Xijun Yan *Editor*

Dan Shen (Salvia miltiorrhiza) in Medicine

Volume 3. Clinical Research

人民卫生出版社
PMPH PEOPLE'S MEDICAL PUBLISHING HOUSE

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Editor
Xijun Yan
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Foreword

Danshen was originally recorded in *Shen Nong's Classic of the Materia Medica*, and detailed information on the herb was also recorded in *Thoroughly Revised Materia Medica* and *The Grand Compendium of Materia Medica* in later ages. Danshen is bitter in taste and slightly warm in nature, and is a commonly used but important drug with the function of activating blood circulation and dissipating blood stasis. Danshen has wide applications and good therapeutic effects, is neutral in nature and non-venomous, and its source is widespread and inexpensive, so it is worthy of research and promotion in clinical settings.

Based on other researchers' and our own long-term clinical experience in the application of Danshen, we have found that Danshen has extensive pharmacologic actions and its unique therapeutic actions can be obtained by flexible combination with other drugs. Clinically, Danshen can be used alone to treat various diseases, and pharmacologic actions can be obtained by combination with other drugs. It can ascend and descend along the channels, and has good therapeutic effects on deficiency syndrome and excess syndrome; thus it can be applied extensively in the clinical treatment of various diseases. Based on a summary of the clinical experience with Danshen of prominent TCM doctors, we propose the following principles and methods which could be used as a reference for clinical medical professionals.

Invigorating Blood and Dissolving Stasis, Treating Upper and Lower Diseases, as Well as the Syndromes of Deficiency and Excess

Treating Upper Diseases

Anemarrhena, Phellodendron, and Rehmannia Decoction combined with Danshen, magnetite, cicada moulting, and cyathula root can be used for treatment of patients with symptoms of *sudden deafness* or hearing loss caused by deficiency in the liver and kidney and stagnation of blood, which has not been cured by long-term use of western medicines. The combination

of Danshen, magnetite, chrysanthemum flower, common self-heal fruit-spike, rehmannia root, Chinese gentian, and cyathula root can be used to treat hyperpyrexia of the liver to eliminate liver fire and to dissolve stagnant blood and promote blood circulation, and good therapeutic effects have been obtained. Danshen and magnetite can be used to treat *hypertension* according to the differentiation of the symptoms, and excellent therapeutic effects have been achieved. Danshen combined with almond, platycodon root, and Sichuan fritillaria bulb etc., has the function of diffusing the lung, activating blood circulation, depressing qi, and stopping coughing.

Treating Lower Diseases

Danshen has the functions of unblocking blood vessels and meridians, activating blood circulation, and removing obstruction in collaterals, and the drug is bitter in taste and acts in lower meridians, so it is especially suitable for chronic diseases of the lower part of the body. For example, when combined with asper-like teasel root, double teeth angelica root, cyathula root, and Chinese taxillus herb belongs, Danshen can be used to treat rheumatic arthralgia in the lower limbs. Combined with honeysuckle stem, swordlike atractylodes rhizome, cyathula root, amur corktree bark, red peony root, cortex moutan, and Chinese pine nodular branch, etc., Danshen can be used to treat beriberoid pyretic arthralgia with the symptom of red swelling joint. Combined with Chinese angelica, suberect spatholobus stem, figwort root, rehmannia dride rhizome, Japanese honeysuckle flower bud, cassiabarktree twig, and pangolin scales, etc., Danshen can be used to treat vasculitis in lower limbs. Combined with Chinese angelica, nutgrass galingale rhizome, common motherwort herb, Danshen can be used to treat menoxenia, menischesis, or blood stasis and abdominal pain after childbirth, and marked effects can be obtained. The same effect can be achieved using Danshen alone: just take Danshen powder with white spirit. Danshen can be combined with rehmannia dride rhizome, prepared rhizome of rehmannia, common anemarrhena, cyathula root, amur corktree bark, hindu lotus stemen, tremolite, fructus corni, wenchow turmeric root tuber, incised notopterygium rhizome and root, and white peony root, etc., to treat liver kidney yin insufficiency or heat accumulation and impotence and prospermia. The above formula is called Essence-Securing and Yang-Raising Decoction (固精启阳汤), with significant therapeutic effects.

Treating Deficiency Syndromes

The symptoms of deficiency syndromes include asthenia of healthy energy due to long duration of disease, weakness of blood circulation, prolonged deficiency, and excessive stasis. Danshen has the functions of removing

blood stasis and producing new blood, promoting blood circulation but not disintegrating blood stasis. It was described by the ancients that the effect of Danshen is equivalent to that of Four Substances Decoction. Although the effect of Danshen might be exaggerated, Danshen does activate blood circulation and dissipate blood stasis. According to *The Grand Compendium of Materia Medica*, Danshen's function is to nourish the blood. Yishen Dingxuan Decoction (益肾定眩汤), which is Lycium Berry, Chrysanthemumm, and Rehmannia Decoction with the addition of Danshen, magnetite, szechwan lovage rhizome, tall gastrodia rhizome, can be used to treat *dizziness* due to deficiency syndrome, especially kidney deficiency combined with blood stasis with the symptoms of *dizziness*, soreness, and weakness of waist and knees, gloomy tongue, deep thin and unsmooth pulse, etc. Danshen is usually combined with stir-baked semen ziziphi spinosae, Chinese angelica, rehmannia dride rhizome, and Chinese magnoliavine fruit, etc., to treat palpitation due to deficiency of blood and insomnia, which was called "cultivating the spirit and calming the mind" in *The Materia Medica of Ming Dynasty* (《大明本草》). Danshen can be combined with mongolian milkvetch root, Chinese angelica, tuber fleeceflower root and medicinal morinda root to treat deficiency-consumption diseases with symptoms of extreme deficiency of qi and blood, deficiency of kidney qi, and stagnant blood.

Treating Excess Syndromes

The six pathogenic factors and the seven emotions can hurt the body, and eventually will cause the stasis of qi and blood and show the symptoms of qi stagnation and blood stasis. Danshen has the functions of activating blood circulation and eliminating stagnation, thus it has been used to treat excess syndromes with certain therapeutic effects. For example, Danshen Beverage is usually combined with sandalwood, villous amomum fruit, and turmeric root tuber to treat patients with hepatogenous gastralgia caused by the depression and stagnation of qi and stagnation of blood; thus it can benefit the patients by regulating vital energy and activating blood circulation. Also, these drugs can complement each other very well. Henoch-Schonlein purpura can be treated with the combination of Danshen, suberect spatholobus stem, Indian madder root, redroot gromwell, and red date. It is called "disintegrating stagnated blood, producing fresh blood"; thus the blood escaped from blood channels could return to the meridians. Patients with mania usually suffer from excessive fire, stagnation, and phlegm, and they can be treated with large doses of Danshen based on the symptoms. Menostasis with the symptom of edema usually can be treated with Five Substances Powder with Poria combined with Danshen, amber, common motherwort herb, mongolian milkvetch root, etc.

Nourishing Blood, Calming the Mind, Eliminating Deficiency-Heat, Stopping Shock, Alleviating Palpitations, and Treating Heart Diseases

Danshen is bitter in taste and cold in nature, and acts on blood and returns to the heart, with the functions of eliminating cardiopyrexia and blood heat, calming the mind and palpitations. Thus, these kinds of diseases can be cured rapidly with correct application of the drug.

Danshen can be combined with Chinese arborvilae seed, Chinese angelica, rehmannia dride rhizome, Chinese magnoliavine fruit, and stir-baked semen ziziphi spinosae, etc., to treat palpitations and insomnia due to deficiency of blood. Yang Supplementing and Five Returning Decoction can be combined with Danshen, prepared liquorice root, and dwarf lilyturf root tuber, etc., to treat severe palpitations which belong to deficiency of heart-qi, qi asthenia, and blood stasis.

Trichosanthes and Chinese Chive Decoction or Kuanxiong Tongbi Decoction (宽胸通痹汤) (Danshen, mongolian snakegourd fruit, longstamen onion bulb, sandalwood, cassiabarktree twig, Chinese pyrola herb, Chinese hawthorn fruit, szechwan lovage rhizome, dwarf lilyturf root tuber, sanchi. red peony root) can be used to treat hypofunction of yang qi in the chest. Pulse-Engendering Powder and Yimai Tongbi Decoction (益脉通痹汤) (Danshen, different leaves pseudostellaria root tuber, dwarf lilyturf root tuber, Chinese magnoliavine fruit, mongolian snakegourd fruit, prepared liauorice root, stir-baked semen ziziphi spinosae, rosewood heart wood, Chinese hawthorn fruit, Chinese pyrola herb) can be used to treat deficiency in both qi and yin. Based on the principle of Honey-Fried Licorice Decoction, Sishen Anxin Decoction (四参安心汤) (Danshen, american cinseng, lightyellow sophora root, figwort root, stir-baked semen ziziphi spinosae, dwarf lilyturf root tuber, prepared liauorice root, cassiabarktree twig, Chinese hawthorn fruit, Chinese pyrola herb) can be used to treat pectoral stuffiness pain and chest pain, insomnia and pavor, *arrhythmia*, etc., and good effects have been obtained in clinical treatment. This formula is especially suitable for patients who have taken other prescriptions for a long time without any effects: in treatment according to pattern differentiation, the drug can rapidly improve the *electrocardiogram* or return it to normal. Stagnation of blood and blood stasis can be induced by hypofunction of yang qi in the chest or deficiency in both qi and yin. According to the theory that "stagnation of qi and blood may bring about pain," Danshen, which has the function of dissipating blood stasis, can be added to prescriptions to obtain good therapeutic effects. It was recorded in *The Grand Compendium of Materia Medica* that Danshen has the functions of activating blood circulation, dredging the pericardium or the envelope of the heart, and treating inveterate diseases of the heart, and it is also recorded in *Materia Medica of South Yunnan* that Danshen has the functions of supplementing the heart, calming the nerves, and treating memory loss, severe palpitation, pavor, and sleeplessness, which demonstrates that Danshen has wide clinical application.

Removing Blood Stasis, Promoting Fresh Blood Production and Circulation, and Treating Acute and Chronic Diseases

Danshen has the functions of activating blood circulation and dissipating blood stasis, promoting defecation and urination, and harmonizing qi and blood; thus, extraordinary effects on the treatment of acute and chronic deathly diseases can be obtained when the drug is used correctly. For example, "Tongmai Shuluo Injection" (通脉舒络注射液) (main components include mongolian milkvetch root, Danshen, and szechwan lovage rhizome, etc.), which was developed according to the theory of "Yang-Supplementing and Five-Returning Decoction" and invented by Wang Qingren of *Qing Dynasty*, has significant therapeutic effects on the treatment of apoplexy; "Naoqiaotong Oral Liquid" (脑窍通口服液) (main components are Danshen, peach seed, forest musk, and lalang grass rhizome, etc.), which was developed according to the theory of "Tongqiao Huoxue Decoction" (通窍活血汤) and invented by Wang Qingren, can be used for patients with the symptoms of water stagnation of the brain, such as apoplexy, brain tumor, and hydrocephalus.

Qingnao Tongluo Tablets (清脑通络片) (main components include Danshen, florists dendranthema, etc.) can be used to prevent and treat threatened apoplexy and apoplexy attacks, and good therapeutic effects can be obtained in both animal experiments and clinical trials, with no toxicity or *side effects* observed so far. The decoction of Angong Niuhuang Wan (安宫牛黄丸) and Danshen can be administered by drench or nasal feeding to coma patients due to obstruction of pathogen and pyretic block. The decoction of Suhexiang Wan (苏合香丸) and Danshen can be administered by drench or nasal feeding to patients with cold retention. However, Danshen Injection by intramuscular or intravenous administration can be used for patients with either cold or pyretic block. The drug can be taken orally with Pujindan Ye (蒲金丹液) (tatarinow sweetflag rhizome, wenchow turmeric root tuber, Danshen, etc.) for coma patients that belong to phlegm and dampness block. 4–20 ml of Danshen Injection can be administered by intramuscular injection or intravenous drip at the same time, and the symptoms can be alleviated or out of danger. Clinical practice has demonstrated that Danshen has the functions of activating blood circulation, dredging collaterals, removing blood stasis and promoting fresh blood production, and promoting defecation and urination.

Danshen has the function of activating blood circulation and dissipating blood stasis, and thus it can be used to treat ischemic stroke. The effect depends on the function of removing blood stasis and promoting fresh blood production. Pharmacological studies have demonstrated that Danshen can inhibit blood clotting and enhance fibrinolysis activity. According to the theory of Traditional Chinese Medicine, "It is better to promote blood circulation, but not stop bleeding" and "It is better to disperse blood stasis to stop bleeding." Danshen has the functions of improving microcirculatory blood flow and increasing blood capillary networks, which can reduce blood vessel pressure at the hemorrhage site and thus explains its function of

stopping bleeding. Therefore, the theory of activating blood circulation and dissipating blood stasis has special effects on hemorrhagic stroke. The effects and the formulas can vary based on normal prescriptions, and reaches the best of using drugs flexibly.

Epilepsy can be treated with Danshen, tatarinow sweetflag rhizome, thinleaf milkwort root, white Indian buead, stiff silkworm, and reddish jackinthepulpit tuber. Yang hyperactivity due to insufficiency of yin in the liver and kidney and phlegm stagnation in superficial venules and lymph vessels can be treated with Danshen combined with dragon's teeth, medicinal cyathula officinalis root, amber, glossy privet fruit, cortex moutan and antelope horn, etc. The above complicated miscellaneous diseases can usually be treated by taking oral decoctions combined with 4 ml of Danshen Injection by intramuscular injection according to the patient's symptoms and signs, and the symptoms can usually be relieved in nonresponders to long-term treatment. To sum up, strange diseases are usually caused by stagnation and prolonged diseases are accompanied by phlegm, which is a key to the treatment of difficult and complicated diseases. As is recorded in *Seeking Accuracy in the Materia Medica*, with its function of eliminating stagnation, Danshen can treat all kinds of diseases.

Clearing Liver, Promoting Gallbladder Function, Dredging Constraint and Stagnation, and Treating Concretions, Conglomerations, Accumulations, and Gatherings with Good Effects

Symptoms such as concretions, conglomerations, accumulations, and gatherings (four types of diseases in TCM) are usually initially induced by liver-gallbladder damp-heat, qi flow disorder in the liver, disturbance of qi movement, or spleen deficiency with damp exuberance, which lead to the disharmony of liver and spleen and dysfunctions of liver, spleen, and kidney. Eventually, these illnesses will result in qi stagnation, blood stasis, and water retention which will accumulate in the abdomen and cause the diseases of concretions, conglomerations, accumulations, and gatherings. Danshen can come into the blood through the liver meridian, and has the functions of promoting blood circulation and qi stagnation, removing blood stasis and promoting water movement, and activating collaterals and subsiding swelling, and thus it is commonly used. For example, hepatitis B belongs to yin insufficiency of the liver and kidney, and can be treated with Effective Integration Decoction, with Danshen usually added into the Decoction. Drugs treating *jaundice* in different phases usually contain Danshen. Patients with dampness and stagnation can also be treated with Danshen in combination with Chinese thorowax root, Chinese angelica, turtle carapace, common oyster shell, chicken's gizzard-membrane, areca peel, Indian buead, common burreed tuber, blue turmeric rhizome, etc. Patients with gallstones can be

treated with Danshen combined with rhubarb, chicken's gizzard-membrane, christina loosestrife herb, Chinese thorowax root, and immature bitter orange.

All of these prescriptions have reliable therapeutic effects in improving liver function, softening the liver and spleen, shrinking lumps, eliminating stagnation, and removing urinary calculus. Pharmacological studies on Danshen have demonstrated that it has the functions of reducing the activity of transaminase, protecting injured hepatocytes, promoting cell regeneration and anti-hepatic fibrosis, etc. This is what is meant in *Shen Nong's Classic of the Materia Medica* when Danshen has the functions of eliminating accumulations and gatherings of cold and heat, breaking concretions, and removing conglomerations.

Dissipating Blood Stasis, Clearing *Sanjiao* Dampness, and Both Yin Edema and Yang Edema can be Treated

Danshen has the functions of promoting blood circulation, clearing waterways, and alleviating edema; thus it can be used to treat edema caused by water retention and blood stasis. Animal experiments have demonstrated that Danshen has the functions of improving renal function, reducing azotemia, and increasing urinary production. Edema belongs to the category of yin water; patients with this disease have symptoms of lower limb and general edema. The symptoms of soreness and hypodynamia are caused by blood stasis and kidney deficiency (e.g., *chronic glomerulonephritis*, chronic pyelonephritis, *nephrotic syndrome*), which can be treated with Yishen Huaru Lishui Decoction (益肾化瘀利水汤) (Five Substances Powder with Poria combined with Danshen, mongolian milkvetch root, Chinese taxillus herb, common motherwort herb, medicinal cyathula officinalis root, Chinese hawthorn fruit, lalang grass rhizome, rice paper plant pith). Patients with edema of the lower limbs, drowsiness acratia, abdominal distension, gloomy tongue with stagnation, knotted and intermittent pulse, etc., caused by deficiency of kidney qi and dampness and blood stasis, usually can be treated with True Warrior Decoction combined with Danshen, peach seed, mongolian milkvetch root, and lalang grass rhizome. Patients with symptoms of deficiency of kidney yang can be treated with Golden Cabinet's Kidney Qi Decoction combined with Danshen, Lalang Grass Rhizome, Eucommia Bark, etc. Patients with symptoms of qi stagnation and water retention can be treated with Bupleurum Liver-Soothing Powder combined with Five Substances Powder with Poria and Danshen, etc. Patients with facial edema (acute renal glomerulus nephritis), which belongs to invasion of the lung by pathogenic wind and disturbance of qi movement in *sanjiao*, can be treated with Maidservant From Yue Decoction with White Atractylodes Rhizome (越婢加术汤) combined with Danshen, Indian buead, asiatic plantain seed, weeping forsythia fruit, etc. Patients with symptoms of lung qi deficiency-cold and impaired waterways can be treated with Linggan Wuwei Jiangxin Decoction (苓甘五味姜辛汤) combined with Danshen, etc., and the therapeutic effects can be enhanced by Danshen.

Clinically, if the symptoms are defined correctly and the prescription and drugs are reasonably used, Danshen can normally help improve urine abnormalities in patients. The movement of fluid in the body depends on the regulatory function of lung qi, the transfusion function of spleen qi, and the transpiration function of kidney qi. When the body is invaded by exogenous pathogens, the functions of visceral organs are disturbed or the visceral organs are deficient in qi, the functions of *sanjiao* will be impaired, waterways will be blocked, and water overflows under the skin and muscle, which will lead to edema. Water and blood are homologous. According to *On Hyperlipidemia* (《血症论》), water and blood have mutual dependence and they hold together; so water retention and blood stasis are interactive. However, both yin edema and yang edema can coexist with stagnation and the only difference is the order of importance and urgency, which is referred to as "unsmooth blood circulation results in water, and water retention results in blood stasis" in TCM.

Cooling Blood, Detoxication, Subsiding Swelling, and Eliminating Carbuncles and Sores

Danshen also has functions of subsiding swelling and relieving pain, cooling blood and detoxication, discharging pus, and promoting the growth of flesh. Danshen can be combined with drugs such as weeping forsythia fruit, snakegourd root, mongolian dandelion herb, mongolian snakegourd fruit, etc., to treat mammary abscess. The drug can be combined with Japanese honeysuckle flower bud, weeping forsythia fruit, frankincense, or myrrh to treat swelling. Patients with acute abdominal pain (acute appendicitis, etc.) can be treated with Dahuang Mudan Decoction (大黄牡丹汤) combined with Danshen, sargentgloryvine stem, etc., and good therapeutic effects have been obtained. Patients with chronic appendicitis can usually be treated with Danshen combined with Chinese thorowax root, Indian buead, Chinese goldthread rhizome, widely costusroot, yanhusuo tuber, nutgrass galingale rhizome, mongolian dandelion herb, medicated leaven, etc.

Danshen also has the function of cooling blood and detoxication, and thus various *poisoning*s can be treated with Lüdou Gancao Jiedu Decoction (绿豆甘草解毒汤) (mung bean, liquorice root, weeping forsythia fruit, noble dendrobium stem herb, Danshen, rhubarb, lalang grass rhizome). Patients with dampness, stagnation, pruritus vulvae, and morbid leukorrhea (e.g. cervical erosion, condyloma acuminatum, etc.) can usually be treated with Danshen combined with amur corktree bark, lightyellow sophora root, raw liquorice root, largehead atractylodes rhizome, swordlike atractylodes rhizome, rhiizoma dioscoreae from Henan of China, glabrous greenbrier rhizome, belvedere fruit, wild dendranthema flower, ginkgo seed, etc. The drugs can be taken orally or used as a washing solution, and significant therapeutic effects have been obtained. Patients with dampness and stagnation and dysentery can usually be treated with Pulsatilla Decoction combined with Danshen. Patients with hyperpyrexia and coma can be treated with Peaceful

Palace Bovine Bezoar Pill decocted with Danshen and taken orally, which can enhance the therapeutic effects and shorten the course of treatment. Patients with scabies with dampness-heat can be treated with Danshen, lightyellow sophora root, and common cnidium fruit, etc., by washing the affected part. It is recorded in *The Materia Medica of Ming Dynasty* that Danshen has the function of treating ulcers and carbuncles, goiters and swelling and erysipelas, discharging pus, relieving pain, and promoting the growth of flesh. Modern pharmacological research has shown that Danshen has strong inhibitory effects against *Staphylococcus*, *Escherichia coli*, *Bacillus proteus*, *Bacterium typhosum*, and has a certain degree of inhibitory effect against *Bacillus dysenteriae*.

In summary, drugs cannot be classified into noble or humble classes; the important thing is how and where to use them. Danshen is cold in nature and bitter in taste, has the function of activating blood circulation and dissipating blood stasis, activating collaterals and dredging *bi* symptoms, promoting blood circulation but not breaking stagnated blood, reaching viscera and all bones, calming the nerves and relieving restlessness, detoxicating and cooling blood, subsiding swelling and relieving pain, promoting tissue regeneration, and treating ulcerative carbuncles and scabies. When a flexible and changeable prescription is made according to the symptoms, good effects usually can be obtained by application of Danshen. However, we need to pay attention to the fact that large doses of the drug can induce diarrhea, and thus people with loose stool due to spleen deficiency and pregnancy should use the drug with caution. There is a great difference in the dosage of Danshen between ancient and modern society; the dosage for adults usually ranges from 10 to 30 g, reaching up to 60 g for some people. The dosage should be small at the beginning and can be increased gradually.

Preface to Dan Shen (Salvia miltiorrhiza) in Medicine

In the 2008 press conference on the publication of the Chinese edition of the *Dan Shen* (*Salvia miltiorrhiza*) *in Medicine*, several volume editors suggested that the book should be translated into English and distributed internationally. They all believed that the medical communities are enthusiastic about TCM research, and that among the studies on single herbs, the study of Danshen has taken the lead. Therefore, it was a worthy undertaking to introduce the study conducted by the Chinese people over the past 1,000 years, and especially in the past 30 years, to the world. Meanwhile, I was asked unanimously to be its editor-in-chief. After several years of hard work by nearly 100 professors and research scientists, the translation is finally complete.

The English edition of *Dan Shen* (*Salvia miltiorrhiza*) *in Medicine* is based on its Chinese edition. Modifications include changing the five-volume format to one volume and deleting some duplicated portions in the Chinese edition. Since the chapters in each volume of the Chinese edition were written by many individuals, details such as biological properties and ancient literature reviews were repeated many times, and the duplications were deleted in the English edition. Also, the various names of Danshen were unified. The appendix in the fifth volume, the prescriptions or formulas in ancient China, and the chapter on information management in the fourth volume were also deleted. The introduction to the production region, common names, and phytochemical components had appeared in the first three volumes, while this time only their first appearance was preserved. Some typos and oversights were corrected after consulting with volume editors. New progress in Danshen research was included in this book, such as the development of Salvianolate Lyophilized Injection, which finally came on the market in 2011 after 8 years of strict examination, and it was a landmark event in the development of TCM injections. It is unfortunate that we could not include the data on Qishenyiqi Dripping Pills, as the papers have not been published yet. The drug, developed by academician Boli Zhang, passed large-scale, evidence-based medicine clinical research trials in 2010, the first for a TCM drug, and won the 2011 National Science and Technology Progress Award.

In principle, the English edition of *Dan Shen (Salvia miltiorrhiza) in Medicine* is the translation of the Chinese edition, thus preserving the latter's framework. Because the Chinese edition was written by more than 100

scholars and published in five volumes, the styles and layouts were not identical. For example, some references were listed at the end of the chapter, while some were listed at the end of the section. The English edition did not change the style.

Dan Shen (*Salvia miltiorrhiza*) *in Medicine* has amassed Danshen research results since the times of ancient China—it is not only a magnificent historical scroll, but also a huge work which shines the light of modern science and technology.

I sincerely thank academicians Yongyan Wang and Boli Zhang. They have given me so much substantive guidance and encouragement despite their busy schedules. Without their help, it would have been impossible to finish the work. I also want to thank every author and volume editor who has participated in the writing and editing of both editions of this book; they have solved various problems which arose during the writing and translating processes. Last but not least, I want to thank the comrades working in the office of *Dan Shen* (*Salvia miltiorrhiza*) *in Medicine*, who have worked patiently and diligently over the past 15 years, collecting and organizing data and information.

The publication of the English edition of *Dan Shen* (*Salvia miltiorrhiza*) *in Medicine* is a testimony of our sincere desire for the communication and discussion of TCM among international communities. We earnestly welcome suggestions and criticism from our colleagues around the world.

Xijun Yan

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About the Chief Editor

Dr. Xijun Yan was born in 1953 in Zhenyuan, Gansu province. Dr. Yan is a chief pharmacist, and enjoys the Special Expert's Allowance from the State Council of China. At present, he is a President of Tianjin Tasly Group; serves as a member of traditional Chinese medicine (TCM) Standardization Technical Committee; the deputy director of Science Popularization Committee of Chinese Pharmaceutical Association; a member of Expert Committee of The National Pharmaceutical Industry Policy Research Project of Chinese Pharmaceutical Association; the vice president of Tianjin Pharmaceutical Association. Dr. Yan is the first person to propose the concept of "modern TMC drugs" and the new mode of TCM R&D, and has engaged for a considerable length of time in research and industrial development of modern Chinese medicine. Dr. Yan has actively undertaken key national projects on the research and development of important new drugs, supervised or participated in 38 projects in the National Key Science and Technology Projects in the 9th and 10th "Five Year Plans"; National Level Promotion Program of Scientific and Technological Achievements; National High-tech Industrialization Demonstration Project, etc. Dr. Yan has 69 patents and more than 50 publications, including The Standards of Diagnosis, Efficacy, and Medication in TCM's Heart Disorder (one of the editors-in-chief); How TCM Drugs Enter the EC Market (associate editor-in-chief); The Ideas and Methods of Modernization of TCM Research (one of the editors-in-chief); The Reflection and Practice of the Modernization of TCM Preparations; On the Trends of Modern TCM Industry, etc. Dr. Yan has been awarded honorary titles like National Model Worker; National Outstanding Scientific and Technological Worker; National Outstanding Pharmaceutical Entrepreneur; National Health Industry and Enterprise Advanced Individual; National Model Worker in Chinese Medicine System. Dr. Yan has received numerous awards, including the Third National Prize for Scientific Advancement, the Second Prize for Scientific Advancement by the People's Liberation Army, and the First Prize for Scientific Advancement by Tianjin Municipal Government.

Introduction by Chief Editor

After the hard efforts of an entire decade, by nearly 100 experts from home and abroad, the *Dan Shen* (*Salvia miltiorrhiza*) *in Medicine* is finally going to the press.

Danshen (*Salvia miltiorrhiza*) has a time-honored history of research, development, and application in China's traditional medicine, and is held in very high esteem by the medical community. We hope that the five-volume series now made available to the readership will make a worthwhile contribution to its research and application.

Salvia Carries the Dream of Internationalization of Traditional Chinese Medicine

In 1996, China began to formulate and implement a strategy for the modernization of traditional Chinese medicine (TCM). However, the question of how in practice to systematically develop traditional medicine, passed on from generation to generation over several millennia, remained a real and persistent challenge to the academic and industrial dimensions of TCM. In 1998, a discussion among several TCM experts from home and abroad gave us the idea of compiling the *Dan Shen (Salvia miltiorrhiza) in Medicine*. The experts discussed not only the present state and the future prospects of modernizing Chinese medicine itself, but also the growth of the Chinese medicine industry, and the issues in developing big brand modern TCM drugs. The discussion was especially centered on the utilization of Danshen, and the topics ranged from its collection and processing in ancient times to the widespread application of various Danshen preparation, from its effective components to its pharmaceutical action, from its cultivation and plantation to its modern industry chain, from its compound prescriptions and to modern Compound Danshen Dripping Pill (Dantonic™), from its R&D to the rapid growth of a modern TCM enterprise—the Tasly Group. Is it possible that a unique industrial technology and economy grow out from a single TCM drug and a series of research activities focused on the drug? Is it possible that the unique industrial technology and economy stimulate new lines of thinking and novel approaches to the modernization and internationalization of TCM? Is it possible the unique industrial technology and economy push forward the systematic project of TCM research and development? These and several other questions roused profound interest

among experts in deepening the research on Danshen, and the compilation of the *Dan Shen* (*Salvia miltiorrhiza*) *in Medicine* was originated from this initial driving force.

For thousands of years, TCM has made enormous contribution to the health and multiplication of the Chinese people. But why is it so hard for TCM to be accepted and acknowledged in the international community? Why do some people still have doubts about the scientific nature of TCM? To be able to continually promote the modernization and internationalization of TCM, these questions must have affirmative answers. In order to introduce Chinese medicine to the rest of the world, and let the international community understand, accept, and use TCM, we must resort to modern technology to re-develop TCM again. We also have to give TCM a fresh interpretation, using the standardized scientific and digitized languages. It is indeed necessary to select a certain Chinese medicine for an exploratory trial, and this Chinese medicine must meet a number of requirements. First, it should have both a long history of inheritance and deep accumulation of clinical knowledge; second, it has been systemically studied with modern means of science and technology, and its effective substances and the mechanism of action have been elucidated, relatively speaking; third, it has made a comparatively great contribution to human health, especially in terms of satisfactory effects in the treatment of serious diseases; fourth, its industrialization has been successful, having representative name brand products; fifth, it has sufficient resources to ensure the sustainable industrialization; and sixth, it should be conducive to a progressive growth of Chinese medical research. We believe that Danshen meets all these requirements, and it could showcase a wealth of innovative achievements and profound knowledge, and become a model in promoting the modernization and internationalization of TCM.

Hundreds of Scientists Involved in the Work

It is with this underlying ambition in mind that we started data collection, collation, and *compilation of the this book*. *Nearly 100 experts* from home and abroad have participated in this huge project. The expert team includes both world renowned senior scientists and young scholars with outstanding achievements. Some of them are from prestigious research institutions and universities, others from industrial regulatory bodies, and still others from the frontline of industrial development. Their expertise covers multiple research areas, including medicinal botany, phytochemistry, pharmaceutical analytics, pharmacology, toxicology, medical preparation, medicine reviewing, TCM, and integrative medicine. We have been particularly fortunate in that our research and compilation work has received strong support and guidance from the academicians Yongyan Wang and Boli Zhang, as well as from several relevant leaders and experts. Each writer adhered to the mission of "being responsible for both past and future generations" and followed stringent scientific spirit and serious academic attitude, searching extensively, and studying strenuously and carefully. They referenced nearly 50,000 pieces of literature, including books, research articles, trial reports,

and others, directly quoted 7,235 references, thus laying a solid literature foundation for the work.

Botany of Danshen documents Danshen herbal research, medical source survey, identification of medicinal characteristics, distribution and ecological environment, biological features, in vitro culture, and genetic breeding; describes and reviews research on Danshen germplasm resources and genetic diversity. The detailed research provides guidance for scientific and large-scale cultivation of Danshen, and contributes to the securing of resources for its further development and industrialization.

The phytochemical research of Danshen originated in the 1930s. Centered on the extraction and isolation of the effective components from Danshen, researchers have utilized various techniques and spectral analytical methods, including the 2D nuclear magnetic resonance. These developments are all accounted for in *Phytochemistry of Danshen*. The volume also systematically describes the chemical structure of Danshen's liposoluble ingredients (tanshinones) and water-soluble ingredients (salvianolic acids), methods for extraction and isolation, spectral characteristics, the chemical and physical properties, the biosynthesis pathways, and chemical synthesis. The chemical ingredients of other plants in the genus *Salvia* are also described.

Since the 1930s, domestic and international experts have carried out in-depth, or even spectacular, intensive pharmacological research into the effective ingredients of Danshen. They have analyzed its pharmacological action and mechanisms in the cardio-cerebrovascular system, the nervous system, the digestive system, and its anti-bacterial and anti-inflammatory effects. In the *Pharmacology of Danshen*, the liposoluble and water-soluble ingredients of Danshen are described in detail for their pharmaceutical functions. The lipo-soluble ingredients have the functions of anti-bacteria and regulation of the endocrine, while the water-soluble ingredients have the functions of anti-oxidation, anti-ischemia, and inhibiting the expression of cell adhesion molecules. The multi-target effects of Danshen and its preparations in the treatment of microcirculatory dysfunction have been recognized by the international pharmacological scholars. The volume reviews and summarizes the achievements of these researches in considerable detail, revealing the leaps and bounds of modern pharmacology in recent years.

Quality Control of Danshen is based on research into the pharmacologically effective components of Danshen. The volume introduces a QC system which combines fingerprinting technology with multi-indicator analysis. In fact, this QC system is a full range of Danshen quality control system, integrating modern TCM chemistry, pharmacological pharmacodynamic, and pharmacokinetics, covering Danshen identification, content determination, fingerprinting spectra, in vivo metabolic processes of major ingredients, and the effect of the preparation process on the quality of drugs, etc. The volume shows comprehensively and systematically the present state of Danshen quality control and highlights the most recent achievements.

Clinical Research of Danshen records 1,261 carefully selected Danshen-containing prescriptions from over 2,000 medical works since the Qin and Han dynasties. It reports the summarized results of mathematical and

statistical analysis, showing how Danshen-containing drugs were processed, with which herbs Danshen was combined, and what kinds of preparations were used. The changes in the frequency of other herbs combined with Danshen, and the indications of these prescriptions have been compared. The ancient Chinese pointed out explicitly a long time ago that the basic functions of Danshen are to invigorate blood and dissolve stasis, and clear blood vessels. They also summarized that "the functions of a single Danshen is equal to those of Four Substances." In the field of modern medicine, Danshen enjoys an even wider application. The authors of the volume have carried out exhaustive documentation and summarization of the clinical applications Danshen, especially the experience from famous TCM doctors. In this volume, the methods of evidence-based medicine have been used to summarize the functions of modern TCM drugs, Compound Danshen Dripping Pill (Dantonic™) in the prevention and treatment of coronary heart disease and its multiple risk factors, and proposes for the first time the multiple-target mechanism of Dantonic™'s effects on the treatment of coronary heart disease and angina. In addition to their wide application in the treatment of cardio-cerebral vascular diseases like coronary heart disease and ischemic stroke, Danshen preparations are used to treat other diseases, and it has proved to be effective for chronic hepatitis, chronic nephritis, chronic kidney failure, type II diabetes, blood diseases, infectious diseases, and skin diseases. All of these are systematically described in the volume. Such an integration will doubtlessly be beneficial to clinical workers in the fields concerned.

Looking at the history, it is safe to say that Danshen has been one of the most extensively used drug in TCM since ancient times, and it is one of the TCM herbs studied with modern techniques the earliest and most thoroughly. Through the research on Danshen in botany, biology, chemistry, pharmacology, and clinical trials, we now have comprehensive understanding of its effective components, clinical effects, and indications. The study on the effective components of Danshen serves as the foundation for the study on its pharmacological effects, and based on the pharmacological study, a batch of widely applied and effective modern Danshen preparations have been developed. Danshen research is a model of multidisciplinary, multi-domain, multi-faceted integration, and cooperation and will surely be an important milestone in the process of modernization of TCM.

New Challenges and Opportunities in the Era of Health Care

Since the 1970s, the spectrum of human diseases has shifted from the infectious to lifestyle diseases, geriatrics, and degenerative diseases. This has brought about significant changes in medical modes and treatment philosophies; from the biological medicine mode to a "biological-psychological-social" mode; from the purely passive disease treatment to the combination of "prevention–healthcare–treatment–rehabilitation." Also, people are paying more attention to a timely adjustment of, and recovery from, sub-health state. These trends suggest that the society has entered an

era of "enlarged health." People hope to attain the objective of enjoying a longer and healthier life by means of full care and comprehensive protection. To put it simply, we now strive to have a life journey which consists of "eugenic birth, longevity life, delayed aging, and peaceful departure." These changes have posed new challenges to medical research, and guided medical R&D into a new age.

Started from searching for the chemical basis of life substances in 1780s, the drug development mode of modern medicine has gradually evolved into looking for chemical compounds. The trends of contemporary drug development show that a new drug can only be successfully developed after screening thousands of compounds, and the cost of R&D for listed drugs increasing annually, while the speed of new drug development is slowing down, which leads to a vicious circle characterized by high input, high risk, and low output. There is urgent need for a fresh drug R&D mode.

Very different from the Western mode, the TCM mode started from a holistic concept, based on individualized diagnosis and treatment and knowledge accumulation, used the resources of plants, animals, and minerals, and developed preparations of pills, powders, pastes, etc. These TCM preparations, tested through clinical application over thousands of years, contained a variety of pharmacodynamic active substances, and their action mechanisms integrated antagonistic, supplement, and regulation as one. Thus, our ancestors have left us a drug resource treasure, which is our unique advantage. This advantage is also a more economical and efficient path to the discovery of new drugs.

The promotion of TCM modernization strategy, and the implementation of policies such as the Scientific and Technological Action of TCM Modernization (Outline), and the Development Outline for TCM Modernization, has enabled the construction of a system for scientific innovation of Chinese medicine. Contemporary high-tech innovations are increasingly used in the field of TCM, engendering a diversified research and development of TCM. Although the most varieties and the most widely used TCM drugs are traditional preparations, modern TCM drugs have gradually matured, and the exploration of chemical TCM, biological TCM, and metabolic TCM is receiving increasing attention. Modern TCM drugs are those based on TCM formulas and prescriptions, but manufactured using modern technology to extract effective components, using fingerprinting and chromatographic techniques for qualitative and quantitative quality control, using online data collection, analysis and feedback function of information technology to adapt to the new industrialized production requirements. Chemical TCM drugs are drugs obtained using chemical methods to isolate from TCM or herbal drugs single effective ingredients that could not be totally synthesized, and use them as the lead compounds to generate monomer compounds drugs with defined structures after in-depth study of chemical and biological activities, and by structural modification and transformation.

The priorities in the exploration of biological TCM drugs are planting of medicinal plants, extraction of the effective components, and manufacture of the preparations. In addition, bio-techniques could be used to discover or invent new effective components, to improve the effectiveness of TCM

drugs and the recovery of the effective components, as well as to reduce toxic and side effects. The so-called metabolic TCM drugs are to be searched for new active substances (effective components, effective fractions, or new lead compounds) from the metabolic process of TCM drugs in human or animal bodies, and use them for new drug development. It can be predicted that new techniques and new fields of Chinese medicine R&D will keep springing up. The key is to encourage diversified innovation and exploration based on different technical routes.

The aim of *Encyclopedia of Danshen* is not just to focus on a single TCM herb, but to use the rich TCM drugs and prescriptions as a medical resource treasury, to combine innovative thinking in TCM with modern medical techniques, and to explore new modes for pharmaceutical R&D.

Cooperation to Develop a Blockbuster of Traditional Chinese Medicine

Historically, the typical mode of practicing TCM has been to run a mom-and-pop style operation, composed of a storefront and a backroom workshop. The introduction of modern industrialization has changed the modes of both innovation and industrial organization of TCM. Multidisciplinary cooperation and industry—academia—research integration have become the best approaches to TCM pharmaceutical R&D.

China has a large number of TCM preparations, but few have a market sales in excess of 500 million Yuan, and even fewer with a market sales over 1 billion Yuan. For TCM drugs to meet the standards of modernization and internationalization, for TCM enterprises to become large industry, characteristic industry, or even competitive industry, name brand products and large-scale production are essential. Analyzing the knowledge economy, industry economy, and technology economy of TCM from the point of view of economics, we can see both the huge potential of TCM and the gap between TCM industry and modern pharmaceutical industry.

Starting with a single TCM herb Danshen, bringing together the elite researchers at home and abroad, through a comprehensive and systematic study, *Dan Shen* (*Salvia miltiorrhiza*) *in Medicine* has demonstrated the quality, effectiveness, safety, and toxicological and pharmacokinetic characteristics of Danshen-containing drugs. Moreover, it has demonstrated the scientific nature of TCM with detailed and accurate research results, which will unquestionably contribute to the understanding, acceptance, and utilization of TCM drugs by more people, and this is in turn laying a scientific foundation for the expansion and further strengthening of the TCM industry.

The comprehensive and systemic study of Danshen shows that a "blockbuster" type of TCM drug can be developed. The industrialization of TCM has a character of close connections among multiple industries, so the key is to actively exert the gathering and coordinating role of TCM industrial chain to promote the technological transformation, standards upgrades, and structural optimization in the entire industry, and realize the economic value of TCM in various links of the chain, including TCM

agriculture, TCM industry, TCM commerce, and TCM knowledge industry.

A single TCM herb can be used in a variety of prescriptions to benefit the health of many patients; a TCM industrial chain can also boost the economy of certain areas. I believe that the *Encyclopedia* can provide inspiration for the development of TCM resources and TCM industry.

Inheritance and Innovation

A comprehensive summary of Danshen research over thousands of years is both a grand event to revitalize TCM and a difficult task. This series contains not only the original research on Danshen by ancient people and contemporary scientists, but is also the fruit of strenuous labor and a large amount of pioneering work on the part of each author. To summarize Danshen research is to shoulder not only the burden of inheriting previous experience, but also the burden of opening the future and deepening innovation.

As the titled Encyclopedia indicated, this series not only strives to be "extensive and comprehensive," but also attempts to be "excellent and profound." Therefore, in terms of compilation style, we not only try to maintain the uniformity in style and systematicness in content, but also take into consideration the uniqueness of each volume, so that the characteristics and progress in each field can be reflected. The book is based on a single herb, Danshen, thoroughly going through the literature from ancient till modern times, with the purpose of reflecting from a certain angle the progress and development of TCM through generations. We divide the series into volumes in terms of botany, phytochemistry, pharmacology, quality control, and clinical research, in order to reflect the entire picture of Danshen research on one hand, and extract the essence of the research on the other, so as to reach the goal of integrating the practicality, comprehensiveness, and prospectiveness in one book. We adopted the approach of "breaking down the institution barriers," bringing together nearly 100 experts from the forefronts of their relevant fields. We advocated brainstorming and free debate, as well as the accumulation of collective knowledge and wisdom to develop the Encyclopedia into a genuine milestone in Danshen research.

Memories pass through thousands of years, and science is an endless frontier. The modernization and internationalization of TCM is an ongoing process, science is being advanced, technology is being innovated, cross-disciplinary achievements are being integrated, and in-depth research into Danshen is being pushed forward in multiple sectors. There is every reason to believe that this research will continue to be enriched and replenished with an ever-increasing number of new and even more in-depth fruits. The modernization of Chinese medicine is of course more than just producing a collection of academic and technical research papers and awards. It also calls for more TCM products to drive the relevant industries, even new cultural and humanitarian philosophies, which in turn pose new themes and topics to Danshen research for our continuously to explore and innovate. With further research and accumulation of findings, we will no doubt be able

to come up with an additional volume or a sequel to this book, bringing Danshen research to ever deeper and higher levels.

The publication of the book is first of all made possible by the creative achievements of our predecessors in various ages, and by the long history and timeless essence of Chinese culture and Chinese medicine. Our most deeply felt gratitude, then, goes to our ancestors, for this precious scientific and cultural heritage.

In the process of compilation, the associate editors of the book, leaders of various institutions and agencies, colleagues, and friends from home and abroad who are enthusiastic about TCM have given strong support and great help. The chief editors, associate editors, and editors of individual volume, as well as colleagues of the *Encyclopedia* compilation office, have made enormously strenuous efforts toward the publication of the book, and it is to them that I hereby extend my sincerest gratitude. A special mention is due to these experts who participated in this project. They themselves are accomplished experts on Danshen research. They bear the heavy research work of their own, and shared the work of writing this book. Thanks go to the experts for their research accomplishment and hard work. The academicians Yongyan Wang and Boli Zhang sacrificed from their precious time to review the manuscript and to author the Prefaces. All of our editors and compilers extend their deepest gratitude to them.

In terms of compilation style, we applied uniform requirements while leaving relatively great room for each volume in order to allow the chief editors of each volume to exercise judgment according to discipline-specific features and the particular status of research. Therefore, it was impossible to achieve perfect coherence in the writing style and length. The research literature on Danshen transcends several millennia and country borders, and covers multiple disciplines. Despite arduous research and diligent search efforts on the part of various editors and compilers, errors and mistakes may still exist. Collective authoring of a five-volume encyclopedic series calls for enormous amounts of work. Therefore, even repeated elaboration and modification by multiple experts may still leave some room for improvement. We sincerely hope that friends and colleagues in the Chinese medicine research and industry, as well as the hopefully vast readership at large will offer their criticism and comments.

Xijun Yan

Application in Medicine Systems

1

Yi Zheng, Xuewen Zhang and Jiaoli Guo

Modern pharmacological studies on Danshen have shown that the pharmacologic actions of Danshen mainly include dilating vessels, promoting blood flow, improving microcirculation, changing blood viscosity, increasing myocardial blood and oxygen supplies, reducing myocardial consumption of oxygen, etc. The drug is used to treat diseases of the cardio-cerebrovascular system. In addition, Danshen also has antitumor, antibacterial, and anti-inflammatory functions. Therefore, Danshen has wide clinical application. In recent years, there has been an increase in the number of reports on the clinical application of Danshen extract and Danshen compound preparations. Danshen is seldom used alone; rather, it is usually combined with other drugs to form compound preparations. Various Danshen preparations have been developed, such as Compound Danshen Tablets, Compound Danshen Dropping Pill (Dantonic™), Compound Danshen Granules, Compound Danshen Capsule, Compound Danshen Oral Liquid, Compound Danshen Aerosol, and Compound Danshen Injection (CDI), etc. The successful development of these preparations has improved product quality, enhanced efficacy, and opened up broader prospects for Danshen's clinical application.

Y. Zheng (✉) · X. Zhang · J. Guo
Shengli Hospital of Shengli Petroleum Authority, Shandong, China
e-mail: zhengyiphd@yahoo.com.cn

1.1 Diseases of Circulation System

Danshen has the function of effectively dilating the coronary artery, increasing coronary blood flow, reducing heart rate, inhibiting platelet aggregation and thrombopoiesis induced by platelet activation factors, promoting the recovery of injured cardiac muscle, increasing cardiac contractility, and protecting cardiac muscle cells; thus it can be widely applied in treating the diseases of the circulation system.

1.1.1 Coronary Heart Disease and Angina Pectoris

The preparations of Danshen used in the clinical treatment of coronary heart disease are mainly decoctions and compound injections. Compound Danshen decoctions are usually combined with other drugs such as the qi-boosting drugs ginseng and astragalus root, qi-moving drugs common aucklandia root, Sichuan lovage root, and sandalwood, and the blood-invigorating drug safflower. Compound injections are usually combined with drugs for supplementing qi, nourishing yin, and activating blood circulation. The application of Danshen preparations can also be adjusted in timing and dosage.

Liu [1] observed the effect of modified Danshen Beverage on the treatment of 120 patients with coronary heart disease and Angina pectoris. 120 patients in the treatment group were

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administered modified Danshen Beverage; the prescription included 20 g Danshen, 10 g ginseng, 10 g American ginseng, 10 g villous amomum fruit, 10 g Leech, 10 g Sanchi, and 6 g sandalwood, with a course of treatment lasting 4 weeks. 86 patients in the control group were orally administered Compound Danshen Tablet. The results showed that the total effective rates in the treatment group and control group were 91.67 and 71.07 %, respectively, and there was a significant difference between the two groups ($P < 0.001$). ECG efficacies in the treatment and control groups were 55.1 and 39.5 %, respectively, and the difference was statistically insignificant ($P > 0.05$). The blood lipids and hemorheology indices in the two groups changed after treatment. The rate of reduced or ceased use of nitroglycerin in the treatment group was 91.4 %, and in the control group was 67.8 %; the difference was significant ($P < 0.01$). The authors concluded that the modified Danshen Beverage has the functions of improving coronary artery blood supply, reducing blood lipids, reducing blood viscosity, and inhibiting myocardial ischemia.

Li et al. [2] observed the clinical therapeutic effects of combined Chinese and Western medicines on the treatment of unstable angina pectoris (UAP). 98 patients with UAP were randomly divided into treatment and control groups, 49 patients in each group. The patients in the control group were administered with 5-isosorbide dinitrate (5-ISMN2) by intravenous drip; the patients in the treatment group were administered with, in addition to 5-ISMN2, Compound Danshen Aerosoleach, four sprays per time, three times a day. The results showed that in the treatment group, some therapeutic effects on improving angina pectoris symptoms, physical signs, and ischemic electrocardiogram, etc. were observed; the drug also has the function of reducing total cholesterol, LDL level, and platelet adhesion rate, and stabilizing plaques. They found that combined treatment with Danshen for UAP was better than that of 5-ISMN2 used alone.

Meng and Zou [3] reported the effect of modified Pulse-Engendering Powder combined with Danshen Beverage on the treatment of 60 patients with coronary heart disease and angina pectoris. The patients in the treatment group were administered with 30 g of heterophylly false satarwort root, 15 g of Radix ophiopogonis, 10 g of Chinese magnolia vine fruit, 10 g of Danshen, 6 g of villous amomum fruit, and 6 g of liquorice root. The above drugs were decocted with water and taken one dose twice a day for 2 weeks as one course of treatment. The patients in the control group were administered with 10 mg of isosorbide dinitrate three times a day. The results showed that angina pectoris in the two groups after treatment was significantly relieved and the average number of days in the treatment group and control group was 3.6 ± 3.2 days and 3.5 ± 4 days, respectively. The average number of days when angina pectoris disappeared in the treatment group and control group was 11.1 ± 8.9 and 13.8 ± 9 days ($P < 0.05$), respectively.

Hu and Yang [4] reported the effect of modified Muxiang Danshen Beverage (木香丹参饮) on the treatment of coronary heart disease and angina pectoris. The basic prescription contained 15 g of common aucklandia root (木香), 6 g of clove flower (丁香), 12 g of round cardamon kernel (白蔻仁), 6 g of villous amomum fruit (砂仁), 12 g of agastache (藿香), 6 g of sandalwood (檀香), 30 g of Danshen, and 6 g of liquorice root (甘草). The above drugs were decocted and administered with water and divided into two parts, to be taken as one part twice per day. The results showed a therapeutic effect on the symptoms of angina pectoris: of the 42 patients, there were 15 patients with a marked effect, 23 patients with an effect, and 4 patients without effect. The effective rate was 90.48 %. Regarding therapeutic effects on the electrocardiogram ST-T segment, of the 42 patients, 11 patients had a marked effect, 16 patients had an improving effect, and 15 patients had no effect; the effective rate was 64.29 %.

Chen and Gao [5] reported the effect of modified Harmonious Yang Decoction and Danshen Beverage on the treatment of 43 patients with coronary heart disease and angina pectoris. 42 patients in the control group were treated with western medicines; 20 mg of

isosorbide mononitrate was orally administered twice a day, along with 75 mg of enteric-coated aspirin once a day. The patients in the treatment group were administered with the above western medicines plus TCM decoctions, i.e., modified Harmonious Yang Decoction and Danshen Beverage, which contained 30 g of prepared rhizome of rehmannia (熟地), 30 g of Danshen, 15 g of antler glue (鹿角胶), 15 g of mongolian snakegourd fruit (全瓜蒌), 6 g of cassia bark tree twig (桂枝), 6 g of villous amomum fruit (砂仁), 6 g of sandalwood (檀香), 6 g of raw liquorice root (生甘草), 10 g of szechwan lovage rhizome (川芎), and 10 g of white mustard seed (白芥子). The above drugs were decocted and taken with water, one dose twice a day, for 15 days as one course of treatment, and the two groups were treated in two consecutive courses. The therapeutic effects were evaluated at the end of the treatment. The result showed that effective rate in the treatment group was 97.67 %, which was significantly higher ($P < 0.01$) than that of the control group, which was 76.19 %.

In the clinical application of Danshen's modern preparations, Compound Danshen Injection (CDI) occupies a very important position. CDI can significantly improve blood viscosity, so that blood flow is accelerated and intravascular pressure is reduced. CDI can antagonize calcium, dilate blood vessels, increase blood flow, and improve microcirculation of the heart. It also has the function of inhibiting platelet adhesion, aggregation and release, and improving prostacyclin metabolism, etc. These functions have been documented in large amounts of clinical literature, and CDI has been proven to have reliable therapeutic effects. On the basis of using CDI alone, various injections with the function of activating blood circulation, such as daidzein, and with the function of supplementing qi and nourishing yin, such as Shenmai Injection, etc., have been developed.

Lu and Xu (1996) observed 84 patients with average ages of 53 ± 8 years in a control group, and 124 patients with average ages of 56 ± 9 years in the Danshen treatment group. The patients in the control group were administered with 250 ml of low molecular dextran combined with 5 ml of 25 % magnesium sulfate, 5 ml of 10 % potassium chloride, and 8 IU human insulin by intravenous drip at 30–40 drops/min, once a day, for 2–3 weeks as one course of treatment. The patients in the Danshen treatment group received the same treatment as those in the control group, but received an additional 8–12 ml of Danshen Injection. The therapeutic effects were evaluated according to clinical symptoms and electrocardiograms. The results showed that the marked effective rate and improvement rate in the Danshen treatment group were higher than those in the control group, the total effective rates of the two groups were 90.8 and 81.3 %, respectively, with a significant difference ($P < 0.01$). Judging by ischemic electrocardiograms, the marked effect rate and improvement rate in the Danshen treatment group were significantly higher than those in the control group, and the total effective rates were 62 and 41 %, respectively ($P < 0.01$). The effective rates of reducing arrhythmia recurrence in the two groups were 71.7 and 48 %, respectively ($P < 0.01$), which demonstrated that the recurrence rate of arrhythmia in the Danshen treatment group was significantly reduced compared to that in the control group. During the treatment period, neither abnormal changes nor any adverse reactions were shown in blood and urine routine assays, and the blood sugar and liver and kidney functions were normal.

Yang [6] reported the application of Shenmai and Danshen injections in the treatment of 35 patients with coronary heart disease and angina pectoris. The patients were administered with 30 ml of Shenmai Injection and 30 ml of Danshen Injection by intravenous drip, once per day for 3 weeks, and the results showed the treatment had significant anti-angina pectoris effects.

Fu et al. [7] reported the application of 0.5/250 ml of puerarin and glucose injection combined with 16 ml of CDI in the treatment of 44 patients with coronary heart disease and angina pectoris, and the results showed that in the treatment group there were 31 patients with a marked effect, 10 patients with an effect, 3 patients without effect, and the total effective rate was 93.2 %.

There is a report showing that the effectiveness of Danshen drugs might vary with the timing of drug administration. Xing [8] reported the application of CDI in the treatment of 120 patients (treatment group: 80 patients, control group: 40 patients) with coronary heart disease and angina pectoris and blood stasis based on temporal rhythm. The patients were divided into a morning group and afternoon group, with the same drug and dosage (16 ml of CDI) administered by intravenous drip. The results showed that the total effective rates of the treatment group in the morning and control group in the afternoon were 95.0 and 77.5 %, respectively, and the difference between the two groups was significant ($P < 0.01$). The results demonstrated that better therapeutic effects of Danshen could be obtained when the heart of the patient was in a vigorous condition.

Mao et al. [9] reported the application of CDI and Danshen injection in the treatment of 102 patients with coronary heart disease, based on the theory that Danshen has the effects of activating blood circulation, dissipating blood stasis, nourishing the heart to promote blood circulation, and benefiting vital energy and strengthening yang. 6 ml of CDI and 6 ml of Danshen injection were mixed together, then the acupoints of Inner Pass (PC 6), Heart Shu (BL 15), and Jueyinshu (BL 14) were selected and the liquid was injected after needle sensation. Heart Shu and Jueyinshu received 2 ml of the injection each time, and Inner Pass received 1 ml. The acupunctural injection was performed once every other day for 20 days as one course of treatment, and usually two courses of treatment were necessary. The synergistic effects were obtained by the combination of acupuncture and medication. The effects were judged according to clinical symptoms, electrocardiogram and hemorheology. The total effective rate of clinical symptoms was 96.5 %, the total effective rate of improvement of electrocardiogram ST-T was 82.9 %, and both whole blood viscosity and serum viscosity were significantly reduced.

Zhang [10] reported the application of compound Danshen Aerosol on the treatment of 80 patients with coronary heart disease and angina pectoris. The patients were sublingually administered with 3–5 sprays of the aerosol three times a day, for 7 days as one course of treatment. 40 patients in the control group were administered with Isosorbide Dinitrate Tablet. The results showed that the total short-term effective rates for angina pectoris in the treatment group and control group were 92.25 and 85 %, respectively; judging by electrocardiograms, the total short-term effective rates were 70 and 50 %, respectively, and the differences were significant ($P < 0.05$). The immediate effective rates in the two groups were 95 and 30 %, respectively; the onset times were 3.24 ± 1.37 and 3.41 ± 1.36 min, respectively. The therapeutic effects on angina pectoris in short term, immediate effects, and the effects on severe angina pectoris and unstable angina in the treatment group were significantly better than those in the control group ($P < 0.01$).

The mechanisms for the treatment of coronary heart disease by Danshen Injection were clinically investigated.

Kong et al. (2002) found that after treatment with Danshen preparations, the platelet aggregation test (PAgT), β-TG (β-thromboglobulin) TXB_2 (thromboxane B_2), and PGF1α (prostaglandin F1α) in patients with coronary heart disease were significantly reduced, and there were downward trends in PAgT (22 μmADP) and PF4 (platelet IV factor) after treatment, though the differences were not statistically significant. There were no significant changes in the ratios of β-TG/PF4 and TXB_2/PGF1α. The results demonstrated that Danshen had wide cardiovascular pharmacologic actions (e.g., inhibiting platelet aggregation, dilating coronary artery blood vessels, cleaning oxygen radicals, anticoagulation, etc.) and reducing oxygen consumption by the myocardium so as to antagonize angina pectoris.

Zhang et al. [11] reported the application of Danshen in the treatment of patients with coronary heart disease and angina pectoris by *injectio ad acumen* at Heart Shu (BL 15). The results showed that the blood plasma ET-1 and MDA were significantly reduced to a normal level after treatment. The authors concluded that Danshen injection at Heart Shu point could remit the impairment of blood vessel endothelial cells in

the patients with coronary heart disease and angina pectoris and alleviate angina pectoris.

Xing [12] used Danshen Injection to treat 24 patients with coronary heart disease, and observed the changes in the contents of lipid peroxides (LPO) and superoxide dismutase (SOD) before and after the treatment. 20 healthy individuals were used as the control. The results showed that LPO of patients with coronary heart disease was significantly higher than that of healthy individuals ($P < 0.01$), but blood SOD was lower significantly than that of healthy individuals ($P < 0.01$); after treatment with Danshen, LPO was significantly reduced ($P < 0.01$), and SOD was significantly increased ($P < 0.05$). The results demonstrated that Danshen had the function of reducing LPO and enhancing the activity of SOD in serum.

1.1.2 Acute Myocardial Infarction

Lin [13] used Danshen powder injection combined with nitroglycerin to treat high myocardial infarction patients with ST segment elevation, and obtained satisfactory therapeutic results. Danshen (lyophilized) powder has the function of dilating the coronary artery, inhibiting platelet aggregation, inhibiting thrombopoiesis, and improving hemorheology and microcirculation. Danshen powder injection can be used to substitute long-term use of aspirin in the treatment of coronary heart disease. Drug resistance can be induced by long-term use of nitroglycerin, and thus the therapeutic effect can be reduced to some extent. When Danshen powder injection was added to the comprehensive treatment scheme (nitroglycerin, low molecular heparin, etc.), the total effective rate was 93.5 %, the blood rheology was significantly improved, and no apparent toxicity or side-effects on liver and kidney function was observed.

Qi et al. [14] observed the therapeutic effects of sodium tanshinone II_A sulfonate (STS) injection on the treatment of acute myocardial infarction (AMI). 94 patients with AMI were randomly divided into an observation group (46 cases) and control group (48 cases). Conventional therapy methods were performed in the control group, but STS injection in addition to conventional therapy was performed in the observation group. The results showed that the incidence of angina pectoris after infarct in the treatment group was significantly reduced 2 weeks after treatment, and there was a significant difference between the treatment group and control group but no significant difference in arrhythmia and hospital mortality rate between the two groups. The results demonstrated that ventriculus sinister function and myocardial ischemia in patients with AMI can be improved by STS injection, and it was safe and effective in clinical application.

How to reverse left ventricular remodeling and slow down congestive heart failure after myocardial infarction (AMI) is an important issue for physicians. Clinically, β receptor blockers, angiotensin converting enzyme inhibitors, angiotonin II receptor antagonists, and aldosterone receptor antagonists have been used for left ventricular remodeling treatment after AMI. Chao et al. [15] observed the therapeutic effect of tanshinone II_A (TSN) on left ventricular remodeling after AMI, and they found that TSN had significant inhibitory effects on remodeling compared with the control group. The results showed that TSN could significantly reduce the levels of LEDVI and LESVI and increase the levels of LVEF and E/A 2–6 weeks after treatment, thus inhibiting the post-AMI enlargement of left ventricular internal diameter at the end of diastasis and left ventricular remodeling. The results demonstrated that TSN had a marked effect on the disease. It was revealed that the main pharmacologic actions of TSN on the cardiovascular system included anticoagulation and antiplatelet aggregation, improving coronary artery collateral circulation, reducing infarcted cardiac muscle area, reducing left ventricular end-diastolic pressure, reducing myocardial consumption of oxygen, and increasing left ventricular work.

1.1.3 Old Myocardial Infarction and Premature Ventricular Beats

Cheng et al. [16] reported the application of San Shen Decoction (三参汤) in the treatment of 50

patients with old myocardial infarction (OMI) and premature ventricular contractions (VPC). 3–7 days later after taking antiarrhythmia drugs, the patients began to take San Shen Decoction which contains 20 g of Danshen, 20 g of light-yellow sophora root (苦参), 20 g of pilose asiabell root (党参), 6 pieces of common jujube (大枣), one dose taken twice a day (morning and evening), continuing for 20–30 days. The dilatation drugs and cardiac diuretic were not discontinued while taking San Shen Decoction. The results showed that the total effective rate was 78 %. There were three patients who suffered from accidental nausea and vomiting, but no significant side effects were observed in the other patients. Danshen has the function of dilating vessels, enhancing the cardiac muscle's resistance to hypoxia, and improving heart function; combining the three drugs for the treatment of OMI accompanied by VPC is an effective method.

1.1.4 Congestive Heart Failure

Danshen has the function of dilating the coronary artery, enhancing resistance of the cardiac muscle to hypoxia, dilating peripheral vessels, and improving microcirculation. It especially has the function of improving cardiac contractility in the situation of can't affecting oxygen consumption when the patient is suffering from cardiac insufficiency, reducing the heart rate, significantly improving heart function, accelerating blood flow, and opening more capillary beds. These improvements are very important for patients with chronic congestive heart failure. In the treatment of chronic congestive heart failure, the dosage of CDI is usually 40 ml or more; the therapeutic effect will be lessened if the dosage used is less than 40 ml. The drug has poor efficacy on edema, which might have something to do with the amount of activity, salt intake, age, and other complications.

Huang and Chen [17] reported the application of True Warrior Decoction combined with Danshen Beverage in the treatment of 60 patients with deficiency in heart-yang and kidney-yang types of heart failure; the prescription includes 6–10 g of red ginseng, 6–15 g of prepared common monkshood daughter root (熟附子), 10–12 g large head atractylodes rhizome (白术), 10–30 g of indian buead (茯苓), 30 g of Danshen, 10 g of villous amomum fruit (砂仁), 10 g of sandalwood (檀香), 10–20 g of oriental waterplantain tuber (泽泻), and 10–30 g of asiatic plantain seed (车前子) (decocting in wrapped condition), with 20 days for one course of treatment. After the treatment, 30 cases were clinically cured, 11 cases showed a marked effect, 14 cases showed an effect, and 5 cases showed no effect; the effective rate was 91.67 %.

Liu [18] observed the effect of CDI combined with Shenmai Injection on the treatment of 25 patients with chronic congestive heart failure, of which there were 18 males and 7 females; 12 cases of pulmonary heart disease, 5 cases of coronary heart disease, 5 cases of hypertensive cardiopathy, 1 case of rheumatic heart disease, 1 case of coronary heart disease, 1 case of lung cancer; 7 cases of Class II cardiac function, 15 cases Class III, 3 cases Class IV; 7 cases of left congestive heart failure, 5 cases of right congestive heart failure, and 13 cases of whole congestive heart failure. 100 ml of 10 % glucose was mixed with 30 ml of Shenmai injection and administered by intravenous drip; 100 ml of 10 % glucose was mixed with 12 ml of CDI and administered by intravenous drip. The drugs were given once daily for 7–10 days as one course of treatment. The patients were usually treated for 1–4 courses, with an average period of 2.5 courses and an interval of 2–3 days between the courses. After various symptoms and physical signs were improved, the patients took Compound Danshen Tablet and Shengmai Beverage orally to consolidate the therapeutic effect. The results showed that there were 10 patients with marked effect, 12 patients with effect, 3 patients with no effect, and the total effective rate was 88 %.

Hong et al. [19] reported that 64 patients with congestive heart failure were randomly divided into two groups; 30 cases were treated with conventional therapy, and 34 cases were treated with conventional therapy plus Mongolian

Milkvetch Root (黄芪) and CDI by intravenous drip. The changes of clinical therapeutic effect, heart function, and LPO and SOD in the two groups were observed. The results showed the total effective rate in TCM group was 94.12 %, which was higher than that in the conventional group (76.67 %) ($P < 0.05$). The heart functions of the two groups were improved after the treatments ($P < 0.05$). The therapeutic effect in the TCM group was significantly better than that in the conventional group ($P < 0.05$). The LPO levels in the two groups were reduced after the treatments, SOD levels were increased ($P < 0.05$), LPO in the TCM group was reduced, and SOD was significantly increased compared to the conventional group. The authors concluded that the treatment of congestive heart failure with Mongolian Milkvetch Root and CDI has the effects of strengthening the heart, relieving cardiac load, and improving blood circulation. The combination of the two drugs has the effects of benefiting vital energy and activating blood circulation, and promoting diuresis, which is consistent with TCM principles of treating heart failure.

1.1.5 Restenosis Post Percutaneous Transluminal Coronary Angioplasty (PTCA)

With thorough understanding of the etiological factors of coronary heart disease and the increasing maturation, improvement, and advancement of cardiac cathetenization, percutaneous transluminal coronary angioplasty (PTCA) is becoming an important method for physicians to treat coronary heart disease with. However, clinical studies have shown that about one-third of patients with a successful PTCA operation suffer from coronary artery restenosis within 6 months, which seriously affects the long-term therapeutic effects of PTCA. The occurrence of restenosis is a complex biological process involving various factors. So far, there are no marked effective drugs for the prevention and treatment of restenosis, therefore the research and development of such drugs which can effectively prevent coronary artery restenosis is of great significance. Danshen Injection can inhibit the propagation of rabbit aorta smooth muscle cells cultured in vitro, and also has the function of inhibiting in vivo hyperplasia after the operational removal of endothelium in rabbit artery, which suggests that the development of Danshen into an effective drug for restenosis is hopeful.

1.1.6 Dilated Cardiomyopathy

Xu [20] observed the application of CDI in the treatment of 22 patients with dilated cardiomyopathy. 500 ml of 10 % glucose solution or 500 ml of 0.9 % physiological saline were added into 40–80 ml of CDI and administered by intravenous drip, once daily for 15 days as one course of treatment. The dosage of CDI in the treatment of dilated cardiomyopathy was usually greater than 40 ml/time; a lesser amount will give a poor therapeutic effect. Glucose solution should be substituted by 0.9 % physiological saline for patients with diabetes. A small amount of patients after using CDI suffered from side effects such as active bowel sounds, loose stool, or increased number of dejection, etc., but the majority of patients suffered no adverse reactions.

Zhu et al. [21] observed the therapeutic effects of Mongolian Milkvetch Root injection combined with CDI on the treatment of 32 patients with dilated cardiomyopathy. The patients were divided into two groups; both groups were treated with conventional therapy (low salt diet, using cardiotonic and diuretic drugs and converting enzyme inhibitors, etc.), then the patients in the control group were administered by intravenous drip with 40 mg of ATP, 200 units of coenzyme A, 2 g of vitamin C, 0.2 g of vitamin B_6, and 20 ml of trommcardin, in 250 ml of 5 % glucose, once daily for 7 days as one course of treatment, and the patients were treated for 2–3 courses. 30 ml of Mongolian Milkvetch Root Injection (10 ml injections contains 20 g of Mongolian Milkvetch Root) and 20 ml of CDI were mixed with 250 ml of 5 % glucose injection and administered by intravenous drip to the patients in

the treatment group, once daily for 7 days as one course of treatment, and the patients were treated for 2–3 courses. The results showed that 19 cases in the treatment group showed marked effect, 10 cases effect, 3 cases no effect (3 cases died), and the total effective rate was 90.6 %; in the control group, 10 cases showed marked effect, 8 cases effect, 12 cases no effect, 7 cases died, and the total effective rate was 60 %. The differences in effective rates and fatality rates between the two groups were statistically significant ($P < 0.05$). It was concluded that CDI has the function of activating blood circulation and dissipating blood stasis, regulating vital energy and inducing resuscitation, inhibiting platelet aggregation, dilating the coronary artery, increasing blood flow, reducing heart rate, and promoting the repair of damaged myocardial cells. In the combination of the two drugs, the 30 ml of Mongolian Milkvetch Root injection is the principal drug which has the major function of nourishing qi and the adjutant function of diuresis; the 20 ml of CDI is the adjutant drug which has the function of activating blood circulation. The combination of the two can complement each other. In this study, the total effective rate of the treatment group was 90.6 %, and the difference was significant compared with the control group. No toxicity or side effects were observed and no tolerance was induced.

1.1.7 Idiopathic Sick Sinus Syndrome

Yan Wanying and He Jianping reported the application of a self-made decoction in the treatment of 35 patients with elderly sick sinus syndrome; the prescription included 15 g of pilose asiabell root (党参), 20 g of mongolian milkvetch root (黄芪), 10 g of Chinese angelica (当归), 10 g of red peony root (赤芍), 15 g of Danshen, 5 g of szechwan lovage rhizome (川芎), 10 g of rehmannia dride rhizome (生地), 10 g of spine date seed (酸枣仁), 5 g of cassia-barktree twig (桂枝), 15 g of common motherwort herb (益母草), 15 g of lobed kudzuvine root (葛根), 10 g of fried submature bitter orange (炒枳壳), and 15 g of prepared liquorice root (炙甘草). Among the 35 patients treated, 8 cases showed marked effect, which was defined as the disappearance of clinical symptoms and an increase in heart rate by 5 beats/min in 1 month of treatment; 21 cases showed effect, which was defined as improvement of the clinical symptoms and an increase in heart rate by 1–5 beats/min in 2 months of treatment. 6 cases were classified as no effect, which means there were some improvements in clinical symptoms, but no changes in heart rate after 2 months of treatment.

Fu [22] reported the application of salbutamol and Danshen in the treatment of 21 patients with idiopathic sick sinus syndrome. The patients were administered with 4.8 mg of salbutamol by intravenous drip, three times a day, and 30 ml of Danshen Injection, one time a day. A half month after treatment, the patients were administered orally with Compound Danshen Tablet, three times a day, three tablets each time, for 6 months as one course of treatment. The results showed that 6 months after salbutamol and Danshen treatment, all 21 patients showed some degree of alleviation of clinical symptoms. The sinoauricular node recovery time (SNRT) and sinoatrial conduction time (SACT) were significantly shortened in 18 patients; the maximal shortened SNRT was 1,200 ms, the minimal was 600 ms, and average was 1,000 ms; the maximal shortened SACT was 120 ms, the minimal was 80 ms, and average was 100 ms. There was no significant change in SNRT and SACT in three patients. There are many causes of sick sinus syndrome, but after examining the electrocardiograms, echocardiograms, sternum X-rays, blood fat, and blood sugar of the 21 patients, no definite etiological causes were confirmed and thus they were classified as having idiopathic sick sinus syndrome. Salbutamol is a β2 receptor stimulant which has the function of dilating vessels, improving sinoauricular node blood supply and enhancing pacing. Danshen preparation has the function of activating blood circulation, promoting qi, dilating vessels and increasing coronary artery blood supply, increasing sinoauricular node blood supply, and reducing blood viscosity, thus preventing fibrosclerosis of the sinoauricular node. The therapeutic effects were enhanced by

the combination of the two drugs, and satisfactory clinical therapeutic effects were obtained.

1.1.8 Protecting Effect on Myocardial Ischemia Reperfusion After Open Heart Surgery

Shi et al. [23] reported that 20 patients having intracardiac operations under direct vision were randomly divided into a treatment group and control group, with 10 patients each. The patients in the treatment group were administered with 200 mg/kg CDI by intravenous injection before operation and after heart resuscitation after rewarming, and the patients in the control group were administered with physiological saline. The results showed that CDI has the function of increasing the PGI_2/TXA_2 ratio in the reperfusion phase, effectively inhibiting the production of endothelin and promoting the recovery of cardiac function after ischemia-reperfusion.

Base upon the above reviewed data, we can see clearly that Danshen has significant therapeutic effects on the treatment of heart and circulation system diseases such as coronary heart disease, myocardial infarction, heart failure, cardiomyopathy, myocardial ischemia, sick sinus syndrome, and so on. The therapeutic effects are especially better when Danshen is combined with other traditional Chinese drugs.

1.2 Nervous System Disease

Besides the functions of antiplatelet aggregation, reducing thromboxane A_2 and promoting prostacyclin production, Danshen also has the function of blocking Ca^{2+} channels, improving the tolerance of brain cells to ischemic and hypoxic conditions, reducing free radical content, stabilizing cell membranes, and improving microcirculation. Danshen has the function of increasing brain blood flow, and improving brain circulation. It is widely applied in the treatment of stroke (such as nervous system diseases, cerebral thrombosis, cerebral hemorrhage, subarachnoid hemorrhage (SAH), etc.) in TCM, and satisfactory therapeutic effects can be obtained.

1.2.1 Cerebral Hemorrhage

Li et al. [24] demonstrated that the function of Danshen was mild and comprehensive. Large doses of mannitol could induce pachyemia, aggravate the high viscosity and hypercoagulability of the blood, and aggravate ischemic damage after cerebral hemorrhage. However, Danshen can reduce blood viscosity, inhibit platelet aggregation, and improve microcirculation, and has the function of regulating the fibrinolysis system and promoting fibrin degradation, has anti-free radical activity, and relieves ischemic damage after cerebral hemorrhage and promotes hematoma absorption. When combined with dehydrating agents, Danshen can relieve cerebral edema, promote the absorption of hematoma, promote the repair and regeneration of brain tissue, and alleviate sequelae. Patients with cerebral hemorrhage were treated with CDI, and the rates of recovery and significant improvement in the treatment group were significantly better than those in the control group, and no side effects were observed. Especially for patients with a small amount of hemorrhage, Danshen can improve neurologic impairment and enhance the recovery rate. It is believed that senile patients usually suffer from blood system abnormalities, and the majority of research has reported that fibrinolysis activity in the elderly is low, thus they can easily suffer from thromboembolic disease. However, special attention needs to be paid to the possibility of hyperfibrinolysis or rehaemorrhagia or hematoma enlargement, which can be induced by various causes, in patients with cerebral hemorrhage.

Pang et al. [25] observed the therapeutic effect of Danshen Injection on the treatment of cerebral hemorrhage. 35 patients with cerebral hemorrhage were randomly divided into two groups; 20 patients in the treatment group, and 15 patients in the control group. The basic prescription in two groups was the same, namely, 125 ml of 20 % mannitol by intravenous drip, each for 8–12 h,

continued for 7–10 days. 3 days after the onset, the patients in the treatment group received 250 ml of Danshen Injection by intravenous drip, once a day for 2 weeks. CT examination was performed before and 2 and 3 weeks after treatment to measure hematoma volume. Nerve function was also evaluated for the patients in the two groups. There was no significant difference in hematoma volume between two groups before the treatment ($P > 0.05$), and hematomas in the treatment group were smaller than in the control group after treatment ($P < 0.05$). There was no significant difference in neurological deficit between the two groups before treatment ($P > 0.05$), but it was significantly reduced after treatment in the treatment group compared to the control group ($P < 0.05$). The difference was especially obvious 2 months later ($P < 0.01$). These results demonstrate that Danshen Injection can promote hematoma absorption and nerve function recovery.

Pang et al. [26] investigated the preventive nerve protective effect of Dantonic™ on hypertensive patients. A large-sample epidemiological survey was conducted, and 561 patients with hypertension who met the diagnostic criteria were selected. The patients were divided into 2 groups. 286 cases in the treatment group were administered with Dantonic™ and nifedipine or captopril. 275 cases in the control group were administered with nifedipine or captopril alone. They were followed up for 24 months, and the changes in blood pressure, blood lipids, microcirculation, blood flow, thrombin, and other indices and the incidence of cerebral ischemic stroke were monitored. After treatment, there were significant differences in the clinical marked effective rate; effective rate and average pressure decrease between the two groups ($P < 0.05$). The improvements in blood lipids, microcirculation, blood flow, and thrombin etc. in the treatment group were significantly better than those in the control group ($P < 0.01$). The incidences of cerebral ischemic stroke in the treatment group and control group were 0.69 % (2/286) and 10.5 % (29/275), respectively, and the difference was significant ($P < 0.05$). The results demonstrated that Dantonic™ has a good prophylactic neuroprotective effect on patients with hypertension.

1.2.2 Cerebral Infarction

Zhang (1988) reported the application of a prescription with the function of unblocking the orifices, invigorating blood, and promoting urination in the treatment of 66 patients with apoplexy. The CT examination showed 19 patients with cerebral hemorrhage, 47 patients with cerebral infarction, and 19 patients with brain atrophy. The prescription included Danshen, szechwan lovage rhizome (川芎), red peony root (赤芍), peach seed (桃仁), safflower (红花), common motherwort herb (益母草), medicinal cyathula officinalis root (川牛膝), indian buead (茯苓), forest musk (麝香) [or taiwan angelica root (白芷), synthetic borneol (冰片)], mongolian milkvetch root (黄芪), suberect spatholobus stem (鸡血藤), and earthworm (地龙). The above drugs were decocted and taken with water, one dose a day. After treatment, 23 patients almost completely recovered, 19 patients showed marked effect, 2 cases showed no effect, and the total effective rate was 96.9 %. The prescription was especially effective on slurred speech.

Qi [27] reported the application of Sanqi Panax notoginseng and CDI in the treatment of 132 patients with cerebral infarction. The patients were 45–73 years old and all hospitalized 6 h to 4 days after onset; among them there were 38 mild cases, 54 moderate cases, and 40 severe cases. The patients were divided into two groups, with 66 cases in each group. The patients in the treatment group were administered with Sanqi Panax notoginseng and CDI by intravenous drip, and the patients in the control group were administered with CDI by intravenous drip. The two groups were comparable in gender, age, number of cases, and clinical classification. The patients in both two groups were treated according to the conventional procedure for cerebral infarction: those without significant anticoagulation contraindication or ulcer or hemorrhagic diseases were administered with anticoagulation drugs, such as 50 mg heparin by

intravenous drip for 24–48 h; 100 mg antiplatelet aggregation drug aspirin, one time a day. 20 % mannitol and dexamethasone were administered according to individual situations to reduce intracranial pressure, relieve cerebral edema and clean free radicals, and maintain water and electrolyte equilibria. The patients in the treatment group received 6 ml of Sandi Panax notoginseng in 250 ml of 5 % glucose solution and 16 ml of CDI in 250 ml of 5 % glucose solution, both administered by intravenous drip once a day. The patients in the control group received 16 ml of CDI in 250 ml of 5 % glucose solution, with 10 days as one course of treatment, and the patients were treated for 3 courses. The interval between courses was 4 days. For cured patients, the treatment was stopped immediately, and these patients were treated for 17–29 days. The results showed that there were 28 patients with near complete recovery in the treatment group, 20 patients with significant improvement, 5 patients with improvement, 13 patients without improvement, and the total effective rate was 80.3 %. In the control group, there were 20 cases of recovery, 12 cases of significant improvement, 6 cases of improvement, 28 cases of no improvement, and the total effective rate was 57 6 %. The difference in effective rates of the two groups was significant ($P < 0.01$).

Huang et al. [28] observed the therapeutic effect of intravascular irradiation by a low energy He–Ne laser and Danshen treatment on acute cerebral infarction. In addition to traditional neurological treatment, 100 cases of cerebral infarction (research group) were treated with intravascular irradiation by a low energy He–Ne laser and Danshen, and there was a corresponding control group. The hemorheology and blood fat indexes were determined before and after the treatment. The results showed that the effective rate in the research group was 81.3 % compared to 62.4 % in the control group, and the difference between the two groups was significant ($P < 0.05$). The results demonstrate that intravascular irradiation by low energy He–Ne laser combined with intravenous drip of Danshen is a good method for the treatment of acute cerebral infarction.

Zhai et al. [29] observed therapeutic effect of high-dosage Danshen on the treatment of 45 patients with acute cerebral infarction; 30 ml of Danshen Injection was added into 500 ml of low molecular dextran and administered by intravenous drip to 22 patients in the treatment group, and mannitol and antibiotics etc. were administered according to pathogenetic conditions. Anticoagulation, thrombolysis, and dilating vessel drugs were not used in the treatment. The patients in the control group were administered with the same drugs as in the treatment group, except for CDI. The drugs were administered by intravenous drip once a day, for 2 weeks as one course of treatment. The results showed that there were 2 cases with a clinical cure, 8 cases with marked effect, 10 cases with improvement, 7 cases without effect, and the total effective rate was 91 % in treatment group. In the control group, there were 5 cases with marked effect, 11 cases with improvement, 7 cases without effect, and the total effective rate was 69.6 %. There was a significant difference in therapeutic effects between the two groups ($P < 0.05$). It was revealed that compound Danshen can significantly improve the majority of cerebral hemodynamic indexes, especially those of brain blood flow speed, vessel wall elastic wave speed, and critical pressure, which demonstrated that it had important functions in promoting cerebral blood flow, improving the elasticity of cerebral vessels, and reducing blood viscosity. Therefore, application of Danshen in the early stage can enhance the therapeutic effect and reduce disability rate.

1.2.3 Subarachnoid Hemorrhage

Sun [30] investigated the cerebral hemodynamic change of patients with SAH, and the protective effect of Danshen on brain ischemic damage. 68 patients with SAH were divided into two groups, with patients in both groups on absolute bed rest. The patients were administered conventional drugs with the function of reducing intracranial pressure and antifibrinolysis. 20 ml of CDI was added into 500 ml of 5 % glucose injection and administered by intravenous drip to the patients

in the Danshen treatment group once a day, and the maximal length of the treatment was 3 weeks. The cerebral hemodynamic changes and fatality rate in the two groups, ECG abnormal incidence, and cerebral vessel spasm incidence were observed. The results showed that the cerebral hemodynamic parameters of patients with SAH were significantly changed, especially the minimum blood flow speed and cerebral vessels peripheral resistance; the cerebral hemodynamic changes between the Danshen group and control group were very significant ($P < 0.01$). It was revealed that SAH can induce cerebral hemodynamic abnormality, and Danshen preparation has a protective effect on brain ischemic change due to SAH.

With further pharmacology and clinical research on Danshen, an increasing number of clinical documents have demonstrated that there are satisfactory therapeutic effects of Danshen and its preparations on the treatment of cerebral vessel diseases, including cerebral hemorrhage and cerebral infarction. Numerous facts have demonstrated that Danshen can be actively used in the prevention and treatment of cerebral vessel diseases.

1.2.4 Trigeminal Neuralgia

Zhang [31] reported the application of integrated medicine to the treatment of trigeminal neuralgia. TCM preparations were anointed on the surface of the trigeminal neuralgia site. After locating the "trigger points" in the trigeminal neuralgia site, about 2 ml of 2 % lidocaine was injected at each point. 5 min later, 300 μg of vitamin B_{12} combined with 2 mg dexamethasone were injected in the same site, once every 7 days. During the blocking period, the patients took Compound Danshen Tablet orally, 2 tablets each time, 3 times a day, plus 0.2 g of spiramycin each time, 3 times a day. The results showed that 46 patients were cured by 3 times of blocking treatment, 30 patients were cured by 6 times of blocking treatment. The patients were followed up for 3–6 months, and there were no recurrences during the 6 months to 2 years period; the curative rate was 100 %. The results demonstrate that integrated medicine can be used to treat trigeminal neuralgia, which can rapidly control the onset of the pain. The method is simple and practical, and can be further extended.

Wu [32] reported the treatment of 28 trigeminal neuralgia cases with CDI and "Wu Bai Decoction" (五白汤). The patients were administered with 4 ml of CDI by intramuscular injection, twice a day. Traditional Chinese drug "Wu Bai Decoction" contains 50 g of White Peony Root (白芍), 10 g of Giant Typhonium Tuber (白附子), 10 g of Taiwan Angelica Root (白芷), 10 g of white Stiff Silkworm (白僵蚕), 20 g of Troubles territories (白蒺藜). The above drugs were decocted twice with water and administered one dose a day. The recovery rate was 64.28 %, the total effective rate was 92.86 %, and therapeutic effects were significantly better than those in the control group. It was revealed that compound Danshen by intramuscular injection has the function of dilating microcirculation and improving local blood supply; a high dosage of White Peony Root has the function of nourishing blood and retaining yin with astringent, nourishing liver, and relieving pain. There was no toxicity or side-effects in clinical application, and the courses of treatment were short.

1.2.5 Facial Neuritis

Gao et al. [33] reported the application of Dantonic™ in the treatment of 32 patients with middle-aged and elderly facial neuritis. The patients in the control group received treatment with hormones, vitamins, antiviral drugs, physical therapy, and anti-inflammatory drugs, etc., and the patients in the treatment group received the same treatment as the control group plus 10–15 pills of Dantonic™, 3 times a day for 10 days as one course of treatment, and 3 courses of treatment were performed. The results showed that the total effective rates in the treatment group and control group were 81.58 and 51.35 %, respectively, and there was a significant difference in the total effective rate between the two

groups. The study demonstrated that Dantonic™ has the function of relieving vasospasm, improving local blood circulation around the facial nerves, and relieving inflammatory edema, thus it can be used to treat the disease.

1.2.6 Migraine

Zhang [34] reported the treatment for 20 cases of migraine. 12–16 ml of CDI was added into 5 % glucose salt water, and administered by intravenous drip for 10 days as one course of treatment. Patients without improvement after the first course received another course of treatment after 2–4 days. The results showed that five cases significantly improved after one course, and 10 cases improved after the second course of treatment. It was believed that Danshen's effects might be related to its function of stabilizing vasoconstriction and improving microcirculation.

Ge et al. [35] reported the treatment of serious migraine with Danshen, diclofenac sodium, and β-sodium aescinate. 51 cases of serious migraine were treated with 10 ml of Danshen, 0.1 g of diclofenac sodium, and 10 mg of β-sodium aescinate, and the effects were compared with those in 62 cases of serious migraine treated by diclofenac sodium alone. The results showed that the total effective rates of the combined drug treatment group and single diclofenac sodium group were 96 and 64 %, respectively, and the differences in total effective rate and control rate between the two groups were significant ($P < 0.01$).

Wang [36] reported the treatment of migraine with Compound Danshen and 654-2 in 47 cases. 10 mg of 654-2 injection and CDI was added into 250 ml liquid and administered by intravenous drip to the patients in the treatment group once per day, and 7 days later they were orally administered with three tablets of Compound Danshen Tablet and 5 mg of 654-2 tablets, three times a day for 1 month as a course of treatment. The patients in the control group were administered orally with not more than six tablets of Ergotamine and Caffeine tablets each day, then 40 mg of nimodipine tablets twice a day after pain remission. The results showed that in the treatment group, 28 cases showed marked effect, 17 cases showed effect, 2 cases showed no effect, and the total effective rate was 95.7 %. In the control group, 21 cases showed marked effect, 13 cases showed effect, 12 cases showed no effect, and the total effective rate was 73.9 %, with a significant difference ($P < 0.05$). It was believed that the effect of Compound Danshen and 654-2 on migraine treatment was related to their functions of vessel dilation and vasospasm relief; the study demonstrated that there was both blood vessel constriction and vasospasm during the migraine attack phase, Compound Danshen and 654-2 has the function of regulating vasoconstriction to stabilize blood vessels, thus controlling the migraine attack. There was a synergistic effect when the two drugs were used together, and with gentle adverse reactions; a few patients suffered from dry mouth, pharyngalgia, and other symptoms which might be related to the side effects of 654-2.

1.2.7 Functional Insomnia

Zhou et al. [37] administered a mixture of 16 ml of Danshen Injection and 20 ml of cerebrolysin by intravenous drip to 35 elderly patients with functional insomnia. The results showed that the clinical recovery rate and effective rate were 65.7 and 94.3 %, respectively, which were significantly better than those of the control group ($P < 0.01$). It was believed that Danshen has the functions of cleaning oxygen radicals and antilipid peroxidation, so it can delay the degeneration of brain cells and improve sleep.

Tong [38] reported on 86 patients with insomnia randomly divided into two groups; the patients were, respectively, treated with Danshen Zaoren Decoction (丹参枣仁汤) and diazepam tablets, and the therapeutic effects in the two groups were observed. The patients in the treatment group were treated with self-made Danshen Zaoren Decoction, which contains 15 g each of Danshen, raw dragon's bones (生龙骨), raw common oyster shell (生牡蛎), tuber fleeceflower stem and leaf (夜交藤), silktree albizia

bark (合欢皮), and 10 g each of stir-baked semen Ziziphi spinosae (炒枣仁), and Chinese arborvilae seed (柏子仁). The patients in the control group were administered with 2.5 mg of diazepam tablets orally before sleep, once a day. The therapeutic effects were evaluated 15 days after the treatment. The results showed that the effective rate in the treatment group (96.3 %) was significantly higher than that in the control group (65.6 %), and the difference was significant ($P < 0.05$).

1.2.8 Meniere's Disease

Li [39] reported the treatment of Meniere's disease with a combination of CDI and Qingkailing Injection (清开灵注射液) for 35 cases. 16–20 ml of CDI was added to 250–500 ml of 10 % glucose injection and administered by intravenous drip, and 40–60 ml of Qingkailing Injection was added to physiological saline or 250–500 ml of 10 % glucose injection and administered by intravenous drip in the treatment group. For the control group, 20 mg of anisodamine injection was added to physiological saline or 250 ml of 10 % glucose injection and administered by intravenous drip, 500 ml of low molecular dextran was administered by intravenous drip, and 40 mg of ATP, 100 U of coenzyme A, 400 mg of inosine, 100 mg of Vitamin B_6, and 3 g of Vitamin C were added to 500 ml of 10 % glucose injection and administered by intravenous drip. The symptoms of acid–base imbalance and electrolyte disturbances were treated at the same time. The therapeutic effects in the two groups were compared 5 days after the drug administrations. The results showed that the recovery rate (82.86 %) in the treatment group was significantly higher than that in the control group (59.38 %). It was revealed that CDI has the function of activating blood circulation and dissipating blood stasis, regulating vital energy, and inducing resuscitation. Qingkailing Injection has the function of clearing heat and resolving toxins, cooling the blood and dissipating blood stasis, calming the liver and extinguishing wind, awakening the brain and opening the orifices, and eliminating sputum and dredging collaterals. The treatment using the combination of the two drugs targets both the causes and symptoms of Meniere's disease, so satisfactory therapeutic effects were obtained.

1.2.9 Polyneuritis

Liu et al. [40] reported that 4 ml of Danshen Injection and 10 mg of 654-2 injection were administered by intramuscular injection every 6 h; or 250 ml of 10 % glucose combined with 20 ml of Danshen and 25 ml of 10 % glucose combined with 40 mg of 654-2 injection were administered by intravenous drip each day. 3 days after administration, the dosage of 654-2 was gradually reduced to 30 mg, 20 mg or complete withdrawal, depending on the patients' conditions and whether a toxic effect was induced by 654-2. The dosage of Danshen was not changed. 4 patients with polyneuritis were treated and all of them were cured. The course of treatment was 20–75 days.

1.2.10 Dizziness

Xiao [41] observed the therapeutic effect of CDI combined with Banxia Baizhu Tianma Decoction (半夏白术天麻汤) on acute dizziness. 83 patients with acute dizziness were randomly divided into a treatment group and control group. In the treatment group, 20 ml of CDI was added to 250 ml of 5 % GS and administered by intravenous drip for 3 days, once a day; modified Banxia Baizhu Tianma Decoction was administered for 3 days, one dose per day. In the control group, 0.4–0.6 g of venoruton injection was added into 250 ml of 5 % GS and administered by intravenous drip for 3 days, once a day. The results showed that among the 43 cases in the treatment group, 35 cases were cured, 6 cases showed an effect, and only 2 cases showed no effect; the total effective rate was 95.47 %. In the control group, 15 cases were cured, 12 cases showed effect, 13 cases showed no effect, and the total effective rate was 67.5 %, There was a

significant difference between the treatment group and control group ($P < 0.01$).

1.2.11 Pulmonary Encephalopathy

Liu et al. (1996) reported that 63 cases of pulmonarye encephalopathy were randomly divided into a treatment group (30 cases) and control group (33 cases). The patients in the two groups were treated with the conventional therapy. 16 ml of CDI was added to 500 ml of 10 % glucose solution and administered by intravenous drip to the patients in the treatment group, and 4 ml of Niuhuang Xingnao Injection (牛黄醒脑注射液) I and II were administered by intramuscular injection, 2–3 times a day. The results showed that in the treatment group, the remission rate was 80 % and mortality was 20 %, and in the control group, the remission rate was 48.5 % and mortality was 51.5 %. The difference in fatality rate between the two groups was significant ($0.01 < P < 0.025$). It is believed that Danshen has the functions of reducing blood vessel fragility and permeability, relieving the stagnation and aggregation of erythrocytes, reducing blood hypercoagulability, improving microcirculation in important organs such as the brain, heart, lung, and kidney, regulating tissue repair and regeneration, enhancing the body's compensatory ability, and promoting blood circulation. Niuhuang Xingnao Injection was developed from the prescription of Angong Niuhuang Wan, which has the function of clearing heat and resolving toxins, and calming the nerves and relieving spasms. It promotes consciousness recovery, and has significant anti-inflammatory effects. It can improve the body's tolerance to hypoxia. Some therapeutic effects have been obtained by the combination of the two drugs in the treatment of pulmonary encephalopathy.

1.2.12 Craniocerebral Injury

Lin [42] investigated the effect of compound Danshen preparations on the treatment of craniocerebral injury. 270 patients with craniocerebral injury confirmed by head CT were selected in the study and randomly divided into two groups. The patients in the treatment group were administered with compound Danshen preparations in addition to conventional therapy. The total effective rates in the treatment group and control group were 91.1 and 71.1 %, respectively. The results showed that better therapeutic effect was obtained in the treatment of craniocerebral injury by application of compound Danshen preparations, and no significant side effects were observed.

Danshen has extensive applications to the treatment of nervous system diseases. Besides on the pathological changes of cerebral vessels, it also has satisfactory therapeutic effects on trigeminal neuritis, facial neuritis, migraine, insomnia, dizziness, etc., so it is worthy of physicians' consideration when they face these diseases.

1.3 Respiratory System Disease

1.3.1 Chronic Bronchitis

Li and Yi [43] reported the treatment of 78 elderly patients with lower respiratory tract infections. Among the patients, there were 23 with pneumonia, 32 with chronic bronchitis acute attack, 13 with bronchiectasis accompanied by infections, and 10 with pulmonary infection caused by chronic diseases. The patients were randomly divided into two groups, 40 cases (26 male, 14 female) in the treatment group, and 38 cases (24 male, 14 female) in the control group. There was no significant difference ($P > 0.05$) in common condition (gender, ages, pathogenesis), levels of infection (body temperature, symptoms, physical signs, X-ray, blood routine assays, bacteriology examination, etc.), and baseline disease and so on between the two groups. The patients in the two groups were treated according to their disease conditions. Besides the above treatments, 20 ml of CDI was added into 500 ml of 5 % glucose and administered by intravenous drip for the patients in treatment group, once a day. All patients were treated for 14 days.

The results showed that in the treatment group, 15 cases recovered, 9 cases showed marked effect, 10 cases showed effect, 6 cases showed no effect, and the effective rate was 85.0 % (34/40); in the control group, there were 8 cases of recovery, 5 cases of marked effect, 12 cases of effect, 13 cases with no effect, and the effective rate was 65.8 % (25/38). The effective rate in the treatment group was significantly higher than that in the control group ($P < 0.05$). No toxicity or side-effects were observed. It was believed that CDI has the function of activating blood circulation and dissipating blood stasis, dilating vessel and restoring blood capillary relaxation ability, relieving blood vessel obstructions and blood stasis, relieving lung arteriola spasm, improving and promoting lung microcirculation, recovering pulmonary ventilation function, enhancing pulmonary oxygen function, promoting absorption of rales, and improving dyspnea conditions. In recent years, it has been demonstrated by research that Danshen has inhibitory effects on Gram-positive bacteria and some Gram-negative bacteria, enhancing the body's immunity and thus enhancing the body's ability to fight infection. In addition, CDI also has the function of changing the blood rheology, improving pulmonary hypertension, shortening the course of lower respiratory infection in senile patients, and reducing mortality.

Shi (2005) reported the treatment of 13 patients with persistent pneumonia who had been treated with various antibiotics, gamma globulins, plasma or fresh blood transfusions, physical therapy, and cortical hormones for more than 1 month, but had obtained no significant therapeutic effects. The patients in the study were administered by intravenous drip with 40–60 mg of tanshinol, twice a day. 5–9 days after the treatment, 7 patients were cured and 6 patients had improved. It was revealed that in the pathogenesis of pneumonia, viruses and anoxia act upon the lung tissues to produce vasoactive substances and thus induce lung arteriola spasm and microcirculatory disturbance. Compound Danshen has the function of vascular dilation and improving microcirculation, thus promoting the patients' recovery from pneumonia.

1.3.2 Bronchial Asthma

Xu et al. (1987) used the ultrasonic atomizing inhalation of CDI to treat bronchial asthma. 4 ml of CDI was diluted with 15 ml of distilled water, and ultrasonic atomizing inhalation was performed once a day for 10 days as one course of treatment. Among the patients treated, there were 26 cases of acute bronchitis, 16 cases of chronic bronchitis, 29 cases of asthma, and the average number of treatments was 2–27 times. The results showed that 45 cases showed marked effect, 24 cases showed effect, and the total effective rate was 97.2 %. The effect of the treatment on asthma patients began slowly, but the therapeutic effect was strengthened after the asthma was relieved. 5 cases were followed up, and the disease did not recur one year after treatment.

Li et al. [44] reported the application of CDI in the treatment of 23 cases of bronchial asthma during the attack phase. The patients in the control group were treated with regular treatments such as oxygen inhalation, spasmolysis, β_2 agonists, glucocorticoids, antibiotics, and so on. The patients in the treatment group were treated in the same way as those in the control group, but received an additional 20 ml of CDI which was added into 500 ml of 5 % glucose and administered by intravenous drip, once a day for 15 days as a course of treatment. The results showed that the total effective rates in the treatment group and control group were 95.7 and 80 %, respectively. Statistical analysis showed that there was a significant difference in therapeutic effect between the two groups. The mechanism of CDI in the treatment of bronchial asthma might be: ① inhibiting the release of bioactive compounds, reducing the high reactivity of airway, improving lung ventilation; ② improving microcirculation, enhancing the body's tolerance to anoxia; ③ dilating the coronary artery, increasing coronary blood flow, improving myocardial blood supply, enhancing cardiac contractility, and promoting remission of asthma; and ④ the obvious of antibacterial and anti-inflammatory functions have adjuvant therapeutic effects on lung infections.

1.3.3 Pulmonary Heart Disease

Zhang [45] reported that 87 patients with acute aggravating stage pulmonary heart disease were randomly divided into a treatment group (44 cases) and control group (43 cases). Comprehensive treatments (relieving cough and eliminating sputum, cardiotonics, anti-inflammation, low flow oxygen inhalation, etc.) were performed on the patients in the two groups, and 20 ml of CDI in 250 ml of 5 % glucose was administered by intravenous drip to the patients in the treatment group, once a day for 2 weeks as one course of treatment. The results showed that in the treatment group there were 18 cases with marked effect, 21 cases with improvement, 5 cases without effect, and the total effective rate was 88.6 %. In the control group, there were 12 cases with marked effect, 19 cases with improvement, 11 cases of no effect, 1 case of death, and the total effective rate was 72 %. The effective rate in the treatment group was significantly higher than that in the control group ($P < 0.05$). Patients with chronic pulmonary heart disease have some changes in their hemorheology, which include three characteristics: "dense" (increased erythrocytes), "sticky" (increased whole blood viscosity), and "accumulation" (enhanced erythrocyte aggregation). Compound Danshen has the function of improving the blood rheology, reducing blood viscosity, inhibiting erythrocytes and platelet aggregation, promoting the activity of fibrinolysis system, dilating vessels, promoting blood flow, improving microcirculation, increasing heart renal blood supply and anti-infection, enhancing body immunologic function, and so on, so it has significant clinical therapeutic effects. To calculate the effect of Danshen on the pulmonary artery pressure (PAP) of patients with chronic lung disease, the cardiac output (CO), lung circulation resistance (RVR), and lung blood vessel compliance (PVC) were compared for some patients before and after treatment. The results showed that after injection of Danshen, the extents of PAP reduction in the high pressure group and normal pressure group were 0.35–1.07 and 0.18–0.91 kPa, respectively, and the differences before and after the treatment were significant. The results demonstrated that Danshen has the function of reducing PAP, and the reduction period was usually about 3–5 min with no cases taking longer than 10 min, suggesting that Danshen has circulation dynamic effects similar to those of dihydropyridines.

Zhang and Chen [46] reported the use of CDI to treat 30 patients with chronic pulmonary heart disease. The patients were administered by intravenous drip with 60 ml of CDI in 250 ml of 5 % glucose, once a day for 10 days as one course of treatment, and four indexes (LPO, erythrocytes SOD, whole blood GSH-Px, and catalase activity) were observed. The results showed that Danshen could significantly reduce enhanced lipid peroxidation and correct the imbalance of antioxidant enzymes in patients with chronic pulmonary heart disease. The studies demonstrated that the drug has the function of cleaning and inhibiting free radicals, thus inhibiting the occurrence and development of pulmonary hypertension in patients with chronic obstructive pulmonary emphysema.

It is believed in traditional Chinese medicine that the heart controls blood circulation and the lung controls respiration; the normal circulation of blood depends on the pushing power of qi, and the movement of qi depends on the normal circulation of blood. For this reason, Danshen and its preparations, which are good drugs for activating blood circulation and dissipating blood stasis, can exert satisfactory therapeutic effects on pulmonary system diseases, which has been shown in the above examples.

1.4 Diseases of the Digestive System

Experimental research has already demonstrated that Danshen can improve disturbances in liver microcirculation, has the functions of anti-lipid peroxidation, protecting hepatocytes, promoting the repair of liver damage, increasing fibrin levels in plasma, enhancing the phagocytic function of the reticuloendothelial system, inhibiting hepatic fibrosis, and promoting the resorption of

fiber. In addition, Danshen also has the function of promoting the secretion of mucus by the stomach mucous membrane, relieving intracellular calcium overload, increasing blood flow in mucous membranes, improving microcirculation, inducing the synthesis and release of endogenous prostaglandin, and inhibiting gastrointestinal motility. Therefore, it can be extensively used in the treatment of digestive system diseases such as chronic hepatitis B, hyper-bilirubinemia, cirrhosis, peptic ulcers, chronic gastritis, etc.

1.4.1 Virus Hepatitis

viral hepatitis is a complex and high incidence disease, and there are no effective drugs available for its treatment. In recent years, it has been found by pharmacological research and validated by clinical practice that Danshen has the function of improving liver as well as systemic blood circulation, promoting the regeneration of liver cells, preventing and curing hepatic fibrosis, detoxication, regulating immunity, recovering liver function, etc.

Lu et al. [47] reported the treatment of 109 patients with HAV IgM positive and hyper-bilirubinemia. After one course of treatment, the degrees of bilirubin reduction were compared. The results showed that Danshen Injection's effective rate of jaundice elimination was 100 %, which was better than those of Yinzhihuang (茵栀黄), (85.7 %), aspartate potassium magnesium (70 %), and potenlin (60 %).

Zhao [48] reported that significant therapeutic effects were obtained by the application of Danshen Injection to the treatment of 117 patients with chronic hepatitis B. 30 ml of Danshen Injection (2 ml of injection was equivalent to 3 g of raw Danshen) was added to 500 ml of 10 % glucose injection in the treatment group, and the drug was administered by intravenous drip once a day. A traditional Chinese drug decoction (no Danshen) was used in the control group. The results showed that the total effective rates in the treatment group and control group were 88.9 and 59.2 % ($P < 0.01$), respectively. There were 81 cases (69.2 %) in the treatment group with marked effect, 23 cases (19.7 %) with effect, 13 cases (11.1 %) without effect, and the total effective rate was 88.9 %. Danshen Injection can improve blood circulation in the liver and has the function of relieving ischemia anoxia and stagnant blood in the liver and relieving toxic injury from oxygen radicals; therefore, it has significant therapeutic effects on chronic hepatitis B.

Sun [49] clinically observed the protection effect of Danshen on hepatocyte ischemia in 7 patients with hepato-vascular disease and liver cancer. The porta hepatis was blocked by operation and Danshen Injection by preoperative and intraoperative intravenous drip was administered, and the protecting function of Danshen on ischemia in hepatocytes was observed. 20 ml of CDI was added to 500 ml of 5 % glucose and administered by intravenous drip to the patients within 5 days before the operation in the treatment group, and 20 ml of CDI was added to 200 ml of 5 % glucose and administered by intravenous drip before blocking the porta hepatis. During the partial hepatectomy, blood was collected from the hepatic vein before blocking the porta hepatis for 15 min and recovering blood flow for 30 min; at the same time, the residual hepatic tissue was observed under a light microscope and electron microscope. The results showed that the content of oxygen radicals in the hepatic tissue and hepatic vein during the ischemia and reperfusion phase in the treatment group was significantly reduced, and pathological changes were significantly relieved.

Zhang and Sun [50] observed the therapeutic effects of tiopronin combined with CDI on the treatment of 125 patients with chronic hepatitis B. The patients were divided into two groups; 70 in the treatment group were orally administered with 200 mg of tiopronin 3 times a day, and 20 ml of CDI was added to 250 ml of 10 % glucose injection and administered by intravenous drip once a day. 55 cases in the control group were administered orally with 200 mg of tiopronin, 3 times a day. Patients in both groups received 2 g of vitamin C injection and 20 mg of vitamin K1 injection by intravenous drip once a day. The course of treatment was 3 months. The results showed that in the treatment group, there

were 54 cases (77.2 %) with marked effect, 12 cases (17.1 %) with effect, and 4 cases (5.7 %) without effect; the total effective rate was 94.3 %. In the control group, there were 30 cases with marked effect (54.5 %), 14 cases with effect (25.5 %), and 11 cases with no effect (20 %); the total effective rate was 80.0 %. The total effective rate in the treatment group was significantly higher than that in the control group ($P < 0.05$). It was believed that the combination of tiopronin and CDI has a synergistic effect on the treatment of chronic hepatitis B and can promote the recovery of liver function.

1.4.2 Cirrhosis

There are some important factors acting on the formation of cirrhosis, such as disturbance of liver microcirculation, overactivation of lipid peroxidation, deposition of collagen fibers, and specific binding of plasma fibronectin (PFN) and the corresponding PFN decrease and phagocytic function weakening in the reticuloendothelial system. Danshen has the function of improving liver microcirculation, enhancing PFN levels, and enhancing the phagocytic function of the reticuloendothelial system. In addition, Danshen has the function of inhibiting the growth and propagation of fibroblasts, promoting reabsorption of the formed fibrous tissue of the liver, and delaying and blocking the process from chronic hepatitis to cirrhosis. Danshen has the function of promoting degradation of the formed collagen fiber and enhancing reabsorption of the fibrous tissue of the liver. Experimental research has shown that salvianolic acid is an important component of Danshen with the function of inhibiting hepatic fibrosis, and its strength is equivalent to that of raw Danshen and colchicine.

Li et al. [51] reported changes in the hemodynamics of the portal vein of patients with cirrhosis 10–12 weeks after orally taking Danshen Decoction. The hemodynamics were monitored by Doppler ultrasound, and it was revealed that both the internal diameter and blood flow of the portal vein and the internal diameter and blood flow of the splenic vein in the patients were significantly reduced, and there were improvements on acratia, anorexia, and abdominal distension, as well as on liver function. There were no side effects. The study demonstrated that Danshen is a safe and effective drug for the treatment of portal hypertension. In addition, Danshen has the function of preventing hepatic fibrosis, reducing blood viscosity, inhibiting TXA production, etc., and can reduce resistance from the portal vein.

Zhou [52] observed the therapeutic effect of Danshen Injection on cirrhosis in 60 cases. 122 cases with cirrhosis were randomly divided into two groups. 0.5 g/kg Danshen Injection was added to 250 ml of 10 % GS and administered by intravenous drip to 60 patients in the treatment group, and common hepato-protection treatment was performed for the 62 patients in the control group. The course of treatment was 1 month, and the patients were treated for a total of three courses. The changes in five indices of liver function and hepatic fibrosis were observed. The results showed that the liver function of the patients in the treatment group was significantly improved at the end of treatment, five indices of hepatic fibrosis were significantly reduced, and there was a significant difference between two groups ($P < 0.05$). It was revealed that Danshen Injection has the function of inhibiting liver damage and hepatic fibrosis in patients with cirrhosis.

Wang [53, 54] combined diammonium glycyrrihizinate with Danshen Injection to treat hepatic fibrosis. 160 cases of patients with chronic viral hepatitis were randomly divided into three groups: 80 cases in the treatment group (Diammonium Glycyrrihizinate + Danshen); 40 cases in control group 1 (Diammonium Glycyrrihizinate); 40 cases in control group 2 (Danshen), and hepatic fibrosis indices were detected at the end of the treatment. The results showed that the symptoms and physical signs of the patients from the three groups improved to different extents after treatment, liver function improved as time elapsed, hepatic fibrosis indices were significantly reduced in the treatment group after treatment ($P < 0.05$), and hepatic fibrosis indices in the control group were also reduced

after treatment, but the extent of reduction was less than that in the treatment group. It was revealed that Diammonium Glycyrrihizinate combined with Danshen Injection can improve the symptoms and physical signs of chronic viral hepatitis, recover liver function, significantly reduce hepatic fibrosis indices, and has good anti-hepatic fibrosis function. It was demonstrated that there was an additive effect in the combination.

Ma et al. (2003) observed the therapeutic effect of compound Danshen combined with Mongolian Milkvetch Root (黄芪) and aspartate potassium magnesium on the treatment of old cirrhosis ascites. The patients were allowed to rest, on a low-salt diet, and treated for hepatoprotection and diuresis. However, after 2 weeks' treatment, no effects were observed and ascites volume was not significantly changed. 16 ml of CDI, 40 ml of Mongolian Milkvetch Root injection, and 20 ml of Aspartate Potassium Magnesium injection were added to 250 ml of 5 % glucose and administered by intravenous drip to the patients in the treatment group once a day. 16 ml of CDI was added to 250 ml of 5 % glucose and administered by intravenous drip to the patients in the control group once a day. The ascites volume was determined by B-ultrasound each week. The liver function and magnesium and potassium ion levels were determined before and after treatment, with 15 days as one course of treatment, and the patients were treated for two courses. There was a significant difference in liver function, magnesium ion, and potassium ion levels between the two groups, and before and after treatment ($P < 0.05$). The total effective rates of the treatment group and control group were 90.62 and 66.66 %, respectively, and the difference was statistically significant ($\chi^2 = 6.215$, $P < 0.05$).

Ye [55] observed the effect of compound Danshen on the 5-year mortality of decompensated liver cirrhosis. Based on comprehensive treatment, 46 cases in the treatment group were treated with a high dosage of CDI (or tablets) for a long term, and the changes in 5-year mortality and alimentary tract hemorrhage rate were observed. The results showed that the 5-year mortality in the treatment group was 45.7 % (20/46 cases), and in control group was 72.7 % (16/22 cases), and there was a significant difference between the two groups ($P < 0\ 05$); the incidence of upper gastrointestinal hemorrhage within 5 years in the treatment group was 45.7 % (21/46 people), and in the control group was 81.8 % (18/22 people), and the difference between the two groups was significant ($P < 0.05$). It was concluded that an early and continued high dosage of Compound Danshen preparations benefits the stabilization of the disease condition, reduces complication, and thus enhances the long-term survival rate.

1.4.3 Peptic Ulcer

It has been discovered that Danshen has a strong inhibitory function against *Helicobacter pylori*. The tanshinol in Danshen can rapidly eliminate necrotic tissue in ulcer sites and has the function of activating macrophages and promoting cell regeneration, thus promoting ulcer healing.

Liu and Yi [56] reported the application of CDI in the treatment of 30 patients with peptic ulcer disease, and the effects were compared with those in 30 patients in the ranitidine treatment group. 20 ml of CDI was added to 250 ml of 5 % glucose and administered by intravenous drip to the patients in the treatment group once a day; 0.3 g of ranitidine was administered orally twice to the patients in the control group. The two groups were treated for 8 weeks, and then the therapeutic effects were recorded. The results showed that in the treatment group, there were 24 recovery cases, 5 effective cases, and 1 case without effect; the recovery rate was 80.0 %. In the control group, there were 26 recovery cases, 3 effective cases, and 1 case without effect; the recovery rate was 86.7 %. There was no significant difference in recovery rate between the two groups ($P > 0.05$). peptic ulcers usually belong to the category of chronic disease, and according to TCM theory, chronic illness is usually associated with stasis, and prolonged disease and pathogens usually intrude into the collaterals. Danshen has the function of activating blood

circulation and dissipating blood stasis. It is believed in modern medical research that Danshen has an inhibitory function against *Helicobacter pylori*, and that tanshinol in Danshen can effectively clean necrotic tissue in ulcer sites, activate macrophage function, and promote cell regeneration, thus promoting healing. There was no significant difference in the therapeutic effects of Compound Danshen and ranitidine for the treatment of peptic ulcers. However, Compound Danshen had scanty side effects and was welcomed by the patients.

Liu et al. [57] observed the treatment of peptic ulcers with Danshen and ranitidine; ① The treatment group: Danshen and ranitidine were administered at the same time. 60 g of raw Danshen each day was soaked in 200 ml of water for 15 min, then 600 ml of water was added and decocted by slow fire for three times. The physic liquor was concentrated to 100 ml and taken orally in two times. 150 mg of ranitidine was administered in two times a day. ② The control group: 150 mg of ranitidine was administered in two times in a day. The course of treatment for the two groups was 6 weeks. The therapeutic effects were evaluated by endoscopy. The results showed that after 6 weeks of treatment, the peptic ulcer recovery rates of the control group and treatment group were 69 and 93.9 %, respectively, and there was a significant difference ($P < 0.05$). The LPO and ET plasma contents in the control group were 0.111 ± 0.006 μg/ml and 70.2 ± 7.9 pg/ml, respectively, which were lower than 0.15 ± 0.12 μg/ml and 86.3 ± 13.5 pg/ml before treatment ($P < 0.05$). In the treatment group, the numbers were 0.08 ± 0.006 μg/ml and 52.9 ± 7.52 pg/ml, respectively, which were significantly lower than 0.16 ± 0.11 μg/ml, 85.9 ± 12.2 pg/ml before treatment ($P < 0.001$). The results demonstrated that Danshen's mechanism of action in the treatment of peptic ulcers might include ① cleaning oxygen radicals and inhibiting lipid peroxidation, which could protect the mucous membrane of the stomach and duodenum from injury, thus promoting ulcer healing. ② reducing blood plasma ET levels, improving microcirculation, and increasing blood flow in the mucous membranes of the stomach and duodenum. It has been demonstrated in recent years that ET can be produced by the intestinal mucosa epithelial cells of the stomach, and the mechanism through which ET causes ulcers is related to its ability to cause vasoconstriction in the stomach and duodenum, which leads to mucous membrane ischemia, anoxia and acidosis. On the other hand, ischemia, anoxia and endothelium cell damage can stimulate the release of ET, creating a vicious cycle. Danshen can be used as an ET antagonist, and it has the function of reducing ET content in the blood plasma and improving the blood supply of the gastroduodenal hemorragemucous membrane, thus preventing ulcer formation.

1.4.4 Chronic Gastritis

In TCM, chronic gastritis belongs to the category of blood stasis. Research has shown that there is a close relationship between blood stasis and microcirculatory disturbance. Danshen is one of the traditional drugs with the function of activating blood circulation and dissipating blood stasis; it can improve microcirculation, eliminate metabolism disturbances of the stomach mucous membrane, and antagonize inflammation, thus promoting the regeneration of tissue, softening the proliferative pathological changes, and enhancing absorption function.

Li [58] reported the application of modified Danshen Beverage in the treatment of 50 patients with chronic gastritis. The patients in the treatment group were treated with modified Danshen Beverages according to their symptoms. The basic prescription contains 30 g of Danshen, 5 g of sandalwood (檀香), and 5 g of villous amomum fruit (砂仁). The patients in the control group were orally administered 20 mg of omeprazole twice a day, 0.5 g of amoxicillin three times a day, and 0.4 g of metronidazole three times a day. The above three drugs were administered together for 2 weeks, and then omeprazole was administered for another 2 weeks. During the treatment period, the patients should correct their poor eating habits, have a regular diet, avoid eating various

stimulatory foods or drugs, and avoid smoking and drinking alcohol or strong tea. There was a significant difference ($P < 0.05$) between the two groups in therapeutic effects; the effective rate of the treatment group was 94 %, which was significantly higher than the 77 % of the control group.

1.4.5 Severe Pancreatitis

The research in recent years has shown that hemorheology abnormality is one of the important etiological factors of severe pancreatitis. It is the main cause of blood circulation disturbance in the pancreas. Compound Danshen has the function of inhibiting platelet adhesion, aggregation and release, and it can significantly reduce erythrocyte aggregation, improve the blood rheology, regulate blood viscosity, improve microcirculation, enhance the tolerance of pancreatic tissue to anoxia, reduce the production of oxygen radicals, and relieve pathological changes in pancreatic tissue. In addition, tanshinol in Danshen has the function of rapidly cleaning necrotic tissue in the pancreas, promoting the regeneration of pancreatic cells, dilating pancreatic blood vessels, and promoting recovery from pancreatitis.

Xie [59] reported the treatment of 28 severe pancreatitis cases with CDI. 12 ml of CDI was diluted with 500 ml of glucose solution and administered by intravenous drip once a day, for 7–14 days as one course of treatment. The patients were treated after operation, and 13 cases in the control group were treated with normal western medicine. The results showed that the fatality rate in the treatment group was only 3.6 %, while the fatality rate in the control group was higher (30.8 %), and the difference was significant ($P < 0.05$). The hematocrit levels in the treatment group were reduced from 46 ± 5.2 % before operation to 33.2 % ± 3.9 % after operation, and the difference was significant ($P < 0.05$). It was concluded that hematocrit can be reduced to the normal lower limit by CDI after severe pancreatitis surgery, reducing blood viscosity, improving circulatory disorders of the body organs, promoting pancreatic tissue recovery, and contributing to the correction of serious complications such as adult respiratory distress syndrome (ARDS), so that mortality in the treatment group was significantly lower than in the control group.

1.4.6 Ulcerative Colitis

Zhang and Liu [60] reported the treatment of 48 ulcerative colitis cases. 23 cases in the treatment group were treated with the general treatment plus Danshen injection. 20 ml of Danshen injection was added into glucose solution and administered by intravenous drip for 3 weeks, once a day. The results showed that no significant differences were found in the levels of platelet α granule membrane protein (GMP-140), thromboxane 2 (TXB_2), 6-ketone-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) and von Wilebrand factor related antigen (vWF:Ag) before and after the general treatment. In the Danshen treatment group, however, the levels of GMP-140, TXB_2, and vWF:Ag were significantly reduced compared with those before the treatment ($P < 0.01$), and there was no significant changes in 6-ke-to-PGF1α. It was believed that the combined treatment of active phase patients with Danshen injection and conventional methods could correct hypercoagulability, relieve inflammation responses, and improve disease conditions.

Blood stagnation is one of the most common types of syndromes in TCM. It exists in many systemic diseases, including diseases of the digestive system. Based on clinical practice and observation, different degrees of stagnation could be induced by the prolonged pathogenesis of both lung and stomach intestinal diseases. Therefore, the application of Danshen and its preparations in the treatment of chronic diseases of the digestive system has its theoretical and practical foundations.

1.5 Urinary System Diseases

1.5.1 Acute Nephritis

Wang and Wen [61] observed the effect of 654-2 and CDI by intravenous drip on the treatment of 68 patients with acute nephritis. The patients in the treatment group were treated with conventional therapy (mainly benzylpenicillin, low salt diet, symptom relief, etc.), and at the same time, 20 mg of 654-2 and 12–16 ml of CDI were, respectively, added into 250 ml of 10 % glucose and administered by intravenous drip, once a day, for 7–10 days as one course of treatment. If necessary, the drugs were discontinued for 3 days, then the second course of treatment was performed, and the treatment could be stopped if no effect was obtained. Urine-routine was measured before and after treatment. The patients in the control group were administered with the traditional treatment. The results showed that in the treatment group 27 cases were cured, and among them 21 cases had their symptoms of nephritis all disappear after one course of treatment (spirit and appetite were recovered, edema was dissipated, and urine protein turned negative) and 6 cases had their urine protein turn negative after 2 courses of treatment. Five cases showed improvement, and two cases showed no effect. The average time for edema to subside was 5.37 ± 1.26 days, the average time for blood pressure to return to normal was 3.84 ± 1.26 days, the average time for urine protein to turn negative was 14.57 ± 3.08 days, and the average time of hospitalization was 12.4 days. In the control group, 22 cases were cured, 7 cases improved, and 5 cases showed no effect. The average time for edema to subside was 9.08 ± 2.63 days, the average time for blood pressure to return to normal was 6.48 ± 2.62 days, the average time for urine protein to turn negative was 14.57 ± 3.08 days, and the average time of hospitalization was 14.3 days. CDI has the function of reducing platelet aggregation and adhesion, inhibiting platelet generation, inhibiting blood coagulation, promoting fibrinolysis, improving hemorheology, and so on. The combination of 654-2 with Danshen has the function of dilating the renal arteries, reducing blood viscosity, increasing renal blood flow, improving kidney microcirculation, increasing the flow rate of urine in renal tubules, and preventing and relieving the occlusion of cast and cast-off cells on the distal convoluted tubules, thus realizing the effects of diuresis, subsiding edema, and eliminating proteinuria in a short time. 3 months of follow-up was performed, with affirmative therapeutic effects.

1.5.2 Chronic Glomerulonephritis

Patients with chronic glomerulonephritis (CGN) usually suffer from a disequilibrium of thromboxane-prostacyclin (TXA-PGI), which can result in kidney vessel and mesangial constriction, reducing the filtration area of the renal glomerulus, promoting the adhesion and aggregation of platelets and leucocytes, and participating in thrombopoiesis, inflammation response, and nephridial tissue and cell damage; thus, it is one of the causes of the sustained development of chronic glomerular lesions and renal dysfunction. Experiments have demonstrated that Danshen has the function of improving microcirculation, increasing the content of cyclic adenosine monophosphate in blood capillaries, and increasing PGI synthetase. It also has the function of inhibiting TXA synthetase, which can improve the balance of TXA-PGI. With the improvement of TXA-PGI balance, renal blood flow and glomerular filtration rate increased and urine protein was reduced. In addition, Danshen can enhance fibrinolysis activity, thus promoting fibrinolysis, relieving fibrin deposition in the renal glomerulus, and relieving renal glomerulus damage.

Shen [62] reported the treatment of CGN with Danshen. 20 ml of CDI was added to 250 ml of 5 % glucose injection and administered by intravenous drip to 67 patients with CGN, once a day, for 12 days as one course of treatment. The results showed that there were 18 cases of complete remission (26.9 %), 15 cases of general remission (22.3 %), 4 cases of partial remission

(6.1 %), and 0 cases of no effect. The total effective rate was 100 %.

1.5.3 Chronic Renal Failure

Patients with chronic renal failure (CRF) usually suffer from reduced plasma-albumin and increased fibrin. Fibrin is related to the increase in cholesterol. High levels of fibrinogen will increase blood viscosity, thus leading to blood hypercoagulability and fibrinolysis disturbance in patients with CRF. Danshen is a traditional drug with the function of activating blood circulation and removing blood stasis. It has functions of anticoagulation, thrombolysis, reducing blood lipids, etc., and improving CRF-induced disorders in renin and blood plasma volume and the chain reactions induced by the increase of renin, such as increased renal tubule resistance, deposition of erythrocytes, blood vessel occlusion, reduced renal blood flow, local disturbance of circulation, reduced oxygen supply and renin release, etc.

Jiang [63] reported the use of CDI for the intervention of peritoneal dialysis; 34 cases with acute or CRF were treated, and the drug was added together with anisodamine (654-2) into peritoneal dialysis solution for 30 cases in the control group. The results showed that the serum creatinine (SCr) of 18 cases in the treatment group was reduced by more than 50 %, 12 cases by more than 30 %, and 4 cases by more than 10 %; 10 cases in control group reduced by more than 50 %, 11 cases by more than 30 %, and 9 cases by more than 10 %. The blood urea nitrogen (BUN) of 20 cases in the treatment group was reduced by more than 50 %, 9 cases by more than 30 %, and 5 cases by more than 10 %; 12 cases in control group reduced by more than 50 %, 10 cases by more than 30 %, and 8 cases by more than 10 %. The total effective rate in the treatment group was 88.3 %, and in the control group was 73.4 %; the total effective rate in the treatment group was significantly better than that in the control group.

Zhang [31] reported the treatment of CRF with CDI combined with energy mixture. 41 patients with CRF were randomly divided into 2 groups; 21 cases in the treatment group were treated according to their symptoms and administered with CDI and energy mixture by intravenous drip. 20 cases in the control group were treated according to their symptoms and administered with glucose and insulin by intravenous drip. The therapeutic effects in the two groups were observed after one course of treatment. The results showed that the total effective rate in the treatment group was 85.71 %, while the total effective rate in the control group was 35.00 %, and the treatment group was significantly better than the control group ($P < 0.01$). BUN and SCr were reduced after CDI treatment, and there was a significant difference before and after the treatment ($P < 0.05$). There was no significant difference in BUN and SCr in the control group before and after the treatment ($P > 0.05$). It showed that CDI combined with energy mixture can protect residual renal function, delay the development of CRF, and there was a promising perspective.

1.5.4 Acute Renal Failure

Acute renal failure (ARF) belongs to the category of “difficulty in urination-defecation” and “disuria and urine retention” in traditional Chinese medicine. Its pathological feature is that the root is deficient and the branches are excessive, namely, the cause is kidney deficiency and blood stasis is the symptom, which may also include water-dampness and heat bind. Danshen has the function of activating blood circulation and removing blood stasis, cooling the blood and clearing heat. Rosewood heart wood (绛香) has the function of activating blood circulation and relieving pain. The combination of the two drugs has the function of breaking the constraint of qi and dispersing the stasis of blood, so as to recover renal function. Modern medical research has shown that tanshinone and tanshinol in Danshen can dilate small blood vessels, increase microcirculatory flow rate, increase capillary networks, etc., and that rosewood heart wood has anticoagulation function. When the drugs are combined with western medicine, the functions

of dilating kidney vessels, correcting hypercoagulability, improving microcirculation, increasing renal blood flow, enhancing glomerular filtration rate, and improving renal function can be obtained. In addition, microcirculation can be directly improved by intraperitoneally administered Danshen, thus increasing the peritoneal dialysis rate, and it also has antibacterial and anti-inflammatory effects and prevents the occurrence of peritonitis.

Huang et al. (1993) reported the effect of Danshen on the treatment of AFR. 110 patients with ARF were treated with 20 ml of CDI in 250 ml of 10 % glucose by intravenous drip, once a day, for 14–21 days as one course of treatment. The results showed that all patients were cured, and that BUN was reduced by 8.3 mmol/L within 7 days and the diuresis stage began within 4–8 days (average of 7 days) of treatment.

Jiang [63] used CDI in peritoneal dialysis solutions to obtain a concentration of 6 ml. 34 cases were treated with a total effective rate of 88.3 %, and the total effective rate in the 654-2 injection control group (concentration was 20 mg) was 73.4 %. There was no significant difference ($P > 0.05$) between the two groups, but the effects in the treatment group were significantly better than those in the control group, and no patient was complicated by peritonitis in the treatment group during hospitalization.

1.5.5 Primary Nephrotic Syndrome

Patients with nephrotic syndrome (NS) usually experience hypercoagulability; the blood viscosity is increased, microcirculation is dysfunctional, and even vascular microthrombosis is complicated, which aggravates NS treatment. Modern pharmacological studies have shown that Danshen has the function of dilating peripheral arteries, improving local blood circulation, reducing inflammation effusion, promoting absorption, etc., thus localizing the nonspecific inflammation in nephridial tissue, which is conducive to renal tissue repair. Danshen also activates blood circulation, removes blood stasis, and acts as an anticoagulant. In addition, Danshen can cool the blood and eliminate carbuncles, relieve restlessness and calm the nerves. Thus, it can be used to alleviate the blood-heat and stasis induced by taking hormones, and to treat hormone-induced sore swelling and sore toxin, as well as sleeplessness.

Huang and Wu [64] reported that good effects on the treatment of nephrotic syndrome were obtained by using CDI and hormones. 16 ml of CDI was added to 500 ml of 10 % glucose and administered by intravenous drip to 33 cases in the treatment group, once a day, and 10 mg of prednisone was administered orally, three times a day, for 20 days as one course of treatment. The 33 patients in the control group were administered prednisone only. The results showed that the remission rate in the treatment group was 94 %, and in the control group was 54.8 %, and the difference between the two groups was significant ($P < 0.005$). When people suffer from nephrotic syndrome, their blood capillary filter membrane in the renal glomerulus experiences immunoinflammatory reactions, their glomerular basement membrane proliferates, their blood is in a state of hypercoagulability, and their kidneys have different degrees of fibrosis. Compound Danshen has the function of reducing cholesterol, inhibiting fibroplasia, relieving fibrin deposition, improving hypercoagulability induced by renal insufficiency, and recovering renal function, thus it can effectively treat nephrotic syndrome.

Liu et al. [65] reported therapeutic effects of Compound Danshen and Mongolian Milkvetch Root (Huangqi, 黄芪) in the treatment of nephrotic syndrome. 42 patients with nephrotic syndrome were randomly divided into two groups, and patients in the control group were administered orally with prednisone and dipyridamole. The patients in the treatment group were administered orally with prednisone and by intravenous drip with dipyridamole plus 20 ml of CDI and 20 ml of Huangqi Injection, once a day, for 2 weeks as one course of treatment. Before and after treatment, plasma-albumin, urine protein, cholesterol, and triglyceride levels in each group were determined. The results showed that plasma-albumin levels in the two groups

increased after treatment compared to before treatment, and the levels in the treatment group were significantly higher than in the control group ($P < 0.01$). Urine protein, cholesterol, and triglycerides in the two groups were reduced after treatment, and the reductions in the treatment group were significantly larger than those in the control group ($P < 0.01$, $P < 0.05$). It was concluded that the therapeutic effects in the treatment of nephrotic syndrome can be increased when the conventional prednisone and dipyridamole treatments are combined with compound Danshen and mongolian milkvetch root.

1.5.6 Purpura Nephritis

Purpura nephritis, or Henoch-Schönlein nephritis (HSN), belongs to the category of bruising and urine hemorrhage in TCM, which is usually caused by the heat injury of blood collaterals. The main clinical manifestations include hemorrhage and stagnant blood symptoms. Danshen is bitter in taste and slightly cold in nature, and has the function of activating blood circulation, cooling blood, eliminating congestion, and stopping bleeding. Pharmacological studies have demonstrated that compound Danshen has the function of promoting microcirculation, regulating the metabolism and immunologic function, and increasing renal blood flow and filterability, thus increasing urinary production, eliminating edema, reducing blood pressure, eliminating haematuria and proteinuria, and promoting HSN recovery.

Meng et al. (1999) reported that CDI 0.5–1 ml/(kg·d) was added to 5 % glucose injection and administered by intravenous drip to 24 patients with HSN. The results showed that 18 cases were cured, 5 cases improved, 1 case showed no effect, and the total effective rate was 95.8 %.

Zhang et al. (1992) reported that a high dosage of CDI, 20–40 ml, was added to 500 ml of 5 % glucose solution and administered by intravenous drip to 21 patients with HSN, once a day. The results showed that 13 cases were cured, 5 cases improved, 3 cases showed no effect, and the total effective rate was 86 %.

1.5.7 Diabetic Nephropathy

Research has shown that Diabetic nephropathy (DN) is related to factors such as microangiopathy of the renal glomerulus, increased plasma viscosity, abnormal platelet function, abnormal coagulation and anticoagulant mechanisms, etc. In addition, patients with DN also suffer from SOD activity reduction, glomerular basement membrane thickening, and glomerulosclerosis, which are typical pathological changes of DN. Danshen has the function of activating blood circulation, removing blood stasis, improving microcirculation, inhibiting platelet aggregation, and reducing blood lipids and blood viscosity, etc. It can also increase SOD activity, eliminate oxygen radicals, relieve small vasospasms, and improve renal anoxia conditions, thus it could eventually reverse the pathological changes of the glomerular basement membrane, so as to cure DN and delay the process of renal dysfunction.

Yang [66] mixed 40 ml of CDI in 250 ml of physiological saline and administered by intravenous drip to 38 patients with DN, once a day, for 1 week as one course of treatment. 20 patients in the control group were administered with Western medicine only. The results showed that the total effective rate in the treatment group was 89.5 %, while in control group was 55 %, and the difference was significant ($P < 0.05$).

Li et al. [67] divided 66 patients with DN randomly into a treatment group (36 cases) and control group (30 cases). The patients in the treatment group were treated with normal therapy plus 20 ml of Danshen Injection, administered for 4 weeks by intravenous drip, once a day. The results showed that blood plasma endothelin (ET-1), type IV collagen (CIV), and 24-h urinary protein excretion rates in the treatment group were significantly reduced ($P < 0.05$). The results demonstrated that Danshen has some preventative and treatment effects on DN at the early stage, and the mechanism the drug's

inhibition of the production of ET-1 and synthesis of CIV.

1.5.8 Lupus Nephritis

Zhang [68] showed that Danshen had inhibitory effects on renal desmocytes and inducing cell apoptosis by promoting the high level expression of C-myc protein. Taking high dosages of Danshen for a long period of time could have some therapeutic effects on interstitial fibrosis, thus preventing or reducing the production of lesions and delaying the occurrence of uremia, demonstrating that Danshen could promote the absorption of excessive connective tissue.

1.5.9 Chronic Allograft Nephropathy

Huang and Wu [64] reported the effect of Danshen on the treatment of chronic allograft nephropathy. Besides the routine anti-rejection therapy, 30 ml of Danshen was added to physiological saline and administered by intravenous drip to 20 patients with chronic allograft nephropathy for 4 weeks. The results showed that the improvement in renal function indexes in patients in the treatment group was better than that in the control group ($P < 0.05$), and Danshen has the function of reducing urine NAGase activity ($P < 0.01$). It was concluded that Danshen has protective effects against acute or chronic renal damage, and the mechanism is Danshen's inhibition of the overproduction of nitric oxide and peroxide. Danshen has the function of preventing chronic rejection and thrombopoiesis induced by the ciclosporin damage to the renal tubule, thus improving transplanted kidney function.

1.5.10 Hypertensive Renal Damage

Zhang et al. [69] reported the treatment of hypertension accompanied by renal injury with CDI combined with benazepril hydrochloride in 30 cases, and the changes in urinary albumin were observed. Blood pressure was measured twice each day for all patients with hypertension over the 3 days before treatment, and the average of the six blood pressure values was used as the baseline blood pressure before treatment. Urinary albumin was measured within 24 h before drug administration. The patients in the control group were administered with 10 mg of benazepril once a day, and the patients in the treatment group were administered orally with 10 mg of benazepril once a day, and 30 ml of CDI in 250 ml of 5 % glucose injection was administered by intravenous drip once a day. Blood pressure was measured once each day for the patients in the two groups. Two weeks after treatment, if the blood pressure was not reduced to 140/90 mmHg or lower, benazepril would be increased to 20 mg, once a day, treated for 4 weeks. The average blood pressure over 3 days at the end of treatment was used as the blood pressure after treatment, and urinary albumin was measured within 24 h after treatment. Urinary albumin was examined by radiation immunity. The results showed that there was no statistical difference in blood pressure reduction between the two groups after treatment ($P > 0.05$). There was, however, a statistical difference in the reduction of urine protein between the two groups after treatment ($P < 0.05$). The results demonstrated that the effect of Danshen and benazepril treatment on urinary albumin was significantly better than that of benazepril alone, and significant therapeutic effects could be obtained by the combination of the two drugs. The method is convenient and the side effects are few, making it an effective method for the treatment of hypertensive renal injury.

1.5.11 Prostatic Hyperplasia

He et al. [70] reported the use of CDI in the treatment of 112 patients with benign Prostatic hyperplasia by local injection to the perineal prostate capsule, 4 ml each time, once every 2 days, for 10 injections as one course of treatment. The results showed that the International Prostate Symptom Score (IPSS) was reduced compared to

the conditions of patients before treatment ($P < 0.01$), the maximal urinary flow rate increased ($P < 0.01$), and the residual urine volume was significantly reduced ($P < 0.01$). Danshen activates blood circulation and dissipates blood stasis, promotes blood circulation and nourishes blood, promotes the excretion of prostatic fluid, shrinks the gland, and improves urination function.

1.5.12 Chronic Prostatitis

Huang (1993) reported the administration of Danshen and metronidazole mixture by prostate injection. One course of treatment later, symptom disappearance occurred in 20 cases, improvement in 8 cases, and the total effective rate was 93.3 %. Reexamination showed that in 13 cases, the swollen gland was significantly shrunken and tubercles were softened.

1.5.13 Impotency

Tian [71] reported the use of CDI to treat impotency. CDI was administered by injection to acupoint Qugu (RN 2) in 30 patients with impotency; the patients were 22–47 years old, the average age was 29.3, and the course of disease was 1–10 years. Before treatment, the patients were asked to empty their bladder, then normal skin disinfection was performed. 1.5–5 ml of CDI was injected at Qugu, once every 2 days, 7 times as one course of treatment, and sexual intercourse was prohibited during the treatment period. The results showed that 23 cases were cured, 2 cases showed effect, 2 cases showed marked effect, 3 cases showed no effect, and the total effective rate was 90.0 %.

Although the application of Danshen in the urinary system is not as popular as in the cardiocerebrovascular and digestive systems, what is affirmed is that Danshen and its components have relatively good therapeutic effects on acute or chronic nephrosis due to the retention of stagnant blood, interior harmful retention of toxin and heat, such as acute nephritis, acute and CRF, nephrotic syndrome, DN, chronic prostatic hyperplasia, and so on.

1.6 Diabetes

Jiang [72] reported the treatment of 40 cases of type 2 diabetes mellitus (the majority were complicated with angioneuropathy) with CDI. The patients were randomly divided into the treatment group and control group, 20 cases each. The patients in both groups had reasonable dietary control, and one or more hypoglycemic agents were used for blood sugar control according to their conditions. Some patients were treated with vitamin B_1, B_{12} and other treatments according to their symptoms. 10–16 ml of CDI in 250–500 ml of physiological saline was administered by intravenous drip to the patients in the treatment group, once a day for 2–3 weeks. The results showed that in the treatment group there were 7 cases showing marked effect, 11 cases showing improvement, 2 cases showing no effect, and the total effective rate was 90 %. In the control group, 3 cases showed marked effect, 9 cases showed improvement, 8 cases showed no effect, and the total effective rate was 60 %. The therapeutic effects in the treatment group were significantly higher than those in the control group ($P < 0.01$). The mechanism of the effects might be that the activity of SOD, which has the function of cleaning oxygen radicals, was reduced in patients with type 2 diabetes mellitus, and there was lipid peroxidation damage. CDI has the function of enhancing the tolerance of pancreatic tissue to anoxia, reducing the production of oxygen radicals, increasing SOD activity, and effectively relieving lipid peroxidation damage. Danshen also reduces blood sugar and protects pancreatic islet β cells in experimental diabetes. Therefore, CDI will have important clinical significance in the prevention and treatment of diabetic complications.

Lü [73] observed the therapeutic effects of Huangqi injection combined with Danshen Powder Injection on the treatment of type 2 DN at the early stage. 26 cases in the control group

received conventional hypoglycemic antihypertensive therapy. The 28 patients in the treatment group received conventional therapy plus 100 ml of Huangqi Injection and 0.8 g of Danshen Powder Injection in 250 ml of physiological saline, administered by intravenous drip, once a day, for 1 month as one course of treatment. The changes in urinary albumin excretion (UAE) within 24 h were observed. The results showed that there was no significant change in UAE in the control group before and after the treatment ($P > 0.05$), but in the treatment group, the UAE was significantly reduced after treatment compared to before ($P < 0.01$). It was concluded that Huangqi Injection combined with Danshen Powder Injection has therapeutic effects on DN at the early stage.

1.6.1 Diabetic Gastropathy

Chen [74] observed the therapeutic effect of CDI combined with domperidone on Diabetic Gastropathy. 112 inpatients and outpatients suffered from type 2 diabetes mellitus, 58 male, 54 female; 34 cases were complicated with coronary heart disease; fasting plasma glucose was 5.9–13.4 mmol/L; average fasting plasma glucose was 7.6 ± 1.6 mmol/L. All patients received the conventional diabetes treatment, and those who had complications of peptic ulcers, stomach and duodenum operation, and ketosis acidosis were excluded. 25 cases in the control group had no dyspepsia symptoms or peptic ulcer history, and liver and kidney functions were normal. 53 cases with DG were divided into 3 groups based on gastric emptying function and medication condition. 15 cases in the domperidone group were administered orally with 10 mg of domperidone, three times a day; 15 cases in the Danshen group were administered by intravenous injection with 16 ml of CDI, once a day; 23 cases in the domperidone + Danshen group were administered with domperidone and Danshen, and the dosage and administration were the same as the above therapies. The course of treatment was 4 weeks, and fasting plasma glucose, liver and kidney functions, and gastric emptying function were reviewed within 3 days after treatment. There were no significant differences in gender, age, or disease condition and fasting plasma glucose among the 3 groups. The results showed that the gastric emptying half-times in the diabetes group and control group were 67.1 ± 14.4 min and 48.3 ± 11.7 min, respectively, and the difference between the two groups was significant ($P < 0.01$). The gastric emptying function of patients with Diabetic Gastropathy was significantly improved, and that of the drug combination group was the most significant. There were different extents of improvement in the pathological changes of the peripheral nerves and cardiovascular system after treatment with Danshen, but there was no significant difference in fasting plasma glucose before and after treatment.

1.6.2 Diabetic Peripheral Neuropathy

Li et al. [75] observed the treatment of diabetic peripheral neuropathy (DPN) with Danshen combined with mecobalamin (Methycobal). 50 cases of DPN were randomly divided into two groups. 30 cases in the treatment group received 16 ml of Danshen Injection in 500 ml of physiological saline, administered by intravenous drip each day, and 500 μg of methycobal, administered by intramuscular injection, once a day for 4 weeks. 20 cases in the control group received the conventional diabetes treatment. The results showed that the marked effect rate and the total effective rate in the treatment group were 56.67 and 90 %, respectively, which were significantly higher than those in the control group, 18.18 % ($P < 0.05$) and 44.45 % ($P < 0.01$), respectively. Therefore, it was concluded that better therapeutic effects were obtained by Danshen combined with Methycobal in the treatment of DPN.

Gong [76] observed the therapeutic effect of Yinxing (Ginkgo) Damo Injection combined with Danshen Injection on the treatment of DPN. 95 patients with type 2 diabetes mellitus complicated with DPN were randomly divided into three groups according to the chronological order of hospitalization. There were 31 patients in

group 1 administered with Yinxing Damo Injection combined with Danshen Injection, 32 patients in group 2 administered with Yinxing Damo Injection, and 32 patients in group 3 administered with Danshen Injection. The treatment period in the above three groups lasted for 2 weeks. All three treatments showed some degree of therapeutic effects on DPN; they could improve symptoms such as numbness, pain, chill, fever and others, and neural conduction function was significantly enhanced. The clinical therapeutic effects in group 2 were better than those in treatment group 3 ($P < 0.05$), but those in group 1 were better than in group 2 and group 3 ($P < 0.05$). There were significant therapeutic effects of Yinxing Damo Injection combined with Danshen Injection in DPN treatment.

Diabetes is a common clinical disease and is one of the three diseases which threaten human health. The patients' quality of life is usually directly reduced due to related complications which appear during the later stages of the disease. From the related documents we have found, Danshen and its preparations are mainly used in the treatment of DN, stomach diseases, and peripheral nerve pathological changes etc., and satisfactory therapeutic effects have been obtained, so it is worthy of consideration.

1.7 Effects on Hemorheology

Lin [77] reported the application of Danshen Injection in the treatment of 300 cases of high blood viscosity syndrome, and observed the effect of Danshen on the hemorheology Hemorheology. 30 ml of Danshen Injection in 5 or 10 % glucose was administered by intravenous drip, one time a day, 10 times as one course of treatment. After 1–2 courses of treatment, the rate of total plasma viscosity reduction was 94.7 %; among them, improvement in 1–2 indexes was 47.33 %, and in 3–4 indexes or more was 52.67 %. It was revealed that the drug can effectively improve hematocrit, erythrocyte electrophoretic time, fibrinogen and blood plasma viscosity, and thus can be used as one of the adjuvant therapies for polycythemia, pulmonary heart disease, heart failure, burn, frostbite, ischemic stroke induced by fibrinogen and blood plasma viscosity increase, myocardial infarction, diabetes, hyperlipidemia, globulin increase, and other diseases.

Yan et al. [78] investigated the effect of salvianolate on platelet function and its clinical therapeutic effect on stable angina pectoris. 56 patients with stable angina pectoris were randomly divided into the salvianolate low dosage group (group A), high dosage group (group B) and Danshen Injection control group (group C). The patients were treated for 14 days, observing symptom remission, treadmill tests, platelet aggregation rate, and changes in P-selectin level. platelet aggregation reduction rate and P-selectin in group A and group B were better than in group C, but symptom remission and treadmill tests were similar to those in group C. Salvianolate significantly inhibits platelet aggregation and activation, and improves angina pectoris and ST-T changes in electrocardiograms.

Secondary increases in erythrocytes and blood viscosity can be induced by anoxia during an attack of pulmonary heart disease. Qian [79] reported the application of normal therapy combined with CDI in the treatment of pulmonary heart disease in 17 cases. The results showed that there were significant changes in whole blood viscosity in hemorheology, viscosity, and plasma viscosity in the treatment group before and after treatment ($P < 0.01$).

The treatment period for primary nephrotic syndrome is lengthy and the recurrence rate is high. Blood hypercoagulability plays an important role in the occurrence, development and turnover of the disease. To search for a safe anticoagulation drug, 67 cases with primary nephrotic syndrome were treated with Compound Danshen by Li et al. (1997). The patients were treated with prednisone and Compound Danshen Tablet (Danshen, sanchi, synthetic borneol), one tablet a day, two times a day for patients younger than 7 years old and three times a day for patients older than 7 years old, for 1 month as one course of treatment, 1–6 courses of treatment were observed. 5 indexes (platelets, blood clotting

time, plasma viscosity, packed red cell volume, blood sedimentation) were observed. The results showed that there was a significant difference between the observation group and control group before and after treatment ($P < 0.01$).

Hui [80] observed platelet recovery in 103 cases with epidemic hemorrhagic fever treated with Danshen Injection. The patients in the treatment group were treated with conventional therapy plus Danshen Injection, 20 ml each time, 2 times a day. Administration was discontinued until platelet levels were 70×10^9/L or more, which was used as the standard for marked effect. The results showed that there were 94 cases (91.3 %) with marked effect and 9 cases (8.73 %) without effect. The effective rate in the control group, who were treated with conventional therapy only, was 33.33 %, the ineffective rate was 66.66 %, and there was a significant difference between the two groups. It was revealed that Danshen can directly or indirectly reduce damage to platelets and promote platelet production, so the platelet number was rapidly recovered.

In theories of traditional Chinese medicine and Western medicine, there are common and different aspects of stagnant blood in TCM and hyperviscosity in Western medicine. However, Danshen's functions in activating blood circulation and dissipating blood stasis are confirmed by both TCM theory and modern pharmacological experiments. From this point of view, the effect of Danshen and its preparations on hemorheology is self-evident, and the data presented above are corroborative evidence.

References

1. Liu H. J New Chin Med. 2003;2(35):34–5.
2. Li B, Yang Q, Jin S. Shaanxi J Tradit Chin Med. 2006;11(27):1332–3.
3. Meng Y, Zou A. Tianjin J Tradit Chin Med. 2002;19 (2):273.
4. Hu J, Yang D. Henan Tradit Chin Med. 2000;20 (4):45.
5. Chen Y, Gao Y. J Pract Tradit Chin Intern Med. 2004;3(18):237.
6. Yang XR. Yunnan J Tradit Chin Med Mater. Medica. 2004;25(4):61.
7. Fu D, Shang Y, Cui T. Cent. Plains Med J. 2005;32 (6):24.
8. Xing Q. J Integr Tradit Chin West Med. 1998;18 (8):506.
9. Mao X, Li P, Wang Y. J Clin Acupunct Moxibustion. 1995;11(2):16–8.
10. Zhang J. Hubei J Tradit Chin Med. 2005;27(1):51.
11. Zhang Q, Zhang P, Mingzhuang L, et al. Guizhou Med J. 2002;8(26):686–7.
12. Xing Z. J Integr Tradit Chin West Med. 1996;16 (5):287.
13. Lin Y. J Integr Tradit Chin West Med. 2007;5 (27):465.
14. Qi H, Zhao X, Li Y. China Med Herald. 2006;23 (3):22–4.
15. Chao S, Wang L, Fan J, et al. Chin J Integr Tradit West Med Intensive Crit Care. 2007;3(14):145–6.
16. Cheng W, Zhao J, Zhang S. J Integr Tradit Chin West Med. 1995;12:712–3.
17. Huang B, Chen L. Henan Tradit Chin Med. 2000;20 (6):42.
18. Liu F. China's Naturopathy. 2003;4(11):43–4.
19. Hong Y, Xian S, Huang Y. J Guangzhou Univ Tradit Chin Med. 2000;17(3):225.
20. Xu Z. Tianjin J Tradit Chin Med Drug. 2003;4 (20):74–6.
21. Zhu F, Wang L, Liu Z. J Shandong Med Coll. 2002;25:7–8.
22. Fu B. Mod Med Health. 2003;1(19):40.
23. Shi X, Xia Z, Fan J, et al. J Integr Tradit Chin West Med. 2000;20(12):896–8.
24. Li R, Zhao H, Zhang Y, et al. Chin J Integr Tradit West Med Intensive Crit Care. 1999;10(6):462–5.
25. Pang Z, Sun H, Ji H. Shandong Med J. 2003;1 (43):43–4.
26. Pang X, Song B, Wang J. Chin J Tradit Med Sci Technol. 2007;2(14):121–2.
27. Qi G. Chin J Rural Med Pharm. 2002;1(9):12.
28. Huang B, Liu Q, Xu Z, et al. China J Mod Med. 2003;1(13):62–3.
29. Zhai Z, Sun J, Zhang J. J Hebei Med. 2001;2 (7):1110–1.
30. Sun J. Integr Tradit Chine West Med Pract Crit Care Med. 1998;2(5):60–2.
31. Zhang L. Mod J Integr Tradit Chin West Med. 2003;12(13):1389–90.
32. Wu Q. J Snake. 1999;11(3):66–7.
33. Gao S, Peng J, Lan Z. Chin J Clin. 2002;30(9):46.
34. Zhang A. Chin Pract J Rural Doct. 1997;13(1):31–2.
35. Ge L, Li L, Zhang J. Chin J Clin Pharmcol Ther. 2002;7(3):250–1.
36. Wang F. Cent Plains Med J. 2003;5(30):32.
37. Zhou J, Zhang S, Chen Q. J Tradit Chin Med. 1995;2 (36):92–4.
38. Tong L. J Zhejiang Univ Tradit Chin Med. 2007;1 (31):71.
39. Li J. Guangxi J Tradit Chin Med. 2001;4(24):20–1.
40. Liu S, et al. J Integr Tradit Chin West Med. 1987;7 (6):359.

41. Xiao X. Pract Clin J Integr Tradit Chin West Med. 2003;2(3):14.
42. Lin K. Shaanxi J Tradit Chin Med. 2006;11 (27):1352–3.
43. Li W, Lai Y. J Guiyang Med Coll. 2003;3 (28):259–60.
44. Li F, Wang F, Chen Y, et al. Mod J Integr Tradit Chin West Med. 2002;11(16):1560.
45. Zhang Z. Chin J. 1997;2:95–6.
46. Zhang P, Chen Z. J Integr Tradit Chin West Med. 1994;8(14):474–7.
47. Lu M, Ding Z, Yang J, et al. Shanghai Med J. 1989;2:101–2.
48. Zhao H. J Integr Tradit Chin West Med. 1995;15 (10):624.
49. Sun J. Chin J Integr Tradit West Med. 1995;15 (3):172.
50. Zhang X, Sun J. Herald Med. 2003;4:244.
51. Li X, Yao X, Li T, et al. Chin J Intern Med. 1997;36 (7):450.
52. Zhou H. J Huaihai Med. 2003;2(21):70–1.
53. Wang L. Northwest Pharm J. 2003;18(2):78.
54. Wang L. Northwest Pharm J. 2003;2(8):78–9.
55. Ye F. Chin J Clin. 2003;3(31):82.
56. Liu P, Yi X. Chin J Rural Med Pharm. 2002;9(7):44.
57. Liu Y. Harbin Med J. 2003;1(23):28.
58. Li B. J Jining Med Coll. 2003;2(26):65.
59. Xie M. J Integr Tradit Chin West Med. 1995;15 (5):269.
60. Zhang L, Liu J. Chin J Dig. 2002;22(6):383–4.
61. Wang X, Wen J. Jiangxi Med J. 2001;36(6):441.
62. Shen Y. Mod J Integr Tradit Chin West Med. 2005;4 (20):2764–6.
63. Jiang M. J Tradit Chin Med. 1998;10(39):612–3.
64. Huang Z, Wu K. J Chin Phys. 2002;4(1):19–20.
65. Liu H, et al. Mod J Integr Tradit Chin West Med. 2003;12(8):232.
66. Yang L. J New Chin Med. 1998;9(30):11–2.
67. Li Z, Zhang J, Huo F. Clin Med China. 2002;18 (7):621–2.
68. Zhang G. J Integr Tradit Chin West Med. 1997;17 (8):173.
69. Zhang W, Lu Y, Lin Q. Clin Focus. 2003;11 (18):637–8.
70. He Z, Zhao J, Zhang J. Shandong Med J. 2002;42 (11):3.
71. Tian Z. Hebei J Tradit Chin Med. 1994;16(5):48.
72. Jiang Z. J Integr Tradit Chin West Med. 1997;17 (1):32.
73. Lv C. Acta Med Sinica. 2003;1:26.
74. Chen Z. Chin J Clin Gastroenterol. 2001;5(13): 225–6.
75. Li X, Lin X, Chen G. Mod Recovery. 2001;12 (5):31–2.
76. Gong Z. Hainan Med J. 2005;7(16):88.
77. Lin L. Tradit Chin Med Res. 1989;14(5):13.
78. Yan P, Luo X, Shi H. Mod J Integr Tradit Chin West Med. 2005;14(16):2902.
79. Qian B. Chin J Inf Tradit Chin Med. 1996;4:23.
80. Hui H. Heilongjiang J Tradit Chin Med. 1991;5:15.

Application in Surgical Systems

2

Yi Zheng, Xuewen Zhang and Jiaoli Guo

2.1 Surgical System Diseases

2.1.1 Thromboangiitis Obliterans

Li and Zhang [1] reported the treatment of Thromboangiitis Obliterans with Danshen Tongmai Decoction (丹参通脉汤), taken orally and used for washing in 52 cases. The decoction included Danshen 30 g, mongolian milkvetch root (黄芪) 30 g, red peony root-drug (赤芍药) 30 g, Chinese angelica (当归) 20 g, earthworm (地龙) 20 g, leech (水蛭) 20 g, szechwan lovage rhizome (川芎) 40 g, peach seed (桃仁) 10 g, safflower (红花) 20 g, common achyranthes (牛膝) 30 g, sappsn wood (苏木) 30 g, tangerine peel (陈皮) 10 g, liquorice root (甘草) 10 g. The above drugs were decocted in water, one dose a day, for 15 days as one course of treatment. The remnants of the above drugs were decocted with water again for 5 min, and the liquid was used to wash the feet for 30 min, 1–2 times a day. The results showed that there were 25 (48.1 %) clinical recovery cases, 19 (36.5 %) marked effective cases, 5 (9.6 %) improved cases, 2 (3.9 %) ineffective cases, and 1 (1.9 %) deterioration case. The total effective rate was 98.1 %. The longest treatment period was 247 days, the shortest was 30 days, and the average was 81 days. It was concluded that the disease is closely related to blood stasis. The treatment should be performed mainly with drugs with the function of activating blood circulation and dissipating blood stasis, and the disease should be treated with the decoction modified by adding or subtracting certain drugs according to the specific types of symptoms; for example, drugs with the function of warming meridians and scattering cold, activating blood circulation and dredging collaterals, clearing away heat pathogens and expelling superficial pathogens, benefiting vital energy and nourishing blood, etc.

Zhongshan Hospital in Shanghai examinated some patients cured by Danshen treatment with Doppler ultrasound, and the results showed that the pulse in their dorsalis pedis artery and anterior tibial artery was enhanced or recovered to normal levels, compared to their conditions before treatment.

2.1.2 Varicose Veins Complications

Sui et al. [2] reported the treatment of 39 patients with eczematous dermatitis by intravenous administration of 20 ml of Compound Danshen Injection, which was supplemented by local treatment. After one course of treatment, 7 of 12 cases with chronic leg ulcers were cured, and the total effective rate was 98 %. The mechanism of Danshen's effects are mainly its functions of improving microcirculation, increasing tissue blood supply, and promoting tissue repair and regeneration.

Y. Zheng (✉) · X. Zhang · J. Guo
Shengli Hospital of Shengli Petroleum Authority, Shandong, China
e-mail: zhengyiphd@yahoo.com.cn

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2.1.3 Hepatic Veno-Occlusive

Hepatic veno-occlusive disease (VOD) is one of the key complications after hematopoietic stem cell transplantation, and early manifestations of the disease include jaundice, ascites, hepatomegaly, and other symptoms and physical signs. To prevent VOD, Zhang [3] used 6–12 ml of Danshen combined with prostaglandin E1 lipid microsphere (Lipo-PGE) in peripheral hematopoietic stem cell transplantation, and obtained satisfactory therapeutic effects. All 8 cases treated did not suffer from VOD nor any side effects. It was concluded that Danshen combined with prostaglandin E1 lipid microsphere is safe and feasible for the prevention of hepatic VOD.

2.1.4 Adhesive Intestinal Obstruction

Compound Danshen has the function of improving blood circulation and increasing plasminogen activator activity, which promotes the conversion of plasminogen into plasmin and induces fibrinolysis, preventing the formation of adhesion substances. Wang et al. [4] reported that Compound Danshen Injection was directly injected into the peritoneal cavity after enterolysis surgery in 47 cases of adhesive intestinal obstruction. 1–9 years of follow up showed an excellent therapeutic effect rate of 100 % in the treatment group. In the control group, where antibiotics were directly injected into peritoneal cavity in 38 cases, the excellent therapeutic effect rate was 73.7 %. The therapeutic effect in the treatment group was significantly better than that in the control group ($P < 0.01$).

2.1.5 Traumatic Subarachnoid Hemorrhage (t-SAH)

Shen et al. [5] reported 307 cases diagnosed with t-SAH, randomly divided into the treatment group (159 cases) and control group (148 cases). Besides treatment as in the control group, 20 ml of Danshen Injection in 5 % glucose was administered by intravenous drip to the patients in the treatment group once a day. The results showed that there were significant differences in the fatality rate and disability rate between the two groups. It was concluded that significant therapeutic effects by compound Danshen on preventing and treating cerebral vessel spasm (CVS) after t-SAH were obtained, and CVS incidence, fatality rate, and disability rate were significantly reduced.

2.1.6 Craniocerebral Injury

You Hongxing et al. (2003) investigated the optimal stage for using Danshen Injection to treat cerebral edema and increased intracranial pressure (ICP) after craniocerebral injury. 98 cases with craniocerebral injury were randomly divided into the administration group at the ultra-early stage (6–12 h after craniocerebral injury, T1), administration group at early stage (24–72 h after craniocerebral injury, T2), and the control group (C). The patients in the administration groups were treated with Danshen Injection, and the conditions of ICP at 1, 3, 5, 7 days and cerebral edema at 7, 14 days after craniocerebral injury were observed and compared among the groups. The results showed that ICP at 3, 5, 7 days after craniocerebral injury in group T1 was significantly lower than in group C ($P < 0.05$), and ICP in group T2 at 7 days was significantly lower than in group C ($P < 0.05$). The severe cerebral edema rate of group T1 at 7 days was significantly lower than that in group C ($P < 0.05$), and there was no significant difference between group T2 and group C ($P > 0.05$); the cerebral edema regression rate in group T1 and group T2 at 14 days was significantly higher than in group C ($P < 0.05$), but that in group T1 was more significant ($P < 0.01$).

2.1.7 Aphasia After Traumatic Craniocerebral Injury

Wang [6] reported that one patient with aphasia after severe craniocerebral injury was treated with normal western medicine, but no effect was

obtained. The patient was then treated with Compound Danshen by intravenous drip and cured. Danshen has the function of significantly improving brain tissue microcirculation, promoting collateral circulation production. In recent years, the scientists have also found that it has the function of promoting blood edema regression, eliminating lipid peroxides, and so on. These findings help elucidate the mechanism of Danshen's treatment of cerebral vascular diseases and confirm its clinical value.

2.1.8 Secondary Epilepsy

Li [7] reported the therapeutic effect of Compound Danshen Tablet combined with sodium valproate on the treatment of secondary epilepsy of children caused by external injury, tetanus, encephalitis, etc.

2.1.9 Skin Flap Necrosis After Breast Cancer Surgery

Xiang et al. [8] observed the therapeutic effect of Compound Danshen on preventing skin flap necrosis after breast cancer surgery. The results showed that in the group where Compound Danshen Injection was not used during the operation, 5 patients suffered from darkening of the skin flap (28.5 %), 2 patients suffered from local necrosis (7.4 %), and 1 patient suffered from partial dehiscence (3.4 %). In the group where Compound Danshen Injection was used, 3 patients suffered from skin flap darkening (10.7 %), and no necrosis or dehiscence was observed. Meanwhile, in the CDI group, pain symptoms were alleviated and pain time was shorted.

2.1.10 Postkidney Transplantation

Tian et al. [9] investigated the effect of Danshen on the recovery of transplanted kidney function after transplantation. 112 patients with renal transplantation received conventional treatments plus 60 ml of Danshen Injection administered daily after operation for 10 days. Meanwhile, 109 patients with renal transplantation in the control group were administered conventional therapy without Danshen Injection. The following indexes were observed in the two groups: volume of urine, serum creatinine, endogenous creatinine clearance rate, incidence of delayed graft function and acute rejection reaction, blood viscosity, platelet aggregation rate, and blood flow resistance in the graft measured by color Doppler ultrasonography. Urinary production and endogenous creatinine clearance rate after operation for patients using Danshen Injection were significantly higher than those in the control group ($P < 0.05$). However, serum creatinine, delayed incidence of renal function recovery, blood viscosity, platelet aggregation, and blood flow and resistance were significantly lower than in the control group ($P < 0.05$). There was no significant difference in incidence of acute reject reaction between the two groups ($P > 0.05$). Danshen has the function of improving blood microcirculation and decreasing the incidence of renal function recovery retardation, so it is beneficial to the recovery of kidney function after transplantation.

2.1.11 Kidney and Ureter Stone Cramps

Song [10] treated kidney and ureter stone cramps with magnesium sulfate combined with Danshen in 108 cases. The patients in the treatment group received 20–30 ml of 25 % magnesium sulfate in 250 ml of 5 or 10 % GS injection, administered in two times by intravenous drip, and 20 ml of Danshen Injection in 250 ml of 5 % glucose or 0.9 % sodium chloride injection, administered by intravenous drip for 2–5 days. The patients in the control group received conventional treatment such as atropine, 654-2, and progesterone, etc., for 5–12 days. Neither group received painkillers. The pain remission time, therapeutic effects, and side effects were observed, and the patients were advised to drink larger amounts of water and to perform some jumping activities after drug administration. The results showed that in the treatment group, there were 36 cases with marked

effect, 20 cases with effect, 5 cases without effect, and the total effective rate was 91.8 %. In the control group, there were 20 cases with marked effect, 16 cases with effect, 11 cases with no effect, and the total effective rate was 76.6 %. It was concluded that Danshen has the function of dilating arteriola and improving microcirculation, enhancing hypoxia tolerance of tissues, and blocking calcium ion channels. The drug can be used to treat urinary pain and has the function of dilating spasmodic ureter arteriola and improving ureter spasm caused by ischemia and anoxia conditions. In addition, the drug blocking calcium ion channels and thus can directly act on the ureter smooth muscle, inhibiting the slow internal flow of calcium to smooth muscle cells during repolarization and thus inhibit ureter smooth muscle constriction. The above pharmacologic actions can effectively relieve ureteral cramps and improve the functions of the heart, brain, and other organs, so it is especially suitable for old patients. Intravenous administration of magnesium sulfate and Danshen Injection has the effects of spasmolysis and pain relief on the smooth muscle of the urinary tract. The two drugs have synergistic effects, and if used alternatively, the function time can be prolonged. There was no significant toxicity or side effects.

2.1.12 Cervical Lymphadenitis

Zhang [11] reported the application of Compound Danshen Tablet combined with erythromycin ethylsuccinate in the treatment of cervical lymphadenitis in 20 cases; significant synergistic effects were obtained, and the course of treatment was significantly shorter than that of the control group. It was concluded that Danshen has the function of activating blood circulation and dissipating blood stasis, cooling blood, treating boils, nourishing blood, and calming the nerves. Modern pharmacological research has shown that tanshinone in Danshen has anti-inflammatory function, reduces body temperature, inhibits the transmigration and ambulation of leucocytes in inflammatory areas, and enhances the anti-inflammatory actions of antibiotics. The combination of the two drugs has the function of significantly shortening the course of treatment.

2.1.13 Acute Mastitis

Wang [12] injected compound Danshen into the acupoint Xi Shang (郄上) on the forearm contralateral to the breast. A total of 57 cases were treated, and the cure rates were 95 %.

2.1.14 Bartholin's Cyst

Cai [13] reported the application of Compound Danshen Injection in the treatment of Bartholin gland cysts in 62 cases. The method was to pierce the cyst and aspirate the fluid, and inject CDI, in the amount of one-half volume of the fluid, into the cyst. In the control group, after local drainage or laser fenestration, anti-infection and sitz baths were performed. The results showed that the cure rate and recurrence rate in the treatment group were better than those in the control group. It was concluded that Danshen has the function of activating blood circulation and dissipating blood stasis, inhibiting platelet aggregation, cleaning oxygen radicals, improving prostaglandin metabolism and inhibiting chemotaxis and aggregation reactions of leucocytes, protecting glandular cells and blood vessel epithelial cells, promoting microcirculation, reducing effusion, enhancing absorption, and avoiding and reducing lipid peroxides of gland epithelial cells, thus protecting glands and reserving their function, and helping the recovery.

2.1.15 Anal Fissure

Xiang [14] used CDI to treat 200 cases of Anal fissure. A 10-ml syringe was used to draw 4 ml of CDI, 3 ml of 2 % lidocaine, and 5 mg of 654-2, and the syringe was connected to a No. 5 dental needle. Before treatment, patients were allowed to empty their stool and lie in the lateral position.

After regular local disinfection, the index finger of the left hand was inserted into the anus for conducting, avoiding penetration of the anus vessel wall or into the rectum. The needle was inserted at the bottom of the anal fissure and 0.5 cm from the anal verge, and the physic liquor was slowly injected; the depth was about 3 cm. The needle was withdrawn to subcutaneous tissue, then injected on the two sides of the anal fissure in fan shape; after light massage for a moment, two index fingers were inserted into the anus to perform anal dilatation. The accompanied hypertrophy of anal papilla, sentinel pile and subcutaneous fistula were removed after anal dilatation. The dosage for one injection was 3–7.5 ml. The patients were re-examined 1 week later, and if necessary, the injection was performed again. Usually 1–3 injections were needed. The results showed that among the 200 cases in the treatment group, 172 cases were cured, 25 cases showed clinical effect, and 3 cases showed no effect. 172 cured patients were followed up with for 2–-36 months, with an average period of 18 months. Recurrence was not observed in 48 cases in Phase I and 92 cases in phase II. Among the 32 Phase III cases, there were 4 cases of recurrence within 1 year, 3 cases of recurrence within 2 years, and 4 cases of recurrence within 3 years; partial internal sphincterotomy combined with anal dilatation was performed for the patients and all of them recovered. It was concluded that Danshen has the function of improving microcirculation, increasing local blood flow, promoting the repair and regeneration of tissue, etc., and its function can be enhanced by combining with 654-2. CDI can significantly relieve local tissue ischemia, nutritional disorders, and pain caused by spasms of the internal sphincter, and can reduce inflammatory effusion on the wound surface and accelerate tissue regeneration and repair, thus promoting the healing of the ulcer.

2.1.16 Hemorrhoids

Wang [15] reported the application of CDI by *injectio ad acumen* in the treatment of hemorrhoids. The method was to find the pain spot along the Tai Yang lung meridian under the acupoint Chi Ze (LU 5), around acupoint Kong Zui (LU 6), perform normal local disinfection, and after needle sensation and no blood coming with the withdrawing needle, inject 2 ml of CDI. The patients were treated once every 2 days for 5 times as one course of treatment, with 3 days between two courses. The patients were usually cured in 1–2 courses of treatment. A total of 20 patients were treated this way and were all cured. The theoretical foundation of the treatment might be that lung controls the skin and hair, and the lung and the large intestine being interior–exteriorly related, thus hemorrhoids can be treated by acupoint Kong Zui, and the double effects of acupuncture and medication can be obtained.

2.2 Skin Diseases

2.2.1 Lupus Erythematosus

Lupus erythematosus is an autoimmune disease. There are two TCM theories about its etiology, namely the deficiency of the kidney and blood stasis. For patients whose main symptom is blood stasis, Danshen can be administered by intravenous drip and by intramuscular injection during the consolidation phase. Danshen has significant effects on Raynaud's disease and skin damage regression, but has no significant effects on immunological indexes. The injective preparation of tanshinol, one of Danshen's many components, has the same effect as Danshen on the treatment of lupus erythematosus. Li et al. [16] reported the application of CDI in the treatment of systemic lupus erythematosus in 32 cases. CDI was administered by intravenous drip, 16–20 ml per day, for 14 days as one course of treatment. The results showed that the marked effective rate was 81.3 %, the effective rate was 93.8 %, and the effect was significantly different compared with the group treated with prednisone ($P < 0.01$). The treatment of systemic lupus erythematosus with compound Danshen mainly depends on its anticoagulation function, which can improve blood circulation in the tissues and

organs, and relieve wide small vasculitis changes induced by systemic lupus erythematosus.

2.2.2 Scleroderma

Scleroderma is accompanied by a series of blood stasis (e.g., blood circulation disturbance). Research has shown that Danshen has the function of regulating blood vessel function, improving blood circulation, and anti-inflammation. Qin [17] reported the application of Danshen Injection in the treatment of scleroderma. 16 patients with scleroderma were administered by intravenous drip with 8–16 ml of Danshen Injection in low molecular dextran or 500 ml of 5–10 % glucose solution. The total effective rate was 68.8 %. Tanshinol, the water-soluble component of Danshen, has a similar effect on the disease.

2.2.3 Dermatomyositis

The characteristics of dermatomyositis include inflammation of the skin, muscle, and small blood vessels. Shan Yijun (1986) reported the application of Danshen in the treatment of the disease. 4 ml of Danshen Injection was administered by intramuscular injection each time, 1–2 times a day. 50 patients were treated, with 40 cases of marked effect, and the therapeutic effects for patients with blood vessel damage were enhanced by intravenous drip.

2.2.4 Sjogren's Syndrome

The disease is closely related to collagen diseases, and it also belongs to chronic inflammatory autoimmune diseases. During the treatment, it was found that the therapeutic effect could be enhanced by the combination of common Threewingnut root (雷公藤) with Danshen tablets or tanshinol injection by intramuscular or intravenous administration, and symptom improvement was better than that when treated by common Threewingnut root alone.

2.2.5 Infectious Diseases

Gao Yugui et al. (1993) reported the application of Danshen extractive tablets for oral use and 2 % total tanshinone in Vaseline for external use in the treatment of *Staphylococcus aureus* and beta-*Streptococcus* infection. 455 cases with symptoms of furuncle, phlegmon, traumatic infection, and burn infection were treated. Clinical observations confirmed that Danshen indeed has antibacterial and anti-inflammatory functions, and can activate blood circulation and dissipate blood stasis, promote wound surface healing, etc. The total effective rate was 90 %. It has the advantage of high therapeutic effects and no side effects for long term use. It has relatively good therapeutic effects on infections of the drug resistant strains of *Staphylococcus aureus*.

The pharmacological studies performed by the Institute of Materia Medica of Chinese Academy of Sciences showed that Danshen has strong antibiotic activity against Gram-positive cocci, especially *Staphylococcus aureus*. 58 strains resistant to penicillin, erythromycin and various antibiotics were tested in drug sensitivity tests, and the results showed that all strains were sensitive to Danshen. They also discovered that Danshen has antibacterial action against hemolytic *streptococcus* and human tubercle *bacillus*. Danshen extracts were used to treat *Staphylococcus aureus* infection in 354 patients, and satisfactory therapeutic effects were observed. No toxicity, side effects, or resistance was observed after long-term application.

2.2.6 Alopecia Areata

Huang Shunde et al. (2002) reported the application of Danshen in the treatment of alopecia areata. 25 ml of prednisone, 2 ml of compound Danshen and 2 ml of 2 % lidocaine were mixed and subcutaneous punctiform blocking was performed. 50 cases were treated in this manner once every 1–3 weeks for 1–3 times. The patients were administered with 25 mg of doxepin, 3 times/day. The results showed that 34 cases

(70.8 %) recovered, 13 cases (27.1 %) had clinical effect, 1 case (2.1 %) had no effect, and the total effective rate was 97.9 %.

2.2.7 Acne

Acne is a skin damaging disease with very high incidence. The causes of the disease include endocrine disorder, infection by acne *Corynebacterium*, increase in blood viscosity, etc. Tanshinone is the ethanol extract of Danshen studies have shown that it can significantly inhibit Gram-positive bacteria and *Corynebacterium*; it has the function of antibiotics and male hormones. It also has an anti-inflammatory function similar to hydrocortisone. There was no endocrine disorder or other side effects after long-term usage.

Wang [15] reported the application of CDI by *injectio ad acumen* in the treatment of acne and its induced pigmentation. The therapeutic method was to select acupoints Hegu (LI 4) and Zusanli (ST 36), perform normal local disinfection, insert the needle and after needle sensation and no blood coming with the withdrawing needle, inject 2 ml of CDI in each acupoint, alternating left and right with the acupoint injections, once every 2 days for 10 times as one course of treatment. There was a 5-day interval between 2 courses of treatment, and 1–3 courses were usually needed. Among the 45 cases treated, 36 cases were cured (the skin returned to normal and pigmented spots disappeared by 90 % or more), 7 cases were improved (symptoms changed from severe to mild, pigmented spot area shrank by 10 % or more, or pigment turned lighter), and 2 cases showed no effect (no significant change after treatment). Facial acne and pigmentation are usually caused by blood deficiency, lack of nutrients in the face; or obstruction of the meridian by blood stasis preventing blood from reaching the face. CDI has the function of improving blood circulation, and the face is split in the fields of Hand and Foot-Yang Ming Channels, which are distributed on the face. Thus, Hegu and Zusanli acupoints were selected for CDI injection, and significant therapeutic effect were obtained.

Yu et al. [18] reported the curative effect of tanshinone on acne. 100 patients diagnosed with common type acne and without a history of general medication within 1 month were selected. The patients were 14–32 years old (20.41 ± 4.18), and the course of the disease ranged from 3 months to 10 years (median: 113 days). The skin lesions of the patients were all mainly facial damage, and some were accompanied by damage on the back, shoulder, and chest. The above patients were randomly divided into two groups: 56 people in the treatment group; 21 male, 35 female, 24 papule type, 20 pustule type, 8 cyst type, and 4 conglomerate type. 44 patients in the control group, 15 male, 29 female, 20 papule type, 16 pustule type, 6 cyst type, and 2 conglomerate type. The age, gender, course of disease, disease typing, and severity in the two groups were similar. The patients in the treatment group were administered orally with 4 capsules of tanshinone (3 capsules for patients between 15 and 17 years old and with body weight less than 50 kg), 3 times a day, for 4 weeks. The patients who were not cured continued to be treated, but the treatment would not last more than 6 weeks. The patients were applied externally with chloramphenicol tincture, three times a day. The patients in the control group were administered orally with 0.25 g of erythromycin, 4 times a day, and chloramphenicol tincture was applied externally. All patients were examined once each week for 6 weeks. 56 cases in the treatment group and 44 cases in the control group were observed regularly, and a rank test was performed for therapeutic effects, with a significant difference observed. The therapeutic effect of the treatment group was better than that of the control group. The onset times of effectivity in the tanshinone treatment group were: 8 cases after 1 week, 29 cases after 2 weeks, and 13 cases after 3 weeks. The onset time for most patients (80 %) with marked effect was 2–3 weeks after treatment. The clinical characteristics of tanshinone treatment showed varying degrees of efficacy on various types of acne. It was observed that tanshinone treatment had very good efficacy on pustule type and papule type acnes, but poor efficacy on cyst type and conglomerate type acnes. The adverse reactions during tanshinone treatment involved

4 females who suffered from different degrees of excessive menstruation, and they recovered to normal after drug reduction. No abnormality was observed by examination of blood routine, blood clotting time and liver function before and after treatment.

2.2.8 Burns and Scalds

Zhong et al. [19] reported the application of CDI in the treatment of 50 cases of sub-second degree burns and scalds. The patients in the control group received conventional therapy, which was washing with 1 % benzalkonium bromide (benzalkonium bromide), cutting off the dead skin and blisters, cleaning the necrotic tissue, spraying gentamicin and lidocaine in physiological saline for disinfection and pain relief, applying burn moist paste, which was changed once everyday, and irradiating with ordinary 60–100 W incandescent lamps until a scab formed. The patients in the treatment group received the conventional therapy plus 5–50 ml of CDI by intravenous injection; the exact dosage was determined based on the area of the burn and scald, deepness and gradient of infection, and body weight. The results showed that compared with patients in the control group, patients in the treatment group had less wound exudate, milder edema, and slighter pain; the average wound healing times in the treatment group and control group were 12 and 20 days, respectively. The times for the scab to crack and come off in the treatment group were 8–13 days, and in the control group, 10–16 days. There were significant differences in wound surface infection rate and healing times between the two groups. Therefore, integration of CDI into the comprehensive treatment of burns and scalds is beneficial to the tissue regeneration and repair. Danshen has the function of antiplatelet aggregation and activating blood circulation and dissipating blood stasis, improving microcirculation, increasing blood flow supply to wound surface, especially to the muscular layer under the infection lesions, enhancing local cell metabolism, supplying nutrients, and promoting granulation, thus promoting tissue repair at an early stage. Due to improvements in local blood circulation, immunological substances increased in the body and the body's phagocytic capacity and resistance to damage were enhanced, such that it could prevent and control infection.

2.2.9 Infected Wounds

Ren and Ren [20] reported the treatment of 63 patients with infected wounds with Mayinglong Shexiang Zhichuang Haemorrhoids Paste (马应龙麝香痔疮膏) combined with Danshen Injection. The wounds were cleaned thoroughly and the paste was applied on the surface of the wounds. For patients with deep wounds, the paste was applied on the surface of a drainage strip and the drainage strip was inserted in the wound. The drug was changed every 3 days. In addition to the anti-infection treatment, 250 ml of Danshen was administered by intravenous dip, once a day for 15 days as one course of treatment. The second course of treatment was performed 1 week after drug discontinuance. The results showed that all 63 patients were cured within 2 months: 44 cases within 10–15 days, 16 cases within 15–30 days, and 3 cases within 2 months. The average healing time was 12.5 days, and there was a significant difference in therapeutic effect before and after the treatment. No adverse effects were observed.

2.2.10 Stasis Eczema

Li and Gao [21] reported that 6–10 ml of CDI in 250 ml of 5 % glucose was administered by intravenous drip to 25 patients with stasis eczema, once a day. The results showed that the drug could cure the disease. There was mild pigmentation or decrescence after the treatment. One month later the patients recovered, with no recurrence observed. Compound Danshen Injection has the function of activating blood circulation and dissipating blood stasis, and thus can improve the skin's blood supply, enhance immunologic function in the lesions, and promote the disappearance of inflammation.

2.2.11 Keloids

Yang Wei (2002) reported that 40 cases of keloid were treated with Danshen Injection or Compound Danshen Injection by external application and local obturation. 20 cases received external application treatment, which was performed as follows: a disinfected absorbent cotton or bandage was saturated with Danshen Injection and used to cover the skin lesions until the liquid dried naturally, 2–3 times a day, with a daily dosage of 2–8 ml. 20 cases received local obduration: the skin was disinfected and a No. 5 dental needle or 25 ml syringe for single use was used for injection in the skin around the lesions. The needling directions were inclining to the muscle under the lesions, and 1–4 sites were selected based on the conditions of the lesions, 0.5–1 ml each site, for 10 days as one course of treatment, with 2–3 days between two courses. The above two methods were performed until the color of the damaged skin turned to normal, the damaged skin became soft, and severe itching disappeared; the treatment time ranged from 6 days to 9 months. It was concluded that the methods were effective, quick, low-cost, and without toxicity and side effects.

2.2.12 Verruca Planae

Ma et al. [22] reported the application of fresh Danshen leaf in the treatment of 26 patients with Verruca planae. Fresh Danshen leaves were gathered, washed clean with water, and used to rub the damaged skin until the wart and its surrounding skin turned reddish and the patients felt a burning pain, indicating that Danshen leaf juice had penetrated the verruca planae. The debris was washed off with water 1 h later. The treatment was performed twice a day, once in the morning and once in the evening. All 26 patients were cured, the skin was smooth and glossy, and no scar was formed, and no toxicity or side effects were observed.

2.2.13 Psoriasis

Wang and Zhang [23] observed the effect of Danshen on the treatment of 32 patients with psoriasis. Patient profile: 20 male and 12 female; 26–42 years old; course of disease 6 months to 5 years; psoriasis vulgaris 30 cases (guttiform skin 5 cases, map like 12 cases, coin like and plaque 13 cases), erythrodermic psoriasis 2 cases; 12 cases had been treated by antitumor drugs. All patients were administered with 20 ml of CDI in 500 ml of 5 % glucose solution by intravenous drip, once a day, for 15 days as one course of treatment. There was a 5-day interval between two courses, and no other treatments were applied during the treatment period. The therapeutic effects were observed and nail fold circulation was reviewed. The results showed that 21 cases were cured (erythema and scaling were dissipated), and 11 cases were improved (attenuation of skin damage, partial dissipation of erythema and scaling). Among the cured patients, the shortest time of treatment was two courses, and the longest was four courses. During the treatment period, there were 3 cases with mild dizziness, but no other adverse reactions were observed in the other patients. The nail fold microcirculation in the left ring finger before and after treatment was observed. Among the 30 cases with blurred blood vessels, 28 cases became clear after treatment; among the 20 cases with reduced capillary loop density, 18 cases returned to normal after treatment; among the 19 cases with widened and enlarged capillary loops, all returned to normal after treatment; among the 22 cases with distorted and disorganized capillary loops, 21 cases returned to normal after the treatment; among the 20 cases with slow blood flow, all returned to normal after treatment; among the 18 cases with shrunken diameter in input part and enlarged diameter in output part, 17 cases returned to normal after treatment; among the patients with erythrocyte aggregation, 11 cases mild, 16 cases moderate, and 5 cases severe, all symptoms disappeared after treatment.

2.2.14 Herpes Zoster

Deng et al. [24] reported the application of CDI combined with acyclovir in the treatment of herpes zoster in 60 cases. Both control and treatment groups received acyclovir treatment, but the patients in the treatment group received an additional 20 ml of CDI which was mixed with 500 ml of 5 % glucose and administered by intravenous drip once a day for 7 days as one course of treatment. The results showed that the incidence of neuralgia was significantly reduced in the treatment group. The mechanism may be through Danshen's function of improving the permeability of blood capillary microcirculation, promoting absorption of antiviral drugs, inhibiting ganglion and hyperemia of corresponding sensory nerve fibers, edema and necrosis, and preventing adhesions, thus preventing the occurrence of neuralgia.

2.2.15 Scrotal Eczema

Li [25] reported the application of anti-itching lotion combined with Danshen tincture in the treatment of 30 patients with scrotal eczema with satisfactory therapeutic effects. The 30 patients were 18–65 years old and the course of the disease ranged from 3 days to 5 years. All patients suffered from flushing in the scrotum and perineum, intense itching, pleomorphic skin damage, erythema or papule, blister or pustule, and a few with erosion, and chronic patients could have scale and moss like damage. Clinically, there was a tendency of recurrence, fusion, and effusion. The therapeutic method was to apply the anti-itching lotion on the lesions, which consists of the following drugs: light yellow sophora root (苦参) 60 g, common cnidium fruit (蛇床子) 60 g, common capsicum fruit (鹤虱) 30 g, hydnocarpus (大枫子) 30 g, belvedere fruit (地肤子) 30 g, dense fruit pittany root-bark (白鲜皮) 30 g, amur corktree bark (黄柏) 30 g, radix et rhizoma rhei from sichuan of china (川军) 30 g, paniculate swallow wort root or herb (徐长卿) 30 g, hairyvein agrimony herb (仙鹤草) 30 g, raw almond (生杏仁) 13 g, sessile stemona root tuber (百部) 13 g, sulfur (硫黄) 10 g, and wasps nest (蜂房) 15 g.

2.2.16 Progenital Hypopigmentation

Xu Chengkang et al. (2003) reported the therapeutic effect of Compound Danshen Injection on the treatment of progenital hypopigmentation. 50 patients with progenital hypopigmentation who had been unsuccessfully treated by other methods were divided into 3 groups. The 25 cases in the research group received 5–10 ml each of 1 % procaine and CDI injected into the lesions, twice a week, for 8 times as one course of treatment. The 15 cases in the procaine control group received 1 % procaine by local injection, and the dosage and courses of treatment were the same as in the research group. The 10 cases in the blank control group received no treatment. The therapeutic effects were compared among the 3 groups 1 month later. The results showed that in the research group there were 12 cured cases (48 %), 8 improved cases (32 %), and the total effective rate was 80 %. There were no cured cases and 3 improved cases (20 %) in the procaine control group, and the total effective rate was 20 %. There were neither cured nor improved cases in the blank control group. The differences among the three groups were statistically significant ($P < 0.01$). It was concluded that satisfactory therapeutic effects could be obtained by local injection of CDI and 1 % procaine to treat progenital hypopigmentation, and it could be used as a complementary method to the conventional therapy.

Zhang Yanqin (2000) reported the application of CDI in the treatment of white lesions of the vulva in 46 cases. The patients were 16–70 years old, with an average age of 43, and 2 cases were under 40 years old; 35 cases were from he countryside and 11 cases from cities; the shortest course of disease was 2 months, and the longest was 3 years. The therapeutic method was to disinfect the area around acupoint Hui Yin (RN 1) with iodine tincture and alcohol, pierce needle straight into the acupoint, and after no blood coming with the withdrawing needle, inject 4 ml

of CDI. After injection, the patient usually had the sense of defecation, soreness and numbness. The drug was administered once each day 10 times as one course of treatment, with 2–3 days between the courses. Normally after one course of treatment improvement could be observed, and recovery achieved in 2–4 courses. Among the 46 patients in the treatment group, there were 43 recovery cases (93.48 %) and 3 improvement cases (6.52 %), and the total effective rate was 100 %.

2.2.17 Pigmentary Purpuric Dermatosis

Yu Huijuan (2002) reported the application of Dantonic™ with vitamin C in the treatment of pigmentary purpuric dermatosis (PPD). Among the 40 PPD patients, 11 had pigmentary purpuric dermatosis, 15 had pigmentary purpura, and 14 had purpura annularis telangiectodes. 9 cases were accompanied with cardiovascular disease. 10 pills of Dantonic™ were administered each time, three times a day; 0.1 g of vitamin C was taken orally, three times a day. One course of treatment lasted for 20 days, and 2 courses of treatment were observed. The results showed recovery in 9 cases (22.5 %), marked effect in 13 cases (32.5 %), effect in 11 cases (27.5 %), and no effect in 7 cases (17.5 %); the total effective rate was 82.5 %. pigmentary purpuric dermatosis belongs to the category of lymphocytic periductal capillaritis, which is similar to "blood malnutrition" disease in tradition Chinese medicine. Gravity and increased venous pressure can cause slowed blood circulation in the lower limbs, which could cause stagnation and generate heat after a prolonged period, damaging blood vessels and the collaterals. The blood fails to circulate in the vessels, thus leading to the disease. The disease can be treated by drugs for activating blood circulation and dissipating blood stasis, cooling blood and removing ecchymoses. It is believed in TCM that Danshen has the function of cooling blood, activating blood circulation, and eliminating stasis; Sanchi has the function of activating blood circulation and dissipating blood stasis, and stopping bleeding; synthetic borneol has the function of clearing heat, activating blood circulation, and dredging collaterals. Dantonic™, which contains the three drugs, can be used in the treatment of PPD to reduce capillary permeability and intravascular pressure by dilating the capillaries and increasing the opening of capillary beds, improving microcirculation, regulating body fibrinolysis and blood clotting, promoting blood flow speed in blood capillaries, promoting normal hemorheology, and promoting the absorption of hemorrhage, edema and stagnant blood. Vitamin C has the function of reducing the permeability and fragility of capillary walls. The two drugs have synergistic effect, so good efficacy was achieved.

In summary, Danshen is a suitable and common drug for the treatment of diseases in the departments of surgery and dermatology. Stagnant blood can be easily induced by wound and surgery, and there is a close relationship between the stagnation of blood stasis and lupus erythematosus, scleroderma, keloid, and psoriasis. Animal and clinical experiments have demonstrated that Danshen has the function of activating blood circulation and dissipating blood stasis, clearing the heat and expelling toxin; thus the drug is effective and safe.

References

1. Li Q, Zhang F. Hebei J Tradit Chin Med. 2003;6 (25):426–7.
2. Sui B, Chen S, Chen J. People's Mil Surg. 1965;2:24.
3. Zhang L. Leukemic lymphadenoma. 2003;3 (12):146–7.
4. Wang R, et al. J Integr Tradit Chin W Med. 1994;10 (14):252–597.
5. Shen Y, He Z, Song H, et al. J Integr Tradit Chin W Med. 2000;20(12):943.
6. Wang H. Jiangxi J Tradit Chin Med. 1992;23(1):62.
7. Li L. Jiangxi Med J. 1985;(6):24–25.
8. Xiang J, et al. Mod J Integr Tradit Chin W Med. 2003;12(6):623–4.
9. Tian X, Xue W, Ding X. J Integr Tradit Chin W Med. 2005;5(25):404.
10. Song C. J Huaihai Med. 2003;1(21):178.
11. Zhang S. J Integr Tradit Chin W Med. 2001;21 (2):148.
12. Wang B. J Integr Tradit Chin W Med. 1993;13 (5):295.

13. Cai H. Sichuan Tradit Chin Med. 2002;20(1):55.
14. Xiang J. Chin J Surg Integr Tradit W Med. 2003;1(9):9.
15. Wang B. J Anhui Coll Tradit Chin Med. 1995;1 (14):48.
16. Li H, Zhang S, Lv X. Clin Focus. 1999;14(21):999.
17. Qin W. Prog Tradit Med Sci Technol Home Abroad. (1992);(4):90.
18. Yu Z, et al. J Chengde Med Coll. 2003;2(20):25.
19. Zhong Z, Xin L, Xue W. J Clin Medicineprogression. 2003;4(12):296.
20. Ren H, Ren H. Aerosp Med. 2003;1(14):41.
21. Li X, Gao S. Lishizhen Med Materia Med Res. 2001;12(4):369.
22. Ma S, Liu X, Liu A. China's Naturopathy. 2003;11 (1):30.
23. Wang S, Zhang Z. Mod J Tradit Chin W Med. 2003;12(3):245.
24. Deng X, Hong Y, Huang Z. J Integr Tradit Chin W Med. 2001;12(1):39.
25. Li Z. China's Naturopathy. 2003;6(11):30.

Application in Orthopedics and Traumatology

3

Yi Zheng, Xuewen Zhang and Jiaoli Guo

Numerous facts have demonstrated that Danshen is one of the most common clinically used drugs with the function of activating blood circulation and dissipating blood stasis. It can improve microcirculation, increase blood flow volume, enhance the intake and utilization of oxygen in tissue, promote the repair and regeneration of tissue, reduce blood viscosity, and so on. In addition, other pharmacological functions, such as antibacterial, anti-inflammation, and anticoagulation activity, activating fibrinolysis, and regulating immunologic function, have received more and more attention in recent years. Therefore, the wide clinical use of Danshen in orthopedic diseases has been increasing.

3.1 Acute or Chronic Soft Tissue Injury

Xue [1] reported the treatment of 30 acute soft tissue injury cases with Compound Danshen Tablet, used orally and externally. The results showed that all patients were cured within 3–10 days. Wang Fengshan reported that Compound Danshen Tablet was ground to a powder and mixed with distillate spirit to obtain a paste for external application. 60 patients with soft tissue blunt injury were treated with the paste, and all were cured within 1–4 days on average.

Zhang and Wu [2] reported that CDI was injected into acupoint Zhongping to treat acute damage of parascapular muscle. Among the 39 cases treated, 31 recovered, and the total effective rate was 100 %. They received 1–6 injections. Shi Kuiwei reported that 36 cases of shoulder periarthritis were treated with Danshen by *injectio ad acumen*; the cure rate was 91.6 % and the effective rate was 100 % after one course of treatment.

3.2 Periarthritis of the Shoulder

Wang [3] reported the treatment of periarthritis of the shoulder with CDI by *injectio ad acumen*. The spot with the most pain in the shoulder and the contralateral pain spot about 1 in. under the acupoint Zusanli were selected. After regular disinfection, needle sensation, and no blood coming out, 2 ml of CDI was injected into each acupoint. The treatment was performed once every 2 days for 10 times as one course of treatment, with 5 days between two courses and 1–3 courses of treatment usually performed. Among the 21 cases treated, more than 15 cases were cured (shoulder joint function recovery normal and no pain), 71.43 %, and 6 cases were improved (shoulder joint function disturbance improved, slight pain at times), 28.57 %. The method not only employs

Y. Zheng (✉) · X. Zhang · J. Guo
Shengli Hospital of Shengli Petroleum Authority, Shandong, China
e-mail: zhengyiphd@yahoo.com.cn

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Danshen's function of activating blood circulation and dissipating blood stasis, but also validates the acupuncture theory of TCM that by using the pain spot as an acupoint, left pain is treated in the right side, and upper disease is treated by targeting the lower part.

Zhang [4] reported the treatment of periarthritis of the shoulder in 37 cases with Danshen Injection by *injectio ad acumen*. The majority of patients were older than 45 years. The local acupoint of the shoulder joint was selected, and l ml of Danshen Injection was injected into each acupoint, 2–3 acupoints each time, 3 times a week, 10 times as one course of treatment. The results showed that 33 cases (91.67 %) were cured (the patients felt that the symptoms completely disappeared and their upper arms could move freely), and 3 cases (8.33 %) had clinical effect. 24 cases were cured after one course of treatment, and 9 cases after 2 courses. The method has satisfactory therapeutic effects and is easy to use, convenient, economical, and suitable for wide application in primary health care units.

3.3 Bone Fracture

Tang et al. [5] reported the application of Danshen and compound amine acids in the treatment of bone fracture. 122 patients with femoral neck fracture were divided into treatment and control groups, and they were all treated with traction. The 62 patients in the treatment group received additional treatment with the administration of Danshen and compound amine acids. After 4 courses of treatment, the treatment group and control group had 50 and 18 cases of recovery, respectively. The total effective rates of the two groups were 90.3 and 68.3 %, respectively. The difference was significant ($P < 0.01$).

The Ruijin Hospital of Shanghai Second Medical University used Danshen to treat 10 cases of femoral shaft fracture by intravenous drip. The healing time was shortened from the original 55.5–50.9 days, which demonstrated the promoting function of Danshen in the repair and healing of bone fracture. Danshen can promote local blood circulation, correct ischemia and hypoxia conditions in damaged tissue, promote the transportation of calcium, zinc, and various trace elements to the fracture site, promote the production of embryo and deposition of calcium, promote the growth and calcification of connective tissue and bony callus, and promote fracture healing.

3.4 Acute Osteomyelitis

There is a report showing a 93.7 % effective rate of Danshen on acute osteomyelitis, and 81.2 % on chronic osteomyelitis.

3.5 Lumbocrural Pain

Yang and Hou [6] treated 82 patients with neck and lower back nerve root compression and spinal cord compression with Danshen by intravenous drip. After one course of treatment, there were 19 cases showing marked effect, 57 cases showing effect, and 6 cases showing no effect; the total effective rate was 92.6 %.

3.6 Cervical Spondylosis

Wu and Li [7] reported the treatment of intractable cervical spondylosis with anisodamine, CDI, and normal physical therapy. 47 outpatient cases were treated with common physical therapy (traction, massage, iontophoresis, etc.), and the patients were hospitalized and treated if no satisfactory therapeutic effect was obtained. Among the 47 cases, there were 31 male and 16 female; ages ranged from 19–56 years with an average age of 45.3 years; disease history ranged from 2 months to 8 years; and diagnostic classifications were: nerve root type 13 cases, vertebral artery type 21 cases, sympathesis type 2 cases, mixed type 11 cases. The diagnosis was performed according to the diagnostic criteria and

classification defined in the cervical spondylosis Conference in China in 1984, and all cases were confirmed by X-ray cervical spine radiography, with some patients confirmed by MRI, CT, and neck ultrasonography. After hospitalization, the patients were treated by intravenous drip with 10 mg of anisodamine injection plus 10 ml of CDI in 500 ml of 10 % glucose, once a day. Traction, massage and electrotherapy were performed after infusion, with 15 days as one course of treatment. Among the 13 cases of nerve root type cervical spondylosis, 7 cases were clinically cured, 2 cases showed marked effect, 2 cases showed improvement, and 2 cases had no effect; among the 21 cases of vertebral artery type, 16 cases were clinically cured, 3 cases showed marked effect; 1 case showed improved, and 1 case had no effect; of the 2 sympathesis type cases, 1 case showed improvement and 1 case had no effect; among the 11 mixed type cases, 3 cases were cured, 3 cases showed marked effect, 3 case showed improvement, and 2 cases had no effect. The total effective rate was 87.23 %, and the recovery rate was 55.32 %. The basic principles of rehabilitation are brake, antispasmodic, analgesic, and orthopedic. Anisodamine is a blocker of M choline receptors and has the function of relieving blood vessels, smoothing muscle spasm, improving microcirculation, and relieving pain. It is also a free radical scavenger and can directly clean OH and oxygen radicals produced in cellular and chemical systems, improving pathological lipid peroxidation in diseased tissue. CDI has the function of activating blood circulation, dissipating blood stasis, dilating vessels, improving microcirculation, increasing blood flow, relieving pain, reducing inflammation, eliminating edema, and calming the nerves. The application of the two drugs in combination with physical therapy has effects in both internal and external treatment, which can regulate and change the interrelations between the cervical vertebrae and the surrounding soft tissue, relieve, or eliminate the compression and stimulation of nerves and blood vessels, improve local blood circulation, eliminate inflammatory edema and pain, accelerate tissue metabolism and inflammation absorption, promote tissue repair and recovery or improve compression imbalances of cervical vertebra, and stabilize cervical vertebra.

3.7 Sciatica

Wang [3] reported the application of CDI *injectio ad acumen* to the treatment of sciatica. The method used acupoints Huantiao (GB 30) and Yanglingquan (GB 34) in group one and the pain spot and acupoint Juegu in group two. After normal local disinfection and needle sensation, 2 ml of CDI was injected in each acupoint, once every two days, 10 times as one course of treatment. There were 5 days between courses, and effects could usually be obtained in 1–3 courses of treatment. Among the 40 cases treated, 3 cases (7.5 %) were cured (symptoms and physical signs disappeared, capable of physical labor); 11 cases (27.5 %) showed marked effect (symptoms basically or largely disappeared, occasional pain in lateral or posterior regions of the legs, capable of normal work); and 6 cases (15 %) showed improvement (symptoms and physical signs relieved, but pain in cloudy and rainy weather or after exertion). Patients with acute sciatica usually suffer from stagnant blood, and CDI has the function of dredging the meridians, activating blood circulation, and dissipating blood stasis; *injectio ad acumen* sends the drug directly to the lesions, exerting the dual functions of acupuncture and medication and accelerating the dissipation of stagnant blood, thus realizing the therapeutic effect.

Cheng and Wu [8] reported the treatment of sciatica with CDI by *injectio ad acumen* in 184 cases. Acupoint selection was based on the principle of following the pain to select the meridians, and then selecting the acupoints on the meridians. Thus, for patients with the main pain in the foot shaoyang gall bladder channel, the acupoints selected were Huantiao (GB 30), Fengshi (GB 31), Yanglingquan (GB 34), and Xuanzhong (GB 39); for patients with the main pain in the foot taiyang bladder channel, the acupoints selected were Zhibian (BL 54), Yinmen (BL 37),

Weizhong (BL 40), Kunlun (BL 60); for patients with the main pain in the foot yangming stomach channel, the acupoints selected were Biguan (ST 31), Futu (ST 32), Zusanli (ST 36), and Jiexi (ST 41); for patients with severe pain, acupoint Ashi was selected. The treatment method was to select two acupoints (pain-affected side) each time, once a day, and apply in turn. 2 ml of CDI was injected into each acupoint using a No. 6.5–8 needle; acupuncture was performed first, then the drug was rapidly injected after needle sensation. Each acupoint was injected once, 7 times as one course of treatment. There was a 2–3 day rest before the next course was started. Satisfactory therapeutic effects were obtained.

3.8 Lumbar Intervertebral Disc Protrusion

Feng et al. [9] observed the therapeutic effect of CDI by intravenous drip on nitric oxide (NO) and superoxide dismutase (SOD) in the blood serum of patients with lumbar intervertebral disc protrusion (LIDP). 62 cases with LIDP were randomly divided into a Danshen group (31 cases) and contol group (31 cases). The NO content and SOD activity in the serum were determined with nitrate reductase and hydroxylamine oxygen methods, respectively, before and after treatment. Visual analogue scales (VAS) were used for pain evaluation, and therapeutic effects were evaluated by a LIDP quantitative assessment table. The results showed that after CDI treatment, NO content was reduced and SOD activity was increased in the patients with LIDP, and there was a significant difference between the treatment group and control group ($P < 0.05$); the therapeutic effect of the treatment group was better than that of the control group. It was concluded that CDI by intravenous drip can reduce NO levels in patients with LIDP while enhancing SOD activity and the body's antioxidation capability.

Wu [10] reported that 52 cases with LIDP, confirmed by X-ray, B-ultrasound, CT scanning and MR, with the course of disease from 3–9 years, were treated with pelvic traction, local thermotherapy and anti-inflammatory drugs, and then 20 ml of CDI in 500 ml of 5 % glucose was administered by intravenous drip daily for 7–14 days. The patients were then administered orally with Compound Danshen Tablet for 1 month, 3 tablets/day. The results showed that the total effective rate was 96.2 %, and there was a significant difference between the treatment group and control group ($P < 0.01$).

3.9 Piriformis Syndrome

Min [11] reported that 86 patients with piriformis syndrome were randomly divided into a treatment group and control group, with 43 patients each. Besides the conventional therapy such as massage, etc., 20 ml of compound Danshen in physiological saline was administered by intravenous drip to the patients in the treatment group. The results showed that the therapeutic effect in the treatment group was significantly better than that in the control group ($P < 0.01$). The mechanism for the effect might be that compound Danshen has the function of improving hyperemia and edema in the tissues surrounding the piriformis muscle and eliminating inflammatory mediators, which would help the massage to relieve spasm and eliminate adhesions, thus enhancing the therapeutic effects.

3.10 Acute Muscle Damage Around the Scapula

Zhang and Wu [2] observed the effect of Danshen Injection by *injectio ad acumen* on the treatment of Acute muscle damage around the scapula in 39 cases. The acupoint is located on the fibular side of the leg, connecting the lines between the capitulum fibulae and lateral malleolus spire, 5 in. down the patella line, or 1/3 connecting lines between the patella line and superior border of the lateral malleolus. It corresponds to the circulation line of the stomach meridian on the leg. 1 in. down, acupoint

Zusanli, usually the acupoint on the healthy side, was selected. Using a 5 ml syringe and No. 6–8 injection needle, draw 2 ml × 2 Danshen (or Compound Danshen) injection, remove the air, disinfect acupoint Zhongping, insert the needle with a slight slope, and after needle sensation and no blood coming out, rapidly inject all the drugs, withdraw the needle, and press with a disinfected dry tampon to avoid liquorrhoea or hemorrhage from the pore. The treatment was performed once a day. The 39 patients were treated at least once and at most 6 times; most people were treated 3–5 times. There were 31 recovery cases (79 %) and 8 improvement cases (21 %), and the total effective rate was 100 %.

3.11 Lumbar Transverse Process Syndrome

Min [11] observed the effect of massage combined with Danshen injection on the treatment of third lumbar vertebra transverse process syndrome. 43 patients diagnosed with third lumbar vertebra transverse process syndrome were randomly divided into two groups, 22 cases in the treatment group, and 21 cases in the control group. The patients in the treatment group were treated with massage combined with CDI by intravenous drip, and the patients in the control group were treated with massage only. 20 ml of CDI in 300 ml of physiological saline was administered by intravenous drip, and the patients had a rest for 30 min after administration and then continued with massage. The following massages were performed for the patients in the treatment group and control group: (1) rubbing and rolling the lumbar part and the third lumbar vertebra transverse process surrounding; (2) deeply pressing and pulling the third lumbar vertebra transverse process with two thumbs; (3) clapping and hitting the lumbar part and the third lumbar vertebra transverse process surrounding. The massage should not cause significant pain in the patients, and the above three types of massage can be performed in turn, with light and heavy pressing in turn, to prevent muscle tension and muscle fatigue, 20 min each time with a 10-min break after treatment. Treatment was performed once a day in both groups, 10 times as one course of treatment. The results showed that the complete recovery and marked effect rate in the treatment group was 86.4 %, and in the control group was 38.1 %; the average treatment times for marked effect or better were 4.5 times in the treatment group and 8.9 times in the control group; the differences between the two groups were statistically significant.

Orthopedic and traumatological diseases are a class of very complicated diseases, mainly including bone pathological changes and soft tissue damage, but the common characteristics of the diseases are pain; whether lumbar muscle strain, periarthritis of the shoulder, bone fracture, intervertebral disk pathological changes, or sciatica, the obvious manifestation is pain. Danshen has the function of activating blood circulation and dissipating blood stasis, therefore Danshen and its preparations have obvious function in the treatment of the diseases. If combined with acupuncture, massage, medicated bath, and other TCM therapies, Danshen's effect will be even better.

References

1. Xue S. Chin Rural Med J. 1990;(9):41–42.
2. Zhang H, Wu L. J Pract Tradit Chin Med. 1994;(2):30–43.
3. Wang B. J Anhui Coll Tradit Chin Med. 1995;1(14):48.
4. Xu Z. People's Mil Surg. 2004;47(10):618–9.
5. Tang L, Hou G, Dang H. Chin J Integr Tradit West Med. 1992;7:441–2.
6. Yang Z, Hou B. Shanghai J Tradit Chin Med. 1997;(2):28.
7. Wu B, Li Z. J Hubei Inst Nationalities (Med Ed). 2003;2(20):49.
8. Cheng R, Wu Y. J Shanxi Coll Tradit Chin Med. 2003;1(4):35.
9. Feng D, et al. Chin J Phys Med Rehabil. 2003;6(25):368–70.
10. Wu S. Guangxi Med J. 1998;6(20):431–2.
11. Min K. Chin J Med. 2000;35(7):52.

Application in Pediatrics

4

Yi Zheng, Xuewen Zhang and Jiaoli Guo

Danshen and its preparations have the function of protecting anoxic tissue, promoting cell regeneration, regulating immunologic function, and promoting inflammation regression, and they have extensive application prospects in pediatrics. Unexpected therapeutic effects usually can be obtained if it is used properly. Therefore, the drug is worth further research. In this chapter, we review Danshen's application in this area.

4.1 Pneumonia

As is demonstrated in many studies, free radicals mediate the pathogenesis of pneumonia, thus leading to cytolysis and tissue damage, promoting the diffusion of inflammation and local vasoconstriction, and aggregating platelets and local microcirculatory disturbance. Danshen can inhibit oxygen radicals, and thus can be used in the treatment of pneumonia.

Yang [1] reported the treatment of bronchiolitis with Compound Danshen Injection by ultrasonic atomizing inhalation in 40 patients with significant therapeutic effects; the total effective rate was 92.5 %. The author believed that bronchiolitis was a disease induced by respiratory syncytial virus, the main manifestations including serious wheeze and even heart failure and respiration exhaustion. CDI has the function of activating blood circulation and dissipating blood stasis, improving lung microcirculation, relieving bronchiole smooth muscle spasm, and rapidly expelling phlegm. It also has anti-inflammatory and sedative effects. Thus, it can be used to relieve cough and asthma.

Wang [2] reported the application of CDI in the treatment of 33 children with severe pneumonia, with 30 patients in the control group. Both groups received comprehensive treatments such as anti-inflammation, cardiotonic, diuresis, oxygen inhalation, and phentolamine, etc. The treatment group received also 4–8 ml of CDI in 10 % glucose, administered by intravenous drip once a day. The results showed that in the treatment group and control group, the remission time of dyspnea was 3.7 days and 5 days, respectively ($P < 0.05$); the correcting time of congestive heart failure was 3.2 days and 4.6 days; disappearance time of lung rales was 10.13 and 14.1 days; and length of hospitalization was 15.2 and 19.9 days, respectively, and the difference was highly significant ($P < 0.01$). Patients with severe pneumonia can be affected by anoxia, acidosis, and viral and bacterial toxins, which produce vasoactive substances and induce lung arteriola spasm and microcirculatory disturbance, even leading to organ function exhaustion. CDI has the function of dilating blood vessels, improving myocardial ischemia, inhibiting platelet aggregation, promoting microcirculation, and enhancing the adaptability of lung

Y. Zheng (✉) · X. Zhang · J. Guo
Shengli Hospital of Shengli Petroleum Authority, Shandong, China
e-mail: zhengyiphd@yahoo.com.cn

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tissue. In addition, CDI has anti-inflammatory function and the function of improving tissue organ anoxia and promoting the recovery of multiple organ functions, therefore it could rapidly relieve the severe symptoms.

Gan et al. [3] reported that 47 children with severe pneumonia were treated with compound Danshen. The patients, having reduced platelet count (PLT), significantly increased mean platelet volume (MPV), and platelet distribution width (PDM), were administered with compound Danshen by intravenous drip. The results showed that platelet abnormality rapidly returned to normal. Clinical symptoms, physical signs, and complications were alleviated, and the total effective rate was 96 %. The mechanism might be that on the one hand, Danshen has the function of inhibiting platelet activation by inhibiting platelet calcium influx, and on the other hand, Danshen has broad-spectrum antibiotic actions and could inhibit allergic responses. Its anti-M-cholinergic receptor function is similar to that of atropine, which relieves smooth muscle spasms.

4.2 Viral Hepatitis

Danshen has the function of dilating peripheral blood vessels, reducing portal vein pressure, and improving blood circulation in the liver, thus reducing blood stasis so as to retract the liver and spleen, improve nutrition and oxygen supply to hepatocytes, promote cell regeneration and inflammation regression, promote necrotic tissue absorption, and recover the physiological function of the liver.

Wang et al. [4] reported the treatment of 50 children with Viral hepatitis with Danshen. Fifty children in the control group were administered with inosine. 6 ml of CDI in 25 % glucose solution was administered by intravenous injection to patients 2–5 years old, then 2 ml was administered by intramuscular injection, once a day. Patients older than 5 years received 10–20 ml of CDI in 500 ml of 5 % glucose, once a day, for 10 days as one course of treatment, and the treatment usually lasted for 1–2 courses. The results showed that in the treatment group, there were 24 clinically cured cases, 17 improved cases, and nine non effective cases; the total effective rate was 82 %. In the control group, the numbers were 6, 26, 18, and 64 %, respectively.

The mechanism for Danshen's treatment of Viral hepatitis might be that CDI is an oxygen radical scavenger and can improve blood circulation in the liver, thus relieving ischemia and blood stasis, enhancing antioxidation, and significantly relieving hepatocyte degeneration, necrosis, and fibrosis, and promoting cell regeneration. Therefore, Danshen should be a drug for the treatment of acute or chronic hepatitis.

4.3 Viral Myocarditis

Danshen has the functions of cleaning free radicals and inhibiting calcium channels. Danshen Injection or Danshen Tablet was used for the treatment of Viral myocarditis in children. The treatment group received conventional therapy plus Danshen, with two weeks as one course of treatment. The results showed that improvements in subjective symptoms and electrocardiograms were better than those in the control group.

According to Li and Huang [5], viral myocarditis was usually treated with western medicine. Although the therapeutic effect was affirmed, sequelae and recurrence were not uncommon. However, by combining western drugs with traditional Chinese drugs such as Danshen Injection and Compound Danshen Tablet, satisfactory therapeutic effects in the treatment of viral myocarditis can be obtained. Danshen has the function of improving cardiac contractility and increasing myocardial reserves, and promoting myocarditis recovery. Danshen can activate blood circulation and dissipate blood stasis, cool blood and relieve pain, and remove cardiopyrexia for tranquilization. Danshen acts on the heart, pericardium, and liver meridian, especially in the treatment of stagnation of the heart. CDI at 0.2 ml/(kg d) in 250 ml of 10 % glucose was administered by intravenous drip, once a day, for two weeks. Two weeks later, the patients were administered orally

with Compound Danshen Tablet, 1–2 tablets/time, three times a day, for 3–6 months as one course of treatment.

Zhang et al. (1993) reported 60 children with viral myocarditis, randomly divided into an observation group and control group, each with 30 cases. Conventional therapy was given to the control group, and hormones were not given to the observation group; instead, in addition to the conventional treatment, the dosage of vitamin C was increased to 500 ml/(kg d) which was divided into two parts, dissolved in 50–100 ml of 10 % glucose, and administered by intravenous drip. Children younger than 1 year were given 1–2 injections/day of CDI; 1–3 years old, 3–4 injections/day; 3–7 years old, five injections/day; 7–14 years old, 6–8 injections/day. CDI was mixed with 250 ml of 10 % glucose solution and administered by intravenous drip for 2 weeks as one course of treatment. The results showed that the observation group had 26 cured cases, two effective cases, and two non effective cases, and the total effective rate was 93.34 %. The control group had 16 cured cases, five effective cases, and nine non effective cases, and the total effective rate was 70 %. The difference in the total effective rates between the two groups was significant ($P < 0.05$). The mechanism for the treatment might be that high dosages of vitamin C can reduce the damage to myocardial cells caused by free radicals and promote the recovery of damaged myocardial cells. Compound Danshen can protect the mitochondria and myocardial fibers under hypoxic conditions, promote the regeneration of myocardial cells, dilate coronary arteries, improve circulation, increase myocardial blood flow, and promote the recovery of ischemic or damaged myocardium.

4.4 Protection of Asphyxia Neonatal Myocardium

Wang et al. [6] reported the significant protective effect of compound Danshen on the myocardium of neonates with asphyxia. In neonates with asphyxia, besides hypoxic-ischemic encephalopathy, myocardial damage can be caused by reperfusion, and the release of oxygen radicals. The active components in CDI can improve oxygen utilization in tissues by directly cleaning oxygen radicals and regulating microcirculation so that the production of oxygen radicals is reduced, the consumption of SOD is reduced, and its activity is increased. The myocardium can be effectively protected by blocking the pathogenesis of myocardial hypoxic-ischemic damage. The dosage was 5–10 ml of CDI each time, diluted with water and administered by intravenous drip, for 10–12 days as one course of treatment.

Xu et al. [7] investigated the relationship between the functional disturbance of blood clotting and bilirubin and the treatment value of CDI in neonatal asphyxia. The patients were randomly divided into a treatment group and control group, and a normal group was set. D-dimeride and bilirubin values were determined at birth and at 24 and 72 h after birth. There was some degree of relationship between D-dimeride and bilirubin levels in neonatal asphyxia; CDI has the function of effectively reducing D-dimeride and bilirubin after birth. The disturbance of blood clotting in neonatal asphyxia might be related to neonatal jaundice, and CDI has value in the prevention and treatment of the disease.

4.5 Kawasaki Disease

Jiang (1992) reported the treatment of Kawasaki disease with CDI in 33 children. The baseline treatment for the two groups was the same (administration of aspirin), but 4–10 ml of CDI in 100–250 ml of 10 % glucose was administered to the patients in the treatment group by intravenous drip once a day for 7 days as one course of treatment, and the treatment lasted for 1–2 courses. The patients in the control group were administered with 1–2 mg/kg gamma globulin by intravenous drip once a day. The results showed that there was no significant difference in the therapeutic effect between the two groups, and it was demonstrated that the treatment method was suitable for patients with economic difficulties

and who were allergic to gamma globulin. The mechanism might be Danshen's protection of the mitochondria and myocardial fibers, promotion of myocardial fiber regeneration, increasing the blood flow in myocardium, regulating capillary blood flow, and inhibiting platelet aggregation and reducing blood viscosity, inhibiting thrombopoiesis.

4.6 Neonatal Scleredema

When a child suffers from scleredema neonatorum, blood flow in the tissue is slow and stagnant, leading to tissue hypoxia, damage to the capillary walls, and increased permeability, and in severe cases, even acidosis and microcirculatory disturbance. Compound Danshen has the function of activating blood circulation and dissipating blood stasis, inhibiting platelet aggregation and thrombopoiesis, and reducing blood viscosity, thus improving local microcirculation, increasing renal blood flow and urinary production, and eliminating scleredema.

Qian [8] reported the treatment of neonatal scleredema in 96 cases. CDI was administered by intravenous drip, and drugs with the function of activating blood circulation and dissipating blood stasis were prepared to obtain an ointment for external application. The effects were compared with those from the conventional therapy of western medicine in 60 cases. The results showed that in the CDI treatment group and conventional treatment group, the numbers of respective marked effective cases were 75 and 12, of effective cases were 15 and 30, and of ineffective cases were 6 and 18; the total effective rates were 93.75 and 70 % ($P < 0.01$). The CDI group was better than the western medicine control group.

Tan [9] reported the treatment of 159 cases of severe neonatal scleredema with Compound Danshen, and the therapeutic effect was significant. 4 ml of Compound Danshen was added to 20 ml of 10 % glucose and administered by intravenous drip once a day to the 159 cases in the treatment group until the scleredema receded; the other comprehensive treatment was the same as in the control group. Fifty-five cases in the control group were administered with comprehensive treatment, including rewarming, energy supply, fluid replacement, anti-infection, and according to each patient's pathogenetic condition, treatments of oxygen inhalation, cardiotonic, diuresis, intracranial pressure reduction, etc. were given. The results showed that the time for platelet counts to return to normal (treatment group/control group) was 7.27 ± 1.81/8.08 ± 1.81 days ($P < 0.05$); complete scleredema regression time was 8.68 ± 2.70/9.90 ± 2.28 days ($P < 0.01$); hospitalization time was 13.14 ± 2.65/14.33 ± 3.39 days; and fatality rate was 15.1 %/27.3 % ($P < 0.05$). The treatment mechanism might be because in severe neonatal scleredema, cold, anoxia, and infection could induce microcirculatiory disturbance, acidosis, insufficient blood supply to organs, renal damage, cardiac muscle damage, platelet reduction, and DIC and other blood clotting disorders accompanied by the production of oxygen radicals. Compound Danshen has the function of inhibiting blood clotting, platelet adhesion, and the synthesis of prostaglandin, and promotes the depolymerization of erythrocytes and enhances fibrinolysis function. It also has the function of cleaning oxygen radicals, stabilizing membranes, and antagonizing calcium, thus it has satisfactory therapeutic effects on severe neonatal scleredema.

4.7 Acute Nephritis

Xie (1988) reported the treatment of Acute nephritis in 24 children. The mild cases were treated with 2 ml of CDI by intramuscular injection, two times a day. 2–3 ml/per year of age/day of CDI in 10 % glucose solution was administered by intravenous drip for the severe cases. Urinary production was usually significantly increased on the day of administration, a high peak was reached on the third day, swelling subsided in an average of 5.79 days, blood pressure reduced to normal levels in 7.9 days, hematuria turned negative in an average of 7.05 days, proteinuria turned negative in 9.08 days, 22 cases were clinically cured, and the recovery rate was 91.73 %.

Ni [10] reported the application of CDI in the treatment of 25 children with acute renal glomerulus nephritis. Twenty children in the control group were administered with conventional therapy (e.g., bed rest, benzylpenicillin intramuscular injection to control infection, diuresis, pressure reduction, etc.). Besides the above treatments, the children in the treatment group were also administered with 8–10 ml of CDI by intravenous drip once a day for 7–10 days as one course of treatment. The results showed that times for swelling to subside, pressure to reduce, and urine routine to turn negative in the treatment group were significantly shorter than those in the control group ($P < 0.05$). It was concluded that CDI has satisfactory therapeutic effects on the treatment of nephritis.

The disease is related to the disturbance of the prostacyclin system and increased immune complexes and free radicals, and it is usually complicated by different degrees of microcirculatory disturbance and blood hypercoagulability. CDI has the function of inhibiting immune complexes, correcting prostacyclin system disturbance, anticoagulation, improving renal microcirculation, improving renal blood flow, increasing glomerular filtration rate and relieving renal glomerulus inflammation, strengthening antioxidation, inhibiting lipid peroxidation, preventing damage to nephridial tissue by free radicals, and protecting renal function.

4.8 IGA Nephritis

Cao et al. [11] reported the satisfactory therapeutic effects of Compound Danshen Tablet on the treatment of IGA nephritis. It was demonstrated that the pathological manifestations of various nephritis and nephrotic syndromes involved local and (or) general blood stasis, and thrombopoiesis could be reduced and renal function be recovered by a suitable anticoagulation treatment. Danshen has the function of activating blood circulation and dissipating blood stasis, improving body microcirculation, regulating metabolism, immunity and the nervous system, and promoting repair and regeneration. Usage: Compound Danshen Tablet, 3–6 tablets/days, for 3–6 months.

4.9 Nephrotic Syndrome

Patients with Nephrotic syndrome usually suffer from hypercoagulability, viscous blood, slow blood flow, increased platelet aggregation, and may even be complicated with blood vessel microthrombus. It has been shown by modern pharmacological studies that Danshen has the function of dilating peripheral arteries, improving local blood circulation, reducing inflammation effusion, promoting absorption, etc., and it can limit nonspecific inflammation in nephridial tissue, which is beneficial to nephridial tissue repair. In addition, Danshen also has the function of cooling the blood, eliminating carbuncles, relieving restlessness, calming the nerves, and relieving the blood-heat and stasis induced by taking hormones.

Zhou et al. [12] reported the treatment of nephrotic syndrome with Dantonic™ in 22 cases, and the times for proteinuria to turn negative and for edema to regress were significantly shorter than those in the control group, which had 20 cases ($P < 0.05$, $P < 0.01$).

Dong et al. (2003) reported the application of CDI in the treatment of nephrotic syndrome in 33 children, and significant therapeutic effects were obtained. The disease was accompanied by immune inflammation changes in the renal glomerulus blood capillary filter membrane, proliferation of glomerular basement membrane, increased permeability, blood hypercoagulability, and different degrees of fibrosis. CDI has the function of improving microcirculation, reducing cholesterol, inhibiting fibroplasia, relieving fibrin deposition, and improving renal function and hypercoagulability induced by chronic kidney insufficiency, and the therapeutic effect can be enhanced if used together with hormones.

4.10 Purpura Nephritis

Yu (1991) reported the application of Danshen Injection by intravenous drip and Wilfordii tablets (雷公藤片) by oral administration in the treatment of childrens' purpura nephritis in 15 cases. The results showed that the effective rate of controlling proteinuria, haematuria and hypertension etc. was 100 %.

Meng and Li [13] reported the treatment of purpura nephritis in children with CDI in 24 cases; 0.5–1 ml/(kg d) of CDI in 5 % glucose was administered by intravenous drip, while special treatment was given according to the symptoms. Patients with toxic-heat and blood stasis were administered with modified Jiedu Huoxue Decoction (解毒活血汤), patients with blood heat were administered with modified Rhinoceros Horn and Rehmannia Decoction, patients with syndromes of dampness-heat and stasis were administered with modified Field Thistle Drink, and patients with qi and yin deficiency were administered with modified Double Supreme Pill. The results showed that 18 cases were cured, 15 cases improved, and 1 case showed no effect.

4.11 Neonatal Unconjugated Hyperbilirubinemia

Li [14] reported the treatment of neonatal unconjugated hyperbilirubinemia in 55 cases. The patients in the treatment group were irradiated with blue light for 15–20 h each day. 5 mg of phenobarbital was taken orally three times a day, and 2 ml of CDI in 10 ml of 10 % glucose solution was administered by intravenous drip each day, with 5 days as one course of treatment. The patients in the control group were not treated with CDI, and the other treatments and courses of treatment were the same as those in the treatment group. The results showed that the patients in the two groups were all cured. The recovery time in the treatment group was 3.9 days, in the control group was 4.3 days, and there was a significant difference between the two groups ($P < 0.05$); the jaundice elimination time in the treatment group was significantly shorter than that in the control group. It was believed that CDI has the function of reducing oxygen radical production, thus reducing free radical damage to erythrocytes and reducing bilirubin production; meanwhile, because oxygen radicals were reduced, damage to the blood cerebrospinal fluid barrier was relieved, and thus, the occurrence of kernicterus could be prevented. In addition, the erythrocyte and hemoglobin levels in neonatal blood were high, and phototherapy can induce the loss of moisture from the body and the increase in blood viscosity, which is harmful to metabolism and excretion. CDI has the function of activating blood circulation and dissipating blood stasis, reducing blood viscosity, and promoting metabolism and the excretion of unconnected bilirubin, thus promoting the recovery.

4.12 Newborn Diseases

Feng [15] reviewed the application of the combination of Danshen and Mongolian Milkvetch Root Injection (黄芪注射液) in the treatment of newborn diseases. Patients in five groups (neonatal perinatal asphyxia, neonatal hypoxic-ischemic myocardial injury, myocardial damage caused by neonatal hyperbilirubinemia, neonatal hypoxic-ischemic encephalopathy, and neonatal pneumonia) were divided into a treatment group and control group. Besides the normal comprehensive treatment, the patients in the treatment group were administered with Danshen and Mongolian Milkvetch Root injection by intravenous drip for 7–9 days, and the therapeutic effects were observed. The total clinically effective rates of the five diseases in the treatment group were 93.5581.82, 95.65, 85.71, and 92.86 %, respectively, and were all higher than those in the control group. When Danshen and Mongolian Milkvetch Root injection were combined in the treatment of the five newborn diseases, clinical symptoms were rapidly improved and the therapeutic effects were satisfactory. It is safe and economical, and without toxicity or side-effects.

4.13 Neonatal Hypoxic-Ischemic Encephalopathy

Yang (1998) reported the application of high dosage CDI combined with high frequency jet ventilation (HFJV) in the treatment of 23 cases of Neonatal hypoxic-ischemic encephalopathy, and 23 cases in the control group were treated with conventional western medicine. There was a significant difference in the total effective rate between the two groups ($P < 0.01$). The more severe the disease conditions were, the more significant the difference in therapeutic effect would be. The effective rate in severe cases in the treatment group was 83.3 %, but in the control group was only 20.0 %.

Wang [16] reported the treatment of Neonatal hypoxic-ischemic encephalopathy. The patients were treated with CDI and citicoline, respectively, and the effects were compared with those in the normal group. It was found that in the CDI treatment group, there was a significant increase in serum SOD ($P < 0.05$) and a significant decrease in serum CK-BB ($P < 0.05$), returning back to normal levels. The abnormality rates of 20 items in the Neonatal Behavioral Neurological Assessment were reduced compared to in the citicoline group ($P < 0.05$), and mortality was slightly reduced ($P > 0.05$). There was no significant difference between the growth and development or the results of The Denver Developmental Screening Test of the two groups after treatment. The author believes that the active components in Compound Danshen have the function of blocking the pathogenesis of HIE, thus relieving brain injuries.

Zheng [17] reported the treatment of 76 cases of neonatal hypoxic-ischemic encephalopathy. The treatment method was the control of cerebral edema and rapid control of convulsion. 4 ml of Compound Danshen, 5 g of vitamin C1, 50 units of coenzyme A, 125 mg of citicoline, and 2 ml of cerebrolysin were mixed in 50 ml of 10 % glucose and administered by intravenous drip, for 7–10 days as one course of treatment. The results showed that the all 20 mild cases showed marked effect, while 27 of 40 moderate cases showed marked effect and 10 showed effect; the effective rate was 93 %. 3 of 16 severe cases showed marked effect and 5 showed effect; the effective rate was 50 %, and the total effective rate was 86 %. The author believes that cerebral ischemia and hypoxia can produce large amounts of oxygen radicals which damage brain cell membranes and cause brain cell degeneration and necrosis. Compound Danshen, vitamin C, and coenzyme A have the function of cleaning oxygen radicals; therefore, it is necessary to treat neonatal hypoxic-ischemic encephalopathy with a sufficient dosage of oxygen free radical scavengers at an early stage.

4.14 Viral Encephalitis

Xue [18] reported the treatment of Viral encephalitis with high doses of CDI in 69 cases. 2–3 ml/kg CDI in 100–200 ml of 10 % glucose solution was administered by intravenous drip once a day for 1 week as one course of treatment. The 46 patients in the control group received antiviral, anti-inflammatory, antispasmodic, and antipyretic treatment, as well as treatment to reduce intracranial pressure and activate brain cells. The results showed that there were 60 and 14 cases in the two groups, respectively, with marked effect (treated for 3 days, clinical symptoms, and cerebral edema disappeared), 6 and 17 cases with effect, and 3 and 15 cases without effect; the total effective rates were 95.7 % and 67.4 % ($P < 0.01$), respectively.

4.15 Infant Diarrhea in Autumn and Winter

Zhang [19] reported the treatment of viral enteritis with conventional therapy combined with Compound Danshen, and there was q significant difference in the effect of stopping diarrhea, defervescence time, and total course of the disease between the treatment group and the

control group (no Danshen was used). The therapeutic effect was significantly higher than in the control group ($P < 0.05$). Compound Danshen has the function of activating blood circulation and dissipating blood stasis, improving intestinal microcirculation, and promoting the recovery of desquamated and damaged intestinal mucosa. In addition, Danshen is a diuretic, promotes the discharge of viruses from the body, eliminates pyrogen, and reducs the body temperature to normal levels. The earlier the drug was taken the better the therapeutic effect was, demonstrating that Danshen has antiviral function.

Yang [1] injected 1 ml of CDI into the bilateral acupoints Zusanli of children; 30 infants with autumn diarrhea were treated, and the recovery rate was 100 %. The average healing time was 2.35 days, which was better than the 4.08 days in the antibiotics control group.

CDI has the function of improving intestinal microcirculation and promoting the recovery of injured intestinal mucosa. In addition, Danshen has the function of significantly increasing glomerular filtration rate, renal blood flow, and diuresis function, promoting the discharge of viruses from the body, eliminating pyrogens, and reducing the body temperature to normal levels.

4.16 Allergic Purpura

Allergic purpura is an allergic disease of blood capillaries, usually caused by various factors, and the main pathological change is aseptic vasculitis. Currently, there is no effective therapeutic method. The disease is called hematohidrosis in TCM, and belongs to the category of hemorrhagic symptoms. The manifestation of the disease in the acute phase is usually in heat toxin symptoms. Danshen is bitter in taste and slightly cold in nature, and has the functions of activating blood circulation, cooling blood, removing blood stasis, and stopping bleeding. Pharmacological studies have demonstrated that Compound Danshen has the function of reducing whole blood viscosity and plasma viscosity, changing the electric charge of cell membranes, increasing the charge capacity of cells, improving microcirculation, regulating metabolism and immunologic functions, and increasing renal blood flow and filterability, thus promoting urinary production, eliminating edema, reducing blood pressure, eliminating haematuria and proteinuria, and promoting recovery from purpura nephritis.

Zhang et al. (1992) reported the treatment of allergic purpura with Compound Danshen and vitamin C in 20 cases. The total effective rate was 90 %, which was better than hormone treatment group. The experimental results showed that Compound Danshen has anti-anaphylactic function and stabilizes mastocyte membranes, inhibits the release of grana and mediators, reduces IgE production, and enhances C_3 and lgG. Danshen can effectively inhibit allergic reactions at the first and second stages. Danshen also has the function of improving intestinal and renal microcirculation and increasing renal blood flow. Dosage: 6–10 ml/days CDI in 250 ml of 10 % glucose solution, administered by intravenous drip.

4.17 Recurrent Aphtha

Xiao Zhengzhong [21] used Danshen decoction combined with methyl testosterone to treat 24 children with recurrent aphtha recurrent aphtha and obtained satisfactory therapeutic effects. 30 g of Danshen was decocted with water and taken orally once a day; 10 mg of methyl testosterone was taken 3 times/week, within the first 5 days of the week and discontinuing for 2 days, for two weeks as one course of treatment. There were 20 patients in the control group; prednisone and 10 mg of vitamin B_1 were administered orally 3 times/weeks. The results showed that the treatment group had 13 cases (65 %) heal within 5 days, 5 cases (25 %) heal within 7 days, and 2 cases (10 %) heal in another 7 days; during the corresponding periods, the numbers of healed cases in the control group were 2 cases (10 %), 8 cases (40 %), and 10 cases (50 %) ($P < 0.01$). Recurrence rates: in the treatment group, there were 7 cases (35 %) without recurrence after 14 months, 6

recurrent cases (30 %) within 6–12 months, 4 recurrent cases (20 %) within 3–6 months, and 3 recurrent cases (15 %) within 3 months. In the control group, the corresponding numbers were 1 (5 %), 4 (20 %), 6 (30 %), and 9 (45 %). The difference between the two groups was significant ($P < 0.05$). Comprehensive therapeutic effect evaluation: the treatment group was better than the control group. The mechanism might be related to Danshen's functions in activating blood circulation and dissipating blood stasis, improving microcirculation, improving local blood supply, and increasing macrophage and T lymphocyte numbers, as well as antibacterial function.

4.18 Viral Enteritis

Wang et al. [22] conjectured that, since Danshen has the function of inhibiting calcium influx and is a calcium channel blocking agent, Danshen might be able to reduce the secretion of cryptae cells, inhibit the damage to intestinal mucosa by platelet activating factors, and dilate vessels and improve microcirculation. So, to treat severe enteritis caused by rotavirus, satisfactory results could be achieved by combining Danshen with polyinosinic acid, which has the function of increasing cell immunity, and ribavirin, which has antiviral function. 4 ml of Compound Danshen was added to 1/2–1/3 glucose and administered by intravenous drip once a day. 10–15 mg/kg of ribavirin was added into 1/2–1/3 glucose and administered by intravenous drip once a day; 1 ml of polyinosinic acid was administered by intramuscular injection once a day. For patients less than 1-year old, the doses of polyinosinic acid and Compound Danshen were reduced by half.

4.19 Congenital Hydrocephalus

Zhang [23] reported the treatment of 21 children with congenital hydrocephalus based on the theory of craniocerebral water and stagnation; drugs with the function of promoting blood circulation, and diuresis were used. The prescription included Danshen 15–30 g, szechwan lovage rhizome (川芎) 10–12 g, red peony root (赤芍) 10–12 g, peach seed (桃仁) 10–15 g, safflower (红花) 10–15 g, common motherwort herb (益母草) 15–30 g, medicinal cyathula officinalis root (川牛膝) 10–15 g, indian buead (茯苓) 15–24 g, and forest musk (麝香) 0.1–0.2 g. The medicine was taken with boiling water. Taiwan angelica root (白芷) 10–12 g and synthetic borneol (冰片) 0.1–0.15 g could be added. By adding antler glue (鹿角胶) 6–10 g, cassiabarktree twig (桂枝) 6–10 g, tatarinow sweetflag rhizome (石菖蒲) 6–9 g, and amber (琥珀) 1–2 g (taking with boiling water), the medicine can increase the dissipation of blood stasis and alleviate water retention, activating yang, and inducing resuscitation. Ten cases were basically cured, 7 cases showed marked effect, and 2 cases showed effect; the total effective rate was greater than 90 %.

4.20 Toxic Intestinal Paralysis

Chen (1994) reported on 48 children treated with conventional treatment plus Danshen. 2–8 ml of Danshen Injection in 5 % glucose was administered by intravenous drip, and 0.5–1 mg/kg of phentolamine in 10 % glucose was administered by intravenous drip for 2–4 days, 1–2 times a day. The results showed that there were marked effects in 38 cases within 48 h. It was revealed that both drugs have the function of relieving intestinal wall vasospasm and blood stagnation, increasing blood flow to intestinal wall tissue, relieving intestinal wall edema, improving microcirculation, recovering intestinal function, and relieving abdominal distension.

Compound Danshen Injection has good qualities such as high-therapeutic effect and few side-effects, thus, it has become increasingly welcomed by pediatricians. It is believed that with further clinical and experimental research on the drug, there will be more extensive prospects of application in clinical pediatrics.

References

1. Yang J. J Clin Pediatr. 1993;11(4):287.
2. Wang X. J Appl Clin Pediatr. 1992;7(4):212.
3. Gan J, Xiong A, Xiao X. Chin J Contemp Pediatr. 2000;3(2):156.
4. Wang Y, et al. Guangdong Med J. 1988;9(2):31.
5. Li P, Huang X. J Appl Clin Pediatr. 1995;10(1):4.
6. Wang X, He P, Zhang L. J Appl Clin Pediatrics. 1995;10(l):22.
7. Xu S, Xu G, Jiang H. J Emerg Tradit Chin Med. 2005;7(14):637.
8. Qian X. Integr Tradit Chin West Med Pract Crit Care Med. 1998;5(7):301.
9. Tan Y. Integr Tradit Chin West Med Pract Crit Care Med. 1996;3(7):302.
10. Ni J. Pract J Integr Tradit Chin West Med. 1991;4 (16):333.
11. Cao B, Jiang B, Li X, et al. J Appl Clin Pediatr. 1995;10(4):22.
12. Zhou X, Jiang R, Qian J, et al. Chin J Pract Pediatr. 2001;16(1):14.
13. Meng Q, Li X. Heilongjiang J Tradit Chin Med. 1990;1:17–8.
14. Li Y. J Integr Tradit Chin West Med. 1995;15 (9):235.
15. Feng L. J Emerg Tradit Chin Med. 2006;7(15):743.
16. Wang B. Chin J Misdiagnosis. 2007;12(7):2718.
17. Zheng Z. J Appl Clin Pediatr. 1996;11(4):212.
18. Xue Y. J Sichuan Tradit Medicine. 1991;6:25.
19. Zhang E. J Clin Pediatr. 1988;6(4):267.
20. Wang J. Guangdong Med J. 1998;9(2):31.
21. Xiao Z. J Tradit Chin West Med. 1989;9(5):304.
22. Wang X, Lin R, Huang L, et al. Chin J Pract Pediatr. 1997;12(2):91.
23. Zhang X. Shaanxi J Tradit Chin Med. 1984;5 (1):1–3.

Application in Gynecology

5

Yi Zheng, Xuewen Zhang and Jiaoli Guo

5.1 Intrauterine Growth Retardation

Intrauterine growth retardation (IUGR) is one of the important reasons for the disease and death of perinatal infants. It used to be called placental dysfunction syndrome, and was then named chronic placental dysfunction by Gruenwald in 1963. The pathogenesis is considered to be related to reduce placental blood flow. When a fetus suffers from placental dysfunction, oxygen and nutrient intake from the mother is reduced and fetus growth will be affected. During normal pregnancy, blood flow in the placenta gradually increases with the development of the pregnancy. However, a large number of foam cells appear in the uterine spiral artery wall in patients with IUGR, which is called acute atherosclerotic phenomenon, leading to the decrease in placental blood flow. Meanwhile, a series of changes such as delayed growth of villi, inflammation, infarct, and so on can be induced in the placentas of patients with IUGR, and ischemia and hypoxia of the villus will be accelerated. Abnormal blood circulation in the placenta, excessive thickening of the tunica intima of the placenta arteriola, and narrowing of lumens affect the blood flow and transport function.

Zhou [1] reported the treatment of IUGR with Danshen and salbutamol in 87 cases. The pregnant women were 21–34 years old; gestational age was 27–36 weeks; 83 cases were primiparas, four cases were multiparas; one case was complicated with chronic nephritis renal hypertension, 11 cases had mid-term pregnancy-induced hypertension (PIH). Among the 87 patients, 50 patients received 10 ml of Danshen Injection by intravenous administration and 4.8 mg of salbutamol by oral administration, three times a day for 7 days as one course of treatment, and a total of 2–3 courses of treatment were performed. The 37 patients in the control group received 250 ml of compound amine acid injection and 500 ml of 10 % glucose injection with 40 mg of triphosadenine and 100 μ of coenzyme A by intravenous administration once a day for 7 days as one course of treatment, and 2–3 courses of treatment were performed. The uterine height was examined once a week and the biparietal diameter (BPD) and femur length (FL) were examined by B-ultrasound once every 2 weeks at the end of the first course of treatment for the pregnant women in both groups. The results showed that the growth rates of uterine height, BPD, and FL of pregnant women in the Danshen + salbutamol treatment group were significantly higher than those in the control group. Danshen has the functions of activating blood circulation and dissipating blood stasis, promoting microcirculation, and improving blood viscosity. Salbutamol is an adrenergic receptor stimulant and has the functions of reducing uterine muscular

Y. Zheng (✉) · X. Zhang · J. Guo
Shengli Hospital of Shengli Petroleum Authority, Shandong, China
e-mail: zhengyiphd@yahoo.com.cn

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tension and uterine contractility, relaxing uterine muscles, dilating the blood vessels of the placenta, increasing blood flow to villus interspaces, and improving placental blood supply. The combination of the two drugs can promote placental blood flow, increase perfusion, and enhance substance transportation, thus enhancing the intake of oxygen and nutritive materials by the fetus and promote the growth of fetuses with IUGR. No side-effects were observed in the application of the two drugs, it was revealed that the therapeutic effect of Danshen + salbutamol on the treatment of IUGR was good, safe, and reliable.

Zhang and Zhang [2] observed the clinical therapeutic effect of hyperbaric oxygen and Danshen in the treatment of IUGR in 12 cases. Thirty-two qualified pregnant women with IUGR were randomly divided into a control group (20 cases) and treatment group (12 cases). The patients in the control group received 30 g of Danshen in 500 ml of 5 % glucose solution which was administered by intravenous drip; they also received 250 ml of compound amino acids, with 7 days as one course of treatment. The patients in the treatment group received the same treatment as those in the control group, plus they were treated with hyperbaric oxygen; the treatment pressure was 0.18 Mpa, and the patients inhaled pure oxygen twice for 30 min, with a 10-min interval between inhalations. Two weeks later, uterine height, abdominal circumference, and body weight were measured, and the increased values of fetus BPD and FL were measured with B-ultrasound. The results showed that the uterine height, abdominal circumference, and body weight of the pregnant women in the treatment group were significantly higher than those in the control group, and there were significant differences in the increased values of fetus BPD and FL. Various indexes of pregnant women and fetuses with IUGR were significantly improved by hyperbaric oxygen and Danshen. Hyperbaric oxygen can significantly alter hypoxia in the uterus, placenta, and placental fetus, promote fetal development, and reduce fetal mortality and complication during the perinatal period. Danshen reduces blood viscosity, has anticoagulant and thrombolytic effects, promotes microcirculation, etc., and thus improves blood circulation in the uterus and placenta, promoting the growth of fetuses with IUGR. The treatment has no significant effect on the blood sugar and platelet levels of fetuses with IUGR, and had no significant change in blood clotting time. It was concluded that marked effects on the treatment of IUGR were obtained by combining hyperbaric oxygen with Danshen and amino acids.

5.2 Ovarian Hyperstimulation Syndrome

Ovarian hyperstimulation syndrome (OHSS) is the manifestation of an excessive reaction of the ovaries to gonadotrophic hormones and complications of superovulation. The incidence of the disease is 23.3 %, and the incidence of severe OHSS is 0.008–10 %. The fundamental causes of OHSS have not been found, but most researchers believe that it is related to abnormalities in blood E2 and the activation of the ovarian renin-angiotonin-aldosterone system. Some people believe that there might be ovarian factors which act on blood vessels. The main pathological changes of the disease include increases in blood vessel permeability, hemoconcentration, and transudate retention.

She [3] observed the therapeutic effect of Danshen on the treatment of 12 cases with severe OHSS, aged between 25 and 41 years. The causes for infertility included four cases of polycystic ovaries, five cases of oviduct adhesions and occlusion, and three cases of undefined causes. In the ovulation induction treatments, eight cases received gonadotropin releasing hormone agonist (GnRHa) + follicle stimulating hormone (FSH) + human chorionic gonadotrophin (HCG), and four cases received HMG + HCG. In Vitro Fertilization Pre-Embryo Transfer (IVF-ET) was performed on nine cases, with successful pregnancy in eight cases, and simple artificial insemination was performed on four cases. The 12 patients had apparent subjective symptoms, significant ascites

and ovarian increase, and oliguria, and half of the patients suffered from pleural effusion. Group A: low molecular dextran, albumin 10–20 g/day, crystalloid solutions by intravenous infusion. Group B: same treatments as group A, plus administration of Danshen at 6–12 g/day (added into low molecular dextran and administered by intravenous drip). Patients with pulmonary interstitial edema and oliguria can be administered with furosemide 20–40 mg/day by intravenous injection, and 1,000 ml of urinary production or more a day was maintained. One course of treatment lasted for 7–10 days, and the treatment was repeated if necessary. The patients could orally take indomethacin and prednisone. Group C: there were three cases with very severe OHSS, and ascites and follicular fluid suction were performed based on drug treatment. Puncture was performed by abdominal or vaginal B-ultrasound. The ascites was drained by 1,000–1,500 ml/time. The number of ovarian follicles punctured in the patients in this group ranged from 5 to 9. The E2 content of follicular fluid was >400 pmol/L. After treatment, the clinical symptoms of all patients disappeared; urinary production increased to more than 1,000 ml/day; ascites and hydrothorax reduced or disappeared; and ovaries were shrunken. Blood E2, hematocrit, whole blood viscosity, high shear, and low shear values before treatment were 2091.9 pmol/L, 41.67, 7.38, and 5.23 %, respectively, and after treatment, the values were 1781.1 pmol/L, 37.28, 5.35, and 4.49 %, respectively. The differences were significant ($P < 0.05$). The reduced values of blood E2 and hematocrit in group A were 634.2 pmol/L and l %, respectively; in group B, 840.8 pmol/L and 3 %, respectively; in group C, 1,018 pmol/L and 6.67 %, respectively. The average treatment period in group A was 45.36 days, group B 36.25 days, group C 22.67 days. Groups B and C differed from group A significantly ($P < 0.05$), and group B and group C were statistically the same ($P > 0.05$). Patients with severe OHSS should correct the blood volume and prevent pachyemia. Danshen has the function of promoting microcirculation, reducing blood viscosity, and inhibiting thrombopoiesis. The eight cases in group A were treated with Danshen on the basis of expansion treatment with low molecular dextran and albumin, and the therapeutic effect was better than that from expansion treatment alone ($P < 0.05$). Ascites and follicular fluid suction can rapidly reduce abdominal pressure and significantly reduce E2 and angiotonin II, exerting the fundamental therapeutic functions.

5.3 Chronic Dystrophy of Vulva

The etiological factors for white lesions of the vulva have not been identified, and the disease is difficult to cure but easy to recur. The causes of the pathological changes of skin disease mainly involve neurovascular nutritional disorders of the dermis. In pathological sections, there is usually excessive cornification of the cuticular layers, atrophy of the epidermis, swollen derma, and reduced cell components of blood vessels, and they are usually accompanied by mild to moderate chronic nonspecific inflammation.

Chen [4] reported the application of Compound Danshen ointment in the treatment of white lesions of the vulva. 368 patients were selected for the experiment, aged 44–76 years old and with the course of disease ranging from half a month to 26 years. 106 patients in the study were administered with various soft gels; 17 patients were administered with boom laser therapy; 26 patients were administered with local drug injections; 4 patients suffered from local recurrence after vulvectomy. The vulva was cleaned, then the afflicted part was smeared with Compound Danshen ointment (main constituents included Danshen, synthetic borneol, and dictamni cortex (白藓皮), the adjuvant was various vitamins), 1–2 times a day for 1 week. The patients then returned for examination and were followed up with every 1–3 months. Samples from 62 cases that could be followed up with were collected and examined before, during and after the treatment. The results showed that among the 368 cases, 84 recovered, 212 showed marked effect, 67 showed improvement, two cases stopped treatment because of local burning pain, and three cases showed no changes after

treatment. The total effective rate was 98.64 %. Samples were collected from 32 cases before treatment, with 13 cases of hyperplasia type malnutrition, 14 cases of lichen sclerosis type malnutrition, and five cases of mixed type malnutrition. Pathological examination showed different degrees of excessive hyperkeratinization of the surface layer, incomplete cornification, acanthosis, interstitial edema, hyperemia, significant infiltration of lymphocytes and plasmocytes in the dermis, and even the production of cornification, local necrosis, early stage calcification, etc. These changes are related to the duration and severity of the disease. After treatment, the pathological sections showed different degrees of squamous epithelium hyperplasia, swollen derma, hyperemia, blood vessel dilation, light inflammation reactions or small amounts of cell infiltration, fibroplasias and hyperemia, and edema. Some sections showed plenty of small blood vessels, pigment cells, and pigmentation. The epidermis of cured patients was basically normal by pathological examination; only mild hyperplasia was observed, and the inflammation reaction was also relatively mild. These changes coincided with the degree of improvement in the patients' disease condition and healing. Danshen has the function of activating blood circulation, dissipating blood stasis, improving microcirculation, and dilating blood vessels; synthetic borneol has anti-allergy and anti-inflammation functions; and dictamni cortex and various vitamins have the functions of improving vascular and peripheral nerve nutrition. Posttreatment pathological sections showed improvement in the blood circulation of the vulvar lesions, controlled inflammation, and different degrees of increases in fibrous connective tissue and pigment granules. The drug is convenient to use, and the therapeutic effect is obvious.

5.4 Chronic Salpingitis

Zheng [5] observed the therapeutic effects on chronic salpingitis of millimeter-wave and Compound Danshen introduced into the body by direct current. 100 patients with chronic salpingitis were randomly divided into two groups. The 50 cases in the treatment group were 19–40 years old, with 6 months to 2 years of disease history. The 50 cases in the control group were 21–41 years old with 5 months to 2 years of disease history. The patients in the treatment group were treated with an 8-mm-wave therapy instrument, with frequency 35–75 GHz, wave length 8.4 mm, and output 10 mW/cm^2. The diameter of the cylindrical radiation head was 7.3 cm. The radiation head clung to one or two sides of the body surface over the oviducts. The patients were radiated for 30 min each time, and patients with bilateral chronic salpingitis were radiated for 30 min on each side. AC induction diathermy was used at the same time as the treatment: 8 ml of CDI was sprinkled on padding filter paper, the main pole padding (8 cm × 15 cm × 2) was placed on the two sides of the abdomen, introducing the positive pole, and the auxiliary pole padding (12 cm × 12 cm) was placed at the lumbosacral region. The current intensity was 0.05−0.1 mA/cm^2, 20 min each time, once a day, 18 times for one course of treatment.

The control group received treatment with an ultrashort wave therapy instrument, with wavelength 7.2 m, frequency 40.68 MHz, and output 200 W. Two poles (1 cm × 22 cm × 2) were placed on the lower abdomen and lumbosacral area with an interspace of 2–4 cm, 15 min each time. After treatment, 8 ml of 10 % potassium iodide was used at the same time, and negative pole was introduced; the method and time was the same as in the introduction of Compound Danshen, once a day, 20 times for one course of treatment, and no other treatment was performed in the treatment period. The clinical treatment was analyzed by the Ridit method, showing that the therapeutic effect in the treatment group was better than that in the control group, and the difference was highly significant, $P < 0.01$. In the treatment group, 15 cases were cured, 26 cases showed marked effect, seven cases showed improvement, and two cases showed no effect. In the control group, 11 cases were cured, 13 cases showed marked effect, 17 cases showed improvement, and nine cases showed no effect.

It was revealed that when the electromagnetic oscillation frequency of the millimeter-wave synchronizes with the inherent oscillation frequency of the biomembrane, they undergo resonance, which has the effects of anti-inflammation, relieving pain, subsiding swelling, dilating blood capillaries, improving local tissue perfusion and microcirculatory blood flow of the pain site, and improving immunologic functions and related pathological processes. Tanshinone and tanshinol, the components of Danshen, inhibiting angiotonia and can significantly improve hemorheology indexes, relieve local stagnant blood, and improve blood circulation. Tanshinone also has antibacterial and anti-inflammatory functions. Observation of the curative effects of millimeter waves combined with CDI direct current introduction in the treatment of chronic salpingitis has shown that local blood circulation can be effectively increased, eliminating inflammatory swelling and pain and promoting the softening and absorption of hyperplasia tissue.

5.5 Salpingitis Infertility

Salpingemphraxis, which is one of the important causes of female infertility, is mainly caused by acute or chronic salpingitis or chronic pelvic inflammatory disease, etc. Currently, there are no effective treatments for this disease.

Liang et al. (2003) reported the application of CDI in the treatment of Salpingitis infertility. The patients suffered from both primary infertility and secondary infertility, and were diagnosed with infertility caused by salpingemphraxis by iodolography in the uterus oviduct. The patients were 23–35 years old, with an average age of 29 years, the infertility time was 2–7 years, with an average of 4.5 years. Six patients (about 38 %) suffered from primary infertility, 10 patients (about 63 %) suffered from secondary infertility, 1 patient suffered from infertility after an exfetation operation, 9 patients suffered from infertility after induced abortion operations, and 12 patients (about 80 %) had a history of chronic pelvic inflammatory disease or appendagitis. Hysterosalpingography JOLECTTHIN imaging was conducted with a gastrointestinal imaging machine. The 16 patients were examined before treatment and after 3 or 6 courses of treatment. According to TCM theory, most salpingemphraxis type infertility cases are caused by blood stasis in the lesser abdomen, and the treatment principle for this kind of disease is to activate blood circulation, dissipate blood stasis, and unblock the collaterals. 20 ml of CDI was injected into the uterus or until the uterus was full. The detailed method was: after urination, disinfect the bladder lithotomy position, examine the vagina, expose and clamp the cervix, insert the catheter, inject 20 ml of CDI in a syringe slowly into the catheter at a speed of 5 ml/min. If the injection met no resistance, and the patient felt discomfort at bilateral abdomen, then it indicated that the oviduct was not obstructed; if the injection was difficult to process, the volume of CDI injected was 10 ml or less, the patient felt abdominal distension and pain, or CDI flew back into the syringe after the injection was stopped, then it indicated that there was tubal occlusion. If the injection could continue after adding pressure, it indicated that the fallopian tube had a mild adhesion which was separated.

The patients were administered orally with anti-inflammatory drugs for 3 days after the operation. The patients were treated each month when menstruation stopped within 2–3 days after treatment, once every 2 days for 3–5 times as one course of treatment, and 3–6 courses of treatment were performed in total. Oral administration of TCM decoctions was used as an adjuvant treatment which was given to the patients according to their symptoms, and it was stopped when the symptoms were improved. After treatment there was a different degree of oviduct deoppilation in the majority of patients, and the primary stiffness of the oviducts and reduced peristalsis function due to surrounding adhesions were significantly recovered. The total effective rate was 81.25 % after treatment. CDI has the function of promoting qi, activating blood circulation, and dilating vessels. The concentration of the drug in the lesion area was enhanced by direct local administration with pressure, which dilates local

blood vessels, softens lesions, and eliminates adhesions. Meanwhile, the drug for oral use has the function of regulating yin-yang and qi-blood balances, inhibiting the hyperplasia of fibrocytes, reducing the infiltration of inflammation cells, and inhibiting the degeneration and necrosis of epithelial cells of mucous membranes, thus accelerating the deoppilation of lumens and providing conditions for pregnancy.

5.6 Pregnancy-Induced Hypertension Syndrome

The main pathophysiological changes of PIH syndrome include general arteriola spasm, pachyemia, and reduced blood volume, and the above factors are also the main causes of fetal growth and development restriction. General arteriola spasm can lead to abnormalities of blood rheology and microcirculation of the whole body and placenta, thus leading to intrauterine ischemia, anoxia, poor tolerance, low burn scores, and even intrauterine death of the fetus.

Wang [6] reported the adjuvant treatments of PIH with Ligustrazine and CDI in 60 cases. Their effects were compared against each other, the differences between the two drugs in improving microcirculation and fetal intrauterine anoxia were discussed, and advice for clinical application was provided. Sixty hospital patients with PIH were divided into two groups. Based on treatments of calming, spasmolysis, pressure release and low flow oxygen inhalation, the patients were, respectively, administered with Ligustrazine Injection and CDI by intravenous drip. 80 mg of ligustrazine hydrochloride sodium chloride injection was administered by intravenous drip for the patients in the Ligustrazine injection group, once a day for 10 days as one course of treatment. 16 ml of CDI in 250 ml of 5 % glucose was administered by intravenous drip for the patients in the CDI group, once a day for 10 days as one course of treatment. The results showed that the hemorheology, fibrinolysis function, TG, TC, and fetus umbilical artery S/D values of the patients in the two groups before treatment were significantly higher than those in the normal control group. Biophysics scores and placental function E3 of the fetus in the two groups were significantly lower than those in the control group, and there was no significant abnormality in blood clotting function. Fetal biophysics scores were significantly increased by the treatment of ligustrazine hydrochloride sodium chloride injection and CDI in the two groups. HCT, Fg, TG, FDP, D-D, and S/DD values were significantly reduced, but E3 was significantly increased after treatment in the Ligustrazine group. HCT, TC, TG, S/D values were significantly reduced after CDI treatment, but there were no significant changes in BT, PT, ESR, and PLT between the two groups before and after treatment. It was concluded that the two drugs do have therapeutic effects on PIH in the two groups, but the mechanisms for the improvement of blood rheology and microcirculation are not the same.

Ye [7] reported the prevention of PIH by the combination of Compound Danshen and calcium. The MP PIH syndrome monitoring system was used to predict PIH in 764 patients who had been pregnant for 20–28 weeks, and 84 patients selected as at high risk for PIH were randomly divided into a prevention group (42 cases) and placebo group (42 cases). The patients in the prevention group were administered orally with 4 tablets of Compound Danshen, twice a day, and 1,200 mg of Caltrate-D, once a day, until delivery. The patients in the placebo group were administered orally with 100 mg of vitamin C, three times a day, until delivery. The incidences of PIH syndrome, hemodynamic changes before and after drug administration, delivery conditions, and neonatal conditions were observed in the two groups. The results showed that there were three cases of PIH in the prevention group; the incidence was 7.14 %, and no severe cases were observed. There were 12 cases of PIH, 7 mild cases and 2 severe cases, in the placebo group; the incidence was 28.57 %. There was a significant difference between the two groups ($P < 0.001$). There were no significant changes in hemodynamic indexes in the prevention group

before and after treatment; however, the changes in the placebo group were significant ($P < 0.01$). The average neonatal body weight in the prevention group was 3,367 ± 328.6 g, and in the placebo group was 3,057 ± 237.2 g; the difference between the two groups was significant ($P < 0.05$). It was revealed that oral administration of Danshen and calcium tablets can reduce the risk of PIH and improve maternal and newborn health. PIH syndrome is related to the imbalance of prostacyclin (PGI_2) and thromboxane A_2 (TXA_2). PGI_2 has the function of inhibiting platelet agglutination and enhancing blood vessel dilation, but TXA_2 has the function of inducing platelet aggregation and enhancing blood vessel constriction. During normal pregnancy, the contents of the two agents increase with the progression of the pregnancy. When the patients suffer from placental ischemia, there are great changes in the levels of PGI_2 and TXA_2 in the body. Low concentrations of lipid peroxides can significantly stimulate epoxy synthetase, increasing the synthesis of PGI_2 and TXA_2, but high concentration of lipid peroxides can inhibit epoxy synthetase, reducing the synthesis of PGI_2 and increasing the synthesis of TXA_2, reducing the PGI_2/TXA_2 ratio. Thus, a series of manifestations of PIH syndrome are induced, such as excessive small blood vessel spasm and platelet aggregation, increased blood pressure, and ischemia of important organs. Danshen has the function of activating blood circulation, dissipating blood stasis, dilating blood vessels, reducing blood viscosity, changing hemorheology characteristics, and improving microcirculation. It also has the function of cleaning free radicals, inhibiting lipid peroxidation in cells, and increasing the PGI_2/TXA_2 ratio, thus, it can prevent the incidence of PIH in high-risk patients.

Hao [8] observed the effect of Compound Danshen on microcirculation in 56 pregnant women with PIH syndrome, who were between 23 and 34 years old and with gestational age between 35 and 40 weeks. 47 cases were primiparas and nine cases were multiparas. There were 26 cases with mild PIH syndrome, 18 cases with moderate PIH, and 12 cases with severe PIH syndrome. 16 ml of CDI in 500 ml of 5 % glucose solution was administered by intravenous drip once a day for 5 days as one course of treatment. The patients were recommended the left recumbent position, and given adjuvant treatments such as tranquilizers and oxygen inhalation, etc. The changes in mean arterial pressure (MAP) and nailfold microcirculation were observed before and after treatment. The results showed that the MAP of pregnant women with mild, moderate and severe PIH syndrome was significantly reduced after treatment ($P < 0.05$). Observation of 16 indexes of nail fold microcirculation in pregnant women with PIH syndrome demonstrated that the characteristics of fold microcirculation in pregnant women with PIH syndrome include narrowed capillary caliber, slowblood flow speed, significant erythrocyte aggregation, graininess, shortened loops and tortuosity, and obfuscated and crossed loops. There were different degrees of improvement after the treatment. The main manifestations included increased blood flow speed in the nailfold microcirculation, significantly relieved erythrocyte aggregation, dilated capillary caliber, and opening of some loops. It demonstrated that Danshen can be used in the treatment of pregnant women with PIH syndrome, and it can reduce the MAP of pregnant women and adjust microcirculatory shape, regulate microcirculatory fluid state, and improve microcirculation It was believed that while Danshen could improve nail fold microcirculation, it must be able to improve the microcirculation of the placenta, thus increasing the perfusion volume to the placenta.

5.7 Threatened Preterm Labor

Zhang [9] reported the application of Danshen and salbutamol in the treatment of threatened preterm labor in 42 cases. The patients were 22–40 years old; eight cases were 22–25 years old, 18 cases were 26–30 years old, 10 cases were 31–35 years old, and six cases were 36–40 years old. Gestational age: 28–32 weeks, 26 cases; 33–36 weeks, 16 cases. Pregnancy times: pregnant once,

24 cases; pregnant twice, 12 cases; pregnant three times, six cases. The therapeutic method: 4.8 mg of salbutamol, three times a day, taken orally; 9.6 mg if necessary, three times a day, taken orally. 16 ml of Danshen Injection in 500 ml of 5 % glucose was administered once a day by intravenous drip, and vitamin E and C were administered adjuvantly and diazepam was administered if necessary, until no abdominal pain or discomfort was felt. 2.4 mg of a maintenance dose of salbutamol was administered after the symptoms of threatened preterm labor were eliminated, three times a day, po, for 3 days. The results showed that 24 cases had marked effect, 14 cases had improvement, and four cases had no effect; the total effective rate was 90.5 %. The pregnancy continued in 36 cases, maintained for more than 37 weeks. Five cases suffered from symptoms of threatened preterm labor after treatment, and the symptoms disappeared and the pregnancy continued after the above treatments. Danshen has the function of activating blood circulation and dissipating blood stasis, cooling blood, relieving pain, nourishing blood, and calming the nerves. Danshen's chemical constituents include protocatechualdehyde, protocatechuic acid, and tanshinones. The combination of these components can dilate vessels, which can improve microcirculation, increase blood supply to the uterus and placenta, increase the blood oxygen content of the umbilical cord, promoting nutritional supply to the fetus, and maintain a quiet environment in the uterus. Salbutamol has the function of relaxing uterine smooth muscle, mainly via the function of stimulating β_2 receptors, thus inhibiting uterine contraction. The excitation of β_2 receptors, the relaxation of uterine smooth muscle, and the dilation of arteries can all increase the blood flow to the uterus and placenta, and synergistic effects can be obtained by combination with Danshen.

5.8 Endometriosis

Endometriosis is one of the most concerning diseases in clinical gynecology and obstetrics. The etiological factors of the disease have not been identified, thus its treatment is very difficult. The endometriosis tissue, cyclical bleeding, and deciduous uterine endometrial debris shedding cannot be discharged out of the body like normal menstrual bleeding; instead, they are detained in the pelvic cavity, which could be regarded as foreign material by the immune system, leading to immune response and resulting in the disturbance of immunologic function.

Liao et al. (2003) observed the effect of Danshen mixture and tamoxifen on the immunologic functions of patients with endometriosis. Monoclonal antibodies against human CD_{20}, CD_3 and their subgroups were used for detecting the percentages of CD_{20}, CD_3, CD_4 and CD_8 in 43 females with endometriosis and 27 females with normal menstrual cycles. 10 ml of venous blood was collected from the patients in the treatment group and control group during the second half phase of menstruation, heparin (50 U/ml) was used for anticoagulation, and indirect immunofluorescence was used for detecting CD_{20}, CD_3, CD_4, CD_8, and antibodies against human CD_{20}, CD_3, CD_4, CD_8. 24 cases with severe endometriosis were treated with Danshen mixture by retention enema and tamoxifen; the Danshen mixture contained: Danshen 20 g, dahurian patrinia herb (败酱草) 20 g, mongolian dandelion herb (蒲公英) 20 g, sargentgloryvine stem (红藤) 20 g, philippine violet herb (紫花地丁) 20 g, common burreed tuber (三棱) 10 g, blue turmeric rhizome (莪术) 10 g, peach seed (桃仁) 10 g, rhizoma corydalis (延胡) 10 g, costusroot (木香) 10 g, and nutgrass galingale rhizome (香附) 10 g. The above drugs were decocted with water to obtain 100 ml of decoction, and administered by retention enema at the end of menstruation, once a day for 20 days as one course of treatment. At the same time as the administration of Danshen mixture, tamoxifen treatment was given until menstruation, twice a day, 10 mg each time, and the changes in the ratios of CD_{20}, CD_3, CD_4, CD_8, CD_4/CD_8 were observed before treatment and after two courses of treatment. The results showed that the value of whole blood B lymphocytes of the patients with endometriosis in each group was significantly higher than that in the control group ($P < 0.01$). The percentage

average value of CD_{20} in the moderate and severe group was significantly higher than that in the mild group ($P < 0.01$). There was no significant difference in the percentage value of CD_3 between the moderate group and severe group ($P > 0.05$). There was no significant difference in CD_3 value between the treatment group and control group ($P > 0.05$). There was no significant difference in the percentage value of CD_4 between the mild and moderate group and control group ($P > 0.05$). The percentage value in the severe group was significantly lower than that in the control group ($P < 0.05$). The CD_8 values in the moderate group and severe group were significantly lower than those in the control group ($P < 0.01$), and there was no significant difference between the mild group and control group ($P > 0.05$). Two months after treatment with Danshen by retention enema and tamoxifen, the percentage values of CD_{20} and CD_3 and the percentage ratio of CD_4/CD_8 were significantly reduced ($P < 0.01$); the CD_8 value was significantly increased ($P < 0.05$), and there were no significant changes in the percentage value of CD_4 before and after treatment. The follow up results showed that among the 24 patients who were treated with Danshen mixture by retention enema and tamoxifen for 2 courses of treatment, 17 patients no longer had dysmenorrhea, 6 patients had dysmenorrhea alleviation, and one case had no effect. The clinical signs were reviewed by B-ultrasound and gynecological examination; pelvic cavity tubercle disappearance, one case; pelvic cavity lump or tubercle reduction, nine cases; no significant change, 14 cases. The 14 patients were treated with laparotomy operations (six cases), or continued treatment (eight cases), and were reviewed 3 months after treatment. One case suffered from a duck egg-like pelvic cavity lump before treatment, which completely disappeared after the treatment, and the other seven cases with pelvic cavity lumps and tubercles also showed shrinkage. It was demonstrated that there was significant disturbance of immunologic function in patients with the disease, and the disturbance degree was increased with the pathological changes of endometriosis. The combination of Danshen mixture and tamoxifen has a good effect on the regulation of the body's immunologic functions and on the improvement of clinical symptoms caused by endometriosis. It demonstrated that the effects were obtained by inhibiting the immune response and regulating body immunity. The majority of patients in the study suffered from recurrent attacks and received several rounds of medical treatment, and there were different degrees of inflammation surrounding the endometriosis lesions. Danshen mixture by retention enema has the function of activating blood circulation and dissipating blood stasis, removing heat and cooling the blood, and softening lumps and loosening knots, and satisfactory therapeutic effects on improving symptoms can be obtained by combination with tamoxifen, which is an antiestrogen agent. Their function of eliminating lesions needs further study.

5.9 Oligohydramnios

Oligohydramnios directly influences the growth and development of the fetus in utero, and leads to different degrees of fetal malformatios, delayed growth, intrauterine asphyxia, and even dead fetus and stillbirth; the perinatal mortality rate is extremely high. A pregnant woman who is clinically diagnosed with oligohydramnios is usually complicated by PIH syndrome, pregnancy hypertension, IUGR and excessive pregnancy, fetal malformation, etc.

Zhou (2003) reported the application of Danshen in the treatment of 15 cases of oligohydramnios. The patients had been clinically ruled out for fetal malformation and premature rupture of membranes; the average gestational age was 34 weeks, the shortest was 28 weeks and the longest was 39 weeks; seven cases were complicated with IUGR, and three cases were complicated with mild and moderate PIH. In the past 6 years, 48 patients with oligohydramnios were treated; among them, 15 women were similar in age, pregnancy age, and pregnancy complications, etc. with those in the Danshen

treatment group, and they were selected as the control. Oxygen inhalation and left recumbent position were first performed for the patients in the two groups after hospitalization, and the patients in the control group were only treated for their corresponding complications. For patients complicated with IUGR, compound amine acids were administered by intravenous drip each day; for patients complicated with PIH, blood pressure greater than 16.0/13.3 kPa, or positive urine protein, magnesium sulfate was first administered; for patients with oligohydramnios without complications, an energy mixture was administered to improve the general conditions of mother and fetus. The patients in the Danshen treatment group were treated with, besides oxygen inhalation and left recumbent position after hospitalization, 5 CDIs in 250 ml of 10 % glucose by intravenous infusion, once a day, for 7–10 days as one course of treatment. The patients complicated with IUGR were treated with Danshen and then 500 ml of compound amine acids. The blood pressures of three cases complicated with mild to moderate PIH were reduced to normal levels after administration of Danshen, and urine protein tests became negative; thus they were not treated with magnesium sulfate for spasmolysis. Five pregnant women with simple oligohydramnios were administered with one set of CDI each day. The therapeutic effects of the patients in the two groups were observed 7–10 days later. The indexes determined by B-ultrasound include the maximal area opaca of amniotic fluid and BPDs, etc. The results showed that all 4 indexes in the control group were not as good as those in the Danshen group, and the differences between the two groups were significant ($P < 0.05$). It is noteworthy that in the Danshen treatment group, the greatest increase in amniotic fluid was more than 3.2 cm, and the least was 1.2 cm, nearly two times greater than in the control group. In addition, BPDs and uterine height increase were especially significant for seven pregnant women with IUGR who were treated with Danshen and amine acids; the average increase in BPD was 0.22 cm, and the average increase in uterine height was 2.8 cm, but the average increase in BPD diameter in IUGR patients in the control group was 0.13 cm, and the average increase in uterine height was 2 cm. There were significant differences between the two groups ($P < 0.05$). The administration of CDI before amine acid treatment to correct IUGR had a better therapeutic effect than did amino acid administration alone. Besides the function of activating blood circulation and dissipating blood stasis, Danshen also has the function of calming the nerves. When applied in gynecology and obstetrics, Danshen has the function of expending fluid, reducing blood viscosity, dissolving microthrombus in the microcirculation, reducing the pressure load of the heart, increasing circulation volume, and ensuring normal osmotic pressure in the maternal plasma through the amniotic membrane. It can also relieve the afterload of the heart in patients with PIH syndrome or pregnancy complicated with hypertension, activate blood circulation, dissipate blood stasis, promote dredging of the obstructions of villous vessels caused by placental lesions, increase placental circulation volume, and regulate the dynamic balance of maternal, fetal, and amniotic fluid circulation. In addition, the drug can be combined with amine acids for fluid expansion and increasing placental circulation to ensure the maximum utilization of amine acids. To sum up, Danshen was used in the treatment of 15 pregnant women with oligohydramnios; it has the function of activating blood circulation and dissipating blood stasis, and the function of fluid expansion and spasmolysis can be realized in gynecology and obstetrics. It can be used for the treatment or remission of oligohydramnios, PIH syndrome, and IUGR.

5.10 Primary Dysmenorrhea

Shen et al. (1995) reported the treatment of primary dysmenorrhea with Danshen and Four Substances Decoction in 65 cases. Self-made Danshen and Four Substances Decoction included Danshen 15 g, Chinese Angelica (当归) 15 g, peony (川芍) l0 g, Red Peony Root (赤芍) 10 g, and prepared rhizome of rehmannia (熟地)

12 g. The drug was administered within 3–4 days before menstruation, one dose a day, and discontinued on the third day of menstruation, for 6–7 doses each month. Chinese Angelica essence was administered after menstruation, three times a day, 10 ml each time, and the decoction was administered until 3–4 days before the next menstruation, for 3 months as one course of treatment. The results showed that recovery (symptoms completely disappeared for more than 3 months after one course of treatment) was shown in 31 cases, marked effect (symptoms remission during menstrual period, only scanty slight pain, without affecting normal life and work) in 28 cases, effect (symptoms appeared during menstrual period, but the degree was significantly relieved, normal life and work could be maintained without other drugs) in four cases, and no effect in two cases. The total effective rate was 96.9 %, marked effect rate was 90.7 %.

Ji et al. [10] reported the treatment of primary dysmenorrhea with tanshinone. 273 patients with primary dysmenorrhea were selected; 203 patients were randomly assigned to the research group, and the other 70 cases were assigned to the control group. The patients in the research group were administered orally with tanshinone capsules on the fifth day of menstruation, each capsule containing 250 mg of tanshinone, 2 times a day, two capsule/time, 20 days per month, for 3 months as one course of treatment. The patients in the control group were administered orally with diethylstilbestrol tablets on the fifth day of menstruation, one time a day, 0.5 mg a time for 20 days, and medroxyprogesterone acetate (depogeston) was administered 5 days later, 10 mg a day, for 3 months as one course of treatment. The results showed that among the 203 cases in the research group, there were 162 cases cured and 25 cases improved for a total effective rate of 92.2 %, and there was no effect in 16 cases, 7.8 %. Among the 70 cases in the control group, 57 cases were cured, five cases were improved, five cases showed no effect, and the total effective rate was 93.1 %. There was no significant difference between the two groups ($P > 0.05$). Tanshinone is the ethanol extract of Danshen; it contains various components of Danshen which are collectively called tanshinone. Tanshinone has anti-inflammatory and estrogen like bioactivities, and its effect is milder than that of estradiol. It can inhibit the excessive secretion of progesterone, reduce the content of blood prostacyclin (PGF2a), thus inhibiting the constriction of uterine muscles and relieving pain, and it achieved a clinical therapeutic effective rate of 92.2 %, which is statistically the same as that of estrogen (93.1 %) ($P > 0.05$). The clinical therapeutic effects of tanshinone are reliable. The side-effects of tanshinone were scanty (2.46 %), and there was a significant difference compared with the side-effects of estrogen (87.14 %) ($P < 0.01$), which demonstrated that tanshinone has the good qualities of significant therapeutic effect and few side-effects in the treatment of primary dysmenorrhea.

5.11 Chronic Pelvic Inflammatory Disease

Li [11] reported the application of Danshen Baijiang Decoction (丹参败酱汤) in the treatment of chronic pelvic inflammatory disease in 65 cases. The main therapy was to activate blood circulation and dissipate blood stasis, which was aided by the therapy of clearing heat and draining dampness. The prescription was Danshen Baijiang Decoction: Danshen 30 g, dahurian patrinia herb (败酱草) 30 g, red peony root (赤芍) 15 g, peach seed (桃仁) 9 g, sargentgloryvine stem (红藤) 15 g, amur corktree bark (黄柏) 9 g, ma-yuen jobstears seed (薏苡仁) 30 g, nutgrass galingale rhizome (香附) 15 g, cassia bark (肉桂) 3 g, and liquorice root (甘草) 6 g. The above drugs were decocted with water and taken one dose a day, once in the morning and once in the evening. 15–20 doses were taken as one course of treatment, and usually for 2–3 courses of treatment. The results showed that among the 65 cases, 34 cases were cured, 27 cases were improved, four cases had no effect, and the total effective rate was 93.7 %. The recipe of Danshen Baijiang Decoction is the modified version of Exfetation I combined with Yiyi Fuzi Baijiang Powder (薏苡

附子败酱散). Danshen was the principal agent of the prescription, and it is recorded in *Miscellaneous Records of Famous Physicians* that "Danshen acts especially at the blood level… reach viscera and dissipate blood stasis and qi stagnation." Dahurian Patrinia Herb is bitter in taste and calm in nature, has the function of clearing heat, subsiding swelling, dissipating stagnation, and relieving pain; it is a good drug for inflammation in gynecology. The prescription has better clinical effects in anti-inflammation and relieving pain, dissipating lumps, and releasing adhesions.

Zhang et al. [12] observed the therapeutic effect of Danshen on the treatment of chronic pelvic inflammatory disease by multiple means of drug administration. 100 patients with chronic pelvic inflammatory disease were randomly divided into a multiple route administration group (TCM orally, by enema, external application of gruffs, Danshen by intravenous drip) and a single traditional Chinese drug group, with 50 cases each. The results showed that the total effective rate in the multiple route administration group was 96 %, which was significantly better than that in he single traditional Chinese drug group (84 %). Improvements in symptoms and clinical signs, pelvic cavity lump regression, and immune indexes in the multiple route administration group were significantly better than those in the single traditional Chinese drug group. It was revealed that by multiple route administration of the main drug, Danshen has the function of effectively eliminating symptoms of chronic pelvic inflammatory disease, promoting inflammatory lump absorption, improving cell immunity, and shortening treatment time.

5.12 Menopausal Syndrome

Liu [13] reported the treatment of a 50 year old patient with menopausal syndrome. The patient suffered from subjective scorching hot in the lung muscle for 3 years, which was worse during the night, like warmness, dry mouth, especially during the night, thirst, soreness and tiredness of the waist and knee, acratia, and bad sleeping. The patient had normal defecation, red tongue, white musci and thin pulse, and amenorrhea 2 years before. The symptoms of scorching hot and like warmness were from true cold with false heat syndrome. The patient was treated with three doses of modified Harmonious Yang Decoction to warm the yang to promote blood circulation. There was no change in symptoms, and scorching hot was not relieved. The prescription with the function of nourishing yin and clearing heat was then used; the main prescription was Anemarrhena, Phellodendron, and Rehmannia Decoction, and it was combined with sweet wormwood herb (青蒿) and Chinese wolfberry root-bark (地骨皮). Three doses later, no effect was obtained either. Then, 30 g of Danshen was added to the prescription. One dose later, the burning sensation was significantly relieved, the patient could fall asleep intermittently, and dry mouth was improved. Another three doses later, the burning sensation was completely relieved, the spirit improved, and sleeping improved. Another two doses were taken to strengthen the therapeutic effect. A half year follow up observed no recurrence. It was revealed that the patient had suffered from amenorrhea for 2 years, was in the menopausal period, kidney qi was deficient, kidney-essence was exhausted, and there was disharmony of the *chong* and *ren mai*. So, the treatment should be based on nourishing the heart, boosting the yin, and calming the nerves. The subjective symptoms of scorching hot in lung, worsening in nights, dry mouth and worsening in nights, soreness and tiredness of the waist and knee were caused firstly by deficiency of kidney yin, and secondly by disharmony of the *chong* and *ren mai*. The functions of Anemarrhena, Phellodendron and Rehmannia Decoction are to nourish yin and clear heat, which was not enough to relieve the symptoms, so Danshen should be used adjuvantly to realize the function of nourishing blood and calming nerves, as well as regulating *chong* and *ren mai*. Modern medicine has already found that ovarian function in females with menopause begins to degenerate, and the regulating function of the body is not used to the change. Thus, a disturbance is induced in the

hypothalamus-hypophysis-ovaries loop, affecting nerve, spirit, and metabolism functions, with the main manifestations of the disturbance in the cardiovascular and autonomic nervous systems and changes in substance metabolism. Research has also demonstrated that Six-Ingredient Rehmannia Decoction has the function of enhancing immunity and regulating the nervous system. Danshen has the function of improving microcirculation, and it affects the metabolism, immune, and nervous systems. The combination of Six-Ingredient Rehmannia Decoction with Danshen can complement each other's functions, improving the therapeutic effects.

The function of Danshen is similar to the function of Four Substances Decoction. It was believed in ancient times that the function of Danshen was similar to that of Four Substances Decoction, and furthermore, Four Substances Decoction has been a classic formula for female menstruation. From this view, it is easy to understand why Danshen has been widely used in the treatment of diseases in gynecology. According to the literatures we have collected, Danshen and its prescriptions can be used for pathological changes of the uterus, ovaries, oviduct, vagina and vulva, and good therapeutic effects on pregnancy, abortion, oligohydramnios and dysmenorrhea, mastitis, pelvic inflammatory disease, and so on have been obtained. However, the diseases treated by Danshen should belong to the category of blood stasis, otherwise there will not be any effects, and even worse, some side-effects could be induced.

References

1. Zhou G. Zhejiang J Prev Med. 1999;6:30–1.
2. Zhang Y, Zhang Y. Herald Med. 2003;3(22):174.
3. She R. Guangzhou Med J. 1998;29(4):59.
4. Chen L. Med Pharm Yunnan. 1998;3(19):198–9.
5. Zheng M. Mod Rehabil. 2000;4(1):144.
6. Wang X. J First Mil Med Univ. 2003;23(9):969–71.
7. Ye L. Mod Prev Med. 2000;27(3):384–7.
8. Hao C. J Pract Obstet Gynecol. 1998;4(144):203–4.
9. Zhang X. J Binzhou Med Univ. 1998;21(3):298.
10. Ji X, et al. J Chin Physician. 2001;6(l3):12.
11. Li X. Shandong J Tradit Chin Med. 1998;3(17):113.
12. Zhang L, et al. J Shandong Univ Tradit Chin Med. 2003;3(27):120–2.
13. Liu D. J Shanxi Coll Tradit Chin Med. 2001;3(2):36–7.

Application in Ophthalmology and Otorhinolaryngology

6

Yi Zheng, Xuewen Zhang and Jiaoli Guo

6.1 Ophthalmology Diseases

The application of Danshen and its preparations in ophthalmology is mainly in the treatment of blood syndrome, stagnation, and ocular fundus diseases. It has the function of activating blood circulation, dredging collaterals, eliminating inflammation, improving microcirculation, increasing hypoxia tolerance of retina blood vessels and optic nerve fibers, promoting absorption of lesions, and regulating tissue repair and regeneration. In recent years, it has been revealed by research on the mechanism and clinical application that it has unique therapeutic effects on ophthalmology diseases, especially ocular fundus diseases. It has good effects on treatment of the retina, vein occlusion, subhyaloid hemorrhage, optic neuropathy, and macula lutea, etc.

6.1.1 Retinal Hemorrhage

Compound Danshen Injection can act on various blood coagulation factors and has the function of activating the fibrinolytic enzyme system and promoting fibrinolysis and the absorption of retinal hemorrhage, edema, and exudation. It also has the function of promoting microcirculatory blood flow rate, improving ischemia anoxia conditions, dilating retinal blood capillaries, ensuring blood and oxygen supply to the entoretina, and recovering the physiologic function of the retina. The drug also has the function of promoting the absorption of proliferative lesions, promoting clot dissolution and absorption of vitreous body hematocele, and avoiding retinal detachment induced by vitreous organization.

Danshen can be combined with other traditional Chinese decoctions, and it is an effective method for the treatment of retinal hemorrhage. Linzhen [1] reported that Yang-Supplementing and Five-Returning Decoction was combined with Danshen, Chinese angelica (北当归尾), safflower (红花), red peony root (赤芍), szechwan lovage rhizome (川芎), etc., and used in the treatment of retinal hemorrhage due to arteriosclerosis in 35 cases; Hongjian [2] reported that Four Substances Decoction was combined with Danshen, safflower (红花), peach seed (桃仁), etc., and used in the treatment of highly myopic macular hemorrhage; Songhua [3] reported the application of Danshen, red peony root (赤芍), rehmannia dride rhizome (生地), peach seed (桃仁), safflower (红花), submature bitter orange (枳壳), seaweed (海藻), etc. in the treatment of old vitreous body hematocele in 34 cases and satisfactory therapeutic effects were obtained.

Yuandong [4] and Xiaorong [5] reported the treatment of retinal hemorrhage in 18 and 24 cases, respectively, with CDI in 500 ml of 5 % glucose (or dextran), plus inosine and vitamin etc. The results showed that the total effective rate in Qiu's

Y. Zheng (✉) · X. Zhang · J. Guo
Shengli Hospital of Shengli Petroleum Authority, Shandong, China
e-mail: zhengyiphd@yahoo.com.cn

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group was 100 %, and the rate of marked effect was 88.2 %. Among the 24 cases treated by Qi, 16 cases were cured, 6 cases showed marked effect, and 2 cases showed effect. No patient suffered from hemorrhage in the treatment period, and no recurrence was observed by follow up from 3 months to 3 years. Yongqiang [6] reported the application of CDI on the treatment of 23 patients with hyphema. 14–16 ml CDI in 500 ml of 5 % glucose was administered by intravenous drip, once a day; Compound Danshen Tablet was administered orally after hemorrhage absorption, and the therapeutic effect was significant, compared to the control group ($P < 0.05$). Weier [7] reported the treatment of vitreous body hematocele in 22 cases with CDI combined with urokinase by intravenous drip. The results showed that marked effect (hematocele absorption, fundus clear, vision >5 line) was shown in 15 eyes, effect in four eyes, and no effect in three eyes. Li Ruizhen reported the treatment of traumatic hemorrhage with Danshen Injection by intravenous drip in 32 cases. The results showed 59.3 % of the cases were cured, 28 % showed marked effect, 6.2 % showed improvement, 6.2 % showed no effect, and significant therapeutic effects were obtained.

Luping [8] investigated the clinical therapeutic implications of iontophoresis of Danshen by direct current in patients with retinal vitreous hemorrhage. 103 cases were treated with and without Danshen iontophoresis, and he improved conditions of visual function and eye ground of the patients after treatment were evaluated and analyzed. The results showed that the enhanced effective power of vision in the treatment group was 86 %, and there was a significant difference compared with control group ($P < 0.05$). It was revealed that Danshen had satisfactory therapeutic effects on improving symptoms, promoting hematocele absorption, and enhancing vision.

6.1.2 Retinal Arterial and Vein Obstruction

Yiqin [9] observed the effect of Dantonic™ on treatment of central retinal vein obstruction. 83 patients were randomly divided into an observation group (52 cases) and control group (31 cases). The patients in the observation group were administered with Dantonic™, 15 pills each time, three times a day. The shortest length of drug administration was 30 days and the longest was 1 year. 5,000–10,000 U of urokinase in 500 ml of 5 % glucose was administered by intravenous drip to the patients in the control group, once a day. The total effective rate in the observation group was 90.39 %, and in the control group was 78.13 %, but there was no significant difference between the two groups ($P > 0.05$). However, there were 31 cases (59.6 %) with marked effect in the observation group, and only 11 cases (34.38 %) with marked effect in the control group, and the difference between the two groups was significant ($P < 0.05$). The examination results of eye ground after treatment showed that there was no significant difference in the average time of edema regression and the recovery of retinal hemorrhage induced by branch occlusion in the two groups ($P > 0.05$); but the average recovery period for retinal hemorrhage induced by general obstruction in the observation group was 33 ± 18.6 days, compared to 48 ± 10.9 days in the control group, and the difference between the two groups was significant ($P < 0.05$). The vision of the patients with central retinal vein obstruction rapidly improved in the observation group, venous engorgement of the eye ground was relieved, and absorption of subhyaloid hemorrhage was regressed, and especially the treatment period for patients with general obstruction was shortened. A marked effect can be rapidly obtained, and adverse reaction was scanty. The drug was easy to take so that the patient can adhere to the treatment. Long-term use of Dantonic™ can reduce blood viscosity, clean oxygen radicals, reduce lipid peroxides, improve microcirculation, regulate capillary permeability, reduce tissue edema, promote edema regression and promote hemorrhage absorption, and enhance vision, thus the therapeutic effect is satisfactory.

6.1.3 Glaucoma

Wu Zhenzhong (1994) reported 121 cases (153 eyes) of middle stage or late stage glaucoma, treated first with miotic agents or anti-glaucoma operation to control intraocular pressure within a normal range, then Danshen preparations (3 compound Danshen, one simple Danshen) were administered by intramuscular injection. After the treatment with four preparations, 43.7 % of eyes had increased vision, and 87.5 % of visual field maintain was not changed or slightly increased. There was no statistical difference in the therapeutic effect among the four Danshen preparations, but the therapeutic effects were better than those in the control group. The long-term efficacy of 19 eyes was followed up with, and therapeutic effects were preserved in 14 eyes.

6.1.4 Optic Neuropathy

Daian [10] reported the treatment of acute ischemic optic neuropathy in 27 cases (38 eyes) with CDI by intravenous injection and retrobulbar injection. Marked effects were obtained, with a recovery rate of 81.58 %, and there was a significant difference in visual field chi-square tests after treatment ($P < 0.01$), as well as a significant difference in wall-retina circulation time before and after treatment ($P < 0.05$). It was revealed that Danshen Injection was an ideal drug for the treatment of the disease.

6.1.5 Central Serous Chorioretinopathy

Yun [11] administered 18–20 ml of CDI in 500 ml of 5 % glucose by intravenous drip to 30 patients (30 eyes) once a day for 10 days as one course of treatment, with a 3-day interval between courses. The 28 cases in the control group (28 eyes) were treated with bandazol, vitamin B_1, vitamin C, troxerutin (venoruton), corticosteroids, prolonium iodide (Entodon), etc. Besides CDI, the other drugs in the control group were administered to the patients in the treatment group. The results showed that the treatment group had 23 cured eyes, six improved eyes, and one noneffective case, with a total effective rate of 96.7 %. The control group had 15 cured cases, six improved cases, and seven noneffective cases, and the effective rate was 75 %.

Xing [12] reported the treatment of 19 cases (20 eyes) with Danshen Injection combined with cerebrolysin. The results showed a total effective rate of 94.74 %, (marked effect 12 cases, effect six cases, no effect one case).

6.1.6 Diabetic Retinopathy

Naixin [13] investigated the therapeutic effects of the combination of Dantonic™ with Lycium Berry, Chrysanthemum and Rehmannia Pill (LBCRP) on the treatment of diabetic retinopathy. 32 patients with simple diabetic retinopathy were randomly divided into two groups. The patients in one group were administered with Dantonic™, three times a day, 10 pills each time; the patients in the other group were administered with LBCRP, three times a day, 10 pills each time. One course of treatment lasted 2 weeks. The results showed that the effective rate in the Dantonic™ group was 87.5 %, and the effective rate in LBCRP group was 56.2 %. For the treatment of diabetic retinopathy, the drug with the function of activating blood circulation and dissipating blood stasis (Dantonic™) was better than that for nourishing the liver to improve visual acuity (LBCRP).

6.1.7 Corneal Injury

Xin [14] studied the effect of CDI on neovascularization after corneal injury. Large doses of CDI were administered to the corneal alkali burn model in rabbit for a long period. The results showed that there was a significant difference in therapeutic effect ($P < 0.05$); the pannus area in the treatment group was significantly smaller than that in the control group, and histological examination showed that the density and degree of the

differentiation of corneal neovascularization were also decreased. The conclusion was that CDI has the function of inhibiting neovascularization after corneal injury, and does not affect the healing of injured cornea.

6.1.8 Dacryocystisis

Qingshan [15] reported the treatment of dacryocystisis in 46 cases by washing the lacrimal duct with Danshen Injection and Ligustrazine Injection; the total effective rate was 91.3 %, and the therapeutic effect was significantly better than that when treated with gentamicin and chloramphenicol eyedrops.

6.1.9 Acute Retinal Necrosis

Currently, this disease has a low cure rate and poor prognosis. Jiacheng [16] reported the application of Danshen Injection and hormones by intravenous drip in the treatment of the disease in three cases. Before treatment, the vision of two patients was 0.1 and 0.05, respectively. After treatment with Danshen Injection combined with hormones, the vision was 0.5 (2 eyes) and 1.5 (2 eyes), respectively. It was revealed that the injection has a significant therapeutic effect on the disease.

6.1.10 Traumatic Vitreous Opacities

Wu Defen (1994) reported that 20–40 ml of Danshen Injection in physiological saline or 500 ml of 5–10 % glucose was administered to 61 patients with Traumatic vitreous opacities by intravenous drip for 7–14 days. The results showed, under a slit lamp, that the eye ground changed from occultation to obfuscation in four cases, from obfuscation to clearness in three cases, and from occultation to clearness in eight cases.

Danshen is a valuable heritage in the medical treasure trove of China; it has wide applications and scanty side-effects, and good therapeutic effects can be achieved by simple or combined application. Meanwhile, the drug can be made into a variety of preparations. CDI in current clinical use consists of Danshen and Rosewood Heart Wood (绛香); the latter has the function of regulating vital energy and eliminating stagnation, and it can help Danshen to realize pharmacologic actions. Danshen has obvious effects on eye diseases, and thus we expect it will have a wider range of applications.

6.2 Otorhinolaryngology Diseases

6.2.1 Chronic Rhinitis

Aimin [17] reported that 2 ml of CDI and 2 ml of sodium chloride injection mixture was administered to 38 patients with chronic simple rhinitis by nasal dropping for two weeks, three times a day, and two drops on each side of the nostrils. 1 % ephedrine was administered to 37 cases in the control group by nasal dropping. The results showed that the total effective rate in the treatment group was 92.11, 78.38 % in the control group, and the difference was significant ($P < 0.05$). It was revealed that Danshen has the function of activating blood circulation, dissipating blood stasis, increasing blood circulation, enhancing the anti-inflammatory ability of the nasal cavity, and accelerating the recovery of lesions, thus improving the symptoms of nasal obstruction.

Han [18] reported the treatment of 410 cases of various types of chronic rhinitis with CDI by double inferior turbinate injection, and the therapeutic effects were analyzed by disease typing. The results showed that the treatment has a satisfactory therapeutic effect on rhinitis sicca, Allergic Rhinitis and chronic simple rhinitis, and the total effective rates were 97.35, 88.52, 80.12 %, respectively. The therapeutic effects on chronic hypertrophic rhinitis and atrophic rhinitis were so–so.

6.2.2 Allergic Rhinitis

Jiang Limei et al. (1995) reported the application of CDI in the treatment of 60 cases of Allergic

Rhinitis by double inferior turbinate mucosa injection, 1 ml each side, 1–2 times each week, 5–7 times as one course of treatment. The results showed that 12 cases were cured, 34 cases showed marked effect, eight cases improved, six cases showed no effect, and the total effective rate was 90 %.

6.2.3 Sudden Deafness

Guosong [19] reported the application of CDI in the treatment of 50 cases of sudden deafness. 20 ml of CDI in 500 ml of 10 % GS was administered by intravenous drip to the patients in the treatment group, once a day, for 7 days as one course of treatment. Based on the disease conditions, some patients were treated for one more course. One course of treatment later, pure tone audiometry was reviewed. 10 mg of dexamethasone in 500 ml of 5 % GS was administered by intravenous drip to the patients in the control group, once a day, and 3 days later the dosage was reduced gradually, with one course of treatment lasting 7 days. At the end of treatment, pure tone audiometry was reviewed. Adenosine triphosphate, vitamin B1 and B12 were used as adjuvant drugs for patients in both groups. Patients with basis disease were treated accordingly. The total effective rate in the treatment group was 72 % and in the control group was 52 %; the difference was significant ($P < 0.05$). The effective rate was 83.33 % for the patients in the treatment group whose disease course was less than 7 days, and the corresponding number in the control group was 58.82 %. There were no cured or marked effective cases in either group for patients whose disease course was longer than 7 days. For patients with disease course less than 7 days, the cure rate in the treatment group was 38.89 %, and effective rate was 83.33 %; the cure rate in the control group was 17.65 %, and the effective rate was 58.82 %. The treatment group was better than the control group. The main components in CDI are tanshinol, theophylline, protocatechuic acid, and a small amount of tanshinone; tanshinol has the function of dilating vessels, enhancing microcirculation perfusion, improving microcirculatory disturbance, regulating blood consistency, and promoting the repair of nervous system disturbance, thus relieving symptoms of tinnitus, deafness, and dizziness. CDI has the function of inhibiting platelet aggregation and anticoagulation, calming the central nervous system, recovering damaged nerve cells, and correcting the repair of internal ear nerve tissue caused by ischemia, anoxia, and inflammation, thus increasing the compliance and coordinating the relaxation and constriction of blood vessels, promoting hearing recovery from sudden deafness.

6.3 Stomatology Diseases

6.3.1 Recurrent Aphtha

YU Zidong (1995) reported the application of Compound Danshen in the treatment of 30 cases of recurrent mouth ulcer by *injectio ad acumen*. The acupoints Hegu (LI 4), Laogong (PC 8), Qianzheng (牵正), and Chengjiang (RN 24) were injected with 0.1–0.3 ml of CDI, each acupoint in turn, one acupoint each time, one injection every 3 days. When the injection needle was injected into the acupoint, patients undergo a subjective sour feeling and apathetic feeling, and the needle was repeatedly twirled to enhance the needle sensation. The operation was maintained for 1–2 min, and then CDI was administered. Thirty-nine cases were treated and nine cases were lost; the shortest observed time was 1 year, the longest was 4 years; there were marked effects in five cases, remission in 24 cases, and no effect in one case.

Weihong [20] reported the application of integrated medicine in the treatment of recurrent aphtha in 64 cases. The patients in the treatment group received conventional therapy plus 30 ml of Danshen Injection in 500 ml of 5 % glucose sodium chloride injection, which was administered by intravenous drip once a day; Gynostemma Total Glycosides Capsules were taken orally, 0.8 g each time, three times a day,

for 14 days as one course of treatment. The patients in the control group were treated with conventional therapeutic methods (compound vitamin B and zinc gluconate tablets taken orally and gentamicin sensitive layer by local application). The clinical therapeutic effects in both the treatment group (64 cases) and control group (62 cases) were observed. The results showed that the total effective rate in the treatment group was 84.38 %, in the control group was 56.45 %, and there was a significant difference between the two groups. It was revealed that the method of integrated medicine has the function of improving local blood circulation, eliminating inflammation, rapidly relieving pain, and promoting ulcer surface healing for patients with recurrent mouth ulcers. Danshen and Fiveleaf Gynostemma Herb or Root (绞股蓝) extract significantly inhibit platelet aggregation and thromboxane A_2 release, and improve microcirculation both in vivo and in vitro. The therapy of activating blood circulation and dissipating blood stasis combined with western medicine conventional therapy has the function of significantly promoting ulcer healing, and is an effective method for treating recurrent aphtha.

6.3.2 Atrophic Pharyngitis

Wang Qi (1990) reported the treatment of atrophic pharyngitis with Danshen by ultrasonic atomizing inhalation in 85 cases, in which there were 65 primary cases, 18 cases of secondary atrophic otitis and naso sinusitis, and two cases of secondary dry pharyngeal portion after cancer of nasopharynx radiotherapy and atrophy of mucous membrane. 8 ml of Danshen Injection was stored in a Type 402 Ultrasonic Atomizing Inhalation Apparatus, and the drug was inhaled for a half hour each time, two times a day, for 4 weeks as one course of treatment. The results showed that clinical symptoms in 60 cases disappeared; the mucous membrane of the pharyngeal portion thickened and bloomed, normal folliculus lymphaticus was observed, and touch sensation of the pharynx was good; 81 % were cured, 10 cases (12 %) improved, and 6 cases (7 %) showed no effect. The shortest course of treatment was 3 weeks, and the longest was a half year. The results showed that satisfactory therapeutic effects on the treatment of atrophic pharyngitis were obtained by ultrasonic atomizing inhalation of Danshen.

6.3.3 Abnormal Sensation of Throat

Wu Qiang (1995) used 1 % teracainum solution to anesthetize the pharyngeal mucous membrane, and used 2 % merbromine solution to smear the posterior pharyngeal mucosa. 2 ml of CDI was used in the treatment group; a No. 5 needle and 5 ml syringe were used for drawing, and 1 ml was injected into the pharyngeal mucous membrane to produce hummocky swelling. The patients in the control group were injected with 1 ml of physiological saline with the same method, once every 4 days, four times as one course of treatment, and two courses of treatment was performed in both groups. The results showed that the effective rate in the treatment group was 87.88 % and in the control group was 54.55 % ($P < 0.01$). It was revealed that Danshen has the function of dilating microvascular caliber, reducing blood viscosity, and improving the blood rheology. The effect of the drug can be enhanced by local application.

6.3.4 Epidemic Parotitis

Tieshan [21] reported the application of CDI combined with dipyridamole in the treatment of epidemic parotitis in 100 cases. 4 ml of CDI was administered by intramuscular injection, 1–2 times each day. Dipyridamole was administered orally; the dosage for children was 5 mg/(kg d), and for adults was 25–50 mg/time, 2–3 times a day, with one course of treatment lasting 5 days. The results showed that the therapeutic effect was significantly better than that in the control group, which received treatment with indigowoad root (板蓝根) and moroxydine.

References

1. Linzhen W. Hubei J Tradit Chin Med. 1995;17:16.
2. Hongjian Z. J Tradit Chin Ophthalmol. 1996;6:16.
3. Songhua C. Jiangsu J Tradit Chin Med. 1995;16:27.
4. Yuandong Q. J Integr Tradit Chin West Med Ophthalmol. 1994;12:35.
5. Xiaorong Q. Jilin J Tradit Chin Med. 1994;6:24.
6. Yongqiang L, Yalin Ji. J Tradit Chin Ophthalmol. 1996;6:4.
7. Weier J. J Fujian Coll Tradit Chin Med. 1996;6:8.
8. Luping G, et al. Chin J Optom Ophthalmol. 2003;1 (5):41–2.
9. Yiqin G. Tianjin Pharm. 2001;12(13):54.
10. Daian Z, Wenqiang W. J Tradit Chin Ophthalmol. 1995;5:819.
11. Yun L, Naipeng F. J Tradit Chin Ophthalmol. 1994;4:249.
12. Xing Z. Integr Tradit Chin West Med Ophthalmol J. 1995;13:139.
13. Naixin Q. Strait. Pharm J. 2003;2:67–8.
14. Xin M, Jing W. J Tradit Chin Ophthalmol. 1995;5:11.
15. Qingshan H. J Integr Tradit West Med Ophthalmol. 1994;12:97.
16. Jiacheng L. J Tradit Chin Ophthalmol. 1994; 4:13.
17. Aimin N. J Integr Tradit Chin West Med. 1994;14 (7):439.
18. Han L, Dong Liu. Railway Med J. 1997;25 (4):247.
19. Guosong J, Yezhong Q. Chin Arch Tradit Chin Med. 2001;06:595.
20. Weihong Y. J Nanjing Univ Tradit Chin Med (Nat Sci). 2005;05:323.
21. Tieshan S. Pract J Integr Tradit Chin West Med. 1994;7(4):219–20.

Application in Other Diseases

7

Yi Zheng, Xuewen Zhang and Jiaoli Guo

7.1 Malignant Tumor

7.1.1 Lung Cancer

Luo [1] observed the treatment of malignant pleural effusion with Danshen Injection combined with cisplatin in 34 cases. Conventional pleural aspiration was performed; 800 ml of pleural fluid was aspirated at first, thereafter around 1,200 ml each time. After aspiration, 30 ml of Danshen Injection and 60–100 mg of cisplatin were injected, once each week. After 3 consecutive times, if bone marrow was significantly inhibited, Danshen Injection was administered alone. The combination treatment was performed again after the hemogram returned to normal. All patients were treated 3 times or more. Complete remission (hydrothorax complete regression, maintained for more than 1 month) occurred in 11 cases, partial remission (hydrothorax reduced by more than half, maintained for more than 1 month) in 20 cases, no effect (hydrothorax reduced by less than half) in 2 cases, progression (hydrothorax increased) in 1 case, and the total effective rate was 91.2 %. The main chemical constituent of Danshen is tanshinone, which has the function of inducing the differentiation of tumor cells in vitro. It has been reported that the treatment of late stage non-small-cell lung carcinoma with CDI combined with 654-2 during chemotherapy had an effective rate of 37 %. Local application of Danshen Injection in the thoracic cavity has the function of inhibiting platelet aggregation, reducing blood viscosity, improving microcirculation, and reducing the permeability of blood capillaries, thus promoting the absorption of liquid. Danshen can enhance immunologic function, and some researchers believe that Danshen has a sensitizing effect on cancer patients with chemotherapy.

7.1.2 Leukemia

Zhu Haihong (1996) reported the treatment of leukemia with CDI. 20–26 ml of CDI in 500 ml of 5 % glucose was administered by intravenous drip to 9 patients with recurrent refractory leukemia one day before chemotherapy, and was continued until the end of chemotherapy, with one course of treatment lasting 7–10 days. The effective rate was 88.8 %. The reasons for the relapse of acute leukemia and the ineffectiveness of chemotherapy are mainly due to the existence of a large number of drug-resistant leukemia cells in the blood. CDI has the function of improving immature cells in the stagnant state, reducing the resistance of leukemia cells to chemotherapy drugs, and enhancing the therapeutic effect.

Y. Zheng (✉) · X. Zhang · J. Guo
Shengli Hospital of Shengli Petroleum Authority, Shengli, Shandong, China
e-mail: zhengyiphd@yahoo.com.cn

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7.1.3 Liver Cancer

Based on experimental data, Yuan [2] believed that tanshinone inhibits the growth and induces the differentiation of liver cancer cells by regulating the expression of cellular proto-oncogene SMMG7712, thus suppressing cells from entering S phase. It has been demonstrated by research that the combination of Danshen and chemotherapy drugs can increase blood flow in tumors and improve the anaerobic glycolysis of tumor cells, which is conducive to the penetration of chemotherapy drugs, and increase the sensitivity of liver cancer cells to chemotherapy drugs.

Zhang and Wang [3] reported that hepatic arterial infusion and postoperative intravenous drip of Danshen Injection were used in combination with anticancer agent intervention. The results showed that the remission rate in Danshen group was 85 % (17/20), and the remission rate in the western medicine group was only 45 % (9/20), and the difference between the two groups was significant. In addition, the toxicity and side effects of the Danshen group were significantly lower than those of the control group.

Xue [4] reported that 16 ml of Danshen in glucose was administered by intravenous drip to patients with late-stage liver cancer in 23 cases, once a day for 1–2 weeks as one course of treatment. The results showed that 1 week after administration, pain in 6 cases was significantly relieved and analgesics could be discontinued; 2 weeks after administration, pain in 12 cases was relieved and narcotic analgesics could be discontinued; the total effective rate was 78.3 %. Danshen has the function of improving liver microcirculation and clearing the tumor thrombus obstructions of the hepatic vessels, so as to reduce the tension of the liver capsule and relieve pain.

7.1.4 Renal Damage After Gynecological Chemotherapy

Guo and Wang [5] investigated the effects of Mongolian Milkvetch Root (黄芪) and Danshen injections on acute kidney insufficiency induced by gynecological chemotherapy. Both Mongolian Milkvetch Root and Danshen injections are TCM injections, which could induce some adverse reactions with various manifestations, such as sinus tachycardia, digestive system symptoms (nausea, vomiting, etc.), headache, and dyspnea, and severe cases could suffer from larynx edema and even anaphylactic shock, etc. The symptoms of such adverse reactions should be closely monitored in a clinical setting, especially at the beginning of infusion. The speed should be slower than 20 drops/min, adjusting to higher speeds only if no adverse reactions are observed, and the speed should be controlled under 60 drops/min. Adverse reactions can be reduced or relieved when the infusion speed is effectively controlled. Although it has been demonstrated by the above research that Mongolian Milkvetch Root and Danshen injections have marked effects on acute renal injury caused by gynecological chemotherapy, patients who meet the hemodialysis indications should be treated with dialysis as soon as possible.

7.1.5 Gastric Cancer After Operation

Yu et al. [6] reported that 30 ml of Danshen in glucose solution was administered by intravenous drip to patients with early intraperitoneal chemotherapy after gastric cancer operation. The results showed that the side effects were significantly lower than those in the control group with chemotherapy alone. The mechanism might be that Danshen has the function of controlling the effusion of the peritoneal cavity and the formation of adhesions, and promoting wound healing. It was also revealed by research that Danshen can significantly inhibit DNA synthesis in tumor cells and directly kill tumor cells, thus preventing and treating tumor metastasis and recurrence.

7.1.6 Pancreatic Cancer

Chen et al. [7] reported 81 cases with advanced pancreatic cancer, randomly divided into two

groups: group A (41 cases) was treated with gemcitabine hydrochloride and cisplatin combined chemotherapy (GP regimen), as well as Dantonic™; group B (40 cases) was treated with chemotherapy (GP regimen) alone. The therapeutic effect, quality of life, and adverse reactions were evaluated. The effective rates (complete remission + partial remission) in groups A and B were 46.3 and 35.0 % ($P > 0.05$), respectively; the clinical benefit rates (CR + PR + Stable Disease) in Groups A and B were 73.2 and 50.0 % ($P < 0.05$), respectively. T lymphocyte subpopulations CD4/CD8 ratios were significantly enhanced in group A after treatment ($P < 0.01$), but the CD4/CD8 ratio was significantly reduced in group B after treatment ($P < 0.01$); the quality of life in group A was higher than that in group B ($P < 0.05$), and nausea and vomiting and leukopenia in group B were higher than in group A ($P < 0.05$). The treatment of pancreatic cancer with Dantonic™ and chemotherapy has the function of enhancing the clinical benefit rate of the treatment, improving quality of life, and decreasing the side effects of chemotherapy.

7.1.7 Esophageal Cancer and Cardia After Radical Operation

Yao et al. [8] reported the use of Danshen treatment in radical operations of esophageal cancer and cardia. Nail fold microcirculation and blood rheology were observed 2 weeks after the operation. The results showed that there were significant changes in visual field articulation, effusion, and hemorrhage of nail fold microcirculation between the Danshen group and control group after operation; the lack of hemorrhage manifestation was the most significant. The main manifestation of blood rheology was that the whole blood viscosity was not significantly increased after operation, which demonstrated that Danshen has the function of improving microcirculatory disturbance after operation and relieving or inhibiting blood viscosity increases after operation. Surgical hemorrhage was not increased, and tumor transfer was not observed by the application of Danshen. Therefore, it was beneficial and safe to use Danshen with the operation.

7.1.8 Malignant Lymphoma

Zhang et al. [9] observed the effect of Danshen on high blood plasma fibrinogen in patients with malignant lymphoma. 35 patients with malignant lymphoma were divided into groups. The results showed that cyclophosphamide (COP) treatment was enhanced by Danshen. The results of blood plasma fibrinogen (fig) determination showed that there was a significant difference between the malignant lymphoma group and normal control group. Blood plasma fig was reduced after COP treatment, but the difference was not significant. Blood plasma fig of Danshen-COP treatment group was significantly reduced after treatment, and the content of blood plasma fig was negatively correlated with therapeutic effect. It was revealed that the antitumor activity of the chemotherapy drug was enhanced by Danshen in the Danshen-COP treatment group; the synergistic effect was related to reduced high blood plasma fibrinogen, and this relationship can be related to the fibrinolytic function of Danshen.

7.1.9 Nasopharyngeal Carcinoma

Huang et al. [10] observed the clinical therapeutic effects of Shanghuanglian Powder for Injection (SPFI) combined with CDI on the treatment of nasopharyngeal carcinoma. 56 patients were randomly divided into 2 groups; 31 cases in the treatment group were administered with SPFI combined with CDI, and 25 cases in the control group were administered with CDI alone. The clinical therapeutic effects of pain relief and quality of life were observed. The results showed that the total remission rate in the treatment group was 87.1 %, while the total remission rate in the control group was 64 %; the difference between the two groups was very significant ($P < 0.01$). Changes in the quality of life: the improvement rate in the treatment group

was 58 %, and in the control group was 36 %, and the difference between the two groups was significant ($P < 0.01$). The onset times of pain relief in both the treatment and control groups were 0.82 ± 0.4 h and 1.12 ± 0.6 h, respectively; the cure times were 10.82 ± 3.47 days and 14.28 ± 3.12 days, respectively. There was a significant difference between the two groups ($P < 0.01$). It was believed that SPFI clears heat and resolves toxins, and has antiviral and anti-inflammatory function, significantly enhancing the immunologic function of the host and killing pathogens; CDI activates blood circulation, dissipates blood stasis, dredges collaterals, relieves pain, improves the blood rheology, and regulates blood viscosity. The combination of the two drugs has anti-inflammatory and analgesic effects, and can be used to treat the disease from both its root cause and its symptoms.

The pain caused by tumors is complicated, but their common feature is pain and lump, which is also the clinical manifestation of the disease. According to the theory of traditional Chinese medicine, the occurrence of pain and lump is closely related to qi stagnation, blood stasis, and phlegm coagulation. It is generally believed that the occurrence of stagnant blood is one of the foundations of tumor pathogenesis. Danshen has the function of activating blood circulation, dissipating blood stasis, and detoxication, thus satisfactory therapeutic effects for benign and malignant tumors can be obtained.

7.2 Poisoning

Yuan et al. [11] observed the therapeutic effect of CDI and Naloxone Hydrochloride on rescuing acute severe diazepam poisoning. 70 patients with acute severe diazepam poisoning were randomly divided into 2 groups. 34 patients in the control group were treated with traditional methods, and 36 patients in the treatment group were treated with CDI and Naloxone Hydrochloride in addition to the traditional treatment. The time to recover consciousness and the subjective symptom improvement and disappearance times were observed. The results showed that the onset time, marked effect time, and recovery time in the treatment group were 0.84 ± 0.52 h, 6.58 ± 3.21 h, and 18.64 ± 7.15 h, respectively, which were significantly shorter than those of the control group, which were 72.35 ± 7.83 min, 110.86 ± 11.17 min, and 231.51 ± 16.25 min, respectively ($P < 0.01$). It was revealed that the course of the disease can be shortened and therapeutic effects can be enhanced in the treatment of acute severe diazepam poisoning by applying CDI and Naloxone Hydrochloride together.

Yuan et al. [11] observed the therapeutic effect of CDI and Naloxone Hydrochloride on rescuing acute severe alcohol alcohol poisoning. 89 patients with acute severe alcohol poisoning were randomly divided into 2 groups. 39 patients in the control group were treated with traditional methods, and 50 patients in the treatment group were treated with CDI and Naloxone Hydrochloride in addition to the traditional treatment. The time to recover consciousness and the subjective symptom improvement and disappearance times were observed. The results showed that the onset time, marked effect time, and recovery time in the treatment group were 30.46 ± 5.62 min, 55.85 ± 8.14 min, and 140.28 ± 12.63 min, respectively, which were significantly shorter than those of the control group, which were 72.35 ± 7.83 min, 110.86 ± 11.17 min, and 231.51 ± 16.25 min, respectively ($P < 0.01$). It was revealed that the course of the disease can be shortened and the therapeutic effect can be enhanced in the treatment of acute severe alcohol poisoning by the combined application of CDI and Naloxone Hydrochloride.

7.3 Infectious Diseases

7.3.1 Epidemic Hemorrhagic Fever

Li [12] treated 224 patients with epidemic hemorrhagic fever in the early period with furosemide and Danshen to prevent the occurrence and development of the oliguria stage, in an attempt to find a way to shorten the disease course of

oliguria and find a better treatment. On the basis of the comprehensive treatment, patients with late phase fever in the treatment group were administered with furosemide and Danshen, and the drugs could be administered repeatedly until the diuresis stage. The patients in the control group were treated when oliguria tendency appeared. The majority of the patients in the treatment group directly entered the diuresis stage, and the combination of the two drugs had the function of preventing serious complications of oliguria at the migration stage. Furosemide has the function of dilating general small blood vessels and improving the hemodynamics of renal blood vessels, increasing antidiuretic hormones and urinary production. Danshen has the function of relieving kidney vessel spasm, preventing blood cell aggregation in renal tubules, improving the blood rheology of renal microcirculation, and increasing urinary production. The combination of two drugs can enhance the recovery rate and reduce the fatality rate.

7.3.2 Schistosomiasis

He [13] reported the application of Danshen combined with Thymopeptides in the treatment of 20 patients with late-stage blood fluke infection. 400 mg of Danshen Powder Injection and 40 mg of Thymopeptides Powder Injection were dissolved in 250 ml of 5 % glucose separately and administered by intravenous drip for 14 days. Based on the disease conditions, diuretics and other hepatoprotective drugs were administered. 1 month after treatment, liver function was reviewed and B-ultrasound examination was performed. 10 cases showed marked effect, which included significant improvement of clinical symptoms and signs, basically normal liver function, no ascites rebound after subsidence within 1 month, and recovery of basic physical working capacity. Among the 10 cases, 4 cases had a shrunken spleen, and 4 cases had ascites regression. 6 cases showed effect, which meant that the clinical symptoms and signs and liver functions were improved, and ascites was reduced but not eliminated completely. 4 cases showed no effect. It was revealed that Danshen Injection has the function of improving the blood circulation of the liver and increasing hepatic blood flow, thus improving congestive splenomegaly and reducing or eliminating ascites. Danshen also has significant antihepatic fibrosis and immunologic enhancing functions. All 20 patients who received treatment were elderly with general declines in resistance and immunity. The combination of Danshen and Thymopeptides injection has the function of improving clinical symptoms and signs and enhancing immunologic function, with few adverse reactions, definite short-term therapeutic effect, and is worthy of clinical application.

7.3.3 Pulmonary Tuberculosis

Li et al. [14] reported that in addition to the normal antituberculosis treatment, 10–16 ml of CDI in 500 ml of solution was administered by intravenous drip to patients with tuberculosis, once a day, for 3 months as one course of treatment. After one course of treatment, the patients were administered orally with Danshen Tablet, 3–5 tablets/time, three times a day, for 3 months as one course of treatment. 56 cases with pulmonary tuberculoma and bulk caseous focus were treated; the total effective rate was 94.4 %, which was significantly better than the 76.5 % of the simple antituberculosis treatment group ($P < 0.05$). The mechanism might be the drug's function of activating blood circulation and dissipating blood stasis and improving blood supply to the lesions, which leads to an increase in the concentration of anti-TB drugs, so that *Mycobacterium tuberculosis* could be more efficiently killed, promoting the liquefaction and absorption of caseous focus and thus achieving clinical effectiveness.

7.3.4 Tuberculous Exudative Pleurisy

Xu et al. [15] observed the therapeutic effects of compound Danshen on tuberculous pleuritis. 60 cases with tuberculous pleuritis were randomly divided into a therapeutic group (30 cases) and

control group (30 cases). Both groups were treated with isoniazid (H) 0.4 g/day, rifampicin (R) 0.45 g/day, pyrazinamide (Z) 1.5 g/day, streptomycin (S) 0.75 g/day, plus thoracentesis. The patients in the therapeutic group received an additional intravenous drip of Compound Danshen. The results showed that at the end of the treatment, absorption of pleural effusion in the therapeutic group was significantly promoted, and the course of disease was shortened. It was revealed that Compound Danshen by intravenous drip can significantly prevent the occurrence of pachynsis pleurae adhesions. There was a significant difference between the two groups ($P < 0.05$).

7.3.5 Tuberculous Exudative Peritonitis

Shi et al. [16] reported the treatment of patients with the conventional method combined with Danshen. 52 cases in the treatment group and 48 cases in control group were treated with conventional therapy, and 30 ml of Danshen Injection in glucose solution was administered by intravenous drip to the patients in the treatment group, once a day for 3 months; adrenal cortex hormone was administered to the patients in the control group. The results showed that the total effective rates were 94.2 and 81.3 %, respectively ($P < 0.01$); the median times of ascites absorption was 33.4 days and 63.9 days, respectively ($P < 0.01$); and the times for ascites removal were 8 and 15.7 times, respectively ($P < 0.05$). The mechanism might be through Danshen's function of promoting fibrinogen degradation, increasing plasminogen activator activity, promoting the conversion of plasminogen to plasmin, inducing fibrinolysis, inhibiting the formation of intestinal adhesions parcels; dilating vessels, improving local blood circulation, and promoting the absorption of inflammation.

Zhang and Shao [17] observed the clinical adjuvant therapeutic effects of CDI on tuberculous peritonitis. 78 patients with tuberculous peritonitis were randomly divided into a treatment group (40 cases) and control group (38 cases). Both groups received regular chemotherapy for 6 months. 60 ml of CDI was administered to the patients in the treatment group by intravenous drip, once a day, for a half-month as one course of treatment. The results showed that in the treatment group, the times for body temperature to return to normal, night sweats to disappear, abdomen to soften, abdominal pain to disappear, ascites to disappear, and the clinical marked effect rate and total effective rate all were significantly better than those in the control group ($P < 0.01$), which demonstrated that CDI does have certain clinical adjuvant therapeutic effects on tuberculous peritonitis.

7.3.6 Tuberculous Meningitis Hydrocephalus

Shi [18] divided 82 cases with tuberculous meningitis randomly into a treatment group (42 cases) and control group (40 cases). Both groups received the same therapy, but the patients in the treatment group received an additional 40 ml of CDI by intravenous administration once a day for 3 months. The results showed that the effective rate in the treatment group was 85.1 %, and in the control group was 70 % ($P < 0.05$). It was revealed that Danshen has the function of promoting hydrocephalus absorption and is worthy of clinical application.

References

1. Luo J. J Tradit Chin Med. 2003;01:19.
2. Yuan S. Med Liaoning. 2001;16(3):36–9.
3. Zhang W, Wang Y. Jiangsu J Tradit Chin Med. 1997;1:23.
4. Xue Y. Clin Focus. 1994;17:45.
5. Guo Z, Wang S. Forum Tradit Chin Med. 2006;4(21):28.
6. Yu Q, Wang W, Wang X, et al. Chin J Surg Integr Tradit W Med. 2002;6(8):393–6.
7. Chen X, Liang Q, Li X. J Oncol. 2005;1(11):46.
8. Yao Y, Chen Y, Zhang D, et al. J SE Univ (Med Sci Ed). 2000;4(19):267–8.
9. Zhang Y, Xue Y, Zhang B. J Integr Tradit Chin W Med. 1988;(10):582,607–608.
10. Huang Z, Li H, Tan M, et al. Hebei J Tradit Chin Med. 2000;(5).

11. Yuan Z, Gao J, Ou Y, et al. Obs Pract Clin Med. 2001;3(2):48.
12. Li J. Infect Dis Inf. 2006;2(26):13.
13. He F. Occup Health. 2007;16(23):1446.
14. Li A, Xu Y, Yan H, Zhang Y. Chin J Antituberculosis. 1998;1(20):21–3.
15. Xu S, Han Q, Bai Y, et al. J Clin Pulm Med. 2005;4 (10):449–50.
16. Shi H, Tang X, Zheng S. J Integr Tradit Chin W Med. 2000;20(10):766.
17. Zhang Q, Shao X. Herald Med. 2003;6(22):407.
18. Shi H. Clin Med China. 2002;18(3):247.

Precautions, Side-Effects and Adverse Reactions

8

Yi Zheng, Xuewen Zhang and Jiaoli Guo

8.1 Precautions

Clinically, Danshen should be used together with black false hellebore root (藜芦). The usual dose is about 10–15 g and the largest dose is 30 g. 3–4 tablets of Compound Danshen Tablet can be used each time, 3 times a day. 10–20 ml of Compound Danshen Injection can be diluted with 250 ml of 5 and 10 % glucose injection and administered at 5 ml/min by intravenous drip, once a day. When the dropping speed is greater than 10 ml/min, the patient usually suffers from headache, nausea and vomiting, etc. The drug cannot be combined with vitamin C and gentamicinone, as the combination produces red precipitates. The drug is cold in nature; healthy qi and spleen and stomach can be damaged by long term use, leading to side-effects such as discomfort in the gastric cavity and abdomen, nausea, vomiting, diarrhea, etc. Thus, elderly people should not take large doses for a long period of time.

8.2 Side-Effects and Adverse Reactions

Danshen is widely applied in clinical settings with satisfactory therapeutic effects. The adverse reactions caused by Danshen are rare, and it is relatively safe. However, Danshen preparations do generate some adverse reactions in clinical application.

8.2.1 Itchy Skin

Hou [1] reported that that a 42 year old male patient with myocardial blood supply deficiency, hypertension and coronary heart disease received 16 ml of CDI in 500 ml of low molecular dextran by intravenous drip, once a day. One week later, the patient experienced general itchy skin, but erythra was not observed. The above drugs were discontinued, and chlorphenamine maleate and calcium gluconate were administered to the patient. After 2 days, the itch was gradually relieved, and after 5 days the itch disappeared. 16 ml of CDI was administered again by intravenous drip, once a day. 2 days later the patient again suffered from general itch, and the itch disappeared gradually after the discontinuation of CDI administration. It was believed that the itch was induced by CDI.

Y. Zheng (✉) · X. Zhang · J. Guo
Shengli Hospital of Shengli Petroleum Authority, Shengli, Shandong, China
e-mail: zhengyiphd@yahoo.com.cn

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8.2.2 Urticaria

Yin [2] reported a 62 year old male patient with coronary heart disease and angina pectoris, who received CDI in 500 ml of 5 % glucose by intravenous drip. 5 min later, the patient suffered from pale facial expression, shortness of breath, general itching, and then irregular sized wheals appeared on the skin. The infusion was immediately stopped, and promethazine (phenergan) was administered by intramuscular injection. 20 min later, the itch began to gradually disappear, and the condition was improved.

8.2.3 Drug Eruption

Wang et al. [3] reported that a 70 year old male patient with coronary heart disease was administered by intravenous drip with CDI in 500 ml of 5 % glucose, once a day. 3 days later, the patient suffered from burning pain on the inner side of his left medial leg. Examination revealed a large sheet of coarctated red petechia, and it was considered to be drug eruption. CDI administration was discontinued, chlorphenamine maleate and prednisone were administered orally, and the erythra disappeared. One month later, CDI was again administered by intravenous drip, and 2 days later the patient suffered from the same symptoms as the previous time, and was diagnosed with purpuras type of drug eruption induced by CDI.

8.2.4 Dermatitis Medicamentosa

Chen [4] reported that a 51 year old male patient with coronary heart disease received 10 ml of CDI in 250 ml of 5 % glucose by intravenous drip, once a day. After 2 courses of treatment, there was a scattered rash in the back of the hand and neck skin which was extremely itchy. The rash then spread to the four limbs, back, and axillaris. The rash was bright red and grain sized, The patient was diagnosed with dermatitis medicamentosa. Danshen was discontinued immediately, and the symptoms were treated. 10 days later, the rash regressed.

8.2.5 Hyperpyrexia and Abdominal Pain

Han [5] reported that a 55 year old female patient with lumbar intervertebral disc herniation was administered orally with Large Channel-Activating Elixir and CDI by intravenous drip. 6 h later, the patient suffered from hyperpyrexia (body temperature was 39.5 °C). 4 ml of anileridine (antondin) was administered by intramuscular injection, and the body temperature was reduced to 37.8 °C. CDI was administered by intravenous drip the next day, about 6 h later, the patient suffered from hyperpyrexia again, accompanied by upper left abdominal pain, nausea, vomiting, and mild abdominal distension. The reactions were considered to be related to CDI. The patient was administered with 5 mg of dexamethasone. 1 h later, the body temperature returned to normal. CDI was discontinued on the 3rd day, but Large Channel-Activating Elixir was taken until the patient was discharged from the hospital and no hyperpyrexia occurred.

8.2.6 Anaphylactic Shock

Zhang and Yu [6] reported that a 39 year old male patient with compensated alcoholic liver cirrhosis was treated with 10 ml of CDI in 500 ml of 5 % glucose, which was administered by intravenous drip. One hour later, the patient suffered from fear of heat, irritability, and palpitations. The infusion was discontinued, and 25 mg of promethazine was administered by intramuscular injection. Several minutes later the patient got out of bed to urinate and suffered from dizziness and amaurosis, then fell down unconscious with apnea and coma for about 10 min, accompanied by urinary and fecal incontinence. The blood pressure was 8/5.33 kPa, and the limbs were cold. The patient was administered with 1 injection of dexamethasone, nikethamide and lobeline by intravenous injection. 100 mg of hydrocortisone and 100 mg of dopamine were then administered by intravenous drip. The patient recovered consciousness gradually. 3 days after the blood pressure rose, the above symptoms disappeared and disease

conditions improved. Craniocerebral diseases were excluded by consultation and examination, and allergic shock induced by CDI was diagnosed.

8.2.7 Allergic Asthma

Dong [7] reported that a 65 year old male patient with hypertension was hospitalized due to chest pain and palpitation. CDI in 500 ml of 5 % glucose was administered by intravenous drip. About 3 h later, the patient suffered from nasal obstruction, itching pharynx, dyspnea, gasping, cyanosis of the lips, and wheezing rale of the lung. The patient was treated according to the symptoms, and the symptoms were gradually relieved. The next day, CDI was administered by intravenous drip under close observation, and about half an hour later the patient suffered from the above asthma again, and asthma was relieved after emergency treatment. On the third day, 120 mg of ligustrazine was added into a 5 % glucose injection and administered by intravenous drip, and the above symptoms did not appear.

8.2.8 Hemolytic Uremic Syndrome

Zhu [8] reported that a 69 year old female patient with coronary heart disease without allergic reaction history was administered by intravenous drip with 16 ml of CDI combined with 500 ml of 706 plasma substitute. The patient suffered from fear of cold, chill, vomiting, and soy sauce like urine during the infusion, and gradually returned to normal after drug discontinuance. 2 days after drug discontinuance, 5 % glucose injection was combined with 16 ml of CDI and administered by intravenous drip. The patient again suffered from similar conditions. The examination showed that urine protein was positive, and RBC was positive. Physiological saline was combined with 16 ml of CDI and administered by intravenous drip and the patient suffered for the third time from the above symptoms; the urine color was deeper and urine was scanty. It was diagnosed as hemolytic uremic syndrome caused by CDI. The patient was treated with adrenal cortex hormone and diuretics for 2 days, but the urine output did not increase. Blood dialysis was performed, and the disease condition was improved.

8.2.9 Jaundice

Wu [9] reported that a 48 year old male patient was hospitalized due to dizziness and mild hyperosteogeny of 5–6 cervical vertebra. Besides regular treatment, 12 ml of CDI was added to 250 ml of 5 % low molecular dextran and administered by intravenous drip. No abnormality was observed for 4 days, but infusion reaction appeared on the 5th day when 50 ml of glucose solution was administered, and about 3 h later the patient suffered from abdominal pain and diarrhea. Examination showed that the blood routine and acidophilic cell count were normal. The patient had subjective burning sensations and pain in the stomach and esophagus. The patient was administered with promethazine and dexamethasone by intramuscular injection, physical cooling, and hypophosphorous acid was administered orally. The fever subsided and diarrhea stopped, but the patient suffered from sclera and systemic yellow skin. Liver function examination: transaminase 46 u/L, jaundice index > 20 u, urobilinogen positive. The patient was treated according to the symptoms; 10 days later jaundice was dissipated, liver functions were normal, and urobilinogen was negative.

8.2.10 Tachycardia

Huang Luming (1998) reported that a 58 year old male patient was hospitalized because of repeated chest tightness and suffocation; the heart rate was 84 beats/min, and the rhythm was regular with no noise. The electrocardiogram examination showed there was sinus rhythm and myocardial ischemia. Besides conventional vasodilators and myocardial nourishing treatment, 16 ml of CDI in 500 ml of 5 % glucose

was administered by intravenous drip. 30 min after administration, the patient suffered from rapid heart beat; the heart rate was 110 beats/min, and the rhythm was regular and accompanied by chest tightness. The electrocardiogram examination showed that the patient suffered from sinus tachycardia, and the administration was immediately discontinued. The patient was administered orally with 5 mg of diazepam, and the symptoms gradually disappeared. The patient was administered with CDI again the next day, and suffered from the above symptoms again about 20 min after administration. The administration was immediately discontinued, and no treatment was performed. About a half hour later the patient sensed that the symptoms gradually disappeared. An energy mixture was administered by intravenous drip on the 3rd day, and the above reactions were not observed. The patient had no history of tachycardia, and none of the patients in the same section of the hospital who were administered with CDI from the same lot suffered the same reactions.

8.2.11 Muscle Tremors

Wang and Cui [10] reported a 55 year old female patient with rheumatic mitral stenosis complicated by atrial fibrillation. The electrocardiogram showed myocardial ischemia. 20 ml of CDI in 250 ml of 10 % glucose was administered by intravenous drip. When the infusion amount reached 200 ml, the patient felt facial fever, back cold, and muscle tremors of the chest and abdomen. The tremors gradually aggravated and spread to both sides and the thighs, and the body temperature was 36.8 °C. The condition lasted for 15 min, and the drug administration was discontinued upon the request of the patient. The energy mixture (Cytochrome C + coenzyme A + inosine + vitamin C + vitamin B6 + 10 % glucose injection) was administered, and in 15 min the above symptoms disappeared. CDI in glucose solution was administered again on the second day, and the patient again suffered from the same symptoms when the input reached 200 ml. The energy mixture was administered, 15 min later, and the above symptoms disappeared. Thus, CDI was considered to be the cause of the symptoms.

8.2.12 Sublingual Edema

Dai [11] reported a 70 year old female patient who visited the doctor because of dizziness, headache, chest tightness, and palpitation. 20 ml of CDI in 250 ml of 5 % glucose was administered by intravenous drip. After 20 min of drug infusion, the patient experienced a tingling mouth and tongue, but no other indispositions. At the end of the infusion, when the needle was withdrawn, there was significant swelling between the upper extremity and the elbow. The doctor then found that the patient suffered from slurred speech. Examination showed that there was significant sublingual edema and blood stasis. It was considered to be an allergic reaction induced by CDI. 25 mg of promethazine was administered by intramuscular injection, dexamethasone and hydrocortisone etc. were added into 5 % glucose injection respectively and administered by intravenous drip for 2 days, and the patient was treated according to symptoms. The symptoms improved on that day, and the patient recovered on the 3rd day.

In recent years it has been reported in various documents that Danshen and its preparations have induced adverse reactions, such as dizziness, headache, tinnitus, nasal obstruction, blurred eyes, palpebral edema, larynx edema, dyspnea, face flushing, limb coldness, palpitation and irritability-restlessness, nausea and vomiting, abdominal pain and diarrhea, numbness of limbs, maculopapular rash, etc. Tang [12] reported the application of CDI in 1,409 cases, and 21 cases (1.49 %) had adverse reactions. Adverse reactions occurred in 3 cases of 656 male patients (0.46 %), and 18 cases of 753 female patients (2.39 %), and the difference between the two groups was highly significant ($P < 0.01$). The incidence of adverse reactions was not related to age, type of disease, or dosage. The characteristic of the adverse reactions was that they could appear anywhere from the beginning to the end

of the administration. The allergic reaction rate for patients with allergic constitution was higher; thus a skin test should be performed before treatment to ensure safety.

8.3 Editor's Note

By reviewing the medical literatures of Danshen and its preparations, we have found that they have wide clinical application and have been used in the treatment of 90 types of disease in 7 departments, such as internal medicine, surgery, ophthalmology, otorhinolaryngology, gynecology, pediatrics, dermatology, and so on. The majority of previous clinical research on Danshen mainly focused on cardiovascular diseases in internal medicine such as coronary heart disease, cardiomyopathy and arrhythmia, etc., and nervous system diseases such as cerebral infarction, migraine and subarachnoid hemorrhage, etc. It has been demonstrated that Danshen has very good therapeutic effects in these areas. With the further development of medical science and continuous clinical investigation, the boundary of Danshen's clinical application, which was mainly as a drug for activating blood circulation and dissipating blood stasis, has been broken. In other words, not only it is used in the treatment of vascular diseases, but also gradually used in the treatment of various rare diseases and difficult and complicated miscellaneous diseases.

During the compilation process of this part, we have found that with the advance of Danshen preparation manufacturing technology, the clinical research on Danshen has become increasingly wide and reliable, especially over the past 20 years. For example, Danshen's protective effect on myocardial ischemia reperfusion in intracardiac operation under direct vision has surpassed the therapeutic range of cardiovascular diseases in traditional Chinese medicine. Another example is that Danshen has achieved certain therapeutic effects on chronic allograft nephropathy by combination with Western medicine. The important functions of Danshen in dermatology have also been obtained in the treatment of Sjogren's syndrome, eczema, and various diseases. Danshen has played a positive role in surgery, such as intestinal obstruction, secondary epilepsy etc. Danshen has been applied in orthopaedics and traumatology diseases, and can be used in the treatment of various contusion and soft tissue damage to realize the function of relieving pain and activating blood circulation. The drug has been applied in gynecology, and can be used in the treatment of oligohydramnios, ovarian hyper-stimulation syndrome, and other rare diseases. Danshen also can be used in the treatment of malignant tumors, poisoning, and Infectious diseases.

Faced with such a broad array of clinical literature, we endeavored to show as much as possible of its scope of clinical application, treatable diseases, and various methods of administration of Danshen and its preparations. We hope that the book can provide some inspiration for clinical workers so that the treatment range and application methods of Danshen and its preparations could be further expanded, making a great contribution to Danshen and its preparations and even to the development of traditional Chinese medicine.

References

1. Hou Y. J Clin Dermatol. 1995;24(1):44.
2. Yin H. Chin Pract J Rural Doct J. 1994;22(6):40.
3. Wang D, Yang J, Wang D. Harbin Med J. 1994;14(2):67.
4. Chen H. Chin J Pract Nurs. 1989;5(1):26.
5. Han G. J Chin Pharm Sci. 1997;8(4):306.
6. Zhang M, Yu L. Med Pharm Yunnan. 1995;16(4):316.
7. Dong L. Chin J Pharmacoepidemiol. 1994;3(4):227.
8. Zhu Y. Lishizhen Med Mater Med Res. 1999;10(7):552.
9. Wu L. Xinjianng Med J. 1995;25(2):104.
10. Wang X, Cui H. Chin Pharm Aff. 1997;11(3):212.
11. Dai J. Chongqing Med. 1999;28(5):400.
12. Tang Q. China J Chin Mater Med. 1999;24(1):57.

Overview of Dantonic™

9

Guoguang Zhu

9.1 Introduction

Compound Danshen Tablet contains three ingredients: Danshen, Notoginseng, and Borneol. The formula is recorded in the Chinese Pharmacopoeia. In 1977, Shanghai TCM Pharmaceutical Plant developed the formula into a tablet preparation, which was manufactured by more than a hundred factories. Compound Danshen Tablet has the shortcomings of slow clinical onset, necessity of large dosage, and instability of product quality. In the 1990s, Mr. Yan Xijun and his research team, after numerous trials, made great improvements in the extraction process. Their high-tech-based process could maximize the extraction of active ingredients from raw medicinal materials. They also developed the formula into the preparation of Dropping Pill, which could improve clinical effects with a lower dosage. Dropping Pill belongs to a solid-state molecular dispersion system; the drug substance is in a state of molecular dispersion, which ensures the fastest dissolution and overcomes the shortcoming of slow onset. For quality control, the salvianolic acids content of Danshen and total saponins of Panax notoginseng were measured with HPLC and borneol content was measured by gas chromatography, so as to effectively control the quality of the drug. The dropping pill preparation mainly provides the following two advantages:

First, the drug substances are evenly dispersed in the matrix after eutectic melting, and scattered into eutectic solution in the form of molecules or fine crystals after congelation, which makes it easily absorbed and fast to exert therapeutic effect, thus improving bioavailability and reducing side effects.

Secondly, the fine crystals and molecules of the drug substances are tightly embedded in the matrix; the interspace is minimal and the drug substances have little chance of contact with air, so they are not vulnerable to oxidization and volatilization. In addition, the matrix is not liquid, so the drug substances will not undergo hydrolysis. All of these have increased the stability of the drug.

In addition, by means of sublingual administration, the drug is absorbed into the blood by mucous membranes, which overcomes the first-pass effect caused by absorption through the gastrointestinal tract and liver. Therefore, a lower dosage and rapid effect are achieved. So far, besides Compound Danshen Tablet, Dantonic™ is the only preparation based on the same formula which has been included in the Chinese Pharmacopoeia.

In 2004, the market share of Dantonic™ in Chinese patent medicines for the treatment of coronary heart disease was 35.59 % (Fig. 9.1).

G. Zhu (✉)
The European Federation of Pharmaceutical Society, Stockholm, Sweden
e-mail: ggz68111@yahoo.com

X. Yan (ed.), *Dan Shen (Salvia miltiorrhiza) in Medicine*,
DOI 10.1007/978-94-017-9466-4_9,

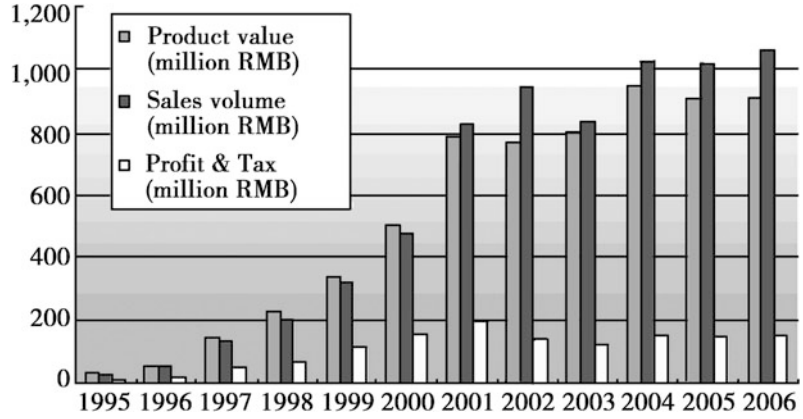

Fig. 9.1 Yearly product value and sales volume of Dantonic™

The development and production of Dantonic™ began with the adaptation of Good Agricultural Practices (GAP) in the planting and harvesting of Danshen, notoginseng, and *Cinnamomum camphora* (containing borneol). At the same time, Dr. Yan Xijun, the inventor of Dantonic™, proposed for the first time in the world the concept of Good Extracting Practice (GEP) and its detailed operating procedures. The concept and procedures have standardized the key links in the production of TCM or herbal medicinal products and ensured that the contents of the components of the TCM or herbal medicinal products will not be affected by factors like weather and geographic locations, and thus guaranteed their quality. The standardized extracts attained through GEP are manufactured according to GMP into the finished products and fully comply with the pharmaceutical regulatory requirements. Meanwhile, the current internationally accepted standard GSP requirements are also adopted in the marketing practice, with a set of strict drug sales and supervision systems, so that the safety of the patients and the effectiveness of the drugs are ensured to the greatest extent.

In 2002, the production, sales, and profits and taxes of Dantonic™ reached 920,000,000, 1 billion, and 250,000,000 RMB, respectively, which were 28.8, 41.6, and 27.7 times of those in 1995, respectively. Cumulative sales volume reached 3 billion RMB from 1995 to 2002. In 2002, the sales volume rose to 3.33 % of the entire cardiovascular drug market in China, occupied l5.57 % of China's market of Chinese patent medicines for the treatment of cardiovascular diseases, and took the first place in market shares of Chinese patent medicines. In 2002, the sales volume of Dantonic™ in sample hospitals reached 73,590,000 RMB in 16 major cities (Beijing, Tianjin, Shijiazhuang, Zhengzhou, Shenyang, Harbin, Xi'an, Shanghai, Nanjing, Hangzhou, Jinan, Chongqing, Chengdu, Wuhan, Changsha, Guangzhou, Shenzhen),

Table 9.1 A list of countries where Dantonic™ is registered

Registered countries	Registration category
Vietnam	Prescription drug
UAE	Prescription drug
Russia	Prescription drug
Cuba	Prescription drug
South Korea	OTC drug
USA	Health product
South Africa	Supplement
Hong Kong	TCM
Singapore	TCM
Mongolia	Cardiovascular medicine

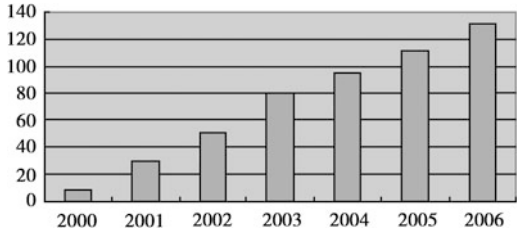

Fig. 9.2 Yearly exports of Dantonic™ (10 K USD)

accounted for 14.75 % of market shares of Chinese patent medicines sold in sample hospitals, and sold 558,810,000 minimum packaging units (pills, tablets or sticks), with a market share of 49.68 %.

Dantonic™ is registered as a prescription drug in Russia, the United Arab Emirates, Mongolia, Vietnam and Cuba. It is registered as a non-prescription drug in South Korea, and registered as a nutritional supplement in the United States and South Africa (Table 9.1). As shown in Fig. 9.2, Dantonic™ has been exported since 1999 and reached a sale of 1.31 million US dollars in 2006, a 100-fold increase.

Since its invention over 10 years ago, Dantonic™ has shown good clinical effects which are closely related to its quality management. Dantonic™ has strict quality standards; it was the first TCM drug to adopt an HPLC based fingerprint detection system in China, which has been recorded in *Chinese Pharmacopoeia*, 2000 edition.

Therapeutic Effects of Dantonic™ on Coronary Heart Disease

10

Guoguang Zhu, Naifeng Wu, Yonghong Zhu, Danyong Wu, Ruizhi Luo and Yan Liu

By the end of October 2007, a total of 1,222 papers on Dantonic™ published in China and the rest of the world were collected, as shown in Table 10.1. There are two monographs available. One is "Danshenform" (Chinese and English version), prepared by The Herbal Expert Working Group of the Pan-European Federation of TCM Societies, Chief Editor Dr. Guoguang Zhu. The other is "FAQ of the Compound Danshen Dropping Pill."

10.1 Dantonic™ in Treatment of Angina Pectoris

Many studies on the effect of Dantonic™ on stable angina pectoris have been reported recently, and the results show that Dantonic™ had some advantages. Zhang et al. [1] made a systemic evaluation of Dantonic™ in the treatment of stable angina pectoris. Meta-analysis was implemented based on 20 randomized studies (Table 10.2), and the results showed that Dantonic™ can significantly alleviate angina (test of heterogeneity: $P = 0.08$; fixed effect model analysis: OR = 2.68 [2.03, 3.55], $P < 0.00001$). An efficacy analysis showed that Dantonic™ can significantly improve the ischemic ECG (test of heterogeneity: $P = 0.29$; fixed effect model analysis: OR = 1.89 [1.54, 2.30], $P < 0.0001$). Analysis of 8 randomized trials on reducing cholesterol: test of heterogeneity: $P < 0.00001$, OR = −0.54 [−0.91, −0.71], $P = 0.005$. Analysis of 8 randomized trials on reducing triglycerides: test of heterogeneity: $P = 0.001$; WMP = −0.34, [−0.57, −0.12] $P = 0.03$. Analysis of 5 studies on reducing high blood viscosity: test of heterogeneity: $P < 0.00001$; WMD = −0.69, [−0.80, −0.58], $P < 0.00001$. The above results strongly suggest that Dantonic™ can lower the levels of total cholesterol and triglycerides and improve blood rheology. The effects were significantly superior to those of the control group. The author also made a funnel plot analysis (Fig. 10.1) and sensitivity analysis, showing that the literature collected in the Meta-analysis was neutral and stable.

10.1.1 Effect of Dantonic™ on Alleviating Angina, Improving Subjective Symptoms, and Reducing Nitroglycerin Administration

Li et al. [2] used the treadmill test to observe the effect of Dantonic™ before and after treatment. Seventy cases of stable angina patients were observed. The control group took Isosorbide. The course of treatment lasted 2 months. The results showed that the total effective rate in the treatment

G. Zhu (✉) · N. Wu · Y. Zhu · D. Wu · R. Luo
Y. Liu
The European Federation of Pharmaceutical Society, Stockholm, Sweden
e-mail: ggz68111@yahoo.com

X. Yan (ed.), *Dan Shen (Salvia miltiorrhiza) in Medicine*,
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Table 10.1 A list of research literature on Dantonic™ (from 1993 to October 2007)

Type	Number
Basic studies	80
Clinical studies and reports	1,074
Reviews	47
Others	21
Total	1,222

Table 10.2 Sensitivity analysis of the overall therapeutic effects of Dantonic™ on angina and ECG (on)

Items	Randomized model	Fixed model
Angina pectoris	2.61	2.68
ECG	1.85	1.89

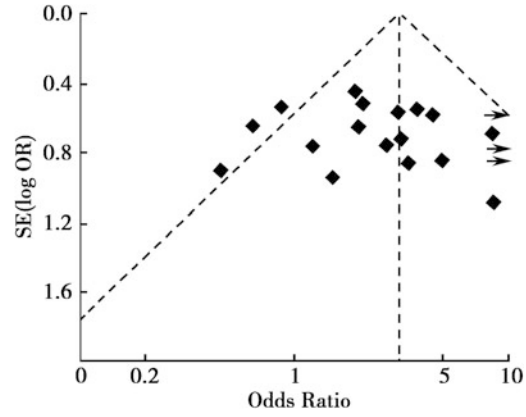


Fig. 10.1 Funnel plot

group was 91.4 %, and in the control group was 69.6 %. The frequency of angina attacks in the treatment group was significantly reduced while the duration was shortened. Also the administration of nitroglycerin tablets was reduced. The differences were statistically significant between the treatment group and the control group. The improvement rate of Dantonic™ on myocardial ischemia reached 70.5 %. Compared with 57.1 % in the control group, the difference was statistically significant (Table 10.3).

Dantonic™ can alleviate angina pain and reduce the number of angina attacks, with the advantages of a lower dose, fast absorption, and rapid effect. Li et al. [3] used Dantonic™ to treat angina pectoris and observed the rate of recurrence (number of attacks per week). They found that the rate of recurrence was reduced from 12.4 times a week to 3.7 times a week. The duration of attacks decreased from 7.6 to 2.6 min. The author

Table 10.3 Indicators of movement ECG before and after treatment with Dantonic™ ($\bar{X} \pm S$)

Items	Treatment group		Control group	
	Before treatment	After treatment	Before treatment	After treatment
Duration required for exercise evoked ST decreasing of 0.1 mV (s)	25.00 ± 125.20	414.70 ± 203.20	249.77 ± 124.65	363.73 ± 208.65
Amount of exercise evoked ST segment decreasing 0.1 mV (METS)	2.75 ± 0.76	5.25 ± 0.96	250.00 ± 125.20	3.43 ± 0.83
Maximum ST segment decrease (mm)	1.38 ± 0.48	0.75 ± 0.96	250.00 ± 125.20	0.82 ± 0.85
Maximum workload (METS)	6.50 ± 1.00	12.75 ± 2.87	250.00 ± 125.20	8.10 ± 0.89
Oxygen consumption [ml/(kg ml)]	27.20 ± 4.50	48.25 ± 6.50	250.00 ± 125.20	33.98 ± 6.15
Heart rate when reaching maximum workload (times/min)	160.70 ± 2.70	123.30 ± 5.70	250.00 ± 125.20	110.80 ± 5.57
Duration required to reach target heart rate (s)	480.50 ± 48.60	824.00 ± 106.30	250.00 ± 125.20	600.40 ± 107.25
Lasting duration of ST segment decrease (s)	390.00 ± 60.00	210.00 ± 51.90	250.00 ± 125.20	329.00 ± 51.55
Duration of heart rate recovery (s)	372.10 ± 79.60	180.50 ± 69.30	250.00 ± 125.20	244.00 ± 69.30

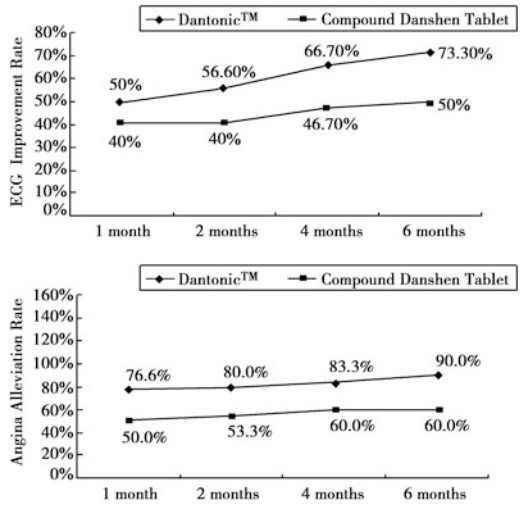


Fig. 10.2 ECG improvement rate

believed that Dantonic™ not only could relieve angina pectoris but also reduce the rate of recurrence after a period of time of treatment, and that this medicine could improve the patients' condition and improve (reduce) the attack duration. The study concluded that Dantonic™ not only had the effect of treating the "symptoms", i.e., relieving angina pectoris, but also had the effect of treating the cause, i.e., improving the ischemic conditions of the cardiac muscle. The author reported a total of 19 cases in which the rate of nitroglycerin reduction was 94.74 % (Fig. 10.2).

Shi [4] reported that 64 patients with coronary heart disease (CHD) were grouped in a randomized double-blind control study. The first 2 weeks were the elution period, and the patients were treated with a placebo and no drugs, except for nitroglycerin if necessary. In the 8 weeks following the elution period, one group was administered with 10–15 pills of Dantonic™, 3 times/day, and another group with 10–15 mg of Isosorbide, 3 times/day. The average number of angina attacks in the Dantonic™ group was reduced from 1.93 ± 3.10 to 0.46 ± 1.33, and the difference was statistically significant ($P < 0.01$). The daily usage of nitroglycerin was reduced from 1.88 ± 2.96 tablets to 0.51 ± 1.44 tablets, which indicates a significant statistical difference ($P < 0.01$). Dantonic™ was found to be similar to nitroglycerin in its ability to quickly relieve pain. The time taken to remove pain with Dantonic™ was found to be slightly slower than that of nitroglycerin. The total effective rate for 3 to 8 min was 88.24 % versus 93.33 %, and the difference was not significant ($P > 0.05$). The effect of Dantonic™ was obviously related to the degree of angina pectoris; the lower the degree, the lower the effect. The author concluded that Dantonic™ had almost the same effect as Isosorbide in its ability to relieve pain quickly.

Qian [5] compared the effect of Dantonic™ (10 pills) with nitroglycerin (0.5 mg) on pain relief in angina pectoris patients, and the results are shown in Table 10.4.

Gao [6] observed 310 patients with CHD or cardiovascular angina pectoris after Dantonic™ administration for 30 days. The rate of recurrence (times/day) was reduced from 3.8 ± 1.8 before the treatment to 0.6 ± 0.4 after the treatment. The rate of angina pectoris was reduced 93 % for this group compared to 60 % for the control group, which had 302 cases treated with Isosorbide.

Dantonic™ could markedly alleviate the level of pain and lower the frequency of attacks in angina pectoris patients. Also, the subjective symptoms were improved and the demand (both in frequency and dosage) for nitroglycerin was reduced significantly. In the past 10 years, 13 pieces of literature reported a total of 604 cases in detail (Table 10.7). Most researchers reported that the nitroglycerin dosage (daily or weekly) was reduced significantly after the patients were treated with Dantonic™ for 2–8 weeks. Sun et al. [7] reported that among 35 cases of angina pectoris, 88.57 % began to reduce or even stop taking nitroglycerin 24 h after taking Dantonic™. Eight

Table 10.4 Comparison of Dantonic™ with nitroglycerin for pain relief in angina pectoris patients

Group	Cases	Pain relief in 3 min	Pain relief in 3–8 min	Total efficiency (%)
Dantonic™	102	41 (40.2 %)	49 (48.04 %)	88.24
Nitroglycerin	30	16 (53.33 %)	12 (40 %)	93.33

authors compared Dantonic™ with Isosorbide. The results indicate that Dantonic™ was identical with Isosorbide in reducing the dosage of nitroglycerin. Two of the authors even reported that Dantonic™ was statistically more effective than Isosorbide in nitroglycerin reduction. Ye et al. [8] reported that 60 angina patients were treated with an energy mixture, Taponin and aspirin 40 mg. Thirty of these cases were treated with additional Dantonic™. The results showed that the nitroglycerin consumption in Dantonic™ treatment group was significantly lower than that of the control group after Dantonic™ treatment ($P < 0.05$). Zhang et al. [9] reported that 59 patients with angina pectoris were treated with conventional therapy including nitroglycerin, calcium antagonist, β-receptor blocker, aspirin, thiophene pyridine, heparin, or low molecular weight heparin. They were randomly grouped, with 31 cases in the Dantonic™ treatment group and the other 28 cases in the control group. After 4 weeks, the nitroglycerin amount was reduced by 50 % in 90.3 % patients in the treatment group, while in the control group, the number was 82.1 %. It seemed that the effect of Dantonic™ in reducing the nitroglycerin amount was related to the type of angina. Zhang et al. [10] found that Dantonic™ reduced the nitroglycerin amount more effectively in patients with stable angina. Dong (1996) observed the effect of Dantonic™ on different TCM types of CHD. The type of heart blood obstruction was more sensitive to Dantonic™; 58 patients of this type were treated with Dantonic™, and 2 weeks later, all of them stopped taking nitroglycerin. Dantonic™ was less effective in phlegm-turbid internal obstruction type (22 cases) and qi deficiency, heart-kidney obstruction and deficiency type (20 cases). After 2 weeks' treatment with Dantonic™, only 54.5 and 18.2 % of these patients, respectively, stopped taking nitroglycerin.

Wu et al. (1999) reported that l3 cases of cardiovascular angina pectoris were treated with Dantonic™. Ten patients experienced rapid relief within 3 min after taking the pills. The rate of marked relief of angina pectoris was 76.92 %.

Yang [11] used Dantonic™ to treat 100 cases of cardiovascular angina pectoris, and the 40 cases in the control group were treated with Isosorbide. The results are shown in Table 10.5.

Qian [5] compared Dantonic™ with nitroglycerin in terms of the time needed to relieve angina pectoris. The analgesic effect in 102 patients administered with Dantonic™ was 40.2 % in 3 min and 48.4 % in 3–8 min, while in the patients administered with nitroglycerin, the numbers were 53.3 and 40 %, respectively. The difference between the two groups was not statistically significant. Wang and Wang [12] chose 108 patients with stable angina pectoris and randomized them into two groups: Dantonic™ sublingual group (56) and nitroglycerin sublingual group (52), and the results are shown in Table 10.6.

Angina pectoris is a medical emergency with needs for emergency treatment and rapid pain relief. The conventional treatment is sublingual administration of nitroglycerin to alleviate symptoms and to improve myocardial blood supply. In recent years, many adverse effects of nitroglycerin have been reported, such as dysuria, urine retention, constipation, abdominal distension, induced glaucoma, etc. It has also been reported that some patients with CHD suffered allergic shocks and other severe reactions after taking nitroglycerin. Therefore, Dantonic™ has unique advantages over nitroglycerin in alleviating angina.

Table 10.5 Treatment for angina pectoris with Dantonic™

Group	Case	Marked effect		Effect		Ineffect		Total effective rate (%)
		cases	%	cases	%	cases	%	
Treatment	100	52	52.0	41	41.0	7	7.0	93.0
Control	40	12	30.0	21	52.0	7	17.5	82.5

Table 10.6 Comparison of the marked effects on angina pectoris within 30 min of administration of Dantonic™ and nitroglycerin (min)

Group	*n*	3 min	5 min	8 min	10 min	15 min	30 min	Total	%
Dantonic™	56	3	9	24	6	5	3	50	89.28
Nitroglycerin	52	4	8	22	6	3	4	47	90.38

$T = 1.592$, $P = 0.187$

Dai et al. [13] reported that 67 cases of cardiovascular angina pectoris were treated with oral administration of 75 mg aspirin daily, and 12.5 mg of Betaloc twice a day. Patients with hypertension or diabetes were treated accordingly to relieve the symptoms. The patients were randomized into two groups. The treatment group received Dantonic™, 10 pills a day, and the control group did not. After 4 weeks, the angina relief rate reached 86.1 % in the treatment group and 71.0 % in the control group. ECG improvement rate was 63.9 % in the treatment group and 54.8 % in the control group. The differences were not statistically significant, however. The amounts of nitroglycerin used by the patients before and after treatment were also not markedly different. The authors found significant improvements in blood lipids, blood glucose, average systolic blood pressure, and blood rheology in patients in the treatment group, yet no such changes were found in the control group. The authors considered that Dantonic™ had comprehensive intervention effects on a variety of risk factors (blood lipids, blood glucose, blood pressure, hyperviscosity syndrome, etc.), and could improve the short-term and long-term symptoms as well as the prognosis of CHD.

Dantonic™ can reduce the frequency of angina attacks, relieve pain, and decrease nitroglycerin consumption by patients. Liu [14, 15] randomly divided 86 cases of cardiovascular angina pectoris into two groups: 50 patients took Dantonic™ and 36 took long-acting Isosorbide. After 3 weeks, the frequency of angina attacks for both groups was reduced, but the Dantonic™ group was markedly better than the Isosorbide group. The difference was statistically significant. The nitroglycerin consumption by the patients in Dantonic™ group was also obviously reduced ($P < 0.01$).

Yang et al. (2001) observed 30 cases of cardiovascular patients used Dantonic™ for 6 months. He found that the longer the patients used the medication, the greater the improvement in the angina-relieving effect and in the patients' electrocardiogram.

For patients with unstable angina, additional administration of Dantonic™ to conventional treatment can decrease nitroglycerin consumption. Ren [16] reported a study in which 249 cases of unstable angina patients were treated with 250 mg of Dantonic™, 3 times a day, in addition to conventional treatment (nitrates, calcium antagonists, β-receptor blockers, low molecular weight heparin, enteric coated aspirin, etc.) for 3–6 weeks. The author found that the average duration of an angina pectoris attack was 6.4 ± 3.9 min before the treatment and 3.5 ± 1.7 min after the treatment. The difference was significant ($P < 0.05$). The average daily number of attacks was 0.7 ± 0.33 after treatment, which was significantly lower than that of pre-treatment 2.6 ± 1.2 ($P < 0.01$). The average daily nitroglycerin consumption was 0.3 ± 0.1 mg after treatment, which was significantly lower than that of pre-treatment, 1.6 ± 0.8 mg ($P < 0.05$).

Hong et al. [17] studied the treatment of unstable angina with Dantonic™ in addition to conventional therapy in a randomized and controlled trial, and found that nitroglycerin consumption in the treatment group was significantly lower than that in the control group ($P < 0.0$ l). Analgesic consumption in the treatment group was also significantly lower than that in the control group ($P < 0.05$). The authors also found in a half year follow-up that the rate of cardiac events was 10 % in the Dantonic™ group, which was significantly lower than that of the routine treatment group, which was 20 % ($P < 0.05$).

10.1.2 Effect of Dantonic™ on Electrocardiogram

Dantonic™ can significantly alleviate angina and improve ST segment changes on ECG. Qin et al. [18] reported 84 cases of CHD patients treated with Dantonic™ for 4 weeks. The use of other cardiovascular drugs (including vasodilator, antiplatelet and hypolipidemic drugs, etc.) was ceased for 1 week before treatment. Nitroglycerin could be used if angina pectoris occurred. Conventional 12-lead ECG was used for all patients. The number of ST segment decreases (NST) and total ST segment depression (ΣST) demonstrated the area and level of myocardial ischemia. Their results are shown in Table 10.7.

Zhang et al. [19] divided 60 cases of angina pectoris into four groups. The improvement in the ECG after treatment with different herbal medicines was 26.6 % for the Compound Danshen Tablet (CDT), 40 % for Suxiaojiuxin Pill, 33 % for Diao Xinxuekang, and 60 % for Dantonic™.

Hu et al. [20] randomly divided 63 cases of angina pectoris into two groups: Dantonic™ group (32 cases) and the Isosorbide Dinitrate group (31 cases). The ST-T segment changes were measured by Holter using electrocardiogram recordings before and 24 h after taking the medication. The results showed that the measurements of ST-T segment changes in both groups were markedly decreased. The efficiency of Dantonic™ (82.4 %) was significantly greater than that of Isosorbide Dinitrate (74.5 %) ($P < 0.05$).

Shi (1999) reported the changes in ST-segment on ECG that occurred after treatment with Dantonic™ in 34 patients with stable angina pectoris. The patients were grouped with the double-blind method. The time of ST-segment depression ≥1 mm on the electrocardiogram was significantly delayed, and the duration of exercise and evoked angina pectoris occurrence time was also delayed. The degree of myocardial ischemia without symptoms was markedly improved.

Hu [21] used Dantonic™ to treat 60 cases of CHD and blood hyperviscosity. The rate of improvement in clinical symptoms was 91.7 % for chest distress, 87 % for chest pain, 62.5 % for vexation, 94.2 % for lacking in strength, and the recovery on ECG was 83.3 % after 4 weeks of treatment. The author believed that the first choice of medication for the patients with CHD accompanied with hyperviscosity should be Dantonic™.

Li et al. [22] reported that 109 cases of CHD were randomized into two groups. One group used 10 pills of Dantonic™ 3 times a day. The control group used 10–15 mg of Isosorbide Dinitrate 3 times a day. The results showed that the efficacy of Dantonic™ in relieving angina pectoris was 93 % compared with 86.5 % in the Isosorbide Dinitrate group. The difference was not significant ($P > 0.05$). The improvement of the ECG in the group using Dantonic™ was 61.4 % (Table 10.8). The times for the onset of exercise-induced angina pectoris and ST segment depression ≥0.1 mV were delayed, the maximum ST segment depression was reduced, and the maximum load increased.

Jia et al. [23] divided 102 CHD patients into two groups using a randomized double-blind method: Dantonic™ group ($n = 52$) and Isosorbide Dinitrate (control) group ($n = 50$). The use of all other anti-angina pectoris drugs was ceased prior to the treatment. It was observed that after treatment for 2 months, the standard deviation of

Table 10.7 Changes in $\sum$ST, NST, HR, SBP and RPP after treatment with Dantonic™ ($\bar{X} \pm S$)

Treatment	$\sum$ST (mm)	NST (number)	HR (times/min)	SBP (kPa)	RPP
Before	3.6 ± 1.3	3.6 ± 1.5	79 ± 14	16 ± 3	1,412 ± 210
After	1.0 ± 0.9**	2.1 ± 1.3*	77 ± 11	15 ± 2	1,309 ± 181*

Comparison before and after treatment *$P < 0.05$, **$P < 0.01$

Note HR Heart Rate, *SBP* Systolic Blood Pressure, *RPP* HR·SBP, representing the extent of myocardial oxygen consumption, i.e., myocardial oxygen consumption index

Table 10.8 Comparison of exercise treadmill test indexes between the Dantonic™ group and Isosorbide Dinitrate group before and after treatment

Group	Cases	Treatment	Exercise evoked angina pectoris time (s)	Exercise evoked ST segment decreasing 0.1 mV time (s)	Amount of exercise evoked ST segment decreasing 0.1 mV (MET)	Maximum ST segment decrease (mm)	Maximum loading dose (mm)
Dantonic™	49	Before	228 ± 60	204 ± 79	4.2 ± 2.0	2.5 ± 1.8	7.3 ± 1.2
		After	301 ± 94*	268 ± 92*	5.6 ± 2.3*	1.8 ± 1.1*	9.8 ± 2.1*
Isosorbide Dinitrate	47	Before	230 ± 39	210 ± 76	4.5 ± 1.8	2.2 ± 0.9	7.8 ± 1.6
		After	303 ± 89	257 ± 85	5.8 ± 2.6	1.6 ± 0.8	10.1 ± 2.2

*Compared with the treatment group before treatment: $P < 0.01$; compared with the control group after treatment: $P > 0.05$

R-R Intervals (SDNN) had markedly improved in the Dantonic™ group ($P < 0.01$), but there was no significant change in the Isosorbide Dinitrate group ($P > 0.05$). It was concluded that Dantonic™ was able to improve the coronary patients' heart rate variability and adjust the equilibrium of the autonomic nervous system.

Mao [24] used Dantonic™ to treat 98 patients with myocardial ischemia symptoms, showing in ECG as ST segment depression, T-wave lowing, flatness, diphase, or inversion as well as QT-interval prolongation and so on, caused by the administration of antipsychotics (chlorpromazine, clozapine, haloperidol and lithium carbonate etc.) The results showed that improvement in myocardial ischemia was 80 %.

10.1.3 Comparison of Dantonic™ with Isosorbide Dinitrate

Nitrate is one of the most widely used drugs in the treatment of CHD, owing to its ideal therapeutic effects in reducing the number of angina pectoris attacks, improving ECG ST-segment depression in the treadmill test, and increasing exercise tolerance of the patients. But as with other chemical substances, a great quantity of long-term nitroglycerin administration and long-acting nitrate preparation will lead to drug tolerance, and the practical effects of treating angina pectoris will be reduced in most patients. It would also affect the improvement of blood flow dynamics in angina pectoris patients and reduce the effect of anti-platelet aggregation. Since 1994, with the thorough study of Dantonic™, it was found that Dantonic™ is effective in increasing coronary blood flow, reducing myocardial oxygen consumption, preventing myocardial ischemia, inhibiting platelet activation, stabilizing atherosclerotic plaques, and protecting against ischemia-reperfusion injury. Some doctors have proposed to solve the clinical problems brought about by nitroglycerin by means of Dantonic™. More and more randomized clinical trials comparing Dantonic™ and nitrate preparations have been reported, and the efficacy and superiority of the former have been systemically evaluated and clinically affirmed. Based on the literature in the second half of 2000, as well as the latest statistical analyses, the Ad hoc Expert Group of Pan-European Federation of TCM Societies implemented "An Evaluation of the Therapeutic Effects of Dantonic™ on Coronary angina pectoris" as a formal research study in June 2001, and collected relevant information on Dantonic™ from 1993 to June of 2001. Based on the literature collected, at least l7 different Chinese or Western medicines have been compared with Dantonic™ and reported in clinical studies, and among them, Isosorbide Dinitrate was the most common medication. Forty-nine papers including a total of 6,910 cases have been collected; among them, 4 were non-randomized controlled studies and 45 were randomized controlled trials. Of the randomized controlled trials,

6 studies only had abstracts available (the original texts were lost and/or could not be located), 5 trials did not adopt the WHO diagnosis criteria for CHD and angina pectoris, or the diagnosis criteria were unclear, and 2 trials did not examine and/or record the angina alleviation rate and ECG improvement rate. In all, 32 papers can be treated with statistical methods. The weighted treatment of each statistic, the statistics of angina-alleviation rate and ECG-improved rate, and the tests of the homogeneity of statistics were completed.

10.1.3.1 Functional Comparison

Clinical applications have fully demonstrated that Dantonic™ has the advantages of quick, efficient, safe, nontoxic and side effects in the treatment of angina pectoris. Dantonic™ is significantly superior to ISDN in terms of the clinical effective rate and the ECG effective rate in long-term administration. Although nitrate is used as the classical medicine to treat angina pectoris, a disadvantage of its long-term usage is "drug tolerance," which can decrease its therapeutic effect. The possible reasons may be as follows: (1) ISDN significantly decreases the internal pressure of blood vessels, which results in the activation of the endogenous neurohumoral system and an increase in blood volume. (2) ISDN depends on sulfur groups in the vascular walls, which become exhausted through long-term administration of ISDN. Dantonic™, however, ameliorates myocardial cells in a multi-target, multilevel, and multi-route manner. It produces the angiectasis effect by means of an effective slow calcium channel blocking action and improves myocardial ischemia by some fundamental actions such as stabilizing myocardial cell membranes, eliminating body free radicals, modulating the energy metabolism of myocardial cells, ameliorating systemic platelet aggregation, and decreasing cholesterol and blood viscosity, thus bringing anti-angina action into play. Many reports have demonstrated that Dantonic™ has better long-term therapeutic effect. The similarities and the differences between Dantonic™ and ISDN have been compared (see Table 10.9).

Wu et al. (1999) randomized 40 patients with stable angina pectoris into two groups: Groups A and B. There were no significant differences ($P > 0.05$) between the two groups in terms of age, sex, and average course of the disease. Both groups were double-blindly administered for 8 weeks, Group A taking 10 pills of Dantonic™, 3 times/day, and Group B taking 10 mg of Isosorbide Dinitrate 3 times/day. The results showed that during the first 2 weeks, there was no difference between the groups in terms of the angina effective rate. At the 4th, 6th, and 8th weeks, they were 90 % versus 75 % ($P > 0.05$), 90 % versus 70 % ($P < 0.05$), and 95 % versus 65 % ($P < 0.01$), respectively, with Group A superior to Group B. During the first 2 weeks, there was no difference between the two groups in terms of the ECG effective rate. At the 4th, 6th, and 8th weeks, the ECG effective rates were 80 % versus 65 % ($P < 0.05$), 75 % versus 55 % ($P < 0.05$), and 80 % versus 50 % ($P < 0.01$), respectively, with Group A superior to Group B (Fig. 10.3). Long-term administration of Dantonic™ can increase the angina alleviation rate and ECG improvement rate, and this effect has been found to be greatly superior to the effect of Isosorbide Dinitrate. Long-term administration of Isosorbide Dinitrate is associated with drug tolerance, which decreases the therapeutic effect. Dantonic™ has a long-term, stable therapeutic effect and is not associated with drug tolerance.

The results shown by Professor Wu Keng were validated by many clinical studies. Liu and Li [25] reported a randomized controlled trial (RCT) with a huge number of samples: the Dantonic™ group had 380 cases and the ISDN group had 400 cases. There was no statistical difference in the relief rate of angina pectoris and ECG improvement rate between the two groups within 2 weeks, which means that Dantonic™ has similar effects to ISDN over short-term treatment of angina pectoris. However, after 8 weeks of treatment, the relief rate of angina pectoris in the Dantonic™ group (92.1 %) was significantly higher than that of the ISDN (65.0 %), $p < 0.05$. The authors believed that the effectiveness of ISDN on the relief of angina pectoris and the improvement of ECG had a

Table 10.9 A comparison between Dantonic™ and Isosorbide Dinitrate (ISDN)

Dantonic™	Isosorbide Dinitrate (ISDN)	Reference
Long-term (8 weeks) administration of Dantonic™ does not decrease the angina alleviation rate and the ECG improvement rate, and is superior in effect to that of ISDN. The angina alleviation rate and the ECG improvement rate increase if Dantonic™ is administrated for over 6 months	Six-week administration results in drug tolerance, which significantly decrease the ECG improvement rate	Wu et al. [67]; Wu (2001)
Improve blood rheological properties, decrease blood viscosity and prevent the formation of thrombi	No obvious effect on blood rheological properties	Li et al. [22]
Improve indices such as myocardial contraction, left ventricular function, myocardium oxygen consumption, variability of heart rate and hemodynamics	No obvious effects on such indices as myocardial contraction, left ventricular function, myocardium oxygen consumption, variability of heart rate and hemodynamics	Jia et al. [23], [42]; Shi et al. (1997)
Significant improvement in Hyperlipemic apolipoprotein A and B100, lipid peroxide and super-oxide dismutase	No obvious effect on Hyperlipemic apolipoprotein A and B100, lipid peroxide and super-oxide dismutase	Wang et al. [48]
Inhibiting ET-1 gene expression in endothelial cells of peripheral circulation system	No obvious effect on ET-1 gene expression	Feng et al. [68]
An obvious therapeutic effect on SMI in senile coronary heart disease patients. It can be used as a Class I medication	A therapeutic effect on SMI, but its effect was slightly inferior to Dantonic™	Fan (1998); Zhu [43]
Inhibiting the hyperactivity of the sympathetic nerve and adjust the autonomic nervous equilibrium	No such effect	Liu and Yang [69]
Almost no noticeable headache or dizziness occurred	Headache, dizziness, flushed face and a feeling of burning	Yang et al. (2001)

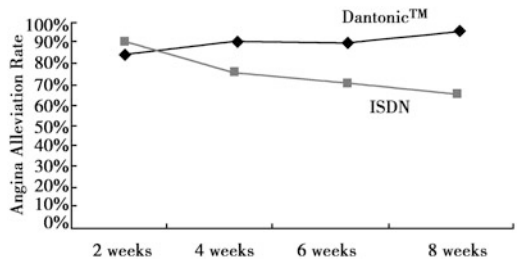


Fig. 10.3 Effect of long-term administration of Dantonic™ and Isosorbide Dinitrate on angina alleviation rate

downward trend after a long period of administration. Drug resistance was obviously generated, while Dantonic™ could compensate for the drug resistance to ISDN. The authors observed the changes in whole blood, blood plasma, and fibrinogen in both groups within the period of drug administration, and all these indexes were significantly improved in the Dantonic™ group, but were not in the ISDN group. The authors presumed that Dantonic™ was capable of improving blood rheology without drug tolerance after a long period of treatment, which is also one of the reasons that the therapeutic effect of Dantonic™ was superior to ISDN.

10.1.3.2 Meta-analysis

Dantonic™ has been compared with 15 Chinese patent medicines and Western medicines, especially ISDN. There were a total of 49 papers in comparison to Dantonic™ and ISDN, and among them 5 papers were based on randomized controlled design. There were 6,880 cases in total; 3,975 were treated with Dantonic™, and 2,905 with ISDN. In 2001, the Ad hoc Expert Group of the Pan-European Federation of TCM Societies systematically analyzed the therapeutic effect of Dantonic™ and ISDN on angina pectoris. In all, 20 papers met the criteria.

The weighed treatment of each statistic and homogeneity test was completed. Statistics of angina alleviation rate and ECG improvement rate were also carried out.

There were 20 trials using either Dantonic™ or Isosorbide Dinitrate, but not any other coronary artery dilating or anti-anginal drugs at the same time. The data from these trials were used for Meta-analysis.

The statistical methodology was to first conduct the test of homogeneity. If the variances were homogeneous, the Peto method of the Fixed Effect model was adopted; if the variances were heterogeneous, the DerSimonian and Laird method of the Random Effect model was adopted.

For comparison between Dantonic™ and ISDN in terms of angina pectoris relief, there were 20 papers that met the criteria. Meta-analysis showed that there was a statistically significant difference, with alleviation rates of 90.1 % versus 78.8 %, OR = 1.86 (95 % Confidence Interval was 1.24, 2.80), $P = 0.000$ (Table 10.10).

For comparison of Dantonic™ with Isosorbide Dinitrate in terms of ECG improvement, there were 20 papers that met the criteria. Meta-analysis showed that there was a statistically significant difference, with improvement rates of 64.7 % versus 48.8 %, OR = 1.89 (95 % Confidence Interval was 1.61, 2.22), $P = 0.000$ (Table 10.11). Black squares refer to the odd ratio and beelines with arrows refer to the 95 % confidence intervals.

According to the Meta-analysis results, Dantonic™ is superior to ISDN in terms of relief of angina pectoris and ECG improvement.

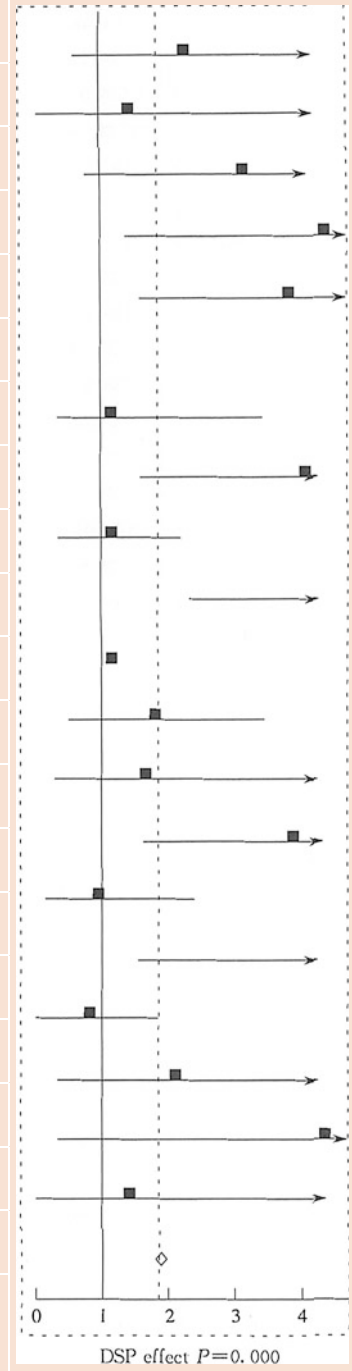
Wang et al. [26] systematically evaluated the therapeutic effect and safety of Dantonic™ and nitrate preparations in treating stable angina pectoris as a registered study of an international evidence-based medicine center. The authors collected 118 papers comparing Dantonic™ and nitrate preparations. The quality of these trials collected was evaluated with the Jadad scale, and 17 of them met the criteria. The 17 trials were also evaluated with Cochrane systematic reviews. The combined effective quantity RR (relative risk) and 95 % confidence interval of angina therapeutic effect and ECG improvement was l.12 [1.06, 1.19] and l.42 [l.20, 1.57], respectively, for the two groups. According to Cochrane systematic evaluation, the authors concluded that Dantonic™ was superior to the nitrate preparations in alleviating angina and improving ECG for stable angina pectoris. Dantonic™ also had the advantage of fewer side effects and better drug tolerance. Stratified analysis for the different treatments (≤1 month, ≥1 month) indicated that the therapeutic effect of Dantonic™ was superior to ISDN in every course of treatment, especially in longer courses. The ECG improvement rate was among the best therapeutic effects, with RR 1.41 (treatment course >1 month) and 1.16. The author objectively pointed out that the quality of each study included was generally low (with Jadad score l-2), which was the main problem in systematic evaluation. The low quality showed in the following: lack of multi-center randomized clinical trials, no estimation of sample size, no description of specific randomized methods and hidden protocol, lack of basic comparability guarantee for both randomized allocated groups, and no description of the quitting cases in most trials. The author also proposed the good suggestions that reasonable design, strict execution and multi-center, large sample, randomized, controlled double-blind trials should be used from now on to further verify the therapeutic effect of excellent Chinese patent medicines, so as to make more reliable conclusions.

The author recommends that for Dantonic™, the trial should choose as much as possible meaningful endpoint indexes, such as mortality, myocardial infarction incidence, and other indicators closely related to the quality of life, such as activities, number of hospitalizations for angina pectoris, the duration of hospitalization, etc.

The conclusion that Dantonic™ is superior to ISDN in treating stable angina pectoris has also been validated by another Meta-analysis report. Zhang et al. [1] reported a Meta-analysis of the treatment of stable angina pectoris with Dantonic™. The analysis of 14 clinical trials showed that in the heterogeneous test $P = 0.099$, OR = 3.16 [2.28, 4.27], $P < 0.00001$. For ECG improvement rates, the results of 13 clinical trials showed that in the heterogeneous test $P = 0.57$,

Table 10.10 Comparison between Dantonic™ and ISDN in terms of angina alleviation rate (no other anti-angina drugs were administrated)

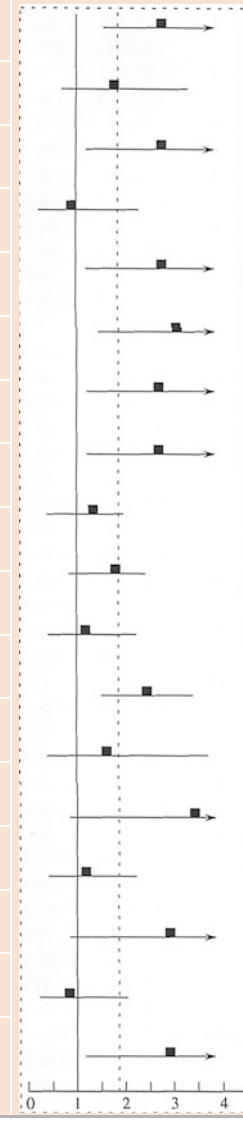
Trial	Dantonic™	Adjusted control	Weight	Odds ratio and 95 % confidence interval		
				OR	OR_L	OR_U
1	112/120 (93.3 %)	104/120 (87.0 %)	1.27	2.15	0.77	6.06
2	48/52 (92.2 %)	45/50 (90.0 %)	1.09	1.33	0.34	5.28
3	76/80 (95.0 %)	68/80 (84.5 %)	0.81	3.35	0.89	12.66
4	34/35 (89.4 %)	25/38 (66.7 %)	0.77	4.50	1.21	16.74
5	43/50 (86.0 %)	30/50 (61.1 %)	1.10	3.91	1.38	11.098
6	76/80 (95.0 %)	28/80 (34.0 %)	0.40	35.29	10.66	116.82
7	51/60 (85.0 %)	50/60 (83.3 %)	1.33	1.13	0.34	3.74
8	55/60 (91.6 %)	42/60 (70.0 %)	0.83	4.71	1.42	15.70
9	119/143 (83.8 %)	117/142 (82.5 %)	2.17	1.11	0.59	2.06
10	130/140 (93.3 %)	98/140 (70.0 %)	1.56	5.57	2.66	11.65
11	85/101 (84.2 %)	84/96 (87.5 %)	1.74	0.76	0.28	2.08
12	148/160 (92.5 %)	143/160 (89.1 %)	1.80	1.48	0.67	3.28
13	35/40 (87.5 %)	33/40 (81.6 %)	1.19	1.48	0.43	5.14
14	54/60 (90.0 %)	41/60 (68.9 %)	1.09	4.06	1.42	11.65
15	61/69 (88.4 %)	59/66 (89.4 %)	1.56	0.90	0.31	2.65
16	58/60 (96.7 %)	46/60 (76.6 %)	0.43	8.83	1.71	45.68
17	19/31 (61.3 %)	26/36 (72.3 %)	1.76	0.61	0.22	1.70
18	39/42 (92.9 %)	36/42 (85.7 %)	0.88	2.17	0.50	9.31
19	58/60 (96.0 %)	52/60 (86.7 %)	0.48	4.46	0.77	25.91
20	57/62 (92.0 %)	54/60 (90.0 %)	0.97	1.27	0.28	5.69
total	1,358/1,507 (90.1 %)	181.5/1500 (78.8 %)	23.21	1.86	1.24	2.80



Test for heterogeneity $x^2_{19} = 65.65$, $P = 0.000$
Crude, unadjusted control for total = 873/1,101

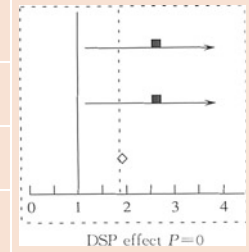
Table 10.11 Comparison of Dantonic™ with ISDN in terms of ECG improvement (no other anti-angina drugs were administrated)

Trial	Dantonic™	Adjusted control	O − E	Variance	Odds ratio and 95 % confidence interval			
					zOR	OR_L	OR_U	
1	76/120 (63.3 %)	46/120 (38.0 %)	10.00	9.96	2.78	1.47	5.27	
2	33/52 (63.5 %)	26/50 (52.0 %)	2.92	6.28	1.60	0.73	3.54	
3	54/80 (67.5 %)	34/80 (43.5 %)	6.67	6.50	2.81	1.29	6.14	
4	24/38 (63.9 %)	27/39 (69.9 %)	−0.94	3.54	0.76	0.26	2.20	
5	32/50 (64.0 %)	21/54 (38.9 %)	5.26	5.27	2.79	1.15	6.77	
6	50/80 (62.5 %)	28/80 (35.0 %)	7.33	6.69	3.10	1.40	6.83	
7	38/60 (63.3 %)	24/60 (40.0 %)	4.67	4.99	2.59	1.05	6.37	
8	42/60 (70.0 %)	28/60 (46.7 %)	4.67	4.75	2.67	1.08	6.59	
9	109/142 (76.8 %)	105/142 (73.7 %)	2.00	13.23	1.16	0.68	2.00	
10	84/140 (60.0 %)	69/140 (49.0 %)	7.50	17.41	1.54	0.96	2.48	
11	47/101 (46.5 %)	42/96 (43.8 %)	0.91	8.13	1.12	0.56	2.23	
12	100/160 (62.5 %)	64/160 (40.0 %)	16.80	18.70	2.50	1.57	3.98	
13	31/40 (77.5 %)	28/40 (71.1 %)	1.50	3.92	1.48	0.54	4.03	
14	54/60 (90.0 %)	42.6/60 (71.1 %)	4.86	3.85	3.66	1.26	10.57	
15	45/69 (65.2 %)	42/66 (63.6 %)	0.53	7.79	1.07	0.53	2.17	
16	38/60 (63.3 %)	26/60 (43.0 %)	4.00	4.97	2.26	0.92	5.52	
17	16/31 (51.6 %)	21/36 (58.3 %)	−1.12	4.18	0.76	0.29	2.00	



(continued)

Table 10.11 (continued)

Trial	Dantonic™	Adjusted control	O − E	Variance	Odds ratio and 95 % confidence interval			
					zOR	OR_L	OR_U	
18	26/42 (61.9 %)	15/42 (35.7 %)	5.50	5.31	2.93	1.21	7.10	
19	37/60 (61.7 %)	22/60 (36.7 %)	5.00	5.03	2.78	1.12	6.88	
20	39/62 (62.9 %)	24/60 (40.0 %)	4.63	5.05	2.54	1.04	6.22	
total	975/1,507 (64.7 %)	734.6/1,505 (48.8 %)	92.68	145.54	1.89	1.61	2.22	

Test for heterogeneity $x^2_{19} = 25.6$ NS
Crude, unadjusted control for total = 563/1101
Note Trial serial number of papers that met the criteria, $O - E$ observed significant minus the expected significance, *OR* odds ratio, OR_L lower limit of 95 % confidence interval, OR_U upper limit of 95 % confidence interval

OR = 1.73 [1.37, 2.20], P = 0.00001, which showed that Dantonic™ is superior to ISDN in terms of relief of angina pectoris and ECG improvement. Dantonic™ especially has advantages in treating angina pectoris.

10.1.4 Comparison of Dantonic™ with the CDT

In June 2001, the Ad hoc Expert Group of the Pan-European Federation of TCM Societies performed systemic research on the project of "Comparison of the Therapeutic Effects of Dantonic™ and CDT in the Treatment of angina pectoris." A total of 25 papers were collected, and 17 of them used randomized controlled clinical study design. In the 17 papers, a total of 1,054 cases were treated with Dantonic™, and 931 treated with CDT. There were 7 papers in which the diagnostic criteria and/or therapeutic effect were not clearly defined, and the remaining 10 papers met the criteria. The patients were divided into three groups according to whether the administration of Dantonic™ or CDT was accompanied with other anti-anginal (nitroglycerin, if taken when necessary, was not included) or anti CHD drugs.

Group 1: Anti-anginal or anti CHD drugs were not administrated

Comparison of Dantonic™ with CDT in terms of relief of angina pectoris. Meta-analysis showed that the difference in alleviation rates, 92.6 % versus 68.7 %, was statistically significant, OR = 4.54 (95 % confidence interval [2.55, 8.10]), P = 0.000 (Table 10.12).

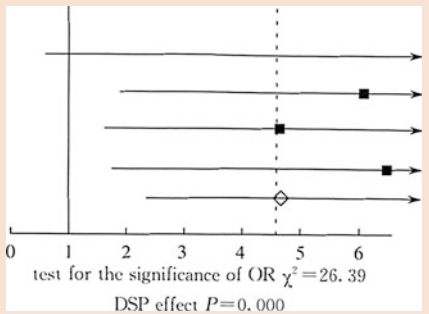
Comparison of Dantonic™ with CDT in terms of ECG improvement. Meta-analysis showed that the difference in ECG improvement rates, 61.9 % versus 40.3 %, was statistically significant, OR = 2.36 (95 % confidence interval [1.44, 3.87]), P = 0.000 (Table 10.13).

Group 2: Anti-anginal or anti CHD drugs were administrated

Comparison of Dantonic™ with CDT in terms of relief of angina pectoris. Meta-analysis showed that the difference in alleviation rates, 94.3 % versus 73.7 %, was statistically significant, OR = 4.89 (95 % confidence interval [2.80, 8.53]), P = 0.000 (Table 10.14).

Comparison of Dantonic™ with CDT in terms of ECG improvement. There were three papers that met the criteria. Meta-analysis showed that the difference in ECG improvement rates, 69.38 % versus 60.49 %, was statistically

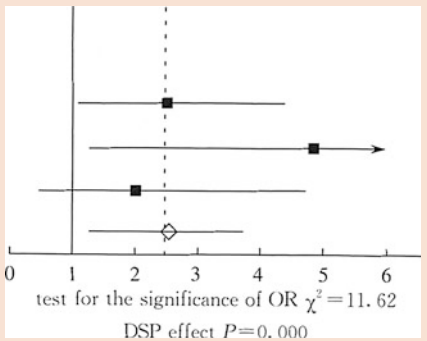
Table 10.12 Comparison of Dantonic™ and Compound Danshen Tablet in terms of the relief of angina pectoris (Group 1)

Trial	Dantonic™	Adjusted control	O − E	Variance	Odds ratio and 95 % confidence interval			
					OR	OR_L	OR_U	
1	22/23 (95.65 %)	16/23 (71.69 %)	2.755	1.606	8.68	0.96	78.32	
2	56/60 (93.3 %)	43/60 (71.67 %)	6.489	4.371	5.50	1.73	17.51	
3	33/36 (91.7 %)	24/34 (70.60 %)	3.689	2.680	4.60	1.14	18.57	
4	27/30 (63.34 %)	18/30 (60.0 %)	4.500	2.860	6.00	1.48	24.30	
Total	138/149 (92.6 %)	101/147 (68.7 %)	17.434	11.517	4.54	2.55	8.10	

Test of heterogeneity: $X_3^2 = 0.13$ NS

Table 10.13 Comparison of Dantonic™ with Compound Danshen Tablet in terms of ECG improvement rate (Group 1)

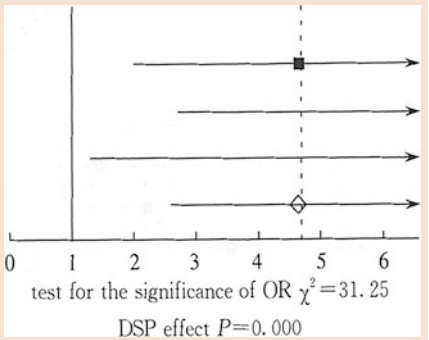
Trial	Dantonic™	Adjusted control	O − E	Variance	Odds Ratio and 95 % confidence interval			
					OR	OR_L	OR_U	
1	35/60 (58.33 %)	24/60 (40.0 %)	5.499	7.560	2.10	1.01	4.35	
2	24/36 (66.70 %)	11/34 (32.25 %)	6.024	4.435	4.21	1.55	11.42	
3	19/30 (63.34 %)	15/30 (50.0 %)	2.001	3.745	1.73	0.62	4.85	
Total	78/126 (61.90 %)	50/124 (40.3 %)	13.524	15.741	2.36	1.44	3.87	



Test of heterogeneity: $X_3^2 = 1.63$ NS

Table 10.14 Comparison of Dantonic™ with Compound Danshen Tablet in terms of relief of angina pectoris (Group 2)

Trial	Dantonic™	Adjusted control	O − E	Variance	Odds ratio and 95 % confidence interval			
					OR	OR_L	OR_U	
1	85/93 (91.4 %)	64/89 (71.94 %)	8.85	6.78	4.15	1.75	9.79	
2	54/56 (96.43 %)	39/56 (69.64 %)	7.50	3.98	11.78	2.57	53.96	
3	58/60 (96.67 %)	48/60 (80.0 %)	3.34	1.64	7.26	1.37	38.56	
Total	197/209 (94.3 %)	151/205 (73.7 %)	19.69	12.40	4.89	2.80	8.53	



Test of heterogeneity: $X_3^2 = 1.22$ NS
Crude, unadjusted control total = 127/175

significant, OR = 1.39 (95 % confidence interval [0.90, 2.13]), $P = 0.100$ (Table 10.15).

Group 3: Whether anti-anginal or anti CHD drugs were administered or not was unknown

Comparison of Dantonic™ with CDT in terms of relief of angina pectoris. Meta-analysis showed that the difference in alleviation rates, 86.70 % versus 70.18 %, was not statistically significant, OR = 2.00 (95 % confidence interval [0.86, 4.62]), $P = 0.100$ (Table 10.16).

Comparison of Dantonic™ with CDT in terms of ECG improvement. Meta-analysis showed that the difference in ECG improvement rates, 50.58 % versus 34.88 %, was statistically significant, OR = 2.08 (95 % confidence interval [1.28, 3.38]), $P = 0.000$ (Table 10.17).

The black squares refer to the odd ratio and the beelines and beelines with arrows refer to the 95 % confidence intervals.

10.2 Treatment of Unstable Angina Pectoris with Dantonic™

10.2.1 Unstable Angina Pectoris

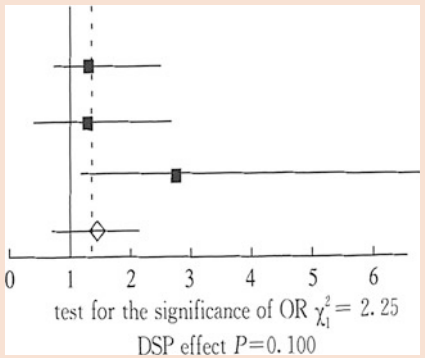
Unstable angina pectoris (UAP) is an unstable clinical myocardial ischemic syndrome between angina pectoris and myocardial infarction. It is considered at present that its occurrence and development is closely associated with the following factors: plaque rupture and erosion, platelet over-activation and aggregation, inflammation, increase of sympathetic nerve excitability, increase of vascular TXA_2, white blood cell activation, decrease of fibrinolytic capacity, thrombosis (obvious signs include the increase of serum fibrin related antigen D-dimer, the increase of serum tissue plasminogen activator and the fibrinolytic activator inhibitor-1, as well as the increase of prothrombin, etc.), coronary artery spasm and stenosis (dysfunction of coronary artery endothelium, such as the release of endothelin (ET) which promotes the vascular contraction, and the release of prostacyclin, which inhibits vascular relaxing factor). UAP is one of the clinical manifestations of acute coronary artery syndrome. About 15 % of UAP cases will develop into acute myocardial infarctions. According to clinical research, about 50 % of myocardial infarctions were developed from UAP. Reaching the goal of relieving the symptoms and preventing myocardial infarction and sudden death by active treatment of UAP is the hottest topic in current CHD therapy. Since 1994, when Dantonic™ was on the market, it was mainly used for anti-angina purposes and for reducing nitroglycerin consumption. Since 1999, clinicians have found that Dantonic™ has the function of anti-platelet activation and stabilizing atherosclerotic plaques. More and more doctors began to use Dantonic™ as an important adjunctive drug in the treatment of UAP.

Liu [27] reported a study in which 34 cases of UAP were treated with Dantonic™ and the results were compared with those with ISDN. The total effective rates of these two drugs were 94.1 and 74.2 %, respectively. Statistical analysis showed that Dantonic™ was more effective than ISDN in treating UAP ($P < 0.05$). The author concluded that this medicine had good effect not only for stable-type CHD but also for UAP. It was believed that Dantonic™ could prevent myocardial infarction as well.

He et al. [28] reported the treatment of 16 cases of UAP with Dantonic™, and the effective rate was 75 % (Table 10.18).

Wang et al. [29] randomly divided 40 cases of UAP into two groups: the conventional treatment group (20 cases) and Dantonic™ group (20 cases). The patients in the conventional treatment group received low molecular weight heparin for 5–-7 days, aspirin, nitrates, Ca^{++} antagonists, β-receptor blockers, etc. The patients in the Dantonic™ group received Dantonic™ in addition to conventional treatment for 4 weeks. The levels of GMP-140, plasminogen activator (t-PA) and its inhibitor (PAI-1) in the patients before treatment were determined. The results showed that there were no significant differences in GMP-l40, PAI-1 and t-PA between the two groups before treatment.

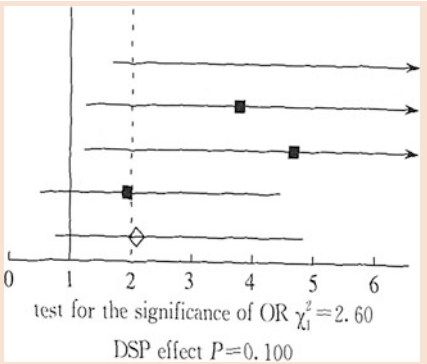
Table 10.15 Comparison of Dantonic™ with Compound Danshen Tablet in terms of the ECG improvement rate (Group 2)

Trial	Dantonic™	Adjusted control	O − E	Variance	Odds ratio and 95 % confidence interval			
					OR	OR_L	OR_U	
1	67/93 (72.04 %)	61/89 (68.53 %)	1.60	9.54	1.18	0.63	2.24	
2	35/56 (62.28 %)	33/56 (58.93 %)	0.94	6.75	1.15	0.54	2.46	
3	43/60 (71.67 %)	30/60 (50.0 %)	4.33	4.63	2.53	1.02	6.28	
Total	145/209 (69.38 %)	124/205 (60.49 %)	6.87	20.92	1.39	0.90	2.13	

Test of heterogeneity: $X_3^2 = 2.20$ NS
Crude, unadjusted control total = 109/175

Table 10.16 Comparison of Dantonic™ with Compound Danshen Tablet in terms of the relief of angina pectoris (Group 3)

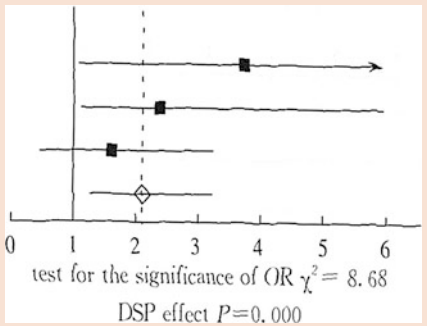
Trial	Dantonic™	Adjusted control	O − E	Variance	Odds ratio and 95 % confidence interval			
					OR	OR_L	OR_U	
1	29/30 (96.7 %)	20/30 (66.7 %)	4.50	2.08	14.63	1.72	124.63	
2	41/45 (91.0 %)	33/45 (73.3 %)	3.98	3.34	3.68	1.09	12.42	
3	43/46 (93.5 %)	36/46 (78.2 %)	3.52	2.82	4.01	1.02	15.71	
4	76/97 (78.86 %)	64/97 (65.8 %)	3.76	5.45	1.94	0.86	4.35	
Total	189/218 (86.70 %)	153/218 (70.18 %)	15.77	13.89	2.00	0.86	4.62	



Test of heterogeneity: $X_3^2 = 2.72$ NS
Crude, unadjusted control total = 116/162

Table 10.17 Comparison of Dantonic™ with Compound Danshen Tablet in terms of the ECG improvement rate (Group 3)

Trial	Dantonic™	Adjusted control	O − E	Variance	Odds ratio and 95 % confidence interval			
					OR	OR_L	OR_U	
1	17/30 (55.6 %)	9/30 (28.54 %)	4.06	3.72	3.14	1.07	9.15	
2	30/45 (67.2 %)	20/45 (44.4 %)	5.13	5.61	2.57	1.09	6.04	
3	40/97 (41.54 %)	31/97 (32.25 %)	2.68	6.89	1.49	0.69	3.22	
Total	87/172 (50.58 %)	60/172 (34.88 %)	11.87	16.22	2.08	1.28	3.38	



Test of heterogeneity: X_3^2 = 1.48 NS
Crude, unadjusted control total = 42/116
Note Explanations for Tables 10.12, 10.13, 10.14, 10.15, 10.16, 10.17: same as the note at the end of Table 10.11

Table 10.18 The Effect of Dantonic™ on the treatment of stable and unstable angina pectoris

Group	Cases	Markedly effective rate (%)	Effective rate (%)	Total effective rate (%)
Stable angina pectoris	46	60.87	30.43	91.3
Unstable angina pectoris	16	31.25	43.75	75

However, there were obvious decreases in GMP-140 and PAI-1 and increases in t-PA in both groups after treatment. The increase in the content of GMP-140 (32.7 ± 22.58 μg/L) and the activity of t-PA (0.49 ± 0.28 Iu/m1) in the Dantonic™ group were significantly higher than those in the conventional treatment group (18.25 ± 16.69 μg/L, 0.34 ± 0.16 Iu/ml, respectively, $P < 0.05$). The decrease in PAI-l activity in the Dantonic™ group (3.77 ± 1.70 Au/ml) was bigger than that in the conventional treatment group (2.86 ± 1.54 Au/ml), but the difference was not statistically significant ($P > 0.05$). It indicated that Dantonic™ was able to inhibit platelet activation and improve fibrinolytic activity. The authors pointed out the fact that the effect of Dantonic™ on reducing PAI-l was statistically similar to that of the conventional treatment, so Dantonic™'s effect on the increase of t-PA activity in UAP might not be implemented by decreasing PAI-1 and decreasing the inactivation of t-PA. Rather, the mechanism might be related to the increased synthesis and release of t-PA.

Judging from the change in GMP-140 levels, Dantonic™ has a long-term and stable effect on the treatment of UAP. Recently it has been found that coronary artery endothelium injury, platelet dysfunction, and thrombogenesis form the pathological basis and are important causes of UAP, and abnormality of platelet activation is the most important. Plasma α-Granule membrane protein-140 (GMP-l40) is a membrane protein located mainly in the granular membrane of platelets and Weibel-palade bodies of vascular endothelial cells. When platelets are activated, the granular content is released and GMP-140 immediately binds to the plasma membrane. The concentration of GMP-140 in plasma can accurately reflect the activation state of platelets. It is believed at present that GMP-140 is the specific molecular marker of platelet activation.

Lu [30] was the first person who reported the effect of Dantonic™ on the treatment of UAP. The patients were divided into the Dantonic™ group and the control group randomly. The patients in the Dantonic™ group were administered with aspirin and Dantonic™ for 4 weeks, and the patients in the control group were treated with aspirin only. Twenty healthy people were set as the normal control. The results are shown in Fig. 10.4. Before the treatment, the patients with UAP had markedly higher GMP-140 levels than did the healthy people ($P < 0.01$). After treatment, the symptoms of angina pectoris and ECG improvement of the Dantonic™ group were significantly superior to those of the control group, and their GMP-140 levels were markedly lower than in the control group ($P < 0.05$) and similar to those of the healthy people ($P > 0.05$). The patients in the control group still had higher GMP-140 levels than did healthy people after treatment ($P < 0.05$) (Fig. 10.5).

By October of 2007, there was a total of 37 reports on the treatment of 1661 UAP patients with Dantonic™. Most authors adopted Dantonic™ in addition to routine treatment (nitrates, Ca^{++} antagonists, β-receptor blockers, enteric coated aspirin or low molecular weight heparin). Among the 37 reports, 31 (83.8 %) used randomized controlled design in their trials.

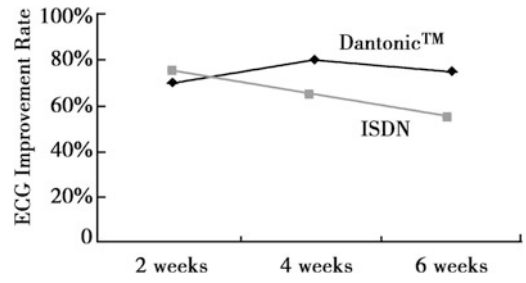


Fig. 10.4 Effect of long-term administration of Dantonic™ and Isosorbide Dinitrate on ECG improvement rate

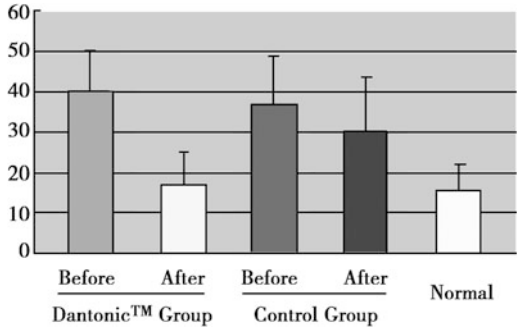


Fig. 10.5 Effect of Dantonic™ on plasma GMP-140 concentration in UAP patients

10.2.2 Systemic Assessment of Randomized Trials of Treating UAP with Dantonic™ as an Adjuvant Therapy (Meta-analysis)

UAP is a serious and potentially dangerous accident and emergency, and can easily develop into acute myocardial infarction (AMI) or sudden death. It is a syndrome between chronic stable angina pectoris and AMI. In recent years, numerous clinical reports have demonstrated that UAP is a common type of CHD. According to evidence-based medical research, especially the extensive application and development of cardiac percutaneous coronary intervention technology, a large amount of clinical evidence about the disease has been obtained. The European Heart Association, the Heart Association of the United States, and the WHO have proposed UAP treatment guidelines. The current consensus is that UAP is a complex clinical syndrome with dynamic changes and should be recognized as the precursor to myocardial infarction. Both UAP and myocardial infarction have common pathophysiological links, and UAP has an even closer relationship with the pathophysiological characteristics of non-ST-segment elevation myocardial infarction. All clinicians should have to comply with this conventional treatment for critical emergency patients with unstable angina. Therefore, we believe that routine treatment is essential to the patients which have been diagnosed with UAP. Dantonic™ has a significant effect in improving platelet activation, stabilizing atherosclerotic plaques, and alleviating angina. Someone speculated from a clinical and pharmacological point of view that Dantonic™ might have effects on UAP. Since Dantonic™ entered the market in 1994, several authors have used a sound treatment protocol for UAP patients, that is, treating them with conventional therapy plus Dantonic™, and compared the results with the conventional therapy. There are no systemic evaluations of the new treatment regime. Our research group collected the relevant documents to implement a Meta-analysis and evaluate the effect and safety of Dantonic™ in combination with conventional treatment for UAP.

10.2.2.1 Method

Literature Adoption Criteria

a. The diagnostic criteria for UAP were formulated by the World Health Organization.
b. The trial was randomized and controlled.
c. The conventional treatment followed the Guidelines for the Management of Patients with unstable angina, and Dantonic™ was used as an adjuvant therapy.

Diagnostic Criteria and Outcome Indicators

According to the diagnosis criteria of WHO, clinical angina pectoris improvement and ECG abnormality improvement were used as outcome indicators.

Literature Retrieval

Chinese Medicine Conference Proceedings (1994–2006), Chinese Academic Journal (1994–2006), Wan Fang Database (1994–2006), Medline (1994–2006), EbmASE (1994–2006), Biological Abstracts (1994–2006), Chinese Biomedical Database (1994–2006), The Cochrane, a clinical trial registration database in the field of Evidence-based medicine. Manually retrieved from several nervous system diseases conference proceedings and obtaining the relevant literature from the Tianjin Tasly Company Institute and other pharmaceutical companies.

Table 10.19 Jadad's Scale

Content	Score
Adoption and description of the randomization methodology	0/1
Adoption and detailed description of the randomization methodology	0/1
Double–blind design	0/1
Description of double–blind methodology (placebo and positive control drug)	0/1
Records of withdrawal and missing cases	0/1
Records with a starting point by adopting the random method	0/1
Records of studies adopting the double-blind methodology, but the blind methodology is not appropriate	0/1

Clinical Research Papers Quality Scoring Method

Use the Jadad scoring method (Table 10.19).

According to RCT grading rules, a score of 3–5 corresponds to high-quality research; scores below 3 correspond to low-quality research. All RCTs were evaluated independently by two evaluators with expertise in statistics and epidemiology who used a Jadad grading sheet to choose the clinical trial papers and collected information strictly with pre-designed forms. In case of disagreement, it was decided through discussion and a meeting of whole group participated in by all members. If papers were found to be lacking of information, the author(s) would be contacted, if possible, to obtain firsthand information.

Statistics

Adoption of Rev Man4.1 software. Relative Risk was adopted for numeration data and Weighted Mean Difference was adopted for continuous variable. Both were expressed by 95 % of confidence intervals. If the result showed good homogeneity, the Fixed Effects Model was adopted to implement the Meta-analysis. If the result showed heterogeneity, the Random Effects Model was adopted.

10.2.2.2 Results

Literatures Adopted by Meta

By October 2007, there were a total of 37 papers reporting the treatment of 1,661 UAP patients with Dantonic™. After reading the papers, 25 RCT were identified, with 1,060 cases. Among the 25 RCT papers, 4 papers had brief descriptions about their randomized studies, so they were rated as 2 points. The other 21 papers were rated as 1 point according to the Jadad scale. None of the papers had descriptions of withdrawals and dropouts, nor had estimations of sample sizes. The maximum sample size included in the trials was 91 cases. Only 7 papers (28 %) had more than 50 samples, and none more than 100 (Table 10.19). Since Dantonic™ is a medicine favored by many patients, the trials should be designed in strict accordance with the multi-center, large sample, randomized controlled double-blind principles, so that the conclusions will be more reliable.

Major Conclusion

The combination of Dantonic™ with conventional therapy has better therapeutic effects on UAP than conventional therapy alone. Meta-analysis showed that the difference between the two therapies is significant ($P < 0.00001$) (See Fig. 10.6) (Table 10.20).

10.3 Treatment for Silent Myocardial Ischemia (SMI) with Dantonic™

Silent myocardial ischemia (SMI) is also called asymptomatic myocardial ischemia, or occult myocardial ischemia in some papers. The disease has no objective evidence, like pain, for myocardial ischemia, and there are no symptoms of angina apparent in the patients. SMI often occurs

Review: a study on the treatment of unstable angina pectoris with Dantonic™
Comparison: 01 Danshen group v.s. a routine treatment group
Outcome: 01 effective rate of relief of angina pectoris, Dantonic™ group vs. conventional treatment group

Study or sub-category	Treatment group n/N	Control group /N	OR(fixed) 95%CI	Weight	OR(fixed) 95%CI
2003-1	1/20	3/20		1.12	0.30[0.03,3.15]
2000-1	3/21	9/21		3.03	0.22[0.05,0.99]
2001-1	3/38	9/35		3.39	0.25[0.06,1.01]
2003-2	3/42	10/38		3.83	0.22[0.05,0.85]
2003-3	2/25	4/16		1.76	0.26[0.04,1.63]
2003-4	3/86	10/82		3.88	0.26[0.07,0.98]
2003-5	3/22	10/22		3.39	0.19[0.04,0.83]
2003-6	3/30	12/30		4.24	0.17[0.04,0.67]
2003-7	4/32	10/30		3.55	0.29[0.08,1.04]
2004-1	2/35	8/35		2.96	0.20[0.04,1.04]
2004-2	2/20	10/18		3.72	0.09[0.02,0.50]
2004-3	4/33	8/32		2.80	0.41[0.11,1.54]
2004-4	4/40	14/40		4.95	0.21[0.06,0.70]
2004-5	3/36	11/34		4.07	0.19[0.05,0.76]
2004-6	0/34	1/34		0.58	0.32[0.01,8.23]
2005-1	3/60	28/60		10.45	0.06[0.02,0.21]
2005-2	2/40	8/40		2.98	0.21[0.04,1.06]
2006-1	3/50	13/48		4.90	0.17[0.05,0.65]
2006-2	3/31	9/26		3.47	0.20[0.05,0.85]
2006-3	9/40	20/40		6.09	0.29[0.11,0.76]
2006-4	6/76	18/70		6.78	0.25[0.09,0.67]
2006-5	4/35	8/31		2.95	0.37[0.10,1.38]
2006-6	4/57	9/52		3.44	0.36[0.10,1.25]
2006-7	7/66	14/62		5.07	0.41[0.15,1.09]
2007-1	6/91	18/91		6.60	0.29[0.11,0.76]
Total (95% CI)	1060	1007		100.00	0.23[0.18,0.30]
Total events:87(treatment group),274(control group) Test for heterogeneity:Chi?=9.84,df=24(P=1.00),I?=0 Test for over all effect:Z=10.93(P< 0.00001)					

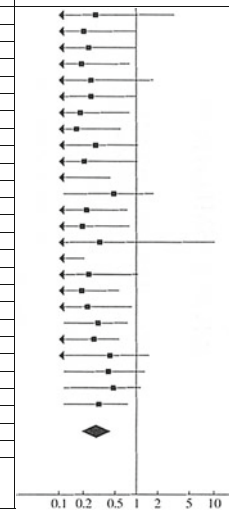


Fig. 10.6 Meta-analysis of the trials of treating unstable angina pectoris with Dantonic™

in the following clinical backgrounds: (1) ECG exercise test is positive, but asymptomatic; (2) Coronary angiography shows significant stenosis of blood vessels, while asymptomatic; (3) There is myocardial infarction which is not identified or asymptomatic; (4) No symptomatic history, but there are old myocardial infarctions; (5) Angina is chronic and stable, and sometimes asymptomatic when myocardial ischemia occurs.

There are three types of SMI: Type I: Complete SMI; Type II: SMI after myocardial infarction; Type III: angina pectoris accompanied with SMI. Between 60 and 67 % of patients with chronic CHD were found to have symptoms of ST segment decrease by means of Ambulatory electrocardiogram, and the ratio was even greater for patients with UAP. Currently, it is believed that the clinical significance of SMI is as important as that of anginal myocardial ischemia. SMI is often overlooked because of the absence of symptoms, which is generally acknowledged as a risk factor for poor prognosis of CHD, which is especially true for missed SMI: its prognosis is even worse than that of angina myocardial ischemia. Investigators believe that the cause of myocardial infarction or sudden death is not the symptom, but the duration and degree of myocardial ischemia. SMI patients may not be sensitive to pain caused by myocardial ischemia. For myocardial ischemia, the symptom of pain is actually a very good warning sign. SMI patients often have no knowledge of the occurrence of myocardial ischemia which will be developed into myocardial infarction and sudden death in the future. Therefore, in order to reduce the occurrences of myocardial infarction and sudden death, clinicians put increasing attention toward the prompt diagnosis and treatment of SMI.

The mechanism for SMI occurrence is still unclear, and may be related to the following factors: (1) myocardial ischemia occurs within a small area and is of short duration, the degree of ischemia is light, the degree of pain stimulus is too weak to meet the threshold of angina, or some patients have a higher threshold for pain; (2) Some investigators believe that in some patients there may exist problems in their pain conduction system. In particular, patients with diabetes or myocardial infarction have a significantly increased occurrence rate of SMI. The nociceptive afferent nerve

Table 10.20 Jadad scoring of the papers on the treatment of UAP with Dantonic™

No.	Volume of sample	Randomized design	Description of Randomized Methodology	Double-blind	Description of double-blind methodology	Description of case loss	There is evidence that random method is inappropriate	There is evidence that double-blind method is inappropriate	Side Effect	Jadad Grading
2000-1	21	✓	–	–	–	–	–	–	✓	1
2001-1	38	✓	–	–	–	–	–	–	✓	1
2003-1	20	✓	–	–	–	–	–	–	✓	1
2003-2	42	✓	–	–	–	–	–	–	✓	1
2003-3	25	✓	–	–	–	–	–	–	?	1
2003-4	86	✓	–	–	–	–	–	–	?	1
2003-5	22	✓	–	–	–	–	–	–	?	1
2004-1	35	✓	–	–	–	–	–	–	?	1
2004-2	20	✓	–	–	–	–	–	–	?	1
2004-3	33	✓	–	–	–	–	–	–	✓	1
2004-4	40	✓	✓	–	–	–	–	–	✓	2
2006-1	50	✓	–	–	–	–	–	–	✓	1
2006-2	31	✓	–	–	–	–	–	–	✓	1
2006-3	40	✓	✓	–	–	–	–	–	✓	2
2005-1	60	✓	✓	–	–	–	–	–	✓	2
2006-4	76	✓	–	–	–	–	–	–	✓	1
2005-2	40	✓	–	–	–	–	–	–	✓	1
2006-5	35	✓	–	–	–	–	–	–	✓	1
2006-6	57	✓	–	–	–	–	–	–	✓	1
2003-6	30	✓	–	–	–	–	–	–	✓	1
2003-7	32	✓	✓	–	–	–	–	–	✓	2
2007-1	91	✓	–	–	–	–	–	–	?	1
2004-5	36	✓	–	–	–	–	–	–	?	1
2004-6	34	✓	–	–	–	–	–	–	✓	1
2006-7	66	✓	–	–	–	–	–	–	✓	1

terminals of these patients might suffer from abnormalities, degeneration, and necrosis, or the patient may have an autonomic nervous system disease. (3) Some patients may have an anomaly of the pain reception system, as endogenous analgesic substances (such as endogenous opioids, endogenous endorphin) and the content of pain-producing substances may affect the pain threshold and pain stimulation when myocardial ischemia occurs. This plays an important role for the symptoms occurrence of myocardial ischemia. Most investigators do not believe that the degree of coronary artery stenosis is a factor in determining whether or not symptoms occur during myocardial ischemia.

SMI is a common disease in elderly CHD patients. It is a reversible disorder in myocardial perfusion and electric activities, without angina symptoms, ECG showing ST segment depression, coronary arteriography or pathological examination showing coronary artery stenosis. Some researchers believe that the cause of myocardial ischemia is the change in the tension of blood vessels due to coronary artery stenosis.

Zhu et al. (1997) treated 60 cases of coronary artery insufficiency with isosorbide mononitrate plus Dantonic™ for 12 weeks. The clinical symptoms and cardiograms were markedly improved in the group that took isosorbide mononitrate and Dantonic™ compared with the

control group, which was treated with isosorbide mononitrate alone.

Fan and Jia [31] reported 71 cases of CHD diagnosed in accordance with the WHO criteria. The SMI diagnosis was based on a 24-h dynamic electrocardiogram, and the criteria were adopted from the 1992 Chinese National myocardial ischemia and Reperfusion Injury and SMI Thematic Studies, i.e. ST segment flat or droop-type depression ≥ 0.01 mv, duration ≥ 1 min, and at least 1 min apart from the last ischemia to be counted as an attack. If angina pectoris occurred, it would be diagnosed as symptomatic myocardial ischemia. Cohn's SMI typing was adopted: type I complete SMI, 2 cases; type II myocardial infarction with SMI, 30 cases; type III angina pectoris accompanied with SMI, 39 cases. The authors divided these cases into two groups: Dantonic™ treatment group (36 cases) and ISDN control group (35 cases). The results showed that both Dantonic™ and ISDN reduced the occurrence of SMI and shortened SMI duration. Both groups showed significant differences before and after treatment. A comparison between the two groups showed that Dantonic™ was obviously superior to ISDN. The authors concluded that Dantonic™ should be the medicine of first choice in the treatment of SMI.

Zhu and Gu [32] observed 52 SMI patients who were treated with Dantonic™ and 52 SMI patients who were treated with ISDN, both for 4 weeks. The results showed that the efficacy gradually improved as the treatment prolonged. The effective rates after 4 weeks' treatment were 75 and 38.5 % in the Dantonic™ group and ISDN group, respectively. In addition, both the number of premature ventricular contractions and the average occurrence were markedly reduced after treatment with Dantonic™. The dynamic ECG recorded frequency and duration of premature ventricular contractions before and after Dantonic™ treatment was shown in Table 10.21.

SMI has hidden symptoms, so it is often overlooked by patients and physicians. It is difficult to diagnose in the early stage of the disease, and the prognosis could be worse than that of symptomatic myocardial ischemia. SMI patients are also in danger of myocardial infraction and sudden death. SMI needs to be treated in time with Dantonic™ in order to reduce the risk of myocardial infraction and sudden death.

Single-photon emission computed tomography (SPECT) with ^{99m}TC-MIBI as the myocardial imaging agent can be used to measure myocardial ischemia area (MIA), which directly reflects the viability of the myocardial cells and the distribution of myocardial blood flow. It is one of the best methods of noninvasive diagnosis of CHD. Zhang and Wang [33] reported the status of 32 cases of CHD patients after being treated with Dantonic™ for 4 weeks: the MIA value of the 32 patients after using Dantonic™ for 4 weeks was l4.2 ± 6.8 %, which was markedly lower than the value before the treatment, 32.6 ± 7.4 % ($P < 0.01$).

Wang et al. [34] used Dantonic™ to treat 30 cases of SMI, and the control group was treated with ISDN. The recovery of ST segment ST-segment depression in ECG was adopted as the evaluation criterion. It was found that Dantonic™ was superior to ISDN in terms of improving SMI, and the therapeutic effect increased with treatment time (Fig. 10.7).

Niu [35] also demonstrated that Dantonic™ was the first choice to treat SMI. Chen and Yu [36] randomized 64 cases of SMI patients into two groups: 36 cases in the Dantonic™ group and 28 cases in the ISDN group. The results

Table 10.21 ECG recorded frequency and duration of *premature ventricular contractions* before and after Dantonic™ treatment

Treatment	Number of premature beats (time)	Accumulated time of premature beats (min)	Average attack duration (min/time)
Before	95	510	5.37
After	24	38	1.58

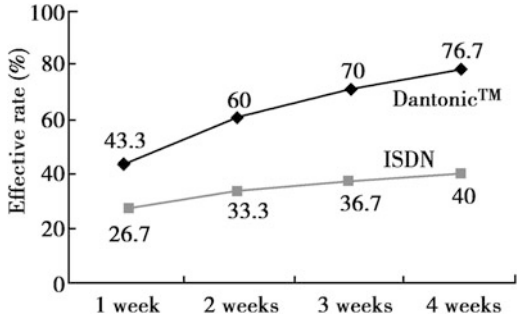


Fig. 10.7 The effective rates of Dantonic™ and ISDN on the treatment of SMI

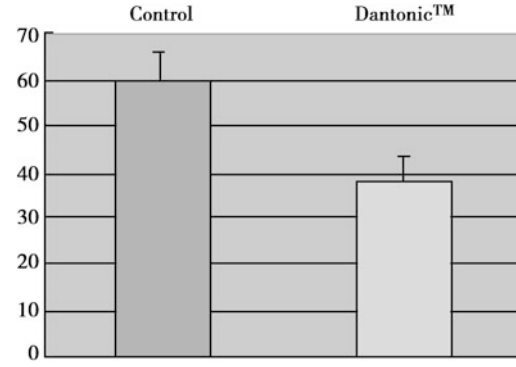


Fig. 10.8 Control, Dantonic

showed that the ST segment improved rate in Dantonic™ group was 83 %, which is higher than that of the ISDN group (57 %), $P < 0.05$. According to 24-hour Holter recordings, the ST segment improved rate in Dantonic™ group was 78 %, which was higher than that in the ISDN group (50 %), $P < 0.05$.

10.4 The Effect of Dantonic™ on Arrhythmia in Patients with Angina Pectoris

CHD arrhythmia refers to myocardial ischemia evoked arrhythmia which is caused by coronary atherosclerosis. Arrhythmia may be the only ischemic heart disease symptom. In this case, a coronary angiography should be carried out to confirm a coronary obstructive disease (WHO 1979). A serious cardiac rhythm disturbance can damage the pump function of the heart and endanger the patient's life. Obstructive diseases caused by coronary artery stenosis will result in chronic myocardial ischemia. The ischemic damage to myocardial metabolism, functions, and structure, and electrophysiological changes are the primary factors causing CHD arrhythmia (Figs. 10.8, 10.9, 10.10, 10.11).

Cheng et al. (1994) used Dantonic™ to treat 99 cases of CHD, angina pectoris, and cardiac arrhythmia. He divided them into two groups; the treatment group in which the patients received conventional Western medicine plus Dantonic™ treatment (51 cases), and the control group in which the patients received Western medicine treatment only (48 cases). The effective rates were 85 and 64 % in the treatment and control groups, respectively, ($P < 0.01$).

Shou et al. [37] reported 66 cases of premature ventricular contractions with Lown Criteria ≤III, the total over 24 h of ventricular premature contractions and upper ventricular premature contractions was less than 2,000 but more than 1,100, and the heart function of patients was ≤III. There were 26 cases of ventricular premature contractions, 16 cases of upper ventricular premature contractions, and 24 mixed cases. The authors eliminated arterial fibrillation and sinus arrhythmia. 66 cases were randomized into two groups: Dantonic™ group (35 cases) and control group (31 cases). Aspirin, ISDN, nitroglycerin, antihypertensive, and anti-myocarditis medicines (nom–β-receptor blockers or Ca^{++} antagonists) were allowed to use during the treatment period. After 4 weeks' treatment, Dantonic™ showed therapeutic effects on coronary premature contractions. The results also showed that Dantonic™ interacted with the anti-arrhythmic medicine Propafenone; pharmacologically, the two drugs had an additive and synergistic effect. These effects were statistically significant.

Zheng et al. (1999) observed 56 cases of CHD arrhythmic (sinus bradycardia, arterial premature beats, junctional premature beats, premature ventricular contractions, atrioventricular junction block, and bundle branch block, etc.). After

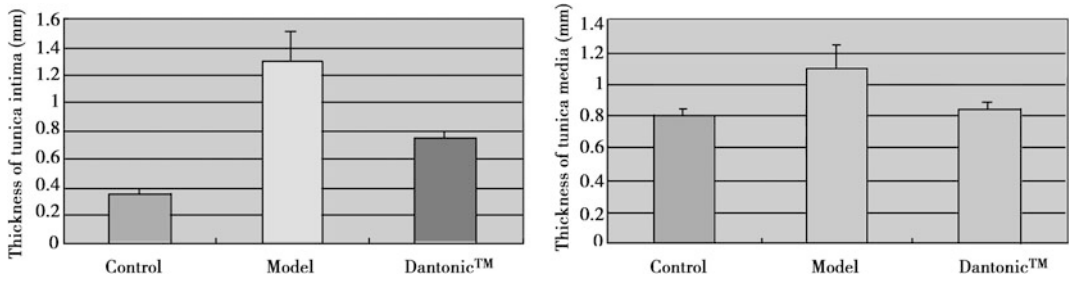


Fig. 10.9 Thickness of tunica intima, tunica media

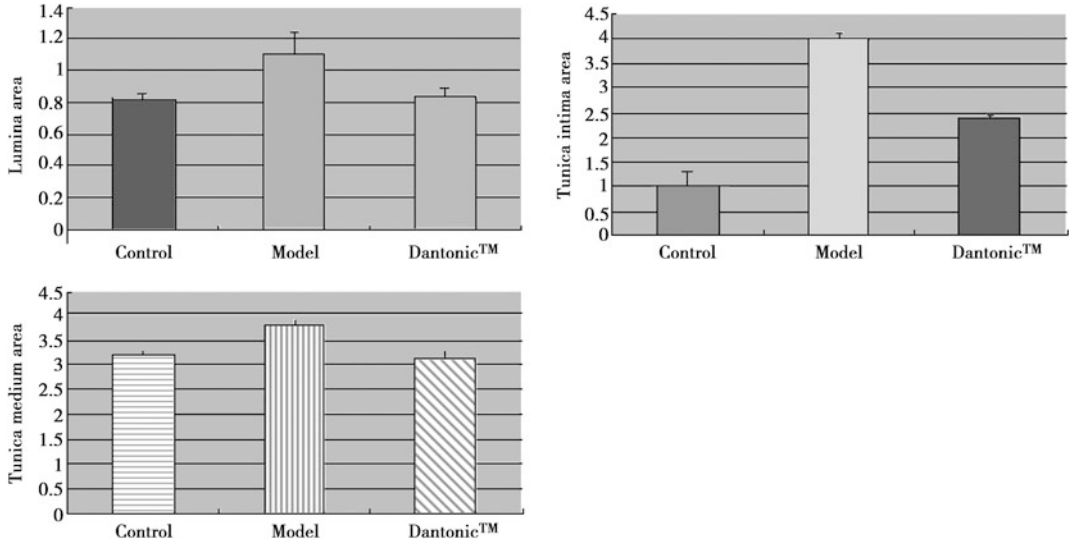


Fig. 10.10 Lumina area, tunica intima area, tunica medium area

2 weeks' treatment with Dantonic™, all arrhythmic symptoms were improved with the exception of bundle branch block.

Duan et al. [38] used berberine combined with Dantonic™ to treat premature ventricular contraction, and the results showed that the effect was significantly superior to that of Propafenone. Dantonic™ has the effect of improving myocardial ischemia, reducing heart rate, lowering the ectopic pacemaker, and bringing about the disappearance or reduction of premature ventricular contraction.

Zhang et al. [39] treated 60 CHD patients with Dantonic™ and Astragalus Injection for 30 days. 38 of these patients had cardiac arrhythmia

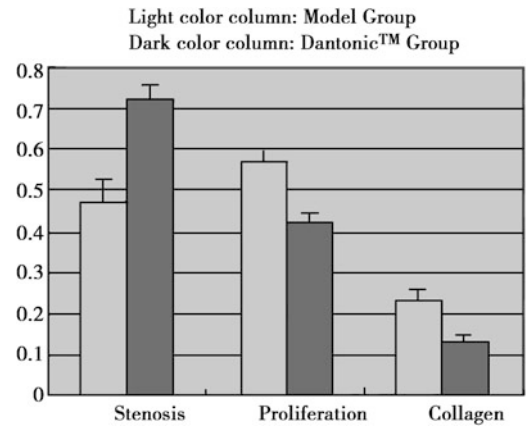


Fig. 10.11 Model Group, Dantonic™ Group

(arterial premature ventricular contractions, premature AV junctional beats, arterial premature ventricular contractions with paroxysmal ventricular tachycardia, premature nodal contraction with arterial fibrillation, and so on). After treatment, 29 cases were improved, and the anti-arrhythmic effective rate was 76.3 %. In the control group (34 cases), which was treated with Astragalus Injection and ISDN, the effective rate was 54.8 %.

Zheng and Ci (2000) treated 56 cases of CHD arrhythmia with Dantonic™. After treatment, all arrhythmic symptoms were improved significantly (Table 10.22).

The authors believed that Dantonic™ had a significant curative effect on arrhythmia, and the possible mechanisms could be the following: (1) Calcium antagonism. The Danshen components in Dantonic™ could reduce the concentration of intracellular free calcium and prevent calcium overload. (2) Protection of myocardial cell membrane. Damage to myocardial cell membranes is caused by myocardial ischemia and the membrane potential of myocardial cells is also changed. (3) Elimination of free radicals. The overload of free radicals can cause arrhythmia. (4) Tanshinol could increase ATP synthesis and energy supply.

Ni et al. [40, 41] observed that Dantonic™ can enhance the heart rate variability of soldiers who carried out emergency training, which indicated that Dantonic™ could protect the myocardia of these soldiers.

In recent years, more and more investigators believe that ventricular repolarization dispersion (QT) reflects ventricular repolarization, and is an indicator for cardiac instability. QT thus has the significance of predicting ventricular arrhythmia, especially malignant arrhythmia. Some authors believe that ventricular fibrillation in AMI is positively correlated with QTd, and recent statistics showed that ventricular fibrillation is the primary cause of early AMI. At present, the QT interval is measured from the starting-point of QRS to the intersection of the T wave descending branch and isoelectric baseline. The QT intervals are measured at each lead of the 12-lead surface ECG for three consecutive cycles, and then an average is taken. $QTd = QT_{max} - QT_{min}$.

Since 1999, several authors have observed the effect of Dantonic™ on the ECG QT value of CHD patients. Jia et al. [23, 42] found Dantonic™ was able to improve the QT value in old patients. Zhu [43] confirmed that Dantonic™ could improve the QT value of CHD patients. Zhang [44] and Qiao [45] used Dantonic™ to treat patients with myocardial infarction and confirmed that Dantonic™ did improve QT (Table 10.23)

It has been also reported that Dantonic™ has positive effects on arrhythmic patients without CHD. Clozapine is widely used as a clinical antipsychotic. Clozapine has strong anti-choline and anti-epinephrine effects. It was reported that ECG changes were found in 43 % of the patients and most of them were suffering from sinus tachycardia and T-wave changes. The abnormal cardiac rate increases with Clozapine dosage and the proportion of ECG QTc prolongation. It has important clinical significance in the reduction of sudden death in the course of the treatment with Clozapine to reduce the T-wave changes and prevent QTc interval prolongation.

Zhou and Zhu [46] used Dantonic™ to treat 35 patients with T-wave changes, S-T segment depression and sinus tachycardia ECG changes caused by Clozapine. The study was a RCT. It was found that Dantonic™ was superior to potassium chloride in treating tachycardia caused by Clozapine, and the total effective rate of treating T-wave and S-T segment was also better than that of potassium chloride. The duration of treatment for QTc interval prolongation with Dantonic™ was shorter than that with potassium chloride. The

Table 10.22 Arrhythmia situation before and after Dantonic™ treatment (cases)

Treatment	Sinus Bradycardia	Atrial PVC	Premature AV junctional beats	PVC	Atrioventricular block	Bundle branch block
Before	14	21	7	32	11	5
After	3	5	2	8	4	5

Table 10.23 Effect of Dantonic™ on the QT value of ECG

References	Diagnosis	Clinical design	Results
Jia et al. [23, 42]	Presbycardia	Non-randomized controlled study	Authors treated 80 cases of presbycardia (Lost 4 cases) with Dantonic™, l0 pills/day, Tid, for 2 months
			QTcd < 50 ms (21 cases in the normal group): there was no difference 2 months before the treatment
			QTcd50 ~ 80 ms (39 cases in the increased group): there was significant decrease one month after treatment ($P < 0.05$) and two months after treatment ($P < 0.01$)
			QTcd > 80 ms (16 cases in the markedly increased group): there was significant decrease one month after treatment ($P < 0.05$) and two months after treatment ($P < 0.01$)
Zhu [43]	Coronary Artery Disease	Non-randomized controlled study	The author observed 58 cases of coronary heart disease. QT was (48.3 ± 12.6) mm before taking Dantonic™. QT was (44.1 ± 13.1) mm after administration of the drug for 2 months. The difference was significant ($P < 0.05$)
Zhang [44]	Acute myocardial infarction	Randomized controlled study	The author randomly divided 60 patients with acute myocardial infarction into 2 groups, and both groups were treated with AMI routine therapies without using anti-arrhythmia drugs against myocardial cathode. Dantonic™ was administered in the treatment group, 10 pills/day, tid, for 21 days. After the treatment, QTd (21 days) was 37.33 ± 16.52 ms, which was significantly lower than that of the control group (48.74 ± 22.84 ms), ($P < 0.05$)
Qiao [45]	old myocardial infarction	Randomized controlled study	The author chose 97 patients with OMI (1997–2001) as the treatment group, and patients with OMI (1993–1994) as the control group. QT was 30 ± 24 ms after treatment, which was significantly lower than that before treatment (60 ± 32 ms). There was no such difference in the control group

authors presumed the following possible mechanism for the effectiveness of Dantonic™:

1. The effective ingredients of Dantonic™, such as phenolic aldehydes and acidic aldehyde, can effectively relieve the inhibition of myocardial Na^+/K^+-ATPase by Clozapine, so as to normalize the ionic distribution inside and outside myocardial cells.
2. Dantonic™ can effectively improve blood rheology, prevent erythrocyte aggregation, and improve myocardial microcirculation.
3. Dantonic™ is able to reduce the heart rate, enhance ventricular contractility, reduce wall tension, and completely repolarize the myocardium, so as to effectively cure myocardial ischemia and hypoxia.

Mao [24] observed the effect of Dantonic™ on 98 patients with ECG changes caused by antipsychotics (Chloropromazine, Clozapine, Aloperidin, Lithium carbonate, etc.). 80 % of the patients had improvement in myocardial ischemia ECG after the treatment.

Since the sympathetic-adrenal system is the main factor affecting heart rate variation, Dantonic™ can affect the activity of the sympathetic vagus nerve by adjusting catecholamine levels to protect myocardia. The other functions of Danshen, such as relieving vasospasm and improving myocardial ischemia, also have an important effect on the elimination of cardiac dysrhythmia.

10.5 The Effect of Dantonic™ on the Left Ventricle

Echocardiography (cardiac ECHO) studies have shown that 49 % of female and 33 % of males over the age of 70 suffer from left ventricular hypertrophy (LVH). This phenomenon usually increases with age

and is sometimes referred to as "aging heart." LVH affects heart function on the left side, oxygen consumption of the heart muscle, and arrhythmia. Moreover, it is believed that this is related to cardiovascular accidents in elderly people.

CHD with LVH is one of the most common causes of sudden death, myocardial infraction, and arrhythmia. Early detection and arrest of LVH is a hot issue in cardiovascular research. Clinical doctors pay great attention to LVH reversal. According to several reports, Dantonic™ has a definite effect on the reversal of LVH.

Yan et al. [47] studied 54 patients, recruited from clinics and hospitals, who were diagnosed with LVH by cardiac ECHO. Other conditions such as secondary hypertension, CHD, cardiomyopathy, diabetes, and other organic heart diseases were excluded by ECG (including exercise tests) and cardiac ECHO. The patients were randomized into two groups: the treatment group had 34 patients who received Dantonic™ (10 pills each time, tid), and the control group had 20 patients who received Metoprolol (50 mg each time, tid) over a treatment course of 6–-12 months. There was no apparent difference between the two groups in terms of age, sex, and symptoms. The patients were examined by HP Color Doppler 7200 AC for their left ventricular diameter (LVID), intraventricular septum thickness (IVST), and left ventricular posterior wall thickness (LVPWT) in the diastolic phase.

$$\text{Left Ventricular Weight (LVW)} = 1.04 \times [3(\text{LVID} + \text{LVPWT} + \text{LVST}) - 3\text{LVID}] - 1.36$$

$$\text{Left Ventricular Weight Index (LVWI)} = \text{LVW}/\text{surface area}$$

The author found that Dantonic™ could significantly reverse some indexes of LVH (Table 10.24).

Wang et al. [48] investigated 56 patients with CHD in a treatment group that received Dantonic™, 10 pills each time, tid for 3 months, and 50 patients in a control group who received isosorbide dinitrate (ISDN), 10 mg each time, tid for 3 months. The patients were examined by the Color Doppler 7200 AC for their LVID, IVST and LVPWT. LVMT and LVW were calculated. The results showed that Dantonic™ had a reversal effect on LVH caused by CHD, but ISDN had no such effect (Table 10.25).

The authors also found that after treatment with Dantonic™ for 3 months, the patients' heart rate, oxygen consumption by the heart muscle, blood viscosity, Blood reduction viscosity, plasma viscosity, microcirculation conditions (microcirculation turnover rate, turnover time, time taken for microcirculation retention) and indexes of anti-arteriosclerosis (apolipoproteins A and B100, lipid peroxide, superoxide dismutase) were all improved. However, those who took ISDN had none of these changes.

Table 10.24 Comparison of the effects between Dantonic™ and Metopolol on LVH Using B Ultrasound ($\bar{X} \pm s$)

Index	Dantonic™		Metopolol	
	Before treatment	After treatment	Before treatment	After treatment
LVID (mm)	5.58 ± 0.59	5.21 ± 0.33*	5.62 ± 0.64	5.59 ± 0.66
IVST (mm)	13.6 ± 1.3	10.9 ± 1.4**	12.8 ± 1.6	12.4 ± 1.8
LVPWT (mm)	13.0 ± 1.7	11.0 ± 1.2*	12.6 ± 1.5	11.9 ± 1.6
LVW (g)	252.6 ± 58.2	198.7 ± 30.96**	238.6 ± 59.8	229.8 ± 42.5
LVMI (g/m^2)	136.9 ± 22.6	108.9 ± 18.6	139.8 ± 19.3	135.7 ± 20.6

Before and after treatment comparison: $^{*}P < 0.05$; $^{**}P < 0.01$

Table 10.25 Changes of LVH indexes before and after treatment with Dantonic™ or ISDN ($\bar{X} \pm s$)

Group	Treatment	LVID (mm)	IVST (mm)	LVPWT (mm)	LVW (g)	LVMI (g/m^2)
Dantonic™ (56 cases)	Before	5.59 ± 0.56	13.79 ± 1.58	13.21 ± 1.87	245.67 ± 56.21	149.15 ± 20.83
	After	5.21 ± 0.33*	10.2 ± 1.22**	10.66 ± 1.69**	208.3 ± 45.67**	117.82 ± 16.92
ISDN (50 cases)	Before	5.56 ± 0.61	13.47 ± 1.53	13.52 ± 1.67	239.66 ± 57.39	138.75 ± 19.17
	After	5.56 ± 0.42	13.21 ± 1.56	13.81 ± 1.61	235.28 ± 51.32	131.36 ± 18.56

Before and after treatment comparison: $^{*}P < 0.05$; $^{**}P < 0.01$

Dantonic™ has an obvious reversal effect on LVH caused by CHD. The mechanism for this may be as follows:

1. Dantonic™ can effectively decrease lipid peroxide and apolipoprotein B levels and increase SOD and apolipoprotein A, which are beneficial in alleviating damage to blood vessels by oxygen free radicals, thus decreasing the occurrence of arteriosclerosis.
2. Dantonic™ can decrease blood viscosity and peripheral vascular resistance, so as to eliminate the factors of hypercoagulability and hyperviscosity, improve microcirculation, and adjust myocardial compliance. Dantonic™ can improve all of these hemodynamic factors which induce LVH.
3. Dantonic™ can expand the coronary artery, improve blood flow in the coronary artery, increase cardiac output (CO), reduce heart rate, decrease oxygen consumption, adjust and maintain the supply and demand balance of myocardial oxygen and energy metabolism, and reduce the cardiac pressure overload and myocardial work, so as to eliminate or reduce the inducing factors of LVH.

One characteristic of hypertension and atherosclerosis is ventricular remodeling and hypertrophy, which leads to cardiac microvascular disease. The increase in coronary perfusion pressure results in the decrease in coronary flow reserve, therefore, LVH is related to hypertension and local growth factor. ET, angiotensin, catecholamine, and fibroblast growth factor can all stimulate the proliferation and hypertrophy of vascular smooth muscle. Therefore, LVH reversal and coronary artery circulation improvement are important goals in the treatment of hypertension.

Luo Zhurong et al. [49] used Color Doppler technology to determine the concentration of plasma catecholamine (including noradrenaline NE, epinephrine E), arterial natriuretic polypeptide (ANP), ET, and nitric oxide (NO). They studied 140 patients with hypertension combined with CHD and the effect of Dantonic™ on the remodeling of the left ventricle. The authors showed that Dantonic™ could improve the diastolic function of the left ventricle, decrease the thickness of the intraventricular septum and left ventricular posterior wall, and the weight index of the left ventricle, demonstrating that Dantonic™ can contribute to LVH reversal. It was also found that Dantonic™ had a statistically significant effect on the decrease of ET, ANP, NE and E, and the increase of NO. Therefore, Dantonic™ should be the first choice in medication for patients with CHD complicated with hypertension. In theory, the LVH reversal effect of Dantonic™ is related to its ability to adjust the balance of neurohormones.

Fu et al. [50] used Dantonic™ to treat 92 patients with CHD, and ISDN was used in the control group. They used Color Doppler technology (Doppler 8200 AC) cardiac ECHO to measure stroke volume (SV), minute CO, ejection fraction (EF), and left ventricular fractional shortening (FS). After 3 months' treatment, SV, CO, EF, and FS were increased in the Dantonic™ group, and the differences were significant ($P < 0.05$). No significant differences were found in the ISDN group. The authors believed that the mechanism for the effect of Dantonic™ on the treatment of CHD was that Dantonic™ can expand the coronary artery, improve blood flow in the coronary artery, reduce the heart rate, decrease oxygen consumption, improve

microcirculation, accelerate blood circulation, increase the coronary flow, improve the contractility of the left ventricle, decrease the tension of the left ventricle wall, and increase CO.

Dantonic™ has an effect on the insufficiency of the diastolic function of the left ventricle with CHD. Zhang et al. [51] randomly divided patients with CHD into two groups, and both were treated with conventional treatments such as Ca^{++} antagonists, converting enzyme inhibitor, and β-receptor blockers. Dantonic™ was administered in the treatment group for 6–8 weeks. All patients were examined by cardiac ECHO before and after treatment, and LVDd, EFVE, VA were determined (Table 10.26). The results in Table 10.26 indicate that early diastolic dysfunction in CHD patients could easily lead to an increase in left ventricular diastolic filling pressure, decrease in the blood flow in early diastolic rapid filling, decrease in VE peak filling rate, increase of VE peak, and a ratio of VE/VA less than 1. After treatment with Dantonic™, these parameters were all improved, which indicated that in CHD, Dantonic™ had a significant effect on the efficiency of left ventricle diastolic function.

Wang [52] reported that angina pectoris patients were treated with Dantonic™ and found that the CO, SV and EF all increased ($P < 0.01$).

Hu et al. [20] divided 63 cases of angina pectoris patients into two groups: Dantonic™ group (32 cases) and ISDN group (31 cases). Cardiac ECHO was used to determine CO, SV, EF and shortening fraction of the left ventricle (FS); the results are shown in Table 10.27.

To sum up, Dantonic™ usually has an LVH reversal effect on aging patients with LVH, LVH combined with CHD, and LVH combined with hypertension and CHD.

10.6 Dantonic™ and Interventional Cardiac Surgery

In 1964, Dotter and Judkins adopted a percutaneous and transluminal vasodilatation surgery using the coaxial nylon dilating catheter, initiating minimally invasive treatments in clinical medicine around the world and creating the Percutaneous Transluminal Angioplasty (PTA) method. With the development of polyvinyl chloride (PVC), the double-lumen dilating catheter with a single-end pore balloon was deployed in percutaneous transluminal coronary angioplasty (PTCA) for the treatment of CHD, which has been considered to be an epoch-making revolution. PTCA, believed to be one of the most effective methods in treating CHD, has been the basic method in modern interventional cardiovascular therapy. However, restenosis (RS) after interventional therapy became the greatest obstacle affecting its long-term curative effect. The RS rate after PTCA can reach 30–50 %. In all, there are about one million post PTCA patients in the world according to statistics, with half of them in America, among whom 150,000 may develop RS and need interventional surgery again. Although various angioplasty and stenting and different kinds of laser and peeling operations have been applied, the RS rate did not decrease. It is calculated that 250 million US dollars are needed to pay for RS-related symptoms every year. Therefore, it has become a hot issue in seeking anti-RS measures and resolving the problem of post-PTCA RS in cardiovascular diseases. It is of great importance in decreasing operation rates, reducing operation risks, lowering the incidence of acute cardiovascular disease, raising the life quality and survival rate of CHD patients, and cutting down social

Table 10.26 The changes in the indexes examined by cardiac ECHO before and after the treatments ($\bar{X} \pm s$)

Groups	Treatment	LVDd (mm)	EF (%)	VE (cm/s)	VA (cm/s)	E/A
Control ISDN	Before	55.4 ± 7.2	64.8 ± 7.2	56 ± 16	65 ± 17	0.86 ± 0.24
	After	54.8 ± 8.7	65.2 ± 8.4	63 ± 18	58 ± 12	1.09 ± 0.20
Treatment Dantonic™	Before	54.8 ± 8.1	64.7 ± 8.2	56 ± 15	65 ± 17	0.86 ± 0.21
	After	55.2 ± 7.6	65.1 ± 7.2	67 ± 16	54 ± 11	1.24 ± 0.26

Table 10.27 The effect of heart function before and after treating angina pectoris with Dantonic™ and ISDN

Items	Dantonic™ (32 cases)		ISDN group (31cases)	
	Before treatment	After treatment	Before treatment	After treatment
SV	75.38 ± 8.32	83.45 ± 9.11	74.96 ± 8.44	79.47 ± 8.72
CO	5.61 ± 1.34	6.94 ± 1.39	5.64 ± 1.36	6.12 ± 1.41
EF	0.57 ± 0.02	0.79 ± 0.02	0.59 ± 0.03	0.70 ± 0.03
Fs	17.14 ± 3.4	19.69 ± 3.6	17.32 ± 3.1	18.46 ± 4.2

medical expenses, as well as improving interventional therapy.

Wang et al. [53] reported the preventive intervention effect of Dantonic™ and trimetazidine (TMZ) on instant myocardial ischemia and post-ischemia reperfusion during CHD interventional therapy. There were 78 patients who had previously taken nitroglycerin, β-receptor blockers, aspirin, hypolipidemic drugs, angiotensin converting enzyme inhibitors, and antiplatelet drugs. However, they had not taken drugs that interfere with ST-segment changes, such as amiodarone, monoamine oxidase inhibitor and Dipyridamole. Thirty-three patients were administered with TMZ; fifteen patients were administered with both TMZ and Dantonic™. Thirty patients in the control group took neither TMZ nor TMZ with Dantonic™. The authors used the ST-segment elevation value in intracoronary electrocardiogram, angina pectoris relief rate, arrhythmia and EF as the clinical assessment indexes. As shown in Table 10.28, in patients with UAP and AMI, Dantonic™ combined with TMZ could improve myocardial blood supply and increase the ischemic tolerance of myocardial cells during PTCA and post-PTCA. It was concluded that Dantonic™ combined with TMZ had a preventive intervention effect on UAP and also on instant ischemia during AMI treated with PTCA and postischemia reperfusion, as shown in Table 10.29. It is suggested that Dantonic™ combined with TMZ should be widely used one week before PTCA and patients should continue taking it for 30 days after PTCA. PTCA is the most widely used and successful method among cardiac interventional operations. It has become the most effective method in CHD treatment, with extensive applications. The main problem for PTCA is that the RS rate can reach 30 % or even more half a year after the operation. According to statistics, intra-coronary stenting could markedly decrease the RS rate after PTCA. However, there were still more than 15 % of patients suffering from RS after having been treated with LEPU stenting. Therefore, the long-term effect of PTCA and stent implantation remains a big problem.

RS after PTCA may be related to the following factors: vascular elastic recoil, thrombogenesis, and intimal hyperplasia. Although there are many theories, the exact mechanism is still unclear. A majority of researchers are inclined to believe that intimal hyperplasia is the major cause of RS. Intimal hyperplasia includes the extracellular matrix and smooth muscle, etc. Gao Xiaoge et al. (2003) reported that many traditional Chinese medicines could effectively protect vascular endothelial cells. The major

Table 10.28 The effect of TMZ combined with Dantonic™ on CHD PTCA ($\bar{X} \pm s$)

Group	n	IcECG increased value of ST segment (mV)		Duration of angina attack (min)	Increased value of ST segment (mV)	Arrhythmia	EF (%)
		The first expansion	The second expansion				
TMZ	33	0.5208 ± 1.049	1.0792 ± 1.0380	1.0909 ± 2.9934	0.6591±	15	63.75 ± 6.3509
TMZ + Dantonic™	15	0.5733 ± 0.5892	0.24 ± 0.3699	2.6667 ± 3.7161	0.8667±	8	53.6667 ± 15.7211
Conventional treatment	30	2.8476 ± 1.6696	2.3988 ± 1.6108	1.87 ± 5.6663	0.5667±	9	62.2143 ± 8.6218

Table 10.29 The clinical effect of TMZ combined with Dantonic™ on various kind of CHD PTAC ($\bar{X} \pm s$)

Type	Group	n	IcECG increased value of ST segment (mV)		Duration of angina attack (min)	Increased value of ST segment (mV)	Arhythmia	EF (%)
			The first expansion	The second expansion				
Stable	TMZ	9	2.2750 ± 0.35	1.7625 ± 0.2250	3.3333 ± 5.0	0.0 ± 0.0	6	62.5 ± 2.7386
	TMZ + Dantonic™	0						
	Conventional treatment	5	3.6 ± 2.0075	3.1667 ± 1.893	7.0 ± 13.0384	0.0 ± 0.0	3	69.0 ± 2.6458
Unstable	TMZ	19	1.2357 ± 1.1441	0.8143 ± 1.1950	3.3333 ± 3.5355	0.697 ± 0.8522	8	66.1 ± 6.3136
	TMZ + Dantonic™	9	0.40 ± 0.3279	0.1111 ± 0.2205	0.3158 ± 1.1572	0.388 ± 0.4167	6	53.0 ± 18.8225
	Conventional treatment	18	3.025 ± 1.74	2.5563 ± 1.7011	1.1722 ± 2.2528	0.472 ± 0.0214	6	61.4 ± 9.2075
Acute myocardial infarction	TMZ	5	0.5	0.2	0	1.7 ± 1.4405	4	50.0 ± 4.125
	TMZ + Dantonic™	6	0.8333 ± 0.8162	0.4333 ± 0.4810	0	1.58 ± 1.0206	5	55.0 ± 8.7178
	Conventional treatment	7	2.1167 ± 1.3497	1.7 ± 1.2570	1.6667 ± 4.0825	1.21 ± 1.0746	6	55.0 ± 6.3640

components of Dantonic™, tanshinol and notoginsenosides, could inhibit smooth muscle cell migration and alleviate intimal hyperplasia. The combined use of the two drugs has a better effect than any one drug used alone (Gao Hongcai et al. 2003). Huang et al. [54] investigated the effect of Dantonic™ on the iliac artery of hyperlipidemic rabbits after endothelial denudation. The pathomorphology of the iliac artery was observed. The intimal area and internal elastic lamina area was measured by the image analysis system. The results showed that Dantonic™ could suppress intimal hyperplasia independent of hyperlipidemia modulation. The author also detected proliferating cell nuclear antigen (PC-NA) and found that in the Dantonic™ group, the level of PC-NA protein of new endomembranes in the iliac artery was significantly lower than that of the control group. The level of PC-NA in the endangium could sufficiently reflect the proliferation of smooth muscle cells in endomembrane vascular haemorrhage. The results of this study suggested that Dantonic™ could inhibit intimal hyperplasia through the suppression of smooth muscle cell proliferation.

Li et al. [55] used adult white rabbits (healthy, male, second-grade) to make a balloon endarterectomy and they were fed a high cholesterol diet. The rabbits were randomly divided into a control group, a model group and a treatment group (taking Dantonic™). The experiment lasted for 8 weeks. It was confirmed by pathomorphological examination of the iliac artery sample of the rabbits that Dantonic™ could significantly suppress intimal hyperplasia after vascular injury. The authors also observed matrix cell metalloproteinase MMP2 and MMP9, which could specifically bind to the extracellular matrix, degrade the extracellular matrix, and promote smooth muscle cell migration and proliferation. The results showed that the expression of MMP2 and MMP9 were significantly lower in the treatment group than in the model group (Table 10.30).

Table 10.30 MMP changes in Japanese rabbits after iliac artery intima destruction by balloon

Group	N	MMP_2	MMP_9
Control	9	11.3 ± 3.65	17.2 ± 1.88
Model	8	$23.4 \pm 4.61^{\triangle}$	$28.2 \pm 2.38^{\triangle}$
Dantonic™	8	$16.2 \pm 3.03^{*\triangle}$	$20.1 \pm 4.01^{*\triangle}$

Note Compared with the model group, $^{*}P < 0.05$, compared with the control group $^{\triangle}$ $P < 0.05$

Table 10.31 Experimental study of Dantonic™ on stenosis

Author (year)	Animal and type of model	Methods	Results
Huang Weiqiang (2003)	Hyperlipidemic rabbit after iliac artery endothelial denudation	20 Japanese rabbits, balloon injured on right iliac artery after 2 weeks of high-cholesterol diet, were randomly divided into a Dantonic™ group (300 mg/day per rabbit, 3 days before operation, $n = 10$) and a control group ($n = 10$). Pathomorphology analysis of the iliac artery and immunohistochemistry of PCNA were made 4 weeks after the operation	The neointimal area and the level of PCNA protein in Dantonic™ group increased ($P < 0.05$), the lumen area also increased significantly ($P < 0.05$), compared with the control group. Conclusion: Dantonic™ can reduce the proliferation of smooth muscle cells in rabbits and alleviate intimal hyperplasia after iliac artery injury, thus reducing experimental artery stenosis. The effectiveness was independent of the modulation of hyperlipidemia
Li et al. [55]	Rabbit, intima destroyed by balloon, hypercholesteroic diet	The rabbits were randomly divided into a control group, a model group and a treatment group (intima destroyed by balloon + hypercholesteroic diet + Dantonic™ administration 150 mg/d × 8 weeks). Pathomorphology of the rabbits' iliac artery sample was made. Metalloproteinase (MMP_s) MMP_2 and MMP_9 were analyzed by immunohistochemistry method	Compared with the modal group, the stenosis of artery lumen diameter decreased 27.8 % in the treatment group, the thickness of intima decreased 41 %, intima area decreased 52 %, intima thickness/medium thickness ratio decreased 22 %,area ratio decreased 38 % ($P < 0.01$) in the treatment group. MMP_2, MMP_9 of the model group > MMP_2, MMP_9 of the control group MMP_2, MMP_9 of the treatment group < MMP_2, MMP_9 of the model group Intimal hyperplasia and stenosis degree of vascular lumen correlated well with MMP_2, MMP_9 ($r = 0.896$, $P < 0.01$) Conclusion: Dantonic™ can markedly inhibit intimal hyperplasia after vascular injury
Ma et al. [70]	Rabbit, model whose iliac artery was injured by balloon	24 New Zealand Rabbits were randomly divided into Dantonic™ group (300 mg/day) and the control group. The iliac arteries of the rabbits in both groups were injured by balloon dilation 7 days later. The endothelium reparation and intimal hyperplasia of the injured arteries were observed 4 weeks later. The pathology parameters were also determined. Venous blood samples of the rabbit's ear were taken before and 1, 2, 4 weeks after the operation to measure the NO concentration	The pathological results showed that NO concentration of Dantonic™ group 2 and 4 weeks after the operation was significantly higher than that of the control group 4 weeks after operation. The level of intimal hyperplasia in Dantonic™ group was lower than in the control group. Vascular smooth muscle cells and fiber tissue in neointima decreased significantly in Dantonic™ group compared with the control group. The endothelium was comparatively complete and smooth. The level of stenosis was low. The lumen area was significantly larger than in the control group ($P < 0.05$). The neointima area and the intimal hyperplasia ratio was markedly smaller than in the control group ($P < 0.05$). The author concluded that Dantonic™ could promote the recovery of intima cells and reduce intimal hyperplasia, thus reducing restenosis rate

Zeng et al. [56] of Guangxi Medical University studied the effect of Probucal and Dantonic™ on in-stent restenosis (ISR) after intracoronary stenting. 141 CHD patients with successful intracoronary stenting were randomly divided into a control group, a Dantonic™ group, a Probucal group and a Probucal plus Dantonic™ group. The course of treatment was 6 months. A quantitative coronary analysis (QCA) was conducted pre-operation, post-operation, and as a follow-up to find coronary impact factors.

All three groups took conventional drugs such as enteric coated aspirin, Clopidogrel, Elantan 20, β-receptor blockers, angiotensin converting enzyme inhibitors, and statins. The Dantonic™ group began to take Dantonic™ 24 h after stenting, 10 pills each time, tid. The results are shown in Tables 10.32, 10.33 and 10.34. The results suggest that Dantonic™ had a definite effect on preventing RS after intracoronary stenting. The minimum luminal diameter of stenting, net luminal gain, net gain index, lesion area net gain, late loss and late loss index, which followed up after the combined usage of Probucal and Dantonic™, were significantly different from the control group. It was confirmed that Probucal and Dantonic™ had a synergistic effect in preventing ISR, suggesting that Probucal and Dantonic™ worked on ISR in different ways (Table 10.31).

The sample size of this study was small and the follow-up rate was low, but it began a new way of combining TCM and modern technology in CHD treatment. It created an idea of the significance of TCM administration after interventional therapy. Actually, any interventional operation is an invasive therapy which may destroy the stability of the plaques. Viewed from the long-term interests of the patients, these operations could only temporarily alleviate the symptoms of the disease. At present, drugs are always needed no matter what kinds of stents are planted. After the application of drug-eluting stents and intravascular brachytherapy, ISR is still being studied further. Likewise, the above questions need the contemplation of all scientific researchers.

10.7 Combination of Dantonic™ with Other Drugs for CHD

Over the history of human's struggle against diseases, CHD is the disease on which humans

Table 10.32 The coronary angiographic data of four groups of patients before stent implantation ($\bar{X} \pm s$)

Item	Control	Dantonic™	Probucol	Dantonic™ + Probucol
Number of coronary artery lesions	42	49	48	52
One branch (cases)	21	27	28	30
Two branches (cases)	6	5	4	5
Three branches (cases)	3	4	4	4
Stent planted in coronary artery	42	49	48	52
Left anterior descending (cases)	26	30	31	29
Left circumflex artery (cases)	6	5	8	10
Right coronary artery (cases)	10	14	9	13
Diameter of related artery (l/mm)	2.69 ± 0.15	2.75 ± 0.17	2.70 ± 0.25	2.68 ± 0.10
Stenosis of lesion (%)	90.0 ± 5.5	90.9 ± 6.7	90.9 ± 7.2	89.0 ± 5.3
Length of lesion (l/mm)	12.0 ± 3.5	12.5 ± 3.3	11.5 ± 4.7	11.3 ± 2.5
Minimum luminal diameter before dilation (l/mm)	1.20 ± 0.16	1.21 ± 0.13	1.16 ± 0.14	1.20 ± 0.10
Minimum pathological stenosis area before operation (A/mm^2)	1.16 ± 0.26	1.16 ± 0.23	1.08 ± 0.25	1.15 ± 0.18

Table 10.33 The coronary angiographic data of four groups of patients after stent implantation ($\bar{X} \pm s$)

Item	Control	Dantonic™	Probucol	Dantonic™ + Probucol
Diameter of the stent (l/mm)	3.00 ± 0.25	3.05 ± 0.30	3.00 ± 0.20	3.05 ± 0.25
Length of the stent (l/mm)	14.0 ± 4.7	13.8 ± 4.1	15.4 ± 5.0	14.3 ± 3.5
maximum dilation pressure (p/kPa)	1,236 ± 61	1,212 ± 81	1,192 ± 121	1,242 ± 91
dilation duration (t/s)	7.90 ± 1.49	7.92 ± 1.48	7.83 ± 1.53	7.80 ± 1.39
Residual stenosis (%)	4.28 ± 4.80	4.31 ± 4.67	4.33 ± 4.12	4.54 ± 4.32
Maximum luminal diameter after dilation (l/mm)	3.05 ± 0.22	3.08 ± 0.19	3.05 ± 0.27	3.10 ± 0.25
Minimum luminal diameter after dilation (l/mm))	2.64 ± 0.16	2.70 ± 0.16	2.67 ± 0.24	2.68 ± 0.16
instant luminar gain (l/mm)	1.44 ± 0.18	1.49 ± 0.17	1.51 ± 0.24	1.48 ± 0.21
instant luminar gain index	53 ± 6	54 ± 5	56 ± 7	55 ± 7

Table 10.34 The coronary angiographic data of four groups of patients 6 months after stent implantation ($\bar{X} \pm s$)

Item	Control	Dantonic™	Probucol	Dantonic™ + Probucol
Follow up time (t/d)	206 ± 56	204 × 51	210 ± 58	211 ± 62
Followed up Patients (cases)	17	21	22	25
Followed up rate (%)	56.67	58.33	61.11	64.10
Followed up stent (number)	21	26	30	31
Restenosis stent (number)	6	7	7	7
Restenosis rate (%)	28.6	$26.9^{\triangle}$	$23.3^{\triangle}$	$22.6^{\triangle}$
cholesterol changes during follow up (c_B/μmol·L^{-1})	−0.69 ± 0.25	−0.69 ± 0.27	−0.71 ± 0.32	−0.75 ± 0.25
Triglyceride changes during follow up (c_B/μmol·L^{-1})	−0.20 ± 0.09	−0.22 ± 0.11	−0.23 ± 0.11	−0.24 ± 0.11
Reexamination minimum luminal diameter (*l*/mm)	1.85 ± 0.44	1.90 ± 0.38	$2.11 \pm 0.39^{\triangle\star}$	$2.19 \pm 0.36^{\blacktriangle\bigstar}$
Late luminal diameter loss (*l*/mm)	0.79 ± 0.40	0.79 ± 0.35	$0.56 \pm 0.33^{\triangle\star}$	$0.50 \pm 0.31^{\blacktriangle\bigstar}$
Late loss index	230 ± 14	29 ± 13	$21 \pm 11^{\triangle\star}$	$19 \pm 12^{\blacktriangle\bigstar}$
Net gain (*l*/mm)	0.66 ± 0.40	0.70 ± 0.34	$0.95 \pm 0.38^{\triangle\star}$	$0.98 \pm 0.39^{\blacktriangle\bigstar}$
Net gain index	25 ± 15	25 ± 12	$35 \pm 13^{\triangle\star}$	$36 \pm 14^{\blacktriangle\bigstar}$
Lesion area net gain (A/mm^2)	1.75 ± 1.12	1.81 ± 0.95	$2.55 \pm 1.22^{\triangle\star}$	$2.69 \pm 1.15^{\blacktriangle\bigstar}$

Note Compared with the control group, $^{\triangle}$ $P < 0.05$, $^{\blacktriangle}$ $P < 0.01$; compared with Dantonic™ group: * $P < 0.05$; $^{\bigstar}$ $P < 0.01$

have spent the most effort. After nearly a hundred years of research, its mechanisms have become increasingly clear. It has been concluded that it is impossible to treat CHD with only one medicine. The risk factors causing CHD have reached as many as 254, and people have realized the necessity of compound drugs. In the last 10 years or so, many clinical doctors have treated CHD with Dantonic™ combined with western medicines, or with other Chinese medicines, and achieved good therapeutic effects. They have also accumulated plenty of clinical experience. Which medicine combined with Dantonic™ could enhance the efficacy? Which drug should not be combined with Dantonic™? A summary of published clinical reports on Dantonic™ will

be reviewed in this section. The purpose of the review is to provide more ideas for clinical doctors to use drugs to treat CHD more rationally, enhance the therapeutic effect, and reduce the side effects.

Based on the analysis of clinical reports on Dantonic™ over the past 10 years, the following can be summed up:

1. Dantonic™ has a certain effect on CHD angina pectoris, particularly in relieving angina pectoris and reducing nitroglycerin consumption, improving clinical indications, improving patients' quality of life, reducing cardiovascular accidents, and minimizing risk factors of CHD.
2. Dantonic™ can be safely combined with a large number of drugs conventionally used for CHD treatment. The combination is particularly effective when used to prevent angina pectoris from developing into UAP and myocardial infarction, or to prevent a cardiocerebral vascular accident after UAP and myocardial infarction. The combinations of Dantonic™ with other conventional medicines have significant synergistic effects on the improvement of endpoint observation on CHD.
3. The combination of Dantonic™ with commonly used CHD drugs, such as aspirin, ISDN, Ca^{++} antagonists, β-receptor blockers, has special complementary, collaborative, and synergistic effects.
    a. Combined with aspirin: decrease "aspirin resistance", has the effect of anti-platelet activation.
    b. Combined with ISDN: improves drug tolerance problems.
    c. Combined with β-receptor blockers: improves heart rate and eliminates the decrease of myocardial contractile force.
4. When used after the conventional treatment of CHD, or during the interventional treatment of CHD, Dantonic™ combined with other drugs can improve the prognosis.
5. There are no incompatibilities, and no enhancement of toxicity or side effects in the combination of Dantonic™ with other drugs.
6. TMZ has an effect on inhibiting the oxidative phosphorylation of fatty acids, promoting the use of glucose as an energy source, increasing the efficiency of energy generation by myocardial cells, reducing the side effects caused by fatty acid oxidation, and relieving the symptoms of myocardial ischemia. TMZ is an effective anti-angina pectoris drug, and its effectiveness can be enhanced by combining with β-receptor blockers, Ca^{++} antagonists, and nitrates. But, TMZ cannot increase coronary blood flow, unlike nitrates and calcium channel blockers, and it cannot reduce heart rate, weaken myocardium contraction and decrease blood pressure, unlike β-receptor blockers. TMZ is able to limit the extension of myocardial damage, reduce the instability of cardiac cell electrophysiology, and prevent early left ventricular expansion, etc. The possible mechanism for TMZ's functions is that it may affect the metabolism of myocardial cells and improve the hypoxia tolerance of the tissue. TMZ can bind to mitochondrial permeability transition pores to inhibit Ca^{++} induced mitochondrial swelling and exert anti-neutrophil actions, reduce the extent of tissue damage, and decrease the content of adenosine cyclophosphate in platelets; thereby, it is able to inhibit platelet aggregation. TMZ is a new kind of metabolic medicine in the treatment of CHD with good anti-ischemic effects. The combination of Dantonic™ with TMZ can enhance and improve the therapeutic effects, which are shown in Table 10.35.

Clinically, Dantonic™ is commonly used in treating CHD, angina pectoris and hyperlipidemia. With a wide clinical application, it was found that Dantonic™ has other effects if combined with other drugs, such as in combination with Vitamin C for pigmented purpuric dermatosis; in combination with Clarithromycin and Terazosin for Chronic Prostatitis; in combination with Cidomycin for chronic gastritis; in combination with anti-epileptic drugs for intractable epilepsy; in combination with anisodamine for dizziness caused by vertebral artery ischemia; in combination with Nimodipine and Metoprolol

Table 10.35 Combination of Dantonic™ with other drugs for the treatment of coronary heart disease

Compatible drugs	Diagnosis (cases)	Evaluation		Toxic and side effects	Source
TMZ (combined with nitrates, β-receptor blockers, Aspirin, drugs for decreasing blood fat, antiplatelet, ACHI)	CDH (18) 1UAP (2) AMI (5) SAP (1)	Angina relief 50 % 90.9 %	Increased ST segment fell back 50 % 80 % 90.9 %	Not reported	Wang et al. [29, 34, 53, 71]
TMZ, combined with β-receptor blockers, nitrates, Ca^{++} antagonists, Drugs for anticoagulation and decreasing blood fat	Administration before CHD PTCA (10)	Significantly reduced myocardia ischemiaof PTCA, and reduced subepicardial myocardia ischemia		Not reported	Lu et al. (2003)
TMZ + nitrates + β-receptor blockers + Aspirin + drugs for decreasing blood fat + angiotensin converting enzyme + antiplatelet drugs + drugs for blood fat adjustment					Wang [72]
Routine nitrates, β-receptor blockers, Ca^{++} antagonists, enteric Aspirin	UAP (60)	After combination with Dantonic™, the doses of nitroglycerin and number of Paregoric were less than that of the control group ($P < 0.05$) It was indicated by hemorheology that the indexes had clearly improved. Blood fat + total cholesterol + triacylglycerol + low density lipoprotein had decreased and high density lipoprotein had increased		No	Hong et al. [17]
Oral antianginal drugs	UAP (42)	After treatment with combined drugs, a better effect was indicated by clinical and hemorheology observation		Two cases felt light dizziness, abdominal distension and nausea. There was one case of headache and head-fullness in the control group	Shen [73]
Nitrates, β-receptor, Ca^{++} antagonists, low molecular weight Heparin, enteric Aspirin	UAP (249)	The average duration, daily occurrence of angina pectoris, and the average daily consumption of nitroglycerin were significantly reduced after Dantonic™ administration The patients' rheology indexes were improved after the treatment (the difference was significant)		No description	Ren (2003)

(continued)

Table 10.35 (continued)

Compatible drugs	Diagnosis (cases)	Evaluation	Toxic and side effects	Source
β-receptors, Ca^{++} antagonists, Aspirin and Heparin	SAP (25)	The total effective rate was higher than that in the control group (ISDN)	No description	Ai [74]
Low molecular weight Heparin + nitroglycerin 10 mg + 5 % GS 50 m + oral Aspirin	UAP	The combination of Dantonic™ with low molecular weight Heparin had better effect than the two drugs used separately	No description	Yuan [75]
Nitroglycerin + Enteric Aspirin + nifedipine	UAP (46)	The effective rate of angina pectoris improvement in the observation group (86.9 %) is significantly higher than that in the control group (70 %) ($P < 0.05$); the improvement rate of the ECG in the observation group is higher than that in the control group. The heart rate is decreased after treatment	No description	Li and Wen [76]
VitC + nitrates + Ca^{++} antagonists	UAP (44)	(Dantonic™ + Ticlopidine) The overall angina pectoris relief rate in the treatment group (86.3 %) was significantly higher than that in the control group (54.5 %) ($P < 0.05$); the ECG improvement rate in the treatment group was also significantly higher than that in the control group ($P < 0.05$). Compared with the control group, the plasma GMP-140 was greatly decreased, and there was no significant difference compared with the healthy group	No description	Zhang and Wang [77]
Aspirin, nitrates and Ca^{++} antagonists	UAP (21)	The total ECG improvement rate and effective rate of Dantonic™ treatment group was significantly higher than that of the control group ($P < 0.05$)	No side-effects	Lu [30]
Low molecular weight Heparin + Aspirin + nitrates + Ca^{++} antagonists + β-receptor blockers	UAP (20)	There was no significant difference in angina pectoris relief rate between Dantonic™ (97 %) and the conventional treatment groups (86 %): the reduction of GMP-140 in Dantonic™ group was greater than that of the conventional treatment group ($P < 0.05$)	No side-effects	Wang Shanling [29]
ISDN + Enteric Aspirin	UAP (60)	In Dantonic™ group, ET was significantly reduced ($P < 0.01$) and CGRP was significantly increased ($P < 0.05$), compared with the levels before treatment	No description	Liang et al. (2002)

(continued)

Table 10.35 (continued)

Compatible drugs	Diagnosis (cases)	Evaluation	Toxic and side effects	Source
Urokinase 100 million − 500 million U + Aspirin 300 mg/d	MI (48)	Compared with 45 cases without Dantonic™ administration, there was no significant difference in the re-occurrence rate. The total ischemia burden in dynamic ECG was significantly decreased ($P < 0.05$) in Dantonic™ group, and cardiovascular ischemia events were also significantly reduced ($P < 0.05$)	No description	Wu et al. [78]
Aspirin + Ca-antagonist + Nitrate + β-receptor blockers + ACEI + drugs for blood fat adjustment + drugs for blood sugar decrease	AP (45)	The total heart event occurrence rate in the period of 3 years in the Dantonic™ group was 11.1 %, which was significantly lower than that of 28.6 % ($P < 0.05$)	No description	Shen et al. [79]
Dipyridamole + nitrates + β-receptor blockers + Ca^{++} antagonists	UAP (30)	The total effective rate of Dantonic™ group was superior to the control group; compared with before treatment, the seizure frequency and duration of angina attacks were reduced. ECG S-T and T waves were improved. Ultrasoundcardiogram showed improvement in LVH and the left ventricle diastolic function	Two cases felt stomach upset and 1 case felt dizzy	Hu and Suo [79]
ISDN + Enteric Aspirin + CPT + nitroglycerin 5 mg + polarized solution	MI (28)	The serum TnT peak of Dantonic™ group was significantly lower than that of the control group ($P < 0.01$). The times of both TnT increase and recovery were significantly earlier than in the control group ($P < 0.05$)	No description	Liang et al. (1998)
Platelet-antagonists + thrombolysis treatment + nitrates	AMI (21)	Compared with the captopril group, there was no difference in the death rate. LV mass index was relieved in both groups. Compared with the status before the treatment, the change was significant ($P < 0.01$), but there was no difference between the two groups. It indicated that combined with the platelet antagonist thrombolysis and Nitrate, Dantonic™ is similar to captopril which can inhibit ventricle remodeling, improve the blood flow and reduce congestive heart failure in acute myocardial infarction patients	one case felt stomach upset and head fullness	Li and Jiang [80]

(continued)

Table 10.35 (continued)

Compatible drugs	Diagnosis (cases)	Evaluation	Toxic and side effects	Source
Isosorbidi mononitras	UAP (33)	With the combination of Dantonic™ and Isosorbidi mononitras, the clinical angina pectoris relief rate was 82.9 % and the rate of ECG improvement was 75.8 %, both were superior to the treatment with only Isosorbidi mononitras	No	Liu [81]
Isosorbidi mononitras + defibrase, etc.	UAP (76)	There was a synergistic effect	No	Fan and Dong (2006)
Lovastatin	CHD, hyperlipidemia (36)	The total effective rate in the group of Dantonic™ combined with Lovastatin was 86.11 %. The ECG improved rate was 61.11 %, which was significantly higher than that of the control group. Blood fat improvement was significant in both groups, but there was no significant difference	No description	Sun [82]
Isosorbidi mononitras	CHD with AP (309)	The combination group was superior to the control group in terms of the total angina pectoris relief rate and ECG improvement rate	No side effects	Wang [83]
TMZ 20 mg	elderly unstable angina (40)	The angina pectoris relief rate in Dantonic™ combination group (77.5 %) was significantly higher than that of the control group (50 %), and the occurrence rate of arrhythmia, acute myocardial infarction and sudden death was significantly reduced		Wang et al. [84]
Nitrates + β-receptor blockers + Aspirin, drugs for blood fat decrease, (ACEI) TMZ	CHD with MI	Both the seizure frequency and the maximum duration of angina pectoris were significantly reduced in Dantonic™ group and the TMZ addition group. The total ECG improvement rate was 90 %, which was significantly higher than that of the control group (60 %)	Two cases suffered from stomach upset, one case from diarrhea and one case felt dizzy	Zhao et al. [85]
Nitrates + β-receptor blockers + Aspirin, drugs for blood fat decrease	Stable exertional angina (32)	Both Dantonic™ and TMZ had a good synergistic effect combined with these drugs above. The seizure frequency of angina pectoris and nitroglycerin consumption were reduced. ECG ischemia was improved, and the duration of exercise, time to induce angina, and time for ST segment depression to decrease 1 mm were all clearly prolonged	Patients in the TMZ group suffered from headaches and stomach upsets with a reddish face	Li and Chen (2005)

for dizziness; and in combination with Flunarizine or Domperidone for hemicrania [57]. These applications have solved or relieved the suffering of many patients with difficult and complicated illnesses. From a scientific point of view, the study of Dantonic™ in terms of pharmacology has provided many materials and ideas.

10.8 The Effect of Dantonic™ on the Prognosis of CHD and the Life Quality of CHD Patients

Dantonic™ has the effect of relieving angina pectoris, improving coronary flow, myocardial ischemia, platelet activation and aggregation, blood flow changes in organism blood vessels including coronary vessels, and stabilizing atherosclerotic plaques, etc. Dantonic™ has a significant effect on the prognosis of CHD. People will ask, what is the effect of Dantonic™ on the outcome indexes proposed by evidence-based medicine? Shen et al. [58] from Jiangsu Hospital of Integrated Medicine randomly divided 87 cases of stable angina pectoris patients into a control group (42 cases) which was treated with routine western medicines such as aspirin, Ca^{++} antagonists, nitrates, β-receptor blockers, ACEI and drugs for blood lipid adjustment and drugs to reduce blood sugar. The remaining patients were in the treatment group, which was treated with the same western conventional therapy as the control group, plus Dantonic™, 250 mg each time, three times a day, for more than 300 days. The authors observed the total occurrence rate of heart attacks and the death rate in both groups. Patients were followed up for 3 years and it was found that there were five acute cardiac events in the treatment group (11.1 %), which was significantly lower than the 28.6 % in the control group ($P < 0.05$). The number of patients that died of CHD during the 3 years was one case (2.2 %) in the treatment group, which was lower than the two cases in the control group (4.8 %), but there was no significant difference ($P > 0.05$). Dantonic™ is an important decreasing factor in the number of acute heart attacks (including cardiogenic sudden death, CHD with angina pectoris, UAP, AMI interventional therapy or bypass graft surgery for coronary artery) within 36 months of trials.

The evolution of medical models makes people further realize that the effect of drugs cannot be evaluated only by the recovery rate. The patient's quality of life, psychology, sociology, and other aspects must also be considered to implement a comprehensive assessment. In order to improve the patient's life quality, the prevention of angina re-occurrence is the most important. Does Dantonic™ have a preventive effect on angina re-occurrence? Yan [59] divided 60 cases of CHD into two groups. There was no significant difference in age, sex, duration of illness, and clinical characteristics of the patients. Dantonic™ was administered at 250 mg each time, tid for a period of 8 weeks to the treatment group (total 30 cases, 26 cases of stable angina pectoris, and 4 cases of UAP). Diao Xinxuekang was administered at 200 mg each time, tid for a period of 8 weeks to the control group (total 30 cases, 25 cases of stable angina pectoris, and 5 cases of UAP). The patients were observed for one course of treatment, and followed up with 6 months after treatment. The clinical improvement rate in the Dantonic™ group was 80 %, and in the control group, it was 70 %. There was no statistical difference between the two groups ($P > 0.05$). The follow-up observation showed that 56.67 % of the patients in the Dantonic™ group did not have a recurrence of angina, which was significantly higher than the 26.67 % in the control group ($P < 0.05$). After one course of treatment, there was no significant difference in the improvement of the ECG changes between the two groups. 6 months after treatment, the improvement rate of the ECG changes in Dantonic™ group was 43.33 %, which was significantly higher than the 16.67 % in the control group ($P < 0.05$).

Yan Liang's study gave us an important reminder that Dantonic™ has an important effect on the prevention of further development of angina (secondary prevention). In recent years, many international scholars have expressed

concerns about the use of drugs for secondary prevention. "Polypill" is an anti-platelet agent commonly used for secondary prevention, as are statins, β-receptor blockers, ACEI, and other mixed formulations. Scholars estimated that they would reduce the occurrence rate of cardiovascular events in the high-risk population by 80 % world widely, if secondary prevention was put into practice. It shows that western scholars have gradually realized that the effect of a single drug for the prevention of secondary effects is not as effective as that of combined therapy. Of course, the idea of compound preparations could have been influenced by the "westward movement" of TCM, and TCM theory in particular, over the past decade. Compound preparations have been used by TCM to treat diseases for thousands of years. Even a single herb drug can be considered as a compound preparation from the point of view of chemical composition. Dantonic™ has significant effects on angina pectoris treatment: reducing the frequency of angina attacks, alleviating pain, reducing nitroglycerin consumption, expanding the coronary arteries, improving myocardial ischemia, reducing myocardial oxygen consumption, improving the endothelial function of blood vessels, stabilizing atherosclerotic plaques, and inhibiting platelet activation. All of these effects show that the drug treats CHD in multiple channels, at multiple levels, and on multiple targets. This kind of effect cannot be achieved by only one single chemical drug. For instance, some people used high-dose statin drugs as a secondary prevention, but it was reported that there were clinical side effects of statins, such as muscle weakness, rhabdomyolysis, and polyneuropathy disease, which could have serious consequences. Chinese drug preparations such as Dantonic™ have a moderate action and a reliable effect, with little or no side-effects, and it is a suitable medication for secondary prevention for long-term use.

There have been many reports by clinical doctors showing that Dantonic™ does improve CHD patients' quality of life. The improvements in non-angina pectoris symptoms, such as episodes of chest tightness, shortness of breath, and palpitations, are all remarkable. Zhang et al. [9, 39] reported 59 cases of coronary angina pectoris who were treated with standard medications including nitrates, Ca^{++} antagonists, β-receptor blockers, aspirin, pyrantel, heparin or low molecular weight heparin, etc. Of this group, 31 patients were selected randomly and treated additionally with Dantonic™. The control group used standard western medication only. In terms of accompanying symptoms, the total efficiency in the Dantonic™ group was 87.1 % compared to 50 % in the control group. The difference between the two groups was significant ($P < 0.01$). It was demonstrated that Dantonic™ could relieve angina pectoris, and also improve another non-angina pectoris symptoms, improve the quality of life, and thus play a unique role which western drugs like aspirin or nitrates could not play. Long-term use of Dantonic™ will gradually relieve angina pectoris and improve the cardiogram, and also improve heart function (Karnofsky Performance Status, KPS) and the activities of daily life (ADL) (see [60]).

Yang et al. [60] used a survey questionnaire to study the quality of life. The survey included 14 general symptoms of cardiovascular diseases and 5 grades of symptoms: very serious, serious, medium, light, and no symptoms. The ability to carry out 14 kinds of daily life activities was assessed: housework, dining, dressing, and washing were graded 1–4 (total score 56). KPS was used to grade the patients' heart function and ranged from normal activity (10 marks) to severely ill (1 mark). The survey included self-assessment of mental health and included 90 questions relating to depression, stress, terror, crankiness, strength, physical/body symptoms, and relationships with others. The author randomly divided 60 patients into two groups: the first group only used Dantonic™ (10 pills each time, 3 times a day for 5 weeks) and the second group used Dantonic™ plus bio-feedback relaxation therapy. The results are shown in Tables 10.36, 10.37 and 10.38, which demonstrate that Dantonic™ not only can relieve angina pectoris, but also can improve patients' quality of life and the activity of daily life. Combined with bio-feedback therapy, the effects are even better.

Table 10.36 The effect of Dantonic™ and Bio-feedback therapy on angina pectoris patients' symptoms (%)

Group	Chest distress		Chest pain		Asthenia		Hypomnesia		Insomnia	
	Marked effective rate	Effective rate	Marked effective rate	Effective rate	Marked effective rate	Effective rate	Marked effective rate	Effective rate	Marked effective rate	Effective rate
Dantonic™	50.0	28.6	40.0	43.3	62.1	24.1	55.0	30.0	46.1	38.4
Total Effective Rate	78.6		83.3		86.2		85.0		84.5	
Dantonic™ + Bio-Feedback	67.9	28.6	50.0	43.3	75.9	17.1	73.3	17.2	84.6	11.5
Total Effective Rate	95.5		93.3		93.1		90.5		96.1	
P Value Between the Groups	<0.01		<0.05		<0.05		<0.05		<0.01	

Table 10.37 The effect of Dantonic™ and Bio-feedback therapy on angina pectori patients' activity of daily life (ADL) and heart function (KPS)

Group	ADL		*P* value	KPS		*P* value
	Before treatment	After treatment		Before treatment	After treatment	
Dantonic™ Group	50.60 ± 7.83	49.12 ± 6.38	<0.05	6.27 ± 0.83	7.15 ± 0.94	<0.05
Dantonic™ + Bio–Feedback	50.83 ± 8.46	48.34 ± 6.14	<0.01	6.29 ± 0.57	8.03 ± 1.06	<0.01
P Value Between the Groups		<0.05			<0.05	

Table 10.38 The effect of Dantonic™ and the bio-feedback therapy on CHD patients' psychological indicators

	Total marks	A	D	E	F
Dantonic™ Group					
Before treatment	117.25 ± 23.897	19.85 ± 4.185	16.70 ± 4.414	12.45 ± 4.071	10.10 ± 3.194
After treatment	115.20 ± 20.20	19.34 ± 4.183	15.06 ± 4.188	11.40 ± 3.747	9.55 ± 2.907
P value	<0.05	<0.05	<0.05	<0.05	<0.05
Dantonic™ + bio-feedback					
Before treatment	199.22 ± 20.62	28.35 ± 10.40	36.90 ± 8.379	33.35 ± 8.79	19.56 ± 8.61
After treatment	195.45 ± 20.20	25.45 ± 9.64	32.25 ± 6.887	28.80 ± 7.92	17.65 ± 7.56
P value	<0.01	<0.05	<0.01	<0.01	<0.05

Note SCL-90 includes 10 classes (of varying degrees); this table shows four classes that are closely related to the Quality of Life: *A* body symptoms; *D* depression; *E* anxiety; *F* hostility

B. T. Gugaisi of the Russian Ministry of Health treated 75 patients with CHD with Dantonic™ in the three largest medical centers in Russia. The outcome measure was a bicycle test with cardiograms, and special attention was paid to the patients' subjective feelings. The dependence on nitroglycerin decreased to 65.93 % after 7 days' treatment, and 43.2 % after 4 weeks; the ST segment depression decreased from 6.5 ± 0.5 to l.7 ± 0.25, a decrease of 84 %. Assessment of the patients' subjective feeling showed that 80 % of patients felt that the medicine had an effect and improved their quality of life. The patients reported that: (1) they generally felt better; (2) the number of angina pectoris episodes had decreased; (3) their working ability, physical strength and energy had improved; (4) their depression was reduced and (5) their adaptability to society had improved.

Ma and Liu [61] reported a study in which 120 cases of angina pectoris patients used Dantonic™ and bio-feedback therapy. The result also demonstrated that Dantonic™ could relieve angina pectoris, improve the cardiogram and patients' subjective symptoms, increase their quality of life, and improve psychological indicators. The effect was better when the drug was combined with bio-feedback therapy.

10.9 The Effect of Dantonic™ on Hypertension with CHD

Hypertension is one of the most important risk factors for CHD. In recent years, the standard for high blood pressure was repeatedly revised and the current international standard for the diagnosis of high blood pressure is not uniform in practice. These should be attributed to a number of large-scale, multi-center, multinational joint randomized trials which are carried out in Europe and the United States since the 1990s. The results of these trials advanced our awareness of the dangers of high blood pressure.

First, it was considered in the past that the standard of high blood pressure should be changed with age. A blood pressure suitable for old people might be considered high blood pressure for young people. But nowadays, this is not considered correct.

Secondly, in the past, people believed that the increase in diastolic pressure was the most important warning signal, while the systolic blood pressure was not important. Currently, it has been shown by many researches that systolic blood pressure is closely related to CHD, congestive heart failure, and the occurrence rate of cerebral vascular attacks and mortality rate. It has been demonstrated by Framingham Heart Study that the increase in systolic pressure has a more decisive effect on cardiovascular diseases compared to the increase in diastolic pressure. In addition, it has been observed that as the pulse pressure and age increase, so do cardiovascular events. An elevated systolic blood pressure is the most common type of clinical hypertension without treatment, especially for people who are over 60. According to The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, systolic pressure was given high attention in the meeting on this special topic.

Thirdly, there are three types of elderly hypertension: isolated systolic hypertension, isolated diastolic hypertension and mixed hypertension. Among all elderly hypertension cases, 65 % are classified as isolated systolic hypertension. According to a follow-up with these patients, 80 % of critical isolated systolic hypertension will develop into diagnosed hypertension. Those with clinical isolated systolic hypertension are 2–4 times more likely to have cardiovascular disease, myocardial infarction, LVH, stroke, or to die from cardiovascular disease, than normal old people. Research has shown that patients with isolated diastolic hypertension are likely to have lipid metabolism disorders, diabetes, obesity, peripheral vascular diseases, and LVH. The above risk factors are the most important risk factors for CHD. The coexistence of these risk factors forms the most lethal danger to human health, especially to the elderly. Currently, it is considered that isolated systolic hypertension is caused by accumulation of a multitude of factors, and it significantly increases the danger of other morbidity factors and forms multiple marginal abnormalities.

Fourthly, modern medicine emphasizes that hypertension should be treated comprehensively. The idea of focusing only on blood pressure reduction has changed, and now it has been turned to the protection of target organs, and the reversal or reduction of damage to target organs, and special attention has been paid to the heart and brain protection. Clinical doctors have noticed since 2000 the therapeutic effect of Dantonic™ on hypertensive CHD, especially on the CHD accompanied with elderly patients' isolated systolic hypertension. Dantonic™ could reduce blood pressure and improve circulation in the heart and organs in patients with hypertensive heart disease and hypertensive CHD (Bei 2000; He [62]; Lu Guangzhao 2003). See Table 10.39. Most authors believed that the effect of

Table 10.39 The clinical summary of hypertension treatment by Dantonic™

Author (year)	Diagnosis	Protocol	Results
Bei [86]	Hypertensive heart disease	Randomized control trial. The treatment group (86 cases) was treated with Dantonic™ + Composite Captopril; The control group (61 cases) was treated with Composite Captopril, both for 4 weeks	The total effective rate of the treatment group was 95.35 %, which was significantly higher than that of the control group (83.61 %), $P < 0.05$. Five cases suffered from stomach upsets and were relieved several days later
He [62]	Hypertensive heart disease	Randomized controlled trial. The treatment group (57 cases) was treated with Dantonic™ + Metoprolol; The control group (50 cases) was treated with Metoprolol	The effect of blood pressure control was good. The effective rate of the treatment group was 96, and 90 % in the control group; ECG ST-T improved rate was 90 % in the treatment group. The effective rate of ST-T and arrhythmia was 75 %. Both numbers were higher than those of the control group (65, 61 %) ($P < 0.01$)
Lu and Cai [87]	Hypertensive heart disease	Randomized controlled trial. The treatment group (38 cases) was treated with Dantonic™ + Captopril or Felodipine for 4 weeks	Blood pressure reduction effect was 100 % in both groups. The total effect for angina pectoris was 89.5 % in the treatment group, the improved rate of the ECG was 36.8 %, both were significantly higher than those of the control group, 61.8 % ($P < 0.01$) and 26.5 %($P < 0.05$), respectively. Side effects occurred in both groups: two cases had a headache with cough
Lu [88, 89]	(Blood Stasis Syndrome)	Randomized controlled trial. The treatment group (40 cases) was treated with Dantonic™; the control group (40 cases) was treated for 4 weeks	The total effective rate of the treatment group was 95 %, which was significantly higher than that in the control group, 70 % ($P < 0.05$). The symptoms of hyperlipemia and blood stasis syndrome in Dantonic™ group were improved. The author believed that Dantonic™ had a good effect on the treatment of I, II level hypertension
Cao et al. [63]	hypertension	40 cases were treated with Dantonic™ in addition to combined rehabilitation treatment. The 42 cases in the control group were treated with combined rehabilitation for 2 months	blood rheology indexes in the treatment group were all significantly improved compared with those before the treatment, and compared with the control group after treatment
Huang (2001)	Sub-acute hypertension	Non-randomized trials, 37 cases. They used Nifedipine and Diazepam combined with Dantonic™	The symptoms of 30 cases were significantly relieved. Symptoms were relieved basically after 60 min. The effect was stable within 5 h
Yang et al. [64]	Primary hypertension	286 cases in the treatment group were treated with Dantonic™ in addition to Nifedipine or Captopril; 275 cases in the control group were treated with Nifedipine or Captopril, and both were treated for a period of 24 months	The marked effective rate, effective rate, and the average blood pressure reduction in the treatment group were significantly different from those in the control group ($P < 0.05$)

Dantonic™ might be the improvement of blood rheology in hypertensive disease patients [63]. Yang et al. [64] reported that Dantonic™ had a good protective effect on some organs of primary hypertension patients. According to the follow-up of patients treated with Dantonic™, the occurrence rate of ischemic vertigo was significantly lower than that of the control group.

Dantonic™ can significantly reduce the rate of apoptosis of left ventricular myocardial cells, exert anti-myocardial fibrosis activity, reduce the concentrations of Ang II and aldosterone in blood plasma and of Ang II in the local cardiac muscle [65] of spontaneously hypertensive rats when combined with Fosinopril, and significantly reduce the apoptosis rate of myocardial cells [66].

References

1. Zhang M, Wang L, Chen B, et al. Chin J Integr Med Cardio-/Cerebrovasc Dis. 2004;2(6):311.
2. Li X, Zhou Z, Huang H. Chin J Gerontol. 2003;23 (3):183.
3. Li F, Yan F, Wang J. Comparsion of the clinical effect of dinitrosorbide plus composite salviae dropping pill and dinitrosorbide plus compound salviae tablet. In: The 99 national workshop on the modernization of traditional Chinese medicine (composite salviae), 1999. p. 34.
4. Shi Y. Comparsion of the effect of composite salviae dropping pill and isosorbide dinitrate in the treatment of stable angina. In: 96 national symposium on composite salviae medicament form, 1996. p. 29
5. Qian T. Observation of the rapid pain relieving effect of composite salviae dropping pill. In: 96 national symposium on composite salviae medicament form, 1996. p. 36.
6. Gao C. Clinical effect of composite salviae dropping pill on 310 Patients with. In: The 99 national workshop on the modernization of traditional Chinese medicine (composite salviae), 1999. p. 105.
7. Sun Z, Guan Y, Sun D. Shandong Pharm Ind. 2000;9(1):51.
8. Ye L, Shen Y, Zhe J. J Integr Tradit Chin West Med. l998;8(4):242.
9. Zhang Y, Zhang L, Li M. Mod J Integr Tradit West Med. 2000;9(10):874.
10. Zhang W, Yang Z. Strait Pharm J. l996;8(4):31.
11. Yang J. Clinical observation of the effect of composite salviae dropping pill in the treatment of 100 patients with and angina. In: The 99 national workshop on the modernization of traditional Chinese medicine (composite salviae), 1999. p. 31.
12. Wang Y, Wang H. J Henan Med Coll Staff Workers. 2004;16(3):227.
13. Dai X, Gu J, Wang L, et al. J Anhui Tradit Chin Med Coll. 2002;21(6):12.
14. Liu X. Hunan Guiding J TCM. 1999;5(5):30.
15. Liu X. Clinical observation of composite salviae dropping pill in treatment of and angina. In: The 99 national workshop on the modernization of traditional Chinese medicine (composite salviae), 1999. p. 95.
16. Ren S. Hebei J Tradit Chin Med. 2002;24(7):496.
17. Hong Y, Ren P, Zhang T. Mod J Integr Tradit Chin West Med. 2003;12(1):3.
18. Qin P, Fan L, Liu K, et al. Chin Tradit Patent Med. 2000;22(9):630.
19. Zhang G, Xu J, Gong L. Chin Tradit Herbal Drugs. 1999;30(5):365.
20. Hu X, Wang L, Xiong F. The effect of composite salviae dropping pill in the treatment of and the experimental study of composite salviae dropping pill's impact on. In: 96 national symposium on composite salviae medicament form, 1996. p. 48.
21. Hu B. Curative effect of composite salviae dropping pill on coronary heart disease accompanied with blood hyperviscosity syndrome. In: The 99 workshop on the modernization of traditional Chinese medicine (composite salviae), 1999. p. 106.
22. Li Y, Chen C, Feng H. J Snake. 1998;10(3):15.
23. Jia L, Ding X, Wang C. Clin Med J China. 1999;6 (1):21.
24. Mao L. Mod Med Health. 2003;19(1):57.
25. Liu Y, Li H. J Liaoning Coll Tradit Chin Med. 2003;5(4):354.
26. Wang L, Xiong Z, Wang G, et al. Chin J Integr Tradit West Med. 2004;24(6):500.
27. Liu Z. Analysis of the effect of composite salviae dropping pill in the treatment of angina of the unstable type. In: The 99 national workshop on the modernization of traditional Chinese medicine (composite salviae), 1999. p. 61.
28. He G, Liu X, Wang Y. Tradit Herbal Drugs. 1999;30(3):211.
29. Wang S, Wang L, Sun Y. Chin J Cardiovasology. 2003;8(5):354.
30. Lu J. Chin J Integr Tradit West Med. 2000;20 (6):415.
31. Fan S, Jia L. J Henan Coll Tradit Chin Med. l998;77 (13):96.
32. Zhu B, Gu J. Chin Tradit Herbal Drugs. 2000;31 (5):366.
33. Zhang S, Wang K. J Luoyang Med Sch. 2000;18 (1):25.
34. Wang Z, Zheng C, Zhao Y. Heilongjiang Med J. 2003;27(6):475.
35. Niu S. Harbin Med J. 2006;26(5):61.
36. Chen N, Yu H. Mod J Integr Tradit Chin West Med. 2006;15(14):1925.

37. Shou J, Zhao H, Xu B. Chin J Primary Med Pharm. 2001;8(5):421.
38. Duan H, Yang B, Qi H, et al. Central Plains Med J. 2002;29(3):5l.
39. Zhang Y, Zhao B, Li Y, et al. Chin J Integr Tradi West Med. 2000;20(5):378.
40. Ni J, Zhang S, Wei S, et al. Chin J Integr Med Cardio-/Cerebrovasc Dis. 2003;1(8):438.
41. Ni J, Zhang S, Wei S, et al. Chin J Integr Med Cardio-/Cerebrovasc Dis. 2003;1(7):384.
42. Jia J, Li X, Jia N. Res Tradit Med. 1999;15(4):15.
43. Zhu H. J Handan Med Coll. 2000;13(2):149.
44. Zhang Y. Chin J Cardiovasc Rehabil Med. 2001;10 (4):371.
45. Qiao H. Chin J Gerontol. 2004;2(8):758.
46. Zhou H, Zhu Y. Zhejiang J Integr Tradit Chin West Med. 2003;13(11):675.
47. Yan C, Gao M, Wang X. Observation of the clinical effect and discussion of the mechanism of action of the reversal effect of composite salviae dropping pill on LVH. In: 96 national symposium on composite salviae medicament form, 1996. p. 7.
48. Wang X, Huang H, Jiao L, et al. The reversal effect of composite salviae dropping pill on LVH of. In: The 99 national workshop on the modernization of traditional Chinese medicine (composite salviae), 1999. p. 52.
49. Luo Z, Zheng B. Fujian J Tradit Chin Med. 1999;30 (6):7.
50. Fu X, Li Q, Feng J. Observation of the effect of composite salviae dropping pill in treating from the change of of nail fold. In: The 99 national workshop on the modernization of traditional chinese medicine (composite salviae), 1999. p. 74.
51. Zhang G, Xu J, Gong L. Chin Tradit Heart Drugs. (1999);30(5):365.
52. Wang L. Chin Tradit Herbal Drugs. 1999;30(6):448.
53. Wang H, Wang F, Lin Y, et al. Shaanxi Med J. 2003;32(3):252.
54. Huang W, Zeng Z, Yin R, et al. Guangxi Med J. 2003;25(11):2095.
55. Li H, Zhang H, Ji K, et al. Prevention and treatment of cardio-cerebral-vascular disease. 2005;5(5):17, 21.
56. Zeng Z, Wu M, Liu T, et al. J Guangxi Med Univ. 2004;21(6):809.
57. Xu S. Chin J Rural Med Pharm 2006;13(10):43.
58. Shen J, Yan Q, Hu Z, et al. Heilongjiang J Tradit Chin Med. 2003;6:11.
59. Yan L. Clin J Tradit Chin Med. 2007;19(1):9.
60. Yang J, Sha W, Chen P, et al. Chin J Cardiovasc Rehabil Med. l997;3(6):20.
61. Ma S, Liu J. Mod Med Rehabil. 1999;3(9):1113.
62. He Y. Chin New Med. 2003;4(14):1269.
63. Cao S, Teng C, Chen R, et al. Guangxi Med J. 2004;26(11):1634.
64. Yang D, Wang J, Yang D. Shandong J Tradit Chin Med. 2006;25(6):373.
65. Wu T, Chen J, Xie W, et al. Chin J Integr Med Cardio-/Cerebrovasc Dis. 2004;2(11):645.
66. Chen J, Xie W, Wu T, et al. Chin J Integr Med Cardio-/Cerebrovasc Dis. 2005;3(11):969.
67. Wu K, Chen H, Wei B, et al. Chin J Mod Appl Pharm. 2001;18(6):493.
68. Feng P, Tai N, Tan Y, et al. Chin J Integr Tradit Med. 1999;19(5):286.
69. Liu M, Yang Z. Regulating function of composite salviae dropping pill on the of patients with and angina caused by stagnation of Qi and blood stasis. In: 96 national symposium on composite salviae medicament form, 1996. p. 27.
70. Ma X, Zhang X, Ma H, et al. J Clin Cardiol. 2006;22 (7):437.
71. Wang F, Wang H, Lin Y, et al. Chin J Gerontol. 2003;23(6):342.
72. Wang H. Shaanxi Med J. 2003;3(32):252.
73. Shen X. Chin J Integr Med Cardio-/Cerebrovasc Dis. 2003;1(5):266.
74. Ai F. J Med Forum. 2003;24(6):37.
75. Yuan Q. Chin J Med Theory Pract. 2003;8:1071.
76. Li Q, Wen L. Chin J Rural Med Pharm. 2003;10 (11):5.
77. Zhang H, Wang X. Shaanxi J Tradit Chin Med. 2003;24(10):925.
78. Wu X, Cheng J, Zhang Z. Mod J Integr Tradit Chin West Med. 2002;11(4):303.
79. Hu G, Cai F. Chin J Cardiovasc Rev. 2003;1(1):38.
80. Li J, Jiang T. Tian Jin Pharm. 2003;l5(1):36.
81. Liu L. Sichuan Med J. 2004;25(4):419.
82. Sun L. Guizhou Med J. 2006;30(4):341.
83. Wang Z. J Chin Compr Med J (Harbin). 2005;6 (3):238.
84. Wang Y, Cai W, Qian H, et al. Chin J Pract Chin West Med. 2006;19(2):123.
85. Zhao J, Zang W, Wang G. Shandong Med J. 2004;44(34):40.
86. Bei Q. Guilin Med J. 2000;3:20.
87. Lu K, Cai W. Tian Jian Pharm. 2003;15(6):27.
88. Lu X. Guangxi J Tradit Chin Med. 2004;27(4):6.
89. Lu X. J Guangxi Tradit Chin Med Univ. 2004;7 (2):28.
90. Zhang L, Yang H. Treatment of retinal haemorrhage with composite salviae dropping pill. In: The 99 national workshop on modernization of traditional chinese medicine (composite salviae), 1999. p.114.
91. Zhang H, Liu D, Guo J, Zhang X. Abstract of experience of aristocratic family of TCM. Xian: Shanxi Science and Technology Press; 2004. p. 115–120.
92. Xie J. J New Chin Med. 1992;24(8):1–3.
93. Guo J. China newspaper of traditional Chinese medicine. 2005;Cumulated No. 2343phase.
94. Zhang X. Treatment of intractable diseases. 1st ed. Beijing: People's Medical Publishing House; 2005.
95. Luo S, Shaanxi J. Tradit Chin Med. 1987;8(2):540.
96. Xing Q. J Integr Tradit Chin West Med. 1998;18 (8):506.
97. Xi G, Wu F. Foreign Med Sci Trad Chin Med. 1991; (5):17.

98. Yan P, Luo X, Shi H, et al. Mod J Integr Tradit Chin West Med. 2005;14(16):2092–4.
99. Tian Y. Trad Chin Med Res. 1994;(6):47.
100. Yuan X. J Integr Trad Chin West Med. 1996;16 (6):325.
101. Zheng S. J Integr Tradit Chin West Med. 1998;18 (11):690.
102. Zhang J. J Integr Tradit Chin West Med. 1993;13 (2):109.
103. Chen Y. Tradit Chin Med Res. 1998;14(3):8.
104. Pan L. J Nanjing Univ Tradit Chin Med. 1998;14 (4):213.
105. Li L. J Integr Tradit Chin West Med. 1997;(7):435.
106. Cai Z. J Integr Tradit Chin West Med. 1993;(3):187.
107. Wang H. J Integr Tradit Chin West Med. 1990; (11):694.
108. Guo L, Li S, Zhang W. Clinical observation of compound salvia dropping pill anti angina pectoris. J Linyi Med Coll. 2001;23(2):113–5.
109. Guo H, Zhejiang J. Integr Tradit Chin West Med. 1997;7(3):153.
110. Wang S. Chin Heart J. 2000;12(4):323.
111. Zhang X. Chin Tradit Pat Med. 2001;23(3):227–8.
112. Wang S, Clin J. Anhui Tradit Chin Med. 2000;12 (6):510–1.
113. Zhao X. Chin Trad Herbal Drugs. 1999;30 (9):688–9.
114. Sun D, Zhang Z. Mod Med Health. 2000;16(5):397–8.
115. Qin P. Chin Tradit Patent Med. 2000;2(9):630–2.
116. Yang Y, Lin K, Feng X. Chin Tradit Herbal Drugs. 2000;31(3):208.
117. Tan S, Liu C. Heilongjiang Med J. 2001;14(2):125.
118. Zhao J. J Chin Pract Med. 2002;4(6):57–8.
119. Wang G, Shen Y. Clin Focus. 2001;16(15):700–1.
120. Zhang Y, Zhao B, Li Y, et al. J Integr Tradit Chin West Med. 2000;20(5):378–9.
121. Wei Y, Zhang X. J Integr Trad Chin West Med. 2001;21(8):614.
122. Zhang S. J Fujian Univ Tradit Chin Med. 2001;11 (3):10–2.
123. Zhang B, Han Y, Lin L. J New Chin Med. 2001;33 (2):23–4.
124. Wu X, Cheng J, Zhang Z. Mod J Integr Tradit Chin West Med. 2002;1(4):303–4.
125. Ru C. J Chin Clin Med. 2002;3(1):86–7.
126. Ma J, Tianjin J. Tradit Chin Med. 1998;15(1):24.
127. Zhang R, Li Z. Chin J Cardiovasc Rehabil Med. 2002;11(1):81–2.
128. Qian H, Sheng H. Gansu J Tradit Chin Med. 2002;15(1):29–30.
129. Yuan G, Chin J. Clin Pharmacol. 2002;7(2):162–3.
130. Zhang D. J Integr Tradit Chin West Med. 1993;13 (4):234.
131. Zhou S. Clin Focus. 1993;8(20):956.
132. Li B, Yan D, Yang Z, et al. Beijing J Tradit Chin Med. 1992;3:30.
133. Zhang H, Gao Y, Shi Q. J Clin Pediatr. 1994;12 (1):71.
134. Wang Z. J Appl Clin Pediatr. 1994;9(1):59.
135. Yue R. J New Chin Med. 1997;23(11):54.
136. Gu J. J Pract Med, 1994 (5): 48.
137. Yang W. Acta Pharmacol Sinica. 1990;6(2):118.
138. Lang Y. J Integr Tradit Chin West Med. 1990;10 (9):567.
139. Li Y. Beijing J. Tradit Chin Med. 1992;3:30.
140. Yuan X. J Integr Tradit Chin West Med, 1996, l6 (6): 325.
141. Yang M. J Integ Trad Chin West Med. 1996;16 (7):427.
142. Cha J. J Integr Tradit Chin West Med. 1989;9 (4):241.
143. Xue Z. Chin J Pract Pediatr. 1993;(supplement):156.
144. Zhang H. J Clin Pediatr. 1994;12(8):71.
145. Ding M. Chin J Pract Pediatr 1994;167.
146. Wang X. J Appl Clin Pediatr. 1992;7(4):212.
147. Wu N, Yan X. China Pharm. 1992;3(6):32.
148. Jiang W, Chen Y, Wang Y, et al. Acta Acad Med Primae Shanghai. 1982;9(1):13.
149. Wu N, Yan X, Zhu Y. Chin Tradit Patent Med. 1993;15(8):24.
150. He G, Liu X, Wang Y. Chin TraditHerbal Drugs. 1999;30(3):211.
151. Zhou Y, Li C, Zhang N, et al. Integr Tradit Chin West Med Pract. Crit Care Med. 1999;6(2):53.
152. Li F, Ma J, Zhang Z, et al. Chin Tradit Patent Med. 1998;20(3):29.
153. Hlatky MA, Calliff RM, Harre FE, et al. J Am Coll Cardiol. 1990;15:1.
154. Gan ZR, Goulg RJ, Jacobe JW, et al. J Biol Chem. 1988;263:19827.
155. Davis MJ, Thomas AC. Br Heart J. 1985;53:363.
156. Ma H, Zhao Z. Chin Tradit Herbal Drugs. 1999;30 (5):364.
157. Zhao X, Cheng B, Zhang S. Chin Tradit Herbal Drugs. 1999;30(9):688.
158. Bao Y, Xu Z, Jin Z, et al. Chin Tradit Herbal Drugs. 1999;30(4):287.
159. He B, Rao S. Chin Tradit Herbal Drugs. 2000;31 (2):121.
160. Liu Z, Gao S, Deng J, et al. Chinese Traditional Patent Medicine. 1997;19(7):20.
161. Ding X, Jia L, Wang C. Acta Acad Med Suzhou. 1999;19(5):512.
162. Jia L, Ding X, Wang C. Chin Clin Med. 1999;6 (1):21.
163. Xu X. Chin Tradit Herbal Drugs. 2000;31(1):44.
164. Holmes DR Jr, Vliestra RE, Smith HC, et al. Am J Cardiol. 1984;53(Suppl):77c–81c.
165. Zhou X, Lu Z, Wang D. J Integr Tradit Chin West Med. 1996;16(8):480.
166. Jiang H. J Integr Tradit Chin West Med. 2002;22 (8):640.
167. Zhang X. J Integr Tradit Chin West Med. 1993;13 (2):109.
168. Chen S. Clin Focus. 1994;9(17):782.
169. Ding Q, Chen Z, Wang W. J Integr Tradit Chin West Med. 2000;20(3):210–1.
170. Xue Y. Clin Focus. 1994;9(17):809.
171. Lin J, Yang F. Liao Y. J New Chin Med. 1998;5:34–5.

172. Liu X, Zhang J, Zhang S. J Integr Tradit Chin West Med. 2000;20(7):529.
173. Yang M, Lan H. Chin J Neonatol. 2002;17 (1):28–31.
174. Wang F, Wang L, Gu L. China J Mod Med. 2000;10 (5):1–2.
175. Sun D, Chin J. Pract Chin Mod Med. 2000;1 (10):918.
176. Huang D, Zhang D, Feng Z. J Pract Med. 2002;18 (1):16.
177. Zhao Y, Li X, Dong M. Chin J New Drugs Clin Remedies. 2002;21(6):358–60.
178. Su P. Trad Chin Med J. 2000;41(6):376–7.
179. Zhang X. J Clin Med. 2000;20(4):51–2.
180. Li Z. Clin Focus. 2002;17(4):230.
181. Wang X, Chin J. Hos Pharm. 1999;17(4):187.
182. Tu J, Ju H. Tianjin J Tradit Chin Med. 1991;1(2):51.
183. Zhang Y, Zhang Q, Zuo F. Tianjin J Tradit Chin Med. 2001;18(1):10.
184. Zhang D, Zhang X, Yuan X. J Integr Tradit Chin West Med. 1993;13(4):234.
185. Xun J, Xue B, Chen Z. Chin J Phys Ther. 1991;14 (2):6.
186. Jiang L, Wang Y, Sun W. Chin J New Drugs Clin Remedies. 1995;9(5):315.
187. Huo X. J Pract Med. 1992;8(1):38.
188. Xiong L, Cao G, Wu L. Chin J Integr Tradit West Med. 1993;13(8):533.
189. Yang M. J Integr Tradit Chin West Med. 1996;1 (7):427.
190. Sun R, Hebei J. Tradit Chin Med. 1994;16(5):23.
191. Li S. Clin Focus. 1994;9(6):282.
192. Luo N, Liu S. J Clin Dermatol. 1994;23(6):360.
193. Ming Z. Herald Med. 1997;16(6):299.
194. Huang L, China J. Chin Materia Medica. 1996;21 (9):570.
195. Wang X, Cui H. Chin Pharm Aff. 1997;11(3):212.
196. Huang X, Shu Z. China Pharm. 2002;13(3):162.
197. Guo B, China J. Chin Materia Medica. 2002;27 (7):492.
198. Min K, Chin J. Med. 2000;35(7):52.
199. Zheng X. Capital Med. 2002;3:36.
200. Lv H. Chin J. New Drugs Clin Remedies. 1998;17:58–9.
201. Guo L, Lu Q, Chen X. Lishizhen Medi Materia Medica Res. 2001;12(7):644.
202. Tan S. J Clin Dermatol. 1994;15(2):27–8.
203. Cao P, Feng R, Feng Z. Guangxi J Tradit Chin Med. 1994;1(4):3–4.
204. Li J, Jiang T. Tianjin Pharm. 2003;2(2):263.
205. Liang C. Inner Mongolia Med J. 2001;5(33):36.
206. Zheng M. Mod Rehabil. 2000;4(1):144.
207. Wang S. Henan Tradit Chin Med. 2004;24(3):73.
208. Bai C. Shaanxi Med J. 2005;8(34):1001.
209. Wang M, Appl J. Gen Pract. 2005;1(3):91.
210. Ke Y, Wu W. Hubei J Tradit Chin Med. 2005;11 (27):73.
211. Zhao Q, Chin J. Misdiagnosis. 2005;14(5):2647.
212. Pang X, Song B, Wang J. Chin J Tradit Med Sci Technol. 2007;2(14):121–2.
213. He Q, Chen F, Xu Y. J Chin Physician. 2005;11 (17):11.
214. Ma Z, Meng F, Deng Z. J Med Intel. 2007;5 (20):865–6.
215. Guo Z, Wang S. Forum Tradit Chin Med. 2006;4 (21):28.
216. Li J. Infect Dis Info. 2006;2(19):88.
217. Liu R, Du X. Hebei J Tradit Chin Med. 2006;9 (28):687–8.
218. Yan Z. et al. J Pract Tradit Chin Inter Med. 1990;3:33.
219. Liu F. China's Naturopathy. 2003;4(11):43–4.
220. Yan W, He J. Shanghai J Tradit Chin Med. 1999;3:14.
221. Li J, Guangxi J. Tradit Chin Med. 2001;4(24):20–1.
222. Liu Y. Harbin Med J. 2003;1(23):28.
223. Xie M, Jin Z, Ye G, et al. J Integr Tradit Chin West Med. 1995;1(5):269.
224. You H, Chin J. Clin Neurosurg. 2003;2(8):117–9.
225. Wang F. New J. Tradit Chin Med. 1995;9:9.
226. Shi K. J Integr Tradit Chin West Med 1989, (2):116.
227. Yao C, Su A. Chin J Clin Pharm Ther. 2003;8 (3):339–40.
228. Zhang D, Zhang X, Yuan X. et al. J Integr Tradit Chin West Med. 1993;4:234.
229. Shen Z, Zhang M, Liu S. Jiangxi J Tradit Chin Med 1997;Supplement:103-104.
230. Zhou H. J Tradit Chin Ophthalmol. 1996;6:16.
231. He X. J Tradit Chin Ophthalmol. 1997;7(4):205.
232. Qiu N, Chen T. Strait Pharm J. 2003;02:67–8.
233. Liu J. J Tradit Chin Ophthalmol. 1994;4:13.
234. Yu X. J Clin Stomat 1995, (4):132.
235. Wang Q, et al. J Integr Tradit Chin West Med. 1990;10(5):307.
236. Wu Q, et al. J Yunyang Med Coll. 1995;14(1):37–8.
237. Ni A. J Integr Tradit Chin West Med. 1994;14 (7):439.
238. Wang X, et al. Chin J Oncol. 1996;18(6):412–4.
239. Yuan Z, Gao J, Ou Y, et al. Pract Clin Med. 2001;1 (2):46.
240. Zheng S, et al. J Integr Tradit Chin West Med. 1998;18(11):690.
241. Zhu Y. Lishizhen Med Materia Medica Res. 1999;10(7):552.

The Therapeutic Effect of Dantonic™ on High Risk Factors of Coronary Heart Disease

11

Guoguang Zhu, Jinping Liu, Jia Liu and Ruizhi Luo

11.1 The Stabilizing Effect of Dantonic™ on Atherosclerotic Plaques

11.1.1 General Introduction

The research on atherosclerosis has been one of the most in-depth studies on human diseases in the last hundred years or so. In his revised "Injury Responsive Theory," Russell Ross proposed that risk factors such as dyslipidemia, high blood pressure, immune complexes, and viral infections could damage the endodermis, which was considered the initial link of atherosclerosis. The concept of damage includes changes in morphology, metabolism, and function. This endothelial injury can result in changes in endothelial permeability, adhesiveness, and blood coagulation, and the release of a large number of cytokines and growth factors, which lead to a series of chain reactions of atherosclerosis. All of these require a precondition of existence of hyperlipidemia. It is believed at present that among the 246 risk factors for atherosclerosis, hyperlipidemia is the most dangerous. It has been confirmed that the lipid deposition of atherosclerosis is mainly of free cholesterol and cholesterol esters, as well as triglycerides and phospholipids, etc. Modern technology has also demonstrated that the increase of lipids in the intimae is the result of lipoprotein infiltration from blood plasma. In some parts of the aorta and moderate arteries, the intimae thicken with the deposition of a large amount of lipids and the infiltration of monocytes and lymphocytes; medial smooth muscle cells migrate to the intima and proliferate, accompanied with the aggregation of collagen proteins and an increase in extracellular matrix. The central part of an atherosclerotic plaque (ASP) is often soft, and microscopic observation reveals that it is mainly composed of foam cells and tissue fragments. The surface of the prominent luminal part of the ASP is a hard, fibrous capsule, which can be ruptured to form a thrombus and block the lumen. The patients are thus transformed from a subclinical state into severe clinical manifestation, and even sudden cardiac accidents and sudden death can occur.

11.1.1.1 Atherosclerotic Plaque and Coronary Heart Disease

ASP leads to coronary heart disease, which is still the main cause of human mortality in most parts of the world. Low-density lipoprotein (LDL) is a major risk factor for AS. LDL becomes oxidized lipoprotein after certain physical and chemical modifications, which has a very important significance on vascular sclerosis. With the announcement and implementation of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment

G. Zhu (✉) · J. Liu · J. Liu · R. Luo
The European Federation of Pharmaceutical Society, Stockholm, Sweden
e-mail: ggz68111@yahoo.com

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Panel III Final Report, ATP-III), a whole new concept of the prevention of coronary heart disease has been revealed.

11.1.1.2 The Importance of Lipoproteins

In research on AS, more attention is focused on the dynamic process of the entry of lipoproteins into the artery wall, and especially on several types of cells and the interactions among these cells.

Endothelial Cells

The research on endothelin- and endothelium-dependent relaxation factors (EDRFs) has become a hotspot for the last 20 years or so. The imbalance of endothelin and EDRFs, i.e., the decrease of EDRF activities, will easily result in vasoconstriction → stenosis → myocardial ischemia, and this imbalance is not formed at the time of atherosclerosis but in the early stages of the disease. The damage to endothelial cells and hyperlipidemia can easily cause atherosclerosis, lipid deposition in the intima, and the hyperlipidemia itself can damage the endothelial cells.

Mononuclear Macrophage Cells

The mononuclear macrophage cells are one of the most important cell types involved in ASP pathological changes; they act as the initiating factors, and play an important role in the entire process of pathological changes. Mononuclear macrophage cells can uptake modified lipoprotein in the absence of feedback regulation through scavenger receptors and form foam cells. In addition, they can secrete a variety of toxic substances and a variety of cytokines to accelerate the disease and promote ASP rupture.

Smooth Muscle Cells

The proliferation of smooth muscle cells and smooth muscle cells on blood vessel walls and the synthesis of a large amount of extracellular matrix are also among the key factors of ASP pathological changes. Currently it has been confirmed that stimulation by fibroblasts and platelet-derived growth factors and vasoconstrictors can cause the proliferation of smooth muscle. It is believed that smooth muscle cells can be transformed into foam cells as a result of lipoprotein uptake in an environment of high blood fat or anomalous blood fat.

Foam Cells

Foam cells are transformed from Mononuclear macrophage cells and smooth muscle cells, and they constitute the substance of the central area of ASPs. It is believed that the number of foam cells is related to plaque rupture. Therefore, foam cells are closely related to thrombosis incidence in coronary heart disease and other acute coronary heart diseases.

In recent years, it has been proven by noninvasive techniques, such as ultrasound Doppler angiography, that ASP development can be stopped or even dissipated. The scientific evidence changed the previous idea that ASP can only develop but never dissipate.

11.1.1.3 New Development

There have been some new developments in the understanding of ASPs in the past few years. ASP was considered irreversible in the past, but now it has been proven by an increasing amount of studies that ASP is reversible. More and more doctors have realized that ASP is preventable and treatable.

In the past, ASPs were considered to be the accumulation of dead cells. These cells lose their metabolic activity after excessive fat deposition. Current studies have confirmed that the insides of ASPs are full of living cells, and their biological functions and information transmission are closely related to the clinical symptoms caused by AS. It was considered in the past that the greater the plaques are, the greater the risk is. Luminal stenosis and insufficient myocardial perfusion caused by ASP are the mechanisms for angina pectoris and myocardial infarction. In fact, there is no evidence showing that interventional therapy, such as bypass and PTCA, could prevent the reoccurrence of myocardial infarction. With the increase in the occurrence of the intermediate syndrome (since the 1940s), unstable angina pectoris (UAP), ST-segment elevation and non-ST-segment elevation myocardial infarction (since the 1970s), and the relationship between UAP and non-ST segment elevation myocardial infarction and acute coronary syndrome, people have

gradually realized the importance of stabilizing plaques. With the development of coronary artery imaging, interventional cardiology, molecular cardiology, and other related sciences, it has been found that the stability of ASPs is related to the foam cells derived from mononuclear macrophage and smooth muscle cells (related to the expression of matrix metalloproteinases and macrophage-related degradation of matrix collagenase).

11.1.1.4 Plaque Rupture

The main symptom of acute coronary syndrome is plaque rupture, and plaque rupture depends on the structure of the plaque and the exterior force which acts on the plaque.

Inflammation plays an important role in the occurrence and development of atherosclerosis, and is considered one of the most important factors involved in acute coronary syndrome. The studies on vascular inflammatory markers have been carried out more thoroughly in recent years; these markers are P-selectin, IL-6, IL-l, TNF-2, soluble intercellular adhesion molecules, and C-reactive protein.

William S. Tillett and Thomas Francis first discovered CRP in 1930, which was the first discovered acute phase protein in the human body, and a very sensitive marker for inflammatory tissue injury. CRP is produced by the human liver and is partially regulated by IL-6, TNF-2, and IL-l.

Studies have showed that peripheral lymphocyte cells are also able to produce CRP. Human CRP is composed of five nonglycosylated peptide subunits which are similar to each other. Each subunit contains about 200 residues and forms an annular pentameric disc inside cells through noncovalent bonds. The molecular mass of the pentameric disc is 111.8×10^3. CRP has the following features: (1) By means of a classic pathway it activates the complement system, releases inflammatory mediators, promotes adhesion and phagocytic cell responses, and dissolves target cells. (2) It acts on the receptors in lymphocytes and mononuclear cells, resulting in the necrosis and proliferation of lymphocytes, and promotes lymphokine production, leading to the proliferation of T lymphocytes and increasing phagocytosis; (3) It inhibits the aggregation and release response of platelets; and (4) It causes tissue factor expression on the surface of monocytes and immune regulation. The normal level of CRP in the serum of the human body is 2 mg/L, which is not related to satiation and measurement time.

Recently, it has been verified that serum CRP is located in ASP, and has an ability to regulate monocyte aggregation, complement activation, and stimulate endothelial cells. CRP can lead to the secretion of intercellular adhesion molecule-l, and enables macrophages to uptake LDL and transform into foam cells. A European research group followed up for 2 years on the CRP levels in 2,000 patients with angina pectoris, and they found that patients with increased serum CRP were 1.81 times more at risk of a nonfatal myocardial infarction or sudden death than were patients with normal serum CRP. According to studies, the CRP levels are related to age, smoking, body mass index, triglycerides, the extent of coronary artery stenosis, myocardial infarction lesion, and left ventricular ejection fraction. By multiple regression analysis and elimination of these factors, CRP level is still an independent predictor of acute coronary events in angina pectoris patients. In recent years, a number of studies have shown that the CRP level is a reliable indicator for neointimal hyperplasia and restenosis following coronoid stenting.

The effect of Dantonic™ on the stabilization of coronary atheromatous plaques is an integration of multiple actions. Dantonic™ is able to significantly reduce CRP. Research has shown that atherosclerosis is a process of chronic inflammation, which is the main factor affecting the stability of coronary plaques. Inflammation results in the production of neutrophils and monocytes in parts of the blood vessels. The atherosclerosis cap can activate macrophages and lead to further development of plaque rupture. This is one of the main causes of acute coronary syndrome. CRP is an important indicator of the inflammatory response of the body. It was indicated in a study by Bruneck et al. that an increase of CRP is an independent and additional risk factor of chronic bacterial infection. An examination of a total of 985 patients of coronary artery disease diagnosed by angiography showed that increased CRP was an

Table 11.1 Effect of Dantonic™ on CRP levels (means ± SEM)

Group	Before treatment	After treatment
Unstable angina pectoris (48)	15.6 ± 8.14	8.65 ± 4.37*
Stable angina pectoris (116)	13.23 ± 3.03	11.58 ± 2.65
Old myocardial infarction (22)	13.05 ± 3.11	10.82 ± 4.06

*$P < 0.05$, normal value of CRP is less than l0 mg/L

independent risk factor. Zou et al. [1] observed 186 patients with coronary heart disease, including 116 cases of stable angina, 48 cases of unstable angina, and 22 cases of elderly myocardial infarction. Serum CRP was determined before treatment with Dantonic™ and 2 months after treatment with Dantonic™, and the results showed that Dantonic™ could reduce significantly CRP in unstable angina patients (Table 11.1).

There are reports showing that Dantonic™ has the antiinflammatory function and can decrease CRP value. Currently it is believed that fibrates, angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, β-receptor blockers, antiplatelet drugs, etc., all have a certain effect on decreasing CRP. Thus, the effect of Dantonic™, when used in combination with these drugs, must be evaluated accordingly. Clinically, further studies are needed on the effect of Dantonic™ on decreasing CRP.

Zhuge Limin et al. (2005) observed 93 cases of acute coronary syndrome patients with conventional treatments such as nitroglycerine, long-acting isosorbide dinitrate tablets, aspirin, or urokinase. The patients were randomly divided into a treatment group (47 cases) and a control group (46 cases). The patients in the treatment group received the conventional treatment plus 250 mg of Dantonic™, 3 times a day for 1 month. The results showed that Dantonic™ could significantly reduce the CRP value.

11.1.1.5 The Structure of ASP

Matured plaque is composed of two parts:

1. The lipid core: composed of cholesterol esters, a small amount of triglycerides, and macrophage-derived foam cells which release cholesterol esters after cell rupture. The lipid core accounts for more than 40 % of the plaque, and this kind of plaque is inclined to rupture. The debris of dead macrophages and tissue factors secreted by activated macrophages have a strong promotive effect on thrombosis. Endothelial cells and smooth muscle cells also can secrete this tissue factor.
2. The fibrous cap: the important component is collagen fiber (mainly type I collagen). Smooth muscle is the source of the fiber cap. The process of proliferation, migration, and the formation of a fibrous cap by smooth muscle cells is a trauma reparative response. To maintain a steady-state in this process, serine protease, cysteine proteinase, and matrix metalloproteinases play important roles.

Plaques are eccentric, and the part connecting the plaque and endometrial tissue is called the "shoulder." The shoulder bears the greatest external force and the fibrous cap is the thinnest part. Therefore, these two parts are inclined to rupture. Easily ruptured plaques are called "unstable plaques" or "vulnerable plaques" and they have the following features:

(a) Lipid core >40 %;
(b) Thin fibrous cap;
(c) Inflammatory cell infiltration (increase in macrophages and T lymphocytes)
(d) Reduction and apoptosis of smooth muscle cells (related to Interleukin 1-β converting enzyme);
(e) External force: from mechanical forces, hemodynamic forces, decrease of high pressure, lumina volume, and blood vessel wall tension caused by blood pressure (Laplace's law).

This could explain the majority (more than 75 %) of external factors which trigger acute coronary syndrome: the early morning (particularly, a few hours after waking up), Monday, winter, emotional excitement, post-vigorous exercise. These factors can cause excitement of the sympathetic nerves, resulting in a sudden increase in blood pressure, pulse, cardiac contraction, and coronary blood flow, and finally plaque rupture.

11.1.2 Stenosis and Rupture Caused by Atherosclerotic Plaques

Each year, nearly 20 million people die from acute cardiovascular events in the world, and the majority of the patients were asymptomatic before the attacks. With the wide use of coronary angiography, it has been found in the recent coronary angiographies of acute myocardial infarction patients that in 65 % of the patients, the coronary artery diameter had narrowed by >50 %, in 85 % of the patients, it had narrowed by >70 % (Fig. 11.1). Therefore, scholars gradually changed their idea from the concern of narrow lumen to the emphasis on "stabilizing the plaques" in the past 10 years. In 1980, Mailer first created the concept of "vulnerable plaque," and indicated that the transition of the plaques from stable state to unstable and damaged state, and the eventual thrombosis are the core of the pathological basis of acute coronary syndrome. Coronary intervention therapy can correct severe coronary artery stenosis. It is indeed a revolutionary milestone in the history of coronary heart disease treatment, but it cannot change the basic biological processes of ASP and cannot solve the fundamental conflict of cardiovascular events, the unstability of the plaques. In 2003, a group of world famous experts in the area of cardiovascular diseases further developed a new concept, "from vulnerable plaque to vulnerable patient." This concept stressed that the risk of cardiovascular events should be assessed overall, and quantified from each coronary artery, each plaque, from the vulnerable blood and vulnerable myocardium, and from the point of view of the patients, and finally optimize the treatment solution to prevent the occurrence of cardiovascular events. Dantonic™ shows the advantages of comprehensive treatment of stable plaque (Fig. 11.2).

Studies in the past 10 years showed that the main cause of acute coronary syndrome is ASP rupture, rather than narrow, and followed by thrombosis. And the researches have showed the most ASP causing myocardial infarction is mild and moderate. Therefore, while it is important for the clinical doctors to prevent the production and development of ASP, it is even more important to prevent ASP rupture and the aftermath. This idea was one of the most important topics among the cardiovascular scientists from all over the world in the 2005 annual meeting of European Society of Cardiology. After comparing the changes of the vascular stenosis before and after treatment by means of a quantitative coronary angiography, it has been found that Statin drugs can dilate vascular minimum diameter by 3 %, while the occurrence rate of acute coronary events and the mortality rate from coronary heart disease can be reduced by 30 %. Therefore,

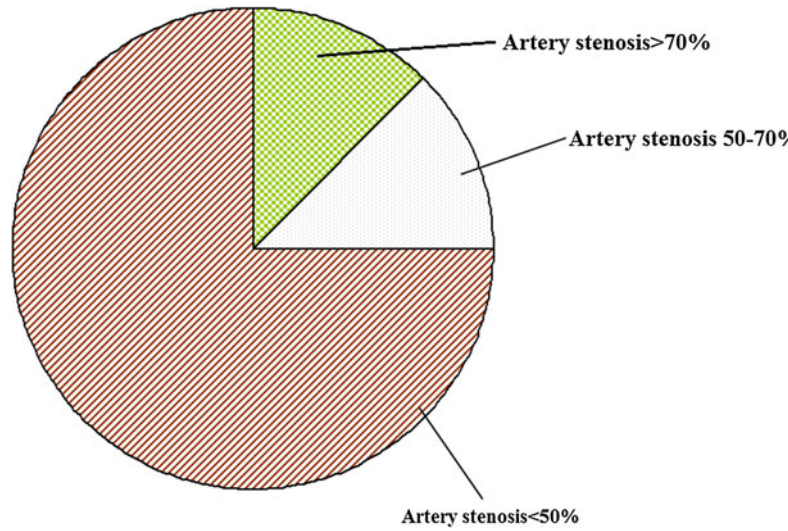

Fig. 11.1 The proportion of artery stenosis in myocardial infarction accidence [based on the data statistics of papers by Ambrose et al. (1988), Nobuyoshi et al. (1991), and Giroud et al. (1992)]

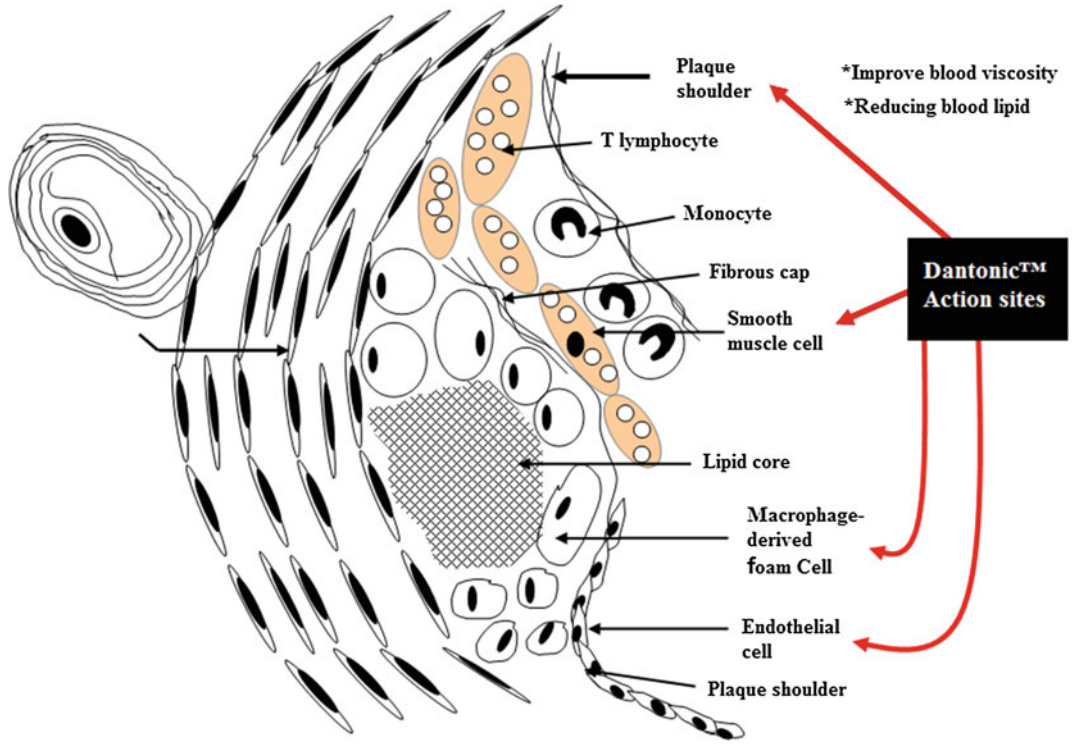

Fig. 11.2 The possible mechanism for the function of Dantonic™ in stabilizing the ASP

Statin drugs were recommended for preventing plaque rupture. This is one of the main outcomes of "The Statin Revolution," and it is generally believed that Statin drugs are the secondary preventive drugs for stabilizing ASP.

11.1.3 The Animal Trials of Dantonic™ on ASP

Lin et al. [2] reported that Dantonic™ had effect on rabbits with experimental hyperlipidemia and atherosclerosis. The medication was able to significantly decrease the concentration of serum total cholesterol (TC), triglyceride (TG), LDL cholesterol (LDL-C), and very low-density lipoprotein cholesterol (VLDL-C), as well as the ratio of TC/high-density lipoprotein cholesterol (HDL-C) (Table 11.2), significantly increase the concentration of HDL-C and decrease the contents of TC in the aorta, TG, and malondialdehyde (MDA) in liver. It has been verified that Dantonic™ can significantly reduce ASP area, thickness, and the amount of the foam cells formed (Table 11.3). Dantonic™ could reduce the rate of coronary artery disease, and the

Table 11.2 The effect of Dantonic™ on the lipid content in the aorta (mg/g, wet tissue, Means ± SEM)

Group	Dosage(/kg·d)	No. animals	TC	TG
Normal		8	$0.51 \pm 0.08^{***}$	$3.36 \pm 1.16^{***}$
High grease		8	7.80 ± 2.07	10.40 ± 2.81
Dantonic™	4 g Crude drug	8	$5.30 \pm 1.62^{*}$	9.21 ± 1.40
	2 g Crude drug	8	$0.51 \pm 0.08^{***}$	$3.36 \pm 1.16^{***}$

Compared with high grease group, $^{*}P < 0.05$, $^{***}P < 0.01$

Table 11.3 The effect of Dantonic™ on the formation of foam cells

Group	Dosage (/kg·d)	No. animals	Level of foam cells formation				*P* value[b]
			+[a]	++	+++	++++	
Normal		8	–	–	–	–	
High fat control		8	0	1	2	5	
Dantonic™	4 g Crude drug	8	2	3	2	1	<0.05
	2 g Crude drug	8	1	2	3	2	>0.05

[a]Level +, ++, +++ and ++++ represent light, moderate and severe respectively;
[b]Compared with high-fat control group

Table 11.4 Comparison of coronary atherosclerosis

Group	Dosage (/kg·d)	Number of artery transection (N)	Vascular number and level of plaque formation						Total scores	Average scores (x ± SD)	Rates of pathologic (%)
			Vessels with lesion	Levels							
				0.5	1	2	3	4			
High-fat control group		333	150	20	21	28	32	49	380	2.53 ± 1.30	45.0
Dantonic™	4 g Crude drug	316	121	24	14	23	30	30	382	2.33 ± 1.31	38.3
	2 g Crude drug	309	134	24	18	22	33	37	322	2.40 ± 1.32	43.4

average score of coronary lumen stenosis (Tables 11.4, 11.5 and 11.6).

Zhang [8] reported that 224 patients with coronary artery diseases or cerebral circulation insufficiency were diagnosed by carotid ultrasonography to confirm the existence of carotid ASPs. They were randomly divided into two groups: Dantonic™ group (111 cases) and the control group which was treated with enteric-coated aspirin (113 cases). The patients with hypertension were treated with Nifedipine also. After 6 months' treatment, the plaques were found to be thinner than before in Dantonic™ group ($P < 0.05$), but there was no difference in the control group. There was no statistical difference in carotid intima-media thickness (IMT) between soft and hard plaque groups. The author believed that Dantonic™ had a significant effect on the early ASP, i.e., flat plaques. But there was no similar significant effect on either soft or hard plaques.

Chen et al. [7] observed the effect of Dantonic™ on the formation of carotid ASP in experimental rabbits and VCAM-1 expression. They found that the plaque areas were significantly reduced compared to the control group and the effect was dose dependent. The plaque area in the high-dosage subgroup was the smallest. (Table 11.7). The positive expressions of VCAM-1 in three different Dantonic™ dosages subgroups were significantly higher than in the normal group. (Table 11.7). The author used the image analyzer (Leica Q550IM) and image analysis software (QWin) to measure LA, PA, and the ratio of PA/LA. It was proven that Dantonic™ can significantly inhibit ASP formation.

Table 11.5 The effect of Dantonic™ on blood lipid in animals with Hyperlipoidemia

Authors (year)	Animals	Experiment design	Dosage of Dantonic™ and course of treatment	Experimental model of AS, method	Results
Shi and Li [3]	New Zealand Rabbits 10 × 3	Randomized	5 mg/(rabbit·d)	AS group: a diet contains l % of Cholesterol, 15 % of yolk powder, 5 % of lard for a period of 8 weeks, Dantonic™ group: fed and treated as above; The control group: Non-high fat diet	1. After treatment for 2 weeks, TC, TG and LDL-C levels in the AS group were significantly higher than those of the normal control group and Dantonic™ group ($P < 0.05$)
Huang et al. [4]	Japanese maleness rabbits	Randomized	From 3 days to 4 weeks after treatment, 300 mg/Day	2 weeks before treatment and 4 weeks after treatment, cholesterol (2 g) + peanut oil (6 g/rabbit), Vascular endothelial endarterectomy	1. There no difference in lipid levels during the same period in both groups. After 2 weeks of high-fat feeding, TC and LDL-C were both significantly increased 2. The new intima area of Dantonic™ group was significantly smaller than that of the control group ($P < 0.05$),the lumen area was bigger than that of the control group ($P < 0.05$), and there was no significant difference in the surrounding area of internal elastic lamina ($P < 0.05$)
Cheng et al. [5]	Japanese rabbits		10 g/L, Two times of man–rabbit equivalent dose, 100 mg/(kg·d) × 4 weeks	High fat diet l00 g (cholesterol 1 g, yolk powder 7.5 g, lard 5 g, standard feed 86.5 g) × 6 weeks	In Dantonic™ group, TG level was significantly lower than the model group ($P < 0.05$).

11.1.4 Effect of Dantonic™ on Stabilizing and Decreasing ASP: Clinical Studies

Dantonic™ can improve the blood lipid level in patients. There are 32 reports with a total of 1,957 patients with Hyperlipoidemia, and after the treatment with Dantonic™, their blood lipid levels were reduced to some extent compared with those before the treatment. The difference was a statistically significant. (Table 11.12). The decrease of blood lipids has a very important significance for the reformation of ASP and the stability of ASP already formed.

Cao et al. [9] observed the effect of Dantonic™ on the early carotid ASP formation, and on the blood lipids, and hemorheology. They also compared the results with the patients treated with aspirin. The patients were selected from those who were suspected of coronary heart disease and diagnosed having carotid artery ASP formation by carotid ultrasound. Only those patients without obvious ischemic clinical manifestations caused by arteriosclerosis were selected. The intima-

Table 11.6 Animal study of Dantonic™ on vascular intima

Authors (Year)	Animals	Trial design	AS model and method	Dantonic™ dosage and course of treatment	Results
Zongpei et al. [6]	Rabbits (29)	Randomized	Chronic hyperviscosity syndrome model	30 mg/kg (10 times of adult's dsoage)	1. TXB_2: In Dantonic™ group it was significantly lower than that of the model group
					2. 6-ketone: There was no difference between the two groups, but it was significantly lower than that in the blank group
					3. ET: In Dantonic™ group it was significantly lower than that of the model group ($P < 0.05$) and significantly higher than that of the blank control group ($P < 0.01$)
					Remark:
					It indicated that long-term administration of Dantonic™ can improve the secretion function of vascular endothelia, while the immediate effect of Dantonic™ was not significant
	Wistar Rats	Randomized	acute hyperviscosity syndrome model	Low dosage, 15 mg/kg; moderate dosage, 30 mg/kg; high dosage, 75 mg/kg	There was no significant difference in TXB_2, 6- ketone and ET among the groups
Chen et al. [7]	New Zealand White Rabbits	Randomized	ASP formation in carotid artery	Compound Danshen extract 0.013 g/(kg·d) (5 times of adult's dosage); 0.039 g/(kg·d) (15 times of adult's dsoage); 0.117 g/(kg·d) (45 times of adult's dosage)	1. Compared with the control group, the lumen area of the model group and the treatment groups were clearly reduced ($P < 0.01$) 2. The plaque areas in the treatment groups were clearly smaller than those in the model group ($P < 0.01$). The plaque areas of the Simvastatin group was clearly smaller than that of 3 Dantonic™ subgroups with different dosage ($P < 0.01$). The plaque areas of Dantonic™ group had a linear relationship with the different dosage: Small dosage group > moderate dosage group > high dosage group. 3. VCAM-1 expression in carotid artery: model group > Dantonic™ group with small dosage > moderate dosage group > high dosage group > Simvastatin group

Table 11.7 The ratio of carotid lumen and ASP area, VCAM-1 expression in Dantonic™ groups with different dosage

Group	Cases	LA (μm^2)	PA (μm^2)	PA/LA (%)	Positive rate of VCAM-1 expression
Normal	8	410 238.4 ± 39 710.1	0	0	31.7 ± 1.2 %
Model	8	302 749.8 ± 32 094.5	47 832.7 ± 7 904.6	15.8	74.1 ± 2.8 %**
Simvastatin	8	343 023.4 ± 29 834.3*	9 790.6 ± 675.8**	2.8**	30.8 ± 2.1 %*
Low dosage Dantonic™ (0.013 g/kg)	8	357 381.5 ± 43 827.0*	29 347.8 ± 1 003.2$^{**\triangle\triangle}$	8.2$^{**\blacktriangle\blacktriangle}$	49.0 ± 3.0 %$^{**\blacktriangle\blacktriangle}$
Moderate dosage Dantonic™ (0.013 g/kg)	8	372 045.2 ± 39 874.3*	20 133.7 ± 8 631.2$^{**\blacktriangle\triangle}$	5.4$^{**\blacktriangle\triangle}$	43.4 ± 4.3 %$^{**\blacktriangle\blacktriangle}$
High dosage Dantonic™ (0.013 g/kg)	8	374 652.3 ± 43 526.8*	13 876.4 ± 7 403.2$^{**\triangle\triangle\blacktriangle\blacktriangle}$	3.7$^{**\triangle\triangle\blacktriangle\blacktriangle}$	38.5 ± 2.6 %$^{*\blacktriangle\blacktriangle}$

*Compared with the normal group and the model group, $^{*}P < 0.05$, ** $P < 0.01$
$^{\blacktriangle}$Compared with the Simvastatin group, $^{\blacktriangle}P < 0.05$, $^{\blacktriangle\blacktriangle}P < 0.01$
$^{\triangle}$The high Dantonic™ dosage group was compared with the low and moderate dosage groups, $^{\triangle\triangle}P < 0.01$

media thickness (IMT) of the 53 patients selected was between 1.2 and 2.6 mm, and ultrasound image (using infrasonic waves) showed that the plaques were soft. They were randomly divided into two groups: a treatment group and a control group. There were 25 patients in the treatment group: 17 males, 8 females, age between 40 and 69 with an average age of 56.8 years old. Of this group, 9 had lesions on both side of the heart. There were 28 patients in the control group, 18 males and 10 females, age ranged between 39 and 71 with an average age of 58.2 years old. Of this group, 13 patients had lesions on one side and 15 had lesions on both sides of the heart. Six patients in both groups had hypertension, and they were treated with ISDN. The treatment group and the control group were comparable in terms of sex and age. The treatment group was treated with Dantonic™, 10 pills each time, three times a day, for 6 months. The control group was treated with enteric aspirin, 50 mg each time, once a day. The carotid IMT was measured using the Acuson 128XP10 computer sonograph (the frequency of the probe was 7.0 MHz). IMT at lesion site was observed before and 1, 2, 3, and 6 months after the treatment. The whole artery was examined along the long axis and short axis for the internal carotid artery, external carotid artery, and subclavian artery. The thickest place was measured at the ventricular diastolic phase (R wave of the cardiogram) and a slice of long axis of blood vessels. The Doppler blood flow test was used and included measurement of blood vessel's visual internal diameter, maximum speed of blood flow at systolic and diastolic phase, and time integral of speed of blood flow. The NXE-I type laminectomy viscosimeter was used and blood rheology including ηHB, ηLB, ηP, and AIR were also measured. Blood lipid was measured by enzyme-linked immunosorbent assay, fasted for 12 h before taking the samples; the major targets were TC and TG. The cardotid IMT before and after treatment is shown in Table 11.8. The results of blood rheology tests are shown in Table 11.9. All patients in both groups were found to have

Table 11.8 Carotid IMT before and after Dantonic™ and Aspirin treatments (means ± SEM)

Group	Number of cases	Treatment	IMT (mm)
Dantonic™	25	Before	2.2 ± 0.7
		After	2.1 ± 0.6*
Aspirin	28	Before	2.0 ± 0.8
		After	2.1 ± 0.7

Note $^{*}P < 0.05$

Table 11.9 Changes in blood rheology in the patients before and after the treatments (means ± SEM)

Group	Cases	Treatment	ηHB (mpa.s)	ηLB (mpa.s)	ηP (mpa.s)	AIR
Dantonic™	25	Before	6.23 ± 1.67	10.92 ± 2.21	1.95 ± 0.08	1.79 ± 0.13
		After	4.35 ± 1.02*	8.30 ± 1.14*	1.77 ± 0.08*	1.39 ± 0.11*
Aspirin	28	Before	6.12 ± 1.56	10.38 ± 1.96	1.89 ± 0.12	1.82 ± 0.17
		After	4.28 ± 1.07*	8.21 ± 1.03*	1.67 ± 0.07*	1.40 ± 0.10*

Note Compared with before treatment, $^{*}P < 0.01$

increased blood rheology initially which decreased after 6 months' treatment. There was no significant difference in the magnitude of decrease between the treatment and control groups ($P > 0.05$). The results of the blood lipid tests before and after the treatment are presented in Table 11.10. All patients had elevated blood lipids prior to treatment. After the treatment, TC and TG were found to be reduced in the treatment group ($P < 0.01$), but no significant changes in blood lipids were found in the control group.

The author found: (1) Carotid artery IMT changes: the carotid artery IMT became thin after Dantonic™ treatment ($P < 0.05$), but in the control group there were no significant changes. (2) Changes in blood rheology: patients in both groups had increased blood viscosity before the treatments, the viscosity was decreased after 6 months' treatments. There was no significant difference between the two groups in terms of the magnitude of decrease ($P > 0.05$). (3) Changes in blood lipids: all patients had elevated blood lipids before treatment. In the treatment group, the TC and TG were found to be decreased after treatment ($P < 0.01$), but there were no significant changes in blood lipid levels in the control group. The results show that Dantonic™ not only can reduce the blood lipid level and improve the blood flow, but also can reverse ASP formation.

There were four reasons why Dantonic™ can reverse ASP formation. (1) Reduction of blood lipids: previously, it was believed that atherosclerosis was an irreversible process, but the follow-up studies by Mack et al. [10] and Wendelhag et al. [11] showed that lipid-lowering drugs could make the abnormal thickening of carotid IMT subside. Many clinical studies have shown that Dantonic™ can reduce blood lipid levels; (2) Antioxidant effect: it has been found that the combination of lipid-reducing medication with antioxidants had a better preventive effect on the development of atherosclerosis than using lipid-lowering alone. Experimental studies in rabbits with high blood lipids showed that when treated with only an antioxidant, although the level of blood lipids was 40 % higher than that of the control group, the rate of atherosclerosis development was reduced by half. The effect of the antioxidants was exerted by inhibiting the oxidation of LDL; (3) The effect of Ca^{++} antagonists: Ca^{++} antagonists can reduce Ca^{++} influx, inhibit the activity of lipid oxidase, and reduce the formation of oxidized LDL; and (4) Protecting vascular endothelium: injury of the vascular endothelium is believed to be the initial factor in the formation of atherosclerosis.

There is a close relationship between plasma α-lipoprotein, [Lp(α)], and atherosclerotic diseases such as the coronary heart disease,

Table 11.10 Blood lipid level before and after the treatments (means ± SEM)

Group	Cases	Treatment	TC (mmol/L)	TG (mmol/L)
Dantonic™	25	Before	6.08 ± 1.5	1.91 ± 0.68
		After	4.91 ± 1.44*	1.54 ± 0.56*
Aspirin	28	Before	6.10 ± 1.67	1.83 ± 0.82
		After	5.92 ± 1.81	1.76 ± 0.94

Note Compared with before treatment, $^{*}P < 0.01$

cerebrovascular accident, and the restenosis after heart surgery. Lp(α) can contribute to atherosclerosis and thrombosis and is one of the most important (and dangerous) risk factors for the coronary heart disease. Han et al. [12] studied two groups of patients, all of them were treated with ISDN, aspirin, and Vitamin E. The patients in the treatment group were treated with additional Dantonic™ for 4 weeks (all other lipid-lowering medications were ceased during this period). The results showed that the levels of Lp (α) and blood lipids were markedly decreased. There were 2 cases of angina pectoris, 1 case of arrhythmia, and 1 case of cardiac insufficiency in the treatment group. There were 5 cases of angina pectoris, 1 case of arrhythmia, 1 case of cardiac insufficiency, 1 case of myocardiac infraction, and 1 case of sudden death in the control group. This study demonstrates that Dantonic™ can reduce the levels of Lp(α) and blood lipids in CHD patients, and reduce the occurrence of cardiac accidents.

Rongtang and Jianfu [13] treated 68 cases of coronary heart disease complicated with congestive heart failure with Dantonic™. The patients were randomly divided into two groups: the conventional treatment group which was treated with Dixina, Hydrochlorothiazide, and ISDN, and the combination group which was treated with the conventional treatment plus Dantonic™. This study was used to test the calcitonin gene-related peptide (CGRP) and endothelin (ET) level in plasma. They found that the CGRP level in patients with a coronary heart disease was significantly lower than that of normal people ($P < 0.05$), the ET level was significantly higher than normal people ($P < 0.05$). The CGRP level was increased and the ET level was decreased after treatment in both groups ($P < 0.05$), but it was more significant in Dantonic™ group.

Qingfu et al. [14] used randomized controlled single-blind method to divide 68 cases of coronary angina pectoris into two groups: Dantonic™ group (36 cases) and the conventional treatment group (32 cases). The course of treatment was 3 weeks. High-resolution vascular ultrasound was used to monitor the change of carotid blood flow mediated dilatation function. The results showed that the vascular endothelial function in the Dantonic™ group was significantly improved.

Zongpei et al. [6] built the chronic hyperviscosity syndrome model in rabbits with high-polymer dextran, adnephrin, bovine serum albumin, etc. One time IV Injection of high-polymer dextran was given. They also built the acute hyperviscosity syndrome model in Wistar rats by intravenous injection of polymer dextran and subcutaneous injection of epinephrine. Both animals were treated with Dantonic™, and it was found that Dantonic™ could significantly increase thromboxane B2 (TXB2), and decrease 6-keto-prostaglandin F_{1a} (6-ketone), in animals with either acute or chronic hyperviscosity syndrome (Tables 11.11, 11.12).

Han et al. of Keio University [15] studied the continuous changes of microcirculation in rat mesentery by monitoring multiple indicators and dynamic process, and they demonstrated that Dantonic™ could inhibit the adhesion between leukocytes and venules induced by ischemia and reperfusion, inhibit the production of peroxides in venular walls and mast cell degranulation in mesentery, etc. These effects were related to tanshinol and panax notoginseng saponins in Dantonic™. It was also found that the effects of

Table 11.11 The effect of Dantonic™ on the secretive function of vascular endothelium in chronic hyperviscosity syndrome rabbit model (means ± SEM)

Group (*n*)	Dosage	TXB2	6-ketone
Blank (9)	–	218.29 ± 74.29	149.75 ± 25.38
Model (9)	–	845.89 ± 79.88**	58.0 ± 21.94**
Treatment (11)	30 mg/kg	275.18 ± 84.72##	66.67 ± 25.22**

**Compared with blank groups, $P < 0.01$
##Compared with model groups, $P < 0.01$

Table 11.12 The effect of Dantonic™ on the secretive function of vascular endothelium in acute hyperviscosity syndrome rat model (means ± SEM)

Group(n)	Dosage	TXB2	6-ketone
Blank(8)	–	599.57 ± 269.27	157.84 ± 61.87
Model(8)	–	398.87 ± 224.37	174.31 ± 111.26
Low dosage Dantonic™ (8)	15 mg/kg	440.96 ± 292.21	225.81 ± 109.29
Moderate dosage Dantonic™ (8)	30 mg/kg	431.38 ± 260.55	238.97 ± 148.99
High dosage Dantonic™ (8)	75 mg/kg	347.73 ± 282.90	244.11 ± 150.44

tanshinol and panax notoginseng saponins were related to the inhibition of the expression of granulocyte adhesion molecules CD11b and CD18. They showed immunohistochemically that Dantonic™ might inhibit the expression of vascular endothelial ICAM-1 and leukocyte adhesion factor CD11b. They used the flow cytometry to prove that tanshinol and panax notoginseng saponins could inhibit the expression of CD11b and CD18.

They also used the toluidine blue stain method to show that Dantonic™ could inhibit mast cell degranulation caused by ischemic reperfusion, reduce the release of vascular active substances such as TNF2, histamine, and 5-hydroxytryptamine, and prevent blood vessel damage caused by these factors. Panax notoginseng saponins play a major role in these effects.

Chen et al. [7] also showed that in rabbits with carotid artery wall atherosclerosis, Dantonic™ had an effect on vascular cell adhesion molecule-1 (VCAM-1) similar to Statins.

11.1.5 Summary

From animal experiments to clinical observation, the function of Dantonic™ in stabilizing and reducing ASP has showed multiple action points:

(a) Reducing blood lipids;
(b) Protecting endothelial cells, inhibiting adhesion factors;
(c) Reducing foam cells inside ASP;
(d) Inducing the apoptosis of smooth muscle cells;
(e) Improving blood viscosity and local hemodynamics around Plaque shoulders; and
(f) Alleviating inflammatory responses (C-reactive protein, tumor necrosis factor, etc.)

Recently, it has been found that the plaques that cause cardiovascular damage are not necessarily the vulnerable plaques. It is believed that plaque rupture might be related to systemic factors. Many scientists proposed a new concept which covers the scope from vulnerable plaque to vulnerable patient, which has undoubtedly advanced our scientific understanding of ASP and ASP-related diseases.

11.2 The Antiplatelet Activation Effect of Dantonic™

The role of platelets in the development and treatment of coronary heart disease has been the focus of scientific community for a long time. In 1852, Von Rokitansky proposed that the lesions of atherosclerosis were formed as a result of mural thrombus being embedded in the arterial wall. Duguid (1946) also believed that atherosclerosis was caused by the thrombosis of the artery wall. This theory has not been accepted by the academic community because there is no sufficient evidence showing that thrombus could directly develop into atherosclerosis. But most people believed that among many ingredients for thrombosis formation, such as fibrin (fibrinogen), platelets and thrombin, were involved in the development of atherosclerosis. In recent years, with the gradual clarification of the critical nature and the pathological mechanism of acute coronary syndrome, the importance of platelets becomes more and more realized. The main

pathological mechanism for the acute coronary syndrome is that plaque rupture activates platelets, which leads to thrombosis, and a high degree of coronary artery obstruction or complete occlusion, which may or may not accompanied by remote microcirculation embolism.

The laboratory studies and clinical observation in the past 10 years or so have demonstrated that Dantonic™ has a definite inhibitory effect on platelet activation. Therefore, besides the effect of coronary expansion, Dantonic™ has more important function in the prevention of atherosclerotic formation, and the reduction of sudden cardiovascular and cerebrovascular accidents in the patients with a coronary heart disease.

11.2.1 The Experimental Studies of the Effect of Dantonic™ on Platelet Aggregation

Platelet aggregation experiments: Dantonic™ was dissolved in physiological saline and diluted to a certain concentration. The solution was filtered before use.

Rabbit blood was collected from the carotid artery, mixed with anticoagulated, and centrifuged at 1,000 rpm for 10 min to obtain platelet-rich plasma (PRP); centrifuged at 3,000 rpm for 10 min again to obtain platelet-poor plasma (PPP). The recording instrument was calibrated with PPP to a graduation of "20" and with PRP set to a graduation of "80". The platelet aggregation and the drug's action on platelet aggregation were determined according to Born's turbidimetric method by using ADP (2 μM) as the inducer. The control batch was: 200 μl of PRP + 10 μl of drug + 2 μl of ADP. The treatment group was 200 μl of PRP + 10 μl of drug + 2 μl of ADP. The aggregation rate of each group was calculated according to the following formula:

$$\text{Aggregation Rate} = \text{Scales of Aggregation}/60 \times 100\,\%.$$

Dantonic™ showed a significant inhibitory effect on platelet aggregation when the final concentration was between 14 and 58 mg/ml. The effect was dose dependent.

Li et al. [16] studied the effect of Dantonic™ on the platelet adhesion rate and thrombosis index in the experimental hyperlipidemia rats. The platelet adhesion rate in the experimental hyperlipidemia rats was significantly higher than that in the normal rats ($P < 0.05$). The thrombosis index in hyperlipidemia rats was significantly higher than that in the normal rats ($P < 0.01$). Dantonic™ at 150 and 450 mg/kg, polysaccharide sulfate at 25 mg/kg could significantly reduce the platelet adhesion rate in the experimental hyperlipidemia rats ($P < 0.05$). Dantonic™ at 50, 150, and 450 mg/kg, polysaccharide sulfate at 25 mg/kg could significantly reduce the thrombosis index in the experimental hyperlipidemia rats ($P < 0.01$) (Table 11.13).

Table 11.13 The Effect of Dantonic™ on platelet adhesion rate and thrombosis index in Hyperlipoidemia rats (Means ± SEM)

Group	Dosage (mg/kg)	*n*	Platelet adhesion rate	*n*	Thrombosis index
Normal	0	10	25.5 ± 5.6	11	16.4 ± 1.0
Model	0	10	38.4 ± 14.5^{b}	12	21.3 ± 2.0^{c}
Dantonic™	50	10	30.2 ± 11.2^{adg}	9	17.8 ± 1.0^{cdi}
	150	8	26.7 ± 5.5^{bdg}	10	16.4 ± 1.9^{ceg}
	450	11	26.1 ± 6.6^{bd}	11	16.3 ± 0.8^{ef}
PSS	25	9	24.6 ± 8.6^{b}	9	18.3 ± 1.5^{c}

[b, c]Comparison between model and normal control groups, $^{b}P < 0.05$, $^{c}P < 0.01$
Comparison between Dantonic™ and model group, $^{a}P > 0.05$, $^{b}P < 0.05$, $^{c}P < 0.01$
Comparison between PSS and model groups, $^{b}P < 0.05$, $^{c}P < 0.01$
Comparison between Dantonic™ and PSS groups, $^{d}P > 0.05$, $^{e}P < 0.01$, $^{f}P < 0.01$
Comparison between 50, 150 mg/kg Dantonic™ groups and 450 mg/kg Dantonic™ group, $^{g}P > 0.05$, $^{i}P < 0.01$

Li et al. [17] used fluorescence polarization method to determine rabbit platelet membrane fluorescence polarization P, microviscosity η, and Lipid membrane fluidity (LFU). The results showed that Dantonic™ was able to significantly increase the fluidity of the platelet membrane and reduce microviscosity η.

Ma and Deng [18] put 16 normal Wister rats and 26 atherosclerosis (AS) model Wister rats (Among them, 10 rats were treated with 50 mg of Dantonic™) in a decompression chamber which was lifted to 8,000 M. The rats were kept at that altitude for 30 min. The plasma of the rats was isolated from the blood before and after decompression and made into a PC suspension. GMP-140 and TXB2 were measured by radioimmunoassay. The results showed that decompression stress led to the increase in GMP-140 in the rats' PC, and the increase in AS rats was the most markedly, which demonstrated that the extent of PC activation in AS rats was higher than that of normal rats, and Dantonic™ could weaken the increase.

11.2.2 The Clinical Studies of the Effect of Dantonic™ on Platelet Aggregation

11.2.2.1 Antiplatelet Aggregation Effect in CHD Patients

There were 26 clinical reports which studied the effect of Dantonic™ on platelet aggregation. A total of 2,277 cases of cardia and cerebral disease with platelet aggregation increase were treated with Dantonic™. platelet aggregation was measured after treatment, and the results showed that Dantonic™ had significant inhibitory effect on platelet aggregation.

Dai and Shao [19] divided 40 cases of Hyperlipoidemia into Dantonic™ group and Xuezhikang group. The former was treated with 10 pills of Dantonic™ each time, three times a day, and the latter was treated with 0.6 g of Xuezhikang each time, twice a day. Both were treated for a period of 4 weeks. The platelet aggregation rate was determined by measuring the fasting venous blood at the end of the treatments. The results showed that Dantonic™ could significantly inhibit the platelet aggregation (1, 5 s) ($P < 0.01$) (Table 11.14).

Bai and Wang [20] randomly divided the patients into treatment group (50 cases) and control group (45 cases). The patients in both groups received the conventional treatment. After 2 weeks, the treatment group received additional Dantonic™, 10 pills each time, 23 times a day for 2 courses of treatment. The control group received Troxerutin tablets, 40 mg each time, three times a day for 2 courses of treatment. Fasting blood was collected before and after the treatments and tested for whole blood viscosity, plasma viscosity, thrombus length, thrombus humidity, thrombus dryness, and platelet aggregation rate. The SZ-4A thrombosis instrument and the SZ-4B blood viscosity detector, both were manufactured by Suzhou Wangting Precision Instrument Factory, were used for the measurements. The results showed that Dantonic™ could significantly reduce blood viscosity, thrombus length, thrombus wet/dry weights, and platelet aggregation rate.

Ma et al. [21] treated 86 abnormal blood fat and hemodynamics patients (53 male and 33 female cases, age: 58 ± 7 years old) with Dantonic™, 10 pills each time, three times a day for 2 months. The changes of blood fat and hemodynamics after the treatment were observed. The results showed

Table 11.14 Platelet aggregation in the Hyperlipoidemia patients before and after the treatments (means ± SEM)

Group	Cases	Treatment	Rate of platelet aggregation (1 s) %	Rate of platelet aggregation (5 s) %
Dantonic™	20	Before	35.56 ± 3.80	42.21 ± 3.82
		After	26.10 ± 2.82**	30.88 ± 3.01**
Xuezhikang	20	Before	35.25 ± 2.97*	41.41 ± 3.22
		After	33.75 ± 2.56	40.25 ± 2.78

Compared with the status before treatment, *$P < 0.05$, **$P < 0.01$

Table 11.15 Changes of blood rheology in two groups of patients before and after the treatments ($\overline{X} \pm s$)

	Treatment group (n = 50)		Control group (n = 50)	
	Before treatment	After treatment	Before treatment	After treatment
Volume packed cells (L/L)	0.49 ± 0.03	0.42 ± 0.02$^{\triangle}$	0.48 ± 0.04	0.47 ± 0.02
Whole blood viscosity (60 $s^{-1)}$	5.23 ± 0.81	4.51 ± 0.74$^{\triangle}$	5.24 ± 0.63	5.22 ± 0.76
Plasma viscosity (120 $s^{-1)}$	1.84 ± 0.16	1.35 ± 0.12$^{\triangle}$	1.81 ± 0.63	1.80 ± 0.68
Blood sedimentation [mm/h]	24.60 ± 9.74	22.38 ± 8.32	25.01 ± 9.34	23.50 ± 8.26
Profibrin [g/L]	4.78 ± 0.65	4.66 ± 0.72	4.75 ± 0.68	4.67 ± 0.87
Platelet adhesion rate (%)	35.26 ± 7.48	28.35 ± 5.89$^{\triangle}$	35.75 ± 6.92	34.10 ± 8.51

$^{\triangle}$Compared with the status before treatment, $P < 0.05$

that the platelet aggregation rate, whole blood viscosity, plasma viscosity, total cholesterol, triacylglycerol, and LDL were all significantly decreased after the treatment ($P < 0.001$).

Zhao and Yin [22] treated 62 cases of coronary heart disease patients with Dantonic™ and compared them with 36 healthy people. The whole blood specific viscosity, plasma specific viscosity, whole blood reduced viscosity, hematocrit, platelet adhesion rate and fibrinogen were all significantly improved after the treatment. The dry mass, wet mass, and length of thrombus in vitro were also significantly improved. The treatment significantly decreased the patients' serum total cholesterol and triglycerides, and improved the clinical symptoms and ECG.

Wei [23] collected 100 cases of coronary heart disease patients which met the WHO Diagnosis Criteria of 1979. There were 42 cases of common CHD and 58 cases complicated with angina pectoris. These patients were randomly divided into two groups: the Dantonic™ treatment group (50 cases, 31 male cases, and 19 female cases, age between 46 and 75 years old, the average age was 56 and average course of illness was 5.13 years), and the Isosorbide dinitrate control group (50 cases). The results are shown in Table 11.15.

Gou et al. [24] treated 57 patients with stable angina pectoris (31 cases), UAP (19 cases), and silent myocardial ischemia (7 cases).

The patients were treated with Dantonic™ 10 pills each time, three times a day for 2 months. Aspirin, Bo'er Xin, and any other anticoagulant drugs were discontinued before the treatment. The platelet aggregation and the blood viscosity were determined. The results indicated that Dantonic™ had an obvious improving effect on the platelet aggregation rate and blood viscosity (Table 11.16).

Fang [25] treated 80 patients with coronary heart disease with Dantonic™, 10 pills once orally, and for a course of 3 months. The use of aspirin, Persantine, and any anticoagulants were discontinued before measurement. The platelet aggregation was

Table 11.16 The effect of Dantonic™ on platelet aggregation rate and blood viscosity (means ± SEM)

Targets	Before treatment	After Treatment	P
platelet aggregation (%)	78.61 ± 15.70	55.97 ± 14.12	<0.05
High shear viscosity of whole blood	7.37 ± 1.20	5.01 ± 1.18	<0.05
Volume packed cells (%)	44.41 ± 5.01	43.87 ± 4.23	>0.05
Blood viscosity	2.21 ± 0..76	1.98 ± 0.80	<0.05
Platelet aggregation rate (%)	8.87 ± 1.22	6.57 ± 3.07	<0.05
Profibrin	5.05 ± 1.61	3.19 ± 1.57	<0.05

Table 11.17 The effect of Dantonic™ on the hemorheology indexes (means ± SEM)

Index	Before treatment	After treatment
Platelet aggregation rate (%)	79.60 ± 15.73	56.96 ± 15.11*
High shear rate of whole blood viscosity (mPa/s)	7.39 ± 1.22	5.11 ± 1.27*
Volume of packed red blood cells (%)	2.22 ± 0.76	1.99 ± 0.81*
Blood viscosity	44.5 ± 5.01	41.99 ± 4.46
Platelet aggregation rate (%)	8.89 ± 1.23	6.59 ± 3.06*
Profibrin (g/L)	5.06 ± 1.06	3.20 ± 1.58*

*Compared with the status before and after treatment, $P < 0.05$

determined with an ADP inducer. A comparison was made between the platelet aggregation rate, high shear rate of whole blood viscosity, plasma viscosity, the volume of packed red blood cells, erythrocyte aggregation rate and profibrin and other indexes, before and after Dantonic™ treatment. It was concluded that Dantonic™ had a significant effect on the platelet aggregation rate and blood viscosity (Table 11.17).

Li and Long [26] treated 52 cases of stable angina pectoris (SAP) and 29 cases of UAP with Dantonic™, 10 pills each time, three times a day for 2 months. The patients were also treated with ISDN and other basic drugs. The drugs for antiplatelet aggregation and for hemorheological improvement (such as aspirin) were discontinued. The results are shown in Table 11.18.

Hu et al. [27] randomly divided 63 CHD cases into Dantonic™ group and ISDN group. The authors found that Dantonic™ could significantly reduce β platelet microglobulin and thromboxane B2 in patients' blood (Table 11.19).

Wang [28] observed the effect of Dantonic™ on platelet aggregation in 87 CHD patients, who were treated with Dantonic™ for 2 months, without taking aspirin and Curantyl. platelet aggregation was measured 1 and 5 min after adding the inducer. The maximum aggregation was also recorded. The results are shown in Fig. 11.3.

11.2.2.2 Antiplatelet Aggregation Effect in Non-CHD Patients

Ye et al. [29] studied the effect of Dantonic™ on platelet aggregation in patients with noncoronary heart diseases. The results showed that Dantonic™ had a significant inhibitory effect on platelet aggregation in noncoronary heart disease patients. The difference in the results before and after the treatment in the treatment group was statistically significant ($P < 0.01$). Other reports showed similar results (Table 11.20).

Ma et al. [18] found that stress could lead to the increase of platelet aggregation. They observed the platelet aggregation in fighter pilots

Table 11.18 Blood rheology changes in CHD patients with AP before and after the treatment ($n = 81$, means ± SEM)

Index	Before treatment	After treatment
Platelet aggregation rate (%)	80 ± 16	57 ± 15[a]
Whole blood viscosity (mPa·s) (high shear)	7.39 ± 1.22	5.11 ± 1.27[a]
Whole blood viscosity (mPa·s) (low shear)	6.69 ± 2.12	7.25 ± 2.56[a]
Plasma viscosity (mPa·s)	1.98 ± 0.23	1.34 ± 0.16[b]
Volume of packed red blood cells (L/L)	0.44 ± 0.03	0.43 ± 0.03
Profibrin/(g/L)	5.1 ± 0.5	3.3 ± 1.2[b]

Compared with treatment group, [a]$P < 0.05$, [b]$P < 0.01$

Table 11.19 The effect of Dantonic™ on the levels of β platelet microglobulin and Thromboxan B2 in CHD patients (means ± SEM)

		Treatment group	Control group	*P*
β Platelet microglobulin	Before treatment	62.44 ± 14.37	59.89 ± 15.42	>0.05
	After treatment	45.65 ± 12.25	54.56 ± 13.18	<0.0001
Thromboxanβ_2	Before treatment	1,312 ± 535	1,315 ± 507	>0.05
	After treatment	738 ± 384	1,218 ± 445	<0.01

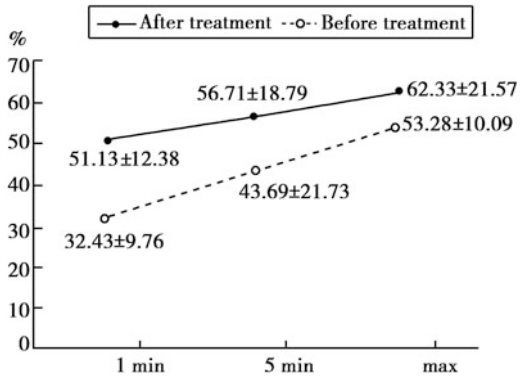

Fig. 11.3 The effect of Dantonic™ on platelet aggregation in CHD patients

under the stress condition and found Dantonic™ had an inhibitory effect on platelet aggregation.

Fan et al. [32] randomly divided 120 patients with transient ischemic attack (TIA) into two groups: Dantonic™ group (60 cases divided further into three subgroups: 50 mg qd, 250 mg bid, and 250 mg tid) and aspirin group (60 cases further divided into three subgroups: 50 mg qd, 50 mg bid, and 50 mg tid). The patients in both groups were followed up for 18 months. The platelet aggregation rate was measured by turbidimetric method with multiple inducers: adenosine diphosphate (ADP), epinephrine (EPI), collagen (COL), and arachidonic acid (AA) 4 weeks after the drug administration. The results showed that the inhibitory effect of Dantonic™ on platelet aggregation were similar to that of aspirin, but its side-effects were smaller than those of aspirin. The follow-up results showed that 18 months after the treatment, Dantonic™ was slightly superior to aspirin. (Tables 11.21, 11.22, 11.23 and 11.24).

Fan et al. [32] treated 180 TIA patients with Dantonic™ for 18 months, and found that Dantonic™ had an effect of antiplatelet aggregation and prevention of cardiovascular and cerebrovascular accidents.

11.2.2.3 The Effect of Dantonic™ on GMP-140

Platelet activation plays an important role in the occurrence of coronary angina pectoris. The activation of platelets is also one of most important factors for thrombogenesis. Granule membrane protein-140 (GMP-l40) is a membrane glycoprotein located in platelet α-granules and Weibel-palade bodies of the vascular endothelial cells (VECs). GMP-l40 exists in two forms: the platelet membrane GMP-140 and blood plasma GMP-l40. When platelets are activated or endothelial cells are damaged, the content of GMP-140 increases. According to recent data, the plasma concentration of GMP-140 can more directly reflect the extent of platelet activation than endothelial cell damage does. So far, GMP-140 is considered as the specific molecular marker of platelet activation. During the formation of a thrombosis, GMP-140 acts as the initiator, makes platelets adhere with neutrophils, aggregate, and form thrombus. In addition, GMP-140 can increase monocyte expression of tissue factor, which causes hemostatic abnormalities. Lu [33] studied the effect of Dantonic™ on plasma GMP-140 in patients with CHD and UAP, and found that the GMP-140 level in plasma was greatly decreased after Dantonic™treatment ($P < 0.05$). Dantonic™ was able to inhibit the abnormal platelet activation in UAP patients, and has a good antiangina effect.

Table 11.20 The effect of Dantonic™ on platelet aggregation in noncoronary heart disease patients

Authors (year)	Diagnosis	Treatment (cases)	Dosage/ course of treatment	Platelet aggregation rate (means ± SEM)				Remarks
				Measurement	Instrument	Before treatment	After treatment	
Ye et al. [29]	Children Nephritic Syndrome	Dantonic™ (15)	l0 pills each time, 3 times per day for 8 weeks	Turbidimetric method	Not described	55.81 ± 10.36	34.93 ± 12.52	(1) Randomized, controlled trial. (2) The difference in the results before and after treatment in the treatment group was statistically significant ($P < 0.01$)
		Conventional (15)				56.65 ± 10.14	68.48 ± 8.55	
		Normal children (20)				33.75 ± 10.26		
Yang et al. [30]	Nephrotic syndrome	15	l0#tid/8 wk		Not described	61.42 ± 2.32	32.56 ± 2.03	The author also determined the second phase platelet aggregation-pagwax. There was statistical difference between the status before treatment and after treatment with the composite salviae dropping Pill ($P < 0.05$)
		15 (control group)	Routine treatment		Not described	65.08 ± 3.52	58.63 ± 2.86	
Huang et al. [31]	Oral lichen planus		l0#tid/8 wk		LBY-N6A of Beijing Pu Li Company	16.58 ± 3.01	11.79 ± 2.15	

Table 11.21 The maximum platelet aggregation in Dantonic™ and Aspirin groups

Group	Cases	ADP	EPI	COL	AA
Dantonic™	60	63.0	50.3	35.3	18.5
Aspirin	60	67.6	57.9	23.5	33.9
P		0.30	0.32	0.14	0.07

Table 11.22 The side-effect incidence in Dantonic™ and Aspirin groups

Side effect	Dantonic™ (n = 60)	Aspirin (n = 60)	p
Gastrointestinal tract	0	5	
Gingival bleeding, and epistaxis	0	3	
Efflorescence	0	0	
Numbness of mouth	1	0	
Total	1	8	$P < 0.05$

Table 11.23 The occurrence of cardiovascular and cerebrovascular accidents in Dantonic™ and Aspirin groups

Cordis and cerebral accident	Dantonic™ (n = 60)	Aspirin (n = 60)
TIA attacks		
Carotid artery system	2	3
Vertebral artery	3	3
Cerebral infarction	1	2
Cerebral hemorrhage	0	0
SAH	0	0
Myocardial infarction	0	1
Death	0	0
Total	6	9

Wang et al. [34] studied 40 UAP cases. The patients were divided into two groups randomly. The 20 cases in the conventional treatment group were treated with low molecular weight heparin, aspirin, nitrates, Ca^{++} antagonists, β-receptor blockers, etc., and the 20 cases in Dantonic™ group were treated the same way as those in the conventional group, plus with Dantonic™, 10 pills each time, three times per day for 4 weeks. Blood was collected before and after the treatment to measure GMP-140, plasminogen activator (t-PA) and its inhibitor (PAI-1), and the results showed that Dantonic™ was able to prevent platelet activation and improve plasminogen activation (Tables 11.25 and 11.26).

Zhou et al. [35] observed changes in platelet activation in patients with primary nephrotic syndrome (PNS), and investigated the clinical effect of Dantonic™ on the activation. Method: A total of 42 PNS patients (children) were divided into a Dantonic™ treatment group (22 cases) and a control group (20 cases). 20 healthy children were selected as the normal group. The Dantonic™ group was treated with Dantonic™, 3 pills each time, three times a day for preschool children, and 5 pills each time, three times a day for school age children. Patients in both groups took Prednisone at a dosage of 2 mg/(Kg·d) for a period of 8 weeks. ELISA was used to determine the level of plasma GMP-140 before and after the treatment. The changes in platelet count and the time needed for proteinuria to turn negative and edema to dissipate were observed. Results: before the treatment, the GMP-140 levels in both the Dantonic™ group and control group were obviously higher than that of the normal group ($P < 0.01$). After the treatment, the time for proteinuria to turn negative and edema to dissipate in the Dantonic™ group was significantly shorter than that of the control group ($P < 0.05$, $P < 0.01$, respectively), while GWP-140 was

Table 11.24 The occurrence rate of cardiovascular and cerebrovascular accidents in the subgroups of Dantonic™ and Aspirin groups

	Number of cases	Carotid artery system TIA	VBI	Cerebral infarction	Myocardial infarction	Side effect
Dantonic™						
250 mg qd	20	1	2	1	0	0
250 mg bid	20	0	1	0	0	0
250 mg tid	20	1	0	0	0	1
Aspirin						
50 mg qd	20	1	2	1	1	1
50 mg bid	20	1	1	1	0	1
50 mg tid	20	1	0	0	0	6

Table 11.25 The changes in the content of plasma GMP-140 and the activities of t-PA and PAI-1 before and after the treatments (means ± SEM)

Groups	Treatment	Cases	GMP-140 (μg/L)	t-PA (IU/ml)	PAI-1(AU/ml)
Conventional	Before	20	61.81 ± 24.36	1.21 ± 0.45	11.33 ± 3.1
	After		43.56 ± 21.67*	1.55 ± 0.47*	8.46 ± 2.1
Dantonic™	Before	20	61.49 ± 25.23	1.20 ± 0.43	11.78 ± 3.3
	After		28.78 ± 19.97**	1.69 ± 0.49**	8.01 ± 2.4

Compared with status before treatment $^{*}P < 0.05$; $^{**}P < 0.01$

clearly decreased compared with the control group ($P < 0.01$) and there was no difference compared with the normal group ($P > 0.05$). The GMP-140 level of some children in the control group was still higher than that in the normal group ($P < 0.05$). The difference in platelet count was not significant. Conclusion: there was platelet activation in children with PNS and Dantonic™ can inhibit platelet activation abnormality, improve symptoms, and relieve the occurrence and development of PNS.

Zhang [36] reported that 60 PNS cases were randomly divided into a treatment group (32 cases) and a control group (28 cases). The patients in both groups took Prednisone tablets at 2 mg/(kg·d), and the patients in the treatment group took Dantonic™ additionally at 3 pills/time for preschool children, 5 pills/time for school-aged children, three times a day for a period of 8 weeks. GMP-140 levels and blood platelet count were determined before and after the treatment. The results are shown in Table 11.27.

11.2.3 The Effect of Dantonic™ on Aspirin Resistance

11.2.3.1 Introduction to Aspirin Resistance

The use of salicylic acid (extract of willow bark) for the treatment of pain caused by rheumatic and other diseases, inflammation, and fever can be traced back to the fifth century B.C. during the Hippocrates era, but its strong side-effect on the digestive tract has been disturbing clinical doctors ever since. At the end of the nineteenth century, a German chemical scientist, Felix Hoffmann, in order to treat his father's arthritis, synthesized acetylsalicylic acid (ASA), which was more stable and had fewer side-effects. In l899, Friedrich Bayer & Co. marketed ASA under the name of aspirin. Aspirin has been considered an epoch-making drug for inhibiting fever, pain, and inflammation since the beginning of its sales. Today, aspirin is widely used around the world, and can be freely bought anywhere as an OTC drug. Aspirin has a wide range of

Table 11.26 The effect of Dantonic™ on plasma GMP-140 content

Author (year)	Diagnosis (cases)	Treatment group			Control group			Remarks
		Medication	GMP-140		Medication	GMP-140		
			Before treatment	After treatment		Before treatment	After treatment	
Lu [33]	UAP (21) (control group, 21 cases)	SAS + Dantonic™ group × 4 wk	39.8 ± 10.2	17.0 ± 7.9	SAS × 4 week	37.1 ± 11.7	30.4 ± 13.6	Healthy people (22) 15.2 ± 6.5 Dantonic™ group was clearly lower than the control group after treatment ($P < 0.05$)
Wang et al. [34]	UAP (20)	Conventional treatment + Dantonic™ 10 pills × tid × 4 week	61.49 ± 25.23	28.78 ± 19.97	Heparin, SAS, Nitrates, Ca^{++} antagonists, β-receptor blockers	61.81 ± 24.36	43.56 ± 21.67	There was a statistical difference in the contents before and after the treatment
Zhang et al. (2000)	UAP	Conventional Treatment + Dantonic™ 10 pills × tid × 4 wk	There was no data available. But it was lower compared with the status before the treatment ($P < 0.05$). It was also significantly lower compared with the control group ($P < 0.05$)		Vitamin C, Ticlid see Ticlopidine (250 mg/time × 7 days), Nitrates, Ca^{++} antagonists × 4 week			

Table 11.27 A comparison of plasma GMP-140 content and platelet count between Dantonic™ and the control groups (means ± SEM)

Author (year)	Diagnosis	Groups	Cases	GMP-140 (μg/L)			Blood platelet count ($\times 10^9$/L)		
				Before treatment	Treated for 4 week	Treated for 8 week	Before treatment	Treated for 4 week	Treated for 8 week
Zhang [36]	PNS	Dantonic™	32	45.79 ± 7.60	28.25 ± 3.12	15.76 ± 5.25	20.5 ± 4.7	22.1 ± 2.8	22.1 ± 3.5
		Control group	28	48.67 ± 8.95	39.33 ± 3.46	23.40 ± 3.72	22.0 ± 3.4	20.5 ± 4.1	22.2 ± 4.8
Zhang [36]	Simple nephropathy	Dantonic™	14	32.21 ± 4.20	16.15 ± 3.35	16.30 ± 5.75	22.4 ± 4.2	21.7 ± 3.7	20.8 ± 4.5
		Control group	11	31.98 ± 11.24	23.75 ± 3.87	17.54 ± 3.69	20.5 ± 4.7	22.1 ± 2.8	21.4 ± 5.6
	Nephritis nephropathy	Dantonic™	8	45.79 ± 7.60	28.25 ± 3.02	15.76 ± 5.25	23.1 ± 5.2	20.9 ± 4.8	22.1 ± 3.5
		Control group	9	48.67 ± 8.95	39.33 ± 3.46	23.40 ± 3.72	22.0 ± 3.4	20.5 ± 4.1	22.2 ± 4.8
	Healthy	Normal group	19	15.33 ± 5.20			21.0 ± 4.5		

applications which not only covers antipyretic analgesics, but also can inhibit swelling at high doses (3 g/day), and has a significant effect on treating rheumatic inflammation. In the mid-twentieth century, there were reports showing that aspirin could cause massive hemorrhage, and it was confirmed that the mechanism of the effect was aspirin's inhibition of platelet aggregation. In the early 1950s, American scholars also found that the occurrence of myocardial infarction and cerebral infarction mortality had been significantly reduced among patients with rheumatoid arthritis who used aspirin perennially. Incidences of coronary heart disease were also reduced for women who took aspirin to treat dysmenorrhea. In 2002, a joint international antithrombotic group, Antithrombotic Trialists' Collaboration, published a Meta-analysis report on antiplatelet therapy for the prevention of death, myocardial infarction, and stroke in high risk patients. Based on the analysis of 65 clinical trials of aspirin, they estimated that by using aspirin, high-risk patients lowered their risk for cardiovascular events by 23 %. Aspirin also has a very good therapeutic effect on acute myocardial infarction patients, and early administration can significantly increase the curative rate and reduce the mortality rate by 23 %. The internationally well-known Boston health study (a physicians' health study) studied 20,000 physicians whose treatment group took 325 mg aspirin every other day while the placebo group took β carotene (it was said to reduce the occurrence of cancer). It was found that aspirin can significantly reduce the incidence of myocardial infarctions of middle-aged doctors. However, the incidence of cerebral apoplexy was higher than that of the control group and there was a major increase in cerebral hemorrhage, but no statistical significance.

These large-scale, worldwide, strictly designed and highly managed and controlled trials, which were carried out in developed western countries, undoubtedly confirmed the dominant position of aspirin in preventing cardiovascular and cerebrovascular accidents, even though side-effects of aspirin have been found in clinical application, such as hemorrhage, gastrointestinal reactions, asthma, and poor antithrombotic effects in women. In clinical studies, people still do not know the exact extent of platelet function reduction or at which level aspirin is the most effective and the safest for thrombosis prevention. However, it is the reduction of thrombosis disease incidence whose statistical significance has been accepted by the academic world. To achieve this, there must be a large number of cases and long-term observation. For example, if a clinical trial is conducted on transient ischemic disease using a new antiplatelet drug with uncertain therapeutic effect, then there would be a large ethical problem. Clinical trials on the prevention of myocardial infarction and the recurrence of cerebral infarction require long-term drug administration and are very expensive, which is why it is so difficult to develop new antiplatelet drugs and determine their effectiveness. Therefore, aspirin has been widely involved and used in the treatment of cardiovascular diseases, especially in the treatment of ischemic heart disease. Aspirin also plays an important role in the secondary prevention of coronary heart disease, as well as in primary prevention in some selective patients.

However, it has been found clinically that even if some patients took aspirin regularly, they still experienced cardiovascular accidents. It has been estimated that about 1/8 of high-risk patients who, even if they took aspirin regularly, still had attacks of vascular accidents within a period of 2 years. Using different methods to determine platelet activity, several reports have shown that aspirin's effect on individuals varies greatly. Some patients do not respond to aspirin treatment according to clinical and laboratory examinations. It is termed "aspirin resistance" (AR) in the literature, and has caught the attention of cardiovascular and cerebrovascular disease researchers, patients, and the media.

11.2.3.2 Identification and Classification of Aspirin Resistance

The fact that aspirin could not meet clinical expectations has been known for quite a long time. By the end of the 1970s, aspirin was used to treat patients at high risk for cardiovascular

and cerebrovascular diseases. Many reports showed that the drug did not work equally well in every case. By measuring platelet aggregation, platelet activity, bleeding time and thromboxane formation, it has been confirmed that aspirin's inhibitory effect on platelets does not show in every patient. Recently, several researchers have proposed a diagnosis of AR as follows:

(1) The average platelet aggregation ≥70 %, when ADP concentration is 10 μm;
(2) The average platelet aggregation ≥20 %, when arachidonic acid concentration is 0.5 mg/ml.

If both criteria are met, then it is aspirin resistance; if only one criterion is met, it is aspirin semi-resistance (ASR).

Based on biochemical and in vitro experiments on platelets, Artur-Aron Weber et al. (2002) proposed the classification of AR into three types. The classification is helpful for the understanding of AR. As a control, the normal aspirin response is defined as oral aspirin at 100 mg per day for 5 days with the complete inhibition (>95 %) of collagen-induced platelet aggregation and thromboxane formation. The three types of AR are described as follows:

Type I (pharmacokinetic): To patients with type I AR, oral administration of aspirin is ineffective. However, aspirin at 100 μM is able to completely inhibit collagen-induced platelet aggregation and thromboxane formation in vitro, suggesting that the pharmacokinetics of the drug are abnormal.

Type II (pharmacodynamics): To type II AR patients, aspirin is ineffective either taken orally or added to an in vitro assay. The mechanism of this type of resistance is unknown, but the involvement of the genetic diversity in the enzyme metabolic pathway, or the diversity of aspirin sensitivity, is suspected.

Type III (pseudoresistance): Although the formation of thromboxane can be completely inhibited by orally taking aspirin, collagen at a low concentration (1 μg/ml) still can induce platelet aggregation, which is called pseudoresistance, since aspirin does not exert its clinical function of platelet aggregation inhibition even if it totally inhibited thromboxane formation. Does this mean that the platelet has an increased sensitivity to collagen fibers in some AR patients? This complex clinical question has not been clarified.

The above AR classification actually is an attempt to use in vitro assays to solve the mystery of weakened antithrombotic capability of aspirin in vivo. For type I AR, an increase in the dosage of aspirin has been proposed. For types II and III AR, other kind of antiplatelet drugs might be considered. This classification will be helpful to clarify the mechanisms of aspirin resistance, the actual incidence, and possible clinical outcomes. Of course, one can only draw a conclusion on the actual clinical significance through follow-ups on AR patients and relevant clinical studies.

Although AR as a definition or a concept is still problematic, as a clinical phenomenon it does exist. Many clinical reports have revealed its significance: the occurrence of vascular accidents, i.e., myocardial infarction, cerebral infarction, and peripheral artery embolization has been increased in AR patients. Currently, nearly 10,000 research papers and news reports related to AR can be retrieved via the Internet, suggesting that the problem has been causing widespread concern to the scientific community and the public.

11.2.3.3 A Trial

From October, 2003 to January, 2004, the Tasly Institute aspirin resistance Study Group conducted an AR screening among retired cadres and their families in Beijing Military Region. 86 AR patients (M 57, F 29; age 70.94 ± 10.9) were identified, which was 15.6 % of the total individuals screened.

Method

Selection criteria:

(1) Patients who had continuously taken a small dose of aspirin for more than 2 weeks;
(2) The maximum platelet aggregation rate induced by arachidonic acid was more than 30 %, as determined by the Platelet Aggregometers 540VS (Chrono-log, USA).

Patients who met both criteria were selected.

Exclusion Criteria:

(1) Patients with hematological system diseases, especially hemorrhagic diseases;
(2) Patients with cancer;
(3) Patients with chronic obstructive pulmonary diseases.

Patients who met one of the above conditions were excluded.

Groups

Group A: 55 AR patients were randomly selected. They continued taking aspirin, and received additional Dantonic™ treatment (30 pills per day for 2 weeks).

Group B: 31 AR patients were randomly selected and treated with Dantonic™ alone, 30 pills per day for 2 weeks.

In Group A, there were 55 patients with complete documentation. In the second examination, blood samples were collected from 44 patients; one patient was hospitalized due to rectal cancer, and 10 patients were out of town. There were 31 patients in Group B with complete documentation.

The average age in Group A was 71.97, in Group B, 70.2; 12.7 % of the patients in Group A were smokers, in Group B, none; 45.5 % of the patients in Group A were complicated with hypertension, in Group B, 29.2 %; 14.5 % of the patients in Group A were complicated with diabetes, in Group B, 4.2 %; 38.1 % of the patients in Group A were complicated with coronary heart disease, in Group B, 20.8 %; 16.4 % of the patients in Group A were complicated with cerebrovascular diseases, in Group B, 8.3 %; 1.8 % of the patients in Group A were complicated with peripheral vascular diseases, in Group B, 0 %; 5.5 % of the patients in Group A were complicated with vascular diseases, in Group B, 0; no one in either group was complicated with hepatic cirrhosis. The above differences between the two groups were not statistically significant.

Results

The Effect of the Combination of Aspirin and Dantonic™ on the Maximum Platelet Aggregation Rate 55 patients took aspirin and Dantonic™. After 2 weeks' treatment, 46 patients (83.6 %) had their maximum platelet aggregation rate return to a normal level. 120 days after treatment, 44 patients were examined again, and 26 patients (59.1 %) had maximum platelet aggregation rates in the normal range. There was no occurrence of cardiac-cerebro and peripheral vascular accidents in these patients. The average value of the maximum platelet aggregation rate (27.76 ± 26.74) after 2 weeks' treatment was significantly lower than that before treatment (67.45 ± 22.76) ($P < 0.0001$, $n = 55$). The average value of the maximum platelet aggregation rate 120 days after the treatment (46.66 ± 31.84) was significantly lower than the value of the first test ($P = 0.0002$, $n = 44$). The average value 120 days after the treatment was significantly lower than the value 2 weeks after treatment ($P = 0.0197$, $n = 44$).

The Effect of Dantonic™ on the Maximum Platelet Aggregation Rate The maximum platelet aggregation rate after 2 weeks' treatment was determined in 31 patients from Group B, which was treated with Dantonic™ only, and the average value was 60.67 ± 38.41, which was significantly lower than the value before treatment (81.64 ± 1 1.73) ($t = 2.985$, $P = 0.0051$). 120 days after treatment, the average value was significantly lower than that before treatment ($t = 4.791$, $P = 0.0001$, $n = 27$). The average value 120 days after treatment was lower than the average value 2 weeks after treatment, but the difference was not statistically significant ($n = 26$, $t = 1.879$, $P = 0.0719$).

There was no occurrence of cardiac-cerebro and peripheral vascular accidents in Group B patients. 2 weeks after treatment, 15 patients (40.5 %) had maximum platelet aggregation rates reduced to below the normal level. 120 days after treatment, 13 of the 28 patients tested (46.4 %) had their values decreased to within the normal range.

A Comparison Between the Two Groups

Before treatment, the average value of the maximum platelet aggregation rate in Group B (81.64 ± 11.31) was significantly higher than that

in Group A (69.15 ± 22.76), $t = 3.082$, $P = 0.0027$. After 2 weeks' treatment, the average value in Group B (60.69 ± 38.41) was significantly higher than that in Group A (27.76 ± 26.73, $P < 0.05$). 120 days after treatment, the average value in Group B (49.74 ± 34.60) was significantly higher than that in Group A (46.66 ± 31.84), but the difference was not statistically significant (t = 0.383, P = 0.7028). After 2 weeks of treatment, the number of cases in Group A whose maximum platelet aggregation rate decreased to a normal level (83.6 %) was significantly higher than that in Group B ($x^2 = 16.31$, $P < 0.001$). There was no difference in the two groups 120 days after treatment ($x^2 = 0.654$, $P > 0.05$).

Conclusion: A total of 83.6 % of the patients whose maximum platelet aggregation rate had increased after taking aspirin were back to normal levels after treatment with aspirin and Dantonic™ for 2 weeks. There were still 59.1 % of patients remaining below the normal level 4 months later. 40.5 % of patients' platelet aggregation rates dropped to normal levels after 2 weeks' treatment with Dantonic™, and 4 months later, 46.4 % of the patients had maximum platelet aggregation rates within the normal range. Dantonic™ has a relative strong anti-AR effect, and it works synergistically with aspirin.

11.2.3.4 The Possible Mechanism of AR

Aspirin has an inhibitory effect on the formation of TXA2, which has a strong effect on platelet aggregation and vasoconstriction. TXA2 is formed from arachidonic acid which is separated from the phospholipids of platelets by phospholipase. Under the actions of PGH_2 synthase (cox-1, cox-2, peroxidase) and thromboxane synthase, arachidonic acid is transformed to prostaglandin H_2 and then TXA2. Aspirin acetylates serine-529 near the active site of cyclooxygenase and inactivates the enzyme, thus blocking the formation of TXA2 from prostaglandin H_2 and inhibiting platelet aggregation. The acetylation process is irreversible; therefore, aspirin's effect still exists even if aspirin disappears from the blood. The duration of activity depends on the lifetime of the platelets. In other words, the effective duration of aspirin does not depend on the duration of its effective concentration in the blood. Theoretically, all platelet function in the blood will be inhibited if aspirin is given once in full dosage. The average platelet life is 9 days. Therefore, new platelets can be inhibited for 9 days, while platelets which have already existed for 8 days can only be inhibited for one day. In theory, the antiplatelet effect of aspirin can last a long time, and it will take a stable effect with one oral administration daily. On the other hand, in patients with UAP, MI, HBP, diabetes, and cerebral vessel ischemic palsy, the formation of platelet TXA2 increases significantly, and the expression of TXA2 receptor (TP receptor) also increases. Aspirin can reduce the formation of TXA2 by inhibiting Cox-l so as to inhibit platelet aggregation, which means that aspirin is very important in the treatment of these kinds of diseases.

Clinically, some patients were not sensitive, responsive, or resistant to aspirin, and the mechanism has not been clarified completely, but it must be related to the following factors:

(1) The dosage of aspirin: many researchers believe that a low dosage of aspirin is enough to completely inhibit Cox-1 while a high dosage may be required for some patients to achieve antiplatelet effects. Helgason et al. (1993) reported that patients with cerebral infarction were studied with platelet aggregation assays to find whether they were sensitive to aspirin. The AR occurrence rate was 25 % with aspirin at 325 mg/day, while it was reduced to 8 % with a dosage of 1,300 mg/day. However, a recently published Meta-analysis report did not support this view. Some researchers believe that many patients developed side-effects in the gastrointestinal tract because of the high dosage. Eikelboom believes that AR is not related to ASA dosage. The problem of aspirin dosage also involves the diagnosis of AR. According to the definition of drug resistance in materia medica, it is considered "drug resistance" when the drugs have no effect or a lower effect than normal when the curative concentration has been reached. However, there are hardly any concentration determinations

of ASA in the AR related papers. Many authors believe that AR was not in accordance with the commonly used terms. The half-life of ASA is about 15 min. As described above, taking ASA once is enough to make the antiplatelet effect out of proportion to the blood concentration of ASA.

The ideal dosage of ASA has always been a disputed question, and there has been no convincing evidence showing that the antithrombus effect of ASA is dosage-related. According to a recent Meta-analysis, a high dosage of ASA (500–l,500 mg/day) was no more effective on the reduction of vascular accidents in high-risk people than was a low dosage (75–150 mg/day). A high dosage of ASA is accompanied with not only a higher incidence rate of side-effects, which makes it difficult for clinical application, but also with the inhibition of vascular endothelial Cox-1, which acts upon arachidonic acid (AA) in the blood vessel endothelium or on platelet AA adhered and aggregated on the injured vessel wall, forming prostaglandin I_2 (PGI_2). The effect of PGI2 is opposite to that of TXA2: it expands blood vessels and blocks thrombopoiesis. There is evidence showing that a small dose of ASA had a weak inhibitory effect on PGI2, while having a stronger inhibitory effect on TXA2. Theoretically and clinically, a very high dose of ASA should be avoided. There are reports showing that aspirin could aggravate angina (coronary stenosis) (Fig. 11.4).

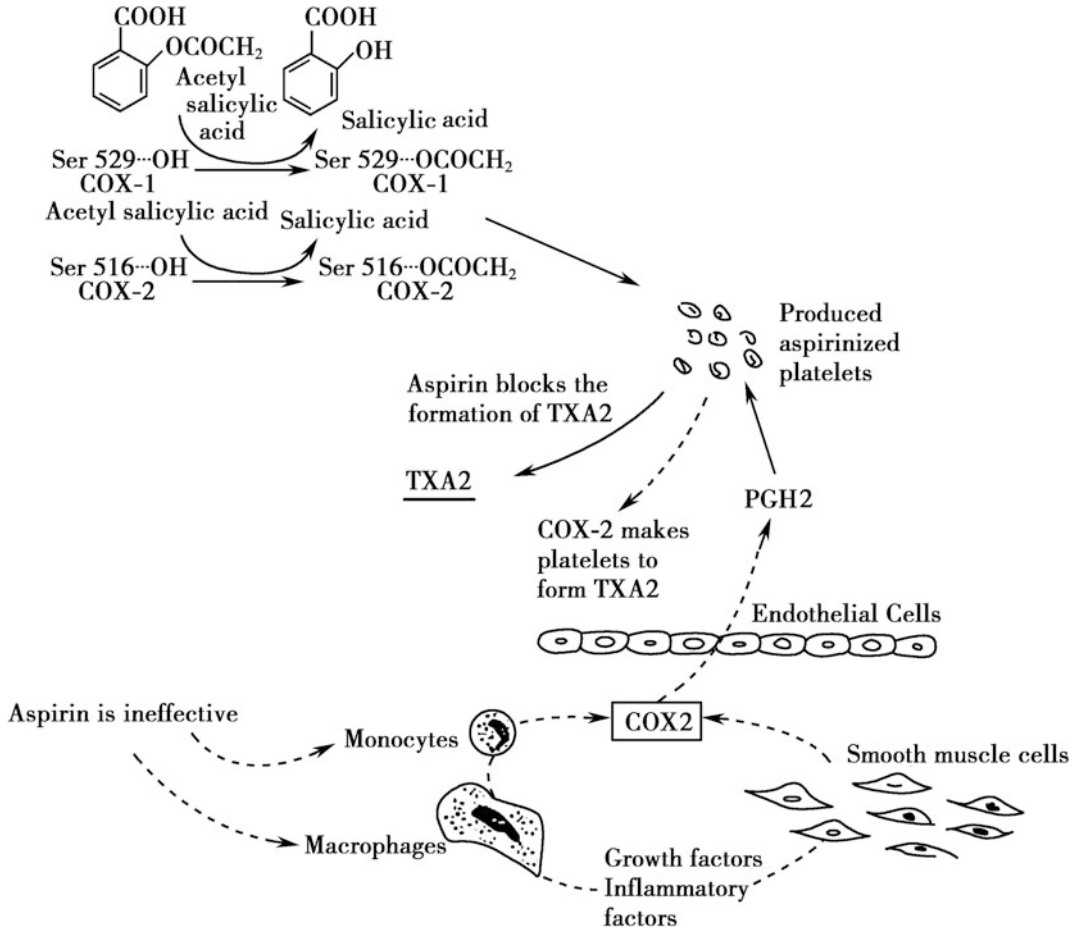

Fig. 11.4 Possible mechanism for aspirin resistance

(2) Smoking, hyperlipidemia, heart surgery, etc., could affect platelet turnover rates, which might affect the antiplatelet effect of ASA. Hung et al. (1995) showed that ASA in CHD patients could not block the increase in platelet thrombus formation induced by smoking. At present, studies have shown that after lipid oxidation, arachidonic acid changes to PGF2, which has important effects on cardiovascular and cerebrovascular diseases. For instance, both plasma F2-isoprostanes and urin 8-iso-PGF2, a lipid peroxidation marker, are increased in people with a long history of smoking. Aspirin at conventional doses can inhibit the activity of platelet Cox-1, but it cannot inhibit egestion of 8-iso-PGF2 in urine.

Friend et al. (2003) reported that among a group of 56 patients with coronary artery disease or with at least two risk factors for coronary heart disease, the average total cholesterol and LDL cholesterol levels of 14 patients with aspirin resistance were significantly higher than those of 42 cases which had a good response to aspirin. There were 9 cases of AR among 13 patients with hyperlipidemia. The authors also compared AR patients with patients who were sensitive to ASA, and there were no statistical differences in HDL and triglyceride levels, smoking history, high blood pressure, or diabetes between the two groups. Zimmermann et al. (2001) found that patients had increased ASA resistance after coronary artery bypass grafting.

11.2.3.5 AR or Secondary AR Caused by Drug Interactions

Physicians normally know that aspirin may cause a series of problems if it is combined with hypoglycemic drugs (tolbutamide, methyl chloride C urea), anticlotting drugs, gout treatment medicine (probenecid), blood pressure drugs, angiotensin-converting enzyme inhibitors (ACEI-captopril), Betamethasone, and so on. However, these drugs do not result in AR.

Like aspirin, nonsteroidal antiinflammatory drugs (NSAIDs) are very common drugs, and many patients may have used them together for a long period. Even some physicians believed that they could be used in combination, since they both belong to NSAIDs. In fact, both of these drugs can inhibit Cox enzymes and thus they might have competitive effects on each other. The inhibition of Cox-1 by NSAIDs is reversible. It has been shown that ibuprofen is able to inhibit aspirin's effects of antiplatelet aggregation and cardiovascular system protection, and it can even cause the development of secondary AR (SAR) in the original aspirin-sensitive patients. According to studies, the reason for the induction of SAR by NSAIDS is that the latter could competitively inhibit the active site of Cox-1 so as to stop the binding of aspirin to the target. This notion is validated by clinical observation. MacDonald and Wei (2003) reported that people who take aspirin and ibuprofen have increased risks of cardiovascular mortality.

Even if aspirin is not used together with other drugs, the volume of water used for taking the medicine can also affect the absorption of the drug. When taking aspirin with a low volume of water (25 ml), the absorption rate was lower than with a large volume of water (250 ml). It has also been reported that if aspirin was taken with soft drinks, the blood concentration of aspirin was only 50 % of that taken with water.

A. Cox-2

The key problem of AR is that there is no inhibition of TXA2 after taking aspirin. Aspirin's inhibitory effect on TXA2 is exerted by inhibiting Cox-l. People have always thought that the mature platelets in the human body contain only Cox-1 isozymes, but it has been shown by recent studies that platelets also contain Cox-2 mRNA, and the expression of *cox*-2 in each patient is different. Some patients may have very high levels of Cox-2, especially when they are in a state of nervousness. Cox-2 is not inhibited by a low dose of aspirin. Some people have estimated that aspirin is 166 times more active against Cox-1 than against Cox-2. Cox-2 can also produce a large amount of TXA2, and make ASPs unstable and vulnerable to rupture. This is the key to acute cardiovascular syndrome, and might be the key to AR as well.

B. Cox-1

Currently, it has been found that there are polymorphisms and various degrees of maturity in Cox-1. Some researchers believe this is the molecular basis of AR. The single nucleotide polymorphisms (SNPs) of Cox-l could affect the sensitivity of an individual to aspirin. SNPs are considered the genetic basis of drug reactions and the intermediates of phenotype changes.

There is another cytological reason for AR. Besides platelets, nucleated cells (monocytes/macrophages) may play a role in AR, since these cells also have the potential for TXA2 synthesis. Compared with nonnuclear platelets, these cells have the ability to regenerate these enzymes, including Cox-l; therefore, they can cause insensitivity or resistance to aspirin, that is, the production of TXA2. These cells can also synthesize Cox-2, and if stimulated by inflammation, the expression of Cox-2 in nucleated cells could be increased by 10- to 20-fold. TXA2 synthesized by nucleated cells can reverse platelet activity so as to begin a chain reaction. The existence of Cox-2 has been identified in atherosclerotic tissue, and there are macrophages in these plaques, which are very important for the production of TXA2. However, aspirin cannot exert all these effects, which leads to the production of AR and acute coronary syndrome. It is also worth studying that red blood cells have effects on prethrombosis and the enhancement of platelet activity, which cannot be blocked by aspirin for a long period of time.

C. The effects of red blood cells on platelets

The interaction between red blood cells and platelets has effects on platelet aggregation, because red blood cells can regulate the generation of arachidonic acid substances in platelets. Aspirin cannot inhibit the effects of red blood cells on the enhancement of platelet reactiveness. Therefore, further studies are needed to clarify whether the interaction between red blood cells and platelets can cause aspirin resistance.

The glycoprotein IIb/IIIa receptor complex is located on the platelet surface, and is the common pathway to platelet activation. The complex binds fibrinogen and is essential for platelet aggregation. Genetic differences in the glycoprotein IIb/IIIa receptor complex may be the reason for different reactions to aspirin in different patients. Common polymorphisms include Leu 33 ($P1A_1$) to Pro ($P1A_2$). Most studies have shown that $P1A_2$ carriers not only have enhanced platelet activation but also are less responsive to aspirin's antithrombotic effects. Therefore, it is basically confirmed that glycoprotein IIb/IIIa has an effect on aspirin, but it has still not been clarified how much clinical aspirin resistance has been affected by glycoprotein IIb/IIIa polymorphism.

Others

Tension, excessive movement and some factors which may cause sympathetic nervous excitement and increase the level of catecholamine may lead to enhanced platelet function, which can lead to vascular accidents. The inhibitory effect of aspirin is relatively weak, so some researchers considered that this may be one of the reasons for AR's occurrence.

D. Countermeasure to AR

Since there are no universally accepted diagnostic criteria for AR, and the mechanism for AR has not been elucidated, the treatment of AR is difficult. The factors involved in AR generation are shown in Table 11.28. The dosage of aspirin should be considered and platelets should be rechecked in time so as to determine the existence of AR. This is essential to reduce thrombosis.

Several investigators proposed that the inhibition of platelet aggregation by Clopidogrel was through ADP receptors, and thus Clopidogrel could be used by AR patients. However, there have already been reports of Clopidogrel resistance cases. Attention should be paid to the platelet TXA2 receptor (TP receptor) which has a certain effect on artherosclerosis. Besides

Table 11.28 Factors related to producing AR

Gender differences/females are AR-prone
Smoking
Overexercise
Mental stress
Advanced age
Taking nonsteroidal and antiinflammatory drugs
Heart surgery, interventional treatment, etc.

platelets, mononuclear cells, and macrophages can also produce this receptor, and therefore a TP receptor antagonist is valuable to the prevention of angiosclerosis and even acute cardiovascular events. The ideal antithrombus treatment should choose the selective inhibitors to Cox-l and Cox-2 and consider the antagonists of the TP receptor.

Lu [33] randomly divided 42 patients with UAP into a Dantonic™ group and a control group. Both groups were treated with aspirin, nitrates, calcium antagonists, etc. The author used ELISA to determine GMP-l40 levels in the plasma of all patients before and after treatment, and observed the symptoms of angina and ECG ischemia. After 4 weeks' treatment, exciting results were obtained. The plasma GMP-140 levels in both groups before the treatment were significantly higher than in those of healthy people ($P < 0.01$); after treatment, angina symptom improvement in the treatment group was 85.7 % compared to 57.1 % in the control group, and the difference in the total effective rates between the two groups was significant ($P < 0.05$). The ECG ischemia improvement rate was 57.1 % in the treatment group, which was significantly higher than that of the control group (23.8 %) ($P < 0.05$). At the same time, the plasma GMP-140 level was clearly reduced compared with the control group ($P < 0.05$) and was almost the same as that of healthy people, while the GMP-140 level of the control group was still higher than that of healthy people ($P < 0.05$). This study showed that the plasma GMP-140 level was reduced by 4 weeks of aspirin treatment, but the level was still higher than that of healthy people, suggesting that aspirin alone was not enough to completely inhibit the abnormal activation of platelets in UAP patients. To these patients, a combination of aspirin with Dantonic™ was recommended.

Li [37] reported that 70 UAP patients were randomly divided into two groups. In the treatment group, Dantonic™ was administered in addition to conventional treatment (including heparin + nitrates +β-receptor blockers + Ca^{++} antagonists). The control group was treated with conventional western drugs only. The symptoms of the angina pectoris patients in both groups were compared after 1 week and the occurrence rate of MI was compared after 2 months. The results indicated that the total improvement rate was 71 % in the treatment group and 60 % in the control group. There was a statistical difference ($P < 0.05$), but no significant difference in the occurrence rate of MI.

11.2.4 The Mechanism for the Effects of Antiplatelet Activation and Aggregation by Dantonic™

Li et al. [17] used fluorescence polarization to determine the fluorescence polarization P of rabbit platelets, microviscosity η, and membrane fluidity. The results indicated that Dantonic™ was able to significantly increase the fluidity of platelet membranes and reduce the microviscosity η, and the effect was clearly dose dependent.

Zongpei et al. [6] used high-polymer dextran, adnephrin, bovine serum albumin, and other composite factors to induce the chronic hyperviscosity syndrome model in rabbits. They also induced the acute hyperviscosity syndrome model in Wistar rats by intravenous injection of high-polymer dextran and subcutaneous injection of adnephrin. Both animals were treated with Dantonic™, and it was discovered that Dantonic™ can significantly increase TXB2 in the acute and chronic hyperviscosity syndrome models, and decrease the 6-Ketone- prostaglandin F1a.

Professor Han Jingyan from Keio University et al. [15] studied the continuous changes of microcirculation in rat mesentery by means of multiple targets and dynamic study, and proved that Dantonic™ can inhibit the adhesion of leukocytes and veins induced by ischemia and reperfusion, and inhibit the production of peroxides in venular walls and mast cell degranulation in mesentery and other multiple target effects. The author also used toluidine blue intravital staining and preagonal staining to prove that Dantonic™ was able to inhibit the mast cell degranulation induced by ischemia and reperfusion, reduce TNF2, histamine, 5- HTA, and the release of vasoactive substances, and prevent vasoactive damage caused by vascular attack factors, which

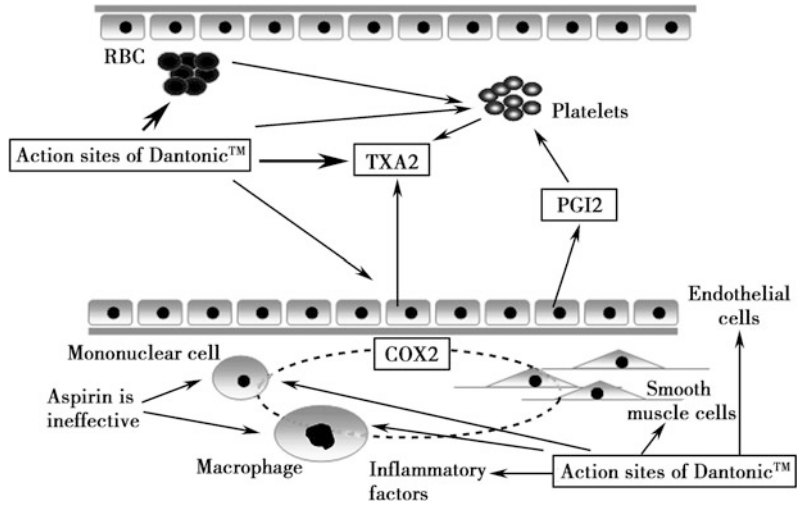

Fig. 11.5 The inhibitory effects of Dantonic™ on platelet activation and aggregation

also has been proven to be the main effect of panax notoginseng saponins.

Chen et al. [7]) also proved that Dantonic™ has a similar effect to that of statins for vascular cell adhesion molecule-1 under the condition of angiosclerosis of rabbit arterial blood vessel walls.

Chen [38] randomly divided 40 male Wistar rats into a Dantonic™ treatment group and a control group. The platelet aggregation rate was determined by ADP-induction. The platelet aggregation rate in the treatment group (31.05 ± 4.01) was significantly lower than that of the control group (69.53 ± 2.01). The author also observed the effect of Dantonic™ on the contents of platelet cAMP and found that Dantonic™ was able to greatly increase the contents of platelet cAMP and proteins, and the effect was positively related to the dosage of Dantonic™.

In the nearly 10 years of animal studies and clinical observations on Dantonic™, it has been validated that Dantonic™ has a definite inhibitive effect on platelet activation, and the effect involves multiple sites, multiple links, multiple targets, and multiple layers (Fig. 11.5). Besides the curative effect on coronary heart diseases and angina pectoris, Dantonic™ can particularly prevent the development of artherosclerosis and reduce the occurrence of sudden cardiovascular and cerebrovascular accidents in patients with coronary heart disease.

11.3 The Effect of Dantonic™ on Endothelial Dysfunction Correction

Vascular endothelium is composed of flat cells, which was considered as a relatively inactive cell layer before the 1970s. Over the last 30 years, many studies have revealed that endothelial cells are the largest endocrine cells in the body, and they have significant effects on blood coagulation, fibrinolysis, arterial function, and blood vessel growth. Endothelial cells have functions specific to their host organs, such as heart myocardial function, pulmonary gas exchange, hepatosplenic phagocytosis, etc. In 1976, Ross et al. proposed the endothelial cell damage theory, and opened a new area of vascular etiology. With recent progress in molecular biology and biochemistry, it has become a specialized area: vascular disease syndrome.

11.3.1 Dysfunction of Vascular Endothelium

Vascular endothelial dysfunction is one of the earliest changes in atherosclerosis. Since arteries with vascular endothelial dysfunction lose their expansion function during increased blood flow, which is normally induced by the release of a

relaxing factor, vascular endothelium dysfunction is considered the initial link of coronary heart disease and has an important effect on the development of coronary heart disease and acute coronary heart disease events. At present, it is believed that the occurrence of many acute coronary events is not merely related to the degree of coronary stenosis; rather, coronary endothelial dysfunction plays a leading role in the events.

In 1992, Celemajer et al. invented a noninvasive method for the detection of peripheral vascular endothelial dysfunction, high-resolution ultrasound. The diameters of the superficial femoral and brachial arteries at rest, during reactive hyperaemia, and after sublingual glyceryl trinitrate were measured, and the percentage of brachial artery expansion during reactive hyperaemia and after sublingual nitroglycerin could be calculated and compared with the status under quiescent conditions.

Wang et al. [39] used human umbilical vein endothelial cell (HUVEC) culture to prepare a lipopolysaccharide injury model, and the effects of Dantonic™ at different concentrations were observed. Cell viability, NO, NOS, ET-1, and intracellular calcium were measured. The cells were observed under a measuring microscope, an inverted phase contrast microscope, and a laser confocal scanning microscope and transmission electron microscope. The results showed that treatment of the cells with Dantonic™ before adding LPS could significantly relieve structural injury in VECs. Dantonic™ at 0.58 and 0.25 g/L could offer significant protection ($P < 0.05$); at higher (1 g/L) or lower (0.1 g/L) concentration, Dantonic™ could alleviate the injury, but the results were not statistically significant ($P > 0.05$). It was concluded from this test that Dantonic™ has a protective effect on VECs.

Xu et al. [40] used H_2O_2 to induce HUVEC injury, and Dantonic™ at different concentrations was added before or after the induction. Cell viability was measured by MTT assay to observe the effect of Dantonic™. The author used the immunocytochemical method to study the effect of Dantonic™ on H_2O_2 injured endothelial cells. The expressions of nitric oxide synthases 2 and 3 (NOS2, NOS3) and NF-κB were monitored. The results showed that Dantonic™ was able to significantly increase the activity of the cells, inhibit the production of H_2O_2-induced MDA, and adjust NO in two ways; therefore, Dantonic™ had a significant antagonistic effect on endothelial cell injury. The authors believed that the mechanism for that was related to the expressions of NOS2, NOS3, and NF-κB.

Dantonic™ not only can protect ex vivo endothelial cells, but also can improve and adjust abnormalities of the vascular endothelial secretory system, which has been validated in the experiment on a chronic hyperviscosity syndrome rabbit model (2003 and 2006). The authors drew a conclusion from the changes in rabbit plasma thromboxane B (TXB) and ET: Dantonic™ with long-term administration has a significant effect on rabbits with chronic hyperviscosity syndrome, but it was not apparent for the instant effect of improving vascular endothelial secretory function (Table 11.29).

11.3.2 Dantonic™ and Endothelin

The VEC is a cell monolayer located between the circulating blood and the subendothelial tissue of the vessel wall. According to many studies in recent years, people have changed the concept of VEC as a canal lining. VEC has wide physiological functions, such as anticoagulant, antithrombosis, fibrinolysis, synthesis of connective tissue components, metabolism, and secretion of active substances. VEC is directly related to vasospasms, thrombosis, atherosclerosis, and luminal stenosis, so this blood vessel endothelium actually is responsible for the dynamic equilibria of coagulation–anticoagulant; fibrinolysis–antifibrinolysis; platelet aggregation–antiaggregation; vasodilation–contraction; and proliferation of smooth muscle–antiproliferation. In recent years, endothelium-derived contracting factors (EDCF), synthesized and secreted by VEC, have attracted a lot attention. These factors include TXA2, arachidonic acid metabolites (such as endoperoxide), and peptide

Table 11.29 The effect of Dantonic™ on vascular endothelium dysfunction in coronary heart disease patients (means ± SEM)

Author (year)	Trial design and disease	Medicine and cases	Brachial artery flow mediated dilation (FMD)			ET-1		Remarks
			Before treatment	After treatment	P	Before treatment	After treatment	
Liu et al. [41]	Randomized controlled single-blind, brachial artery, CHD	Dantonic™ (40 cases)	4.46 ± 1.98	10.08 ± 2.16		60.81 ± 11.21	30.51 ± 11.21	
		Conventional (40 cases)	4.5 ± 1.8	5.3 ± 1.9	$P < 0.01$	60.98 ± 11.21	58.88 ± 8.98	
Yang et al. (2003)	Randomized controlled single-blind, carotid artery, angina with coronary heart disease	Dantonic™ (36 cases)	4.86 ± 1.80 %	9.10 ± 1.70 %		6.68 ± 2.10	4.10 ± 1.51	Comparison between Dantonic™ and the conventional control group after treatment, $P < 0.0$ l
		Conventional (32 cases)	4.69 ± 3.10 %	4.70 ± 2.01 %	$P < 0.01$	6.64 ± 1.77	6.28 ± 1.77	
Wang et al. (2007)	Randomized control, brachial artery, coronary heart disease	Dantonic™ (43 cases)	2.51 ± 1.88	6.51 ± 2.04				The authors observed no difference in clinical end-point events, $P > 0.05$
		Conventional (42 cases)	2.09 ± 1.92	4.23 ± 1.99	$P < 0.01$			
Zhang [8]	Randomized controlled, brachial artery	Dantonic™ (47 cases)	2.46 ± 0.21	6.53 ± 0.41		119.7 ± 21.48	72.98 ± 20.75	
		Conventional (46 cases)	2.48 ± 0.24	2.51 ± 0.26	$P < 0.05$	121.13 ± 20.56	104.96 ± 21.02	

Table 11.30 Comparison of a relative amount of ET-1 PCR product in stable angina patients before and after treatment with Dantonic™ and ISDN (means ± SEM)

Groups	Number of cases	Relative amount of ET-1 PCR (OD nm)	
		Before treatment	After treatment
Dantonic™	29	294.48 ± 12.05	69.55 ± 80.83*#
ISDN	30	290.68 ± 10.12	288.09 ± 1.32

*Compared with the control group after the treatment, $P < 0.01$
#Compared with the treatment group before the treatment, $P < 0.01$

vasoconstriction substances (such as endothelin, ET), etc. ET is by far the strongest vasoconstrictor, and it has a strong effect on vascular contraction, promoting the proliferation of smooth muscle, having a positive inotropic effect, promoting the release of EDCF, and inhibiting the release of norepinephrine, etc. ET has dose-dependent positive inotropic and positive frequency effects on the heart, which enables strong contractions of the heart and stimulates the release of atrial natriuretic peptide. When a CHD patient has an angina attack, his/her plasma ET-1 concentration is significantly higher than that in healthy people. During acute myocardial infarction, the plasma ET-1 concentration also increases, and the extent of the increase is positively proportional to the infarct size and the degree of heart failure.

Since the isolation of ET from porcine aortic endothelial cells by Japanese scholar Yamagisawa in 1988, three types of ET (ET-1, ET-2, and ET-3) have been identified. They all contain 21 amino acids and two disulfide bonds. The three ETs are encoded by distinct genes with somewhat different functions. ET-1 is the only endothelin secreted by endothelial cells. Human ET-l mRNA encodes a precursor protein (pre-pro ET-1) with 212 amino acids which is cut into 38 amino acid peptides (big ET-1) by proteolytic enzymes, and ET-1 is formed by the endothelin converting enzyme. The coronary artery smooth muscle is rich in ET receptors, and coronary artery's response to ET is the most sensitive. ET-l adjusts its changes in local plasma levels by paracrine regulation; however, the increase in the local release of ET does not necessarily reflect changes in the plasma levels. Therefore, it is necessary to check the expression of ET-1 mRNA in VECs.

Under normal physiological conditions, there is a small amount of natural replacement of exfoliated cells in the blood, i.e., circulating endothelial cells. They are the only specific indicator directly reflecting vascular endothelial injury and have an important clinical value. Feng et al. [42] randomly divided 70 cases of stable angina patients into two groups, one treated with Dantonic™ and the other treated with isosorbide dinitrate, and determined ET-1 gene expression in peripheral blood circulating endothelial cells with RT-PCR. 30 healthy people were used as a pretreatment control. The results showed that a 546 bp band was detected in 69 of the 70 angina pectoris patients, while none of the healthy people showed a positive result. After the treatment with Dantonic™, 6 of 29 patients in the group showed negative results in the RT-PCR assay, while there were no negative cases in the ISDN group. The relative amount of ET-1 PCR product (optical density) decreased significantly in the Dantonic™ group, and there was a statistical difference compared with the ISDN group ($P < 0.05$) (Table 11.30), which indicated that Dantonic™ was able to inhibit the expression of ET-l in peripheral blood endothelial cells. It has now been confirmed that Dantonic™ can directly alleviate angina attacks through the regulation of ET-1 mRNA expression levels in VECs. This is an important revelation in the mechanism of the effect of Dantonic™ on angina from a molecular level.

The literature (Zhu et al. (1995); Yanagisawa et al.) has shown that ET concentration, renin activity (RA), and angiotensin II (AT-II) levels in patients with coronary heart disease and angina were significantly higher than those in normal people. In addition, an increase in ET secretion

could induce or exacerbate myocardial ischemia. Plasma ET concentrations in angina patients are positively correlated with the severity of the illness.

11.4 The Effect of Dantonic™ on the Metabolic Syndrome

The metabolic syndrome (MS) has been proposed as early as the 1960s; the content mainly showed the close relationships among obesity, high blood pressure, blood lipid disorders, and atherosclerotic heart disease stents, thus forming a concept of a clinical syndrome. The research afterward found that insulin resistance (IR) was the basis of the syndrome, so it is also called IR syndrome. The National Institutes of Health (NIH) of the United States calls it "Treatment of High Blood Cholesterol in Adults."

Dantonic™ was able to regulate blood lipids, stabilize ASPs, correct endothelial dysfunction, protect VECs, improve blood rheology, resist platelet activation and aggregation, improve microcirculation and antioxidants, and exhibit anticoagulant effects, showing a certain advantage in the field of MS prevention and treatment.

IR is an independent risk factor for cardiovascular disease. It refers to the decreased sensitivity of body tissues to insulin in the promotion of cellular uptake of blood glucose, which leads to an increase in blood sugar levels and stimulation of insulin secretion. Hyperinsulinemia promotes vascular smooth muscle cell proliferation, resulting in stenosis of the lumen of blood vessels and a decrease in blood vessel elasticity, strengthening the effect of the renin-angiotensin system by increasing sympathetic activity and affecting transmembrane ionic transport, etc., to affect the activities of the heart. According to a recent study by People's Liberation Army No. 254 Hospital, Dantonic™ was found to be able to protect blood vessels under conditions of IR, and the effect might be related to the inhibition of the excessive apoptosis of vascular smooth muscle cells. Chen et al. [43] studied 80 cases of high blood pressure patients with IR and randomly divided them into two groups: one group was treated with Amlodipine and Dantonic™, and another group was treated with Amlodipine only. The results showed that the blood levels of insulin and the ratios of blood insulin/glucose in 40 patients had been decreased significantly after taking Dantonic™ for 4 weeks. The insulin sensitivity had increased, while the blood plasma endothelin had decreased (Table 11.31).

Table 11.31 The effects of Amlodipine and Dantonic™ treatment on patients with hypertension and IR

Observed parameters		Amlodipine and Dantonic™ treatment		Amlodipine only treatment	
		Before treatment	After treatment	Before treatment	After treatment
Glucose (mmol/L)	Fasting	5.26 ± 0.84	5.01 ± 0.78$^{*\triangle}$	5.19 ± 0.56	5.27 ± 0.59
	Glucose load 60 min	9.63 ± 1.94	7.26 ± 0.31$^{*\triangle}$	9.83 ± 0.65	9.76 ± 0.52
	Glucose load 120 min	7.64 ± 0.80	6.21 ± 0.15$^{*\triangle}$	7.69 ± 0.81	8.01 ± 0.76
Blood insulin (mv/L)	Fasting	26.24 ± 1.83	20.32 ± 1.57$^{*\triangle}$	25.34 ± 1.74	25.31 ± 1.73
	Glucose load 60 min	126.79 ± 1.90	99.16 ± 2.00$^{*\triangle}$	122.01 ± 1.91	121.65 ± 1.89
	Glucose load 120 min	90.53 ± 1.75	71.42 ± 1.96$^{*\triangle}$	91.26 ± 1.96	92.56 ± 1.66
Ratio of blood insulin/glucose		5.06 ± 1.29	4.19 ± 0.93$^{*\triangle}$	5.24 ± 1.01	5.18 ± 1.07
Blood plasma endothelin (ng/l)		56.4 ± 6.78	38.7 ± 4.62$^{*\triangle}$	59.2 ± 7.31	42.6 ± 4.78

Compared with the before treatment data, $^{*}P < 0.05$
$^{\triangle}$compared with the after treatment data of amlodipine only group, $^{\triangle}P < 0.05$

Qu et al. [44] studied patients with severe acute pancreatitis complicated with multiple organ dysfunction syndrome (MODS). They found that the levels of ET and NO were increased in these patients. The patients were treated with Ceftazidime and Dantonic™ and the results showed that Dantonic™ had a therapeutic effect on MODS and could reduce ET and NO levels, suggesting that Dantonic™ does have regulatory effects on the ET system.

11.5 The Effect of Dantonic™ on Hemorheology

Hemorheology is the study of blood flow properties and its components. This is an important branch of biorheology with the most extensive and in-depth research. Ever since the blood and blood vessels were viewed as an organic whole, the concept of the blood vessel organ was formed. Abnormal hemorheology exists in many diseases, including coronary heart disease, hyperlipemia, acute myocardial infraction, respiratory failure, cerebrovascular accident, and Acute Renal Failure, and it is a basic pathological process. Clinically, these processes, which are caused by one or more abnormal blood viscosity factors, are called hyperviscosity syndrome. In a sense, hyperviscosity syndrome includes coronary heart disease and hyperlipidemia. Arteriosclerosis is a systemic vascular wall lesion. Although some people believe that the initial trigger is injury in the endothelial cells and the central link is the formation of foam cells and proliferation of smooth muscle cells, the whole pathological process involves cellular adhesion, aggregation, deformation and movement, and changes in platelet function and blood rheological properties. Therefore it can be said that there are promoting interactions between abnormal blood rheology and the factors in the pathogenesis of atherosclerosis. So, finding and correcting blood hyperviscosity as early as possible is very important for the prevention and the treatment of hyperlipidemia, angina pectoris, and myocardial infarction.

The effect of Dantonic™ on hyperviscosity syndrome has been studied by several investigators. At present, there are no unified methods nor uniform standards for measuring blood rheology parameters in the laboratories in China. So, we chose to list the changes in parameters before and after treatment, and the comparison with the control groups. However, none of the authors reported whether these values reached normal levels after the treatment. Of the 16 papers, 11 have relatively more complete information. The following is a summary of these data:

1. Seven papers tested ηHB and ηLB, and they all showed that Dantonic™ could improve these properties.
2. Nine papers tested plasma viscosity. Except for one report, all of the other reports showed that Dantonic™ could significantly improve plasma viscosity. The one exception was a study by Feng [45] who found that for the male group, Dantonic™ had no statistically significant effect.
3. Five papers measured hematocrit, and four of them found that Dantonic™ had an improving effect on this parameter. Ji et al. [46] reported 121 cases of hyperlipidemia syndrome (including 37 cases of coronary and 34 cases of cerebral infarction) and they found no changes after treatment with Dantonic™. Xu Zongpei et al. reported that Dantonic™ could improve the distortion of red blood cells, and at a dosage range of 15–75 mg/kg, the changes in red blood cell distortion increased with dosage. Red blood cells are the predominant cells in blood; therefore distortion has a great influence on blood viscosity. Red cell distortion has a fundamental effect on microcirculation perfusion.
4. Five authors measured the rate of platelet aggregation. Bi [47] reported 60 cases of pulmonary heart disease accompanied with hyperviscosity syndrome and found that Dantonic™ had an improving effect. Feng [45] reported 80 cases of cardiac and cerebrovascular diseases accompanied with hyperviscosity syndrome. It was found that blood platelet aggregation decreased markedly in the male group who were treated with

Dantonic™; however, no effect was found in the female group.
5. Seven papers measured fibrinogen and they all found that Dantonic™ could reduce its level.

In the past several years, many investigators have reported that Dantonic™ was able to treat angina pectoris patients accompanied with hyperviscosity syndrome. In 24 papers, blood rheology indexes in 1455 CHD patients were determined before and after the treatment.

1. Dantonic™ had a definite effect on whole blood viscosity. Compared with the control group which was treated with dinitrosorbide and compared with the control group taking Compound Danshen Tablet [48], Dantonic™ had a better effect on reducing whole blood viscosity than these two drugs.
2. Dantonic™ had a definite effect on plasma viscosity. The results in 15 papers showed that compared with the data obtained before the treatment, the viscosity levels after treatment with Dantonic™ decreased markedly, and the differences were statistically significant.
3. 5 papers measured RBC aggregation rates, and they all showed an improvement after treatment with Dantonic™. 7 papers measured the specific volume of RBC, and they all showed positive results.
4. 10 papers reported that fibrinogen level was clearly improved after treatment with Dantonic™. Liu [49] compared Dantonic™ with ISDN and found that Dantonic™ had a more significant effect on reducing fibrinogen.
5. Two reports determined platelet adhesion rate and aggregation rate, and found that the indices decreased significantly after treatment with Dantonic™.
6. Two papers measured the changes in erythrocyte sedimentation rate, and their results showed no significant changes.

In summary, after analyzing 26 reports, it can be concluded that Dantonic™ has a significant improving effect on whole blood, blood plasma, and fibrinogen.

Chen Xinyi et al. (1996) determined Dantonic™'s effect on the formation and resolution of blood stasis using a thromboelastography instrument. They found that a low dose (5 pills/time, 3 times a day) of Dantonic™ had no obvious effect on the thrombus elasticity graph or the microcirculation of the bulbar conjunctiva. Under the normal dose (10–15 pills/time, 3 times a day), Dantonic™ showed effects 10 min after administration, with a maximum effect occurring between 20–90 min. The effect was maintained for 240 min. The effect time recorded on the thromboelastography instrument, namely, the formation time of the prothrombin activator and the formation time of fibrin from start to finish was prolonged, and the rigidity of the thrombus (in the experimental group) decreased. Thus, Dantonic™ can clearly improve the thrombus elasticity graph.

11.6 The Effect of Dantonic™ on Microcirculation Disturbance

Microcirculation is the blood circulation in the arterioles, venula, and capillaries, where the substance exchange between blood and tissue is conducted, oxygen and nourishing supplements are provided, metabolites are carried away, and the stable internal environment within the tissues is maintained. Two important research areas in microcirculation are the fluidity and deformability of blood in capillaries. Patients with coronary heart disease not only have obstructions in general blood circulation, but also in microcirculation to a varying extent. For patients with coronary heart disease, there must be microcirculatory obstructions. However, because the three criteria for microcirculatory disturbance are difficult to quantify, whether microcirculation obstruction is an etiological factor for coronary heart disease is still to be verified.

However, the fact that lack of exercise can increase the morbidity and mortality of cardiovascular diseases is widely recognized among medical workers. Regular exercise coupled with other measures for the reduction of the risk factors for cardiovascular events is helpful for the

primary prevention and treatment of these events. It is also helpful for the bypass surgery for myocardial infarction and stroke, and for the rehabilitation after interventional surgery and the secondary prevention of the recurrence of cardiovascular events. The most direct result of exercise is that it speeds up blood flow and improves the microcirculation. It has been found in recent years that the half turnover rate and other indexes are decreased in most patients with a coronary heart disease, suggesting there is an obvious systemic disturbance in microcirculation .

In the past several years, many researchers have made special observations on and researched the effects of Dantonic™ on microcirculation in CHD patients. We set out an independent section particularly to summarize the progress in this area. Han Jingyan (2003) from Japan reported that Danshen was able to significantly improve mesenteric circulation obstruction caused by ischemia reperfusion in rats, and had an effect superior to that of SOD on eliminating leukocytes adhered to capillary endothelia. Chinese scholars have been using nail fold microcirculation as a window to observe the systemic microcirculation. Fu et al. [50] observed nail fold microcirculation in 92 patients with coronary heart disease and found that the number of capillary loops was reduced, cross-loop deformity was increased, the diameter of the pipe loops were reduced, blood flow was slowed, thread flow was reduced by 19.6 %, granular flow was increased by 80.4 %, significant aggregation of red blood cells occurred, and weighted scores were greatly increased. Their indicators were improved significantly after being treated with Dantonic™ (Table 11.32).

By graphing the microcirculation of the bulbar conjunctiva in patients with coronary heart disease and graphing the improvement of thrombus elasticity, Chen et al. (1996) analyzed the effects of

Table 11.32 The effect of Dantonic™ on nail fold microcirculation in CHD patients

Configuration	Observed item		Before treatment	After treatment
	Density of vessel loop (strip mm^2)		6.1	8.9*
	Number of vessel loop (strip mm^2)		3.25	2.00*
	Abnormality		0.92	0.32*
	Diameter of input brunch (mm)		3.02	4.40*
	Diameter of output brunch (mm)		5.00	6.02*
	Diameter of overhead coil of vessel loop (mm)		7.64	8.80*
	Length of vessel loop (mm)		147	205*
	Speed of Blood flow (mm/s)		675	1,011*
State of blood stream	Flow state	Thread flow (%)	19.6 %	71.7 %
		Granular flow (%)	80.4 %	28.3 %
	Red blood cell aggregation	No	0	4.2 %
		Light	4.2 %	65.3 %
		Moderate	65.3 %	30.4 %
		Serous	30.4 %	0 %
Weighted scores	State of vessel loop		1.34	0.98
	State of blood stream		2.63	0.91
	State around vessel loop		0.74	0.32
	Total aggregation value		4.71	2.21

*Compared with status before treatment $P < 0.01$

Note This table was created from data presented in the paper with the title of "observed effect of composite salviae dropping pill on coronary heart disease from change of microcirculation of nail fold" by Fu et al. [50]

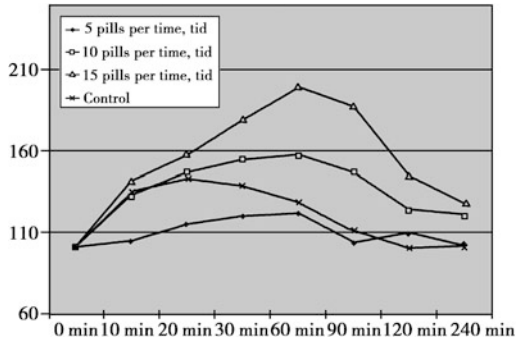

Fig. 11.6 The effect of Dantonic™ on the inner diameter of arterioles of bulbar conjunctiva microcirculation in CHD patients

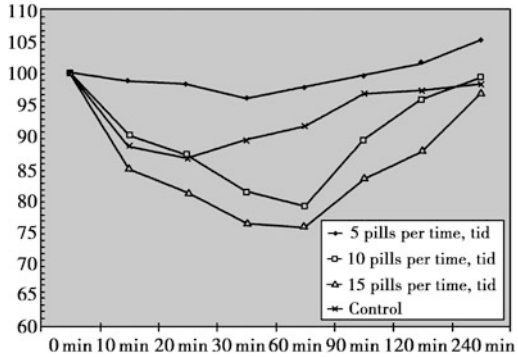

Fig. 11.7 The effect of Dantonic™ on the inner diameter of venula of bulbar conjunctiva microcirculation in CHD patients

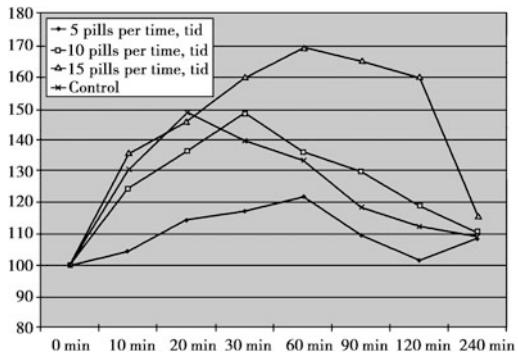

Fig. 11.8 The effect of Dantonic™ on blood flow speed in bulbar conjunctiva in CHD patients

Dantonic™ on microcirculation with a low dose (5 pills each time, three times a day), moderate dose (10 pills each time, three times a day) and high dose (15 pills each time, three times a day) of Dantonic™. They found that low dose Dantonic™ had no effect on the microcirculation. However, with increasing doses, there were increasing effects on the inner diameter of the arteriole in bulbar conjunctiva microcirculation (Fig. 11.6), inner diameter of venula (Fig. 11.7), speed of blood flow in arterioles (Fig. 11.8), and blood flow in arterioles. The onset of action was 10 min, culminating at 20–90 min, and was maintained for 240 min (Fig. 11.9).

Wang et al. [51] reported the effect of Dantonic™ on left ventricular hypertrophy (LVH) in CHD patients. The results showed that after treatment with Dantonic™, the turnover rate, turnover time, and detention time of microcirculation were markedly improved, compared with the values before the treatment. The control group was treated with ISDN and there were few changes after treatment (Table 11.33).

There have been 12 papers on the effect of Dantonic™ on microcirculation in patients with coronary heart disease, diabetes syndromes, and nephropathy syndromes. The results showed that Dantonic™ could significantly improve the microcirculation of the bulbar conjunctiva and nail folds in these patients (Table 11.34).

11.7 The Regulatory Effect of Dantonic™ on Autonomic Dysfunction

The fact that coronary heart disease is related to personality factors and psychological factors has been accepted by the academic world. Type A behavior pattern includes three features: a sense of time urgency, competitive impulses, and proneness to hostility. This type of personality has been regarded as one of the risk factors for coronary heart disease. It is believed at present that the reason that individuals with type A behavior patterns have a higher risk for coronary heart disease is due to hormones, such as increases in adrenaline and noradrenaline secretion. An increase in this type of hormone may cause fluctuations in blood pressure and

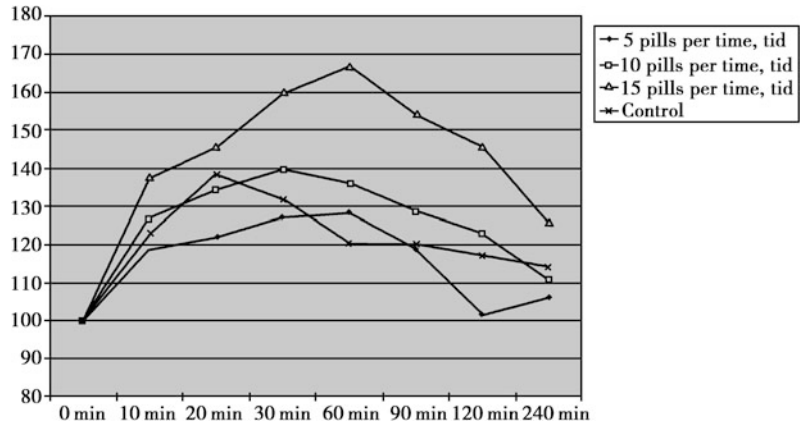

Fig. 11.9 The effect of Dantonic™

Table 11.33 The effect of Dantonic™ on microcirculation (means ± SEM)

Index	Dantonic™		ISDN	
	Before treatment	After treatment	Before treatment	After treatment
Microcirculation turnover rate (%)	0.067 ± 0.005	0.052 ± 0.004*	0.069 ± 0.006	0.065 ± 0.004
Microcirculation turnover time (s)	25.13 ± 1.31	16.58 ± 1.21*	26.12 ± 1.35	25.68 ± 1.42
Microcirculation detention time (s)	28.31 ± 1.16	22.15 ± 1.02*	28.54 ± 1.23	25.62 ± 1.31

*Compared with the status before the treatment $P < 0.01$

autonomic dysfunction, enhance stress responses, and accelerate the development of coronary heart disease: they not only lead to the increased risk of coronary heart disease attack, but also the increased risk of coronary heart disease death.

The occurrence and development of a coronary heart disease is closely related to emotions. Epidemiological and neurocardiological investigations have concluded that stimulation from emotions can severely affect the course and prognosis of coronary heart disease. The central nervous system excites the sympathetic nerves to promote the secretion of catecholamines, which can cause coronary arteries to be in a state of shrinkage and spasm. Friedman and Rosenman (1959) first described the type A behavior pattern and proposed its association with coronary artery disease. In 1979, the National Heart, Lung and Blood Institute in the United States found that coronary heart disease was correlated with type A behavior, and considered it an independent causing factor of coronary heart disease; it is more dangerous than risk factors such as age, increased systolic pressure, increased serum cholesterol or smoking. In fact, its danger is equivalent to the sum of the latter three risk factors. Since the type A behavior pattern is related to the nervous system and hormones, an important topic is of how to regulate the balance of the autonomic nerves to treat angina and reduce the risk of sudden death and arrhythmia. Unfortunately, almost no western medicines have been found to be effective as a therapy for this purpose.

Liu and Yang [58] randomly divided 54 CHD patients with angina pectoris into two groups: 30 patients in the Dantonic™ treatment group, and 23 patients in the ISDN control group. The course of treatment was 4 weeks. The autonomic nervous system equilibrium index was measured, and 24-hour continuous ECG recordings were used to calculate the standard deviation of normal R-R intervals (SDNN) which was used to represent heart rate variability (HRV). The results are shown in Tables 11.35 and 11.36.

Table 11.34 Reports on the effect of Dantonic™ on microcirculation

Author	Diagnosis	Cases	Medication	Result
Wang et al. [51]	LVH caused by coronary heart disease	56	10 pills each time, 3 times per day, for 3 months	The turnover rate, turnover time and detention time of microcirculation were improved significantly after the treatment with Dantonic™, compared with the status before the treatment ($P < 0.01$)
Zheng et al. (1999)	Nephropathy syndrome	6	10 pills each time, 3 times per day, sublingually at 10 min, 30 min, 1, 1.5, 2, 3.5 h	From 10 min to 3.5 h after drug administration, the ring finger nail fold microcirculation on the left hand was improved significantly with respect to the following endpoints: blood vessel readability of microcirculation of nail fold, vessel loop amount, diameter of input and output branch of vessel loop, ratio of input/output branch, diameter of overhead coil of vessel loop decreased, light or moderate effusion and flattened papilla altered, and white microembolus disappeared
Fu Xiaoliang et al. [50]	Coronary heart disease	92	10 pills each time, 3 times per day, for 3 months.	Dantonic™ treatment showed an obvious positive effect (improvement) on microcirculation endpoints: morphology of nail fold, condition of blood flow, and weighted scores
Zou et al. [52]	Senile diabetes	40	10 pills each time, 3 times per day, for 3 months	Dantonic™ treatment showed obvious improvement in senile diabetes with respect to the following endpoints: amount of vessel loops of microcirculation, diameter of output/input branch of vessel loop, diameter of overhead coil of vessel loop, length of vessel loop, amount of crossed and abnormality vessel loop, motility of blood vessel. The following endpoints were all improved significantly: amount of WBC, general integral, fluid state integral, integral of state around vessel loop, and general integral of microcirculation of nail fold after the treatment
Peng [53]	coronary heart disease	36	10 pills each time, 3 times per day, for 1 month	Dantonic™ treatment showed ameliorative effects on microcirculation dysfunction; general integral of the improvement in microcirculation of nail fold reached statistical significance
Liu et al. [54]	Diabetes	62	10 pills each time, 3 times per day	Dantonic™ treatment showed a better ameliorative effect on the microcirculation dysfunction caused by coronary heart disease than the control group (treated with diet and Dazmegrel)
Mou et al. [55]	hyperviscosity syndrome	56	10 pills each time, 3 times per day for 30 days	Integrals of four markers of microcirculation in Dantonic™ group improved clearly, showing the advantage of Dantonic™ over the control group (treated with Compound Danshen Tablet)

(continued)

Table 11.34 (continued)

Author	Diagnosis	Cases	Medication	Result
Chen et al. (1996)	coronary heart disease	90	5–15 pills each time, 3 times per day	Moderate and large dose of Dantonic™ could enlarge the diameter of microcirculation, and increase the speed of blood flow in the bulbar conjunctiva in patients with coronary heart disease
Yan et al. (1988)	LVH	34	10 pills each time, 3 times per day for 6–12 months	After receiving Dantonic™, the fluid state and fluid speed of microcirculation in the patients improved
Li et al. [56]	Coronary heart disease	187	10 pills each time, 3 times per day for 4 weeks.	After receiving Dantonic™, all aspects of the microcirculation of the nail fold improved clearly as follows: density of vessel loop (crossed, abnormal), diameter of overhead of vessel loop, length of vessel loop, speed and fluid state of blood, and weighted scores
Zou et al. [52]	Senile diabetes	140	10 pills each time, 3 times per day for 3 months	After Dantonic™ treatment, all aspects of nail fold microcirculation improved significantly as follows: amount of vessel loops, length of vessel loops, amount of crossed and abnormal vessel loops, the diameter of input and output brunch of vessel loops, motility of blood vessel; generalized integral, fluid state integral, integral of state around vessel loop, and general integral of microcirculation of nail fold upon a group of patients with diabetes and diabetic retinopathy
He and Rao [57])	coronary heart disease	30	10 pills each time, 3 times per day for l month	Compared with the state before the treatment, half turnover rate, half turnover time, and average detention time of microcirculation of nail fold were improved significantly ($P < 0.01$)

Table 11.35 The effect of Dantonic™ on the autonomic nervous system equilibrium index

Group	Cases	$Y > +0.56$		$Y < -0.56$	
		Before treatment	After treatment	Before treatment	After treatment
Dantonic™	30	13 (43.33 %)	7 (23.33 %)*	3 (10 %)	2 (6.67 %)
ISDN	23	10 (43.48 %)	9 (39.13 %)	3 (13.04 %)	1 (4.35 %)

*Compared with status before treatment, $P < 0.05$

Table 11.36 The effect of Dantonic™ on heart rate variability (HRV)

Groups	Number of Cases	Standard deviation of R-R interval		P
		Before treatment	After treatment	
Dantonic™	30	4.20 ± 0.19	4.41 ± 0.029	<0.01
ISDN	23	4.18 ± 0.20	4.23 ± 0.21	>0.05

It is shown in the tables that Dantonic™ has a significant effect on the equilibrium index of the autonomic nerve ($P < 0.05$) and is able to improve the HRV in CHD patients. It also demonstrated that Dantonic™ is able to inhibit adrenergic nerve abnormality, adjust the balance of the vegetative nerve and reduce the risk of sudden death and other accidents.

Jia et al. [48] studied 102 patients with typical exertional angina who were diagnosed according to the WHO standard. Patients were divided into the Dantonic™ group and the ISDN (control) group, and were treated for 8 weeks. The results showed that Dantonic™ is able to improve heart rate variability, inhibit adrenergic nerve abnormality, adjust the balance of the vegetative nerve, and oppose serious cardiac arrhythmias so as to reduce the risk of sudden death and other accidents.

11.8 The Protective Effect on Myocardial Cells

The studies on the mechanism for Dantonic™'s effect on myocardial cells have already entered the molecular level. Dantonic™ can clear obstructions in blood vessels and protect myocardial cells.

11.8.1 Effect of Dantonic™ on the Myocardial Energy System

Danshensu is an excellent radical scavenger; its effect on O^{2-}elimination is even better than that of SOD. Danshen can reduce the content of lipid peroxides, improve the fluidity of cell membranes, and even improve the fluidity of the mitochondrial inner membrane. Danshen can scavenge O^{2-}generated either by the xanthine oxidase-xanthine system or by PMA-induced white blood cells. Dantonic™ can maintain a stable level of myocardial adenylic acid.

Zhao et al. (2000) used the isolated Wistar rat heart perfusion technique to prepare a myocardial ischemia/reperfusion model. They monitored the content changes of high-energy phosphate compounds in the myocardial tissue with HPLC. The results are shown in Table 11.37.

In the Dantonic™ pre- or post-protective groups, AMP, ADP, ATP, and TAN were all higher than in the ischemic reperfusion group ($P < 0.01$) and the ISDN pre- and post-protective groups ($P < 0.01$). In addition, in both Dantonic™ groups, the ATP levels were within the normal range (there was no significant difference compared to normal control group, $P > 0.05$), which suggests that Dantonic™ is able to protect myocardial tissue from ischemic reperfusion injury.

Table 11.37 The content of high-energy phosphates in anoxia/reoxygenation myocardium in different groups (mg/100 g myocardial tissue (means ± SED)

Group	*n*	AMP	ADP	ATP	TAN
Control	7	36.30 ± 15.31	38.75 ± 15.10	43.62 ± 0.71	118.6 ± 12.02
Ischemic reperfusion	7	3.56 ± 1.29$^{\triangle}$	2.97 ± 1.07$^{\triangle}$	12.47 ± 3.76$^{\triangle}$	18.99 ± 4.88$^{\triangle}$
Dantonic™ pre-protection	7	8.77 ± 2.40$^{\triangle\square}$	9.21 ± 0.49$^{\triangle\square}$	42.07 ± 8.13$^{\square}$	60.05 ± 9.25$^{\square}$
Dantonic™ post-protection	7	8.10 ± 2.92$^{\triangle\square}$	8.45 ± 2.23$^{\triangle\square}$	30.84 ± 10.89$^{\square}$	47.39 ± 10.24$^{\square}$
ISDN pre-protection	7	5.76 ± 1.31$^{\triangle *}$	7.93 ± 1.20$^{\triangle *}$	16.21 ± 5.22$^{\triangle\square *}$	29.04 ± 7.40$^{\triangle\square *}$
ISDN post-protection	7	4.97 ± 1.47$^{\triangle\star}$	4.25 ± 1.38$^{\triangle\star}$	14.99 ± 2.13$^{\triangle\square\star}$	27.38 ± 7.79$^{\triangle\square\star}$

$^{\triangle}P < 0.01$ versus control group
$^{\square}P < 0.01$ versus I/Rgroup
$^{*}P < 0.01$ versus Dantonic™ pre-protection group
$^{\star}P < 0.01$ versus Dantonic™ post-protection group
TAN = AMP + ADP + ATP

Table 11.38 Comparison of myocardium necrosis among all groups (means ± SED)

Group	*N*	HW (g)	AAR (g)	IS/AAR (%)
Ischemic reperfusion (IR)	10	1.15 ± 0.12	0.41 ± 0.16	45 ± 19
Sham ischemic preconditioning (SIPC)	10	1.16 ± 0.12	0.39 ± 0.14	47 ± 17
Ischemic preconditioning (IPC)	10	1.14 ± 0.13	0.33 ± 0.13	30 ± 11
Drug + IPC	10	1.09 ± 0.13	0.35 ± 0.13	20 ± 9**
Drug + IR	9	1.10 ± 0.16	0.33 ± 0.16	35 ± 11
SIPC in late stage (SWOP)	10	1.14 ± 0.09	0.28 ± 0.09	45 ± 13
IPC/SWOP	10	1.09 ± 0.13	0.31 ± 0.15	41 ± 14
Drug + IPC/SWOP	10	1.17 ± 0.23	0.32 ± 0.18	29 ± 13

Compared with SIPC, $^{**}P < 0.01$

Although AMP and ADP levels in the ISDN preprotective group were higher than in the ischemic reperfusion group ($P < 0.01$), the AMP, ADP, ATP, and TAN levels in the ISDN pre- and post-protective groups were lower than in the normal group. The contents of myocardial energy-rich phosphate and total adenylic acid in the Dantonic™ treatment groups were significantly higher than those in the ISDN groups, suggesting that Dantonic™ has a better capability of improving the energy reserves in ischemic myocardial tissue than does ISDN.

Table 11.39 Changes in myocardial enzymes in different groups (means ± SED)

Group	*N*	LDH (u/L)
Control	13	888.54 ± 294.22
IR	17	2,422.18 ± 656.06**
SIPC	18	2,170.06 ± 1,002.45**
IPC	15	2,005.94 ± 818.92
DIPC	16	1,467.93 ± 807.06
DIR	16	1,746.06 ± 1094.37
SIPC/SWOP	15	2,345.94 ± 759.47**
IPC/SWOP	16	2,137.06 ± 817.70**
DIPC/SWOP	15	1,291.44 ± 462.62▲

**Compared with the control group, $P < 0.01$
▲Compared with SIPC in late stage group, $P < 0.05$

11.8.2 Effect of Dantonic™ on Myocardial Ischemic Preconditioning

Zhang et al. (2002) prepared a classical ischemic preconditioning rat model (ischemia for 5 min, reperfusion for 5 min, repeat 3 times as an ischemic preconditioning model; ischemia for 30 min, reperfusion for 2 h as an ischemia reperfusion model). They used the necrotic tissue weight of the cardiac muscle divided by the ischemic weight of the cardiac muscle (IS/AAR), the amount of myocardium enzyme, arrhythmia frequency, histomorphology and free radicals as evaluation indicators, observing the protective effect of Dantonic™ pretreatment simulation and enhanced ischemic preconditioning (ICP) on myocardial ischemia. The influence of Dantonic™ on the expression of the signal transduction substance protein kinase C (PKC) was also observed. The results showed that after pretreatment with Dantonic™, IS/AAR was reduced by 10–17 %, compared with the reperfusion model and IPC model. The LDH release was also reduced. The results are shown in Tables 11.38 and 11.39.

Using electron microscopy, it was found that abnormalities (including myocardial fiber atrophy and disturbance, reduction of mitochondrion density, vacuolation, loss of ribose, endothelial cell swelling, vessel contraction, platelet aggregation in some vessels, inflammatory cell adherence and obstruction, red blood cells and fragmented red blood cells around capillaries, and collagen proliferation around vessels and vessel fibrinogen) were separated out in the

Table 11.40 Changes in myocardial SOD and MDA in different groups (means ± SED)

Group	MDA (u/L)	SOD (u/L)
Control	4.21 ± 0.72	285.04 ± 84.49
IR	6.89 ± 2.13*	215.56 ± 85.47
SIPC	7.95 ± 2.23**	222.51 ± 56.74
IPC	5.42 ± 1.40	277.68 ± 103.42
DIPC	4.62 ± 0.86▲▲	336.74 ± 85.32
DIR	5.88 ± 1.30	302.28 ± 146.47
SIPC/SWOP	6.51 ± 1.29	211.48 ± 60.67
IPC/SWOP	5.41 ± 0.94	242.15 ± 77.59
DIPC/SWOP	4.87 ± 0.74	283.75 ± 105.10

**Compared with the control group, $P < 0.01$
▲Compared with SIPC and SIPC in late stage groups, $P < 0.05$

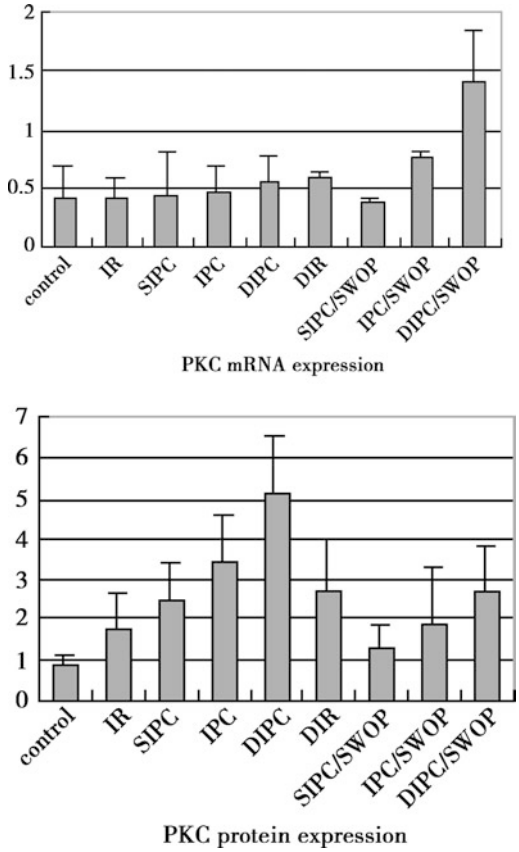

Fig. 11.10 PKC expression in different treatment groups

ischemic reperfusion group and in the early and late stages of the sham ischemic preconditioning group. The early stage of IPC can also manifest the injuries described above in different degrees, but the reduction of myocardial cells has been found to be smaller. The later stage is more serious than the early stage. In the DIR group and the DIPC (in early and late stage) group, the myocardial cells were swollen and partial blood plasma effusion could still be observed.

After Dantonic™ pretreatment, MDA was reduced in the blood plasma and SOD activity was increased. The expression of PKC mRNA and protein in myocardial cells in the early and later IPC groups and the reperfusion group were significantly increased, $P < 0.05$. The results are shown in Table 11.40 and Fig. 11.10.

It was found that Dantonic™ was able to generally mimic and enhance the effect of IPC. Compared with early stage IPC, Dantonic™ treatment was not better than IPC, but if compared with late stage IPC, the effect of Dantonic™ treatment was better. The primary mechanism for the action might be the enhancement of SOD activity or reinforcement of PKC expression.

The four pathophysiological changes in the process of myocardial ischemic reperfusion injury include reperfusion arrhythmia, myocardium contraction incoordination, myocardium cell death, and microcirculatory disturbance.

11.8.3 Inhibition of Myocardium Cell Apoptosis by Dantonic™

Ischemic reperfusion can cause myocardial cell death, including necrosis and apoptosis. Apoptosis differs from necrosis in that it is an initiated, energy-consuming, and programmed cell death. In the early stage of ischemia, most cell deaths are due to apoptosis, but in the late stage, most are due to necrosis. Many pathological factors can cause the activation of endonucleases which degrade DNA into 180–200 bp fragments, or oligonucleotide fragments. The ladder printing can be detected by DNA gel electrophoresis. The

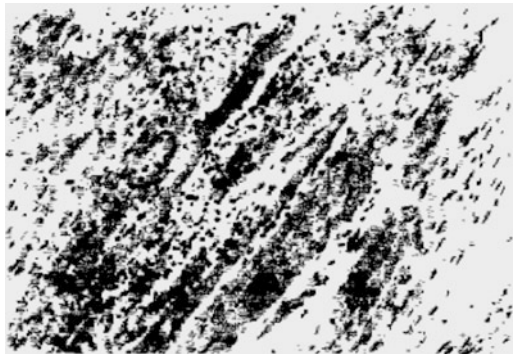

Fig. 11.11 Inflammatory cell infiltration around the infarcted area

major morphological features of apoptosis include cell shrinkage, cell membrane budding, chromatin clustering, and formation of apoptotic bodies.

The process of apoptosis is controlled and regulated by several genes. In mammalian cells, the protein product of apoptotic stimulating gene *Fas* is a cell membrane protein, and it is also a tumor necrosis factor. The apoptosis suppressor gene (*Bcl*-2) blocks *Fas*-induced apoptosis. The two genes are most closely related to apoptosis. Zhao et al. [59] prepared an ischemic reperfusion model with an obstruction of the left coronary artery in rats, and observed the apoptosis and the expression of *Fas* and *Bcl-2*. The results showed that Dantonic™ could significantly downregulate the expression of *Fas* and slightly up-regulate the expression of *Bcl-2*, so as to inhibit the apoptosis of myocardial cells induced by ischemic

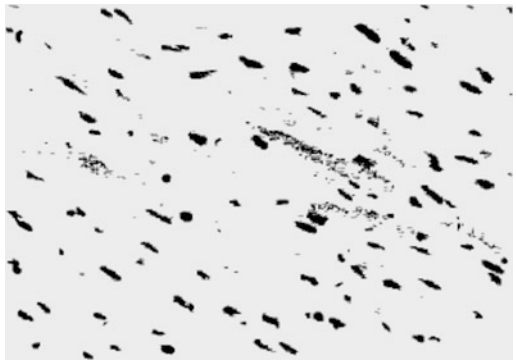

Fig. 11.12 The apoptotic cells in the border between infarcted and noninfarcted areas

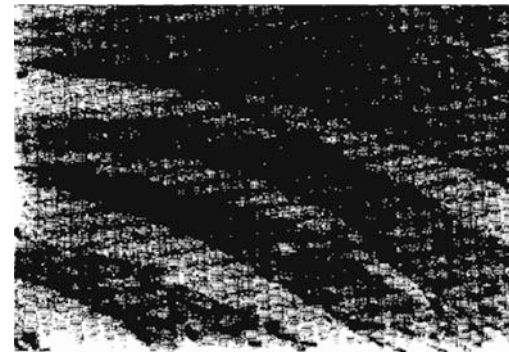

Fig. 11.13 Bcl-2 protein positive cells located in the border between the infarcted and noninfarcted areas

Fig. 11.14 Fas protein positive cells located in the border between the infarcted and noninfarcted area

reperfusion injury. Moreover, the regulatory effect of Dantonic™ was dose dependent, which means that Dantonic™ has an effect on the expression of apoptosis-related genes when myocardium cell apoptosis occurs.

The histopathological changes in the myocardium can be observed under a light microscope after HE staining. In myocardial tissue after ischemic reperfusion, the cells had obvious swelling and were blurry, local necrosis foci were numerous and occasionally merged together, and the infarcted area was surrounded by inflammatory cell infiltration (Fig. 11.11). After treatment with Dantonic™, the degree of cellular swelling and the size of the infarct area were reduced; moreover, a higher dose of Dantonic™ could produce a more significant effect. As shown in Figs. 11.11, 11.12, 11.13, and 11.14, apoptotic cells and cells with *Fas* and *Bcl-2*

Table 11.41 Effect of Dantonic™ on *Fas/Fas*L expression in neonatal mice

Group	Fas protein PEI (%)		FasL protein PEI (%)	
	Untreated	Dantonic™ treated	Untreated	Dantonic™ treated
Control	2.59	2.61	2.27	2.26
Hypoxia for 4.5 h	18.01*	9.62*	19.67*	10.74**
Reperfusion for 4 h	19.02*	10.00*	20.71*	10.69**

*Compared with the control group, $P < 0.05$
**Compared with untreated group, $P < 0.05$

positive expression were mainly located in the border between infarcted and noninfarcted areas, and only a few of these cells were located inside the infarcted areas.

Liu et al. [60] found that after myocardial ischemia and reperfusion, older rats had larger area of myocardial infarction and more apoptotic cells than did the younger rats, suggesting that the adaptability, reactivity, and tolerance of older rats to the harmful stimulations were weakened, resulting in more apoptotic cells. They also found that Dantonic™ had inhibitory effects on apoptosis, and the effect was stronger in older rats than in younger rats, which suggested that Dantonic™ might be more suitable for older patients.

Wang et al. [61] found that the expression of *Fas* and *Fas*L was upregulated in both hypoxia and reoxygenation periods, which demonstrated the existence of apoptosis during ischemic reperfusion. Dantonic™ could downregulate the expression of *Fas/Fas*L (Table 11.41).

11.8.4 Calcium-Antagonistic Effect of Dantonic™

Myocardial ischemia results in intracellular calcium overload, which is the major cause of cell death, because cells generate free radicals after hypoxia, causing a decrease in cell membrane stability and leading to injury. In addition, intracellular hydrogen ions increase during hypoxia, which leads to the increase in intracellular sodium ions via the hydrogen-sodium exchange mechanism, and via the sodium-calcium exchange mechanism, a large amount of extracellular calcium flows into cells. Meanwhile, the stores of intracellular calcium, the sarcoplasmic reticulum, and Golgi complex, also transfer calcium into the cytoplasm. All of these result in the excessive intracellular accumulation and overload of calcium, which damages or kills the cells.

Li et al. [17] observed the change of intracellular calcium ion fluorescence intensity with the administration of Dantonic™ under the

Table 11.42 The effect of Dantonic™ on calcium ion fluorescence intensity under hypoxia and reoxygenation condition (means ± SED)

Group	Number of cells	Average intensity of Ca^{++}
Normal control (I)	12	1,005.75 ± 264.25
Hypoxia for 10 min (II)	23	1,509.43 ± 508.58*
Hypoxia for l0 min + Dantonic™ (III)	9	1,217.78 ± 312.07#
Hypoxia for l0 min + reoxygenation for l0 min (IV)	9	1,617.60 ± 477.53
Hypoxia for l0 min + reoxygenation for l0 min + Dantonic™ (V)	11	1,567.91 ± 577.61△

*$P < 0.05$ versus.control
△$P < 0.05$ versus group IV
#$P < 0.05$ versus group II

condition of myocardium hypoxia and reoxygenation (Table 11.42). The hypoxia control group showed significantly enhanced fluorescence intensity ($P < 0.05$), and the treatment with Dantonic™ reduced it to the normal level, which suggests that Dantonic™ can act as a calcium antagonist.

Liang et al. [62] randomly divided patients with acute myocardial infarction into two groups: patients in the control group were treated with conventional western medicine, and patients in the treatment group were treated with Dantonic™ in addition to the conventional western medicine. The content of serum troponin T (TnT) was determined. The results showed that in the Dantonic™ group, serum TnT significantly increased 3–6 h after onset ($P < 0.05$) and reached the maximum level 47 h after onset; the increase lasted about 9 days and returned to a normal level 11 days after onset. In the conventional western medicine group, serum TnT significantly increased 4–6 h after onset and reached the maximum level 48 h after the onset; the increase lasted 10 days and returned to normal level about 12 days after onset. The peak value in the Dantonic™ group was obviously lower than that in the western medicine group ($P < 0.01$). The lasting time of increased TnT and the time required to return to a normal level in the Dantonic™ group were obviously shorter than those in the control group ($P < 0.05$).

Studies have shown that in cardiac myocytes, TnT mainly exists in the conjugation form and only small portion exists in a free state in the cytoplasm. When myocardial cells are slightly damaged from ischemia or hypoxia, free TnT enters the blood through the damaged cell membrane first. When cardiac myocytes undergo denaturation and necrosis, which results in the activation of proteases, conjugated TnT is degraded and released in a large quantity. There are reports showing that serum TnT could be detected in 50 % of patients 3 h after a myocardial infarction. Recently, it has been proposed that TnT is the most sensitive serum marker for myocardium injury. Dantonic™ can decrease the peak value of TnT and significantly reduce the duration of increased TnT, as well as reduce the time required to return to a normal level, which suggests that Dantonic™, if combined with routine western medicines, has a protective effect on myocardial cells in patients with acute myocardial infarction.

References

1. Zou H, Pan W, Fan Y. J Chin Mod Inter Med. 2006;3 (1):68.
2. Lin C, Shi T, Wang M et al. The experimental study of the influence of composite salviae dropping pill on hyperlipimia and atherosclerosis in rabits. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 77.
3. Shi Y, Li J. Chin J Cardiovasc Rehabil Med. 2002;11 (3):226.
4. Huang W, Zeng Z, Ruixing Yin, et al. Guangxi Med J. 2003;25(11):2095.
5. Cheng C, Tan Y, Tan S, et al. Chin J Integr Tradit West Med Intensive Crit Care. 2003;10(3):170.
6. Zongpei X, Boli Z, Jizheng Z, et al. J Hubei Coll Tradit Chin Med. 2003;5(3):15.
7. Chen J, Zhao Y, Cui D, et al. Chin J Clin Rehabil. 2005;9(19):208.
8. Zhang X. Chongqing Med J. 2005;34(11):1755.
9. Cao T, Duan Y, Yang B. Chin J Ultrasound Med. l999;15(6):457.
10. Mack WT, et al. Stroke. 1993;24:1779.
11. Wendelhag I, et al. Ateriosclerosis. 1995;117:225.
12. Han Q, Chai X, Lv J. Chin J Integr Tradit Western Med. 2000;20(7):514.
13. Rongtang Li, Jianfu Hu. Chin J Gerontol. 2003;23 (7):424.
14. Qingfu Yang, Cailing Li, Jian Chen, et al. J Xinxiang Med Coll. 2003;20(2):127–8.
15. Han J-Y, Akiba Y, Suzuki H, et al. Symp. Life Sci. Med. Tokyo. 2005;13:247.
16. Li J, Lin J, Li Z, et al. Study J Tradit Chin Med. 2002;20(4):496.
17. Li Y, Liu F, Sun J, et al. Chin J Hemorheology. 2001;11(2):100.
18. Ma F, Deng L. Research on effect of anti-platelet gathering by fliying. In: 96th national symposium on composite salviae medicament form. 1996; p. 21.
19. Dai X, Shao J. Chin J Hemorheology. 2002;12 (4):328.
20. Bai J, Wang N. J Shanxi Med. 1997;26(4):307.
21. Ma W, Yang J, Gong C, et al. Pharm J Chin People's Liberation Army. 2001;17(1):47.
22. Zhao S, Yin X. Mod J Integr Tradit Chin Western Med. 2001;10(9):799.
23. Wei J. J Chin Microcirc. 2001;5(2):14B.
24. Gou L, Zhao Q, Liu X. J North Sichuan Med Coll. 2001;16(3):56.

25. Fang Y. Zhejiang J Integr Tradit Chin Western Med. 2001;11(11):686.
26. Li C, Long J. Chin Heart J. 2002;14(2):176.
27. Hu X, Wang L, Xiong F. The effect of composite salviae dropping pill in the treatment of coronary heart disease and the experimental study of composite salviae dropping pill's impact on blood rheology. In: 96th national symposium on composite salviae medicament form. 1996; p. 48.
28. Wang Y. Clin J Anhui Tradit Chin Med. 2001;13 (4):250.
29. Ye Q, Li Z, Huang T, et al. Appl J Gen Pract. 2004;2 (1):30.
30. Yang Q, Liu D, Chen D, et al. Clin J Med Officers. 2000;28(2):9.
31. Huang H, Dong Z, Xu H, et al. J Pract Stomatology. 2002;18(2):140.
32. Fan W, Wang H, Xu C, et al. Chin J Tradit West Med. 2003;4(10):1463.
33. Lu J. Chin J Integr Tradit West Med. 2000;20(6):415.
34. Wang S, Wang L, Sun Y. Chin J Cardiovasology. 2003;8(5):354.
35. Zhou X, Jiang R, Qian J, et al. Chin J Pract Pediatr. 2001;16(1):14.
36. Zhang D. Henan Med Inf. 2001;9(9):11.
37. Li Z. Clinical observation of adjunct treatment of unstable angina pectoris with composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae)' 99. 1999; p. 96.
38. Chen Y. Research on the pharmacological action of composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 82.
39. Wang D, Wang X, Xu J. Chin J Pathophysiol. 2006;22(5):933.
40. Xu J, Wang X, Wang D. Chin J Pathophysiol. 2006;22(5):929.
41. Liu H, Hu Y, Chen J. Tianjin Pharm. 2003;15(2):39.
42. Feng P, Tai N, Tan Y, et al. Chin J Integr Tradit Med. 1999;19(5):286.
43. Chen Y, Li Y, Hu Y. People Mil Surg. 1999;42(8):461.
44. Qu Z, Qu J, Yang C, et al. Chin Crit Care Med. l998;10(10):599.
45. Feng H. The change in blood rheology of patients with cardiovascular disease treated with composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 50.
46. Ji H, Yao S, Wei Y. China J Tradit Chin Med Pharm. 1999;14(5):68.
47. Bi C, Wang S. Observation of the effect of composite salviae dropping pill in the treatment of 60 patients with chronic pulmonary heart disease. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 70.
48. Jia L, Ding X, Wang C. Clin Med J China. 1999;6 (1):21.
49. Liu Z. Analysis of the effect of composite salviae dropping pill in the treatment of angina of the unstable type. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 61.
50. Fu X, Li Q, Feng J. Observation of the effect of composite salviae dropping pill in treating coronary heart disease from the change of microcirculation of nail fold. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; 74.
51. Wang X, Huang H, Jiao L, et al. The reversal effect of composite salviae dropping pill on LVH of coronary heart disease. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 52.
52. Zou J, Wu P, Xu M, et al. Chin Med Factory Mine. 1999;27(5):357.
53. Peng Y. Observation of the effect of composite salviae dropping pill on improving microcirculation obstruction of coronary heart disease. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 90.
54. Liu G, Yu R, Ma X, et al. Effect of composite salviae dropping pill on biood lipid, hemorrheology, and microcirculation patients with diabetes. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 107.
55. Mu N, Zuo Z, Song C, et al. Effect of composite salviae dropping pill on hemorrheoligy and the microcirculation of patients with blood hyperviscosity syndrome. In: 99th national workshop the modernization of traditional Chinese medicine (composite salviae). 1999; p. 107.
56. Li F, Zhang Z, Ma J, et al. Clinial observation of composite salviae dropping pill in the treatment of coronary heart disease. In: 96 national symposium on composite salviae medicament form. 1996;p. 76.
57. He B, Rao S. Chin Tradit Herbal Drugs. 2000;31(2):121.
58. Liu M, Yang Z. Regulating function of composite salviae dropping pill on the autonomic nervous system of patients with coronary heart disease and angina caused by stagnation of qi and blood stasis. In: 96th national symposium on composite salviae medicament form. 1996; p. 27.
59. Zhao M, Wang J, Wei J, et al. Chin J Clin Pharmacol. 1999;15(4):288.
60. Liu L, Zhao M, Gao C. The intervention effect of composite salviae dropping pill on cardiac cell apoptosis caused by ischemia reperfusion in senile rats. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 18.
61. Wang X. Cell and molecule mechanism of composite salviae dropping pill in cardiac protection. In: 96th national symposium on composite salviae medicament form. l996; p. 1.
62. Liang T, Zhang C, Zhao X. Liaoning J Tradit Chin Med. 2002;29(3):163.

The Effect of Dantonic™ on Diabetes and Its Serious Complications

12

Guoguang Zhu, Renshu Li, Ying Zhao and Ruizhi Luo

With improvements in living standards and the spread of Western lifestyle, the prevalence of diabetes has been growing. Epidemiological studies have proven that type 2 diabetes has increased year by year, which is also related to the aging of the population. Therefore, diabetes has become the third largest noncommunicable disease, following cardiovascular diseases and cancer. In 1998, according to the World Health Report of the WHO, it was estimated that there were more than 143 million diabetes patients in the world, and the figure was expected to increase to 300 million by 2025. In recent years, the conception of the metabolic syndrome in the prevention and treatment of coronary heart disease has integrated a variety of risk factors, including the increase of fasting blood glucose, insulin resistance, and impaired glucose tolerance, which are closely related to the glucose metabolism of the body. Diabetes is also one of the most important risk factors for coronary heart disease, and coronary heart disease is the most common complication of diabetes.

According to a WHO report, 26–35 % of diabetics have coronary heart disease, and the number is even higher among women and the elderly. The annual incidence rate was 1–3 %, which was 3 times higher than that of nondiabetics. Diabetic patients are normally complicated with coronary heart disease at a younger age, and the mortality rate of coronary heart disease in patients with diabetes is higher than in nondiabetic patients. It was reported that after adjusting the risk factors for coronary heart disease, the risk of male diabetic patients dying from coronary heart disease was 1.9 times higher than that of nondiabetes, and it was 3.3 times that for female patients.

Therefore, the prevention and the treatment of cardiovascular and cerebrovascular diseases cannot be separated from the prevention and treatment of diabetes. Over nearly 14 years of clinical application, the excellent therapeutic effect of Dantonic™ on the treatment of coronary heart diseases and angina pectoris has become well-known. Meanwhile, many clinical workers have objectively observed the preventive effect of Dantonic™ on microcirculation in diabetes, blood rheology, and improvement of hyperliposis, as well as diabetic retinopathy (DR), diabetic nephropathy (DN) and diabetic neuropathy, to which wide attention was paid by a majority of professional medical diabetes workers. Nowadays, there is a saying for diabetes treatment: "The treatment for coronary heart disease needs Dantonic™, the prevention of diabetes also needs Dantonic™". In this chapter, we review the literature in this area.

G. Zhu (✉) · R. Li · Y. Zhao · R. Luo
The European Federation of Pharmaceutical Society, Stockholm, Sweden
e-mail: ggz68111@yahoo.com

X. Yan (ed.), *Dan Shen (Salvia miltiorrhiza) in Medicine*,
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12.1 Diabetic Retinopathy

The greatest harm of diabetes to humans is arteriosclerosis and microvascular diseases, and the various chronic complications developed on these diseases, such as diabetic encephalopathy, diabetic extremital gangrene, diabetic cerebrovascular diseases, DN, DR, and neuropathy, etc. Most complications occur after diabetes has developed to a certain stage. If there are no preventive measures, these complications can usually cause irreversible and progressive development. Therefore, with population growth and increasing life expectancy, the number of diabetes patients is growing. Diabetes is the most common disease in the middle-aged and elderly, particularly within groups of people with obesity and a family history of diabetes; these are the high-risk groups. The etiology of diabetes is complex and diverse; the development of the disease forms the syndrome of chronic hyperglycemia. The problem of how to protect the microvessels in patients with diabetes and chronic hyperglycemic syndrome must be resolved urgently.

In China, the morbidity of diabetes in 1980s was 0.6 %, according to a sampling survey. It rose to 2 % in the early 1990s; among them, 50 % had DR, and of the DR patients, 6 % were of the proliferative type. In 1980, Beijing Union Medical College Hospital surveyed 662 patients with diabetes, and the morbidity of DR was 51.3 %. In 1985, Luo Chengren of Sichuan Province surveyed 411 patients with diabetes, and the morbidity of DR was 44 %. In 1986, Xhou Peirong of Beijing studied juvenile and youth diabetes, and the morbidity of DR was 28 %, of which 17 % had a history of diabetes for less than 4 years, and 62.5 % had a history of diabetes for more than 10 years.

Since 1922, when insulin began to be used as an effective hypoglycemic agent, patients gained more effective control over their diabetic conditions, their state of health improved, their life expectancy increased, and their resistance increased. However, the morbidity of DR did not decline; instead, it soared. Before the application of insulin in diabetes treatment, Wagener (1921) reported that the DR morbidity rate was 8.3 %, while it was 17.7 % in 1934 and 30.6 % in 1945. Therefore, diabetic patients, under the condition of well-controlled blood sugar, should more actively prevent the occurrence of DR.

DR patients, especially early stage DR patients whose macula lutea in the fundus of the eye is unaffected, have normal vision and no subjective symptoms. Sometimes they may experience decreased vision or floaters. The pathological changes of DR are microangiopathy with the characteristics of exudation, obstruction, and hyperplasia, which is shown as enhanced platelet aggregation, reduced fibrinolytic activity, decreased deformation of red blood cells, and increased whole blood viscosity, as well as vascular endothelial injury and capillary occlusion, etc. Fundus changes are divided into two types, namely, nonproliferative and simple proliferative.

(1) Nonproliferative DR: Von Jaeger first reported the special changes that appeared in the fundus of patients with diabetes in l856. In 1857, Leber considered this to be diabetic retinitis. Many scholars made a long-term study on the most serious diabetes complications and found that it was not caused by inflammation, but by increased blood sugar over a long period, with the metabolic disorders leading to systemic microcirculatory disturbance. Because the retinal blood vessels are the most vulnerable to injury, a majority of scholars believe the disease should be called DR. At present, it has been generally acknowledged as one of the factors that lead to blindness in diabetes patients. It has been proven by epidemiological studies that about 75 % of diabetic patients who have not paid attention to controlling their blood sugar will be attacked by DR within 15 years. There are about 40 million people with diabetes in China, and the incidence of DR was 30–60 % according to statistics, that is, between 12 and 24 million people. In the United States, the number of diabetic blindness cases is 25 times greater than that of nondiabetic blindness. Klein et al. (1984) reported that 3 % of patients in the adult diabetes group

had moderate visual impairment, and 1.6 % were legally blind. The disease lesions, such as microvascular bleeding spots, exudation, and sclerosis of retinal vessels, are mainly in the macular area and surroundings of the posterior pole. Diabetic maculopathy is the main cause of central vision loss. In the macula lutea area of the fundus, there are arteriovenous changes in the retina, microcirculation obstructions, ischemia, and diffuse edema; there are large wax-like plaques and cholesterol crystals. Central vision loss cannot be recovered.

(2) Proliferative DR: lesions are in the optic disc and retinal vascular area. The disc has a large area of neovascularization and forms the so-called florid retinopathy; hemorrhage resulting in a sharp decline in vision, and there is no red light reflection in the fundus. The disease can also lead to severe retinal hemorrhage and vitreous hemorrhage. Fong et al. concluded, based on a 5-year follow up study, that the severe loss of vision was firstly due to subretinal hemorrhage and preretinal hemorrhage; secondly to macular edema and pigment change; and thirdly to amotio retinae and neovascular glaucoma. Therefore, proliferative DR is a serious complication of diabetic disease. Meanwhile, the occurrence of eye complications often indicates severity of lesions in systemic blood vessels, the nervous system, and the liver.

12.2 Effect of Dantonic™ on DR

12.2.1 Effect of Dantonic™ on Improving Visual Acuity and Mean Defect

The basic pathological change of DR (DR) is retinal capillary damage. Currently, the treatment for DR is mainly hypoglycemic and diet control, which can prevent DR fundamentally. The treatment also includes Doxium (2,5-hydroxy acid calcium), which has the effect of reducing blood viscosity and improving microcirculation. It is believed at present that this drug has a certain effect on nonproliferative DR. It was also reported that erythropoietin was able to absorb the hardy exudation of retinopathy, reduce macular dropsy, and improve vision. Over the past 20 years, blue–green argon laser treatment has been used to treat preproliferative and proliferative DR around the world; people have also used krypton-red and krypton-yellow lasers to treat macular degeneration. Some scholars tried partial hypophysectomy on some patients to relieve the vascular disease of retinopathy based on the discovery of the relationship between DR and growth hormone. In sum, there are plenty of DR treatments, but there has not been a method with an especially good effect. Dantonic™ has the effect of increasing the anticoagulant and fibrinolytic activity of the body, is an anticoagulant, inhibits thrombosis, platelet activation and aggregation, lowers blood viscosity; improves microcirculation, blocks the production of hydroxyl radicals, and prevents lipid oxidation and the adhesion of cells to the vascular wall. The occurrence of DR is mainly due to increased blood viscosity, damaged fibrinolytic functions, decreased free radical scavenging function, decreased red blood cell deformability, increased red blood cell aggregation, slowed blood flow, and obstructed microcirculation which leads to clinical microarteriopathy of the retina, such as retinal ischemia and hypoxia, hemorrhage and exudation, etc. It seems that Dantonic™ could act upon each phase of DR, which is why it has been used to treat DR since the end of the 1990s (Table 12.1).

So far, more and more clinical workers have found that Dantonic™ has a good effect on the prevention and treatment of DR, and that it could significantly improve the visual field index of early DR disease. Sun Jianghong et al. (2007) reported that 107 patients with I–III stage DR were divided into two groups: 50 cases were treated with Dantonic™; 57 cases were treated with Vit B, Vit C, Vit E, and carnine tablets, for 6 months. Visual acuity (0.71 ± 0.16) was significantly improved in the Dantonic™ treatment group compared with the status before treatment (0.52 ± 0.12) ($P < 0.01$).

Table 12.1 A summary of the clinical application of Dantonic™ in the treatment of DR

Author (Year)	Trial design	Diagnosis criteria	Medication (cases)	Results
Wang [2]	Randomized and controlled	Chinese ophthalmology association, 1985; American Diabetes Association, 1997	Treatment group (28): Dantonic™ + Calcium dobesilate 500 mg × 4 months Control group (16), Calcium dobesilate 500 mg × 4 months	Total effective rate was 85.7 %, which was significantly higher than that in the control group (62.5 %) ($P < 0.05$); there was no difference in 24-h urinary albumin excretion rate (24HUAER). 24HUAER of the treatment group (104.6 ± 18.5 mg/24 h) was significantly lower compared with the status before the treatment (156.8 ± 28.7 mg/24 h) ($P < 0.01$). In the control group, there was no statistical difference between the status before the treatment 154.1 ± 30.1 mg/24 h) and after the treatment (134.6 ± 17.9 mg/24 h) ($P > 0.05$) *Note* The patients in both groups took adjuvant drug, Venoruton Tablets, Vit C, Vit E, Vit B6, Rutosids, etc.
Deng [1]	Nonrandomized	Type 2 diabetes, third Chinese national conference of ophthalmology, 1984	Dantonic™ group (l0): 3 months Calcium dobesilate group (l0): 3 months	Vision: there was no significant difference in both groups before and after treatment ($P > 0.05$) Mean defect of visual field: it was significantly lower compared with the status before the treatment in Dantonic™ group ($P < 0.05$); it was significantly lower compared with status before treatment for right eyes of Calcium dobesilate group ($P < 0.05$). Number of microaneurysms was significantly reduced compared with the status before the treatment in both groups ($P < 0.05$); there was no difference between the two groups ($P > 0.05$)

(continued)

Table 12.1 (continued)

Author (Year)	Trial design	Diagnosis criteria	Medication (cases)	Results
Bao [3]	Randomized and controlled	WHO diagnosis criteria	Treatment group (37): Dantonic™, l5 pills, tid. Control group (30) Calcium dobesilate, 500 mg, tid	Improvement in microangiopathy, small bleeding points and bleeding spots in the treatment group were better than those in the control group ($P < 0.05$), while yellow exudation and macular edema in neither groups were improved. The values of low shear, high shear and erythrocyte aggregation of hemorheology were significantly lower than those of the control group ($P < 0.05$)
Sun Jianghong et al. (2007)	Non-randomized	The third Chinese conference of ophthalmology, 1985	Treatment group (50): Dantonic™ l0 pills, tid + Vit Bl, Vit C, for 6 months; control group (57): × 6 months	In the treatment group, vision was significantly improved after the treatment ($P < 0.05$). There was no difference before and after treatment in the control group Mean defect of visual field: the gray value of MD in the treatment group was significantly improved compared with the status before the treatment ($P < 0.01$). While there was no significant difference before and after treatment in the control group. MD of the treatment group was greatly superior to that of the control group after the treatment ($P < 0.01$) Changes in fundus: the number of microaneurysms in the treatment group was significantly reduced compared with the status before treatment ($P < 0.05$); number of bleeding spots were significantly reduced ($P < 0.O5$); but there was no significant difference in these indicators in the control group. The treatment group had significantly fewere microaneurysms ($P < 0.05$) and bleeding spots ($P < 0.01$) than the control group

(continued)

Table 12.1 (continued)

Author (Year)	Trial design	Diagnosis criteria	Medication (cases)	Results
Liu Junhai et al. (2007)	Randomized and controlled	WHO Diagnosis Criteria, 1999	Group A: Dantonic™ l0 pills, tid × 4 weeks Group B: Lycii and Chrysanthemi and Rehmanniae Bolus, 10 pills × 4 weeks	The total effective rate in Group A was 83.3 %, which was significantly higher than that of the control group (50 %). The treatment of promoting blood circulation and removing blood stasis on background diabetic retinopathy was superior to that of Lycii and Chrysanthemi and Rehmanniae Bolus
Qi Chaoxiu et al. (2007)	Randomized and controlled	The third Chinese conference of ophthalmology, 1985	Treatment group with Dantonic™ (43 eyes), 10 pills, tid × 3 months Control group (35 eyes): Vit Bl, Rutosids, Vit C	Patients' vision in Dantonic™ group was improved compared with the status before treatment. There was a significant difference compared with the control group ($P < 0.05$); Small ecchymosis in retina, number of microangiomas and MD were greatly reduced compared with the status before treatment and there was a significant difference compared with the control group ($P < 0.05$) The incubation period of visually evoked potential P100 wave in the treatment group was less than that of the control group and the amplitude was higher than that of the control group. The incubation period of electroretinogram a, b waves were less than those of the control group and the amplitudes were higher than those of the control group, there was a significant difference ($P < 0.05$)

Qi Chaoxiu et al. (2007) reported that 42 patients with I–III stage DR were randomly divided into two groups: 43 eyes were treated with Dantonic™, 10 pills/time, Tid, for 3 months; 35 eyes in the control group were treated with Vit B_1, Rutosids, and Vit C. The results showed that visual acuity was significantly improved in the Dantonic™ treatment group, and there was a significant difference compared to that in the control group ($P < 0.05$). The visual field improvement in DR patients after Dantonic™ treatment is shown in Fig. 12.1.

Deng [1] observed the treatment of 20 cases of DR with Dantonic™ and calcium dobesilate for a period of 3 months. The results showed that there were no statistical differences between the

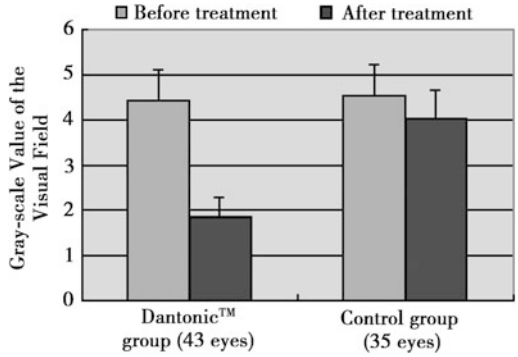

Fig. 12.1 The effect of Dantonic™ on visual field improvement

treatment group and the control group (nonrandomized trials) before and after the treatment, suggesting that visual acuity was not significantly improved. They found that the gray-scale value of the visual field (MD) in both left and right eyes after treatment with Dantonic™ was obviously improved compared to that before the treatment.

12.2.2 The Effect of Dantonic™ on the Fundus Lesions in DR Patients

According to the criteria for typing and staging DR drafted by The Third Chinese Conference of Ophthalmology, 1985, DR pathogenesis was divided into 6 stages:

Stage 1: There are microaneurysms with bleeding points in the retina;

Stage 2: There are proteinous hard exudates with bleeding spots in the retina;

Stage 3: There are white soft exudates with bleeding spots in the retina;

Stage 4: There are new blood vessels or vitreous hemorrhage in the retina;

Stage 5: There are new blood vessels or fibrous proliferation in retina;

Stage 6: There are new blood vessels and fibrous proliferation, plus retinal detachment.

The first 3 stages comprise simple DR and the last 3 stages comprise proliferative DR. Qi Chaoxiu et al. (2007) studied the treatment of stages I–III DR with Dantonic™ in a randomized controlled trial, which showed that the fundus lesion was improved after treatment. Both microangiopathy and small bleeding spots were significantly improved compared with the status before the treatment ($P < 0.05$). Wang [2] reported a randomized controlled study in which DR patients were either treated with Dantonic™ or calcium dobesilate for a course of 4 months. Microaneurysms and bleeding spots were adopted as the curative criteria for evaluation. After treatment, the total effective rate of the Dantonic™ group was 85.7 %, which was significantly higher than that of the control group (62.5 %), ($P < 0.05$). Deng [1] used Dantonic™ to treat early DR. Table 12.2 shows that Dantonic™ was obviously superior to calcium dobesilate in DR treatment.

Sun Hongjiang et al. (2007) used fundus photography and fundus fluorescein angiography methods to observe the effect of Dantonic™ on the treatment of stage I–III DR patients. The results confirmed that microangioma and bleeding spots were significantly reduced compared with the status before taking Dantonic™. There was also a significant difference compared with

Table 12.2 Comparison of fundus fluorescein angiography of DR patients before and after treatments

Group	Number of eyes	Number of microaneurysms		Hemorrhagic foci area		Exudative foci area	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Dantonic™	20	17.8 ± 7.5	11.2 ± 5.4[a]	2.00 ± 1.03	2.20 ± 1.03[c]	1.00 ± 0.67	1.20 ± 0.80[c]
Calcium dobesilate	20	19.7 ± 16.4[b]	14.9 ± 12.2[ab]	1.87 ± 1.06[d]	1.84 ± 0.87[d]	0.86 ± 0.61[d]	0.94 ± 0.83[d]

[a] Intragroup comparison, $P < 0.05$
[b] intergroup comparison, $P > 0.05$
[c] intragroup comparison before and after treatment, $P > 0.05$
[d] intergroup comparison before and after treatment, $P > 0.05$

Table 12.3 Comparison of the effects between Dantonic™ and calcium dobesilate on retinal lesions in DR patients

	Dantonic™ group (n = 37)				Calcium dobesilate group (n = 30)			
	Before treatment	Improved	Not changed	Aggravated	Before treatment	Improved	Not changed	Aggravated
Microangioma and small bleeding spots	37	12 (32.43)[a]	19 (51.35)	6 (5.4)	30	7 (23.33)	16 (53.33)	7 (23.34)
Ecchymosis	18	7 (38.89)[a]	7 (38.89)	4 (22.22)	19	6 (31.57)	3 (15.78)	10 (52.63)
Yellow–white exudates	20	0	15 (75.00)	5 (25.00)	20	0	15 (75.00)	5 (25.00)
Macular edema	9	2 (22.22)	4 (44.44)	3 (33.33)	9	0	7 (77.78)	2 (22.22)

[a] Compared with the control group, $P < 0.05$

the control group after treatment. Bao [3] reported a randomized controlled trial of 37 patients with DR, who were treated with either Dantonic™ or calcium dobesilate. The results are shown in Table 12.3.

The authors believed that both Dantonic™ and calcium dobesilate indeed have a control effect on DR, but their effects were not good enough to improve macular edema, which was caused by changes in vasopermeability or tissue hypoxia in the macular region. Dantonic™ was able to improve blood rheology; however, once the vessel walls were damaged enough, the blood vessels could not be recovered even if the microcirculation of blood flow was improved.

Electroretinograms and visual evoked potentials can reflect the function and state of the retina and the function of visual cells and the visual transduction pathway. The changes in these parameters are related to the severity of the fundus lesions. Some researchers used them as quantitative indicators of the disease. Qi Chaoxiu et al. (2007), of Affiliated Hospital of Sun Yat-Sen University, found that the latent period of visually evoked potential P100 wave was shorter than that of the control group after taking Dantonic™, and the amplitude was higher than that of the control group. The latent period of electroretinogram a, b wave was shorter than that of the control group, and the amplitude was higher than in the control group. There was a significant statistical difference between the two groups. The authors used DR quantitative indicators to prove that Dantonic™ had the effect of improving ischemia and hypoxia in retinal tissue.

12.3 The Effect of Dantonic™ on DN

DN is one of the blood capillary complications of diabetes. In 1839, Richard Bright indicated that albuminuria was the main complication of diabetes. DN has become the primary cause of dialysis for patients in the United States and Europe. Statistically, the proportion of diabetic kidney

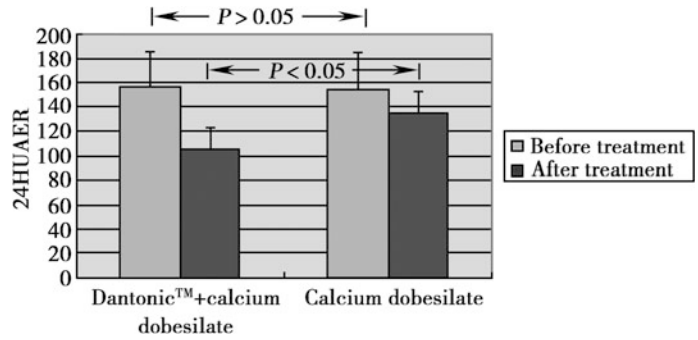

Fig. 12.2 The effect of Dantonic™ on 24-h urinary albumin excretion rate (24HUAER)

Table 12.4 Clinical treatment of diabetic nephropathy with Dantonic™

Author (year)	Diagnosis criteria	Design	Treatment	Results
Qiu Xiaotang (2001)	WHO Standard, 1985	Randomized and controlled	Patients in both groups were alimentary controlled and treated with dimethyl biguanide as a basic drug. Dantonic™ was additionally taken in the treatment group, 5 pills each time, tid for 3 months; Lotensin was taken additionally in the control group, l0 mg/time, tid for 3 months	Microalbuminuria was improved within 24 h in both groups after the treatments. The improvement in the treatment group was particularly evident. The difference between the two groups was significant ($P < 0.05$)
Xiao Wenliang, etc. (2005)	Not described	Randomized and double-blind	The observation group (29 cases), enalapril in 5 mg/time, twice a day + Dantonic™	The total effective rate of urine protein reduction was 82.5 % in the observation group, which was significantly higher than that in the control group (42.3 %) ($P < 0.01$)
			The control group (28 cases), enalapril in 5 mg/time, twice a day	
Zhao Yuebin (2007) [4]	WHO	Randomized and controlled	The treatment group (78 cases): iletin + benazepril, 10 mg/Day + kallidinogenase, 240u tid + Dantonic™, 10 pills each time, tid for 3 months	The urinary albumin excretion in the treatment group was significantly reduced ($P < 0.0$ l). Urea nitrogen and creatinine in both groups were improved ($P < 0.01$). It was significantly improved in the observation group ($P < 0.01$)
			The control group (70 cases): iletin + benazepril, 10 mg/Day	
Guo Yujie (2007) [5]	American Diabetes Association, Denmark Mogensen diagnosis of diabetic nephropathy in stages, 1997	Randomized and controlled	All patients were alimentary controlled. With egg albumen of 0.8 g/(kg·d), iletin or Gliguidone and (or) dimethyl biguanide to control blood sugar. The treatment group was additional treated with Dantonic™, l0 pills/time, tid. Control group + ADT	Albumin excretion in urine was 30–300 mg/24 h. The total effective rate of urinary albumin excretion reduction of early DN in the treatment group was 89.74 % which was significantly higher than that of the control group (61.5 %), ($P < 0.0$l). Blood urine β2- microglobulin in the treatment group was significantly reduced compared to the status before treatment ($P < 0.01$), while there was no significant difference before and after treatment in the control group. There was clearly a difference between the treatment group and the control group after treatment ($P < 0.01$)

diseases has been rising to second place in Chinese dialysis patients. Type I diabetes with renal failure amounted to 8.9 %, and incidences of type 2 diabetes with renal failure accounted for between 3 and 8 %, of which most cases ended in death caused by cardiovascular attacks when renal failure occurred. Incidences of cardiovascular events in diabetic patients with proteinuria were 4 times that of patients without proteinuria, and 37 times that of normal people; thus, DN has received increasing attention from clinical cardiovascular doctors and metabolic disease practitioners. Dantonic™ has significant relieving effects on DR. Both DR and DN are microvascular diseases, and clinically the two diseases are often found coexistent with each other. In addition, the severity of the two diseases has a parallel relationship.

Wang [2] used Dantonic™ to treat stage I–III DR patients, and used calcium dobesilate (500 mg each time, 3 times/day) to treat the patients in the control group. The results showed that Dantonic™ had advantages in the treatment of DR. Meanwhile, a 24-h urinary albumin excretion rate (24HUAER) was determined, and the results are shown in Fig. 12.2, which showed that the combination of Dantonic™ and calcium dobesilate had a better improving effect on 24HUAER in diabetic patients.

There have been several reports showing that Dantonic™ has an excellent therapeutic effect on DN (Table 12.4). The reason for that is obviously that DN is a microangiopathy with symptoms of exudation, obstruction, and proliferation. Patients usually suffer from hyperactivated platelet activity, decreased fibrinolytic activity, and reduced red blood cell deformability. Hemorheological changes in DN include increased blood viscosity and damaged capillary endothelia. Dantonic™ has positive activities in all of these aspects, so it could exert its effects on multiple targets, in multiple ways, and from multiple layers, resulting in an integrated and regulated balance.

Li Yousheng et al. (2003) explored the effect of Dantonic™ on early stage DN in type 2 diabetes rat models for a period of 12 weeks. The results showed that a high dose of Dantonic™ could decrease blood glucose levels, reduce urinary microalbumin, alleviate renal hypertrophy, and reduce urinary volume. A moderate or low dose of Dantonic™ could decrease blood triglyceride levels in the rats, and the effect was better than Losartan. It was concluded that high doses of Dantonic™ could ameliorate microalbuminuria and thus improve DN.

References

1. Hui D, Ming J, Wei Y, et al. J Tradit Chin Ophthalmol. 2005;15(2):72.
2. Bin W. Chin J Gen Med. 2004;3(11):58.
3. Lingzhi B, Guang Y, Haibin W. Hebei J Tradit Chin Med. 2006;28(4):304.
4. Yuebin Z, Ruihua W, Guoqing W. Chin J Integr Tradit West Nephrol. 2007;8(2):112.
5. Yujie G. Med J Chin People's Health. 2007;19(3):117.

Effect of Dantonic™ on Prevention of High Altitude Myocardial Hypoxidosis

13

Guoguang Zhu, Keqin Han and Ruizhi Luo

Highland areas 3,000 m above sea level are called plateaus, and air pressure and oxygen partial pressure are relatively lower here than in the plains. Hypoxia occurs when people enter highland areas a short time after living in the plains, or after having originally lived in high altitude regions but stayed in the plains for a period of time. When they return to the highland area, they suffer from headache, dizziness, cardiopalmus, and shortness of breath. Some people even suffer from decreased food appetite, nausea, vomiting, insomnia, fatigue, abdominal distension, tightness of the chest, cyanotic lips, and limb numbness. The pathogenesis involves the slowing of oxygen exchange between the atmosphere and alveolar gas and of oxygen release from the blood, which causes organism hypoxia and high altitude sickness.

Recently, attention has been paid to high altitude myocardial hypoxidosis (HAMH), which is the myocardial hypoxic ischemic change shown on an ECG when a person is adjusting to the plateau climate. HAMH might also be accompanied by other high altitude idiopathic symptoms which have undesirable manifestations. The diagnostic criteria of HAMH require that patients be considered healthy in examinations (including ECG) in a plain area or at an altitude of 2,500 m base, but after living in a highland area (>3,000 m), they have two of the following abnormalities:

(1) For any R-wave dominant lead, an ST-segment level or dropped pressure appears ≥0.1 mV.
(2) For any R-wave dominant lead, the T-wave is in the place of inversion or two-way.
(3) T-wave with symmetrical two limbs becomes narrow, sharp, and high.
(4) ECG changes dynamically, and the following items have been excluded:
   a. The patient has been diagnosed with high altitude chronic cardiopathy (HACC) or HACC-related symptoms;
   b. The patient's ST-T changes above were located in the right ventricular lead;
   c. The patient has elevated blood lipids, suspected coronary artery disease, or ST-T changes caused by electrolyte disturbances in the blood.

Zhang et al. [1] reported that 617 male workers, whose physical examinations were normal at sea level, entered an elevation of 5,000 m. These workers were randomly divided into a medication group (186 cases) treated with Dantonic™, and a control group (431 cases) treated with a placebo. There was no statistical difference in average age, body height, body weight, blood pressure, heart rate, or oxygen saturation between the groups. The results showed that over the 6-month trial period, those in the Dantonic™ treatment group had significantly lower ECG myocardial ischemia rates than did those in the control group. Dantonic™

G. Zhu (✉) · K. Han · R. Luo
The European Federation of Pharmaceutical Society, Stockholm, Sweden
e-mail: ggz68111@yahoo.com

X. Yan (ed.), *Dan Shen (Salvia miltiorrhiza) in Medicine*,
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Table 13.1 Comparison of the ischemic ECG rates of the Dantonic™ and placebo groups

Group	Myocardial ischemia (by people)			Myocardial ischemia (by case)		
	Number	Number with myocardial ischemia	Percentage (%)	Number	Number with myocardial ischemia	Percentage (%)
Dantonic™	186	21	11.29	595	33	5.55
Placebo	431	112	25.99	1,029	193	18.76
X^2			16.59			54.92
P			<0.01			<0.01

reduced the relative risk of HAMH in the first-time high altitude workers by 0.57 (by people) or 0.7 (by case) ($P < 0.01$), and the efficiency index was 0.23 (by people) or 0.34 (by case); the anticipation of myocardial ischemia tested by movement ECG was reduced by 35 % ($P < 0.01$). For people with myocardial ischemia, after taking Dantonic™ the recovery rate was 39 % ($P < 0.01$) (Tables 13.1, 13.2 and 13.3). They also tested serum H_2S content: the content of the Dantonic™ group ($n = 34$) was 51.14 ± 14.99 μmol/L, and that of the control group ($n = 65$) was 44.91 ± 13.94 μmol/L. The difference between the two groups was significant ($P < 0.05$). It demonstrated that Dantonic™ was able to increase the content of serum H_2S and significantly decrease blood pressure and heart rate, as well as the abnormality rate of SpO2 ($P < 0.05$ or $P < 0.01$). By applying partial correlation, the improvements of myocardial ischemia and physiological parameters were related to Dantonic™ treatment ($P < 0.05$ or $P < 0.01$).

Chen and Fan [2] randomly divided 246 HAMH patients into the Dantonic™ group and the Compound Danshen Tablet group. After taking Dantonic™ for 14 days, the symptoms of nervousness, chest tightness, precordial spasms, and so on disappeared, and the ECG improvement was significantly superior to that of the Compound Danshen Tablet group.

Lin et al. [3] randomly divided 385 healthy people, who entered a highland area (3,800 m) for the first time, into Group A (200 cases) with Dantonic™ and oral Dexamethasone and Group B (185 cases) with "dummy" (author did not indicate what the drug was). The result: The occurrence of high altitude pulmonary edema in Group A (4 cases) was significantly lower than that of Group B (9 cases) (Tables 13.4, 13.5 and 13.6).

Zhao et al. [4] studied 128 patients, who had entered the highlands for the first time and had various extents of headache, dizziness, cardiopalmus, chest tightness, dry mouth, and insomnia. The patients were randomly divided into groups and treated with various methods:

Group A (30 cases): Rhodiola Oral Solution, 10 ml each time, 3 times a day; chlorine theophylline 0.2 g each time, 3 times per day.

Group B (57 cases): Gao Yuan'an Capsule, 4 pills each time, 4 times a day.

Table 13.2 Dantonic™'s intervention effect on the treadmill ECG predication rate and the rehabilitative effect on the ischemic ECG

Group	Number of positive people by treadmill test in low altitude	Predicated number ischemic people after entering high altitude	Predication rate (%)	Number of ischemic people in high altitude	Number of rehabilitated people	Rehabilitation rate (%)
Dantonic™	31	8	25.81	29	14	48.28
Placebo	25	15	60.00	182	17	9.34
X^2			6.685			30.25
P			<0.012			<0.01

Table 13.3 Comparison of blood pressure, abnormal heart rhythm rate, and blood oxygen saturation in the Dantonic™ and placebo groups

Group	*N*	BP ≥ 140/90 (mm Hg)		HR ≥ 100 (beats/min)		SpO2 (≥80 %)	
		n	Rate (%)	*n*	Ratio (%)	*n*	Ratio (%)
Dantonic™	575	205	35.65	173	30.09	306	53.22
Placebo	1,021	417	40.84	391	38.30	463	45.35
X^2			3.847		10.848		8.778
P			$p < 0.05$		$p < 0.01$		<0.01

Table 13.4 Acute altitude sickness symptoms grading and scoring criteria

	Symptom	Grade	Scoring
Headache	l. The symptom was not significant without pain expression, and it did not affect daily activities	±	1
	2. The symptom was light with pain expression. It was markedly improved after taking painkillers and did not affect daily activities	+	2
	3. The symptom was heavy with pain expression. It was improved after taking painkillers and affected daily activities	++	4
	4. The symptom was too heavy to tolerate. Patients were bedridden and unable to get up. General painkillers were ineffective	+++	7
Vomit	1. Vomiting about 1–3 times a day, and the vomit was food-based. Improvement was noticeable after taking general antiemetics and daily activities were not affected	+	1
	2. Vomiting about 3–4 times a day, the vomit was gastric juice. Improvement occurred after taking general antiemetics but daily activities were affected	++	2
	3. Vomiting more than 5 times a day and being bedridden. No improvement after taking general antiemetics	+++	4
Others	Dizziness, nausea, nervousness, shortness of breath, chest tightness, vertigo, insomnia, drowsiness, abdominal distension, diarrhea, constipation, cyanotic lips, hands, feet, and numbness	Each were marked 1 score	7

Table 13.5 Grading and diagnosis of acute high altitude responses

Grading	Criteria
No response basically (±)	Total scores: l–4
Light response (+)	Headache (+), or vomiting (+), or total score was 5–10
Moderate response (++)	Headache (++), or vomiting (++), or total score was 11–15
Severe response (+++)	Headache (+++), or vomiting (+++), or total score was more than 16

Group C (41 cases): Dantonic™, 10 pills each time, 3 times a day; chloro-theophyllin, 0.2 g each time, 3 times a day; somedon, 0.5 g each time, 2 times a day; VhB 20 mg each time, 3 times a day.

After a course of 5 days, the symptoms disappeared and the cure rate in group A was 84.1 %, in group B 94 %, and in group C 88 %. The author adopted pharmacoeconomics to analyze the economics and sensitivity. From the

Table 13.6 Comparison of symptom grading for acute high altitude responses

	No response basically	Light response	Moderate response	Severe response	Number of cases	Incidence rate (%)
Group A	148	24	17	11	52	26.00
Group B	72	51	37	25	113	61.08

$X^2 = 48.29$, $P < 0.01$

pharmacoeconomical view, the best solution for treatment was Dantonic™.

It has been proved by animal experiments that Danshen could increase the blood oxygen carrying capacity. It could also increase the oxygen concentration of important viscus, and effectively reduce the damage to the heart, kidneys, and other organs caused by hypoxia. By inhibiting platelet aggregation, Dantonic™ could activate the fibrinolytic system, lower blood viscosity, improve microcirculation, increase oxygen supply, inhibit arterial systole caused by hypoxia, increase the arterial partial pressure of oxygen and blood oxygen saturation, and enhance the utilization of oxygen and resistance to hypoxia. Zhang et al. [1] and Zhao et al. [5] moved Wistar rats from 2,260 to 5,000 m above sea level, and randomly divided the rats into a Dantonic™ medication group (7 cases) and a control group without Dantonic™ (7 cases). The anatomical study showed that in the control group there was stasis in the small vessels of the endocardium and myocardium. In addition, the myocardial space widened, focal congestion and focal myocardial fiber edema appeared, and eosinophilia was found in the endocardium. The cardiac fibers inside the focus were thinner and the staining was deeper. The nuclear structure was blurred (Fig. 13.1). In the Dantonic™ group, myocardial congestion and hemorrhage-like bleeding were clearly improved (Fig. 13.2). In the heart ultrafine pathomorphology, there was edema of myocardial cells in the control group, the

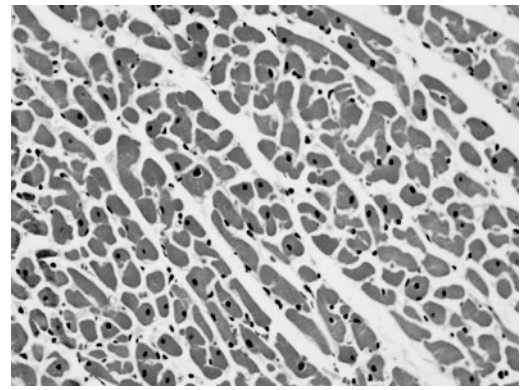

Fig. 13.2 Dantonic™ group, myocardial congestion and hemorrhage-like bleeding were clearly improved

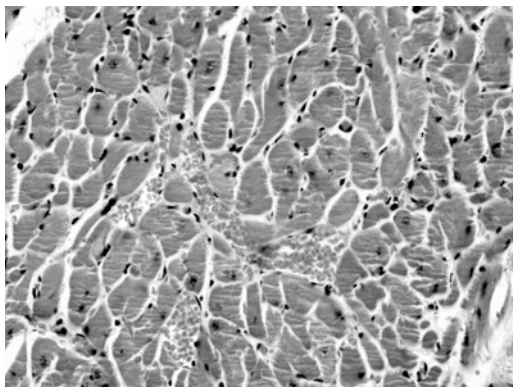

Fig. 13.1 The nuclear structure was blurred

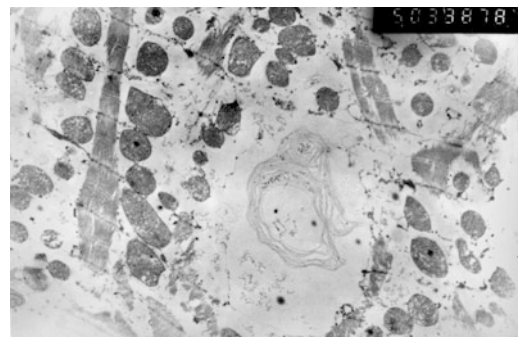

Fig. 13.3 The formation of myelin-like bodies could be observed

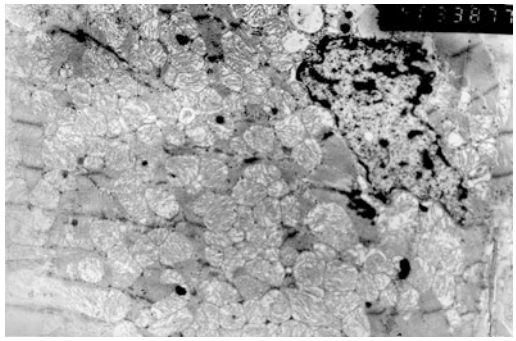

Fig. 13.4 Myocardial necrosis and the congestion of blood vessels between muscle fibers

myofibrillitic gap was widened, and there was necrosis of part of the muscle fibers that had collapsed into a granular state or dissolved. The formation of myelin-like bodies could be observed (Fig. 13.3). Myocardial necrosis and the congestion of blood vessels between muscle fibers in the Dantonic™ group were significantly improved (Fig. 13.4).

References

1. Zhang X, Dong W, Pei Z, et al. Railway Occup Saf Health Environ Prot. 2006;33(4):161.
2. Chen X, Fan X. J Chin Mod Inter Med. 2005;2(9):778.
3. Lin F, Zhao R, Yang Q, et al. Chin J Mod Pract Med. 2005;4(12):9.
4. Zhao C, Ma K, Zhu M, et al. Chin J Gen Med. 2003;2(9):44.
5. Zhao Y, Shi C, Wang X, et al. Chin J Pathophysiol. 2002;18(10):1271.

The Mechanism of Dantonic™ in Treating Coronary Heart Disease

14

Guoguang Zhu and Ruizhi Luo

14.1 Historic Review and Highlights of Dantonic™ in Treating Coronary Heart Diseases

The therapeutic effect of Dantonic™ on coronary heart disease has been accepted by clinical doctors and patients since the medicine was put on the market in 1994. It was believed at the beginning that the effect of Dantonic™ was to relieve coronary spasms and rapidly alleviate angina, and thus the mechanism should be the relief of smooth muscle spasms. Explained in TCM terms, it activates blood circulation and dissipates blood stasis; no obstruction, no pain. So, the therapeutic effect of Dantonic™ on coronary heart disease was generally attributed to its "activating the blood circulation and dissipating blood stasis." However, after in-depth studies, this view has changed. From the summarized clinical application of Dantonic™, we can see that during 1994–1999, Dantonic™ was widely used in treating stable angina pectoris, and since 2000, it has been used for stabilizing atherosclerotic plaques and preventing acute coronary syndrome, myocardial infarction, cerebrovascular accidents, and so on. Currently, the active sites of Dantonic™ on coronary heart disease are as follows:

- Relieves coronary spasms
- Stabilizes atherosclerotic plaques
- Reduces blood lipids and cholesterol
- Protects vascular endothelial cells
- Corrects functional disorder of vascular endothelial cells
- Protects cardiac muscle cells (antioxidation)
- Resists platelet activation and aggregation
- Resists blood hyperviscosity syndrome, improves blood rheology
- Improves cardiovascular circulation and systemic microcirculation
- Anti-metabolic syndrome
- Anti-autonomic nervous system disorder.

Since the introduction of the risk factor concept in a Framingham Study in 1961, the concept has been widely used over the last 50 years not only in the prevention of coronary heart disease, but also in the treatment of the disease. For example, according to Framingham risk factor scores, it has been indicated that the decision of the treatment solution should be based on the patient's risk factors in the prevention and treatment guidelines of high blood pressure and blood lipid abnormality. For acute coronary syndrome, since the 1980s and 1990s the diagnosis and treatment of unstable angina were fundamentally changed, with accurate and standardized indicators to identify high-risk factors in previous studies of people at risk, and with risk stratification. Although there is a fundamental difference in the concept definition between the two, these are the generalizations and extensions of the original "risk factor" concept. At present,

G. Zhu (✉) · R. Luo
The European Federation of Pharmaceutical Society, Stockholm, Sweden
e-mail: ggz68111@yahoo.com

X. Yan (ed.), *Dan Shen (Salvia miltiorrhiza) in Medicine*,
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the idea of risk factors has been expanded from the original qualitative concept to that of quantitative classification, and the absolute risk and relative risk have been implemented in primary and secondary prevention. Therefore, the comprehensive evaluation and disposal of risk factors are important for the prevention, treatment, and curative enhancement of coronary heart disease.

In recent years, the most important update to the understanding and practice of risk factors is, of course, "multiple marginal abnormalities." Traditionally, the estimation of the probability of coronary heart disease occurrence was mainly based on the extent of increase in the risk factors already identified, and high-risk objects were identified accordingly. This assessment was based on a single risk factor. It failed to integrate multiple cardiovascular risk factors for a comprehensive and systematic analysis. In fact, the so called "high-risk" groups should not only include individuals whose certain risk factor has surpassed a certain artificial threshold, but also consider the coexistence of multiple cardiovascular risk factors. Since risk factors often coexist with other risk factors, "multiple marginal abnormalities" should be included in the assessment; that is, even though a risk factor in a patient has not risen to a very high (abnormal) level, the risk of disease occurrence can be aggregated by the accumulation of multiple factors (which are referred to as the risk factor aggregation of individuals). This is especially important for patients who have one or two high-risk factors and a number of marginal abnormalities. Synergies among the aggregated cardiovascular risk factors lead to various subclinical or clinical symptoms. The Framingham Study proposed a "scoring" method based on multiple regression analysis in which each risk factor was quantified as a regression coefficient. The concept of the comprehensive risk of multiple risk factors is another important development. The so-called risk factor for cardiovascular disease syndrome means that the danger of cardiovascular disease occurrence in a certain patient is determined by both the number and the severity of risk factors. Currently, the prevention and treatment of coronary heart disease follows the following principle: determine the intervention intensity based on the risk degree of cardiovascular disease occurrence.

Atherosclerosis is a multi-factorial disease involving genetic, metabolic, and environmental factors, and the main cause of cardiovascular diseases is the metabolic disturbance of fat and sugars, which is why they are also known as metabolic vascular diseases. Most human gene expression (75 %) is not consecutive, which means that their expression only occurs under certain conditions and abnormal expression occurs under circumstances of stress. The environment inside the human body includes the intestinal environment, the pH of body fluids, hormone levels, blood circulation environment, and the intracellular environment. Factors associated with coronary heart disease include cholesterol, triglycerides, insulin, glucose, homocysteine, neurotransmitters such as norepinephrine and acetylcholine, hormones such as thyroxine and adrenaline, local chemical substances such as growth factors, oxygen, carbon dioxide, prostaglandin calcium, potassium proteins, amino acids, nucleotides, vitamins, carbohydrates, lipids, inositol triphosphate, and diacylglycerol, or even metabolism products such as uric acid and lactic acid. Any broken link can cause damage and inflammation in the body and affect the genetic environment. The relationship between the formation of coronary heart disease and genetic environment is often reflected in the increase of blood lipids, lack of chromium ions, low potassium, high sodium, abnormal secretion of insulin, increase in triglyceride and free radicals, local tissue hypoxia, and excitement of nervus sympatheticus, and renin-angiotensin. One or more risk factors and multiple marginal abnormalities compose the whole risk spectra, and any factor and abnormality could cause pathological and sub-pathological changes in the body.

Dantonic™ contains a variety of effective ingredients such as Danshensu, salvianolic acids, and panax notoginseng saponins, which can correct pathological changes caused by a variety of risk factors (including marginal abnormality factors). At present, it has been demonstrated by

epidemiology and evidence-based medicine studies that the aggregation of a variety of risk factors (including marginal abnormalities) has a much higher risk effect on the occurrence of cardiovascular disease compared to any single risk factor. The multifactorial risk increases geometrically instead of arithmetically. Dantonic™ is like a missile with multiple warheads targeted at multiple risk factors of coronary heart disease, which has a better effect on patients' survival than drugs targeting single risk factors. Similarly, it has better therapeutic effects on clinical or subclinical symptoms caused by multiple factors than drugs with single actions. Compared with single action drugs, the potency of multi-targeting drugs to a certain target is relatively weak. For example, the effect of Dantonic™ on correcting dyslipidemia patients is weaker than that of statins. In fact, the aggregation of a number of weak effects on chronic diseases caused by multiple factors cannot be calculated arithmetically. This multi-targeting effect of Dantonic™ on a variety of risk factors for coronary heart disease makes the body reach a new balance.

14.2 Revelation of Dantonic™ Mechanism Discussion

Compared with corresponding western drugs, the indication of Dantonic™ in the treatment of coronary heart disease is basically in a weaker position. For example, although several doctors reported that there was no statistical difference in the rate and degree of angina relief between Dantonic™ and nitroglycerin, many clinical workers objectively pointed out that the effect of nitroglycerin was superior to that of Dantonic™ for a serious angina attack. Another example is anti-platelet activation, and Dantonic™ does not have the same effect as aspirin. Dantonic™ focuses on the treatment of subclinical and

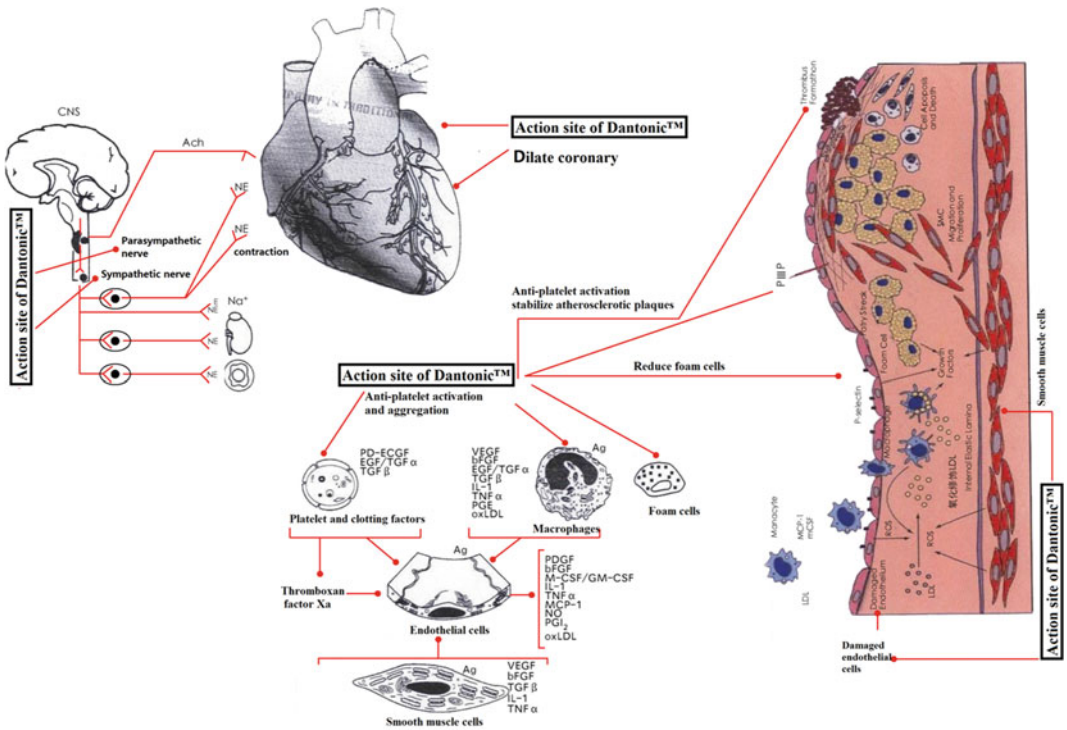

Fig. 14.1 A schematic diagram showing Dantonic™'s cardiovascular targets

clinical changes caused by several high-risk factors and marginal abnormal factors of coronary heart disease; from this arises the curative effect and "marginal treatment" of organisms, and that effect occurs at the same time and on the same organism. This sum of weak forces is calculated geometrically instead of arithmetically. This may be the core mechanism of Dantonic™ in treating coronary heart disease, which is the principle that we call "a multi-warhead missile corresponding to multiple lesions caused by multiple high-risk factors of diseases" (Fig. 14.1). Each compound missile-warhead leads to the formation of a new level of the body, and leads the body gradually away from high-risk factors and multiple marginal abnormalities toward a healthy direction, which might be why compound Chinese medicine succeeds.

Toxicity and Side Effects of Dantonic™ 15

Guoguang Zhu and Ruizhi Luo

Based on nearly 14 years of toxicological research and clinical application in millions of patients in nearly 1,000 hospitals, it can be said that Dantonic™ has no toxicity and few side effects. Among many clinical reports on Dantonic™ we have collected, only one reported a case of hypertension caused by Dantonic™. No other side effects have been reported so far. We have collected as many reports as possible, and summarized the side effects in Table 15.1. There are 66 papers that report definite side effects of Dantonic™. Of a total caseload of 5,169 patients, 161 patients experienced side effects (3.11 %). The main side effects are shown in Table 15.1.

Table 15.1 Side effects of Dantonic™

Side effects	Number of cases	Percentage (%)
Fullness of head, dizziness, facial flushing	100	1.93
Gastrointestinal tract reactions	59	1.14
Skin rash	1	0.02
Increased blood pressure	1	0.02

The main side effects of Dantonic™ are fullness of head, dizziness, or headache with a reddish face. Most are transient (1.93 %). One study reported that after decreasing the dose to 5 pills, 3 times a day, the symptoms disappeared. In other cases, the patients did not need to be treated as their symptoms disappeared naturally with time. The second most common side effect of Dantonic™ is gastrointestinal reactions (1.14 %). 12 patients with original chronic gastritis (of 59 patients experiencing gastrointestinal reactions), felt stomach discomfort after 10 days or so and the treatment was "changed to taking it after dinner and receiving stomach medication"; the authors believe that the patients could gradually adapt without cessation of Dantonic™ treatment.

Intragastric administration of Dantonic™ to mice with a dosage equivalent to 700 times the dosage for adult men, or subcutaneous injection of 350 times the adult dosage, resulted in no mice dead after 1 week. The LD_{50} of mice with oral administration of Dantonic™ is greater than 16.8 g/kg, and for subcutaneous injection it is greater than 8.4 g/kg, which proves that Dantonic™ has very little toxicity. Large-scale clinical application over the past 6 years in China has proved that Dantonic™ is a safe drug.

Wang and Wu [1] reported that Dantonic™ caused one case of allergic response. Zhong et al. [2] reported that Dantonic™ caused two cases of erosive gastritis; Zheng et al. (2005)

G. Zhu (✉) · R. Luo
The European Federation of Pharmaceutical Society,
Stockholm, Sweden
e-mail: ggz68111@yahoo.com

X. Yan (ed.), *Dan Shen (Salvia miltiorrhiza) in Medicine*,
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reported that Dantonic™ caused two cases of syncope; Yang et al. [3] reported that Dantonic™ caused one case of haematuria; Ma Degao et al. (2002) reported that the combination of Dantonic™, ISDN and atenolol caused one case of shock.

References

1. Wang Y, Wu J. Chin J Pract Med. 2003;30(16):32.
2. Zhong Y, Liu J, Wang J. Chin J Pharmacoepidemiol. 2006;15(5):31–6.
3. Yang G, Zhao X, Mu Q. Chin J Hosp Pharm. 2003;23 (6):351.

Effect of Dantonic™ on the Treatment of Other Diseases

16

Guoguang Zhu and Ruizhi Luo

In recent years, the clinical application of Dantonic™ has expanded from the original indications of coronary heart disease and angina pectoris to those of cerebrovascular diseases, based on Danshen's functions of promoting blood circulation, dissipating stasis, strengthening body resistance, and tonifying the deficiency. There are a total of 20 papers reporting that Dantonic™ has been used to treat cerebral infarction, brain hemorrhage, dizziness, transient ischemic attack, and blood stasis type of insomnia and so on with a total of 1,470 cases. The clinical effective rate of Dantonic™ was higher than that of the control group, and the difference was statistically significant (Table 16.1).

Meanwhile, the treatment scope of Dantonic™ has become increasingly wider. It has been used in a wide range of other noncoronary heart diseases (Table 16.2) and achieved very good results. For examples, for hyperlipidemia and high blood viscosity syndrome, clinical studies have shown that Dantonic™ can significantly lower cholesterol, triglycerides, and low-density lipoproteins in blood. It was also found by microcirculation inspection that whole blood viscosity, plasma specific viscosity, wet weight and dry weight of thrombus, and platelet aggregation in the Dantonic™ group were significantly reduced, which means that Dantonic™ has an effect on inhibiting blood agglutination and promoting the fibrinolytic system, and the mechanism is related to the control of platelet adhesion, aggregation, and plasma prothrombin time. In addition, the combination of Dantonic™ and Captopril can expand blood vessels and inhibit platelet aggregation, and has an obvious effect on the treatment of pulmonary heart disease, with fewer side effects. Combined with astragalus and hormone, it can treat nephrotic syndrome, strengthen the effects of diuretic drugs and detumescence, and reduce proteinuria. Dantonic™ also has an improving effect on microcirculation. Dantonic™ can be quickly absorbed sublingually, and promotes blood circulation and stasis dissipation, expands blood vessels, and protects retinal cells. With high-pressure oxygen treatment, the drug has a good effect on patients with central retinal artery occlusion or retinal vein occlusion. Dantonic™ has a significant effect on the treatment of bronchial pneumonia when combined with the conventional anti-infection treatment. It can enhance the anti-inflammatory effect, raise the curative rate, and shorten the course of the disease. On the basis of the conventional treatment of liver protection and diuresis, as well as symptomatic and supportive treatment, Dantonic™ can reduce serum hyaluronic acid, alleviate liver fibrosis, and delay hepatic cirrhosis. If conventional antiepileptic drugs are ineffective, Dantonic™ can be taken additionally. This treatment has a confirmed therapeutic effect on epileptic seizures, with

G. Zhu (✉) · R. Luo
The European Federation of Pharmaceutical Society, Stockholm, Sweden
e-mail: ggz68111@yahoo.com

X. Yan (ed.), *Dan Shen (Salvia miltiorrhiza) in Medicine*,
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Table 16.1 Treatment of cerebrovascular diseases with Dantonic™

Author	Diagnose	*N*	Dosage	Course of treatment	Result
Gao et al. [1]	Cerebral infarction	51	10 pills each time, tid	4 weeks	Total effective rate was 96.5 %. The control group ($n = 51$) received conventional treatment with an effective rate of 72.55 %. The difference was statistically significant ($P < 0.01$)
Wang et al. [2]	Ischemic dizziness	91	10 pills each time, tid	4 weeks	Total effective rate in Dantonic™ group was 92.3 %, in the control group ($n = 51$, received Quke Rutin) was 82.3 %
Wang et al. [3–5]	Cerebral infarction	51	10 pills each time, tid	4 weeks	Total effective rate in Dantonic™ group was 88.2 %, the control group (received injections of dextran-40 glucose, 500 ml, qd) was 70.6 %. The difference was statistically significant
Cao and Yu [6, 7]	Acute cerebral infarction	220			Satisfactory outcomes
Wang et al. [8]	Disorder of cerebral hemodynamics	60	10 pills each time, tid	24 weeks	All parameters of cerebral arteries hemodynamics were improved after the treatment, blood flow in both sides of cerebral arteries increased ($P < 0.05$), peripheral vascular resistance of both sides of the brain decreased ($P < 0.01$), demonstrating that Dantonic™ could increase the blood flow and improve the blood supply to the brain
Gao [9]	Acute cerebrovascular disease	94		–	Excellent outcomes
Zhen et al. (1999)	Cerebral infarction with convalescent sequelae	–		6–8 weeks	Total effective rate in Dantonic™ group was 98.5 %, in the control group was 55.2 %. Recurrence rate in Dantonic™ group was also lower than that in the control group
Li (1999)	Acute cerebral hemorrhage	40		–	Had therapeutic effects
Yu [10]	Cerebral infarction	105		–	The effective rate in Dantonic™ group was 91.94 %, in the control group was 69.76 %. The difference was statistically significant ($P < 0.01$)
Chen and Yan [11]	Vascular head wind disease	–		–	The effective rate was 93 %
Liu (1999)	Coronary heart disease	87	10 pills each time, tid	4 weeks	Dantonic™ had a clear improving effect on the indexes of blood rheology, especially on whole blood viscosity, the platelet and red blood cell aggregation
	Cerebral infarction	34			
Ma et al. [12, 13]	Cerebral infarction	45	10 pills each time, tid	4 weeks	The blood rheology was improved

(continued)

Table 16.1 (continued)

Author	Diagnose	*N*	Dosage	Course of treatment	Result
Xu and Chen [14]	Hypertensive Cerebral hemorrhage	149	10 pills each time, tid	4 weeks	As time passed, the occurrence rates of cerebral-cardiac syndrome in both Dantonic™ and conventional treatment groups were reduced, but the Dantonic™ group was superior to the conventional treatment group, and the differences between the two groups were statistically significant ($P < 0.05$ or 0.01)
Zheng [15]	Dizziness	20	10 pills each time, tid	15 days	Total effective rate in the Dantonic™ treatment group was 90.0 %, which was significantly higher than that in the control group (70.0 %), the difference was significant ($P < 0.05$)
Fan et al. [16]	Transient ischemic attack	60	10 qd, bid, tid	18 months	Dantonic™ has the same effect as aspirin on the prevention of TIA, without significant side effects. The patient's compliance with Dantonic™ is better than with aspirin
Li [17]	Dizziness	40	10 pills each time, tid	15 days	The total effective rate in the Dantonic™ treatment group was 95 %, which was significantly higher than in the control group (75 %), the difference was significant ($P < 0.05$)
Wang et al. [18]	Cerebral infarction	120	10 pills each time, tid	4 weeks	Total effective rate in the Dantonic™ treatment group was significantly different from that in the control group ($P < 0.01$)
Han et al. [19]	Vasovagal syncope	39	10 pills each time, tid	3 months	The effect of Dantonic™ had no significant difference compared with metoprolol and there was no statistical significance
Pu (2005)	Cerebral infarction	150	10 pills each time, 4 times a day	4 weeks	The total effective rate in the Dantonic™ treatment group was 96.08 %, in the control group was 72.55 %. The difference was significant ($P < 0.01$)
Ren and Tian [20]	Stroke	70	10 pills each time, tid	14 days	The effective rate in the Dantonic™ treatment group was 94.3 %, in the control group was 73.2 %
Song [21]	Transient ischemic attack	60	10 qd, bid, tid	18 months	Dantonic™ has the same effect as aspirin on the prevention of TIA, without significant side effects and with better oral compliance than aspirin
Fu [22]	Blood stasis type insomnia	24	10 pills each time, tid	7 days	The total effective rate in the Dantonic™ treatment group was 95.83 %, in the control group was 58.33 %, the difference was significant ($P < 0.01$)
Wang [23]	Early cerebral infarction	40	10 pills each time, tid	2 weeks	The total effective rate in the Dantonic™ treatment group was 97.5 %, in the control group was 80 %, the difference was significant ($P < 0.01$)
Qu and Yang [24]	Transient ischemic attacks	32	10 pills each time, tid	3 months	The total effective rate in the Dantonic™ treatment group was 81.25 %, in the control group was 28.13 %, the difference was significant

Table 16.2 Treatment of diseases other than coronary heart disease with Dantonic™

Author	Diagnose	*N*	Medication	Result
Hu et al. [25]	Retinal vein obstruction	42	15 pills, tid for 12 weeks	Eyesight improved after treatment with Dantonic™, total effective rate was 60 %. The authors concluded that Dantonic™ could substitute Danshen injection for the treatment of this disease
Yang et al. [26]	Hyperviscosity syndrome	41	10 pills, tid for 4 weeks	The symptoms were improved, the blood viscosity and lipids were decreased, and the microcirculation and cardiovascular functions were improved
Zheng et al. [27]	Nephritic syndrome	6	12 pills sublingually	Good improving effect on nail fold microcirculation in the patients
Ci et al. [28, 29]	Central sleep apnea syndrome	48	10 pills, tid for 2 weeks	The apnea index, maximum apnea time, average apnea time, and the lowest oxygen saturation were improved
Bi et al. (1999)	Chronic pulmonary heart disease	60	10 pills, tid for 4 weeks	Dantonic™ had a good effect on chest distress and poor circulation in lower limbs caused by pulmonary heart disease
Fan and Jia [30]	Acute pulmonary heart disease	36	10 pills, tid for 2 weeks	Dantonic™ was helpful in treating cough, phlegm, and dyspnea
Zheng [31]	Myocarditis sequelae	120	10 pills, tid for 3 × 4 weeks	Clinical effective rate was 87 %. Symptoms such as chest tightness, palpitation, shortness of breath, arrhythmia, and lower ST segment, were improved
Fan and Jia [32]	Diabetes, nephropathy	45	–	Dantonic™ had a good effect on relieving or clearing albuminuria; its total effective rate was 64.4 %, in the control group it was 22.5 %
Deng [33]	Chronic hepatitis B	54	10 pills	Total effective rate was 83.2 %, effective on negative conversion of ALT, HBSAg, HBV-DNA

(continued)

Table 16.2 (continued)

Author	Diagnose	*N*	Medication	Result
Pan et al. [34]	Hepatocirrhosis	52	10 pills, tid for 1 year	Liver function improved markedly, blood ammonia decreased, pH of feces lowered, normal bacteria of feces increased, and negative conversion of occult blood in stool was 80.8 %, the diameter of hepatic portal canal and blood flow decreased clearly. It also had some effect on fatigue, loss of appetite, and abdominal distension
Zou et al. [35]	Age diabetes	40	10 pills, tid for 3 months	Had a good effect on nail fold microcirculation
Chen et al. (2001)	Diabetic neuropathy	15	10 pills, tid for 12 weeks	The effective rate in Dantonic™ group was 80 %. Dantonic™ evidently improved the blood viscometer reading, and it could also improve early diabetic neuropathy
Zhi et al. [36]	Glomerular disease	60	10 pills, tid for 4–8 weeks	There was evident improvement in blood rheology
Zhang and Yang [37]	Hemorrhage of the ocular fundus	40	8–10 pills, tid for 4 weeks	Effective cases: 39; ineffective cases: 1
Zhang [38]	Central retinal vein occlusion	22	10 pills, tid for 4 weeks	The effective rate in Dantonic™ group was 83 %. The control group received urokinase 30,000 units in 3 % GS solution by intravenous drip; the effective rate was 44.5 %. The difference was statistically significant
Zhang et al. [39]	Chronic pharyngitis	33		Total effective rate: 94.7 % for the simple type; 88.8 % for the hypertrophic type; 60 % for the atrophic type
Chang et al. (1998)	Hepatocirrhosis in decompensation stage	14	15 pills, tid for 2 weeks	The patients received conventional treatment plus Dantonic™. The effective rate was 94.29 %
Liang and Li [40]	Thrombosis of central vein of retina	2	10 pills, tid for 10–14 days	

(continued)

Table 16.2 (continued)

Author	Diagnose	*N*	Medication	Result
Cai and Li [41]	Pulmonary heart failure	64	10 pills, tid for 2 weeks	The patients received Dantonic™ plus conventional treatment, the total effective rate was 92.1 %; in the conventional treatment group, it was 61.02 %. Dantonic™ group had better results in the relief of cough, asthma, dropsy, cyanosis, and palpitations than the control group
Fang et al. (still waiting for publishing)	Type II diabetes with hyperlipidemia	30	10 pills, tid for 2 months	Dantonic™ improved blood sugar and blood fat levels in the patients. It also improved level of fibrinogen, and prevented the advancement of complications
Fan and He [42]	Chronic liver fibrosis	45	30–40 pills per day for 3 months	The results suggested that after adding Dantonic™, the effective rate increased. Dantonic™ had a positive effect on relieving liver fibrosis, preventing hepatic cirrhosis, and had synergistic effect with potenline
Wei and Zhang [43]	Child viral myocarditis	43	3–6 years old: 8 pills, tid; 7 years and older: 10 pills, tid	Had adjuvant therapeutic effect
Yang [44]	Chronic gastritis	35	10 pills, tid	Had synergistic effect
Zhou [45]	Superficial thrombotic phlebitis (n = 14); thrombosis in brachial veins (n = 2); allergic arteriolitis (n = 2)	18	10 pills, tid	Result: 12 patients recovered (66.7 %), 5 patients had a beneficial effect, and the total effect rate was 94.5 %
Han et al. [46]	Ischemic optic neuropathy	76	10 pills, tid	Marked improvement in visual acuity, 51.7 %, improvement, 41.4 %, no improvement, 6.9 %. Total effective rate was 93.1 %. Marked improvement in visual field, 29.5 %, improvement, 52.5 %, no improvement, 18.0 %. Total effective rate was 82 %. The results suggested that Dantonic™ could dilate intracranial arteries, increase the blood flow, and relieve the state of ischemia and anoxia in the optic nerve lesions

(continued)

Table 16.2 (continued)

Author	Diagnose	*N*	Medication	Result
Tan et al. [47]	Pulmonary heart disease	35	10 pills, tid	The effective rate in the group treated with conventional treatment plus Dantonic™ and captopril was 91.4 %; the control group was treated with conventional treatment (breath oxygen, anti-infection, dispelling phlegm, relieving asthma, cardiac, diuretic, etc.), the effective rate was 71.9 %
Hu et al. [48]	Primary nephrotic syndrome	40	10 pills, tid for one-and-a-half years	All patients were treated with conventional treatment such as deltacortisone, etc. The therapy group simultaneously received Dantonic™. After 8 weeks, there was an obvious difference between the two groups. A half-year later, the total effective rate in Dantonic™ group reached 95 %,which was better than that of the control group (82.5 %), 1.5 years later, the effective rate in Dantonic™ group was 97.5 %, and the control group was 85 %. The difference was statistically significant
Liu et al. [49]	Chronic pulmonary heart disease	24	10 pills, tid for 3 weeks	Dantonic™ improved the symptoms
Chen et al. (2001)	Dizziness	40	10 pills, tid for 15 days	The control group received standard treatment of vessel dilatation; the therapy group received standard treatment plus Dantonic™. The total effective rate was 75 and 95 %, respectively
Weng [50]	Degenerative bone hyperplasia	115	4 pills, tid for 4 weeks	X-ray photos proved that the improvement rate was 97 %
Zhao [51]	Pain from liver cancer	12	3 pills, tid	The total effective rate was 75 %

(continued)

Table 16.2 (continued)

Author	Diagnose	*N*	Medication	Result
Lai and Ma [52]	Chronic hepatitis B	35	8–10 pills, tid	The improvement was evidently better than that of the other two control groups (compound danshen tablet and standard liver protecting drugs)
Yan [53]	Migraine	36	10 pills, tid for 15 days	In the control group, which received ergotamine caffeine tablets, the total effective rate was 72.5 %; in the Dantonic™ group, it was 94.5 %. The difference was statistically significant ($p < 0.05$ %)
Wang [54]	Cervical spondylosis	50	10 pills, tid for 2 months	The improvement rate was 98 %
Yang et al. [55]	Kidney disease	15	5–10 mg/kg/day in 2–3 times	Dantonic™ combined with hormone treatment could improve nephropathy, proteinuria, albumin, and cholesterol. It was shown that Dantonic™ was helpful in relieving hypercoagulability in the patients
Wu and Li [56, 57]	Central retinal artery occlusion	Cases report	In acute period once every 2 h, 3 times in total	Edema in macula area was diminished, and a little bit of degenerative focus was left
Wu and Li [56, 57]	Central retinal artery occlusion	16	Once every 2 h, 20 pills, tid	Combined with therapy of hyperbaric chamber, etc., 82 % patients improved to different extents
Sha et al. [58]	Active hepatic cirrhosis	47	10 pills, tid	All patients received symptomatic treatment. The extents of improvement in hyaluronic acid, type IV collagen, glutamate pyruvate transaminase, and γ-glubin in Dantonic™ group were better than those in the control group, demonstrating that Dantonic™ has an evident antihepatic fibrosis effect
Li et al. [59]	Senile hyperlipemia	52	10 pils, tid	TC, TG, and LDL were decreased significantly, indicating Dantonic™ has lipid-lowering effect

(continued)

Table 16.2 (continued)

Author	Diagnose	*N*	Medication	Result
Zhao and Liu [60]	Breast adenosis	349	10 pills, tid for 30 days	30 days after the treatment, the symptoms were significantly improved, and the tumors in 325 cases were reduced (84.2 %)
Pei and Tang [61]	Elderly fatty liver	60	10 pills, tid for 3 months	The total effective rate in the observation group was 91.67 %, in the control group was 68.34 %, $P < 0.01$, indicating that Dantonic™ had a good synergistic effect on fatty liver syndrome in aged patients
Li and Guan [62]	Hyperlipidemia	25	10 pills, tid for 2 months	Dantonic™ had a similar effect to inositolniacinate on the improvement of blood-fat and liver function
Zong [63]	Facial neuritis	43	10 pills, tid for 45 days	The total effective rate in Dantonic™ group was 81.4 %, in the control group, 66.7 %. The difference was significant ($P < 0.05$)
Liu and Zhang [64]	Hyperlipidemia	68	10 pills, tid for 5 months	TL and TG levels were significantly ($P < 0.01$) reduced after treatment with Dantonic™
Yu and Qi [65]	Pigmentary peliosis	40	10 pills, tid for 40 days	The total effective rate of treatment with vitamin C in addition to Dantonic™ was 82.5 %
Li et al. [66]	Soft tissue injury	30	10 pills, tid, external application	All patients were cured in 3–10 days
Ye [67]	Chronic cardiopulmonary disease	36	10 pills, tid, 2 weeks	The total effective rate in Dantonic™ group was 88.9 %, in the control group, 67.7 %. The difference was statistically significant
Yang [68]	Hyperlipemia	40	10 pills, tid, 6 weeks	Dantonic™ greatly reduced the levels of TC, TG, and LDL-C. There was a significant difference before and after treatment ($P < 0.01$); HDL-C was increased, but the difference was not significant ($P > 0.05$)

(continued)

Table 16.2 (continued)

Author	Diagnose	*N*	Medication	Result
Qiu [69]	Children primary nephrotic syndrome	20	5 pills, tid, 8 weeks	Dantonic™ had a distinct advantage in terms of improvement of symptoms. Urine protein was negative and blood viscosity was lowered
Chen et al. [70, 71]	Fatty liver	36	10 pills, tid, 3 months	The rate of ALT returning to normal was 57.1 % in the treatment group and 37.5 % in the control group; the difference between the two groups was significant ($P < 0.01$)
Liu and Liu [72]	Hyperlipemia	62	10 pills, tid, 4 weeks	Among 62 patients, there were 4 cases without significant changes of blood fat, the total effective rate was 93.5 %
Pang [73]	Diabetic peripheral neuropathy	12	10 pills, tid, 10 days	The total effective rate was 83.3 %
Zhao [74]	Traumatic vitreous hemorrhage	28	10 pills, tid, 40 days	The total effective rate was 92.86 % in Dantonic™ group, and 57.40 % in the control group, the difference was significant ($P < 0.01$)
Liu [75]	Type 2 diabetes combined with microangiopathy	30	10 pills, tid, 3 months	Dantonic™ had an obvious improving effect on microcirculation, especially on the improvement of microvascular structure, which was clearly better than that of the aspirin treatment group ($P < 0.01$)
Lu [76, 77]	Primary hypertension	40	10 pills, tid, 4 weeks	The total effective rate in the treatment group was 95 and 70 % in the control group; There was a significant difference in the effect of blood pressure reduction between the two groups ($P < 0.05$); Dantonic™ could greatly improve objective signs of blood stasis and blood fat disorder ($P < 0.01$)
Wang and Han [78]	Hyperlipemia	76	10 pills, tid, 6 months	Dantonic™ had a significant effect on reducing blood fat and improving blood rheology

(continued)

Table 16.2 (continued)

Author	Diagnose	*N*	Medication	Result
Zhu et al. [79]	QTc interval extension caused by antipsychotic drugs	38	10 pills, tid, 4 weeks	After taking Dantonic™, the QTc interval was significantly shortened compared with the status before treatment. The difference was significant ($P < 0.01$)
Chen and Fan [80]	High-altitude myocardial hypoxidosis	123	10 pills, tid, 14 days	Palpitation, chest tightness, precordial pain, and other symptoms disappeared in Dantonic™ group, the electrocardiogram showed normal results. The improvement of electrocardiogram and the disappearance of symptoms were superior to those of the control group
Deng et al. [81]	Early diabetic retinopathy	10	15 pills, tid, 90 days	Retinal microvascular eye tumors in both treatment and control groups were greatly reduced ($P < 0.05$), and the gray value perspective (MD) was lower than before treatment ($P < 0.05$); there was no significant difference between the two groups ($P > 0.05$)
Chen et al. [82]	Advanced pancreatic cancer	41	10 pills, tid, 8 weeks	The combination of Dantonic™ with chemotherapy can increase the clinical effect on treating pancreatic cancer, improve life quality, and relieve the side effects of chemotherapy
Zhu [83]	Clozapine-induced liver enzyme abnormalities	51	10 pills, tid, 4 weeks	The ALT and AST were distinctly reduced in the Dantonic™ group compared with the status before treatment, and the difference was significant ($P < 0.01$); there was a reduction of ALT and AST in the control group, but the difference was not statistically significant ($P > 0.05$)

(continued)

Table 16.2 (continued)

Author	Diagnose	*N*	Medication	Result
Wei et al. [84]	Chronic prostatitis	134	10 pills, tid, 4 weeks	The total effective rate was 88.1 % in the Dantonic™ group and 76.7 % in the control group ($P < 0.05$)
Zhang et al. (2006)	Liver cirrhosis	40	10 pills, tid, 3–6 months	Compared with the control group, liver function and liver fibrosis indicators in the Dantonic™ group were improved to varying degrees ($P < 0.05$)
Qiu et al. [85]	Oral lichen planus	40	10 pills, tid, 6 months	Dantonic™ could improve the blood rheology of OLP patients and has a curative effect on OLP
Zhang et al. [86]	High-altitude myocardial hypoxidosis	186	10 pills, tid, 6 months	Dantonic™ was able to prevent myocardial ischemia in people who had been predicted to have a 35 % risk of the expected occurrence of the disease by exercise ECG ($P < 0.01$). For patients who already had the sickness, the net recovery rate was 38.94 % after taking Dantonic™ over a short period ($P < 0.01$)
Ma et al. (2006)	Breast cancer	21	10 pills, tid, 6 weeks	Dantonic™ reduced the acute cardiac toxicity of breast cancer radiation therapy. ECG abnormalities were decreased and there was a significant difference ($P < 0.05$)
Yang et al. [87]	Primary hypertension	286	10 pills, tid, 24 months	Dantonic™ was greatly superior to the control group in improving blood fat, microcirculation, blood rheology, thrombin, and other unusual aspects ($P < 0.01$)
Bao et al. [88]	Diabetic retinopathy	37	15 pills, tid, 6 months	Dantonic™ had an enhancing effect on vision and improving effect on fundus, and it was superior to calcium dobesilate in the improvement of blood rheology

(continued)

Table 16.2 (continued)

Author	Diagnose	*N*	Medication	Result
Yang et al. [89]	Hypertensive retinal vein thrombosis	38	10 pills, tid, 60–90 days	The total effective rate was 84.2 % in the Dantonic™ treatment group and 44.7 % in the control group; the difference between the two groups was significant ($P < 0.01$)
Zhai et al. [90]	Migraine	41	10 pills, tid, 8 weeks	The total effective rate was 90.24 % in the treatment group and 69.57 % in the control group, the difference between the two groups was significant ($P < 0.05$). The control rates in the two groups were 43.90 and 17.39 %, respectively, and the difference between the two groups was very significant ($P < 0.01$)
Zhang et al. [91]	Hyperlipidemia with phlegm and blood stasis type	40	10 pills, tid, 3 months	The lipid-lowering effect of Dantonic™ was related to resolving phlegm and removing blood stasis as well as protection of the liver during lipid lowering, this might be related to reducing lipid peroxidation and the level of inflammatory factors. This has a great significance in furthering the study of the mechanism of Dantonic™ for the effect on resolving phlegm and removing blood stasis in lipid metabolism
Guo [92]	Early diabetic nephropathy	39	10 pills, tid, 8 weeks	Both significant efficacy rate and total effective rate were higher in the Dantonic™ group. There was a significant difference between the two groups. Improvement of urinary albumin, blood, urinary β2 microglobulin, fasting blood glucose, blood lipid, blood rheology, and other indicators in the treatment group were better than those of the control group

significant electroencephalogram improvement. Dantonic™ can be used as an adjunctive therapy in addition to the long-term use of antiepileptic drugs. In the area of noncoronary heart disease treatment, it is most helpful to further explore the mechanism of Dantonic™.

References

1. Gao Y, Li X, Zhang X, et al. Comparison of the effect of composite salviae dropping pill in the treatment of coronary heart disease and angina. In: 96th national symposium on composite salviae medicament form. 1996; p. 78.
2. Wang C, Ding A, Chen Y, et al. Clinical observation of effect of composite salviae dropping pill in the treatment of coronary heart disease. In: 96th national symposium on composite salviae medicament form. 1996; p. 76.
3. Wang C, Ding A, Lu X, Clinical investigation of treatment of stable angina pectoris with composite salviae dropping pill and compound salviate tablet. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 96.
4. Wang C, Ding A, Lu X. Clinical investigation of treatment of cerebral infarction with composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 109.
5. Wang C, Ding A, Lu X. Clinical investigation of ischemic vertigo with composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 112.
6. Cao L, Yu M. Clinical effect of composite salviae dropping pill on acute cerebral infarction. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 110.
7. Cao L, Yu M. Effect of composite salviae dropping pill on platelet function with cerebral infarction. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 110.
8. Wang Y, Bi D, Sun W, et al. Clinical investigation of improvement of cerebral artery hemodynamics with composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 110.
9. Gao W. Some experience of emergency treatment of patients with acute cerebral vascular disease with composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 111.
10. Yu S. Clinical application of composite salviae dropping pill in treatment of cerebral infarction. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 116.
11. Chen G, Yan K. A discussion of treatment of wind syndrome of the head with composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 112.
12. Ma J, Li F, Shi J. Clinical analysis of the influence of composite salviae dropping pill on blood rheology and cellular rheology of patients with cerebral infraction. In: 96th national symposium on composite salviae medicament form. 1996; p. 85.
13. Ma J, Li F, Shi J, et al. Clinical observation of composite salviae dropping pill in the treatment of 75 cases with coronary heart disease and angina. In: 96th national symposium on composite salviae medicament form. 1996; p. 97.
14. Xu X, Chen X. Mod J Integr Tradit Chin West Med. 2003;12(13):1347.
15. Zhang J. Clin J Anhui Tradit Chin Med. 2003;15(1): l0.
16. Fan W, Zhou X, Xu C, et al. Chin J Clin Rehabil. 2004;8(4):612.
17. Li L. Chin Pract Med. 2004;6(19):26.
18. Wang W, Li Y, Li Y, et al. Chin Tradit Herbal Drugs. 2004;35(10):1165.
19. Han Y, Wang Z, Wang Z, et al. Chin J Integr Tradit West Med. 2004;24(5):452.
20. Ren S, Tian J. Chin J Clin Med Res. 2005;11 (8):1107.
21. Song L. Shan Dong Med J. 2005;45(8):50.
22. Fu S. Hebei J Tradit Chin Med. 2005;27(2):139.
23. Wang Y. Shaanxi J Tradit Chin Med. 2006;27 (9):1093.
24. Qu Y, Yang W. J Henan Univ Chin Med. 2007;22 (1):59.
25. Hu W, Yao Y, Jin Y. J Integr Tradit Chin West Ophthalmol. 1998;16(2):294.
26. Yang L, Xu H, Zhao X. Tradit Herbal Drugs. 1998;29 (12):821.
27. Zheng Q, Wu G, Yang X. The influence of composite salviae dropping pill on microcirdulation of nail fold of patients with nephrotic syndrome. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 54.
28. Ci S, Yang C, Hu R. The clinical study of composite salviae dropping pill in the treatment of central sleep apnea syndrome. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 63.
29. Ci S, Xu J, Zhang J. The study of the use of composite salviae dropping pill in the treatment of arrhythmia. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 92.
30. Fan S, Jia L. The influence of composite salviae dropping pill on blood rheology of patients with pulmonary heart disease during the acute and aggravating period. In: 99th national workshop on

the modernization of traditional Chinese medicine (composite salviae). 1999; p. 72.
31. Zheng X. Long- term effect observation of treatment of myocardutic sequel with composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 98.
32. Fan X, Jia L. Clinical effect of composite salviae dropping pill on diabetes and nephrosis Accompanied by proteinuria. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 102.
33. Deng Z. Clinical observation of treatment of 54 patients with chronic hepatitis B with composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 180.
34. Pan S, Dang C, Mu Q. Clinical investigation of decompensated cirrhosis with composite salviae dropping pill and Li Zhu Chang Le. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 108.
35. Zou J, Wu P, Xu M, et al. Chin Med Factory Mine. 1999;27(5):357.
36. Zhi S, Meng B, Wang J. Effect of composite salviae dropping pill on hemorrheoiogy of patients with glomerulopathy. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 113.
37. Zhang L, Yang H. Treatment of retinal haemorrhage with composite salviae dropping pill. In: 99th national workshop on modernization of traditional Chinese medicine (composite salviae). 1999; p. 114.
38. Zhang W. Effect of composite salviae dropping pill on retinal on vein occlusion. In: 99th national workshop on the modernization of traditional Chinese (composite salviae). 1999; p. 115.
39. Zhang Z, Cui C, Ji G. Clinical observation of treatment of 33 patients with chronic pharyngitis with composite salviae dropping pill. In: 99th national workshop on modernization of traditional Chinese medicine (composite salviae). 1999; p. 117.
40. Liang R, Li C. J Chin Med Mater. l998;21(10):540.
41. Cai J, Li X. Tianjin Pharm. 2002;14(2):44.
42. Fan W, He Y. Research on anti-hepatic fibrosis effects of composite salviae dropping pill. Chin J Integr Med. 1997;10(19):1874.
43. Wei L, Zhang X. Discussion on the effect and course of composite salviae dropping pill in the treatment of infantile viral myocarditis. In: 96th national symposium on composite salviae medicament form. 1996; p. 46.
44. Yang Y. Clinical observation of composite salviae dropping pill in treating chronic gastritis. In: 96th national symposium on composite salviae medicament form. 1996; p. 57.
45. Zhou Y. Composite salviae dropping pill treatment of 18 cases with disease of the peripheral vessels. In: 96th national symposium on composite salviae medicament form. 1996; p. 85.
46. Han X, Zhang S, Wang Z, et al. Clinical observation of composite salviae dropping pill in the treatment of 76 cases with anterior ischemic lesion of optical nervepart. In: 96th national symposium on composite salviae medicament form. 1996; p. 89.
47. Tan S, Zeng Z, Song Y. Hebei Med Sci. 1999;5(3):35.
48. Hu Y, Hu Y, Su X, et al. J Integr Tradit West Med Intensive Crit Care. 1999;6(4):186.
49. Liu X, Zhang D, Peng X. Tradit Herbal Drugs. 2001;32(11):1022.
50. Weng J. Observation of the effect of composite salviae dropping pill in the treatment of retrograde hyperosteogeny. In: 96 national symposium on composite salviae medicament form. 1996; p. 90.
51. Zhao X. Observation of effect of oral intake of composite salviae dropping pill on relieving pain of liver cancer. In: 96th national symposium on composite salviae medicament form. 1996; p. 90.
52. Lai J, Ma A. Observation of effect of composite salviae dropping pill on patients with chronic hepatitis B and symptoms of accumulation of blood stasis in channel. In: 96th national symposium on composite salviae medicament form. 1996; p. 90.
53. Yan J. Composite salviae dropping pill treatment of 36 patients with migraine. In: 96th national symposium on composite salviae medicament form. 1996; p. 90.
54. Wang D. Chin Tradit Herbal Drugs. 2000;31(7):544.
55. Yang Q, Liu D, Chen D, et al. Clin J Med Officers. 2000;28(2):9.
56. Wu L, Li J. Chin J TCM Ophthalmol. 1999;9(2):111.
57. Wu L, Li J. Jiangxi Med Sci. 1999;34(4):225.
58. Sha Q, Cheng H, Xie X. J Integr Tradit West Med Liver Dis. 1999;9(6):50.
59. Li L, Yu F, Jia H. Chin J Geriatr. 2003;22(11):706.
60. Zhao Z, Liu S. Inner Mongolia Med J. 2003;35(4):356.
61. Pei D, Tang S. Shanghai J Tradit Chin Med. 2003;37(9):12.
62. Li X, Guan X. J Emerg Tradit Chin Med. 2003;12(4):338.
63. Zong S. Shaanxi J Tradit Chin Med. 2003;24(8):705.
64. Liu J, Zhang H. Tian Jin Pharmacy. 2003;15(3):38.
65. Yu S, Qi J. Heilongjiang J Tradit Chin Med. 2003;(3):31.
66. Li A, Li X, Du W. J Pract Tradit Chin Intern Med. 2003;17(3):188,189.
67. Ye L. Zhejiang J Integr Tradit Chin West Med. 2003;13(1):42.
68. Yang L. Clin J Tradit Chin Med. 2004;16(6):561.
69. Qiu B. J Med Thoer Pract. 2004;17(8):934.
70. Chen J, Guo J, Gao J, et al. Chin J Inf Tradit Chin Med. 2004;11(6):530.
71. Chen J, Tian J, Gu Y, et al. Chin J Clin Rehabil. 2004;8(24):5048.
72. Liu L, Liu C. J Chin Clin Med (Beijing). 2004;5(3):96.
73. Pang D. Public Med Forum Mag. 2004;8(11):1033.
74. Zhao K. Chin J Pract Med. 2004;31(14):39.

75. Liu Z. Chin J Hemorheol. 2004;14(2):197,203.
76. Lu X. Guangxi J Tradit Chin Med. 2004;27(4):6.
77. Lu X. J Guangxi Tradit Chin Med Univ. 2004;7(2):28.
78. Wang Y, Han T. Chin Tradit West Med J. 2004;2 (5):52.
79. Zhu Y, Lu S, Zhou H. Pract Clin J Integr Tradit Chin West Med. 2004;4(2):3.
80. Chen X, Fan X. J Chin Mod Intern Med. 2005;2 (9):778.
81. Deng H, Jin M, Yuan W, et al. J Tradit Chin Ophthalmol. 2005;15(2):72.
82. Chen X, Liang Q, Li X, et al. J Oncol. 2005;11(1):46.
83. Zhu Y. J Integr Tradit Chin West Med. 2005;5(2):5.
84. Wei D, Zhao Y, Wang X. Chin J Integr Tradit West Med. 2005;25(1):85.
85. Qiu F, Hui J, Hua L. Chin J Hemorheol. 2006;l6 (4):552,682.
86. Zhang X, Dong W, Pei Z, et al. Railway Occup Saf Health Environ Prot. 2006;33(4):161.
87. Yang D, Wang J, Yang D. Shandong J Tradit Chin Med. 2006;25(6):373.
88. Bao L, Yang G, Wang H. Hebei J Tradit Chin Med. 2006;28(4):304.
89. Yu Y, Wang S, Ma S, et al. Jilin J Tradit Chin Med. 2006;26(5):37.
90. Zhai S, Chen R, Wu X. J Pract Tradit Chin Med. 2006;22(1):26.
91. Zhang S, Chen Z, Lin Y, et al. Chin J Chin Mater Med. 2007;32(5):440.
92. Guo Y. Med J Chin People's Health. 2007;19(3):117.

Ancient and Modern Literature Research on Danshen Prescriptions

17

Guoguang Zhu, Xinde Shi and Jingsheng Zhao

Danshen is a drug with a long history of clinical application, recorded as early as in the Eastern Han dynasty's *Shen Nong's Classic of the Materia Medica*, in which it was called "Xichan Cao." Danshen was called "Chishen" and "Mu Yang Ru" in *Wu Pu's Materia Medica*, "Zhu Ma" in *Collective Commentaries on the Classic of Materia Medica*, and "Shanshen" in *Ri Hua-zi's Materia Medica*. In modern times, Danshen has the names of Zi Danshen, Hong Gen, Huoxue Gen, Da Hong Pao, Xueshen Gen, Hong Danshen, etc. in various botanical and materia medica records.

To further explore the functions and clinical compatibilities of Danshen, we have completely and thoroughly studied its prescription literatures, which, we believe, can best reflect the actual clinical effectiveness of the drug. The following is our research report.

17.1 Research Method

17.1.1 Data Collection

17.1.1.1 Range of Collection

Encyclopedia of Chinese Medicinal Formulas (10 volumes) was used as the primary source for formulas and prescriptions. The book is the most comprehensive, with the most prescriptions ever. It contains nearly 2,000 formulas with titles, collected from the medical literature as early as the Qin and Han dynasties and as recently as 1986.

Drug Specifications Promulgated by the Ministry of Public Health, P. R. China, Chinese Patent Medicine (《中华人民共和国卫生部药品标准·中药成方制剂》) (20 volumes).

17.1.1.2 Criteria of Collection

Any prescriptions in the above two books containing Danshen, no matter how many ingredients the prescription had, were collected.

17.1.2 Results

1,263 prescriptions containing Danshen were collected from the above two books. They were recorded in 218 ancient and modern literatures, including in literatures which have already been lost. Among the 218 literatures, 21 literatures containing 144 prescriptions were written in and before the Tang Dynasty; 27 literatures containing 391 prescriptions were written in the Song and Jin Dynasties; 43 literatures containing 76 prescriptions were written in the Yuan and Ming Dynasties; 83 literatures containing 272 prescriptions were written in the Qing Dynasty; and 44 literatures containing 380 prescriptions, including 240 Chinese patent medicines, were written in modern times.

G. Zhu (✉) · X. Shi · J. Zhao
The European Federation of Pharmaceutical Society, Stockholm, Sweden
e-mail: ggz68111@yahoo.com

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17.1.2.1 The Tang Dynasty and Before (Before 907 AD)

There are 144 prescriptions containing Danshen in the literatures written in or before the Tang Dynasty (see Table 17.1), and more than one half of them were recorded in *Important Formulas Worth a Thousand Gold Pieces* and *Supplement to 'Important Formulas Worth a Thousand Gold Pieces'*, both written by Sun Simiao. *Emergency Formulas to Keep Up One's Sleeve* and *Liu Juan-zi's Ghost-Bequeathed Formulas* also contain some formulas. Besides the formulas from the above four books, all other formulas were originally recorded in the literatures which have all been lost, such as *Fan Wang Formulas* (《范汪方》), *Master Seng Shen's Formulas*, *Simplified Formulas* (《删繁方》), and *Ancient and Modern Records of Proven Formulas*. The formulas recorded in these lost literatures were quoted in *Arcane Essentials from the Imperial Library*, *Refined Medical Prescriptions* (《医心方》), *A New Book of Pediatrics*, and *Yongle Encyclopedia*.

The earliest Danshen-containing formulas were recorded in Chaps. 5 and 8 of *Emergency Formulas to Keep Up One's Sleeve*, which were named "Danshen Paste".

Table 17.1 Source of Danshen-containing prescriptions in the Tang Dynasty and before

Number of prescriptions	Medical work and number of prescriptions in the work	Number of medical works	Total number of prescriptions
≥50	Important Formulas Worth a Thousand Gold Pieces 66	1	66
≥10	Supplement to 'Important Formulas Worth a Thousand Gold Pieces' 13	2	24
	Instant effect Formulas (《近效方》) 11		
≥5	Liu Juan-zi's Ghost-Bequeathed Formulas 8	5	3 1
	Formulas for Infants and Juveniles (《婴孺方》) 7		
	Longevity Secrets (《延年秘录》) 6		
	Ancient and Modern Records of Proven Formulas 5		
	Cui' s Prescriptions (《崔氏方》) 5		
≥2	Universal Aid Formulas (《广济方》) 3	6	16
	Simplified Formulas 3		
	Fan Wang Formulas 3		
	Master Seng Shen's Formulas 3		
	Xu Renze's Formulas (《许仁则方》) 2		
	Emergency Formulas to Keep Up One's Sleeve 2		
1	Illustration of five viscera and six bowels (《五脏六腑图》)	7	7
	Long Shu Pusa Yan Lun (《龙树菩萨眼论》)		
	Zang Wenzhong's Prescriptions (《张文仲方》)		
	Jing Xin Lu (《经心录》)		
	Ji Ji Fang Lun (《济急方论》)		
	Su Nv Jing (《素女经》)		
	Compilation of Proven Formulas (《集验方》)		
Total		21	144

17.1.2.2 The Song and Jin Dynasties (960–1234 AD)

The number of Danshen-containing prescriptions ranked highest in the Song and Jin Dynasties, but the literatures containing these prescriptions were not abundant. The main reason for this was that Danshen prescriptions in and before the Song dynasty were collected in two prescription works compiled by the Song government; *Formulas from Benevolent Sages Compiled during the Taiping Era* and *Comprehensive Recording of Divine Assistance*. The two works collected more than 80 % of Danshen prescriptions during that time. Among the prescription works compiled by individuals, *Chen Suan's gynecology* (《陈素庵妇科补解》) contains the most formulas, which reflected the fact that Danshen was widely used by some doctors in gynecology in the Song dynasty (Table 17.2).

Table 17.2 Source of Danshen-containing prescriptions in the Song and Jin Dynasties

Number of prescriptions	Medical work and number of prescriptions in the work	Number of medical works	Total number of prescriptions
≥100	Formulas from Benevolent Sages Compiled during the Taiping Era 179	2	316
	Comprehensive Recording of Divine Assistance 137		
≥5	Chen Suan's gynecology 18	3	32
	Ji Feng Universal Relief Formulas (《鸡峰普济方》) 9		
	Yu Yao Yuan Formulas (《御药院方》) 5		
≥3	Experiential Formulas for Universal Relief 4	5	19
	Treatise on Diseases, Patterns, and Formulas Related to the Unification of the Three Etiologies 4		
	An Elucidation of Formulas 4		
	Shen Qiao Wan Quan Formulas (《神巧万全方》) 4		
	Bo Ji Formulas (《博济方》) 3		
2	Beneficial Formulas from the Taiping Imperial Pharmacy	7	14
	Secrets from the Orchid Chamber		
	A New Book of Pediatrics		
	Chuang Jia Mi Bao (《传家秘宝》)		
	The Complete Compendium of Fine Formulas for Women		
	Secret Formulas of the Yang Family		
	Treatment of Beriberi (《脚气治法总要》)		
1	Wei Ji Bao Shu (《卫济宝书》)	10	10
	Xiaoer Wei Sheng Zong Wei Lun Fang (《小儿卫生总微论方》)		
	Wang Yue's gynecology and Obstetrics (《王岳产书》)		
	Dong-yuan's Proven Formulas		
	Chan Ru Bei Yao (《产乳备要》)		
	Proven Secret formulas (《经验秘方》)		
	Suwen Bingji Qiyi Baoming Ji (《素问病机气宜保命集》)		
	Yan's Treatise on Formulas for Children		
	Simple and Easy Formulas		
	Jian Yao Ji Zhong Formulas (《简要济众方》)		
Total		27	391

17.1.2.3 The Yuan and Ming Dynasties (1271–1644 AD)

The number of Danshen-containing prescriptions in the Yuan and Ming Dynasties was the smallest, with 76 prescriptions in total. Although the biggest prescription book in history, *Formulas for Universal Relief*, was written at that time, the majority of prescriptions in the book were derived from *Formulas from Benevolent Sages Compiled during the Taiping Era* of Song dynasty. Therefore, there were only 18 prescriptions in the book which were new inventions. However, the number of literatures containing Danshen-containing prescriptions, especially those containing only one Danshen prescription, was relatively large. There were 32 medical works including works in the department of internal medicine, gynecology, pediatrics and ophthalmology, etc., indicating that Danshen was applied in various clinical departments during that time (Table 17.3).

17.1.2.4 The Qing Dynasty (1644–1911 AD)

The number of Danshen-containing prescriptions in the Qing Dynasty was large, and the number of medical works involved was the highest. The great physicians, such as Fei Boxiong, Chen Shiduo, and Cheng Guopeng, were skilled at using Danshen for the treatment of diseases. Their medical works, *The Refined in Medicine Remembered* (by Fei Boxiong), *Syndrome Differentiation* (《辨证录》) (by Chen Shiduo), *Medical Revelations* (by Cheng Guopeng), contained 76 Danshen prescriptions, which accounted for 28 % of Danshen prescriptions during the dynasty. At that time, Danshen was widely used, and Danshen prescriptions appeared in medical texts on internal medicine, gynecology, pediatrics, ophthalmology, etc. In addition, Danshen was recorded in a great number of monographs on externally contracted diseases, such as *Revised Popular Guide to 'Treatise on Cold Damage'*, *The Grand Compendium of Measles* (《麻症集成》), *Collected Annotations and Explainations of Measles and Pox* (《痧痘集解》), *Yang Mao Wen Zheng Lun* (《羊毛温症论》), and *Systematic Differentiation of Warm Diseases*. Danshen was not recorded in the first monograph on externally contracted diseases, *Treatise on Cold Damage*, which appeared in the Eastern Han dynasty (Table 17.4).

17.1.2.5 Modern Era (After 1911)

There are mainly two categories of literature on Danshen-containing prescriptions the in modern era: one collected from the prescriptions and clinical literatures, with 43 medical works and 140 prescriptions in total, and the other collected from *Drug Specifications Promulgated by the Ministry of Public Health, P R China, Chinese Patent Medicine* (20 volumes), with 240 prescriptions in total, which accounted for about 16 % of the total prescriptions (3,867). There were 44 literatures and 380 prescriptions in total.

The great physicians who used Danshen in their prescriptions include Ding Ganren, Zhang Xichun, Xie Liheng, Zhao Bingnan, Guan Youbo, Zhu Renkang, Liu Huimin, Xia Duheng, et al. Zhang Xichun invented 11 Danshen-containing prescriptions which makes him the person with the most such inventions, suggesting that he was good at the application of Danshen in his practice (Table 17.5).

17.2 The Historical Evolution of the Name, Processing, and Compatibility of Danshen

17.2.1 Name

Although Danshen has had many synonymies both in ancient and modern times, our study showed that the name of "Danshen" appears in the majority of prescriptions, and there are no other names except for Chishen, Zi Danshen, and Hong Danshen.

The name of "Chishen" was only recorded in one prescription which was "24-Ingredient Panacean Pill" in volume 4 of *Bo Ji Formulas* in the Song dynasty.

The name of "Zi Danshen" was recorded in 12 prescriptions and appeared in the literatures in the Qing Dynasty, such as "Tiaojing Pill" (调经丸)

Table 17.3 Source of Danshen-containing prescriptions in the Yuan and Ming Dynasties

Number of prescriptions	Medical work and number of prescriptions in the work	Number of medical works	Total number of prescriptions
≥10	Formulas for Universal Relief 18	1	18
≥2	Safeguarded Formulas from the Lu Mansion 4	11	26
	Zun Sheng Ba Jian (《遵生八笺》) 4		
	Prolonging Life and Preserving the Origin 3		
	Wan's gynecology 2		
	Restoration of Health from the Myriad Diseases 2		
	Quintessence of Exernal Medicine 2		
	Hong Lu Dian Xue (《红炉点雪》) 2		
	Xing Yuan Sheng Chun (《杏苑生春》) 2		
	Standards for Diagnosis and Treatment 2		
	The Complete Works of Jing-yue 2		
	Dou Zhen Ren Duan Lu (《痘疹仁端录》) 2		
1	Precious Mirror of Health	31	32
	Dan Tai Yu An (《丹台玉案》)		
	Yun Qi Zi Bao Ming Ji (《云歧子保命集》)		
	Guide to Benevolence		
	Ren Zhai Zhi Zhi Fu Yi (《仁斋直指附遗》)		
	Effective Formulas from Generations of Physicians		
	The Complete Compendium of Ancient and Modern Medical Works		
	Gu Ji Yi Jian (《古今医鉴》)		
	Effective Prescription of Surgery (《外科百效》)		
	Wai Ke Huo Ren Ding Ben (《外科活人定本》)		
	Extensive Notes on Medicine from Xian Xing Studio		
	Required Readings from the Medical Ancestors		
	Yi Lin Fang (《医林方》)		
	Black Pearl from Red Waters		
	Fine Formulas of Wonderful Efficacy		
	Song Ya Yi Jing (《松崖医径》)		
	Experience Prescription for Wind (《治风经验方》)		
	Shang Ke Xuan Cui (《疡科选粹》)		
	Experience Secret Recipe (《经验秘方》)		
	Huo Ren Xin Tong (《活人心统》)		
	A Compendium of Male Disorders		
	A Compendium of Female Disorders		
	Complete Manual of Experience in the Treatment of Sores		
	Patterns and Treatment Based on Pulse and Etiology		
	Corrections and Annotations to Fine Formulas for Women		
	The Secret Transmission of Long-mu's Ophthalmology		
	Complete Collection of Ophtalmology		
	Numerous Miraculous Prescriptions for Health Cultivation		
	Jie Wei Yuan Sou (《解围元薮》)		
	Zeng Bu Nei Jing Shi Yi (《增补内经拾遗》)		
	Empirical Formulas from the Treasured Scroll Chamber		
Total		43	76

Table 17.4 Source of Danshen-containing prescriptions in the Qing Dynasty

Number of prescriptions	Medical work and number of prescriptions in the work	Number of medical works	Total number of prescriptions
≥10	The Refined in Medicine Remembered 28,	4	90
	Syndrome Differentiation (《辨证录》) 28,		
	Medical Revelations 20,		
	Essence of Ancient Prescription (《古方汇精》) 14		
≥3	Rhymed Discourse on External Remedies 9,	24	110
	Hui Yue Medical Mirror (《会约医镜》) 8,		
	The Grand Compendium of Measles (《麻症集成》) 7,		
	Yi Fang Jian Yi (《医方简义》) 6,		
	Yi Lue Liu Shu (《医略六书》) 6,		
	Ma Pei-zhi's Case Records in External Medicine 5,		
	Buju Ji (《不居集》) 5,		
	Sisheng Xinyuan (《四圣心源》) 5,		
	Hui Zhi Tang Prescription (《惠直堂方》) 5,		
	Collected Annotations and Explainations of Measles and Pox (《痧痘集解》) 5,		
	Selected Prescription for Cixi and Guangxu (《慈禧光绪医方选议》) 5,		
	Understanding the complicated diseases (《杂症会心录》) 4,		
	Experience Gained in Treating External Sores 4,		
	Si He Ting Ji Fang (《饲鹤亭集方》) 4,		
	Orthodox Lineage of Medicine 4,		
	New Compilation of Proven Formulas 4,		
	Bu Zhi Yi Bi Yao (《不知医必要》) 3,		
	Xian Nian Ji (《仙拈集》) 3,		
	Wondrous Lantern for Peering into the Origin and Development of Miscellaneous Diseases 3,		
	Yi Ji (《医级》) 3,		
	Qing Nang Quan Ji (《青囊全集》) 3,		
	Revised Popular Guide to 'Treatise on Cold Damage' 3,		
	Chong Qing Tang Medical Essays (《重庆堂医学随笔》) 3,		
	Sha Zhang Yu Heng (《痧胀玉衡》) 3		
2	Wei Sheng Hong Bao (《卫生鸿宝》),	17	34
	Ye's gynecology (《叶氏女科》),		
	Mental Cultivation Methods of gynecology and Obstetrics (《产科心法》),		
	Tong Shou Lu (《同寿录》),		
	Zhu Lin gynecology (《竹林女科》),		
	Yi Xue Chuan Deng (《医学传灯》),		
	Medical Collection (《医学集成》),		
	Qi Fang Lei Bian (《奇方类编》),		
	Complete Collection for Rashes (《治疹全书》),		
	Complete Dictionary for Surgeon (《疡医大全》),		
	Cheng Shu (《诚书》),		
	Fine Writings and Medical Mirror (《笔花医镜》),		
	Gu Song Yuan' Medical Mirror (《顾松园医镜》),		
	Chuan Mo You De Ji (《揣摩有得集》),		
	Ci Hang Collection (《慈航集》),		
	Lü Shuang Collection (《履霜集》),		
	Hao Jing Zhi Zhi (《镐京直指》)		

(continued)

Table 17.4 (continued)

Number of prescriptions	Medical work and number of prescriptions in the work	Number of medical works	Total number of prescriptions
1	Wan' s Private Clinical Experience (《万氏家传点点经》),	38	38
	Da Sheng Yao Zhi (《大生要旨》),		
	Nü Ke Zhi Zhang (《女科指掌》),		
	Heats Differentiation in Pediatric (《小儿诸热辩》),		
	Nei Wai Mi Fang Wai Chuan (《内外验方秘传》),		
	Gu Ji Yi Che (《古今医彻》),		
	Surgery Collection (《外科大成》),		
	Shi Shi Mi Lu (《石室秘录》),		
	Fu Ke Yu Chi (《妇科玉尺》),		
	Cheng Fang Bian Du (《成方便读》),		
	Yang Mao Wen Zheng Lun (《羊毛温症论》),		
	He' s Ji Sheng Lun (《何氏济生论》),		
	Precepts for Physicians,		
	Golden Mirror of the Medical Tradition,		
	Yi Lin Zuan Yao,		
	Medical Description,		
	Comprehensive Medicine According to Master Zhang,		
	Danger Zone of Medicine,		
	Systematic Differentiation of Warm Diseases,		
	Yi Chao Lei Bian (《医钞类编》),		
	Yi Bu Quan Lu (《医部全录》),		
	New Compilation of Prolonging Life (《寿世新编》),		
	Shi Fang Ge Kuo (《时方歌括》),		
	Gang Mu Shi Yi (《纲目拾遗》),		
	Liang Fang Ji Ye (《良方集腋》),		
	Liang Peng Hui Ji (《良朋汇集》),		
	Zheng Zhi Bao Jian (《证治宝鉴》),		
	Cock Crowing Records (《鸡鸣录》),		
	Collection of Private Prescription (《经验各种秘方辑要》),		
	Zheng' s Private gynecology Prescriptions (《郑氏家传女科万金方》),		
	Huo Ren Fang Hui Ji (《活人方汇编》),		
	Complete Collection of Li Symtom (《疡科全书》),		
	Question and answer of gynecology and		
	Obstetrics (《胎产问答》),		
	Bing Ji Sha Zhuan (《病机沙篆》),		
	Measles Notes (《麻疹阐注》),		
	Complete Collection of Cholera (《痧症全书》),		
	Ji Yan Liang Fang (《集验良方》),		
	Song Ya Zun Sheng (《嵩崖尊生》)		
Total		83	272

Table 17.5 Source of Danshen-containing prescriptions in modern era

Number of prescriptions	Medical work and number of prescriptions in the work	Number of medical works	Total number of prescriptions
≥10	Chinese Patent Medicine Formulary (《全国中药成药处方集》) 19,	4	53
	Diagnosis of Traditional Chinese Medicine (《中医症状鉴别诊断学》) 12,		
	Records of Chinese Medicine with Reference to Western Medicine 11,		
	TCM gynecology (《中医妇科治疗学》) 11		
≥5	Prescription and Case Reports for Clinical Practice (《临证医案医方》) 8,	7	43
	Beijing Chinese Patent Medicine Selection (《北京市中药成方选集》) 7,		
	Famous Prescription in Ancient and Modern Times (《古今名方》) 7,		
	Dermatology of Traditional Chinese Medicine (《中医皮肤病学简编》) 6,		
	Zhu Renkang's Clinical Experience (《朱仁康临床经验集》) 6,		
	Qian Jia Miao Fang (《千家妙方》) 5,		
	The Textbook of TCM Traumatology (《中医伤科学讲义》) 5		
≥2	Zhao Bingnan's Clinical Experience (《赵炳南临床经验集》) 4,	9	19
	Chinese Pharmacopoeia (《中国药典》) 3,		
	Gu' s Medical Experience (《顾氏医径》) 2,		
	Ding Ganren's Private Prescriptions (《丁甘仁家传珍方选》) 2, Traditional Chinese Medicine of Gynecology (《中医妇科学》) 2,		
	Manual of Chinese Materia Medica Preparation (《中药制剂手册》) 2,		
	Research of the Treatment of Common Diseases with Traditional Chinese Medicine (《常见病的中医治疗研究》) 2,		
	Case Record of Liu Huimin (《刘惠民医案》) 2		

(continued)

Table 17.5 (continued)

Number of prescriptions	Medical work and number of prescriptions in the work	Number of medical works	Total number of prescriptions
1	Standards of Chinese Patent Medicine of Beijing (《北京市中成药规范》),	24	25
	Drug Standards of Shanghai (《上海市药品标准》),		
	Shandong Medical Journal (《山东医刊》),		
	New Prescriptions of Pediatrics of Integrated Medicine (《中西医结合儿科试用新方》),		
	Internal Medicine of Traditional Chinese Medicine (《中医内科学》),		
	Therapeutics of internal Medicine of Traditional Chinese Medicine (《中医内科临床治疗学》),		
	Knowledge Manual of Traditional Chinese Medicine (《中药知识手册》),		
	Surgery of Traditional Chinese Medicine (《中医外科学》),		
	Journal of Traditional Chinese Medicine (《中医杂志》),		
	Treatment of Psychosis with Traditional Chinese Medicine (《中医治疗精神病》),		
	Selected Readings of Original Work of Traditional Chinese Medicine (《中医原著选读》),		
	Great Dictionary of Chinese Medical Books (《中国医学大辞典》),		
	Obstetrics and gynecology (《妇产科学》),		
	Selection of Medical Documents (《医学资料选编》),		
	Medical Suijin Lu (《医学碎金录》),		
	Selection of Apoplexy and Syncopecollapse (《卒中厥证辑要》),		
	Xia Duheng's Case Record (《夏度衡医案》),		
	Common Chinese Patent Medicine (《常用中成药》),		
	Six Meridians of Ophtalmology (《眼科六经法要》),		
	Clinical Notes of Ophtalmology (《眼科临症笔记》),		
	Wen' s Good Prescription (《温氏经验良方》),		
	Xie Liheng's Private Prescription (《谢利恒家用良方》),		
	Integrated 300 Good Prescriptions (《集成良方三百种》),		
	Preparations of Chinese Medicinal (《中药成分制剂》),		
	Selections from the Clinical Experience of Guan You-bo		
Total		44	140

in *Ji Yan Liang Fang*, "Sanyu Qinghong Zhitong Decoction" (散瘀清火止痛汤) in *New Compilation of Prolonging Life*, "Xuanfu Daizhe Decoction" (旋覆代赭汤) in *Yi Liu Liu Shu*, "Hui Lan Beverage" (回澜饮) in *Collection of Experience Private Prescriptions*, and "Taiyi Jiuku Biwen Dan" (太乙救苦辟瘟丹) in *Liang Fang Ji Ye*, and so on.

The name of "Hong Danshen" was recorded in one prescription in "5-Ingredient Blood-Invigorating Decoction" (五味活血汤) in *Qian Jia Miao Fang*.

Therefore, although Danshen has a variety of names, the name of "Danshen" was the most popular in the medical literature.

17.2.2 Processing

There are few descriptions of the processing method of Danshen in the materia medica literatures. The scanty descriptions are mainly like the following: "moistening with wine and baking slightly" (in *Penetrating the Mysteries of the Materia Medica*); "frying with wine" [in *Yao Pin Bian Yi* (《药品辨义》)]; "frying with pig heart blood" [in *Ben Cao Hai Li* (《本草害利》)], and so on.

We have found in this study that there is a large amount of discussion on the preparation and processing of Danshen in prescriptions and clinical literatures. According to the ages of the literatures, prescriptions prior to the Tang Dynasty only recorded the method of "cutting" (citing *Ancient and Modern Records of Proven Formulas* by *Arcane Essentials from the Imperial Library*), and no other methods were described.

During the Song dynasty, the preparation methods included removing soil, removing soil from the plant, removing the basal part of the stem, removing root nodes, washing, etc. [in Kushen Pill (苦参丸), Huangqi Pill (黄耆丸) and Aconite Decoction in *Comprehensive Recording of Divine Assistance*, and Tianwang Buxin Pill (天王补心丸) in *Secret Formulas of the Yang Family*.] The processing methods included stir-frying, slight stir-frying, slight frying, etc. [in Bupleurum Pill (柴胡丸), Antelope Horn Beverage (羚羊角饮) and Danshen Pill in *Comprehensive Recording of Divine Assistance*].

Besides removing the basal part of the stem, removing soil from the plant, and washing with water from the Song dynasty, the preparation methods in the Yuan and Ming Dynasties also included removing the yellow cortex (in Celestial Emperor Heart-Supplementing Elixir in *Extensive Notes on Medicine from Xian Xing Studio*). Besides stir-frying, the processing methods also included "soaking in wine overnight, drying under the sun," and "frying with wine" (in Danshen Pill in *Black Pearl from Red Waters* and Xiexue Decoction (泻血汤) in *Secrets from the Orchid Chamber*).

In the Qing Dynasty, besides cutting, the preparation methods also included removing the head and tail [shown in Yuhuan Pill (玉环丸) and Shenxiang Eight-Gem Paste (参香八珍膏) in *Jottings from Hall of Repeated Celebration*]. Besides frying and frying with wine, the processing methods also included soaking with ginger juice, washing with wine and fumigating, steaming with wine, frying to a black color, steeping in wine, and baking [in Qingfu Jin Dan (青附金丹) and Shenxiang Eight-Gem Paste in *Jottings from Hall of Repeated Celebration*, Hezhong Pill (和中丸) in *Medical Revelations*, Donkey-Hide Gelatin Pill in *Yi Lue Liu Shu*, Mizhi Wuguji Pill (秘旨乌骨鸡丸) in *Wei Sheng Hong Bao* and Taiyi Jiuku Biwen Dan in *Liang Fang Ji Ye*].

Besides steaming with wine, most prescriptions in the modern era did not mention the processing methods.

From the above review, we can see that the most common processing method for Danshen was processing with wine, including washing with wine, soaking in wine, frying with wine, fumigating with wine, steaming with wine and so on. Theoretically, the wine has the function of dispersing acrid, running and scurrying. After processing with wine, Danshen's function of invigorating blood could be enhanced, and its effect on blood stasis diseases could be even better. However, whether the function of Danshen is really enhanced by processing with wine requires validation by modern processing science.

17.2.3 Number of Ingredients in the Prescriptions

Among the 1,263 Danshen-containing prescriptions, there are 6 prescriptions, one ancient and 5 modern, which contain only Danshen. The

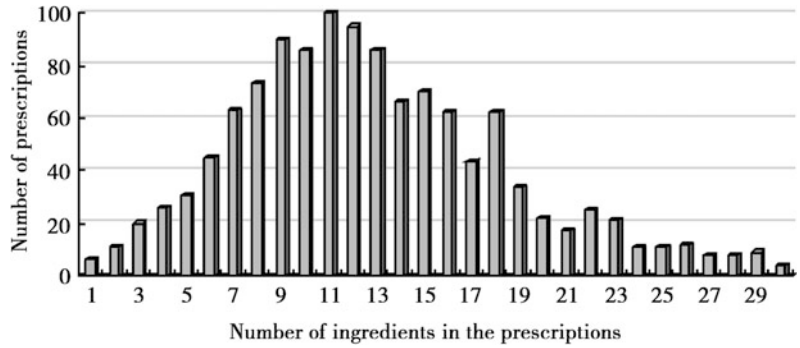

Fig. 17.1 Distribution of the number of ingredients in the prescriptions

prescription with the most ingredients is Qingyang Paste (清阳膏) in *Rhymed Discourse on External Remedies* in the Qing Dynasty, which contains 106 ingredients. However, there are not many prescriptions containing more than 30 ingredients. Statistical analysis of the prescriptions with fewer than 30 ingredients shows that the majority of Danshen prescriptions were medium-sized prescriptions containing about 10 ingredients (Fig. 17.1).

As is shown in Fig. 17.1, prescriptions containing 11 ingredients were of highest abundance, followed by those containing 12, 9, 10, and 13 ingredients.

17.2.4 Preparations

The Danshen prescriptions include preparations for both oral and external uses; the former contains 1,169 prescriptions which account for 92 % of the total, and the latter includes 94 prescriptions and accounts for about 8 %. The traditional Danshen preparations are mainly pills, decoctions, powders, pastes, and alcoholic agents. The preparations for oral use are mainly decoctions, and for external use mainly pastes (Fig. 17.2). Modern preparations are mainly tablets, capsules, beverages, syrups, granules, instant herbal medicines, mixtures, injections, enemas and so on.

17.2.5 Medicinal Herbs Used Together with Danshen

17.2.5.1 The Tang Dynasty and Before

There were 144 Danshen-containing prescriptions before and during the Tang Dynasty. These prescriptions used a total of 253 different medicinal ingredients (including Danshen), which appeared in the prescriptions 1927 times. On average, each ingredient appeared in 7 prescriptions. There were 73 ingredients which appeared in 7 or more prescriptions. Their frequencies of appearance are shown in Table 17.6.

As is shown in Table 17.6, the 10 ingredients which were most frequently used together with Danshen were cinnamon bark, ginseng, siler, dried ginger rhizome, Sichuan lovage root, licorice root, two-toothed achyranthes root, white atractylodes rhizome, poria, and fresh ginger. These herbs belong to five functional categories: warm the interior, supplement qi, dissipate wind-cold, invigorate blood, and calm the mind.

The 73 ingredients are in the 15 major functional categories, and according to their total number of appearances in the prescriptions, they are, from highest to lowest: supplement and boost, warm the interior, dispel wind-damp, clear heat, treat blood, calm the mind, dissolve phlegm and relieve cough, purgation, remove and percolate dampness, rectify qi, dissipate wind-heat,

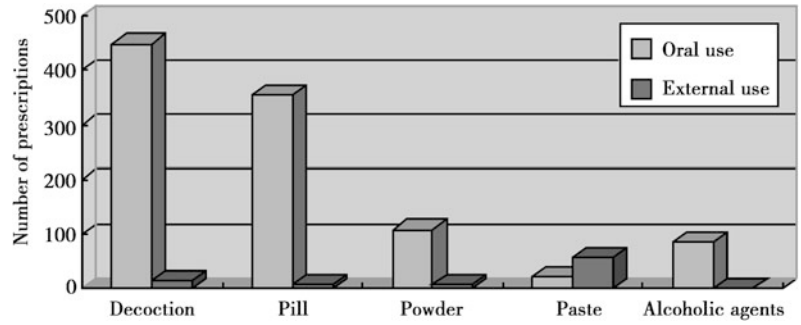

Fig. 17.2 Major Danshen preparations

Table 17.6 The frequencies of the medicinal ingredients used together with Danshen before and during the Tang Dynasty

Frequency of appearance in the prescriptions	Medicinal ingredients and number of appearances	Number of ingredients
≥50 prescriptions	Cinnamon bark (桂心) 61, ginseng (人参) 58, siler (防风) 51	3
≥40 prescriptions	Dried ginger rhizome (干姜) 48, Sichuan lovage root (川芎) 48, licorice root (甘草) 47, two-toothed achyranthes root (牛膝) 46, white atractylodes rhizome (白术) 44, poria (茯苓) 44, fresh ginger (生姜) 41, Manchurian wild ginger (细辛) 40, Chinese angelica (当归) 40	9
≥30 prescriptions	Monkshood (附子) 37, rhubarb root and rhizome (大黄) 33, peony root (芍药) 31	3
≥20 prescriptions	Double teeth pubescent angelica root (独活) 29, pricklyash peel (蜀椒) 29, large leaf gentian root (秦艽) 28, dried rhemannia (干地黄) 28, dendrobium (石斛) 27, astragalus root (黄耆) 26, scutellaria root (黄芩) 22, figwort root (玄参) 21, angelica root (白芷) 20, platycodon root (桔梗) 20	10
≥10 prescriptions	Eleutherococcus root-bark (五加皮) 19, tangerine pericarp (橘皮) 19, cornus (山茱萸) 18, common monkshood mother root (乌头) 18, eucommia bark (杜仲各) 18, light yellow sophora root (苦参) 17, black cohosh rhizome (升麻) 16, croton seed (巴豆) 16, apricot kernel (杏仁) 16, adenophora root (沙参) 16, dwarf lilyturf tube (麦门冬) 16, coix seed (薏苡仁) 16, dried rhemannia (生地黄) 15, gypsum (石膏) 15, Chinese magnolivine fruit (五味子) 14, four stamen stephania root (防己) 14, ephedra (麻黄) 14, desert cistanche (肉苁蓉) 14, monkshood (天雄) 13, pinellia rhizome (半夏) 13, medicinal evodia fruit (吴茱萸) 13, Chinese wolfberry root-bark (地骨皮) 12, thin-leaf milkwort root (远志) 12, Chinese date (大枣) 12, water plantain rhizome (泽泻) 12, dioscoreae deltoideae root (薯蓣) 12, magnolia bark (厚朴) 11, rhinoceros horn (犀角) 11, (莽草叶) 10, (蒴藋) 10, Magnetite (磁石) 10	31
≥7 prescriptions	Monkshood (侧子) 9, oriental arborvitael (柏子仁) 9, tatarian aster root (紫菀) 9, hogfennel root (前胡) 8, Indian bread with hostwood (茯神) 8, grassleaf sweetflag rhizome (菖蒲) 8, cinnabar (朱砂) 7, oyster shell (牡蛎) 7, (茵芋) 7, Stalactite (钟乳) 7, rice paper plant pith (通草) 7, polyporus (猪苓) 7, Himalayan teasel root (续断) 7, antelope horn (羚羊角) 7, hypoglaucous collett yam rhizome (薯蓣) 7, coptis rhizome (黄连) 7, chrysanthemum flower (菊花) 7	17
Total		73

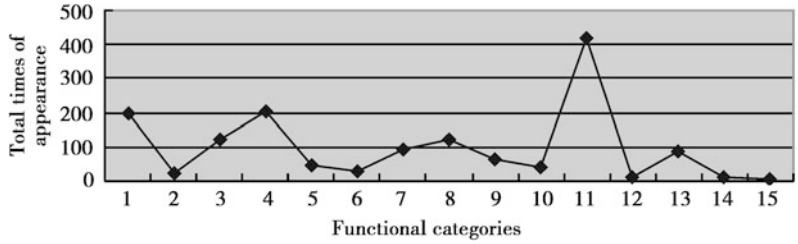

Fig. 17.3 Frequency distributions of the functional categories of medicinal ingredients used together with Danshen before and during the Tang Dynasty. The functional category codes: (*1*) dissipate wind-cold; (*2*) dissipate wind-heat; (*3*) clear heat; (*4*) warm the interior; (*5*) purgation; (*6*) rectify qi; (*7*) treat blood; (*8*) dispel wind-damp; (*9*) dissolve phlegm and relieve cough; (*10*) remove and percolate dampness; (*11*) supplement and boost; (*12*) consolidate and astringe essence; (*13*) calm the mind; (*14*) calm the liver and extinguish wind; (*15*) open the orifices

calm the liver and extinguish wind, consolidate and astringe essence, and open the orifices (Fig. 17.3). Among these categories, the one which appeared the most frequently was the supplementing and boosting category, which includes medicinal herbs that supplement qi, blood, yin, and yang, etc.

The next most frequently used categories are warm the interior, dispel wind-damp, and clear heat. Most of these herbs are acrid-warm medicinals, indicating that before and during the Tang Dynasty, Danshen was mainly used for deficiency syndromes and most likely used together with drugs with warm nature to treat deficiency-cold diseases and wind-cold damp *bi* syndromes. For example, in *Important Formulas Worth a Thousand Gold Pieces*, there is a Huangqi Lizhong Decoction (黄耆理中汤) used for the treatment of deficiency cold in upper *jiao*, shortness of breath, and faint voice. The decoction was a combination of Danshen with drugs for supplementing qi, warming interior, dissolving phlegm, and invigorating blood. The same book also recorded another prescription, Stalactite Liquor, which was used for wind-asthenia disease, cold arthralgia, and thinness and weakness. It is a compound prescription of Danshen combined with drugs with the functions of supplementing yin, yang, and qi, invigorating blood, dispelling wind and dampness, and warming the interior. Also, Danshen Pill for the treatment of lumbodynia and cold arthralgia was a compound prescription of Danshen combined with drugs with the functions of supplementing yang, warming the interior, and invigorating blood.

In addition, frequently used drugs included those with the functions of clearing heat, activating blood circulation and calming the mind, suggesting that Danshen prescriptions were also used for the treatment of fire-heat, static blood, and restlessness of heart spirit, etc.

17.2.5.2 The Song and Jin Dynasties

There were 391 Danshen-containing prescriptions during the Song and Jin Dynasties, and these prescriptions used 421 different ingredients (including Danshen). These ingredients appeared in the prescriptions 5,013 times. On average, each ingredient appeared in 12 prescriptions. There are 102 ingredients which appeared in 12 or more prescriptions, and their frequencies of appearance are shown in Table 17.7.

As is shown in Table 17.7, the top 10 ingredients combined most often with Danshen were: Chinese angelica, two-toothed achyranthes root, Sichuan lovage roo, ginseng, cinnamon bark, licorice root, monkshood, poria, double-teeth pubescent angelica root, and fresh ginger. They belong to six categories: nourishing blood, treat blood, supplement qi, warm the interior, calm the mind, and dissipate wind-cold.

The 102 ingredients belong to 15 functional categories, and according to their total number of appearances in the prescriptions, they are, from highest to lowest: supplement and boost, dissipate wind-cold, dispel wind-damp, clear heat,

Table 17.7 The frequencies of the medicinal ingredients used together with Danshen during the Song and Jin Dynasties

Frequency of appearance in the prescriptions	Medicinal ingredients and number of appearances	Number of ingredients
≥100 prescriptions	Chinese angelica (当归) 147, two-toothed achyranthes root (牛膝) 134, Sichuan lovage root (川穹) 134, ginseng (人参) 129, cinnamon bark (肉桂) 111, licorice root (甘草) 105	6
≥50 prescriptions	Monkshood (附子) 96, Poria (茯苓) 86, double teeth pubescent angelica root (独活) 86, fresh ginger (生姜) 80, astragalus root (黄耆) 80, bitter orange (枳壳) 78, ephedra (麻黄) 74, notoptetygium root (羌活) 72, eleutherococcus root-bark (五加皮) 71, Manchurian wild ginger (细辛) 71, prepared rehmannia root (熟地黄) 69, dried rhemannia (干地黄) 6, white atractylodes rhizome (白术) 69, hypoglaucous collett yam rhizome (薯蓣) 68, figwort root (玄参) 64, eucommia bark (杜仲) 64, dendrobium (石斛) 63, dried rhemannia (生地黄) 62, cinnamon twig (桂枝) 62, dwarf lilyturf tuber (麦冬) 54, light yellow sophora root (苦参) 53, large leaf gentian root (秦艽) 53, antelope horn (羚羊角屑) 51	22
≥30 prescriptions	White peony root (白芍药) 48, peony root (芍药) 29, Indian bread with hostwood (茯神) 48, betel nut (槟榔) 45, tall gastrodis tuber (天麻) 44, dried ginger rhizome (干姜) 43, adenophora root (沙参) 43, red peony root (赤芍) 43, thin-leaf milkwort root (远志) 40, coix seed (薏苡仁) 40, Chinese magnolivine fruit (五味子) 39, scutellaria root (黄芩) 36, caltrop fruit (白蒺藜) 36, spiney date seed (酸枣仁) 35, grassleaf sweetflag rhizome (石菖蒲) 34, rhubarb root and rhizome (大黄) 32, Chinese wolfberry root-bark (地骨皮) 32, Himalayan teasel root (续断) 32, pricklyash peel (蜀椒) 32, black cohosh rhizome (升麻) 31, four stamen stephania root (防己) 31, stephania tetrandra (汉防己) 14, common aucklandia root (木香) 30, apricot kernel (杏仁) 30, oriental arborvitael (柏子仁) 30	23
≥20 prescriptions	Chrysanthemum flower (菊花) 28, desert cistanche (肉苁蓉) 27, platycodon root (桔梗) 27, (乌蛇肉) 25, Gypsum (石膏) 25, tiger bone (虎骨) 25, rhinoceros horn (犀角屑) 25, tangerine pericarp (陈橘皮) 24, cornus (山茱萸) 23, asparagus tuber (天冬) 23, aerial part of epimedium (仙灵脾) 23, donkey-hide gelatin (阿胶) 23, monkshood (天雄) 22, angelica root (白芷) 22, common monkshood mother root (乌头) 22, common monkshood mother root (川乌头) 14, Cape jasmine fruit (山栀) 20, coptis rhizome (黄连) 20	17
≥12 prescriptions	Caltrop fruit (白蒺藜) 19, (茵芋) 19, Magnetite (磁石) 19, dioscoreae deltoideae root (薯蓣) 19, tree peony bark (牡丹皮) 18, typhonium rhizome (白附子) 17, erythrina bark (海桐皮) 17, musk (麝香) 17, aquilaria wood (沉香) 16, deer velvet (鹿茸) 16, scorpion (全蝎) 15, common anemarrhena rhizome (知母) 15, magnolia bark (厚朴) 15, akebia stem (木通) 14, silkworm (白僵蚕) 14, cinnabar (朱砂) 14, Monkshood (侧子) 14, Chinese clematis root (威灵仙) 14, Chinese lovage root (藁本) 14, pinellia rhizome (半夏) 13, agkistrodon (白花蛇) 13, bupleurum (柴胡) 13, kudzuvine root (葛根) 13, shrub chastetree fruit (蔓荆子) 13, turtle carapace (鳖甲) 13, Chinese date (大枣) 12, hemp seed (大麻仁) 12, morinda root (巴戟天) 12, cow bezoar (牛黄) 12, Chinese photinia leaf (石南叶) 12, Halloysite (赤石脂) 12, tortoise plastron (龟板) 12, white mulberry root-bark (桑白皮) 12, (紫参12)	34
Total		102

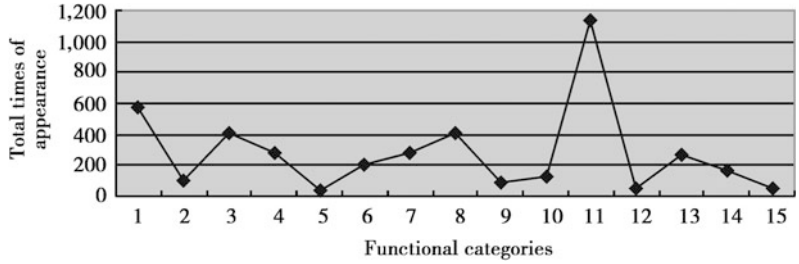

Fig. 17.4 Frequency distributions of medicinal ingredient categories used together with Danshen during the Song and Jin Dynasties (For the category codes, see Fig. 17.3.)

warm the interior, calm the mind, treat blood, rectify qi, calm the liver and extinguish wind, remove and percolate dampness, dissipate wind-heat, dissolve phlegm and relieve cough, open the orifices, consolidate and astringe essence, and purgation (Fig. 17.4).

Ingredients in the supplementing and boosting category were combined with Danshen most often, and the number of ingredients (24) is also the largest. These 24 ingredients belong to the subcategories of supplementing qi, blood, yin, and yang, and among them, the subcategory of supplementing yin is the largest, containing nine ingredients.

Following the category of supplementing and boosting were the categories of dissipating wind-cold and dispelling wind-damp. The obvious changes from the previous era were that the category of warming the interior moved from second place to the place, and the category of clearing heat moved from fifth place to fourth place, indicating that during this period, Danshen-containing prescriptions were not only used mainly for the diseases of weakness, wind-cold, and dampness, but also often for heat syndromes, either deficiency-heat or excess-heat. For example:

Chinese Angelica Blood-Supplementing Decoction (当归和血汤), recorded in *Chen Suan's gynecology* and used for women's qi stagnation, blood heat, and irregular menstruation, was a compound prescription of Danshen combined with drugs with the functions of nourishing blood, activating blood circulation, clearing heat, regulating qi, and nourishing yin.

The Donkey-Hide Gelatin Pill, recorded in *Formulas from Benevolent Sages Compiled during the Taiping Era* and used for postpartum profuse uterine bleeding and weakness, was a compound prescription of Danshen combined with drugs with the functions of nourishing yin, nourishing blood, hemostasis with astringents, and activating blood circulation.

The Donkey-Hide Gelatin Pill, recorded in *Comprehensive Recording of Divine Assistance*, and used for deficiency-consumption cough, fever, thin and weak, was a compound prescription of Danshen combined with drugs with the functions of nourishing yin and blood, clearing heat, supplementing qi, astringing lung, and relieving cough.

The Wu Shen Pill (五参丸), recorded in *Formulas from Benevolent Sages Compiled during the Taiping Era*, and used for lung with wind-toxin, skin rash and itching, sore and swelling, was a compound prescription of Danshen combined with drugs with the functions of supplymenting qi, clearing heat, nourishing yin, calming the mind, regulating qi, dispelling wind, and purgation.

17.2.5.3 The Yuan and Ming Dynasties

There were 76 new prescriptions containing Danshen during the Yuan and Ming Dynasties, and they contained 278 different ingredients (including Danshen), which appeared in the prescriptions 1,251 times. On average, each ingredient appeared in 4 prescriptions. The number of prescriptions in this period was not large, but the number of ingredients was considerable. There were 97 ingredients (excluding Danshen) which appeared in 4 or more prescriptions, and their frequencies of appearance in the prescriptions are shown in Table 17.8.

As is shown in Table 17.8, the top 10 ingredients most frequently used together with Danshen were: Chinese angelica, Sichuan lovage root, ginseng, white peony root, poria, licorice root, dried rhemannia, prepared rehmannia root, figwort root, and siler. The 10 ingredients belong to 6 categories: nourishing blood, invigorating blood, supplementing qi, calming the mind, clearing heat, and dissipating wind-cold. Compared with the previous period, the obvious changes were that drugs for clearing heat appeared in the list, and drugs for warming the interior disappeared. In addition, the number of drugs for nourishing blood was significantly larger than that of other drugs.

The 97 ingredients are in 15 major functional categories, and according to the numbers of these categories' appearances in the prescriptions, they are, from highest to lowest: supplement and boost, clear heat, dissipate wind-cold, treat blood, rectify qi, calm the mind, warm the interior, dispel wind-damp, dissolve phlegm and relieve cough, dissipate wind-heat, remove and percolate dampness, purgation, consolidate and astringe essence, calm the liver and extinguish wind, and open the orifices (Fig. 17.5).

One of the obvious changes in ranking was the increase in clearing heat drugs, moving to second place. The rank of the drugs for warming the interior continued to fall to seventh place. The drugs for rectifying qi appeared more often, moving to fifth place, and their variety also increased; there were nine such drugs. In the previous periods, the drugs for treating blood contained only those for invigoration. However, during this period, hemostatic drugs such as common bletilla tuber and longleaf garden burnet root were used in combination with Danshen. In addition, the variety of the drugs in this category also increased, from 2 to 8. These facts indicate that the Danshen prescriptions during this period were mainly used for the treatment of weakness diseases, and also for the treatment of the syndromes of qi-stagnancy and blood stasis, and heat diseases. For example:

Menstruation-Regulating Four Substances Decoction (调经四物汤), recorded in *Safeguarded Formulas from the Lu Mansion*, used for irregular menstruation, was a compound prescription of Danshen combined with drugs for nourishing blood, activating blood circulation, and rectifying qi.

Both Celestial Emperor Heart-Supplementing Pill, recorded in *Standards for Diagnosis and Treatment*, and Celestial Emperor Heart-Supplementing Elixir, recorded in *Restoration of Health from the Myriad Diseases*, used for amnesia, severe palpitation, pavor, feverish dysphoria, and dry pharynx were compound prescriptions of Danshen combined with drugs for rectifying qi, nourishing blood, nourishing yin, and clearing heat.

Safflower Chinese Angelica Pill (红花当归丸), recorded in *Song's gynecology* (《宋氏女科》), used for female deficiency in blood viscera, irregular menstruation, stasis developing into lumps, pricking pain in abdomen, and thin and weak, was a compound prescription of Danshen combined with the drugs for invigorating blood, nourishing blood, rectifying qi, and warming the interior.

In addition, the prescriptions with drugs for invigorating blood were not only used for the treatment of gynecological diseases, but also for traumatic diseases and external diseases such as ulcers and furuncles.

17.2.5.4 The Qing Dynasty

There were 272 Danshen-containing prescriptions in the Qing Dynasty. The number of different ingredients in these prescriptions was 386 (including Danshen), and these drugs appeared 3,379 times in the prescriptions. On average, each ingredient was listed in 9 prescriptions. There were 99 ingredients (not including Danshen) which were listed in 9 or more prescriptions, and their frequencies of appearance in these prescriptions are shown in Table 17.9.

As shown in Table 17.9, the top 10 herbs most frequently combined with Danshen in the Qing Dynasty were Chinese angelica, licorice root, white peony root, dried rhemannia, dwarf lilyturf tuber, poria, ginseng, tree peony bark, white atractylodes rhizome, and Indian bread with hostwood. The 10 herbs belong to six categories: nourishing blood, reinforcing qi, clearing heat,

Table 17.8 The frequencies of the medicinal ingredients used together with Danshen during the Yuan and Ming Dynasties

Frequency of appearance in the prescriptions	Medicinal ingredients and number of appearances	Number of ingredients
≥30 prescriptions	Chinese angelica (当归) 38	1
≥20 prescriptions	Sichuan lovage root (川芎) 28, ginseng (人参) 26, white peony root (白芍药) 24, poria (茯苓) 22, licorice root (甘草) 19	5
≥10 prescriptions	Dried rhemannia (生地黄) 19, prepared rehmannia root (熟地黄) 19, figwort root (玄参) 18, siler (防风) 18, white atractylodes rhizome (白术) 16, cinnamon bark (桂心 (官桂)) 16, dwarf lilyturf tuber (麦门冬) 16, light yellow sophora root (苦参) 16, aged tangerine peel (陈皮) 16, double teeth pubescent angelica root (独活) 15, Chinese magnolivine fruit (五味子) 13, Manchurian wild ginger (细辛) 13, scutellaria root (黄芩) 13, platycodon root (桔梗) 12, cyperus (香附) 12, two-toothed achyranthes root (牛膝) 12, astragalus root (黄耆) 12, grassleaf sweetflag rhizome (石菖蒲) 11, asparagus tuber (天门冬) 11, angelica root (白芷) 11, oriental arborvitael (柏子仁) 11, fresh ginger (生姜) 10, fresh ginger (羌活) 10, thin-leaf milkwort root (远志) 10, coptis rhizome (黄连) 10	25
≥6 prescriptions	Rhubarb root and rhizome (大黄) 9, cornus (山茱萸) 9, adenophora root (沙参) 9, common anemarrhena rhizome (知母) 9, common monkshood mother root (乌头), common monkshood mother root (川乌头) 5, kusnezoff monkshood root (草乌) 2, amur cork-tree bark (黄柏) 9, Chinese lovage root (藁本) 9, common yam rhizome (山药) 8, dried ginger rhizome (干姜) 8, tall gastrodis tuber (天麻) 8, eucommia bark (杜仲) 8, atractylodes rhizome (苍术) 8, villous amomum fruit (砂仁) 8, combined spicebush root (乌药) 7, dolomiaea root (木香) 7, Indian bread with hostwood (茯神) 7, Chinese clematis root (威灵仙) 7, fineleaf schizonepeta spike (荆芥穗) 7, Chinese date (大枣) 6, eleutherococcus root-bark (五加皮) 6, pangolin scales (穿山甲) 6, ampelopsis (白蔹) 6, gypsum (石膏) 6, donkey-hide gelatin (阿胶) 6, honeysuckle flower (金银花) 6, large leaf gentian root (秦艽) 6, cnidium fruit (蛇床子) 6, spiney date seed (酸枣仁) 6	29
≥4 prescriptions	Tree peony bark (牡丹皮) 5, apricot kernel (杏仁) 5, fennel (小茴香) 5, snakegourd root (天花粉) 5, fritillary bulb (贝母) 5, pinellia rhizome (半夏) 5, corydalis rhizome (玄胡索) 5, pricklyash peel (蜀椒) 5, dendrobium (石斛) 5, Chinese wolfberry root-bark (地骨皮) 5, garden burnet root (地榆) 5, fleeceflower root (何首乌) 5, weeping forsythia capsule (连翘) 5, Monkshood (附子) 5, magnolia bark (厚朴) 5, bupleurum (柴胡) 5, Himalayan teasel root (续断) 5, shrub chastetree fruit (蔓荆子) 5, red peony root (赤芍) 4, bitter orange (枳壳) 4, black cohosh rhizome (升麻) 4, flying squirrel faeces (五灵脂) 4, croton seed (巴豆) 4, bletilla rhizome (白及) 4, 豆蔻typhonium rhizome (白附子) 4, desert cistanche (肉苁蓉) 4, medicinal evodia fruit (吴茱萸) 4, water plantain rhizome (泽泻) 4, slender dutchmanspipe root (青木香) 4, peach kernel (桃仁) 4, chrysanthemum flower (菊花) 4, ephedra (麻黄) 4, (紫参4) 4Centipede (蜈蚣) 4, betel nut (槟榔) 4, Chinese pine node (松节) 4, tree peony bark (牡丹皮) 5, apricot kernel (杏仁) 5, fennel (小茴香) 5, snakegourd root (天花粉) 5, fritillary bulb (贝母) 5, pinellia rhizome (半夏) 5, corydalis rhizome (玄胡索) 5, pricklyash peel (蜀椒) 5, dendrobium (石斛) 5, Chinese wolfberry root-bark (地骨皮) 5, garden burnet root (地榆) 5, fleeceflower root (何首乌) 5, weeping forsythia capsule (连翘) 5, Monkshood (附子) 5, magnolia bark (厚朴) 5, bupleurum (柴胡) 5, Himalayan teasel root (续断) 5, shrub chastetree fruit (蔓荆子) 5	37
Total		97

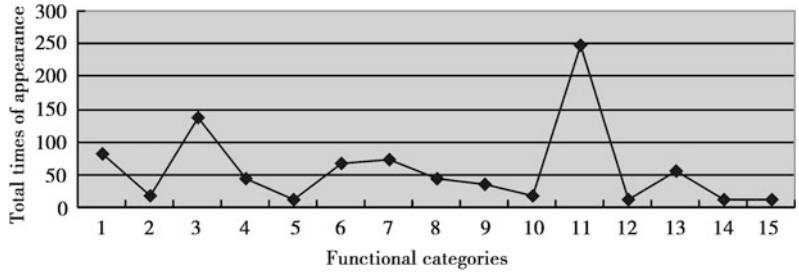

Fig. 17.5 Frequency distributions of medicinal ingredient categories used together with Danshen during the Yuan and Ming Dynasties (For the category codes, see Fig. 17.3.)

nourishing yin, and calming the mind. The variety of herbs in the category of calming the nerves increased, compared with the previous era.

The 99 herbs were in 15 major functional categories, and according to the total number of times they appeared in the prescriptions, they are, from highest to lowest: supplement and boost, clear heat, calm the mind, treat blood, rectify qi, dissolve phlegm and relieve cough, dissipate wind-cold, remove and percolate dampness, dissipate wind-heat, consolidate and astringe essence, warm the interior, dispel wind-damp, open the orifices, calm the liver and extinguish wind, and purgation. The frequency of supplementing and boosting drugs was significantly higher than those of the other drugs (Fig. 17.6).

The drugs for clearing heat still ranked second; the drugs for warming the interior still ranked seventh; the drugs for calming the mind were significantly increased, ranked third. There were nine herbs in the category of treating blood, all belonging to the subcategory of invigorating blood, indicating that the Danshen prescriptions during that period were mainly used for the treatment of amnesia, insomnia, depressed psychosis, mania, epilepsy, and other diseases and syndromes in the heart meridian. For example:

Intelligence-Boosting Pill (益明长智丸), recorded in *Zheng Zhi Bao Jian* and used for amnesia, clearing the mind, and boosting intelligence, was a compound prescription of Danshen combined with drugs with the functions of nourishing yin, calming the mind, rectifying qi, dissolving phlegm, and nourishing blood.

Qin Lian Heart-Clearing Pill (芩连清心丸) recorded in *Wondrous Lantern for Peering into the Origin and Development of Miscellaneous Diseases* and used for depressive psychosis and mania, was a compound prescription of Danshen combined with drugs with the functions of clearing heat, draining fire, nourishing yin, calming the mind, and opening the orifices.

Tongshen Blood-Supplementing Pill (通神补血丸), recorded in *Cock Crowing Records* and used for deficiency in spirit and blood, amnesia, insomnia, palpitation, and easy to fear and sweat, was a compound prescription of Danshen combined with drugs with the functions of clearing heat, calming the mind, nourishing blood, rectifying qi, dissolving phlegm, and opening the orifices.

Thin-leaf Milkwort Root Decoction (远志汤), recorded in *Gu Jin Yi Che* and used for postpartum trance, prolonged lochia or lochiorrhea, was a compound prescription of Danshen combined with drugs with the functions of calming the mind, opening the orifices, invigorating blood, rectifying qi, and supplementing yang and qi.

17.2.5.5 Modern Times

There were 140 Danshen-containing prescriptions in the modern literatures; these prescriptions used 336 different ingredients (including Danshen), and these ingredients were listed 1,851 times in the prescriptions. On average, each ingredient appeared in six prescriptions. There were 79 ingredients in 6 or more

Table 17.9 The frequencies of the medicinal ingredients used together with Danshen in the Qing Dynasty

Frequency of appearance in the prescriptions	Medicinal ingredients and number of appearances	Number of ingredients
≥100 prescriptions	Chinese Angelica 140	1
≥50 prescriptions	licorice root (甘草) 90, white peony root (白芍药) 90, dried rhemannia (生地黄) 88, dwarf lilyturf tuber (麦冬) 78, poria (茯苓) 72, ginseng (人参) 64, tree peony bark (丹皮) 64, white atractylodes rhizome (白术) 58, Indian bread with hostwood (茯神) 56, figwort root (玄参) 54, Sichuan lovage root (川芎) 53	11
≥30 prescriptions	Prepared rehmannia root (熟地黄) 47, coptis rhizome (黄连) 46, oriental arborvitael (柏子仁) 43, spiney date seed (酸枣仁) 43, thin-leaf milkwort root (远志) 43, cyperus (香附) 42, aged tangerine peel (陈皮) 40, fritillary bulb (贝母) 36, paniculate bolbostemma (大贝) 4, tendrilled fritillaria bulb (川贝) 16, two-toothed achyranthes root (牛膝) 34, scutellaria root (黄芩) 33, Chinese magnolivine fruit (五味子) 33, common yam rhizome (山药) 32, fresh ginger (生姜) 32, pinellia rhizome (半夏) 30	14
≥20 prescriptions	Grassleaf sweetflag rhizome (石菖蒲) 29, weeping forsythia capsule (连翘) 27,Himalayan teasel root (续断) 27,platycodon root (桔梗) 26, red peony root (赤芍) 25, astragalus root (黄耆) 25, Cape jasmine fruit (山栀) 25, turmeric root tuber (郁金) 25, bupleurum (柴胡) 25, asparagus tuber (天冬) 24, safflower (红花) 24, eucommia bark (杜仲) 22, peach kernel (桃仁) 22, Chinese date (大枣) 20, adenophora root (沙参) adenophora root (南沙参) 1, straight ladybell root (北沙参) 2, common anemarrhena rhizome (知母) 20, large leaf gentian root (秦艽) 20	18
≥15 prescriptions	Donkey-hide gelatin (阿胶) 18, bitter orange (枳壳) 18, akebia stem (木通) 17, siler (防风) 17, water plantain rhizome (泽泻) 17, red tangerine peel (橘红) 17, amur cork-tree bark (黄柏) 16, dendrobium (石斛) 16, atractylodes rhizome (苍术) 16, double teeth pubescent angelica root (独活) 16, Chinese hawthorn fruit (山楂) 16, mulberry twig (桑枝) 15, cinnabar (朱砂) 15, motherwort (益母草) 15, amber (琥珀) 15	15
≥11 prescriptions	Chinese wolfberry root-bark (地骨皮) 14, Schizonepeta (荆芥) 14, salvia root (淡竹叶) 14, jackinthepulpit tuber (天南星) 14, chrysanthemum flower (菊花) 13, rhubarb root and rhizome (大黄) 13, corydalis rhizome (延胡) 13, Manchurian wild ginger (细辛) 13, rhinoceros horn (犀角) 13, magnolia bark (厚朴) 12, perilla leaf (苏叶) 12, green tangerine peel (青皮) 12, villous amomum fruit (砂仁) 12, Cattail Pollen (蒲黄) 12, snakegourd root (天花粉) 11, plantago seed (车前子) 11, common monkshood mother root (乌头) common monkshood mother root (川乌) 9, kusnezoff monkshood root (草乌) 2, tortoise plastron (龟板) 11, honeysuckle flower (银花) 11, apricot kernel (杏仁) 11	21
≥9 prescriptions	Common aucklandia root (木香) 10, double teeth pubescent angelica root (独活) 10, white mulberry root-bark (桑白皮) 10, dried ginger rhizome (干姜) 10, cinnamon bark (肉桂) 10, fleeceflower root (何首乌) 10, light yellow sophora root (苦参) 10, codonopsis root (党参) 10, coix seed (薏苡仁) 10, gallnut of Chinese sumac (五倍子) 9, black cohosh rhizome (升麻) 9, Chinese wolfberry fruit (枸杞子) 9, pangolin scales (穿山甲) 9, dragon bones (龙骨) 9, juncus (灯芯) 9, Prepared Dried Ginger (炮姜) 9, lotus leaf (荷叶) 9, field mint (薄荷) 9, oyster shell (牡蛎) 9	19
Total		99

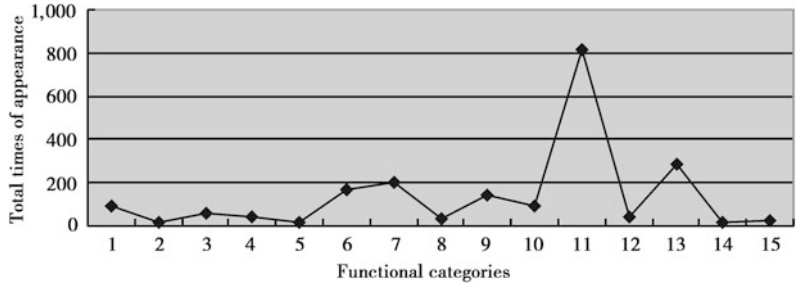

Fig. 17.6 Frequency distributions of medicinal ingredient categories used together with Danshen during the Qing Dynasty (For the category codes, see Fig. 17.3.)

prescriptions, and their frequencies of appearance in the prescriptions are shown in Table 17.10.

As is shown in Table 17.10, the top 10 ingredients which were used most frequently together with Danshen were Chinese angelica, liquorice root, white peony root, cyperus, Sichuan lovage root, dried rhemannia, poria, safflower, red peony root, and white atractylodes rhizome. They belong to five categories: nourishing blood, rectifying qi, supplementing qi, invigorating blood, and clearing heat. The number of drugs for invigorating blood increased significantly.

The 79 ingredients were in 13 major functional categories. Compared with those in previous periods, the drugs in the categories of dispelling wind-damp and removing and percolating dampness disappeared from the list. According to their total number of appearances in the prescriptions, from highest to lowest, they are: supplement and boost, treat blood, clear heat, rectify qi, calm the mind, dissipate wind-cold, dissipate wind-heat, dissolve phlegm and relieve cough, warm the interior, open the orifices, calm the liver and extinguish wind, consolidate and astringe essence, and purgation (Fig. 17.7).

The drugs for supplementing and boosting were still ranked first, and the drugs for treating blood rose to second place. There were 17 varieties of drugs in this category, and except for mugwort leaf, all were drugs for invigorating blood. The drugs for warming the interior fell to ninth place, indicating that the treatment scope of Danshen-containing prescriptions was narrowed; besides for diseases of deficiency, they were mainly used for the treatment of various blood stasis diseases. For example:

Effective Channel-Activating Elixir, recorded in the *Records of Chinese Medicine with Reference to Western Medicine* and used for stagnation of vital energy and blood, indigestion, concretions and conglomerations, pain in epigastrium, abdomen, leg and arm, sores, ulceration, and viscera obstruction, was a compound prescription of Danshen combined with drugs with the function of nourishing and invigorating blood.

Both Xiaoru Decoction (消乳汤), recorded in the *Records of Chinese Medicine with Reference to Western Medicine* and used for mammary swelling or mammary abscesses and all red swelling and sores and ulceration of the skin, and Qingliang Huagai Beverage (清凉华盖饮), recorded in the same book and used for lung ulcers, lung abscesses, vomiting pus and blood, chest pain, or pain below the costal region, were compound prescriptions of Danshen combined with drugs with the functions of clearing heat, removing toxin, and invigorating blood.

Taohong Xiaoyu Decoction (桃红消瘀汤) in *TCM gynecology* and used for the treatment of puerperal fever, prolonged lochia or lochiorrhea, muddy section, pain in lower abdomen, frequent micturition and obstipation, pale tongue, and string-tight pulse, was a compound prescription of Danshen combined with drugs with the functions of invigorating blood.

Xinshang Xuduan Decoction (新伤续断汤), recorded in *The Textbook of TCM Traumatology* and used for new bone fractures, was a

Table 17.10 The frequencies of the medicinal ingredients used together with Danshen in modern times

Frequency of appearance in the prescriptions	Medicinal ingredients and number of appearances	Number of ingredients
≥50 prescriptions	Chinese angelica (当归) 84, licorice root (甘草) 50	2
≥30 prescriptions	white peony root (白芍) 49, cyperus (香附) 45, Sichuan lovage root (川芎) 43, dried rhemannia (生地黄) 32, poria (茯苓) 31	5
≥20 prescriptions	Safflower (红花) 29, red peony root (赤芍) 28, white atractylodes rhizome (白术) 26, prepared rehmannia root (熟地黄) 25, aged tangerine peel (陈皮) 25, astragalus root (黄耆) 24, corydalis rhizome (延胡索) 23, bupleurum (柴胡) 20, common aucklandia root (木香各) 20	9
≥10 prescriptions	Motherwort (益母草) 19, Ginseng (人参) 18, pach kernel (桃仁) 18, Himalayan teasel root (续断) 18, Frankincense (乳香) 18, eucommia bark (杜仲) 17, scutellaria root (黄芩) 17, myrrh (没药) 17, two-toothed achyranthes root (牛膝) cyathula root (川牛膝) 4, turmeric root tuber (郁金) 16, villous amomum fruit (砂仁) 16, Chinese date (大枣) 16, figwort root (玄参) 16, tree peony bark (丹皮) 15, donkey-hide gelatin (阿胶) 15, dwarf lilyturf tuber (麦冬) 15, hirsute shiny bugleweed herb (泽兰) 15, thin-leaf milkwort root (远志) 14, codonopsis root (党参) 14, suberect spatholobus stem (鸡血藤) 12, honeysuckle flower (金银花) 12, combined spicebush root (乌药) 11, pinellia rhizome (半夏) 11, green tangerine peel (青皮) 11, Chinese wolfberry fruit (枸杞) 11, common yam rhizome (山药) 11, asparagus tuber (天冬) 10, mugwort leaf (艾叶) 10, bitter orange (枳壳) 10, pangolin scales (穿山甲) 10, platycodon root (桔梗) 10	32
≥6 prescriptions	Rassleaf sweetflag rhizome (菖蒲) 9, cicada moulting (蝉蜕) 9, cinnamon bark (肉桂) 9, fritillary bulb (贝母) tendrilled fritillaria bulb (川贝母) 7, Chinese magnolivine fruit (五味子) 8, Siler (防风) 8, oyster shell (牡蛎) 8, curcumae rhizome (莪术) 8, dodder seed (菟丝子) 8, deer antler (鹿角) 8, fleeceflower root (何首乌) 8, common burr reed tuber (三棱) 7, rhubarb root and rhizome (大黄) 7, angelica root (白芷) 7, adenophora root (沙参), adenophora root (南沙参) 2, straight ladybell root (北沙参) 1, notoptetygium root (羌活) 7, common anemarrhena rhizome (知母) 7, Manchurian wild ginger (细辛) 7, Indian bread with hostwood (茯神) 7, turtle carapace (鳖甲) 7, amur cork-tree bark (黄柏) 7, cornus (山萸肉) 6, Chinese hawthorn fruit (山楂) 6, toosendan fruit (川楝子) 6, aquilaria wood (沉香) 6, weeping forsythia capsule (连翘) 6, oriental arborvitael (柏子仁) 6, oriental arborvitael (黄连) 6, dandelion (蒲公英) 6, Indian madder root (茜草) 6	31
Total		79

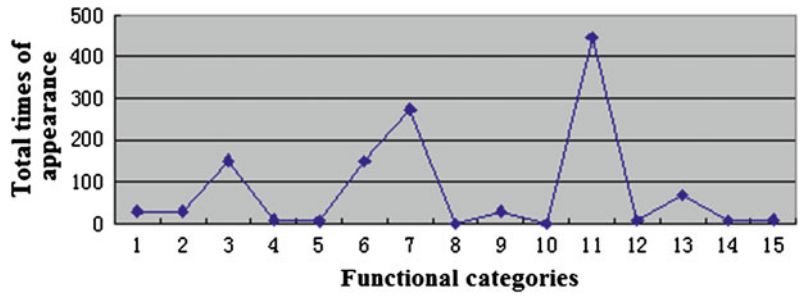

Fig. 17.7 Frequency distributions of medicinal ingredients categories used together with Danshen in modern time (For the category codes, see Fig. 17.3.)

compound prescription of Danshen combined with drugs with the functions of invigorating blood, dredging collaterals, strengthening bones and muscles.

Toxin-Resolving Blood-Moving Decoction (解毒活血汤), recorded in *Famous Prescription in Ancient and Modern Times* and used for blood stasis and toxicity and heat syndrome, scleroderma, and Raynaud's disease, was a compound prescription of Danshen combined with drugs for nourishing blood, clearing heat, resolving toxins, and invigorating blood.

17.2.5.6 Modern Chinese Patent Medicines

To comprehend the development of Modern Chinese Patent Medicines, we performed statistical analysis on the Danshen-containing formulas of Chinese patent medicines. 240 formulas of Chinese patent medicines were collected from *Drug Specifications Promulgated by the Ministry of Public Health, P. R. China, Chinese Patent Medicine* (20 volumes) promulgated by the pharmacopoeia committee, the Ministry of Public Health, P. R. China. These formulas contained 438 different drugs, and these drugs appeared in the formulas 3,281 times. On average, each drug was listed in 7 formulas. There were 135 drugs which appeared in 7 or more formulas, and their frequencies of appearance in the formulas are shown in Table 17.11.

As is shown in Table 17.11, the top 10 ingredients which were combined with Danshen were Chinese angelica, Sichuan lovage root, safflower, licorice root, ginseng, astragalus root, poria, prepared rehmannia root, cyperus, and white peony root. They belonged to five categories: nourishing blood, invigorating blood, supplementing qi, calming the mind, rectifying qi.

The 135 ingredients belonged to 16 major functional categories. Compared with the previous periods, drugs for promoting digestion were used with Danshen for the first time. According to the frequency of appearance in the formulas, these categories were sorted in descending order: supplement and boost, treat blood, rectify qi, clear heat, calm the mind, open the orifices, calm the liver and extinguish wind, remove and percolate dampness, consolidate and astringe essence, warm the interior, dissipate wind-cold, dissipate wind-heat, promote digestion, dispel wind-damp, dissolve phlegm and relieve cough, and purgation (Fig. 17.8).

The drugs for supplementing and boosting were still the top category, and the variety in the category increased significantly to 36 drugs. The drugs for treating blood were still in second place and the variety increased to 21; all except for mugwort leaf and pagoda tree flower were drugs for invigorating blood and dissolving stasis. The drugs for rectifying qi ranked third, and the drugs for warming the interior fell to tenth place, indicating that the Danshen drugs were mainly used for diseases of deficiency, qi stagnation, and blood stasis. For example:

Two Immortals Paste (二仙膏), used for the treatment of qi and blood deficiency, weakness, neurasthenia, and other symptoms, was a compound prescription of Danshen combined with drugs with the functions of supplementing qi, nourishing yin, and nourishing blood.

Wan Nian Chun Liquor (万年春酒), used for the treatment of qi deficiency, weak spleen, waist sour, soft knee, rheumatism, and joint pain, was a compound prescription of Danshen combined with drugs with the functions of rectifying qi, nourishing yin, warming yang, invigorating blood, and strengthening bones and sinews.

Both Xinkeshu Capsule (心可舒胶囊) for the treatment of chest tightness, angina pectoris, hypertension, dizziness, headache, neck pain, arrhythmia, and hyperlipemia caused by coronary heart disease of qi-stagnancy and blood stasis type, and Guanxinkang Granules (冠心康颗粒) for the treatment of coronary heart disease and angina pectoris caused by blood stasis, qi stagnation, blockage of the cardiac vessels, were compound prescriptions of Danshen combined with drugs with the functions of activating blood circulation and rectifying qi.

In addition, the three drugs in the category of promoting digestion, Chinese hawthorn fruit, medicated leaven, and barley sprout, were not combined with Danshen for the treatment of food retention. Rather, they were used with drugs in the category of supplementing and boosting,

Table 17.11 The frequencies of the medicinal ingredients used together with Danshen in the Modern Chinese Patent Medicines

Frequency of appearance in the prescriptions	Medicinal ingredients and number of appearances	Number of ingredients
≥50 prescriptions	Chinese angelica (当归) 109, Sichuan lovage root (川芎) 83, safflower (红花) 70, licorice root (甘草) 66, ginseng (人参) 64, astragalus root (黄芪) 64, poria (茯苓) 55, prepared rehmannia root (熟地黄) 54, cyperus (香附) 51, white peony root (白芍) 50	10
≥30 prescriptions	White atractylodes rhizome (白术) 48, fleeceflower root (何首乌) 47, dried rhemannia (生地黄) 45, Chinese magnolivine fruit (五味子) 44, red peony root (赤芍) 42, two-toothed achyranthes root (牛膝) 40, pseudoginseng root (三七) 39, common yam rhizome (山药) 38, Chinese hawthorn fruit (山楂) 36, dwarf lilyturf tuber (麦冬) 36, Chinese wolfberry fruit (枸杞子) 36, common aucklandia root (木香) 35, aged tangerine peel (陈皮) 32, water plantain rhizome (泽泻) 32, thin-leaf milkwort root (远志) 31, turmeric root tuber (郁金) 31, corydalis rhizome (延胡索) 30, codonopsis root (党参) 30	18
≥15 prescriptions	Borneol (冰片) 29, cinnamon bark (肉桂) 28, grassleaf sweetflag rhizome (石菖蒲) 26, myrrh (没药) 25, kudzuvine root (葛根) 25spiney date seed (酸枣仁) 25tree peony bark (丹皮) 23, peach kernel (桃仁) 23, aerial part of epimedium (淫羊藿) 21, suberect spatholobus stem (鸡血藤) 20, frankincense (乳香) 20, dodder seed (菟丝子) 20, scutellaria root (黄芩) 20, figwort root (玄参) 19, earthworm (地龙) 19,eucommia bark (杜仲) 19, amber (琥珀) 19, Manchurian wild ginger (细辛) 18, Bupleurum (柴胡) 18, Motherwort (益母草) 18, deer velvet (鹿茸) 18, Siberian solomon's seal rhizome (黄精) 18, rhubarb root and rhizome (大黄) 17, privet fruit (女贞子) 17, Himalayan teasel root (续断) 17, Chinese clematis root (威灵仙) 16, villous amomum fruit (砂仁) 16, coptis rhizome (黄连) 15	28
≥l0 prescriptions	Common burr reed tuber (三棱) 14, oyster shell (牡蛎) 14, bitter orange (枳壳) 14, curcumae rhizome (莪术) 14, musk (麝香) 14, Chinese date (大枣) 13, tall gastrodis tuber (天麻) 13, rosewood (降香) 13, oriental arborvitael (柏子仁) 13, virgate wormwood herb (茵陈) 13, Chinese taxillus (桑寄生) 13, platycodon root (桔梗) 13, toosendan fruit (川楝子) 12, combined spicebush root (乌药) 12, asparagus tuber (天冬) 12, donkey-hide gelatin (阿胶) 12, cow bezoar (牛黄) 11, angelica root (白芷) 11, scorpion (全蝎) 11, cinnabar (朱砂) 11, red ginseng (红参) 11, aquilaria wood (沉香) 11, reishi mushroom (灵芝) 11, tortoise shell (龟甲) 11, magnolia bark (厚朴) 11, medicated leaven (神曲) 11, drynaria rhizome (骨碎补) 11, amur cork-tree bark (黄柏) 11, pagoda tree flower (槐花) 11, Chinese quince fruit (木瓜) 10, pinellia rhizome (半夏) 10, desert cistanche (肉苁蓉) 10, notoptetygium root (羌活) 10, psoralea fruit (补骨脂) 10, isatis root (板蓝根) 10, green tangerine peel (青皮) 10, gambir plant (钩藤) 10, black-haired vine (首乌藤) 10, lotus seed (莲子) 10	39

(continued)

Table 17.11 (continued)

Frequency of appearance in the prescriptions	Medicinal ingredients and number of appearances	Number of ingredients
≥7 prescriptions	Cornus (山茱萸) 9, common monkshood mother root (乌头) 9, mugwort leaf (艾叶) 9, dragon bones (龙骨) 9, atractylodes rhizome (苍术) 9, dandelion (蒲公英) 9, stiff silkworm (僵蚕) 9, dried ginger rhizome (干姜) 8, flying squirrel faeces (五灵脂) 8, buffalo horn (水牛角) 8, fritillary bulb (贝母) 8, fragrant solomonseal rhizome (玉竹) 8,cassia seed (决明子) 8, dragon's blood (血竭) 8, flattened milkvetch seed (沙苑子) 8, Monkshood (附子) 8, hirsute shiny bugleweed herb (泽兰) 8, giant knotweed rhizome (虎杖) 8, pearl (珍珠) 8, mother-of-pearl (珍珠母) 8, cinnamon twig (桂枝) 8, chrysanthemum flower (菊花) 8, ephedra (麻黄) 8, glabrous greenbrier rhizome (土茯苓) 7ground beetle (土鳖虫) 7, fennel (小茴香) 7, smoked plum (乌梅) 7, morinda root (巴戟天) 7, siler (防风) 7, euryale seed (芡实) 7, storax (苏合香) 7, cardamom (豆蔻) 7, germinated barley (麦芽) 7, Siberian ginseng (刺五加) 7, large leaf gentian root (秦艽) 7, deer antler glue (鹿角胶) 7, Cattail Pollen (蒲黄) 7, cicada moulting (蝉蜕) 7, yerbadetajo (墨旱莲) 7, toad venom (蟾酥) 7	40
Total		135

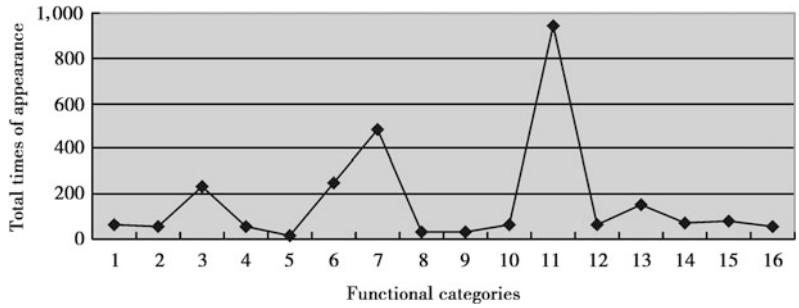

Fig. 17.8 Frequency distributions of functional categories of medicinal ingredients used together with Danshen in Modern Chinese Patent Medicines. The functional category codes: (*1*) dissipate wind-cold; (*2*) dissipate wind-heat; (*3*) clear heat; (*4*) warm the interior; (*5*) purgation; (*6*) rectify qi; (*7*) treat blood; (*8*) dispel wind-damp; (*9*) dissolve phlegm and relieve cough; (*10*) remove and percolate dampness; (*11*) supplement and boost; (*12*) consolidate and astringe essence; (*13*) calm the mind; (*14*) calm the liver and extinguish wind; (*15*) open the orifices; (*16*) promote digestion

such as astragalus root, codonopsis root, Chinese angelica, and fleeceflower root, for the treatment of weakness diseases, for example, in Chan Hou Kang Paste (产后康膏), Kuangshai Fuchun Tablet (抗衰复春片), and Caffeine and Calcium Glycerophosphate Tablet (益脑宁片), etc.

17.2.5.7 Summary of Danshen-Containing Drugs

The 1,263 drugs used together with Danshen in ancient and modern times are the clinically commonly used drugs. There are 44 drugs which have appeared in prescriptions more than 100 times, and they are shown in Table 17.12.

As is shown in Table 17.12, the drug used most frequently with Danshen is Chinese angelica, followed by ginseng (including red ginseng and codonopsis root). The 44 drugs are in 12 major functional categories, and their frequency distributions in the Danshen-containing prescriptions are shown in Fig. 17.9.

The supplementing and boosting drugs were used most often with Danshen, wherein the drugs supplementing blood, qi, and kidney, nourishing

Table 17.12 The drugs frequently used together with Danshen in both ancient and modern times

Frequency of appearance in the prescriptions	Medicinal ingredients and times of appearance	Number of ingredients
≥400 prescriptions	Chinese angelica (当归) 558, Ginseng (人参) 424	2
≥300 prescriptions	Sichuan lovage root (川芎) 389, licorice root (甘草) 377, poria (茯苓) 310	3
≥200 prescriptions	White Peony Root 292, Common Achyranthes 288, Largehead Atractylodes Rhizome 262, Rehmannia Root 261, Cassia Bark 236, Mongolian Milkvetch Root 231, Radix Ophiopogonis 215	7
≥l50 prescriptions	Figwort root (玄参) 192, prepared rehmannia root (熟地黄) 179, fresh ginger (生姜) 163, Manchurian wild ginger (细辛) 162, aged tangerine peel (陈皮) 156, Chinese magnolivine fruit (五味子) 151, cyperus (香附) 150, thin-leaf milkwort root (远志) 150	8
≥100 prescriptions	Eucommia bark (杜仲) 148, double teeth pubescent angelica root (独活) 146, red peony root (赤芍) 142, scutellaria root (黄芩) 141, Monkshood (附子) 136, safflower (红花) 126, tree peony bark (丹皮) 125, Indian bread with hostwood (茯神) 126, bitter orange (枳壳) 124, common yam rhizome (山药) 120, spiney date seed (酸枣仁) 119, dried ginger rhizome (干姜) 117, large leaf gentian root (秦艽) 114, oriental arborvitael (柏子仁) 112, rhubarb root and rhizome (大黄) 111, dendrobium (石斛) 111, notoptetygium root (羌活) 109, platycodon root (桔梗) 108, Himalayan teasel root (续断) 106, coptis rhizome (黄连) 104, common aucklandia root (木香) 102, siler (防风) 101, grassleaf sweetflag rhizome (石菖蒲) 100, ephedra (麻黄) 100	24
Total		44

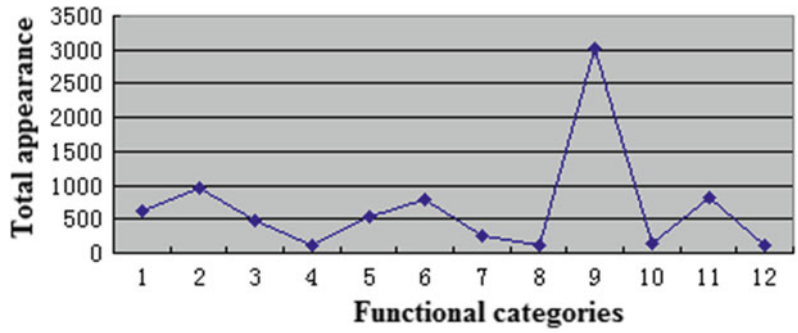

Fig. 17.9 Frequency distributions of functional categories of the drugs most often used together with Danshen at all times. The functional category codes: (*1*) dissipate wind-cold; (*2*) clear heat; (*3*) warm the interior; (*4*) purgation; (*5*) rectify qi; (*6*) invigorating blood; (7) dispel wind-damp; (*8*) dissolve phlegm and relieve cough; (*9*) supplement and boost; (*10*) consolidate and astringe essence; (*11*) calm the mind; (*12*) open the orifices

yin, strengthening bones and sinews were in the majority, indicating that Danshen was usually combined with these drugs to treat various deficiency diseases: blood, qi, yin, and kidney deficiency, and so on. Chinese angelica was the most frequently used drug in Danshen-containing prescriptions, which was widely used in the treatment of diseases and syndromes in gynecology.

The drugs for clearing heat ranked second, wherein most were clearing heat and cooling the blood drugs, indicating that these drugs were mainly used to treat the diseases of heat in the blood level.

The drugs for calming the mind ranked third. In addition, Chinese magnolia vine fruit, which was classified into the category of consolidating and astringing essence, also had the function of calming the mind. In total, there were six drugs of calming the mind normally combined with Danshen, indicating that Danshen had relatively high usage rates in heart channel diseases.

Although there were not many drugs for treating blood in the list, these drugs did appear in many prescriptions, so the category ranked fourth, indicating that Danshen was also used in the treatment of various blood stasis diseases and was usually combined with Sichuan lovage root, two-toothed achyranthes root, and safflower.

Both the fifth ranked dispelling wind-cold drugs and the eighth ranked dispelling wind-damp drugs were wind dispelling drugs. Externally contracted diseases such as cold damage syndromes and warm diseases, leprosy, various skin diseases, and wind-damp bi syndromes were all related to wind evil. So, Danshen was usually used for the treatment of various diseases caused by wind evil, and the indications of some ancient Danshen-containing prescriptions declared that the drugs could be used to treat every wind-related disease.

The drugs for rectifying qi ranked sixth, indicating that Danshen was also combined with these drugs for the treatment of qi stagnation syndromes.

The drugs for warming the interior ranked seventh, wherein cinnamon bark was used most often, indicating that Danshen was usually combined with drugs for warming the interior and unblocking the collaterals to treat various cold diseases.

There was only one purgation drug, rhubarb root and rhizome, in the list. This drug, however, appeared in many prescriptions. The prescriptions containing both Danshen and rhubarb root and rhizome were not only used for the treatment of intestinal accumulation and stagnation diseases, but also used in prescriptions for the treatment of deficiency-consumption diseases, eclampsia, concretions, conglomerations, accumulations, and gatherings. The purpose of including this drug in these prescriptions might be that it could enhance Danshen's function of invigorating blood and dissolving stasis.

Among the drugs with the functions of dissolving phlegm and relieving cough, platycodon root was used most often. The use of the drug in the ancient prescriptions was not limited to the treatment of sore throat or cough, asthma and other lung channel diseases; many miscellaneous diseases, such as deficiency-consumption, accumulations and gatherings, and intestinal welling-abscess also were treated with prescriptions containing the drug, possibly because the physicians believed the theory that lung qi could regulate systemic qi movement.

There was only one drug for opening the orifices in the list, i.e., grassleaf sweetflag rhizome. It was usually combined with Danshen for the treatment of heart channel diseases.

17.3 Indications

17.3.1 The Tang Dynasty and Before

There were 70 indications in the 144 Danshen-containing prescriptions invented before and during the Tang Dynasty. The indications appeared in the prescriptions 182 times, involving diseases in the departments of internal medicine, gynecology, pediatrics, dermatology, ophthalmology & otorhinolaryngology, etc., but mainly in the departments of internal medicine, surgery and gynecology. The diseases for the indications were mainly related to wind, dampness, qi, and blood, such as beriberi, impediment pattern, concretions, conglomerations, accumulations and gatherings, deficiency-consumption, cold damage, aversion to wind, lumbar and back pain, and water swelling. Among the diseases in the internal medicine domain, most were related to disorders in channels and collaterals in the limbs and body; qi, blood, liquid and humor; liver and spleen channel. These diseases were much more common than were the diseases involving the heart channel. The diseases involving the lung channel were the fewest in number. The gynecological diseases listed in the

indications included the diseases and syndromes in menstruation, morbid leukorrhea, pregnancy and circumnatal period, and diseases in pregnancy and postpartum periods were in the majority. The categories of the diseases and syndromes and their frequencies in the prescriptions are shown in Table 17.13.

17.3.2 The Song and Jin Dynasties

In the 391 Danshen-containing prescriptions in the Song and Jin Dynasties, there were 134 indications appearing 429 times in the prescriptions. The involved departments were the same as those in the previous period. The diseases in the Department of Internal Medicine and Gynecology were significantly greater in number than the diseases in the other departments. The indications mainly involved *bì* syndrome, deficiency-consumption, beriberi, lumbar and pedal pain, lepra, lumbodynia, apoplexy, skin itching, scall, menoxenia, and other diseases, and they were mainly manifested in the muscles and sinews on the skin and limbs. The internal diseases were mainly of systemic channels and collaterals, of qi, blood, and body fluid. After these were diseases of the liver, spleen, and heart channels. The number of externally contracted diseases was the fewest. The gynecological diseases were mainly menstrual disorders and postpartum diseases. Compared with the previous period, the major difference was that Danshen prescriptions for skin diseases increased significantly (Table 17.14).

17.3.3 The Yuan and Ming Dynasties

In the 76 Danshen-containing prescriptions in the Yuan and Ming Dynasties, there were 57 indications which appeared 110 times in the prescriptions. The departments of these diseases involved were the same as those in the previous periods. The diseases were mainly limited to the Departments of Internal Medicine, gynecology and Dermatology, such as deficiency-consumption, lepra, amnesia, bì syndrome, sterility, concretions and gatherings, menoxenia, surgical inflammatory swelling, etc. The internal diseases were mainly involved in systemic channels and collaterals, and qi, blood, and body fluids; the diseases of the kidney channel were the fewest. There were no externally contracted diseases. The number of heart channel diseases began to exceed that of liver and spleen channel diseases. The gynecological diseases were mainly emmeniopathy. Leprathe ranked first among the dermatological diseases. The detailed listing is shown in Table 17.15.

17.3.4 The Qing Dynasty

There were 135 indications in the 272 Danshen-containing prescriptions in the Qing Dynasty, and the indications appeared a total of 540 times. The departments involved were the same as those in the previous periods, and mainly in the departments of internal medicine and gynecology. The diseases were mainly deficiency-consumption, menoxenia, pestilence, nocturnal emission, sleeplessness, hematemesis, micturition disorders, amenorrhea, cough, concretions and gatherings, severe palpitation, irritability-restlessness, wasting thirst, uterine bleeding, morbid leukorrhea, etc. In the department of internal medicine, the number of heart, liver, and spleen channel diseases was significantly more than that of the other diseases; the variety of heart diseases, such as insomnia, epilepsy, severe palpitation, precordial pain and amnesia, and so on was significantly greater than that in previous periods; the variety and the number of prescriptions of externally contracted diseases were significantly increased, and the number of the lung channel diseases was the smallest. The variety of gynecological diseases was less than half that of the internal diseases, but the frequency of prescriptions was almost the same, indicating that Danshen was widely used in the treatment of gynecological diseases in the Qing Dynasty (Table 17.16).

Table 17.13 The indications of Danshen-containing prescriptions before and during the Tang Dynasty

Department	Categories of diseases and syndromes (number of prescriptions)	Number of diseases and syndromes	Total prescriptions
Internal medicine	**Externally contracted diseases**: cold damage 7, warm diseases 2, malaria	34	110
	Heart channel diseases: panic 3, heart pain, irritability-restlessness, depressive psychosis, captation, pavor		
	Lung channel diseases: asthma 2, cough		
	Liver and spleen channel diseases: concretions and gatherings 8, dysentery 4, vomiting 2, abdominal distension 2, hypochondriac pain 2, food retention, constipation, jaundice, abdominal tympanites		
	Kidney channel diseases: strangury 4, nocturnal emission 4, hemuresis		
	Diseases of systemic channels and collaterals: *bì* syndrome l4, lumbar and back pain 6, hemiplegia 4, wilting pattern 2		
	Diseases of qi, blood, and body fluids: beriberi l5, deficiency-consumption 8, water swelling 5, wasting thirst, dizziness		
Surgery	Scrofula 8, carbuncle-abscess 3, carbuncle of the back 3, intestinal abscess 2, ulcer 2, eczema of scrotum, mammary abscess, ulcer, gall	9	22
Gynecology	Fetal irritability 4, menoxenia 3, postpartum deficiency-consumption 3, female concretions and conglomerations 2, pruritus vulvae 2, puerperal lumbago, postpartum abdominal pain, amenorrhea, pregnancy abortion, morbid leukorrhea, dystocia, uterine bleeding	12	21
Dermatology	Serious attack by wind (leprosy) 7, itch 2, scall, urticant eruptions	4	11
Pediatrics	Pediatric convulsive epilepsy 4, pediatric chills and fever 3, pediatric heart in epigastrium and abdomen 2, pediatric constipation	4	10
Otorhinolaryngology	Deafness, bone sticking, odontia, nasal polyps, coagulated phlegm in throat	5	5
Ophtalmology	Optic atrophic blindness 2, blurred vision	2	3
Total		70	182

17.3.5 Modern Times

There were 96 indications in the 140 Danshen-containing prescriptions collected from the modern literatures. The distribution of the diseases in various departments was the same as that of previous periods, and internal medicine and gynecology were the major departments. The modern Danshen prescriptions were primarily used for the treatment of menoxenia, morbid leukorrhea, dysmenorrhea, uterine bleeding, leg pain, deficiency-consumption, insomnia, cardiopalmus, gastric and duodenal ulcer, coronary heart disease, arthralgia syndrome, amenorrhea, urticaria, wound, and prosopodynia, etc., and menoxenia ranked first. In the Department of Internal Medicine, heart channel diseases ranked first, followed by liver and spleen channel diseases and diseases of the systemic channels and collaterals. In the Department of Gynecology, emmeniopathy was significantly more frequent than the other diseases and syndromes. The variety of

Table 17.14 The indications of Danshen-containing prescriptions during the Song and Jin Dynasties

Department	Categories of diseases and syndromes (number of prescriptions)	Number of diseases and syndromes	Total prescriptions
Internal medicine	**Externally contracted diseases**: warm diseases, corpse transmission 2	56	253
	Heart channel diseases: panic 5, pavor 5, amnesia 3, cutting pain in chest and back 3, captation 5, depressive psychosis 2, syncopecollapse 2, apoplexy 2, precordial pain, severe palpitation, irritability-restlessness, abalienatio mentis, cona due to apoplexy		
	Lung channel diseases: cough 5, shortness of breath 3, hemoptysis 2		
	Liver and spleen channel diseases: concretions and gatherings 6, liver wind 6, abdominal pain 4, abdominal distension 3, hypochondriac pain3, abdominal tympanites 2, vomiting 2, fullness in the chest and hypochondrium, constipation, food retention, mass in the abdomen, hematemesis		
	Kidney channel diseases: sthenic heat in kidney 3, micturition disorders, gonoblennorrhea, urinary incontinence, nocturnal emission, essence exhaustion, bone exhaustion		
	Diseases of systemic channels and collaterals: *bì* syndrome 42, lumbar and pedal pain 21, lumbodynia 10, apoplexy 10, all the wind evil 6, flaccidity syndrome 5, tetanus 2, peripheral facial paralysis2, acute arthritislike diseases 2, harsh 2, flech exhaustion, arthralgia due to stagnation of blood, syndrome from wind-cold evil involving the skin, rigidity of nape		
	Diseases of qi, blood, and body fluids: deficiency-consumption 31, beriberi 23, dizziness 4, headache 3, wasting thirst		
Gynecology	Menoxenia 8, morbid leukorrhea 7, amenorrhea 5, uterine bleeding 5, vulvar swelling 2, yin cold, dysmenorrhea, pain during menstruation, heat invading blood chamber, indurated mass in the uterus, female pruritus vulvae, pregnancy cold damage and fever, pregnancy fetal irritability, pregnancy apoplexy, abortion, prolonged labor 2, dystocia puerperal lumbago 4, postnatal abalienatio mentis 3, puerperal fever 3, postpartum faintness 3, postnatal lockjaw 2, postnatal profuse uterine bleeding 2, postnatal captation 2, postnatal unable to drink, postnatal cephal hidrosis, postnatal headache, postnatal extravasated blood, postnatal abdomen pain, postnatal consumption diseases	30	65
Dermatology	Lepral 8, sore of skin 9, scall 9, tinea 4, itch of skin 4, dermatophyma 3, skin urticant eruptions 2, freezed ear, purpura	10	52

(continued)

Table 17.14 (continued)

Department	Categories of diseases and syndromes (number of prescriptions)	Number of diseases and syndromes	Total prescriptions
Pediatrics	Pediatric convulsive epilepsy 3, pediatric erysipelas 3, pediatric carbuncle-abscess 3, pediatric abdominal mass below the costal region 2, pediatric scall 2, pediatric sore 2, pediatric lingual retardation 2, pediatric fever, pediatric lymphademectasis, pediatric nasal obstruction, pediatric urticant eruptions	11	21
Surgery	Scrofula 3, Haemorrhoids 3, intestinal abscess, erysipelas, swelling, carbuncle, ce11ulitis, multiple metastatic abscess, sores ulceration, mole cricker, worm in anus, red pain in anus	12	16
Ophtalmology	Internal and external oculopathy 3, presbyopia 2, sore pain of eye 2, red pain of eye 2, dim vision 2, delacrimation 2, blurred vision	7	14
Otorhinolaryngology	Aphtha, tongue sores, aphonia, non-traumatic hemorrhage, dryness in the nasal cavity, soer throat, tinnitus, deafness	8	8
Total		134	429

Table 17.15 The indications of Danshen-containing prescriptions in the Yuan and Ming Dynasties

Department	Categories of diseases and syndromes (number of prescriptions)	Number of diseases and syndromes	Total prescriptions
Internal medicine	**Heart channel diseases**: amnesia 6, severe palpitation 3, captation, epileptic syndrome, dysphasia	25	56
	Lung channel diseases: hemoptysis 2, lung abscess, cough		
	Liver and spleen channel diseases: concretions and gatherings 4, hematochezia 2, vomiting, dyspeptic disease, dysentery		
	Kidney channel diseases: micturition disorders		
	Diseases of systemic channels and collaterals: *bì* syndrome 5, lumbodynia 2, paralysis 2, headache, spasm of foot muscle, gout, buffeting		
	Diseases of qi, blood, and body fluids: deficiency-consumption 10, edema 3, beriberi 3		
Gynecology	Sterility 5, Menoxenia 4, amenorrhea 3, uterine bleeding 2, preceeded menorrhea, fetal irritability, postnatal apoplexy, female pruritus vulvae, female abdominal pain, yin cold, morbid leukorrhea	11	21
Dermatology	Lepra 8, itch, frambesial sore, scabies, macula, sore, whelk, tinea	8	15
Surgery	Swelling 4, scrofula 2, deep-rooted boils, carbuncle of the back, chancre, sore	8	12
Pediatrics	Pediatric fever 2, pediatric ecthyma	2	3
Ophtalmology	Vitamin-deficiency ophthalmopathy, presbyopia	2	2
Otorhinolaryngology	nasal polyps	1	1
Total		57	110

Table 17.16 The indications of Danshen-containing prescriptions in the Qing Dynasty

Department	Categories of diseases and syndromes (number of prescriptions)	Number of diseases and syndromes	Total prescriptions
Internal medicine	**Externally contracted diseases**: pestilence l2, malaria 6, common cold 6, cholera 5, cold damage 4, macula 3, cholera 2, summer febrile prevalent diseases, rubella, wind febris, autumn dryness, eruptive abdominalgia	72	254
	Heart channel diseases: sleeplessness 9, severe palpitation 7, irritability-restlessness 7, epileptic syndrome 6, depressive psychosis 5, madness 5, mania 5, amnesia 4, pavor 3, night sweat 3, precordial pain 4, captation 2, syncopecollapse, perspiration syndrome		
	Lung channel diseases: cough 8, dyspnea-asthma syndrome 3, hemoptysis3, knotted chest		
	Liver and spleen channel diseases: hematemesis 9, concretions and gatherings 8, thirsty 7, dysentery 6, hematochezia 5, stomachache 4, abdominal pain 4, vomiting 3, achalasia of cardia 3, abdominal pain 2, hypochondriac pain 2, diarrhea 3, abdominal tympanites 2, constipation 2, fullness in the chest and hypochondrium, gastric distention, regurgitation, food-poisoning, food retention, ructation, difficulty in urination-defecation, dysentery		
	Kidney channel diseases: nocturnal emission l0, micturition disorders 8, hemuresis 3, gonoblennorrhea 3, impotence		
	Diseases of systemic channels and collaterals: *bì* syndrome 3, flaccidity syndrome 3, lumbodynia 3, apoplexy 3, headache 3, syndrome from wind-cold evil involving the skin, tortoise back, muscular spasm, gout		
	Diseases of qi, blood, and body fluids: deficiency-consumption l4, tuberculosis-like consumptive disease 4, phlegm syndrome, wasting thirst, dizziness, beriberi		
Gynecology	Menoxenia l4, amenorrhea 8, uterine bleeding 7, morbid leukorrhea 7, aberratio menses 4, blood chamber heat invasion4, dysmenorrhea 3, delayed menstruation 3, infertility 2, pyretic abundance, blood emaciation, female pruritus vulvae, Yin cold, fetal irritability 3, feeling of distension in the thorax during pregnancy 2, abortion 2, habitual abortion 2, dystocia 3, postnatal prolonged lochia or lochiorrhea 4, postpartum abdominal pain 3, puerperal fever 2, postnatal dysentery2, postnatal cholera 2, postnatal agalactia, postnatal uterine bleeding, postpartum faintness, postpartum abdominal pain, postnatal painful foot, postnatal rush, puerperal malaria, postnatal cough, postnatal captation, postnatal stagnant blood	33	217
Otorhinolaryngology	Mouth and tongue sore 6, non-traumatic hemorrhage 5, tinnitus 2, throat-moth 2, aphonia, pharyngodynia, bleeding tongue, glossoncus, cheiloschisis, obstructive sore throat, otalgia	11	22

(continued)

Table 17.16 (continued)

Department	Categories of diseases and syndromes (number of prescriptions)	Number of diseases and syndromes	Total prescriptions
Pediatrics	Pediatric convulsion 6, measles 5, ecthyma 4, pediatric malnutritional stagnation 2, pediatric dysentery 2, pediatric terrified fever 2	6	21
Surgery	Carbuncle-abscess 4, scrofula 4, wound 3, carbuncle 2, Haemorrhoids 2, carbuncle of the back, nodules of breast, ecthyma, tuberculosis	9	19
Dermatology	Leprosy 4, acne	2	5
Ophtalmology	Blurred vision, eye bleeding	2	2
Total		135	540

dermatological diseases was large, and so was the number of prescriptions (Table 17.17).

17.3.6 Modern Chinese Patent Medicines

The 240 Danshen-containing prescriptions, collected from *Drug Specifications Promulgated by Ministry of Public Health, P. R. China, Chinese Patent Medicine*, contained 144 indications which appeared 675 times. The distribution of the diseases in various departments was the same as that in previous periods. The diseases were mainly in the departments of internal medicine and gynecology. These patent drugs were usually used for the treatment of coronary heart disease, angina pectoris, insomnia, menoxenia, cardiopalmus, dizziness, dysmenorrhea, amnesia, pectoral stuffiness pain, hepatitis, arteriosclerosis, headache, deficiency-consumption, hyperlipidemia, neurasthenia, hypertension, apoplectic sequela, morbid leukorrhea, and other diseases and syndromes. In the Department of Internal Medicine, coronary heart disease and other heart channel diseases were in the majority, followed by liver and spleen channel diseases. The externally contracted diseases were the fewest. According to the classification system of Western Medicine, the majority of these Chinese patent medicines were for the treatment of cardiocerebrovascular diseases. In the Department of Gynecology, emmeniopathy was again in the majority (Table 17.18).

17.3.7 Summary

In the 1263 Danshen-containing prescriptions of ancient and modern times, there were 43 indications which appeared more than 10 times. The frequency of appearance of each disease in the prescriptions is shown in Table 17.19.

Danshen prescriptions had wide indications, which were mainly diseases in the domains of internal medicine and gynecology, followed by diseases of dermatology, surgery, and otorhinolaryngology. These diseases included exterior pattern, interior pattern, deficiency pattern, excess pattern, cold pattern, and heat pattern, etc. The varieties of ophthalmological and pediatric diseases were relatively diverse, which is why they were not included in the list in Table 17.19.

Most diseases of internal medicine were heart channel diseases, which included almost all varieties of the disease in that category. In terms of modern medicine, encephalopathy, such as insomnia, amnesia, irritability-restlessness, madness, dizziness, headache, apoplexy, tinnitus, etc., accounted for the largest proportion of heart channel diseases, indicating that Danshen had better effects on the treatment of encephalopathy.

Table 17.17 The indications of Danshen-containing prescriptions in modern times

Department	Categories of diseases and syndromes (number of prescriptions)	Number of diseases and syndromes	Total prescriptions
Internal medicine	**Externally contracted diseases**: cholera, pestilence, septicaemia	42	80
	Heart channel diseases: insomnia 5, cardiopalmus 5, coronary heart disease 4, amnesia 3, myocarditis 2, irritability-restlessness, angina pectoris, precordial pain, leukopenia, hyperthyroidism, severe palpitation, depressive psychosis		
	Lung channel diseases: lung abscess		
	Liver and spleen channel diseases: gastric and duodenal ulcer 5, concretions and gatherings 3, hepatitis 3, cirrhosis, stomachache, esophageal stenosis, oesophageal diverticulum, esophageal cancer, abdominal distension, abdominal pain, hepatosplenomegaly		
	Kidney channel diseases: micturition disorders 2, prostatitis, nocturnal emission		
	Diseases of systemic channels and collaterals: leg pain 6, *bì* syndrome 4, apoplexy paralysis 3, cerebral thrombosis 2, Sciatica, limb numbness, crane-like arthropathy, convulsion, spine hyperplasia, demylinization of brain stem		
	Disease of qi, blood, and body fluids: deficiency-consumption 5, obesity		
Gynecology	Menoxenia 23, morbid leukorrhea 9, dysmenorrhea 7, uterine bleeding 6, amenorrhea 4, ectopic pregnancy 3, prolonged lochia 3, preceeded menorrhea 2, delayed menorrhea 2, hypomenorrhea 2, yin cold 2, sterility 2, menorrhagia, anemic emaciation asthenia 2, damaging fetus, mammary fistula, aberratio menses, eclampsia, pelvic inflammation, puerperal fever, postnatal weakness	21	75
Dermatology	Urticaria 4, peliona 2, psoriasis 2, lupus erythematosus 2, vitiligo, eczema, keratoma, itch of department of dermatology, erythroderma, lupus erythematosus, scrotum eczema, neurodermitis, exfoliative dermatitis, scleroderma, Raynaud's phenomenon	15	21
Surgery	Wound 4, postconcussion syndrome 2, appendicitis 2, mastofibroma, mammary abscess, hernia, sores ulceration, multiple metastatic abscess, scrofula, gall, pemphigus, vasculitis	12	17
Ophthalmology and otorhinolaryngology	Prosopodynia 4, tinnitus, swelling pain of throat	3	6
Ophtalmology	Blurred vision, subhyaloid hemorrhage	2	2
Pediatrics	Pediatric epilepsy	1	1
Total		96	202

The encephalopathic diseases were followed by cardiovascular diseases, such as coronary heart disease, angina pectoris, cardiopalmus, severe palpitation, pavor, precordial pain and so on, indicating that Danshen's major target of action is the heart. Danshen prescriptions were

Table 17.18 The indications of Danshen-containing prescriptions of Modern Chinese Patent Medicines

Department	Categories of diseases and syndromes (number of prescriptions)	Number of diseases and syndromes	Total prescriptions
Internal medicine	**Externally contracted diseases**: heat stroke	81	493
	Heart channel diseases: coronary heart disease 45, angina pectoris 44, insomnia 36, cardiopalmus 29, amnesia 21, pectoral stuffiness pain l8, arteriosclerosis 14, hyperlipidemia l3, neurastheria 12, precordial pain 7, myocardial infarction 7, pavor 6, arrhythmia 5, severe palpitation 5, irritability-restlessness 4, chest pain 3, night sweat 3, senile dementia 2, leukopenia 2, dyspnea 2, neurosis, myocardial strain, myocarditis, epilepsy, hyperthyroidism, hypothyreosis, aplastic anemia, thrombocytopenic purpura		
	Lung channel diseases: chronic bronchitis 3, cough 2, bronchial asthma, pulmonary heart disease, dyspnea-asthma syndrome, obstructive emphysema		
	Liver and spleen channel diseases: dizziness 29, hepatitis 17, headache]4, hypertension 12, cerebral thrombosis 9, stomachache 6, hypochondriac pain 4, concretions and gatherings 3, gastritis 3, constipation 3, hepatosplenomegaly 3, cirrhosis 2, deafness 2, abdominal distension 2, peptic ulcer 2, food retention, convulsion, fatty liver, postconcussion syndrome		
	Kidney channel diseases: lumbodynia 4, renal failure 4, chronic nephritis 2, impotence 2, premature ejaculation 2, pyelonephritis, kidney stone, cystitis, vesical calculus, urinary tract infection, nocturnal emission, ureteral calculus		
	Diseases of systemic channels and collaterals: apoplectic sequelal 2, arthralgia syndrome 9, limb numbness 6, rheumatic arthritis 4, Sciatica, rheumatoid arthritis, syringomyelia, gout		
	Disease of qi, blood, and body fluids: deficiency-consumption l4, diabetes 4, premature white hair 3, Simple obesity 2, Behcet's disease, lupus erythematosus, erythema nodosum		
Gynecology	Menoxenia 31, dysmenorrhea 28, morbid leukorrhea 14, infertility 5, climacteric syndrome 4, uterine bleeding 4, amenorrhea 2, pelvic inflammation 2, postpartum abdominal pain 3, prolonged lochia 2, puerperal lumbago, postnatal asthenia, postnatal anemia, vaginitis, appendagitis	15	100

(continued)

Table 17.18 (continued)

Department	Categories of diseases and syndromes (number of prescriptions)	Number of diseases and syndromes	Total prescriptions
Dermatology	Breast lobular hyperplasia 5, Thromboangiitis Obliterans 3, wound 3, furuncle2, sores ulceration 2, bone fracture 2, Cervical spondylosis 2, lumbar muscle strain 2, thrombophlebitis, mammary abscess, mastitis, hernia, scapulohumeral periarthritis, hyperplasia of prostate, hyperosteogeny, osteomyelitis, carbuncle, panniculitis, synovitis, appendicitis, phlegmon, Haemorrhoids	22	35
Ophthalmology and otorhinolaryngology	Tinnitus l3, vocal nodules 2, polyp of vocal cord2, increased mucous membrane of vocal cord2, hoarseness 2, pharyngitis, tonsi11itis, aphtha, otitis externa	9	25
Surgery	Baldness 3, vitiligo 2, acne 2, scleroderma 2, Dermatomyositis, Itch of department of dermatology, perniosis, pityriasis rosea, drug eruptions, burns, acne, psoriasis, impetiginous sores, seborrheic dermatitis	14	19
Ophtalmology	Cataract, nebula of comea	2	2
Pediatrics	Pediatric pneumonia	1	1
Total		144	675

Table 17.19 Summary of indications of Danshen prescriptions

Department	Categories of Diseases and syndromes (number of prescriptions)	Number of disease and syndrome	Total prescriptions
Internal medicine	**Externally contracted diseases**: pestilence l2	32	845
	Heart channel diseases: coronary heart disease 49, angina pectoris 45, insomnia 41, amnesia 37, cardiopalmus 34, severe palpitation 17, pavor 15, irritability-restlessness 14, madness, arteriosclerosis l4, precordial pain 13, hyperlipidemia 13, neurastheria l2 disease in lung meridian: cough l7 Liver and spleen channel diseases: dizziness 35, concretions and gatherings 32, headache 21, hepatitis 20, hypertension l2, cerebral thrombosis 11, hypochondriac pain 11, stomachache 11, hematemesis 10 Kidney channel diseases: nocturnal emission 29, micturition disorders l6		
	Diseases of systemic channels and collaterals: arthralgia syndrome 77, lumbodynia (skelalgia) 54, apoplexy 25, flaccidity syndrome 10 Diseases of qi, blood and body fluids: deficiency-consumption 82, beriberi 42		
Gynecology	Menoxenia 83, postnatal diseases 67, morbid leucorrhea 39, dysmenorrhea 39, uterine bleeding 25, amenorrhea 22	3	275
Dermatology	Leprosy 37, tineal 5	2	42
Surgery	Scrofula l8, wound	2	28
Ophthalmology and otorhinolaryngology	Strepitus aurium 17	1	17
Total		43	1,207

mainly used for the treatment of pavor and severe palpitation in ancient times, but it is mainly used for the treatment of precordial pain in modern times.

The syndrome of deficiency-consumption appeared most frequently in the indications, suggesting that Danshen's application in the treatment of the syndrome was high. This characteristic was reflected by the fact that the supplementing and boosting drugs appeared most often in the Danshen prescriptions in every time period.

The skin, muscle, and joint diseases such as leprosy, tinea, arthralgia syndrome, lumbodynia (skelalgia), and flaccidity syndrome also appeared in the indications, indicating that Danshen was usually used for the treatment of these diseases.

There were few applications of Danshen in the treatment of diseases of the respiratory system, alimentary system, and urinary system.

Among the gynecological diseases, emmeniopathy, and postpartum diseases were in the majority, wherein the frequency of menoxenia was the highest, followed by postpartum diseases, including puerperal fever, prolonged lochia, postpartum abdominal pain, postpartum faintness, postnatal deficiency-consumption, puerperal lumbago, morbid leukorrhea, dysmenorrhea, uterine bleeding, and amenorrhea, indicating that Danshen was widely used in gynecology.

Among the surgical diseases, scrofula ranked the first, followed by traumatic injuries, indicating that Danshen had the function of invigorating blood, dissolving stasis, dispersing swelling, and dissipating masses.

17.4 Reflection on the Danshen Prescriptions of the Past

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It has been demonstrated by this investigation that Danshen prescriptions are mainly combined with drugs from 15 categories: 1. dissipating wind-cold; 2. dissipating wind-heat; 3. clearing heat; 4. warming the interior; 5. purgation; 6. rectifying qi; 7. treating blood; 8. Dispelling wind-damp; 9. dissolving phlegm and relieving cough; 10. removing and percolating dampness; 11. supplementing and boosting; 12. consolidating and astringing essence; 13. calming the mind; 14. calming the liver and extinguishing wind; and 15. opening the orifices.

The indications of these prescriptions involved diseases in the Departments of Internal Medicine, Gynecology, Pediatrics, Ophthalmology & Otorhinolaryngology, and Dermatology, with the most diseases from internal medicine and gynecology. Among the internal medicine diseases, there were not many cold damages and warm diseases; rather, miscellaneous internal damage diseases were in the majority, in which most diseases were of the heart, liver, and spleen channels, and less of the lung and kidney channel diseases. Among the gynecological diseases, emmeniopathy, and postpartum disease were in the majority.

The supplementing and boosting drugs ranked first in every dynasty, both in the number of varieties and the frequency of listing, indicating that the indications of Danshen prescription were closely related to deficiency patterns. Except for the etiological factors that the diseases in the departments of internal medicine and gynecology were usually accompanied by deficiency, there were a larger number of special Danshen prescriptions in the treatment of deficiency-consumption diseases. Based on the statistical analysis, the frequent appearance of these diseases was obvious. This is concordant with the ancient materia medica works that Danshen had the functions of supplementing qi, nourishing blood, reinforcing the heart, and generating blood.

Chinese angelica was the most frequently used drug with Danshen. It appeared in 558 prescriptions, accounting for 44 % of the total number of prescriptions. The fact that nearly half of the Danshen prescriptions contained Chinese angelica suggests that Chinese angelica was the most common drug accompanying Danshen. Chinese angelica has the functions of both

nourishing and invigorating the blood, which makes it an important drug in gynecology. It was said by ancient people that the functions of Danshen were equivalent to the functions of four drugs. Although some physicians thought that the saying was a little exaggerated, it demonstrated, however, that the functions of Danshen were similar to those of Chinese angelica and that it was an important drug in gynecology. According to the compatibility theory of TCM, the two drugs have a relationship of "mutual reinforcement," so the combination of the two drugs could generate a synergistic effect.

The utilization of drugs with the function of warming the interior and dispelling cold in different dynasties varies greatly. During and before the Tang Dynasty, they were second only to the supplementing drugs. However, they fell to fifth place during the Song and Jin Dynasties, to seventh place during the Yuan and Ming Dynasties, and to eleventh place in the Qing Dynasty. In other words, the earlier the time period, the more often Danshen was used together with drugs of warm nature. The possible reason for this was that Danshen prescriptions in the earlier periods were mainly used for the treatment of cold-damp diseases, such as wind-cold damp impediments, beriberi (pedal edema, flaccidity of feet and knees), deficiency-consumption, and edema and so on.

The fate of the clearing heat drugs was the opposite of that of the warm drugs. It ranked fifth during and before the Tang Dynasty, fourth in the Song and Jin Dynasties, second in the Yuan and Ming Dynasties, and second in the Qing Dynasty. These facts suggest that in early times Danshen was less often used for the treatment of febrile illness, but it was widely used for these illnesses in later periods. For example, Ying Level Heat-Clearing Decoction, recorded in *Systematic Differentiation of Warm Diseases* and used for the treatment of summer warm pathogens infecting the pericardium, and Sanyu Qinghuo Zhitong Decoction, recorded in *New Compilation of Prolonging Life* and used for the treatment of stasis with fire from constraint and heart and stomach pain, and Qin Lian Heart-Clearing Pill, recorded in *Wondrous Lantern for Peering into the Origin and Development of Miscellaneous Diseases* and used for the treatment of heart heat and mania, were all compound prescriptions of Danshen combined with drugs for clearing heat and draining fire.

It was thus evident that Danshen, after combination with other drugs, could be used for the treatment of cold pattern diseases, including deficiency cold and excess cold, as well as for the treatment of heat pattern diseases, including deficiency-heat and excess-heat. Namely, the clinical application of Danshen is not restricted by the nature of the diseases; rather, the key is its combination with other drugs. That is why there have been different opinions on the nature of Danshen: some believed it was "slightly cold" (*Shen Nong's Classic of the Materia Medica*), and some believed that it was "heat nature" (*Collected Commentaries on 'Shen Nong's Classic of the Materia Medica'*). Based on this investigation, Danshen is a drug of neither cold nor heat, but is "neutral in nature".

The drugs with the function of activating blood circulation and dissipating blood stasis ranked sixth during and before the Tang Dynasty, seventh during the Song and Jin Dynasties, fourth in the Qing Dynasty, and second in modern times. Also, the varieties of the drugs in this category increased over time. There were only two drugs (Sichuan lovage root and two-toothed achyranthes root) during the Tang, Song, and Jin Dynasties, but six drugs (pangolin scales, corydalis rhizome, flying squirrel faeces, safflower, sappsn wood, peach kernel) were added in the Yuan Dynasty; two drugs (Chinese hawthorn fruit, motherwort) were added in the Qing Dynasty; and seven drugs (frankincense, myrrh, turmeric root tuber, hirsute shiny bugleweed herb, suberect spatholobus stem, curcumae rhizome, common burr reed tuber) were added in modern times. In the Modern Chinese Patent Medicines, pseudoginseng root, earthworm, dragon's blood, and ground beetle were added to the prescriptions. These changes reflected the fact that later doctors paid more and more attention to Danshen's function of activating blood circulation, especially the combination of Danshen with other drugs of activating blood circulation for the

treatment of various cardiovascular and cerebrovascular diseases. Although Danshen prescriptions in ancient times were used for the treatment of chest *bì*, precordial pain, palpitations, and apoplexy in TCM, which corresponded to coronary heart diseases, angina pectoris, and cerebrovascular accident in western medicine, the drug was rarely combined with other drugs of similar functions, suggesting that the understanding of the pathogenesis of cardiovascular and cerebrovascular diseases was different at different times. Among the activating blood circulation drugs, Sichuan lovage root was used most often, appearing in 389 prescriptions, which was 31 % of the total number of Danshen prescriptions, demonstrating that the two drugs had a long-term combination history.

The appearance of dispelling wind-evil drugs, such as siler, double teeth pubescent angelica root, notoptetygium root, large leaf gentian root, and eleutherococcus root-bark, in the Danshen prescriptions was relatively high, which was related to the application of Danshen prescriptions in the treatment of the diseases induced by wind, such as rheumatic arthralgia, spasm of foot muscle, lumbodynia due to wind-damp, deficiency-consumption due to wind, apoplexy and peripheral facial paralysis, postnatal wind invasion due to asthenia and lepra, and so on. In the Song dynasty, there were even several prescriptions claiming to "treat every wind-related disease," suggesting that Danshen, when combined with other wind dispelling drugs, could be used for the treatment of all exterior and interior winds, namely the diseases induced by wind evils, including skin diseases induced by affection of exogenous wind-poison, the diseases of joint, muscle, tendon, and pulse induced by the infection of exogenous wind-dampness, apoplexy induced by liver wind stirring, head and eye diseases (headache, dizziness) induced by disturbing upward of liver wind, and so on. It was recorded in ancient materia medica works that Danshen had the function of eliminating pathogenic wind and dispelling wind-evil.

Danshen prescriptions were widely used for the treatment of insomnia, amnesia, pavor, severe palpitation, epilepsy, irritability-restlessness, madness and other heart-mind diseases. Therefore, the mind-calming drugs appeared often in the Danshen prescriptions; in the Qing Dynasty, they ranked third. They also ranked third in the entire history. Among the mind-calming drugs, poria was used most often, appearing in 310 prescriptions. Following, poris were thin-leaf milkwort root, Indian bread with hostwood, spiney date seed, and oriental arborvitae, indicating that Danshen had some effects of nourishing the heart and calming the mind. These effects were recorded in ancient materia medica works.

Danshen prescriptions were also widely used for the treatment of concretions and gatherings, stomach ache, abdominal distension, and other digestive tract diseases, and usually combined with qi-regulating drugs such as aged tangerine peel, cyperus, bitter orange, common aucklandia root, and so on. Based on the statistical analysis of prescriptions, the qi-regulating drugs ranked sixth. Because there was a close relationship between qi and blood, stagnant blood was usually induced by long-term qi stagnation, and qi stagnation and blood stasis usually existed together. Thus, Danshen should be combined with qi-regulating drugs in the treatment of blood stasis and qi stagnation.

In addition, there were both simple and complex Danshen prescriptions; the former could contain as few as one ingredient, and the latter could contain as many as several dozens of ingredients. The preparations of the prescriptions included oral use and external application; the former included decoction, pill, powder, paste and wine, etc., the latter included paste and balneum.

To sum up, Danshen is an extremely common drug in both ancient and modern times, and it can be used in the treatment of various diseases. More effective Danshen prescriptions must be developed to benefit human health.

References

1. Wu N. J New Chin Med. 1992;24(8):1–3.
2. Yan X, Wu N. Tianjin Pharm. 1992;4(4):22.
3. Wu N, Yan X, Zhu Y. Chin Tradit Pat Med. 1993;15 (8):24.

4. Wu N, Yan X, Guo H, et al. China Pharm. 1993;4 (4):37.
5. Huang J. Chin Manipulation Qigong Ther. 1995;3:46.
6. Yan Y, Ye L, Sun J. Forum Tradit Chin Med. 1995;6:45.
7. Chen Y. Pharm Bull S China. 1996;26(2):12.
8. Chen Y, Qiu C. J Emerg Tradit Chin Med. 1996;5 (5):225.
9. Feng S, Ma Y. Tian Jian Pharm. 1996;8(3):42.
10. Zhang L, Guo Y. The research report on basic pharmacology of composite salviae dropping pill. In: 96th national symposium on composite salviae medicament form. 1996; p. 14.
11. Chang Z, Tang P, Ren B. Research and analysis of composite salviae dropping pill in our clinical apply. In: 96th national symposium on composite salviae medicament form. l996; p. 17.
12. Yan X, Wu N. Why does composite salviae dropping pill have a rapid effect. In: 96th national symposium on composite salviae medicament form. 1996; p. 17.
13. Tang Z. Clinical report of 100 caes with coronary heart disease and angina treated with composite salviae dropping pill. In: 96th national symposium on composite salviae medicament form. 1996; p. 55.
14. Ji H, Yao S. Analysis of the clinical effect treatment of obstruction of Qi in the chest with composite salviae dropping pill. In: 96th national symposium on composite salviae medicament form. 1996; p. 68.
15. Zhang J, Lin J. The effect of treatment of 60 patients with coronary heart disease and angina with composite salviae dropping pill (Attached comparsion with 30 cases treated with dinitrosorbide). In: 96th national symposium on composite salviae medicament form. 1996; p. 71.
16. Li Q, Feng X, Jiao L, et al. The influence of composite salviae dropping pill on blood viscosity, blood platetel aggregation and microcirculation of patients with coronary heart disease. In: 96th national symposium on composite salviae medicament form. 1996; p. 73.
17. Xu Y, Wang H, Li A, Hua C, Jin X. The supplement and experience of composite salviae dropping pill in the treatment of chronic renal embolism. In: 96th national symposium on composite salviae medicament form. 1996; p. 76.
18. Li F, Zhang Z, Ma J, et al. Clinial observation of composite salviae dropping pill in the treatment of coronary heart disease. In: 96th national symposium on composite salviae medicament form. 1996; p. 76.
19. Liu Z, Gao S, Deng J, et al. Clinical research on composite salviae dropping pill in the treatment of coronary heart disease. In: 96th national symposium on composite salviae medicament form. 1996; p. 76.
20. Du A, Li H. Summary of the clinical effect of composite salviae dropping pill in the treatment of coronary heart disease and angina. In: 96th national symposium on composite salviae medicament form. 1996; p. 77.
21. Lin D, Chen J. Clinical observation of composite salviae dropping pill in the treatment of 62 cases with coronary heart disease. In: 96th national symposium on composite salviae medicament form. 1996; p. 77.
22. Wang S, Liu C, Han S, et al. Composite salviae dropping pill treatment of 206 cases with coronary heart disease and angina. In: 96th national symposium on composite salviae medicament form. 1996; p. 78.
23. Fan X, Huang Y. clinical observation of composite salviae dropping pill in the treatment of coronary heart disease and angina. In: 96th national symposium on composite salviae medicament form. 1996; p. 79.
24. Liang K. Clinical observation of composite salviae dropping pill in the treatment of 120 cases with coronary heart disease and angina. In: 96th national symposium on composite salviae medicament form. 1996; p. 80.
25. Zhu D, Xu D. Analysis of effect of composite salviae dropping pill in the treatment of coronary heart disease and angina. In: 96th national symposium on composite salviae medicament form. 1996; p. 80.
26. Xing Z, Gu Q. Observation of the effect of composite salviae dropping pill in the treatment of 60 cases with coronary heart disease and angina. In: 96th national symposium on composite salviae medicament form. 1996; p. 80.
27. Hu S, Fang Q, Cheng W, et al. The clinical study of composite salviae dropping pill in the treatment of coronary heart disease and angina. In: 96th national symposium on composite salviae medicament form. 1996; p. 81.
28. Lv Y. Clinical observation of the effect of composite salviae dropping pill in the treatment of 128 cases with angina. In: 96th national symposium on composite salviae medicament form. 1996; p. 81.
29. Yun Y, Yang L, Xie Y, et al. Clinical observation of composite salviae dropping pill in the treatment of senile coronary heart disease. In: 96th national symposium on composite salviae medicament form. 1996; p. 81.
30. Shi Y. Comparsion of composite salviae dropping pill and compound salvia miltiorrhiza tablet in the treatment of coronary heart disease. In: 96th national symposium on composite salviae medicament form. 1996; p. 82.
31. Luo Z. Clinical observation and discussion of the mechanism of composite salviae dropping pill in the treatment of coronary heart disease and angina combined with hypertension. In: 96th national symposium on composite salviae medicament form. 1996; p. 82.
32. Ai L, Hu P. Clinical observation of composite salviae dropping pill in the treatment of obstruction of Qi in chest. In: 96th national symposium on composite salviae medicament form. 1996; p. 82.

33. Huang W. The experimental study of composite salviae dropping pill on blood rheology of excitable rats. In: 96th national symposium on composite salviae medicament form. 1996; p. 84.
34. Jia W. The experimental report about the influence of composite salviae dropping pill on microcirculation and blood rheology. In: 96th national symposium on composite salviae medicament form. 1996; p. 84.
35. Ma J, Li F, Shi J. Clinical analysis of the influence of composite salviae dropping pill on blood rheology and cellular rheology of patients with cerebral infraction. In: 96th national symposium on composite salviae medicament form. 1996; p. 85.
36. Liu Y. Clinical observation of composite salviae dropping pill in the treatment of 78 cases with abnormal blood lipid. In: 96th national symposium on composite salviae medicament form. 1996; p. 85.
37. Shen Y, Li R. Clinical experience of composite salviae dropping pill in the treatment of many diseases. In: 96th national symposium on composite salviae medicament form. 1996; p. 88.
38. Zhao X. Observation of effect of oral intake of composite salviae dropping pill on relieving pain of liver cancer. In: 96th national symposium on composite salviae medicament form. 1996; p. 90.
39. Zhang K, Lin X. Observation of the effect of composite salviae dropping pill in the treatment of coronary heart disease and angina. In: 96th national symposium on composite salviae medicament form. 1996; p. 97.
40. Ma J, Li F, Shi J, et al. Clinical observation of composite salviae dropping pill in the treatment of 75 cases with coronary heart disease and angina. In: 96th national symposium on composite salviae medicament form. 1996; p. 97.
41. Chen H. Clinical analysis of composite salviae dropping pill in the treatment of coronary heart disease. In: 96th national symposium on composite salviae medicament form. 1996; p. 97.
42. Lin W. Comparsion of composite salviae dropping pill and quick acting pill for heart recovery in the treatment of coronary heart disease and angina. In: 96th national symposium on composite salviae medicament form. 1996; p. 94.
43. Zhu L, Gong Y, Wang B. Observation of the effect of composite salviae dropping pill in treating hyperlipemia. In: 96th national symposium on composite salviae medicament form. 1996; p. 98.
44. Geng J. Observation of the effect of composite salviae dropping pill in the treatment of senile coronary heart disease. In: 96th national symposium on composite salviae medicament form. 1996; p. 98.
45. Cong P, Sun X, Shi X, et al. Clinical study of composite salviae dropping pill combined with heparin in the treatment of angina of unstable angina pectoris combined with high blood viscosity. In: 96th national symposium on composite salviae medicament form. 1996; p. 98.
46. Zhang Q, Li Shuyi. Observation of the effect of composite salviae dropping pill in the treatment of coronary heart disease and angina. In: 96th national symposium on composite salviae medicament form. 1996; p. 99.
47. Bai J, Wang N. J Shanxi Med. 1997;26(4):307.
48. Sun D, Guo J, Li G. J Linyi Med Coll. 1997;2:113.
49. Wang G, Wang S. Hainan Med J. 1997;36.
50. Li QB, Yan Y, Lin F, Fu J. J Tradit Chin Med. 1997;28(5):1.
51. Du J, Liu L, Dai Y. Heilongjiang Med J. 1997;161 (11):23.
52. Liu Z, Gao S, Deng J, et al. Chin Tradit Pat Med. 1997;19(7):20.
53. Zheng Z, Lu G, Pei Z, et al. Hunan Med J. 1997;14 (3):l45.
54. Gao Y, Li X. J Integr Tradit W Pract Clin Emerg. 1997;4(3):100.
55. Guo H, Zhe J. J Integr Tradit Chin W Med. 1997;7 (3):153.
56. Wang S, Xu H, Guo Y, Li S, et al. Med Mater Med Res. 1998;9(2):112.
57. Zhang G, Li Y, Liu W, et al. Traditi Chin W Med Commun. 1998;26:63.
58. Lou M, Jia L. J Henan Coll Tradit Chin Med. 1998;13(77):99.
59. Wang H, Li R, Fan X, et al. Nei Mongol J Tradit Chin Med. 1998;S1:3.
60. Yu J, Ji S. Shandong Med J. 1998;38(11):58.
61. Li Z. Appl J Tradit Chin Intern Med. 1998;12(4):29.
62. Zhou Y. Chin J New Drugs Clin Remedies. 1998;17 (6):375.
63. Guo H. Tianjin Pharm. 1998;10(1):27.
64. Sun D, Zhang Z. J Changchun TCM Coll. 1998;14 (4):6.
65. Li F, Ma J, Zhang Z, et al. Chin Tradit Pat Med. 1998;20(3):29.
66. Ma J. Tianjin J Tradit Chin Med. 1998;15(1):24.
67. Zhang Y, Ren J. J Emerg Tradit Chin Med. 1998;7 (3):139.
68. Zhu S, Wang H. Clin J Hui Tradit Chin Med. 1998;10(3):142.
69. Lu G, Li X. Fujian Med J. 1998;20(4):55.
70. Zhao M, Wang J, Wei J, et al. Chin J Clin Pharmacol. 1999;15(4):288.
71. Liang T, Gao S, Wang A. Lishizhen Med Mater Med Res. 1999;10(2):90.
72. Luo L, Peng J. Cent China J Med Sci. 1999;26 (2):54.
73. Li W. Chin J Cardiovasc Rehabil Med. 1999;8(1):33.
74. Fu C, Zha Y. Chin J Microcirc. 1999;3(4):253.
75. Liu JA. Hunan J Tradit Chin Med. 1999;15(5):29.
76. Zeng Z, Wei Y. Chin J Rehabil Med. 1999;8(3):57.
77. Ma H, Zhao Z. Tradit Herbal Drugs. 1999;30 (5):364.
78. Hu G, Yu X. Chin J Cardiovasology. 1999;4(4):238.
79. Qiu Q, Lin X. Strait Pharm J. 1999;11(2):84.
80. Bo S, Song Z, Xue X. Herald Med. 1999;18(6):38.
81. Chen N, Zhou S. Hainan Med J. 1999;10(6):14.

82. Bao Y, Xu Z, Jing Z, et al. Chin Tradit Herbal Drugs. 1999;30(4):287.
83. Gu X. Harbin Med Sci. 1999;19(4):21.
84. Zhang A, Liya A. Chin J Rehabil Med. 1999;14 (1):47.
85. Ye N, Yang C, Lai S. Lishizhen Med Mater Med Res. 1999;10(2):139.
86. Tan JN. Jiangsu J Prev Med. 1999;10(3):58.
87. Wang B, He Z. Mech Electr Eng Mag. 1999;16 (1):20.
88. Meng L, Wang N. Tradit Chin Drug Res Clin Pharmacol. 1999;10(5):290.
89. Liao F, Feng L, Cao H, et al. J Zhejiang TCM Coll. 1999;23(6):39.
90. Zhao X, Zhang S. Chin Tradit Herbal Drugs. 1999;30(9):688.
91. Li Y, Dong S. Zhejiang J Integr Trdit Chin W Med. 1999;9(2):79.
92. Zhang G, Wang Y. Jilin J Tradit Chin Med. 1999;19 (6):23.
93. Li Z, Qu Y. Acta Chin Med Pharm. 1999;27(6):16.
94. Gao F, Zhang X. J Emerg Tradit Chin. 1999;8 (5):205.
95. Zou J, Shi Z. Chin J Med Fact Min. 1999;12(5):357.
96. Wang S, Zhou X, Zhang Y. J Changchun TCM Coll. 1999;15(2):10.
97. Zhu J. Anthology Med. 1999;18(2):152.
98. Li F, Zhang Z, Wang C, et al. J Anhui Tradit Chin Med Coll. 1999;18(1):10.
99. Zhang G, Cao Y, Dai X, et al. Jilin J Tradit Chin Med. 1999;19(3):10.
100. Mu Z, Lin W. Hebei J Integr Tradit W Med. 1999;8 (4):540.
101. Ji H, Yao S. Chin J Tradit Med Sci Technol. 1999;6 (1):43.
102. Wang X, Qin L, Huang Y. J Emerg Med. 1999;8 (8):395.
103. Liang L, Yang W, Zhang Y. Chin Doct. 1999;13 (4):252.
104. Dong X, Zhang S. Pract Clin Med. 2001; (3):143–145.
105. Hu J, Chen H. Railway Med J. 1999;27(3):192.
106. Ding X, Wang C. Acta Acad Med Suzhou. 1999;19 (5):512.
107. Zhou Y, Li C, Zhang N, et al. Integr Tradit W Med Pract Clin Emerg Treat China. 1999;6(2):53.
108. Zhu Z, Sun H. Hubei J Tradit Chin Med. 1999;21 (1):34.
109. Cao T, Duan Y, Yang B, et al. The observation and study of composite salviae dropping pill on treatment of hyperlipimia and atherosclerosis using h-resolution ultrasonic blood vessel imaging. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 9.
110. Zhao M, Wei J, Gao C, et al. The experimental study of the protective effect of composite salviae dropping pill on damaged heart muscle caused by ischemia reperfusion. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 15.
111. Guan Z. Observation of the clinical effect of composite salviae dropping pill in the the treatment of 2 patients with coronary heart diseases and angina of stable type following the clinical protocol of FDA Phase II of USA. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 24.
112. Luo Z. The influence of composite salviae dropping pill on restructuring left ventricle and influence on neurohormones of patients with hypertension combined with coronary heart disease. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 29.
113. Jia L, Shen R. Comparsion study of composite salviae dropping pill and compound salviae tablet in the treatment of coronary heart disease. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 40.
114. Wang W. Observation of the effect of composite salviae dropping pill in the treatment of coronary heart disease and the influence of composite salviae dropping pill on blood rheology. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 44.
115. Li M, et al. Observation of effect of composite salviae dropping pill in the effect of 56 patients with coronary heart disease and angina. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 55.
116. Xu G. Clinical observation of composite salviae dropping pill in the treatment of coronary heart disease and angina. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 57.
117. Ci S, Yang C, Hu R. The clinical study of composite salviae dropping pill in the treatment of central sleep apnea SynDrome. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 63.
118. Gao Y, Mao L, Zhao W, et al. The clinical study of composite salviae dropping pill in the treatment of cerebal infraction. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 65.
119. Fan S, Jia L. The influence of composite salviae dropping pill on blood rheology of patients with pulmonary heart disease during the acute and aggravating period. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 72.
120. Li Z, Lin J, Li J, et al. The influence of composite salviae dropping pill on blood rheology of rats with hyperlipimia. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 84.

121. Yang G. The clinical application of composite salviae dropping pill (a summary). In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 86.
122. Li Y, Tianwen, Hao Xu, et al. Observation of the effect of composite salviae dropping pill in the treatment of senile coronary heart disease and angina. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 89.
123. Liu Y. Clinical observation of composite salviae dropping pill in the treatment of 60 patients with coronary heart disease. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 89.
124. Ma X. Observation of the effect of composite salviae dropping pill in the treatment of coronary heart disease and angina. In: The 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 90.
125. Lu Z. The clinical observation of composite salviae dropping pill in the treatment of 120 patients with coronary heart disease. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 90.
126. Xia J. A little experience of the clinical application of composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 90.
127. Chen G. The clinical analysis of composite salviae dropping pill in the treatment of 68 patients with coronary heart disease. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 91.
128. Yan Y, Yang J. Observation of the effect of composite salviae dropping pill in the treatment of 60 patients with coronary heart disease. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 91.
129. Ci S, Xu J, Zhang J. The study of the use of composite salviae dropping pill in the treatment of arrhythmia. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 92.
130. Yang X, Zhang X. The influence of composite salviae dropping pill on the LPO content in blood and the diastole function of the left ventricle. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 92.
131. Cheng M, Pei J, Zhang Y, et al. Observation of the effect of composite salviae dropping pill in the treatment of 51 patients with coronary heart disease. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 93.
132. Zhang C, Zhang L. Observation of the effect of composite salviae dropping pill in the treatment of coronary heart disease. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 93.
133. Yu Z. The clinical observation of composite salviae dropping pill in treating ischemic heart disease. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 94.
134. Liu G. A pilot clinical study of composite salviae dropping pill in the treatment of coronary heart disease and its influence on blood triglycerides. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 94.
135. Wang S, Fu H, Li S, et al. The effect of composite salviae dropping pill, the effect of composite salviae dropping pill in treatment of coronary heart disease combined with hyperviscosity syndrome. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 95.
136. Zhang X, Shi S, Wang J. The clinical observation of the use of composite salviae dropping pill in the treatment of coronary heart disease and angina. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae)' 99. 1999; p. 95.
137. Liang S, Li G. Clinical observation of treatment of angina pectoris, hyperlipmia and blood hyperviscosity syndrome with composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae)' 99. 1999; p. 96.
138. Rao S, Jiang Q. Comaprsion study of prevention and treatment of coronary heart disease with composite salviae dropping pill and sitalong. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 97.
139. Jia L, Zhu S. Effect of composite salviae dropping pill on ventricular late receptor potential of patients with coronary heart disease. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 97.
140. Hu P, Hu Y, Ai L. Clinical observation of treatment of obstruction of Qi in the chest with composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 99.
141. Ding Q, Tan W. Clinical observation of treatment of 30 patients in the acute phase ofpulmonary heart disease with composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 99.
142. Xu C, Wang J, Zou X. Clinical observation of treatment of 60 patients with stable angina pectoris with composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 99.

143. Qiao Y, Wang B. Treatment of 50 patients with coronary disease with composite salviae dropping pill. In: 99 national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 99.
144. Huang Q, Huang W. Clinical effect of composite salviae dropping pill on 45 patients with angina pectoris. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 100.
145. Zhang S, Fan J, Zhang Z. Clinical observation of treatment of 47 patients with A ngina pectoris of coronary heart disease with composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 100.
146. Li J, Yang J, Li X, et al. Effect of composite salviae dropping pill on negative-trans of ventricular late receptor potential of patients with coronary heart disease. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 101.
147. Yuan L. Clinical effect of composite salviae dropping pill combined with lsosorbide dinitrate on coronary heart disease. In: 99th national workshop on modernization of traditional Chinese medicine (composite salviae). 1999; p. 101.
148. Guo G. Clinical effect of composite salviae dropping pill on angina pectoris. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 102.
149. Wang S. Effect of composite salviae dropping pill on ECGs of patients with coronary heart disease. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 102.
150. Yu Z. Clinical effect of composite salviae dropping pill on 102 patients with heart disease. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 103.
151. Wang Y. Clinical observation of treatment of angina pectoris with composite salviae dropping pill combined with lsosorbide dinitrate. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 104.
152. Gao H, Ma L. Clinical effect of composite salviae dropping pill on 130 patients with angina pec-toris. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 104.
153. Guo R. Treatment of 280 patients with angina pectoris of coronary heart disease with composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 105.
154. Lin X, Chen J. Clinical observation of treatment of 30 patients angina pectoris with composite salviae dropping pill and discussion. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 105.
155. Liu Z. Clinical effect of composite salviae dropping pill on angina pectoris. In: 99th national workshop the modernization of traditional Chinese medicine (composite salviae). 1999; p. 105.
156. Yang J. Clinical effect of composite salviae dropping pill on angina pectoris. In: 99th national workshop the modernization of traditional Chinese medicine (composite salviae). 1999; p. 106.
157. Chen Z, Tian W, Li Z. Effect of composite salviae dropping pill on blood lipid abnormity and hemorrheology. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 106.
158. Guo D, Chen R, Fu X. A hemorrheological study: composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 107.
159. Huang C, Li Q, Feng X, et al. Effect of composite salviae dropping pill on blood viscosity, platelet aggregation and microcirculation of patients with coronary heart disease. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 108.
160. Huang Y. Application of composite salviae dropping pill in treatment of chronic hepatitis B (including 57 case reports). In: 99th national workshop on modernization of traditional Chinese medicine (Composite Salviae). 1999; p. 109.
161. Long Z, Wen G, Liao X, et al. Effect of composite salviae dropping pill on blood lipids of patients with cardiao-cerebral-vascular disease. In: 99th national workshop on the modernization of traditional Chinese medicine (Composite Salviae). 1999; p. 110.
162. Cao L, Yu M. Clinical effect of composite salviae dropping pill on acute cerebral infarction. In: 99th national workshop on the modernization of traditional Chinese medicine (Composite Salviae). 1999; p. 110.
163. Cao L, Yu M. Effect of composite salviae dropping pill on platelet function with cerebral infarction. In: 99th national workshop on the modernization of traditional Chinese medicine (Composite Salviae). 1999; p. 110.
164. Zhang X. Case report of typical patients with cardiac infarction and cerebral infarction with composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Chinese medicine (Composite Salviae). 1999; p. 111.
165. He Z. Treatment of 61 patients with vertebral-basilar artery ischemic vertigo composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Chinese medicine (Composite Salviae). 1999; p. 112.
166. Zhen Y, Li H. Clinical observation of treatment of convalescent cerebral infarction and its sequelae with composite salviae dropping pill. In: 99th national workshop on the modernization of

traditional Chinese medicine (composite salviae). 1999; p. 113.
167. Zhou J. Clinical observation of treatment of meniere's syndrome with composite salviae dropping pill, mannitol and flunarizine. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 113.
168. Ma J. Treatment of hemorrheological index changes caused by hyperviscosity with composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Chinese (composite salviae). 1999; p. 116.
169. Sang M. Clinical observation of treatment of blood hyperviscosity with composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Chinese medicine (composite salviae). 1999; p. 116.
170. Wu H. Clinical observation of treatment of obstruction of Qi in the chest with composite salviae dropping pill. In: 99th national workshop on the modernization of traditional Medicine (composite salviae). 1999; p. 119.
171. Zheng X. Chin Pract Med. 2000;2(3):13.
172. Wu X, Guo X. Hebei J Tradit Chin Med. 2000;22 (9):671.
173. Liu G, Yuan S, Su S. China's Nat. 2000;8(2):33.
174. Zheng R. Zhoushan Med Sci. 2000;28(3):52.
175. Hu S. J Pract Tradit Chin Med. 2000;16(2):34.
176. Yao C. Jiangsu J Clin Med. 2000;4(6):574.
177. Wang L, Liu G, Chen G. J Pract Tradit Chin Med. 2000;16(7):33.
178. Hua Y, Wang M, Wang S. Shanxi Tradit Chin Med. 2000;16(2):64.
179. Gao B, Wu Y. J Binzhou Med Coll. 2000;23(1):68.
180. Liu Y, Zhangyong. Fujian J Med Sci, 2000;22 (3):83.
181. Liu R, Li S. Hubei J Tradit Chin Med. 2000;22 (1):30.
182. Fu C. Liangang Technol Manage. 2000;(5):60.
183. Quan H, Liu X, Quan D, et al. Chin J Integr Tradit W Med. 2000;20(12):943.
184. Zheng C. Jilin Med Info. 2000;17(6):39.
185. Tang Q, Chen Y. J Guangdong Med Coll. 2000;18 (3):251.
186. Li Q, Wang X, Xu C, et al. Chin J Pathophysiol. 2000;16(10):1026.
187. Li P. Yinshan Acad J. 2000;15(6):89.
188. Sun C, Zhang Z. Changkuang Med Health. 2000;16 (5):397.
189. Pan X, Zhang S. J Yichun Med Coll. 2000;12 (4):283.
190. Zheng H. Chin J Dis Control Prevention. 2000;4 (3):284.
191. Jiang H, Li L, Wang L, et al. Chin J Cardiovasc Rehabil Med. 2000;9(5):64.
192. Liu X, Song Y. J Clin Cardiol. 2000;16(11):520.
193. Yan X. Chin Tradit Pat Med. 2000;22(12):863.
194. Hong X, Mi S, Wang N. New Tradit Chin Drug Res Clin Pharmacol. 2000;11(5):286.
195. Wang F. Chin J Dis Control Prevention. 2000;4 (4):381.
196. Lin D. Mod J Integr Tradit W Med. 2000;9 (20):2012.
197. Huang T. Chin J Tradit Med Sci Technol. 2000;7 (5):327.
198. Zheng L, Ci S. J Zhenjiang Med Coll. 2000;10 (3):512.
199. Shi J. J Zhenjiang Med Coll. 2000;10(2):253.
200. Wang S, Sun H. Clin J Anhui Tradit Chin Med. 2000;12(6):510.
201. Huang L. Anthol Med. 2000;19(4):469.
202. Ge Z, Pan S. Zhejiang J Integr Tradit Chin W Med. 2000;10(12):720.
203. Gong W, Dai H, Zhang X. Chin J Med Writ. 2000;7 (1):96.
204. Han G, Zhao Z, Liu T, et al. Chin Tradit Pat Med. 2000;22(12):872.
205. Yang Y, Wu YG. J Anhui TCM Coll. 2000;19 (5):15.
206. Gao H, Wu N. Pharm J Chin People's Liberation Army. 2000;16(2):114.
207. Cheng L, Zhao L, Gao C, et al. J Liaoning TCM Coll. 2000;2(1):62–3.
208. Ren X. Shanxi Clin Med. 2000;9(9):694.
209. Zhou D. Chin Tradit Pat Med. 2000;22(8):578.
210. Yang L. Chin Tradit Herbal Drugs. 2000;31(5): W002–3.
211. Lv Y, Jia M. Chin Heart J. 2000;12(5):418.
212. Pan L, Sun H, Fang H. Chin Rural Doct. 2000;15 (4):6.
213. Yang Y, Li K, Feng X. Chin Tradit Herbal Drugs. 2000;31(3):208.
214. Wang B, Wang J. Manufact Autom. 2000;22(8):25, 31.
215. Chen Z. J Hunan TCM Coll. 2000;20(2):38.
216. Wang X, Li C. Chin J Pract Med. 2000;27(9):16.
217. Li W, Xie M, Wei P, et al. Shanxi J Tradit Chin Med. 2000;16(4):25.
218. Wan Y, Wan M, Xu P. Shanxi J Tradit Chin Med. 2000;l6 (4):45.
219. Zhou X, Zhu H. Hebei Tradit Chin Med. 2000;22 (5):338.
220. Wang S. Chin J Heart Dis. 2000;12(4):323.
221. Fang Y. Zhejiang J Integr TCM W Med. 10(9):537.
222. Sheng Y, Wang J, Li C. Chin J Cardiovasc Rehabil Med. 2000;9(1):54.
223. Dai W, Jia S, Zhao L. Hebei Med Sci. 2000;6 (2):132.
224. Xu X. Chin Tradit Herbal Drugs. 2000;31(1):44, 72.
225. Sun L, Dai P. Tianjin J Tradit Chin Med. 2000;17 (3):6.
226. Pan H. Guangxi Med Sci. 2000;22(4):758.
227. Liu X, Wang D, Xu L. Beijing J Tradit Chin Med. 2000;19(3):64, F003.
228. Jia L, Du Y. J Emerg Tradit. 2000;9(3):106.
229. Chai J, Zhang W. Mod J Integr Tradit W Med. 2000;9(10):879.
230. Wang N, Mi S. New Tradit Chin Drug Res Clin Pharmacol. 2000;11(3):141.

231. Ma J, Ye Z, Yang Y. World Sci Technol Mod Tradit Chin Med. 2000;2(2):44.
232. Quan Y. Hubei J Tradit Chin Med. 2000;22(8):13.
233. Wu S, Liu H. Ningxia J Med Sci. 2000;22(7):407.
234. Qiao Y, Qiao Y. Bull Med Res. 2000;29(4):54.
235. Sun L, Shao J, Yang X. J Pract Tradit Chin Med. 2000;14(1):38.
236. Chen R, Zheng X. Zhejiang J Integr Tradit Chin W Med. 2000;10(3):127.
237. Wang Q. J Pract Tradit Chin Med. 2000;16(4):33.
238. Ding Q. Mod J Integr Tradit W Med. 2000;9(8):698.
239. Guo Z. Chin J Inf Tradit Chin Med. 2000;7(4):14.
240. Du C. Zhejiang J Integr Tradit Chin W Med. 2000;10(1):18.
241. Qiao Y, Qiao Y, Zhang H. J Integr Tradit W Med. 2000;29(4):54.
242. Xu Z, Zhang B, Wang Y, et al. Chin Tradit Herbal Drugs. 2000;31(4):283.
243. Li T, Geng B, Wang H, et al. Heilongjiang Anim Sci Vet Med. 2000;3:22.
244. Sun S, Li M, Zhang L, et al. Tradit Herbal Drugs. 2001;32(9):W003–4.
245. Liu J. Li Jianhua. Chin J Med Theory Pract. 2001;5:587.
246. Zhang Y. Chin J Clin Pharmacol Ther. 2001;6 (2):160.
247. Ma Y, Zhang H, Ma J. Mod Tradit Chin Med. 2001;14(2):15.
248. Wang Yichen. China Labor, 2001, (11):1010.
249. Mao J. Fu Jian J Tradit Chin Med. 2001;32(2):22.
250. Shi L, Xu C, Wang X, et al. J Harbin Med Univ. 2001;35(5):335.
251. Jia L, Wang D. Shaanxi J Tradit Chin Med. 2001;22 (8):485.
252. Jiang P. Forum Tradit Chin Med. 2001;16(5):32.
253. Gu Y. J Pract Tradit Chin Med. 2001;7(12):10.
254. Xue F, Liu S. J Tradit Chin Med Univ Hunan. 2001;21(2):36.
255. Fu S, Shen L. Hebei Med J. 2001;23(2):147.
256. Xiao H. Med J Ind Enterp. 2001;14(6):10.
257. Guan Y. Tian Jian Pharm. 2001;13(6):54.
258. Li X, Liang Y, Ding N. Tian Jian Pharm. 2001;13 (5):23.
259. Lu J, Sheng H. Gan Su J Tradit Chin Med. 2001;14 (6):22.
260. Zhang F, Wang H, Dong Y. Pharm J Chin People's Liberation Army. 2001;17(3):165.
261. Huang X, Li G. China Pharm. 2001;10(12):6.
262. Liu Y. Henan J Diagn Ther. 2001;15(4):250.
263. Li J, Wang Q. Shanxi J Tradit Chin Med. 2001;17 (5):56.
264. Wang B, Shi X. Tianjin Sci Technol. 2001;4:60.
265. Zhang Y, Li M, Zhang L. Mod J Integr Tradit Chin W Med. 2001;10(12):110l.
266. Li S, Sun S. Chin Ophthalmic Res. 2001;19(4):334.
267. Huang T, Wang N. Tradit Chin Drug Res Clin Pharm. 2001;12(5):354.
268. Yan Y, Li B. Chin J Rural Med Pharm. 2001;8 (12):24.
269. Yan L, Yue L. Heilongjiang Med. 2001;14(4):316.
270. Guo G. Clin Med. 2001;21(9):40.
271. Yuan G. Henan Tradit Chin Med. 2001;21(5):35.
272. Li J. Shihezi. Sci Technol. 2001;4:51.
273. Peng Z. Lishizhen Med Mater Med Res. 2001;12 (9):818.
274. Qiu X. Chin J Inf Tradit Chin Med. 2001;8(9):69.
275. Lu J, Wang F, Lin Y, et al. J Clin Cardiol. 2001;1 7 (8):377.
276. Shi A, Xie M. Shanxi Clin Med. 2001;10(8):585.
277. Zheng J, Dai P. Pract J Cardiac Cereb Pneumal Vasc Dis. 2001;9(4):209.
278. Lin X, Chen L. Fu Jian J Tradit Chin Med. 2001;32 (3):39.
279. Zhang Y. J Jinzhou Med Coll. 2001;22(4):36.
280. Zheng X. Chin Tradit Herbal Drugs. 2001;32 (7):636.
281. Qi F, Tian Y. J Med Theory Pract. 2001;14(8):745.
282. Wei Y, Zuo F, Zhang X. J Med Theory Pract. 2001;14(8):808.
283. Zhang S. J Fujian Coll Tradit Chin Med. 2001;11 (3):10.
284. Cai M. Zhejiang J Integr Tradit Chin W Med. 2001;11(8):516.
285. Wang G, Shen Y. Clin Focus. 2001;16(15):700.
286. Li G, Liu G. Jiangxi Med Sci. 2001;36(3):215.
287. Yang J, Dai G. J Postgrad Med. 2001;24(8):22.
288. Peng Z. New J Tradit Chin Med. 2001;33(9):55.
289. Guo Z. J Med Theory Pract. 2001;14(6):501.
290. Chu Z, Wang X. Acta Acad Med Wannan. 2001;20 (3):190.
291. Yang S, Huang T, Wang H. Acta Acad Med Wannan. 2001;20(3):198.
292. Wei Y, Zhang X. Chin J Integr Tradit W Med. 2001;21(8):614.
293. Sun C. Heilongjiang Med Pharm. 2001;24(3):77.
294. Zhu W, Li S. J Zhenjiang Med Coll. 2001;11 (6):808.
295. Zhu Y. Gansu Tradit Chin Med. 2001;14(2):52.
296. Wei F. Chin J Tradit Med Sci Technol. 2001;8 (3):184.
297. Xie C. J Liao Ning Coll Tradit Chin Med. 2001;3 (2):112.
298. Huang Z, Ou Y, Wang Q, et al. Strait Pharm J. 2001;13(2):56.
299. Lin P, Chen X. Guangzhou Med J. 2001;32(3):73.
300. Guo L, Li S, Zhang W. J Linyi Med Coll. 2001;23 (2):113.
301. Wang X. Pharm J Chin People's Liberation Army. 2001;17(2):78.
302. Xie S, Liu C. Heilongjiang Med J. 2001;14(2):125.
303. Zhang X. Chin Tradit Pat Med. 2001;23(3):227.
304. Lv X, Zhang W, Yu X. Cent Plains Med J. 2001;28 (4):56.
305. Zhu Y. Jiangxi J Tradit Chin Med. 2001;32(2):28.
306. Wei Y, Wang S, Xu Q. Shandong Med J. 2001;41 (8):30.
307. Mao J, Gan Z. Pharm J Chin People's Liberation. 2001;17(1):49.
308. Zhang B. HanYun, Lin Lin. Shanghai J Tradit Chin Med. 2001;35(2):19.

309. Zhang H, Yang Y. Fujian J Tradit Chin Med. 2001;32(1):10.
310. Zhao N. J Zhejiang Coll TCM. 2001;25(1):22.
311. Zheng D, Chen C. Guangxi J Tradit Chin Med. 2001;24(1):4.
312. Wu D, Li F, Xu G. Clin Med China. 2001;17(1):40.
313. Li Q, Wang X, Zhu S, et al. Chin J Pathophysiol. 2001;17(7):690.
314. Wu Y, Wang J. Chin J Ethnomed Ethnopharm. 2001;48:13.
315. Gong Q, Mao Z. Youjiang Med J. 2001;29(1):53.
316. Guan X, Lin X, Guo H, et al. Zhejiang J Integr Tradit Chin W Med. 2001;11(3):143.
317. Jiang H. Zhejiang J Integr Tradit Chin W Med. 2001;11(2):96.
318. Yang Z, Fan H, Yu C, et al. Clin Med. 2001;21 (3):24–5.
319. Zhang B, Han Y, Lin L. J New Chin Med. 2001;33 (2):23.
320. Han J, Liu J, Yang B. Chin J Synthetical Med. 2001;2(11):1024.
321. Wu X, Zengqiang Z. Pract New Med. 2001;3 (8):722.
322. Liu W. Chin Clin J. 2001;1(2):86.
323. None. Durgs for Cardio-Cerebrovascular-Composite Salviae Dropping Pill, Home Medicine. 2002;(7):32.
324. Pan W. Int J Med. 2002;6(24):55.
325. Zhang X. Suzhou Univ J Med Sci. 2002;22(6):649, 661.
326. Lai R, Liu J. Jiangxi Med J. 2002;37(6):479.
327. Ding N. Chin Tradit Herbal Drugs, 2002. 33(12):1, 147.
328. Chen D. Hebei J Tradit Chin Med. 2002;24(12):946.
329. Zheng Y, Yang B, Lin Y, et al. Int Tradit Chin W Med Pract Crit Care Med. 2002;9(6):353.
330. Hu Z, Hu S. Hainan Med J. 2002;13(10):67.
331. Yu W. Hunan Guiding J Tradit Chin Med and Pharmacol. 2002;8(12):746.
332. Yu F. Heilongjiang Med J. 2002;26(12):975.
333. Ge Y, Fang L, Li J. Chin Tradit Pat Med. 2002;24 (11):872.
334. Guo Jian Yu, Jianzhong Shi Huijuan. Central Plains Medical Journal. 2002;29(1):42.
335. Liu M, Jiang L. Yunnan J Tradit Chin Med Mater Med. 2002;23(6):20.
336. Wang Y. Nei Mongol J Tradit Chin Med. 2002;5:11.
337. Qian J. Tianjin Pharm. 2002;14(5):46.
338. Deng W. J Pract Tradit Chin Med. 2002;18(12):23.
339. He H, Luo Y. J Pract Tradit Chin Med. 2002;18 (12):22.
340. Fan Z. Shandong Med J. 2002;42(21):28.
341. Liang D. Mod J Integr Tradit Chin W Med. 2002;11 (19):1913.
342. Wei Z, Zhang S, Liu Y. Chin J Integr Tradit W Nephrol. 2002;3(9):547.
343. Liu P. Shaanxi Med J. 2002;31(9):840.
344. Kou L. J North China Coal Med Coll. 2002;4 (5):588.
345. Hu Y. Chin J Clin Med (Beijing). 2002;3(17):67.
346. Zhao L, Zhao Y, Zhang Z. Pract New Med. 2002;4 (2):105.
347. Zhou Y, Dai X, Gu J, et al. China J Tradit Chin Med Pharm. 2002;17(6):344.
348. Zhu H. Chin J Misdiagn. 2002;2(9):1345.
349. Chang Q. Chin J Pract Med. 2002;29(9):43.
350. Kang J, Zhang Y, Zhao L. Chin Heart J. 2002;14 (4):321.
351. He J, Zhu A. Chin Heart J. 2002;14(4):352.
352. Zhou X. Youjiang Med J. 2002;30(4):283.
353. Sun Y. Chin J Med Thoery Pract. 2002;(8):995.
354. Gao S, Peng J, Lai Z. Chin J Clin. 2002;30(9):46.
355. Huang X, Wen T. Hebei J Tradit Chin Med. 2002;24 (8):566.
356. Deng G, He J, Li B. Tianjin Pharm. 2002;14(4):48.
357. Wang Y, Gao X, Zhang B. J Tianjin Coll Tradit Chin Med. 2002;21(3):53.
358. Chen D, Chen L. Taishan Health J. 2002;26(4):37.
359. Weng H. J Shandong Univ Tradit Chin Med. 2002;26(4):282.
360. Yao X. J Emerg Tradit Chin Med. 2002;11(1):26.
361. Tu Y, Yang Z. Mod J Integr Tradit Chin W Med. 2002;11(15):1449.
362. Li Z. J Changzhi Med Coll. 2002;16(1):32.
363. Hong X, Mi S. Tradit Chin Drug Res Clin Pharm. 2002;13(4):247.
364. Yang S. Chin J Cardiovasc Rehabil Med. 2002;11 (3):274.
365. Feng Z, Gao X. Port Health Control. 2002;7(3):19.
366. Xu L, Xu Xu. Shandong Med J. 2002;21(3):49.
367. Pan Y, Song A, Liu L. Shandong Med J (Intrnal Med). 2002;42(11):65.
368. Zhao X. Mod J Integr Tradit Chin W Med. 2002;11 (13):1296.
369. Wu K, Guan L, Lin Y. Strait Pharm J. 2002;14(3):54.
370. Wang Y, Kang L, Shi H, et al. Tianjin J Tradit Chin Med. 2002;19(3):48.
371. Yan W. Tianjin Pharm. 2002;14(3):44.
372. Feng Y, Lv X, Zhao X. Chin Tradit Herbal Drugs. 2002;33(6):539.
373. Hu Y, Tan S, Tan Y, et al. J Hunan Tradit Chin Med Univ. 2002;22(2):45.
374. Jin Z, Song L. Chin J Clin Med. 2002;3(9):96.
375. Cui S, Zhao J. Shandong Med J. 2002;42(10):28.
376. Liu B. J Pract Med. 2002;18(5):532.
377. Wu Z, Chen D. Acad Periodical Changchun Coll Tradit Chin Med. 2002;18(2):14.
378. Lin X, Qiu Q. Chin Commun Doct. 2002;18(11):32.
379. Yao C. Occup Health. 2002;18(4):112.
380. Li Y, Li J, Zhang S, et al. J Zhangjiakou Med Coll. 2002;19(1):70.
381. Sun J, Liang J, Yan Y, et al. Mod J Integr Tradit Chin W Med. 2002;1I (11):1087.
382. Huang Y, Wang N. Tradit Chin Drug Res Clin Pharm. 2002;13(3):174.
383. Liang Y, Chu X. Chin J Integr Tradit W Med. 2002;22(5):382.
384. Huang Y, Chen J. Gansu J Tradit Chin Med. 2002;15(3):69.

385. Yi C. Guangming J Chin Med. 2002;17(2):37.
386. Yuan G. Chin J Clin Pharm Ther. 2002;7(2):162.
387. Sui Q, Gao Y, Wang Y. Shan Dong J Tradit Chin Med. 2002;21(5):273.
388. Ma D, Jiang C, Yu G. J Health Care Med Chin P.L. A. 2002;4(1):29.
389. Yang Z, Wang X. J Harbin Med Univ. 2002;36 (2):115, F003.
390. Wang Z, Tian Y, Li X. Heilongjiang Med Pharm. 2002;25(2):9.
391. Li J, Tan S. Liaoning J Tradit Chin Med. 2002;29 (3):163.
392. Zhao J, Li F, Zhao W. Chin Pract Med. 2002;4 (6):57.
393. Yun X. Henan Med Inf. 2002;10(6):39.
394. Wu S, Shi Y. Chin J Med Writ. 2002;9(6):434.
395. Yao F, Zhang Y, Huang M, et al. Shandong J Tradit Chin Med. 2002;21(3):147.
396. Wang Z, Hu J, Xu S. J Luoyang Med Coll. 2002;20 (1):62.
397. Zhao J, Zhao W. Shandong Med J. 2002;21(1):56.
398. Shi D, Liu J, Zhou T. Shandong Med J. 2002;42 (1):65.
399. Zheng J. J Sichuan Tradit Chin Med. 2002;20(3):40.
400. Zhang R, Li Z. Chin J Cardiovasc Rehabil Med. 2002;11(1):81.
401. Ru C, Zhao J. Chin J Clin Med. 2002;3(1):86.
402. Qian H, Sheng H. Gansu J Tradit Chin Med. 2002;15(1):29.
403. Li J. Pract J Card Cereb Pneumal Vasc Dis. 2002;10 (1):24.
404. Wang Q, Rui Y. Clin J Anhui Tradit Chin Med. 2002;14(1):21.
405. Wang B, Liu F, Hou L. J Med Thoery Pract. 2002;15(1):53.
406. Lin Y, Hu G. Fu Jian J Tradit Chin Med. 2002;33 (3):13.
407. Jiang Y. Chin J Med Thoery Pract. 2003(12):1659.
408. Tang Y, Liu Y. J Chin Clin Med (Guangzhou). 2003;(68):93.
409. Guo Z, Wang L. Chin Tradit Herbal Drugs. 2003;34 (3):U004.
410. Shi F. Chin J Clin Med Prof Res. 2003, (74):94.
411. Liu Z, Wang T. Chin Tradit Herbal Drugs. 2003;34 (10):945.
412. Yuan X, Chen F. Chin J Med Today. 2003;3(16):33.
413. Wang G, Zhang X, Han H, et al. J Chengdu Univ Tradit Chin Med. 2003;26(4):10,14.
414. Zhang T, Hong Y. J Integr Tradit Chin W Med. 2003;3(6):3.
415. Lv Z, Chen Z. Chin J Tradit W Med. 2003;4(4):506.
416. Chen H, Zhang Y, Wu M, et al. J Anhui Tradit Chin Med Coll. 2003;22(6):13.
417. Zhang D, Zhu G. Lishizhen Med Mater Med Res. 2003;14(12):764.
418. Liu K. Proc Clin Med. 2003;12(11):847.
419. Wu H. Yunnan J Tradit Chin Med Mater Med. 2003;24(4):16.
420. Liu J. J Pract Diagn Ther. 2003;17(6):492.
421. Xu M, Sheng H, Chen Y. Shanxi J Tradit Chin Med. 2003;19(5):16.
422. Wang X, Shen L, Yan L. Acta Acad Med Neimongol. 2003;25(3):204.
423. Yuan X. Shandong Med J. 2003;22(5):50.
424. Fan W, Zhang J, Wang L, et al. Chin J Integr Med Cardio-/Cerebrovasc Dis. 2003;1(10):571.
425. Wu S, Wu C, Ma H, et al. Pharm J Chin People's Liberation Army. 2003;19(5):344.
426. Shi Y, Li J. Chin J Med Thoery Pract. 2003;10:1315.
427. Gong P, Li T, Zhang C. J Taishan Med Coll. 2003;24(3):301.
428. Wu W. Guo Xiaoling. Chin Med Focus. 2003;2 (4):23.
429. Wang H. Chin Tradit Herbal Drugs. 2003;34(9):838.
430. Guo J. Qinghai Med J. 2003;33(8):61.
431. Zhao Y. J Integr Tradit Chin W Med. 2003;3(5):21.
432. Gao C, Wang J, Feng C. J Henan Univ (Med Sci). 2003;22(3):35.
433. Gu J, Dai X, Zhou Y, et al. J Emerg Tradit Chin Med. 2003;12(5):431.
434. Liang Y. J Emerg Tradit Chin Med. 2003;12(4):375.
435. Guo Z, Jia W, Gao W, et al. Chin J Nat Med. 2003;1 (2):124.
436. Xie S, Yang X, Wang X. J Med Forum. 2003;24 (14):69.
437. Lin W. J Med Theory Pract. 2003;16(7):745.
438. Fang P, Shu Z, Zhao S. Chin J Integr Tradit W Med Liver Dis. 2003;13(4):242.
439. Xiao D, Huang C. Chin J Integr Tradit W Med Digestion. 2003;11(4):244.
440. Mao X, Zhang M, Bai P, et al. Chin J Cardiovasc Rehabil Med. 2003;12(4):350.
441. Zhao Y, Zhu S, Shi C, Jet al. J Harbin Med Univ. 2003;37(4):290.
442. Chu X, Jia G. Heilongjiang J Tradit Chin Med. 2003;4:16.
443. Wang B, Zhang G. Tianjin J Tradit Chin Med. 2003;20(4):38.
444. Tian G, Feng Y, Xue D. China's Naturopathy. 2003;11(7):39.
445. Liu L, Tong W. Shanxi Med J. 2003;32(4):394.
446. Yin X, Wang X, Teng J. Med J Ind Enterp. 2003;16 (2):39.
447. Liu J, Zhang H. Tian Jin Pharm. 2003;15(3):38.
448. Wang Y, Gao X, Zhang B. J Tianjin Univ Tradit Chin Med. 2003;22(2):18.
449. Peng F. Mod J Integr Tradit Chin W Med. 2003;12 (13):1377.
450. Bao M, Zhang L. Chin J Primary Med Pharm. 2003;10(6):525.
451. Chi Y. J Binzhou Med Coll. 2003;26(4):296.
452. Liu R. Pract J Card Cereb Pneumal Vasc Dis. 2003;11(3):F003.
453. Yang Z. J Shanxi Med Coll Continuing Educ. 2003;13(2):34.
454. Yin H. Gan Su J Tradit Chin Med. 2003;16(6):16.
455. Xia Z. Chin J Chin W Med. 2003;4(i):65.

456. Cui S, Li G. Mod J Integr Tradit Chin W Med. 2003;11(11):1029.
457. Li T, Wang X, Zhao Q, et al. Chin J Integr Med Cardio-/Cerebrovasc Dis. 2003;I(4):215.
458. Sun H. Lishizhen Med Mater Med Res. 2003;14 (5):315.
459. Hui X, Qu Y, Xue Y, et al. Shanghai J Tradit Chin Med. 2003;37(5):30.
460. Li D. Shanghai J Tradit Chin Med. 2003;37(5):33.
461. Zhou J, Xiong P. Proc Clin Med. 2003;12(4):264.
462. Qiu N, Chen T. Strait Pharm J. 2003;15(2):67.
463. Shen H, Wu R. J Integr Tradit Chin W Med. 2003;3 (2):7.
464. Xu M, Li Q, Zhang W, et al. Chin J Pathophysiol. 2003;19(4):499.
465. Wang G, Liu Z, Gao Y, et al. Chine J Pract Med. 2003;30(8):47.
466. Wang J, Yuan X, Zhao X. Chin J Inf Tradit Chin Med. 2003;10(3):58.
467. Zhang A. J Chin Clin Med (Beijing). 2003;4(5):77.
468. Wang W, Kuang M, Wu F, et al. Chin J Integr Tradit W Med Liver Dis. 2003;13(1):42.
469. Gao K, Liu J. Acad Periodical Changchun Coll Tradit Chin Med. 2003;19(1):36.
470. Guo D, Niu X. Chin Commun Doct. 2003;19(6):48.
471. Yao N. Guangxi Med J. 2003;25(3):363.
472. Wang Z. Jilin J Tradit Chin Med. 2003;23(2):46.
473. Lai Z, Lai C, Fan W. Shenzhen J Integr Tradit Chin W Med. 2003;13(1):27.
474. Gao X, Wang Y, Shang H, et al. Tianjin J Tradit Chin Med. 2003;20(1):23.
475. Zhang A. Henan Tradit Chin Med. 2003;23(1):62.
476. Guo X. For All Health. 2003(1):53.
477. Tang S, Feng L, Zhang T. Guangzhou Med J. 2003;34(1):43.
478. Bai H, He X, An C. Mod J Integr Tradit Chin W Med. 2003;12(2):140.
479. Zeng R, Jing L, Sun W, et al. Med J National Defending Forces Southwest China. 2004;14(1):11.
480. Cao F, Meng J. Econ Outlook Bohai Sea. 2004;12:51.
481. Zhu G, Wu Q, Lou Z. Chin Arch Tradit Chin Med. 2004;22(11):2114.
482. Liang X, Zhao X, Sui X. Mod J Integr Tradit Chin W Med. 2004;13(19):2563.
483. Wang X, Gong A. Henan J Oncol. 2004;17(4):290.
484. Liu J. J Tianjin Med Univ. 2004;10(2):195.
485. Chen J, Guo J, Gao J, et al. Chin J Inf Tradit Chin Med. 2004;11(6):530.
486. Hu Y, Tian J. J Sichuan Continuing Edu Coll Med Sci. 2004;23(1):23, 33.
487. Wen D, Guo D, Tong C. J Emerg Tradit Chin Med. 2004;13(4):222.
488. Liu P, Wang B, Yang D. Manufact Autom. 2004;26 (3):65.
489. Sun Q, Jiang Y. Acta Med Sin. 2004;8(1):59.
490. Sheng X, Zhao Q. J Chin Med Res. 2004;4(3):255.
491. Shi C, Wu C, Ma H, et al. Pharm J Chin People's Liberation Army. 2004;20(1):34.
492. Tian J, Chen J, Gu Y, et al. Chin J Clin Rehabil. 2004;8(9):1708, F003.
493. Li J. Lishizhen Med Mater Med Res. 2004;15 (2):127.
494. Guo X. Med Health Care. 2004;12(3):39.
495. Ge Y, Duan Y, Ruan L, et al. Chin J Clin Rehabil. 2004;8(6):1096.
496. Chen X, Liang Q. Chin J Intergr Tradit W Med Digestion. 2004;12(1):42.
497. Ling Z. Chin Commun Doct. 2004;20(4):20.
498. He Y. Health Vocat Educ. 2004;22(2):107.
499. Zhao Z, Wang C, Shao P. Mod J Integr Tradit Chin W Med. 2004;13(1):72.
500. Yao W, Gao L. Chin Tradit Pat Med. 2004;26(B1 2):l–6.
501. Zhang J, Xiao K, Zhao Z, et al. Chin Tradit Pat Med. 2004;26(B12):19.
502. Liang L, Li H. Chin Tradit Pat Med. 2004;26 (B12):81.
503. Fang L. Chin Commun Doct. 2004;6(20):38.
504. Li Y, Yang N, Liu G. Chin Med Res Clin. 2004;2 (19):23.
505. Li G. Chin Clin New Med. 2004;4(10):881.
506. Rong J, Gu J, Qian X. Acta Acad Med Nantong. 2004;24(4):448.
507. Li X, Hou J, Qiao R. Chin J Pract Med. 2004;31 (24):30.
508. Chen J, Xie W, Wu T, et al. Chin J Integr Med Cardio-/Cerebrovasc Dis. 2004;2(12):718.
509. Li W, Zhang W, Wei F. Chin J Pharm Anal. 2004;24(6):642.
510. Liu J. Acta Chin Med Pharm. 2004;32(3):37.
511. Zhang W. J Pract Tradit Chin Intern Med. 2004;18 (6):547.
512. Chen C. J Med Forum. 2004;25(21):34.
513. Huang S, Zou X, Li P. Mod Diagn Treat. 2004;15 (6):349.
514. Chen K. Health Vocat Educ. 2004;22(21):125.
515. Sun X, Wu G. Chin J Tradit W Med. 2004;2(7):26.
516. Ni R, Chen Y, Li W. Chengdu Med J. 2004;30 (5):266.
517. Wang B. Shaanxi J Tradit Chin Med. 2004;25 (10):888.
518. Deng X, Yutai Feng. Chin J Prim Med Pharm. 2004;11(9):1057.
519. Xiao F, Zhang J, Tian Y, et al. Chin J Prim Med Pharm. 2004;11(9):1142.
520. Wang S. Chin Mod Med. 2004;2(7):70.
521. Chen T, Dai X. Chin J Tradit W Med. 2004;2(10):28.
522. Hu J. Chin J Med Writ. 2004;11(20):1718.
523. Yu Z, Lu Y. J Pract Tradit Chin Intern Med. 2004;18(5):459.
524. Cheng Z, Zhang A. Chin Pract Med. 2004;6(14):l04.
525. Zhong Y, Tang Y. Chin Tradit Herbal Drugs. 2004;35(9):l037.
526. Chen J, Tian J, Gu Y, et al. Chin J Clin Rehabil. 2004;8(24):5048.
527. Xu F, Xiao H, Huang Y, et al. Chin J Cardiovasc Rehabil Med. 2004;13(4):393.

528. Cao F, Meng J. Med World. 2004;7:22.
529. Zhao X, Zhu Z, Liu A, et al. Chin Tradit Pat Med. 2004;26(6):490.
530. Wang C. Chin Med Focus. 2004;1(1):23.
531. Zhang L, Wang S, Zheng L. J Pract Tradit Chin Intern Med. 2004;18(3):253.
532. Fang Y, Shi Z, Fan W, et al. Chin J Cardiovasc Rehabil Med. 2004;13(3):290.
533. Wang Y, Gao X, Zhang B. Chin Tradit Herbal Drugs. 2004;35(6):672.
534. Meng J. China Econ Trade Herald. 2004(9):51.
535. Xue Z. Strait Pharm J. 2004;16(2):104.
536. Xu Z, Zhang B, Zhang J, et al. Tianjin J Tradit Chin Med. 2004;21(2):95.
537. Chen B. Int Med Health Guidance News. 2004; (10):49.
538. Chen W. Mod Hosp. 2004;4(5):24.
539. Guo J, Zhang L, Zeng Z, et al. Chin J Hemorheol. 2004; 14(1):1, 42.
540. Huang J. Chin J Rural Med Pharm. 2004;11(5):8.
541. Xiang N, Li X. Chin J Clin Healthc. 2004;7(2):110.
542. Chen G. China Med Herald. 2005;11(12):12.
543. Jiao H. China J Modern Med. 2005; 15(22):3485.
544. Zhang M, Gou Z, An G. J Gansu Coll Tradit Chin Med. 2005;22(6):36.
545. Tian Y, Li L, Wang R, et al. Acta Chin Med Pharmacol. 2005;33(6):60.
546. Wei B, Zong L, Dong J, et al. Guangdong Pharm. 2005;15(6):22.
547. Zhang J, Shen L, Lu W, et al. J Shanghai Second Med Univ. 2005;25(10):1045.
548. Zhang L, Sun Z, Li H, et al. Int Med Health Guidance News. 2005;22:9.
549. Xiao W, Shi R, Li W, et al. J Huaihua Med Coll. 2005;4(2):45.
550. Meng M. Chin J Pract Chin Western Med. 2005;18 (10):1411.
551. Wang G. Hainan Med J. 2005;16(12):77.
552. Zhang J, Niu Q. Chin J Integr Tradit Western Med Intensive Crit Care. 2005;12(5):312.
553. Li X, Zhang W. Tianjin Pharm. 2005;17(5):8.
554. Huang F. J Appl Clin Pediatr. 2005;20(6):587.
555. Cao X, Fu H, Wang Y, et al. Hebei Med. 2005;11 (12):l062.
556. Yang X, Ling H. Jiangxi Med J. 2005;40(10):633.
557. Dai T. Med Inf. 2005;18(9):1164.
558. Fan X, Ye Z, C Y. Chin J Pharm Anal. 2005;25 (9):1122.
559. Nie X, Yang J, He L, et al. Guizhou Med J. 2005;29 (9):822.
560. Zhang P. J Pract Tradit Chin Med. 2005;21(9):556.
561. Suo D, Chen J. Central Plains Med J. 2005;32 (17):60.
562. Li Y, Tan J, Chen J, et al. Chin J Integr Med Cardio-/Cerebrovasc Dis. 2005;3(10):886.
563. Liao X, Geng X, Lai Z. Chin J Integr Med Cardio-/ Cerebrovasc Dis. 2005;3(9):765.
564. Qiu Z, Ma H, Wang D. Chin J Integr Tradit West Med. 2005;25(9):787.
565. Feng Z, Cai Q, Xie G. Guangdong Med J. 2005;26 (10):1422–4.
566. Zhang S. J Henan Med Coll Staff Workers. 2005; l7 (5):293.
567. Fan W, Meng C, Zhang J, et al. Chin J Clin Rehabil. 2005;9(33):144.
568. Gao M, Gong J. China's Naturopathy. 2005;13(11):32.
569. Zhang X. Mod Med Health. 2005;21(24):3450.
570. Shi Y, Li J. Chin J Med Thoery Pract. 2005; 15(10): l567, l445.
571. Wang L, An X. Chin J Clin Med Res. 2005;11 (16):2368.
572. Yang P, Hu Z. J Henan Med Coll Staff Workers. 2005;17(6):366.
573. Li W, Dong J, Mi S, et al. Chin Tradit Patent Med. 2005;27(9):1092.
574. Fu X, Hu D, Zhi S, et al. J Navy Med. 2005;26 (3):223.
575. Fu Z. China's Naturopathy. 2005;13(8):32.
576. Yang L, Cai W. Eval Anal Drug-Use Hospital China. 2005;5(4):254.
577. Jiao W, Li G. Chin Community Doctors. 2005;21 (16):37.
578. Li T, Qiao Y. Anhui Med Pharm J. 2005; 9(4):2, 6l.
579. Tian S, Lu L. Chin Med Factory Mine. 2005;18 (4):365.
580. Wang D, Wang X, Xu J, et al. Chin J Pathophysiol. 2005;21(8):1656.
581. Xu J, Wang X, Wang D. Chin J Pathophysiol. 2005;21(8):1659.
582. Chen X, Liang Q, Li X. Chin J Surg Integr Tradit West Med. 2005;11(4):300.
583. Zhang Y. Jilin J Tradit Chin Med. 2005;25(8):16.
584. Huang J. Med J Liaoning. 2005;19(4):206.
585. Zhu W, Jia M. J Emerg Tradit Chin Med. 2005; 14 (8):742,747.
586. Zheng Y. Heilongjiang Med J. 2005;29(8):640.
587. Shi J. Chin Community Doctors. 2005;21(15):39.
588. Rong C. U.S. Chin Health Hygiene J. 2005; 8(2):45.
589. Zhang J, Wang Y, Shen L, et al. Chin J Arterioscler. 2005;13(5):571.
590. Wang P. Practical Clin Med (Jiangxi). 2005;6 (10):43.
591. Li Z. Chin J Modern Clin Med. 2005;3(11):1023.
592. Chen J. Guiding J TCM. 2005;11(7):13.
593. Zheng B, Guo Y. Modern J Integr Tradit Chin West Med. 2005;14(15):2075.
594. Lou C. J Med Forum. 2005;26(13):68.
595. Jia M, Zhu W. Shaanxi J Tradit Chin Med. 2005;26 (7):630.
596. Gan B, Zhao Y. J Guiyang Coll Tradit Chin Med. 2005;27(3):14.
597. Miu Z. Chin J Clin Med. 2005;6(6):66.
598. Yao P, Zhu J, Lei Y. China Pharm. 2005;14(7):81.
599. Wan X. Guiding J TCM. 2005;11(5):11.
600. Chen Y, Wu L, Wang W, et al. Chin J Primary Med Pharm. 2005;12(5):548.
601. Kang Y, Wang Y, Zhi L. Clin Focus. 2005;20 (10):596.

602. Zhu G, Wu Q, Lou Z. J Zhejiang Coll Tradit Chin Med. 2005;29(4):13.
603. He T. Public Med Forum Mag. 2005;9(5):423.
604. Yi X. J Mil Surg Southwest China. 2005;7(3):28.
605. Li Y, Wu S. J Chengde Med Coll. 2005;22(2):118.
606. Ren S, Tian J. Chin J Clin Med Res. 2005;11 (8):1107.
607. Wang C, Xu H. Chin J Clin Pharmacol Ther. 2005;10(5):570.
608. Chen Q. J Pract Med. 2005;21(11):1228.
609. Jia B, Li X. J Chin Med Res. 2005;5(5):458.
610. Fang X, Hu R. Chin J Clinical Med Res. 2005;11 (6):756.
611. Liang Q, Chen X, Li X, et al. Pract J Cancer. 2005;20(1):78.
612. Zhu Y. Chin J Med Writ. 2005;12(7):577.
613. Zhang L. China Med Hyg. 2005;6(1):33.
614. Wa Q. Chin J Curr Tradit West Med. 2005;3(1):30.
615. Wu M. Chin J Tradit West Med. 2005;3(4):87.
616. Zou E. Chin Mod Med. 2005;3(1):70.
617. Zhang A, Shi J, Zhang H, et al. Hebei J Tradit Chin Med. 2005;27(2):134.
618. Li M, Quan G, Lu X. Clin Focus. 2005;20(7):393.
619. Zheng A, Hao D. Tradit Chin Med Res. 2005;18 (3):47.
620. Li L, Yang H. J Handan Med Coll. 2005;18(1):34.
621. Shen M. Mod J Integr Tradit Chin West Med. 2005;14(4):447.
622. Zhang Y, Wei S. J Clin Hepatol. 2005;8(1):45.
623. Wang M. Appl J Gen Pract. 2005;3(1):91.
624. Wei B, Wang M, Kuang C. J Chin Med Mater. 2006;29(12):1340.
625. He H, Zeng Y. Med Monthly. 2006;3(12):97.
626. Qiu F, Wan G. Tianjin Pharm. 2006;18(6):33.
627. Pan H. J Pract Med Tech. 2006;13(23):4175.
628. Fan X, Dong H. Shandong Med J. 2006;46(32):6l.
629. Li Y, Xi Y, Zhou C, et al. Clin J Med Officer. 2006;34(6):673.
630. Hu Z, Li J, Gai L, et al. Clin J Tradit Chin Med. 2006;18(6):537.
631. Wang Z, Wang B, Wang J. Harbin Med J. 2006;26 (6):52.
632. Mei F, Zhang Y, Wang Z, et al. Heilongjiang J Tradit Chin Med. 2006;6:4.
633. Lin C, Liu C. Mod Hosp. 2006;6(12):53.
634. Yao Y, Sun C, Gu Y. J Nanjing Univ Tradit Chin Med. 2006;22(6):348.
635. Luo Y. Hebei J Tradit Chin Med. 2006;28(11):859.
636. Yang W, Li Y. China J Chin Materia Medica. 2006;31(23):2008.
637. Tu Y, Nian L, Shang B. Eval Anal Drug-Use Hosp China. 2006;6(4):241.
638. Sun H, Yang S. Chin Commun Doctors (Compr Ed). 2006;8(22):60.
639. Zhong H, Liang Z, Ou W. Chin J Primary Med Pharm. 2006;13(10):l679.
640. Fu W, Ding S, Jiang J, et al. Mil Med J South China. 2006; 20(5):5, 12.
641. Lou G, Xu D, Feng P. Zhejiang J Integr Tradit Chin West Med. 2006; 16(11):665.68.
642. Liu J, Yuan B, Luo W, et al. Youjiang Med J. 2006;34(6):602.
643. Li Y, Tan J, Chen J, et al. New J Tradit Chin Med. 2006;38(11):23.
644. Wang Q, Niu H. China's Naturopathy. 2006;14 (10):16.
645. Wu X. China J Clin Med Hyg. 2006;4(8):13.
646. Li H, Zhang H, Ji K, et al. Chin J Gerontol. 2006;26 (9):1226.
647. Zhou S. Clin J Tradit Chin Med. 2006;18(5):474.
648. Zhu H, Yu W, Wan H. China Jo Mod Tradit Chin Med. 2006;2(4):357.
649. Wang Q, Niu H. Tradit Chin Med J. 2006;5(4):54.
650. Xiao W, Shi R, Li W, et al. Modern J Integr Tradit Chin West Med. 2006;15(19):2631.
651. Liu A, Li Y, Huang G. Chin J Pract Med. 2006;33 (19):83.
652. Ding H, Li Q, Yuan Y. Mod Tradit Chin Med. 2006;26(5):13.
653. Xu S. Chin J Rural Med Pharm. 2006;13(10):43.
654. Li H, Cui G, Tong Y. Herald of Med. 2006;25 (9):887.
655. Zhao J. Zhejiang J Integr Tradit Chin West Med. 2006;16(9):560.
656. Wang X, Gu Z, Wang D, et al. Chin J Integr Med Cardio-/Cerebrovasc Dis. 2006;4(9):789.
657. Dong H, Li Z. Mod J Integr Tradit Chin West Med. 2006;15(17):2310.
658. Hu Q, Fang W, Wu R, et al. Sichuan J Cancer Control. 2006;19(3):190.
659. Yuan X, Xu Y, Huang L. Chin J School Doctor. 2006; 20(4):448, F0003.
660. Han G. Tianjin Pharm. 2006;18(4):68.
661. Xiao W, Shi R, Li W, et al. People's Mil Surg. 2006;49(7):383.
662. Hu R. Hebei J Tradit Chin Med. 2006;28(8):613.
663. Meng M. J Youjiang Med Coll Nationalities. 2006;28(5):746.
664. Zhou J. J Emerg Tradit Chin Med. 2006;15(8):864.
665. Gong Y. J Anhui Health Vocat Tech Coll. 2006;5 (4):34.
666. Zhang W, Liu R, Zhu H. Guangming J Chin Med. 2006;21(7):F0003.
667. Huang T, Ye S, Ou W, et al. Tradit Chin Drug Res Clin Pharmacol. 2006;17(4):265.
668. Fang J, Fan L. Chin Community Doctors. 2006;8 (14):115.
669. Ma J, Jia X, Qiu Z, et al. J Clin Res. 2006;23 (7):1160.
670. Xu Y, Yang B. Hebei Med. 2006;12(7):615.
671. Dong J, Gao Y, Du X, et al. Infect Dis Inf. 2006;19 (2):84.
672. Wang J, Cui Z. J Shanxi Med Coll Continuing Educ. 2006;16(2):34.
673. Ran Q, Jiang H. J Chin Mod Med. 2006;3(6):652.
674. Wang Y. Hubei J Tradit Chin Med. 2006;28(7):14.
675. Zhao G, Wang W, Tian Y, et al. Shanghai J Tradit Chin Med. 2006;40(7):19.
676. Wei B, Chen X, Zong L. J Mod Food Pharm. 2006;16(3):21.

677. Guo B. Fujian J Tradit Chin Med. 2006;37(3):7.
678. Zhou Y, Wang C, Ding Y. Chin J Clin Rehabil. 2006;10(23):167.
679. Liu C, Wu H. China's Naturopathy. 2006;14(6):33.
680. Wang W, Zhao G. (director). Gansu J Tradit Chin Med. 2006;19(6):12.
681. Cheng G (partially selected). People's Mil Surg. 2006; 49(6):372.
682. Chen Y, Tao R, Chen Y. World J Infect. 2006; 6 (3):211,218.
683. Feng J, Wang S. Chin J Misdiagnostics. 2006;6 (12):2261.
684. Wang Q, Niu H. Chin J Pract Chin West Med. 2006;19(17):2028.
685. Guo Y, Luo L, Yang H. J Integr Tradit Chin West Med. 2006;6(3):7.
686. Liang B. Chin Community Doctors. 2006;22(9):36.
687. Min Y, Zhang X. Chin J Geriatr Heart Brain Vessek Dis. 2006;8(6):415.
688. Feng J, Xu Y, Pei B. J Pract Diagn Ther. 2006;20 (6):437.
689. Jiang F. Chin J Clin Pharmacol Ther. 2006;11 (4):418.
690. Peng L. J Pract Tradit Chin Med. 2006;22(6):382.
691. Ke B, Liu X, Chen Y, et al. Chin Tradit Herbal Drugs. 2006;37(5):685.
692. Li G, Chu C. Chin Community Doctors. 2006;22 (6):48.
693. Huang J. Hunan J Tradit Chin Med. 2006;22(3):17.
694. Chen L, Zhang M, Zhang Y, et al. Chin J Ultrasound Med. 2006;22(5):360.
695. Ji H, Shu L. Shaanxi J Tradit Chin Med. 2006;27 (5):566.
696. Liu Y, Chen H. J Liaoning Coll Tradit Chin Med. 2006;8(3):272.
697. Geng X, Li X, Wang Y, et al. Chin J Inf Tradit Chin Med. 2006;13(5):11.
698. Li Y, Zhou C, Liu A, et al. Clin J Med Officer. 2006;34(2):164.
699. Chen X, Li S, Guan J. J Med Thoery Pract. 2006;19 (4):377.
700. Wang M. Chin J Compr Med (Harbin). 2006;7 (3):234.
701. Qiao C, Sun Y, Jiang S. J Lanzhou Univ (Med Sci). 2006;32(1):41.
702. Han L, Feng G, Dong F, et al. J Med Forum. 2006;27(5):63.
703. Zheng X. J Emerg Tradit Chin Mad. 2006;15 (3):234.
704. Chen R, Zhao Y, Zhao X, et al. Chin J Proper Tech Diagn Ther. 2006;24(1):7.
705. Yu Ke K, Hu C, Cheng Y. Chin Pharm J. 2006;41 (3):226.
706. Li H, Zhang H, Ji K, et al. Chin Heart J. 2006;8 (1):94.
707. Ma X, Zhang C, Jia F. Mod J Integr Tradit Chin West Med. 2006;15(4):420.
708. Zheng Y, Wei Q. Jiangxi J Tradit Chin Med. 2006;37(1):26.
709. Liang Q, Chen X, Li X, et al. Chin Arch Tradit Chin Med. 2006;24(1):186.
710. Xiang B, Pan Z, Cao D. China Pharm. 2007;18 (9):708.
711. Wang Z, Huang S. Hainan Med J. 2007;18(4):17.
712. Huang Y. Inner Mongol J Tradit Chin Med. 2007;26 (3):5.
713. Qiao C, Zhang C, Guo X, et al. J Lanzhou Univ (Med Sci). 2007;33(1):14.
714. Ma J. Chin J Inf Tradit Chin Med. 2007;14(3):81.
715. Zhao X, Qiang G, Guo Y, et al. J Chin Mass Spectrom Soc. 2007; 28(1):23, 30.
716. Zheng X, Wang S, Zhao X, et al. J Fourth Mil Med Univ. 2007;28(5):435.
717. Xu X. J Pract Tradit Chin Med. 2007;23(3):145.
718. Yan J, Diao L, Chang X, et al. Chin J Inf Tradit Chin Med. 2007;14(2):14.
719. Lin Y. Chin J Pract Med. 2007;34(4):79.
720. Zhang Q. Chin Primary Health Care. 2007;21(2):94.
721. Zheng L. J Int Tradit Chin West Med. 2007;7(1):9.
722. Hu Y, Zuo H, Huang J. J Integr Tradit Chin West Med. 2007;7(1):10.
723. Zhang H. China Med Herald. 2007;4(1):71.
724. Chen S, Shi P, Huang D. J Med Thoery Pract. 2007;20(1):40.
725. Huang W, Huang X. Chin J Integr Med Cardio-/ Cerebrovasc Dis. 2007;5(1):9.
726. Li Y, Wang W, Ma Y, et al. Chin Tradit Patent Med. 2007;29(1):40.
727. Yue Z, Zhu Y, Jing C, et al. Chin Gen Pract. 2007;10(1):64.
728. Liang Q, Zhang Y, Xie J, et al. Shanghai J Tradit Chin Med. 2007;41(1):22.
729. Yang X. Chin J Pract Med. 2007;34(1):78.
730. Mack WT, et al. Stroke. 1993;24:1779.
731. Bjorkhen I, et al. Aterioscler Thromb. 1991;11:15.
732. Yana Gisawa M, Kurihara H, Kimura S, et al. Nature l988; 332(3):411.
733. Ling S, Dai A, Guo Z, et al. Clin Exp Pharmacol Physiol. 2005;32:571.
734. Han* J-Y, Fan J-Y, Horie Y, et al. Amwliorating effects of compounds derived from salvia miltiorrhiza root extract on microcirculatiory disturbance and targetorgan injury by ischemia-reperusion. Pharmacol Ther. 2007 (in press).
735. Guo J, Sun K, Wang C-S, Fang S-P, et al. Protective effects of dihydroxylphenyl lactic acid and salvianolic acid B on lipopolysaccharide-induced mesenteric microcirculatorv disturbance in rats. Shock. 2007 (in press).
736. Han* J-Y, Horie Y, Miura S, et al. World J Gastroenterol. 2007; 13(26): 3581.
737. Wang F, Liu Y-Y, Liu L-Y, et al. Clin Hemorheol Microcirc. 2006;33:131.
738. Hork Y, Han* J-Y, Mori S, et al. World J Gastroenterol. 2005; 11:511.
739. Horie Y, Han J-Y, Ishii H. Microcirc Ann. 2004;20:31.
740. Han J-Y, Akiba Y, Miura S, et al. Microcirc Ann. 2004; 20:23.

741. Horie Y, Han J-Y, Kajihara M, et al. Microcirc Ann. 2003; l9:31.
742. Han J-Y, Akiba Y, Suzuki H, et al. Microcirc Ann. 2003; l9:39.
743. Han J-Y, Akiba Y, Suzuki H, et al. Microcirc Ann. 2002; l8:31.
744. Han J-Y, Akiba Y, Suzuki H, et al. Microcirc Ann. 2001; l7:33.
745. Han J-Y, Akiba Y, Suzuki H, et al. The 7 World Congress for Microcirculation, 2001. p. 369.
746. Han J-Y, Suzuki H, Mori M, et al. Microcirc Ann. 1997. 13:25.
747. Oda M, Han J-Y. Microcirc approach to Asian traditional medicine, 1996. p. 117.
748. Han J-Y, Kurose I, Miura S, et al. Microcirc Ann. 1996; 12:151.
749. Han J-Y, Miura S, Fukumura D, et al. Progress Microcirc Res. 1994; 85.
750. Han JY, Miura S, Fukumura D, et al. Microcirc Ann. 1993; 9:41.

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