The Pharmacological Actions of Danshen ThemeD Formulas

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2.1 Composite Danshen Dropping Pill

Danshen has been used for medicinal purposes in China for more than 1,000 years. In clinical applications, Danshen is usually used in combination with other drugs; for the treatment of cardiovascular diseases, Danshen's partner is normally Notoginseng (*Panax pseudoginseng*). Many Chinese patent medicines have been developed mainly based on this combination, such as Compound Danshen Tablet, Composite Danshen Dropping Pill, Cardio Danshen Dropping Pill, Danshen Notoginseng Tablet, etc. Compound Danshen Tablet originated from the classic TCM formula and contains Danshen, Notoginseng, and Borneol. This formula has the function of removing blood stasis and relieving pain, and is used specifically for the treatment of angina pectoris and atherosclerosis. Since it was developed in 1977, the formula has generated many preparations which have been manufactured by more than 100 pharmaceutical companies.

Danshen drug preparations include tablet, dropping pill, injection solution, capsule, granule, sprayer, slow release formulation, soft gel, oral liquid, etc. Because the composition and proportions of these preparations are not exactly the same, their clinical effects are different. Composite Danshen Dropping Pill is an advanced product developed from Compound Danshen Tablet. The preparation is based on a solid molecular dispersion system, which enlarges the surface area of the components. As a result, its dissolution rate, utilization rate, and curative effect are higher than those of the tablets and it is more popular clinically.

2.1.1 Compatibility Studies on Compound Danshen Dropping Pill (CDDP)

2.1.1.1 The Compatibility of Danshen and Notoginseng

Experimental Method: Baseline Geometric Proportion Increasing and Decreasing Design

Baseline geometric proportion increasing and decreasing (BGPID) design is a method suitable to the research on combination ratios for the majority of small complex prescriptions of Chinese medicines. The method is guided by TCM theory and professional knowledge. With the CDDP's functions already known and the optimal ratio of the components unclear, this method is particularly useful. Specifically, the detailed combination ratio of the compound of Danshen and Notoginseng is studied and analyzed. The experiment design followed the principle of pharmacopoeia standards for these two

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medicines. 10/3 (Danshen/Notoginseng) was set as the baseline, with the ratio of the two components decreasing or increasing by 10–30 %. The endpoints were 10/0 and 0/10, respectively, with several variance groups in between (10/1, 10/6, 10/10, 1/10), totaling seven groups. Each group was set as the independent variable, and effect indicators at each time point were set as the dependent variables. The relationship between the variables was analyzed. The key indicators were the major functions of the two medicines. Animal models were used and multi-indicator optimization and multidimensional time series analyses were processed. Moreover, other results from in vitro organ and cellular experiments were integrated, and all data was fed into Intelligent Information Processing methods to finalize the ultimate report.

The Effect of Different Ratios of Danshen and Notoginseng on the Function of Myocardial Ischemic Model and Cardiac Hemodynamics [1–3]

A Myocardial ischemic model from the ligated coronary arteries of dogs was made and integrated with a hemodynamic model. Furthermore, by the baseline method, seven ratio groups (Danshen/Notoginseng: 10/0, 10/1, 10/3, 10/6, 10/0, 1/10, 0/10) were prepared for the pharmacodynamic research. The entire dosage for each group was 1.31 g/kg. Meanwhile, a sham group, model group and positive control group (isosorbide dinitrate) were set to complete the experiment. The indicators used for effect evaluation were epicardial electrocardiogram (Epi-ECG), scale of myocardial ischemia area, cardiac markers, coronary blood flow, oxygen consumption of myocardium, hemodynamic, nitric oxide, endothelin, free radicals, etc.

The results show as the following:

1. Effect on myocardial ischemia: Four groups in which Danshen was the major component (l0/6, l0/3, 10/1, l0/0) showed a significant effect on improving pathologic status. Epi-ECG showed that the treatment groups mitigated myocardial ischemia. TTC staining indicated that the ischemic area decreased in treatment groups, especially the 10/6 and 10/3 groups.
2. Effect on cardiac markers: Treatment groups with Danshen as the major component showed significant inhibition of the increase of cardiac Troponin. They showed that Danshen was more effective than Notoginseng on the cardiovascular system, and the result was the same as those obtained with Epi-ECG and myocardial staining methods.
3. Effect on coronary blood flow and oxygen consumption of myocardium: Treatment groups (10/0, 10/3, 10/6) with Danshen as the major component showed better results. Compared with the positive control group (isosorbide dinitrate), which had a fast effect (30 min after medication) but a very short active duration, TCM groups lasted for a longer period of time and acted steadily.
4. Effect on hemodynamics: All TCM groups showed certain effect. Groups l0/6 and l0/3 were much more effective than other groups in improving systole and diastole, cardiac output, and reducing total systemic vascular resistance. However, left ventricle work did not show a significant increase, and the mean atrial pressure and heart rate showed fewer changes.
5. Effect on nitric oxide (NO), endothelin (ET), and free radicals: Group 0/10 acted better than the other groups in improving NO release, keeping SOD active, decreasing ET and Malondialdehyde (MDA).

The Effect of Different Ratios of Danshen and Notoginseng on the Function of Thrombocyte Aggregation and Adhesion [4]

New Zealand Rabbits were medicated orally for 4 days, then the common carotid arteries were exsanguinated. Thrombocyte aggregation was measured via turbidimetric analysis. Six treatments (10/0, 10/1, 10/3, 10/6, 1/10, 0/10) were conducted. Results: Groups 10/3, 10/6, 0/10 showed obvious inhibition of platelet adhesion. Group 0/10 was the best. Groups 10/0, 10/1, and 1/10 had no significant effect.

The Effect of Different Ratios of Danshen and Notoginseng on the Function of CMEC [5]

Under normal culture conditions, groups with different Danshen to Notoginseng ratios could lower the levels of LDH in CMEC. The levels of NO and ET were also decreased in the treated groups. Groups 10/0–1/10 had a positive effect on raising cell activities; group 10/0 showed the best result, while pure Notoginseng (0/10) showed no effect.

Under hypoxic conditions, the results from all groups showed lowered LDH release by CMEC. All groups showed reduced NO release by CMEC, and except for group 10/6, the reductions were statistically significant. In ET secretion, all groups showed reduced secretion, and the results from groups 10/1 and 10/6 were better than those from other groups. Group 10/0 showed the best result in increasing cell viability, while results of group 0/l0 showed a decrease. From groups 10/1 to 10/6, the effect increased with an increasing proportion of Notoginseng . From groups 10/0 to 1/10, the effect was attenuated with a decrease in Danshen.

Nonlinear Systems Model: Multi-objective Optimization [6, 7]

After the multiple effects of compound Danshen were observed, ED-NM-MO triplex method was employed to perform nonlinear curve fitting and multi-objective optimization on the results from the above experiments [8]. Method: based on the data obtained using BGPID, seven indicators including myocardial ischemia, Hemodynamics, etc. were used as targets for analysis. Results: seven pharmacodynamic indicators and the six best ratios of combinations were obtained through the whole process. ED-NM-MO triplex method is suitable for the optimization of compound formulas. Conclusion: Danshen targets blood vessels and is better than Notoginseng regarding vasodilatory activity; Notoginseng focuses on cardiac muscles which leads to a better effect in protecting myocardial ischemia than Danshen. The best ratio range for myocardial ischemia in the combination of Danshen and Notoginseng was 10/3–10/6.

2.1.1.2 Assisting Function of Borneol in CDDP and Research on Its Target

Borneol is a fragrant herb which has an assistive function in compound formulas. *Chinese Pharmacopoeia* (2000 edition) has recorded more than 20 Chinese Patent Medicines containing Borneol. It is used commonly in the treatment of cardiovascular diseases. However, the targets of borneol in most of the formulas are not clear. Because the human body is an organic whole, in normal physiological conditions, the cardiovascular systemular system is regulated by nerves and body fluids. However, in pathological conditions, the regulation becomes chaotic. Therefore, the aim of this research is to clarify the dosage and effect of borneol on myocardial ischemia, and to identify its targets.

Dosage and Effect of Borneol in CDDP [9]

An acute myocardium ischemia rat model was established by the sublingual venous injection of Pituitrin (Pit). The changes in ECG, myocardial enzymes, and oxygen free radicals were recorded, and the relationship between effect and dosage was investigated by using five dosages of borneol in the compound Danshen formula. Result: All five dosages showed an effect on the resistance to the acute myocardium ischemia induced by Pituitrin, improvement of ECG, reduction of MDA, and suppression of myocardial enzymes like CK and LDH. However, no significant difference was found among these five borneol dosages.

Borneol's Effect on the Regulation of Cerebral Neurotransmitters [10, 11]

The effects of borneol on plasma and hypothalamus neurotransmitters and other active substances were observed to investigate the definite targets of Borneol. Result: borneol decreased the levels of hypothalamic monoamine neurotransmitters NE and E at all five dosages. The effects decreased with a decrease in dosage, and could last for 24 h. On the other hand, borneol did not make significant changes in hypothalamus acetylcholine. Borneol increased MAO significantly

in the hypothalamus and the effect lasted for more than 24 h compared to the control. In summary, the effect of borneol on **myocardial ischemia** was partly due to the regulation of the central nervous system via balancing the content of monoamines.

Borneol's Effect on the Blood-Brain Barrier (BBB) [12, 13]

A BBB model was constructed through the co-culture of brain microvascular endothelial cells (BMEC) and astrocytes (AS) in vitro. Borneol's permeability in BBB and salvianolic acid B's permeability were observed. RT-PCR was utilized to evaluate the effect of borneol and salvianolic acid B on the expression of *Mdrla* and *Mdrlb* mRNA. Result: The BBB model was successfully constructed, and borneol had no effect on opening the BBB; the combination of borneol and salvianolic acid B could inhibit P-protein expression in BMEC to improve the permeability of other medicines.

2.1.2 Pharmacological Research

CDDP can enlarge coronary arteries, lower blood lipid levels, resist atherosclerosis, inhibit platelet aggregation, ameliorate hemorheological status, scavenge free radicals, and restrain lipid peroxidation (LPO).

2.1.2.1 Protection of Cardiac Muscle [14, 15]

The myocardial ischemic model of rats was built and the function of CDDP was observed. Results: The infarct size (IS)/area at risk (AAR) ratios in the animals of the re-perfusion group and preconditioning groups in early and late periods were 45, 47, 45 %, respectively; arrhythmia incidence rates were higher than normal at 76.46, 55.56, 73.33 %; LDH in plasma was also much higher than the control group. After ischemic preconditioning (IPC), the early group's IS/AAR ratio was reduced by 17 %, and that of the late group by 4 %; Arrhythmia incidence rates in these two groups were 11.76 and 43.75 %, respectively, much lower than the re-perfusion group and preconditioning groups; the release of IPC and LDH also decreased. These results showed that ischemic preadaptation could minimize the ischemic range and lessen the risk of an arrhythmia incident. After CDDP preconditioning, IS/ARR was reduced by 10–17 % in further step and LDH release also decreased. Also, MDA in serum deceased and SOD activities increased.

Gao et al. [16] observed the compound Danshen's effect on proteinkinase C (PKC) expression in IPC. Expression of PKC mRNA and the effect of compound Danshen were studied via immuno-histochemical method and RT-PCR. The objective was to test the hypothesis that the mechanism of strengthening IPC with compound Danshen was by promoting the expression of PKC at protein or mRNA levels. Results showed that PKC, which is normally located in the cytosol, was also found in the membrane and nucleus after IPC or compound Danshen medication. PKC's expression was higher in both the early and late IPC groups than in the false preconditioning group, and the early IPC group was higher than the late group. After compound Danshen medication, PKC expression was much higher than the re-perfusion group and IPC groups, and the compound Danshen-IPC (DIPC) group was much higher than the early IPC group. There was no obvious difference in PKC mRNA levels between normal myocardial tissue, the re-perfusion group, and the false preconditioning group, but IPC groups were higher than the false preconditioning ones, and the late IPC group gave more obvious results. The medication of compound Danshen could promote the expression of PKC mRNA in the early and late IPC groups and re-perfusion group. Conclusion: compound Danshen can activate and translocate PKC. This may be the main mechanism of IPC enforcement. Experiments showed that the mechanism of compound Danshen's protective functions for cardiac muscles could involve multiple pathways aimed at multiple targets.

Myocardial cell death is the worst injury of re-perfusion. In recent years, Zhao et al. [17] used ligation on the left coronary artery muscle to make re-perfusion models of myocardial

ischemia in order to study CDDP's function on myocardial cell death. In addition, TUNEL and immune histochemical staining were used to test cells death and changes in *Fas*, *Bcl*-2 mRNA expressions. Results showed that compared to the control group, the re-perfusion group's apoptosis index and the levels of *Fas* and *Bcl*-2 expression increased significantly; both indices decreased in the medication group. Furthermore, when the dosage of medication increased, these two indices decreased further. The conclusion was that CDDP could protect myocardial cells by inhibiting cell death and down-regulating the expression of *Fas* and *Bcl*-2 mRNA.

Xu et al. [18] studied CDDP's effect on *Fas*/*Fas*L expression under hypoxia. The results: in the time between 4.5 and 10.5 h of hypoxia, *Fas*/*Fas*L expressions were much higher than those in the control group, and the two indicators had no obvious difference. The protein levels in the medication group were much lower than those in the hypoxia groups. After 30 min of hypoxia, oxygen was supplied for 4 and 10 h. The levels of *Fas*/*Fas*L were obviously higher than in the control group, but there was no difference between the two oxygen supply groups. In the medication group, the levels of the two proteins were much lower than in the hypoxia- re-oxygenation groups. Conclusion: hypoxia and re-oxygenation made *Fas*/*Fas*L increase and CDDP could reduce these levels to protect cardiac muscles.

Wang et al. [19] studied the mechanism of CDDP's effect on re-perfusion of rat cardiac muscles at whole animal and cell levels. An acute MRI (myocardial reperfusion injury) model was built by loosening ligations of rat LAD (left anterior descending coronary). Myocardial cells with oxygen-glucose deprivation were cultured in vitro, then resupplied with oxygen and glucose. The changes in ECG, lactate Dehydrogenase, creatine kinase leakage, free calcium concentration, SOD, MDA, ET-1, and NO content caused by CDDP were observed. Results: CDDP could improve MRI rats' ECG, lactate Dehydrogenase, creatine kinase leakage, free calcium concentration, SOD, MDA, ET-1, and NO contents. Conclusion: CDDP probably acted on MRI by helping with calcium overload, oxygen free radicals, and endothelial cell injury.

Zhao et al. [20, 21] made hypoxia/re-oxygenation models in rats with the Langendorff method and medicated with CDDP and isosorbide dinitrate to protect cardiac muscles before or after hypoxia. HPLC was used to test the content changes of high-energy phosphate compounds and change in LPO. H-600 Transmission Electron Microscope was used to observe the ultrastructure of cells. Conclusion: CDDP acted well in both occasions because it increased the content of high-energy phosphate compounds and protected cells and myocardial ultrastructure. It was much better than isosorbide dinitrate.

2.1.2.2 Effect on Hyperlipidemia and Atherosclerosis

Using a rat hyperlipidemia model, Li et al. [22] observed CDDP's dosage effect (50, 150, 450 mg/kg). The positive control group was set with medication of Alginic Sodium Diester (25 mg/kg). After 13 days of oral medication, thrombosis index, high shear whole blood viscosity variability and low shear rate, and whole blood reduced viscosity were measured. Results showed an obvious increase in the platelet adhesion rate and thrombosis index in hyperlipidemic rats. CDDP at 150 and 450 mg/kg and the positive control reduced these indices. These data suggest that CDDP could prevent atherosclerosis.

Guan et al. [23] also used hyperlipidemic rats to test many indicators to analyze the effect of CDDP on the function of blood lipids. Results showed that both preventive administration and treatment with CDDP medication could reduce total cholesterol (TC), triglyceride (TG), and low-density lipoprotein (LDL), and increase the ratio of HDL/LDL in the blood of hyperlipidemic rats.

Using adrenaline and high molecular dextran injections, Xu et al. [24] made a rat model of high-viscosity-hyperlipidemia to analyze the functional mechanism of CDDP. CDDP was applied once 90 min before model establishment. 60 min after model establishment, femoral artery samplings were performed and deforming red

blood cells were measured. Results: CDDP can ameliorate red blood cell deformation and dosage effects were found in a range from 15 to 75 mg/kg.

Guo et al. [25] studied the effect of CDDP on hemorrheology and red blood cell micro-rheology in hyperlipidemia model dogs. Methods: The model was maintained for 6 months, then medicated with CDDP for 4 months. After that, the contents of triglyceride, cholesterol, and hemorrheology, RBC-EPM, osmotic fragility, membrane fluidity, and Ch/Pl were measured. Results: CDDP reduced the model's whole blood viscosity, osmotic fragility, Ch/Pl, and improved the deformation index, orientation index, RBC-EPM value, and membrane fluidity. Conclusion: CDDP can improve blood lipid disorders and hemorrheology value.

Tian et al. [26] studied the effect of CDDP on rabbits fed with high fat food. Methods: 48 rabbits were divided into five groups: control group, atherosclerosis group, simvastatin group, and large and small CDDP dosage groups. Animals in the control group were fed normally, and animals in other groups were fed with high fat food. Results: CDDP reduced the contents of cholesterol, triglyceride, and LDL, and increased HDL content. In addition, it could attenuate the endangium and reduce the endangium/Intima-media thickness (IMT) ratio. Compared with the control group, the inhibition rate on IMT of the simvastatin group, small, and large CDDP dosage groups were 32, 24, and 41 %, respectively. In conclusion: CDDP can effectively reduce blood lipid levels of the model rabbits and prevent atherosclerosis.

Chen et al. [27] observed CDDP's function and mechanism on rabbit vascular smooth muscle cells (VSMCs) induced by high blood sugar or high insulin. Methods: VSMCs were first cultured, then high blood sugar or high insulin was used to induce an increase in VSMCs. The model group had a lower content of nitric oxide synthase (NOS) and NO than the control group, but he CDDP groups increased NOS and NO significantly, which could be partially blocked by L-Nitro-Arginine Methyl Ester (L-NAME). Conclusion: CDDP can inhibit the proliferation of VSMCs by the mediation of NO.

Shi et al. [28] studied CDDP's effect on atherosclerosis (AS) in rabbits. Results: CDDP could ameliorate blood lipids. In the AS group, the NO content of the CDDP group was much higher than that of the AS group, but the ET level was reversed. Conclusion: CDDP can improve the levels of blood lipids, NO, and ET much better in AS rabbits.

Wang et al. [29] found that CDDP could inhibit the increase of blood lipids and prevent atherosclerosis, and reduce atheromatous plaque caused by arterial stenosis.

2.1.2.3 Effect on Blood System

Feng et al. [30] studied CDDP's effect on ADP, thrombin, and thrombocyte aggregation induced by collagen. Results: CDDP had inhibitive effects in all these aspects, and the effect was dosage-dependent.

Li et al. [31] studied CDDP's effect on coronary heart diseases and angina pectoris by utilized fluorescence polarization immunoassay to measure the fluorescence polarization P of platelet membrane, micro-viscosity, and membrane fluidity (LFU). Results: in CDDP treated rabbits, LFU increased, micro-viscosity decreased, and the difference between the treatment and control was highly significant. Conclusion: CDDP can efficiently improve LFU and lower micro-viscosity.

Zhang et al. [32] analyzed CDDP's effect on insulin resistant dogs. Results: A high fat diet for 6 months resulted in abnormal metabolism in the animals and insulin resistance, as well as excessive platelet activation. CDDP could reduce blood cholesterol significantly, and showed resistance to oxidation. Both aspirin and CDDP could inhibit platelet activation, but CDDP's inhibition of platelet aggregation and the expression of platelet surface adhesion molecules were more significant. Conclusion: CDDP was able to efficiently inhibit insulin resistance and platelet overactivity.

2.2 The Pharmacological Functions of Other Danshen-Containing Prescriptions

Danshen is widely used in a variety of compound preparations (both in traditional formulas as well as in new modern medicines), and its efficacy has been demonstrated through clinical pharmacology research and experimental studies. This section introduces some commonly used Danshen-containing Chinese patent medicines and compound preparations, and analyzes and summarizes the results of the clinical and experimental research. The patent medicines and preparations are: Compound Danshen injection (CDI), Xinmaitong Tablet (XT), Quanxinning injection, Xinkening Capsule, the Danqi Hemiplegia Capsule, Yangxinshe Tablet, Ningxin-anshen Capsule, Bushenyishou Capsule, Compound Dangshen Tablet, Rukuaixin Tablet (RT), Ningshenbuxin Tablet (NT), Huganning Tablet, Compound Xueshuantong Capsules, etc.

2.2.1 Composite Danshen Injection

CDI is also named Xiangdan injection, and its main ingredients are Danshen and rosewood (Lignum Dalbergiae Odoriferae), which are extracted with water and precipitated with ethanol. This medicine has the function of expanding coronary arteries and blood vessels, inhibiting blood clotting, removing free radicals, reducing lipids, enhancing the blood flow of the liver and kidney, improving immune functions, promoting bone fracture, and wound healing, etc.

2.2.1.1 Explanation of the Formula

The main ingredients of CDI are Danshen and rosewood. Rosewood has other names such as Jiangzhenxiang (降真香), Zijiangxiang (紫降香), and Hualimu (花梨母). It has an acrid flavor and warm nature, and its meridian distribution belongs to the liver and heart. The effects of this medicine include activating blood circulation to dissipate blood stasis, and stopping bleeding and pain. It contains naphtha, which is mainly β-bisabolene, *trans*-β-farnesene, *trans*-nerolidol, etc. It can be used for abdominal pain, liver depression and hypochondriac pain, thoracic obstruction and tingling, injuries from falls, and traumatic hemorrhage. Danshen's nature and flavor are slightly cold and bitter, respectively. The combination of the two herbs can expand blood vessels and increase the blood flow of the coronary artery muscle, and can be used for the symptoms like angina, myocardial infarction, etc. It also has the function of dissipating blood stasis to stop pain, activating blood to promote menstruation, and clearing heart heat to repel vexation.

2.2.1.2 Clinical Application

CDI is commonly used clinically for ischemic cardio- and cerebro-vascular diseases (CCVD). As research on the medicine has deepened, its clinical application has expanded to the areas of the CCVD system, respiratory system, urinary system, digestive system, as well as to orthopedic, neonatal, ophthalmology, surgery and other treatment of diseases. It also Functions as an adjuvant therapy for some infectious diseases. Its clinical application has occasional allergic reactions. It should not be used together with anticancer drugs like cyclophosphamide and combined with cytochrome c.

2.2.1.3 Pharmacological Research

Clinical Research

Cardiovascular Disease

The conventional treatments of dilated cardiomyopathy with heart failure include salt and water restrictions and medication with Western drugs such as Digitalis, diuretics, and vasodilators. If these drugs are used in combination with a large dose of CDI, it can improve heart functions, such as reducing the heart rate, increasing left ventricular ejection fraction (LVEF), and eliminating pulmonary rales and lower limb edema. Occasionally CDI can cause intestinal noise and loose stool. The effects will decrease with lower dosages [33].

The combined use of CDI with Shengmai injection and Huangqi injection in the treatment of coronary heart disease in the elderly can ameliorate the symptoms of chest tightness, palpitation, and fatigue, reduce the seizure frequency of angina, and recover the resting electrocardiogram. The combined use of CDI with Shengmai injection is better for patients with hypotension, infirmities, and complications. The combined use of CDI with Huangqi injection is better for patients with qi-deficiency (qi is the traditional Chinese medicine term meaning body energy) after diagnosis [34, 35]. CDI also has certain effects on unstable angina pectoris [36]. Some research showed that Danshen injection's treatment of blood stasis types of coronary heart disease could increase endothelial nitric oxide synthase mRNA, decrease the positive rate of ET-1 mRNA, and improve endothelial function [37].

The combined use of CDI with Propafenone or Shengmai injection shows good effects on the treatment of coronary heart disease, various cardiac arrhythmias like ventricular premature beat, junctional premature beat, a atrial premature beat complicated by myocarditis. It also has the best effect for blood stasis type patients, and can improve the heart function of congestive heart failure patients [38, 40].

CDI is also used in the treatment of pulmonary heart disease in the acute exacerbation stage, acute exacerbation of chronic pulmonary heart disease, refractory heart failure with pulmonary heart disease, etc.

Cerebrovascular Disease

48 h after subarachnoid hemorrhage (SAH), combined with treatments to stop bleeding, reduce intracranial pressure, and treat dehydration, CDI can significantly relieve headaches, reduce cerebral vasospasms and the incidence of recurrent bleeding, and decrease the death rate. For the treatment of hypertensive cerebral hemorrhage, the application of CDI 12 days after bleeding can effectively prevent cerebral edema and then increase cerebral vascular permeability, and showed better effects of relieving vasospasm, improving microcirculation, promoting absorption of the hematoma, and recovering regional cerebral blood flow, and the effects are better than if treated with Nimodipine. Danshene has a two-way adjustment function on the fibrinolytic system and can improve the redistribution of blood flow, prevent re-bleeding and increase in brain hemorrhage, and relieve the degree of disability and sequelae under the condition of maintaining or reducing vascular pressure [41–43].

For the treatment of acute cerebral infarctions, this medicine can reduce the levels of serum lipid peroxide and apolipoprotein Bl00 (ApoB100) and increase the level of SOD and ApoAl, thereby removing free radicals, regulating the metabolism of Apo, and preventing atherosclerosis. The injection can improve hemorrheology (whole blood viscosity, plasma viscosity, erythrocyte electrophoresis, fibrinogen, platelet adhesion rate), and the degree of the neurologic deficits of patients with cerebral infarction [44, 45].

Respiratory Diseases

For treatment of pneumoconiosis with acute infection, effective antibiotics should be used to improve ventilation function, stop coughing and asthma, regulate low-flow oxygen, expand coronary artery muscle, strengthen the heart, and correct electrolyte imbalance. In addition, CDI and Venoruton injection can be combined with these treatments to promote the improvement of symptoms like cough, asthma, fever and phlegm, and significantly reduce moist and dry rales in the lung. The combination treatment shows good effects on the restoration of complete blood count, and on the improvement of the lung inflammation, as shown by X-ray [46].

For the treatment of bronchopneumonia, the use of CDI can promote the improvement of symptoms such as cough, asthma, fever and phlegm, and significantly clear the moist rales in the lung [47].

The pathogens of lower respiratory tract infections in the elderly are mainly *Streptococcus pneumoniae* and *Haemophilus influenzae*. Antibiotics are usually used for treatment in the early stage. However, antibiotic treatment alone has some shortcomings, such as a longer disease course, more complications, and slower

absorption. But combined with CDI, it can shorten the course of the disease, promote absorption of inflammation, and reduce complications [48].

The combined use of CDI and other conventional methods such as anti-tubercular drugs and hormones to treat tuberculous exudative pleurisy can improve the cure rate and lower the relapse rate [49].

The acute exacerbation of chronic pulmonary heart disease can be treated with conventional treatments plus CDI alginic sodium diester. The combined treatments can increase the partial pressure of oxygen in arterial blood (PaO_2) and the percentage of available hemoglobin that is saturated with oxygen (SaO_2), decrease the atrial partial pressure of carbon dioxide ($PaCO_2$), adjust hypoxia and carbon dioxide retention, release elements like ET, eliminate pulmonary artery spasm, reduce pulmonary hypertension, expand the renal artery, promote diuresis, lower blood viscosity and pulmonary blood flow resistance, and so on, in this way achieving therapeutic effects [50].

For the treatment of chronic obstructive pulmonary disease, in addition to the conventional effects such as stopping cough, decreasing spasm, reducing phlegm, etc., the use of CDI can improve vital capacity, maximum voluntary ventilation, and atrial blood gas [51].

For the treatment of pulmonary encephalopathy, respiratory stimulants should be used, and measures of reducing intracranial pressure, supplying oxygen, correcting acid-base and water-electrolyte imbalances, and controlling heart failure should be adopted. Meanwhile, the use of CDI and Angongniuhuang Pill (one pill, twice or three times daily) can reduce the death rate [52].

Forty patients with carcinoma of the esophagus were randomly divided into two groups: control group and CDI group. During anesthesia, the former group was given sodium lactate Ringer's injection and the latter group was given sodium lactate Ringer's containing 10 ml of CDI. The same method of anesthesia was used. Serum superoxide dismutase (SOD), glutathione peroxidase (GSH2PX) and malindialdehyde (MDA) levels were measured before and 1, 2, 4, and 6 h after anesthesia. The ultramicroscopic structure of the lungs of both groups was investigated. Results: Group D's SOD activity was significantly decreased at the 4th and 6th hour after inspiring, the GSH2PX activity of group D significantly increased at the 1st hour after breathing oxygen and the MDA level of group D significantly decreased at the 2nd hour of inspiring. The ultramicroscopic changes of the pulmonary tissue of group C were worse than those of group D at the 4th and 6th hour after inspiring oxygen. Conclusion: CDI can relieve human lung injury caused by breathing pure oxygen, the possible mechanism being that it can eliminate oxygen free radicals and enhance the activity of SOD and GSH2PX [53].

Liver Diseases

The basic treatment for ascites due to cirrhosis is sodium restriction, diuresis, liver protection, plasma transfusion, antibiotics, and so on. The application of CDI and potassium aspartate and magnesium aspartate injection (one 14 day course of treatment) can reduce the levels of alanine aminotransferase and aspartate aminotransferase, and relieve the clinical symptoms. However, the albumin globulin ratio (A/G) has no significant change before and after treatment [54].

30 and 60 days after the treatment of cirrhosis with CDI, nailfold microcirculation and changes in hepatic portal hemodynamics were observed. It showed that there was improvement of microflow speed, Dpv, Vpvx, Vpvm, Dspv, Vspvx, and Qpv, but no significant effect on Qspv and Vspvm. It suggested that this injection could lower the portal vein pressure without affecting blood supply to the liver and could effectively improve the microcirculation of the liver [55].

Earlier and sustained high-dosage applications of compound Danshen preparations could contribute to the stability of the disease and to reduced complications so as to improve long-term survival [56].

CDI was combined with other medications to treat hepatic fibrosis. The results showed reductions in serum hyaluronic acid, laminin, collagen

type IV, procollagen type III, MDA, lipid peroxides (LPO), and an increase in SOD activity, indicating that the free radical cleaning function of this injection is the key mechanism of preventing and curing hepatic fibrosis [57].

Diammonium glycyrrhizinate can act as an adrenal cortex hormone, with functions of anti-inflammation, liver cell membrane protection, bilirubin metabolism promotion, and liver function improvement. It has a special effect on the increasing of alanine aminotransferase caused by liver cell injury, but no obvious effect in reducing jaundice for chronic hepatitis B. However, when combined with CDI, the treatment can obviously reduce jaundice and Transaminase. It can also decrease total bilirubin and increase the value of A/G. The rebound of ALT and the symptoms would be reduced after cessation of intravenous infusion. So, this injection can significantly relieve liver cell injury, promote the recovery of liver function, and slow down the development of chronic hepatitis to liver cirrhosis [58, 59].

The combined use of CDI and diammonium glycyrrhizinate in the treatment for fatty liver can obviously reduce the TC, TG, ALT, AST, and GGT and the effect is better than any single application of the two medicines [60].

The combined use of CDI and other conventional methods in the treatment of stasis cholestatic hepatitis can enhance the regeneration of epithelial cells, maintain an unobstructed bile canaliculus, improve the stasis of bile, clear liver inflammation, and dilute bile so as to reduce jaundice [61].

The combination of CDI and interferons in the treatment of chronic hepatitis B has a certain synergistic effect on the inhibition of Hepatitis B virus (HBV) replication and on the protection of liver cells from fibrosis. Whether it can have long-term anti-HBV effects and prevent the formation of liver fibrosis is not exact [62].

Using CDI for pretreatment is the effective way to prevent hematopoietic stem cell transplantation from hepatic veno-occlusive disease (HVOD). CDI can reduce the incidence of abdominal pain, liver expansion and ascites, reduce AST, ALT, PT, APTT and other indices, and prevent the incidence of HVOD. It is presently believed that HVOD is caused by multiple factors, but endothelial cell injury is the foremost critical factor. CDI's function of relieving endothelial cell injury might be its mechanism of HVOD prevention [63].

Many drugs for blood diseases have certain side effects on the liver. The combined use of Chuanxiong injection and CDI can prevent these side effects. Reports showed that the two drugs can reduce liver damage in the treatment of leukemia, and reduce liver damage as well as increase curative effects [64].

Nervous System Disease

Diabetic peripheral neuropathy disease (DPND) is a common complication of diabetes, and the pathogenesis is related to metabolic disturbance, diabetic microangiopathy, nerve growth factor reduction, etc., with the symptoms including pain, numbness, and hypoaesthesia. The combination of CDI and Methycobal or mexiletine has certain clinical effect on DPND. With mexiletine, it can relieve pain, and with Methycobal, it can relieve the symptom of numbness. CDI can reduce the level of Thromboxane A2, arteriolospasm and platelet aggregation, improve microcirculation, accelerate blood flow, reduce aggregation of RBC, and increase blood and oxygen supply to the tissues. So, the addition of CDI to the treatment of DPND can improve the clinical effect [65, 66].

CDI is widely used in the treatment of kidney diseases (chronic and acute glomerulonephritis, nephrotic syndrome, chronic renal failure, diabetes, and so on), and is usually combined with Astragalus injection, Ligustrazine injection, and Shengmai injection. Together they can improve clinical symptoms and increase kidney function.

CDI has an adjuvant therapeutical effect on pediatric diseases such as neonatal hypoxic-ischemic encephalopathy, neonatal sclera edema, infantile pneumonia, bronchopneumonia, allergic purpura, nephrotic syndrome, etc.

CDI can prevent steroid-induced necrosis of the femoral head, and has clinical effects on scapulohumeral periarthritis, osteoarthritis, and other osteopathy. It also has therapeutic effects

and auxiliary therapeutic effects on dermatological, surgical, ENT, mental, gynecological, and other diseases.

Experimental Research

It has been reported that CDI could improve the activity of SOD and reduce the content of MDA in rat cardiac tissue. The increased activities of Na^+-ATP, K^+-ATP, and Ca^{2+}-ATP had a protective effect against acute myocardial ischemia reperfusion injury in rats, and the protective mechanism was related to the function of CDI (including improving the microcirculation of cardiac muscle, cleaning free radicals, reducing LPO, resisting the toxicity of free radicals and calcium overload, and maintaining the function of myocardial cell membranes and mitochondria) [67].

Ischemic cerebrovascular disease is caused by the expression of surface adhesion molecules in vascular endothelial cells and white blood cells, which leads to the infiltration of peripheral blood leucocytes in the ischemic area. This movement blocks microcirculation and affects the blood supply to the tissue. On the other hand, the activated white blood cells release many inflammatory mediators and cytokines which can damage local blood vessels, increasing their permeability which leads to tissue edema; damage neurons and neuroglial cells which worsen nervous tissue injury, making more WBC attack the tissue, and causing more damage. Aided by micromanipulation techniques, researchers found that CDI can inhibit the changes in adhesion of Polymorphonuclear leukocytes and cerebral capillary endothelial cells of rats, which confirmed the observation that CDI reduced adhesion of cells (4th, 12th, 24th hour of cerebral ischemia reperfusion) [68].

Mesenchymal stem cells are derived from the mesoderm during the early period of mesenchymal stem cells, and they are non-hematopoietic stem cells found in bone marrow. The effect of CDI on the differentiation of rat bone marrow mesenchymal stem cells (rMSCs) has been studied. The results showed that CDI could induce the differentiation of rMSCs into neuron-like cells. However, in in vitro culture, there was less than 5 % neuroglia cells, which might indicate the process of MSC's differentiation: from pluripotent stem cells, to neural stem cells, to neural precursor cells, and then to mature nerve cells. It was suggested that the antioxidant activity of Danshen is one of the main factors in inducing the differentiation of rMSCs [69].

Spinal cord injury (SCI) model rats were prepared with the improved Allen's method, CDI was injected intraperitoneally, and the locomotion of the rats on a inclined plane was measured using the Basso Beattie and Bresnahan Locomotor rating scales. Results: CDI could promote motor function recovery in rats with acute SCI, and the application of cycloheximide and CDI could significantly reduce the apoptosis of spinal cord cells [70, 71].

The combined use of methylprednisolone and CDI can promote the recovery of motor function in the hind limbs of SCI rats, protect nerve conduction, stabilize mitochondrial structure, and maintain the normal morphology and function of neurons. Light and electron microscopy showed that hydromyelia, axonal degeneration, changes in myelin, and mitochondrial and capillary injuries in SCI rats were reduced with treatment with methylprednisolone and CDI. The treatment also returned synaptic vesicle numbers to normal [72].

2.2.2 Dan-Qi Hemiplegia Capsules

Dan-qi hemiplegia capsule is a new medicine to cure strokes and is suitable for strokes from qi-deficiency blood stasis and for meridians stopped by wind and phlegm. The drug has the function of dissolving cerebral thrombosis, improving blood circulation, increasing blood flow in the brain, and repairing nerve cells. There are 14 main ingredients in the drug, including Danshen, astragalus root, Rhizoma Chuanxiong, leech, calculus bovis artifactus, cornu saigae tataricae, scorpion, etc. The principle of this formula is mainly to enhance qi, activate blood circulation, reduce stasis, unblock the collaterals, repel wind, and open the orifices (all in traditional Chinese medicine terms). Its main indications are dyskinesia and mental disturbance after stroke.

2.2.2.1 Explanation of the Formula

Astragalus root has a sweet flavor and warm nature, and it belongs to the meridian of lung and spleen. A large dosage of this herb can nourish qi, which in traditional Chinese medicine terminology means body energy, unblock the collaterals, repel blood stasis without harming healthy qi, and is prescribed as a chief medicine.

Rhizoma Chuanxiong has an acrid and dispersing nature. It can promote blood circulation by removing blood stasis and is best for repelling wind. It also can free the qi and repel the wind in blood, which makes other herbs move to head.

Leech can remove blood stasis and stop pain, free the blood and meridian, and clear the mind by removing depression. Combined with the chief medicine astragalus root, they can nourish qi, free blood, remove blood stasis, and free the meridian. It is used as a deputy drug.

Calculus bovis artifactus, antelope horn, and scorpion enter the meridian of the liver and belong to comforting liver and repelling wind medicines; they can stop pain and free the meridian, calm the liver and wind, and relieve distortion. The combined use of the three herbs can clear heat and free phlegm. Rhizoma Acori Tatarinowii and other herbs dispel dampness and remove turbidity, functioning mainly in opening the orifices. Combined with calculus bovis, they can **clear heat** and eliminate phlegm. The above are assistant drugs.

So, the entire formula can nourish qi and restore body energy, refresh and clear the mind, and free the blood and meridian.

2.2.2.2 Clinical Application

It is used for hemorrhagic strokes from qi deficiency and blood stasis and has significant effects on the late stage of this disease.

2.2.2.3 The Pharmacological Research

The main pathological changes of the cerebral hemorrhage are the hematoma and the surrounding edema. The hematoma is the fundamental factor in causing cerebral edema. Many animal experiments, clinical research studies, and iconography data such as MRI and CT scans have confirmed that the local blood flow in the brain in the hematoma area is reduced, the affected area is far larger than the hemorrhage area, and the edema area is the same as the area with reduced brain blood flow.

Experimental studies have showed that the hematoma oppresses the surrounding brain tissue, causing large reduction of brain blood flow in areas near and far from the hematoma, resulting in delayed ischemia and hypoxia. This phenomenon did not disappear with the disappearance of the hematoma, suggesting that injury to nerve function is related to the delayed ischemia and hypoxia. So, the measures to prevent injury to nerve function are to prevent ischemia and hypoxia in area. Many animal experiments revealed that herbs such as Danshen, astragalus root, Sichuan lovage root, etc., could reduce hematocrit and fibrinogen blood levels, lower blood viscosity, accelerate blood flow, relieve injury to brain tissue, shorten the recovery time of the Edema area, and greatly protect nerve functions. Dan-qi hemiplegia capsule can improve paralysis of the face, upper and lower limbs, and fingers and toes, decrease blood lipids, and significantly affect recovery from late stage hemorrhagic stroke [73].

2.2.3 Compound Radix Codonopsitis Tablet

This medicine contains the herbs radix codonopsitis, Danshen, angelica, radix glehniae, radix tinosporae, etc. It can promote blood circulation by removing blood stasis, nourishing qi, and calming the heart, and is used for angina and chest distress caused by myocardial ischemia. Recent research on the medicine has shed more light on its pharmacological mechanism and scope of indications.

2.2.3.1 Explanation of the Formula

This medicine is a pure Chinese traditional medical preparation and contains mainly radix codonopsitis, Danshen, angelica, radix glehniae, radix tinosporae, etc. Radix codonopsitis can nourish spleen qi and lung qi; Danshen can

promote blood circulation by removing blood stasis; angelica can nourish and activate blood; radix glehniae can nourish yin and clear the lung; and radix tinosporae can clear heat and repel toxins. Together, they nourish qi and activate blood.

2.2.3.2 Clinical Application

It is used for the treatment of angina and chest tightness caused by myocardial ischemia cerebrovascular disease, and for injuries to the heart, brain, and lung under the hypoxic environment of high altitudes.

2.2.3.3 Pharmacological Research

Clinical Studies

To study the effects of Compound Radix Codonopsitis Tablet (CRCT) on the protection and improvement of brain functions, healthy people living at an altitude of 3,700 m were asked to take CRCT orally, and then their intelligence, and memory functions were measured in several psychological tests. The results showed that CRCT can significantly improve Verbal IQ, Performance IQ and Full-scale IQ. The results of memory comparison revealed that the indexes of orientation, l00-1, picture memory, imagination, touch, recite and memory quotient are significantly higher than those measured before CRCT administration. Several psychological tests of DX-A also revealed a significant change after administration. The above tests showed that this medicine can reduce hypoxic brain injury and can maintain and improve brain functions for people in hypoxic environments. The comparison of hemodynamic parameters 1 month after the administration revealed that pulse (P), total peripheral resistance (TPR), whole blood viscosity (η), altering latter time (ALT), pulmonary artery wedge pressure (PAWP), and Coronary perfusion pressure (CCP) were all reduced, and stroke volume (SV), effective blood volume (BV) and mean arterial blood pressure (mAP) were all increased (statistically significant). Thus, CRCT can reduce oxygen consumption, improve the circulation system and brain function, and protect from myocardial injury. Other tests on humans also showed similar effects [74, 75].

The main cause of high altitude pulmonary hypertension is hypoxic pulmonary vasoconstriction. Hypoxia causes the worsening of pulmonary vasoconstriction and the tension of pulmonary vascular smooth muscles, which increases the pulmonary artery pressure. Pulmonary vasoconstriction caused by hypoxia is the result of the depolarization of PVSM cell membranes and the transmembrane backflow of calcium ions. Improved heart function can delay the development of pulmonary artery pressure and reduce its injury. CRCT belongs to nourishing medicines, and many studies have confirmed its function of resisting hypoxia, and its mechanism is to reduce anoxic symptoms in an oxygen-deficient environment and to maintain normal physiological and biochemical functions. Long-term use of CRCT can turn changes under adverse conditions back to normal. Research results have shown that long-term use of this medicine can prevent the pulmonary artery pressure for people living above an altitude of 5,000 m [76].

CRCT was administered to people between the age of 50–77, twice daily, five tablets each, continued for 3 months. The results showed that the indexes of picture memory (PM), velocity of mental arithmetic (VMA), step velocity (SV), SD, and AFWL were significantly improved. There was no significant improvement for SDMEMA and FSM were not significantly improved until the 3rd month. The results show that this medicine can significantly improve brain function and delay aging [77].

CRCT has been used to treat angina of qi deficiency and blood stasis style. Patients more than 35 years of age were given CRCT three times daily, three tablets at each time, over 30 days. The results showed that CRCT could greatly relieve the main symptoms such as chest pain and tightness and TCM symptoms such as qi deficiency and blood stasis. ECGs were back to normal or basically normal. The depression segment returned to 0.05 mV, the T wave was reduced by more than 25 % or change from flat

to erect, and the atrioventricular block was also reduced. Meanwhile, it was observed that CRCT had no effect on liver and kidney function, as indicated by serum ALT, inosine, and blood urea nitrogen. It could reduce cholesterol levels, but had no influence on triglyceride content [78].

Experimental Studies

An acute decompression hypoxia and confined hypoxic condition at an altitude of 8,000 m was simulated. After 7 h under such a condition, the changes of cytochrome oxidase and succinic dehydrogenase of myocardial cells in mice were tested. CRCT (0.2 ml/each) was orally delivered to mice 1 day before hypoxia, and the same volume of distilled water was delivered to the control group. 1 h before hypoxia, the same dosage of CRCT or water was delivered by abdominal cavity injection. The animals were placed in a decompression chamber, where the pressure was reduced to that at an altitude of 8,000 m, maintained for 7 h, and then returned to pressure at sea level. The mice were executed and the hearts collected to measure cytochrome oxidase and succinic dehydrogenase activities. The results showed that the activities of cytochrome oxidase and succinic dehydrogenase in the hypoxic group were reduced when compared to those of the normal pressure group, and the difference was statistically significant. The levels of the two enzymes in the CRCT treatment group were higher than in the hypoxia group and close to those in the normal pressure group, but statistically insignificant. Acute hypoxia can reduce the activity of cytochrome oxidase and succinic dehydrogenase, which is harmful to body. However, CRCT could increase these activities and the levels were close to normal, suggesting that the medicine can prevent the reduction of enzymatic activities and improve anoxia tolerance of their bodies [79].

2.2.4 Xinkening Capsules

This medicine contains Danshen, Notoginseng, safflower, bezoar, borneol, senso, cornu bubali, and ginseng fibrous root. It can promote blood circulation by removing blood stasis, stop pain, and refresh the mind. It is used for the treatment of CCVD clinically.

2.2.4.1 Explanation of the Formula

Danshen is the chief drug in a prescription, and with the aid of Notoginseng and safflower, it can promote blood circulation and remove blood stasis, free meridians, and stop pain. Bezoar, borneol, senso, and cornu bubali can refresh the mind and dispel filth. Ginseng fibrous root can powerfully nourish original qi, restore vessels, and rescue from desertion, promote fluid production, calm the mind, and protect the body energy by reinforcing healthy qi and dispelling pathogens. The nature of senso is pungent and scurrying, the flavor is warm, and it has the function of opening the orifices and dispelling filth. *Convenient Reader on Materia Medica* says, "senso is good at clearing the mind and repelling harm, and is used to protect the body in an emergency." The major chemical components of senso are steroids, and collectively they are called toad diene lipid. Senso has the cardiotonic effect of digitalis and the boosting pressure effect and central respiratory stimulation effect of adrenaline. In addition, it can stop pain, activate striated muscle, uterus and fallopian tube, relieve coughing and panting, resist inflammation, cancer and radiation, increase white blood cells, etc. Senso is used clinically for respiratory and circulatory failures. Ginseng is also used for the symptoms of asthenia, cool limbs and weak pulse.

2.2.4.2 Clinical Application

This medicine is used for coronary heart disease, angina, chest tightness, palpitations, and dizziness. It can relieve hypertension, and reduce blood lipid.

2.2.4.3 Pharmacological Research

Patients were selected in line with WTO diagnostic criteria: at least 3 months of angina history, angina pectoris at least 5 times per week, symptoms able to be relieved with resting or sublingual nitroglycerin, and no liver, heart, or kidney disorders. After treatment with Xinkening

capsules for 4 weeks, the myocardial oxygen consumption index (expressed as rate-pressure product) and the degree of myocardial ischemia decreased significantly. The total incidence of myocardial ischemia within 24 h reduced by 41 %, both the sustained and total time of ST segment depression within 24 h were reduced, and the maximal platelet aggregation (MPAG) was significantly lowered compared to before treatment. Blood sugar and liver and kidney function were not affected. The mechanism of this drug's Functions is unclear, possibly acting by expanding the coronary artery muscle, reducing vascular resistance, increasing blood flow, improving myocardial nutrition and myocardial ischemia, and reducing the area of ischemia, myocardial oxygen consumption. Meanwhile, it can reduce blood lipids, regulate blood viscosity, accelerate blood flow, etc. [80].

2.2.5 Fufang Xueshuantong Capsule (Copound Xue-Shuantong Capsule)

This drug is mainly used for treating vascular diseases by removing blood stasis, and nourishes qi and yin. It has been used for eye problems. Its main ingredients include Danshen, Notoginseng and astragalus root, etc.

2.2.5.1 Explanation of the Formula

The main ingredient in this medicine is Notoginseng, which is aided by Danshen, astragalus root, and figwort. The flavor of Notoginseng is sweet and slight bitterly and the nature is warm, which can remove blood stasis, stop bleeding, and free meridians. The flavor of astragalus root is sweet and the nature is slightly warm, and it belongs to the meridian of lung and spleen. It can nourish qi, free meridians, and repel blood stasis without hurting the healthy qi. The nature of Danshen is slightly cold and the flavor is bitter, which can free meridians, remove blood stasis, and promote blood. The nature of radix scrophulariae is slightly cold and the flavor is bitter, sweet, and salty, which can cool blood and promote yin, clear heat and reduce toxins. The combined use of these herbs can improve blood circulation by removing blood stasis and nourishing qi and yin, without hurting the blood.

2.2.5.2 Clinical Application

This medicine can expand the coronary artery muscle, improve microcirculation, and reduce blood lipid and platelet aggregation, and is used for coronary heart disease, angina, eye problems, and other vascular diseases.

2.2.5.3 Pharmacological Research

Compound Xue-shuantong Capsule (CXSC) can expand blood vessels, improve microcirculation, and reduce lipid and platelet aggregation. It is used for the treatment of cerebrovascular disease, coronary heart disease, angina, and a variety of other vascular diseases of the fundus and traumatic bleeding.

Clinical Application

CXSC stops bleeding and repels stasis simultaneously, activating blood circulation without leaving the stasis. It has an anti-inflammatory analgesic effect. The clinical studies showed that it can shorten the clotting time, promote clot lysis, resist thrombosis, improve microcirculation and increase blood flow, and is used for heart, brain, and eye problems of blood stasis and hemorrhagic style.

CXSC and gingko leaf tablets were used together to treat atherosclerosis-related vertigo. The patients receiving the treatment should meet the following criteria: (1) over the age of 50; (2) eye-base arteriosclerosis was above level II; (3) high blood lipid or blood viscosity; (4) cerebral arteriosclerosis proven by either transcranial Doppler (TCD) or cerebral blood flow diagram; (5) no other diseases considered blood stasis type of vertigo by TCM. The patients were treated for 6 months, receiving three capsules/time, 3 times daily for CXSC, and 40 mg/time and 3 times daily for the gingko leaf tablet [81]. The results showed that the treatment reduced TC, TG and LDL, increased HDL, and maintained the above four indexes around the normal level. The combination of the two drugs gave better results than gingko leaf tablets used alone. The mechanism of

these drugs might be related to the function of reducing blood viscosity and thrombosis and increasing peripheral blood flow.

CXSC has been used to treat migraine patients, who were selected based on the diagnostic criteria in the 1995 edition of the "Chinese Medical Association Neural Science." Each patient received two capsules of CXSC, and at 50 and 100 min post administration, color TCD ultrasound technology was used to detect the bilateral middle cerebral artery (MCA), and peak systolic velocity (VS) changes in the anterior cerebral artery (ACA) and posterior cerebral artery (PCA). The results showed that MCA, ACA, and VS of PCA were significantly reduced 50 min after the administration, and MCA, ACA, and VS of PCA continued to decrease 100 min after the administration, which was statistically significant. This medicine can increase peripheral, carotid artery and brain blood flow, improve brain circulation, increase blood hypoxia tolerance and inhibit various vascular diseases. The peak function time is from 50 to 100 min after administration, and this drug only has an effect on the flow velocity of the headache side, but has no obvious effect on the normal flow [82].

CXSC has been used for the treatment of vitreous hemorrhage. Patients were administered 2 capsules each time, three times daily, for 2 months. Patients with diabetes and hypertension were also given hypoglycemic and antihypertensive drugs, respectively. Among the 46 cases, 28 % showed an obvious effect, and 52 % showed improvement. Vitreous hemorrhage results from accumulation of blood in the vitreous chamber, which is caused by rupturing of the retinal and uveal blood vessels. Since the metabolism of the vitreous body is low, it can cause proliferative vitreoretinopathy and obvious reduction of eyesight if not treated in time. Meanwhile, surgical treatment of the disease requires certain equipment and technique, which is not available everywhere. CXSC promotes the absorption of vitreous hemorrhage, and improves vision in a simple and practical way [83].

CXSC has a good effect on curing hyphema. The indications also include the concomitant symptoms such as bleeding under the eyelid skin, injury of the eyelid skin, corneal abrasion, iridodialysis, secondary glaucoma, commotio retinae, vitreous hemorrhage, etc. The clinical effects showed that it could quickly promote the absorption of hematoceles and improve eyesight [84].

Diabetic retinopathy is one of the most common complications of diabetes and its cause is related to retinal ischemia and hypoxia. The total saponins of Notoginseng in this medicine stop the α-receptor of vascular smooth muscle cells to control calcium channels, which can expand blood vessels, reduce blood viscosity, promote blood circulation, and improve tolerance of hypoxia. Clinically, the common treatment for diabetic retinopathy is retinal photocoagulation, combined with oral administration of CXSC, or a single treatment with CXSC. The dosage is 2–3 capsules each time, three times a day, continued for more than 3 months. Meanwhile, hypoglycemic and antihypertensive drugs should be administered. The treatment can improve eyesight by more than 1–2 lines, control fundus diseases, and stop the development of retinal hemorrhage, exudation, and microaneurysm. It has good effects on central retinal vein occlusion, central retinal artery and artery branch occlusion, central serous chorioretinopathy, age-related macular degeneration, optic disk vasculitis, etc., hence improving patients' quality of life [85].

In treating glaucoma of controlled intraocular pressure, this drug shows good effects on glaucomatous optic neuropathy. It can broaden the view and improve the visual function of the patients, but the effects are not stable for elderly patients. The pharmacological foundation of controlling intraocular pressure and preventing deterioration of visual function from glaucoma is to improve microcirculation of the optic nerve and ischemia and anoxic conditions, and enhance the excitability of visual cells [86].

Experimental Studies

CXSC has been tested on rats and rabbits, and results showed that it could expand the mesenteric artery and vein, improve blood circulation, prolong the survival time of tissues under hypoxia, resist thrombosis, promote clot lysis,

and shorten the clotting time. The above function is the result of synergy of all herbs. It showed that Notoginseng could increase thrombin levels, shorten the clotting time, and also promote clot dissolution, while diminishing inflammation and stopping itching. The other herbs in this medicine can expand blood vessels, improve blood circulation, resist thrombosis, clear heat, nourish yin, etc. [87].

In a study on the protection of ischemic heart muscle in dogs, CXSC has been shown to enhance cardiac muscle systole, maintain blood pressure stability after acute myocardial infarction, make glucogen and lactic acid contents close to the levels of the normal control group, make the contents of MDA and LDH lower than those of ischemic group, and the activity of SOD higher than those of the ischemic group. These data revealed that CXSC can maintain cardiac pump function, promote blood and oxygen supply, normalize the aerobic oxidation of sugar, regulate cardiac muscle injury, and reduce the leakage of LDH. Myocardial ischemia causes the blockage of aerobic oxidation, the reduction of ATP, and disorder of the ion gradient and membrane stability; meanwhile, the generation of oxygen free radicals would damage the cardiac muscle. CXSC can enhance aerobic oxidation, increase the activity of SOD, maintain ATP generation and membrane stability, reduce the content of MDA, and remove free radicals [88].

Another study has shown that CXSC can improve the ischemic change of epicardial electrocardiograms of myocardial infarction in experimental dogs. CXSC can significantly reduce the degree of myocardial ischemia ($\sum$-ST) and the area of the myocardial ischemia (N-ST). Compared with the ischemic group, the $\sum$-ST and N-ST at the corresponding time points are significantly reduced. So, CXSC's ability of resisting myocardial ischemia is confirmed. The pharmacological pathway of this medicine is possibly that the medicine can activate blood circulation, remove stasis, and promote blood and oxygen supply, which normalizes the pump function of Na^+-K^+ in the membrane of cardiac muscle cells, and promotes the index of cardiac electric activity of the epicardium in ECG [89].

In a study on hypoxia tolerance, it has been shown that 1 h after administration of CXSC, both the atmospheric hypoxia tolerance and the ability of isoproterenol to increase hypoxia tolerance in mice were increased, the survival time of mice was prolonged, and the electrophysiology of myocardial ischemia was maintained. These results suggest that CXSC can reduce myocardial oxygen consumption, improve metabolism and improve anoxia tolerance.

2.2.6 Guanxinning Injection

This medicine contains Danshen and Sichuan lovage root. The two herbs together can improve blood circulation, remove blood stasis, nourish the mind, free meridians, free qi, and stop pain.

2.2.6.1 Explanation of the Formula

The flavor and nature of Danshen is slightly cold and bitter, which can invigorate blood, remove blood stasis, and nourish blood. According to TCM classics, although Danshen by itself is only one herb, it has the functions of four different herbs. The flavor and nature of Sichuan lovage root is pungent and enters the liver and gallbladder meridian, which is the qi medicine in blood, and can promote blood circulation, free qi, and repel depression, wind and pain, which is used for stopping pain, reducing pressure, expanding the coronary artery muscle, increasing coronary artery muscle blood flow and resisting myocardial ischemia. The combination of the two herbs can easily remove blood stasis and promote blood circulation, greatly free qi and meridians, effectively nourish the mind and stop pain, and largely enhance the clinical effects without causing too much dryness.

2.2.6.2 Clinical Application

It is used for CCVD such as coronary heart disease, angina, diabetic nephropathy (DN), gynecological and pediatric diseases.

2.2.6.3 Pharmacological Research

Cardiovascular Effects

The clinical effects of Guanxinning injection (GI) treatment for coronary heart disease and angina have been observed. GI was delivered to coronary heart disease and angina patients at 20 ml/day, with a treatment lasting 15 days. Those with high blood pressure used hypotensive drugs, those with acute cardiac insufficiency used digitalis preparations and diuretics, and those with angina used nitrate medications. The results showed that after administration of the drug, the same level of fatigue did not cause or reduce the frequency of angina, and the ECG ST segment rebounded [90].

Another research group studied the effect of combining conventional therapies, such as a low-salt and low-fat diet and using aspirin and Betaloc, with GI and ginkgo leaf injections. Each administration (intravenous drip) was 10 ml per day continued for 14 days. The results showed that the incidence of angina, ST-T (ECG) and WBV were greatly improved over a single conventional therapy [91].

In treating cough, cyanosis, dyspnea, oliguria, edema of lower extremities, lung noise, and hepatojugular reflux of some pulmonary heart disease positive patients, GI relieved the above symptoms in 60 % of the patients, and the total effective rate was 90 % [92].

Effects on Microvessels

DN is one of the chronic complications of diabetes microvascular disease. Combining conventional therapy (like control of blood pressure, sugar, lipid, weight, and other indexes) with GI showed that fasting plasma glucose, postprandial 2 h glucose, glycosylated hemoglobin, blood urea nitrogen, serum creatinine, blood and urine β2-microglobulin, morning urine microalbumin, urinary protein excretion, fibrinogen, and whole blood viscosity were significantly reduced after two periods of treatment. Meanwhile, the thromboplastin time and thrombin time were prolonged, but plasma viscosity was not changed. The dosage was 20 ml/time, once daily, for a course of 14 days [93].

To sum up, GI can reduce platelet surface activity, inhibit platelet aggregation, improve the activity of fibrinoclase, adjust blood rheology, and improve immune function. Danshen can inhibit α and M receptors, expand blood vessels, reduce blood viscosity, increase renal blood flow and glomerular filtration rate, inhibit immune complex allergic reactions and the form of Thromboxane, resist blood capillary spasm and platelet aggregation, free the blockage of renal blood vessels, protect GBM and promote diuresis, and also has calming, antibacterial, and anti-inflammatory effects. Sichuan lovage root can alleviate the spasmodic smooth muscle of the trachea, inhibit the accumulation of Ca^{2+} in cells, reduce the activity of ospholipase, ATPase, cathepsin, lipoxidase, Cyclooxygenase and TXA_2, clear oxyradicals, resist LPO, maintain the balance of Thromboxane (A_2) and prostacyclin, expand blood vessels, reduce blood viscosity, improve microcirculation, and reduce the blood anoxic symptoms of tissue. The combination of the two herbs can even better change the abnormal hemodynamics and hypercoagulative state of Glomeruli, reduce urinary albumin excretion, and positively affect diabetes and renal diseases. Reduction of pulmonary hypertension and right heart load has a therapeutic effect on coronary heart disease, angina, and pulmonary heart disease.

2.2.7 Bushenyishou Capsule

This capsule contains famous Chinese herbs like ginseng, glossy ganoderma, and Danshen, etc. In TCM, these herbs can nourish qi and kidneys, and this medicine can relieve many clinical symptoms related to kidney qi-deficiency and improve cellular immune function and to increase the quality of life of the patients. Recent research shows that this capsule can resist LPO and stress and regulate immune function, adrenocortical function, and hypogonadism.

2.2.7.1 Explanation of the Formula

In this formula, red ginseng and licorice can nourish qi, and the lung and spleen. Glossy

ganoderma, lycium fruit, epimedium and polygonati rhizome can nourish qi, yin, and kidneys. Fleeceflower root and Danshen can nourish and activate blood, and clear and calm the mind. Pearl can calm the liver and subdue yang, tranquilize the heart and repel horror. All together, these herbs nourish kidney and qi.

2.2.7.2 Clinical Application

It is used for clinical symptoms of kidney qi-deficiency (like fatigue, short breath, spontaneous sweating, aching and weakness at the waist and knee, and nocturia), has a therapeutic effect on male ED, and improves the quality of life. It can improve cellular immune function, has a significant antioxidant effect, and can delay aging in experimental animals.

2.2.7.3 Pharmacological Research

Clinical Research

Kidney Qi-deficiency

80 patients with kidney qi-deficiency symptoms (shortness of breath, mental and physical fatigue, spontaneous sweating, weak knees, dizziness, tinnitus, long urination, incomplete urination, nocturia, loss of sex drive) were treated for 1 month. The T achroacyte subgroup (CD3, CD4, and CD8) was observed before and after treatment. The results show that this medicine can improve the clinical symptoms of kidney qi-deficiency and the quality of life of the patients, improving cellular immune function, and increasing serum levels of CD3, CD4, and CD8.

Atypical Organic ED

The patients who scored below 21 on the International Index of Erectile Function and had been sick for 3 months to 2 years were treated with this medicine for 8 weeks. Compared with the control group, the treated group showed a significant improvement. Within the treated group, patients with mild or moderate ED had a better improvement than those with serious ED. It suggests that the level of ED is related to the medical effect; the milder the symptoms are, the better the therapeutic effect of the drug will be [94].

Immune Function of the Elderly

Three groups of people were studied; a normal adult group, normal elderly control group, and normal elderly treatment group. The normal elderly treatment group was given six capsules each time, three times daily for 2 months. No drugs were given to the other two groups. Blood samples were collected to check the Ts function, ConA, and PHA. The results showed that after treatment, PHA returned to normal, ConA increased to close to normal adult levels, and the Ts function also increased, but these changes were statistically insignificant.

Experimental Study

Anti-Stress Effect and Influence on Immune Function

The effects of the medicine on the tolerances of high temperature, cold, hypoxia, swimming endurance, anti-inflammation, the peritoneal macrophage phagocytic function, the production of antibodies, and the impact of delayed hypersensitivity were studied on mice. The results showed that after several administrations, the drug can improve the mice's ability to tolerate high and low temperatures, survive longer in high or freezing temperatures, and that the mice's tolerance of cold temperature was stronger than of high temperature. The drug extended the time of death in mice in occlusion hypoxia at atmospheric pressure, and similarly in the treated with isoproterenol to increase their cardiac load. The drug strengthened the endurance of the mice and prolonged their swimming time. The drug had an inhibitive effect on ear edema in mice induced by croton oil, but the effect was not as good as that of aspirin.

In a test of macrophage cell function in the abdominal cavities of mice, the experimental animals were administered continuously for seven days, injected with 0.2 ml of hepatic glycogen solution on the 5th day, 1 ml of 5 % chicken red blood cells (CRBC) with normal saline solution 1 h after the last administration. The animals were executed 1 h later, and the percentage of macrophage cells was counted. The results showed that this medicine can improve the phagocytic activity of mouse

peritoneal macrophages, as both the phagocytic percentage and phagocytic index increased significantly.

Mice were injected with CRBC intraperitoneally, and the post-immune serum was collected and mixed with guinea pig serum (mouse: guinea pig = 1:10) and 10 % CRBC. The hemolysis value was measured after incubation at 37 °C. The drug's effect on of antibody generation was observed and compared. The results showed that this capsule can significantly promote hemolysis of the antibody against CRBC.

A high dose of this capsule could significantly inhibit DNFB-induced delayed hypersensitivity (DTH). The effects of medium and low dosages were not remarkable, but they could inhibit DTH induced by cyclophosphamide [95].

Antioxidation and Neurohumoral Regulation

An anti-aging experiment was carried out on *Drosophila melanogaster* using culture medium containing 0, 0.5, 1, and 5 % of the medicine. The results showed that this medicine could prolong the life of *D. melanogaster*. Compared with the control group, the longest and the average age increased (with no difference between genders). This suggested that this capsule could delay the aging and death of *D. melanogaster* to some extent [96].

The drug's effect on the antioxidation activity of aged mice was studied. Five groups of mice aged 18 months, were fed a solution containing different concentrations of this drug, vitamin E or drinking water, and young control mice were fed drinking water. The administration was once per day, six times per week, and continued for one and a half months. 1 h after the final administration, the eyeballs were excised to collect blood, and the livers and hearts were quickly excised to prepare serum, liver and myocardial extracts. The activity of SOD in serum and liver tissue was measured by the hydroxylamine method, the content of LPO was measured with the thiobarbituric acid method, the content of glutathione peroxidase in red blood cells was measured with the improved Hafeman method, and the content of lipofuscin in heart muscle was measured with fluorescence spectrophotometry. The results showed that this medicine could obviously increase the activity of SOD in serum and liver tissue and glutathione peroxidase in red blood cells. It could reduce the content of LPO and lipofuscin. Since the levels of LPO and lipofuscin are positively related to the degree of aging, the results suggest that long term intake of this capsule can delay aging. This function may be related to the increased activity of SOD and glutathione peroxidase and reduced LPO, which prevents injury to the biomembrane.

The drug's effect on vitamin C levels in the adrenal glands of SD rats was studied by randomly dividing the rats into six groups (half male and female), and feeding them the drug or drinking water, once daily. The administration continued for 1, 7, and 14 days. The results showed that this drug could reduce the content of vitamin C in adrenal glands and excite the adrenal cortex, but a one-time administration showed no obvious effect. The pituitaries of the control and treatment groups were extracted, and the extracts could reduce the content of vitamin C in the adrenal glands. It was suggested that this might be caused by adrenocorticotropic hormone (ACTH) contained in the pituitary that could quickly excite the adrenal cortex. Since this medicine could increase the content of ACTH in pituitary, it could delay aging.

The effects of Bushenyiqi Capsule on T-cell apoptosis: The model and treatment groups (SD rats) were injected 10 mg/kg CORT to make the model. Meanwhile, they both were given the drug once daily, for 14 days. After that, their spleens were collected in germ free conditions and the T-cells were isolated and purified. The whole process was finished and cells were cultured on six-well incubation plate pre-coated with CD3 monoclonal antibody. 14 h later, they were prepared as specimens for electron microscopy. TUNEL labeled apoptotic cells were detected by flow cytometry, and the rate of apoptosis was calculated with area integral methods.

Morphological studies showed that CD3 monoclonal antibody could induce apoptosis of T-cells of any group. The apoptotic cells had typical nucleolus changes; nuclear chromatin

formed chromatin clumps which showed high electron density under electron microscopy. The test of TUNEL by flow cytometry and the mark of apoptosed cells showed a significant difference between model and normal control groups on T-cell apoptosis. Results showed that Bushenyishou Capsule could downregulate the inducement of T-cell apoptosis [97].

Another test showed that continuous administration of this capsule for 1 or 2 weeks could obviously increase serum corticosterone, but that a single administration had no obvious effect.

In a clinical study on the effect of this capsule on SOD, MDA, and GSH-Px levels in kidney qi-deficiency patients, the results showed that the levels of SOD and GSH-Px increased and MDA decreased after the treatment. The effects of Bushenyishou capsule were more obvious than those of Guifudihuang Pill. The experiment was conducted as follows: 80 kidney qi-deficiency patients were randomly divided into two equal groups, the treatment group and the control group. The treatment group had Bushenyishou Capsule (two capsules per time, three times per day, 0.26 g per capsule), the control group had Guifudihuang Pill (6 g per time and twice daily), and the treatment cycle for both groups was 30 days.

2.2.8 Huganning Tablet

This medicine is a commonly used Chinese medicine that can clear heat and dampness, relax liver, stop pain, and reduce jaundice and ALT. This is used for acute and chronic hepatitis with the effect of improving blood circulation in the liver, inhibiting liver fibrosis, and increasing immune function. The ingredients of this medicine are stringy stonecrop, giant knotweed rhizome, Danshen, and glossy ganoderma.

2.2.8.1 Explanation of the Formula

The sarmentosin of stringy stonecrop can promote metabolism in liver cells and enhance the liver's detoxification ability. Giant knotweed rhizome can repel wind and dampness, stop pain, stasis, cough and phlegm, reduce lipids in the liver, free fatty acids in serum, ALT, AST, etc. Glossy ganoderma can nourish the qi in five organs, promote body energy and restore the vital qi, inhibit the HBV, regulate immune function and inhibit platelet aggregation, etc. Danshen can nourish and activate blood, free meridians, and repel stasis. The mixture of these can clear heat, repel dampness, protect and free the liver, stop stasis, and stop pain.

2.2.8.2 Clinical Application

This medicine can relieve common symptoms related with hepatitis (fatigue, abdominal distension, hypochondriac pain, dark urine, etc.). Clinical observations showed that this medicine could also cure hepatitis and liver damage caused by alcohol-induced liver disease and fatty liver, etc. It also has an anti-hepatic fibrosis function.

2.2.8.3 Pharmacological Research

Research on the protective effects of Huganning Tablet on liver damage caused by carbon tetrachloride revealed that this medicine could obviously reduce the level of ALT and AST in the serum of poisoned mice. Pathological examination of the liver tissues showed that carbon tetrachloride could cause edema or diffuse edema of the liver cells centered around the central vein, with focal necrosis and patchy necrosis of liver tissue, inflammatory cells, neutrophile granulocyte, and lymphocyte infiltration, surrounding the blood vessels and lymphatics. Tissues from mice treated with Huganning Tablet only showed edema of the liver cells and inflammatory cell infiltration (surrounding the blood vessels) and slight necrosis of liver cells. The results suggest that this medicine could protect the liver tissue of mice poisoned with carbon tetrachloride [98].

2.2.9 Xinmaitong Tablet

This medicine is used for the prevention and treatment of cardiovascular diseases. It can promote blood circulation, remove stasis, free meridians, nourish the heart, improve microcirculation, increase coronary blood flow, reduce

myocardial oxygen consumption, lower blood pressure and blood lipids, and soften blood vessels, and is suitable for thromboembolic diseases.

2.2.9.1 Explanation of the Formula

There are 11 main ingredients in XT; they are hairy holly root, cassia seeds, gambir plant, angelica, Danshen, Notoginseng, two-toothed achyranthes root, pueraria root, pagoda tree flower, common self-heal fruit-spike, etc. Danshen and Notoginseng can repel stasis and stop pain. The nature and flavor of two-toothed achyranthes plant is even, bitter and acidic, and it can repel stasis and free meridians, and promote the blood to the lower part of the body. The nature and flavor of hairy holly root is cold and bitter, and can clear heat and toxins, free blood and meridians, and reduce the heat in stasis. The nature and flavor of angelica is warm, sweet and pungent, and can nourish and free blood. The above herbs together can nourish, activate blood, free meridians, and reduce stasis without affecting the body energy. Radix puerariae can clear heat, generate body fluid and stop spasms. Common self-heal fruit-spike is cold and pungent, and can clear heat and improve eye function. Cassia seed has the same function as common self-heal fruit-spike. The flavor and nature of gambir plant is cool and sweet, and can clear heat and calm the liver, repel wind and reduce horror. Pagoda tree flower can cool and stop blood, and clear heat in the liver. The combined use of these can promote blood circulation, remove stasis, free meridians, and nourish the heart.

2.2.9.2 Clinical Application

This medicine can improve microcirculation, increase coronary blood flow, reduce myocardial oxygen consumption, lower blood pressure and blood lipids, soften blood vessels, and is clinically used for hypertension and hyperlipidemia.

2.2.9.3 Pharmacological Research

Clinical Research

In a study on reducing myocardial oxygen consumption, XT was used to treat the patients of myocardial infarction, coronary heart disease, myocardial ischemia, and angina, and the myocardial oxygen consumption and blood supply were observed. Rate-pressure product (RPP) was used to represent the myocardial oxygen consumption index, and $\sum$ST and NST were used to express the total reduction of ST part of conventional 12 lead and the lead index of reduction (≥0.25 mm), respectively. This medicine was administered four pills at a time, three times a day. The control group used conventional western drugs, isoamyl nitrite, Compound Danshen Pill and Aspirin Enteric-coated Tablet. The dose of isoamyl nitrite was l0 mg, Compound Danshen Pill was three pills three times a day (orally), and Aspirin Enteric-coated Tablet was 75 mg once and three times daily (orally). The treatment cycle lasted 1 month. The results showed that the level of myocardial ischemia was close between the treatment and control groups, but the RPP of the treatment group was better than the control group. This revealed that this medicine could reduce myocardial oxygen consumption and protect the Cardiac Muscle [99].

Experimental Research

The effect of the medicine on carotid artery thrombosis and clotting time was studied, and the results showed that XT had a strong antithrombotic effect. New Zealand rabbits were divided into an XT group, Compound Danshen group, and saline group. Each group had six rabbits. Different drugs were administered 3 days before the experiment, three times per day for 3 days. On the 4th day, drugs were given only once, then the animals were anesthetized with urethane, a 4 cm segment of carotid artery was selected, and its two ends were clamped, stopping blood flow in the segment. 3 cm of No. 1 silk thread was put into the selected artery, and the end of the thread farther from the heart was floating in the blood. At this time the clamps were loosened and blood began to flow. 2 h later, this 4 cm segment was departed and cut open. The thread was also taken out and put on filter paper to absorb the blood. Then, the threads with thrombus were weighed to figure out the net weight of thrombosis by deducting the weight of the threads. Meanwhile,

once again carotid artery sampling and blood clotting time was measured by slide method. Results showed that the thrombosis weights of XT groups with intermediate and high dosages were significantly lighter than those of the saline group, and the time of clotting was also prolonged, which was the same as the Compound Danshen group [100].

2.2.10 Ningxinanshen Capsule

This medicine can clear heat and depression, calm the mind, and comfort the chest and heart which can largely relieve symptoms such as palpitations, insomnia, irritability, hot flashes, night sweats, zygomatic redness, and thirst, which are caused by yin deficiency and vigorous fire. There are 11 main ingredients in this medicine, including Danshen and coptis rhizome, etc.

2.2.10.1 Explanation of the Formula

There are 11 main ingredients in Ningxinanshen Capsule (NC): coptis rhizome, amber, acorus, thin-leaf milkwort root, poria, Danshen, licorice, red jujube, wheat, magnet (calcined), and mother-of-pearl. The nature and flavor of coptis rhizome is bitter and cold, which is used for irritability and insomnia caused by heat of heart. The nature and flavor of amber is even and sweet, and can clear and calm the mind. The nature and flavor of magnet is cold and pungent, and can oppress yang, contain qi, oppress horror, and calm the mind. The nature and flavor of mother-of-pearl is salty, sweet and cold, and can calm liver, oppress yang and calm the mind. Thin-leaf milkwort root and acorus can repel phlegm, fresh the mind, regulate heart and kidney, and nourish heart. Licorice and wheat can improve spleen and calm the mind. Danshen and red jujube can nourish blood and calm the mind. The combination of them can regulate the emotion and spirit, nourish yin and calm the mind.

2.2.10.2 Clinical Application

It is used for menopause syndrome and neurasthenia, etc.

2.2.10.3 Pharmacological Research

Insomnia is a common sickness caused by yin-deficiency with vigorous fire, and it can be treated with NC with good effect. Taking four pills of NC orally each time, three times per day, and continuously taking this medicine for 4 weeks can greatly relieve the symptoms caused by yin-deficiency with vigorous fire. Of 32 patients with the symptom of insomnia and treated with NC, 12.5 % slept normally, accompanied with the disappearance of other symptoms, without recurrence for more than 3 months; 43 % of them had better sleep (time to fall asleep <20 min, sleep time >5 h), and 40 % fell asleep in a shorter amount of time for a prolonged sleep time, with the disappearance of other problems. The depth of sleep increased and the mental state was good after waking up [101].

There were 40 cases which western medicine diagnosed with menopausal syndrome and TCM diagnosed with yin-deficiency and excess of heart fire. They were treated with NC for 30 days (three times per day, four pills each time). 15 % of them had improved menopausal syndrome symptoms. Another 15 % had significant improvement of symptoms, and 67 % of them had their symptoms eased. It was shown that this medicine had better effects on female menopausal syndrome (western medicine), yin-deficiency and excess of heart fire [102].

2.2.11 Ningshenbuxin Tablet

This medicine is used for treating the symptoms of dizziness, tinnitus, palpitation, forgetfulness, insomnia, etc. caused by Kidney yin-deficiency, and has the function of nourishing the blood, liver and kidney and calming the mind.

2.2.11.1 Explanation of the Formula

NT contains 10 main ingredients, including Danshen, schisandra, fresh rehmannia, prepared rehmannia root, prepared privet fruit, eclipta, mother-of-pearl, etc. Danshen can nourish and activate blood, free meridians, repel distress, and calm the mind. The nature and flavor of schisandra is acidic and warm, and can restrain,

nourish, and calm mind and body. Prepared privet fruit, prepared rehmannia root and eclipta can **nourish yin** and blood, and supplement and boost liver and kidney. The mixture of prepared privet fruit, schisandra, prepared rehmannia root and eclipta together can **nourish yin**. Cortex albizziae and mother-of-pearl can free qi, repel depression and calm the mind. Acorus is pungent, bitter, warm and aromatic, and can nourish the heart, liver, eyes, ears, and throat. The combination of these can nourish the liver and kidney, calm heart, and mind, and in traditional Chinese terminology is the balance and the mutual promotion of coordination between water and fire so as to calm the heart and mind.

2.2.11.2 Clinical Application

This medicine is suitable for symptoms such as insomnia, forgetfulness, heart palpitations, dizziness, tinnitus, etc., caused by liver and kidney yin-deficiency.

2.2.11.3 Pharmacological Research

Clinical research was performed on the influence of this medicine on insomnia; there were 300 cases diagnosed as insomnia or restlessness, with profuse dreaming and easiness to wake from sleep, tinnitus, dizziness, dry mouth and throat, palpitations, sweating, forgetfulness, weak waist (men), nocturnal emission (men), irregular menstruation (women), red and dry tongue (women), etc. The medicine was administered three times daily, six pills each time, and continued for 30 days. 35 % of patients improved their sleep duration to normal levels or to more than 6 h during the night, and 93 % had their symptoms relieved. The clinical effects were better than those of oryzanol pill and doxepin pill.

According to TCM theory, insomnia is caused by yin-deficiency in the kidney and liver; the yin and yang are in disorder, yin is in short supply, and yang is out of control. Yin-deficiency results in vigorous fire, which goes up and disturbs the mind. Because there is no interaction between the heart and the kidney, the mind is uneasy, resulting in insomnia. NT can nourish the yin of liver and kidney and calm the heart and mind, reaching a balance between water and fire and establishing the interaction between heart and kidney, returning sleep back to normal [103].

2.2.12 Yangxinshi Tablet

This medicine contains 13 ingredients, including astragalus root, codonopsis root, Danshen and pueraria root, etc. It is a Chinese medicine used to treat coronary heart disease. It can improve the blood and oxygen supply to ischemic myocardium, ease the symptoms of myocardial ischemia, and has two-way regulations on abnormal heart rate. According to TCM, this medicine can nourish qi, activate blood, free meridians, and stop pain.

2.2.12.1 Explanation of the Formula

There are 13 main ingredients; astragalus root, codonopsis root, Danshen, pueraria root, epimedium, Chinese hawthorn, rehmannia, angelica, coptis rhizome, corydalis rhizome, glossy ganoderma, ginseng, and licorice. The chief herbs in this formula are astragalus root and codonopsis root, which can powerfully supplement the original qi, and restore the pulse and stem desertion. The chief herbs are aided by the deputy herbs Danshen, radices rehmanniae and angelica, etc., which can activate blood circulation and nourish yin. Chinese hawthorn and Danshen can promote blood circulation and remove stasis. The nature and flavor of glossy ganoderma is even and bitter, not toxic, and it can nourish qi of the heart, activate blood, and promote meridians. Rhizoma corydalis belongs to the heart meridian, and can activate blood, free qi and stop pain. Modern pharmacological studies show that astragalus root can improve heart function and increase cardiac output effect. Danshen and angelica can resist platelet aggregation and improve peripheral microcirculation. Hawthorn can expand the blood vessels and reduce blood lipids. Glossy ganoderma can nourish the body and kidney and free urine. Used together they can activate the blood, stop pain, and nourish qi.

2.2.12.2 Clinical Application

This medicine is used for coronary heart disease, angina, cardiac arrhythmia and heart diseases associated with diabetes, and shows good effects on ischemic cerebro-vascular disease.

2.2.12.3 Pharmacological Research

Clinical Research

Treatment of Coronary Heart Disease and Angina

All patients were diagnosed according to the criteria established by the WHO for angina pectoris. The effective criteria are according to the Guidelines for Clinical Research of cardiovascular system Drugs, published by the Pharmaceutical Council of the Ministry of Health of the People's Republic of China (1993 version). The clinical effect criteria are, Significant effect: The occurrence of angina disappeared, or the incidence is 90 % less at the end of treatment than before. Effect rate: Significantly alleviated the symptoms of angina, or the incidence is 50–89 % less than before treatment. No effect: There was no alleviation of angina or the incidence, or it is 49 % less than before treatment. The effects of ECG, Effect: ST-T returns to normal or close to normal, stress ECG test changes from positive to negative. No effect: no improvement on ST-T, stress ECG still positive.

Yangxinshi Tablet (YT) was used to treat patients for 30 days (three pills per time, three times per day). The clinical results were that 15 cases showed a significant effect, 22 cases showed improvement, and 3 cases showed no effect. The total effective rate was 92.5 %. The ECG results were that a significant effect was found in 10 cases, improvement in 15 cases, and no effect in 15 cases, and the total effective rate was 62.5 %. The hemorrheological study showed that whole blood viscosities at high shear (HBV), low shear (LBV), packed cell volume (PCV), plasma viscosity, and platelet aggregation rate were all reduced. The indexes of nailfold microcirculation showed improvement after treatment [104].

Regarding improvement of the clinical symptoms of CHD and angina, the document showed that this medicine (1.8 g, three times daily, continued for 2 months) could relieve symptoms of chest tightness, heart palpitations, shortness of breath, paroxysmal retrosternal pain, arrhythmia, and reduce the indexes of serum TC and triglycerides, etc. [105].

Isosorbide dinitrate was combined with YT to treat angina for 2 months, and the blood, urine, blood lipids, liver function, kidney function, blood pressure, heart rate and ECG, and the incidence of angina were observed. The results showed that the effects of the combination were much better than when isosorbide dinitrate was used alone [106, 107].

YT and isosorbide dinitrate were used to treat patients for 3, 6, and 10 weeks. The results showed that the longer the treatment took, the better the results were. It showed that the combined use of the above two medicines could have a longer effect on stable angina [108].

YT was also used for diabetic CHD and angina. The results showed that YT could relieve the symptoms of diabetic CHD and angina, and was best for type I and II angina and had significant effects on the symptoms of CHD (headaches, heart palpitations, chest tightness, shortness of breath, and weakness, etc.), and the corresponding ST changed obviously. It could also obviously reduce blood sugar and lipids [109, 110].

YT could be used to treat ventricular premature beat associated with CHD, myocarditis and hypertensive heart diseases. YT was given 4 pills each time, three times per day, and for 30 days as one treatment cycle. The results showed that the average number of hourly premature beats in six of 30 patients was reduced by more than 90 % or totally disappeared after the treatment, and in 20 patients, the reduction was more than 60 % after the treatment [111].

Treatment of Cerebrovascular Diseases

Patients of cerebral infarction were treated 5 h to 16 days after the onset, and the conventional therapies were Danshen injection, Mannitol injection, ATP injection, CoA injection and cerebrolysin vials. Meanwhile, nimodipine and YT (5 pills each time, three times per day) were administered orally. The treatment cycle was 4 weeks. The results showed that the main

symptoms, body function, and the degree of disability were improved. The clinical effects were better than in the groups without YT [112].

YT has affirmative effects on cerebral arteriosclerosis and hypercalcinuria. It could treat dizziness, headache, fatigue, sleepiness, forgetfulness, and improve blood lipids, and blood rheology. Published results showed that it could significantly relieve the symptoms mentioned above, and the total effective rate was 87.80 % in a total of 82 patients after four treatment cycles. Side effects on liver and kidney function were observed by checking the blood and urine, with no abnormal changes found [113].

The patients were sent to the hospital within 48 h after the occurrence, and head CTs or MRIs were checked and the blood rheology and brain blood flow were measured before and after the treatment. 100 patients were randomly divided into two groups; the control group had 20 ml of Compound Danshen **injection** (added with 250 ml of NS, intravenous, once daily), the treatment group had Compound Danshen **injection** plus YT (5 pills each time, three times daily) added into their prescription, and both groups were treated for 2 weeks. The results showed that blood supply to the frontal lobe, parietal lobe, temporal lobe, occipital lobe, area centralis, brain stem, the focus areas and the surrounding area increased after treatment, and the indexes of the blood rheology (whole blood viscosity, plasma viscosity, hematocrit value, platelet adhesion rate, erythrocyte sedimentation rate and maximum platelet aggregation rate) improved. The blood flow in each cerebral area (excluding area centralis) and the indexes of the blood rheology of the treatment group of YT were better than the control group [114].

Experimental Research

The Effect of YT on Pharmacokinetic Parameters of Ciclosporin A

Cyclosporine A (CsA) is an immunosuppressive agent and at present is commonly used to prevent organ transplant rejection and in the treatment of immune diseases. CsA can interact with many drugs, and its bioavailability in different individuals is different. It also has liver and kidney toxicity. Long-term consumption of CsA may cause symptoms of arrhythmia and high blood pressure. Clinically, YT was usually used to offset the side effects caused by CsA. In the study of YT's effect on CsA, results showed that YT could cause an increase in CsA concentration in the blood and shorten the elimination phase half-life. The study was done as follows: Rabbits were without food and water for 12 h. The CsA group was given medicine at 30 mg/kg, blood samples (2.0 ml) were collected at intervals of 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 h, and CsA blood concentration was measured by RP-HPLC. After one week, YT (25 mg/kg) was delivered to the rabbits for 3 days, CsA (30 mg/kg) was given 0.5 h after the 4th day of administration, blood samples (2.0 ml), were collected at the same time points of the CsA group, and CsA was again measured by RP-HPLC. The pharmacokinetic parameters were calculated according to pharmacokinetic procedure. The results suggest that the blood concentration of CsA during the combined use of the two medicines should be monitored and the dosage adjusted to prevent the occurrence of side effects from CsA [115].

2.2.13 Rukuaixin Tablet

This medicine is a Chinese medicine which can treat hyperplasia of the breast. It is effective against unilateral or bilateral breast pain and against enlarged and hardens breast bumps. It can also relieve pain, soften the lumps of the breast and partly inhibit hyperplasia. The medicine can be used alone or combined with Western medicines. The main ingredients are tangerine leaf, Danshen, Chinese honeylocust spine, cowherb seed, Sichuan chinaberry, earthworm, etc.

2.2.13.1 Explanation of the Formula

The main ingredients are tangerine leaf, Danshen, Chinese honeylocust spine, cowherb seed, Sichuan chinaberry, earthworm, etc. Tangerine leaf belongs to the liver meridian, and it can free liver and qi, and reduce phlegm, bumps, and toxin. Danshen can activate blood circulation, remove stasis, cool blood, and repel carbuncles. The

nature of cowherb seed is even and the flavor is bitter, and it can free the blood and meridian, and reduce bumps and pain. The nature of earthworm is cold and the flavor is salty, and it belongs to the meridians of liver, spleen and lung. It can clear heat, reduce toxins, free meridians and stop spasms. The above four medicines work together to activate blood circulation, remove stasis, and free qi and meridians. Sichuan chinaberry belongs to the liver and stomach meridians, and can repel liver heat, free qi, reduce depression, and stop pain. The nature of Chinese honeylocust spine is warm and the flavor is pungent. It can reduce swelling, draw out pus, remove abscesses, and is suitable for mammary abscesses. The mixture of these herbs can free the liver and meridians, soften hard lumps, dispel nodes, activate blood circulation, and reduce stasis.

2.2.13.2 Clinical Application

It is used for the treatment of breast hyperplasia and related pain, hard lumps and nodes.

2.2.13.3 Pharmacological Research

In numerous clinical study reports, there have been 3 ways of using RT to treat breast hyperplasia: alone, combined with other TCM drugs, and combined with Western drugs.

There is a report showing the use of RT alone to treat 80 cases, with five pills each time, three times per day, for 2 months. The cure rate was 45.0 %, the significant efficacy rate was 41.2 %, and the efficacy rate was 10.0 % [116].

Another report showed that 60 patients of breast hyperplasia were treated with RT alone. After 1 month, the cure rate was 25 % and the significant efficacy rate was 36 %. After 2 months, the cure rate was 46 % and the significant efficacy rate was 25 %. After treatment for 3 months, the cure rate was 65 % and the significant efficacy rate was 25 % [117].

Some reports showed RT combined with antiphlogistic tablets (0.6 g/time) to treat 340 breast hyperplasia patients with 1 month to 3 years of disease history. The results: the cure rate was 32.0 % (128 cases), the significant efficacy rate was 45.0 % (180 cases) and the efficacy rate was 19.25 % (77 cases) [118].

In an integrated TCM and Western medicine treatment of 820 patients, tamoxifen (10 mg per time and twice per day) and RT (five pills each time and three times daily) were used, and the treatment time was 6–18 months (average of 8 months). The cure rate was 93.54 % (767 cases), partial cure rate was 6.46 % (53 cases) and the total efficacy rate was l00 %.

Tamoxifen is an estrogen receptor antagonist, competing with the hormone in the body for the receptor, thus inhibiting hormonal stimulation of the hyperplasia of the glandular tube and the surrounding tissues. Clinically, it can quickly relieve the pain and soften the lumps of the breast. However, once the medication is stopped, the recurrence of the disease is more likely. Also, tamoxifen's efficacy is not satisfactory in moderate to severe hyperplasia. Tamoxifen can also cause side effects such as menstrual disorders, even amenorrhea. Long term intake of RT has few side effects, except for occasional gastrointestinal tract discomfort, so it is better to take RT after meals. The combined use of the two medicines can reduce side effects and improve efficacy [119].

The above summarized the information about Danshen-containing Chinese patent medicines approved by the Chinese government, which have special production sites and are used clinically. Many of them have been studied extensively in recent years. There are more than a hundred formulas in *Chinese Pharmacopoeia* of which Danshen is the main ingredient or is one of many components. They are not included in this article.

Danshen is currently widely used, and its research is deepened. However, some problems need to be pointed out. First, the production processes and technique levels are uneven, which makes quality control of the product difficult. Second, the lack of supervision of the raw material sources and quality is serious. Third, the contraindications of clinical use of Danshen are not very clear, and the studies in this area need improvement. There are some adverse reactions in the clinical application of Danshen which should be taken seriously. So, further research is needed and the data should be reviewed and integrated so that the foundation of Danshen's clinical application is solid.

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