

Progress of Research on Clinical Application of Xuefu Zhuyu Decoction in Cardiovascular Diseases

Zhengfang Zhou^{1,a}, Panpan He^{1,b}, Peng Lei^{2,c,*}

¹Shaanxi University of Chinese Medicine, Xianyang, 712046, China

²Shaanxi Provincial People's Hospital, Xi'an, Shaanxi, 710068, China

^a1531652654@qq.com, ^b1594184383qq.com, ^cleipengml163.com

*Corresponding author

Keywords: Xuefu Zhuyu Decoction; cardiovascular disease; research progress

Abstract: Xuefu Zhuyu Decoction is a classic prescription, which is mainly used for the treatment of chest blood stasis. In recent years, with the in-depth study of this formula and related drugs, it is found that it is widely used in the prevention and treatment of cardiovascular diseases such as coronary heart disease, angina pectoris, arrhythmia, chronic heart failure and restenosis after interventional treatment. Through the literature search, this paper combs, analyzes and summarizes the three aspects of prescription, pharmacology and clinical treatment of the decoction, aiming to provide more thinking directions for its clinical application. Xuefu Zhuyu Decoction has a long history and precise therapeutic effect ^[1]. In the prescription, Peach kernel, Radix Paeoniae Rubra, safflower and hyssop can promote menstruation, relieve pain, activate Blood circulation and remove Blood stasis; Angelica sinensis and Rhizoma Ligustici Chuanxiong can promote Yang and disperse knots, activate Blood circulation and nourish Blood; Hovenia dulcis can relieve depression and dredge the Liver. Modern pharmacology has confirmed that Xuefu Zhuyu Decoction can promote neovascularization, reduce blood lipid levels, inhibit inflammatory reactions, inhibit vascular remodeling, anti-fibrosis, and has an important role in the repair of nerves and blood vessels, and anti-oxidative stress, etc. ^{[2][3]}, it is widely used in clinical practice, especially effective in the treatment of cardiovascular diseases. Cardiovascular diseases, also known as circulatory diseases, are a group of heart and blood vessel diseases, usually closely related to atherosclerosis. With the continuous improvement of people's economic living standard and the rapid change of life style, cardiovascular disease has become one of the most serious chronic non-communicable diseases threatening people's health, and it is also the leading factor leading to the death of the disease.

1. Analysis of the prescription of Xuefu Zhuyu Decoction

Shuowen Jiezi: "Blood stasis, also known as stagnant blood" The stagnation of blood stasis in the human body will not only impede normal blood circulation, but also adversely affect the blood circulation of the whole body or the local blood circulation, thus triggering bodily diseases, therefore, in clinical treatment, blood circulation should be activated and blood stasis should be

eliminated as the main therapeutic principle. There are three main features of Xuefu Zhuyu Decoction: First, the combination of blood activation and qi activation methods, which can not only activate blood stasis, but also relieve the stagnation of qi; second, dispelling blood stasis and nourishing blood are used together, so that blood can be activated without depleting blood, and qi activated without injuring yin; third, Up and fall, not only can rise to Qingyang, but also can lower down, thus qi and blood and adjustment.

Aiwu Yin and Saijin Huang^[4] isolated 11 compounds from the decoction of Xuefu Zhuyu Decoction, including pregnenolone, stearic acid, β -sitosterol, oleanolic acid, 4-hydroxy-3-butyl-phthalide, corkyphenol, β -ecdysone, etc. Currently, there are 11 compounds in Xuefu Zhuyu Decoction, which can be used to promote blood circulation, exhaust blood and injure yin. At present, there are fewer studies on the composition of the compound formula of Hematopoietic Stasis Relief Soup, and more studies on single drugs, in which the monarch drug peach kernel and safflower often appear as a pair of drugs to activate blood circulation and remove blood stasis; the results of Fang Joy, Yanbin Chen, etc.^[5] showed that peach kernel and safflower contain linoleic acid, catechin, safflower pigment, gluten sterol, and so on, 16 major compounds, which have the effect of anti-atherosclerosis (AS).

2. Progress in pharmacological action studies of Xuefu Zhuyu Decoction

2.1 Improvement of blood rheology

According to the theory of blood rheology, the onset of coronary heart disease is closely related to the elevation of blood viscosity, because high blood viscosity can increase the resistance of cardiac microcirculation, thus making the myocardium of the blood supply ischemia, hypoxia, and the blood rheology has a potential impact in the diagnosis and treatment of a variety of cardiovascular diseases^[6]. Tingting Zhu and Fajun Liang investigated the effects of Xuefu Zhuyu Decoction on blood rheology and related serological indexes in hyperlipidemic rats and found that this prescription could well regulate the lipid viscosity of rats, thus restoring blood rheology and helping to reduce the levels of LDL-C, APO-A, APO-B, and LP(a)^[7]. Another study showed that^[8], Xuefu Zhuyu capsule can significantly increase the amount of microcirculation perfusion in the tongue of patients with primary dysmenorrhea with qi stagnation and blood stasis syndrome, enriching the blood flow in the tongue, thus indirectly improving the blood rheology of the patients.

2.2 Improvement of microcirculation

Microcirculation is an important part of the cardiovascular system, and with the development of new technologies, information about changes in microcirculation in health and disease conditions is becoming more and more accurate. Medical literature shows that most people suffering from coronary heart have some degree of coronary microcirculation disorders due to the influence of one or more unfavorable factors, mainly poor vascular blood flow, blood blockage, and changes in blood flow patterns.

Studies in rats with microcirculation disordered pathology model showed that Xuefu Zhuyu Decoction can significantly dilate microvessels and accelerate blood flow in rats with microcirculation pathology disordered^[9]. Chun Jin^[8] used VAS score and average blood flow of tongue microcirculation as the main observational indexes to investigate the efficacy of Haifu yuyu capsule in improving the state of tongue microcirculation of PD patients with qi stagnation and blood stasis and the symptoms related to qi stagnation and blood stasis syndrome.

2.3 Protection of vascular endothelial cells

Vascular endothelial cells are monolayer mononuclear cells that can synthesize and secrete a variety of antithrombotic substances, and changes in their structure and function are the common pathological basis of many cardiovascular diseases. Studies have shown that endothelial structure and function are severely impaired in patients with hypertension and coronary artery disease^[10].

Experiments on the rabbit model of blood stasis syndrome showed^[11] that the ET and NO contents in the blood stasis syndrome + Chinese medicine group were significantly lower than those in the control group, indicating that the blood stasis in experimental rabbits can be improved by Xuefu Zhuyu Decoction, which improves the endothelial endocrine function of the vasculature and has a better antithrombotic effect.

2.4 Reducing inflammatory factors

More and more experimental evidence and epidemiological data show that inflammatory factors are one of the "killers" that significantly increase cardiovascular disease, and inflammatory markers may be a powerful predictor of the risk of coronary heart disease and provide a new method for the treatment of coronary heart disease.

Clinical treatment of post-PCI studies have shown^[12] that the control group (aspirin and clopidogrel) plays a positive role in improving the Chinese medicine syndrome, inhibiting platelet aggregation, and down-regulating CD62P, CD63, GPIIb/IIIa and inflammatory factors, promoting cardiac function recovery, compared with the observation group (Xuefu Zhuyu Decoction combined with conventional dual antiplatelet therapy). This is also an important mechanism to protect cardiomyocytes and prevent ISR and major cardiovascular adverse events. There is also a study on constructing a COPD mouse model (fumigation combined with LPS nasal drip) to observe the inflammatory factors and TLR4/MyD88/NF- κ B signaling pathway^[13], which showed that the level of inflammatory factors in the blank group of mice was reduced compared with that of the mice that had undergone the intervention of Xuefu Zhuyu Decoction. The levels of TLR4, MyD88, and NF- κ B in the lung tissues of mice were significantly decreased, which indicated that Xuefu Zhuyu Decoction was involved in the release of inflammatory factors in COPD.

3. Progress of clinical application research in cardiovascular diseases

3.1 Angina pectoris of coronary heart disease

More than 2,000 years ago, *the Spiritual Pivot* and *Su Wen* recorded that Promoting blood circulation and removing blood stasis is one of the main treatments for coronary heart disease^[14]. Zhiliang Chen^[15] selected 75 cases of coronary heart disease angina pectoris patients, clinical experiments will be set up in the control group of conventional Western medicine treatment, the research group on this basis, the application of Xuefu Zhuyu Decoction with additional subtraction. According to the patient's clinical symptoms of the addition and subtraction of the treatment, if the patient has a heartburn, According to the clinical symptoms of the patients, if the patients have heartburn and insomnia, add 10 g of sour jujube kernel and 10 g of cypress kernel; if there are palpitation symptoms, add 15 g each of oyster and dragon bone; the decoction should be taken in morning and evening and serve for 3 weeks continuously. The results show that the treatment of angina pectoris in coronary heart disease with the addition and subtraction of Xuefu Zhuyu Decoction has remarkable efficacy.

3.2 Arrhythmia

Cardiac arrhythmia is firstly listed in "*Nei Jing*", which can be categorized as "palpitation" in Chinese medicine, with the main symptoms conscious tachycardia with precordial discomfort. Clinically, the heart-blood stasis and obstruction type is the most common. Yuping Yin and Wenying Yin^[16] applied Xuefu Zhuyu Decoction to treat a patient with palpitations, who palpitations worsened in the last month and were accompanied by dizziness and fatigue. At the time of treatment, the heart rate was measured to be 48 beats/min. Administering Xuefu Zhuyu Decoction for Treatment. The decoction was warmly taken in the morning and evening, totaling 5 doses, after one month of treatment, the patient's heart rate was improved, and the electrocardiogram showed sinus rhythm, indicating that the efficacy of this prescription in the application of cardiac arrhythmia is considerable.

3.3 Chronic heart failure

Chronic heart failure is attributed to the category of "heart failure" in traditional Chinese medicine, The onset of heart failure is closely related to the metabolic abnormalities of qi.^[17] Huairong Chen^[18] selected 26 patients with chronic heart failure and randomly divided them into the control group (conventional Western medicine) and the study group (Xuefu Zhuyu Decoction with addition and subtraction of combined Western medicine). The decoction was added and subtracted according to the different clinical manifestations of the patients, and the water decoction was taken warmly in the morning and evening. The clinical study showed that after fifteen days of treatment, the quality of life of the patients was better than that of the patients treated with western medicine alone, indicating that the study group performed well in the treatment of chronic heart failure, and the effect was more effective compared with that of the control group.

3.4 Restenosis after intervention

Restenosis refers to the re-stenosis of local vascular lumen after intervention or bypass surgery. It belongs to the category of "blood stasis syndrome" in Chinese medicine. In recent years, Chinese medicine has been used in clinical trials to treat post-interventional restenosis by tonifying qi, resolving phlegm and expelling blood stasis to improve cardiac endothelial function and coronary blood supply, preventing thrombosis, and achieving remarkable results, proving the therapeutic advantages of traditional Chinese medicine^[19].

Yan Wang^[20] randomly divided patients after PCI treatment for coronary artery disease into 40 cases each in the treatment group and the control group. The control group was treated with conventional Western medicine, and the treatment group was treated on the basis of the control group by adding Xuefu Zhuyu Decoction, with additions and subtractions according to the specific conditions of the patients. The results showed that the therapeutic effect of the treatment group was better than that of the control group, and the incidence of restenosis was greatly reduced by adding Xuefu Zhuyu Decoction. There is also a clinical experiment showed^[21], PCI postoperative angina patients taking bloodfu yiuchu soup, angina and other symptoms significantly improved, blood lipid levels decreased, the application of this treatment provides more choices for patients, but also improve the patient's condition and improve the quality of life.

3.5 Others

Through the "active ingredient - key target - pathway", Hejiao Li and Naiyu Xue et al.^[22] demonstrated that Xuefu Zhuyu Decoction can reduce inflammation, lower oxidative stress and

promote neovascularization, which has a therapeutic effect on uterine fibroids; ZiBei Zhu and Lin Wang et al. [23] investigated the mechanism of the disease, indications for its application, and experimental studies, and concluded that Xuefu Zhuyu Decoction has a better therapeutic effect in perimenopausal constipation and geriatric constipation; moreover, it has been widely used in a wide range of conditions caused by stagnation of qi and blood stasis, and has been found to have a definite therapeutic effect on chest tightness type variant asthma (CTVA) [24].

4. Conclusion

In the basic theory of Chinese medicine, blood stasis is defined as one of the Chinese medicine symptoms of poor blood circulation, blood stasis symptoms may appear in many different diseases, and can occur to varying degrees between tissues of the body as well as between internal organs and organs. Usually, if the blood leaving the meridians cannot dissipate quickly or stagnate somewhere, or if the blood flows poorly, resulting in the accumulation of blood in the meridians or organs to form stagnation, this condition is known as Blood stasis. Clinically, it is often treated with medicines that activate blood circulation and eliminate blood stasis, so as to unclog the meridians and internal organs of the whole body and improve blood circulation. Xuefu Zhuyu Decoction can activate blood circulation, remove blood stasis and move qi to relieve pain. When applied clinically after diagnosis, the related symptoms can be improved and cured.

The diseases mentioned above are usually characterized by a long duration of illness, persistence and recurrence; most of the time, they are caused by poor blood circulation, which is considered as "Qi is the commander of blood" and "blood is the mother of Qi" in the basic theory of traditional Chinese medicine. "Qi can generate blood, and qi can move blood"; "qi can regulate blood, blood can be angry, and blood can carry qi". By applying the Xuefu Zhuyu Decoction with reasonable additions and subtractions, which can not only solve the problem of stagnation of blood, but also eliminate the stagnation of qi. In conclusion, as a classic formula, Xuefu Zhuyu Decoction has shown remarkable efficacy in the treatment of coronary angina pectoris, arrhythmia, chronic heart failure, restenosis after interventional therapy and other cardiovascular diseases, and its application is obviously superior to the treatment method of using only a single western medicine, so it is worthwhile to popularize and learn from the formula, and strive for a better service in the clinic for the benefit of the patients.

References

- [1] Qingren Wang. *Medical forest correction*[M]. Beijing: People's Health Publishing House, 1963:45.
- [2] Yanhong Kang, Jinxing Wang, Fang Fang et al. *Visualization and analysis of the research literature on Xuefu Zhuyu Decoction*[J]. *China Journal of Traditional Chinese Medicine Information*, 2023, 30(07):56-61. DOI:10.19879/j.cnki.1005-5304.202211681.
- [3] Jiao Wang. *Discussing the effects of Xuefu Zhuyu Decoction on blood lipids, serum inflammatory factors and endothelial function in patients with coronary heart disease*[J]. *Chinese Medicine Guide*, 2020, 18(19):160-161. DOI:10.15912/j.cnki.gocm.2020.19.075.
- [4] Aiwu Yin, Saijin Huang. *Study on the chemical constituents of Xuefu Zhuyu Decoction*[J]. *Chinese Materia Medica*, 2011, 34(10):1553-1555. DOI:10.13863/j.issn1001-4454.2011.10.035.
- [5] Huanle Fang, Yanbin Chen, Xin Zhang et al. *Study on the mechanism of action of peach kernel-safflower drug pair intervening in atherosclerosis based on network pharmacology-molecular docking-experimental validation*[J]. *New Chinese Medicines and Clinical Pharmacology*, 2023, 34(09):1245-1254. DOI:10.19378/j.issn.1003-9783.2023.09.010.
- [6] Beris AN, Horner JS, Jariwala S, Armstrong MJ, Wagner NJ. *Recent advances in blood rheology: a review*. *Soft Matter*. 2021; 17(47):10591-10613. Published 2021 Dec 8. doi:10.1039/d1sm0121
- [7] Tingting Zhu, Fajun Liang. *Effect of Xuefu Zhuyu Decoction on blood rheology and related serological indexes in hyperlipidemic rats*[J]. *Chinese Electronic Journal of Acupuncture and Moxibustion*, 2022, 11(01):4-7.
- [8] Chun Jin. *Discussing the clinical effects of Xuefu Zhuyu capsule on primary dysmenorrhea (Qi stagnation and blood stasis syndrome) based on tongue microcirculation perfusion*[D]. Liaoning University of Traditional Chinese

Medicine,2022.DOI:10.27213/d.cnki.glnzc.2022.000410.

- [9] Qiaoling Fan,Youshun Zheng,Jiang Liu et al.Experimental study on the effect of Hematocrit on microcirculation[J]. Chinese patent medicine,1988(07):29-30.
- [10] Qiu Yahui.Function of vascular endothelial cells and damage repair and atherosclerosis[J].Chinese Tissue Engineering Research and Clinical Rehabilitation,2007(10):1927-1929+1933.
- [11] Qi Wang,Yunbo Chen,Shilong Lai et al.Effects of Xuefu Zhuyu Decoction on the endocrine function of serum-impaired vascular endothelial cells in a rabbit model with blood stasis[J].Chinese Journal of Experimental Formulas,2002(02):12-14.DOI:10.13422/j.cnki.syfjx.2002.02.006.
- [12] You Zhai,LingHua Deng,Dan Gao et al. Effects of bloodfu yuyu tang combined with clopidogrel on CD62P, CD63, GPIIb/IIIa and inflammatory factors after PCI[J].Chinese herbal medicine,2021,44(02):470-475. DOI:10.13863/j.issn1001-4454.2021.02.041.
- [13] Shuangle Wang,Huan Liu,Haibin Ni.Effects of Xuefu Zhuyu Decoction on inflammatory factors and TLR4/MyD88/NF- κ B signaling pathway in COPD model mice[J].China TCM Emergencies, 2022, 31(05):769-772.
- [14] Xiaoyan Lu,Hongxin Cao.Discussion on the treatment of coronary heart disease from "phlegm and stasis related". Journal of Traditional Chinese Medicine,2010,51(2):101-103.
- [15] Zhiliang Chen.Clinical observation on the treatment of angina pectoris in coronary heart disease with Xuefu Zhuyu Decoction[J].China Traditional Chinese Medicine Modern Distance Education, 2023, 21(17):96-98.
- [16] Yuping Yin,Wenyin Yin.Three cases of Xuefu Zhuyu Decoction[J].Journal of Practical Chinese Medicine,2011, 25(11): 92-93.
- [17] Xinggui Cai,Hairong Cai,Huiling Cai,et al.Treatment of heart failure based on the theory of endogenous persistent evil[J].New Chinese Medicine,2022,54(1):235-239.
- [18] Huairong Chen.Experiences on the treatment of chronic heart failure with the adding flavored Xuefu Zhuyu Decoction[J].Electronic Journal of Integrative Cardiovascular Disease of Chinese and Western Medicine, 2017, 5(11): 82-83. DOI:10.16282/j.cnki.cn11-9336/r.2017.11.065.
- [19] Yumin Yang,Jia Zhou.Cheng Zhiqing's experience of preventing postoperative restenosis of coronary artery from stasis[J]. Journal of Traditional Chinese Medicine,2006(03):180-181.DOI:10.13288/j.11-2166/r.2006.03.017.
- [20] Yan Wang.Interventional effect of adding flavored Xuefu Zhuyu Decoction on restenosis after PCI for coronary artery disease[J].Chinese medicine introduction,2015,21(17):90-92.DOI:10.13862/j.cnki.cn43-1446/r.2015.17.037.
- [21] Yan Cui, Xiaopeng Wei,Huijuan Shi et al.Changes of cardiac function and blood lipid levels in patients with postoperative angina after PCI before and after treatment with Xuefu Zhuyu Decoction[J].Jilin Chinese Medicine, 2023, 43 (08):918-921.DOI:10.13463/j.cnki.jlzyy.2023.08.013.
- [22] Hejiao Li,Naiyu Xue,Yi Huang et al.Bioinformatics-based exploration of the mechanism of action of Xuefu Zhuyu Decoction in the treatment of uterine fibroids[J].Journal of Xuzhou Medical University,2023,43(08):565-570.
- [23] Zibei Zhu,Wang Lin,Shumei Ma et al.Discussion on the treatment of constipation with Xuefu Zhuyu Decoction[J].Bright Chinese Medicine,2023,38(10):1977-1980.
- [24] Xuefeng Gong, Hongsheng Cui, Qiuyi Chen et al. 2023. Exploration of the clinical use of Xuefu Zhuyu Decoction in the treatment of chest tightness variant asthma [J].Chinese basic medical science and medicine.