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Study on the application and mechanism of action of Ling Gui Zhu Gan Tang in heart failure

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Abstract: Ling Gui Zhu Gan Tang is a classic formula from Zhang Zhongjing's "Treatise on Miscellaneous Diseases of Typhoid", which has been highly respected by medical practitioners of all times, and is often used in the treatment of cardiovascular diseases in modern times, especially in the treatment of heart failure.The dection has a remarkable therapeutic effect. In recent years, with the in-depth research, some of the mechanisms of ling gui zhu gan tang have been proved, and the article provides an overview on the application of ling gui zhu gan tang and the mechanism of its effect. So that it can provide theoretical guidance and data support for the in-depth research of this formula. The application and mechanism of action of Ling Gui Zhu Gan Tang are reviewed in this article to provide theoretical guidance and data support for the in-depth study of this formula.

1. Introduction

With the rapid social and economic development, people's living standards are increasing and lifestyles are changing, the impact of cardiovascular diseases (cardiovasculardiseases, CVD) risk factors on the health of the population is becoming more and more significant, and the prevalence of CVD in China is still on a rising trend. According to *The China Cardiovascular Health and Disease Report 2023*, it is estimated that there are currently 330 million CVD cases worldwide, including 13 million cases of stroke, 11.4 million cases of coronary heart disease (CHD), 8.9 million cases of heart failure (HF), 5 million cases of pulmonary heart disease, 4.87 million cases of atrial fibrillation, 2.5 million cases of rheumatic heart disease, 2 million cases of congenital heart disease, and 45.3 million cases of peripheral arterial disease (PAD),and hypertension about 245 million[1] In recent years, the State has increasingly emphasized the role of traditional Chinese medicine (TCM) in disease management. In recent years, the state has been paying more and more attention to the role of traditional Chinese medicine in the prevention, diagnosis and treatment of diseases, on the basis of which this article will give a review of the classic formula "Ling Gui Zhu Gan Tang" in the prevention, diagnosis and treatment of heart failure.

2. Ling Gui Zhu Gan Tang Traceability

2.1 Ling Gui Zhu Gan Tang Source

Ling Gui Zhu Gan Tang is a classic prescription from Zhang Zhongjing's "Treatise on Typhoid Fever", which has achieved remarkable development in recent years in cardiovascular system diseases such as coronary heart disease, cardiac hypertrophy, and cardiac arrhythmia. The original text of the theory of typhoid fever recorded: "Typhoid fever, if vomiting, if the heart is full, qi on the chest, the head is dizzy, the pulse is tight, sweating is moving meridian, as a shaking person, Poria Guizhi Baizhu Licorice decoction master" the cause of the syndrome: Typhoid fever should not use the lower method, "after the lower" will be weak in the jiao transport, water wet stop, blocking the qi machine, causing water and qi to reverse, then the qi rushed chest, self-feeling chest tightness, shortness of breath, palpitation. When water-drinking obstructs the middle jiao, the clear yang cannot rise, and at the same time, the clear orifices are blocked, resulting in "the body is vibrating and shaking", and in "The Essentials of the Golden Chamber - Phlegm-drinking and Cough Disease Pulse Witnesses and Treatments XII". "There is phlegm-drinking under the heart, and there is fullness in the chest and hypochondrium, and dizziness, and the Ling-Gui-Ju-Gan Tang is the mainstay of this." Ling Gui Jiu Gan Tang is also recorded[2] In Ling Gui Jiu Gan Tang, there is also a record of Ling Gui Jiu Gan Tang. In Ling Gui Zhu Gan Tang, "fullness in the chest and hypochondrium, dizziness, and vibration of the body" are similar to the symptoms of chest tightness, shortness of breath, and limitation of activity in heart failure in modern medicine.

2.2 Drug composition and analysis of Linggui Zhugan Decoction

The drug composition of Linggui Zhugan decoction is Poria four two, laurel twig three two (peel), white art, licorice two two (moxibustion). The ratio is 4:3:2:2, the decoction takes the dampness and dampness of Poria light tonic as the king medicine, the warm Yang and Pingchong of cassia twig as the minister medicine, and the two medicines are combined to enhance the effect of warming Yang and rehydrating water, with Baizhu strengthening spleen and rehydrating water, regulating middle jiao, and moxibustion licorice supplementing middle Qi [3]. The combination of four medicines, a total of warming Yang Qi, spleen and water effect, simple and effective, for warming Yang and water "Linggui agent" representative of the prescription, the history of doctors have more notes on this prescription, for clinical commonly used prescriptions.

3. Recognition of heart failure in Chinese and Western medicine

3.1 Modern medical understanding of heart failure

(1) Overview: chronic heart failure is a class of diseases in which the function or structure of the heart is impaired, resulting in a decrease in ventricular filling or ejection function, and cardiac output is insufficient to meet the needs of the body.[4] . Heart failure is the end stage of all kinds of cardiovascular disease, the risk and death and disability rate is high, seriously affecting the quality of life and life expectancy of patients. Heart failure has become a public event that the world should face together, the prevention and treatment face no small challenge, there is no time to lose, but prevention should be greater than cure.(2) Diagnosis and staging: "China Heart Failure Diagnosis and Treatment Guidelines 2024[5] The classification and diagnosis of heart failure have been newly explained and updated. According to the different left ventricular ejection fraction (LVEF) of heart failure patients and the changes after treatment, the new guideline is classified into heart failure with reduced LVEF (HFrEF), heart failure with improved LVEF (HFimpEF), heart failure with

mildly reduced LVEF (HFmrEF), and heart failure with preserved LVEF (HFpEF), and newly added HFimpEF, and the 4 stages were also renamed as stages A, B, C, and D, for heart failure risk, preheart failure, symptomatic heart failure, and end-stage heart failure, respectively. (3) Treatment: The first diagnosis of heart failure is very important. The new guidelines [6] point out that the diagnosis of heart failure should first be based on medical history, physical examination, electrocardiogram, and chest imaging, and then the diagnosis of heart failure and LVEF classification should be confirmed by further plasma natriuretic peptide detection and echocardiography. Treatment mainly focuses on improving patients' clinical symptoms and quality of life, preventing or reversing myocardial remodeling, and reducing the risk of death. At this stage, clinical drugs are broadly divided into the following categories: ① diuretics, such as loop diuretics, thiazide diuretics, potassium-preserving diuretics and so on. ② Renin angiotensin system inhibitors (reninangiotensinsysteminhibitor, RASI), such as ARNI, ACEI, ARB class. ③ β-blockers ④ MRA class ⑤ SGLT2i class ⑥ soluble guanylate cyclase (solubleguanylatecyclase, sGC) stimulators ⑦ ivabradine.

3.2 Chinese medicine on the understanding of heart failure

(1) the name of the disease location: "Yellow Emperor's Classic of Internal Medicine" recorded "the heart distension, disturbed shortness of breath, restlessness", "the beginning of the water also, slightly swollen on the case of the eye, such as the new lying up the shape of the neck pulsation, when coughing, the yin and femur between the cold, shins swollen abdomen is large, the water has been carried out. It is recorded in the book that press their hands on the abdomen, with the hands and up, such as wrapped in the shape of water, this is also the wait", "Golden Chamber Essentials" for the first time in the concept of "heart water", "heart water, its body heavy and less gas, not to lie down, annoyance and agitation, the person's yin swollen".[7] In the Tang Dynasty, Sun Simiao wrote in his book, "Preparing an Emergency Thousand Golden Essentials Formula", "Heart failure is ambulatory." For the first time, the name of heart failure. Ancient records of "heart water", "heart failure" symptoms are mostly similar to the symptoms of heart failure. The location of the disease is mostly in the heart, often involving the lungs, spleen, liver and kidneys. (2) Etiology and pathogenesis: heart failure is mostly caused by the influence of external evils, internal injuries due to labor and fatigue, dietary disorders, injuries due to seven emotions, and disorders of internal organs, etc. The symptoms of heart failure are mostly similar to heart failure.[8] The disease is caused by a number of factors. Clinically, the pathogenesis of heart failure is intricate and complex, and overall the common pathogenesis is the underlying deficiency, which is dominated by cardiac qi deficiency and cardiac yang deficiency, and the underlying reality is phlegm, blood stasis, and water and drink as the pathological products throughout the process of disease development.[8] In the initial stage of the disease, the heart qi deficiency is unable to promote the operation of blood vessels, the heart yang deficiency warms and warms the function of water and liquid inappropriately, resulting in water and liquid metabolism malfunction, the disease is long phlegm, stasis blood, water and other pathological products stagnation of the heart veins, and with the development of the disease, the two are interacting with each other, each other intertwined. Eventually, heart failure is formed, and dyspnea, lower limb edema, and dizziness are common clinical symptoms.

4. Modern Pharmacological Studies on Ling Gui Zhu Gan Tang

4.1 Modern pharmacological study of Ling Gui Zhu Gan Tang

Ling Gui Zhu Gan Tang in the "Treatise on Typhoid Fever" in the ratio of 4:3:2:2, the formula is

rigorous, properly matched, modern pharmacological study of Poria cocos in the main chemical constituents for the diterpenoids, triterpenoids, sterols, polysaccharides, as well as other classes of compounds, with diuretic, anti-inflammatory, anti-tumor, anti-aging, and other roles.[9] It has diuretic, anti-inflammatory, anti-tumor, anti-aging and other effects. Gui Zhi contains volatile components, organic acids, glycosides and other chemical components, which have the functions of regulating body temperature, anti-inflammatory, analgesic, anti-tumor, vasodilator and so on [10].In "On Febrile Diseases", Poria and cassia twig are often used, and the effect of warming Yang and detumification is more obvious than that of single medicine, so "Linggui prescription" is often used in clinical treatment of edema diseases, such as: Linggui Zaogan decoction, Linggui Jianggan decoction and other prescriptions. Atractylodes macrocephala contains terpenoids, steroids, alkaloids and other chemical components, which can be anti-inflammatory, anti-tumor, regulate gastrointestinal motility, improve the intestinal microbiota and so on.[11] . Roasted licorice contains polysaccharides, triterpenoid saponins, flavonoids and other chemical components which have pharmacological effects such as anti-inflammatory, anti-tumor, anti-depressant, anti-arrhythmic, etc.[12] The

4.2 Modern application of Ling Gui Zhu Gan Tang

Ling Gui Zhu Gan Tang has been widely used for a variety of systemic diseases such as cardiovascular system, respiratory system, and nervous system. Modern research has proved that it may be related to mechanisms such as anti-inflammatory response, antioxidant, and regulation of lipid metabolism[13] .

Zhang Sheng'an.[14] A systematic evaluation and Meta-analysis of Ling Gui Zhu Gan Tang. Forty-seven studies were included, with a total of 3,933 cases of each disease type. The disease types mainly included chronic heart failure, arrhythmia, type 2 diabetes mellitus, non-alcoholic fatty liver disease, and many other diseases.Meta-analysis showed that linggui jujugan tang had the ability to improve the left ventricular ejection fraction of chronic heart failure (MD = 3.63,95% CI [1.72,5.54],P = 0.0002), brain natriuretic peptide (MD = - 104.35,95% CI [-145.02,-63.67],P < 0.0001), amino-terminal cerebral natriuretic peptide precursor (MD = -140.60,95% CI [-213.40, -67.79],P = 0.0002) levels; reduced the number of premature atrial beats (MD = -288.36,95% CI [-323.21, -253.52],P < 0.0001) and premature ventricular beats within 24h The number of premature ventricular beats (MD = -262.53,95%CI [-301.23,-223.82],P<0.0001) proved clinically significant in improving patients' heart failure.

Zhao Lilong[15] Seventy-two patients with coronary heart disease were randomly divided into two groups of 36 cases each. The control group was given conventional treatment, and the study group was given Ling Gui Jiu Gan Tang treatment. Serum inflammatory factor levels (IL-6, IL-1β, TNF-α), lipids [serum triacylglycerol (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)], and oxidative stress levels [superoxide dismutase (SOD), and malondialdehyde (MDA)] before and after the treatment were compared between the two groups. It was found that serum HDL-C level was higher and TC, TG, LDL-C levels were lower in the study group than in the control group after treatment (P < 0.05). Serum IL-6, IL-1β, and TNF-α levels were lower in the study group than in the control group after treatment (P < 0.05). The serum MDA level of the study group was lower than that of the control group after treatment, and the serum SOD level was higher than that of the control group, and the difference was statistically significant (P < 0.05). It indicated that linggui jujugan tang had obvious anti-inflammatory response, antioxidant, and regulation of lipid metabolism.

Hu Shuangxuan[15] 80 cases of elderly chronic heart failure patients were divided into control group and observation group, 40 cases in each group. The patients in the control group were treated

with western medicines on conventional treatment, and the observation group was given Ling Gui Zhu Gan Tang.By contrast the two groups of elderly chronic heart failure patients clinical treatment effect, cardiac function indexes, the incidence of adverse reactions. The results found that the total effective rate of elderly chronic heart failure patients in the observation group was 95.00%, which was higher than the total effective rate of 80.00% of the patients in the control group.

5. Study on the mechanism of action of Ling Gui Zhu Gan Tang in the treatment of heart failure

5.1 Mechanism of action of Linggui Jinggan Tang on rat model of heart failure

Xueping Li[16] Forty SD rats were divided into blank group, model group, linggui jujugantang group and digoxin group by intraperitoneal injection of azithromycin to replicate the rat chronic heart failure model, and gavage was performed for 4 weeks. The results showed that the end-systolic internal diameter (LVESD) value of the linggui jujugantang group was significantly lower than the model group ($P<0.05$), and the values of the left ventricular ejection fraction (LVEF) and left ventricular end-diastolic internal diameter (LVEDD) were higher than the model group ($P<0.05$); the values of linggui jujugantang group and left ventricular end-diastolic internal diameter were higher than the model group ($P<0.05$). values were higher than those in the model group ($P<0.05$); serum angiotensin II (AngII), endothelin-1 (ET-1) and brain natriuretic peptide (BNP) levels in the linggui juguan tang group and digoxin group were significantly decreased compared with those in the model group ($P<0.05$), which indicated that linggui juguan tang had the effect of improving ventricular remodeling in rats with chronic heart failure, inhibiting the overexpression of endocrine factors, improving It can inhibit the over-expression of endocrine factors, improve the damage of cardiomyocytes, improve the cardiac function of rats with heart failure and delay the process of heart failure.

Wang Xiang et al.[17] The experimental method of coronary ligation was used to prepare a rat model of post-infarction heart failure, which was divided into the model group, linggui juguangan soup group, captopril group, and the sham operation group. It was found that linggui juguangan soup could significantly improve the cardiac function of rats with post-infarction heart failure, reduce the levels of BNP, NT-ProBNP, and ROS, up-regulate the expression of Nrf2 and nuclear translocation, reduce the expression of BNIP3, improve SOD content, and improve the structural damage of mitochondria. The mitochondrial structural damage indicated that the efficacy of Ling Gui Zhu Gan Tang was related to Nrf2/BNIP3, and it could protect mitochondria, reduce oxidative stress damage, decrease cardiomyocyte apoptosis, effectively prevent ventricular remodeling after heart failure, and inhibit the further development of heart failure.

Yao Juan[17] et al. divided SD rats into sham-operated group, atopril group, and linggui jujugangan soup group, and found that left ventricular end-diastolic internal diameter (LVIDd) and left ventricular end-systolic internal diameters (LVIDs) were significantly reduced in the linggui jujugangan soup group versus the captopril group, the left ventricular ejection fraction (LVEF) and the left ventricular shortening short-axis shortening (LVFS) rate were significantly elevated, and the myocardial tissue inflammatory cell infiltration and pathological damage were significantly reduced. ROS, MDA level and cardiomyocyte apoptosis rate were significantly reduced, SOD, ATP content and membrane potential were significantly elevated, p-Drp1, Fis1 and MFF protein expression was significantly down-regulated, and Sirt3, p-AMPK and OPA1 protein expression was significantly up-regulated, indicating that linggui juju gan Tang could alleviate cardiomyocyte oxidative stress and apoptosis, and the effect might be related to mitochondrial split-fusion, Sirt3/AMPK signaling pathway.

6. Summary

Ling Gui Zhu Gan Tang is a representative formula for the treatment of heart failure by doctors of all times, which is simple, economical and effective, and has a remarkable effect in the clinical treatment of heart failure with western drugs, and modern pharmacological studies have also proved that this formula has anti-inflammatory, anti-oxidative stress, and apoptosis-delaying mechanisms, which has a very good prospect for application. However, some mechanisms of action of Ling Gui Zhu Gan Tang are still unknown, and there are some limitations in the current study, and the unclear relationship of drug pairing in the clinic may affect the therapeutic efficacy. In the future, we should carry out more in-depth clinical and basic research, and follow the original dosage of "Typhoid Fever Treatise", so that we can provide the theoretical and data support for further in-depth maneuvers.

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References

[1] Liu Mingbo, He Xinye, Yang Xiaohong, et al. Interpretation of key points in the China Cardiovascular Health and Disease Report 2023[J]. Chinese Family Medicine:1-19.

[2] Zhou Yuan, Li Qizhu, Xu Jingyu. Research progress of Ling Gui Zhu Gan Tang in the treatment of heart failure [J]. Shaanxi Traditional Chinese Medicine, 2022,43(12):1819-1821.

[3] Jiang Deyou, Zhang Wanqiu, Han Jieru. Research progress of Ling Gui Zhu Gan Tang[J]. Journal of Chinese Medicine, 2021,36(12):2562-2567.DOI:10.16368/j.issn.1674-8999.2021.12.531.

[4] Ge Junbo, Lin Guowei, Wang Jiyao. Practical internal medicine [M]. Beijing: People's Health Press, 2018: 818.

[5] Xu Dingli, Song Lin. Interpretation of the Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2024[J]. Journal of Clinical Cardiovascular Disease, 2024,40(06):437-439.DOI:10.13201/j. issn.1001-1439. 2024.06. 002.

[6] Chinese Journal of Cardiovascular Disease Editorial Board Chinese Medical Association Division of Cardiovascular Diseases Chinese Physicians Association of Cardiovascular Physicians Branch Chinese Physicians Association of Heart Failure Specialty Committee. Chinese guidelines for the diagnosis and treatment of heart failure 2024[J]. Chinese Journal of Cardiovascular Disease, 2024.

[7] Lan Yu, Luo Fukun, Yu Yue, et al. Traditional Chinese medicine understanding of heart failure and treatment strategy of meridian prescription[J]. Chinese Journal of Traditional Chinese Medicine:1-14.DOI:10.19540/j. cnki. cjcmm. 20240814.501.

[8] Chen Hao, Xu Fafei, Han Jingbo. Research progress of Chinese medicine in the treatment of chronic heart failure [J]. Research on Traditional Chinese Medicine, 2022,35(06):88-92.

[9] Ye Qing, Liu Dongsheng, Wang Lanxia, et al. Progress of research on chemical composition, pharmacological effect and quality control of Poria[J]. Chinese Medicine Information, 2023,40(02):75-79.DOI:10.19656/j. cnki. 1002-2406. 20230214.

[10] Li Xue, Zhao Jinghan, Wu Wenxuan, et al. Progress in the study of chemical composition and pharmacological effects of Gui Zhi[J]. Journal of Traditional Chinese Medicine, 2023,51(05):111-114.DOI:10.19664/j.cnki. 1002-2392. 230114.

[11] LI Jing, HE Mou, LI Ling, et al. Progress on the chemical composition and pharmacological effects of the volatile

oil of Atractylodes macrocephala[J]. Chinese patent medicine, 2024,46(03):881-889.
[12] XIE Ruiqiang, WANG Changfu. Progress in the study of chemical composition and pharmacological effects of Radix et Rhizoma Glycyrrhizae[J]. Chinese Medicine Information, 2023,40(04):84-89.DOI:10.19656/j.cnki. 1002-2406. 20230414.
[13] Cheng Qian, Zhou Qingwei, Xue Jiaxi, et al. Research progress on modern clinical application and mechanism of Linggui Zhugan Decoction [J/OL]. Journal of Liaoning University of Traditional Chinese Medicine, 1-8 [2024-11-07]. http://kns.cnki.net/kcms/detail/21.1543.R.20241015.0952.008.html
[14] Zhang Sheng'an, Liu Zhidong, Dai Liang, et al. Clinical application of Ling Gui Zhu Gan Tang: 1 systematic evaluation and Meta-analysis[J]. Chinese Herbal Medicine, 2023,54(14):4599-4614.
[15] Zhao LL. Effects of linggui juguangan soup on serum inflammatory factors, lipids and oxidation levels in patients with coronary heart disease[J]. Chinese Community Physician, 2020,36(16):83-84.
[16] HU Shuangxuan, LI Xiangzhong. Clinical efficacy and effect on LVEF of Ling Gui Zhu Gan Tang plus reduction in the treatment of chronic heart failure in the elderly[J]. Heilongjiang Traditional Chinese Medicine, 2020, 49(05): 10-11.
[17] Wang Xiang, Mo Jiajia, Tang Tongjuan, et al. Exploration of the effects and mechanisms of linggui juguangan tang in improving myocardial infarction-induced heart failure in rats based on Nrf2/BNIP3 pathway[J]. Chinese Journal of Pharmacology, 2023,39(12):2390-2397.