

Progress in the application and mechanism of Baoyuan Tang in the treatment of chronic heart failure

Gao Rong^{1,a}, Zhi Liqin^{2,b,*}

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

²*Affiliated Hospital of Integrated Traditional and Western Medicine of Shaanxi University of Chinese Medicine, Xi'an, 710000, China (Xi'an No. 5 Hospital, Xi'an, 710000, China)*

^a877731677@qq.com, ^b377985560@qq.com

**Corresponding author*

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Abstract: Chronic heart failure (CHF) is the end-stage manifestation of cardiovascular disease and the most important cause of death. As a classic formula for heart failure with qi deficiency and blood stasis, Baoyuan Tang, with its unique efficacy of benefiting qi and warming yang, has been widely used in clinical practice with remarkable effects, and has gradually become a hot spot in the research of multi-pathway and multi-targeted treatment of CHF. By reviewing the published literature, this paper found that the addition of Baoyuan Tang and its additive and subtractive formulas to the conventional Western medicine treatment of chronic heart failure was superior to the conventional Western medicine treatment alone in terms of improving the clinical efficacy, increasing the left ventricular ejection fraction, lowering the level of NT-proBNP, alleviating the clinical symptoms, and improving the quality of life, and it also possessed a higher degree of safety. Animal experiments further revealed the mechanism of action of Baoyuan Tang in the treatment of CHF, including the regulation of oxidative stress, the regulation of inflammatory response, the regulation of mitochondrial function and energy metabolism, the improvement of characteristic electrical abnormalities of heart failure cells, and the inhibition of ventricular remodeling. The aim of this paper is to comprehensively summarize and conclude the clinical efficacy and molecular biological mechanisms of Baoyuan Tang and its additive and subtractive formulas in the treatment of CHF, so as to provide reference and reference for subsequent in-depth studies, and to promote the wider application of Chinese medicine in the field of cardiovascular diseases.

Chronic heart failure (CHF) is a complex clinical syndrome characterized by fluid retention, fatigue, and dyspnea, caused by a variety of etiologic factors that alter cardiac function and structure [1]. Over the past 30 years, there has been great progress in the treatment of heart failure, and the treatment strategy for heart failure has evolved from the initial "cardiotonic, diuretic, and vasodilator" to the neurohormonal inhibition therapy based on β -blockers and ACEIs, to the standard "Golden Triangle" treatment program with the addition of aldosterone receptor antagonists, to the "Golden Triangle" treatment program with the addition of aldosterone receptors, to the standard "Golden Triangle" treatment program with the addition of aldosterone receptor antagonists [2]. Although the

latest protocol opens a new pattern for the treatment of chronic heart failure patients, and reduces the morbidity and mortality of heart failure to a certain extent, there are still problems such as poor prognosis and repeated hospitalization of patients. From the aspect of systemic prevention and treatment, Chinese medicine is crucial in the treatment of CHF. There is no "heart failure" in the ancient medical literature of China, but according to its symptoms and signs, it can be roughly summarized as "palpitation", "strangulation", "asthma", "phlegm", "phlegm", "phlegm", "phlegm", "phlegm", "phlegm", "phlegm", "phlegm" and "phlegm"., "phlegm drink", "accumulation", "heart water" and other categories of disease. The main symptoms of heart failure include palpitations, shortness of breath, swelling of the limbs, mostly secondary to palpitations, cardiac paralysis and other conditions, is the end stage of various heart diseases or other visceral diseases. Traditional Chinese medicine has its unique advantages in treating heart failure, and many experienced doctors have summarized a number of prescriptions based on the guiding principle of "benefiting qi and warming yang, activating blood circulation and inducing diuresis". Baoyuan Tang, also known as "Baoyuan Dan", "Baoshen Tang" and "Ginseng Qi Tang", as a classic formula for treating heart and lung qi deficiency, its effect focuses on benefiting qi and warming yang. The formula was first introduced by Wei Zhi in Bo Ai Xin Jian in the Ming Dynasty, and consists of Astragalus, Ginseng, Cinnamon, Radix et Rhizoma Glycyrrhizae, and Ginger. Astragalus and ginseng benefit qi and strengthen the spleen; cinnamon, roasted licorice and ginger help yang and benefit qi. The combination of all the medicines together, play the effect of tonifying qi and warming yang. Clinical studies have shown that Baoyuan Tang and its additions and subtractions can effectively improve clinical symptoms and have a high degree of safety. The authors summarize the clinical efficacy and mechanism of action of Baoyuan Tang and its additions and subtractions in the treatment of chronic heart failure to provide reference for subsequent studies.

1. Mechanism of action of Bao Yuan Tang in the treatment of heart failure

1.1. Inhibition of apoptosis

Apoptosis plays an important role in structural abnormalities and cardiac dysfunction, not only participating in the process of left ventricular remodeling, but also contributing to the onset and development of chronic heart failure. Persistently low levels of apoptosis induce lesions and damage in a variety of myocardial tissues, which can lead to the development of CHF [3]. Studies have shown that the endoplasmic reticulum stress apoptosis pathway is an important pathogenetic mechanism in chronic heart failure. Animal experiments by Yuan Xianying et al [4] showed that the intervention of Paoyuan Tang in the middle and high dose groups significantly down-regulated PERK, eIF2 α , GRP78, CHOP protein levels and mRNA expression. The results suggested that Paoyuan Tang slowed down cardiomyocyte apoptosis by inhibiting the PERK/eIF2 α /CHOP apoptotic pathway and then slowed down cardiomyocyte apoptosis. Gu Xuemei et al [5] found that there are 93 active ingredients in Baoyuan Tang through research and analysis, which contains an active chemical component, kaempferol, which can regulate the MAPK pathway to reduce apoptosis and inflammation to prevent myocardial injury. Wu Shandan et al [6] found that isorhamnetin, another active ingredient in Paoyuan Tang, not only reduces the degree of cardiomyocyte apoptosis by affecting the PI3K-AKT signaling pathway, but also improves the local and overall cardiac function, thus protecting cardiomyocytes.

1.2. Regulation of oxidative stress

Oxidative stress is a negative effect produced in the body by free radicals that interfere with cellular metabolism, modulating and destroying cellular components. General pathogens will

stimulate the host cells to release a variety of pro-inflammatory cytokines, further inducing the defense cells, through the production of a large number of reactive oxygen species to resist cellular invasion, when the production of reactive oxygen species in excess will induce oxidative stress in tissues, so oxidative stress and inflammatory response can be interacted with each other, is an important mechanism for the development of chronic heart failure. Astragaloside, the active ingredient of Astragalus in Baoyuan Tang, inhibits the activation and diffusion of oxidative stress and slows down cardiomyocyte injury by activating the PI3K/Akt signaling pathway, up-regulating the expression levels of SOD2 and HO-1 proteins, and down-regulating the level of MDA, thus exerting a cardioprotective effect [7]. At the same time, Yan Hao et al [8] found that another active ingredient of Astragalus isoflavin reduces adriamycin-induced cardiotoxicity by regulating the PI3K/Akt signaling pathway and Bcl-2, Bax, and increasing H9c2 cell activity, and inhibits oxidative stress and apoptosis to prevent and control CHF. The PI3K/Akt signaling pathway is an important one for myocardial protection. Diao Yuanyuan et al [9] concluded that quercetin, the active ingredient in astragalus and licorice, which plays a major role in the treatment of CHF by Baoyuan Tang, has antioxidant, anti-inflammatory, and vasodilatory effects. It was found that quercetin finally attenuates oxidative stress-induced myocardial injury and apoptosis by increasing the protein expression of Nrf2 and HO-1 and activating the Nrf2/HO-1 signaling pathway [10].

1.3. Regulation of inflammatory response

Inflammatory factors play an important role in the development of CHF. the NF- κ B information pathway, as a classical inflammatory signaling pathway, is closely linked to myocardial injury. il-17A not only promotes the development of inflammation, but also promotes the production of collagen and matrix metalloproteinases, and accelerates myocardial fibrosis [11]. Baoyuan Tang can inhibit the expression of pro-inflammatory factors and reduce myocardial damage, thus improving cardiac function. It was found that ginseng, the active ingredient in Paoyuan Tang, may inhibit inflammatory response and apoptosis by regulating signaling pathways such as TNF, adipocytokines, NF- κ B, and apoptosis through multi-targeted and multi-pathway effects, thus playing a role in the treatment of heart failure [12]. Meng Hui et al [13] suggested that Baoyuan Tang could effectively reduce the degree of fibrosis in the ischemic region of model rats, and then slow down the process of heart failure, verified the mechanism of Baoyuan Tang's anti-inflammatory and anti-ventricular remodeling, and evaluated its clinical efficacy in the treatment of CHF with qi deficiency and blood stasis. Zhou Aimin et al [14] demonstrated that Baoyuan Tang and Blood Fu and Blood Stasis Tang slowed down the development of CHF by decreasing plasma NT-proBNP and inflammatory factor levels, thereby reducing the release of inflammatory factors, protecting endothelial cells.

1.4. Regulation of mitochondrial function and energy metabolism

Abnormal myocardial mitochondrial energy metabolism plays an important role in the development of CHF. In the early stage of CHF, cardiomyocytes prioritize glucose for energy metabolism in order to meet the energy required for normal cardiac function. In the late stage of CHF, cardiomyocytes are severely ischemic and hypoxic, resulting in a loss of energy metabolism and a reduction in glucose uptake, which in turn diminishes the ability of mitochondrial oxidative phosphorylation. Studies have shown that qi-benefiting herbs can regulate energy metabolizing enzymes, such as Astragalus in Baoyuan Tang, which protects the mitochondrial ultrastructure of cardiomyocytes and plays a role in up-regulating the activity of ATP-generating bioenzymes; and ginseng, which can ameliorate the impaired energy metabolism of mitochondrial energy metabolism of cardiomyocytes in CHF by elevating the activity of myocardial succinate dehydrogenase [15]. Luo Yuanlin et al [16] showed that Baoyuan Tang further improved myocardial mitochondrial energy

metabolism by inhibiting p38MAPK activity in myocardial tissues while promoting PPAR- γ protein expression level, thus alleviating CHF lesions.

1.5. Improvement of Characteristic Electrical Abnormalities in Heart Failure Cells

Intracellular Ca²⁺ overload and Ca²⁺ homeostatic imbalance in cardiomyocytes are the initiating factors in chronic heart failure. Second, calcium regulation stems mainly from L-type calcium channel-mediated Ca²⁺ inward flow and sarcoplasmic reticulum-mediated Ca²⁺ release. Ca²⁺ inward flow and release in cardiomyocytes is a key link in chronic heart failure, and it is directly related to the occurrence of arrhythmias, myocardial hypertrophy, and cellular activation in the course of CHF. Ginseng saponin, astragalus saponin, and licorice glycosides can regulate intracellular Ca²⁺ concentration and improve CHF from different perspectives. Meanwhile, calcium-sensing receptor (CaSR) plays an important role in CHF. Studies have confirmed that ginseng saponin can play a protective role against ISO-induced myocardial injury cells by inhibiting the expression of intracellular CaSR and reducing Ca²⁺ concentration [17]. Another study showed that glycyrrhizin can reduce calcium homeostasis and calcium cycling by blocking aconitine, which is detrimental to cardiomyocytes, in order to enhance calcium adaptation and ultimately maintain diastolic as well as contractile effects of the myocardium [18]. Wang Bingbing et al [19] concluded that ginsenoside Rb1 could inhibit the activity of calmodulin kinase II (CaMK II) in cardiomyocytes and significantly reduce the Dox-induced NT-proBNP level in cardiomyocytes, thus improving the cardiac function of damaged cardiomyocytes.

1.6. Inhibition of ventricular remodeling

The structure and function of the heart are affected by continuous stress and pathological stimulation of cardiomyocytes, leading to high morbidity and mortality in CHF. In this process, ventricular remodeling can be regulated through the activation of multiple signaling pathways and cytokines. TGF- β is able to promote myocardial fibrosis and is a promoter of ventricular remodeling. After treatment with Baoyuan Tang, TGF- β , galactoglucan lectin-3, and MMP-9 levels can be reduced in cardiomyocytes, thereby inhibiting ventricular remodeling and improving cardiac function [20]. Another study showed that Baoyuan Tang down-regulated the expression of AT1, ACE1, p-P38 MAPK, TGF- β , and Smad3 pathways by inhibiting collagen production in myocardial tissues of rats with CHF, thus reducing the degree of myocardial fibrosis and improving ventricular remodeling [13]. In addition, Astragalus in Baoyuan Tang has the effect of inhibiting ventricular remodeling, reducing myocardial fibrosis, protecting vascular endothelial cells, and promoting angiogenesis [21]. Periostin protein, as an intercellular matrix protein, ventricular remodeling is closely related to the high and low content of it. And ginsenoside Rb1 inhibits ventricular remodeling in CHF rats by inhibiting the TGF- β pathway, which in turn attenuates the expression of Periostin protein level, and ultimately slows down the development of CHF [22].

2. Clinical application of Baoyuan Tang in the treatment of chronic heart failure

Baoyuan Tang and its additive and subtractive formula for the treatment of chronic heart failure are widely used in clinical practice, and its efficacy is obvious and has high safety advantages. Ma Xuezhu et al.[23] analyzed and evaluated the efficacy and safety of Paoyuan Tang plus and minus formula for the treatment of CHF, and the results showed that the addition of Paoyuan Tang and its plus and minus formula to the conventional treatment could significantly improve the clinical efficacy, reduce the level of NT-proBNP, improve the left ventricular ejection fraction, and slow down clinical symptoms, which was significantly higher than that of simple western medicine treatment. Gao Gao

Yu [24] observed 142 cases of chronic heart failure patients with qi and yin deficiency and found that the combination of Baoyuan Tang and Gui Zhi Gan Cao Tang could reduce the levels of serum IL-6, TNF-alpha, and hs-CRP, and at the same time, the main symptoms such as chest tightness, palpitations, and edema basically disappeared, and the cardiac function was significantly improved, which was safe and highly effective. Kan Zhengang [25] randomly divided 100 cases of chronic heart failure patients, with heart qi insufficiency into experimental group and control group, 50 cases in each group, the control group was given statins and angiotensin-converting enzyme inhibitors for routine treatment, and the experimental group was given Baoyuan Tang (Astragalus 30g, Red Ginseng 6g, Cinnamon 9g, Licorice 6g), the results showed, which the overall efficacy of the experimental group was significantly better than that of the control group, and the levels of the left ventricular end-diastolic internal diameter, LEVF and superoxide dismutase were significantly improved compared with the control group. The results showed that the overall efficacy of the experimental group was significantly better than that of the control group, and the levels of left ventricular end-diastolic internal diameter, LEVF and superoxide dismutase were significantly higher than those of the control group. Wang Zhenkuan [26] used Baoyuan Tang combined with Xifu yuyu Tang to treat patients with freeze-dried recombinant human brain natriuretic peptide in CHF, which could significantly reduce B-type natriuretic peptide level and LV end-diastolic internal diameter, improve myocardial microcirculation, and improve the overall therapeutic efficacy of the patients.

3. Summary and Expectation

Chronic heart failure is categorized as "palpitation" and "asthma" in Chinese medicine. According to its clinical manifestations, medical practitioners in the past generations have concluded that heart failure is an evidence of deficiency, with deficiency of qi, blood, yin and yang, mainly heart qi insufficiency. The real is blood stasis and water-drinking, which affects the five organs. The importance of qi deficiency in heart failure can be seen from the fact that it often leads to blood stasis due to the weakness of the heart's main operation, so it is advisable to use the method of benefiting qi and warming yang in the treatment of CHF.

Baoyuan Tang, as a representative formula for benefiting qi and warming yang, has its significant therapeutic effect and safety in treating chronic heart failure. It is often used in combination with western medicines to alleviate the clinical symptoms of CHF patients, improve the level of cardiac function, improve the quality of patients' survival, slow down the disease process, and then reduce the risk of readmission and death by reducing the inflammatory response, inhibiting apoptosis, oxidative stress, decreasing autophagy, and improving energy metabolism, as well as demonstrating a good safety profile.

In recent years, there have been many studies on the mechanism of Baoyuan Tang, but there are still some limitations. First, the safety of Baoyuan Tang has been verified, but detailed and definitive toxicity studies and its possible adverse effects are lacking. In addition, the studies mainly focused on animal models and small-scale clinical observations, and lacked human cell level and large-sample clinical trials to verify its safety and efficacy. Finally, there is a lack of standardized dosage of Baoyuan Tang, which needs to be explored and clarified in future studies to make further breakthroughs in the study of the efficacy mechanism of Chinese medicine in the treatment of CHF.

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