

## **Advances in the mechanisms of traditional Chinese medicine in the treatment of heart failure**

### **Abstract**

Heart Failure (HF) represents the advanced stage of various cardiovascular diseases and remains a major global public health challenge despite advances in pharmacological and device-based therapies. Traditional Chinese medicine (TCM) has emerged as a promising adjunctive strategy for HF, exerting therapeutic effects through multi-target and multi-pathway mechanisms. This review summarizes the major mechanisms, including the regulation of inflammatory responses, oxidative stress, myocardial energy metabolism, neuroendocrine systems, and ventricular remodeling. A deeper understanding of these mechanisms is expected to facilitate the evidence-based integration of TCM into standard HF management.

**Keywords:** Heart failure; Traditional Chinese medicine; Mechanism of action; Cardiac remodeling; Inflammatory response; Oxidative stress.

### **Introduction**

Heart Failure (HF) is a complex clinical syndrome caused by structural and/or functional cardiac abnormalities that impair ventricular filling and/or ejection [1]. Its major clinical manifestations include dyspnea, fatigue, and fluid retention. With the aging of the population and the increasing prevalence of chronic diseases such as coronary artery disease, hypertension, and diabetes mellitus, HF has become a major global public health challenge. Current guideline-directed medical therapies mainly include Angiotensin Receptor-Nephrilysin Inhibitors (ARNIs),  $\beta$ -blockers, mineralocorticoid receptor antagonists, and Sodium-Glucose Cotransporter 2 (SGLT2) inhibitors [2]. Despite these advances, many patients still suffer from progressive cardiac dysfunction and recurrent hospitalization [3]. Although substantial progress has been achieved through neurohormonal blockade, device therapy, and cardiac resynchronization therapy, a considerable proportion of patients continue to experience persistent symptoms, reduced quality of life, and poor long-term prognosis. In recent years, increasing attention has been paid to the role of TCM in HF management, particularly due to its advantages in holistic regulation, multi-target intervention, and long-term disease management [4]. TCM has demonstrated unique advantages in alleviating HF symptoms, improving exercise tolerance, and reducing rehospitalization rates.

**Dexiu Li\***

*Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing 100091, China.*

**\*Corresponding author: Dexiu Li**

Xiyuan Hospital, China Academy of Chinese Medical Sciences, Beijing 100091, China.

Email: [ldxiuyx123@163.com](mailto:ldxiuyx123@163.com)

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Accumulating basic and clinical evidence has revealed that TCM exerts cardioprotective effects through multiple interconnected mechanisms, including modulation of inflammatory responses, attenuation of oxidative stress, inhibition of myocardial fibrosis and ventricular remodeling, regulation of neuroendocrine systems, improvement of myocardial energy metabolism, and modulation of apoptosis and autophagy [5]. This review systematically summarizes these mechanistic advances, aiming to provide a comprehensive reference for further research and the rational integration of TCM into clinical HF management.

### **Mechanisms of TCM in the treatment of heart failure**

#### **Inhibition of inflammatory responses**

Chronic inflammation is recognized as a critical mechanism in the development and progression of HF [6]. Persistent inflammatory cell infiltration and excessive release of inflammatory cytokines can induce myocardial injury, ventricular remodeling, and deterioration of cardiac function [7]. Studies have shown that inflammatory pathways involving Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ), Interleukin (IL)-1 $\beta$ , IL-6, and Nuclear Factor kappa-B (NF- $\kappa$ B) are significantly activated in HF patients. TCM exerts cardioprotective effects by suppressing inflammatory mediator expression [8]. For instance, Qiliqiangxin capsules have been reported to reduce serum levels of TNF- $\alpha$ ,

IL-6, and C-Reactive Protein (CRP), thereby attenuating inflammatory responses and improving cardiac function [9]. Shenfu decoction can inhibit the activation of the Toll-like receptor 4 (TLR4)/NF- $\kappa$ B signaling pathway, reducing the release of inflammatory mediators and alleviating myocardial injury [10]. Active compounds derived from *Salvia miltiorrhiza* and *Astragalus membranaceus* have also demonstrated anti-inflammatory properties by regulating macrophage polarization and inflammatory signal transduction, thereby improving the myocardial microenvironment [11].

### Amelioration of oxidative stress

Oxidative stress is a key contributor to HF progression [12]. Excessive production of Reactive Oxygen Species (ROS) can lead to mitochondrial dysfunction, lipid peroxidation, and cardiomyocyte injury, ultimately aggravating ventricular remodeling [13]. Previous studies have shown that TCM alleviates oxidative stress by enhancing antioxidant enzyme activity, scavenging free radicals, and improving mitochondrial function [14]. Flavonoids derived from *Astragalus membranaceus* can enhance Superoxide Dismutase (SOD) activity and reduce Malondialdehyde (MDA) levels [15]. Tanshinone IIA has been shown to inhibit ROS generation and attenuate myocardial ischemia-reperfusion injury [16]. In addition, puerarin can activate the nuclear factor erythroid 2-related factor 2/heme oxygenase-1 (Nrf2/HO-1) antioxidant pathway, thereby enhancing cellular antioxidant capacity [17]. Several classical herbal formulas, including Zhenwu decoction and Shengmai powder, have also been reported to improve mitochondrial membrane potential and maintain myocardial energy metabolic homeostasis, thereby delaying HF progression [18].

### Inhibition of myocardial fibrosis and ventricular remodeling

Ventricular remodeling is the central pathological basis of HF progression and is characterized by myocardial hypertrophy, cardiomyocyte apoptosis, and excessive extracellular matrix deposition [19]. Myocardial fibrosis contributes to reduced ventricular compliance and impaired systolic and diastolic function. The Transforming Growth Factor- $\beta$  (TGF- $\beta$ )/Smad signaling pathway plays a pivotal role in myocardial fibrosis. Studies have demonstrated that TCM can inhibit collagen deposition by modulating this pathway. Tanshinone IIA suppresses TGF- $\beta$ 1 expression and reduces the synthesis of type I and type III collagen [20]. Qishenyiqi dripping pills can inhibit fibroblast activation and ameliorate ventricular remodeling [21]. Furthermore, herbal medicines such as *Rhodiola rosea* and *Ligusticum chuanxiong* also exhibit anti-fibrotic effects [22]. In addition, TCM formulas can attenuate cardiac remodeling by improving microcirculation, alleviating ischemia-hypoxia injury, and regulating Matrix Metalloproteinases (MMPs) [23]. For example, Xuefuzhuyu decoction has been shown to regulate MMP-2 and MMP-9 expression, thereby reducing abnormal extracellular matrix degradation and remodeling [24].

### Regulation of the neuroendocrine system

Persistent activation of neuroendocrine systems is an important mechanism underlying HF deterioration [25]. Excessive activation of the sympathetic nervous system and the Renin-Angiotensin-Aldosterone System (RAAS) can lead to tachycardia, vasoconstriction, sodium and water retention, and myocardial remodeling. Certain TCM can alleviate cardiac burden by regulating neuroendocrine activity. Studies have shown that Shenfu injection reduces plasma norepinephrine

and angiotensin II levels while improving left ventricular ejection fraction [26]. Qiliqiangxin capsules have also been reported to decrease Brain Natriuretic Peptide (BNP) and N-Terminal pro-Brain Natriuretic Peptide (NT-proBNP) levels [27]. Some active compounds in herbal medicines can improve cardiac function by modulating  $\beta$ -adrenergic receptor signaling. For example, ginsenosides can attenuate excessive sympathetic excitation and reduce myocardial oxygen consumption [28]. Properly processed aconite-derived compounds may enhance myocardial contractility and increase cardiac output under controlled dosage conditions.

### Improvement of myocardial energy metabolism

The myocardium is a highly energy-dependent organ, and HF is often accompanied by mitochondrial dysfunction and reduced ATP production [29]. Energy metabolism disorder is considered one of the major pathological mechanisms of HF. Recent studies have demonstrated that TCM improves mitochondrial function and regulates metabolic signaling pathways. Qi-tonifying herbs such as *Astragalus membranaceus* and *Panax ginseng* can enhance ATP synthesis efficiency and mitochondrial oxidative phosphorylation. Coenzyme Q10 combined with TCM therapy has also shown synergistic therapeutic effects in HF treatment [30]. The AMP-activated Protein Kinase/peroxisome proliferator-activated receptor gamma coactivator-1 $\alpha$  (AMPK/PGC-1 $\alpha$ ) pathway is a key regulator of cellular energy metabolism [31]. Some active herbal compounds have been reported to activate AMPK signaling, promote fatty acid oxidation and glucose utilization, and thereby improve myocardial energy supply [32]. Furthermore, TCM may improve myocardial metabolic efficiency and delay cardiac dysfunction progression by enhancing microcirculation and alleviating ischemic-hypoxic conditions.

### Regulation of apoptosis and autophagy

Excessive cardiomyocyte apoptosis is an important contributor to HF progression [33]. Imbalance of B-cell lymphoma-2 (Bcl-2)/Bcl-2-associated X protein (Bax), activation of caspase cascades, and related pathways are involved in cardiomyocyte apoptosis. Moderate autophagy is beneficial for maintaining cellular homeostasis, whereas excessive autophagy may lead to cell death [34]. Studies have shown that TCM protects cardiomyocytes by regulating apoptosis- and autophagy-related signaling pathways. Tanshinone IIA increases Bcl-2 expression while decreasing Bax and caspase-3 levels, thereby reducing apoptosis [35]. Astragaloside IV inhibits cardiomyocyte apoptosis through the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signaling pathway [36]. Regarding autophagy regulation, certain herbal medicines can maintain appropriate autophagic activity through mammalian Target of Rapamycin (mTOR) and AMPK signaling pathways, facilitating the clearance of damaged organelles and alleviating myocardial injury [37]. This bidirectional regulatory effect reflects the holistic and balanced therapeutic characteristics of TCM.

### Characteristics and prospects of TCM in the treatment of heart failure

TCM treatment for HF is characterized by holistic regulation, multi-target intervention, and individualized syndrome differentiation therapy [38]. Compared with conventional therapies that often target specific pathological pathways, TCM tends to modulate systemic functions and can simultaneously

target multiple pathological processes, including inflammation, oxidative stress, neuroendocrine activation, energy metabolism disorders, and cardiac remodeling.

However, several limitations remain in current TCM research on HF. First, mechanistic studies are often limited to single pathways and lack systematic integration. Second, high-quality multicenter clinical trials are still insufficient. Third, the active constituents and pharmacodynamic material basis of many herbal medicines remain unclear.

Future studies should strengthen the application of omics technologies, network pharmacology, and artificial intelligence in TCM research, thereby promoting the precision and systematization of mechanistic studies. Moreover, integrative medicine combining evidence-based Western medicine with TCM syndrome differentiation may become an important direction for future HF management, potentially improving long-term prognosis and quality of life in HF patients.

### Conclusion

The pathogenesis of HF is highly complex and involves multiple pathological processes, including inflammatory responses, oxidative stress, neuroendocrine activation, myocardial fibrosis, and energy metabolism disorders. Owing to its multi-component, multi-target, and holistic regulatory characteristics, TCM can exert therapeutic effects by suppressing inflammation, attenuating oxidative stress, improving myocardial energy metabolism, inhibiting ventricular remodeling, and regulating apoptosis. With the continuous advancement of modern biomedical technologies, the mechanisms underlying TCM treatment of HF will be further elucidated, providing a theoretical basis for its broader clinical application and international development.

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