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REVIEW

The traditional Chinese medicines treat chronic heart failure and their main bioactive constituents and mechanisms

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Abstract Chronic heart failure (CHF) is a severe public health problem with increasing morbidity and mortality, any treatment targeting a single session is insufficient to tackle this. CHF is characterized by reduced cardiac output resulting from neurohumoral dysregulation and cardiac remodeling, which might be related to oxidative stress, inflammation, endoplasmic reticulum stress, apoptosis, autophagy, mitochondrial function, and angiogenesis. These molecular mechanisms interact with each other through crosstalk. Historically, Chinese medicinal herbs have been widely applied in the treatment of CHF, and therapeutic effects of Chinese medicinal herbs and their ingredients have been scientifically confirmed over the past decades. Traditional Chinese medicine (TCM) with multiple components can confront the different pathogenesis of CHF through multiple targets. This review analyzes commonly used TCM patent drugs and TCM decoctions that are applicable to different stages of CHF based on clinical trials. Diverse bioactive ingredients in Chinese medicinal herbs have been found to treat CHF *via* multiple molecular mechanisms. This review comprehensively covers the key works on the effects and underlying mechanisms of TCM, herbal ingredients and synergistic effects of constituent compatibility in treating CHF, providing additional ideas to address this threat.

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1. Introduction

Chronic heart failure (CHF) is a set of complicated clinical syndromes triggered by aberrant changes in the structure and/or function of the heart brought on by a variety of factors. This condition results in compromised ventricular systolic and/or diastolic function when the heart is unable to pump sufficient blood to meet the metabolic needs of the tissues[1,2]. It is the outcome of numerous end-stage cardiovascular disorders, which present as dyspnea, dyskinesia, and fluid retention (Fig. 1). The Summary of the 2018 Report on Cardiovascular Diseases in China stated that there are 4.5 million people with CHF. There is a 30-day mortality rate of 4.1% for hospitalized CHF patients in China[3]. CHF has been identified as one of the leading causes of morbidity and mortality, posing a hazard to 1%−2% of adults and tending to affect younger people[4]. Unfortunately, despite significant worldwide efforts and funding invested in the discovery of anti-CHF drugs each year, and even with optimal treatment available after diagnosis, the overall survival rate after five years is still only 46% so far[5,6].

Currently, chemical medications that have evolved from "diuretic, cardiotonic, and vasodilator" to the combination of "diuretics, angiotensin-converting enzyme inhibitors, and β-blockers" are used to support conventional therapy for CHF in clinics. These drugs can rapidly improve the hemodynamic index and reduce myocardial oxygen and energy expenditure to help CHF patients relieve symptoms. However, they are unable to entirely address the root cause of CHF and its complications[7]. The rising prevalence of CHF is a serious issue due to the paucity of drugs that can effectively treat failing hearts.

Traditional Chinese medicine (TCM) remedies are an invaluable source for the creation of new anti-CHF medications. Many Chinese medicinal herbs, including Astragali Radix (Huangqi), Salviae Miltiorrhizae Radix (Danshen), Codonopsis Radix (Dangshen), Notoginseng Radix (Sanqi), etc., have been used successfully in China for thousands of years as CHF treatments. The beneficial effects of TCM formulas made up of Chinese medicinal herbs have recently been further supported by evidence-based medical investigations. Depending on the stages of CHF, different TCM formulas can be selected. At the same time, TCM formulas may be better able to exploit the advantages of multi-targeting and multi-functionality due to the complexity and mixed conditions of CHF patients.

TCM formulas are usually more rapidly adopted into clinical practice, based on thousands of years of rich human experience, whereas chemical agents require a lengthy review process. More profoundly, dozens of TCM formulas, hundreds of Chinese medicinal herbs, and their extracts or constituents have been reported to possess pharmacological research-approved anti-CHF bioactivities, shining a light on the already stagnant development of anti-CHF drugs. For example, cardiac glycosides have been developed as medications to treat CHF and arrhythmias for decades.

Huge efforts have been made over the past few decades to understand how these natural substances impact the pathophysiology of CHF. In this review, we examined the available proprietary TCM formulas from an evidence-based medical standpoint and analyzed their research status as well as potential clinical application situations. Ulteriorly, we summarized the updated progress in the prevention and treatment of CHF with respect to Chinese medicinal herbs and their main ingredients and analyzed their underlying mechanisms.

2. Pathogenesis of CHF

The etiology of CHF is complex and varies with diverse etiologies and phases as a result of the diversity of underlying disorders (Fig. 2). The two main pathophysiological factors that contribute to the formation and progression of CHF are neurohumoral regulation and cardiac remodeling. After myocardial damage, neurohumoral cytokines are initially activated, which causes myocardial structural and phenotypic alterations that emerge as cardiac hypertrophy and overload through a number of

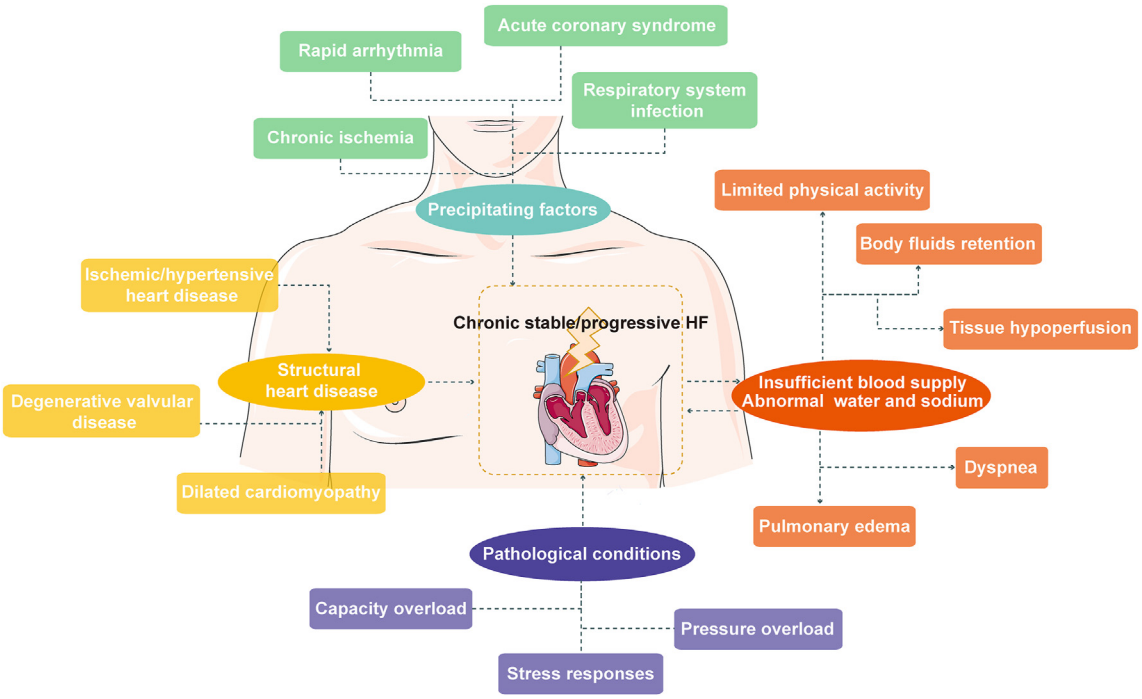


Figure 1 Chronic heart failure is the end stage of multiple cardiovascular diseases.

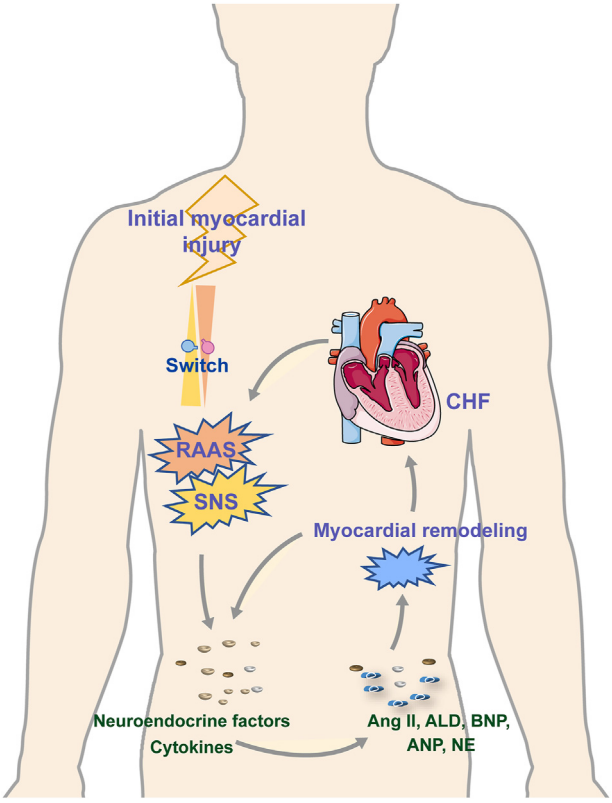


Figure 2 The neurohumoral regulation mechanism is the key, and ventricular remodeling is the pathophysiological basis of chronic heart failure.

signals[8−10]. The mechanical burden on the ventricular wall is then increased by high pressure or volume loads, which in turn triggers more neuroendocrine signals that worsen CHF[10−12]. The overactivation of the renin−angiotensin−aldosterone system (RAAS), a key hormone system, is a significant factor in the incidence and progression of CHF[13]. Angiotensin II (Ang II), an effector molecule of RAAS, activates the downstream Ang II type 1 receptor to control cell proliferation and death and impact the deposition of extracellular matrix (ECM)[14]. Ang II influence the processes of myocardial fibrosis, hypertrophy, and deformation by regulating microRNAs[15]. Additionally, a variety of released fibrogenic and hypertrophied mediators, including transforming growth factor-β (TGF-β), matrix metalloproteinase (MMP), fibroblast growth factor, vascular endothelial growth factor (VEGF), and several chemokines, are included in the activation of neuroendocrine signals. These signals act on all cell types involved in cardiac fibrotic and hypertrophic responses, leading to cardiac remodeling through oxidative stress, inflammation, endoplasmic reticulum stress (ERS), autophagy, apoptosis, mitochondrial energy metabolism, and angiogenesis[16]. Taken together, neurohumoral disharmony and cardiac remodeling eventually cause the reduction of myocardial systolic and/or diastolic function, hemodynamic anomalies, and myocardial fibrosis[17].

2.1. *Pathological manifestations of CHF*

2.1.1. *Myocardial hypertrophy*

Pathological myocardial hypertrophy, in contrast to physiological myocardial hypertrophy brought on by exercise or pregnancy, denotes an increase in cardiac pressure and ventricular wall tension as a result of pressure or volume overload, followed by an increase in cardiomyocyte volume, interstitial fibrosis, and intercellular mass. In cases of volumetric overload, serial sarcomere duplication lengthens cardiomyocytes, resulting in eccentric hypertrophy[18]; in cases of pressure overload, parallel sarcomere duplication and arrangement lengthen cardiomyocytes, resulting in concentric hypertrophy[19]. After significant cardiomyocyte loss caused by ischemic or diffuse myocardial disorders, the remaining myocardium may undergo compensatory hypertrophy. Pathological myocardial hypertrophy weakens myocardial contractility and compliance and increases oxygen consumption, culminating in CHF.

Through multiple signaling pathways, pressure, or volume overload and excessive neurohumors control cellular responses such as gene expression, protein synthesis, and cellular metabolism. As a result, capillary thinning, metabolic disorders, Ca^{2+} overload, inflammatory responses, cell death, and fibrosis occur, causing cardiac hypertrophy. Calcineurin/nuclear factor of activated T cell signaling functions as a master regulator of cardiac hypertrophy[20]. The activation of phosphatidylinositol 3-kinase (PI3K) signaling may encourage cardiac hypertrophy, interstitial fibrosis, and cardiac dysfunction[21].

2.1.2. *Myocardial fibrosis and pathological remodeling*

Myocardial fibrosis, the process through which cardiac fibroblasts proliferate and transform into the myofibroblast phenotype, is one of the main pathological alterations of CHF. An imbalance in collagen synthesis and degradation can be detected during the process, including an increase in the expression of collagen I, collagen III, and α-smooth muscle actin (α-SMA). It is the primary cause of ventricular remodeling, which results in less myocardial compliance, compromised cardiac systolic and diastolic functions, and chronic volume or pressure overload that eventually progresses to CHF[22].

Myocardial fibrosis is characterized by disordered collagen metabolism and excessive diffuse deposition of collagen in the interstitial and perivascular areas[23]. Initially, ECM deposition is an adaptive and protective mechanism, but excessive and continuous ECM deposition eventually leads to irreversible pathological changes, including ventricular dilation, cardiomyocyte hypertrophy, and apoptosis, decreased tissue compliance, and finally accelerates the progression of CHF[24]. TGF-β/Smads, WNT/β-Catenin, and PI3K/AKT/mammalian target of rapamycin (mTOR) signaling pathways all play crucial roles in stimulating fibroblast proliferation and ECM remodeling[25]. Additional factors that contribute to myocardial fibrosis include ATP-dependent chromatin remodeling, apoptosis, autophagy, necrotic cell death, aberrant mitochondrial activity, reactive oxygen species (ROS) generation-stimulated oxidative stress, inflammasome signaling, and the buildup of pro-inflammatory mediators[26].

2.2. *Molecular mechanisms of CHF*

2.2.1. *Oxidative stress*

Oxidative stress occurs as a result of an excessive amount of free radical production, accumulation, or their oxidant metabolites. These oxidants negatively impact subcellular components like lipid peroxidation, mitochondrial dysfunction, ERS, and DNA fragmentation, which together cause myocardial damage and consequently CHF.

Oxidative stress occurs when the oxidative and antioxidant systems in the body are out of balance and large amounts of ROS and their metabolites build up in cells. These accumulations have toxic effects on cells and activate some signaling pathways, triggering a string of tissue damage[27]. Increased oxidative stress and excessive ROS production are present in failing hearts, according to clinical investigations and animal trials. Antioxidant systems are classified into non-enzymatic and enzymatic systems. The former mainly contains antioxidants such as glutathione and vitamins C and E, while the latter includes superoxide dismutase, nicotinamide adenine dinucleotide (NAD^+/NADH) and nicotinamide adenine dinucleotide phosphate (NADPH)-dependent catalase, glutathione peroxidase, thioredoxin, etc.[28]. NADPH oxidases (NOX), such as NOX2 and NOX4, regulate oxidative stress and compartmentalize intracellular signaling in endothelial cells, smooth muscle cells, macrophages, cardiomyocytes, and fibroblasts[29]. There is not only an excess of ROS but also a reduction in the activity of antioxidant enzymes during CHF.

Exposure of cells to elevated levels of ROS provokes an inflammatory cascade and the expression of adhesion molecules, such as nuclear factor-κB (NF-κB) activation[30]. Increased ROS triggers the activation of metalloproteinases and calpain, which contributes to cell swelling and lysis, leading to mitochondrial permeability transition pores (mPTP) opening and mitochondrial swelling and rupture of the outer mitochondrial membrane, thereby facilitating the deposition of pro-apoptotic factors and intensifying apoptosis[31]. Therefore, restoring the equilibrium between the oxidative and antioxidant systems necessitates lowering the excess accumulation of ROS as well as activating antioxidant enzymes or administering antioxidants. The prognosis of CHF benefits from the early maintenance of redox homeostasis through exogenous scavenging of excess ROS.

2.2.2. *Inflammation*

Inflammation is a central mechanism in the emergence of CHF. Cytokines, such as interleukin (IL)-1β, IL-6, and IL-8, have been investigated as potential markers for risk stratification, early diagnosis, and prognostic assessment in CHF[32]. Initiating, integrating, and maintaining myocardial responses to stress are all determined by proinflammatory cytokines, and all clinical manifestations of CHF show signs of a prolonged inflammatory response[33]. The short-term prognosis of CHF patients, including 30- and 90-day hospital all-cause mortalities, is adversely affected by higher levels of systemic immune-inflammation indexes[34]. The early stages of heart healing nonetheless require a moderate inflammatory response. An intense inflammatory response is essential for cardiac repair in the early stages. The protracted, severe inflammation triggers loss of cardiomyocytes and ventricular wall integrity, myocardial rupture, impaired systolic function, and extended fibrotic changes beyond the initial infarction.

The myocardium is mainly composed of cardiomyocytes, fibroblasts, endothelial cells, and leukocytes, all of which are strongly associated with inflammation. Necrotic cardiomyocytes activate innate immune response by releasing a variety of danger signals (high mobility group protein Bl, heat shock protein B1, etc.) to eliminate necrotic cells[35,36]. Cardiomyocytes in the peri-infarct zone may serve as manufacturing sites for a number of pro-inflammatory substances[37]. During the healing process, cardiac fibroblasts distributed in the interstitium and perivascular region activate the inflammasome and secrete cytokines, chemokines and lysosomes to promote inflammation[38]. Proinflammatory cytokines postpone the differentiation of fibroblasts into fibrosis until necrotic cells and stromal components are removed. However, under the volume and pressure overload, fibroblasts in the non-infarct area are activated and transformed into myofibroblasts to promote the formation of interstitial fibrosis. Endothelial cells are the main source of secretion of pro-inflammatory factors, such as monocyte chemoattractant protein 1, CXC motif chemokine 10, and mediate the adhesion and aggregation of circulating leukocytes[39]. The heart-resident leukocytes, especially macrophages, have inflammatory and protective transcriptional signatures in immune compartment[40]. A rise in mono-macrophages can be detected in the early injury and late repair stages of CHF[41]. Macrophages can be classified into M1 and M2 types; the former is thought to have a pro-inflammatory effect [secreting IL-6, IL-1β, and tumor necrosis factor-α (TNF-α)], whereas the latter is involved in resolving of inflammation and reducing collagen production (secreting IL-4, IL-10, and arginase 1)[42,43].

Innate immune responses are triggered when inflammatory signals attach to pattern recognition receptors. Activated Toll-like receptor (TLR) interact with myeloid differentiation factor 88 adaptor protein (MYD88) to activate NF-κB and trigger the inflammatory cascade reaction, aggravating inflammation and transducing TGF-β signal to form myocardial fibrosis[44–46]. Activated NOD-like receptor 3 (NLRP3) inflammasome signal pathway amplifies the inflammatory response and participates in pyroptosis[47]. Furthermore, it is important to consider the role of other immune cells such as neutrophils, mast cells, T cells, and natural killer cells in inflammation[48].

2.2.3. *Endoplasmic reticulum stress*

The endoplasmic reticulum is an intracellular organelle responsible for translation of membrane proteins, post-translational modification of proteins, regulation of cellular Ca^{2+} homeostasis, and lipid synthesis. The collapse of endoplasmic reticulum homeostasis is a trigger for various cardiovascular diseases. When stressors like hypoxia, glucose deprivation, ATP depletion, and calcium overload are present, the accumulation of misfolded and unfolded proteins in the endoplasmic reticulum lumen and disturbance of Ca^{2+} homeostasis turn on unfolded protein responses and apoptotic signaling pathways, which leads to ERS[49].

Moderate ERS is an adaptive response of the cell that facilitates the restoration of endoplasmic reticulum function and guarantees cell survival. Severe or persistent ERS and protein misfolding will induce inflammation and apoptosis, thus accelerating cardiac remodeling[50,51]. Calcium pools in the endoplasmic reticulum regulate intracellular Ca^{2+} level; the balance of its concentration maintains the function of the endoplasmic reticulum, membrane transport, and internal environmental homeostasis. Dysregulation of the Ca^{2+} circulation is one of the key causes of the loss in myocardial contractile capacity in CHF. The imbalance of Ca^{2+} homeostasis is responsible for the aggregation of misfolded or unfolded proteins in the endoplasmic reticulum, which incites inflammatory responses and oxidative stress, resulting in mitochondrial damage, apoptosis, and myocardial fibrosis[52]. Impaired myocardium may trigger persistent ERS by activating inositol-requiring enzyme 1 cleaving X-box binding protein 1 to induce the expression of glucose-regulated protein 78, activated transcription factor 4, and CCAAT enhancer binding protein[53]. The SUMOylation of SERCA2a has been verified to play a critical role in the abnormal Ca^{2+} cycle of CHF[54].

2.2.4. *Apoptosis*

One of the main causes of cardiac dysfunction is cardiomyocyte loss, which is primarily attributed to apoptosis[55]. Excessive

apoptosis of myocardial cells leads to persistent loss of myocardial contractile units and structural lesions, which impair myocardial perfusion capacity and increase the risk of CHF.

Apoptosis is predominately regulated by two signaling pathways: the endogenous pathway associated with mitochondria and the exogenous pathway associated with death receptors (FAS and other TNFR superfamily members and ligands). The former is regulated by the pro- and anti-apoptotic members of the BCL-2 family proteins. To maintain cell survival, the anti-apoptotic proteins BCL-2, BCL-XL, MCL-1, BCL-W, and A1/BFL1 work in tandem with the cell death effectors BAX and BAK[56]. The key apoptosis promoter, the BH3-only protein, is upregulated in response to intracellular stress (such as Ca^{2+} overload, DNA damage, or ERS), and it binds to BCL-2 with a high affinity. This results in the release of BAX and BAK, leading to mitochondrial outer membrane permeabilization (MOMP), which then results in cytochrome *c* and SMAC/DIABLO[57]. These apoptotic stimuli encourage the activation of the caspases' cascade reaction, leading to the cleavage of hundreds of proteins, which results in cell destruction. The exogenous apoptotic pathway is initiated by cell surface death receptors that contain death domains triggered by death ligands, forming the death-inducing signaling complex, and activating caspase-8 and downstream caspase-3 and caspase-7[58]. Caspase-8 also cleaves and activates the BH3-only protein BID, causing MOMP[59], which links exogenous and endogenous apoptosis.

Limiting the flow of Ca^{2+} from the outside to the inside of the cell may inhibit cell disintegration caused by calcium overload; stabilizing the mitochondrial structure by restricting the over-opening of MOMP may effectively prevent the caspases-activated cascade reactions to reduce excessive apoptosis. Downregulating FAS receptor and its ligand proteins, TNF-α, TNFR-1, FADD, caspase-8, and caspase-3 may impair exogenous apoptosis directly.

2.2.5. *Autophagy*

Autophagy is a highly conserved intracellular catabolic process. With the help of lysosomes, autophagy degrades misfolded proteins and damaged organelles, eliminates aging cells, maintains energy homeostasis, and assures cellular survival and function[60]. Autophagy is mainly classified into macroautophagy, microautophagy, and chaperone-mediated autophagy, each of which is mediated by different regulators[61]. The mTOR acts as a negative regulator of autophagy, whereas adenosine monophosphate activated protein kinase (AMPK) and glycogen synthase kinase-3β are positive regulators[62]. In response to a variety of regulatory factors, autophagy plays an integral role in the energy metabolism of cardiomyocytes, the production of collagen, and endothelial−mesenchymal transition (EMT) and thus contributes to cardiac hypertrophy and fibrosis[63,64]. Abnormal autophagy is reported in the myocardium of patients with CHF due to dilated cardiomyopathy, valvular diseases, and coronary artery diseases[65].

An imbalance in autophagy leads to cardiac hypertrophy. In the early stage of CHF, insufficient autophagic activity increases hypertrophic cardiomyocytes and precludes clearance of apoptosis arising from inflammation and oxidative stress; excessive autophagy intensifies of CHF[66,67]; proper autophagy releases free fatty acids (FFAs) and amino acids to degrade senescent and dysfunctional organelles and proteins[68]. Under normal physiological settings, autophagy is at a low level. However, ATP depletion, ROS release, and mPTP opening facilitate a rapid increase in autophagic activity, eventually leading to overactive autophagy[69]. Over-activated autophagy damages important organelles and proteins while eliminating toxic elements, evoking apoptosis and the loss of cardiomyocytes[70]. The activation of autophagy can induce EMT and cardiac fibrosis, and inhibition of autophagy to EMT is a cardioprotective strategy to ameliorate cardiac fibrosis. Excessive activation of autophagy exacerbates cardiac fibrosis through the upregulation of EMT in transverse aortic constriction (TAC)-induced mice[71]. However, in certain circumstances, autophagy restriction might lead to EMT and promote cardiac fibrosis. Autophagy disruption established by autophagy related gene 5-specific deletion significantly induces IL6-dependent EMT and exacerbates cardiac fibrosis[72], while restoration of TFEB-mediated autophagic flux inhibits TGF-β-mediated EMT[73]. Myocardial autophagy may be altered differentially by various etiologies of CHF, and the role of autophagy in the progression of CHF may change over time. Further studies are needed to better understand autophagy and obtain cardioprotective effects without maladaptive effects.

2.2.6. *Mitochondrial function and metabolism remodeling*

There is growing evidence that metabolic remodeling of cardiomyocytes is responsible for cardiac structural remodeling. The apparent alterations in metabolic remodeling are a shift in metabolic substrate usage and the decrease of mitochondrial oxidative capacity in cardiomyocytes. In a healthy heart, cardiomyocytes consume large amounts of FFAs but relatively little glucose to regenerate ATP for contraction. While in a hypertrophic and fibrotic heart, cardiomyocytes switch from using FFAs as a fuel to glucose, which is characterized by decreased metabolism of FFAs and increased glycolysis[74]. Additionally, the sympathetic-adrenal system in CHF is over-activated, which results in excessive Ca^{2+} buildup and mitochondrial mPTP opening, resulting in electron leakage during its transfer. The imbalance of mitochondrial quality control exacerbates myocardial energy metabolism disorders[75]. A diversified analysis of CHF patients proved that the evolution of CHF is linked to the progressive degradation of energy generation and reserve capacity. The endogenous feedback mechanism struggles to balance out the inordinate energy demand after the damage hits the crucial threshold, and CHF worsens[76].

Metabolic intermediates and metabolites can regulate the activities of enzymes essential for cardiac hypertrophy and remodeling, including AMPK signal, peroxisome proliferator-activated receptor γ coactivator 1α signal, mTOR signal, PI3K/protein kinase B signaling, and so on[77]. Alterations in these signals are obvious indicators of energy deficits and energy metabolism disorders, showing a route to a cure for CHF. Disorders of myocardial substrate utilization and metabolism are progressively being recognized as possible causes of cardiac remodeling and dysfunction. Regulatory approaches to cardiac energy metabolism are sensitive and adaptive, allowing the heart to adapt to different states and workloads to maintain its systolic function. Therefore, researchers are looking at myocardial energy metabolism as a new way to try to help CHF patients.

2.2.7. *Angiogenesis*

Angiogenesis is the process of forming new blood vessels from already existing ones. Myocardial hypertrophy is one of the precursors of myocardial remodeling. In ischemia diseases such as coronary artery disease and myocardial infarction (MI), coronary microvascular dysfunction will accelerate the dysfunction of the myocardium[78]. One of the prerequisites to cardiac remodeling is myocardial hypertrophy[79]. The degree of myocardial hypertrophy is closely related to the density of blood vessels. In the early

phases of chronic cardiac hypertrophy, myocardial hypoxia stimulates microvascular dilation by inducing the secretion of angiogenic factors. As hypertrophy worsens, the adaptive angiogenic response is suppressed, and thickening of the inner wall and increased wall/lumen ratio lead to capillary thinning and poor coronary artery remodeling, resulting in a mismatch between capillary density and increased oxygen demand that further weakens cardiac function[80].

Endothelial cells release a range of angiogenic molecules that participate in endothelial growth, microvascular permeability, and angiogenesis[81]. VEGF is an angiogenic molecule that both supports vasodilation and promotes neovascularization. In elderly CHF patients, upregulating VEGF expression can promote angiogenesis and endothelial function and improve cardiac ejection[82]. Endothelin, a powerful endogenous angiogenesis inhibitor, its increase accelerates left ventricular (LV) remodeling in CHF mice due to myocardial ischemia, and its anti-angiogenic activity may be mediated by reducing endothelial neovascularization and plaque growth[83]. Clinical trials revealed that increased endostatin was significantly associated with worsening ventricular systolic and diastolic function in the elderly community[84]. Angiogenesis can improve the blood and oxygen supply, thereby inhibiting the apoptosis of myocardial cells, alleviating fibrosis, and improving cardiac function[85]. Overall, exogenous stimulation of angiogenesis-mediated microvascular recovery by drugs may hold promise for the treatment of CHF.

3. The ameliorating effects of TCM formulas on CHF

TCM, a comprehensive medicinal system, is characterized by holistic theory that emphasizes the regulation of the integrity of the human and the interactions between human individuals and their environments. The diagnostic and therapeutic methods of TCM are based on the differentiation of syndromes (Zheng in Chinese) and the use of herbal formulas (Fang-Ji in Chinese). According to TCM theory, CHF occurs in the heart and also involves the lung, spleen, and kidney, implying that CHF is not only attributed to cardiac conditions. It is characterized by the syndromes of deficiency in origin and excess in superficiality, or the deficiency−excess complex. The deficiency of Qi and Yang of heart is the fundamental cause of CHF, and the blood stasis and phlegm that follow further exacerbate the illness. In the early stages of CHF, both Qi and Yin are deficient; in the middle stages, Qi deficiency, blood stasis, and phlegm are predominant; and in the latter stages, Yang deficiency of the heart and kidney, blood stasis, accumulative phlegm, and sudden Yang collapse are predominant. Overall, Qi deficiency of the heart and blood stasis run through CHF, and Yang deficiency is the main factor. Hence, the therapeutic principles and methods of TCM for CHF concentrate on warming Yang to promote diuresis, supplementing Qi and nourishing Yin, and activating blood circulation to remove blood stasis.

Over the past few years, numerous investigations have been carried out to find evidence-based anti-CHF TCM formulas. This section covered TCM anti-CHF formulas that have been accepted for use in clinical settings by the general population and small bodies of supporting research (Table 1).

3.1. *Patent capsules or pills*

3.1.1. *Shensong Yangxin capsule (SSYX)*

Ginseng Radix Rubra (Hongshen), Ophiopogonis Radix (Maidong), Corni Fructus (Shanzhuyu), Salviae Miltiorrhizae Radix (Danshen), Nardostachyos Radix (Gansong), Ziziphi Spinosae Semen (Suanzaoren), Taxilli Herba (Sangjisheng), Paeoniae Radix Rubra (Chishao), Eupolyphaga Steleophaga (Tubiechong), Coptidis Rhizoma (Huanglian), Schisandra Chinensis Fructus (Wuweizi), and Dragonsbones (Longgu) make up SSYX. The special effect of SSYX is to supplement Qi and nourish Yin, activate blood circulation, and remove blood stasis to treat CHF caused by deficiency of Qi and Yin syndrome[86].

SSYX is a Chinese patent medicine recommended by guidelines for the treatment of ventricular premature beats and is preferred to ameliorate arrhythmia symptoms in patients with CHF[86]. The autonomic imbalance may be an important mechanism for the deterioration of CHF, and heart rate variability is a sensitive indicator commonly used to quantify autonomic function[87]. In a clinical trial enrolled 120 CHF patients, the control group was given conventional therapy, and the experimental group was given the SSYX and conventional therapies. The electrocardiography results demonstrated that the root mean square of the difference value of an adjacent RR interval and the percentage of differences exceeding 50 ms between an adjacent standard number of interval values in the experimental group were higher than those in the control group, indicating that SSYX improved the LV function and normalization of heart rate variability in CHF patients, thus improving therapeutic effects[88]. The congestive CHF patients with frequent ventricular premature complexes given SSYX showed a significantly greater decline in the total number of VPCs and N-terminal pro-B-type natriuretic peptide (NT-proBNP) level than the placebo group did[89]. In addition, the Minnesota Living with Heart Failure Questionnaire score was markedly elevated after SSYX treatment, showing the meliority of SSYX for the quality of life of CHF patients[90].

3.1.2. *Qishen Yiqi dropping pills (QSYQ)*

QSYQ is composed of Astragali Radix (Huangqi), Salviae Miltiorrhizae Radix (Danshen), Notoginseng Radix (Sanqi), Dalbergiae Odoriferae Lignum (Jiangxiang). It can invigorate Qi and promote blood circulation to relieve pain, so it can be applied to CHF patients with Qi deficiency and blood stasis syndrome[91].

QSYQ is recommended by TCM treatment guidelines for coronary heart disease (CHD) before or after percutaneous coronary intervention (PCI) for CHD patients[91]. A clinic trial enrolled 640 CHF patients triggered by MI indicated that 6-min walking distance (6-MWD) and the Minnesota Living with Heart Failure Questionnaire score are significantly improved, while secondary outcomes in composite clinical events (all-cause mortality and emergency treatment or hospitalization due to CHF) and brain natriuretic peptide (BNP) changes were non-significantly greater compared with the placebo group after 6-month QSYQ treatment. Furthermore, a meta-analysis showed that, compared with conventional western medicine alone, such as sacubitril valsartan sodium, trimetazidine, and levosimendan, QSYQ combined with conventional western medicine obviously improved LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), LV ejection fraction (LVEF), BNP, 6-MWD, and weakened adverse reactions[92]. The effect of conventional western medicine combined with QSYQ is better than conventional western medicine alone[93].

3.1.3. *Compound Danshen dripping pills (CDDP)*

CDDP is a widely used TCM medication in China for treating ischemic angina pectoris and consists of Salviae Miltiorrhizae Radix (Danshen), Notoginseng Radix (Sanqi), and Borneolum

Table 1 Category of effects, composition, patterns of syndrome and origin of TCM formulas.

Category of effects	TCM formula	Composition	Pattern of syndrome	Origin
Tonifying Qi	HQI	Astragali Radix (Huangqi)	Deficiency of heart Qi and stagnation of vessel by blood stasis	Approved by CFDA (Z19993151)
	SQFZ	Astragali Radix (Huangqi), Codonopsis Radix (Dangshen)	Deficiency of lung-spleen Qi	Approved by CFDA (Z19990065)
	SBPs	Moschus (Shexiang), Ginseng Radix (Renshen), Bovis Calculus (Niuhuang), Borneolum (Bingpian), CinnamomI Cortex (Rougui), Styrax (Suhexiang), Bufonis Venenum (Chansu)	Qi stagnation and blood stasis	Approved by CFDA (Z31020068)
Tonifying Qi and activating blood	QLQX	Astragali Radix (Huangqi), Ginseng Radix (Renshen), Salviae Miltiorrhizae Radix (Danshen), Descurainiae Semen Lepidii Semen (Tinglizi), Alismatis Rhizoma (Zexie), Polygonati Odorati Rhizoma (Yuzhu), Cinnamomi Ramulus (Guizhi), Carthami Flos (Honghua), Periplocae Cortex (Xiangjiapi), Citri Reticulatae Pericarpium (Chenpi)	Deficiency of Yang Qi and blood stasis	Approved by CFDA (Z20040141)
	QSYQ	Astragali Radix (Huangqi), Codonopsis Radix (Dangshen), Notoginseng Radix (Sanqi), Dalbergiae Odoriferae Lignum (Jiangxiang)	Qi deficiency and blood stasis	Approved by CFDA (Z20030139)
	TXL	Ginseng Radix (Renshen), Eupolyphaga Steleophaga (Tubiechong), Dalbergia Odorifera Lignum (Jiangxiang), Ziziphi Spinosae Semen (Suanzaoren), Paeoniae Radix Rubra (Chishao), Hirudo (Shuizhi), Scorpio (Quanxie), Cicada Periostracum (Chantui), Scolopendra (Wugong), SantaLi Albi Lignum (Tanxiang), Olibanum (Ruxiang), Borneolum (Bingpian)	Deficiency of heart Qi and blood stasis	Approved by CFDA (Z19980015)
	XML	Roach	Deficiency of Qi and Yang, blood stasis	Approved by CFDA (Z20060443)
Tonifying Qi and Yin	SM	Ophiopogonis Radix (Maidong), Ginseng Radix Rubra (Hongshen)	Deficiency of Qi and Yin	Approved by CFDA (Z51021921)
	SI	Ginseng Radix (Renshen), Ophiopogonis Radix (Maidong), Schisandra Chinensis Fructus (Wuweizi)	Deficiency of Qi and Yin	Approved by CFDA (Z51021264)
	YQFM	Ginseng Radix Rubra (Hongshen), Ophiopogonis Radix (Maidong), Schisandra Chinensis Fructus (Wuweizi)	Deficiency of Qi and Yin	Approved by CFDA (Z20060463)
	SSYX	Ginseng Radix (Hongshen), Ophiopogonis Radix (Maidong), Corni Fructus (Shanzhuyu), Salviae Miltiorrhizae Radix (Danshen), Nardostachyos Radix (Gansong), Ziziphi Spinosae Semen (Suanzaoren), Taxilli Herba (Sangjisheng), Paeoniae Radix Rubra (Chishao), Eupolyphaga Steleophaga (Tubiechong), Coptidis Rhizoma (Huanglian), Schisandra Chinensis Fructus (Wuweizi), Dragonsbones (Longgu)	Deficiency of Qi and Yin, blood stasis	Approved by CFDA (Z20103032)
Activating blood to remove blood stasis	DSDP	Salviae Miltiorrhizae Radix (Danshen), Notoginseng Radix (Sanqi), Borneolum (Bingpian)	Qi stagnation and blood stasis	Approved by CFDA (Z20080078)
	DHI	Salviae Miltiorrhizae Radix (Danshen), Carthami Flos (Honghua)	Blood stasis	Approved by CFDA (Z20026866)
	TSD	Chuanxiong Rhizoma (Chuanxiong), Carthami Flos (Honghua), Angelica Sinensis Radix (Danggui), Persicae Semen (Taoren), Paeoniae Radix Alba (Baishao), Rehmanniae Radix (Dihuang)	Blood stasis and blood deficiency	Fu Ke Bing Jian

(*continued on next page*)

Table 1 (*continued*)

Category of effects	TCM formula	Composition	Pattern of syndrome	Origin
Warming Yang	ZWD	Poria (Fuling), Atractylodes Macrocephala Rhizoma (Baizhu), Aconiti Lateralis Radix Praeparata (Fuzi), Zingiberis Rhizoma Recens (Shengjiang), Paeoniae Radix Alba (Baishao)	Edema due to Yang deficiency	Treatise on Febrile Diseases (Shang Han Lun)
	LZD	Poria (Fuling), Cinnamomi Ramulus (Guizhi), Atractylodes Macrocephala Rhizoma (Baizhu), Glycyrrhizae Radix (Gancao)	Dampness due to Yang deficiency	Treatise on Febrile Diseases (Shang Han Lun)
Removing phlegm and resolving stasis	GXBD	Trichosanthis Semen (Gualouzi), Alli Macrostemonis Bulbus (Xiebai), Pinelliae Rhizoma (Banxia)	Phlegm-accumulation stasis	Treatise on Febrile Diseases (Shang Han Lun)
Restoring Yang and tonifying Qi	SFI	Ginseng Radix Rubra (Hongshen), Aconiti Lateralis Radix Praeparata (Fuzi)	Sudden collapse of Yang	Approved by SFDA (Z51020664)

(Bingpian). A majority in treating CHF is implied by CDDP's prominence in promoting blood circulation to reduce blood stasis. With quick dissolution, strong bioavailability, and low adverse reactions, CDDP is the first proprietary Chinese medicine to pass Phase II and is undergoing phase III clinical trials for the prevention and treatment of ischemic cardiovascular disease by the U.S. Food and Drug Administration.

CDDP was shown to improve the cardiac index, LVEF, LVEDD, and LVESD, and reduce C-reactive protein, IL-8, and amino-terminal brain natriuretic peptide precursor (NT-proBNP) levels in aged CHF patients[94]. In CHF patients, an elevated BNP level is a high-risk factor for subsequent readmission; patients with higher BNP level require intensive treatments[95]. The NT-proBNP level in plasma was not significantly decreased after one month of CDDP treatment but apparently mitigated after three and six months of treatment, suggesting better long-term stabilization[96], implying that CDDP could play a role in reducing subsequent readmission rates. CDDP in combination with conventional antihypertensive drugs significantly improved the clinical efficacy in hypertensive myocardial hypertrophy[97]. In addition, CDDP combined with conventional therapy alleviated hemorheology and blood lipid parameters and inflammatory mediators, thus prominently improving vascular endothelial function and cardiac function[98].

3.1.4. *Tongxinluo capsule (TXL)*

TXL was developed under the "collateral disease theory" founded by Professor Wu Yiling[99]. It is composed of Ginseng Radix (Renshen), Eupolyphaga Steleophaga (Tubiechong), Dalbergiae Odoriferae Lignum (Jiangxiang), Ziziphi Spinosae Semen (Suanzaoren), Paeoniae Radix Rubra (Chishao), Hirudo (Shuizhi), Scorpio (Quanxie), Cicada Periostracum (Chantui), Scolopendra (Wugong), SantaLi Albi Lignum (Tanxiang), Olibanum (Ruxiang), and Borneolum (Bingpian). It is adept at supplementing Qi and activating blood circulation. CHF caused by Qi deficiency of heart and blood stasis falls under TXL treatment.

Although coronary revascularization decreases mortality and improves prognosis, CHF remains the most frequent and dangerous complication in MI patients. TXL has the potential to reduce myocardial no-reflow and myocardial ischemia/reperfusion (MI/R) injury. In CHF patients after PCI for MI, TXL notably ameliorated symptoms such as chest tightness and shortness of breath and reduced NT-proBNP expression[100,101]. In MI patients with delayed PCI, TXL not only prevented coronary embolism, attenuated vascular endothelial injury but also enhanced blood flow and strengthened cardiac systolic function to prevent CHF[102]. However, in another study, although TXL reduced primary cardiovascular events (cardiac death, recurrent MI, arrhythmia, and recurrent angina pectoris), it could not lower the incidence of recurrent CHF, which is even more likely to result in gastrointestinal discomfort[103]. Therefore, a prospective, randomized, double-blind, placebo-controlled, multicenter clinical study to evaluate the clinical efficacy and safety of TXL is essential to achieving a tough clinical endpoint.

3.1.5. *Qiliqiangxin capsule (QLQX)*

QLQX is the first Chinese patent drug with evidence-based medical evidence to positively affect CHF in China, and it is composed of Astragali Radix (Huangqi), Ginseng Radix (Renshen), Salviae Miltiorrhizae Radix (Danshen), Descurainiae Semen Lepidii Semen (Tinglizi), Alismatis Rhizoma (Zexie), Polygonati Odorati Rhizoma (Yuzhu), Cinnamomi Ramulus (Guizhi), Carthami Flos (Honghua), Periplocae Cortex (Xiangjiapi), and Citri Reticulatae Pericarpium (Chenpi). QLQX can supplement Qi and warm Yang, activate blood circulation, and induce diuresis (to eliminate edema) is superior in treating mild and moderate congestive CHF specialized by deficiency of Yang, blood stasis, and excessive phlegm. Based on the multidimensional "radar chart" mode, songorin, calycosin-7-*O*-*β*-D-glucopyranoside, astragaloside, tanshinone IIA (tan IIA), ginsenoside Re, hesperidin, and alisol A are screened out to take the best pharmacological effects on CHF[104].

Data from randomized controlled trials (RCTs) suggested QLQX significantly improved quality of life and reduced cardiovascular events, re-hospitalization rates, and mortality in CHF patients[105]. NT-proBNP, as a diagnostic and prognostic criterion, has been incorporated into the original American Heart Association/American College of Cardiology Heart Failure Diagnostic Criteria and Guidelines, and studies have shown that NT-proBNP level is positively correlated with CHF severity and the New York Heart Association (NYHA) classification of cardiac function and negatively correlated with EF and cardiac output[106]. In a multicenter, randomized, double-blind, parallel-group, placebo-controlled study enrolled 512 CHF patients, QLQX for 12 weeks reduced the NT-proBNP level, and demonstrated superior

performance in the NYHA classification of cardiac function, LVEF, and 6-MWD[107].

3.1.6. *Shexiang Baoxin Pills (SBPs)*

SBPs, a classic patent medicine composed of Moschus (Shexiang), Ginseng Radix (Renshen), Bovis Calculus (Niuhuang), Borneolum (Bingpian), CinnamomI Cortex (Rougui), Styrax (Suhexiang), and Bufonis Venenum (Chansu) originating from the Suhexiang Pills of the Song Dynasty in China, has been extensively used to prevent and treat cardiovascular diseases. SBPs may treat CHF characterized by Qi stagnation and blood stasis syndrome by supplementing Qi firmly and rapidly[108].

In a study on therapies in elderly patients with CHF secondary to ischemic cardiomyopathy, compared with trimetazidine alone, SBPs combined with trimetazidine apparently improved the clinical efficacy and indices of cardiac function (increasing LVEF and 6-MWD, decreasing LVEDD and LVESD) without serious adverse reactions[108]. In CHD-related CHF, the combination of SBPs and conventional drugs exerted preferable effects than conventional medications alone, as evidenced by the normalization of indicators reflecting cardiac function, including LVEF, LVEDD, LVESD, and cardiac output, and the reduction of NT-proBNP[109]. Furthermore, SBPs decreased endothelin and nitric oxide (NO) to improve cardiac function in CHF patients without changes in laboratory indicators, including blood count and renal and liver function tests, presenting pleasurable safety[110].

3.2. *Patent injections*

3.2.1. *Xinmailong injection (XML)*

XML is a *Periplaneta americana* extract with various effective bioactive components, including inosine, adenosine, pyroglutamic acid, and saccharin, approved by the China State Food and Drug Administration (CFDA) for treating CHF in 2006. For CHF caused by deficiency of Qi and Yang and blood stasis, XML can improve cardiac function by supplementing Qi and activating blood circulation, warming Yang to promote diuresis, to be an adjuvant therapy for congestive CHF[111].

In a multicenter double-blind RCT, the patients were given XML or a placebo (XML mimetics) in addition to receiving standard treatment[111]. XML (5 mg/kg) was injected intravenously (200 mL of 0.9% NaCl or 5% glucose at a drip rate 20−40 mL/min) twice a day for 5 days. Tests of the NYHA function showed that patients in the XML group had a greater overall efficacy rate than those in the placebo group. The 6-MWD distance was significantly longer (from 364.23 to 435.65 m) in patients taking XML compared to placebo. XML relieved symptoms and improved cardiac function and exercise tolerance in CHF patients, supported by a series of meta-analyses[112,113]. Moreover, age is a potential factor affecting efficacy and early use of XML contributes to improving the prognosis.

3.2.2. *Shengmai injection (SI)*

SI is illuminated by “Shengmai Powder” from “Medicine Origin (Yi Xue Qi Yuan)”, also known as “Shengmai Yin” in the Jin Dynasty (AD 1115−1234), consisting of Ginseng Radix (Renshen), Ophiopogonis Radix (Maidong), and Schisandra Chinensis Fructus (Wuweizi). SI could supplement Qi and nourish Yin to restore Qi and Yin and the feeble pulse in CHF. Shengmai Yin has been verified to control or slow the progression of CHF by inhibiting pathological changes in CHF rat models[114].

SI was revealed to decrease high-sensitivity C-reactive protein (hs-CRP) levels, enhance cardiac pumping function, biphasically regulate arterial blood pressure, reduce myocardial oxygen consumption, and improve vascular compliance[115]. A “real-world study” refers to a study that systematically collects and analyzes real-world data routinely generated from clinical trials[116]. Based on real-world data from the Hospital Information System, a study intensely explored the clinical characteristics of SI, demonstrating that it increased LVEF and cardiac output and improved cardiac function in CHF patients. Moreover, the combination of SI with chemical medicine such as spironolactone, furosemide, acetylsalicylic acid, and spironolactone can further prevent complications such as thromboembolism and respiratory infections and reduce the risk of adverse cardiovascular events[117]. A meta-analysis enrolled 20 RCTs demonstrated that adjuvant treatment with SI significantly improved cardiac function, including LVEF, cardiac output, and index, compared with conventional medicine alone[118]. Interestingly, patients receiving adjuvant therapy with SI showed a higher response to treatment[119].

3.2.3. *Shenmai injection (SMI)*

SMI is extracted from Ophiopogonis Radix (Maidong) and Ginseng Radix Rubra (Hongshen), which supplement Qi and Yin. It can improve the immune competence of tumor patients, increase the efficacy, and reduce the cardiotoxicity of chemotherapy drugs, for instance, anthracyclines[120].

In a multicenter, double-blind RCT, patients received SMI or a placebo except standard medication for CHF. After one week, the SMI group demonstrated a remarkable improvement in NYHA cardiac function classification, 6-MWD, and TCM syndrome score, compared with the placebo group[121]. Increasing evidence indicates that a disruption in myocardial energy metabolism in patients with CHF leads to the progression and deterioration of the disease[122]. SMI regulated energy metabolism as evidenced by changing FFAs, lactic acid, pyroracemic acid, and branched-chain amino acid levels in serum[123]. Besides, SMI could relieve respiratory dysfunction and LV systolic disorder in patients with pulmonary CHF[124]. SMI seeks to capture the attention of patients with pulmonary CHF. But another study found no evidence to support SMI as adjuvant therapy for pulmonary CHF[125]. This may be due to the low methodological quality and tiny sample size.

3.2.4. *Yiqi Fumai injection (YQFM)*

YQFM consists of Ginseng Radix Rubra (Hongshen), Ophiopogonis Radix (Maidong), and Schisandra Chinensis Fructus (Wuweizi), which can supplement Qi and nourish Yin to improve CHF caused by the deficiency of Qi and Yin syndrome caused by CHD in particular. By using lyophilized powder injection to make YQFM, the instability of TCM injection, is taken care of, which makes it easier to store[126].

During the process of CHF, excessive inflammatory factors may lead to elevated expression of soluble CD146 on endothelial cells, inducing neovascularization and rupture. Soluble CD40 may exacerbate the inflammatory response by binding to sCD40 receptors on the surface of smooth muscle cells and endothelial cells[127]. In the treatment of CHF induced by CHD, YQFM in combination with atorvastatin is effective. Their combination effectively reduced the levels of soluble CD146 and CD40 and pregnancy-associated plasma protein A, restored cardiac function, and ameliorated ventricular remodeling, and hence CHF patients may reap huge fruits in terms of prognosis[128]. YQFM can be easily dissolved in normal saline for an intravenous drip, which

implies the advantages of rapid action, a high concentration of active ingredients, and accurate drug delivery[129]. However, it should be properly prepared when used to adequately ensure clinical application safety. In a study comparing the clinical efficacy of YQFM and SI on CHF with Qi and Yin deficiency syndrome, SI was superior to YQFM in improving TCM symptoms, while YQFM exhibited better effects on regulating BNP values and cardiac function[130]. Current evidence suggests that YQFM, as a complementary therapy, significantly improves cardiac function and indicators in CHF patients.

3.2.5. *Huangqi injection (HI)*

HI is extracted from Astragali Radix (Huangqi), containing the total flavonoids of Astragalus, Astragalus polysaccharide, astragaloside, and astragalosaponin[131]. In the case of CHF caused by Qi deficiency of heart and blood stasis, HI contributes to supplementing Qi and invigorating the spleen in order to expel dampness and eliminate pathogens.

A study showed that the combination of HI based on standard treatment improved cardiac function and hemodynamic indexes better in CHF patients compared with standard treatment alone[132]. Additionally, HI was revealed to decrease malondialdehyde (MDA) and reduce NO and heme oxygenase-1 (HO-1) in CHF patients[133], implying that its effect may be associated with the up-regulation of endogenous antioxidation stress. In CHF patients with Qi deficiency syndrome, HI significantly improved 6-MWD, and the therapeutic effect exhibited a positive correlation with the duration and frequency of HI treatment[134]. However, the safety and efficacy of HI remain controversial[135]. More high-quality, evidence-based medical work is pressingly needed to investigate further.

3.2.6. *Shenfu injection (SFI)*

SFI is made up of Ginseng Radix Rubra (Hongshen), and Aconiti Lateralis Radix Praeparata (Fuzi) and originated from Shenfu Decoction in the Song Dynasty. It is irreplaceable in supplementing Qi to solidify and rescuing from collapse by restoring Yang. Thus, it has been widely used to rectify the syndrome of sudden Yang collapse. Since its commercial release in 1987, SFI has demonstrated a remarkable therapeutic effect in CHF patients during the acute phase[136].

In patients with acute aggravation of CHF caused by Yang and Qi deficiency syndrome, an RCT revealed that SFI effectively alleviated the respiratory dyspnea and inappetence and improved cardiac tolerance without adverse reactions[136]. In CHF patients with Yang deficiency of heart and kidney syndrome, SFI could down-regulate NT-proBNP level and main symptom scores[137], and SFI is superior to SMI in improving LVEF, BNP level and TCM syndrome curative effect of CHF[138]. Notably, from the health care system's perspective, a one-year decision tree model was used to estimate the costs and quality-adjusted life years of hospitalized CHF patients in grades III and IV treated with SFI combined with conventional therapy. The incremental cost-effectiveness ratio of SFI (a 14-day course of treatment) was 9016 CNY, far lower than the cost of conventional treatment alone and Chinese GDP per capita. The 7-day course treatment of SFI combined with conventional therapy is a dominant strategy, while the 14-day course of treatment of SFI is a cost-effective strategy[139].

3.2.7. *Shenqi Fuzheng injection (SQFZ)*

SQFZ is extracted from Astragali Radix (Huangqi) and Codonopsis Radix (Dangshen), which can supplement Qi and strengthen body resistance to improve CHF in the deficiency lung-spleen Qi syndrome[140]. Network pharmacology predicts that the Astragali Radix (Huangqi)—Codonopsis Radix (Dangshen) herbal pair targets PI3K/protein kinase B, mitogen-activated protein kinase (MAPK), and NF-κB pathways[141]. Calcitonin gene-related peptide (CGRP), a potent endogenous vasodilator, can improve endothelial cell function, promote vascular repair, reduce blood viscosity, and increase coronary blood flow[142]. It is confirmed that the decrease in CGRP level is highly correlated with myocardial injury in the early stages of CHF, reflecting the degree of cardiac dysfunction in CHF, and can act as an early marker[143]. Meanwhile, NF-κB mediated inflammatory responses were positively correlated with the severity of ventricular remodeling in CHF patients[144]. SQFZ was found to significantly reduce NF-κB level and increase CGRP level to suppress the inflammatory response, improving cardiac function[145].

MMP-9 and tissue inhibitor of MMP-1 regulate ECM alteration, which is a critical pathological factor of ventricular remodeling in CHF[146]. SQFZ was depicted to regulate the dynamic balance of MMP-1 and MMP-9, inhibiting ECM degradation to treat CHF[147]. Moreover, SQFZ could apparently increase heart rate, respiratory rate, BNP, and $PaCO_2$; meanwhile, it elevated the ratio of forced expiratory volume in 1 s[148], implying the potential of SQFZ to improve cardiopulmonary function in CHF patients with chronic obstructive pulmonary disease.

3.2.8. *Danhong injection (DHI)*

DHI contains Salviae Miltiorrhizae Radix (Danshen) and Carthami Flos (Honghua). Since its successful development in 2005, it has been widely used in the treatment of MI and cerebral infarction and is also being gradually applied to CHD and CHF nowadays[149,150].

DHI improved LVEF and reperfusion after MI, thereby significantly reducing the risk of mortality, recurrent angina, arrhythmia, and CHF[151]. Additionally, DHI could increase the 6-MWD and decrease the NT-proBNP level in CHD complicated by CHF[152]. The microcirculation is a complex network of small arteries, veins, and capillaries responsible for providing a dynamic response of tissue perfusion to local tissues in order to meet their oxygen requirements and to participate in nutrient transport and metabolite removal[153]. The microcirculatory dysfunction is correlated with systemic endothelial dysfunction and CHF severity[154]. DHI may reduce microcirculatory resistance to relieve myocardial injury[155]. CHF could activate platelets through the neuroendocrine system, hemodynamics, cytokines, and NO[156]. In turn, the activation of platelets participates in thrombosis and the inflammatory responses, which further play a role in the occurrence and development of CHF[157]. The liquid chromatography-mass spectrometry results demonstrated DHI anti-platelet aggregation in a dose- and concentration-dependent manner, mainly through the nicotinic acid-niacinamide metabolic pathway and the purine metabolic pathway[158].

3.3. *Common decoctions prescribed by physicians*

3.3.1. *Zhenwu decoction (ZWD)*

ZWD is recorded in "Treatise on Febrile Diseases (Shanghanlun)" by Zhang Zhongjing in the Han Dynasty, containing Poria (Fuling), Atractylodes Macrocephala Rhizoma (Baizhu), Aconiti Lateralis Radix Praeparata (Fuzi), Zingiberis Rhizoma Recens (Shengjiang), and Paeoniae Radix Alba (Baishao). It warms Yang

to eliminate diuresis, which is conducive to holding back edema due to Yang deficiency[159].

ZWD could boost LVEF, cardiac index, and stroke volume[160]. Aldosterone (ALD), an indicator of the RAAS, is positively correlated with CHF mortality. Prolonged high levels of ALD can exacerbate CHF caused by water-sodium retention, electrolyte disturbances, collagen deposition, and fibrosis in the myocardium and interstitial vessels, thus exacerbating CHF. However, ZWD was revealed to antagonize the RAAS and down-regulate ALD level by reducing Ang II in a dose-dependent manner[159], indicating ZWD can prevent the progression of CHF and decrease mortality partially. ZWD could induce the activity of the cytochrome P450 proteins (CYP), including CYP3A1, CYP2C6, and CYP2C11[161], which indicates that whether ZWD can be co-administered with these enzyme-mediated drugs and the potential herbal interactions are noteworthy. In short, ZWD may be appropriate for CHF patients complicated by or paired with renal diseases.

3.3.2. *Linggui zhugan decoction (LZD)*

During the Han Dynasty, Zhang Zhongjing wrote "Treatise on Febrile Diseases (Shanghanlun)", which states that LZD is made up of Poria (Fuling), Cinnamomi Ramulus (Guizhi), Atractylodes Macrocephala Rhizoma (Baizhu), Glycyrrhiza Radix (Gancao). LZD is unique in that it warms Yang to eliminate diuresis and strengthens the spleen to get rid of dampness[162].

In contrast to, which is better at warming Yang, LZD emphasizes spleen strengthening, which reduces digestive system difficulties in CHF patients. In CHF patients, especially in the elderly who have gastrointestinal clinical manifestations of impaired gastric motility caused by gastrointestinal stasis, such as abdominal distension, belching, a sense of fullness, and poor appetite, are frequent[163]. In addition to lowering BNP levels and improving LVEF values, LZD had further benefits in lowering the Gastrointestinal Symptom Rating Scale scores and shortening gastric emptying time[164]. Patients exhibit an improvement in appetite and quality of life, with a positive effect on CHF. For CHF patients with type 2 diabetes, LZD markedly decreased blood glucose, glycosylated hemoglobin, fasting insulin, and indices of triglyceride and total cholesterol. By enhancing glycometabolism, LZD, as a therapy for CHF with diabetes and obesity, has favorable elimination effects on risk factors[165].

3.3.3. *Taohong Siwu decoction (TSD)*

It is documented that TSD from "Fu Ke Bing Jian" in the Qing era activates blood circulation to remove blood stasis and enrich blood. It is composed of Chuanxiong Rhizoma (Chuanxiong), Carthami Flos (Honghua), Angelica Sinensis Radix (Danggui), Persicae Semen (Taoren), Paeoniae Radix Alba (Baishao), and Rehmanniae Radix (Dihuang). The prominent active ingredients in TSD are flavonoids, aromatic organic acids, and benzoquinones (from Carthami Flos, Chuanxiong Rhizoma and Angelica Sinensis Radix, respectively)[166].

Blood stasis destroyed the structure and proliferative activity of endothelial cells, with increasing levels of endothelin, NO, and TGF-β1. Endothelial cell structure and proliferative activity were both restored by TSD, and the levels of ET, NO, and TGF-1 were brought back to normal[167]. This proved that TSD is capable of removing blood stasis and attenuating endothelial cell damage caused by blood stasis. TSD also had the ability to dispel acute blood stasis[168]. By enhancing the local ischemia milieu and controlling mitochondrial dynamics, TSD has positive effects on cardiac function in ischemic cardiomyopathies including MI and CHF[169], suggesting TSD may be a promising adjunctive strategy for the treatment of ischemic cardiomyopathies. TSD paired with ZWD may partially reverse myocardial remodeling in congestive CHF with Yang deficiency and blood stasis syndrome by raising LVEF and MMP-1 values while lowering LVEDD, LVESD, BNP, and MMP-9 levels[170].

3.3.4. *Gualou Xiebai Banxia decoction (GXBD)*

Originally stated in "Jin Gui Yao Lue" in the Han era, GXBD is a common TCM formula composed of Trichosanthis Semen (Gualouzi), Alli Macrostemonis Bulbus (Xiebai), and Pinelliae Rhizoma (Banxia)[171]. It is able to treat CHF by activating Yang, removing obstructions, and regulating Qi to dissipate phlegm.

The versatility and effectiveness of GXBD in the treatment of cardiac disorders are backed by a lot of evidence. In individuals with stable angina, GXBD alone or in combination with standard medication dramatically reduced angina symptoms and improved the encephalogram and the blood lipid conditions[171]. Patients with excess phlegm are frequently plagued by lipid metabolism disorders, and GXBD presented eye-catching effects on CHD patients with phlegm stasis syndrome[172]. A number of elementary studies have revealed that GXBD may be a prospective TCM formula for therapy of CHF. GXBD could ameliorate the cardiac dysfunction due to myocardial fibrosis by inhibiting the expression of NF-κB pathway-related inflammatory mediators[173]. GXBD extract significantly alleviated infarct injury in MI rats, and the water-insoluble fraction of GXBD is an effective site of cardioprotective properties[174].

To create synergistic benefits and reduce toxicity, TCM formulas typically mix a number of Chinese medicinal herbs in varying amounts and methods. According to recent research, TCM offers CHF patients with various medical states or consequences more individualized and accurate therapy alternatives than chemical medications. In order to expand the window of on how TCM formulas can treat CHF and benefit more CHF patients, high-quality clinical trials are required.

4. Chinese medicinal herbs and their main ingredients with potential implication for CHF and the underlying mechanism

Chinese herbal compatibility lies at the heart of TCM formulas. The function of TCM formulas is based on diverse actions of natural herbs. A number of Chinese medicinal herbs with implications for the cardiovascular system can be applied to treat cardiovascular diseases. We summarized 15 Chinese medicinal herbs available for CHF from TCM formulas listed above and the rules of TCM prescription in the treatment of CHF that have been reported[175] (Table 2). Furthermore, we categorized and analyzed their main bioactive ingredients (Table 3 and Fig. 3).

4.1. *Astragali Radix (Huangqi)*

Huangqi is the root of *Astragalus membranaceus* (Fisch.) Bge.-var.mongholicus (Bge.) Hsiao or *A. membranaceus* (Fisch.) Bge., which mainly contains flavonoids, saponins, and alkaloids[176]. Flavonoids have antibacterial and antioxidant properties as well as the ability to promote glucose consumption and inhibit α-glucosidase[177]. Several alkaloids and phenolic components have been proved to possess biological activities such as antioxidation, anti-inflammation, and regulating metabolism[178–180]. Astragalus polysaccharide, mainly composed of glucan (water-soluble glucan and water-insoluble glucan) and heteropolysaccharides (mostly

Table 2 Category, main bioactive ingredients of Chinese medicinal herbs and their structure.

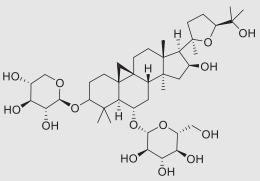
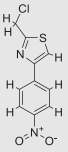
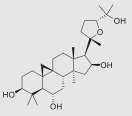
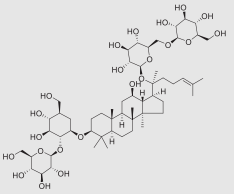
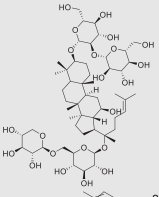
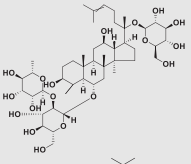
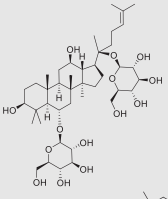
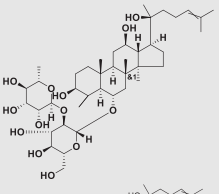
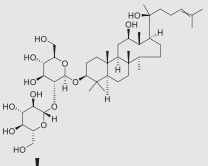
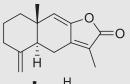
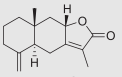
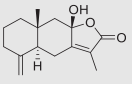
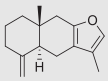
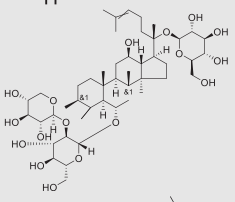
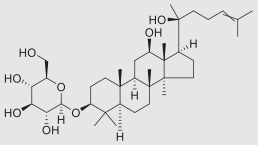
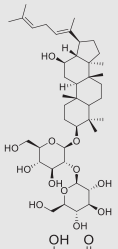
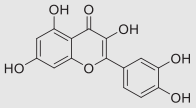
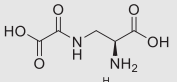
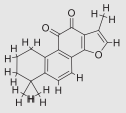
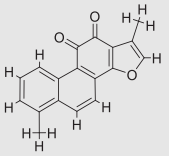
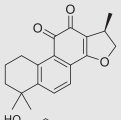
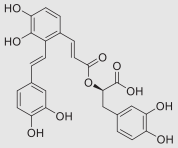
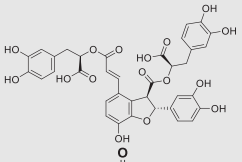
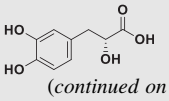
Category	Chinese medicinal herb	Ingredient	Structure
Tonifying Qi	Astragali Radix (Huangqi)	Astragaloside IV	
		Astragalus polysaccharide	
		Cycloastragenol	
	Ginseng Radix (Renshen)	Ginsenoside Rb1	
		Ginsenoside Rb3	
		Ginsenoside Re	
		Ginsenoside Rg1	
		Ginsenoside Rg2	
		Ginsenoside Rg3	
	Atractylodes Macrocephala Rhizoma (Baizhu)	Atractylenolide I	
		Atractylenolide II	
		Atractylenolide III	

Table 2 (*continued*)

Category	Chinese medicinal herb	Ingredient	Structure
		Atractylon	
	Notoginseng Radix (Sanqi)	*Panax notoginseng* saponins	
		Notoginsenoside R1	
		Ginsenoside Rh2	
		Ginsenoside Rg5	
		Quercetin	
		Dencichin	
Activating blood	Salviae Miltiorrhizae Radix (Danshen)	Tanshinone IIA	
		Tanshinone I	
		Cryptotanshinone	
		Salvianolic acid A	
		Salvianolic acid B	
		Danshensu	

(*continued on next page*)

Table 2 (*continued*)

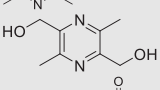
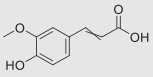
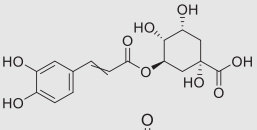
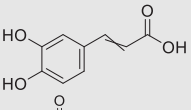
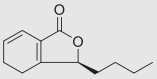
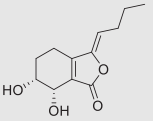
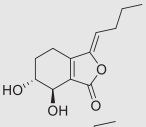
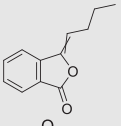
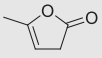
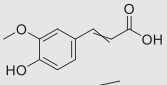
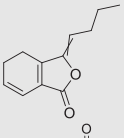
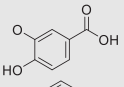
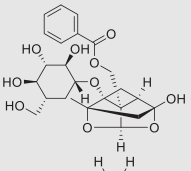
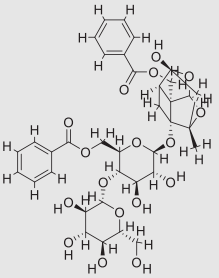
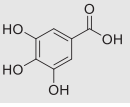
Category	Chinese medicinal herb	Ingredient	Structure
	Chuanxiong Rhizoma (Chuanxiong)	Ligustrazine	
		Liguzinediol	
		Ferulic acid	
		Chlorogenic acid	
		Caffeic acid	
		Senkyunolide A	
		Senkyunolide H	
		Senkyunolide I	
	Angelica Sinensis Radix (Danggui)	Butenyl phthalide	
		α-Angelica lactone	
		Ferulic acid	
		Ligustilide	
		Vanillic acid	
	Paeoniae Radix Rubra (Chishao)	Paeoniflorin	
		Paeoniflorin B	
		Gallic acid	

Table 2 (*continued*)

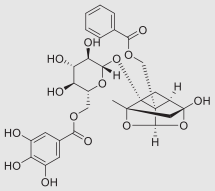
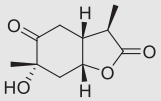
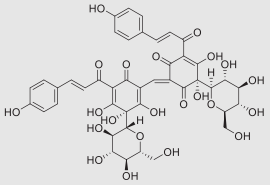
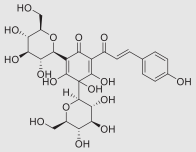
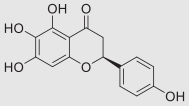
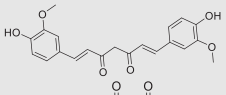
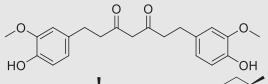
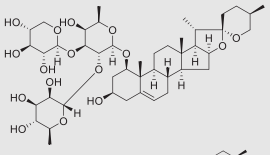
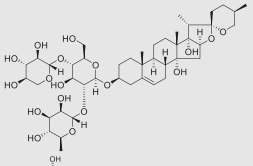
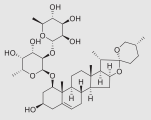
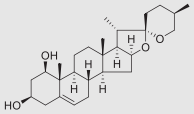
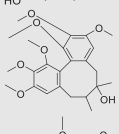
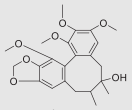
Category	Chinese medicinal herb	Ingredient	Structure
		Galloylpaeoniflorin	
		Paeonilactone A	
	Carthami Flos (Honghua)	Safflower yellow	
		Hydroxysafflor yellow A	
		Carthamidin	
	Curcumae Longae Rhizoma (Jianghuang)	Curcumin	
		Tetrahydrocurcumin	
Tonifying Yin	Ophiopogonis Radix (Maidong)	Ophiopogonin D	
		Ophiopogonin C	
		Ophiopogonin B	
		Ruscogenin	
	Schisandra Chinensis Fructus (Wuweizi)	Schisandrol A	
		Schisandrol B	

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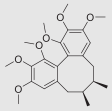
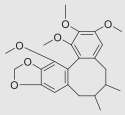
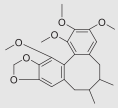
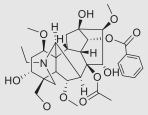
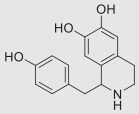
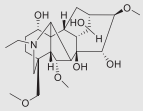
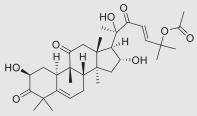
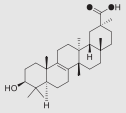
Table 2 (*continued*)

Category	Chinese medicinal herb	Ingredient	Structure
		Schisandrin A	
		Schisandrin B	
		Schisandrin C	
Warming Yang	Aconiti Lateralis Radix Praeparata (Fuzi)	Aconitine	
		Higenamine	
		Fuziline	
Dissipating phlegm	Trichosanthis Fructus (Gualou)	Cucurbitacin B	
		Bryonolic acid	
Inducing resuscitation	Moschus (Shexiang)	Muscone	

water-soluble acidic heteropolysaccharides), can be used as an immune promoter or regulator with the functions of enhancing immunity[181], anti-inflammation[182], antioxidation[183], and remodeling the gut microenvironment[184], act on multiple systems of the human body. Saponins, which include astragalosides I−VIII and isoastragalosides I−III, are important active components of Huangqi because they can stimulate the β-oxidation of FFAs, improve mitochondrial function, and increase the expression of VEGF and basic fibroblast growth factor to promote angiogenesis[185].

Astragaloside is the main active ingredient of saponins in Huangqi and can be used as a qualitative and quantitative index. The antioxidant activity and anti-apoptosis effects of astragaloside IV (AS-IV) on cardiomyocytes, are primarily achieved by reversing overexpressed small ubiquitin-like modifier-specific protease 1[186]. Hypercholesterolemia is a risk factor for the development of cardiac hypertrophy. It is reported that AS-IV could inhibit oxidative stress, regulate cardiac homeostasis, prevent hypercholesterolemia-induced cardiac remodeling, and restore ventricular function[187]. Signal transducer and activator of transcription 3 (STAT3) is a promising molecule for angiogenesis-mediated therapy. AS-IV could activate Janus kinase 2 (JAK2)/STAT3 pathway to increase vascular density to alleviate CHF by inducing the expression of CD31 and VEGF[188]. The molecular docking prediction showed that AS-IV might target MYD88 and subsequently the downstream TLR4 signaling pathway. AS-IV suppressed collagen I, III to ameliorate myocardial fibrosis by reducing inflammation and blocking TLR4/MYD88/NF-κB and suppressor of IKKε/TANK-binding kinase 1/PI3K/AKT pathways[189,190]. Moreover, AS-IV prevented against cardiac malfunction induced by MI/R that initiates from the phase of ischemia, *via* regulating energy metabolism to maintain the integrity of myocardial structure[191].

4.2. *Ginseng Radix et Rhizoma (Renshen)*

Renshen is the dried root and rhizome of *Panax ginseng* C. A. Mey., a medicinal plant of the Araliaceae family. Renshen has extensive pharmacological effects that work on multiple systems in the human body[192]. Research on Renshen focuses on Ginsenosides and ginseng polysaccharides, which have pharmacological effects such as inhibiting lipid accumulation[193], improving insulin sensitivity[194], selectively inhibiting apoptosis[195], repairing the blood−retinal barrier[196], and regulating energy metabolism[197]. Ginsenosides are the vital active components of Renshen that act on the central nervous system, cardiovascular system, immunological system and endocrine system. They are classified into three

Table 3 Targets/pathways and effects of ingredients of Chinese medicinal herbs on CHF.

Ingredients	Targets/Pathways	Effects	Ref.
Astragaloside IV	Senp1 JAK2/STAT3 pathway TLR4/MyD88/NF-κB pathway SIKE/TBK1/PI3K/Akt pathway	Oxidative stress Apoptosis Inflammation Energy metabolism Angiogenesis Myocardial fibrosis	185−190
Ginsenoside Rg1	RhoA signaling pathway AMPK/mTOR pathway MMP-9 α-SMA	Energy metabolism Apoptosis Myocardial fibrosis Autophagy	197,198,201,202
Ginsenoside Rg2	Akt/mTOR pathway	Autophagy	203
Ginsenoside Rg3	AMPK pathway NLRP3 pathway	Autophagy Inflammation Apoptosis	204
Ginsenoside Rb1	RhoA signaling pathway Rho/ROCK pathway PI3K/mTOR pathway MAPK/MEK1/2 signaling pathway miR-155 Gas6 pathway	Apoptosis Autophagy Inflammation Energy metabolism Oxidative stress Apoptosis	197−199,200,205,206
Ginsenoside Rb3	PPARα pathway PERK/Nrf2/HMOX1 pathway	Mitochondrial function Energy metabolism Oxidative stress Apoptosis Myocardial fibrosis	207−209
Ginsenoside Rc	SIRT1	Energy metabolism	210
Ginsenoside Re	TGF-β/Smad3 pathway	Myocardial fibrosis	211
Atractylenolide I	Caspase-3 signaling pathway AMPK pathway PI3K/Akt pathway	Apoptosis Mitochondrial function Energy metabolism	214,220
Atractylenolide II	Akt/p38 MAPK pathway AMPK pathway PI3K/Akt pathway	Energy metabolism	217,220
Atractylenolide III	Caspase-3 Akt/p38 MAPK pathway	Apoptosis Mitochondrial function Energy metabolism	215,217
Panax notoginseng saponins	PPARα, RXRα FoxO3a/Mn-SOD signaling pathway PI3K/Akt signaling pathway AMPK signaling pathway HIF-1α/BNIP3 pathway miR-29c CaMKII Thr287	Energy metabolism Mitochondrial function Oxidative stress Apoptosis Autophagy Myocardial fibrosis	222,225−228
Notoginsenoside R1	ROCK/ATP5D GRP78, P-PERK, ATF6, IRE CHOP, Caspase-12, P-JNK RhoA/ROCK-1/P-MLC pathway	Energy metabolism Oxidative stress ERS Myocardial fibrosis	223,224,377
Tanshinone IIA	NOX4 TLR4 C/EBP-β	Oxidative stress Myocardial fibrosis Inflammation	230−234
Total salvianolic acid	SIRT1 SIRT3	Oxidative stress Mitochondrial function	235
Salvianolic acid A	LncRNA PVT1 NF-κB pathway	Apoptosis	238
Salvianolic acid B	MMP9 α-SMA ERK1/2/GATA4 signaling pathway VEGF signaling	Autophagy Myocardial fibrosis Angiogenesis	236,237
3, 4-dihydroxyl-phenyl lactic acid	SIRT1 RhoA/ROCK-1/P-MLC pathway	Mitochondrial function Oxidative stress Apoptosis Myocardial fibrosis Energy metabolism	239,377
Ferulic acid	VEGF signaling Nrf2 signaling pathway	Apoptosis Oxidative stress Angiogenesis	241,243,244

(*continued on next page*)

Table 3 (*continued*)

Ingredients	Targets/Pathways	Effects	Ref.
		Gut microbiota	
Chlorogenic acid		Oxidative stress	245
		Apoptosis	
		Autophagy	
		Gut microbiota	
Ligustilide	AMPK/GSK-3β/Nrf2 pathway	Oxidative stress	248
		Inflammation	
		Myocardial fibrosis	
Ligustrazine	Ca^{2+} influx	Apoptosis	249–252
	ET-1	ERS	
	Ang II	Pyroptosis	
	PI3K/Akt pathway	Inflammation	
	TLR4/TRAF6/NF-κB/NLRP3/caspase-1 pathway		
	TLR4/caspase-8/caspase-3 pathway		
Liguzinediol	RAAS system	Oxidative stress	253–255,386
	PP1 and PP2A	Inflammation	
	SERCA2a	Myocardial fibrosis	
	TGF-β1/Smads pathway	Apoptosis	
	MMPs		
Angelica sinensis polysaccharide	Akt/hTERT pathway.	Apoptosis	257–262
	PI3K/Akt signal pathway mTOR signal pathway	ERS	
	miR-126	Oxidative stress	
	PI3K/Akt pathway	Myocardial fibrosis	
	JAK1/STAT3 pathway miR-22		
	ATF6 pathway		
Ferulate	PKC and MAPK signaling pathways	Myocardial hypertrophy	263
Vanillic acid	AMPK2	Apoptosis	264
	AMPK3	Oxidative stress	
Butylidenephthalide	PI3K/STAT3 axis	Inflammation	265
		Myocardial fibrosis	
Total glucosides of paeony	miR-181a-5p/ADCY1 axis	Oxidative stress	267–271,274
	NF-κB pathway	Pyroptosis	
	Caspase-1	Myocardial fibrosis	
	NLRP3	Inflammation	
	NOX-2	Apoptosis	
Paeoniflorin	NOX-2	Oxidative stress	271–274
	NOX-4 p38 MAPK pathway	Apoptosis	
	TGF-β1/Smad pathway	Myocardial fibrosis	
	GPCR pathway	Inflammation Immunoregulation	
	MAPKs/NF-κB patway		
	PI3K/Akt/mTOR pathway		
	JAK2/STAT3 pathway		
Hydroxysafflor yellow A	Mitochondrial permeability transition pores	Mitochondrial function	279–287
	HO-1/VEGFA/SDF-1α	Myocardial fibrosis	
	NLRP3	Angiogenesis	
	AMPK/NLRP3 pathway	Autophagy	
	JAK2/STAT1 pathway	Inflammation	
	Nrf2/NQO-1/HO-1 signaling pathway	Oxidative stress	
	PGC-1α/Nrf2 pathway	Apoptosis	
		Myocardial hypertrophy	
Curcumin	β-MHC (GATA site) p300-HAT	Apoptosis	289–294,297–300
	Nrf2 pathway	Cell death	
		Myocardial hypertrophy	
		Oxidative stress	
		Myocardial fibrosis	
		Mitochondrial function	
Tetrahydrocurcumin	PI3K/Akt/mTOR pathway	Apoptosis	299
		Autophagy	
Ophiopogonin D	CYP4F3	Energy metabolism	305–309,311,313–316
	JNK/ERK pathway	Oxidative stress	
	Ca^{2+}/Calcineurin signaling	ERS	
	CYP2J3	Mitochondrial function	

Table 3 (*continued*)

Ingredients	Targets/Pathways	Effects	Ref.
	SERCA2a	Autophagy	
	PI3K/Akt/eNOS pathway	Inflammation	
	CYP2J2	Apoptosis	
	JNK/c-Jun	Gut microbiota	
	CYP2J2/EETs-PPARα pathway		
	NF-κB pathway		
Polysaccharide from *Ophiopogon Japonicus*		Immunoregulation Gut microbiota	317−319
Schizandrin	Smad3/JNK/NF-κB pathway JAK2/STAT3 pathway	Apoptosis Myocardial hypertrophy Inflammation	322,323
Schisandrin B	AMPK/Nrf2 pathway PI3K/Akt pathway ATF6 pathway PERK pathway TGFβ1/NF-κB pathway	Oxidative stress ERS Apoptosis Inflammation Mitochondrial function Myocardial fibrosis	324−326,328,333,334
Schisandrin C	Keap1 Nrf2 pathway	Oxidative stress	327
Schisandrol A	14-3-3θ PI3K/Akt pathway	Oxidative stress Apoptosis Energy metabolism	330−332
Schisandrol B	TGFβ1/NF-κB pathway	Inflammation Myocardial fibrosis	330,333
Schisandra chinensis polysaccharide	TXNIP and Trx-1	Oxidative stress Myocardial hypertrophy	337
Aconitine	SIRT3 Mitochondrial permeability transition pores β-Adrenergic receptor agonist	Energy metabolism Myocardial hypertrophy Apoptosis Inflammation Mitochondrial function	341−344
Higenamine	LKB1/AMPKα/SIRT1 signaling pathway PI3K/Akt Pathway	Mitochondrial function Energy metabolism Oxidative Stress Apoptosis	350,351
Water-soluble alkaloids extracted from *Aconiti Lateralis Radix Praeparata*	Calcium signaling pathway RyR2 RyR3 SERCA2a	Apoptosis Myocardial fibrosis	352
Cucurbitacin B	Akt/mTOR/FoxO3a signal axis	Autophagy Pyroptosis Inflammation Myocardial hypertrophy Myocardial fibrosis	357
Bryonolic acid	Nrf2/HO-1 pathway	Inflammation Oxidative stress Pyroptosis	358
Muscone	SIRT3 NF-κB and NLRP3 inflammasome HIF-1α/VEGF pathway	Oxidative stress Apoptosis Inflammation Angiogenesis	361−365

types: type A (panoxadiol type), type B (panaxatriol type), and type C (oleanolic acid type). Based on the tight binding affinity of Ras homolog gene subfamily member A (RhoA) to ginsenoside Rg1 (GRg1) or ginsenoside Rb1 (GRb1), both of these inhibited RhoA signaling pathway to attenuate energy metabolism disorder and apoptosis to recover myocardial injury[198,199]. GRb1 also could regulate Rho/Rho-associated kinase (ROCK) and PI3K/mTOR pathways against CHF by inhibiting autophagy of cardiomyocytes[200]. GRb1 can act as a natural agonist of glutathione reductase to protect H9c2 cells from oxidative stress-induced apoptosis[201]. By dramatically suppressing AMPK and activating the mTOR pathway, GRg1 improved cardiac hypertrophy by preventing the formation of intracellular autophagosomes[202]. GRg1 also could regulate the interaction between Beclin 1 and BCL-2 and inhibit apoptosis while promoting autophagy[203]. Ginsenoside Rg2 could activate autophagy to

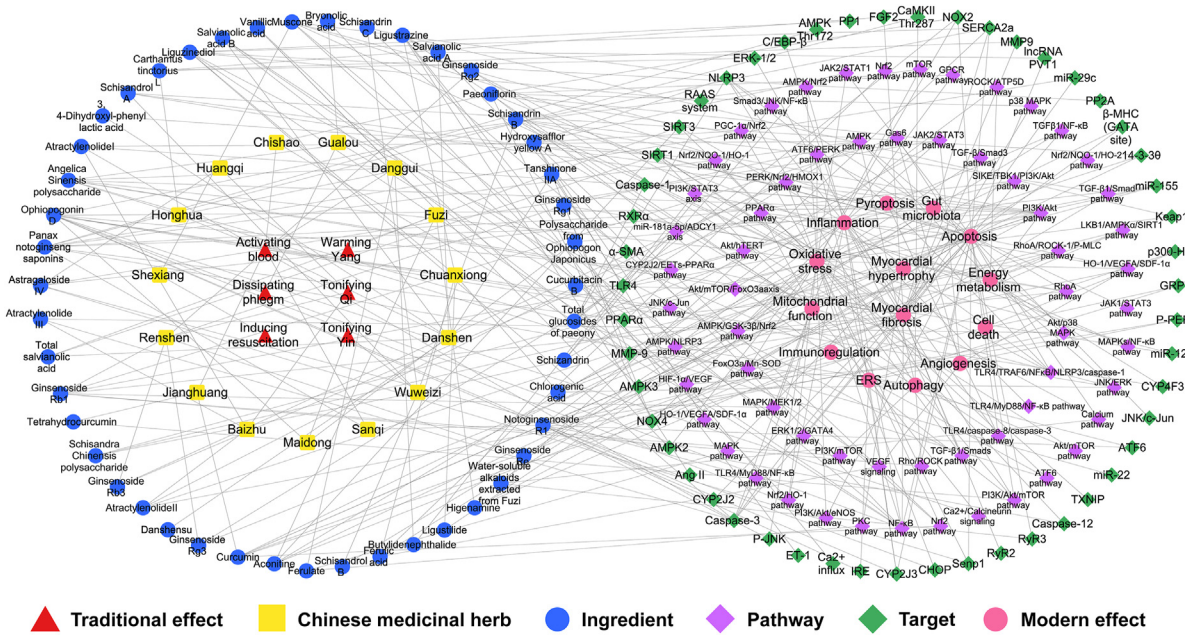


Figure 3 The summary of targets and pathways of natural herbal components against chronic heart failure.

protect human cardiomyocytes against trastuzumab-induced cardiotoxicity *via* upregulating Beclin 1, LC3, and ATG5[204]. Ginsenoside Rg3 protects the heart against isoproterenol (ISO)-induced myocardial injury by activating AMPK mediated autophagy and NLRP3 inflammasome[205]. In addition, GRb1 may reduce IL-1β, IL-6 and TNF-α production and mitigate cardiac inflammation to ease cardiac hypertrophy through MAPK 1/2 signaling pathway[206]. GRb1 could also reduce calcium and collagen deposition in aged mice, suggesting that GRb1 may be a potentially anti-aging-related vascular injury medication[207]. In addition to regulating the oxidation of FFAs by targeting the peroxidase proliferator activated receptor α (PPARα) pathway, Ginsenoside Rb3 (GRb3) could protect mitochondrial membrane integrity and exert anti-apoptotic effects[208]. In order to prevent hypoxia/reoxygenation (H/R)-induced oxidative stress and apoptosis GRb3 could phosphorylate extracellular regulated protein kinases (ERK), induce nuclear translocation of NF-E2-related factor 2 (Nrf2), and stimulate the production of HO-1[209]. Besides, nanoparticle conjugation of GRb3 corrected the low oral bioavailability to inhibit myocardial fibrosis[210], suggesting nano-drug carriers may be a potential solution for the delivery of natural drugs. Recent research found that ginsenoside Rc, as a silent information regulator (SIRT)-1 activator, promotes energy metabolism to improve cardioprotective functions under MI/R injury[211]. Orally administrated ginsenoside Re for four weeks to ISO-induced CHF rats significantly reduced collagen I by regulating the TGF-β/Smad3 pathway to alleviate myocardial fibrosis, thereby enhancing LV function[212]. In short, Renshen may be a fantastic agent for the treatment and management of CHF.

4.3. Atractylodes Macrocephala Rhizoma (Baizhu)

Baizhu, a commonly used tonifying Qi herb in TCM, is the rhizome of *Atractylodes macrocephala* Koidz. of the Asteraceae family. Lactones, polysaccharides, and volatile oil make up its primary chemical constituents. Atractylon is the main active component of volatile oil, and its content is a crucial quality evaluation criterion for Baizhu. Volatile oil from Baizhu is volatile, thus easily oxidized and decomposed into atractylenolides (ATL) I, II, and III[213]. Their content is arranged as follows: ATL III > ATL I > ATL II > ATL IV, and ATL II and ATL III are the main active components among them[214]. However, there have been few studies on the effects of *A. macrocephala* polysaccharides on the cardiovascular system.

ATL I pretreatment suppressed myocardial apoptosis by inactivating the caspase-3 signaling pathway to preserve mitochondrial function, thus improving myocardial morphology[215]. In rat models of MI, ATL III could also inhibit BAX and caspase-3 activity while up-regulate BCL-2 expression to reduce maladaptive apoptosis of cardiomyocytes and reverse mitochondrial malfunction[216].

Platelets are crucial in the development of atherosclerosis-thrombosis and therefore antiplatelet agents are widely used in the treatment of CHD[217]. ATL II and ATL III have been reported to reduce agonist-induced platelet aggregation and ATP release from dense granules, delay the contraction of clots in platelet-containing platelet-depleted plasma, and prolong the time to the first occlusion of iron chloride-induced carotid thrombosis in mice[218]. These results suggest ATL II and ATL III may be potential therapeutic candidates for the prevention of thrombosis.

Diabetes mellitus is a common co-morbidity and is recognized as a risk factor for a worse prognosis in CHF patients[219,220]. Recently, the SGLT2 inhibitors (dapagliflozin and empagliflozin) have been included as Class IA indication in the 2021 ESC guidelines on HF with LVEF $\leq$40% to reduce the risk of hospitalization and death in CHF patients. Similar to how SGLT2 inhibitor function, ATL I and ATL II were revealed to significantly increase GLUT4 expression and promote GLUT4 translocation to the plasma membrane through the activation of AMPK and PI3K/AKT pathways[221]. These compounds will have novel therapeutic applications for cardiovascular diseases accompanied by dysglycemia.

4.4. *Notoginseng Radix et Rhizoma (Sanqi)*

Sanqi is the dried root or rhizome of *Panax notoginseng* (Burk.) F. H. Chen. Using OB $\geq$ 30% and DL $\geq$ 0.15 as the screening conditions, nine main active components of Sanqi were obtained: octadecadiene, lipoxin, diisooctyl phthalate β-sitosterol, stigmasterol, ginsenoside Rh2, enoic acid ester, enoic acid, and quercetin[222]. *P. notoginseng* saponins (PNS) are the major cardioprotective substances of Sanqi, in which the contents of GRg1, GRb1, GRd, GRe, and notoginsenoside R1 (NGR1) are rich. PNS exerts a cardiovascular protective role through multiple pathways.

PNS specializes in regulating energy metabolism and mitochondrial function. Transcriptome analysis shows that PNS effectively increased the expression of PPARα and RXRα, which help control the downstream energy metabolism-related proteins to exert a cardioprotective effect[223]. While NGR1 was demonstrated to inhibit ROCK and enhance mitochondrial ATP synthase δ-subunits to prevent MI/R-induced energy metabolism disorder[224]. NGR1 pretreatment prevented ERS and apoptosis by decreasing the levels of ERS-responsive proteins GRP78, P-PERK, activated transcription factor 6, and IRE and inhibiting the expression of pro-apoptotic proteins CCAAT enhancer binding protein, caspase-12, and p-JNK[225]. Mitochondrial dysfunction leads to an increase in oxidative damage, which plays a key role in apoptosis in cardiomyocytes. PNS was reported to ameliorate aging-related mitochondrial dysfunction in a dose-dependent manner to attenuate oxidative stress damage and exert anti-apoptotic effects, thereby significantly improving myocardial morphological changes in aging rats[226]. PNS also enhanced glucose deprivation-induced mitochondrial autophagy through phosphorylation of AMPK Thr172 and CaMKII Thr287 in cardiomyocytes[227].

Besides, PNS inhibited cardiomyocyte apoptosis and death in the oxygen-glucose deprived-H9c2 cells and reversed hypertrophy through cell cycle arrest, DNA double-strand breakage repair process, and chromosome segregation[228]. Global gene expression analysis revealed that PNS could protect cardiomyocytes by elevating the expression of several non-coding RNAs, such as miRNAs and lncRNAs[229]. The anti-fibrotic microRNA miR-29c is involved in the cardioprotective effects of PNS. PNS promoted the expression of miR-29c directly and down-regulated fibrogenesis genes (collagen 1a1, collagen 1a2, collagen 3a1, and collagen 5a1), fibrillin 1 and TGFβ1 increased by ISO[229].

4.5. *Salviae Miltiorrhizae Radix et Rhizoma (Danshen)*

Danshen is the dried root and rhizome of *Salvia miltiorrhiza* Bge. in the Labiatae family. More than 60 lipid-soluble components and 50 water-soluble components have been isolated. Most of the lipid-soluble components are phenylanthraquinone derivatives, including tanshinone, tanshinone lactone, and tanshinol. Tanshinone, as a research hotspot, is mainly distributed in the root bark. Tanshinones contain *o*-quinone or *p*-quinone structures and are classified into tanshinone I, tan IIA, tan IIB, cryptotanshinone, isocryptotanshinone, 15,16-dihydrotanshinone, hydroxytanshinone, methyl tanshinonate, etc[230]. Among them, tan IIA has the most prominent activity. Most of water-soluble components are phenolic acids, such as salvianolic acid A, salvianolic acid B (Sal B), rosmarinic acid, protocatechualdehyde, and alkannic acid.

Tan IIA treatment prevented myocardial fibrosis to restore LVEF and LV fraction shortening in MI-induced CHF model *via* suppressing oxidative stress in cardiac fibroblasts[231]. Tan IIA injection can effectively improve microcirculation and ventricular remodeling, improve cardiac function, and reduce the occurrence of major adverse cardiac events[232]. In MI mice, the combination of tan IIA and puerarin at a ratio of 1:1 reduced M1 type macrophages, improved M2 type macrophages in the early stages, and reduced collagen synthesis and fibroblast release in the later stages, thereby inhibiting myocardial fibrosis and cardiac remodeling[233]. Sodium TSA sulfonate, the sulfonated product of tan IIA, has been clinically tested to be effective in treating angina pectoris[234]. A clinical trial on MI found that short-term treatment of sodium TSA sulfonate reversed progressive LV remodeling and resulted in better clinical outcomes, which may be relevant to the inhibition of eventual injury of the infarcted myocardium by infiltrating neutrophils[235].

Total salvianolic acid (TSA) is the main water-soluble component of SM, and TSA injection was approved by CFDA (Z20110011) in 2011 for ischemic stroke. TSA could attenuate oxidative stress injury induced by MI/R through upregulating SIRT1 and SIRT3 to restore the activity of mitochondrial respiratory chain complexes[236]. Sal B is the most abundant active ingredient in TSA. Elevated MMP-9 after MI may exacerbate ischemia-induced CHF. Increased MMP-9 inhibited autophagy, whereas Sal B inhibited MMP-9 activity and then increased autophagic flux in the peri-infarct myocardium to mitigate cardiac ECM deposition[237]. Inhibition of ERK1/2/GATA4 signaling pathway is a key mechanism of the anti-CHF effect of Sal B in CHF mice established by TAC-induced pressure overload[238]. Salvianolic acid A may down-regulate lncRNA plasmacytoma variant translocation 1 to prevent doxorubicin (DOX)-induced H9c2 cell injury and apoptosis by inhibiting NF-κB pathway[239]. 3,4-Dihydroxyl-phenyl lactic acid (DLA) is a water-soluble compound and regulates mitochondrial function mediated by SIRT1, a core target of DLA activities. DLA improved myocardial structure and cardiac function after MI/R *via* restoring SIRT1-interceding complex I activity and mitochondrial function[240].

4.6. *Chuanxiong Rhizoma (Chuanxiong)*

Chuanxiong is the dried rhizome of the plant *Ligusticum chuanxiong* Hort. in the Umbelliferae family. The bioactive ingredients in Chuanxiong can be categorized into phenols and organic acids, phthalates, and alkaloids. Phenols and organic acids are distinct bioactive components in Chuanxiong.

Ferulic acid (FA), chlorogenic acid (CHA), and caffeic acid (CAA), the main phenols and organic aids in Chuanxiong, show the prospect for clinical application. Diet or drugs may interact with the host by altering the intestinal flora, thus affecting the prognosis and progression of cardiovascular diseases. CHA and CAA can be derived into FA *via* a range of metabolic pathways. Gut microbiota affects the production of FA[241], and FA itself could regulate the gut microbiota. A daily supplement of 50 mg/kg FA for eight weeks improved LVEF and cardiac remodeling by increasing abundance of *Lactobacillus* and *Parabacteroides* in TAC mice, suggesting FA may be a nutraceutical and dietary option for prevention and treatment of CHF[236,242]. In both human umbilical vein endothelial cells and zebrafish models, FA enhanced the pro-angiogenic effect of Sal B partly through activating VEGF receptors[243]. FA ameliorated CHF by inhibiting apoptosis *via* decreasing Nrf2 signaling pathway-mediated oxidative stress[244]. CHA is metabolized mainly by the gut microbiota through hydrogenation, dehydroxylation, and hydrolysis, exhibiting multiple modulations of pathological cascade responses that reduce oxidative stress-induced apoptosis through the activation of autophagy[245].

The phthalides in Chuanxiong are a large group of substances with the parent nucleus structure of phthalides, for instance, ligustilide, senkyunolide A, senkyunolide H, senkyunolide I are abundant in content and have biological activity. Ligustilide, senkyunolide A, senkyunolide I may aid in the passage of medications across the blood−brain barrier. Therefore, it may be key for Chuanxiong to act as an 'envoy drug' to and trigger the upward movement of medications[246,247]. Ligustilide, the most abundant phthalide in Chuanxiong, could modulate oxidative injury, inflammation, and fibrosis through the AMPK/glycogen synthase kinase-3β/Nrf2 pathway, thereby attenuating glycolipotoxicity-induced cardiomyocyte dysfunction[248]. Ligustilide may represent a potential therapeutic agent against CHF with diabetes mellitus. Ligustrazine is considered the characteristic alkaloid of Chuanxiong and is supported as a metric for assessing the product quality. Ligustrazine inhibited Ca^{2+} influx[249], endothelin 1/Ang II released from endothelial cells[250], excessive apoptosis[251] and ERS[252]. Liguzinediol, 2,5-dimethyl-3,6-dimethylpyrazine, as a lead compound, is a structurally modified derivative of Chuanxiong. For one thing, liguzinediol reduced oxidative stress by inhibiting RAAS activation and the secretion of pro-inflammatory factors. For another, liguzinediol relieved myocardial fibrosis by reducing cardiomyocyte necrosis and collagen deposition[253]. Liguzinediol enhanced sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA2a) activity *via* inhibiting of protein phosphatase (PP1 and PP2A) activities, which contributed to positive inotropic effects in CHF rats[254]. In DOX-induced CHF rats, administration of liguzinediol for two weeks decreased BAX level and increased BCL-2 level, restored cardiac function by suppressing myocardial cell apoptosis. Meanwhile, a decrease in the number of apoptotic bodies and injury to cardiomyocytes could be observed by transmission electron microscope[255].

4.7. *Angelica Sinensis Radix (Danggui)*

Danggui is the dried root of *Angelica sinensis* (Oliv.) Diels, a plant in the Umbelliferae family. There has always been a saying that "nine out of ten prescriptions have Danggui". The main bioactive components in Danggui are *A. sinensis* polysaccharide (ASP), volatile oil, and vanillic acid (VA).

ASP accounts for 15% of the content of Danggui, and its physicochemical properties and biological activities are affected by different drying techniques. Freeze-drying ASP is more suitable for medicinal raw material[256]. ASP could improve the oxidative damage of diverse cells through various pathways[257,258]. ASP might protect the heart against MI by ameliorating the detrimental ERS[259]. ASP pretreatment activated activating transcription factor 6 signaling pathway and thus improved ERS and oxidative stress in hydrogen peroxide treated H9c2 cells[260]. ASP normalized cardiac functions (increasing the LVEF while decreasing the LVEDD, LVESD) by alleviating oxidative stress and apoptosis[261], implying that ASP may be a cutting-edge new natural antioxidant and anti-aging agent.

The volatile oil, another essential practical component, its content in Danggui is about 1%. It can be divided into neutral oil, phenolic oil and acidic oil. Among them, neutral oil accounts for the highest proportion, up to more than 88%, mainly including butylidene phthalide, butenyl phthalide, ligustilide, etc. FA is the representative of organic acids in Danggui. A pharmacokinetic study of FA indicates transdermal administration may be a promising drug delivery route compared with intragastric administration[262]. Ferulate is the sodium salt of FA, proving that it can inhibit protein kinase C and MAPK signaling pathways to downregulate Ang II and endothelin 1 levels to withstand myocardial hypertrophy[263].

VA is another phenolic compound with the high content in Danggui. In H9c2 cells of H/R injury, VA decreased the lactate dehydrogenase activity, accompanied by reduced levels of ROS, alleviated myocardial injury[264]. Butylidenephthalide is an active compound of VA, which promoted macrophage polarization to M2 type to reduce inflammation and myocardial fibrosis targeting the PI3K/STAT3 axis. Impressively, it even reversed aging-related myofibroblast dysregulation[265].

4.8. *Paeoniae Radix Rubra (Chishao)*

Chishao is the dried root of *Paeonia lactiflora* Pall., a plant of the Ranunculaceae family. Its active ingredients mainly contain glycosides, flavonoids, and phenolic acids. Glycosides in Chishao are collectively referred to total glucosides of paeony (TGP), mainly including monoterpene glucosides, which are mainly divided into pinane-type and pinane lactone-type glucosides[266]. The former mainly includes paeoniflorins A−H and desbenzoyl paeoniflorin; the latter includes paeonilactones A−C. These compounds underline the pharmacological effects of Chishao.

TGP can protect cardiomyocytes by regulating the levels of various myocardial enzymes and MDA[267]. TGP is capable of improving cardiomyocyte dysfunction by protecting antioxidative defenses and bioenergetic systems[268]. The onset of pyroptosis is dependent on the activation of caspase-1 as a result of the activation of intracellular inflammasome. TGP whittled caspase-1 and NLRP3 activity *via* miR-181a-5p/adenylate cyclase 1 axis, thus attenuated H/R-induced cardiomyocyte pyroptosis[269]. TGP reduced collagen fibril production by inhibiting the expression and activity of MMPs through the inhibition of NF-κB pathway[270]. Paeoniflorin accounts for more than 40% of TGP, which significantly downregulated the expression of NOX2 and NOX4 to fight with DOX-induced apoptosis and oxidative stress in a dose-dependent manner[271]. In addition, paeoniflorin could relieve myocardial fibrosis to rescue cardiac function *via* down-regulating the p38 MAPK and TGF-β1/Smad pathways in CHF rats[272,273]. In brief, TGP and paeoniflorin restore abnormal signaling pathways to exert broad anti-inflammatory effects and thereby treat CHF[274].

Gallic acid is the highest content of phenolic acid compounds in Chishao. Wistfully, its therapeutic application is limited by poor bioavailability and toxicity[275]. Flavonoids isolated from Chishao include kaempferol, dihydroapigenin, etc. These components may be the material basis of Chishao for promoting blood circulation and removing blood stasis[276].

4.9. *Carthami Flos (Honghua)*

Honghua is the dried tubular flower of *Carthamus tinctorius* L., mainly comprises flavonoids, alkaloids, and polysaccharides. The primary active ingredient in Honghua is safflower yellow, a quinone chalcone carboglycoside derived from flavonoids, whose structure is characterized by the oxidation of the chalcone ring. Nearly all red and yellow pigments in Honghua are classified as quinone chalcone carboglycosides, of which hydroxysafflor yellow A (HSYA) is a typical representative[277].

HSYA is one of the key medicinal substances in TSD[278]. HSYA penetrated the member of cardiomyocytes and was able to repair myocardial injury by interacting with mPTP[279]. Through the HO-1/VEGFA/SDF-1α signaling cascade response, HSYA increased the BCL-2/BAX ratio and decreased cleaved-caspase 3, TGF-β and

Collagen I in post-MI cardiomyocytes to mobilize endothelial progenitor cells to restore impaired LV function and promote myocardial angiogenesis[280]. In addition, HSYA may resist oxidative stress, inhibit the inflammatory response, and protect cardiomyocytes and endothelial cells, thus promoting VEGF release to promote angiogenesis[280]. Nucleolin is a multifunctional DNA−RNA−protein binding protein widely expressed in the nucleolus of eukaryotic cells. It might be a "staging post" for HSYA regulation on angiogenesis[281]. Inflammation, apoptosis, and autophagy play instrumental roles in the pathogenesis of myocardial injury, while HSYA could directly regulate AMPK/NLRP3 and JAK2/STAT3 pathways to suppress NLRP3 inflammasome and apoptosis as well as promote autophagy to protect hearts against MI/R injury[282−284]. Besides, HSYA exerted significant anti-hypertrophic effects[285]. Fibrosis-related factor 2 is engaged in myocardial hypertrophy and collagen deposition caused by pressure or volume overload. The ethanolic extract of Honghua, could antagonize fibrosis-related factor 2 and MMP9 to protect against lipopolysaccharide (LPS)-induced cardiac fibrosis[286]. In primary cardiomyocytes and human-induced pluripotent stem cell-derived cardiomyocytes, the cardioprotective effects of HSYA have in-depth corroboration. Patch-clamp experiments revealed that HSYA restored the contractile function of cardiomyocytes and abnormal field potential signaling[287].

Overall, further development of Honghua for the treatment of CHF is anticipated, given that Honghua injection has been used clinically in China for the treatment of occlusive cerebrovascular diseases and CHD (Approval number: Z14021790).

4.10. *Curcuma Longa Rhizoma (Jianghuang)*

Jianghuang is the dried rhizome of *Curcuma longa* L., a plant of the Zingiberaceae family. The main chemical components of Jianghuang are phenols and terpenoids, with curcumin constituting the majority of the former and volatile oil constituting the majority of the latter[288].

Curcumin attenuated norepinephrine-induced cell death and modulated apoptosis in H9c2 cardiomyocytes[289]. Chronic stress, including hypertension, upregulates the expression of p300 and p300 activation causes the release of BNP, endothelin 1, and atrial natriuretic peptide (ANP), which sharpens LV remodeling[290]. Inhibition of p300 by curcumin markedly reduced hypertension-induced elevations in posterior wall thickness and LV mass index without affecting systolic function in Dahl salt-sensitive rats[291]. Additionally, curcumin and its demethoxy derivatives inhibited cardiomyocyte hypertrophy by inactivating p300[292]. To improve the therapeutic potential of curcumin in CHF, a curcumin analog named GO-Y030 was synthesized. 1 μmol/L GO-Y030 is equivalent to 10 μmol/L curcumin, therefore, it could exhibit stronger curcumin-like effects[293]. Nanocurcumin also presented exceeding cardioprotective effects against DOX-induced cardiac toxicity[294]. Bevacizumab is a human monoclonal antibody with promising efficacy for the treatment of metastatic malignancies. Bevacizumab disrupts mitochondria and exacerbates the risk of cardiovascular diseases with age, including CHF[295,296]. Curcumin in combination with bevacizumab significantly reduced the cardiotoxicity of bevacizumab and avoided deterioration of cardiac function[297].

Exercise intolerance is a typical symptom of HFrEF. Curcumin might target Nrf2 in skeletal muscle to increase oxidative defense capacity to delay force loss and fatigue in HFrEF mice[298]. Nrf2 in skeletal muscle could be an imaginable point for treating severe CHF. Tetrahydrocurcumin (50 mg/kg/day), an essential hydrogenated metabolite of Jianghuang, protected rat hearts from MI/R-induced CHF by increasing LVEF, LV fraction shortening and decreasing LVESD and LVEDD[299]. Curcumin and some of its analogs could improve cardiac dysfunction caused by cardiac fibrosis[300]. Moreover, curcumin may be used as an alternative therapy for the treatment of patients with fibrotic CHF who are intolerant to angiotensin-converting enzyme inhibitors[301]. It is worth noting that adrenergic β-blockers and curcumin may interact and affect each other's pharmacodynamic[302]. Nonetheless, oral curcumin (80 mg/day) for five days had no positive effect on electrocardiographic parameters and echocardiographic parameters, and no differences were demonstrated in arrhythmias and CHF in patients with unstable angina[303]. Still, there is an urgent need for more research to move promising drugs from basic experiments to clinical practice.

4.11. *Ophiopogonis Radix (Maidong)*

Maidong is the dried tuberous root of *Ophiopogon japonicus* (L. f) Ker-Gawl in the Orchidaceae family. A variety of chemical components were isolated from different parts of Maidong, such as steroid saponins, homoisoflavonoids, polysaccharides, volatile oil, etc., among which steroidal saponins and homoisoflavonoids have a variety of pharmacological activities[304].

Steroid saponins are divided into ruscosaponin-type and diosgenin-type structures, of which ruscogenin is dominant and regarded as a landmark component for measuring the quality of Maidong. The steroid saponins belonging to ruscogenin are ophiopogonins A, B, C, and D. In human AC16 cardiomyocytes, ophiopogonin D (OPD) can regulate the metabolic molecules of FFAs to protect the cardiovascular system in a dose-dependent manner[305]; while it also alter gut microbiota composition and fecal metabolites to prevent atherosclerosis[306]. The antioxidative activity of OPD can reduce mitochondrial membrane potential damage, improve mitochondrial productivity disorders, and balance myocardial energy homeostasis; meanwhile, it plays a comprehensive myocardial protective role by regulating the autophagic activity of mitochondria and clearing the inflammatory factors caused by injury[307]. Besides, OPD upregulated fusion proteins mitofusion 1/2 and optic atrophin 1 to manage the dynamic equilibrium of mitochondrial division to allay diabetic myocardial injury[308]. OPD can maintain the Ca^{2+} homeostasis of cardiomyocytes by suppressing ERS[309]. As a member of the cytochrome P450 superfamily, CYP2J3 catalyzes the conversion of arachidonic acid into epoxyeicosatrienoic acids (EETs)[310]. Elevated expression of CYP2J3 and EETs protects the heart by maintaining cardiomyocyte Ca^{2+} homeostasis through upregulation of phospholamban and SERCA2a expression[311]. OPD promoted phospholamban phosphorylation and SERCA2a activity *via* the modulation of CYP2J3 to sustain Ca^{2+} homeostasis, thus rescuing cardiac function[312]. Furthermore, OPD upregulated circulating CYP2J3/EETs, exerting anti-apoptotic, antioxidant, and anti-inflammatory effects to reduce MI/R injury and death of endothelial cells[313−315]. Inhibition of the inflammatory response with the help of CYP2J3 upregulated by OPD also attenuated myocardial hypertrophy *via* NF-κB pathway[316].

Polysaccharides from *O. japonicus* (POJ) are composed of mono- and oligosaccharides, including fructose and glucose. POJ possesses conspicuous immune-enhancing activity and may be a novel immunopotentiator[317]. In addition to slowing a rapid heart rate, POJ could restore cardiac contraction amplitude and coronary flow faster after MI/R[318]. POJ promotes the intestinal

microbial-induced metabolism of ophiopogonin and acts synergistically with ophiopogonin[319].

4.12. *Schisandra Chinensis Fructus (Wuweizi)*

Wuweizi is the dried and mature fruit of *Schisandra chinensis* (Turcz.) Baill. principallycomposed of lignans and volatile oil. Volatile oil contains terpenoids, aliphatic compounds, and aromatic compounds, among which sesquiterpenoids are the most abundant, playing the role of anti-tumor, and anti-inflammation[320]. Lignans account for 8% of Wuweizi, schizandrin, and schisandrol are the primary active components of lignans. The composition of Wuweizi grown in different regions of China varies significantly. Wuweizi from southwest China has the best antioxidant capacity, and the main antioxidants are schisandrol A, schisandrol B, and schisandrin B[321].

LPS induced excessive secretion of pro-inflammatory factors in H9c2 cells, whereas schizandrin reduced inflammation and cell loss, which may be partially reversed by overexpression of Smad3[322]. Schisandrin down-regulated JAK2/STAT3 pathway to decrease the BAX/BCL-2 ratio, increased the ratio of the cell surface area to cardiomyocyte protein/DNA, showing the potential for treating myocardial hypertrophy[323].

Nrf2 is involved in the regulation of the antioxidant system, while myocardial injuries could disrupt the transcriptional activity of Nrf2. In H/R H9c2 cells, schizandrin B activated the AMPK/Nrf2 pathway to confront oxidative stress and inflammation[324]. Also, schisandrin B could reduce oxidative stress and ERS-induced excessive apoptosis caused by MI/R injury[325,326]. Similarly, schisandrin C targeted the Nrf2 pathway to attenuate oxidative stress in endothelial cells[327]. Nrf2 is a central molecule in the mechanism of the antioxidant and anti-inflammatory activity of schisandrin. Pirarubicin is one of the anthracycline anti-cancer drugs, and its cardiotoxicity cannot be ignored. In the cardiotoxicity rat models induced by pirarubicin, schizandrin B inhibited mPTP opening and sustained mitochondrial function to antagonize cardiotoxicity[328]. There is growing evidence that 14-3-3 proteins regulate cell cycle, signal transduction, metabolism, protein transport, necroinflammation, and apoptosis[329]. With rapid absorption (T_{max} = 2.07 h) and a longer duration ($t_{1/2}$ = 9.48 h), schisandrol A binding to 14-3-3θ proteins could resist oxidative stress and reduce apoptosis to attenuate MI/R injury[330,331]. Moreover, schisandrol A could regulate various endogenous amino acid metabolic pathways to protect against cardiac diseases[332].

It has been reported that schisandrol B and schisandrin B had the strongest inhibitory effect on TGFβ1-mediated NF-κB activation[333]. Hence, schisandrol B and schisandrin B might be candidates for anti-myocardial fibrosis. And the antifibrotic effect of schisandrin B has been demonstrated in TAC mice[334]. Although schisandrin B shows a promising future, its poor solubility and low bioavailability may limit its clinical application. Schisandrin B delivery *via* MMP-sensitive peptide-modified PEGylated lipid nanoparticles may be an alternative option[335].

It is noteworthy that *S. chinensis* polysaccharides are also effective at improving cardiac function. Thioredoxin-1 (TRX-1) is among the most important cellular antioxidative systems, reducing oxidized proteins through thiol-disulfide exchange reactions[336]. *S. chinensis* polysaccharides may bind to Arg207, Ser169, Lys166, Lys286, and Ser285 in TRX-interacting protein through hydrogen bonds, which may restrict or interfere with the binding between TXNIP and TRX-1 and its interacting protein, resulting in TRX-1 activation to inhibit oxidative stress to prevent cardiac hypertrophy[337].

4.13. *Aconiti Lateralis Radix Praeparata (Fuzi)*

Fuzi is the processed root of *Aconitum carmichael*, a plant in the Ranunculaceae family, which is regarded as “the first choice for herbs of invigorating Yang and saving lives”. Alkaloids are the main chemical components, representing substantial cardioprotective effects. The raw Fuzi mainly contains diester alkaloids, which can be hydrolyzed into monoester alkaloids after decoction or concoction, and the latter can be further hydrolyzed into alcohol-amine alkaloids[338]. The toxicity is based on the number of ester bonds. In order of decreasing toxicity, diester type > monoester type > alcohol-amine type.

Aconitine is the main active ingredient of diester alkaloids as well as the main component causing cardiotoxicity[339]. Although aconitine has certain cardiotonic effects, it is prone to the occurrence of arrhythmias[340]. The effectiveness of aconitine in the treatment of CHF is debatable. On the one hand, aconitine attenuated Ang II-induced energy metabolism dysfunction in H9c2 cells by activating SIRT3, thus inhibiting mPTP opening, and improving ATP synthesis[341]. Aconitine may alleviate Ang II-induced cardiac hypertrophy by inhibiting hypertrophic factors including ANP, BNP, β-myosin heavy chain, α-SMA and F-actin[342]. Selective activation of β-adrenergic receptor agonist by aconitine inhibits cardiomyocytes apoptosis and prevents MI/R injury[343]. On the other hand, accumulating evidence has proved that aconitine can readily cause heart damage. Aconitine inhibited cardiomyocyte proliferation in a dose- and time-dependent manner and induced inflammation and mitochondria-mediated apoptosis[344]. Although some people believe that the lowest possible concentration of aconitine would not cause cardiotoxicity, a recent result indicated that the aconitine level in blood did not correlate with symptoms or electrocardiogram findings caused by aconitine[345].

Compatibility with other herbs or therapies offers a breakthrough for the clinical application of aconitine. Mass spectrometry analysis revealed that the content of toxic components decreased while the content of protective components increased by compatibility of Glycyrrhiza Radix (Gancao), rapidly ameliorating the inflammation response in HF mice[346]. Paeoniflorin could also significantly reduce the cardiotoxicity of aconitine on H9c2 cells[347]. Combined with electroacupuncture, aconitine can not only improve the systolic function of CHF rats more obviously, but also reduce the toxic reaction of aconitine[348,349]. For long-term drug treatment of CHF, a combination of non-drug therapies, for instance, acupuncture and massage, can be considered as a measure to increase the effectiveness of drugs and reduce their toxicity.

Higenamine is another water-soluble alkaloid in Fuzi. Higenamine in combination with gingerol significantly increased the mitochondrial oxygen consumption rate and extracellular acidification rate and improved mitochondrial dysfunction to alleviate cardiac injury. In addition, the metabonomic analysis showed that the anti-CHF effect of their combination was mainly related to the regulation of the metabolism of FFAs and energy metabolites[350,351]. The aqueous extracts of Fuzi could attenuate the

expression of SERCA2a to maintain intracellular calcium homeostasis and suppress the expression of α-SMA, collagen I, and III, thus inhibiting ventricular remodeling associated with CHF[352].

4.14. *Trichosanthis Fructus (Gualou)*

Gualou is the dried ripe fruit of *Trichosanthes kirilowii* Maxim. or *T. rosthornii* Harms in the Cucurbitaceae family. Gualou is an important herb for the treatment of cardiothoracic obstruction, angina pectoris, MI, CHF, etc. Triterpenoids are the main active substances in Gualou. Cucurbitacin B and bryonolic acid are two characteristic triterpenoids found in Gualou that have a variety of activities, inducing angiogenesis, anti-tumor, triggering pyroptosis, and anti-inflammation[353−355].

The aqueous extract of Gualou protects H9c2 cells from H/R injury by regulating PI3K/Akt/NO pathway to decrease apoptosis[356]. In mice with TAC-induced myocardial hypertrophy and phenylephrine-stimulated human AC16 cardiomyocytes, cucurbitacin B was depicted to promote autophagy, restrain heart weight and interstitial fibrosis, exhibiting a strong resistance to hypertrophy and fibrosis[357]. Bryonolic acid suppressed the inflammatory response by inhibiting the expression of inducible NO synthase in LPS-stimulated RAW 264.7 macrophages. In addition, bryonolic acid steadily induced the HO-1 protein, which relies on Nrf2 to fight against oxidative stress *in vitro* and *in vivo*[358].

4.15. *Moschus (Shexiang)*

Natural Shexiang is the dried secretion of the scent sac of the mature male of *Moschus berezovskli* Flerov, *M. sifanlcu*s Pmew alssi. and *M. moschifems* Linaeu. As natural Shexiang is infrequent, synthetic Shexiang is now widely used, for example, in SBPs. Synthetic Shexiang has the same odor and clinical efficacy as natural Shexiang and can be used as a substitute for musk. Muscone is the main active component of Shexiang, which could activate the mouse muscone receptor MOR215-1 and human musk receptors OR5AN1 and OR1A1 to conduct signal cascades *via* odorant molecules[359,360].

Muscone pretreatment significantly reversed the decrease of MMP and BCL-2, and the increase of lactate dehydrogenase, MDA, creatine kinase, and caspase-3 caused by MI/R injury[361]. Overactive and persistent chronic inflammation leads to worsening ventricular remodeling and depresses cardiac function[362]. Muscone pretreatment could inhibit oxidative stress and inflammation, attenuate MI/R-induced cardiac dysfunction and LV remodeling, relying on the upregulation SIRT3[363]. Muscone also alleviated cardiac macrophage-mediated chronic inflammation by inhibiting NF-κB and NLRP3 inflammasome activation, thereby improving cardiac function in MI mice[364]. Besides, the scavenging of ROS may be its other mechanism[364]. Moreover, muscone could upregulate the expression of VEGFA and HIF-1α, promoting myocardial angiogenesis to repair damaged hearts in CHF mice[365]. Muscone is a chiral compound that can be further divided into *S*-muscone and *R*-muscone, both of which are present in synthetic Shexiang. In a zebrafish model, *S*-muscone and *R*-muscone were found to cause cardiotoxicity in zebrafish embryos through myh6 and myh7 mRNA, Trh, thβ, and Dio3 genes, resulting in pericardial edema and slowing of heart rate[366]. Concerns about safety still need to be raised about the chiral isomer composition and clinical application of synthetic Shexiang.

5. The synergistic effects of constituent compatibility in the treatment of CHF

The purpose of compatibility in TCM formulas is to exert synergistic effects, including enhancing effects and reducing toxicity, through the integration of multiple targets and multiple pathways mediated by specific active substance groups. The compatibility of Chinese medicinal herbs was accurately determined through screening for the compatibility of their effective constituents in order to demonstrate the synergistic effects of TCM formulas.

The compatibility with other Chinese medicinal herbs to increase the efficiency and reduce the toxicity of Fuzi may open a window for its clinical application. By upregulating the expression of CYP3A, Glycyrrhizae Radix (Gancao) can promote the metabolism of toxic components of Fuzi including aconitine, mesaconitine, and hypaconitine; reduce the contents of BNP, Ang II and ALD; improve myocardial energy metabolism, and thus preventing the development of CHF[367]. Moverover, the compatibility could significantly increase the exposure of active components composed of hypaconitine, benzoylmesaconitine, and songorine *in vivo*[368]. Acetyl-11-keto-β-boswellic acid is a major component in Ruxiang. HSYA pretreatment with acetyl-11-keto-boswellic acid reduced the level of mitochondrial ROS while increasing superoxide dismutase activity, effectively attenuating ISO or oxygen-glucose deprivation-induced cardiomyocyte damage[369]. Active fractions were obtained by means of solvent extraction and chromatography from QLQX, and 11 compounds with their own targets were identified that produce cardiotonic, diuretic, and vasodilator effects through synergistic or complementary effects[370]. Ginsenosides Rb1, Rg1, Rf, Rh1, Rc, Rb2, Ro, and Rg3, were isolated and confirmed as the major anti-inflammatory constituents of YQFM[371].

The 24 ingredients from QSYQ were predicted to be bioactive and named combinatorial bioactive ingredients (CBIs) *via* UPLC−Q-TOF/MS and the ChEMBL database. CBIs presented greater cardioprotective potency than the individual ingredients in QSYQ, exhibiting similar potency to QSYQ and synergistic effects[372]. QSYQ without Jiangxiang, on the other hand, significantly weakened myocardial protection. In another study, according to the composition of QSYQ and Jun-Chen-Zuo-Shi theory, supplementing Qi constituents were prepared in the ratio of HQ: Jiangxiang = 148.01:11.97 and activating blood constituents were prepared in the ratio of Danshen:Sanqi:Jiangxiang = 70.35:70.35:11.97. The simultaneous supplementing Qi and activating blood achieved the best therapeutic effect[373]. DLA and NGR1 are major ingredients in QSYQ. DLA inhibited SIRT1 expression, resulting in a decrease in complex I activity. NGR1 reversed the upregulation of RhoA/ROCK-1 expression and myosin light chain phosphorylation, restored mitochondrial complex V activity and F-actin arrangement, and alleviated myocardial fiber rupture. The additive effect of DLA and NGR1 could exert a stronger protective effect on MI/R injury *via* inhibiting oxidative stress and recovering energy metabolism[374]. AS-IV inhibited the abnormal energy metabolic pathway; Danshensu inhibited oxidative stress; NGR1 partially improved myocardial energy metabolism, inhibited oxidative stress injury, and descending aromatic oil up-regulated carnitine palmitoyl transferase 1A. Their

compatibility supplements Qi and activates blood to reverse myocardial hypertrophy and fibrosis with the best effect[375]. GRb1 (G), ruscogenin (R), and schisandrin (S) are selected separately from the composition of "Shengmai Yin", and the three components synergistically exert superimposed therapeutic effects on MI/R injury with best efficacy at the dose of 18.15 mg/kg (G:R:S = 12:0.15:6) to improve myocardial injury[376,377]. Demethylcoclaurine, benzoylaconine, ATL III, paeoniflorin, 6-gingerol, 8-gingerol, pachymic acid, and dehydrotumulosic acid can be defined as quality markers of ZWD for treating CHF[378].

6. Discussions and perspectives

Multiple etiologies and pathophysiological mechanisms that interact with each other make up the complex pathophysiology of CHF. Epidemiological data show a gradual increase in the incidence and prevalence of CHF with aging. According to the majority of earlier research, CHF was driven on by traditional risk factors for cardiovascular disease, including CHD, hypertension, diabetes, and atrial fibrillation, under aging conditions[379]. However, aging is increasingly becoming recognized as a separate factor that damages myocardial, causing progressive decline of cardiac structure and function that eventually manifests as end-stage heart diseases[380]. Finding strategies to prevent the early onset of CHF is therefore valuable, and the fact that so many herbal ingredients have exhibited cardioprotective effects is encouraging. With thousands of years of history and a wealth of theories and knowledge, TCM has been used to prevent and treat heart diseases, including CHF.

TCM significantly affects the symptoms and quality of life of CHF patients, according to a growing body of contemporary, evidence-based medical studies[381–383]. The cornerstone of TCM theory is treatment based on syndrome differentiation, which necessitates different prescriptions according to individual and syndrome differences. For CHF with deficiency of Qi and Yin, SSYX is superior to nourishing Qi and Yin to improve the syndrome, while CHF with blood stasis and phlegm due to Qi deficiency prefers QSYQ and TXL treatment to supplement Qi and promote blood circulation; QLQX is more suitable for CHF with deficiency of heart and kidney Yang by warming Yang and inducing diuresis; and SBPs are more effective for CHF with Qi stagnation and blood stasis syndrome. Exhilaratingly, the gap between TCM theory and modern medicine theory is narrowing. The Qi deficiency is closely relevant to mitochondrial function and energy disorders. Coincidentally, it has been demonstrated that the impact of Qi-supplementing herbs is concentrated on the regulation of energy metabolism[384]. The physiology and pathology of phlegm in TCM are related to the imbalance of autophagy[385]. All of these findings would shed new light on the elaboration of obscure TCM theories and herbal functions.

Even though TCM therapy for CHF worked well, the fact that some key issues remain unresolved has hampered the clinical application of TCM formulas and Chinese herbs in CHF patients. Firstly, a precise connection with objective biological indicators in the diagnosis and treatment system of TCM-based syndrome differentiation has not yet established, which limits the application of TCM in the modern medical system. Hence, it is imperative to incorporate objective indications into TCM theory and establish a unified standard for TCM diagnosis and treatment in order to standardize clinical treatment. The types, quantities, and proportions of the ingredients in Chinese medicinal herbs and TCM formulas are complex, which makes it challenging to grasp their exact mechanisms. It is urgent to put more effort into finding out active constituents and probable action mechanisms of Chinese herbal medications. Besides, the immediate effects of TCM tend

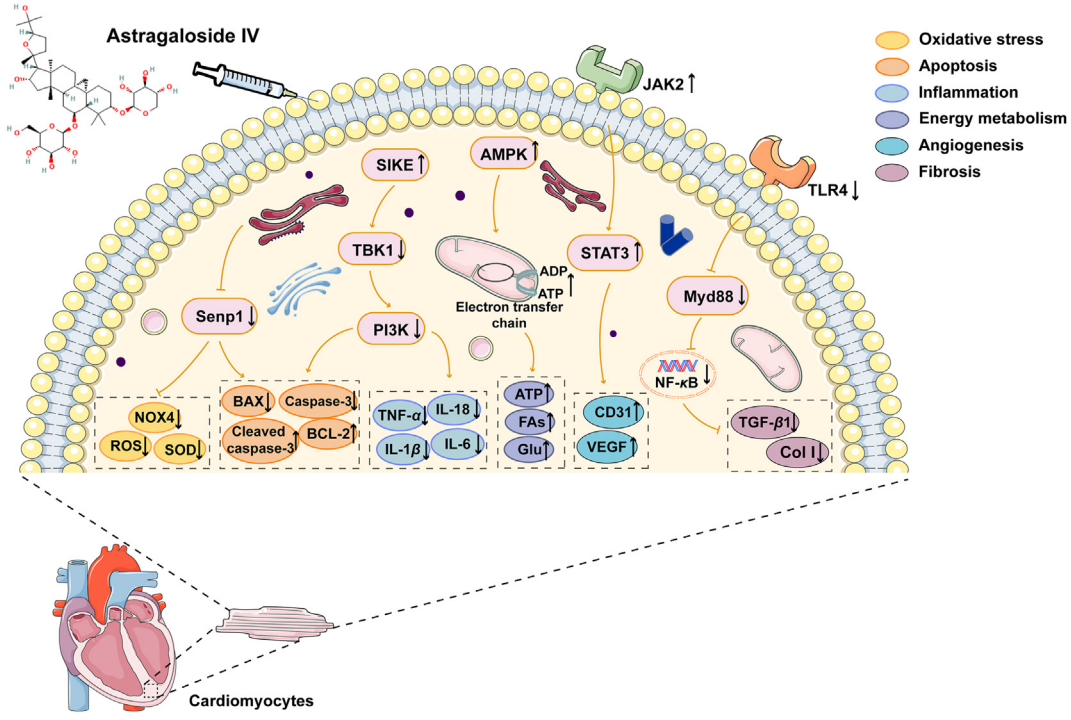


Figure 4 The example showing the superiority of natural ingredients in the treatment of chronic heart failure, attributed to their multi-target potential.

to be overlooked, which may squander the finest chance and effectiveness for treating CHF. TCM is worthy of clinic application as early as possible for the sake of the best effect.

As research into synthetic chemical drugs has reached a bottleneck, the development of pharmaceuticals based on Chinese herbal medicines has become a current direction. Numerous natural components control several pathogenic variables by acting on numerous routes and systems. For example, AS-IV could inhibit oxidative stress, reduce inflammation, and regulate energy metabolism to restore cardiac homeostasis[187,189−191] (Fig. 4); liguzinediol may inhibit inflammation and excessive apoptosis, reduce oxidative stress, and alleviate myocardial fibrosis[255,386]; OPD could maintain mitochondrial function, suppress ERS, and exert anti-apoptotic, antioxidant, and anti-inflammatory effects to treat CHF[307−309,313]. These imply the feasibility and advantage of using natural products to improve complications and comorbidities.

The compatibility of different various components is essential, particularly for medications with large doses and a narrow safety window. Properly formulated drugs can reduce doses, combat drug resistance and mitigate side effects. For example, aconitine combined with liquiritin and glycyrrhetinic acid could regulate the calcium regulation proteins to protect cardiomyocytes from damage, and liquiritin and glycyrrhetinic acid may lessen toxicity and boost the effectiveness of aconitine[387]. With reference to the Jun-Chen-Zuo-Shi principle, the key components that have isolated and identified from Chinese herbs are formulated to work synergistically to produce therapeutic effects. This preserves the benefits and features of TCM formulas while also shedding light on the standardization, modernization, scientification, internationalization, and marketization of TCM. Some Chinese herbs or components, like Wuweizi, *Ginkgo biloba* (Yinxing), and curcumin, may have the potential to improve the efficacy and lessen the toxicity of chemical pharmaceuticals, enlightening traditional medicines[302].

Although Chinese herbal constituents have shown promise in the treatment of CHF, their actual application in clinical settings is still a long way off. In summary, finding bioactive constituents from TCM and exploring their effects and mechanisms are challenging but intriguing tasks.

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Author contributions

Sheng Lin and Hongcai Shang designed the manuscript. Jie Chen and Xiaohong Wei wrote the manuscript. Guiyang Xia and Huan Xia revised the manuscript. Qian Zhang and Yuzhuo Wu searched the literature. Lingyan Wang aided in the design of the illustrations. All authors approved the manuscript for publication.

Conflicts of interest

The authors have no competing interests to declare.

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