



## A Review of Chinese Herbal Medicine for the Treatment of Chronic Heart Failure

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**Abstract:** Heart failure is one of the major causes of mortality worldwide and it is the end stage of several cardiovascular diseases. Traditional Chinese medicine has been used in the management of heart failure for a long time. Only until recently, well-designed clinical trials have been put into practice to study the efficacies of Chinese herbs. Extensive studies have also been carried out to explore the underlying mechanisms of pharmaceutical actions of Chinese herbs. In this study, we will summarize the frequently used Chinese herbs, formulae and patent Chinese drugs in treating patients with heart failure and review published clinical evaluations of Chinese herbs in treating cardiovascular diseases. The mechanisms by which Chinese herbs exert cardio-protective effects will also be reviewed. In the end, we will point out the limitations of current studies and challenges facing modernization of traditional Chinese medicine.

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## 1. INTRODUCTION

Heart failure (HF), as the final stage of cardiac diseases, is an abnormality of cardiac structure or function. Several diseases, including coronary heart disease (CHD), acute myocardial infarction (AMI), high blood pressure, and different kinds of cardiomyopathy, can lead to heart failure [1, 2]. Patients with HF have compromised blood supply as the failing heart is unable to pump sufficiently [3]. According to treatment guidelines, the conventional therapeutic approaches in HF management are angiotensin-converting enzyme inhibitors (ACEIs),  $\beta$ -adrenergic blockers, and diuretics [4, 5]. However, prolonged uses of these chemical drugs may lead to severe side effects, including electrolyte depletion, fluid depletion, hypotension, *etc.* [6-8]. Therefore, traditional Chinese medicine (TCM) has been considered as an alternative therapeutic strategy for the treatment of chronic heart failure (CHF) with lower cost and fewer side effects.

Combining disease with syndrome is an important treatment principle in TCM clinical practice. Generally, syndrome, which is originated from TCM, is a summary of the pathological status that describes severity and stages of the diseases and the patient's individual reaction. Syndrome differentiation is conducted based on the information collected through four traditional diagnostic methods including inspection, listening and smelling examination, inquiry and palpation, and it is also used as the guidance for prescription principle. The top six syndromes of patients with heart failure are *yang* deficiency, *qi* deficiency, blood stasis, water retention, *yin* deficiency and turbid phlegm [9, 10]. Blood stasis is found to be the main syndrome element of heart disease, followed by *qi* deficiency [11]. According to TCM theory, the heart governs mental activities

(*shen*). The heart *qi* maintains blood circulation, whereas heart *yang* promotes fluid metabolism. The fundamental dysfunction in heart failure is the long period of deficiency in heart *qi* and *yang*, which consequently lead to stasis of blood circulation [12]. Therefore, the treatment principles are that they collectively benefit the *qi* and warm *yang* of the heart- specifically by activating blood circulation to dissipate blood stasis and disperse swelling.

Concept of TCM prescriptions is to integrate several medicinal herbs according to syndrome differentiation to form a "formulae" (Fufang). The well-accepted theory of TCM is "Jun-Chen-Zuo-Shi". "Jun" (the emperor) cures the main causes or symptoms of the disease; "Chen" (minister) strengthens the effect of "Jun", or treats accompanying symptoms; the main function of "Zuo" (adjutant) is to reduce or eliminate potential toxic effects of the Jun or Chen herbs, whereas "Shi" (courier) delivers the above herbs to target organs [13]. A number of formulae have been prescribed widely in the treatment of heart failure and several patent drugs (including pills, capsules and injections) have been manufactured by pharmaceutical companies. Exploiting the active components of formulae and investigating the pharmacological actions of TCM have been an ongoing effect in understanding the mechanisms of TCM. Some previous studies have reviewed the effects or the underlying mechanism of some TCM in treating cardiovascular diseases [14-23]. In this review, we will summarize the commonly prescribed Chinese herbs, the clinical evaluations of TCM and the progress made in understanding the mechanisms of TCM in treating cardiovascular diseases and HF.

## 2. COMMONLY PRESCRIBED TCM IN THE TREATMENT OF HF

Chinese herbs have different properties and therapeutic nature. According to TCM theory, cold and cool herbs belong to *yin*, whereas hot and warm herbs belong to *yang*. Balancing *yin* and *yang* in the body is vital for maintaining health. Chinese herbs have been used for the effective treatment of heart failure for thousands of years. The commonly prescribed herbs for treating different heart failure syndromes are as follows: *Radix aconiti carmichaeli* (Fuzi), *Atractylodes* (Baizhu), Cassia twig (Guizhi), Dried ginger (Ganji-

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ang), *Radix pseudostellariae* (Taizishen), *Radix astragali* (Huangqi), *Codonopsis pilosula* (Dangshen), Ginseng (Renshen), *Panax notoginseng* (Sanqi), *Chinese angelica* (Danggui), Safflower (Honghua), *Ligusticum wallichii*(Chuanxiong), *Salvia miltiorrhiza* (Danshen), Red paeony root (Chishao), Peach kernel(Taoren), Hawthorn(Shanzha), *Semen lepidii*(Tinglizi), *Alisma*(Xieze), *Poria cocos*(Fuling); *Radix Ophiopogonis*(Maidong), *Fructus schisandrae*(Wuweizi), *Radix rehmanniae*(Shengdi), Pinellia(Banxia), *Trichosanthes Kirilowii*(Gualou), Dried tangerine or orange peel(Chenpi), Scallions white(Xiebai), etc. [10].

As mentioned above, it is a common practice that several herbs with different amounts are prescribed together, as a formula or “Fufang” in Chinese, to enhance the therapeutic efficacies of each herb and reduce toxicities. There are several most commonly prescribed formulae that have been proven effective clinically for the treatment of heart failure [24-27]. These decoctions prescribed by physicians include: Zhenwu tang, Shengmai san, Baoyuan tang, Xuefuzhuyu tang, Tinglidazaoxiefei tang, Danshen yin, Taohongsiwu tang etc. Meanwhile, several Chinese patent drugs have been successfully produced by standardized procedures and are widely used in health care industry. Drugs in the form of capsules or pills include: Qishenyiqi dripping pill (QSYQ), Fufang danshen dripping pill, Danqi pill (DQP), Qili qiangxin capsule, Shengmai capsule, etc. The produced injections include: Shenmai injection, Shengmai injection, Huangqi injection, Shenfu injection, Danhong injection, etc. The commonly prescribed formulae and their components are listed in Table 1. Several drugs have been put into clinical trials. In the next sections, we will review the published clinical evaluations of TCM and the mechanisms by which TCM exert cardio-protective effects.

### 3. CLINICAL EVALUATIONS OF TCM EFFICACIES

One of the major obstacles in the modernization of TCM is that few remedies have been put into scientifically rigorous clinical evaluations. Even though double-blinded, controlled and randomized trials are rarely carried out to evaluate the efficacies of TCM in treating cardiovascular diseases, some of the most commonly prescribed TCM, including QSYQ, Qili qiangxin capsule, Huangqi injection, Di'ao xinxuekang capsule and Xinmailong, have already been put into clinical evaluations.

QSYQ, a Chinese patent prescription composed of *Radix astragali*, *Salvia miltiorrhiz*, *Panax notoginseng* and *Dalbergia odorifera*, has been applied frequently in the integrative treatment of patients with ischemic heart failure. Some clinical trials of small scales of QSYQ demonstrated that QSYQ could promote left ventricular function, increase exercise capacity and reduce re-admission rate. A randomized clinical trial enrolled 3505 patients and found that QSYQ had similar effects to aspirin for the secondary management of myocardial infarction [28]. A randomized, double-blinded, multicenter, placebo-controlled trial assessed the efficacy of QSYQ on ischemic heart failure. A total of 640 patients with ischemic heart failure from 32 hospitals in China were enrolled and duration of treatment was 6 months [29]. The follow-up phase was 6 months. Outcome data included: six-minute walking test, scores on the New York Heart Association (NYHA) classification and Minnesota quality of life index, all-cause mortality, frequency of cardiovascular events, biomarker of HF-brain natriuretic peptide (BNP) levels, left ventricular ejection fraction (LVEF). Although the results have not been published yet, we can still expect that the rigorous design will provide an objective assessment of the effectiveness and safety of QSYQ in treating HF.

**Table 1. Commonly prescribed formulae and patent drugs in the treatment of heart failure.**

Form	Name	Components
Formulae prescribed by physicians	Baoyuan Tang	Renshen, Huangqi, Gancao, Rougui
	Danshen Yin	Danshen, Tanxiang, Sharen
	Shengmai San	Renshen, Maimendong, Wuweizi
	Taohongsiwu Tang	Danggui, Shudi, Chuangxiong, Baishao, Taoren, Honghua
	Tinglidazaoxiefei Tang	Tingli, Dazao
	Xuefuzhuyu Tang	Taoren, Danggui, Honghua, Chishao, Niuxi, Chuanxiong, Jiegeng, Chaihu, Zhiqiao, Shengdi-huang, Gancao
Patent capsules or pills	Zhenwu Tang	Fuling, Shaoyao, Baizhu, Shengjiang, Fuzi
	Danqi Pill	Danshen, Sanqi, Bingpian
	Fufang danshen Dripping Pill	Danshen, Sanqi, Bingpian
	Shengmai Capsule	Renshen, Maidong, Wuweizi
	Qili Qiangxin Capsule	Huangqi, Renshen, Fuzi, Danshen, Tinglizi, Zexie, Yuzhu, Guizhi, Honghua, Xiangjiapi, Chenpi
Qishen Yiqi Dripping Pill	Huangqi, Danshen, Sanqi, Jiangxiang	
Patent injections	Danhong Injection	Danshen, Honghua
	Huangqi Injection	Huangqi
	Shenmai Injection	Hongshen, Maidong
	Shenfu Injection	Hongshen, Fupian
	Shengmai Injection	Hongshen, Maidong, Wuweizi

Qili qiangxin capsule, another Chinese patent drug, was permitted for the treatment of HF by China Food and Drug administration (CFDA) in 2004. It contains extract of 11 Chinese herbs, including *Radix astragali*, Ginseng, *Radix aconiti carmichaeli*, *Salvia miltiorrhiza*, *Semen lepidii*, *Alismatis rhizoma*, etc. Among them, *Radix astragali* and *Radix aconiti carmichaeli* provide the fundamental active ingredients with pharmacological effect [30]. The efficacy of Qili qiangxin capsule was investigated in a double-blinded, multicenter, and randomized clinical trial, which enrolled 512 participants with systolic heart failure. The researchers reported that after 12 weeks of treatments, N-terminal prohormone of brain natriuretic peptide (NT-proBNP) level, which is considered as the most sensitive biomarker of HF, was down-regulated by Qili qiangxin capsule in 47.95% of patients. Furthermore, Qili qiangxin capsule demonstrated superior performance in comparison to the placebo in terms of NYHA functional classification, 6-min walking distance, LVEF and quality of life [31]. The promising results indicated that Qili qiangxin capsules could be prescribed with other medications for the treatment of chronic heart failure.

Huangqi injection, preparation of an extract of *Radix astragali*, is another commonly used Chinese patent medicine for clinical treatment of chronic heart failure. 62 randomized controlled trials (RCTs) and quasi-RCTs have been reviewed [23]. It was found that the methodologies of the trials were of low qualities and available studies were not robust enough to prove the efficacy and safety of Huangqi injection. Systematic reviews on the effects of hawthorn, cannabinoids and curcumin in treating chronic heart failure have also been conducted [32-34].

Di'ao Xinxuekang capsule was approved by CFDA and has been prescribed routinely in China for several years. Its components are mainly extracted from the rhizomes of *Dioscorea panthaica*. A randomized, multicenter, double-blinded trial was conducted to assess its effects on angina as compared with compound Danshan tablet [35]. Seven hundred and thirty three patients were included in the analysis set. After 20 weeks treatment, Xinxuekang capsule successfully reduced the proportion of angina pectoris patients. According to the results of measurement on the Seattle angina questionnaire score and blood stasis score, the qualities of life of patients were improved significantly by Xinxuekang. A review of randomized clinical trials on the efficacy of Xinxuekang capsule demonstrated that Xinxuekang capsule seemed to have a better effect on patients with angina pectoris as compared with isosorbide dinitrate [36].

Xinmailong is another patent Chinese medicine and the effective components are extracted from *Periplaneta Americana*. Xinmailong has been shown to have protective effects on ischemic myocardial injury [37, 38]. A systematic investigation with 121 patients in a course of 15 days explored the effects of Xinmailong on patients with heart failure, and compared its effects with the standard treatments [39]. In standard treatment group, patients received routine prescription including digitalis preparation,  $\beta$ -blockers, sodium nitroprusside as well as aspirin. Indicators of heart functions, including high sensitivity C-creative protein (hsCRP), NT-proBNP, LVEF and end systolic volume index of left ventricle, were restored towards normal levels by standard treatment and Xinmailong injections after 7 days of treatment. Xinmailong turned out to have a better performance after 15 days of treatment compared with standard treatment. LVEF was increased from 36.9% at the beginning of treatment to 46.4% after 15 days of treatment by Xinmailong (LVEF in normal group was 59.7%). This cardio-protective effect of Xinmailong might be achieved by its inhibition of angiotensin II, which in turn suppressed renin-angiotensin-aldosterone system [39].

Treating patients according to syndrome differentiation is an important aspect of TCM. In a multicenter, randomized control clinical trial with a total of 220 CHF patients, researchers reported that after 28 days, patients treated by Chinese herbs achieved better

improvement of LVEF as compared with the placebo group. Patients in Chinese herbal medicine groups received different kinds of formulae according to syndrome differentiation. TCM syndrome scores also improved significantly in Chinese herbal medicine group compared to the placebo group. The only case of side effect was that one patient in Chinese herbal medicine group experienced atrial fibrillation [40]. The study showed that Chinese herbal medicine treatment according to syndrome differentiation effectively improved heart functions in patients with CHF and appeared to be safe. Another two studies with Nuanxin capsule and Shencao tongmai granule showed that after two weeks of treatment, the TCM syndrome scores of the CHF patients in the Chinese herbal medicine group decreased to levels lower than those observed in the placebo group. Chinese herbal medicine treatment can also markedly relieve the symptoms and signs of CHF patients [41, 42].

An issue facing clinical evaluations is that the concentrations of the effective components are usually unknown and the amounts of bioactive components may vary from one capsule to another [43]. The inconsistency of compounds in formulae or capsules warrants that the results of clinical trials should be received with cautious optimism. Despite the challenges, the clinical trials will open opportunity to explore how the multi-compounds in TCM exert integrated effect on the syndrome of heart failure [44].

#### 4. THE MECHANISMS OF TCM IN TREATING HF

The pharmacological mechanisms of TCM in treating heart failure have been explored in numerous studies. The most commonly used animal model in these studies is acute myocardial ischemia (AMI) model or doxorubicin (DOX)-induced cardiac toxic model. *In vitro* studies on H9C2 cardiac cell lines have also been extensively conducted. The investigated forms of TCM include single herb, extracts of herbs and formulae. The experimental studies demonstrate that TCM possess properties of anti-fibrosis, anti-inflammation, anti-oxidant, anti-apoptosis, pro-angiogenesis and metabolism regulation (Table 2). These biological pathways are interconnected with each other and TCM may function in a multi-components and multi-targets mode.

##### 4.1. TCM that Exert Anti-Fibrotic Effects

Fibrosis results from a number of cardiovascular diseases. The accumulation of fibroblasts and deposition of extracellular matrix often lead to the distortion of organ architecture and cardiac dysfunction. Transforming growth factor  $\beta$ 1 (TGF- $\beta$ 1) acts as one of critical regulatory factors involved in the progression of fibrosis [45]. Progress has been made in the anti-fibrotic treatments by targeting TGF- $\beta$ 1 [46]. Collagen I (Col I), collagen III (Col III), matrix metalloproteinase-2 (MMP-2) and MMP-9 are the most commonly detected molecules, as they are the main contributors to extracellular matrix remodeling [47, 48]. Several herbals have been shown to have anti-fibrotic effects.

Xuefuzhuyu decoction, a TCM used for coronary heart disease, is composed of 11 compounds. A study showed that Xuefuzhuyu decoction treatment could decrease cardiac fibrosis induced by hypertension and inhibit expression of TGF- $\beta$ 1 [49]. The bioactive components of Xuefuzhuyu that attenuate myocardial fibrosis by acting on TGF- $\beta$ 1 signaling pathways may include *carthamin yellow*, *ferulic acid sodium*, *ligustrazine*, *amygdalin* and *paeoniflorin* which are extracted from *Carthamus tinctorius*, *Angelica sinensis*, *Ligusticum striatum*, *Prunus persica* and *Paeonia lactiflora* Pall, respectively.

Shengmai yin, used for treating coronary heart disease with "qi-yin" deficiency, is composed of *Radix ginseng*, *Radix ophiopogonis* and *Fructus schisandrae* at the ratio of 1:2:1. Shengmai yin showed protective effect against cardiac toxicity induced by DOX in rats. Rats treated with Shengmai yin showed reduction of monocyte chemoattractant protein-1 (MCP-1) and B-type natriuretic peptide. Myocardial fibrosis was suppressed by Shengmai yin, as evidenced

**Table 2. Chinese herbs or extracts of herbs with cardio-protective properties.**

Property	Herbs or Extracts	Target or Indicator	Type of Study	References
Anti-fibrosis	Xuefuzhuyu decoction	TGF- $\beta$ 1	<i>in vivo</i>	[49]
	Shengmai yin	BNP, MCP-1, PICP proCol III, TGF- $\beta$ 1	<i>in vivo</i>	[50]
	Shensong yangxin	col I and col III, TGF- $\beta$ 1, MMP2	<i>in vivo</i>	[51, 52]
	Sini tang	TLR-2, TLR-4, TGF- $\beta$ 1	<i>in vivo</i>	[53]
	Nanmu xiang	ERK1/2, TGF- $\beta$ , Sma d2	<i>in vivo, in vitro</i>	[54]
	Qishenyiqi dripping pill	MMP-2, MMP-9, col I, col III, IL6, STAT3, TNF $\alpha$ , NF- $\kappa$ B, TGF- $\beta$ 1	<i>in vivo, in vitro</i>	[55-59]
	Zhenwu tang	collagen	<i>in vivo</i>	[60]
Anti-inflammation	Qishenyiqi dripping pill	PLA2, COX1, COX2, AT1, AT2, NF- $\kappa$ B, JAK1, STAT3, Akt	<i>in vivo</i>	[55]
	PNS	LXR $\alpha$ , ABCA1, NF- $\kappa$ B	<i>in vivo, in vitro</i>	[70]
	Danqi pill	leukotrienes B4, COX1, COX2, PLA2, NF- $\kappa$ B, thromboxane B2, prostaglandin I2	<i>in vivo</i>	[71, 72]
Pro-angiogenesis	Shumai tang	Akt, VEGF, PDGF, PI3K	<i>in vivo</i>	[76]
	Ginsenoside	PI3K, Akt	<i>in vivo</i>	[77]
	Danggui	VEGF	<i>in vivo, in vitro</i>	[78]
	Qishenyiqi dripping pill	HIF-1 $\alpha$ , VEGF, MAPK, PI3K and AKT	<i>in vivo</i>	[80-83]
Anti-oxidation	Danshen	ROS, LDL, ERK1/2, JNK, NAD(P)H oxidase, Bcl-2, Bax, caspase-3	<i>in vivo, in vitro</i>	[91-99]
	Zhuzhi shen	MDA, NO, CK, NOS	<i>in vivo</i>	[100]
	Manshan hong	GSH-Px, SOD, MDA, ROS	<i>in vitro</i>	[101]
	Ginkgo biloba	ROS, VACM-1	<i>in vitro</i>	[102]
Anti-apoptosis	Qiliqiangxin capsule	ROS, Fas, caspase-3	<i>in vivo</i>	[108]
	Buyinhuanwu decoction	Bcl-2, Bax, caspase-3	<i>in vivo</i>	[109]
	Dioscin	Bcl-2, Bax, ROS, MDA, cytochrome c	<i>in vitro</i>	[110, 111]
	PNS	p-AKT, PI3K	<i>in vivo, in vitro</i>	[112]
	Shengmai injection	caspase-12	<i>in vivo</i>	[113]
	Protocatechuic aldehyde	caspase-3	<i>in vitro</i>	[114]
	Tanshinone IIA	P38 MAPK, mir-1	<i>in vivo</i>	[118]
Regulating energy metabolism	Danqi pill	ApoA-I, CD36, FABP, CPT-1A, LPL	<i>in vivo</i>	[72, 122]
	Qishenyiqi dripping pill	ATP, PPAR $\alpha$ , PGC-1 $\alpha$ , SOD, MDA, TNF $\alpha$ , IL-1 $\alpha$	<i>in vivo</i>	[123-125]
	Shenfu decoction	amino acids, arachidonic acid, etc.	<i>in vivo</i>	[126]

by suppression of amino terminal propeptide of procollagen type III, carboxyl terminal propeptide of procollagen type I (PICP) and TGF- $\beta$ 1 [50]. Shensongyangxin capsule has long been used clinically to treat arrhythmias. Experiments in a rabbit model demonstrated that Shensongyangxin capsule could decrease the protein levels of Col I and Col III, down-regulate the mRNA levels of TGF- $\beta$ 1 and MMP2, thereby ameliorating electrophysiological dysregulations in ischemic hearts [51]. It was also demonstrated that Shensongyangxin capsule inhibited fibrosis in streptozocin-induced diabetic rats with high fat-diet and improved cardiac function via TGF- $\beta$ 1/Smad signaling pathway [52].

Sini tang is composed of four herbs: *Aconitum carmichaelii*, *Cinnamomum cassia*, *Zingiber officinale*, and *Glycyrrhiza uralensis*. The concentrations of Toll-like receptors (TLR-2 and TLR-4) in cardiac tissue could be down-regulated significantly by Sini tang. Meanwhile, the levels of collagens in plasma and in cardiac tissue were also reduced. The similar results were got in terms of the plasma and cardiac levels of TGF- $\beta$ 1, suggesting that Sini tang could prevent against early ventricular hypertrophy and improve *post-AMI cardiac* function [53]. Nanmu xiang, also known as *aristolochia yunnanensis*, has been proven to be effective in the treatment of hypertension and chest pain. It was shown that extract of

*Aristolochia yunnanensis* could inhibit angiotensin II induced cardiac fibrosis through extracellular signal regulated kinase 1/2 (ERK1/2) and TGF- $\beta$ /Smad pathways [54].

QSYQ is prescribed frequently for treating cardiovascular diseases including heart failure. Current research demonstrated that QSYQ exerted anti-fibrotic effect in AMI rat models by inhibiting renin-angiotensin-aldosterone system (RAAS), including blocking the type I receptor of angiotensin II (AT1), activating type II receptor of angiotensin II (AT2), down-regulating angiotensin-converting enzyme (ACE), and up-regulating ACE 2. Both Cyclooxygenase 1 (COX1) and COX2 in arachidonic acid (AA) pathway activated by RAAS were also inhibited. Myocardial fibrosis biomarkers, including matrix metalloproteinase-2 (MMP-2), MMP-9, collagen I and collagen III, were regulated by QSYQ treatment. In addition, "therapeutic" QSYQ administration could suppress the release of pre-inflammatory factors including tumor necrosis factor  $\alpha$  (TNF $\alpha$ ) and interleukin 6 (IL-6) [55, 56]. Other studies also confirmed that QSYQ had definite effect on myocardial fibrosis and slowed down the progression of cardiac hypertrophy [57, 58]. Danshen is a composite of QSYQ and study showed that Danshen alone prevented myocardial fibrosis which was induced by chronic iron overload in mice. Further study demonstrated that Danshen treatments was capable of increasing expressions of TGF- $\beta$ 1 and MMP-9, reducing level of iron deposition, fibrotic area and contents of collagen I and collagen III in a dose-dependent manner [59]. Zhenwu tang was shown to inhibit collagen hyperplasia and fibrosis in a myocardial hypertrophy rat model [60].

#### 4.2. TCM that Attenuate Inflammation

Inflammation has been proven to be the major pathological changes in heart failure [61, 62]. An intense inflammatory response can be initiated by ischemic injury in heart tissue, which usually leads to further cardiac dysfunction [63]. Several signaling pathways, including phospholipase A2 (PLA2)/cyclooxygenases (COXs) and IL-6-janus kinase (JAK)/STAT3, are involved in the inflammatory process [64]. Inflammatory responses can eventually lead to fibrosis and ventricular remodeling [65]. Therefore, the effects of TCM on inflammation and fibrosis are inter-connected with each other. Our studies showed that QSYQ could attenuate myocardial fibrosis in AMI model rats by reducing expression of AT1 and increasing expression of AT2 in RAAS pathway. The inflammatory signaling pathway was also attenuated by QSYQ. In particular, the QSYQ had a similar effect with aspirin which could unselectively inhibit both the expressions of COX1 and COX2. Furthermore, QSYQ suppressed levels of NF- $\kappa$ B, JAK1, STAT3 and Akt, the contributing factors to myocardial inflammation and fibrosis [55]. Several specific Chinese herbs, such as *Coptis chinensis* (huanglian), *Scutellaria baicalensis* (huangqi), *Flos Lonicerae* (jinyinhua) and *Forsythia suspensa* (lianqiao), have also been shown to have anti-inflammatory properties [66, 67].

DQP, prepared from equal amounts of *Salvia miltiorrhiza* and *Panax notoginseng*, is frequently prescribed for the treatment of coronary heart disease. The major active ingredients in DQP are salvianolic acids and panax notoginseng saponins (PNS) [68, 69]. PNS could attenuate atherosclerosis by inducing expression of liver X receptor  $\alpha$  (LXR $\alpha$ ), and inhibiting NF- $\kappa$ B DNA binding activity [70]. Our study showed that DQP regulated multiple biological processes, including AA metabolism, in AMI rat model [71]. It down-regulated expression of thromboxane B2 and up-regulated expression of prostaglandin I2. DQP also suppressed productions of COX1, COX2 and leukotrienes B4. Expressions of PLA2 in AA pathways are suppressed by DQP treatment [72].

#### 4.3. TCM that Regulate Angiogenesis

An insufficient supply of blood to the cardiac tissues is characteristic of ischemic heart disease [73]. Therefore, a therapeutic strategy to treat ischemic heart failure is to restore blood supply by

stimulating the growth of new blood vessels [74]. Studies have shown that various angiogenic growth factors and progenitor cells, including vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), recombinant proteins and bone marrow stem cells, can enhance new blood vessels and stimulate angiogenesis [75]. Some components of Chinese herbs have been shown to be able to promote development of new blood vessels. Shumai tang, a TCM for ischemic heart disease treatment, consists of seven medicinal components. The major effective ingredients of Shumai tang include astragaloside, salvianolic acid, sanchinoside, ginsenoside Rg1, etc. A study showed that Shumai tang significantly increased densities of capillaries and arterioles, attenuated myocardial fibrosis, and up-regulated cardiac phosphorylation of protein kinase B (Akt), increased expressions of VEGF and platelet-derived growth factor (PDGF-BB). These effects may be exerted by activation of the phosphoinositide 3-kinase (PI3K)/Akt signaling pathway in AMI rat model [76]. Ginsenoside-Rg1 could also promote angiogenesis and attenuate myocardial fibrosis by activating PI3K/Akt and inhibiting P38 mitogen-activated protein kinases (p38 MAPK) [77]. Study demonstrated that Angelica and Chuanxiong, which are used as treatment for ischemic heart disease, could increase expressions of VEGF in the ischemic heart tissues of rats, stimulate proliferation of endothelial cells and increase densities of vessels on chick embryo chorioallantoic membrane model [78].

MicroRNAs(miRNA) play a key role in regulating gene expression, mainly through blocking translation of target mRNA or inducing degradation of mRNA [79]. MiRNAs also play important roles in angiogenesis and cardiovascular diseases. A study found that QSYQ promoted angiogenesis by targeting mir-223p, one of the key miRNAs in regulating angiogenesis of microvascular endothelial cells without blood supply. Expressions of HIF-1 $\alpha$ , VEGF, MAPK, PI3K and AKT in hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ) signaling pathway were increased remarkably by QSYQ [80]. Other studies showed that the components of QSYQ promoted angiogenesis through activating PI3K/Akt pathway and up-regulating expressions of HIF-1 $\alpha$  and VEGF [81-83]. It is worthy of noting that some herbs are antiangiogenic and have been applied for the treatment of cancers and decompensated heart failure [84].

#### 4.4. TCM with Anti-Oxidative Property

Oxidative stress is caused by excessive production of reactive oxygen species (ROS) and it's an important contributor to cardiac remodeling and heart failure. ROS can be produced by several intracellular enzymes, including NAD(P)H oxidase, xanthine oxidase, and uncoupled nitric oxide synthase. Increased ROS level leads to mitochondrial damage, up-regulation of MMPs and cardiac hypertrophy [85]. The plasma level of malondialdehyde (MDA) produced by lipid peroxidation rose in heart failure patients. NAD(P)H Levels of oxidase-derived ROS and plasma TNF $\alpha$  were also increased [86, 87]. Oxidative stress is also one of the most potent inducers of endothelial dysfunction and is involved in atherosclerotic plaque evolution [88-90]. Antioxidants have the potential to protect against the harmful effects of oxidative stress and many natural plant products have such properties of antioxidants. Trilinolein is extracted from *Panax notoginseng* and has been found to have antioxidant activity [91]. Shanzha and Danshen are used together to treat cardiovascular diseases. Both Shanzha and Danshen exhibited high antioxidant activities [92-94]. The active components of Shanzha are mainly phenolic compounds, whereas the active components of Danshen have been identified as salvianolic acid A and B [95]. Phenolic compounds not only exerted antioxidant activities, but also inhibited formation of oxidized low density lipoprotein (ox-LDL) [96]. Salvianolic acid B was the major effective component of the Shanzha and danshen capsule and exhibited strong antioxidant activity compared with other phenolic compound [97]. Treatment with salvianolic acid B reduced phosphorylation of ERK1/2 and JNK and suppressed production of prostaglandin E2 (PGE2) and NAD(P)H oxidase activity in human aortic smooth muscle cells

treated with LPS, indicating that salvianolic acid B had antioxidant properties [98]. Tanshinone IIA, another main component of Danshen, could significantly inhibit the production of H<sub>2</sub>O<sub>2</sub>-induced ROS. Tanshinone IIA was able to significantly decrease the expression of Bax and caspase-3 evoked by H<sub>2</sub>O<sub>2</sub> *in vitro* and increase the level of anti-apoptotic protein B-cell lymphoma 2 (Bcl-2) in EA.hy926 cells [99]. A study showed that polysaccharides of Zhuzi shen (*Rhizoma panacis majoris*) could alleviate oxidative stress response, reduce levels of its products, MDA and nitric oxide (NO), and inhibit activities of creatine kinase(CK) and nitric oxide synthase(NOS) in a rat model of congestive heart failure [100]. Farrerol, an extract from the Chinese herb Manshan hong (*Rhododendron dauricum*), could significantly inhibit the H<sub>2</sub>O<sub>2</sub>-induced loss of cell viability and enhance activities of protective enzymes in oxidative stress pathway including superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) in EA.hy926 cells. In addition, farrerol inhibited the H<sub>2</sub>O<sub>2</sub>-induced elevation of intracellular MDA and ROS [101]. Extract from Ginkgo biloba could attenuate intracellular ROS formation, redox-sensitive transcription factor activation, and expressions of vascular cell adhesion molecule 1 (VCAM-1) as well as intercellular adhesion molecule 1 in human aortic endothelial cells, thereby suppressing endothelial adhesion induced by inflammatory cytokine to human monocytic cells [102]. Herbs with anti-oxidative properties were summarized by a previous review [14].

#### 4.5. TCM that Suppress Apoptosis

Apoptosis contributes to the progression of a variety of cardiovascular diseases and inhibition of myocardial apoptosis is a potential strategy for the treatment of cardiovascular diseases. Caspases have been considered as the major promising targets, as their induction and execution are essential to evaluate the activation and inhibition of apoptosis. Caspases are used as the common biomarkers for different apoptotic pathways [103]. In addition, Bcl-2 family members, including both pro-apoptotic and anti-apoptotic proteins, play complicated roles in myocardial ischemia/reperfusion (I/R) [104-107]. Some Chinese medicines exert cardio-protective effects by inhibiting apoptosis in myocardium. Qili qiangxin capsule was shown to inhibit cardiomyocyte apoptosis in ischemic heart tissues. The potential mechanism may be involved with its ability to reduce ROS and to depress the expression of Fas and caspase-3 [108]. Buyinghuanwu decoction could attenuate ligation of Left Anterior Descending Artery (LAD)-induced ventricular remodeling, by up-regulating Bcl-2/Bax ratio and down-regulating caspase-3 activity [109]. Dioscin is an extracted saponin from the roots of Huaishanyao (*Dioscorea panthaica*) and Chuanshanlong (*Dioscorea nipponica Makino*) [110]. Dioscin alleviated cell death and reduced level of lactate dehydrogenase (LDH) in I/R-stimulated H9C2 cells. Dioscin also attenuated cellular apoptosis through regulating expressions of Bax and Bcl-2. Cytochrome c release, intracellular ROS and MDA levels were also reduced by dioscin [111]. PNS were shown to exhibit anti-apoptotic effect both *in vitro* and *in vivo*. This effect was probably mediated by activating PI3K/Akt pathway, as the anti-apoptotic effect was neutralized by PI3K inhibitor LY294002 [112]. Shengmai injection could alleviate endoplasmic reticulum stress and inhibit caspase-12 dependent apoptosis, thereby protecting against DOX-induced heart dysfunction [113]. Protocatechuic aldehyde, derived from Danshen, is water-soluble antioxidant. Research found that protocatechuic aldehyde could inhibit apoptosis induced by lipopolysaccharide in human umbilical vein endothelial cells through regulating caspase-3 expression in a dose-dependent manner [114].

Some microRNAs, such as cardiac muscle specific Mir-1, play critical roles in growth of muscle, and therefore it can directly affect the cardiac function [115]. Meanwhile, the activation of phosphorylation of p38 MAPK could result in myocardial damage and apoptosis [116, 117]. Tanshinone IIA was shown to have protective effects against ischemic or hypoxic induced cardiac injury. This

effect was achieved by regulating expression of mir-1 and suppressing activation of p38 MAPK signaling pathway [118].

#### 4.6. TCM that Regulate Mitochondrial Functions and Energy Metabolism in HF

Pumping blood to meet the need of body relies heavily on the supply of adenosine triphosphate (ATP). Oxidation of nutrients, including fatty acids, glucose, lactate, ketone bodies and amino acids, is the source of ATP. Fatty acids provide 70% to 90% of cardiac ATP. Glucose, lactate and a small amount of amino acids provide the left 10% to 30% of ATP needed by the heart [119]. Since the lipid metabolism dominates the energy supply for the heart, lots of studies focused on regulation of it for the treatment of heart disease. Among them, peroxisome proliferator activated receptors  $\alpha$  (PPAR $\alpha$ ) was intensively investigated as it participated in the whole process of lipid metabolism. The level of very low density lipoprotein (VLDL) in plasma could be reduced by activation of PPAR $\alpha$  which inhibits the formation of both triglyceride and cholesterol [120, 121]. Therefore, activating PPAR $\alpha$  by agonists is a potential strategy for the treatment of CHD. Herbal medicine could regulate cardiac metabolism and exert cardio-protective effects in the treatment of heart failure. Previous study showed that DQP up-regulated PPAR $\alpha$  expression significantly in AMI model [72]. Our research also demonstrated that DQP could intervene the transportation, absorption, distribution as well as metabolism of fatty acids in AMI model rats by regulating expressions of essential proteins, including apolipoprotein A-I (ApoA-I), cluster of differentiation 36 (CD36), fatty acid binding protein (FABP), carnitine palmitoyl transferase I (CPT-1A) and lipoproteinlipase (LPL) in the heart tissues. Conclusively, DQP had a comprehensive regulatory effect on lipid metabolic process in AMI rats [72, 122].

Another TCM study on lipid metabolism showed that QSYQ treatment could attenuate DOX-induced cardiac injury and protect against damage of cardiac structure. DOX caused damage to heart function by reducing protein content of ATP 5D, PPAR $\alpha$ , as well as peroxisome proliferator-activated receptor gamma coactivator 1 $\alpha$  (PGC-1 $\alpha$ ) [123]. Meantime, a parallel study found that ATP levels and mitochondrial transmembrane potential (MTP) in AMI heart were restored by QSYQ pretreatment for 7 days. Pretreatment with QSYQ also regulated plasma SOD, MDA, TNF $\alpha$  and IL-1 $\alpha$ . QSYQ improved energy metabolism and reduced oxidative stress by attenuating I/R-induced mitochondrial abnormalities [124]. The effects of QSYQ on energy metabolism were also investigated by proteomic study. The results demonstrated that QSYQ treatment regulated expressions of proteins involved in oxidative stress and energy metabolism. Due to interactions of its bioactive ingredients, QSYQ had a better anti-hypertrophic effect than its single ingredients or combinations of several ingredients. Among those ingredients of QSYQ, 3,4-dihydroxy-phenyl lactic acid was the best candidate for counteracting oxidative stress. Astragaloside IV and notoginsenoside R1 were more potent at regulating energy metabolism [125]. Another well-known prescription, Shenfu decoction, was found to exert therapeutic efficacies in rats with chronic HF. Results of urinary and plasma metabolomics suggested that inflammation and dysfunctions of energy metabolisms were associated with 16 potential urine biomarkers and 13 potential plasma biomarkers. Shenfu decoction could partly restore the disturbed pathways that the differentially expressed biomarkers were enriched on [126].

#### CONCLUSION

Heart failure is related with multiple risk factors. Therefore, multi-target treatments may be more effective in treating HF. The combined application of herbal and chemical drugs is becoming a new trend of modern medicine in preventing and treating diseases nowadays. The promise of Chinese herb-derived compounds as effective therapies for heart failure has been indicated by clinical

evaluations and experimental studies [127]. Chinese herbs have been shown to have anti-fibrosis, anti-inflammation, anti-oxidation, anti-apoptosis, pro-angiogenesis and metabolism regulatory effects. However, the published studies have several limitations. Firstly, most of the clinical studies contain a small sample size or incomplete data. The exclusion and inclusion criteria are not specific or not even mentioned in some of the studies. There is a lack of double-blinded, multi-center, randomized and controlled clinical trial for most of the compounds used in treating HF. Secondly, other than patent drugs, most of the formulae prescribed by doctors contain varied amounts of components and the treatment period also vary from person to person. Therefore, it is difficult to make accurate evaluations of the efficacies of the herbs in TCM practice in a systematic way. Thirdly, it is believed that combination of herbs could attenuate toxicity as well as enhance efficacy. Toxic side effects could occur by treatment with some herbs. However, published *in vivo* studies seldom mention the adverse effects of the treatments. The systemic and organ-specific toxic effects and the minimally toxic dose for most of herbs are still to be investigated by animal studies and clinical studies. Fourthly, in modern medical practice, it is more likely that Chinese herbs are used together with other drugs to treat cardiovascular diseases and heart failure. Therefore, herb-drug interaction should be taken into consideration and should be carefully evaluated in future studies. Moreover, the active ingredients in different compounds are still not clear and their targets are still inconclusive. The development of systems biology and network pharmacology provides us with tools to analyze and predict large-scale drug-target interactions [20, 128-132]. Finally, heart failure is a multiple-stage condition caused by multiple factors. Most of the published investigations are focused on examining the effects of Chinese medicine on one or a few aspects of heart failure. A systematic evaluation of the mechanisms of TCM should be performed. In spite of all these challenges, further well designed clinical trials and experimental studies will facilitate better understanding of the mechanism of TCM and promote the modernization of TCM in the treatment and prevention of heart failure.

#### LIST OF ABBREVIATIONS

AA	=	Arachidonic Acid
ABCA1	=	ATP-binding Cassette A1
Akt	=	Protein Kinase B
AMI	=	Acute Myocardial Ischemia
ApoA-I	=	Apolipoprotein A-I
AT1	=	Angiotensin Type 1 Receptor
ATP	=	Adenosine Triphosphate
Bcl-2	=	B-cell Lymphoma 2
BNP	=	Brain Natriuretic Peptide
CD36	=	Cluster of Differentiation 36
CHD	=	Coronary Heart Diseases
CK	=	Creatine Kinase
Col	=	Collagen
COX	=	Cyclooxygenase
CPT-1A	=	Carnitine Palmitoyl Transferase I
DOX	=	Doxorubicin
DQP	=	Danqi Pill
ERK	=	Extracellular Signal Regulated Kinase
FABP	=	Fatty Acid Binding Protein
FGF	=	Fibroblast Growth Factor
GSH-Px	=	Glutathione Peroxidase

HF	=	Heart Failure
HIF-1 $\alpha$	=	Hypoxia-inducible Factor 1 $\alpha$
I/R	=	Ischemia/reperfusion
IL-6	=	Interleukin 6
JAK	=	Janus Kinase
LPL	=	Lipoproteinlipase
LVEF	=	Left Ventricular Ejection Fraction
LXR $\alpha$	=	Liver X Receptor $\alpha$
MCP-1	=	Monocyte Chemoattractant Protein-1
MDA	=	Malondialdehyde
miRNA	=	microRNA
MMP	=	Matrix Metalloproteinase
NF- $\kappa$ B	=	Nuclear Factor- $\kappa$ B
NOS	=	Nitric Oxide Synthase
NT-proBNP	=	N-terminal Prohormone of Brain Natriuretic Peptide
NYHA	=	New York Heart Association
p38 MAPK	=	P38 Mitogen-activated Protein Kinases
PDGF-BB	=	Platelet-derived Growth Factor
PGC-1 $\alpha$	=	Peroxisome Proliferator-activated Receptor Gamma Coactivator 1 $\alpha$
PI3K	=	Phosphoinositide 3-kinase
PICP	=	Carboxyl Terminal Propeptide of Procollagen Type I
PLA2	=	Phospholipase A2
PNS	=	Panax Notoginseng Saponins
PPAR $\alpha$	=	Peroxisome Proliferator Activated Receptors $\alpha$
QSYQ	=	Qishenyiqi Dripping Pill
RAAS	=	Renin-angiotensin-aldosterone System
ROS	=	Reactive Oxygen Species
SOD	=	Superoxide Dismutase
STAT3	=	Signal Transducer and Activator of Transcription 3
TCM	=	Traditional Chinese Medicine
TGF- $\beta$ 1	=	Transforming Growth Factor $\beta$ 1
TLR	=	Toll-like Receptors
TNF $\alpha$	=	Tumor Necrosis Factor
VCAM-1	=	Vascular Cell Adhesion Molecule 1
VEGF	=	Vascular Endothelial Growth Factor
VLDL	=	Very Low Density Lipoprotein

#### CONSENT FOR PUBLICATION

Not applicable.

#### CONFLICT OF INTEREST

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