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Review article

Qili Qiangxin (QLQX) capsule as a multi-functional traditional Chinese medicine in treating chronic heart failure (CHF): A review of ingredients, molecular, cellular, and pharmacological mechanisms

Tongxing Wang [a,b,1], Bin Hou [a,b,1], Haoran Qin [c,1], Junqing Liang [a,b], Min Shi [a,b], Yanfei Song [e,f], Kun Ma [d], Meng Chen [d], Huixin Li [e], Guoyuan Ding [e,f], Bing Yao [f], Zhixin Wang [f], Cong Wei [a,b,d,**], Zhenhua Jia [a,e,*]

[a] National Key Laboratory of Luobing Research and Innovative Chinese Medicine, Shijiazhuang 050035, China
[b] Key Laboratory of State Administration of TCM (Cardio-Cerebral Vessel Collateral Disease), Shijiazhuang 050035, China
[c] Department of Integrative Oncology, Changhai Hospital, Naval Military Medical University, Shanghai 200438, China
[d] Hebei Provincial Key Laboratory of Luobing, Shijiazhuang 050035, China
[e] Key Disciplines of State Administration of TCM for Luobing, Hebei Academy of Interactive Medicine, Shijiazhuang 050035, China
[f] Shijiazhuang Compound Traditional Chinese Medicine Technology Innovation Center, Shijiazhuang 050035, China

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ABSTRACT

Chronic heart failure (CHF) is a key part of cardiovascular continuum. Under the guidance of the theory of vessel-collateral doctrine, the present study proposes therapeutic benefits of Qili Qiangxin (QLQX) capsules, an innovative Chinese medicine, on chronic heart failure. The studies show that multiple targets of the drug on CHF, including enhancing myocardial systole, promoting urine excretion, inhibiting excessive activation of the neuroendocrine system, preventing ventricular remodeling by inhibiting inflammatory response, myocardial fibrosis, apoptosis and autophagy, enhancing myocardial energy metabolism, promoting angiogenesis, and improving endothelial function. Investigation on the effects and mechanism of the drug is beneficial to the treatment of chronic heart failure (CHF) through multiple targets and/or signaling pathways. Meanwhile, it provides new insights to further understand other refractory diseases in the cardiovascular continuum, and it also has an important theoretical and practical significance in enhancing prevention and therapeutic effect of traditional Chinese medicine for these diseases.

1. Introduction

Heart failure (HF) is a complex clinical syndrome caused by abnormal changes in cardiac structure and/or function caused by dysfunction of ventricular systolic and/or diastolic function caused by a variety of reasons, mainly manifested as dyspnea, fatigue and fluid retention (pulmonary congestion, systemic circulation congestion and peripheral edema) [1]. The high incidence, hospitalization

* Corresponding author. Address: No. 238 Tianshan Road, Gaoxin District, Shijiazhuang, Hebei Province, China.
** Corresponding author.National Key Laboratory of Luobing Research and Innovative Chinese Medicine, Shijiazhuang 050035, China.
E-mail addresses: weitcm@163.com (C. Wei), jzhjiazhenhua@163.com (Z. Jia).
[1] Tongxing Wang, Bin Hou, and Haoran Qin contributed equally to this work.

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and mortality of this cause pose a great challenge to the public health system. According to statistics, there are 64.3 million people suffering from HF in the world [2], and the prevalence of HF in European and American countries is 1.5%–2.0 %. At present, the number of HF patients in China is 8.9 million, and the prevalence of HF in Chinese adults aged ≥35 years is 1.3 % [3–5]. The 1-year mortality rate of HF patients is about 15 %, and the 5-year mortality rate is as high as 50 % [6,7]. The Chinese Heart Failure Patient Registration Study (China-HF) shows that the mortality rate of inpatients with heart failure is 4.1 % [8]. Although modern medicine has deepened the understanding of heart failure, the concept of treatment has changed, and the treatment means have been innovative. To further improves the quality of life of patients, reduce the mortality of heart failure, and improve the long-term prognosis is still a difficult point of clinical treatment in the international medical community.

In recent years, studies have found that the characteristics of multi-component and multi-target regulation of traditional Chinese medicine have certain advantages in the treatment of HF. QLQX is an innovative traditional Chinese medicine (Z20040141) for the treatment of chronic systolic heart failure, which is developed under the guidance of TCM collateral disease theory for the first time and has the evidence of evidence-based medicine research in China. Compared with cardiac drugs, diuretics, angiotensin-converting enzyme inhibitors (ACEI) and β-blockers in the treatment of heart failure, it has more overall regulatory advantages, and is the first choice of Chinese patent medicine for treating Chronic heart failure (CHF). From a preclinical perspective, QLQX can play a role in the treatment of CHF through a variety of mechanisms, such as regulating myocardial contractility, diuresis, inhibiting excessive activation of the neuroendocrine system, inhibiting inflammation, myocardial fibrosis, apoptosis and autophagy, improving myocardial energy metabolism, promoting angiogenesis, and improving endothelial function [9]. Therefore, this article reviews the pharmacological mechanism of QLQX in the treatment of HF in combination with the current research progress at home and abroad, in order to provide scientific theoretical basis for the rational clinical application of QLQX in the treatment of HF.

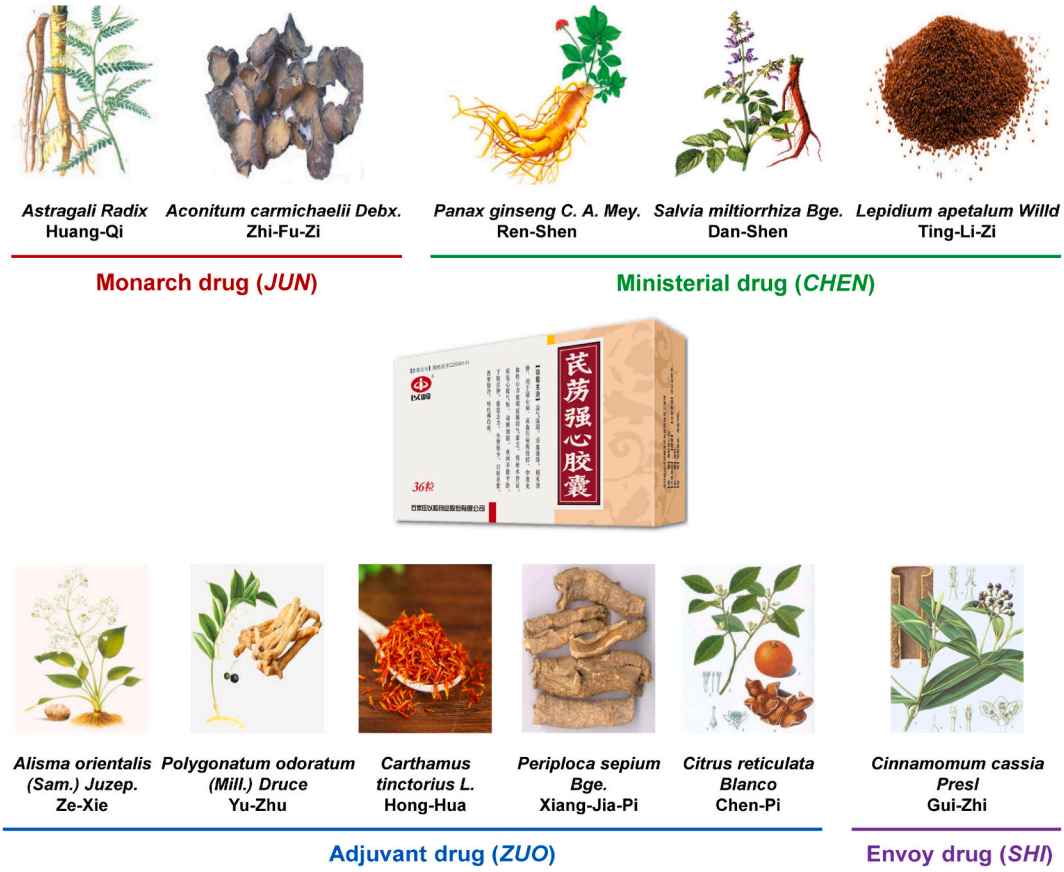

Fig. 1. The herbs included in Qili Qiangxin (QLQX) capsule and the Chinese patent medicine. The QLQX prescription consists of eleven herbs: two monarch drug (JUN)- the *Astragali Radix* (Huang-Qi) and *Aconitum carmichaelii Debx.* (Zhi-Fu-Zi), three ministerial drug (CHEN)- *Panax ginseng C. A. Mey.* (Ren-Shen), *Salvia miltiorrhiza Bge.* (Dan-Shen), and *Lepidium apetalum Willd* (Ting-Li-Zi), five adjuvant drug (ZUO)- *Alisma orientalis (Sam.) Juzep.* (Ze-Xie), *Polygonatum odoratum (Mill.) Druce* (Yu-Zhu), *Carthamus tinctorius* L. (Hong-Hua), *Periploca sepium Bge.* (Xiang-Jia-Pi), and *Citrus reticulata Blanco* (Chen-Pi), one envoy drug (SHI)- *Cinnamomum cassia Presl* (Gui-Zhi). QLQX is orally administered as capsules. The picture of this patent medicine has been permitted to be presented in the manuscript by YILING PHARMACEUTICAL, INC.

Table 1
Compounds in Qili Qiangxin (QLQX) capsule.

Ref.	Compounds	Count
[27]	**Huang-Qi:** Calycosin-7-*O*-β-D-glucopyranoside **Ren-Shen:** Ginsenoside Re; Ginsenoside Rg1; Ginsenoside Rf; Ginsenoside Rb1; Ginsenoside Rc; Ginsenoside Rb2 **Dan-Shen**: Salvianolic acid A; Salvianolic acid B **Hong-Hua**: Kaempferol-3-*O*-rutinoside **Xiang-Jia-Pi**: Periplocoside G	11
[19]	**Huang-Qi**: Astragaloside I; Astragaloside IV; Astragaloside VII; Isoastragaloside I; Isoastragaloside IV; Calycosin-7-*O*-β-D-glucopyranoside; 2′-Hydroxyl-3′,4′-methoxy-isoflavane-7-*O*-β-glucoside **Ren-Shen**: Ginsenoside F1; Ginsenoside F3; Ginsenoside F5; Ginsenoside Ra1; Ginsenoside Ra2; Ginsenoside Ra3; Ginsenoside Rb1; Ginsenoside Rb2; Ginsenoside Rc; Ginsenoside Rd; Ginsenoside Re; Ginsenoside Rf; Ginsenoside Rg1; Ginsenoside Rh1; Ginsenoside Ro; 20 R-Ginsenoside Rg2; 20 S-Ginsenoside Rg2; 20 S-Ginsenoside Rg3; 20 R-Ginsenoside Rg3; Notoginsenoside Fa; Notoginsenoside-K; Notoginsenoside R1; Notoginsenoside R2; Notoginsenoside R4 **Dan-Shen**: Salvianolic acid A; Salvianolic acid B **Hong-Hua**: Kaempferol-3-*O*-rutinoside **Xiang-Jia-Pi**: Periplocoside G; Periploside S-4a; Periploside S-4b; Periploside S-5; Periploside S-6; Russelioside D or isomer; Russelioside D or isomer; Plocoside A **Chen-Pi**: Aurantiamarin **TBD**: Mesuein; Triptoquinone H	45
[28]	**Xiang-Jia-Pi**: Periploside S-4a	1
[20]	**Huang-Qi**: Calycosin-7-*O*-β-D-glucopyranoside; Formononetin; Isoastragaloside I **Dan-Shen**: Violet oxalic acid **Ze-Xie**: 11 Dehydroxyalisol F; Alisol E 23-Acetate **Xiang-Jia-Pi**: Periploside H1; Periploside S-4a **TBD**: Naringin; Rutin; β-Sitosterol	11
[18]	**Huang-Qi**: Formononetin 7-*O*-β-D-glucoside **Ren-Shen**: Ginsenoside Rb1; Ginsenoside Re; Ginsenoside Rf; 20 R Ginsenoside Rh1 **Xiang-Jia-Pi**: Periplocin **TBD**: 2′-hydroxy-3′,4′- dimethoxyisoflavane-7-*O*-β-D-glucoside; 5′,7-dihydroxy-3′-methoxy isoflavones; 5-Hydroxy-2-methoxy-benzyl alcohol; 8*Z*-decaene-4,6-diyne-1-*O*-β-D-glucopyranoside; Adenosine; Quercetin-3-*O*-β-D-*gluco*-pyranosyl-7-*O*-β-gentiobioside	12
[17]	**Huang-Qi**: Astragaloside I; Calycosin **Ren-Shen**: Ginsenoside Rd; 20 S-Ginsenoside Rg2; 20 S-Ginsenoside Rh1 **Chen-Pi**: Aurantiamarin **TBD**: Ethyl rosmarinate; Methyl rosmarinate; Periplocin Δ5-pregnene-3β,20 S-diol-20-*O*-β-D-glucopyranosyl-(1 → 6)-β-D-glucopyranosyl-(1 → 2)-β-D-digitalopyranoside; Kaempferol-3-*O*-rutinoside	10
[29]	**Fu-Zi**: Taradisamin; Neoling; Mesaconine; Jasaconitine; Hypaconitine; Hypaconitine; Deoxyaconitine; Chasmaconitine; Cammaconine; Aconine; Aconitine; Mesaconitine; Fuziline; 10 Hydroxyaconitine **TBD**: Aconitine in 10-hydroxy-14-benzoyl; 14 Benzoylhypaconitine; 14 Benzoyldeoxygenatedaconitine; 14 Benzoylaconitine; 14 Benzoylaconitine; 14 Acetyl Taradisamine	20
[30]	**Huang-Qi**: Astragaloside IV; Calycosin-7-*O*-glucoside **Ren-Shen**: Ginsenoside Rb1; Ginsenoside Rd; Ginsenoside Re; Ginsenoside Rf; Ginsenoside Rg1 **Xiang-Jia-Pi**: Periplocin; Periploside H1 **TBD**: Aurantiamarin; Isoquercitrin; Naringin	12
[31]	**Ting-Li-Zi**: Isorhamnetin; Kaempferol; Quercetin	3
[32]	**Dan-Shen**: Salvianolic acid A*; Salvianolic acid B*; Danshensu*; Violet oxalic acid*; Rosmarinic acid*; Protocatechuic acid*	6
[33]	**Huang-Qi**: Astragaloside*; Calycosin-7-glucoside*; Formononetin*	3
[34]	**Ting-Li-Zi**: Kaempferol*; Quercetin*; Sinapine thiocyanate*	3
[35]	**Ren-Shen**: Ginsenoside F2*; Ginsenoside Rb1*; Ginsenoside Rb2*; Ginsenoside Rc*; Ginsenoside Rd*; Ginsenoside Re*; Ginsenoside Rf*; Ginsenoside Rg1*; Ginsenoside Rg3*	9
[36]	**Fu-Zi**: Aconitine*; Hypaconitine*; Mesaconitine*; Benzoylaconitine*; Benzoylneoaconitine*; Benzoylhypaconitine*	6
[37]	**Huang-Qi**: Astragaloside III; Astragaloside V; Astragaloside VI; Astragaloside VII; Astragaloside IV; Calycosin-7-*O*-β-D-glucopyranoside; Isoastragaloside I **Fu-Zi**: 10 Hydroxyaconitine; 14 Acetyl Taradisamine; 14 Benzoyl Aconitine; 14 Benzoyl Hypaconitine; Aconine; Aconitine; Cammaconine; Chasmaconitine; Deoxaconitine; Hypaconine; Hypaconitine; Jesaconitine; Mesaconitine; Neoline; Talatizamine **Dan-Shen**: Salvianolic acid A; Salvianolic acid B **Chen-Pi**: Hesperidin **Ren-Shen**: 20 R-Ginsenoside Rg2; 20 R-Ginsenoside Rg3; Ginsenoside F1; Ginsenoside G-F3; Ginsenoside G-F5; Ginsenoside Rb1; Ginsenoside Rb2; Ginsenoside Rd; Ginsenoside Re; Ginsenoside Rf; Ginsenoside Rg1; Ginsenoside Rg2; Ginsenoside Rg3; Ginsenoside Rh1; Ginsenoside Ro; Notoginsenoside Fa; Notoginsenoside R1; Notoginsenoside R4 **TBD**: Kaempferol-3-*O*-rutinoside; Mesuein	45
[21]	**Huang-Qi**: Astragaloside III*; Astragaloside II*; Calycosin* **Fu-Zi**: 14 Acetyl Taradisamine*; 2-OH-Mesaconitine*; Aconine*; Aconine*; Aconitane*; Benzoylaconine*; Benzoylhypaconine*; Benzoylmesaconine*; Carmichaeline*; Fuziline*; Higenamine*; Hypaconitine*; Mesaconine*; *N*-deacetyllappaconitine*; Neoline*; Talatisamine* **Ren-Shen**: Ginsenoside F5*; Ginsenoside Rf* **Dan-Shen**: Cryptotanshinone*; Danshenxinkun B*; Formononetin*; Miltionone II*; Ononin*; Sodium Danshensu*; Tanshinone IIA*; Tanshinone IIb* **Ting-Li-Zi**: Descurainolide B* **Xiang-Jia-Pi**: Schisandrin A* **TBD**: Adenosine*; Isochlorogenic Acid A*; Protocatechualdehyde*	34

(*continued on next page*)

Table 1 (*continued*)

Ref.	Compounds	Count
[38]	**Ren-Shen**: Ginsenoside Rb2 **TBD**: Arachidic acid; lauric acid; Pentade-canoic acid; Pexadecanoic acid; Tridecanoic acid; Widdrol	7
[39]	**Huang-Qi**: Astragaloside; Calycosin-7-glucoside; Formononetin **Fu-Zi**: Aconitine; Benzoylaconine; Benzoylhypaconine; Benzoylmesaconine; Hypaconitine; Mesaconitine **Ren-Shen**: Ginsenoside F2; Ginsenoside Rb1; Ginsenoside Rb2; Ginsenoside Rc; Ginsenoside Rd; Ginsenoside Re; Ginsenoside Rf; Ginsenoside Rg1; Ginsenoside Rg3 **Dan-Shen**: Danshensu; Protocatechuic acid; Rosmarinic acid; Salvianolic acid A; Salvianolic acid B **Hong-Hua**: Hydroxysafflor yellow A **Chen-Pi**: Hesperidin **TBD**: Lithospermic acid; Quercetin; Rutin; Sinapine bisulfate	29
[40]	**Huang-Qi**: Astragaloside; Calycosin-7-glucoside; Formononetin **Fu-Zi**: Aconitine; Benzoylaconine; Benzoylhypacoitine; Benzoylmesaconine; Hypaconitine; Mesaconitine **Ren-Shen**: Ginsenoside Rb1; Ginsenoside Rb2; Ginsenoside Rg1 **Dan-Shen**: Danshensu; Rosmarinic acid; Salvianolic acid A; Salvianolic acid B **TBD**: Sinapine	17
[41]	**Huang-Qi**: Calycosin-7-*O*-β-D-glucopyranoside; Astragaloside **Fu-Zi**: Songorine **Ren-Shen**: Ginsenoside Re **Dan-Shen**: Tanshinone IIA **Ze-Xie**: Alisol A **Chen-Pi**: Hesperidin	7
[42]	**Huang-Qi**: Calycosin-gluA*; Formononetin*; Formononetin-gluA* **Fu-Zi**: Fuziline*; Hypaconine*; Mesaconine*; Neoline*; Songorine*; Talatizamine* **Ren-Shen**: Ginsenoside Rb1*; Ginsenoside Rg1* **Dan-Shen**: Neocryptotanshinone* **Ze-Xie**: Alisol A* **Xiang-Jia-Pi**: Periplogenin*	14
[43]	**Huang-Qi**: Astragaloside IV* **Fu-Zi**: Benzoylhypaconine*; Benzoylmesaconine* **Ren-Shen**: Ginsenoside Rb1* **Ze-Xie**: Alisol A* **Xiang-Jia-Pi**: Periplocymarin*	6
[44]	**Huang-Qi**: Calycosin; Calycosin 7-*O*-glucoside; Formononetin; Ononin **Fu-Zi**: 10-Hydroxy Aconitine; Aconine; Aconitine; Benzoylaconine; Benzoylmesaconine; Chasmanine; *Cis*-aconitic acid; Neoline; Talatisamine **Ren-Shen**: Ginsenoside F1; Ginsenoside Rb1; Ginsenoside Rc; Ginsenoside Rd; Ginsenoside Re; Ginsenoside Rg1; Ginsenoside Rg2; Ginsenoside Rg3; Ginsenoside Rg6; Ginsenoside Rh1 **Dan-Shen**: 3′-*O*-monomethyl lithospermic acid B; Cryptotanshinone; Danshensu; Danshenxinkun A; Dehydromiltirone; Dimethyl lithospermate B; Neocryptotanshinone; Rosmarinic acid; Salvianolic acid A; Salvianolic acid B; Salvianolic acid C; Salvianolic acid D; Salvianolic acid F; Salvianolic acid G; Salvianolic acids; Tanshinaldehyde; Tanshindiol C; Tanshinone I; Tanshinone IIA; Tanshinone IIB; Trijuganone A **Ze-Xie**: Alisol A; Alisol B; Alisol B 23-Acetate **Hong-Hua**: Hydroxysafflor yellow A **Xiang-Jia-Pi**: Periplocin **Chen-Pi**: Dihydroisotanshinone I; Hesperidin; Nobiletin **TBD**: 1-Hydroxypinoresinol-1-*O*-β-D-glucoside; 3,4-Dicaffeoylquinic acid; 3,4-Dihydroxybenzaldehyde; 3,4-Dihydroxybenzoic acid; 7α-acetoxyroyleanone; Adenosine; Anacardic acid; Benzoylhypacoitine; Caffeic acid; Caffeoylquinic acids; Chlorogenic acid; Citric acid; Coixol; Coumarin; Cryptochlorogenic acid; Ferulic acid; Gallic acid; Glucosyringic acid; Isochlorogenic acid A; Isochlorogenic acid C; Isocitric acid; Isoquercitrin; Isorhamnetin-3-*O*-glucoside; Kaempferide; Kaempferol; Kaempferol-3-rutinoside; Lithospermic acid; Micranthin B; Narcissoside; Neochlorogenic acid; Prolithospermic acid; Rindoside; Rutin; Sarmentosin; Sheganone; Silymarin; Sophoraflavanone G; Succinic acid; Sugiol; Syringaldehyde; Syringic acid; Tormentic acid; Trijuganone C; Vanillin; Verbascose	97
JKY	**Huang-Qi**: Astragaloside III; Astragaloside IV; Astragaloside V; Astragaloside VI; Astragaloside VII; Astragaloside VIII; Calycosin-7-*O*-β-D-glucopyranoside **Ren-Shen**: Ginsenoside G-F3; Ginsenoside G-F5; Ginsenoside Ra2; Ginsenoside Ra3; Ginsenoside Ra3; Ginsenoside Rb1; Ginsenoside Rb2; Ginsenoside Rc; Ginsenoside Re; Ginsenoside Rf; Ginsenoside Rg1; Ginsenoside Rg2; Ginsenoside Rg3; Notoginsenoside R1; 20 R-Ginsenoside Rg2; 20 R-Ginsenoside Rg3 **Dan-Shen**: Salvianolic acid A; Salvianolic acid B **Xiang-Jia-Pi**: Periplocoside G; Periplocoside G; Periplocoside G; Periplocoside G; Periplocoside S-4a **TBD**: Kaempferol-3-*O*-rutinoside; Plocoside A	32
Other	**Huang-Qi**: Astragaloside I; Astragaloside IV; Astragaloside V; Astragaloside VI; Astragaloside VII; Astragaloside VIII; Isoastragaloside I **Ren-Shen**: Ginsenoside A; Ginsenoside F2; Ginsenoside F3; Ginsenoside F4; Ginsenoside F5; Ginsenoside F7; Ginsenoside La; Ginsenoside P; Ginsenoside Ra1; Ginsenoside Ra2; Ginsenoside Ra3; Ginsenoside Rb1; Ginsenoside Rb2; Ginsenoside Rc; Ginsenoside Rd; Ginsenoside Re; Ginsenoside Rf; Ginsenoside Rg1; Ginsenoside Rg7; Ginsenoside Rh4; Ginsenoside Ro; 20 R-Ginsenoside F1; 20 R-Ginsenoside Rg2; 20 R-Ginsenoside Rg3; 20 R-Ginsenoside Rh1; 20 S-Ginsenoside F1; 20 S-Ginsenoside Rg2; 20 S-Ginsenoside Rg3; 20 S-Ginsenoside Rh1 **Dan-Shen**: Salvianolic acid A; Salvianolic acid B; Salvianolic acid C; Salvianolic acid D; Salvianolic acid E; Salvianolic acid F; Salvianolic acid H **Xiang-Jia-Pi**: Periplocoside; Periplocoside G; Russelioside D; S-4a; S-4b; S-5; S-6 **TBD**: 7-Hydroxy-5,6,8,4′-tetramethoxyflavone; Calycosin; Calycosin-7-*O*-β-D-Glucopyranoside-6′-*O*-malonate; Isomucronulatol-7,2′-di-*O*-glucoside; Isomucronulatol-7-*O*-glucoside; Isoquercitrin; Isorhamnetin-3-*O*-glucoside; Kaempferol-7-*O*-β-D-glucopyranoside; Quercetin; Quercetin-3-*O*-B-D-glucopyranoside; Quercetin-3-*O*-α-L-rhaMnopyranoside; Quercimeritrin; Rutin	63

Notes: * main xenobiotics exposed in rat's plasma. TBD: to be determined.

2. Clinical study of Qili Qiangxin capsule in treating chronic heart failure

A large number of studies have shown that this drug can reduce the level of NT-proBNP in CHF patients and improve the quality of life and cardiac function of patients [10]. A multicenter, randomized, double-blind, placebo parallel controlled trial conducted by Li, X et al. [11] provided the evidence supporting its efficacy for the treatment of CHF. A total of 512 patients with CHF were enrolled and randomly assigned to receive the placebo or QLQX in addition to their standard medications for the treatment of CHF. The primary endpoint was the reduction or percent change in the plasma *N*-terminal pro-B-type natriuretic peptide (NT-proBNP) level during 12 weeks of treatment. At the 12-week follow-up, a significant reduction in the NT-proBNP level from baseline was observed in both groups, but the QLQX group demonstrated a significantly greater reduction than the placebo group ($p = 0.002$); 47.95 % of patients in the WLWX group demonstrated reductions in NT-proBNP levels of at least 30 % compared with 31.98 % of patients in the placebo group ($p < 0.001$). Treatment with QLQX also demonstrated superior performance in comparison to the placebo with respect to New York heart association (NYHA) functional classification, LVEF, 6 MWD, and quality of life. On a background of standard treatment, QLQX further reduced the levels of NT-proBNP. In addition, QLQX could be used in combination therapy for CHF.

Meta-analysis, especially the meta-analysis of comprehensive high-quality randomized controlled trials (RCTs), has been regarded as the highest level of evidence in evidence-based medicine. Zheng et al. [12] conducted a meta-analysis to systematically evaluate the clinical efficacy of QLQX in the treatment of HF by collecting literatures related to randomized controlled trials of QLQX. A total of 26 studies with 5161 patients were included. Results showed that QLQX significantly increased Left ventricular ejection fraction (LVEF) [WMD = 5.63, 95%CI (4.33, 6.93), $P < 0.01$] and 6 MWD distance [WMD = 58.86, 95%CI (39.57, 78.14), $P < 0.01$] in HF patients, decreased left ventricular end-diastolic diameter (LVEDD) [WMD = −3.08, 95%CI (−4.07, −2.10), $P < 0.01$], amino-terminal pro--brain natriuretic peptide (NT-proBNP) [WMD = −572.28, 95%CI (−1022.45, −122.11), $P = 0.01$] and BNP [WMD = −774.96, $P < 0.01$], 95%CI (−1102.41, −44.50), $P < 0.01$]. The results of clinical trials suggest that QLQX can improve cardiac function and quality of life, and has a potential role in improving prognosis. On the basis of standard treatment, QLQX can further improve the clinical efficacy of HF patients without adverse reactions.

3. Main active ingredients of QLQX

According to traditional Chinese medicine, "Yang qi" in the heart can moisturize organs and promote metabolism. The fundamental problem of heart failure is the lack of qi and Yang, which makes the heart so weak that it cannot promote blood flow and fluid transport, and finally leads to blood stasis and fluid retention [13]. Therefore, according to the traditional Chinese medicine (TCM) pathogenesis of heart failure, "Qi and Yang deficiency, collateral stasis and water stagnation" [14], QLQX was developed (Fig. 1). *Astragali Radix* (Huang-Qi) and *Aconitum carmichaelii Debx.* (Fu-Zi) are the monarch drugs (JUN), which exert "*Nourishing Qi and Warming Yang*" effect to treat its root causes. *Panax ginseng C. A. Mey.* (Ren-Shen), *Salvia miltiorrhiza Bge.* (Dan-Shen), and *Lepidium apetalum Willd* (Ting-Li-Zi) are ministerial drugs (CHEN) with the blood-harmonizing and blood-activating, purging lung and diuresis, tonifying qi and dredging collaterals characteristics to treat the symptoms. *Alisma orientalis (Sam.) Juzep.* (Ze-Xie), *Polygonatum odoratum (Mill.) Druce* (Yu-Zhu), *Citrus reticulata Blanco* (Chen-Pi) and other drugs can not only reduce diuresis to alleviate edema, but also prevent injury from excessive diuresis and replenishes stagnant qi [15]. The saponins contained in *Astragali Radix* (Huang-Qi) could improve cardiac function, hemodynamics and mitochondrial membrane potential of cardiomyocytes. The saponins in *Panax ginseng C. A. Mey.* (Ren-Shen) have the functions of strengthening heart, protecting myocardium and improving blood rheology. *Aconitum carmichaelii Debx.* (Fu-Zi) has the effects of enhancing myocardial contractility, anti-arrhythmia, increasing coronary blood flow and improving hypoxia tolerance. *Cinnamomum cassia Presl* (Gui-Zhi) can improve microcirculation, increase myocardial oxygen uptake, and increase coronary blood flow. *Salvia miltiorrhiza Bge.* (Dan-Shen) and *Carthamus tinctorius* L. (Hong-Hua) can effectively improve myocardial ischemia, improve hemodynamic, dilate blood vessels, improve microcirculation and coronary blood circulation, and resist hypoxia. *Alisma orientalis (Sam.) Juzep.* (Ze-Xie) has the effect of diuresis and improving coronary blood flow. Periplocin and periplocoside G are strong cardiosides in *Periploca sepium Bge.* (Xiang-Jia-Pi) [16]. These herbs have protective effects on the heart, as well as positive inotropic, vasodilation, anti-inflammatory and anti-fibrosis effects.

QLQX's compounds were investigated by ultra-performance liquid chromatography combined with quadrupole-time-of-flight mass spectrometry (UPLC-Q-TOF/MS), Silica gel column chromatography, gel column chromatography, medium and low pressure liquid chromatography and high performance liquid chromatography [17–21], the structures were identified by NMR, HRMS and other spectra, and a total of nearly 200 compounds were found (Table 1). More than 60 compounds were obtained by chromatographic separation. Among them, Ginsenoside compounds, including Ginsenoside Rg1, Ginsenoside Re, etc. Have obvious hypoxic resistance, which can slow down heart rate, increase cardiac output and coronary blood flow, and enhance myocardial contractility [22]. Astragalosides, such as astragaloside V and astragaloside VII, have the effects of protecting cardiomyocytes, protecting vascular endothelium and improving blood flow [23]. Phenolic acids, including Salvianolic acid A, Salvianolic acid B, etc., have universal antioxidant, anti-inflammatory activity and anti-platelet aggregation effects [24]. Flavonoids, including isoquercitrin, rutin, etc., have universal antioxidant, anti-inflammatory activity, anti-platelet aggregation and other effects [25]. Cardiac steroids, including periplocoside and periplocoside G, have good cardiac activity [26]. Aconite alkaloids, including aconite spirit, neoline and so on. Experimental studies have demonstrated that QLQX's compounds have effect-enhancing and toxic-reducing effect, which provide theoretical support for elucidating its mechanism of action and guiding clinical rational drug use [21].

4. Pharmacological effects of QLQX on heart failure

QLQX has significant efficacy in the treatment of CHF and was included in the clinical application guidelines of Chinese patent medicine in the treatment of heart failure in 2021 [45]. It can prevent and cure CHF and improve cardiac function in patients with CHF. Many studies have shown that QLQX can enhance myocardial contractility, diuresis, inhibit the over activation of neuroendocrine systems such as renin angiotensin aldosterone system (RAAS), inhibit inflammation, myocardial fibrosis, apoptosis and autophagy, improve myocardial energy metabolism, promote angiogenesis, and improve endothelial function [9].

4.1. Cardiotonic effects

The myocardium pumps blood through moderate contraction and relaxation, and overcomes the resistance of systemic and pulmonary circulation to transport blood and perfuse the whole-body tissues, thus maintaining normal life activities. In CHF, the heart does not perform its function normally and exhibits systolic or diastolic dysfunction. Studies have shown that QLQX can enhance myocardial contractility, improve hemodynamics, and enhance cardiac function. Li et al. [46] found that the oral administration of QLQX capsule increased the blood concentration of digoxin in 165 patients with or without digoxin chronic heart failure for 5–7 days, indicating that QLQX had strong cardiac glycosides effect and could enhance myocardial contractility in patients with CHF. Liu et al. [47] showed that QLQX could significantly increase the maximal left ventricular pressure rising rate (dp/dt max), significantly increase the left ventricular myocardial contractility (LVMCF), decreased left ventricular end-diastolic pressure (LVEDP), increased cardiac output (CO), and effectively improved hemodynamic parameters and cardiac function. QLQX can also reduce left ventricular end-systolic diameter (LVDs) and increase left ventricular end-diastolic diameter (LVSd), left ventricular end-systolic septal thickness (LVSs), left ventricular posterior wall thickness (LVPWd), and left ventricular posterior wall thickness (LVPWs). It can improve the hemodynamic indexes of rats with Qi deficiency type CHF and the morphological structure of left ventricle in heart failure rats to varying degrees [48]. In addition, the efficacy and safety in patients with chronic heart failure (CHF) of western medication plus QLQX was assessed in a prospective, single-blind, randomized, controlled, and multicenter clinical trial, the results showed that the combination can increase 6 MWD (improve exercise tolerance) and quality of life with HF patients [49]. Xiang et al. [50] found that QLQX could reduce the levels of soluble growth STimulation expressed gene 2 (sST2) and NT-proBNP in CHF patients, and improve LVEF and 6 MWD. Therefore, QLQX can play a role in the treatment of CHF by strengthening the heart.

4.2. Diuretic effect

The reduction of cardiac output and redistribution of blood lead to insufficient renal perfusion, which leads to the reduction of glomerular filtration rate, and the increase of reabsorption of water and sodium by renal tubules. Water and sodium retention may cause serious complications such as systemic edema, pulmonary congestion, and significantly increase the mortality of CHF patients. In heart failure, insufficient cardiac output and redistribution of circulating blood volume trigger the renal entry arterioles to activate neuroendocrine compensatory mechanisms. For example, continuous activation of arginine vasopressin (AVP) and up-regulation of aquaporin2 (AQP2) expression can increase water reabsorption by the collecting duct, thus causing water and sodium retention [51]. In the diuretic mechanism, AVP is secreted by the hypothalamus. When the circulating blood volume decreases, arterial blood pressure decreases and plasma osmotic pressure increases, AVP secretion increases compensatively. AQP2 is an important protein regulating renal water balance. Under the regulation of plasma AVP, AQP2 completes the reabsorption of water by renal collecting duct, thus stabilizing the body's water balance. Wu et al. [52] studied the effect of QLQX on AVP in heart failure rats, and the results showed that QLQX treatment could reduce the plasma AVP concentration, accompanied by increased renal drainage and increased urine output. Study has also confirmed that QLQX can regulate water metabolism disorder and improve edema by reducing the protein expression of AQP2 and phosphorylated aquaporin at serine 256 (PS256-AQP-2) in renal collecting duct [53]. Further studies have shown that QLQX can reduce the concentration of AVP in CHF rats, increase renal excretion, reduce cardiac load [54], significantly increase urine volume, reduce urine permeability, significantly reduce AQP-2 protein expression, and exert diuretic effect without excessive loss of K^+ [55]. QLQX could reduce the concentration of plasma AVP, and down regulate the expression of aquaporin-2 (AQP-2) in the kidney through the specific receptor vasopressin V2 receptor (V2-R) on the renal collecting duct, resulting in reducing the renal reabsorption of water and increasing the urine volume of CHF rats [56].

Other studies have shown that the diuretic effect is closely related to the level of antidiuretic hormone (ADH). ADH can improve the water permeability of distal curvature tubules and collecting ducts, thereby increasing the amount of water reabsorption, resulting in urine concentration and urine volume reduction [57]. Numerous studies have found that QLQX can treat HF by down-regulating ADH. Wang et al. found that QLQX could improve clinical symptoms and serum indicators of patients by down-regulating ADH concentration [58]. Yang et al. found that QLQX could treat chronic congestive heart failure and improve cardiac function by reducing the levels of ADH and LVEF [59]. The in-depth study on the mechanism of QLQX in improving the heart and kidney function of CHF may find new targets to correct water retention, alleviate clinical symptoms, and improve heart function in CHF patients, providing a solid theoretical basis for its clinical application.

4.3. Inhibition of the overactivated neuroendocrine system

CHF is closely related to overactivation of the neuroendocrine system [60]. Cardiac function injury is first manifested in cardiac hemodynamic changes, which further leads to the excessive activation of RAAS, sympathetic nerve and other endocrine systems,

including norepinephrine (NE), angiotensin II (Ang II), aldosterone (ALD) and other neurohormones and cytokines [61,62]. They can damage the cardiovascular system through the neuroendocrine system. Meanwhile, some neurohormones and cytokines synthesized and secreted by cardiomyocytes and endothelial cells, such as NE, Ang II, transforming growth factor-β (TGF-β), matrix metalloproteinases (MMPs), inflammatory cytokines, aggravates the damage of myocardium and cardiac function [63]. Therefore, blocking the overactivation of neuroendocrine system is of great significance for preventing and treating cardiac function injury.

4.3.1. Regulation of neuroendocrine system

Studies have shown that QLQX can inhibit the overactivation of neuroendocrine system, inhibit ventricular remodeling, and prevent CHF. Bei et al. [64] used a micro syringe pump to pump QLQX solution into the lateral ventricle of rats with heart failure. After 4 weeks of administration, left ventricular systolic pressure (LVSP), left ventricular end-diastolic pressure (LVEDP), heart weight index (HWI) and other indicators were detected. The results showed that LVEDP and HWI of rats with heart failure decreased after administration. The levels of NE, ACTH, corticotropin releasing hormone (CRH) were decreased, and the mRNA expressions of CRH and TNF-α in the hypothalamus were decreased, indicating that QLQX could improve cardiac function by regulating the central neuroendocrine system. Ma et al. [65] established a CHF model after myocardial infarction and pumped QLQX ultrafine powder solution through the lateral ventricle for 4 weeks. Compared with the model group, the cardiac function of rats in QLQX group was significantly improved. The levels of Ang II, angiotensin converting enzyme (ACE), angiotensin type I receptor (AT1R) in paraventricular nucleus of hypothalamus and NE and NT-proBNP in plasma were significantly decreased. These results showed that QLQX could inhibit RAS in paraventricular nucleus of hypothalamus, reduce renal sympathetic nerve activity, and improve cardiac function in CHF rats.

4.3.2. Regulation of RAAS system

RAAS system runs throughout the course of CHF. Early activation of RAAS is beneficial to increase cardiac output, while excessive activation accelerates the deterioration of CHF [66]. Studies have confirmed that Ang II and ALD are significantly increased in HF patients [67]. In addition, clinical trials have shown that angiotensin converting enzyme inhibitors can slow the development of HF and reduce the morbidity and mortality of cardiovascular diseases [68]. When RAAS is activated in myocardial infarction, plasma renin activity (PRA) levels of Ang II and ALD in tissues are increased, accompanied by increased tissue fibrosis and inflammation, which may lead to left ventricular dysfunction, ventricular remodeling and cardiomyocyte necrosis. Thus, the development of HF is further accelerated [69]. Li's [70–72] study found that atorvastatin combined with QLQX could improve the cardiac autonomic function of patients and the diastolic function of heart failure rats by regulating the RAAS and neuroendocrine system, thus achieving the purpose of treating CHF. QLQX could significantly improve cardiac function in CHF rats by reducing the oxidative stress level in heart failure rats and inhibiting the enhancement of cardiac RAAS activity [73]. Compared with the model group, the cardiac function of rats in QLQX group was significantly improved. The levels of Ang II, angiotensin converting enzyme (ACE), angiotensin type I receptor (AT1R) in paraventricular nucleus of hypothalamus and NE and NT-proBNP in plasma were significantly decreased [65]. These results showed that QLQX could inhibit RAS in paraventricular nucleus of hypothalamus, reduce renal sympathetic nerve activity, and improve cardiac function in CHF rats.

4.4. Improvement of myocardial energy metabolism

Heart failure is essentially an overload cardiomyopathy caused by abnormal gene expression due to insufficient energy. Adenosine triphosphate (ATP) required for myocardial metabolism under normal conditions comes from the metabolism of various substances, such as lipids, lactate, ketone bodies, amino acids and glucose [74]. There are energy metabolism disorders, such as mitochondrial dysfunction and decrease of high-energy phosphate in myocardium during CHF. Among them, myocardial mitochondrial dysfunction plays an important role in ventricular remodeling and imbalance of energy metabolism [75], and improving energy metabolism may be a new way for traditional Chinese medicine to further improve the efficacy of *anti*-HF.

4.4.1. Regulation of glucose and lipid metabolism

Fatty acid β-oxidation (FAO) and glucose aerobic oxidation are the main sources of metabolic energy in normal myocardium, of which 60%–90 % comes from FAO, while the remaining 10%–40 % of energy supply comes from glucose and lactose oxidation, and a very small amount comes from the metabolism of amino acids and ketone bodies. FAO can produce a large number of Reactive oxygen species (ROS), which can inhibit myocardial contraction and lead to the reduction of cardiolipin content, thereby reducing mitochondrial energy generation, damaging mitochondrial structure and function, and causing cardiomyocyte apoptosis [76]. Studies have found that QLQX can improve cardiac function in heart failure rats by removing ROS and improving the antioxidant capacity of cardiomyocytes [77]. In the case of equivalent ATP production, fatty acid (FA) consumes more oxygen than most other substrates, and its production efficiency is low [78]. Zhang et al. found that QLQX could regulate glycolipid substrate metabolism, reduce the accumulation of free fatty acids and lactic acid, and protect cardiomyocyte and mitochondrial function by activating AMPK/PGC-1α axis [79]. Heart failure can cause an imbalance between increased demand for ATP and decreased production of ATP, which is the fundamental cause of decreased myocardial metabolic reserve and cardiac function degradation [80]. Studies have shown that QLQX can significantly increase the amount of ATP and ADP in myocardial tissue, improve the generation and utilization of ATP, and increase the expression of eNOS mRNA and phosphorylated AMPK (*p*-AMPK) protein in myocardial tissue, indicating that QLQX can increase myocardial energy reserve and improve energy metabolism disorders. The mechanism may be related to the activation of AMPK-eNOS pathway [81,82]. Changes in cardiomyocyte metabolism during heart failure reduce ATP levels, leading to an increase in

lactate and accumulation of non-esterified fatty acids, intracellular acidosis, and increased cardiomyocyte damage. QLQX may regulate the glycolipid substrate metabolism by activating AMPK/PGC-1 alpha axis and reduce the accumulation of free fatty acids (FFA) and lactic acid (LA), to protect cardiac myocytes and mitochondrial function [83].

Chang et al. found that QLQX has an effect on lipid metabolism in rats with heart failure after myocardial infarction, and its mechanism is related to the down-regulation of the expression of 8-ISop-PGF2α and 3-NT, the regulation of cholesterol metabolism through SCAP/SREBP-1c/ACC1, LOX and COX pathways [84]. Wang, J et al. found that QLQX improved cardiac diastolic function in spontaneously hypertensive rats, which may be related to the enhancement of myocardial glucose metabolism [85]. Carnitine palmityl transferase I (CPT-I) and Glucose transporter 4 (GLUT4) levels are the key factors of fatty acid and glucose oxidation, respectively. Studies have found that QLQX can improve CPT-I and GLUT4 expression levels [83]. Cheng, W. et al. [86] found that QLQX can enhance the cardiac (18)F-fluorodeoxyglucose uptake and the levels and translocation of GLUT4, suppress GLUT1 in both areas, indicating that QLQX encouraged border myocytes to use more glucose in a GLUT4-dependent manner, indicating its potential for driving the border myocardium into an anaerobic glycolytic pathway against hypoxia injuries and urging the remote myocardium to oxidize FA to maximize energy production. In addition, QLQX treatment improves glucose utilization and metabolism and increased ATP production through regulating glucose uptake, FFA uptake, and key enzymes of energy metabolism, such as GLUT4, HK2, PKM2, PFK1, LDHA, via HIF-1α-dependent and independent mechanisms associated with the regulation of AMPK/mTOR/HIF-1α pathway [87,88].

4.4.2. Regulating mitochondrial metabolism

Abnormal myocardial energy metabolism is an important factor in the development of heart failure. Mitochondrial metabolism plays an important role in myocardial energy metabolism. It exerts both direct and indirect effects on cardiomyocyte physiology by regulating bioenergy, redox reactions, oxidative stress, calcium ion, excitation-contraction coupling, necrosis and apoptosis [89].

The heart is the organ with the largest internal energy consumption in the body, which needs energy to maintain the pumping function and its own metabolic needs [90]. The main source of body energy is ATP, while mitochondria are the main place for energy metabolism. 90 % of the energy required by normal adult myocardium is provided by mitochondrial aerobic oxidation. QLQX can protect mitochondria and improve energy metabolism, which is one of the important mechanisms to improve cardiac function [83]. In addition, QLQX could improve mitochondrial respiratory function through inhibiting peroxisome proliferator-activated receptor--gamma coactivator 1-alpha (PGC-1α) and its downstream factors [83]. PGC-1 has a variety of biological effects [91], such as affecting mitochondrial biosynthesis through nuclear respiration factors and orphan nuclear receptors [92]. QLQX protects cardiomyocytes and mitochondrial function by activating AMPK/PGC-1α axis, and reducing the accumulation of free fatty acids and lactic acid [83].

Bai et al. [93] found that compared with the β-blocker metoprolol, QLQX could significantly improve the ultrastructure of myocardial mitochondria after 4 weeks of intervention in HF rats after MI. The results of the electron microscopy study by Li [94] showed that the degree of mitochondrial swelling in the QLQX group was less than that in the heart failure group. QLQX could enhance oxidative metabolism and mitochondrial uncoupling in H9C2 cell, and increase mitochondrial content and mitochondrial biogenesis-related gene expression levels, including 16sRNA, SSBP1, TWINKLE, TOP1MT and PLOG, via activation of PGC-1α and its downstream effectors [95]. In addition, QLQX could effectively improve mitochondrial function and in hypoxic CMECs in a HIF-1α-dependent manner, which was associated with the regulation of AMPK/mTOR/HIF-1α pathway [88]. Zhang et al. [96] found that QLQX can activate PI3K/Akt signaling pathway, attenuate the mitochondrial pathway of CytC-mediated cardiomyocyte apoptosis induced by Drp1, protect the structure and function of cardiomyocyte mitochondria, inhibit cardiomyocyte apoptosis, improve energy metabolism, and ultimately improve cardiac work and delay heart failure. Shen, S. et al. [97] found that QLQX could facilitate energy metabolism by upregulating Cd36, Fatp, Pdk4, Acadm, Acadl, Acadvl, Cpt1a, Cpt1b and Cpt2 in the MI hearts of the Ovariectomized mice, among which Acadm, Acadl, Cpt1a, Cpt1b, and Cpt2 were the downstream targets of PPARγ.

In summary, the improvement of cardiomyocyte energy metabolism by QLQX is an important part of delaying the progression of heart failure, which can reduce heart mass index, improve hemodynamic parameters, increase myocardial high-energy phosphate capacity, and improve energy reserve and metabolic status [83].

4.5. Inhibition of ventricular remodeling

Ventricular remodeling refers to the structural adaptive response of myocardium to excessive pressure or volume load, including myocardial parenchymal remodeling and interstitial remodeling [98], leading to changes in cardiac structure and function, which is the common pathological change of a variety of heart diseases when they develop to a certain extent. Histologically, ventricular remodeling is mostly manifested as apoptosis and necrosis of cardiomyocytes, proliferation of fibroblasts and collagen deposition [98]. Studies have shown that QLQX can improve cardiac function by reversing ventricular remodeling [99]. The various mechanisms of QLQX in improving ventricular remodeling are discussed below.

4.5.1. Inhibition of myocardial inflammation

Chronic inflammation at the cellular and molecular levels including a variety of cytokines and chemokines is involved in the occurrence and development of CHF disease [100]. Galectin-3 (Gal-3), sST2, hypersensitive *C*-reactive protein (hs-CRP) in cardiac tissue and peripheral blood of patients with HF the expression of hs-CRP, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and other inflammatory factors is increased [101–103], which promotes myocardial remodeling. Therefore, inhibition of inflammatory response is of great significance for delaying CHF. In the study of 142 elderly patients with heart failure, Ma et al. [104] found that QLQX could effectively reduce the serum levels of sST2 and Gal-3, reduce the cascade induced by them, and effectively prevent matrix

degradation and ventricular remodeling. The serum levels of hs-CRP, IL-6 and TNF-α decreased after QLQX treatment, suggesting that QLQX in the treatment of heart failure may be related to the inhibition of inflammatory response to excessive stress [105]. QLQX can delay CHF by inhibiting inflammation via decreasing the expression levels of prostaglandin E2 (PGE2), TNF-α and IL-6 in plasma of CHF rats [106]. QLQX may improve cardiac function of rats with MI through regulation the balance between pro/anti-inflammatory cytokines TNF-alpha and IL-10 [107]. Han et al. [108] showed that QLQX reduced Col-I, a-SMA, TGF-β1, and *p*-Smad3 expression levels but increased *p*-Smad7 levels, and decreased the protein expression levels of Nuclear factor-κB (NF-κB), phosphorylated IκBα (*p*-IκBα), TNF-α and IL-6 in post-myocardial infarct rat hearts, which reveal the protective effects against cardiac remodeling potentially by inhibiting TGF-β1/Smad3 and NF-κB signaling pathways.

4.5.2. Inhibition of myocardial fibrosis

During the course of heart failure, cardiomyocytes and extracellular matrix can undergo remodeling. Ventricular remodeling includes myocardial fibrosis and extracellular matrix changes. Many factors are involved in ventricular remodeling, involving RAAS system, immune system and a variety of cytokines, such as platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), transforming growth factor-β1 (TGF-β1), etc. [94]. Matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinases (TIMPs) are the main factors of extracellular matrix changes. After myocardial infarction, the neuroendocrine system is over-activated, TIMPs is down-regulated, and MMPs is activated, leading to the degradation of extracellular matrix proteins to form fibrous stroma, which increases the deposition of cell matrix, thereby expanding the infarct area, dilating the left ventricle, thinning the myocardium, and finally developing into CHF [109]. Studies have shown that MMPs/TIMPs balance is the key to maintain the balance between collagen synthesis and degradation metabolism in myocardial fibroblasts. Excessive increase of MMPs activity or serious imbalance of MMPs/TIMPs ratio will lead to ventricular remodeling and myocardial fibrosis [110]. However, the increased activity of MMPs can degrade normal collagen, which is replaced by fibrous interstitial tissue, resulting in the serious damage of cardiac fibrous collagen network. Zhang et al. [37] showed that QLQX could effectively inhibit myocardial remodeling and delay the occurrence of heart failure by inhibiting the activity of basal MMP, thereby maintaining the homeostatic balance between matrix MMPs and TIMPs. Xu Tao et al. [111] found that QLQX could significantly reduce the mRNA expression and activity of MMP-2 and MMP-9 in myocardial tissue, and increase the expression of TIMP-1, indicating that QLQX can inhibit ventricular remodeling and delay the occurrence of heart failure by inhibiting the expression and activity of MMP and regulating the balance of MMPs/TIMPs.

TGF-β1 can promote collagen synthesis and up-regulate the expression of MMP, thereby promoting myocardial fibrosis. Li et al. [112] gave QLQX to CHF rats after myocardial infarction for 4 weeks by gavage, and compared with the control group, the cardiac function of rats was improved and the activities of MMP-2 and MMP-9 were decreased, suggesting that QLQX inhibited myocardial fibrosis. Han et al. [108] found that QLQX significantly reduced the expression of TGF-β1, phosphorylated smad3 (*p*-Smad3), collagen I (COL I), α-smooth muscle actin (α-SMA) and increased the expression of phosphorylated Smad7 protein in CHF rats treated with QLQX for 4 weeks after myocardial infarction compared with the control group. In addition, QLQX extract could reduce the expression of Ang II-induced α-SMA and TGF-β1 proteins, reduce the phosphorylation level of Smad3 protein, and increase the expression of Smad6 protein. The results suggested that QLQX could inhibit myocardial fibrosis through TGF-β1/Smads pathway, thereby improving ventricular remodeling in CHF rats [113].

In addition, some studies have shown that neurohumoral factors change is also one of the mechanisms of heart failure. Sun Xin et al. [114] studied the effect and mechanism of QLQX on CHF rats induced by pressure overload, and found that the hydroxyproline content, Ang II concentration and Calcineurin (CaN) protein expression in cardiac tissue of heart failure rats in QLQX group were significantly decreased, suggesting that QLQX inhibits myocardial fibrosis and improves cardiac function, and inhibits cell differentiation and metastasis by inhibiting RAS mediated CaN. Osteoblast-specific factor 2 (Periostin) plays an important role in ventricular remodeling in heart failure by chemotaxis of myocardial fibroblasts, increasing the mobility and contractility of fibroblasts and the synthesis of matrix proteins. QLQX can improve left ventricular function and inhibit the remodeling of cardiac Collagen network in rats with heart failure after myocardial infarction by reducing Ang II in the circulatory system, regulating the expression of Periostin protein, inhibiting collagen-I deposition, and reducing collagen synthesis and fibrosis in infarcted and non-infarcted areas of heart failure after myocardial infarction [115–117]. The expression of myosin heavy chain α (α-MHC) gene in rat myocardium was significantly decreased in end-stage heart failure. Myocardial remodeling, characterized by the transformation of α-MHC into embryonic β-MHC, can reduce the rate of myocardial shortening and systolic function and promote the progression of heart failure [118]. Zhang [119] showed that one of the possible mechanisms of QLQX improving cardiac function and inhibiting ventricular remodeling in rabbits with heart failure after myocardial infarction is to promote the expression of α-MHC mRNA and inhibit the expression of β-MHC mRNA, thereby increasing the ratio of α-MHC/β-MHC mRNA.

QLQX inhibits the expression of growth factors. Zhang Li et al. [120] established a rat model of congestive heart failure by partial coarctation of abdominal aorta, and found that left ventricular mass index (LVWI) and myocardial collagen volume fraction (CVF) of type I, III and I/III were significantly increased in the model rats ($P < 0.01$), indicating that cardiomyocyte hypertrophy occurred in congestive heart failure. Collagen deposition in myocardial interstitium and dysregulated interstitial fibrotic remodeling in the proportion of type I and III collagen were observed. After QLQX intervention, the pathological morphology of rat myocardium was significantly improved, and the type I/III was decreased. The results of Western blot and immunohistochemistry showed that the drug inhibited cardiac remodeling by inhibiting the overexpression of connective tissue growth factor in left ventricular myocardial tissue.

4.5.3. Inhibition of cardiomyocyte apoptosis and autophagy

Loss of cardiomyocytes due to cardiomyocyte apoptosis is the turning point from compensatory to decompensated stage of heart failure. Cardiomyocytes autophagy is one of the adaptive responses of myocardium to pressure overload. However, abnormal

autophagy response is also one of the causes of cardiac dysfunction. Cardiomyocyte apoptosis plays a key role in the pathological mechanism of heart failure. In the process of cell apoptosis, B-cell CLL/lymphoma 2 (BCL2) has the pro-apoptotic effect of inhibiting Bcl2-associated X protein (Bax). Cysteinyl aspartate specific proteinase (Caspase) can inactivate Bc1–2 and other apoptotic inhibitor proteins. Study has found that QLQX shows a positive effect on inhibiting cardiomyocyte apoptosis in heart failure [121]. Xu Tao et al. [122,123] found that QLQX could improve cardiac function indexes, promote cardiac function recovery and inhibit cardiomyocyte apoptosis through reducing the mRNA and protein expression levels of FasL, Fas and Bax. Zhang et al. [124] used isoproterenol to induce the mouse ventricular remodeling model. Compared with the control group, the Bcl/Bax ratio of mouse myocardial tissue was significantly reduced after QLQX ultrafine powder was administered, suggesting that QLQX could inhibit myocardial cell apoptosis, and this effect was related to the up-regulation of peroxisome activator proliferation receptor (PPARγ). QLQX promotes angiogenesis and inhibits cardiomyocyte apoptosis by activating NRG-1/Akt and inhibiting P53 signaling pathway, thereby improving cardiac function and inhibiting cardiac remodeling [125,126].

In addition, cytokines, such as interleukin and tumor necrosis factor, can promote cardiac hypertrophy and cardiomyocyte apoptosis. Zou et al. [127] showed that QLQX could inhibit cardiac hypertrophy, remodeling and dysfunction in mice with pressure overload for 4 weeks. The mechanisms include inhibition of TNF-α and up-regulation of insulin-like growth factor1 (IGF-1) expression to inhibit myocardial inflammation, regulation of C/EBPb/CITED4 to inhibit myocardial apoptosis, and promotion of cell proliferation. Overexpression of Sarco-endoplasmic reticulum ATPase 2a (SERCA2a) increases myocardial oxygen consumption [128]. QLQX inhibits the overexpression of SERCA2a mRNA and its protein content by increasing the expression of regulatory factor PLB mRNA, reduces calcium overload in heart failure cells, and reduces oxygen consumption in heart failure cells, thus indirectly playing a protective role in cardiomyocytes [52].

Ye et al. [129] used QLQX combined with angiotensin converting enzyme inhibitor (ACEI) and Ang II receptor blocker (ARB) to treat cardiac hypertrophy induced by pressure overload in rats, and the results showed that QLQX combined with the two drugs significantly inhibited autophagy in rat cardiomyocytes compared with the control group. Zou et al. [127] found that autophagy level of mouse cardiomyocytes did not increase significantly after 2 weeks of ascending aortic coarctation (TAC), which may be an adaptive stage of cardiac hypertrophy, but autophagy increased significantly after 4 weeks of TAC-which was the time point when adaptive cardiac hypertrophy developed into a maladaptive stage in mice. These results suggest that excessive autophagy promotes the transformation of cardiac hypertrophy induced by pressure overload to heart failure. Within 4 weeks after TAC, QLQX administration significantly inhibited the expression of autophagy related genes p53 and LC3b in cardiomyocytes, which indicated that QLQX could partially inhibit the abnormal cardiomyocyte autophagy during chronic stress overload, thereby inhibiting cardiac remodeling and cardiac dysfunction.

4.5.4. Promotion of angiogenesis

Myocardial hypertrophy and angiogenesis play a synergistic regulatory role in the process of cardiac physiological growth, but the destruction of coordinated growth pressure after hemodynamic overload and/or cardiac injury, along with the down-regulation of factors associated with angiogenesis and the inhibition of angiogenesis, aggravate the progression of heart failure [130]. Wang et al. [131] found that QLQX enhanced the migration and tube formation ability of cerebral microvascular endothelial cells (CMECs) after induced hypoxic injury compared with the control group by up-regulating protein expression levels of HIF-1α and VEGF via HIF-1α/VEGF signaling pathway. The HIF-1α protein expression enhanced by QLQX in hypoxic CMECs was associated with the regulation of AMPK/mTOR/HIF-1α pathway, and the HIF-1α stabilization improved by QLQX were speculated through down-regulating prolyl hydroxylases 3 (PHD3) expression [88]. The angiogenesis enhancement may be mediated via activation of NRG-1/Akt signaling and suppression of p53 pathway by QLQX on improving cardiac function and attenuating cardiac remodeling post MI [132]. In addition, a study found that the pro-angiogenesis effects of QLQX on hypoxic CMECs are mediated by activating miR-21 and its downstream HIF-1α/VEGF signaling pathway possibly [133].

4.5.5. Improvement of endothelial function

In the CHF state, hemodynamics will change, resulting in a decrease in the shear stress of peripheral blood flow on the intima of blood vessels, vascular endothelial injury, and structural remodeling of the vascular wall [134]. Among them, NO and Endothelin-1 (ET1) are important vasoactive substances synthesized by microvascular endothelial cells, and their homeostasis plays a key role in maintaining normal vascular basal tension. When CHF occurs, the synthesis of NO and Vascular endothelial growth factor (VEGF) is significantly reduced and the synthesis of ET-1 is significantly increased, which leads to the rearrangement of vascular wall components including endothelial cells, vascular smooth muscle cells and collagen matrix, and finally structural remodeling [134]. This accelerates the progression of heart failure, so restoring and maintaining normal endothelial function is an effective treatment for cardiovascular diseases. Studies have shown that combined application of QLQX can improve cardiac function and vascular endothelial function in patients with dilated cardiomyopathy and heart failure, and the mechanism of action is related to increasing VEGF and NO levels, decreasing the level of ET-1 content and soluble vascular endothelial adhesion factors [54,135], which has a positive effect on improving microvascular structure and alleviating endothelial damage.

Cardiac microvascular endothelial cells (CMECs) are important angiogenic components and are injured rapidly after cardiac ischemia and anoxia. QLQX could Improve the morphology and function of MMVEC after hypoxia injury, reduce the apoptosis of CMVECs under hypoxia stimulation by reducing Bax/Bcl-2 ratio and Caspase 3 activity [136,137]. The myocardial capillary endothelium in rats under pressure overload can be protected by QLQX through decreasing the expression of ICAM-1 mRNA and increasing the expression of eNOS mRNA. The mechanism of QLQX may be related to the activation of AMPK-eNOS pathway [82]. QLQX significantly reversed these anoxia-induced injuries and up-regulated expressions of NRG-1, phospho-ErbB2, phospho-ErbB4,

Table 2
Studies on pharmacological mechanism of Qili Qiangxin (QLQX) capsule in treating chronic heart failure (CHF) based on different models.

#	Models	Involved mechanisms	Signaling pathway	Pharmacological effects	Ref.
1	Mice: myocardial hypertrophy model	↓: ANP, BNP, PPARγ, PGC-1α	–	Cardiac hypertrophy	[167]
2	NRCMs: hypoxia model	↑: ErbB4, *p*-Akt; ↓: Caspase-3	↑: ErbB4/PI3K/Akt pathway	Cardiomyocyte apoptosis	[168]
3	SD rats: cardiac fibroblasts	↓: IL-6, TGF-β1, α-SMA	↓: CaN-NFAT3	Cardiac remodeling	[169]
4	H9C2 cell: cardiomyocyte metabolism model	↑: 16sRNA, SSBP1, TWINKLE, TOP1MT, PLOG, PGC-1α	–	Cardiac energy metabolism	[170]
5	C57BL/6 mice: cardiac remodeling after MI	↑: Cd36, Fatp, Pdk4, Acadm, Acadl, Acadvl, Cpt1a, Cpt1b, Cpt2, Bcl-2; ↓: Bax	↑: PPARγ pathway	Cardiac remodeling; Cardiac energy metabolism; Cardiomyocytes apoptosis	[171]
6	CMECs: hypoxia model	↑: NRG-1, *p*-ErbB2, *p*-ErbB4, *p*-Akt, *p*-mTOR, HIF-1α, VEGF	↑: NRG-1/ErbB signaling, PI3K/Akt/mTOR pathway	Cardiomyocytes apoptosis; Angiogenesis	[172]
7	CMECs: hypoxia model	↑: HIF-1α, GLUT1, HK2, PFK1, PKM2, LDHA; ↓: PH3D	↑: AMPK/mTOR/HIF-a pathway	Cardiac microvascular endothelial cell apoptosis	[139]
8	SD rats: MI-HF model	↑: NADH oxidoreductase, ATP synthase, MDH, ACADVL, ALD, CK, CaM; ↓: LDHB, Eno, αB-crystallin, HSP27	–	Cardiac energy metabolism; Oxidative stress	[93]
9	SD rats: AMI-HF model	↓: NT-proBNP, RI, Ang II, ALD, 8-iso-pgf2α, 3-nt, AVP, V2R, AQP2; ↑: NRG1, AngPTL4, CGRP	↓: SCAP/SREBP-1c/ACC1; ↓: LOX/COX; ↑: eNOS/sGC/cGMP/PKG	Cardiac energy metabolism	[84]
10	SD rats: cardiac fibroblasts (CFs)	↑: Smad6; ↓: α-SMA, TGF-βl, *p*-Smad3	↓: TGF-βl/Smad3	Cardiac remodeling	[173]
11	SD male rats: AMI model	↓: α-SMA, Col-I, TGF-β1, *p*-Smad3	↓: TGF-βl/Smad3	Cardiac fibrosis	[174]
12	CMECs: hypoxia model	↑: Bcl-2; ↓: Bax, Caspase-3	–	Cardiac microvascular endothelial cell apoptosis	[137]
13	CMECs: hypoxia model	↑: Bcl-2, Akt, *p*-Akt; ErbB4; ↓: Caspase-3, Bax;	↑: ErbB4/PI3K/Akt	Cardiomyocyte apoptosis; Cardiac microvascular endothelial cell apoptosis	[175]
14	SD rats: HF model	↓: TNF-α, IL-1β, IL-6, TLR4, NF-κB p65	↓: TLR4/NF-κB	Myocardial inflammation	[176]
15	SD rats: MI model	↑: miR-133a; ↓: TGF-β1, Smad 2, Smad3	↓: miRNA-133a/TGF-β1/Smads	Cardiac fibrosis	[177]
16	Wistar rats: HF model	↓: Ang II, Col-I	–	Cardiac fibrosis	[178]
17	Wistar rats: MI-ventricular remodeling model	↓: Ang II, TGF-β1, Periostin, Col-I, Mature collagen	↓: Ang II-TGF-β1/periostin pathway	Cardiac fibrosis	[179]
18	NRCMs: myocardial hypertrophy model	↓: ANP, BNP, MYH7, miR-199a-5p	–	Cardiac hypertrophy	[180]
19	SD rats: AMI model	↓: Caspase-3	–	Cardiomyocyte apoptosis	[181]
20	C57BL/6 mice: MI model; H9C2: hypoxia model	↑: Bcl-2, *p*-Erk, Nrf2; ↓: Bax	↑: *p*-Erk/Nrf2 pathway	Cardiomyocyte apoptosis	[182]
21	SD rats: AMI-HF model	↑: nNOS; ↓: PGE2, TNF-α, IL-6	–	Myocardial inflammation	[106]
22	SD rats: HF model after MI	↑: nNOS; ↓: CRH, TNF-α, NE, 5-HT, BNP, NE, ACTH, PGE2	↓: Activation of CRH neurons	Cardiac remodeling; Myocardial inflammation	[183]
23	Wistar rats: CHF model	↑: SOD; ↓: BNP, MDA	–	Oxidative stress	[184]
24	NRCMs: hypoxia model	↑: SERCA2a; ↓: miR-25, Ca^{2+}	–	Cardiomyocyte apoptosis	[185]
25	C57BL/6 mice: MI model	↑: PPARγ, Cd36, Fatp, Pdk4, Acadm, Acad 1, Acadv1, Cpt1a, Cpt1b, Cpt2; ↓: Col-I, Col-III, α-SMA	–	Cardiac remodeling; Cardiac energy metabolism	[186]
26	Wistar rats: pressure overload-CHF model	↓: Hydroxyproline, Ang II, CaN	↓: RAS system	Cardiac remodeling	[114]
27	SD rats: AMI-HF model	↓: BNP, CaMK II, CaMK IIδ	–	Cardiomyocyte apoptosis	[187]
28	SD rats: HF model after MI	↑: HIF-1, VEGF	–	Cardiac remodeling: Angiogenesis	[188]
29	SD rats: HF model after MI	↓: 3-NT, FFA, 8-iso-PGF_(2α), n-6PUFAs; ↑: n-3PUFAs	–	Cardiac energy metabolism: Lipid metabolism	[189]
30	SD rats: HF model after acute myocardial infarction (MAI)	↓: AVP, BNP, V2-R, AQP-2	–	Diuresis	[56]
31	SD rats: MI model	↓: XO, Fas, Caspase-3	–	Cardiomyocyte apoptosis	[190]
32	SD rats: CHF model	↑: Bcl-2; ↓: Bax, Fas, FasL	–	Cardiomyocyte apoptosis	[123]
33	H9C2 cell: oxidative damage model	↑: Bcl-2; ↓: Caspase-3, Bax, Fas, FasL	–	Cardiomyocyte apoptosis	[191]
34	H9C2 cell: oxidative damage model	↑: PPARα	–	Cardiomyocyte apoptosis	[192]
35	SD rats: CHF model	↑: TIMP-1; ↓: ET-1, Ang II, TNF-α, MMP-2, MMP-9	–	Cardiac remodeling	[111]
36	C57BL/6 mice: myocardial hypertrophy model; $ATG^{-/-}$ mice	↓: Ang II, AT1R, *p*-ERK, ANP, BNP	–	Cardiac hypertrophy; Neuroendocrine system	[193]

(*continued on next page*)

Table 2 (*continued*)

#	Models	Involved mechanisms	Signaling pathway	Pharmacological effects	Ref.
37	C57BL/6 mice: pressure overload myocardial hypertrophy model	↑: *p*-ErbB2, *p*-ErbB4; ↓: AT1R, *p*-ERK	–	Cardiac hypertrophy	[194]
38	Wistar rats: Qi Deficiency CHF model	↑: ATP	–	Cardiac energy metabolism	[81]
39	Wistar rats: MI model	↑: P2X2, P2X4, P2X5, P2X6	–	Cardiac remodeling	[195]
40	Male FVB/NJ mice: MI-HF model; H9C2 cell: aging model	↑: CYLD; ↓: SASP (IL-6, EREG, HGF, IL-1α, CXCL-1, CXCL-2, MMP3), Aging proteins (p16, p53, PCNA)	–	Cardiac remodeling	[196]
41	C57BL/6 mice: cardiac remodeling model	↑: PPAR-γ, PGC-1α, Bcl-2; ↓: TGF-β, MMP2, MMP9, Bax	↑: PPAR-γ/PGC-1α axis	Cardiac remodeling: Cardiac fibrosis; Cardiomyocytes apoptosis	[197]
42	CMECs: hypoxia model	↑: miR-21, HIF-1α, VEGF; ↓: cleaved caspase-3/caspase-3	–	Cardiac microvascular endothelial cell apoptosis; Angiogenesis	[140]
43	SD rats: pressure overload-HF model	↑: ATP, eNOS; ↓: ICAM-1	↑: AMPK-eNOS	Cardiac energy metabolism; Cardiac microvascular endothelial function	[198]
44	SD rats: CHF model	↓: CD34, ET-1, NT-pro BNP, Ang II, ALD, NE, v WF	–	Angiogenesis; Cardiac microvascular endothelial function; Neuroendocrine system	[142]
45	SD rats: pressure overload-myocardial hypertrophy and HF model	↑: α-MHC, Mfn2, p-PI3K, *p*-Akt; ↓: β-MHC, Drp1	↑: PI3K/Akt pathway	Cardiomyocyte apoptosis; Cardiac energy metabolism	[96]
46	SD rats: myocardial hypertrophy model	↓: Glycolipid substrate, FFA,LA	↑: AMPK/PGC-1α axis	Cardiac energy metabolism	[199]
47	SD rats: CHF model	↓: TGF-β1, Smad3, Col-I, Col-III	↓: TGF-β1/Smad3	Cardiac fibrosis	[199]
48	SD rats: CHF model	↓: CTGF	–	Cardiac fibrosis	[200]
49	Wistar Kyoto (WKY) rats: hypertension-HF model	↑: PPAR-α, PPAR-γ	–	Cardiac remodeling	[120]
50	SD rats: HF model	↓: Ang II, BNP, cTnI, ALD	↓: RAAS system	Neuroendocrine system	[201]
51	SD rats: MI-CHF model; H9C2 cell: oxidative damage model	↑: SOD, HO-1, CAT, Bcl-2, *p*-AKT/AKT, *p*-GSK3β/GSK3β; ↓: LDH, ROS, Bax, Cytochrome *c*, Apaf-1, Caspase-9, Caspase-3	↑: PI3K/AKT/GSK3β	Cardiomyocyte apoptosis	[202]
52	Male FVB/NJ mice: mycological infection (MI) model; H9C2 cell: oxidative damage model	↑: Pink1, Parkin, LC3 II	↑: Pink1/Parkin	Cardiac remodeling	[203]
53	SD rats: HF model after MI	↑: Bcl-2; ↓: Bax	–	Cardiomyocyte apoptosis	[204]
54	C57BL/6 mice: hypertensive-ventricular remodeling model	↓: ANP, BNP, Col-III, CD68, IL-6, AT1R, *p*-ERK1/2, TGF-β1, *p*-Smad 3	↓: *p*-ERK1/2; TGF-β1/Smad3	Cardiac fibrosis; Myocardial inflammation	[205]
55	SD rats: AMI-HF model	↑: HIF-1α, VEGF, GLUT-1, GLUT-4, Bcl-2; ↓: Bax	–	Angiogenesis; Cardiac energy metabolism; Cardiac microvascular endothelial cell apoptosis	[136]
56	C57BL/6 mice: myocardial hypertrophy model	↑: CBP/p300, *p*-ErbB2, *p*-ErbB4; ↓: CEBPβ, IGF-1, TNFα, AT1R	–	Cardiac remodeling: Cardiomyocytes proliferation; Cardiomyocytes apoptosis; Myocardial inflammation	[206]
57	CMECs: hypoxia model	↑: HIF-1α, VEGF	–	Angiogenesis	[207]
58	Heart failure patients	↓: NT-proBNP	–		[208]
59	C57BL/6 J mice: AMI model	↑: Smad7, PPARα, PPARβ, PGC-1α; ↓: TGF-β1, MMP-2, MMP-9, Col-I, Col-III, α-SMA, Bax/Bcl-2, cleaved PARP/PARP, cleaved caspase-3/caspase-3	–	Cardiac remodeling	[209]
60	CHF patients	↓: NT-proBNP	–		[210]
61	CMECs: apoptosis model	↑: SQSTM1, Bcl-2, *p*-AKT, *p*-FoxO3a, *p*-GSK3β, *p*-ErbB2; ↓: LC3B-II, cleaved-caspase 9, cleaved-caspase 3, cleaved PARP, Bax	↑: ErbB2-AKT-FoxO3a axis	Cardiac microvascular endothelial cell apoptosis	[145]
62	CMECs: hypoxia model	↑: NRG-1, *p*-ErbB2, *p*-ErbB4, *p*-Akt, *p*-mTOR, HIF-1α, VEGF	↑: NRG-1/ErbB signaling, PI3K/Akt/mTOR pathway	Cardiac microvascular endothelial cell	[138]
63	Male FVB/NJ mice: MI model; H9C2 cells: hypoxia model	↑: Pink1, Parkin, *p*-Parkin; ↓: Bax/Bcl-2	↑: Pink1/Parkin signaling	Cardiomyocyte apoptosis	[211]
64	CMECs: hypoxia model	↑: HIF-1α, VEGF, ATP, GLUT1, HK2, PFK1, PKM2, LDHA; ↓: PHD3	↑: HIF-1α/VEGF signaling pathway, AMPK/mTOR/HIF-1α pathway	Angiogenesis; Cardiac energy metabolism	[88]
65	SD rats: MI model	↑: IL-10; ↓: TNF-α	–	Myocardial inflammation	[107]

(*continued on next page*)

Table 2 (*continued*)

#	Models	Involved mechanisms	Signaling pathway	Pharmacological effects	Ref.
66	Wistar rats: congestive heart failure model	↑: TGF-β3, Smad7, miR-345–3p, miR-328a-3p, miR-106 b-3p; ↓: Bax/Bcl-2, Col-I, Col-III, TGF-β1, Smad3, MMP-2, TIMP-2	↓: TGF-β1/Smad3; ↑: TGF-β3/Smad7	Cardiac remodeling	[212]
67	SD rats: MI model	↑: HIF-1α, VEGF, *p*-Akt, Bcl-2, NRG-1; ↓: Bax, Caspase 3, p53	↑: NRG-1/Akt signaling; ↓: p53 pathway	Cardiac remodeling; Cardiomyocytes apoptosis; Angiogenesis	[132]
68	SD rats: AMI model	↑: *p*-Smad7; ↓: Col-I, α-SMA, TGF-β1, *p*-Smad3, TNF-α, IL-6, NF-κB, *p*-IκBα	↓: TGF-β1/Smad3 and NF-κB signaling pathways	Cardiac remodeling; Cardiac fibrosis; Myocardial inflammation	[108]
69	SD rats: cardiac fibroblasts (CFs) model	↓: TGF-β1, α-SMA, IL-6, Col-I, Col-III	↓: calcineurin/NFAT3 signaling	Cardiac remodeling	[113]
70	C57BL/6 mice: cardiac hypertrophy model	↑: ErbB2, ErbB4; ↓: TNF-α, IGF-1, AT1R, Ang II, CITED4, C/EBPβ	–	Cardiac remodeling	[127]
71	CHF patients	↑: BNP	–		[49]
72	Male SD rats: cardiotoxicity model	↑: SOD, GSH, T-AOC, Bcl-2, Bcl-xl, p62, *p*-mTOR, p-PI3K, *p*-AKT; ↓: H2O2, CKMB, c-TnT, LDH, AST, ALT, cleaved caspase-3, cleaved caspase-9, Bax, Bad, LC3 II, BECN, ULK1	↑: PI3K/AKT/mTOR pathway	Oxidative stress; Cardiomyocyte apoptosis; Cardiomyocyte autophagy	[213]
73	Male SD rats: HF model	↑: Lactobacillus; ↓: IL-1β, TNF-α, NF-κB, NLRP3	↑: Gut microbiota; ↓: NLRP3 inflammasome	Cardiac remodeling	[214]
74	NRCMs: hyperglycemia-induced apoptosis model; mice: diabetic cardiomyopathy model	↑: PPARγ, PGC-1α, HO-1, Nrf2; ↓: Bax/Bcl-2, cleaved caspase-3/caspase-3, TNFα, IL-1β, ANP, BNP, Col1a1, Col3a1	↑: PPAR-γ/PGC-1α axis	Cardiomyocyte apoptosis; Oxidative stress; Cardiac fibrosis; Myocardial inflammation	[215]
75	CMECs: hypoxia or normoxia model	↑: miR-21, HIF-1α, VEGF	↑: miR-21-HIF-1α/VEGF pathway	Angiogenesis	[133]
76	SD rats: AMI-HF model	↑: CD31, VEGF, VEGFR2, PGC-1α, Glucose, glycolysis, ATP, HIF-1α, GLUT4, HK2, PKM2, PFK1, LDHA, FFA; ↓: NT-proBNP	↑: HIF-1α/VEGF pathway	Cardiac energy metabolism; Angiogenesis	[87]
77	SD rats: MI-HF model	↑: FDG, GLUT4, *p*-PDH, PDK4, LDH-A, FAT, CPT1; ↓: GLUT1	–	Cardiac energy metabolism	[86]
78	Rabbits: AF model	↑: DHPR; ↓: TGF-β1, *p*-smad2/3, Col-III, MMP9	↓: TGF-β1/p-smad2/3	Cardiac remodeling; Cardiac fibrosis	[216]
79	SD rats: CHF model; H9C2 cell: ISO-induced injury model	↑: Bcl-2, p62, *p*-AKT/AKT, *p*-mTOR/mTOR; ↓: Bax, LC3II/LC3I	↑: AKT/mTOR pathway	Cardiomyocyte apoptosis; Cardiomyocyte autophagy; Oxidative stress	[217]
80	C57BL/6 mice: cardiac hypertrophy model; NRVMs: cardiac hypertrophy model	↑: PPARγ, PGC-1α; ↓: ANP, BNP	–	Cardiac hypertrophy	[218]
81	SD rats: HF model	↑: AngPTL-4, CGRP, NRG-1; ↓: RI, AII, ALD, AVP, FFA, 3-NT, 9, 10, 13-TriHOME, 12, 13-DiHODE, 9, 10-DiHOME, 9-HOTrE, 5, 6-DiHETrE, 12, 13-EpOME, 9, 10-EpOME, 9-KODE, 13-KODE, 16, 17-EpDPE, LPA-C140, LPA-C160, LPA-C161, LPA-C181, LPA-C182, LPA-C183-ω3ω6, LPA-C203, LPA-C204, LPA-C205, LPA-C225, LPA-C226	↓: LPA/cLPA-related pathways	Cardiac hypertrophy; Myocardial inflammation	[219]
82	Female C57BL/6 mice: MI model	↑: Bcl2, PPARγ, Cd36, Fatp, Pdk4, Acadm, Acadl, Acadvl, Cpt1a, Cpt1b, Cpt2; ↓: Bax, Col-I, Col-III, α-SMA, TGF-β	–	Cardiac energy metabolism; Cardiac remodeling	[97]
83	NRVMs: cardiac hypertrophy model; C57BL/6 mice: AMI model	↓: ANP, BNP, MYH7, miR-199a-5p	–	Cardiac hypertrophy	[220]
84	C57BL/6 mice: I/R model	↑: *p*-mTOR, *p*-Akt; ↓: p-4EBP-1	↑: mTOR pathway	Cardiac remodeling	[131]
85	H9C2 cell: cardiomyocyte metabolism model	↑: PGC-1α, NRF1, TFAM, 16sRNA, SSBP1, TWINKLE, TOP1MT, PLOG	–	Cardiac energy metabolism	[95]
86	SD rats: myocardial hypertrophy model	↑: *p*-AMPK, AMPK, PGC-1α, CPT-I, GLUT-4; ↓: FFA, LA	↑: AMPK/PGC-1α axis	Cardiac energy metabolism	[83]
87	C57BL/6 male mice: cardiac remodeling model	↑: PPARγ, PGC-1α; ↓: TGF-β, MMP-9, MMP-2, Bax/Bcl-2	–	Cardiac remodeling; Cardiomyocyte apoptosis; Cardiac fibrosis	[221]
88	SD rats: MI-HF model; NRCMs: hypoxia model	↑: Bcl-2/Bax, VEGF, *p*-Akt; ↓: caspase-3	–	Cardiac remodeling; Cardiomyocyte apoptosis; Cardiac fibrosis	[222]
89	SD rats: AMI-HF model; H9C2 cell: oxidative damage model	↑: Bcl-2, *p*-AKT/AKT, *p*-GSK3β/GSK3β; ↓: Bax, cytochrome *c*, Apaf-1, cleaved-caspase 9, cleaved-caspase 3, mitochondrial fission, MPTP, MMP	↑: PI3K/AKT/GSK3β signaling pathway	Cardiomyocyte apoptosis	[223]

phospho-Akt, phospho-mammalian target of rapamycin (mTOR), HIF-1α and vascular endothelial growth factor (VEGF) in CMECs via NRG-1/ErbB signaling which was most probably dependent on PI3K/Akt/mTOR pathway [138]. QLQX can effectively promote proliferation of hypoxic CMECs, inhibit apoptosis, and promote angiogenesis of CMECs through HIF-1α/VEGF signaling pathway by upregulating HIF-1α and a range of glycolytic related enzymes, including GLUT1, HK2, PFK1, PKM2, and LDHA. The regulation of AMPK/mTOR/HIF-α signaling pathway participate in the QLQX-dependent enhanced expression of hypoxia CMECs HIF-1α protein, and the down-regulation of PHD3 expression may improve the stability of HIF-1α [139]. In addition, up-regulation of microRNA-21 expression by QLQX may play a role in reduces apoptosis and promotes angiogenesis of rat CMECs under hypoxia [140].

CHF patients show a hyperactive renin-angiotensin-aldosterone system (RAAS) with elevated plasma Ang II levels [141]. Microvascular injury interacts with hyperactivation of neuroendocrine function [142]. Excessive Ang II induces endothelial cell damage.

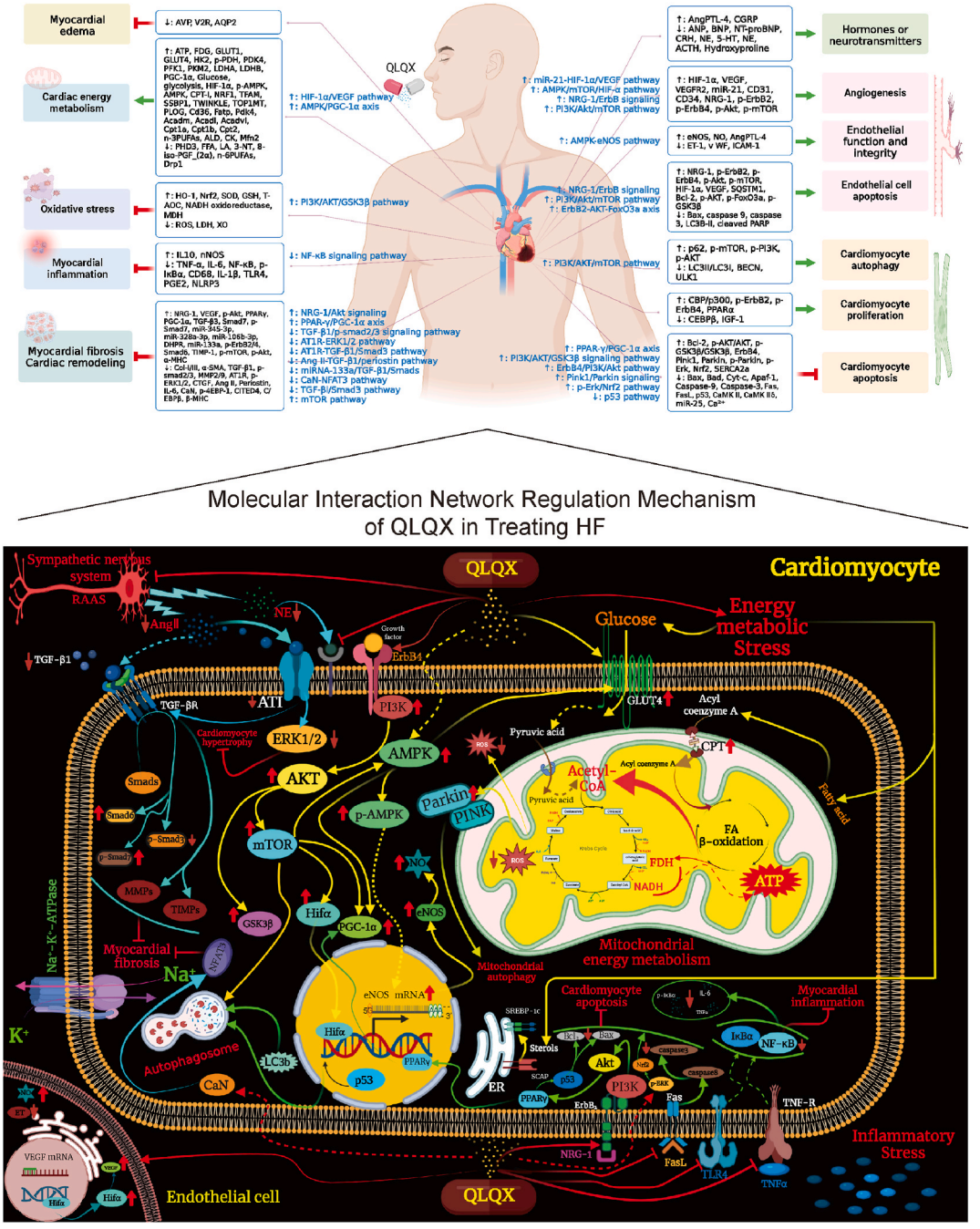

Fig. 2. The therapeutic roles by which Qili Qiangxin (QLQX) capsule protect against heart failure.

This damage eventually leads to coronary microvascular rarefaction and microvascular dysfunction [143], which have recently been proposed to be the primary pathophysiological features of HF [144]. Therefore, inhibition of Ang II-induced endothelial cell injury is particularly important for the management of HF. Li F et al. [145] found that QLQX-induced downregulation of Ang II-activated autophagy and apoptosis was ErbB2 phosphorylation-dependent via the AKT-FoxO3a axis.

5. "Multi-component, multi-target and multi-pathway" mechanism of QLQX in treating chronic heart failure (CHF)

Traditional Chinese medicine (TCM) is characterized by its complex system with multiple components, multiple targets and pathways [146]. In recent years, network pharmacology has been be widely accepted as an efficient research strategy to explore TCM from the perspective of biological network balance [147–149]. Here, we combined chemical and therapeutic properties with the network pharmacology to probe into the molecular mechanisms of QLQX employed for treating HF. A comprehensive target spectrum of QLQX is crucial to investigate the substantial basis and mechanism of action on the treatment of HF. The compounds in Table 1 were standardized through PubChem database, and 146 compounds were obtained for subsequent analysis. To improve reliability, the known targets collected from DrugBank [150], TTD [151], ChEMBL [152], PubChem [153], and CTD [154], and the putative targets predicted from STITCH [155], SEA [156], TargetNet [157], SwissTargetPrediction [158], ChEMBL_prediction [159], and BATMAN-TCM [160] were combined and normalized by UniProt [161]. The whole compound-target (*C*-T) network of QLQX was constructed and visualized by Cytoscape v3.7.1 [162]. And the degree computed by NetworkAnalyzer plugin [163] was used to evaluate the importance of the nodes. In order to further explore the key active compounds and targets of QLQX in treating HF, we collected the targets reported in literatures (Table 2 and Fig. 2) and therapeutic targets from PHARMACODIA (https://www.pharmacodia.com/). And their (*C*-T) subnetworks were extracted to identify the key active components and hub targets exerting therapeutic effects. To interpret the mechanisms of QLQX against HF from a systematic perspective, clusterProfiler version 4.0.3, an R Bioconductor package [164] was used to conduct gene ontology (GO) and KEGG pathway enrichment analysis for targets from literatures [165]. ClueGO plugin in Cytoscape was used to decipher functionally grouped GO terms or KEGG pathways [166].

Notes: ↑: Increased/activated/up-regulated by QLQX at the level of gene and/or protein expression, or enzyme activity content; ↓: Decreased/inhibited/down-regulated by QLQX at the level of gene and/or protein expression, or enzyme activity, or active substance content. QLQX, Qili Qiangxin capsule; CMVECs, Cardiac microvascular endothelial cells; CMECs, Cardiac microvascular endothelial cells; NRCMs, neonatal rat cardiac myocytes; NRCMs, neonatal rat cardiomyocytes; NRVMs, neonatal rat left ventricle myocyte; CHF, chronic heart failure; AF, atrial fibrillation; CFs, cardiac fibroblasts; I/R, ischemia/reperfusion; AMI, acute myocardial infarction; MI, myocardial infarction; MIRI, myocardial ischemia-reperfusion injury; SHRs; spontaneous hypertension; SD, Sprague-Dawley rats; ZO-

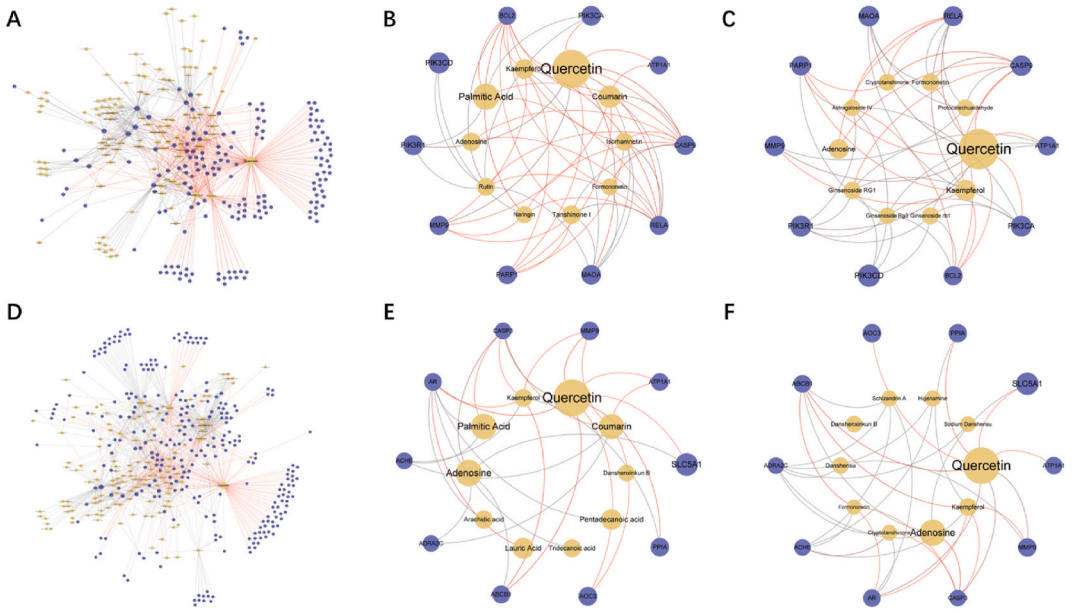

Fig. 3. The compound-target (*C*–T) networks and enrichment analysis results. (A) The (*C*–T) networks for targets from literatures. The network contained 284 nodes (112 compounds and 172 targets) and 859 edges. **(B)** Top 10 key active compounds and hub targets from literatures. **(C)** Top 10 key active compounds highly exposed in plasma and hub targets from literatures. **(D)** The (*C*–T) networks for therapeutic targets from PHARMACODIA. The network contained 403 nodes (131 compounds and 272 targets) and 1289 edges. **(E)** Top 10 key active compounds and hub therapeutic targets from PHARMACODIA. **(F)** Top 10 key active compounds highly exposed in plasma and hub therapeutic targets from PHARMACODIA. If a compound targets on a protein, there is a link between them. The round orange and square blue nodes represent the compound and target, respectively. Node size is proportional to its degree. The degree of a node is the number of its neighbors. *C*-T network, Compound–target network.

1, Zonula Occludens-1; IL10, interleukin-10; IL6, interleukin-6; MMPs, matrix metalloproteinases; TIMPs, tissue inhibitor of metalloproteinases; MMP-2, matrix metalloproteinase-2; MMP-9, matrix metalloproteinase-9; PINK1, PTEN induced kinase 1; Parkin, E3 ubiquitin-protein ligase parkin; LC3-II; CK, creatine kinase; SOD, Superoxide dismutase; GSH, glutathione; MDA, malondialdehyde; NO, nitric oxide; ET-1, endothelin-1; MPO, myeloperoxidase; iNOS, inducible nitric oxide synthase; eNOS, endothelial nitric-oxide synthase; α-SMA, α-smooth muscle actin; PECAM-1, platelet-endothelial cell adhesion molecule-1; *p*-CREB, phosphorated cAMP response element-binding protein; TRAF6, TNF receptor associated factor 6; NF-κB, nuclear factor kappa-B; TNF-α, tumor necrosis factor-α; TGF-β1, transforming growth factor-β; AQPs, aquaporins; Bcl-2, B-cell lymphoma-2; Bax, BCL2-associated X protein; Ang II, angiotensin II; PPAR-α, peroxisome proliferator activated receptor-α; PPAR-γ, peroxisome proliferator activated receptor-γ; Angptl4, angiopoietin-like 4; HIF-1, hypoxia inducible factor-1; vWF, von Willebrand Factor; NRG-1, Neuregulin 1; ErbB2, human epidermal growth factor receptor 2; ErbB4, human epidermal growth factor receptor 4; PI3K, phosphatidylinositol3-kinase; Akt, protein kinase B; VEGF, vascular endothelial growth factor; AMPK, AMP-activated protein kinase; mTOR, mammalian target of rapamycin; LC3, microtubule-associated protein 1 light chain 3; NT-proBNP, *N*-terminal pro-B-type natriuretic peptide; AVP, arginine vasopressin; AQP2, aquaporin2; V2-R, vasopressin V2 receptor; ADH, antidiuretic hormone; NE, norepinephrine; Ang II, angiotensin II; ALD, aldosterone; CRH, corticotropin releasing hormone; ACE, angiotensin converting enzyme; AT1R, angiotensin type I receptor; PRA, plasma renin activity; ATP, Adenosine triphosphate; FAO, Fatty acid β-oxidation; ROS, reactive oxygen species; FA, fatty acid; CPT-I, carnitine palmityl transferase I; GLUT4, glucose transporter 4; NEFA, non-esterified fatty acid; Gal-3, Galectin-3; hs-CRP, hypersensitive *C*-reactive protein; IL-6, interleukin-6; PGE2, prostaglandin E2; phosphorylated IκBα; PDGF, platelet-derived growth factor; bFGF, basic fibroblast growth factor; *p*-Smad3, phosphorylated smad3; COL-I, collagen I; CaN, Calcineurin; Periostin, osteoblast-specific factor 2; α-MHC, myosin heavy chain α; BCL2, B-cell CLL/lymphoma 2; Bax, Bcl2-associated X protein; IGF-1, insulin-like growth factor1.

Based on the multi-dimensional analysis of the compound-target (*C*-T) networks, the potential active monomers of QLQX in the treatment of HF include palmitic Acid, coumarin, tanshinone I, isorhamnetin, rutin, and naringin. In addition, special attention should be paid to high exposure components in plasma, such as quercetin, kaempferol, adenosine, cryptotanshinone, formononetin, ginsenoside RG1, ginsenoside Rg3, ginsenoside rb1, danshensu, sodium danshensu, danshenxinkun B, protocatechualdehyde, astragaloside IV, schizandrin A, higenamine (Fig. 3). Most of them have been reported to have the potential to improve heart failure [40,224–229], laying the foundation for the interpretation of the basis of pharmacological substances and the development of active substance compositions.

Furthermore, we inferred that the following targets, such as PIK3CD, PIK3R1, PIK3CA, MAOA, CASP9, PARP1, MMP9, ATP1A1, RELA, BCL2, etc., are the key targets for most active compounds in QLQX to play a therapeutic role in treating HF (Fig. 3A–C). In addition, the therapeutic targets of SLC5A1, AOC3, PPIA, AR, ABCB1, ADRA2C, CASP3 and ACHE in clinical studies are also worthy of attention in subsequent studies (Fig. 3D–F).

To interpret the mechanisms of QLQX against HF from a systematic perspective, functionally grouped KEGG pathway and biological process (BP) of GO was explored (Fig. 4). The key signaling pathways of QLQX in the treatment of HF include diabetic cardiomyopathy, apelin signaling pathway, lipid and atherosclerosis, fluid shear stress and atherosclerosis, insulin resistance, chemical carcinogenesis-reactive oxygen species, AGE-RAGE signaling pathway in diabetic complications, AMPK signaling pathway, oxidative phosphorylation, HIF-1 signaling pathway, Apoptosis, TNF signaling pathway, etc. (Fig. 4A). In addition, response to hypoxia, ATP metabolic and biosynthetic process, response to oxidative stress, regulation of apoptotic process, regulation of cell death, response to

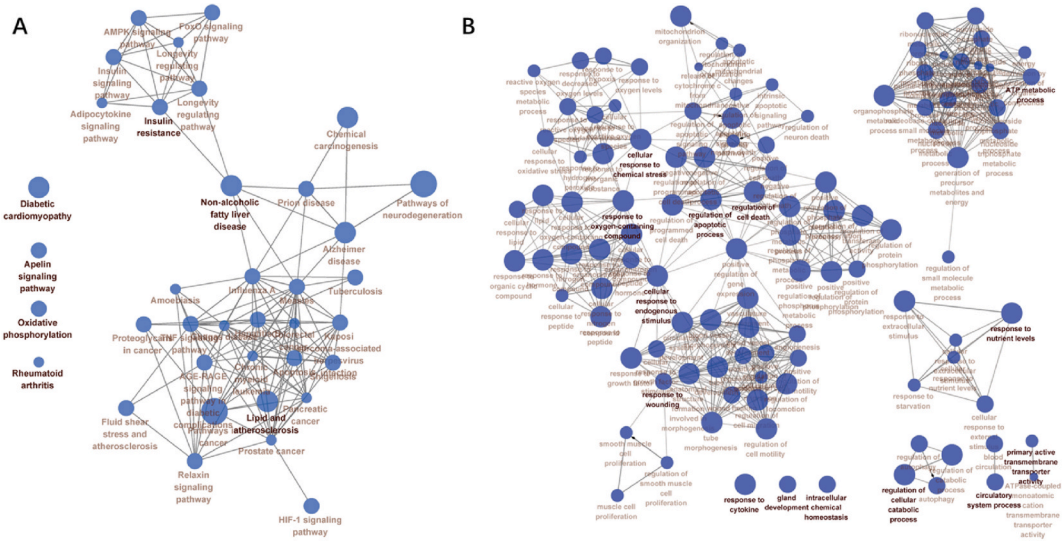

Fig. 4. The enrichment analysis results for targets from literatures. (A) Significantly enriched KEGG pathways. **(B)** Significantly enriched GO biological processes (BP). The smaller the p value, the darker the color of the node and font.

cytokine, circulatory system process, primary active transmembrane transport activity, etc., are the key biological processes for the therapeutic effect of QLQX on HF (Fig. 4B). The above significantly enriched KEGG pathways and GO terms are consistent with the reported mechanism of action of QLQX in the treatment of HF, which can not only reflect the functional characteristics of QLQX "multi-component, multi-target, multi-pathway", but also provide the possibility to explore new mechanisms of action from a systematic perspective.

6. Conclusions

QLQX, developed under the guidance of venation theory, has a solid theoretical basis and clinical efficacy in treating CHF, and is of great significance in improving the prevention and treatment of CHF by traditional Chinese medicine. In the treatment of heart failure, QLQX can play a role of treating both symptoms and root causes from multiple targets and pathways, reverse ventricular remodeling, delay the process of heart failure, improve the prognosis of patients, and have a positive clinical effect on heart failure. Experimental studies have proved that QLQX not only has the role of strengthening cardiac function, diuresis, dilatation of blood vessels, the treatment of heart failure standard, relieving the symptoms of heart failure comparable with the first-line western medicine, It can also intervene in ventricular remodeling and improve the pathological basis of CHF by inhibiting the excessive activation of the neuro-endocrine system, alleviating myocardial inflammation, improving myocardial energy metabolism, and inhibiting myocardial collagen synthesis, so as to cure its root causes, contributing to the long-term prognosis of patients with heart failure. However, heart failure is the pathological development process of multifactorial interaction, and its mechanism has not been fully clarified yet. It is necessary to integrate system biology, bioinformatics, computational biology, and pharmacogenomics for exploring the potential interactions occurring during a holistic treatment. Based on the network pharmacology technique widely used to combine the chemical and therapeutic properties, we conducted a network association analysis of the scattered mechanism information reported in the literatures, which enabled us to achieve a complete understanding of the pharmacology of QLQX in treating HF from a systematic perspective. It is hoped that the systematic review and prospective analysis in this paper can also provide new direction and inspiration for further researches of QLQX in the field of pleiotropic material basis and mechanism. With the improvement of research technologies and the expansion of research fields, on the one hand, more in-depth theoretical, more experimental and clinical researches should be carried out on QLQX to explore the mechanism of multi-target and multi-pathway effects. On the other hand, we should further deepen and expand the therapeutic effect of traditional Chinese medicine on CHF, and provide broader treatment ideas for CHF and other refractory diseases in the cardiovascular event chain.

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Data Availability Statement

Data will be made available on request.

CRediT authorship contribution statement

Tongxing Wang: Conceptualization, Data curation, Visualization, Writing – original draft, Writing – review & editing. **Bin Hou:** Data curation, Software, Visualization. **Haoran Qin:** Conceptualization, Investigation, Methodology. **Junqing Liang:** Investigation, Visualization. **Min Shi:** Data curation, Formal analysis. **Yanfei Song:** Data curation, Formal analysis. **Kun Ma:** Data curation, Formal analysis. **Meng Chen:** Data curation, Formal analysis. **Huixin Li:** Data curation, Formal analysis. **Guoyuan Ding:** Data curation, Formal analysis. **Bing Yao:** Data curation, Formal analysis. **Zhixin Wang:** Data curation, Formal analysis. **Cong Wei:** Conceptualization, Writing – review & editing. **Zhenhua Jia:** Conceptualization, Funding acquisition, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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