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Advances in traditional Chinese medicine for cardiovascular disease therapy in 2020

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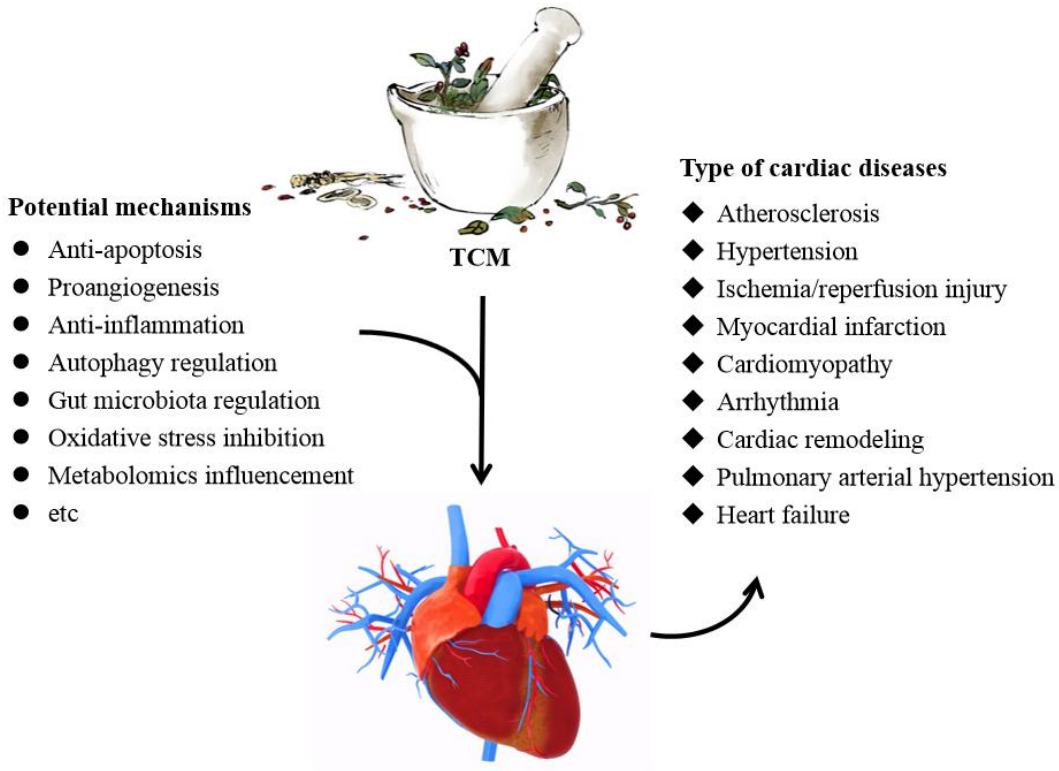
Highlights

The paper reviewed the research progress of traditional Chinese medicine used as cardiovascular diseases therapies in 2020. The research of traditional Chinese medicine in the treatment of atherosclerosis, myocardial infarction, myocardial ischemia/reperfusion injury and heart failure were the research focus for 2020. The anti-cardiovascular diseases effects of Chinese herbal extract such as Ginsenoside and Astragaloside IV have attracted the most attention in the past year.

Tradition

This annual review summarized the research progress on the relevant mechanisms by which traditional Chinese medicine regulates cardiovascular diseases in 2020 with a view to reveal its application for cardiovascular diseases prevention and/or therapy.



Abstract

Cardiovascular diseases are a major cause of morbidity and mortality worldwide and there is an urgent need to develop new pharmacotherapies for managing cardiovascular diseases. In China, traditional Chinese medicine has been used in clinical settings for thousands of years. Although traditional Chinese medicine is very popular, Western medicine experts have not yet accepted it because some ingredients and mechanisms of action for its therapeutic effect are not fully clear. Emerging evidence has established that traditional Chinese medicine inhibits oxidative stress and inflammatory response, suppresses apoptosis, promotes angiogenesis, regulates autophagy and gut microbiota, and modulates metabolomics, among others. Therefore, it has a beneficial role against cardiovascular disease occurrence and progression, such as atherosclerosis, hypertension, myocardial ischemia/reperfusion injury, myocardial infarction, cardiomyopathy, arrhythmia, cardiac remodeling, pulmonary arterial hypertension, and heart failure. In this review, we have summarized the research progress on the relevant mechanisms by which traditional Chinese medicine regulates cardiovascular diseases in 2020 to reveal its application to cardiovascular disease prevention and/or therapy.

Keywords: Traditional Chinese medicine, Cardiovascular diseases, Atherosclerosis, Myocardial ischemia-reperfusion injury, Mechanisms, 2020

***Author contributions*:**

Kun Xiang was responsible for drafted and revised the manuscript. Jin-Fu Yang performed review and revision of the manuscript. Xun Wu was responsible for prepared the relevant references. Jun Peng provided critically opinion. Jian-Jun Guo also provided critically opinion. Cheng-Ming Fan provided critically revision of the final manuscript. All authors read and approved the final manuscript.

***Competing interests*:**

The authors declare no conflicts of interest.

***Abbreviations*:**

CVDs, cardiovascular diseases; TCM, traditional Chinese medicine; AS, atherosclerosis; MI, myocardial infarction; MIRI, myocardial ischemia-reperfusion injury; VSMCs, vascular smooth muscle cells; ECs, endothelial cells; CFDA, China Food and Drug Administration; ApoE−/−, apolipoprotein E-deficient; LXR-α, liver X receptor α; ox-LDL, oxidized low-density lipoprotein; ROS, reactive oxygen species; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; HUVECs, human umbilical vein endothelial cells; PPAR, peroxisome proliferator-activated receptors; AMPK, adenosine monophosphate-activated protein kinase; TNF-α, tumor necrosis factor-α; HFD, high-fat diet; TGF-β, transforming growth factor-β; MAPK, mitogen-activated protein kinases; SD, Sprague-Dawley; QDG, Qingda granule; SOD, superoxide dismutase; LADCA; left anterior descending coronary artery; H/R, hypoxia/reoxygenation; Linc-ROR, long intergenic non-protein coding RNA-regulator of reprogramming; HF, heart failure; mTOR, mammalian target of rapamycin; ISO, using isoproterenol; VEGF, vascular endothelial growth factor; AMI, acute myocardial infarction; SBP, Shexiang Baoxin pill; QQC, Qili Qiangxin capsule; DOX, doxorubicin; GSH-PX-1, glutathione peroxidase-1; PLA2, phospholipase A2; PAH, pulmonary arterial hypertension; CaMKII, calcium/calmodulin-dependent protein kinase II; TLR; toll-like receptor.

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Background

Cardiovascular diseases (CVDs) are the leading cause of disability and death across the globe. Epidemiological studies have shown that CVDs cause about 1/3rd of all deaths in developed countries and 1/4th in developing countries [1]. Since Western medicine has not successfully identified effective treatment methods for CVDs, a complementary and alternative approach for CVDs is required. Traditional Chinese medicine (TCM) has been used in the clinical treatment of CVDs for thousands of years. It is "multi-target and multi-channel" and is, therefore, receiving increasing attention from the cardiovascular research community and becoming popular in many developed countries. TCM mainly uses natural products, such as plants and animals, and processed products [2]. TCM has been effective in preventing and treating several diseases for thousands of years in China. TCM's therapeutic mechanism may be associated with inhibited oxidative stress and inflammatory response, anti-apoptosis activity, promotion of angiogenesis, regulation of autophagy and gut microbiota, modulation of metabolomics, and so on. Further, considering its complex pharmacological activity and potentiality in the prevention and treatment of CVDs (Figure 1), we concluded that the molecular mechanism involved in TCM exerts its beneficial effects on CVD pathology and development, providing new insights into develop new pharmaceuticals and a promising therapeutic regimen to treat CVDs.

Protection of the CVDs with TCM

Atherosclerosis

Atherosclerosis (AS), one of the main pathogenesis of CVDs, could cause critical clinical events, such as myocardial infarction (MI) and unstable angina [1]. AS pathogenesis and development include lipid deposition, endothelial dysfunction, foam cell formation, platelet migration and aggregation, oxidative stress injury, immune-inflammatory response, and vascular smooth muscle cells (VSMCs) proliferation and migration [1]. Extensive research suggests that TCM can exert protective effects against AS by regulating the above-mentioned pathogenesis and development processes (Table 1).

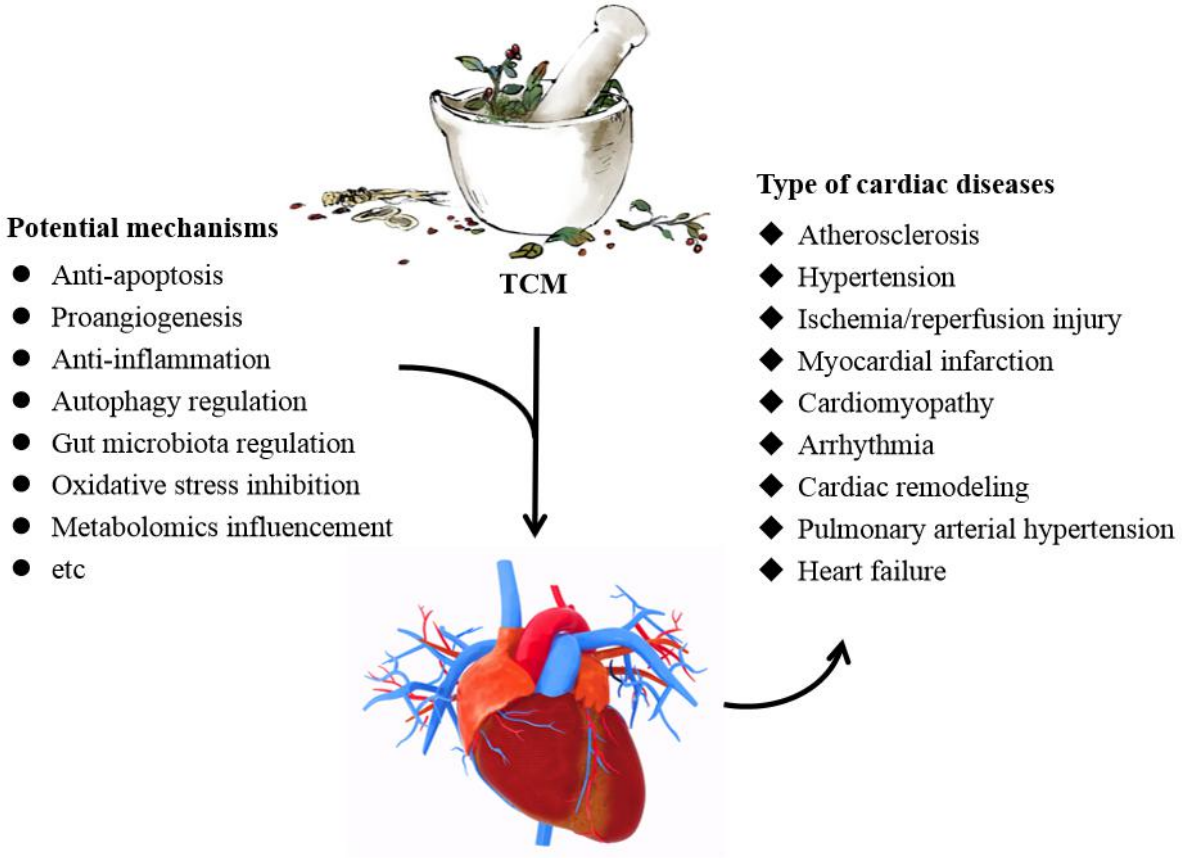

Figure 1 Analysis of the types of cardiac diseases and TCM's potential mechanisms on cardiovascular therapy. TCM, traditional Chinese medicine.

Table 1 Mechanisms of TCM in the treatment of AS

Drugs and prescription	Approval No. by CFDA	Mechanisms and biological effects	Refs
Empirical formula of Chinese medicine Fufang Zhenzhu Tiaozhi capsule	–	Regulates adiponectin signaling pathway, alleviates serum lipids and inhibites foam cell formation	[3]
Chinese patent drug Guanxin Shutong capsule	Z20020055	Inhibites oxidative stress, inflammatory response and foam cell formation	[4]
Ganoderma lucidum spore ethanol extract	–	Promotes expression of LXR-α and downstream genes related to reverse cholesterol transport and metabolism, improves hyperlipidemia	[5]
Gypenoside	–	Improves sirtuin 1-forkhead box O1 mediated autophagy flux restoration and alleviates foam cell formation	[6]
Chinese patent drug *Salvia miltiorrhiza* injection	Z32020161	Inhibits expression of KLF10 and oxidative stress	[7]
Dihydromyricetin	–	Inhibits expression of microRNA-21, oxidative stress and dimethylarginine dimethylaminohydrolase 1-medaited asymmetric dimethylarginine-eNOS-NO signaling pathway	[8]
13-Methylberberine	–	Inhibits activation of NLRP3 inflammasome and improves endothelial dysfunction	[9]
Alisol A	–	Inhibits NF-κB signaling pathway, activates PPARα/β and AMPK/SIRT1 signaling pathways to promote intracellular lipid metabolism	[10]
Arctium lappa root extract	–	Inhibits NF-κB signaling pathway and expression of TNF-α and alleviates inflammatory response	[11]
Classic ancient prescription of the Chinese medicine Buyang Huanwu decoction	–	Regulates TGF-β/Smad2 signaling pathway, inhibits inflammatory response, improves lipid metabolism and stabilizes immune balance between $CD4^+$ T cells	[12]
Berberine	–	Activates MAPK and PI3K-Akt signaling pathway, regulates proteolysis and cell cycles and inhibites inflammatory response and VSMCs proliferation	[13]
Empirical formula of Chinese medicine Dingxin recipe	–	Regulates LXR-α/sterol regulatory element-binding protein 1 signaling pathway and gut microbiota and lipid metabolism	[14]
Classic ancient prescription of Chinese medicine Alisma orientalis beverage	–	Reduces expression of hepatic flavin monooxygenase 3 and trimethylamine N-oxide concentration, alleviates inflammatory cytokine release and regulates gut microbiota	[15]
2,3,5,4'-Tetrahydroxy-stilbene-2-O-β-D-glucoside	–	Suppresses lipid accumulation and inflammatory response and regulates gut microbiota	[16]

TCM, traditional Chinese medicine; AS, atherosclerosis; LXR-α, liver X receptor α; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; MIRI, myocardial ischemia-reperfusion injury; PPAR, peroxisome proliferator-activated receptors; AMPK, adenosine monophosphate-activated protein kinase; TNF-α, tumor necrosis factor-α; TGF-β, transforming growth factor-β; MAPK, mitogen-activated protein kinases; VSMCs, vascular smooth muscle cells; CFDA, China Food and Drug Administration; –, not mentioned.

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Hypolipidemic effects and inhibition of foam cell formation. AS is a lipid-induced inflammatory disease, it occurs in the intima of the arteries. In terms of mechanism, the arterial vessel wall's intensive permeability results from lipid deposition in the endothelial cells (ECs) that exacerbates the oxidation and retention of lipoproteins, ultimately leading to the progression of AS [1]. By establishing the iliac artery restenosis in a New Zealand rabbit model, Tudi L et al. [3] showed that the empirical formula of Chinese medicine Fufang Zhenzhu Tiaozhi capsule, consisting of *Radix Notoginseng*, *Cortex Eucommiae*, *Rhizoma Coptidis*, *Radix Atractylodes Macrocephala*, *Fructus Ligustri Lucidi*, *Radix Salvia Miltiorrhiza*, *Herba Cirsii Jeponici*, and *Fructus Citri Sarcodactylis*, effectively alleviated serum lipids. It improved vascular restenosis by regulating the adiponectin signaling pathway. In an AS apolipoprotein E-deficient ($ApoE^{-/-}$) mice model, Yingdong L et al. [4] showed that the Chinese patent drug Guanxin Shutong capsule, approved by the China Food and Drug Administration (CFDA) (approval No. Z20020055), consisting of *Bamusaeconcretiosilicea*, *Radix Salviae*, *Caryophylliflos*, *Choerospondiatis Fructus*, and *Borneolum Syntheticum*, alleviated AS by reducing foam cell formation and stabilizing the fibrous cap by inhibiting oxidative stress and inflammatory response. *Ganoderma lucidum*, an edible and medicinal fungus, includes sterols, triterpenes, polysaccharides, and other bioactive components. It has been widely used in clinical practice for thousands of years. Peng et al. established a Japanese white rabbit model with hyperlipidemia and AS [5] and found a *Ganoderma lucidum* spore ethanol extract alleviated hyperlipidemia and AS. It upregulated the expression of liver X receptor α (LXR-α) and downstream genes related to reverse cholesterol transport and metabolism, reduced the plasma low-density lipoprotein levels and total cholesterol, and increased the plasma high-density lipoprotein levels. By establishing a human leukemia monocytic THP-1 cells model, treated with oxidized low-density lipoprotein (ox-LDL), Hui B et al. [6] found that Gypenoside, the major biologically active compound of *Gynostemma pentaphyllum*, exerted anti-atherosclerotic effects by alleviating the ox-LDL uptake and foam cell formation by improving sirtuin 1-forkhead box O1 mediated autophagy flux restoration.

Inhibition of oxidative stress. The imbalance between overproduction and purge of reactive oxygen species (ROS) in the cells and tissues was termed oxidative stress, a phenomenon that deteriorates AS under pathological conditions [1]. ROS oxidizes low-density lipoprotein deposits and gathers in the impaired ECs and then to ox-LDL. Moreover, the migrated lymphocytes and monocytes can secrete many ROS that aggravates the early atherosclerotic lesions. ROS favors collagen deposition and VSMCs proliferation, ultimately leading to atherosclerotic plaque development [1]. In an AS mice model, Jing Z et al. cultured and treated mouse aortic VSMCs line [7]. They found that the Chinese patent drug, *Salvia miltiorrhiza* injection that has been approved by the CFDA (approval No. Z32020161), an aqueous extracts of *Salvia miltiorrhiza* Bunge, alleviated oxidative stress and AS by suppressing the KLF10/HO-1 signaling pathway and reducing ROS production. Dafeng Y et al. established an AS $ApoE^{-/-}$ mice of C57BL/6J model [8] and found that dihydromyricetin, the most abundant and bioactive flavanonol compound, alleviated AS by decreasing lipid and endothelial nitric oxide production by reducing the expression of microRNA-21 and then activating the dimethylarginine dimethylaminohydrolase 1 mediated asymmetric dimethylarginine endothelial nitric oxide synthase (eNOS) nitric oxide (NO) signaling pathway.

Alleviation of the inflammatory response. Inflammatory response, mediated by adhesion molecules, chemokines, proinflammatory cytokines, and so on, plays a vital role in atherosclerotic progression stages. The damaged ECs activated by inflammatory factors promote the formation of intercellular adhesion molecule 1, vascular adhesion molecule 1, monocyte chemoattractant protein 1, and proinflammatory cytokines, thereby enabling the accumulation of monocytes in the blood into the endarterium [1]. Migrated monocytes differentiate into macrophages that promote the inflammatory reaction and atherosclerotic plaque formation [1]. 13-Methylberberine is a newly synthesized TCM compound of 13-methyl-substituted derivative of berberine that is distributed in many plants, such as Chinese goldthread, phellodendron, goldenseal, tree turmeric, and European barberry and possesses anti-inflammatory and anti-hypercholesterolemic activities. By establishing the human umbilical vein endothelial cells (HUVECs) model treated with high glucose, Zhihua P et al. [9] demonstrated that 13-methylberberine reduced endothelial dysfunction to exert anti-AS effects by mitigating NLRP3 inflammasome activation via autophagy induction and cytoprotection. Using an AS model in $ApoE^{-/-}$mice of C57BL/6, Ke W et al. [10] showed that alisol A, an alcohol extract of *Alismatis Rhizoma*, alleviated the inflammatory response and AS by activating the peroxisome proliferator-activated receptors (PPAR) α/β and adenosine monophosphate-activated protein kinase (AMPK)/SIRT1 signaling pathway to promote intracellular lipid metabolism that prevents the reduction of I_kB_α and suppresses the activation of NF-κB. By establishing an AS mouse model, culturing, and treating HUVECs and monocyte THP-1 cells, Jangho L et al. [11] found that *Arctium lappa* root alcohol extract alleviated tumor necrosis factor-α (TNF-α)-induced early stage of AS by mitigating the expression of the NF-κB signaling pathway. Using a

high-fat diet (HFD)-induced AS model in ApoE$^{-/-}$ mice of C57BL/6, Shujing C, et al. [12] showed that the classic ancient prescription of the Chinese medicine, Buyang Huanwu decoction, consisting of *Persicae Semen*, *Paeoniae Radix Rubra*, *Carthami Flos*, *Pheretima*, *Chuanxiong Rhizoma*, *Astragali Radix*, and *Angelicae Sinensis Radix*, alleviated AS. It regulated the transforming growth factor-β (TGF-β)/Smad2 signaling pathway to promote Tregs' peripheral differentiation, stabilizing the immune balance between CD4$^+$ T cells, inhibiting inflammatory response, and promoting lipid metabolism and atherosclerotic plaque stability.

Mitigation of VSMCs migration and proliferation. AS plaque formation and intimal focal fibrous thickening were caused by aberrant migration and proliferation of VSMCs [1]. By constructing protein-protein interaction networks pharmacology, Xuejiao X et al. [13] found that berberine alleviated AS. It inhibited the inflammatory response and VSMCs proliferation by activating the mitogen-activated protein kinases (MAPK) and PI3K-Akt signaling pathways, ubiquitin-mediated proteolysis, and cell cycles.

Regulation of gut microbiota. Extensive research has shown that the pathogenesis of AS is associated with the constitution of gut microbiota and their host metabolic phenotype that plays an important role in regulating host cholesterol homeostasis [14]. By establishing an HFD-induced AS ApoE$^{-/-}$ mice model, Yaxin Z et al. [14] found that the empirical formula of the Chinese medicine, Dingxin Recipe IV, consisting of *Coptis chinensis*, *Salvia miltiorrhiza* Bunge, *Ziziphi Spinosae Semen*, and *Ganoderma*, attenuated AS. It regulated gut microbiota and lipid metabolism via the LXR-α/sterol regulatory element-binding protein 1 signaling pathway. Using an HFD-induced AS ApoE$^{-/-}$ mice model, Boran Z et al. [15] demonstrated the classic ancient prescription of Chinese medicine, *Alisma orientalis* beverage, consisting of *Alisma plantago*-aquatica subsp, *Pyrola calliantha Andres*, and *Atractylodes macrocephala* Koidz, reduced the risk of AS. It inhibited the expression of hepatic flavin monooxygenase 3 and trimethylamine N-oxide concentration, inflammatory cytokine release. With an HFD-induced AS ApoE$^{-/-}$ mice model, Fengjiao L et al. [16] showed that 2,3,5,4′-Tetrahydroxy-stilbene-2-O-β-D-glucoside, the main pharmacologically active ingredient of *Polygoni Multiflori Radix Praeparata*, treats hyperlipidemia, suppresses lipid accumulation and inflammatory response, and stabilizes the intestinal microbial balance.

Hypertension

Essential hypertension is a major risk factor of cardiovascular and cerebrovascular diseases. It has an exceedingly high disability rate and death rate caused by damage to the target organs, including the heart, brain, and kidneys. Hypertension results from the interactions among cardiovascular system lesions, genetic factors, and environmental factors; its pathogenesis involves inflammatory reactions, oxidative stress, and endothelial dysfunction, among others [1]. Therefore, comprehensive prevention and treatment of hypertension provide new insights into clinical practice and scientific research [17]. Studies on the clinical application and mechanism of TCM in preventing and treating hypertension have been performed for decades [18]. Several studies have investigated TCM mechanisms in treating hypertension (Supplementary Table 1). With an obesity-related hypertensive C57BL/6J mice model, Yuehua J et al. [19] showed that classic ancient prescription of the Chinese medicine, *Pinelliae* and *Atractylodis Macrocephalae* and *Gastrodiae* decoction, consisting of *Pinellia*, *Gastrodiae*, *Atractylodis Macrocephalae*, *Tangerine Peel*, *Poria Cocos*, *Glycyrrhiza glabra*, *Zingiber officinale*, and *Ziziphus jujuba* Mill., attenuated obesity-related hypertension by reducing endothelial dysfunction and regulating the metabolism of glycerophospholipids. Linhua D et al. established a spontaneous hypertensive Wistar-Kyoto rat model [20] to show that the empirical formula of the Chinese medicine, Tianma Gouteng decoction, consisting of *Poria cocos*, *Uncaria*, *Gardenia*, *Scutellaria baicalensis Georgi*, *Caulis polygoni multiflori*, *Gastrodia elata*, *Achyranthes bidentata*, abalone shell, *Loranthus parasiticus*, *Eucommia ulmoides* Oliv., and *Leonurus japonicas*, decreased blood pressure. It reversed cardiovascular remodeling by inhibiting apoptosis and upregulating the expression of osteoprotegerin, TNF-related apoptosis-inducing ligands, and AKT. By establishing the phenylephrine-induced contraction of mesenteric arteries model in Sprague-Dawley (SD) rat, culturing and treating VSMCs isolated from the thoracic aortas of SD rat, Weijing Y et al. [21] found that uncarialin A (21), an ethanol extract of *Uncaria rhynchophylla* (Miq.) Miq. ex Havil, decreased high blood pressure and suppressed L-type calcium channel subunit alpha-1C (Cav1.2) via an interaction between the hydrogen bond and amino acid residue Met1186, thereby mitigating Ca^{2+} inward current in VSMCs. Humans usually consume lupeol, the main subgroup of pentacyclic triterpenoids, in fruits, vegetables, and medicinal plants worldwide. By culturing and treating the oocytes of *Xenopus laevis*, Sanung E et al. [22] found that lupeol and α3β4 nicotinic acetylcholine receptors suppressed cardiac-sympathetic neurons and decreased blood pressure by inhibiting norepinephrine release. The Chinese patent drug, Qingda granule (QDG), consisting of *Gastrodia*, *Scutellaria baicalensis Georgi*, *Uncaria rhynchophylla* Miz. ex Havil., and *Nelumro nucifera Gaertn*, was approved by the CFDA (approval No. Z10950028) for the prevention and treatment of hypertension. Using an angiotensin II-mediated

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hypertension model in C57BL/6 mice, Na Y et al. [23] found that QDG reduced blood pressure and mitigated the proliferation of aorta VSMCs by inhibiting the expression of the MAPK and PI3K/AKT signaling pathways. By establishing a spontaneous hypertensive Wistar-Kyoto rat model, Fengxia L et al. [24] found that water-decocted solution from *Semen Brassicae* decreased blood pressure, attenuated oxidative stress and inflammatory response, and improved thoracic aortic remodeling.

Myocardial ischemia-reperfusion injury (MIRI) and MI

MIRI and MI refer to blood recovery from ischemic myocardium with or without blood re-supply [25]. Therefore, in addition to timely reperfusion, rescue and reduction of myocardial damage induced by ischemia plays a vital role in coronary artery disease. It involves a series of mechanisms that include the inhibition of oxidative stress, inflammatory response and cardiomyocyte apoptosis, regulation of autophagy, angiogenesis, and metabolomics. Many studies have examined TCM's mechanisms in treating MIRI and MI (Table 2).

Table 2 Mechanisms of TCM in the treatment of MIRI and MI

Drugs and prescription	Approval No. by CFDA	Mechanisms and biological effects	Refs
Oridonin	–	Inhibits oxidative stress and NLRP3 inflammasome signaling pathway and alleviates MIRI	[26]
Calenduloside E	–	Activates AMPK signaling pathways, promotes optic atrophy 1 related-related mitochondrial fusion, improves myocardial energy metabolism and alleviates MIRI	[27]
Astragaloside IV	–	Regulates miR-101a/TGF-β receptor 1/TLR2/MAPK signaling pathway, alleviates inflammatory response and alleviates MIRI	[28]
Panax notoginseng saponins	–	Increases expression of miR-30c-5p and inhibits oxidative stress-induced cardiomyocytes apoptosis	[29]
Chinese patent drug Tongmai Yangxin pill	Z12020589	Activates PI3K/Akt/eNOS signaling pathway, improves NO activity to eclasis coronary microvessels and alleviates apoptosis and MIRI	[30]
Chinese patent drug Tongxin Luo capsule	Z19980015	Activates cardiac microvascular ECs eNOS, increases levels of Linc-ROR and attenuates MIRI	[31]
Catechin	–	Regulates cyclic AMP response-element binding protein/lnc-RNA myocardial infarction-associated transcript/Akt/glycogen synthase kinase-3β signaling pathway and alleviates H/R-induced cardiomyocytes apoptosis	[32]
Tanshinone IIA	–	Regulates AMPK-mTOR signaling pathway, inhibites cardiomyocytes apoptosis, induces autophagy and improves heart function	[33]
Chinese patent drug Qidan Lixin pill	Z20043919	Inhibites mTOR/p70S6k signaling pathway, pro-inflammatory and pro-apoptotic effects, enhances autophagy and improves heart function	[34]
Astragaloside IV	–	Promotes expression of GATA-4, p62 and B cell lymphoma-2, inhibits expression of PARP, light chain 3-II, Beclin-1 and caspase-3 and alleviates apoptosis and autophagy; regulates JAK-signal transducer and activator of transcription 3 signaling pathway, promotes angiogenesis and improves heart function	[35] [37]

Table 2 Mechanisms of TCM in the treatment of MIRI and MI (*Continued*)

Drugs and prescription	Approval No. by CFDA	Mechanisms and biological effects	Refs
Ginsenoside Rg3	–	Activates AMPK, mediated autophagy and improves heart function	[36]
Chinese patent drug Shexiang Baoxin pill	Z31020068	Stimulates macrophages to secrete VEGF-A and uregulates PI3K/Akt signaling pathways and MAPK/Erk1/2 signaling pathways	[38]
Chinese patent drug Qili Qiangxin capsule	Z20040141	Promotes the phosphorylation of lactic dehydrogenase A, pyruvate dehydrogenase kinases 4 and pyruvate dehydrogenase, promotes expression of carnitine palmitoyl transferase-1 protein and fatty acid translocase protein and improves heart function	[39]
Chinese patent drug Suxiao Jiuxin pill	Z12020025	Improves metabolism disorders of galactose, amino acid and fatty acid	[40]
Classic ancient prescription of Chinese medicine Taohong Siwu decoction	–	Promotes fatty acid metabolism, inhibits glucose, glycerophospholipid and arachidonic acid metabolism and improves energy generation	[42]
Classic ancient prescription of Chinese medicine Yiqi Huoxue decoction	–	Regulates AMPK-dependent signaling pathway, promotes expression of p-AMPK, PGC-1α, and CPT-1α, inhibits expression of PGC-1α, CPT-1α and PPARα and improves lipid metabolism disorders and heart function	[43]
Salvianolate	–	Regulates expression of chymase, A-Raf, β-myosin heavy chain, collagen I and collagen V, reduces MI area and improves heart function	[44]

TCM, traditional Chinese medicine; MI, myocardial infarction; MIRI, myocardial ischemia-reperfusion injury; AMPK, adenosine monophosphate-activated protein kinase; TGF-β, transforming growth factor-β; TLR; toll-like receptor; MAPK, mitogen-activated protein kinases; H/R, hypoxia/reoxygenation; eNOS, endothelial nitric oxide synthase; NO, nitric oxide; ECs, endothelial cells; Linc-ROR, long intergenic non-protein coding RNA-regulator of reprogramming; AMPK, adenosine monophosphate-activated protein kinase; mTOR, mammalian target of rapamycin; JAK, Janus kinase; VEGF, vascular endothelial growth factor; PGC-1α, proliferator-activated receptor-gamma co-activator-1α; CPT-1α, carnitine palmitoyltransterase-1α; CFDA, China Food and Drug Administration; –, not mentioned.

Inhibition of oxidative stress. The reasons for myocardial injury and cardiac dysfunction caused by MI are mainly associated with MIRI. Mitochondria produce large amounts of ROS, including malondialdehyde and uncoupled superoxide dismutase (SOD), when myocardial arterial blood supply is disrupted and re-established [1]. Using the left anterior descending coronary artery (LADCA) ligation-induced MIRI mice model, Chuanghong L et al. [26] showed that oridonin, a water extract of *Rabdosia rubescens*, reduced myocardial damage by inhibiting oxidative stress and lowering the expression of the NLRP3 inflammasome signaling pathway. With an MIRI rat model and hypoxia/reoxygenation (H/R) injured cardiomyocytes model, Min W et al. [27] found that calenduloside E, an ethanol extract of *Aralia elata*, improved myocardial energy metabolism and reduced myocardial damage by promoting optic atrophy 1 related mitochondrial fusion and activating the AMPK signaling pathway.

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Inhibition of inflammatory response. MI induces a severe inflammatory response, while inflammation plays a vital role in the pathophysiology of MIRI [1]. During reperfusion, many ROS and proinflammatory mediators are released from the damaged mitochondria to the tissue, resulting in severe inflammatory injury. Using an H/R injured cardiomyocytes model, Yang W et al. [28] found that Astragaloside IV, the main active ingredient of *Astragalus membranaceus*, reduced the inflammatory response and protected cardiomyocytes from H/R injury by regulating the miR-101a/TGF-β receptor 1/toll-like receptor (TLR) 2/MAPK signaling pathway.

Alleviation of apoptosis. Apoptosis is an important form of cardiomyocyte death after MI. It is directly associated with prognoses and outcomes in patients with MI [1]. The mitigation of cardiomyocyte apoptosis can reduce MIRI and is clinically significant for treating MI [1]. By establishing the MIRI rat model and the tert-butyl hydroperoxide-treated H9c2 cell injury model, Linli W et al. [29] found that *Panax Notoginseng* saponins and its active ingredient, ginsenoside Re, inhibited oxidative stress-induced cardiomyocytes apoptosis by regulating the expression of miR-30c-5p and p53. Using the LADCA ligation-induced myocardial no-reflow model in SD rats, Rui C et al. [30] found that the Chinese patent drug, Tongmai Yangxin pill, approved by the CFDA (approval No. Z12020589), consisting of *Cinnamomum cassia Presl*, *Ophiopogon japonicus* (Linn. f.) KerGawl, *Rehmannia glutinosa*, *Chinemys reevesii*, prepared *Radix Polygoni Multiflori*, *Schisandra chinensis* Baill, *Spatholobus suberectus* Dunn, *Codonopsis pilosula* Nannf, donkey-hide glue, and *Ziziphus jujuba* Mill., alleviated MIRI by activating the PI3K/Akt/eNOS signaling pathway, mitigating apoptosis and further improving NO activity to eclasis coronary microvessels. In terms of mechanism, long intergenic non-protein coding RNA-regulator of reprogramming (Linc-ROR) increases the p70s6k1 expression when Linc-ROR was taken into cardiac microvascular ECs. Thereafter, Linc-ROR alleviates miR-145-5p expression, activating the eNOS signaling pathway. Using an MIRI SD rat model and culturing and treating human cardiomyocytes, cardiac fibroblasts, and cardiac microvascular ECs, Guihao C et al. [31] found that the Chinese patent drug, Tongxin Luo capsule that has been approved by the CFDA (approval No. Z19980015), increased the levels of Linc-ROR stem from cardiomyocyte-derived small extracellular vesicles and attenuated MIRI by activating eNOS expression. With an MIRI SD rat model and H/R-induced H9C2 cells model, Lin C et al. [32] showed that catechin, an extract of green tea, alleviated cardiomyocytes apoptosis by regulating the cyclic AMP response-element binding protein/lnc-RNA myocardial infarction-associated transcript/Akt/glycogen synthase kinase-3β signaling pathway.

Regulation of autophagy. Autophagy is a significant physiological activity that maintains cardiac homeostasis and mainly uses lysosomes to digest injured, aging, or excess cytoplasmic materials, such as organelles and long-lived proteins [33]. Targeting autophagy has become a novel and promising therapeutic strategy for CVDs. Using an LADCA ligation-induced heart failure (HF) SD rat model and H_2O_2-induced H9C2 cells injury model, Xuefeng Z et al. [33] found that tanshinone IIA, a fat-soluble component of *Salvia miltiorrhiza*, improved heart function by inhibiting cardiomyocyte apoptosis and inducing autophagy via the regulation of the AMPK-mammalian target of rapamycin (mTOR) signaling pathway. The Chinese patent drug, Qidan Lixin pill, consisting of *Astragalus membranaceus*, *Salvia miltiorrhiza*, *Lepidium* seed, and *Poria cocos*, was approved by the CFDA (approval No. Z20043919) for HF treatment. With an LADCA ligation-induced MI SD rat model, Binhao S et al. [34] found that Qidan Lixin pill slowed the progression of chronic HF following MI by promoting cardiomyocytes autophagy via the suppression of the mTOR/p70S6k signaling pathway and further decreasing the proinflammatory and pro-apoptotic effects. It is noteworthy that overwhelming autophagy was believed to be harmful to maintaining heart function. Therefore, the best autophagic level is vital for maintaining heart function because it helps cardiomyocytes to adapt to stressors and improve cardiomyocytes viability [34]. Jingjing Y et al. [35] showed that Astragaloside IV alleviated H/R injury-induced apoptosis and autophagy in H9c2 cells by promoting the overexpression of GATA-4, p62, and B cell lymphoma-2 and inhibiting the expression of PARP, light chain 3-II, Beclin-1, and caspase-3. Using isoproterenol (ISO)-induced MI Balb/c mice model, Guizhi S et al. [36] showed that ginsenoside Rg3, a water extract of *Panax ginseng*, protected heart function and cardiac tissue against MI injury by activating the AMPK-mediated autophagy signaling pathway.

Promotion of angiogenesis. Cardiac angiogenesis is a physiological program of self-protection; however, it also occurs after MI. When the myocardial tissue is necrotic because of the interruption of arterial blood supply, large numbers of macrophages accumulate in the infarcted myocardium. They secrete massive amounts of proteolytic ferment and growth-stimulating factor. Furthermore, vascular endothelial growth factor (VEGF) and signal transducer and activator of transcription 3 exert important effects on cardiac angiogenesis and are promising molecular targets of angiogenesis-mediated therapy for MI [37]. Using an LADCA ligation-induced acute myocardial infarction (AMI) SD rat model and culturing and treating primary HUVECs, Yanbo S et al. [37] found that Astragaloside IV improved angiogenesis and heart function by

regulating the Janus kinase signal transducer and activator of transcription 3 signaling pathway. The Chinese patent drug, Shexiang Baoxin pill (SBP), consisting of *Borneolum Syntheticum*, *Moschus*, *Cinnamomi Cortex*, *Bovis Calculus Artifactus*, *Ginseng Radix et Rhizoma*, *Styrax*, and *Bufonis Venenum*, was approved by the CFDA (approval No. Z31020068) for the treatment of coronary artery disease (CAD), MI, and angina. With an inflammatory angiogenesis C57BL/6 mouse model and hind limb ischemia C57BL/6 mouse model, culturing and treating the murine macrophage cell line (Raw 264.7) and HUVECs, Jiange Z et al. [38] found that SBP promoted the proliferation and migration of ECs and tubule formation by upregulating the PI3K/Akt signaling pathway and MAPK/Erk1/2 signaling pathway, stimulating macrophages to secrete a series of angiogenic factors (e.g., VEGF-A) to increase the pro-angiogenesis activity.

Influence of metabolomics. The pathogenesis, evolution, and prognosis of AMI are very complex and were involved in the disordered multiple metabolic pathways. Accumulated evidence suggests that metabolic modulation has considerable potential for treating CHD and HF [39]. Using an LADCA ligation-induced AMI SD rat model, Gaosong W et al. [40] found that the Chinese patent drug, Suxiao Jiuxin pill that has been approved by the CFDA (approval No. Z12020025) and consists of extractions from *Borneolum Syntheticum* and *Chuanxiong Rhizoma*, improved more than half of substance metabolism disorders caused by AMI (e.g., galactose, amino acid, and fatty acid). With an LADCA ligation-induced AMI SD rat model, Gaosong W et al. [41] showed that SBP reduced cardiac dysfunction by regulating amino acid metabolisms, lipid, energy, and gut microbiota. The Chinese patent drug, Qili Qiangxin capsule (QQC), consisting of *Citri reticulatae Pericarpium*, *Ginseng Radix et Rhizoma*, *Polygonati Odorati Rhizoma*, *Astragali Radix*, *Carthami Flos*, *Aconiti Lateralis Radix Preparata*, *Alismatis Rhizoma*, *Salvia Miltiorrhiza Radix et Rhizoma*, *Periplocae Cortex*, *Descuraunia Semen*, and *Cinnamomi Ramulus*, has been approved by the CFDA (approval No. Z20040141). Using an HF following LADCA-induced MI model in SD rat, Wenkun C et al. [39] showed that QQC increased metabolic flexibility, protected the surviving cardiomyocytes, and improved heart function. In terms of the mechanism, QQC promoted a shift from glucose oxidation to anaerobic glycolysis in the border area by promoting the phosphorylation of lactic dehydrogenase A, pyruvate dehydrogenase kinases 4, and pyruvate dehydrogenase. Further, QQC upregulated the expression of carnitine palmitoyl transferase-1 protein and fatty acid translocase protein, thereby normalizing fatty acid uptake and oxidation, similar to that in healthy heart tissue. In a randomized, controlled, double-blind clinical study for patients with CHD, Tianqi T et al. [42] showed that the classic ancient prescription of the Chinese medicine Taohong Siwu decoction, consisting of *Paeoniae Radix Alba*, *Angelicae Sinensis Radix*, *Rehmanniae Radix Praeparata*, *Chuanxiong Rhizoma*, and *Carthami Flos*, improved energy generation and heart function by promoting fatty acid metabolism and inhibiting glucose, glycerophospholipid, and arachidonic acid metabolism. Using an LADCA occlusion-induced MI SD rat model and hypoxia-induced H9c2 cells injury model, Lifang H et al. [43] showed that the classic ancient prescription of the Chinese medicine, Yiqi Huoxue decoction, consisting of *Astragalus membranaceus*, *Angelica sinensis*, *Panax ginseng*, *Ligusticum wallichii*, and *Panax notoginseng*, improved heart function and resolved lipid metabolism disorders by regulating the AMPK-dependent signaling pathway and improving the expression of p-AMPK, PGC-1α, and CPT-1α. With an LADCA ligation-induced AMI SD rat model, Cheng C et al. [44] found that Salvianolate, a water-soluble extract of *Salvia miltiorrhiza*, improved heart function and reduced the MI area by regulating the expression of chymase, A-Raf, β-myosin heavy chainMHC, collagen I and V related to cardiomyocytes remodeling.

Cardiomyopathy

Cardiomyopathy, a multifarious group of myocardial diseases, mainly refers to abnormal ventricular hypertrophy or dilatation and is a common cause of HF that increases the risk of sudden cardiac death [45]. Therefore, effective cardiomyopathy therapy is of historic significance in clinical medicine because cardiomyopathy threatens the lives of millions of people all across the world each year. Many studies have investigated the mechanism of TCM in the treatment of cardiomyopathy (Supplementary Table 2). By establishing a doxorubicin (DOX)-induced cardiomyopathy model in C57BL/6 mice and DOX-induced apoptosis model in H9c2 cells, Yueping L et al. [45] found that *Ginkgo biloba* L. leaves alleviated cardiomyopathy by promoting cardiomyocyte survival and inhibiting cardiomyocytes apoptosis and inflammatory response via the modulation of the PI3K-AKT and NF-κB signaling pathways. Using a diabetic cardiomyopathy model in GK rats fed with high-sugar and HFD, Shiying Z et al. [46] found that the empirical formula of the Chinese medicine, Huangqi Danshen compound, consisting of *Glycyrrhiza glabra*, *Santalum album* L., *Trichosanthis Radix*, *Aurantii Fructus Immaturus*, *Radix Salviae*, *Hirudo*, *Platycladi Semen*, *Rehmanniae Radix Praeparata*, *Hedysarum multijugum* Maxim., *Panax ginseng* C.A. Mey, *Folium Nelumbinis*, and *Poria cocos* (Schw.) Wolf alleviated cardiomyopathy by inhibiting the inflammatory response and myocardial apoptosis.

Cardiac hypertrophy refers to the enlargement in the

volume of cardiomyocytes and the ventricular muscle's thickening to cope with the increased workload [47]. Compensatory cardiac growth is initially an adaptive response to maintaining normal heart function. However, it will lead to changes in the metabolism and gene expression of cardiomyocytes, activation of myofibroblasts, and increase in collagen when the imbalance between the adaptive ability and compensatory capacity motivated by sustained pressure or volume load, eventually resulting in pathological myocardial hypertrophy [48] and even HF [47]. Using an Ang II-induced cardiac hypertrophy model in C57BL/6 mice and in primary cardiomyocytes of neonatal rats, Gehui N et al. [47] showed that *Citri reticulatae Pericarpium*, the peel of *Citrus reticulata Blanco*, attenuated myocardial fibrosis and hypertrophy and improved the heart function by upregulating the PPARγ. With an ISO-induced chronic HF mice model and by culturing the neonatal rat ventricular cardiomyocytes treated with ISO, Huiling C et al. [49] demonstrated that *Citri reticulatae Pericarpium* significantly improved heart function and pathological cardiac hypertrophy by alleviating myocardial fibrosis and cardiomyocytes apoptosis and promoting the PPARγ expression. Using an Ang II-induced, cardiac hypertrophy model in C57BL/6 mice and Ang II-induced apoptosis model in H9C2 cells, Ying C et al. [50] showed that QDG significantly resolved hypertension and cardiac hypertrophy by reducing ROS production and activating the PI3K/AKT signaling pathway.

Arrhythmia

AMI caused by acute obstruction of the epicardial coronary artery leads to fatal ventricular arrhythmia, a common condition in patients with CHD. Cumulative evidence has provided new insights into TCM mechanisms that reduce the incidence of ventricular arrhythmia, thus improving the prognosis of ventricular arrhythmia and treatment of arrhythmias (Supplementary Table 3). Using a myocardial ischemia-induced arrhythmia pig model prepared by balloon-expanding the left coronary artery's endothelium, Yusi Y et al. [51] found that the Chinese patent drug, Wenxin granule, the first TCM approved as an antiarrhythmic drug by the CFDA (approval No. Z10950026) that consists of *Nardostachys chinensis Batal*, *Codonopsis, notoginseng*, *Ambrum*, and *Rhizoma polygonati*, shortens the QT interval and decreases heart rate by activating the muscarinic acetylcholine receptor M2 and inhibiting the sodium channel protein type 5 subunit alpha and beta-2 adrenergic receptor. With a metabolic syndrome-induced ventricular arrhythmias Wistar rat model, Hongjie Y et al. [52] showed that the Chinese patent drug, Shensong Yangxin capsule that was approved by the CFDA (approval No. Z20103032) and consisted of *Coptis chinensis*, *Ginseng*, *Paeoniae Radix Rubra*, *Cornus officinalis*, *Ziziphi spinosaesemen*, *Salvia miltiorrhiza*, *Taxilli herba*, *Eupolyphaga seu steleophaga*, *Nardostachyos*, *Ophiopogonis*, *Schisandrae sphenantherae fructus*, and *Os draconis* inhibited electrical remodeling and reduced metabolic syndrome-induced ventricular arrhythmia by upregulating the expression of Cx43, ICa-L and Ito by regulating the TLR4/MyD88/calcium/calmodulin-dependent protein kinase II (CaMKII) signaling pathway. Based on a randomized, double-blind, placebo and positive drug-controlled, multicenter clinical study on patients with premature ventricular contraction, culturing and treating cardiomyocytes isolated from Wistar rats Yuling M et al. [53] showed that the Chinese patent drug, Xinsu Ning that has been approved by the CFDA (approval No. Z20050131) and consisted of *Coptidis Rhizoma*, *Pinelliae Rhizoma*, *Poria*, *Aurantii Fructus Immaturus*, *Dichroae Radix*, *Nelumbinis Plumula*, *Sophorae Flavescentis Radix*, *Artemisiae Annuae Herba*, *Ginseng Radix et Rhizoma*, *Ophiopogonis Radix*, and *Nardostachyos Radix et Rhizoma*, prolonged the human action potential of cardiac ventricular myocytes by blocking hERG potassium channels, hNaV1.5 sodium channel, and whole-cell I_k. Moreover, using an acetylcholine and CaCl2-induced atrial fibrillation SD rat model, Qian Z et al. [54] showed that *Arnebiae Radix* decreased the induction, duration, and susceptibility of atrial fibrillation by reducing atrial fibrosis and inhibiting atrial enlargement induced by acetylcholine and CaCl2. By culturing and treating the Xenopus oocytes, Hui C et al. [55] found that *Ginkgo biloba* extract, consisting of flavonoids (quercetin and rutin) and terpenoids (bilobalide and ginkgolides A, B, C), suppressed pacemaker channels as well as hyperpolarization-activated cyclic nucleotide-gated 2 and 4 channel currents in a concentration-dependent manner.

Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is an intractable CVD that exhibits the destruction and aberrant remodeling of the pulmonary artery wall, causing an increase in pulmonary artery pressure and pulmonary vascular resistance, the cause of cardiac dysfunction right HF, and even death [56]. Although many drugs are available for treating PAH, the prognosis of PAH remains unsatisfactory. However, there are many TCM mechanism studies for PAH treatment (Supplementary Table 4). Using a Su/Hox-induced PAH SD rat model, culturing and treating primary pulmonary arterial vascular smooth muscle cells isolated from healthy donors and patients with PAH, Wande Y et al. [57] showed that berberine alleviated pulmonary arterial vascular smooth muscle cells proliferation and PAH by regulating the Trx1 and β-catenin signaling pathways. With an early-stage

hypoxic PAH model in SD rats and culturing and treating of pulmonary artery fibroblasts of SD rats, Guang L et al. [58] showed that preventive salvianic acid A treatment significantly reduced the elevation of right ventricle systolic pressure and right ventricle hypertrophy index by decreasing the expression of TGF-β, while therapeutic salvianic acid A treatment did not decrease the expression; therefore, salvianic acid A might be suitable for clinical treatment of early-stage hypoxic PAH. Based on a bioinformatics and network topology strategy, Peiliang W et al. [59] found that the empirical formula of Chinese medicine, Qishen Yiqi formula, consisting of *Astragalus membranaceus*, *Salvia miltiorrhiza*, *Panax notoginseng*, and *Dalbergia odorifera*, alleviated PAH by regulating the PI3K-Akt, MAPK, and hypoxia-inducible factor-1 signaling pathways.

Heart failure

HF is a complicated series of clinical syndromes wherein ventricular filling or ejection function is dysfunctional because of deterioration in the heart function or structure [60]. HF has become one of the most severe public health problems worldwide. TCM has unique superiority owing to its multi-target effect on CVD treatment. Several studies have investigated the mechanisms of TCM in the treatment of HF (Table 3). Using an LADCA ligation-induced HF mouse model and oxygen-glucose depletion-induced H9C2 cells model, Mingyan S et al. [61] showed that ginsenoside Rb3, one of the major pharmacological active ingredients of the empirical formula of the Chinese medicine, Danqi pill composed of *Salvia miltiorrhiza* Bunge and *Panax notoginseng* (Burkill) F.H. Chen., attenuated HF by ameliorating ROS-induced energetic metabolism dysfunction, improving mitochondrial function, and facilitating energy metabolism via the regulation of the PPARs-RXRα signaling pathway. Using a DOXs-induced HF model in C57BL/6 mice, culturing, and treating the rat H9c2 cells, Shuai X et al. [62] demonstrated that the Chinese patent drug, Longsheng Zhi capsule that has been approved by the CFDA (approval No. Z20010059), consisting of *Radix Astragali*, *Radix Paeoniae Rubra*, *Radix Angelicae Sinensis*, *Radix aucklandiae*, *Chuanxiong Rhizoma*, *Persicae Semen*, *Carthami Flos*, *Rhizoma Acori Tatarinowii*, *Taxilluschinensis*, *Pheretima*, *Hirudo*, and extract of *Acanthopanacis Senticosi*, alleviated HF. It alleviated oxidative stress by promoting the expressions of anti-oxidative stress enzymes, including SOD1, SOD2, catalase, and glutathione peroxidase-1 (GSH-PX-1) and relieving inflammation/apoptosis by inhibiting caspase 3 expression. Using a DOX-induced HF SD rat model, Qian Z et al. [63] showed that the classic ancient prescription of Chinese medicine, Sini decoction, approved by the CFDA (approval No. Z23020943), consists of *Acontium carmichaeli*, *Zingiber officinale*, and *Glycyrrhiza uralensis*, improved heart function by regulating the phospholipase A2 (PLA2)-cyclooxygenase signaling pathway and the PLA2-cytochrome P450 signaling pathway. Using a transverse aorta constriction-induced HF model in C57BL/6J mice, culturing and treating neonatal rat cardiomyocytes and adult mice cardiomyocytes, HuiHua C et al. [64] found that stachydrine hydrochloride, the main pharmacological active ingredient of *Leonurus japonicus* Houtt, alleviated pressure overload-induced HF and calcium mishandling by inhibiting the transverse aortic constriction/phenylephrine-induced hyper-phosphorylation of CaMKII and sarcoplasmic reticulum Ca^{2+} leak and by improving Ca^{2+} transient amplitude. With a moderate sepsis-induced cardiac dysfunction model in BALB/c mice, Shasha H et al. [65] demonstrated that the empirical formula of Chinese medicine, Qiangxin 1 formula, consisting of *Schisandra chinensis* (Turcz.) Baill., *Polygonum orientale* L., *Salvia miltiorrhiza* Bge., *Astragalus membranaceus* (Fisch.), and *Poria cocos* (Schw.) Wolf., alleviated cardiac dysfunction by suppressing the activity of calcium and MAPK, promoting AKT activation and regulating the TLR4/NF-κB signaling pathways, thereby alleviating cytokine and inflammatory factor storm and stabilizing immune balance. Using an HF and thrombosis model of zebrafish, Miao Y et al. [66] found that dammarane-type triterpenoids extracted from *Rhus Chinensis* root improved the cardiac output and heart rate, suppressed inappropriate heart dilatation and excessive venous congestion, preventing thrombosis formation. In a systematic review and meta-analysis, Qingqing L et al. [67] found that the empirical formula of Chinese medicine, Xinyin tablet, consisting of *Ginseng*, *Astragalus*, *Ophiopogon japonicas*, *Schisandra*, *Motherwort*, *Lex pubescens*, and *Lepidii semen*, improved heart function, myocardial fibrosis, and ventricular remodeling by reducing autophagy and myocardial apoptosis by the regulation of the Akt/AMPK-mTOR signaling pathway and lowering of the serum levels of TNF-α, interleukin-6, endothelin-1, Ang II, and aldosterone. Using a DOX-induced chronic HF Wistar rat model, Fangzhou C et al. [68] showed that the ethanol extract of *Crataegus pinnatifida* Bunge improved heart function by reducing inflammatory response and oxidative stress via down-regulation of mRNA expression of IL-1β and TNF-α and up-regulation of the mRNA expression of GSH-PX-1 and catalase. Based on a randomized controlled trial on patients with HF, Shaomei W et al. [69] found that the Chinese patent drug, Shenmai injection, approved by the CFDA (approval No. Z13020887), consisting of *Ophiopogon japonicus* (Thunb.) Ker Gawl., and *Panax ginseng* C.A. Mey, improved heart function by promoting the myocardial energy metabolism.

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Table 3 Mechanisms of TCM in the treatment of HF

Drugs and prescription	Approval No. by CFDA	Mechanisms and biological effects	Refs
Ginsenoside Rb3	–	Regulates PPARs-RXRα signaling pathway, maintains mitochondrial function, attenuates HF	[61]
Chinese patent drug Longsheng Zhi capsule	Z20010059	Alleviates oxidative stress via inducing expression of SOD1, SOD2, catalase and GSH-PX-1, relieves inflammation/apoptosis via decreasing inflammatory cytokine levels and caspase 3 activity, attenuates HF	[62]
Classic ancient prescription of Chinese medicine Sini decoction	–	Regulates PLA2-cyclooxygenase and PLA2-cytochrome P450 signaling pathway, attenuates HF	[63]
Stachydrine hydrochloride	–	Blocks transverse aortic constriction/phenylephrine-induced hyper-phosphorylation of CaMKII and alleviates calcium mishandling and HF	[64]
Empirical formula of Chinese medicine Qiangxin 1 formula	–	Suppresses activity of calcium and MAPK, increases activation of AKT, regulates TLR4/NF-κB signaling pathways, alleviates cytokine and inflammatory factor storm, stabilizing immune balance and alleviates sepsis-induced cardiac dysfunction	[65]
Dammarane-type triterpenoids	–	Improves cardiac output and heart rate, suppresses heart inappropriate dilatation and venous excessive congestion, prevents thrombosis formation and improves heart function	[66]
Empirical formula of Chinese medicine Xinyin tablet	–	Lowers serum levels of TNF-α, interleukin-6, endothelin-1, Ang II and aldosterone, regulates Akt/AMPK-mTOR signaling pathway, down-regulates autophagy, inhibits myocardial fibrosis and ventricular remodeling and improves heart function	[67]
Ethanol extract of *Crataegus pinnatifida* Bunge	–	Inhibits expression of interleukin-1β and TNF-α, promotes expression of GSH-PX-1 and catalase, reduces inflammatory response and oxidative stress and attenuates HF	[68]
Chinese patent drug Shenmai injection	Z13020887	Ameliorates energy metabolism and improves heart function	[69]

TCM, traditional Chinese medicine; HF, heart failure; PPAR, peroxisome proliferator-activated receptors; SOD, superoxide dismutase; GSH-PX-1, glutathione peroxidase-1; PLA2, phospholipase A2; MAPK, mitogen-activated protein kinases; TLR; toll-like receptor; CaMKII, calcium/calmodulin-dependent protein kinase II; TNF-α, tumor necrosis factor-α; mTOR, mammalian target of rapamycin; AMPK, adenosine monophosphate-activated protein kinase; CFDA, China Food and Drug Administration; –, not mentioned.

Conclusion and perspective

In conclusion, cumulative evidence showed that TCM exerts a strong curative effect and potential CVD treatment potential. TCM exerts prophylactic and/or therapeutic effects in CVDs via a complex set of mechanisms that involve the inhibition of oxidative stress; reduction of inflammatory response-induced damage; promotion of angiogenesis and anti-apoptosis activity; and the regulation of autophagy, gut microbiota, and metabolomics. The multiple-target pharmacological activities of TCM have considerable potential for preventing and treating CVDs, such as AS, hypertension, MIRI, MI, cardiomyopathy, arrhythmia, cardiac remodeling, PAH, and HF. TCM exerts a wide range of preventive and therapeutic effects and has good development prospects and research value. TCM has been used in clinical practice for thousands of years in China, and its curative effect is well established. The most convincing evidence is that TCM exerts great potential and value for the prevention and treatment of corona virus disease 2019

in China and other European and American countries and regions that have attracted medical scientists and researchers worldwide. With continuous advances in the study of pharmacological activity and molecular mechanism of TCM and its bioactive compounds, we expect newer alternative drugs derived from TCM will be available in the future.

Although considerable information regarding the treatment of CVDs with TCM has been introduced in this review, TCM compounds and their bioactive extracts are complex and have numerous targets. Each ingredient potentially plays an independent role or acts synergistically to treat diseases eventually. Moreover, TCM may exhibit adverse effects and physical characteristics while playing a cardiac protective role. However, the specific mechanism and curative effect of TCM remain relatively unclear. Therefore, more research and technical development are required to improve bioavailability. Also, the molecular mechanism and potential targets of TCM compounds and its bioactive extracts in the treatment of CVDs require further examination in a large-scale, randomized, and controlled trial to evaluate the efficacy and safety of the cardiovascular activity of TCM. The results may expand the application of TCM and its preparations as treatments for populations across the world.

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