Cellular and Molecular Mechanism of Traditional Chinese Medicine on Ventricular Remodeling

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Ventricular remodeling is related to the renin-angiotensin-aldosterone system, immune system, and various cytokines involved in inflammation, apoptosis, and cell signal regulation. Accumulated studies have shown that traditional Chinese medicine can significantly inhibit the process of ventricular remodeling, which may be related to the mechanism mentioned above. Here, we conducted a system overview to critically review the cellular and molecular mechanism of traditional Chinese medicine on ventricular remodeling. We mainly searched PubMed for basic research about the anti-ventricular remodeling of traditional Chinese medicine in 5 recent years, and then objectively summarized these researches. We included more than 25 kinds of Chinese herbal medicines including Qi-Li-Qian-Xin, Qi-Shen-Yi-Qi Pill, Xin-Ji-Er-Kang Formula, and Yi-Qi-Wen-Yang Decoction, and found that they can inhibit ventricular remodeling effectively through multi-components and multi-action targets, which are promoting the clinical application of traditional Chinese medicine.

Keywords: ventricular remodeling, traditional Chinese medicine, mechanism, cardiovascular disease, review

INTRODUCTION

Ventricular remodeling, referring to a variety of injuries that change the original substances and cardiac morphology of the heart, is an adaptive response of the body and a pathophysiological process of lesion repair, overall ventricular compensation, and secondary pathophysiology (1). Ventricular remodeling occurs in response to cardiac disease or cardiac damage, and the common causes are myocardial infarction, hypertension, cardiomyopathy, and valvular disease (2, 3). The histological manifestations include the enlargement of the ventricular cavity, a progressive decrease of cardiac function, extracellular collagen deposition, inflammatory cell infiltration, apoptosis, and so on (4). It is also accompanied by neurological and humoral changes, volume overload, and other pathophysiological processes (3, 5). Its mechanism is related to the neuroendocrine system [including sympathetic nervous system (SNS) and renin-angiotensin-aldosterone system (RAAS)], immune system, and various cytokines involved in inflammation, apoptosis, and cell signal regulation (6).

Traditional Chinese medicine, mainly from the East, has shown its idiographic ascendancy in the prevention, therapeutic effect, rehabilitation, and health care of diverse diseases (7, 8). The evidence-based use of traditional Chinese medicine (TCM) keeps a foothold in China and other Asian countries, and with the popularity of TCM in the East, it is increasingly accepted and used by other countries globally (9, 10). Accumulated evidence indicates that TCM has a better effect on ventricular remodeling (VR) compared with western medicine with a single active ingredient, and
the relevant mechanism is being carried out. However, we still cannot fully understand the anti-VR mechanism of TCM. Here, we shed light on recent advances in therapeutic VR of TCM and try to list the main anti-VR mechanisms of TCM. We further summarized preclinical findings and described some current problems and challenges to provide a prospect in this field.

**MOLECULAR PATHWAYS INVOLVED IN CARDIAC REMODELING**

The pathogenesis of VR is associated with several molecular pathways and their relative importance depends on the underlying cause of VR. Inflammatory signals seem to be more important in VR, which are associated with the intense activation of cytokine cascades (11–13). Furthermore, oxidative stress, apoptosis, and autophagy, transforming growth factor β1 (TGF-β1), neuroendocrine system, and peroxisome proliferators-activated receptor γ (PPARγ) are involved in VR regardless of etiology (13, 14).

**Inflammatory Cytokines**

In recent years, a large number of studies have confirmed that the immune response triggered by a myocardial injury, myocardial ischemia, and other factors can produce a variety of cytokines (15), and most of them, especially the inflammatory cytokines, including tumor necrosis factor α (TNF-α), interleukin (IL)-6, IL-1β, and IL-10 are involved in the occurrence and development of VR (13, 16). The major inflammatory cytokines that promote VR are TNF-α, IL-1β, and IL-6. Tumor necrosis factor α and IL-1 may promote VR by its effects on cardiomyocytes, macrophages, and the extracellular matrix (ECM). In cardiomyocytes, TNF-α may trigger apoptosis by activating the inherent pathway of cell death (17, 18). In macrophages, TNF-α can stimulate the synthesis of other pro-inflammatory cytokines (17, 19). In white blood cells, IL-1 can activate white blood cells, and stimulate downstream inflammatory responses (17, 20, 21). In fibroblasts, TNF-α and IL-1 can disrupt the balance between matrix metalloproteinases (MMPs) and their inhibitors, leading to the degradation of the ECM (17). Moreover, TNF-α and IL-1 can induce the expression of endothelial adhesion molecules in the microvasculature, leading to the enhancement of adhesive interactions between circulating leukocytes and the endothelial cell lining. Because of this, the inflammatory cells may accumulate in the cardiac microcirculation, finally leading to tissue damage and cardiac dysfunction (17). Interleukin-6 plays different roles via the gp130/STAT3 pathways (17). Interleukin-6 can promote cardiac hypertrophy in cardiomyocytes (22). In fibroblasts, IL-6 promotes proliferation and stimulates ECM synthesis (23). Additionally, IL-6 can regulate the function of macrophages and lymphocytes (24). However, IL-10 can suppress the release of inflammatory mediators by monocyte macrophages, thus inhibiting the secretion of TNF-α, IL-1β, IL-1, IL-6, IL-8, granulocyte-colony stimulating factors, and granulocyte-macrophage-colony stimulating factors caused by lipopolysaccharide and interferon-γ (25–27). Furthermore, IL-10 enhances the anti-inflammatory factor release, such as IL-1 receptor antagonists and soluble TNF-α receptors (25–27).

Heart-Protecting Musk Pill, prepared using Moschus (Shexiang), Panax ginseng C.A.Mey. (Renshen), Bos taurus domesticus Gmelin (Niuhuang), Cinnamomum cassia (L.) J. Presl (Rougu), Liquidambar orientalis Mill. (Suhexiang), Bufo bufo gargarizans Cantor (Chansu), and Borneol (C_{10}H_{18}O, Bingpian), can inhibit inflammatory reactions and VR after acute myocardial infarction by reducing the levels of TNF-α and IL-6, leading to the increase of the maximum value of left ventricular systolic pressure and left ventricular end-systolic pressure and the reduction of the left ventricular end-diastolic pressure, consequently improving the left ventricular function in rats with acute myocardial infarction (28).

Xi-Ji-Er-Kang Formula, composed of Panax ginseng C.A.Mey. (Renshen), Polygonatum adnatum S.Yun Liang (Yuzhu), Panax pseudoginseng var. Notoginseng (Burkill) G. Hoo & C.L. Tseng (Sanqí), Allium macrostemon Bunge (Xiebai), Angelica sinensis (Oliv.) Diels (Danggui), Ophiopogon japonicus (Thunb.) Ker Gawl. (Maidong), Schisandra chinensis (Turcz.) Baill. (Wuweizi), Salvia miltiorrhiza Bunge (Danshen), Sophora flavescens Aiton (Kushen), Glycyrrhiza uralensis Fisch. (Gancao), Radix Astragali (Huangqí), Epimedium acuminatum Franch. (Yinyanghuo), Trichosanthes kirilowii Maxim. (Gualou), and Dryobalanops aromatica C.F. Gaertn. (Longnáo), can reduce the expression of TNF-α and IL-1β, and increase the expression of IL-10 to restore the balance between the pro-inflammatory and anti-inflammatory state in mice with Angiotensin II (Ang II)-induced human umbilical vein endothelial cells injury (29). Yi-Qi-Wen-Yang Decoction, composed of Radix Astragali (Huangqí), Sedum plantagineum L. (Shengjiang), was capable of inhibiting inflammatory responses through upregulating IL-10 and downregulating TNF-α (30).

The nuclear factor kappa B (NF-κB) transcriptional activation pathway is considered to be the main regulator of inflammation (31). Nuclear factor kappa B can bind to the inhibitor of kappa B (IκB) protein in the cytoplasm (32). Under the action of pro-inflammatory cytokines, IκB is phosphorylated and degraded, releasing NF-κB dimer, so that NF-κB can be transferred to the nucleus, which induces the transcription of many genes and leads to the expression of inflammatory proteins, such as TNF-α and IL-6 (33–35).

Qi-Li-Qiang-Xin, which consists of Panax ginseng C.A.Mey. (Renshen), Radix Astragali (Huangqí), Aconitum carmichaelii Debeaux (Fuzí), Salvia miltiorrhiza Bunge (Rougui), Alisma plantago-aquatica subsp. orientale (Sam.) Sam. (Zexie), Carthamus tinctorius L. (Honghua), Polygonatum adnatum S.Yun Liang (Yuzhu), Citrus reticulata Blanco (Chenpi), Ramulus Cinnamomi (Guízhí), and Semen Lepidii/Semen Descariae (Tinglizi), can reduce the inflammatory response in a rat model of myocardial infarction through inhibiting the activity of NF-κB, which is mainly by reducing the expression of...
NF-κB p65 in the nucleus and the phosphorylation of IkB (32). Moreover, Qi-Li-Qiang-Xin improved cardiac function, reduced left ventricular dimension, inhibited interstitial inflammation and fibrosis, increased neovascularization, and attenuated cardiomyocyte apoptosis through the upregulated hypoxia-inducible factor-1α (HIF-1α), vascular endothelial growth factor (VEGF), and enhanced phosphorylation of Akt (36). Qi-Shen-Yi-Qi Pill, which consists of Radix Astragali (Huangqi), Salvia miltiorrhiza Bunge (Danshen), Panax pseudoginseng var. Notoginseng (Burkill) G. Hoo & C.L. Tseng (Sanqi), and Dalbergia odorifera T. Chen (Jiangxiang), improved cardiac remodeling accompanied with a restoration of the Ang II-NADPH oxidase-reactive oxygen species (ROS)-MMPs pathways and reduction of the TNF-α/NFκB and IL-6/STAT3 pathways (37). Qing-Da Granule, composed of Gastrodia elata Blume (Tianma), Scutellaria baicalensis Georgi (Huangqin), Uncaria rhynchophylla (Miq.) Miq. ex Havil. (Gouteng), and Nelumbo nucifera Gaerth. (Lianzixin), can reduce the infiltration of macrophages and the activation of proinflammatory cytokines (TNF-α, IL-6) by inhibiting the NF-κB pathway in spontaneously hypertensive rats (38).

**Oxidative Stress**

Oxidative stress is due to the loss of balance of redox between the level of ROS and endogenous antioxidant capacity, which causes the relative deficiency of antioxidant capacity and the relative increase of intracellular ROS (39–41). The increase of some toxic ROS leads to the loss of cell function, gene mutation, and even death (14, 42). Studies have shown that ROS is related to myocardial infarction and myocardial hypertrophy (43, 44). The stimulation of VR by oxidative stress involves the activation of several downstream signal pathways. First, ROS can activate a variety of hypertrophic signal kinases and transcription factors, including mitogen-activated protein kinase (MAPK), c-Jun N-terminal kinase (JNK), p38, NF-κB, and Akt kinases, to promote cardiac hypertrophy and cardiomyocyte apoptosis (43, 45, 46). Second, ROS can activate poly [ADP-ribose] polymerase 1 (PARP-1) by causing DNA strand breaks. Poly [ADP-ribose] polymerase 1 can regulate the expression of many inflammatory mediators and promote the progress of cardiac remodeling (43). Third, ROS can cause calcium ion (Ca²⁺) overload, increasing the mitochondrial permeability, and leading to the loss of mitochondrial inner membrane transmembrane potential, and then results in cell death (43, 46). Fourth, ROS can stimulate the proliferation of cardiac fibroblasts, activate MMPs, and lead to ECM remodeling (46, 47).

Xanthine oxidase is the main source of ROS in the cardiovascular system, and the inhibition of its enzyme activity can greatly reduce the production of ROS (48, 49). Qi-Li-Qiang-Xin can significantly reduce the activity of serum xanthine oxidase in rats after myocardial infarction and enhance the ability of myocardial tissue to scavenge oxygen (O₂⁻) and hydroxyl radicals (50). Under the condition of chronic intermittent hypoxia in mice, Sheng-Mai-San can increase the activities of antioxidant enzymes (superoxide dismutase and catalase) and reduce the contents of malondialdehyde and 4-HNE (51). In addition, Sheng-Mai-San can also reduce the level of serum myeloperoxidase (52).

As the main vascular endothelial relaxing factor, nitric oxide (NO) has the effect of relaxing vascular smooth muscles, scavenging free radicals, and inhibiting lipid peroxidation. However, TNF-α can decrease NO content, because TNF-α can not only activate the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and make the superoxide produced by it react with NO, but also can inhibit the initiator of endothelial NO synthases (eNOS) and disturb the stability of the eNOS gene, leading to the decrease of the activity level of eNOS and NO (53, 54). However, Xin-Ji-Er-Kang Formula could significantly decrease the level of TNF-α, inhibit the activation of NADPH oxidase, reduce the uncoupling of eNOS and the production of ROS, and increase the activity of eNOS and NO content, thus improving the function of vascular endothelium (29, 55). The Xin-Ji-Er-Kang Formula has blunted the decrease of superoxide dismutase, NO, and the increase in malondialdehyde and Ang II serum contents, myocardial cross-section area, collagen volume fraction, and perivascular circumferential collagen area compared with the hypertensive model group. It also reduced the serum content of hydroxyproline while increasing the tetrahydrobiopterin levels (56). Moreover, Xin-Ji-Er-Kang Formula could reduce the production of ROS and improve mitochondrial function by down-regulating the expression of NADPH oxidase subunits, such as NOX2, p67 phox, and NOX4 (60). However, due to the lack of experimental data, it is not clear whether TCM can remove all types of ROS.

**Apoptosis Factors and Autophagy**

Cardiomyocyte apoptosis is closely related to the occurrence and development of autophagy and VR (61). Caspase, Bcl-2, and Fas proteins are the major regulators of apoptosis. Many factors, such as AngII, inflammatory factors, and ROS, can promote the expression of apoptosis signals, and then promote apoptosis. Qi-Shen-Yi-Qi Pills could inhibit the expression of Fas ligand and p53 by activating the expression of murine double minute 2 and play an anti-apoptosis role in cardiomyocytes (62). Qi-Shen-Yi-Qi Pills could reduce inflammatory reaction by down-regulating the expression of inflammatory cytokines (TNF-α and IL-6) (62). Cyclooxygenase 2, which is highly linked with inflammatory cytokines, could be inhibited by Qi-Shen-Yi-Qi Pills to limit the conversion of arachidonic acid to prostaglandin E2 (PGE2), and we know that PGE2 and its receptors could induce apoptosis by increasing the transcriptional activity of the p53 gene and the expression of Fas ligand (63–65). Qi-Shen-Yi-Qi Pills could remarkably reduce the production of PGE2 and its receptors (62). The proportion of Bax/Bcl-2 protein is the key factor to determine the inhibitory effect on apoptosis (66). The activation of the PI3K/Akt signal has been proved to prevent cardiomyocyte apoptosis and protect the myocardium (36). Through upregulating the expression of...
neuregulin-1, Qi-Li-Qiang-Xin can activate the PI3K/Akt signal pathway, promote Akt phosphorylation, stimulate the expression of vascular growth factor, and activate the anti-apoptosis protein, leading to the inhibition of the proportion of Bax/Bcl-2 and the expression of Caspase-3 (36). Yi-Qi-Wen-Yang Decoction suppressed the upregulated Bax, cleaved caspase-3 and PARP, and increased the downregulated Bcl-2 through activating the IL-10/Stat3 signaling and inactivating the NF-Kb P65 signaling to inhibit cardiomyocyte apoptosis (30). Qi-Li-Qiang-Xin can also inhibit cardiomyocyte apoptosis in non-infarcted zone rats by reducing the production of ROS (67). In addition, Qi-Li-Qiang-Xin can also reduce the expression of p53 (36, 67).

By upregulating the expression of osteoprotegerin and tumor necrosis factor-related apoptosis-inducing ligand, Tian-Ma-Gou-Teng Decoction, made up of Uncaria rhynchophylla (Miq.) Miq. ex Havil. (Gouteng), Gastrodia elata Blume (Tianma), Scutellaria baicalensis Georgi (Huangqin), Eucommia ulmoides Oliv. (Duzhong), Acanthopanax senticosus Blume (Baihu), Cichlant hus decipiens (D.Don) K.C.Koch (Lurong), and Cichlant hus L. (Yumixu), can reduce the endoplasmic reticulum stress and downregulate the activating transcription factor 6-C/E BP homologous protein signaling pathway to inhibit cardiac fibrosis (13). In addition to TGF-β, the signaling pathways associated with TGF-β are also involved in myocardial fibrosis. The TGF-β/Smads signaling pathway is the classical pathway of myocardial fibrosis. The abnormal activation of the TGF-β/Smads signal pathway can promote the proliferation of fibroblasts and the production of collagen and ECM, leading to the process of the aggravation of the myocardial fibrosis (76, 77). Some research has shown that TGF-β and its signaling pathways can be activated by Ang II, ROS, and inflammatory factors (13, 17, 78, 79).

Lu-Hong Formula can inhibit the expression of TGF-β1, and then inhibit the expression of collagen type I and III, and fibronectin genes and proteins, leading to the inhibition of the proliferation and deposition of collagen in the left ventricle in pressure-overloaded rats (69). Guanxin V could inhibit the TGF-β1 pathway to exert an anti-VR effect (80). Bu-Yang-Huan-Wu Decoction, prepared using Radix Astragali (Huangqi), Angelica sinensis (Oliv.) Diels (Danggui), Paeonia lactiflora Pall. (Chaochao), Rehmannia glutinosa (L.) Man (Dilong), can inhibit the activation of Smad1 and Smad4, which then inhibit the transcription of pro-fibrotic molecules, including the transcription of α-smooth muscle actin, collagen, and tissue inhibitors of MMPs, and finally, reduce the activation of myofibroblasts and matrix deposition, leading to the alleviation of pressure overload-induced cardiac remodeling (81). Dan-Qi soft capsules, Tong-Guan capsules, and Qi-Li-Qiang-Xin can inhibit the differentiation and formation of myofibroblasts by inhibiting the TGF-β1/Smad3 pathway, having an effect of inhibiting VR (32, 82, 83). Moreover, Qi-Li-Qiang-Xin may also promote the TGF-β3/Smad7 signal pathway to play an anti-VR effect (84). Ling-Gui-Zhu-Gan Decoction, composed of Poria cocos (Schw.) Wolf (Fuling), Ramulus Cinnamomi (Guizhi), Atractylis macrocephala (Koidz.) Hand.-Mazz. (Baizhu), and Glycyrrhiza uralensis Fisch. (Gancao), can significantly improve the pathological changes of the myocardial tissues, increase the left ventricular systolic pressure, left ventricular pressure maximum contraction rate, and left ventricular pressure maximum relaxation rate (85). Besides this, it can also decrease the left ventricular end-diastolic pressure and reduce the whole heart weight index and left ventricular weight.
index in rats with acute myocardial infarction (85). All of these are achieved by regulating the TGF-β/Smads pathway (85). Xin-Fu-Li Granule is a compound TCM that consists of extracts from *Radix Astragali* (Huangqi), *Panax ginseng* C.A.Mey. (Renshen), *Salvia miltiorrhiza* Bunge (Danshen), *Ligusticum chuanxiong* (Chuanxiong), *Alisma plantago-aquatica* subsp. *orientale* (Sam.) Sam. (Zexie), *Angelica sinensis* (Oliv.) Diels (Dang gui), *Semen Lepidii/Semen Descriziae* (Tinglizi), *Chaoenomeles speciosa* (Sweet) Nakai (Mugua), *Arecs catechu* L. (Binglang), and *Ophiopogon japonicus* (Thunb.) Ker Gawl. (Maidong), and can improve ventricular reconstruction and inhibit myocardial fibrosis in rats with acute myocardial infarction by regulating the TGF-β/Smads pathway (86).

What we should pay attention to is that TGF-β can also activate several other non-classical pathways, such as ras/methyl ethyl ketone (MEK)/extracellular signal-regulated kinases (ERK), p38, and JNK (78). The Si-Miao-Yong-An Decoction can significantly improve cardiac function and inhibit myocardial fibrosis in pressure-overloaded rats by inhibiting TGF-β1/Smad and TGF-β1/Tak1/p38 signal pathway (87). The connective tissue growth factor (CTGF) is the downstream effect factor of TGF-β1 and only mediates the negative effect of TGF-β1 (88, 89). Transforming growth factor β1 can induce the expression of CTGF, and CTGF can also enhance the TGF-β1 signal pathway (90, 91). Finally, a vicious circle is formed, resulting in the accumulation of ECM, and myocardial fibrosis occurs. Qi-Shen-Yi-Qi pills can inhibit the expression of CTGF protein and mRNA by regulating the TGF-β1/CTGF pathway and reducing the myocardial collagen deposition, leading to the improvement of VR on experimental autoimmune myocarditis rats (92).

Matrix metalloproteinases, acting as an activator in TGF-β (13), also play an important role in myocardial fibrosis. The abnormal increase and excessive deposition of a myocardial ECM plays a very important role in the occurrence and development of myocardial hypertrophy and myocardial fibrosis. Matrix metalloproteinases are a family of zinc-dependent proteases, which mainly participate in the metabolism of ECM and can reduce and release almost all ECM components except polysaccharides (93). After tissue damage, the regulation of MMPs activity is out of control, the ratio of MMPs to tissue inhibitor of metalloproteinase is out of balance, and myocardial ECM accumulates excessively, which leads to myocardial fibrosis and VR (94–96). Si-Miao-Yong-An Decoction can increase the expression of MMP9 and decrease the expression of TIMP2 to promote the degradation of collagen and reduce the synthesis of collagen, leading to the inhibition of myocardial fibrosis (87). Dan-Shen Injection can prevent left VR by inhibiting the activation of MMP2 and MMP9 to improve ejection fraction and left ventricular stroke volume in rats with myocardial infarction (97).

**Nuroendocrine System**

**SNS**

Sympathetic activity is one of the main exogenous factors in the regulation of VR. After any type of myocardial injury, adrenaline can be activated instantly, which is the main means of increasing the heart rate and contractility and playing the role of stabilizing cardiac function (98). However, long-term activation will lead to VR. The increase of catecholamine secretion can cause cardiomyocyte necrosis and apoptosis due to hypoxia, increased sarcomermal permeability, calcium overload, the elevation of cyclic AMP (cAMP), and formation of oxidative cardiomyocyte metabolites (98–101). Norepinephrine can stimulate fetal gene reprogramming, promote fibroblasts and protein synthesis, and aggravate VR (100, 102). Sheng-Mai-San, consisted of *Panax ginseng* C.A.Mey. (Renshen), *Ophiopogon japonicus* (Thunb.) Ker Gawl. (Maidong), and *Schisandra chinensis* (Tierz.) Baill. (Wuweizi), can reduce the contents of norepinephrine and 5-hydroxytryptamine in rats after myocardial infarction by regulating the activity of the SNS, and then the myocardial contraction and heart rate were slowed down (103). Additionally, Sheng-Mai-San may inhibit the activation of the hypothalamic-pituitary-adrenal axis by reducing the levels of IL-6 and TNF-α in patients with heart failure, and then control the activity of SNS and the secretion of neuropeptides. Qing-Da Granule, composed of *Gastrodia elata Blume* (Tianma), *Scutellaria baicalensis* Georgii (Huangqin), *Uncaria rhynchophylla* (Miq.) Miq. ex Havil. (Gouteng), and *Nelumbo nucifera* Gaertn. (Lianzixin), can dilate blood vessels, reduce vascular tension, and inhibit vascular remodeling by suppressing the activation of the L-type Ca$^{2+}$-channel and inhibiting the influx of Ca$^{2+}$ (104). Related research has shown that Ca$^{2+}$ plays an important role in the SNS (105). The generation of sympathetic activity depends on the action potential produced by the influx of Ca$^{2+}$, so the inhibition of Ca$^{2+}$ influx can inhibit the sympathetic nerve activity (101, 106).

**RAAS**

The RAAS plays a very important role in the occurrence and development of VR (107, 108). The chronic activation of RAAS leads to a long-term increase in the levels of Ang II and aldosterone, both of which are involved in pathological processes including cardiomyocyte hypertrophy, interstitial fibrosis, and cardiomyocyte apoptosis (109, 110). Ang II, the main effector of RAAS, can not only activate the SNS and increase the heart rate and contractility but also cause systemic vasoconstriction which leads to an increase in the total peripheral resistance and aggravate cardiac load (110, 111). Ang II can stimulate different cytokines, such as endothelin-1 (ET-1), aldosterone, brain natriuretic peptide (BNP), TNF-α, and IL, and these cytokines are involved in the process of VR via different ways (112–116). Ang II can induce ET-1 by ROS and ERK (78, 117), and ET-1 can not only contract blood vessels but also induce fibroblasts to produce ECM (118). Ang II can induce aldosterone production in the adrenal cortex, and aldosterone can induce cardiomyocyte apoptosis and cardiomyocyte hypertrophy by activating oxidative stress and regulating ion channels (119, 120). Related research has shown that Ang II can increase the secretion of TNF-α and IL-6 (121), and the mechanism of their participation in VR was described in the following paragraphs. Ang II can stimulate the release of natriuretic peptides (122, 123). The long-term overstimulation of RAAS in chronic heart failure promotes increased sodium and water retention, which leads to increased pressure in the left ventricle and atrium.
and finally stimulates the synthesis and secretion of BNP (123). Moreover, Ang II can upregulate the TGF-β1 expression by binding to Ang II type 1 receptors (AT1R) (78, 124), and then the TGF-β1/Smad5 signal pathway is activated which is related to myocardial fibrosis (78).

Guaxin V consists of Codonopsis affinis Hook.f. & Thomson (Dangshen), Ophiopogon japonicus (Thunb.) Ker Gawl. (Maidong), Schisandra chinensis (Turcz.) Baill. (Wuweizi), Rehmanna chinigii H.L. Li (Dihuang), Salvia miltiorrhiza Bunge (Danshen), and Paeonia lactiflora Pall. (Chishao) (80, 125) and has a significant effect on VR (126). Mechanistically, in an animal model, Guaxin V can inactivate RAAS in VR after acute myocardial infarction through the non-angiotensin converting enzyme pathway, which significantly reduces the level of Ang II, reduces the infarct size after acute myocardial infarction, protect cardiac function, reduce myocardial fibrosis, and thus, reduce VR (127). Poge Heart-Saving Decoction, prepared with Aconitum carmichaelii Debeaux (Fuzi), Zingiber officinale Roscoe (Ganjiang), Glycyrrhiza uralensis Fisch. (Gancao), Cornus officinalis Siebold & Zucc. (Shanzhuyu), Os Draconis (Longgu), Concha Ostreae (Muli), Magnetitum (Cishi), Panax ginseng (Wuweizi), and Moschus (Shexiang), can reduce the left ventricular end-diastolic dimension and left ventricular end-systolic dimension by inhibiting the level of RAAS, especially aldosterone and Ang II levels, and finally, decrease the post-load of the heart and increase the ejection fraction, reverse VR, and improve cardiac function (128). Jiajian Yu-Nv-Jian, containing Gypsum (CaSO4·2H2O, Shigao), Anemarrhena asphodeloides Bunge (Zhimu), Scrophularia microdonta Franch. (Xuanshen), Rehmanna chinigii H.L. Li (Dihuang), and Ophiopogon japonicus (Thunb.) Ker Gawl. (Maidong), can significantly reduce the experimental cardiac remodeling by improving hemodynamics and inhibiting the activation of RAAS. It can also reduce the production of ET-1 and the contents of Ang II, aldosterone, and hydroxyproline, and down-regulate the expression of AT1R, TNF-α, and TGF-β1 (113). Morphologically, Jiajian Yu-Nv-Jian decreased the cross-sectional area of cardiomyocytes, collagen volume fraction, collagen types I and III, and the perivascular collagen area (113). RAAS mediates the development of VR mainly by inducing the generation of Ang II, and TCM has confirmed that it can inhibit the level of Ang II not only by classical RAAS but also by the non-angiotensin converting enzyme pathway. However, we do not figure out the mechanism of Ang II produced by the non-angiotensin converting enzyme pathway.

**PPARγ**

PPARγ is a nuclear receptor that can change the transcription of many target genes (129, 130). It is mainly related to energy metabolism. Peroxisome proliferator-activated receptor γ can stimulate the transcription of genes related to lipid metabolism and promotes adipocyte differentiation. Moreover, PPARγ can also suppress the production of proinflammatory cytokines and then inhibit proliferation and migration (130). The PPARγ coactivator 1α (PGC-1α) is the main regulator of lipid catabolism, oxidative metabolism, mitochondrial metabolism, and biogenesis-related genes, reflecting the dysfunction of the mitochondria, which plays an important role in the control of myocardial metabolism (131–133). High levels of PGC-1α may be related to higher levels of oxidative metabolism, higher oxygen consumption, and lower general oxidative stress, while lower levels of PGC-1α may be related to increased dependence on glycolysis, lower oxygen consumption, and higher ROS levels (131, 132). By upregulating the expression of PPARα and PPARγ, Shen-Qi-Fu-Zheng Injection extracted from Codonopsis affinis Hook.f. & Thomson (Dangshen) and Radix Astragali (Huangqí), can interfere with the metabolic process of the injury, inhibit ischemic cardiac structural and functional disorders such as myocardial hypertrophy and VR, effectively improve the damaged cardiac function, and achieve the protective effect of myocardial infarction (134). Qi-Li-Qiang-Xin can improve cardiac energy metabolism by up-regulating PGC-1α and PPARγ, which alleviate myocardial hypertrophy and cardiac remodeling, and significantly improve cardiac function, including ejection fraction and fraction shortening (135–138). However, due to the lack of sufficient experimental data, we do not yet understand the mechanism of TCM suppressing PPARγ and PGC-1α.

**DISCUSSION**

Ventricular remodeling is a process of a series of morphological and structural changes in cardiomyocytes, collagen grids, and vascular beds, which is the basic mechanism of heart failure, so it is of great significance to study the pathogenesis of VR for the prevention and treatment of heart failure.

The inflammatory response is one of the key factors in VR. To promote the repair of injured areas, the damaged myocardium will release its intracellular contents and cause inflammation by activating the innate immune mechanism. Neutrophils were first recruited, followed by pro-inflammatory monocytes/macrophages and lymphocytes (11, 12). These cells remove dead cells and matrix fragments from the damaged areas through different pathways and then activate the repair pathways needed for scar formation. However, the aggravation, prolongation, or expansion of the inflammatory response can lead to more severe remodeling and dysfunction. Excessive early inflammation may increase matrix degradation, leading to heart rupture (11). Prolonged inflammation may damage collagen deposition, resulting in the formation of scars with reduced tensile strength, and finally, the increase of the chamber dilatation (11). The enhanced expression of pro-inflammatory mediators can stimulate the production of ROS, activating the pro-apoptosis pathway, and inducing further loss of cardiomyocytes (43). Finally, defective control of inflammatory response may lead to inflammatory infiltration extending into the non-infarcted myocardium, enhancing fibrosis and worsening the diastolic function (11, 17). In addition, due to the overload of antioxidant defense in the damaged heart, ROS production, and induced inflammatory signals, such as IL-1 β, directly inhibit myocardial function (46).

To maintain the basic function of the damaged heart, SNS and RAAS can be activated. However, the excessive
TABLE 1 | Details of constituents and mechanism of traditional Chinese medicine (TCM) for ventricular remodeling (VR).

| Constituents | Mechanism | Cell type | References |
|--------------|-----------|-----------|------------|
| Codonopsis affinis Hook.f. & Thomson (Danshen), Ophiopogon japonicus (Thunb.) Ker Gawl. (Maidong), Schisandra chinensis (Turcz.) Baill. (Wuweixi), Rehmannia chingii H.L. Li (Dihuang), Salvia miltiorrhiza Bunge (Danshen), and Paeonia lactiflora Pall. (Chishao) | Inactivate RAAS through non-angiotensin converting enzyme pathway, which significantly reduce the level of Ang II, reduce the infarct size, protect cardiac function, reduce myocardial fibrosis, and inhibit TGF-β1 pathway | Myocardial cell and fibroblast | (127) |
| Aconitum carmichaeli Debeaux (Fuzi), Zingiber officinale Roscoe (Ganjiang), Glycerrhiza uralensis Fisch. (Ganjiang), Pogge Heart-Saving Decoction, Scrophularia microdonta subsp. orientale (Sam.) Sam. (Zexie), Carthamus tinctorius L. (Honghua), Panax ginseng C.A.Mey. (Renshen), and Moschus (Shexiang) | Reduce left ventricular end-diastolic dimension and left ventricular end-systolic dimension by inhibiting the level of RAAS, and finally decrease the postload of the heart, increase ejection fraction, reverse VR, and improve cardiac function | Myocardial cell and fibroblast | (128) |
| Gypsum (CaSO₄·2H₂O), Anemarrhena asphodeloides Bunge (Zhimu), Scrophularia microdonta Franch. (Xuanshen), Rehmannia chingii H.L. Li (Dihuang), and Ophiopogon japonicus (Thunb.) Ker Gawl. (Maidong) | Improve hemodynamics, inhibit the activation of RAAS, down-regulate the expression of AT1R, TNF-α, and TGF-β1, and decrease cross-sectional area of cardiomyocyte, collagen volume fraction, collagen types I and III, and perivascular collagen area | Myocardial cell and fibroblast | (113) |
| Panax ginseng C.A.Mey. (Renshen), Radix Astragali (Huangqi), Ophiopogon carmichaeli Debeaux (Fuzi), Salvia miltiorrhiza Bunge (Danshen), Alisma plantago-aquatica subsp. orientale (Sam.) Sam. (Zexie), Carthamus tinctorius L. (Honghua), Polygonatum adnatum S.Yun Liang (Yuzhu), Citrus reticulata Blanco (Chenpi), Ramulus Cinnamomi (Guizhic), and Semen Lepidii/Semen Descurainiae (Tinglzi) | Reduce the inflammatory response though NF-κB pathway; improve cardiac function, reduce left ventricular dimension, inhibit interstitial inflammation and fibrosis, increase neovascularization, and attenuate apoptosis though upregulated HIF-1α, VEGF and enhanced p-Akt; activate P38K/Akt signal pathway, stimulate the expression of vascular growth factor, and activate anti-apoptosis protein and inhibit the proportion of Bax/Bcl-2 and the expression of Caspase3 by up-regulating the expression of neuregulin-1; inhibit cardiomyocyte apoptosis by reducing the production of ROS and the expression of p53; reduce the activity of xanthine oxidase and enhance the ability to scavenge O²⁻ and hydroxyl radical; improve cardiac energy metabolism by up-regulating PGC-1α and PPARγ, and significantly improve cardiac function, including ejection fraction and fraction shortening; inhibit TGF-β1/Smad2 pathway; and activate TGF-β3/Smad7 signal pathway | Myocardial cell, endothelial cell, fibroblast, and inflammatory cell | (32, 36, 50, 67, 84, 135-138) |
| Radix Astragali (Huangqi), Salvia miltiorrhiza Bunge (Danshen), Panax pseudoginseng var. Notoginseng (Burkill) G. Hoo & C.L. Tseng (Sanqi), and Dalbergia odorifera T. Chen (Jiangxiang) | Recover Ang II-NADPH oxidase-ROS-MMPs pathways and reduction of TNF-α/NOx/B and IL-6/STAT3 pathways; inhibit the expression of CTGF, and reduce myocardial collagen deposition via TGF-β1/CTGF pathway; inhibit the expression of FasL and p53 by activating the expression of MDM2 to play an anti-apoptosis role; reduce inflammatory reaction by down-regulating the expression of TNF-α, IL-6, inhibit Cyclooxygenase 2 to limit the conversion of arachidonic acid to PGE2; reduce the expression of Prostaglandin E2 and its receptors | Myocardial cell and inflammatory cell | (37, 62, 92) |
| Gastrodia elata Blume (Tianma), Scutellaria baiacalensis Georgii (Huangqin), Uncaria rhynchophylla (Miq.) Miq, ex Havi, (Gouteng), and Nelumbo nucifera Gaertn. (Lianzixin) | Suppress the activity of the SNS by inhibiting the influx of Ca²⁺; reduce the infiltration of macrophages and inactivating TNF-α, IL-6 by inhibiting NF-κB pathway | Myocardial cell and macrophage | (38) |
### TABLE 1 | Continued

| TCM                        | Constituents                                                                 | Mechanism                                                                 | Cell type                                      | References |
|---------------------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------|------------------------------------------------|------------|
| Heart-Protecting Musk Pill | Moschus (Shexiang), Panax ginseng C.A.Mey. (Renshen), Bos taurus domesticus Gmelin (Niuhuang), Cinnamomum cassia (L.) J.Presl (Rougu), Liquidambar orientalis Mill. (Suhexiang), Bufo bufo gangarizans Cantor (Chansu), and Boroneol (C10H18O, Binguian) | Inhibit the inflammatory reaction by reducing TNF-α and IL-6, increase the maximum value of left ventricular systolic pressure and left ventricular end-systolic pressure, and reduce left ventricular end-diastolic pressure, and improve left ventricular function | Myocardial, cell and inflammatory cell         | (28)       |
| Xin-Ji-Er-Kang Formula    | Panax ginseng C.A.Mey. (Renshen), Polygonatum adnatum S.Yun Liang (Yuzhu), Panax pseudoginseng var. Notoginseng (Burkii) G. Hoo & C.L. Tseng (Sanqi), Allium macrostemon Bunge (Kieba), Angelica sinensis (Oiku) Diels (Danggu), Ophiopogon japonicus (Thunb.) Ker Gawl. (Maidong), Schisandra chinensis (Turcz.) Bail. (Nuweizi), Salvia miltiorrhiza Bunge (Danshen), Sophora flavescens Aiton (Kushen), Glycyrrhiza uralensis Fisch. (Gancao), Radix Astragal (Huangqi), Epimedium acuminatum Franch. (Yinyanghuo), Trichosanthes kirilowii Maxim. (Gualou), and Dryobalanopsaromatica C.F. Gaertn. (Longnag) | Reduce TNF-α and IL-1β, and increase IL-10 to restore the balance between the pro-inflammatory and anti-inflammatory state; decrease TNF-α, inhibit the activation of NADPH oxidase, reduce the uncoupling of eNOS and the production of ROS, and increase the activity of eNOS and NO content; blunt the decrease of superoxide dismutase, NO and the increase in malondialdehyde and Ang II, myocardial cross-section area, collagen volume fraction and perivascular circumferential collagen area; reduce hydroxyproline while increase tetrathydrobiopterin though suppressing JNK/MAPK pathway | Myocardial cell and endothelial cell          | (29, 55, 56) |
| Yi-Qi-Wen-Yang Decoction   | Radix Astragal (Huangqi), Sedum erythrostictum Mq. (Jingtian), Aconitum carmichaelii Debeaux (Fuzi), Polyergus umbellatus (Pers.) Fries (Zhuiling), Cervus nippon Temminck (Lurong), Curcuma phaeocaulis Valeton (zhu), Paeonia lactiflora Pall. (Baishao), and Zingiber officinale Roscoe (Shengjiang) | Attenuate myocardial inflammation, fibrosis, apoptosis, and reverse the impairment of cardiac function by activating the IL-10/Stat3 signaling pathway | Myocardial cell, fibroblast, and inflammatory cell | (30)       |
| Bu-Yang-Huan-Wu Decoction  | Radix Astragal (Huangqi), Angelica sinensis (Oiku) Diels (Danggu), Paeonia lactiflora Pall. (Chishao), Ligusticum chuanxiong (Chuanxiong), Prunus persica (L.) Batsch (Taoren), Carthamus tinctorius L. (Honghua), and Lirubricus (Dilong) | Inhibit the activation of Smad3 and Smap4, then the pro-fibrotic molecules, including transcription of α-smooth muscle actin, collagen and tissue inhibitor of MMPs | Myocardial cell and inflammatory cell         | (81)       |
| Dan-Qi Soft Capsule        | Salvia miltiorrhiza Bunge (Danshen), and Panax pseudoginseng var. Notoginseng (Burkii) G. Hoo & C.L. Tseng (Sanqi) | Inhibit TGF-β1/Smad3 pathway                                              | Myocardial cell and fibroblast.                | (82)       |
| Tong-Guan Capsule          | Radix Astragal (Huangqi), Salvia miltiorrhiza Bunge (Danshen), Hirudo medicinalis (Shuzhi) and Ophiopogon japonicus (Thunb.) Ker Gawl. (Maidong) | Inhibit the differentiation and formation of myofibroblasts; inhibit apoptosis and promote autophagy by activating Sirt1 and down-regulating mTOR/P70S6K/4EBP1 pathway; deacetylate p53 to inhibit apoptosis | Myocardial cell and inflammatory cell         | (72, 83)   |
| Ling-Gui-Zhu-Gan Decoction | Poria cocos (Schw.) Wolf (Fuling), Ramulus Cinnamomoni (Guizh), Atractylis macrocephala (Koiz.) Han. -Mazz. (Baizhu), and Glycyrrhiza uralensis Fisch. (Gancao) | Regulate TGF-β1/Smap3 pathway                                             | Myocardial cells and fibroblast               | (85)       |

(Continued)
| TCM                          | Constituents                                                                 | Mechanism                                                                 | Cell type                           | References |
|------------------------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------|--------------------------------------|------------|
| Xin-Fu-Granule               | Radix Astragali (Huangqi), Panax ginseng C.A.Mey. (Renshen), Salvia miltiorrhiza Bunge (Danshen), Ligusticum chuanxiong (Chuanxiong), Alisma plantago-aquatica subsp. orientale (Sam.) Sam. (Zexie), Angelica sinensis (Oliv.) Diels (Danggui), Semen Lepidii/Semen Deserticae (Tingli), Chaenomeles speciosa (Sweet) Nakai (Mugua), Areca catechu L. (Binglang), and Ophiopogon japonicus (Thunb.) Ker Gawk. (Maidong) | Regulate TGF-β/Smads pathway       | Myocardial cell and fibroblast      | (86)       |
| Lu-Hong Formula              | Cervus nippon Temminck (Lurong), Carthamus tinctorius L. (Honghua), Radix Astragali (Huangqi), Codonopsis affinis Hook.f. & Thomson (Danshen), Cinnamomum cassia (L.) J.Presl (Rougui), and Semen Lepidii/Semen Deserticae (Tingli) | Regulate TGF-β/Smads pathway and reduce apoptosis by down-regulating caspase-3 | Myocardial cell and fibroblast      | (69, 69)   |
| Si-Miao-Yong-An Decoction    | Lonicera japonica Thunb. (Jinyinhua), Scrophularia microdonta Franch. (Xuanshen), Angelica sinensis (Oliv.) Diels (Danggui), and Glycyrrhiza uralensis Fisch. (Gancao) | Inhibit TGF-β1/Smad and TGF-β1/Tak1/p38 signal pathways, and increase MMP9 and decrease TIMP2 to promote the degradation of collagen and reduce the synthesis of collagen | Fibroblast                             | (87)       |
| Dan-Shen Injection           | Salvia miltiorrhiza Bunge (Danshen)                                         | Inhibit the activation of MMP2 and MMP9 to improve ejection fraction and left ventricular stroke volume | Myocardial cell, neutrophil, and macrophage | (97)       |
| Sheng-Mai-San                | Panax ginseng C.A.Mey. (Renshen), Ophiopogon japonicus (Thunb.) Ker Gawk. (Maidong), and Schisandra chinensis (Turcz.) Baill. (Wuweizi) | Inhibit the activity of the SNS and reduce the release of NE and 5-HT, increase the activity of antioxidant enzymes, and reduce malondialdehyde, 4-HNE, and myeloperoxidase | Myocardial cell                             | (51, 52)   |
| Yi-Qi-Fu-Mai Powder Injection | Panax ginseng C.A.Mey. (Renshen), Ophiopogon japonicus (Thunb.) Ker Gawk. (Maidong), and Schisandra chinensis (Turcz.) Baill. (Wuweizi) | Decrease ROS generation, malondialdehyde content, and increase NO content; improve mitochondrial function by down-regulating the expression of NAPD oxidase subunits | Myocardial cell and endothelial cell                             | (57, 60)   |
| Tong-Xin-Luo                  | Panax ginseng C.A.Mey. (Renshen), Buthus martensii Karsch (Quanxie), Hiptropon nipponica Whitman (Shuizhi), Eucommia ulmoides (Turcz.) Baill. (Wuweizi) | Inhibit apoptosis and promote autophagy though AMPK/mTOR pathway                                      | Myocardial cell                                      | (71)       |
| Qi-Dan-Li-Xin Pill            | Radix Astragali (Huangqi), Salvia miltiorrhiza Bunge (Danshen), Epimedium acuminatum Franch. (Yinyanghuo), and Poria cocos (Schw.) Wolf (Fuling) | Inhibit apoptosis and promote autophagy by down-regulating mTOR/P70/S6K/4EBP1 pathway | Myocardial cell                                      | (73)       |
| Yang-Xin-Kang Tablet          | Panax ginseng C.A.Mey. (Renshen), Radix Astragali (Huangqi), Ophiopogon japonicus (Thunb.) Ker Gawk. (Maidong), Schisandra chinensis (Turcz.) Baill. (Wuweizi), and Ilex pubescens Hook. & Arn. (Maodongqing) | Inhibit AMPK/mTOR signal pathway and excessive autophagy                                      | Myocardial cell                                      | (74)       |
activation of SNS will lead to the excessive accumulation of catecholamines, which is linked to cardiomyocyte apoptosis and myocardial fibrosis. The activation of RAAS will cause too much Ang II generation and it can participate in a variety of reactions. Ang II can promote the release of inflammatory cytokines and ROS through AT1R (139). In addition, Ang II is involved in myocardial fibrosis. Ang II can up-regulate the expression of mesenchymal makers by activating the TGF-β1/Smad3 pathway, leading to the formation of myofibroblasts (78, 139). What is more, Ang II can also promote the production of aldosterone, which can upregulate the expression of α-smooth muscle actin and promote myocardial fibrosis (139).

In addition to the mechanism described above, the energy metabolism of cardiomyocytes also affects the process of VR. Abnormal energy metabolism will lead to ROS production and lead to a series of chain reactions, such as inflammation, activation of the neuroendocrine system, and cardiomyocyte apoptosis, thus, improving the myocardial energy metabolism is helpful to improve VR.

Because of its multi-components and multi-targets, TCM has good effects on the prevention and treatment of VR. From the literature we enumerated, Qi-Li-Qiang-Xin is the most studied drug. Based on a variety of studies on Qi-Li-Qiang-Xin, we can find that it can exert the effect of anti-myocardial apoptosis and myocardial fibrosis by inhibiting the production of inflammatory factors, reducing the production of ROS, up-regulating PGC-1α and PPARγ, inhibiting the TGF-β1/Smad3 pathway, and activating the TGF-β3/Smad7 signal pathway. Other TCM, like Qi-Shen-Yi-Qi, can also reduce VR by reducing inflammation and inhibiting the TGF-β1/CTGF pathway. Traditional Chinese medicine improves VR mainly by acting on cardiomyocytes, fibroblasts, and inflammatory cells, but due to the limitations of related experiments, it is not clear what kind of inflammatory cells TCM can reduce. From Table 1, we can find that many TCM has only done related research on one of the mechanism mentioned above, which is not beneficial to our further understanding of the anti-VR mechanism of TCM. Perhaps we can speculate the multiple mechanisms of anti-VR from the same components of different TCM, but we do not know whether the previous interactions of different TCM have changed the structure of the active components of TCM, which requires us to further improve the basic research of TCM against VR.
CONCLUSION

The occurrence of VR is the result of the joint action of a variety of mechanisms (Table 2). In recent years, with the popularity of TCM, the advantages of TCM in the treatment of VR are more and more obvious (140). We do not comment on any monomer here, because the TCM formula consists of dozens of ingredients with numerous chemical molecules, making it difficult to elucidate the therapeutic mechanism of TCM (141–144). Through our research, we verify that TCM inhibits the process of VR through the single or multiple pathways and combined use of multiple drugs again. Some TCM, such as Qi-Li-Qiang-Xin, Qi-Shen-Yi-Qi Pill, Xin-Ji-Er-Kang Formula, and Yi-Qi-Wen-Yang Decoction, could play a role in many pathological conditions, including apoptosis, oxidative stress, and inflammation. From the above discussion, because of its multi-components and multi-action targets, TCM cannot establish treatment standards, which greatly increases the difficulty of clinical trials. In addition, the diversity of components also shows that it is difficult to identify the precise targets, which requires us to continue to improve the relevant technology.

AUTHOR CONTRIBUTIONS

Y-CZ, BL, and NG designed the study, acquired and researched the data for the article, and discussed its content. Y-CZ wrote the manuscript. NG and BL revised the manuscript. All authors read and approved the final manuscript.

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REFERENCES

1. Biere L, Donal E, Jacquier A, Croisille P, Genee O, Christiaens L, et al. A new look at left ventricular remodeling definition by cardiac imaging. Int J Cardiol. (2016) 209:17–9. doi: 10.1016/j.ijcard.2016.02.009
2. Cheng X, Wang L, Wen X, Gao L, Li G, Chang G, et al. TNAP is a novel regulator of cardiac fibrosis after myocardial infarction by mediating TGF-beta/Smads and ERK1/2 signaling pathways. EBioMedicine. (2021) 67:103370. doi: 10.1016/j.ebiom.2021.103370
3. Constant Dit Beaufils A-L, Huttin O, Jobbe-Duval A, Senage T, Filippetti L, Piriou N, et al. Replacement myocardial fibrosis in patients with mitral valve prolapse: relation to mitral regurgitation, ventricular remodeling, and arrhythmia. Circulation. (2021) 143:1763–74. doi: 10.1161/CIRCULATIONAHA.120.050214
4. Azevedo PS, Polegato BF, Minicucci MF, Paiva SA, Zornoff LA. Novel regulator of cardiac fibrosis after myocardial infarction by mediating TGF-beta/Smads and ERK1/2 signaling pathways. EBioMedicine. (2021) 67:103370. doi: 10.1016/j.ebiom.2021.103370
5. Perera-Gonzalez M, Kiss A, Kaiser P, Holzweber M, Nagel F, Watzingter S, et al. Role of tenasin C in cardiac reverse remodeling following banding-debanding of the ascending aorta. Int J Mol Sci. (2021) 22:2023. doi: 10.3390/ijms22042023
6. Fan D-C, Qi J-Y, Zhang M-Z. Insights of Chinese medicine on ventricular remodeling: multiple targets, individualized-treatment. Chin J Integr Med. (2017) 23:643–7. doi: 10.1007/s11655-017-2415-y
7. Chao J, Dai Y, Verpoorte R, Lam W, Cheng Y-C, Pao L-H, et al. Major achievements of evidence-based traditional Chinese medicine in treating major diseases. Biochem Pharmacol. (2017) 139:94–104. doi: 10.1016/j.bcp.2017.06.123
8. Hao P-P, Jiang F, Cheng J, Ma L-Y, Zhang Y, Zhao Y-X. Traditional Chinese medicine for cardiovascular disease: evidence and potential mechanisms. J Am Coll Cardiol. (2017) 69:2952–66. doi: 10.1016/j.jacc.2017.04.041
9. Liang B, Zou F-H, Fu L, Liao H-L. Chinese herbal medicine Dingji Fumai decoction for ventricular premature contraction: a real-world trial. Biomed Res Int. (2020) 2020:5358467. doi: 10.1155/2020/5358467
10. Liang B, Zhou Y, Fu L, Liao H-L. Antiarrhythmic mechanisms of Chinese herbal medicine Dingji Fumai Decoction. Evid Based Complement Alternat Med. (2020) 2020:9185707. doi: 10.1155/2020/9185707
11. Frangogiannis NG. Regulation of the inflammatory response in cardiac repair. Circ Res. (2012) 110:159–73. doi: 10.1161/CIRCRESAHA.111.243162
12. Kologrivova I, Shtatolinka M, Suslova T, Ryabov V. Cells of the immune system in cardiac remodeling: main players in resolution of inflammation and repair after myocardial infarction. Front Immunol. (2021) 12:664457. doi: 10.3389/fimmu.2021.664457
13. Kong P, Christia P, Frangogiannis NG. The pathogenesis of cardiac fibrosis. Cell Mol Life Sci. (2014) 71:549–74. doi: 10.1007/s00018-013-1349-6
14. Liang B, Zhu Y-C, Lu J, Gu N. Effects of traditional chinese medication-based bioactive compounds on cellular and molecular mechanisms of oxidative stress. Oxid Med Cell Longev. (2021) 2021:3617498. doi: 10.1155/2021/3617498
15. He X, Liang B, Gu N. Th17/Treg imbalance and atherosclerosis. Dis Markers. (2020) 2020:8821029. doi: 10.1155/2020/8821029
16. Gouyou B, Grun K, Kerschenmeyer A, Villa A, Matasci M, Schrepper A, et al. Therapeutic evaluation of antibody-based targeted delivery of interleukin 9 in experimental pulmonary hypertension. Int J Mol Sci. (2021) 22:3460. doi: 10.3390/ijms22073460
17. Hann A, Frangogiannis NG. Inflammatory cytokines and chemokines as therapeutic targets in heart failure. Cardiovasc Drugs Ther. (2020) 34:849–63. doi: 10.1007/s10557-020-07071-0
18. Haudek SB, Tafert GE, Schneider MD, Mann DL. TNF provokes cardiomyocyte apoptosis and cardiac remodeling through activation of multiple cell death pathways. J Clin Invest. (2007) 117:2692–701. doi: 10.1172/JCI29134
19. Hamid T, Gu Y, Ortines RV, Bhattacharya C, Wang G, Xuan YT, et al. Divergent tumor necrosis factor receptor-related remodeling responses in heart failure: role of nuclear factor-kappaB and inflammatory activation. Circulation. (2009) 119:1386–97. doi: 10.1161/CIRCULATIONAHA.108.802918
20. Sager HB, Heidt T, Hulsmans M, Dutta P, Courties G, Sebas M, et al. Targeting Interleukin-1β Reduces Leukocyte Production
Wang L, Zhang N, Han D, Su P, Chen B, Zhao W, et al. MTDH
Ding L, Cheng P, Wang L, Hu J, Zhang Y-X, Cai G-W, et al. The
Li H, Gong Z-J, He Y, Huang J-J, Jiang Y-N, Liu Y-Y, et al.
Cen W, Chen Z, Gu N, Hoppe R. Prevention of AMI induced
Xu Y, Hong S, Zhao X, Wang S, Xu Z, Ding S, et al. Acupuncture alleviate s
Kany S, Vollrath JT, Relja B. Cytokines in inflammatory disease.
Li C, Wang Y, Qiu Q, Shi T, Wu Y, Han J, et al. Qishenyiqi protect s
Sackett SD, Otto T, Mohs A, Sander LE, Strauch S, Streetz KL, et al. Myeloid
Nam N-H. Naturally occurring NF-kappaB inhibitors.
Chou CH, Hung CS, Liao CW, Wei LH, Chen CW, Shun CT, et al. IL-6 tra ns-
Res. (2009) 104:699–706. doi: 10.1161/CIRCRESAHA.108.189746
promotes intestinal inflammation by positively regulating TLR
23. doi: 10.1186/s12906-019-2539-z
20:637. doi: 10.1016/j.jep.2014.07.006
221:132–42. doi: 10.2174/157340211166610500520752
301:H2181–90. doi: 10.1152/aphp.00554.2011
PloS ONE. (2014) 9:e102455. doi: 10.1371/journal.pone.0102455
Wu X, Shen A, Bao L, Wu M, Lin X, Wang H, et al. Qingda granules attenuate hypertensive cardiac remodeling and inflammation in spontaneously hypertensive rats. Biomed Pharmacother. (2020) 129:110367. doi: 10.1016/j.biopha.2020.110367
Filomeni G, De Zio D, Cecconi F. Oxidative stress and autophagy; the clash between damage and metabolic needs. Cell Death Differ. (2015) 22:377–88. doi: 10.1038/cdd.2014.150
Sies H. Oxidative stress: a concept in redox biology and medicine. Redox Biol. (2015) 4:180–3. doi: 10.1016/j.redox.2015.01.002
Sinha N, Dhaba PK. Oxidative stress and antioxidants in hypertension-a current review. Curr Hypertens Rev. (2015) 11:132–42. doi: 10.11521/1573402116610500520752
Senoner T, Dichil W. Oxidative stress in cardiovascular diseases: still a therapeutic target? Nutrients (2019) 11:2090. doi: 10.3390/nu11092090
Tsutsui H, Kinugawa S, Matushima S. Oxidative stress and heart failure. Am J Physiol Heart Circ Physiol. (2011) 301:H2181–90. doi: 10.1152/aphp.00554.2011
Pena E, Brito J, El Alam S, Sique S. Oxidative stress, kinase activity and inflammatory implications in right ventricular hypertrophy and heart failure under hypobaric hypoxia. Int J Mol Sci. (2020) 21:6421. doi: 10.3390/ijms21176421
Hirotani S, Otsu K, Nishida K, Higuchi Y, Morita T, Nakayama H, et al. Involvement of nuclear factor-kappaB and apoptosis signal-regulating kinase 1 in G-protein-coupled receptor agonist-induced cardiomyocyte hypertrophy. Circulation. (2002) 105:509–15. doi: 10.1161/01.RES.102863
Hori M, Nishida K. Oxidative stress and left ventricular remodelling after myocardial infarction. Cardiovasc Res. (2009) 81:457–64. doi: 10.1093/cvr/cvn335
Jia G, Hill MA, Sowers JR. Diabetic cardiomyopathy: an update of mechanisms contributing to this clinical entity. Circ Res. (2018) 122:624–38. doi: 10.1161/CIRCRESAHA.117.311586
Mellin V, Isabelle M, Oudot A, Vergely-Vandriess C, Monteil C, Di Meiglio B, et al. Transient reduction in myocardial free oxygen radical levels is involved in the improved cardiac function and structure after long-term allopurinol treatment initiated in established chronic heart failure. Eur Heart J. (2005) 26:1544–50. doi: 10.1093/euheartj/ehi305
Doehner W, Landmesser U. Xanthine oxidase and uric acid in cardiovascular disease: clinical impact and therapeutic options. Semin Nephrol. (2011) 31:433–40. doi: 10.1056/semneph.2011.08.007
Xiao J, Deng S-B, She Q, Li J, Kao G-Y, Wang J-S, et al. Traditional Chinese medicine Qili qiangxin inhibits cardiomyocyte apoptosis in rats following myocardial infarction. Exp Ther Med. (2015) 10:1817–23. doi: 10.3892/etm.2015.2797
Chai C-Z, Mo W-L, Zhuang X-F, Kou J-P, Yan Y-Q, Yu B-Y. Protective effects of Sheng-Mai-San on right ventricular dysfunction during chronic intermittent hypoxia in mice. Evid Based Complement Alternat Med. (2016) 2016:4682786. doi: 10.1155/2016/4682786
Li F, Fan X-X, Chu C, Zhang Y, Kou J-P, Wu Y-B, et al. Strategy for optimizing the combination of active components based on chinese medicinal Sheng-Mai-San for myocardial ischemia. Cell Physiol Biochem. (2018) 45:1455–71. doi: 10.1159/000487572
Neumann P, Gertzberg N, Johnson A. TNF-alpha induces a decrease in eNOS promoter activity. Am J Physiol Lung Cell Mol Physiol. (2004) 286:L452–9. doi: 10.1152/ajplung.00378.2002
Arrirro MM, Rodríguez-Feo JA, Celdrán Á, Miguel LSD, González-Fernández F, Fortes J, et al. Expression of endothelial nitric oxide synthase in human peritoneal tissue: regulation by Escherichia coli lipopolysaccharide. Am J Surg. (2006) 181:1318–23. doi: 10.1016/j.bjps.2006.03.031
Khathavong A, Pungprapakprasert P. Oxidative stress and endothelial dysfunction. Biomed Pharmacother. (2019) 115:108937. doi: 10.1016/j.biopha.2019.108937
Guo K, Lan C-Z, Yu T-T, Huang L-L, Wang X-h, Pan C, et al. Effects of Xin-Ji-Er-Kang formula on 2K1C-induced hypertension and cardiovascular remodeling in rats. J Ethnopharmacol. (2014) 155:1227–35. doi: 10.1016/j.jep.2014.07.006
Li F, Yu Y-S, Chen H, Yan Z, Zhai K-F, Li D-P, et al. Identification of schisandrin as a vascular endothelium protective component in YIQiPuMai Powder Injection using HUVECs binding and HPLC-DAD-Q-TOF-MS/MS analysis. J Pharmacoceut Sci. (2015) 129:1-8. doi: 10.1016/j.jphas.2015.02.003
58. Saberi M, Zhang X, Mobasher A. Targeting mitochondrial dysfunction with small molecules in intervertebral disc aging and degeneration. GeroScience. (2021) 43:517–37. doi: 10.1007/s11357-021-00341-1

59. Chen W, Guo C, Feng H, Chen Y. Mitochondria: novel mechanisms and therapeutic targets for secondary brain injury after intracerebral hemorrhage. Front Aging Neurosci. (2021) 12:615451. doi: 10.3389/fagi.2020.615451

60. Zhang Y, Zhang L, Zhang Y, Fan X, Yang W, Yu B, et al. YiQiFuMai powder injection attenuates coronary artery ligation-induced heart failure through improving mitochondrial function via regulating ROS generation and CaMKII signaling pathways. Front Pharmacol. (2019) 10:381. doi: 10.3389/fphar.2019.00381

61. Xin T, Lu C. Irisin activates Opa1-induced mitophagy to protect against cardiac dysfunction. Front Pharmacol. (2018) 9:589. doi: 10.3389/fphar.2018.00589

62. Wang J, Li L, Cao Y, Wang Q, Lu L, Chang H, et al. Mechanism of QSYQ on anti-apoptosis mediated by different subtypes of cyclooxygenase (2020) 12:615451. doi: 10.3389/fnagi.2020.615451

63. Qiu H, Liu J-Y, Wei D, Li N, Yamoah EN, Hammock BD, et al. Cardiac-generated prostanooids mediate cardiac myocyte apoptosis after myocardial ischemia. Cardiaco Mar. (2012) 59:336–45. doi: 10.1093/cvi/cvs191

64. Liu P, Xu B, Cavalieri TA, Hock CE. Pifithrin-alpha attenuates p53-mediated apoptosis and improves cardiac function in response to myocardial ischemia/reperfusion in aged rats. Shock. (2006) 26:608-14. doi: 10.1097/01.shc.0000223273.11225.f

65. van Engelen BM, Bertolino A, Cislaghi L, Ciapetti G, Doevendans PA, De Windt LJ. Myocyte apoptosis in heart failure. Cardiovasc Res. (2005) 67:21-9. doi: 10.1016/j.cardiores.2005.04.012

66. Xu Y, Zhang Y, Xu Y, Zhang G, Li B, Xia H, et al. Activation of CD137 signaling promotes macrophage apoptosis dependant on p38 MAPK pathway-mediated mitochondrial fission. Int J Biochem Cell Biol. (2021) 120:106003. doi: 10.1016/j.biocel.2021.106003

67. Liang T, Zhang Y, Yin S, Gan T, An T, Zhang R, et al. Cardio-protecteectef of qiliqiangxin capsule on left ventricular remodeling, dysfunction and apoptosis in heart failure rats after chronic myocardial infarction. Am J Transl Res. (2016) 8:2047-58.

68. Deng L-H, Li L, Zhai Y, Michael S, Yang C-Y, Guo R, et al. Tiangmao decoction ameliorates cardiac remodeling, improves cardiac function and attenuates cardiac remodelling by promoting autophagy and inhibiting apoptosis: role of Sirt1. J Mol Cell Cardiol. (2017) 14:301–7. doi: 10.11909/j.issn.1671-5411.2017.05.005

69. Liu Q, Qu H-Y, Zhou H, Rong J-F, Yang T-S, Xu J-J, et al. Luhong formula has a cardioprotective effect on left ventricular remodeling in pressure-overloaded rats. Evid Based Complement Altern Med. (2020) 2020:3439191. doi: 10.1155/2020/3439191

70. Liu Q, Qu H-Y, Zhou H, Zou H, Rong J-F, Yang T-S, Xu J-J, et al. Luhong formula has a cardioprotective effect on left ventricular remodeling in pressure-overloaded rats. Evid Based Complement Altern Med. (2020) 2020:495967. doi: 10.1155/2020/495967

71. Zhou X, Lu B, Fu D, Gui M, Yao L, Li J, Huoxue Qianyang decoction ameliorates cardiac remodeling in obese spontaneously hypertensive rats in association with ATPF-CHOP endoplasmic reticulum stress signaling pathway regulation. Biomed Pharmacother. (2020) 121:195918. doi: 10.1016/j.biopha.2019.105918

72. Li Q, Li N, Cui H, Tian X-L, Jin C, Chen G-H, et al. Tienma decoction ameliorates cardiac remodeling and improves cardiac function and attenuates cardiac remodeling in doxorubicin-induced heart failure rats. Pharm Biol. (2020) 58:417–26. doi: 10.1080/13880209.2020.1761403

73. Wu L, Shi H, Huang J-L, Xu X, Liu P-P, Lingsui Zhuancong inhibition inhibits ventricular remodeling after chronic myocardial infarction in mice by suppressing TGF-beta signaling pathway. Clin J Integ Med. (2020) 26:345-52. doi: 10.1111/cjim.14428

74. Ma S, Ma J, Zhou Y, Guo L, Bai J, Zhang M. Tongqiang capsule derived-herb ameliorates remodeling at infarcted border zone and reduces susceptibility to ventricular arrhythmias in post-myocardial infarction rats. Cell Mol Med. (2019) 23:5454-65. doi: 10.1111/cmm.14428

75. Kunzmann S, Schmidt-Weber C, Zingg J-M, Aziz A, Kramer BW, Blaser K, et al. Connective tissue growth factor expression is regulated by histamine in lung fibroblasts: potential role of histamine in airway remodeling. J Allergy Clin Immunol. (2007) 119:393-407. doi: 10.1016/j.jaci.2007.02.018

76. Kunzmann S, Speer CP, Jobe AH, Kramer BW. Antenatal inflammation induced TGF-beta1 but suppressed CTGF in preterm lungs. Am J Physiol Lung Cell Mol Physiol. (2007) 292:L223–31. doi: 10.1152/ajplung.00159.2006

77. Chen MM, Lam A, Abraham JA, Schreiner GF, Joly AH, CTGF. expression in the heart is induced by TGF-beta in cardiac fibroblasts and cardiac myocytes: a potential role in heart fibrosis. J Mol Cell Cardiol. (2000) 32:1805-19. doi: 10.1006/jmcc.2000.1215

78. Vainio LE, Szabo Z, Lin R, Ulvila J, Yrjola R, Alakoski T, et al. Connective tissue growth factor inhibition enhances cardiac repair and limits fibrosis after myocardial infarction. JACC Basic Trans Sci. (2019) 4:83–94. doi: 10.1016/j.jactbs.2018.10.007

79. Lv S, Wu M, Li M, Wang Q, Xu L, Wang X, et al. Effect and mechanism of QShenYiQi Pill on experimental autoimmune myocarditis rats. Med Sci Monit. (2016) 22:752–6. doi: 10.12659/MSM.895655
93. Toussoulis D, Kampoli AM, Papageorgiou N, Antoniades C, Siasos G, Latsios G, et al. Matrix metalloproteinases in heart failure. Curr Top Med Chem. (2012) 12:11881–91. doi: 10.2174/15680266120108011881

94. Cokkinos DV, Pantos C. Myocardial remodeling, an overview. Heart Fail Rev. (2011) 16:1–4. doi: 10.1007/s10741-010-9192-4

95. Fis C, Carver-Molina A, Chakrabarti M, Azhar M, Carver W. Effects of the isothiocyanate sulforaphane on TGF-β1-induced rat cardiac fibroblast activation and ECM interactions. J Cell Physiol. (2019) 234:13931–41. doi: 10.1002/jcp.28075

96. Vanhoutte D, Heymans S. TIMPs and cardiac remodeling: “Embracing the MMP-independent-side of the family.” J Mol Cell Cardiol. (2010) 48:445–53. doi: 10.1016/j.yjmcc.2009.09.013

97. Wang L, Yu J, Fordjour PA, Xing X, Gao H, Li Y, et al. Danshen protects against cardiac hypertrophy in heart failure patients: A double-blind, placebo-controlled, randomized clinical trial. Eur J Heart Fail. (2015) 17:768–75. doi: 10.1002/ejhf.524

98. Bistrow MR, Quaife RA. The adrenergic system in pulmonary arterial hypertension: bench to bedside (2013 Grover Conference series). Pulm Circ. (2015) 5:415–23. doi: 10.1080/20478177.2015.10862223

99. Lu M, Wang H, Wang J, Zhang J, Yang J, Liang L, et al. Atralagoloside IV protects against cardiac hypertrophy via inhibiting the Ca2+/CaN signaling pathway. Planta Med. (2014) 80:63–9. doi: 10.1055/s-0033-1360129

100. Böhm M, Maack C. Treatment of heart failure with beta-blockers. Mechanisms and results Basic Res Cardiol. (2000) 95 Suppl 1:115–24. doi: 10.1007/s003950070004

101. Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Tousoulis D, Kampoli AM, Papageorgiou N, Antoniades C, Siasos G, Latsios G, Triposkiadis F, Karayannis G, Giamouzis G, Skoularigis J, Louridas G, Tousoulis D, Kampoli AM, Papageorgiou N, Antoniades C, Siasos G, Latsios G. Myocardial remodeling, an overview. Cell Signal. (2008) 20:1609–14. doi: 10.1016/j.cellsig.2008.01.006

102. Bae EH, Ma SK, Lee J, Kim SW. Altered regulation of renal nitric oxide and prosaposin expression in TGRβ-null mice. J Cell Physiol. (2012) 227:698–708. doi: 10.1002/jcp.22732

103. Liu Y, Wu H, Zhang J, Zhao X-S, Pan W, Bekeredjian R, Shohet RV. Endogenous endothelin-1 is required for cardiacmyocyte survival in vivo. Circulation. (2006) 114:830–7. doi: 10.1161/CIRCULATIONAHA.105.577288
131. Fabregat-Andrés O, Ridocci-Soriano F, Estornell-Erill J, Corbí-Pascual M, Valle-Muñoz A, Berenguer-Jofresa A, et al. Blood PGC-1α concentration predicts myocardial salvage and ventricular remodeling after ST-segment elevation acute myocardial infarction. Rev Esp Cardiol. (2015) 68:408–16. doi: 10.1016/j.rec.2014.05.020

132. Fabregat-Andres O, Paredes F, Monsalve M, Milara J, Ridocci-Soriano F, Gonzalez-Hervas S, et al. mRNA PGC-1α levels in blood samples reliably correlates with its myocardial expression: study in patients undergoing cardiac surgery. Anatolian journal of cardiology. (2016) 16:622–9. doi: 10.5152/AnatolJCardiol.2015.6466

133. Sun C-K, Chang L-T, Sheu J-J, Chiang C-H, Lee F-Y, Wu C-J, et al. Bone marrow-derived mononuclear cell therapy alleviates left ventricular remodeling and improves heart function in rat-dilated cardiomyopathy. Crit Care Med. (2009) 37:1197–205. doi: 10.1097/CCM.0b013e31819f0667

134. Liao J, Hao C, Huang W, Shao X, Song Y, Liu L, et al. Network pharmacology study reveals energy metabolism and apoptosis pathways-mediated cardioprotective effects of Shenshi Fuweng. J Ethnopharmacol. (2018) 227:155–65. doi: 10.1016/j.jep.2018.08.029

135. Tao L, Shen S, Fu S, Fang H, Wang X, Das S, et al. Traditional Chinese medicine Qiliqiangxin attenuates adverse cardiac remodeling after myocardial infarction in ovariec tomized mice via activation of PPARγ. Cell Physiol Biochem. (2017) 42:876–88. doi: 10.1159/000478641

136. Balakumar P, Sambathkumar R, Mahadevan N, Muhsinah AB, Alsayar A, Venkateswaramurthy N, et al. A potential role of the renin-angiotensin-aldosterone system in epithelial-to-mesenchymal transition-induced renal abnormalities: Mechanisms and therapeutic implications. Pharmaco Res. (2019) 146:104314. doi: 10.1016/j.phrs.2019.104314

137. Chen R, Zhu C, Xu L, Gu Y, Ren S, Bai H, et al. An injectable peptide hydrogel with excellent self-healing ability to continuously release salvianolic acid B for myocardial infarction. Biomaterials. (2021) 274:120855. doi: 10.1016/j.biomaterials.2021.120855

138. Gu WL, Chen CX, Huang XY, Gao JP. The effect of angoroside C on pressure overload-induced ventricular remodeling in rats. Phytomedicine. (2015) 22:705–12. doi: 10.1016/j.phymed.2015.05.002

139. Gao Y, Gao JP, Chen CX, Wang HL, Guo J, Wu R. Beneficial effects of houttuynin on ventricular remodeling induced by coronary artery ligation in rats. Eur J Pharmacol. (2014) 740:200–8. doi: 10.1016/j.ejphar.2014.07.015

140. Gao Y, Gao J, Chen C, Wang H, Guo J, Wu R. Cardioprotective effect of polydatin on ventricular remodeling after myocardial infarction in coronary artery ligation rats. Planta Med. (2015) 81:568–77. doi: 10.1055/s-0035-1545907

141. Huang XY, Chen CX, Zhang XM, Liu Y, Wu XM Li YM. Effects of ethanolic extract from Radix Scrophulariae on ventricular remodeling in rats. Phytomedicine. (2012) 19:193–205. doi: 10.1016/j.phymed.2011.09.079

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