Mechanisms of action of natural small-molecule drugs in cardiovascular disease

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Abstract

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Review

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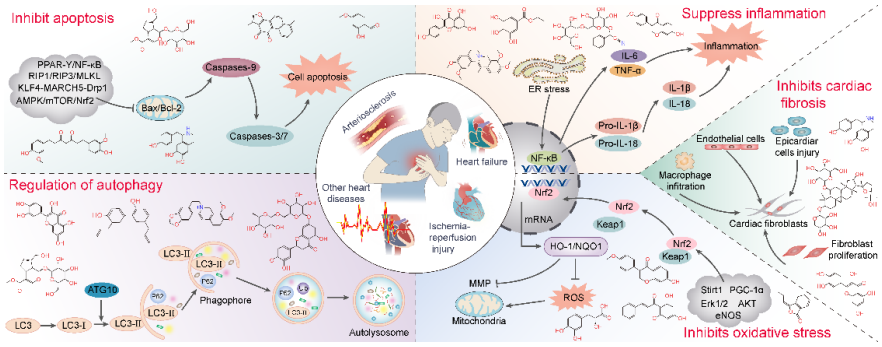
Author contributions

Li Sun, Xuefang Li and Fei Lin contributed to the conception of the manuscript; Hui Luo, Zhigang Chen , Siyu Sun, Xiulong Wang,Dongxu LI ,offers advice ;Fei Lin and Guoan zhao conducts structural reviews; Li Sun wrote the manuscript; All authors discussed the manuscript and all authors read the final manuscript.

Conflict of interest

All authors have no conflict of interest to disclose.

Graphical abstract



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Abbreviations: α-SMA, smooth muscle alpha-actin; Akt, protein kinase B; AMPK, 5' adenosine monophosphate-activated protein kinase; AP-1, activator protein 1; ARE, antioxidant responsive element; AS, atherosclerosis; CaN, calcineurin; CAT, catalase; C/EBP-β, CCAAT-enhancer-binding protein beta; CF, cardiac fibroblasts; CHOP, CCAAT-enhancer-binding protein homologous protein; CRP, C-reactive protein; CTGF, connective tissue growth factor; CVD, cardiovascular disease; Dll4, delta-like ligand 4; ECs, endothelial cells; eNOS, endothelial nitric oxide synthase; ERK1/2, extracellular signal-regulated kinase 1/2; ERS, endoplasmic reticulum stress; FAK, focal adhesion kinase; FOXO1, forkhead box O1; GRP, glucose-regulated protein; GSH, glutathione; H(C)AECs, human (coronary) aortic endothelial cells; HF, heart failure; HIF-1α, hypoxia-inducible factor 1-alpha; HUVECs, human umbilical vein endothelial cells; IκBα, nuclear factor of kappa light polypeptide gene enhancer in B cells inhibitor, alpha; IL, interleukin; I/R, ischemia-reperfusion; JNK, Janus kinase; KLF2/4, Krüppel-like factor 2/4; LVR, left ventricular remodeling; MAPKs, mitogen-activated protein kinases; MI, myocardial infarction; miR, micro RNA; MLKL, pseudokinase mixed lineage kinase domain-like protein; MMPs, matrix metalloproteinases; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NOX-4, NADPH oxidase 4; Nrf2, nuclear factor erythroid 2-related factor 2; ox-LDL, oxidized low-density lipoprotein; PARP, poly (ADP-ribose) polymerase; p-PERK, protein kinase R-like ER kinase; phosphoinositide 3-kinase; PPAR- β/γ, peroxisome proliferator-activated receptor beta/gamma; PKM2, pyruvate kinase isozyme type M2; PTEN, phosphatase and tensin homolog; RIP, receptor-interacting serine/threonine kinase; ROS, reactive oxygen species; Sirt1, sirtuin 1; Smad, suppressor of mothers against decapentaplegic transcription factor; SOD, superoxide dismutase; TAZ, transcriptional coactivator with PDZ-binding motif; TGF-β1, transforming growth factor beta 1; THP-1 cells, human monocytic cell line derived from an acute monocytic leukemia patient; TLR4, Toll-like receptor 4; TNF-α, tumor necrosis factor alpha; TREM2, triggering receptor expressed on myeloid cells 2; TRPM7, transient receptor potential cation channel, subfamily M, member 7; Trx, thioredoxin; UCP2, uncoupling protein 2; VEGF-A, vascular endothelial growth factor A; VR, ventricular remodeling; VSMCs, vascular smooth muscular cells; YAP, yes-associated protein.

Manuscript (without author details)

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Abstract

Cardiovascular diseases (CVDs) cause massive morbidity and mortality. In recent years, natural small-molecule therapeutics have attracted much attention for their significant efficacy. Articles have been published to study the intervention of natural drugs (including monomers, compounds, compound and neo-combinations) on one type of cardiovascular disease, but the number and variety of natural drugs included are small and insufficient, and there are no articles detailing the protective effects of different types of natural small molecule drugs on multiple cardiovascular diseases. Natural small molecule drugs have high biological activity and structural diversity, and are more likely to enter the body to exert their effects. In this article, we describe the efficacy of such drugs for anti-atherosclerosis, cardiomyocyte repair, and antagonism of ventricular remodeling, heart failure, and arrhythmias to provide an experimental basis for clinical research and identification of new therapeutic approaches.

Keywords: cardiovascular disease, natural product, natural medicine, small molecule

Highlights

- This review summarizes pathophysiological mechanisms of cardiovascular diseases.
- It focuses on natural small molecule drugs for cardiovascular disease treatment.
- It shows molecular mechanisms of major components of natural small molecule drugs.

Introduction

Cardiovascular diseases (CVDs) have been increasing in incidence and disability rates year after year, posing serious threats to human life[1, 2]. With the world population aging and growing, 22.2 million people are expected to die from CVDs in 2030 [3]. CVDs include atherosclerosis (AS), heart failure (HF), arrhythmias, valvular disease, peripheral arterial disease, thromboembolic disease, and venous thrombosis, with underlying pathologies of abnormal cardiac, vascular, and electrical remodeling. Many cardiovascular diseases have a long course and poor prognosis, and the current medical approach is mainly based on surgery, supplemented by symptomatic drugs, but these methods can cause intolerance and some side effects in patients. Therefore, it is important to explore new, less side effects and well-tolerated treatments for cardiovascular diseases. Natural small molecules are active ingredients extracted from natural plants, and these natural products have received widespread attention for their advantages such as multi-target effects and fewer adverse effects than synthetic drugs.Natural plants have long played an important role in drug discovery and development; many small-molecule drugs from natural plants are described in classical plant pharmacopoeias such as the 2020 edition of Pharmacopoeia of the People's Republic of China, Indian Pharmacopoeia, U.S. Pharmacopeia/National Formulary U.S. Pharmacopeia/National Formulary," and "Japanese Pharmacopoeia." Examples include digitalis (Maundiflora), aspirin (Willow), ergotamine (Ergot), and quinine (Cinchona) [1, 2, 4]. Multiple reports have described the mechanisms by which natural small molecules are involved in CVD pathophysiologies through complex pathways underlying inflammation, oxidative stress, apoptosis, and autophagy.

Natural plant drugs have many different targets. However, current discussion is mostly about one natural drug for one disease or multiple natural drugs for one disease, including only a small number and insufficient variety of natural drugs and a mixture of complexes and monomers. Data from most randomized clinical trials and meta-analyses do not address the effects of different classes of natural small molecules on different CVDs; moreover, a systematic evaluation of pathways by which they can act is lacking. The aim of this review was to summarize the mechanisms by which natural small-molecule drugs combat CVDs and thus provide useful information for identification of novel compounds.

The effect of natural small molecule drugs on AS

In AS, lipid plaque-like deposits (atheromatous or atherosclerotic plaques) form in the walls of medium or large arteries, resulting in reduced blood flow[5]. Pathological factors that contribute to AS development include increased serum cholesterol levels, impaired vascular endothelial function, and lipid peroxidation

damage. During AS, endothelial permeability increases[6], and oxidized LDL enters the inner layer of the arterial wall, the intima, where a portion of it is retained and modified by proteases and other enzymes. The modified lipoproteins and their products, such as fatty acids and oxidized lipids, induce an inflammatory response, also increasing serum cholesterol level[7] and elevating production of inflammatory factors, including TNF-α, IL-1β, and IL-6. Adhesion molecules induce vascular inflammation by promoting adhesion of monocytes and leukocytes to activated endothelial cells (ECs) [8]. TNF-α can induce apoptosis[9]; moreover, some proatherogenic factors, including oxidized LDL, angiotensin II, nitric oxide, and reactive oxygen species (ROS), induce EC apoptosis [10]. The most important role of oxidized LDL in AS pathogenesis is regulation of oxidative stress [11].

Cholesterol accumulation causes differentiation of monocytes into macrophages [12], which in turn can be functionally and phenotypically modified to respond to microenvironmental stimuli with pro-wound-healing, pro-inflammatory, tissue regeneration, anti-inflammatory, anti-fibrotic, or pro-fibrotic properties[13]. Macrophages become foam cells by phagocytosing lipid droplets and accumulate in plaques, release cytokines to induce inflammatory responses, and induce smooth muscle cell apoptosis [14]. Foam cells and macrophages are also prone to apoptosis. Thin fibrous caps rupture necrotic lipid cores [15] and promote apoptosis, plaque rupture, and thrombosis [16]. Plaque repair requires vascular smooth muscle cell (VSMC) proliferation and matrix synthesis, both of which are altered by cell death and senescence [17]. As AS progresses, lipids, dead cells, and necrotic debris accumulate, requiring increased phagocytosis to prevent formation of a necrotic core, wherein autophagy plays an important role.

Autophagy contributes to intracellular homeostasis in cardiomyocytes, ECs, and arterial smooth muscle cells [18], e.g., activation of autophagy by intercellular and/or extracellular stimulation can prevent VSMC death [19]. Mammalian target of rapamycin inhibitor (mTOR) selectively clears macrophages in rabbit atherosclerotic plaques via autophagy [20]. Some oxidative stress and apoptosis inducers, including oxysterols, oxidized phospholipids (oxPLs), and unesterified free cholesterol, cause macrophage autophagy, which in turn promotes necrosis, apoptosis, and oxidative stress in advanced atherosclerotic plaques [21].

Inflammatory cell infiltration, oxidative stress, apoptosis, and autophagy are central to AS pathophysiology. Many natural small-molecule drugs isolated from plants, such as artemisinin, paclitaxel, ginkgolide B, and curcumin, have been structurally modified to have antioxidant, inflammomodulatory, anticoagulant, hypoglycemic, antihypertensive, anti-atherosclerotic, and anti-ischemic properties and to play important roles in treating CVDs [22, 23]. Therefore, natural small-molecule drugs intervene in AS initiation and progression through inhibition of inflammation and oxidative stress, regulation of apoptosis and autophagy inhibition, intervention in cellular senescence, anti-vascular remodeling, anti-cellular iron death, and anti-cellular adhesion. Their specific mechanisms of action are shown in Table 1.

Table 1. Mechanisms of action of natural small-molecule drugs against AS

Serial number	Chinese medicine	Active ingredient	Classification	Molecular formula	Chemical structure	Cellular/animal models	Role	Molecular mechanisms	Re
1	*Croton tiglium L.*	Phorbol 12-myristate 13-acetate	Phorbol ester	$C_{36}H_{56}O_8$		Japanese white rabbit with large ears	Regulation of inflammation	Regulation of Notch1 and Dll4 signaling	
2	*Corydalis yanhusuo W.T. Wang*	Dehydrocorydaline	Alkaloid	$C_{22}H_{24}NO_4$		Macrophages; *ApoE*$^{-/-}$ mice	Regulation of inflammation	Targeting macrophage p65 and ERK1/2 signaling	[24

Serial number	Chinese medicine	Active ingredient	Classification	Molecular formula	Chemical structure	Cellular/animal models	Role	Molecular mechanisms	Re
3	*Euphorbia fischeriana Steud.*	Ethyl gallate	Polyphenol	$C_9H_{10}O_5$		Macrophages; zebrafish; and *ApoE*$^{-/-}$ mice	Regulation of inflammation	Decreasing lipid content and macrophage number in plaques	[25
4	*Magnolia*	Honokiol	Lignan-like	$C_{18}H_{18}O_2$		*ApoE*$^{-/-}$ mice	Regulation of inflammation	Downregulation of pro-inflammatory marker expression	[26
5	*Spatholobus suberectus Dunn*	Formononetin	Flavonoid	$C_{16}H_{12}O_4$		HASMCs, HUVECs, THP-1 cells and peritoneal macrophages; male *ApoE*$^{-/-}$ mice	Regulation of inflammation	Regulation of interaction between KLF4 and SRA	[27
6	*Lithospermum erythrorhizon Sieb. et Zucc.*	Shikonin	Naphthoquinone	$C_{16}H_{16}O_5$		*ApoE*$^{-/-}$ mice and their macrophages	Regulation of inflammation	Inhibition of CD4+ T cell activation and reduction of interferon-γ secretion via a PKM2-dependent metabolism	[28

Serial number	Chinese medicine	Active ingredient	Classification	Molecular formula	Chemical structure	Cellular/animal models	Role	Molecular mechanisms	Re
7	*Astragalus membranaceus (Fisch.) Bge.*	Calycosin	Isoflavone	$C_{16}H_{12}O_5$		*ApoE*$^{-/-}$ mice	Regulation of inflammation	Regulation of interaction between KLF2 and MLKL	[29
8	*Salvia miltiorrhiza Bunge*	Salvianolic acid B	Phenolic acid compound	$C_{36}H_{30}O_{16}$		ECs and pericytes; *ApoE*$^{-/-}$ mice	Regulation of inflammation	Inhibition of YAP/TAZ/JNK signaling	[30
9	*Kaempferia galanga L.*	Kaempferol	Flavonoid	$C_{15}H_{10}O_6$		HAECs; *ApoE*$^{-/-}$ mice	Regulation of inflammation	Regulation of PI3K/AKT/Nrf signaling	[31
10	*Maclura pomifera*	Morin hydrate	Flavonoid	$C_{15}H_{10}O_7$		*ApoE*$^{-/-}$ mice	Regulation of inflammation	Inhibition of PI3K/Akt1/NF-κB signaling	[32
11	*Cordyceps sinensis (BerK.) Sacc.*	Cordycepin	Nucleoside antibiotic	$C_{10}H_{13}N_5O_3$		HUVECs, THP-1 cells	Regulation of inflammation	Modulation of PI3K/Akt/eNO signaling	[33
12	*Panax ginseng C. A. Meyer*	Ginsenoside-Rb2	Triterpenic compound	$C_{53}H_{90}O_{22}$		Primary HUVECs	Regulation of inflammation	Increasing Smad3 protein expression, inhibition of IκBα degradation, and suppression of NF-κB activation	[34

Serial number	Chinese medicine	Active ingredient	Classification	Molecular formula	Chemical structure	Cellular/animal models	Role	Molecular mechanisms	Re
13	*Prunus amygdalus Batsch*	Amygdalin	Benzaldehyde derivative	$C_{20}H_{27}NO_{11}$		Macrophages; *ApoE*$^{-/-}$ mice	Regulation of inflammation	Modulation of MAPK, AP-1, and NF-κB p65 signaling	[35
14	*Scutellaria baicalensis Georgi*	Baicalin	Flavonoid	$C_{21}H_{18}O_{11}$		*ApoE*$^{-/-}$ mice	Regulation of inflammation	Inactivation of NF-κB and p38 MAPKs signaling	[36
15	*Salvia miltiorrhiza Bunge*	Dihydrotanshinone I	Rosmanol-type diterpenoid	$C_{18}H_{14}O_3$		*ApoE*$^{-/-}$ mice	Regulation of oxidative stress	Stabilization of vulnerable plaques by inhibition of RIP3-mediated macrophage necrosis	[37
16	*Astragalus membranaceus (Fisch.) Bge.*	Formononetin	Flavonoid	$C_{16}H_{12}O_4$		HUVECs	Regulation of oxidative stress	Activation of PPAR-γ signaling	[38
17	*Passiflora coerulea Linn.*	Orientin	Flavonoid	$C_{21}H_{20}O_{11}$		RAW 264.7 cells	Regulation of oxidative stress	Inhibition of ROS generation and increasing eNOS expression	[39
18	*Angelica sinensis (Oliv.) Diels*	Z-ligustilide	Volatile oil	$C_{12}H_{14}O_2$		HUVECs	Regulation of oxidative stress	Activation of several genes downstream of NRF2	[40

Serial number	Chinese medicine	Active ingredient	Classification	Molecular formula	Chemical structure	Cellular/animal models	Role	Molecular mechanisms	Re
19	*Salvia plebeia R. Br.*	Homoplantaginin	Flavonoid	$C_{22}H_{22}O_{11}$		HUVECs; *ApoE*$^{-/-}$ mice	Regulation of oxidative stress	Activation of Nrf2 signaling	[41
20	*Brassica alboglabra L. H. Bailey*	Sulforaphane	Isothiocyanate compound	$C_6H_{11}NOS_2$		HUVECs	Regulation of oxidative stress	Upregulation of Nrf2, inducing changes in the miR-34a/SIRT1 axis	[42
21	*Salvia miltiorrhiza Bunge*	Salvianic acid A	Phenolic aromatic acid	$C_9H_{10}O_5$		HUVECs; adult male Sprague-Dawley rats	Regulation of oxidative stress	Reduction in lipid deposition in the aorta and expression of pro-inflammatory mediators, including interleukin-1β	[43
22	*Eucommia ulmoides Oliver*	Aucubin	Terpene	$C_{15}H_{22}O_9$		SH-SY5Y cells	Regulation of oxidative stress	Regulation of NF-κB, Nrf2/HO-1, and MAPK signaling	[44
23	*Scutellaria baicalensis Georgi*	Baicalin	Flavonoid	$C_{21}H_{18}O_{11}$		H9c2 cells	Regulation of oxidative stress	Activation of Nrf2/HO-1-mediated HIF-1α/BNIP3 signaling	[45

Serial number	Chinese medicine	Active ingredient	Classification	Molecular formula	Chemical structure	Cellular/animal models	Role	Molecular mechanisms	Re
24	*Dioscorea nipponica Makino*	Dioscin	Steroid	$C_{45}H_{72}O_{16}$		$Ldlr^{-/-}$ mice	Regulation of oxidative stress	Activation of PGC-1α/ERα signaling	[46
25	*Rehmannia glutinosa (Gaert.) Libosch. ex Fisch. et Mey.*	Catalpol	Cyclic enol ether terpene Glucoside	$C_{15}H_{22}O_{10}$		Macrophages; $Ldlr^{-/-}$ mice	Regulation of oxidative stress	Activation of PGC-1α/ TERT signaling with subsequent regulation of ROS production, DNA damage, and telomere function	[47
26	*Camellia sinensis (L.) O. Ktze.*	Epigallocatechin Gallate	Tea Polyphenol	$C_{22}H_{18}O_{11}$		HUVECs	Regulation of oxidative stress	Regulation of SIRT1/AMPK signaling in endothelial cells	[48
27	*Pueraria lobate (Willd.) Ohwi*	Puerarin	Flavonoid	$C_{21}H_{20}O_9$		HUVECs	Regulation of oxidative stress	Increasing SIRT-1 expression to reduce ROS overproduction	[49

Serial number	Chinese medicine	Active ingredient	Classification	Molecular formula	Chemical structure	Cellular/animal models	Role	Molecular mechanisms	Re
28	*Gynostemma pentaphyllum (Thunb.) Makino*	Gypenoside	Saponin	$C_{54}H_{92}O_{23}$		Macrophages	Regulation of autophagy	Enhancing recovery of SIRT1/FOXO1-mediated autophagic flux	[50
29	*Clematis chinensis Osbeck*	Clematichinenoside AR	Triterpene saponin	$C_{82}H_{134}O43$		Macrophages	Regulation of autophagy	Activation of autophagy with subsequent reduction of foam cell formation and inflammation	[51
30	*Quercus dentata Thunb.*	Quercetin	Flavonol	$C_{15}H_{10}O_7$		RAW 264.7 cells	Regulation of autophagy	Regulation of MST1-mediated autophagy	[52
31	*Gardenia jasminoides Ellis*	Geniposide	Cyclic enol ether glycoside	$C_{17}H_{24}O_{10}$		*ApoE*$^{-/-}$ mice	Regulation of autophagy	Inhibition of TREM2/mTOR signaling	[53
32	*Coptis chinensis Franch.*	Berberine	Quaternary ammonium alkaloid	$C_{20}H_{18}NO_4$		*ApoE*$^{-/-}$ mice	Regulation of autophagy	Regulation of PI3K/AKT/mT signaling	[54
33	*Gardenia jasminoides Ellis; Panax notoginseng (Burk.) F. H. Chen*	Geniposide,notoginsenoside R1	Cyclic enol ether glycoside; Protopanax triol-type saponin	$C_{17}H_{24}O_{10}$ $C_{47}H_{80}O_{18}$		HUVECs; *ApoE*$^{-/-}$ mice	Regulation of apoptosis	Activation of AMPK/mTOR/ signaling and subsequent inhibition of Bax/Bcl2/caspa 3 signaling	[55

Serial number	Chinese medicine	Active ingredient	Classification	Molecular formula	Chemical structure	Cellular/animal models	Role	Molecular mechanisms	Re
34	*Paeonia suffruticosa Andr.*	Paeonol	Phenolic compound	$C_9H_{10}O_3$		VSMCs	Regulation of apoptosis	Activation of PI3K/Beclin-1 signaling and upregulation of autophagy	[56
35	*Panax ginseng C. A. Meyer*	Ginsenoside Rb1	Tetracyclic triterpene saponin	$C_{54}H_{92}O_{23}$		HUVECs	Regulation of cellular aging	Modulation of the SIRT1/Beclin-1/autophagy axis	[57
36	*Quercus dentata Thunb.*	Quercetin	Flavonol	$C_{15}H_{10}O_7$		*ApoE*$^{-/-}$ mice	Regulation of cellular aging	Regulation of nitrogen metabolism, ECM-receptor interactions, complement and coagulation cascades, as well as p53 and mTOR signaling	[58

Serial number	Chinese medicine	Active ingredient	Classification	Molecular formula	Chemical structure	Cellular/animal models	Role	Molecular mechanisms	Re
37	*Punica granatum Linn.*	Punicalagin	Polyphenol	$C_{48}H_{28}O_{30}$		ECs	Inhibition of vascular remodeling	Attenuation of vascular remodeling by inhibiting force-induced activation of Smad1/5	[59
38	*Salvia miltiorrhiza Bunge*	Tanshinone IIA	Lipid-soluble phenanthrenequinone	$C_{19}H_{18}O_3$		HCAECs	Regulating ferroptosis	Activation of the Nrf2 pathway	[60
39	*Aucklandia lappa Decne.*	Dehydrocostus Lactone	Sesquiterpene lactone	$C_{15}H_{18}O_2$		HAECs	Inhibition of cell adhesion	Inhibition of monocyte attachment to endothelial cells	[61

2.1 Inflammation

AS is a chronic inflammatory disease in which, upon endothelial damage and platelet activation in the arterial vasculature, monocytes adhere to the activated endothelium and differentiate into pro-inflammatory macrophages, promoting release of inflammatory factors and exacerbating AS [62].

Phorbol 12-myristate 13-acetate from croton was shown to reduce the rise in oxidized low-density lipoprotein (ox-LDL)-stimulated reactive oxygen species (ROS) and malondialdehyde (MDA) levels, modulate Notch1 and DLL4 signaling by inhibiting upregulation of nuclear transcription factor (NF)-κB p65 and the related receptor LOX-1. Dehydrocorydaline (DHC), an alkaloid from the traditional Chinese herb yanhuoshao, improved aortic compliance and increased plaque stability in $ApoE^{-/-}$ mice after intraperitoneal injection [63]. DHC reduced lipopolysaccharide (LPS)-induced inflammation in bone marrow-derived macrophages [24]. Ethyl gallate inhibited monocyte chemotactic protein 1 (MCP-1) and interleukin 6 (IL-6) secretion in activated macrophages and attenuated vascular lipid accumulation and inflammatory responses in vivo in zebrafish and $ApoE^{-/-}$ mice [25].

Honokiol downregulated pro-inflammatory marker expression, reduced ROS levels, and enhanced superoxide dismutase (SOD) activity in $ApoE^{-/-}$ mice [26]. Formononetin reduced foam cell formation and its accumulation in the arterial wall by decreasing SRA expression and reducing monocyte adhesion and modulating the interaction between KLF4 and SRA[27]. Shikonin (SKN) inhibited hyperhomocysteinemia (HHcy)-stimulated PKM2 activity, interferon-γ secretion, and T cell ability to promote pro-inflammatory macrophage polarization [28]. Calycosin inhibited foam cell formation, inflammation, and apoptosis by upregulating

KLF2-MLKL-mediated autophagy [29]. Salvianolic acid B, a phenolic acid from *Salvia miltiorrhiza* , inhibited NF-ϰB and TNF-α in ECs and pericytes and decreased the expression of inflammation-related factors (IL-6, IL-1β, TNF-α) and ox-LDL in $ApoE^{-/-}$ serum [30].

Finally, kaempferol, morin hydrate, and cordycepin all reduced inflammation through PI3K/Akt signaling to protect against AS [31-33]. Ginsenoside-Rb2 [34], amygdalin [35], and baicalin [36]were also shown to protect against AS by reducing inflammation through NF-ϰB signaling. These findings suggest that natural small-molecule drugs, as natural antibiotics, intervene in AS by inhibiting EC injury through anti-inflammation, regulation of macrophage polarization, and intervention in smooth muscle cell phenotypic transformation.

2.2 Oxidative stress

Oxidative stress also promotes AS. Natural small-molecule drugs have been shown to alleviate AS by modulating NRF2, peroxisome proliferator-activated receptor (PPAR)-γ, ROS, and endothelial nitric oxide synthase (eNOS) levels [64]. Elevated ROS generation is one of the main factors of cardiomyocyte and EC damage[65, 66]. In addition, oxidative stress can modulate AS by stimulating VSMC proliferation[17].

Dihydrotanshinone I (DHT), a diterpenoid derived from *Salvia miltiorrhiza* , significantly enhanced plaque stability in$ApoE^{-/-}$ mice *in vivo* by reducing oxidative stress, narrowing the necrotic core region, increasing collagen content, and decreasing RIP3 kinase expression; in cultured macrophages, DHT regulated RIP3 through Toll-like receptor 4 (TLR4) dimerization to attenuate necrotic apoptosis[37]. Formononetin (FMNT) is a flavonoid isolated from *Astragalus membranaceus* ; in primary human umbilical vein ECs (HUVECs), FMNT induced damage via ox-LDL. By measuring the expression of cyclooxygenase 2 (COX-2), eNOS, and PPAR-γ, it was shown that formononetin inhibits oxidative stress by stimulating PPAR-γ signaling[38]. RAW 264.7 cells were treated with orientin, a flavonoid isolated from *Passiflora edulis* , along with 80 μg/mL ox-LDL to mimic AS, wherein orientin was found to inhibit ox-LDL-induced lipid droplets. The receptor for ox-LDL, CD36, was significantly downregulated after targeted protein treatment. Alterations in oxidative stress were attenuated by orientin treatment that inhibited ROS generation and increased eNOS expression. In addition, orientin inhibited ox-LDL-induced cellular angiopoietin 2 (Ang-2) and NF-ϰB expression, suppressing oxidative stress and inflammation [39].

Finally, Z-ligustilide [40], homoplantaginin [41], sulforaphane [42], salvianic acid A [43], aucubin [44], and baicalin [45] protected against AS through Nrf2 signaling by inhibiting oxidative stress. Dioscin [46] and catalpol [47] inhibited oxidative stress through PGC-1α signaling. Epigallocatechin gallate [48] and puerarin [49] inhibited oxidative stress through SIRT1 signaling to slow atherosclerotic progression.

2.3 Autophagy

Normal levels of autophagy protect cells from adverse environmental stimuli, but excessive and insufficient autophagy often contributes to CVD development [21]. During AS progression, macrophage autophagy reduces cholesterol deposition in plaque macrophages, promotes cholesterol efflux[67], and inhibits both assembly and activation of NLRP3 inflammatory vesicles.

Gynostemma saponin (GP) is one of the primary bioactive components of the Chinese herb *Gynostemma pentaphyllum* . Incubation of cultured THP-1 cells with ox-LDL induced a significant decrease in LC3-II protein levels and increased the number of autophagosome puncta and p62 expression. Using co-immunoprecipitation assays, GP was found to upregulate Srit1 and FOXO1 expression and enhance their direct interaction, thereby promoting autophagy while inhibiting ox-LDL uptake and foam cell formation [50]. In RAW264.7 macrophages exposed to ox-LDL, clematichinenoside AR (AR), a triterpenoid saponin from Chinese herbal medicine, inhibited foam formation and cholesterol accumulation and promoted cholesterol efflux through upregulation of ABCA1/ABCG1; however, the autophagy inhibitor bafilomycin A1 attenuated these effects, suggesting that AR attenuates AS by activating autophagy [51]. Quercetin is a flavonol extracted from *Quercus serrata* . In ox-LDL-induced cultured RAW264.7 cells, quercetin treatment increased cell survival and LC3-II/I and beclin-1 expression and reduced MST1 expression, lipid accumulation, and senescence [52]. Geniposide [53] and berberine [54] regulates autophagy and alleviates AS through the mTOR signaling

pathway.

2.4 Apoptosis

Apoptosis is a major feature of AS pathophysiology. Apoptosis occurs through extrinsic pathways, involving the death receptor system, cytotoxic stress, and also through intrinsic pathways, involving intracellular injury, hypoxia, and survival factor deprivation; these endogenous stresses can activate endogenous apoptotic pathways [68, 69].

Natural small molecules have been shown to regulate apoptosis through both extrinsic and intrinsic pathways. Geniposide is a cyclic enol ether glycoside from the Chinese plant *Gardenia jasminoides* ; notoginsenoside R1 is a former ginseng triol-type compound extracted from the Chinese plant *Panax ginseng* . *In vivo* , their combination improved lipid levels and attenuated plaque formation; it also inhibited secretion of serum inflammatory factors and oxidative stress factors in $ApoE^{-/-}$ mice on a high-fat diet (HFD). Their combination also reduced expression of NLRP3-containing inflammatory vesicle-associated proteins and Bax/Bcl2/caspase-3 pathway-associated proteins. In cultured cells, their combination activated the AMPK/ mTOR pathway to inhibit H_2O_2-induced inflammation and apoptosis, protecting HUVECs from inflammation and apoptosis [55]. Paeonol is a phenolic compound isolated from peony bark. In cultured ox-LDL-injured VSMCs, it increased LC3II expression, decreased p62 and caspase-3 expression, increased the number of autophagosomes, and decreased that of apoptotic vesicles; paeonol also regulated VSMC autophagy and apoptosis. It inhibited apoptosis in VSMCs by activating PI3K / Beclin-1 signaling and upregulating autophagy [56].

2.5 Senescence

AS is strongly associated with age. Features of aging, such as lower VSMC proliferation, occur in atherosclerotic plaques, one of the first signs of premature VSMC senescence in AS [70]. Senescence of vascular ECs plays a key role in vascular senescence in CVDs [71]. Senescence affects AS through complex pathways, involving sirtuins (Sirts), Klotho, fibroblast growth factor 21 (FGF21), and p53 [72].

Ginsenoside Rb1 is a tetracyclic triterpene saponin from ginseng. In SD rats with hyperlipidemia induced using HFD and in cultured senescent HUVECs induced using ox-LDL, Ginsenoside Rb1 acts through increasing SIRT1 expression to decrease Beclin-1 acetylation and induce autophagy, thereby protecting endothelium and HUVECs from ox-LDL-induced senescence[57]. Quercetin attenuated AS through nitrogen metabolism, ECM–receptor interaction, and p53 and mTOR signaling by inhibiting lipid deposition and increased serum sIcam-1 and IL-6 levels in$ApoE^{-/-}$ mice; it was also found to improve cell morphology, reduce apoptosis, increase mitochondrial membrane potential in HAECs, and regulate EC senescence [58].

2.6 Vascular remodeling

Vascular remodeling refers to structural and functional changes in vessel walls caused by disease, injury, or aging [73]. It is the main determinant affecting vessel lumen areas after AS and balloon injury [74]. In AS, the middle and inner cells of vessels proliferate and the vessel walls thicken, but vascular remodeling is characterized by outward expansion of the vessel walls [75]. Vascular remodeling is generally considered a structural change brought about by cell proliferation, necrosis, and migration and extracellular matrix (ECM) synthesis/degradation [76]. During this change, growth factors, vasoactive substances, and hemodynamics play important roles [77]. Punicalagin, a natural small molecule, prevents vascular remodeling by inhibiting the specific activation of Smad1/5 in human ECs [59].

2.7 Iron death

Iron death is an iron-dependent form of non-apoptotic cell death; oxidative cell death is involved in AS, characterized by increased intracellular iron level and reduced antioxidant capacity leading to lethal accumulations of peroxidized lipids [78]. Lipid peroxidation, intraplaque hemorrhage, and iron death are characteristics of advanced human AS plaques [79].

Tanshinone IIA (TSA) is a lipid-soluble phenanthrene compound isolated from the root of *Salvia divinorum* . It significantly reduced ROS accumulation in HCAEC cells caused by iron death inducers. TSA also restored glutathione (GSH) and increased the expression of NRF2 and downstream genes. It is also shown to protect human coronary artery ECs from iron death by activating NRF2 signaling [60].

2.8 Anti-monocyte adhesion

Monocyte–macrophage adhesion to ECs plays an important role in AS and is promoted by ox-LDL [80]. Monocyte adhesion is closely related to tissue injury and repair; during arterial wall hypoxia, the intima recruits circulating monocytes via a specific integrin receptor (macrophage adhesion ligand 1, or Mac-1) that binds to endothelial adhesion molecules, allowing tight attachment of monocytes [81]. This interaction between cells in the vessel wall can accelerate the formation of early AS lesions.

Dehydrocostus lactone (DHL) is a sesquiterpene lactone naturally occurring in plants of the genus *Xerophyllum* (e.g., *Mucuna pruriens*). It inhibits ox-LDL-induced increases in VCAM-1 and E-selectin expression and reduces their downstream effects (nuclear cell-endothelial adhesion and pro-inflammatory cytokine release), which may be considered a preventive or therapeutic approach against ox-LDL-induced AS [61].

3. Role of natural small molecules in HF

HF refers to decreased myocardial contractile function and inability of the heart's pumping capacity to meet the metabolic needs of the body, resulting in insufficient blood perfusion to tissues and organs; it is often accompanied by stasis in the pulmonary or body circulation [82]. It is an epidemic disease with high mortality and morbidity [83] and is common in the end stages of CVDs.

The pathophysiological mechanisms underlying HF are complex. It is characterized by the failure of innate antioxidant defense mechanisms, including those of SOD, catalase (CAT), and glutathione peroxidase (GPx), leading to ROS inactivation [84]. Ventricular remodeling is the pathological basis for HF development; it involves progressive ventricular dilatation and dysfunction, leading to pressure and volume overload, causing myocardial hypertrophy and fibrosis, while cardiac output decreases, and sustained cardiac overload eventually leads to arrhythmias and sudden death [85-87]. HF converts hemodynamic stress into sterile cardiac inflammation; the resulting increased wall tension and mechanical stretch trigger cardiomyocytes and cardiac fibroblasts to release pro-inflammatory cytokines, including TNF-α, IL-6, IL-1β, and angiotensin II [88].

Systemic inflammation is a common pathobiological feature of both acute and chronic HF [89]. Inflammation and activation of the immune system significantly stimulate cardiac fibrosis and remodeling [90]. Fibrosis is the result of excessive deposition of ECM components, such as collagen and fibronectin, leading to fibrous connective tissue accumulation [91]. Initially, fibrosis is cardioprotective, but persistent fibrosis negatively affects cardiac function. Myofibroblast-mediated fibrosis is a hallmark of pathophysiological cardiac remodeling [92]; paracrine signals from fibroblasts induce cardiomyocyte hypertrophy, involving TGFβ, interleukin 33 (IL-33), fibroblast growth factor 2 (FGF2), and tumor necrosis factor α (TNFα) [93, 94], and hypertrophic stimuli activate cardiomyocytes, inducing apoptosis [95]. During physiological and pathological hypertrophy, the heart cannot pump blood sufficiently, and the cardiac machinery secretes vascular growth factors that promote angiogenesis to maintain myocardial mass and increase blood supply [96]. In addition, macrophages mediate cardiac electrical conduction and metabolic stability under homeostatic conditions and promote early postnatal cardiac recovery by stimulating cardiomyocyte proliferation and angiogenesis [97].

HF is closely associated with myocardial structural changes and activation of multiple molecular signaling pathways of inflammation, oxidative stress, and cardiomyocyte apoptosis, leading to cardiac insufficiency [98]. For HF treatment, the most commonly used clinical drugs are angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and β-blockers; however, their prolonged use can cause adverse effects such as electrolyte disturbances, fluid depletion, and hypotension [99]. Natural drugs in combination with Western medicine have been shown to improve quality of life in patients with HF [100]; drug action mechanisms are shown in Table 3.

Table 2. Mechanisms of action of natural small-molecule drugs against HF

Serial number	Chinese medicine	Active ingredient	Classification	Molecular formula	Chemical structure	Cellular/animal models	Role	Molecular mechanisms	Re
1	*Curcuma longa Linn.*	β-elemene	Sesquiterpenoids	$C_{15}H_{24}$		H9c2 cells; male ICR mice	Regulation of inflammation	Activation of PPARβ, inhibition of NF-κB nuclear translocation, and degradation of IκBα	[10
2	*Lonicera japonica Thunb.*	Chlorogenic acid	Styrene acrylic compounds	$C_{16}H_{18}O_9$		Human induced pluripotent stem cell-derived cardiomyocytes; male C57BL/6N mice	Regulation of inflammation	Inhibition of NF-κB and JNK signaling	[10
3	*Punica granatum Linn.*	Reynoutrin	Flavonoids	$C_{20}H_{18}O_{11}$		H9c2 cells; male Sprague-Dawley rats	Regulation of inflammation	Upregulation of S100 calcium-binding protein A1 expression and inhibition of MMP expression and transcriptional activity of NF-kB	[10

Serial number	**Chinese medicine**	**Active ingredient**	**Classification**	**Molecular formula**	**Chemical structure**	**Cellular/animal models**	**Role**	**Molecular mechanisms**	**Re**
4	*Ligusticum chuanxiong Hort.*	Liguzinediol	Alkaloids	$C_8H_{12}N_2O_2$		Male Sprague-Dawley rats	Regulation of inflammation	Downregulation of TGF-β1/Smad signaling	[10
5	*Brassica oleracea Linnaeus var. acephala Linn.f. tricolor Hort.*	Lutein	Carotenoids	$C_{40}H_{56}O_2$		Neonatal rat cardiomyocytes and CFs	Regulation of inflammation	Inhibition of AP-1/IL-11 signaling	[10
6	*Lycium chinense Miller*	Betaine	Quaternary amines	$C_5H_{11}NO_2$		Wistar rats	Regulation of inflammation	Inhibition of miR-423 and miR-27 expression, restoration of matrix proteins, cardiac biomarker genes to reduce inflammation	[10

Serial number	Chinese medicine	Active ingredient	Classification	Molecular formula	Chemical structure	Cellular/animal models	Role	Molecular mechanisms	Re
7	*Brassica oleracea L. Var. Acpitata L.*	Sulforaphane	Isothiocyanates	$C_6H_{11}NOS_2$		New Zealand white rabbit	Regulation of oxidative stress	Reducing expression of oxidative stress markers and inflammatory markers; increasing superoxide dismutase (SOD) and malondialdehyde (MDA) activity	[10
8	*Lithospermum erythrorhizon Sieb. et Zucc.*	Shikonin	Naphthoquinones	$C_{16}H_{16}O_5$		Neonatal rat cardiomyocytes and CFs; male C57BL/6 mice	Regulation of oxidative stress	Inhibition of PKM2, TGF-β/Smad2/3, and Jak2/Stat3 signaling	[10
9	*Toxicodendron vernicifluum (Stokes) F.A. Barkley*	Butein	Polyphenols	$C_{15}H_{12}O_5$		Male Sprague-Dawley rats	Regulation of oxidative stress	Modulation of ERK/Nrf2 signaling	[10
10	*Alpinia katsumadai Hayata*	Cardamonin	Chalcones	$C_{16}H_{14}O_4$		Isolated mouse cardiomyocytes; C57 mice	Regulation of oxidative stress	Modulation of Nrf2 and NF-κB signaling	[11

Serial number	Chinese medicine	Active ingredient	Classification	Molecular formula	Chemical structure	Cellular/animal models	Role	Molecular mechanisms	Re
11	*Glycine max (Linn.) Merr.*	Soybean isoflavones	Isoflavones	$C_{15}H_{10}O_2$		Patients with ischemic stroke	Regulation of oxidative stress	Upregulation of Nrf2 expression	[11
12	*Panax ginseng C. A. Meyer*	Ginsenoside Rb3	Triterpenic saponins	$C_{53}H_{90}O_{22}$		H9C2 cells; male C57BL/6 mice	Regulation of apoptosis	Activation of PPARα signaling	[11
13	*Spinacia oleracea Linn.*	Lutein	Carotenoids	$C_{40}H_{56}O2$		Male Sprague-Dawley rats	Regulation of apoptosis	Regulation of Nrf2/HO-1 signaling	[11
14	*Ligusticum chuanxiong Hort.*	Liguzinediol	Alkaloids	$C_8H_{12}N_2O_2$		Male Sprague-Dawley rats	Regulation of apoptosis	Regulation of Bcl-2, Bax, caspase-3, and NF-ϰB expression	[11
15	*Cistanche deserticola Ma*	Echinacoside	Phenethyl alcohol	$C_{35}H_{46}O_{20}$		AC-16 cells; male Sprague-Dawley rats	Regulation of VR	Upregulation of SIRT1/FOXO3/ signaling	[11
16	*Veratrum nigrum Linn.*	Resveratrol	Polyphenols	$C_{14}H_{12}O_3$		Neonatal rat CFs; C57BL/6 mice	Regulation of VR	Activation of Sirt1, with subsequent reduction in acetylation and transcriptional activity of Smad3	[11

Serial number	Chinese medicine	Active ingredient	Classification	Molecular formula	Chemical structure	Cellular/animal models	Role	Molecular mechanisms	Re
17	*Tripterygium wilfordii Hook. f.*	Celastrol	Benzoquinone methyl triterpenes	$C_{29}H_{38}O_4$		Rat primary cardiomyocytes and H9C2 cells	Regulation of VR	Modulation of STAT3 activity	[11
18	*Quercus dentata Thunb.*	Quercetin	Flavonoids	$C_{15}H_{10}O_7$		HL-1 cells; male C57BL/6J mice	Regulation of myocardial fibrosis	Enhancement of IDH2-associated desuccinylation via SIRT5	[11
19	*Astragalus membranaceus (Fisch.) Bge.*	Astragaloside IV	Polysaccharides	$C_{41}H_{68}O_{14}$		Neonatal rat CFs and NIH-3T3 cells; male Sprague-Dawley rats	Regulation of myocardial fibrosis	Decreasing TRPM7 channel inhibitory currents and down-regulation of TRPM7 protein expression	[11
20	*Centella asiatica (Linn.) Urban*	Asiatic Acid	Triterpenic compounds	$C_{30}H_{48}O_5$		Male C57BL/6 mice	Regulation of myocardial fibrosis	Inhibition of TGF-β1/Smad and IL-6 signaling	[12
21	*Aconitum carmichaeli Debx.*	Higenamine	Benzylisoquinoline alkaloids	$C_{16}H_{17}NO_3$		Adult mouse cardiac myocytes and CFs; male C57BL/6 mice	Regulation of myocardial fibrosis	Inhibition of TGF-β1/Smad signaling	[12

Serial number	Chinese medicine	Active ingredient	Classification	Molecular formula	Chemical structure	Cellular/animal models	Role	Molecular mechanisms	Re
22	*Astragalus membranaceus (Fisch.) Bge.*	Astragaloside IV	Polysaccharides	$C_{41}H_{68}O_{14}$		Primary HUVECs; male Sprague-Dawley rats	Regulation of angiogenesis	Induction of JAK and STAT3 phosphorylation and STAT3-regulated VEGF promoter activity	[12
23	*Salvia miltiorrhiza Bunge*	Tanshinone IIA	Lipid-soluble phenanthrenequinones	$C_{19}H_{18}O_3$		C57BL/6 mice; HUVECs	Regulation of angiogenesis	Regulation of miR-499-5p	[12

3.1 Inflammation

Inflammatory responses are a major aspect of HF, involving tumor necrosis factor α (TNFα), IL-1β and IL-18. Levels of the downstream factor NLRP3 inflammatory vesicles are elevated in HF [124]. CXC motif ligand 16 (CXCL16) was identified as a novel diagnostic marker for inflammatory cardiomyopathy and HF [125]. C-reactive protein (CRP) level was found to be elevated in 57% of patients who participated in the RELAX (phosphodiesterase 5 inhibition to improve clinical status and exercise capacity in diastolic HF with preserved ejection fraction) trial [126]. This suggests that systemic inflammation is a common pathobiological feature of both acute and chronic HF [89, 127] .

Liguzinediol from Chuanxiong reduces cardiomyocyte necrosis as well as collagen deposition and myocardial fibrosis. It inhibits renin-angiotensin-aldosterone system (RAAS) activation, suppresses pro-inflammatory factors, and also suppresses HF in SD rats by downregulating TGF-β1/Smad signaling [104]. Luteolin is a carotenoid; in cardiac fibroblasts (CFs), it prevented Ang II-induced phenotypic transformation and cardiomyocyte hypertrophy and inhibited inflammation and apoptosis; in vivo, it attenuated Ang II-induced cardiac remodeling in wild type mice. Its mechanism of action is through AP-1/IL-11 signaling inhibition [105]. Betalain was found to abrogate inflammatory signaling by restoring the expression of matrix proteins and cardiac biomarker genes and attenuating that of miR-423 and miR-27 to protect Wistar rats from isoproterenol (ISO)-induced HF [106]. In addition, β-elemene [101], chlorogenic acid [102], and reynoutrin [103] prevented HF progression by blocking lipid-induced inflammatory pathways through NF-ϰB signaling.

3.2 Oxidative stress

Oxidative stress is defined as an imbalance between ROS production and endogenous antioxidant defense mechanisms. During HF development, excessive oxidative stress not only causes cellular dysfunction, myocardial remodeling, protein and lipid peroxidation, DNA damage, and cardiomyocyte apoptosis, but also induces arrhythmias [84].

Sulforaphane corrected elevated malondialdehyde (MDA) level, left ventricular shortening fraction (LVFS), and left ventricular ejection fraction (LVEF) and reduced SOD activity in New Zealand rabbits due to HF and improved cardiac function by inhibiting oxidative stress and remodeling [107]. *In vivo* , pyruvate kinase

isozyme type M2 (PKM2) inhibition by shikonin attenuated Ang-II-induced cardiomyocyte hypertrophy and fibrosis by inhibiting the cardiac remodeling pathway and oxidative stress by inhibiting TGF-β/Smad2/3 and Jak2/Stat3 signaling [108]. Butein inhibited oxidative stress injury-induced ERK/Nrf2 signaling [109]. Cardamonin [110] and soybean isoflavones [111] inhibited oxidative stress and prevented HF through Nrf2 signaling.

3.3 Apoptosis

Cardiomyocyte apoptosis involves the death receptor system (e.g., tumor necrosis factor receptor-1, Apo2, and Apo3) and cytotoxic stress (gamma and UV radiation, cytotoxic drugs, altered mitochondrial permeability, CytoC release, and apoptotic vesicle formation). Among these factors, apoptotic vesicles activate caspases, and the Bcl2 protein family (Bcl2, BclXL) prevents apoptosis [69].

Ginsenoside Rb3 (G-Rb3) is a ginseng-derived triterpenoid saponin. It protects mitochondrial membrane integrity and exerts antiapoptotic effects by increasing the expression of peroxisome proliferator-activated receptor α (PPARα) [112]. Lutein is a carotenoid isolated from spinach. It reduces infarct size and lipid peroxidation product (MDA), lactate dehydrogenase (LDH), and caspase-3 and -9 levels , it significant upregulation of HO-1 and Nrf2 expression protected rats from HF [113]. Liguzinediol is an alkaloid from Chuanxiong. In male SD rats with HF induced by adriamycin injection, it significantly decreased Bax levels in cardiomyocytes and increased Bcl-2 levels, decreased caspase-3 and NF-ϰB expression, and attenuated cardiomyocyte injury [114].

3.4 Cardiac remodeling

Ventricular remodeling refers to changes in ventricular structure, accompanied by increased volume and altered ventricular configuration [128]. Pathological myocyte hypertrophy, myocyte apoptosis, myofibroblast proliferation, and interstitial fibrosis all drive ventricular remodeling [129].

Interventions for ventricular remodeling are part of HF treatment. The natural small-molecule echinacoside is a phenylethanol-like substance isolated from *Cistanche cistanche* . It inhibits mitochondrial ROS, lipid peroxidation, and apoptosis by upregulating SIRT1/FOXO3a/MnSOD signaling and reduces mitochondrial oxidative damage[115]. Resveratrol is a polyphenol derived from quinoa. It protects against adverse cardiac remodeling induced by HF by activating Sirt1 to reduce Smad3 acetylation and transcriptional activity [116]. Celastrol is a triterpenoid compound derived from ragweed. In mouse and rat primary cardiomyocytes and H9C2 cells, it bound to STAT-3 and inhibited its phosphorylation and nuclear translocation and suppressed angiotensin II-induced HF [117, 118].

3.5 Myocardial fibrosis

Cardiac fibrosis is an excessive accumulation of fibrous connective tissue common in HF [91]. Its effects include increased ventricular wall stiffness, reduced cardiomyocyte ratio leading to impaired contraction, and impaired oxygen diffusion leading to ischemia and hypoxia. These effects involve the RAAS, endothelin (ET), nitric oxide (NO), transforming growth factor-β1 (TGF-β1), connective tissue growth factor (CTGF), and intracellular Ca^{2+} [130].

Quercetin is a flavonoid present in many plants. In a TAC mouse model of HF, it inhibited myocardial fibrosis by increasing mitochondrial energy metabolism and regulating mitochondrial fusion/fission. In addition, it inhibited SIRT5 expression and increases IDH2 succinylation, while increasing IDH2 desuccinylation by increasing SIRT5 expression and ameliorating myocardial fibrosis, thereby attenuating HF [118]. Astragaloside IV is a polysaccharide from *Astragalus lycopersicus*with antioxidant, antiapoptotic, and antiviral activities. In hypoxia, it stimulated cardiac fibroblast proliferation and differentiation, upregulated TRPM7 expression, and attenuated isoprenaline (ISO)-induced myocardial fibrosis in rats [119]. Asiatic acid [120] and higenamine [121] attenuated fibrosis by blocking TGF-β1/Smad signaling.

3.6 Angiogenesis

Myocardial hypertrophy is an adaptive response to the increased physiological and pathological loads created by HF. In response to overload, hypertrophy increases oxygen demand, and the myocardium secretes angiogenic growth factors that stimulate coordinated vascular growth [96]. Myocardial angiogenesis is regulated by secreted vascular growth factors, including VEGF, angiopoietins 1 and 2 [131], fibroblast growth factor [132], TGF [133], and platelet-derived growth factor [134].

Natural small molecules can alleviate HF by modulating angiogenesis. Astragaloside reduced infarct size, promoted angiogenesis, and increased vascular density by inducing CD31 and VEGF mRNA expression in ischemic hearts in HF rats. ASI induced JAK and STAT3 phosphorylation as well as the activity of the STAT3-regulated VEGF promoter, attenuating HF [122].

Tanshinone IIA, a lipid-soluble phenanthrene compound isolated from the Chinese herb *Salvia miltiorrhiza* , has been tested in a mouse myocardial infarction model. It administration was found to activate angiogenesis to improve cardiac function. Dual luciferase reporter analysis revealed that PTEN contains a direct binding site for miR-499-5p; thus, tanshinone IIA promotes angiogenesis by regulating miR-499-5p/PTEN signaling [123].

4. Role of natural small molecules on Myocardial ischemia-reperfusion injury (MIRI)

Revascularization is the first treatment option for ischemic cardiomyopathy, but it causes MIRI, a primary mechanism leading to myocardial cell death and permanent structural damage [135]. MIRI is defined as restoration of blood reperfusion to the ischemic myocardium that aggravates structural damage, causing cell death and expansion of myocardial infarction and further damage to cardiac function, worsening the prognosis of patients with myocardial infarction [136].

Several physiological mechanisms promote ischemia and lead to hypoxia and hypoperfusion, including AS, acute myocardial infarction, and HF. Inflammatory infiltration, oxidative stress, ERS, apoptosis, and autophagy are present throughout MIRI. Blocked arterial blood flow leads to hypoxia, when antioxidant concentrations are low and ROS production is increased [136]. In addition, reperfusion generates toxic ROS upon reintroducing oxygen to ischemic tissues. ROS cause oxidative stress and promote endothelial dysfunction, DNA damage, and local inflammation. Ischemia and reperfusion lead to sterile inflammation, associated with host signaling pathways mediating responses to microorganisms, including NF-ϰB, mitogen-activated protein kinase (MAPK), and type I interferon pathways, all of which induce pro-inflammatory cytokines and chemokines [137]. Early in reperfusion, innate immune cells promote inflammatory cell infiltration [138]. MIRI activates multiple cell death programs, including necrosis, apoptosis, and autophagy-related cell death [139]. MIRI causes multiple types of cell damage, leading to nuclear fragmentation, plasma membrane blistering, cell contraction, and loss of mitochondrial membrane potential and integrity, culminating in apoptotic death. With MIRI, cytoplasmic vacuolization, organelle loss, and vesicle and membrane thread accumulation lead to autophagy-associated cell death [138]. Reduced blood flow due to arterial occlusion or hypotension leads to tissue hypoxia, which then rapidly induces protein misfolding and ERS [140]. In contrast, nutritional deficiency, hypoxia, point mutations leading to secretory protein aggregation, and loss of calcium homeostasis have detrimental effects on ERS[141].

Although multivitamin (vitamin E, vitamin C, carotene) treatment of post-coronary patients results in reduction in troponin I levels, it does not reduce the risk of major focal events over a 5-year period [142]. Current clinical approaches to protect against IR injury are exogenous, such as increasing myocardial oxygen and energy supply, reducing cardiac burden, and decreasing energy expenditure [138], but all have shortcomings and side effects. Natural small molecules are effective against IR injury, involving reduction in microvascular perfusion defects, platelet activation, sustained cardiomyocyte death, restoration of blood supply to ischemic myocardium, inhibition of inflammatory cell infiltration, resulting in myocyte necrosis and apoptosis by the mechanisms shown in Table 4.

Table 3. Mechanisms of action of natural small molecules in preventing or treating MIRI

Serial number	Chinese medicine	Active ingredient	Classification	Molecular formula	Chemical structure	Cellular/animal models	Role	Molecular mechanisms	Re
1	*Panax notoginseng (Burk.) F. H. Cheng*	Panax notoginseng saponins	Saponins	$C_{47}H_{80}O_{17}$		Male Sprague-Dawley rats	Regulation of inflammation	Modulation of ATP-sensitive potassium channel activity	[14
2	*Salvia miltiorrhiza Bunge*	Salvianolic acid B	Phenolic acids	$C_{36}H_{30}O_{16}$		Male Sprague-Dawley rats	Regulation of inflammation	Increasing PI3K/Akt expression and decreasing HMGB1 expression	[14
3	*Lycopersicon esculentum Miller*	Lycopene	Carotenoids	$C_{40}H_{56}$		HL-1 cells; male C57BL/6 mice	Regulation of inflammation	Inhibition of ROS production and JNK phosphorylation	[14
4	*Allium sativum L. var. Viviparum Regel*	Allicin	Organosulfur compounds	$C_6H_{10}OS_2$		Sprague-Dawley rats	Regulation of inflammation	Inhibition of p38 signaling	[14
5	*Rosmarinus officinalis Linn.*	Rosmarinic acid	Phenolic acids	$C_{18}H_{16}O_8$		Male C57BL/6 mice	Regulation of inflammation	Inhibition of NF-κB inflammatory signaling and ROS production	[14
6	*Spiraea japonica Linn. f.*	Astilbin	Dihydroflavonol glycosides	$C_{21}H_{22}O_{11}$		H9C2 cells; adult male Sprague-Dawley rats	Regulation of inflammation	Modulation of HMGB1-dependent NF-κB signaling	[14 149

Serial number	Chinese medicine	Active ingredient	Classification	Molecular formula	Chemical structure	Cellular/animal models	Role	Molecular mechanisms	Re
7	*Sophora flavescens Alt.*	Sophocarpine	Alkaloids	$C_{15}H_{22}N_2O$		Sprague-Dawley rats	Regulation of inflammation	Downregulation of JNK and p38 expression; inactivation of NF-κB	[15 15
8	*Glycine max (Linn.) Merr.*	Genistin	Isoflavone glycosides	$C_{21}H_{20}O_{10}$		Male Sprague-Dawley rats	Regulation of inflammation	Inhibition of P2X7/NF-κB signaling	[15
9	*Pueraria lobate (Willd.) Ohwi*	Puerarin	Flavonoids	$C_{21}H_{20}O_9$		H9c 2 cells; male C57BL/6 mice	Regulation of oxidative stress	Increasing protein SUMOization through an ER/ERK/SUM 2-dependent mechanism	[15
10	*Ampelopsis grossedentata (Hand.-Mazz.) W. T. Wang*	Dihydromyricetin	Flavonoids	$C_{15}H_{12}O_8$		Neonatal rat ventricular cardiomyocytes; male wild type and *Sirt3*$^{-/-}$ mice	Regulation of oxidative stress	Increasing Sirt3 expression	[15

Serial number	Chinese medicine	Active ingredient	Classification	Molecular formula	Chemical structure	Cellular/animal models	Role	Molecular mechanisms	Re
11	*Toxicodendron succedaneum (L.) O.Kuntze*	Fisetin	Flavonoids	$C_{15}H_{10}O_6$		Male Wistar rats	Regulation of oxidative stress	Inhibition of mitochondrial oxidative stress, mitochondrial dysfunction, and GSK3β activity	[15
12	*Anemarrhena asphodeloides Bunge*	Mangiferin	Carbofuranoside of tetrahydroxypyrone	$C_{19}H_{18}O_{11}$		H9C2 cells	Regulation of oxidative stress	Increasing glycolytic, citric acid cycle, and fatty acid degradation pathway activity	[15
13	*Panax ginseng C. A. Meyer*	Ginsenoside Rg3	Solid alcohols	$C_{42}H_{72}O_{13}$		H9C2 cells; male Sprague-Dawley rats	Regulation of oxidative stress	Modulation of FoxO3a activity via ROS signaling	[15
14	*Paris polyphylla*	Polyphyllin I	Spirosterolic saponins	$C_{44}H_{70}O_{16}$		Male Sprague-Dawley rats	Regulation of oxidative stress	Alteration of SOD, GSH, ROS, and MDA levels	[15

Serial number	Chinese medicine	Active ingredient	Classification	Molecular formula	Chemical structure	Cellular/animal models	Role	Molecular mechanisms	Re
15	*Cinnamomum cassia Presl*	2'-Methoxycinnamaldehyde	Aldehyde fragrance	$C_{10}H_{10}O_2$		Adult male Sprague-Dawley rats; HUVECs	Regulation of oxidative stress	Reducing HO-1 activity	[15
16	*Salvia miltiorrhiza Bunge: Carthamus tinctorius Linn.*	Alpha-lactic acid; hydroxysafflor yellow A	Phenolic aromatic acids; Flavonoids	$C_9H_{10}O_5$ $C_{27}H_{32}O_{16}$		H9C2 cells; male Sprague-Dawley rats	Regulation of oxidative stress	Modulation of Akt/Nrf2/HO-1 signaling	[16
17	*Astragalus membranaceus (Fisch.) Bge.*	Astragaloside IV	Polysaccharides	$C_{41}H_{68}O_{14}$		Male Sprague-Dawley rats	Regulation of oxidative stress	Regulation of succinate and lysophospholipid metabolism and scavenging of ROS via Nrf2 signaling	[16
18	*Buddleja officinalis Maxim.*	Linarin	Flavonoids; linolenic acid	$C_{28}H_{32}O_{14}$		H9C2 cells	Regulation of oxidative stress	Activation of Nrf-2 signaling	[16

Serial number	Chinese medicine	Active ingredient	Classification	Molecular formula	Chemical structure	Cellular/animal models	Role	Molecular mechanisms	Re
19	*Paeonia suffruticosa Andr.*	Paeonol	Phenolic aromatic acids	$C_9H_{10}O_3$ $C_5H_5NaO_5$		Male Sprague-Dawley rats	Regulation of apoptosis	Inhibition of apoptosis via upregulation of Bcl-2 protein expression and downregulation of caspase-8/caspase-9/caspase-3 and PARP protein expression)	[16
20	*Salvia miltiorrhiza Bunge*	Tanshinone I	Lipid-soluble phenanthrene	$C_{18}H_{12}O_3$	quinones	H9C2 cells; Sprague-Dawley rats	Regulation of apoptosis	Inhibition of RIP1/RIP3/ML signaling and activation of Akt/Nrf2 signaling	[16
21	*Arctium lappa Linn.*	Arctiin	Lignan-like compounds	$C_{27}H_{34}O_{11}$		H9c2 cells; male Sprague-Dawley rats	Regulation of apoptosis	Scavenging ROS and restoring mitochondrial function; targeting RIPK1 and/or MLKL	[16
22	*Curcuma longa Linn.*	Tetrahydrocurcumin	Dominated compounds	$C_{21}H_{24}O_6$		H9c2 cells; Sprague-Dawley rats	Regulation of apoptosis	Activation of PI3K/AKT/mT signaling	[16

Serial number	Chinese medicine	Active ingredient	Classification	Molecular formula	Chemical structure	Cellular/animal models	Role	Molecular mechanisms	Re
23	*Aconitum carmichaeli Debx.*	Higenamine	Benzylisoquinoline alkaloids	$C_{16}H_{17}NO_3$		Neonatal rat ventricular myocytes (NRVM); adult mouse ventricular myocytes; male C57BL/6 mice	Regulation of apoptosis	Activation of β2-AR/PI3K/Akt signaling	[16
24	*Panax ginseng C. A. Meyer*	Ginsenoside Rb1	Tetracyclic triterpenic saponins	$C_{54}H_{92}O_{23}$		Male Sprague-Dawley rats	Regulation of apoptosis	Modulation of mTOR signaling	[16
25	*Carthamus tinctorius Linn.*	Hydroxysafflor Yellow A	Flavonoids	$C_{27}H_{32}O_{16}$		NPCM cells; hiPSC-CMs	Regulation of apoptosis	Inhibition of calcium overload and apoptosis in cardiomyocytes, targeting L-type calcium channels	[16
26	*Scutellaria baicalensis Georgi*	Baicalein	Flavonoids	$C_{15}H_{10}O_5$		H9C2 cells; male C57BL/6 mice;	Regulation of apoptosis	KLF4-MARCH5-Drp1 signaling	[17

Serial number	Chinese medicine	Active ingredient	Classification	Molecular formula	Chemical structure	Cellular/animal models	Role	Molecular mechanisms	Re
27	*Veratrum nigrum Linn.*	Resveratrol	Polyphenols	$C_{14}H_{12}O_3$		Neonatal rat ventricular cardiomyocytes; C57BL/6 mice	Regulation of apoptosis	Antiapoptotic activity through inhibition of STIM1-induced intracellular Ca^{2+} accumulation	[17
28	*Centella asiatica (Linn.) Urban*	Asiatic acid	Triterpenic compounds	$C_{30}H_{48}O_5$		AC16 human cardiomyocyte cells	Regulation of apoptosis	Modulation of miR-1290/HIF-3A/HIF-1α signaling	[17
29	*Glycyrrhiza uralensis Fisch.*	Glycyrrhizic acid	Triterpenic saponins	$C_{42}H_{62}O_{16}$		H9C2 cells;male Sprague-Dawley rats	Regulation of ERS	Reducing protein expression levels of CHOP, GRP78, and p-PERK	[17
30	*Clinopodium chinense (Benth.) O. Ktze.*	Tournefolic acid B	Phenolic acids	$C_{17}H_{12}O_6$		H9C2 cells; adult male Sprague-Dawley rats	Regulation of ERS	Modulation of PI3K/Akt signaling	[17
31	*Citrus reticulata Blanco*	Hesperidin	Flavonoids	$C_{28}H_{34}O_{15}$		Male Sprague-Dawley rats	Regulation of autophagy	Activation of PI3K/Akt/mTO signaling	[17

Serial number	Chinese medicine	Active ingredient	Classification	Molecular formula	Chemical structure	Cellular/animal models	Role	Molecular mechanisms	Re
32	*Magnolia*	Honokiol	Bisphenolic compounds	$C_{18}H_{18}O_2$		C57BL/6 mice	Regulation of autophagy	Enhancing autophagic flux (associated with the Akt signaling pathway) and reducing intracellular ROS production	[17
33	*Centella asiatica (Linn.) Urban*	Asiatic acid	Triterpenic compounds	$C_{30}H_{48}O_5$		H9C2 cells; male C57BL/6 mice	Regulation of autophagy	Modulation of p38 mitogen-activated protein kinase/Bcl-2/Beclin-1 signaling	[17

4.1 Inflammation

After MIRI, the expression of several cytokines increases in the ischemic zone, including the inflammatory mediators IL-6, TNF-α, and TLR4. These cytokines, in turn, can exert effects through multiple signaling pathways such as those involving NF-ϰB and Toll-like receptors (TLRs), which ultimately form the basis of transition from MIRI to inflammatory injury [138].

Pretreatment with Panax notoginseng saponins (PNS) from Chinese*Panax ginseng* restored cardiac function, reduced infarct size, inhibited NLRP3 inflammasome formation, and inhibited the inflammatory mediators IL-6, MPO, TNF-α, and MCP-1 through KATP [143]. PI3K/Akt signaling is important for preventing MIRI. Salvianolic acid B reduced the expression of myocardial injury markers (L-LDH, CK-MB, TNF-α, IL-18) and the inflammatory response by activating PI3K/Akt expression and inhibiting HMGB1 [144]. Lycopene is a carotenoid isolated from tomato. It attenuated inflammation in a murine MIRI model established by ligating the descending branch of the left anterior artery. In culture, hypoxia/reoxygenation (H/R) was induced using HL-1 cells. As little as 1 μM lycopene inhibited MI, ROS production, JNK phosphorylation, and inflammatory in murine heart tissue to prevent MIRI [145]. Allicin is an organosulfur compound isolated from garlic. It significantly reduced cardiac troponin I, serum CK- MB, IL-6, TNF-α, and IL- 8 levels and reduced myocardial pathological injury, MDA expression, and p-p38 expression in myocardial tissue in SD

rats, protecting them from MIRI [146]. In addition, rosmarinic acid [147], astilbin [148], sophocarpine [150], and genistin [152] inhibited inflammation and attenuated MIRI through the NF-ϰB inflammatory signaling pathway.

4.2 Oxidative stress

Excessive ROS production is considered the primary cause of MIRI [136]. SOD, CAT, paraoxonase (PON), glutathione peroxidase (GPx), and heme oxygenase (HO-1), which are endogenous antioxidant enzymes, protect cells from ROS-induced damage [178]. Nrf2 regulates HO-1 to play an antioxidant role in ROS detoxification.

Natural small molecules have been shown to modulate oxidative stress to attenuate MIRI. Puerarin is a flavonoid from *Pueraria lobata* . In vitro and in vivo studies have shown that SUMO 2 overexpression promoted nuclear γ-actin deposition, and SUMO- 2 silencing decreased nuclear γ-actin and SUMOylation levels, exacerbating DNA damage. Puerarin promotes the upregulation of protein SUMOylation via ER/ERK/SUMO 2 led to oxidative stress inhibition and MIRI attenuation in both mice and H9c2 cells [153]. Dihydromyricetin is a flavonoid isolated from *Garcinia cambogia* . It improved mitochondrial function, reduced oxidative stress, and protected *Sirt3*$^{-/-}$ mice and primary cardiomyocytes from MIRI injury by upregulating Sirt3 [154]. Fisetin, a flavonoid from the *Lacertus* wildflower, protected against MIRI by inhibiting mitochondrial oxidative stress, mitochondrial dysfunction, and glycogen synthase kinase 3β (GSK3β) activity [155]. Mangiferin from *C. chinensis* enhanced antioxidant capacity and increased the activity of glycolytic, citric acid cycle, and fatty acid degradation pathways [156]. Finally, ginsenoside Rg3 [157] and polyphyllin I [158] both regulated oxidative stress by inhibiting ROS accumulation to inhibit MIRI. 2'-Methoxycinnamaldehyde [159], alpha-lactic acid, hydroxysafflor yellow A [160], astragaloside IV [161], and linarin [162] exerted antioxidant effects through the Nrf2 and HO-1 signaling pathways.

4.3 Apoptosis

MIRI is closely related to cardiomyocyte apoptosis. In MIRI, cardiomyocyte apoptosis is a gene-regulated process and is affected by time. Many factors cause apoptosis, such as cysteine aspartate-specific protease, the Bcl-2 gene family (Bcl-2, Bcl-x, Bcl-XL), Fas/FasL genes, and c-myc[69].

Paeonol, isolated from peony, attenuated MIRI cardiac impairment by inhibiting apoptosis (upregulating Bcl-2 expression and significantly downregulating caspase-8/9/3 and PARP expression in I/R-injured myocardium) [163]. Tanshinone I exerted cardioprotective effects by inhibiting RIP1/RIP3/MLKL and activating Akt/Nrf2 signaling to inhibit necroptosis [164]. Arctiin is a lignan-like compound isolated from burdock. In rat MIRI, it reduced myocardial infarct size and creatine kinase release, while decreasing the expression of necroptosis-related proteins (RIPK1/p-RIPK1, RIPK3/p-RIPK3, and MLKL/p-MLKL) [165]. Tetrahydrocurcumin [166], higenamine [167], and ginsenoside Rb1 [168] all attenuates apoptosis and MIRI through PI3K/AKT/mTOR signaling. Hydroxysafflor yellow A inhibited calcium overload and apoptosis in cardiomyocytes by targeting the L-type calcium channel (LTCC) [169]. Baicalein inhibited apoptosis through KLF4-MARCH5-Drp1 signaling to inhibit cardiomyocyte-induced mitochondrial apoptosis [170]. Resveratrol inhibited STIM1-induced intracellular Ca2+ accumulation and showed antiapoptotic activity [171]. Asiatic acid regulated the miR-1290/HIF3A/HIF-1α axis to protect cardiomyocytes from hypoxia-induced apoptosis [172].

4.4 ERS

ERS is caused by unfolded and misfolded protein accumulation and disturbance of Ca2+ balance in the ER lumen, one of the mechanisms of reperfusion injury, including uncontrolled intracellular calcium flow and increased release of calcium from sarcoplasmic reticulum stores [179, 180]. Moderate ERS is a protective cellular mechanism that reduces injury by promoting ER processing of unfolded and misfolded proteins; persistent or severe ERS causes apoptosis [140].

Glycyrrhizic acid (GA) is a triterpene saponin extracted from *Glycyrrhiza glabra* . It significantly reduced apoptosis in H9c2 cells, while attenuating left ventricular dysfunction, fibrosis, and apoptosis in MIRI rats,

downregulating CK, CK-MB, LDH, AST, TNF-α, IL-6 and MDA expression and upregulating SOD levels. In addition, GA treatment resulted in decreased expression of CHOP, GRP78 and p-PERK in H9c2 cells and MIRI rats [173]. Tournefolic acid B (TAB) from *Clinopodium chinense* (Benth.) Kuntze decreased the expression of ER proteins, including Grp78, ATF6, PERK and eIf2α, to inhibit ERS. TAB also enhanced PI3K and Akt phosphorylation, inhibited CHOP and caspase-12 expression, decreased JNK phosphorylation, and increased the Bcl-2/Bax ratio to protect against MIRI [174].

4.5 Autophagy

Autophagy plays an important role in IR injury [181]. During myocardial ischemia, activated autophagy protects the myocardium by removing misfolded proteins and necrotic mitochondria that induce cardiomyocyte death [182], whereas during reperfusion, autophagy overactivation induces large number of autophagic vesicles; then, lysosome-dependent autophagosome fusion and clearance become impaired, leading to increased myocardial injury [183].

Hesperidin is a flavonoid isolated from citrus. In male adult rats, hesperidin decreased the expression of LC3II and beclin-1 and increased that of p-mTOR, p-Akt and p-PI3K. These effects were reversed by the PI3K inhibitor LY294002. Hesperidin reduced MIRI by inhibiting excessive autophagy [175]. Honokiol is a low-molecular-weight biphenol compound derived from *Magnolia officinalis* bark. It enhanced autophagic flux (associated with the Akt signaling pathway) to attenuate MIRI in mice. In cultured cells, it reduced ROS production and attenuated mitochondrial damage in neonatal rat cardiomyocytes exposed to H/R by enhancing autophagy [176]. Asiatic acid from *Centella asiatica* protected cardiomyocytes from ROS-mediated autophagy via the p38 mitogen-activated protein kinase/Bcl-2/beclin-1 signaling pathway in MIRI [177].

5. Role of natural small molecules on Other CVDs

Table 4. Mechanisms of action of natural small molecules to prevent or treat Other CVDs

Serial number	**Chinese medicine**	**Active ingredients**	**Classification**	**Molecular formula**	**Chemical structure**	**Cellular/animal models**	**Targeted pathology**	**Molecular mechanisms**	**Re**
1	*Quercus dentata Thunb.*	Quercetin	Flavonoid	$C_{15}H_{10}O_7$		H9C2 cells	Cardiac hypertrophy	SIRT3/PARP1 pass-through	[18
2	*Tripterygium wilfordii Hook. f.*	Triptolide	Epoxyditerpene lactone	$C_{20}H_{24}O_6$		Neonatal rat ventricular myocytes	Cardiac hypertrophy	Increasing expression of mRNAs encoding CDK1, CDK4, p21, and p27	[18

Serial number	Chinese medicine	Active ingredients	Classification	Molecular formula	Chemical structure	Cellular/animal models	Targeted pathology	Molecular mechanisms	Re
3	*Coptis chinensis Franch.*	Berberine	Quaternary ammonium alkaloid	$C_{20}H_{18}C_lNO_4$		A549 and H9C2 cells; Sprague-Dawley rats	Cardiac hypertrophy	Increasing p62 mRNA expression and decreasing Beclin-1 expression	[18
4	*Armeniaca sibirica (Linn.) Lam.*	Amygdalin	Vitamin	C20H27NO11		H9C2 cells	Cardiac hypertrophy	Regulation of Nrf2 and NF-ϰB	[18
5	*Centella asiatica (Linn.) Urban*	Asiatic acid	Triterpenic compound	$C_{30}H_{48}O_5$		Neonatal rat cardiomyocytes and CFs; male C57BL/6 and Sprague-Dawley rats	Cardiac hypertrophy	Inhibition of mTOR and ERK signaling by activation of AMPKα· reduction in overproduction of TGF-β1, inhibition of p38, ERK1/2 phosphorylation, and NF-ϰB activation; upregulation of miR-126/PIK3R2 expression	[18 [18
6	*Glycyrrhiza uralensis Fisch.*	Licoisoflavone A	Isoflavone	$C_{20}H_{18}O_6$		C57BL/6 mice	Cardiac hypertrophy	Activation of Sirt3	[19

Serial number	Chinese medicine	Active ingredients	Classification	Molecular formula	Chemical structure	Cellular/animal models	Targeted pathology	Molecular mechanisms	Re
9	*Sophora japonica Linn.*	Sophoricoside	Isoflavone glycoside	$C_{21}H_{20}O_{10}$		Neonatal rat cardiomyocytes	Cardiac hypertrophy	Increasing autophagy through activation of AMPK/mTORC	[19
10	*Eucommia ulmoides Oliver*	Pinoresinol diglucoside	Lignan-like compound	$C_{32}H_{42}O_{16}$		Sprague-Dawley rats	Cardiac hypertrophy	Modulation of Akt/mTOR/NF-κB signaling	[19
11	*Cyperus rotundus L.*	Tamarixetin	Flavonoid	$C_{16}H_{12}O_7$		H9C2 cells; C57BL/6 mice	Cardiac hypertrophy	Inhibition of NFAT and Akt signaling	[19
12	*Plantago asiatica L.*	Plantamajoside	Phenylpropanoid glycoside	$C_{29}H_{36}O_{16}$		H9C2 cells	Cardiac hypertrophy	Inhibition of HDAC2 and Akt/GSK-3β signaling	[19
13	*Arctium lappa Linn.*	Arctiin	Lignan-like compound	$C_{27}H_{34}O_{11}$		H9C2 cells; male C57BL/6 mice	Cardiac hypertrophy	Inhibition of MAPK and Akt signaling	[19
14	*Rheum officinale Baill.*	Emodin	Anthraquinone glycoside	$C_{15}H_{10}O_5$		NRVM and H9C2 cells; male C57BL/6 mice	Cardiac hypertrophy	Inhibition of histone deacetylase-dependent gene expression; regulation of mitochondrial SIRT3 signaling	[19

Serial number	Chinese medicine	Active ingredients	Classification	Molecular formula	Chemical structure	Cellular/animal models	Targeted pathology	Molecular mechanisms	Re
15	*Lonicera japonica Thunb.*	Luteolin	Flavonoid	$C_{15}H_{10}O_6$		H9C2 cells; male C57BL/6 mice	Diabetic cardiomyopathy	Inhibition of NF-κB-mediated inflammation and activation of Nrf2-mediated antioxidant responses	[19
16	*Phyllostachys nigra (Lodd.) Munro var. Henonis (Mitf.) Stapf ex Rendle*	Syringaresinol	Bis-epoxy lignin	$C_{22}H_{26}O_8$		NRVM; male C57BL/6 mice	Diabetic cardiomyopathy	Modulation of Keap1/Nrf2 and TGF-β/Smad signaling	[20
17	*Leonurus artemisia (Lour.) S. Y. Hu*	Stachydrine hydrochloride	Alkaloid	$C_7H_{14}C_lNO_2$		NRVM; C57BL/6 mice	Diabetic cardiomyopathy	Inhibition of CaN/NFAT signaling	[20
18	*Glycine max (Linn.) Merr.*	Daidzein	Isoflavone	$C_{15}H_{10}O_4$		Male Sprague-Dawley rats	Diabetic cardiomyopathy	Inhibition of NOX-4-induced oxidative stress	[20
19	*Centella asiatica (Linn.) Urban*	Asiatic acid and maslinic acid	Triterpenic compound; pentacyclic triterpenic acid	$C_{30}H_{48}O_5$ $C_{30}H_{48}O_4$		Male BALB/c mice	Diabetic cardiomyopathy	Reducing expression of NF-κB p50, p-ERK1/2, and late glycosylation end product receptors	[20

Serial number	Chinese medicine	Active ingredients	Classification	Molecular formula	Chemical structure	Cellular/animal models	Targeted pathology	Molecular mechanisms	Re
20	*Myrica rubra Siebold et Zuccarini*	Myricitrin	Flavonoid	$C_{21}H_{20}O_{12}$		H9C2 cells; male BALB/c mice	Diabetic cardiomyopathy	Inhibition of Akt and ERK phosphorylation through Nrf2 activation and NF-κB regulation	[20
21	*Panax notoginseng (Burk.) F. H. Chen*	Notoginsenoside R1	Saponin	$C_{47}H_{80}O_{18}$		H9C2 cells; diabetic *db/db* mice	Diabetic cardiomyopathy	Decreasing ROS by promoting estrogen receptor-alpha expression and subsequent activation of Akt and Nrf2 signaling	[20
22	*Magnolia sp*	4-O-Methyl honokiol	Lignan-like compound	$C_{19}H_{20}O_2$		Diabetic *db/db* mice	Diabetic cardiomyopathy	Activation of AMPK-mediated cardiac lipid metabolism	[20
23	*Pseudotsuga menziesii (Mirbel) Franco*	Taxifolin	Dihydroflavonol	$C_{15}H_{12}O_7$		H9C2 cells; male C57BL/6 mice	Diabetic cardiomyopathy	Inhibition of NADPH oxidase and activation of JAK/STAT3 signaling	[20

Serial number	Chinese medicine	Active ingredients	Classification	Molecular formula	Chemical structure	Cellular/animal models	Targeted pathology	Molecular mechanisms	Re
24	*Epimedium brevicornu Maxim.*	Icariin	Flavonoid	$C_{33}H_{40}O_{15}$		Spontaneously hypertensive rats (SHR)	Hypertension-associated heart disease	Inhibition of ERS-induced apoptosis in cardiomyocytes and increased expression of apoptotic proteins such as GRP78	[20
25	*Salvia miltiorrhiza Bunge*	Danshenol A	Diterpenoid	$C_{21}H_{20}O_4$		Spontaneously hypertensive rats (SHR)	Hypertension-associated heart disease	Improvement of mitochondrial dysfunction and inhibition of ROS production	[20

Serial number	Chinese medicine	Active ingredients	Classification	Molecular formula	Chemical structure	Cellular/animal models	Targeted pathology	Molecular mechanisms	Re
26	*Centella asiatica (Linn.) Urban*	Asiatic acid	Triterpenic compound	$C_{30}H_{48}O_5$		CFs cells; spontaneously hypertensive and Sprague-Dawley rats	Hypertension-associated heart disease	Enhancing Nrf2/HO-1 and inhibition of TGF-β1/Smads phosphorylation; recovery of eNOS/iNOS expression; upregulation of eNOS and p47phox expression	[21 [21
27	*Centella asiatica (Linn.) Urban*	Asiatic acid	Triterpenic compound	$C_{30}H_{48}O_5$		Wistar rats	Cardiotoxicity	Activation of the Nrf2 transcription factor	[21
28	*Sophora flavescens Alt.*	Matrine	Alkaloid	$C_{15}H_{24}N_2O$		H9C2 cells; male C57BL/6 mice	Cardiotoxicity	Maintenance of AMPKα/UCP2 signaling	[21
29	*Illicium verum Hook. f.*	Isodunnianol	Lignan-like compound	$C_{27}H_{26}O_3$		H9C2 cells	Cardiotoxicity	Upregulation of autophagy and reduction of apoptosis through activation of AMPK-ULK1 signaling	[21

Serial number	Chinese medicine	Active ingredients	Classification	Molecular formula	Chemical structure	Cellular/animal models	Targeted pathology	Molecular mechanisms	Re
30	*Aconitum carmichaeli Debx.; Zingiber officinale Rosc.*	Higenamine; 6-gingerol	Benzylisoquinoline alkaloid; phenolic compound	$C_{16}H_{17}NO_3$ $C_{17}H_{26}O_4$		H9C2 cells	Cardiotoxicity	Regulation of PPARα/PGC-1α/Sirt3 signaling	[21
31	*Aloe vera (Linn.) N. L. Burman var. chinensis (Haw.) Berg.*	Aloin	Anthraquinone glycoside	$C_{21}H_{22}O_9$		Male Wistar rats	Cardiotoxicity	Restoration of antioxidant defense system by increasing levels of reduced glutathione and catalase; decreasing inflammation by decreasing expression of TNF-α and IL-1β	[21

Serial number	Chinese medicine	Active ingredients	Classification	Molecular formula	Chemical structure	Cellular/animal models	Targeted pathology	Molecular mechanisms	Re
32	*Paeonia suffruticosa Andr.*	Paeonol	Phenolic compound	$C_9H_{10}O_3$		Male Wistar rats	Cardiotoxicity	Inhibition of TLR4/NF-κB/TNF-α/IL-6 signaling and reduction of pro-apoptotic marker expression levels	[21 219

5.1 Myocardial hypertrophy

Cardiac hypertrophy is characterized by an increase in cardiomyocyte volume and dense myonodularity. Persistent hypertrophy leads to cardiac decompensation and systolic dysfunction and exacerbates ventricular remodeling, leading to HF [220]. Multiple natural small molecules treat cardiac hypertrophy through different targets [186-202]; for example, quercetin protects mitochondrial function and inhibits cardiac hypertrophy through SIRT3/PARP-1 signaling [182, 184, 186, 188]. Triptolide increased CDK1 and CDK4 mRNA, CDK1, p21 and p27 mRNA expression[185]. Berberine upregulated p62 mRNA expression and downregulated beclin-1 expression to reduce cardiac hypertrophy[186]. These details are shown in Table 5.

5.2. Diabetic cardiomyopathy

Natural small molecules alleviate diabetic cardiomyopathy through multiple effects. Diabetic cardiomyopathy is characterized by early diastolic abnormalities and later clinical HF in the absence of dyslipidemia, hypertension, and coronary artery disease. Its pathophysiological factors include oxidative stress, inflammation and immune regulatory dysfunction, and systemic metabolic disorders [221].

Luteolin inhibited NF-κB-mediated inflammation and activates Nrf2-mediated antioxidant response to regulate diabetic cardiomyopathy [199, 200, 203]. Syringaresinol prevented type 1 diabetic cardiomyopathy by inhibiting inflammation, as well as oxidative stress through Keap1/Nrf2 and TGF-β/Smad signaling [200, 204]. Natural small molecules can improve diabetic cardiomyopathy by inhibiting CaN/NFAT signaling [201, 202, 205] and NOX-4 [202, 206], decreasing NF-κB p50, p-ERK1/2, and late glycosylation end product receptor cardiac expression [203, 207], and promoting Nrf2 activation and NF-κB inhibition [204-211].

5.3. Hypertension-associated heart disease

Natural small molecules have significant utility in the treatment of hypertensive heart disease. Chronic hypertension causes systolic overload of the left ventricle, leading to its compensatory thickening, which is a major contributor to adverse cardiovascular and cerebrovascular accidents, including sudden cardiac death, myocardial ischemia, HF, ventricular arrhythmias, and cerebral infarction [222].

Icariside (ICA) protected ventricular function and attenuates hypertensive cardiomyopathy by inhibiting ERS-induced cardiomyocyte apoptosis and stimulating increased expression of apoptotic proteins [208, 212].

Salvianol A (DA) attenuated hypertension-induced cardiac remodeling by improving mitochondrial dysfunction and inhibiting ROS production [209, 213]. Asiatic acid enhanced antioxidant activity and inhibited cardiac fibrosis in hypertensive rats through Nrf2/HO-1 and inhibition of TGF-β1/Smad phosphorylation [210, 214]; inhibited oxidative stress and improved hypertensive heart disease by downregulating eNOS expression and upregulating iNOS expression [211, 215]; and enhanced eNOS and p47phox expression by regulating nitric oxide bioavailability to lower blood pressure [212].

5.4 Drug-induced cardiotoxicity

Cardiotoxicity has multiple manifestations; the antineoplastic drug adriamycin causes cardiotoxicity [223]; drugs that reduce body mass, such as sibutramine, can cause cardiomyopathy [224]; cardiotoxicity causes cardiomyopathy (e.g., myocarditis, HF,arrhythmias)with low incidence but high mortality.

Centella asiatica ameliorated adriamycin-induced cardiac and hepatic and renal toxicity in rats through Nrf2 transcription factor activation [213, 217]. Matrine attenuated adriamycin-induced cardiotoxicity by inhibiting oxidative stress and cardiomyocyte apoptosis through activation of AMPKα/UCP2 signaling [214, 218]. Isoduninol attenuated adriamycin-induced cardiotoxicity by activating AMPK-ULK1 signaling to promote autophagy and reduce apoptosis[215]. The natural small molecules higenamine, 6-gingerol, aloin, and paeonol[216-218] attenuated cardiotoxicity by inhibiting TLR4/NF-ϰB/TNF-α/IL-6 inflammatory signaling through the PPARα/PGC-1α/Sirt3 pathway.

6. Conclusions

CVDs are the leading cause of disability and death worldwide [225]. Natural small molecules are from natural botanicals, with a history of 2000 years, and are receiving increasing attention from the cardiovascular research community for their "multi-target, multi-channel, low side effect and good efficacy" characteristics, e.g., digitalis (derived from Trichoderma reesei), aspirin (also known as acetylsalicylic acid, salicylic acid was first extracted from Scutellaria baicalensis), artemisinin (from *Artemisia annua L*).It is important to continue to search for treatments from natural small molecules for CVDs. Natural small molecule drugs has been synthesized, structurally modified and simplified to form a new class of drugs with better efficacy, e.g.,10 hydroxycamptothecin from Camptothecin has been synthesized into Irinotecan and Topotecan; The modification of monomeric drugs long used in clinical practice to reduce adverse reactions, e.g., berberine does not have drug resistance;The bioavailability and toxicity of drugs are altered in the arrangement or conformation of natural small molecules, e.g., the new puerarin crystal , puerarin-V [226], has a better absorption rate and higher plasma drug concentration compared to puerarin.In this paper, we presented the mechanisms of action of natural small molecules on cardiovascular diseases elucidated in recent years. We also presented an in-depth discussion on the molecular mechanisms of natural small molecules for CVDs, aiming to provide information for clinical research and the identification of new treatments, and to provide new ideas for the development of new drugs. Clinically, natural small molecules with flavonoids, saponins, and alkaloids as the main active ingredients have demonstrated therapeutic effects on CVDs such as AS, HF, and MIRI, with high safety and good application prospects.

In addition to the advantages, these small molecules also have limitations. First, natural drugs primarily act as complexes in the form of tonics, prescriptions, and pills as carriers for diseases, while relatively little research has been conducted on single natural small-molecule drugs. Secondly, small-molecule research is primarily based on animal and cultured-cell models. The same natural small molecule and its active ingredients may show bi-directional effects of activation or inhibition in different target cells or different animal models, and few relevant studies explaining these differences are available Third, large-scale, multicenter, randomized and controlled clinical trials for the treatment of CVDs are lacking. Fourth, the systemic and organ-specific toxicities of these natural products remain to be studied [227]. For example, 0.5 μM lycopene treatment did not reduce HL-1 cell death, but 4 μM lycopene only retained 75 ± 15% of cell viability[145], while its dose size and toxicity for humans have not been studied.

Despite these limitations, a better understanding of their active ingredients, mechanisms of action, and adverse effects will be beneficial to help improve efficacy and decrease the side effects of natural drugs. It

can be expected that with the advancement of new technologies (e.g., high-throughput screening of natural compound libraries, bioinformatics, synthetic biology), more cardiovascular drugs will emerge from natural drugs; therefore, our future efforts will be directed toward their development, so that natural small-molecule drugs can be more accurately integrated in the clinical setting.

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