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Review Article

Salvia miltiorrhiza Burge (Danshen): a golden herbal medicine in cardiovascular therapeutics

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Abstract

Salvia miltiorrhiza Burge (Danshen) is an eminent medicinal herb that possesses broad cardiovascular and cerebrovascular protective actions and has been used in Asian countries for many centuries. Accumulating evidence suggests that Danshen and its components prevent vascular diseases, in particular, atherosclerosis and cardiac diseases, including myocardial infarction, myocardial ischemia/reperfusion injury, arrhythmia, cardiac hypertrophy and cardiac fibrosis. The published literature indicates that lipophilic constituents (tanshinone I, tanshinone IIa, tanshinone IIb, cryptotanshinone, dihydrotanshinone, *etc*) as well as hydrophilic constituents (danshensu, salvianolic acid A and B, protocatechuic aldehyde, *etc*) contribute to the cardiovascular protective actions of Danshen, suggesting a potential synergism among these constituents. Herein, we provide a systematic up-to-date review on the cardiovascular actions and therapeutic potential of major pharmacologically active constituents of Danshen. These bioactive compounds will serve as excellent drug candidates in small-molecule cardiovascular drug discovery. This article also provides a scientific rationale for understanding the traditional use of Danshen in cardiovascular therapeutics.

Keywords: *Salvia miltiorrhiza* Burge; Danshen; cardiovascular diseases; herbal medicine; traditional Chinese medicine

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Introduction

Danshen, the dried root of rhizome of *Salvia miltiorrhiza* Burge, has been widely used in Asian countries for treating cardiovascular diseases, including coronary heart disease, myocardial infarction (MI), angina pectoris and atherosclerosis[1-4]. Therefore, Danshen represents a traditional Chinese medicine (TCM) that has a relatively high safety profile. To date, the chemical constituents of Danshen have been well identified, including more than 30 lipophilic compounds that have a diterpene chinone structure (tanshinone I–VI, cryptotanshinone, isotanshinone I–II, Danshenol A *etc*) and more than 50 hydrophilic compounds that mainly have a phenolic acid structure (Danshensu, salvianolic acid A, salvianolic acid B, protocatechuic aldehyde, *etc*)[1, 5-7]. More recently, Tasly Pharmaceuticals, Inc has completed a Phase III clinical trial to evaluate the safety and efficacy of Dantonic® (T89, also known as Compound Danshen Dripping Pills) in patients with chronic stable angina pectoris (ClinicalTrials.gov Identifier: NCT01659580). In this article, we provide a systematic and up-to-date overview of the pharmacological and therapeutic profile of bioactive compounds from Danshen in vascular diseases (atherosclerosis) and cardiac diseases (myocardial infarction, myocardial ischemia/reperfusion injury, arrhythmia, cardiac hypertrophy and cardiac fibrosis), with the aim of providing a scientific rationale for understanding the traditional use of Danshen in cardiovascular therapeutics.

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The pathogenesis of atherosclerosis and the anti-atherosclerotic effects of Danshen

Key events in the pathogenesis of atherosclerosis

Atherosclerosis is a multifactorial, chronic inflammatory disease characterized by an inflammatory response, oxidative stress, and immune disorders[8-12]. Several diet-induced atherosclerotic animal models (such as ApoE$^{-/-}$ mice, LDLr$^{-/-}$ mice, and rabbits) have been widely used to study the pathogenesis of atherosclerosis and evaluate anti-atherosclerotic drugs[13, 14]. There are several sequential and interrelated steps in the development of atherosclerosis (Figure 1). These critical steps have served as excellent models for evaluating atheroprotective drugs, which target one or more of these steps.

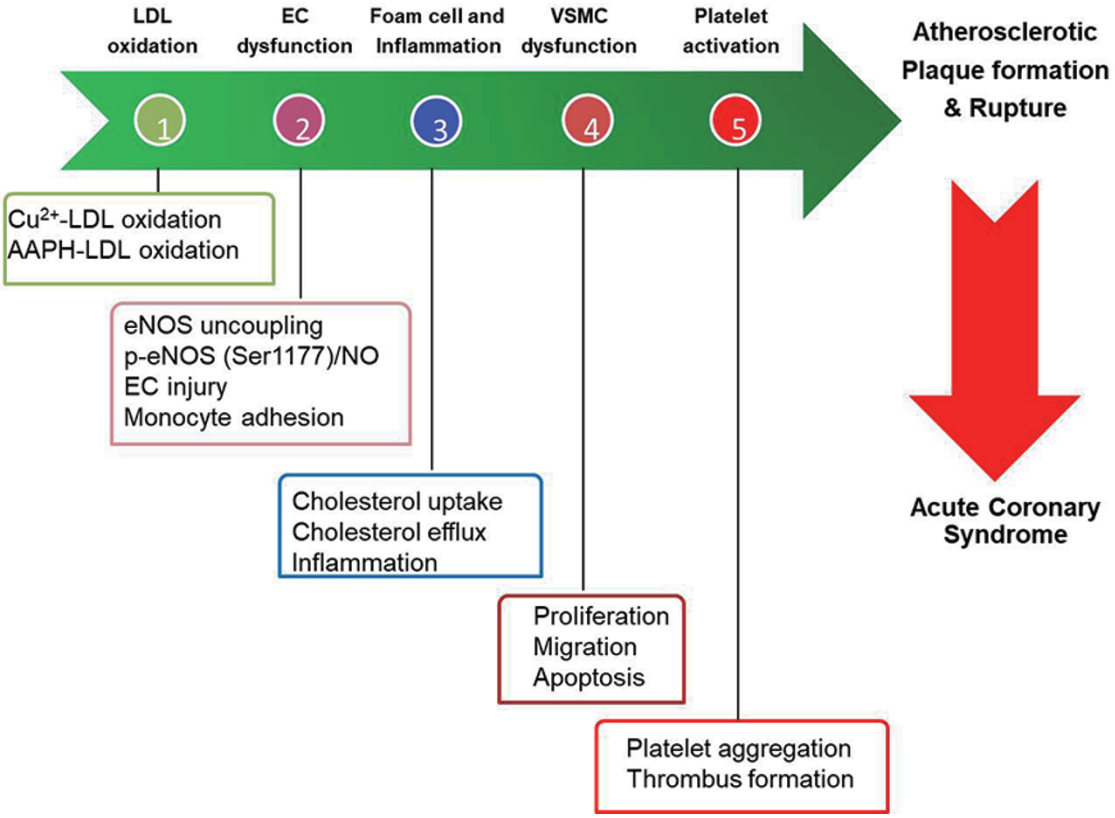

Figure 1. Key cellular events in the pathogenesis of atherosclerosis.

(i) Low-density lipoprotein (LDL) oxidation: a high level of circulating LDL in the hypercholesterolemic microenvironment is prone to modification to form the modified LDL (mLDL). The major form of pathophysiologically mLDL is oxidized LDL (oxLDL), which activates endothelial cells and initiates the vicious cycle of atherosclerotic plaque progression[15].

(ii) Endothelial dysfunction: the combination of multiple pro-atherogenic stimuli (such as oxLDL, high glucose, and homocysteine, among others) injures the integrity of the vascular endothelium, causes a leaky vessel and increases leukocyte (monocytes and neutrophils) adhesion to the diseased endothelium, impairs vasorelaxation, causes endothelial nitric oxide synthase (eNOS) uncoupling and reduces nitric oxide (NO) production[16].

(iii) Vascular smooth muscle cell (VSMC) dysfunction: The injured vascular endothelium induces the phenotypic switch of VSMCs to proliferate and migrate from the media layer of blood vessels to form the neointima (or hyperplasia), the early form of atherosclerosis[17].

(iv) Macrophage-derived foam cell formation and inflammation: Macrophages differentiated from circulating monocytes respond to local inflammatory cytokines or stimuli and are activated. Macrophages also avidly engulf modified LDL via membrane-located scavenger receptors (SR) [such as CD36, SR-A, lectin-like oxidized LDL receptor 1 (LOX-1)] to form foam cells, the hallmark of atherosclerosis[18].

(v) Platelet activation and thrombus formation: After destabilization of atherosclerotic plaques, the plaques are susceptible to rupture, giving rise to platelet activation (adhesion and aggregation) and thrombus formation, which underlie the clinical presentation of atherothrombotic events[19].

Anti-atherosclerotic effects of Danshen components

Danshen is a well-known multi-component and multi-targeting cardiovascular TCM, which can be used alone or together with other TCMs for cardiovascular therapy[1-4] (Table 1). Both the lipophilic components (tanshinone I, tanshinone IIa, cryptotanshinone, and dihydrotanshinone, among others) and hydrophilic components (denshensu, salvianolic acid A, salvianolic acid B, and protocatechuic aldehyde, among others) from Danshen have protective effects in atherosclerotic vascular diseases, including atherosclerosis, calcification and aortic aneurysm formation[1-4]. In this section, we will review and discuss the anti-atherosclerotic effects and molecular mechanisms of individual major component (Table 2 and Supplementary Table S1) with the aim of providing a comprehensive understanding of the pharmacological effects of Danshen.

Major lipophilic components

Tanshinone I

The vasoprotective effects of tanshinone I are mainly observed in cultured cells. For example, in cultured vascular endothelial cells, tanshinone I has potent anti-angiogenic effects via block-

Table 1. Anti-atherosclerotic effects of TCM formula containing Danshen.

Formula	Subjects or models	Effects and mechanisms	References
Cardiotonic Pill	Rabbit+HCD+Ad-p53	↓Plaque vulnerability	[311]
(Fufang Danshen	↓ICAM-1, ↓VCAM-1		
Dripping Pill)	ApoE$^{-/-}$ mice+HFD	↓Lesion size, ↓ICAM-1	[312]
	Hypercholesterolemic patients	↓ICAM-1, ↓E-selectin	[313]
Naoxintong	ApoE$^{-/-}$ mice+HFD	↓Lesion size, vulnerability	[314]
		↓MMP2, ↓TNFα, ↑SM22α	
	Rabbit+HCD	↓Lesion size, ↓iNOS/NO	[315]
	LDLr$^{-/-}$ mice+HFD	↓Lesion size, ↓DC and Mφ content	[316]
Danshen-Gegen Injection	Postmenopausal women with early hypercholesterolemia	↓Carotid intima/media thickness	[317]
Danhong Injection	Rats+HFD	↓Hyperlipidemia, PPARα	[318]
	Rabbits+HCD	↓Lesion size, iNOS, COX2, MDA	[319]
	ApoE$^{-/-}$ mice +HFD		
	LDLr$^{-/-}$ mice+HFD	↓Lesion size, TNFα, IL-1β, IL-6↑ABCA1	[320]

Abbreviations: ABCA1, ATP-binding cassette transporter A1; ApoE$^{-/-}$, ApoE deficient; COX2, cyclooxygenase 2; DC, dendritic cells; HCD, high cholesterol diet; HFD, high fat diet; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; iNOS, inducible nitric oxide (NO) synthase; LDLr, LDL receptor; Mφ, macrophage; MDA, malondialdehyde; MMP-2, matrix metalloproteinase 2; TNFα, tumor necrosis factor alpha; VCAM-1, vascular cellular adhesion molecule-1.

ing endothelial cell proliferation, migration and tube formation as well as vessel sprouting[20]. The molecular mechanism is related to the inhibition of basal as well as hypoxia-induced STAT3 phosphorylation at tyrosine 705[20]. This report suggests that tanshinone I could be a useful therapeutic agent in blocking tumor angiogenesis[20]. Tanshinone I also enhances endothelial integrity by stabilizing cell-cell junctions, thus preventing vascular leakage[21]. Lipopolysaccharide (LPS)-stimulated macrophage cell lines, such as RAW264.7, serve as an excellent *in vitro* model for evaluating anti-inflammatory compounds. Tanshinone I significantly inhibits LPS-induced cyclooxygenase-2 (COX-2)-mediated prostaglandin E2 (PGE2) production[22] as well as IL-12[23] production. The anti-inflammatory effects are mediated by the inhibitory effects on NF-κB and AP-1 activation[23, 24]. Currently, there is no literature reporting the protective effects of tanshinone I against VSMC proliferation, migration, platelet activation and atherosclerosis development.

Tanshinone IIa

Tanshinone IIa is the most well studied bioactive lipophilic constituent of Danshen in cardiovascular medicine. Clinically, sodium sulfate derivatives of tanshinone IIa (STS) have long been used to treat patients with angina pectoris and coronary heart disease[2]. In experimental studies, tanshinone IIa has been shown to attenuate neointima hyperplasia[25, 26], atherosclerotic calcification[27], diet-induced atherosclerosis[28-41] and aortic aneurysm[42, 43]. During the past decade, emerging evidence has suggested that tanshinone IIa modulates multiple key cellular events in vascular diseases, including LDL oxidation, monocyte-endothelial cell interactions, endothelial cell injury, eNOS-dependent vasorelaxation, proliferation, migration of smooth muscle cells, macrophage cholesterol uptake and efflux, and platelet activation[1-4].

Inhibitory effects of Tanshinone IIa on LDL oxidation

In 2000, the preventative effects of tanshinone IIa on inhibiting LDL oxidation were comprehensively analyzed *in vitro*[44]. In both cell-free (Cu^{2+}, peroxyl radical and peroxynitrite-mediated) and macrophage-derived oxidizing systems, tanshinone IIa potently inhibited LDL oxidation by scavenging peroxyl free radical and increasing LDL binding activity[44], suggesting that it can block the initiation of atherosclerosis.

Protective effects of Tanshinone IIa on endothelial function

In endothelial cells, tanshinone IIa improves endothelial function through the following mechanisms. (1) Protecting endothelial cells against endothelial injury: Chronic oxidative stressors, such as H_2O_2 and methylglyoxal (MGO), trigger endothelial injury and subsequent atherogenic events, such as monocyte adhesion and transmigration. Tanshinone IIa has been shown to inhibit endothelial injury induced by H_2O_2[38, 45-48] and MGO[49] via its anti-oxidant, anti-inflammatory, and xenobiotic and endobiotic detoxification effects. Bi *et al* [48] designed and tested the endothelial protective effects of tanshinone IIa derivatives and found that several derivatives have increased efficacy against H_2O_2-induced injury via Nrf2 (nuclear factor (erythroid-derived 2)-like-2 factor) activation and superior water solubility. (2) Preventing inflammatory responses in endothelial cells and endothelial progenitor cells and preventing monocyte adhesion to diseased endothelium: Tanshinone IIa has potent anti-inflammatory effects by blocking the upregulation of pro-inflammatory mediators, such as tumor necrosis factor α (TNF-α), intercellular cell adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), monocyte chemotactic protein 1 (MCP-1), E-selectin, and interleukins (IL-8 & IL-1β), in response to pro-inflammatory stimuli[50-56], thus reducing monocyte adhesion to endothelial cells[50, 54, 56]. (3) Regulation of vascular tone and vasorelaxation by increasing NO and decreasing endo-

Table 2. Therapeutic benefits of bioactive components of Danshen in atherosclerotic vascular diseases.

Compound	Animal Model	Effects and mechanisms	References
Tanshinone IIA	ApoE$^{-/-}$ mice+HFD	↓Lesion size and instability, ↓CLIC1, ↓SRA, ↓CD36, ↓LOX1, ↓PPARγ, ↓CD68, ↓NF-κB, ↓MMP-9	[28-32, 38, 39, 41]
	ApoE$^{-/-}$ (OVX) mice+HFD	↓Lesion size, ↓NF-κB, ↓sICAM-1 ↓AP1, ↓E-selectin, ↓p-ERK1/2, ↓HDL, ↑SOD	[30]
	Rabbits+HCD	↓Lesion size, ↓neointima, ↓CD40, ↓MMP-2/9, SOD, ↓MDA, ↓oxLDL, ↑GPx, ↓VCAM-1, ↓IL-1β	[33-36] [27, 321]
	Rats+HFD	↓Hepatic lipid deposition ↓Aortic calcification, ↓ROS, ↓MDA, ↓oxLDL, ↑Cu/Zn-SOD	
	Rats+balloon injury	↓Intimal hyperplasia, ↓PCNA	[25]
	Mice+carotid artery ligation	↓Intimal hyperplasia, ↓PCNA	[26]
	Rats+ elastase perfusion	↓AAA incidence, ↑elastin fibers, ↑VSMC content, ↓TLR4, ↓pNF-κB, ↓MyD-88, ↓MMP-2, ↓MMP-9, ↓MCP-1, ↓ iNOS	[42, 43]
Cryptotanshinone	ApoE$^{-/-}$ mice+HFD	↓Lesion size and instability, ↓IL-1β, ↓TNFα, ↓IL-6, ↓IL-17A ↓IFNγ, ↓MMP-9, ↓LOX1, ↓ROS	[80]
Dihydrotanshinone	ApoE$^{-/-}$ mice+HFD	↓Lesion size, ↓TLR4, ↓NF-κB, ↓MyD88, ↓ROS, ↓LOX1, ↓NOX4	[88]
Danshensu	Rats+ methionine-rich diet	↓Lesion size, ↓Hcy, ↓TNFα, ↓ICAM-1, ↓ET1, ↑NO	[94]
Salvianolic acid A	ApoE$^{-/-}$ mice+HFD	↓Lesion size, ↓CCL20, ↓CCR6	[105]
	ApoE$^{-/-}$ mice+HFD	↓Aneurysm severity, ↓MMP-2/9 ↓Elastin fragmentation, ↓Macrophage infiltration	[106] [109]
	SHR	↑Relaxation	[111]
	Rat+STZ+HFHS	↓vWF, vasorelaxation, ↓MDA, ↓AGE	[109]
Salvianolic acid B	Rabbits+HCD	↓Lipid deposition, ↓neointimal formation, ↓LDL oxidation	[135]
	ApoE$^{-/-}$ mice+HFD	↓Neointimal formation, ↓foam cell, ↓MMP-2/9, ↓COX-2, ↓CD36	[148, 154, 155]
	Rats+balloon injury	↓Neointimal formation, ↓CXCR-4	[152]
Protocatechuic aldehyde	Rats+balloon injury	↑Re-endothelization, ↓neointima, ↑GPER1, ↑CD31, ↓VCAM-1, ↓CD40	[161]

Abbreviations: AAA, abdominal aortic aneurysm; ABCA1, ATP binding cassette subfamily A member 1; AGE, advanced glycation endproducts; AP1, activator protein-1; CCL20, Chemokine (C-C motif) ligand 20; CCR6, C-C motif chemokine receptor 6; CD36, cluster of differentiation 36; CD40, cluster of differentiation 40; CLIC1, intracellular channel protein 1; COX2, cyclooxygenase 2; CXCR4, chemokine (C-X-C motif) receptor 4; ERK, extracellular signal–regulated kinases; GPER1, G-protein coupled estrogen receptor 1; GPx, glutathione peroxidase; HCD, high cholesterol diet; Hcy, homocysteine; HDL, high density lipoprotein; HFD, high fat diet; ICAM-1, intercellular adhesion molecule 1; IFNγ, interferon gamma; IL, interleukin; iNOS, inducible nitric oxide synthase; LOX1, lectin-like oxidized low-density lipoprotein receptor-1; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; MMP, matrix metalloproteinase; MyD88, Myeloid differentiation primary response gene 88; NF-κB, nuclear factor kappa B; NOX4, NADPH oxidase 4; oxLDL, oxidized LDL; OVX, ovariectomized; PCNA, Proliferating cell nuclear antigen; PPARγ, peroxisome proliferator-activated receptor gamma; ROS, reactive oxygen species; SHR, spontaneously hypertensive rat; SOD, Superoxide dismutase; STAT3, signal transducer and activator of transcription 3; sCD40L, soluble CD40 ligand; sICAM1, soluble intercellular adhesion molecule 1; SRA, scavenger receptor A; TLR4, toll-like receptor 4; TNFα, tumor necrosis factor-alpha; VCAM-1, vascular cell adhesion protein 1; vWF, von Willebrand factor.

thelin-1 (ET-1): Several reports have revealed that tanshinone IIa increases the production of NO[57-59] under different stress conditions in endothelial cells by increasing eNOS levels[58, 60, 61] and eNOS phosphorylation at ser1177[61] while blocking eNOS ser1177 dephosphorylation[61]. Tanshinone IIa also regulates vascular tone via decreasing cyclic strain and TNFα-induced ET1 production[62, 63]. In a model of chronic intermittent hypoxia, tanshinone IIa decreases the expression of ET_A receptors while increasing that of ET_B receptors, thereby dampening ET1 production and induced signaling[64]. (4) Prevention of eNOS uncoupling: Tanshinone IIa ameliorates eNOS uncoupling induced by multiple agents, such as high glucose. The underlying mechanism is linked to the upregulation of key components in the recoupling of eNOS including the following: ratios of eNOS dimer/monomer and tetrahydrobiopterin (BH4)/dihydrobiopterin (BH2), GTP cyclohydrolase I (GTPCH1), dihydrofolate reductase (DHFR) and heat shock protein 90 (HSP90)[11, 61, 65].

Inhibitory effects of Tanshinone IIa on VSMC proliferation and migration

In VSMCs, tanshinone IIa inhibits the proliferation and migration of VSMCs by inhibiting the activation of ERK[25] and PDK1 (3-phosphoinositide-dependent protein kinase 1)[66] while activating the BKCa (large-conductance Ca^{2+}-activated K^+ channel)[67], AMPK (adenosine 5′-monophosphate-activated protein kinase)[68] and Nrf2[69] pathways. Tanshinone IIa also suppresses the apoptosis of VSMCs[39], indicating its potential to reduce plaque vulnerability.

Inhibitory effects of Tanshinone IIa on foam cell formation

In macrophages, tanshinone IIa inhibits LPS-induced inflam-

mation[70-72], oxLDL-induced proliferation and macrophage migration[39] and blocks scavenger receptor-mediated oxLDL uptake[29, 32, 73] while promoting ATP-binding cassette transporters ABCA1 and ABCG1-mediated cholesterol efflux via the Nrf2/HO1 pathway[32], thereby decreasing foam cell formation.

Inhibitory effects of Tanshinone IIa on platelet aggregation

In platelets, tanshinone IIa inhibits platelet aggregation and activation induced by collagen and ADP[74]. All the vasoprotective effects of tanshinone IIa contribute to its atheroprotective effects as observed in different animal models and in cultured cells.

Cryptotanshinone

We[75-78] and others[79] have previously shown that cryptotanshinone is a neuroprotective compound in various models of neurodegenerative diseases *in vitro* and *in vivo*. However, the atheroprotective effects of cryptotanshinone have not been well recognized until very recently.

Endothelial protective effects of cryptotanshinone against atherosclerosis

Considering the potent anti-inflammatory effects of cryptotanshinone in various systems and participation of inflammation in all import phases of atherosclerosis, it is highly plausible that cryptotanshinone may also ameliorate atherosclerosis via its anti-inflammatory effects. Recently, we[80] and several other independent groups[81, 82] have shown that cryptotanshinone shares some of the properties of tanshinone IIa in inhibiting inflammatory stimuli (such as TNFα- and oxLDL)-induced monocyte adhesion to endothelial cells, foam cell formation and platelet activation, thereby attenuating experimental atherosclerosis in ApoE$^{-/-}$ mice. Specifically, cryptotanshinone inhibits monocyte adhesion by suppressing the scavenger receptor LOX1-mediated pro-inflammatory response (ICAM-1 and VCAM-1 upregulation) in endothelial cells[80]. Because LOX1 functions as the upstream major receptor for oxLDL in endothelial cells[18, 83], LOX1 inhibition could be one major anti-atherosclerotic mechanism of cryptotanshinone. The endothelial protective effect of cryptotanshinone is mainly related to the attenuation of endothelial inflammation[80]. Therefore, the potential effects of cryptotanshinone on other critical aspects of endothelial function (such as eNOS phosphorylation and uncoupling) warrant further studies.

Effects of cryptotanshinone on VSMC proliferation and migration

Like tanshinone IIa, the inhibitory effects of cryptotanshinone on the proliferation and migration of VSMCs have also been reported[84]. The underlying mechanism is related to the inhibition of matrix metalloproteinase-9 (MMP-9) expression via the NF-κB (nuclear factor-kappa B) and AP1 (Activator protein 1) pathway[84].

Anti-inflammatory effects of cryptotanshinone in macrophages

Although cryptotanshinone has minimal inhibitory effects against macrophage-derived foam cell formation[85], a recent study has reported that cryptotanshinone displays superior anti-inflammatory effects in LPS-stimulated macrophages compared with tanshinone IIa[86], confirming and extending our previous observation that cryptotanshinone inhibits the LPS-induced inflammatory response in murine macrophages by blocking activation of the NF-κB and MAPK (mitogen-activated protein kinase) pathways[87]. These findings also suggest the necessity to chemically modify cryptotanshinone to increase its therapeutic efficacy. Currently, there is no literature available regarding the thrombo-protective effects of cryptotanshinone *in vitro* and *in vivo*, which merit further studies in the future.

Dihydrotanshinone

A recent study[88] from Chen's laboratory has shown that dihydrotanshinone attenuates diet-induced atherosclerosis in ApoE$^{-/-}$ mice. The underlying mechanism is related to blockade of the NOX4 (NADPH oxidase 4)/ROS (reactive oxygen species)/NF-κB/LOX-1 signaling pathway in LPS-stimulated human endothelial cells and subsequent oxLDL endocytosis and monocyte adhesion to endothelial cells[88]. Dihydrotanshinone also inhibits proliferation, migration and tube formation in endothelial cells, thereby inhibiting angiogenesis[89]. Currently, the regulatory effects of dihydrotanshinone on eNOS-derived NO production remain unknown. Based on a previous study[90] showing that dihydrotanshinone has vasorelaxant activities in an aortic ring assay, it is plausible that dihydrotanshinone may have potential effects on NO production in the endothelium. In LPS-stimulated RAW264.7 macrophages, dihydrotanshinone significantly inhibits LPS induced production of COX2-mediated PGE2 as well as iNOS (inducible NO synthase)-dependent NO by blocking the activation of NF-κB and AP-1[22]. Similarly, dihydrotanshinone also exhibits greater inhibitory effects against LPS-induced IL-12 production than tanshinone I and cryptotanshinone, without affecting IL-10 production[23]. In platelets, dihydrotanshinone functions as a potent thrombin inhibitor compared with tanshinone IIa and cryptotanshinone[91]. It also significantly inhibits collagen induced platelet aggregation (more potent than green tea component EGCG) by suppressing calcium mobilization and thromboxane B2 production[92]. The effects of dihydrotanshinone on VSMC pathophysiology and macrophage-derived foam cell formation warrant further studies.

Major hydrophilic components

Danshensu (or Salvianic acid A)

A high level of circulating homocysteine (Hcy) is a risk factor for cardiometabolic diseases, such as atherosclerosis and hyperhomocysteinemia[93]. In a rat model of hyperhomocysteinemia (by feeding rats with a methionine-rich diet), Danshensu decreases foam cell formation by reducing the expression of TNFα, ICAM-1, and ET-1 while increasing NO production, thus protecting the vascular endothelium from injury[94]. In cultured human endothelial cells challenged with Hcy (5 mmol/L), Danshensu represents the strongest component in the aqueous extract of Danshen that inhibits Hcy-induced injury[95]. Danshensu also prevents H_2O_2 induced endothelial cell injury by inhibiting CD40[96] as well as TNFα-induced endothelial permeability by blocking VEGF (vascular endothelial growth factor) production and ERK activation[97].

In keeping with this function, an excellent study from Zhu's laboratory identified Danshensu as the major component of Danhong injection to exert endothelium-dependent vasodilation in an eNOS/NO-independent, but prostacyclin-dependent, manner[98]. This evidence provides mechanistic insight into the previously observed ability of Danshensu to dilate swine coronary artery[99]. In VSMCs, Danshensu has inhibitory effects on the proliferation of VSMCs by decreasing ET1 production while increasing NO production[100]. In an *in vitro* model of foam cell formation (RAW264.7 macrophages stimulated with oxLDL), Danshensu inhibits lipid accumulation and foam cell formation by decreasing CD36-dependent oxLDL uptake while promoting ABCA1- and ABCG1-dependent cholesterol efflux[101], further extending a previous study that discovered Danshensu as a potential inhibitor of soluble CD36 binding to oxLDL and resultant oxLDL uptake[102]. In platelets, Danshensu displays excellent anti-platelet and anti-thrombotic activities *in vivo* by inhibiting COX2 and normalizing the ratio of thromboxane A2 (TXA2)/prostacyclin (PGI2) [103] despite the low inhibitory effects on platelet aggregation observed *in vitro* [104]. Currently, no literature is available regarding the protective effects of Danshensu in experimental animal models of atherosclerosis.

Salvianolic acid A

In vivo, salvianolic acid A (Sal-A) has recently been shown to inhibit diet-induced atherosclerosis[105] and angiotension II (Ang II)-induced aortic aneurysm formation[106] in $ApoE^{-/-}$ mice. It is one of the strongest anti-oxidant phenolic acids in Danshen due to its polyphenolic structure.

Inhibitory effects of Sal-A on LDL oxidation

In 2002, the effect of Sal-A on $CuSO_4$-mediated LDL oxidation was investigated[107]. The authors observed that Sal-A could chelate Cu^{2+} and inhibit Cu^{2+}-mediated LDL oxidation. As a result, Sal-A scavenges free radicals and decreases the end-product of the lipid peroxidation- malondialdehyde (MDA)[107].

Effects of Sal-A on endothelial dysfunction and vascular remodeling

Seminal studies from Du's laboratory[108-110] and others[111] have recently investigated the effects of Sal-A on endothelial dysfunction and vascular remodeling. The studies have revealed that Sal-A is not hypotensive, but it ameliorates hypertension and high-fat, high-sucrose diet-associated impairment of endothelium-dependent vasorelaxation in spontaneously hypertensive rats[111] and diabetic rats[109], respectively. *In vitro*, Sal-A increases endothelial barrier function in LPS-stimulated endothelial cells [111]. Multiple disease conditions, such as ischemia/reperfusion, impair NO production. Sal-A reverses the ischemia/reperfusion-induced decrease in NO bioavailability by decreasing MKP-3 (mitogen-activated protein kinase phosphatases 3)[112]. Sal-A also inhibits AGE (advanced glycation end products)-induced endothelial cell injury[109]. A more recent study has shown that Sal-A is a safe ET1 type A receptor (ET_AR) antagonist in HEK293 cells overexpressing ET_AR (IC_{50}=5.7 μmol/L)[113], suggesting that Sal-A could have therapeutic effects in hypertension-associated vascular remodeling. Sal-A does not affect basal endothelial cell proliferation and NO production, but it reduces Ang II-induced proliferation of human endothelial cells by inhibiting ROS generation as well as blocking the phosphorylation of Src and Akt[114]. Recent studies have shown that Sal-A represses TGF-β1 (transforming growth factor-β)- and hypoxia-induced endothelial-to-mesenchymal transition by activating Nrf2 and modulating Smads[115, 116]. Sal-A also attenuates PDGF-BB (platelet-derived growth factor-BB)-induced proliferation and migration of VSMCs via the PDGFRβ/ERK[108] and cAMP (cyclic adenosine monophosphate)/PKA (protein kinase A)/CREB (cAMP-response element binding protein) signaling pathways and shows efficacy in preventing neointimal hyperplasia[110].

Effects of Sal-A on macrophages

In macrophages, Sal-A serves as an NF-κB inhibitor by targeting IKKβ (inhibitor of NF-κB kinase) as well as an activator of anti-oxidant HO-1, thereby suppressing LPS-induced upregulation of pro-inflammatory mediators (COX2, iNOS, TNFα and IL-6) and the generation of NO and PDE2[117, 118]. Sal-A also attenuates Ang II-induced macrophage apoptosis by inhibiting the activation of Akt and NF-κB[119], suggesting the occurrence of broad anti-inflammatory activities induced by multiple pro-inflammatory stimuli. It remains to be investigated whether Sal-A affects cholesterol uptake and efflux and resultant foam cell formation in macrophages.

Anti-thrombotic effects of Sal-A, its derivatives and preparations

In 1994, Yu *et al*[120] evaluated the thrombo-protective effects of acetylsalvianolic acid A, a chemically modified derivative of Sal-A. The authors observed that acetyl-Sal-A could inhibit platelet aggregation induced by multiple pro-aggregative stimuli, including thrombin, collagen, ADP, and arachidonic acid, suggesting that acetyl-Sal-A has potent anti-thrombotic activities. Subsequent *in vitro* and *in vivo* studies have confirmed that Sal-A inhibits ADP and collagen-induced platelet aggregation and arterial thrombus formation in mice[121-124]. Salvianolic acids, in particular Sal-A and Sal-C, are core components of Danhong injection exerting anti-thrombotic activity[125]. The cardiovascular actions of salvianolic acids have recently been comprehensively reviewed elsewhere[126].

Salvianolic acid B

Salvianolic acid B (Sal-B) and its derivative magnesium lithospermate B (also known as magnesium tanshinoate B) are commercially available and named Sal-B for simplicity hereafter.

Protective effects of Sal-B on endothelial function

In 2001, two research groups simultaneously reported that Sal-B improved endothelial function by decreasing TNFα-activated monocyte adhesion to endothelial cells[127] as well as VEGF-triggered hyperpermeability in endothelial cells[128], respectively. Subsequent studies have shown that Sal-B decreases TNFα-induced upregulation of PAI1 (plasminogen activator inhibitor-1), ICAM-1 and VCAM-1 by inhibiting NF-κB and AP1 activity as well as upregulating the anti-oxidant Nrf2/HO1 pathway[129-131], underscoring its therapeutic effects in ameliorating inflammation by activating Nrf2 *in vivo*[132]. Sal-B modulates endothelial hemostasis by increasing tissue-type plasminogen activator (t-PA), anti-coagulant

thromomodulin (TM), and eNOS-dependent NO production, while decreasing pro-thrombotic PAI1[133, 134]. Sal-B also inhibits LDL oxidation[135, 136], extravasation[137] and ensuing oxLDL-induced endothelial cell injury[135] and apoptosis[138]. Sal-B also prevents oxidant H_2O_2-induced endothelial cell injury by activating the GRP78 (glucose regulated protein 78 kDa)/ATF6 (activating transcription factor 6) and PI3K (phosphoinositide 3-kinase) pathways[139, 140]. In addition, Sal-B also improves endothelium-dependent vasorelaxation in diabetic rats with fluctuating blood glucose levels [141], as well as angiotensin II-infused mice[142], by inhibiting AT1 receptor and NADPH oxidase-dependent ROS production, as well as restoring eNOS phosphorylation at Ser1177.

Inhibitory effects of Sal-B on VSMC proliferation and migration

In VSMCs, Sal-B attenuated the proliferation and migration of VSMCs (induced by PDGF-BB, serum, LPS and stromal cell-derived factor-1α (SDF-1α)) by cell cycle arrest and blocking CXCR4 as well as activating the Nrf2/HO1 pathway[131, 143, 144]. Another anti-proliferative mechanism of Sal-B is exerted by inhibiting TNFα-induced upregulation of MMP-2 expression and activity[145].

Inhibitory effects of Sal-B on foam cell formation

In LPS-activated RAW264.7 macrophages, Sal-B inhibits iNOS-dependent NO production by activating the HO1 pathway[146]. Sal-B also reduces CD36-dependent oxLDL uptake while promoting cholesterol efflux via the PPARγ/LXRα/ABCA1 pathway[147], thereby inhibiting foam cell formation[102, 147, 148].

Inhibitory effects of Sal-B on platelet aggregation

In platelets, Sal-B significantly inhibits ADP and thrombin-induced platelet aggregation by reducing the release of soluble P-selectin and antagonizing the activity of phosphodiesterase (PDE) and P2Y12 receptor[130, 149, 150]. As a result, Sal-B reduces the adhesion of ADP-activated platelets to endothelial cells via the NF-κB-driven inflammatory response[149] and limits LPS-induced disseminated intravascular coagulation in rabbits[151].

The above-mentioned combined effects potentially contribute to the protective effects of Sal-B against neointimal hyperplasia[135, 152], angiotensin II-induced hypertension[142], hyperglycemia/dyslipidemia[153], and atherosclerosis development in ApoE$^{-/-}$ mice [154, 155].

Protocatechuic aldehyde

In 2004, Chan *et al*[95] compared the efficacy of several components from the aqueous extract of Danshen in preventing Hcy-induced endothelial injury and observed that protocatechuic aldehyde also possesses protective effects, although it is less efficacious than danshensu. Subsequent studies have revealed that protocatechuic aldehyde inhibits LPS-induced endothelial cell injury and apoptosis by inhibiting caspase 3, thereby maintaining endothelial cell barrier integrity[156]. Protocatechuic aldehyde and its precursor compound 3-hydroxybenzaldehyde also inhibit TNFα-induced endothelial inflammation (ICAM-1 and VCAM-1 upregulation) and monocyte adhesion to endothelial cells by inhibiting the activation of JNK, AP1 and NF-κB[157-159]. In VSMCs, protocatechuic aldehyde and its precursor compound 3-hydroxybenzaldehyde show activity in attenuating PDGF-BB-stimulated migration and proliferation (via MAPK and PI3K/Akt pathways) of VSMCs and inhibiting platelet aggregation and the occurrence of neointimal hyperplasia as well as intravascular thrombosis *in vivo*[159, 160]. A more recent study has identified GPER1 (G protein-coupled estrogen receptor-1) as the protective mechanism of protocatechuic aldehyde against endothelial dysfunction both *in*

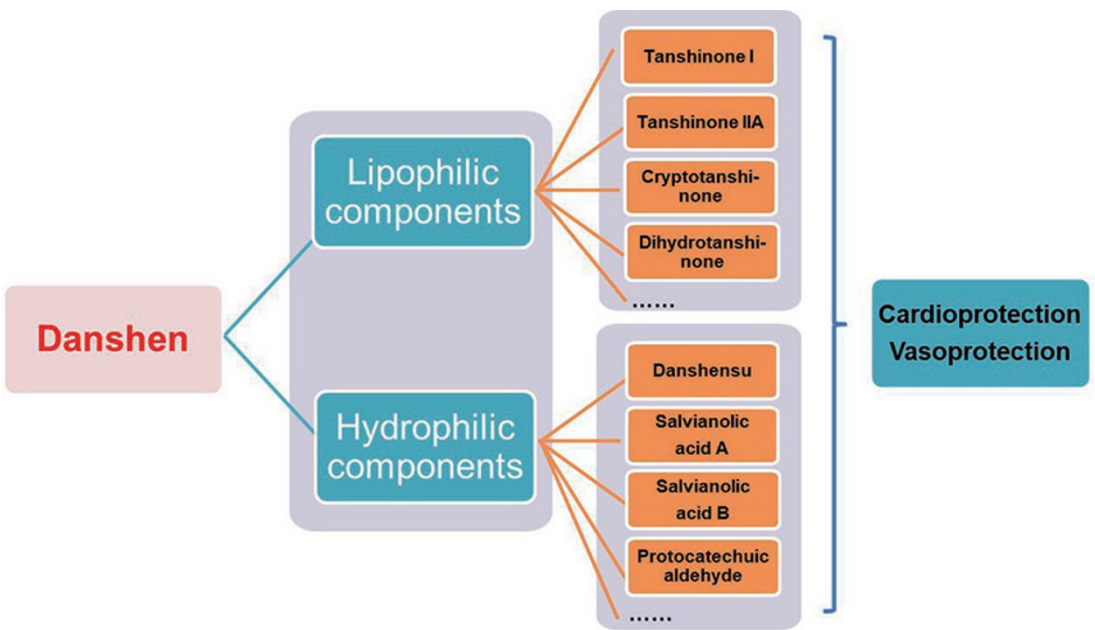

Figure 2. The multi-component nature of Danshen in cardioprotection and vasoprotection.

vitro and *ex vivo* [161]. In TNFα-stimulated macrophages, protocatechuic aldehyde reduces HMGB1 (high mobility group box-1 protein) expression by blocking the activation of NF-κB, underscoring its protective effects against the inflammatory response associated with rat sepsis (induced by cecal ligation and puncture)[162]. Based on the protective effects mentioned above, protocatechuic aldehyde could potentially ameliorate experimental atherosclerosis in animal models, warranting further studies.

In addition to the above-described vasoprotection, bioactive constituents from Danshen also show prominent cardioprotective effects in several heart diseases. In the next section, we will provide an overview of the protective effects and mechanism of individual compounds in cardioprotection.

Cardioprotective effects of Danshen

Pathophysiology of heart diseases

Coronary heart disease is the leading cause of death and disability worldwide. The acute occlusion of the coronary artery commonly induced by atherosclerosis and plaque rupture subjects the myocardium to acute myocardial ischemia [163]. Ischemia of the heart resulting from oxygen and nutrient supply deprivation can lead to cardiomyocyte death and subsequently demarcate the area at risk of myocardial infarction[164]. Restoration of blood flow in the ischemic heart using either thrombolytic therapy or primary percutaneous coronary intervention induces additional cardiac damage, termed "myocardial ischemia-reperfusion injury"[164, 165]. Chronically, the disturbance of cardiac homeostasis, implied by the loss of myocytes, inflammatory events and oxidative stress insult, leads to the development of pathological cardiac remodeling[166]. A prominent feature of the remodeling heart is cardiomyocyte hypertrophy[167], which is due to the dysregulation of a number of cardiac transcription factors[168, 169]. Extracellular matrix remodeling is also involved, which is characterized as fibrosis and activation of MMPs[170]. Cardiac remodeling is the key pathophysiological process leading to heart failure[163, 166, 171].

Effects of Danshen components on heart diseases

A huge amount of experimental and clinical research have reported that Danshen, either the crude medicine or its preparations (Danshen injection, Danshen dripping pill, Danhong injection, and Danshen-Gegen decoction, among others), are favorable for the heart during pathological processes, such as myocardial ischemia, myocardial infarction, and reperfusion injury[172-180]. Danshen components, in particular the lipophilic tanshinone IIa and cryptotanshinone as well as the hydrophilic Danshensu, Sal-A and Sal-B, show potent beneficial effects on the heart. Most of these bioactive components protect the heart against acute ischemic injury due to their anti-oxidant, anti-inflammatory and anti-apoptotic properties. Additionally, some of them show favorable effects on pathological cardiac remodeling, reflecting their potential therapeutic promise in treating chronic heart diseases, such as heart failure. In the following section, we focus on the cardioprotective effects and mechanisms of the major Danshen components (Supplementary Table S2).

Major lipophilic components

Tanshinone IIa

Tanshinone IIa is one of the major components of lipophilic tanshinones in Danshen. Due to its poor absorption through the intestine, its sodium sulfate derivative STS has been developed to enhance the bioavailability[181]. The cardioprotective effects of tanshinone IIa and STS are discussed below with respect to their potent protective effects against acute cardiac ischemic injury, including myocardial infarction, myocardial I/R injury and arrhythmia, as well as chronic pathological cardiac remodeling, including cardiac hypertrophy and cardiac fibrosis.

Protective effects of Tanshinone IIa against ischemic injury of the heart

STS has been widely used in clinics for the treatment of coronary heart disease. Pharmacological studies have demonstrated that tanshinone IIa protects the heart against ischemic injury and would be a promising therapeutic agent in MI, myocardial I/R injury and arrhythmia.

MI is an orchestrated event that combines cardiomyocyte death (reflected as necrosis, apoptosis and autophagy), a massive inflammatory burst and ROS generation, in response to arrhythmic injury[182]. In animal models of MI, tanshinone IIa can reduce the MI size and preserve cardiac function[183-188]. These beneficial effects are not limited to the ability of tanshinone IIA to dilate the coronary artery and increase coronary blood flow but also to its anti-oxidant, anti-inflammatory, and anti-apoptotic effects on cardiomyocytes. The antioxidant effect of tanshinone IIa is attributed to the modulation of the redox-sensitive ERK/Nrf2/HO1 and AMPK/ACC (acetyl-coenzyme A carboxylase)/CPT1 (carnitine palmitoyltransterase-1) pathways[185] and the stimulation of an electron transfer reaction in mitochondria[189]. Inflammation is critically involved in the pathogenesis of MI. In this regard, tanshinone IIa inhibits the activation of NF-κB, eventually attenuating the expression of the inflammatory mediators MCP1, TGF-β1 and TNFα and preventing macrophage infiltration into the infarcted myocardium[184]. Additionally, tanshinone IIa attenuates the formation of the NOD-like receptor (NLR) family, pyrin-domain containing 3 (NLRP3) inflammasome, which has been identified as a mediator of the inflammatory response in MI[190], and subsequently prevents the downstream inflammatory cascades and lipid metabolism disorder[183]. Tanshinone IIa prevents cardiomyocyte apoptosis induced by oxidative stress[191-194], hypoxia[195, 196], and oxygen-glucose deprivation/recovery[197]. The mechanisms underlying these anti-apoptotic effects involve the downregulation of caspase-3 and upregulation of the Bcl-2/Bax ratio via the PI3K/Akt-dependent[192, 195, 198] or JNK/SAPK (stress-activated protein kinase)/MAPK signaling pathway[194], as well as the regulation of microRNAs[192, 196, 199, 200]. MicroRNAs are short, highly conserved, non-coding RNAs that regulate gene expression at the post-transcriptional level by inhibiting translation or promoting degradation of target mRNAs [201]. Tanshinone

IIa upregulates the anti-apoptotic miR-133[192, 196] and miR-152-3p[200], whereas it decreases the apoptotic miR-1[199]. All these observations have yielded promising results indicating that tanshinone IIa might be favorable for the treatment of MI. In addition to its benefits alone, tanshinone IIa also interacts with other agents or therapeutics in MI treatment. Combined therapy of tanshinone IIa and simvastatin reduces circulating inflammatory markers and improves symptoms of angina and blood stasis syndrome in post-MI patients[202]. Due to its ability to increase bone marrow mesenchymal stem cell (BMSC) engraftment in the ischemic myocardium, tanshinone IIa enhances the efficacy of BMSC transplantation treatment, which aims to confine myocardial damage and regenerate the myocardium in acute MI[203, 204]. In contrast, tanshinone IIa can ameliorate the cardiotoxicity effect of adriamycin (also known as doxorubicin), an effective antineoplastic agent, mainly by preventing against cardiac apoptosis and lipid oxidation[205-208].

Myocardial I/R injury refers to the damage to the heart caused by the restoration of coronary blood flow after an ischemic episode[164, 165]. Treatment of tanshinone IIa, prior[209-213] or after[214, 215] I/R injury, reduces the infarct size and ameliorates several consequences of myocardial I/R, including the myocardial zymogram, oxidative status, cardiac dysfunction and microstructure disorder. These observations have confirmed that tanshinone IIa is able to prevent and cure myocardial I/R injury. Optimization of the therapeutic time window for sodium tanshinone IIa sulfonate (8 mg/kg) resulted in 2 h to 4 h after reperfusion[214]. The underlying pathophysiology of myocardial I/R injury likely involves many factors, such as oxidative stress, intracellular calcium overload, altered cardiac energy metabolism, activation of cardiomyocyte apoptosis, and inflammatory responses[164]. Tanshinone IIa can decrease ROS production[209, 214], inhibit inflammation[209, 212, 213], and protect cardiomyocytes against apoptosis[211, 213, 216], potentially contributing to its beneficial effects on myocardial reperfusion injury.

During cardiac ischemia, arrhythmia commonly occurs, which might consequently lead to cardiac death. Tanshinone IIa decreases the incidence of arrhythmias induced by acute cardiac ischemia. This anti-arrhythmic effect is not fully understood. Shan *et al* reported that tanshinone IIa restored the diminished inward rectifying K^+ (Kir) current and Kir2.1 protein level after MI in rat ventricular myocytes by suppressing miR-1[199]. Controversially, Sun *et al* have demonstrated that tanshinone IIa predominantly activates cardiac KCNQ1/KCNE1 K^+ channels without affecting other K^+ channels, including Kir, Kv1.5, or hERG (human ether-a-go-go-related gene)[217]. In addition to K^+ channels, hyperpolarization-activated cyclic nucleotide-modulated (HCN) channels have also been reported to be involved in the anti-arrhythmic effect of tanshinone IIA. The precise underlying mechanisms remain to be determined to draw more definite conclusions.

Protective effects of Tanshinone IIa against pathological cardiac remodeling

The protective effects of tanshinone IIa or STS against pathological cardiac remodeling are associated with its ameliorative effect against cardiac hypertrophy and cardiac fibrosis. The anti-hypertrophic properties of tanshinone IIa have been observed in spontaneously hypertensive rats [218, 219], two-kidney one-clip hypertensive rats[220], two-kidney two-clip hypertensive rats[221], angiotensin II-infused rats[222], and pressure-overloaded rats induced by transverse aortic constriction[223]. In most of these studies, favorable effects of tanshinone IIa have reflected the decrease in the ratio of left ventricular weight to body weight, and the decrease in cardiomyocyte size and diameter are independent of the alteration of systemic blood pressure[218, 220-222], thus eliminating the possibility that tanshinone IIa modulates cardiac hypertrophy by lowering blood pressure. The main drivers of pathological hypertrophy are neurohumoral mediators, particularly the renin–angiotensin system and the beta-adrenergic system[224]. Tanshinone IIa represses the hypertrophic process in response to hypertrophic stimuli, including angiotensin II[222, 225, 226], isoproterenol (ISO)[227], and insulin-like factor-II (IGF-II)[228], suggesting a broad anti-hypertrophic effect of tanshinone IIa. The regulation of tanshinone IIa in cardiomyocyte hypertrophy involves multiple mechanisms: (1) tanshinone IIa suppresses intracellular signaling pathways that regulate expression of the cardiac genes encoding structural proteins or regulatory proteins, including MEK/ERK[222], AP1 (c-jun/c-fos)[225, 226], calcineurin/NFAT3 (nuclear factor of activated T cells 3)[227, 228], and the Cys-C/Wnt signaling pathway[219]; (2) tanshinone IIa upregulates eNOS expression and promotes the phosphorylation of eNOS in the myocardium[187, 219]; (3) tanshinone IIa activates silent information regulator 1 (SIRT1) to attenuate oxidative stress and inflammation involved in cardiac hypertrophy[223]; (4) tanshinone IIa diminishes NADPH oxidase-derived oxidative stress[221]. The anti-fibrotic effects of tanshinone IIa involve inhibition of myofibroblast proliferation [229]; prevention of the deposition of extracellular matrix (ECM) components, such as collagen and fibronectin[230-234]; and regulation of the balance between MMPs and tissue inhibitor of metalloproteinases (TIMPs)[220, 232, 235, 236]. Mechanistically, these anti-fibrotic effects are mainly associated with the reduction of ROS production via the repression of NADPH oxidase[221, 230, 236] and suppression of the typical fibrotic signaling pathway TGFβ1/Smad-2 or -3[233, 234]. It has recently been reported that microRNAs are also involved in the regulation of tanshinone IIa in cardiac fibrosis. Tanshinone IIa upregulates the expression of miR-29b, which inhibits the synthesis of collagen through directly binding to its 3′ untranslated regions[233]. Taken together, these detailed studies suggest a promising effect of tanshinone IIa on attenuating pathological cardiac remodeling. Indeed, clinical studies provide evidence that STS treatment in patients with ST-segment elevation myocardial infarction, when used in combination with current therapies, may significantly reduce adverse left ventricular remodeling and potentially improve clinical outcomes[237, 238]. Because of close association of cardiac remodeling with the development of heart failure, such experimental and clinical observations might suggest an emerging role of tanshinone IIa in chronic heart diseases, such as heart failure.

Cryptotanshinone

A limited number of reports regarding the cardioprotective effect of cryptotanshinone are available to date. We[239] and others[240] have previously reported that cryptotanshinone has protective effects against MI and myocardial I/R injury *in vivo*. In an acute MI experimental model induced by coronary artery ligation, cryptotanshinone dose-dependently ameliorated the disordered arrangement of myocardial tissues and accumulation of inflammatory cells[239]. In a rat model of myocardial I/R injury induced by occluding the left anterior descending coronary artery, pre-treatment of cryptotanshinone significantly reduced the infarct size and improved myocardial contractile dysfunction[240]. The underlying mechanisms were concluded to be the amelioration of microcirculatory disturbances through inhibition of endothelial inflammation. Unfortunately, the effects of cryptotanshinone on cardiac cells were not assessed in that study[240]. Jin *et al* reported that cryptotanshinone prevents cardiomyocyte apoptosis induced by hypoxia, potentially by modulating the mitochondrial apoptosis signaling pathway (referring to the regulation of mitochondrial hyperpolarization, cytochrome *c* release and caspase-3 activity) and expression of pro-apoptosis proteins[195]. In addition, a more recent study has revealed that cryptotanshinone improves mitochondrial function in cardiomyocytes by promoting mitochondrial biogenesis and ATP production and by suppressing the generation of free radicals[241]. These observations might at least partially explain the cardioprotective effect of cryptotanshinone on MI and myocardial I/R injury. Furthermore, the effect of cryptotanshinone against cardiac fibrosis has been investigated by our group[239] and others[242]. The underlying mechanisms are mainly related to the suppression of MMP-2 production and NADPH oxidase-dependent ROS production[239, 242]. The therapeutic potential of cryptotanshinone in the treatment of heart diseases must be further elucidated.

Tanshinone IV

Tanshinone IV and its water-soluble derivatives can recover cardiac contractility during hypoxia/reoxygenation injury by improving myocardial energy production and inhibiting calcium overloading[243-245]. These observations suggest the potential role of tanshinone IV against cardiac ischemia. In addition, tanshinone IV has been reported to prevent cardiomyocyte hypertrophy and cardiac fibrosis after stimulation by several humoral factors, including Ang II, ET1, IGF1 and the α-adrenoceptor agonist phenylephrine[246, 247]. Further *in vivo* studies are still needed to assess the cardioprotective effects of tanshinone IV.

Major hydrophilic components

Danshensu

Protective effects of Danshensu against myocardial ischemia injury and I/R injury

In a rat model of myocardial ischemia injury induced by ISO, Danshensu can reverse changes in heart morphology and electrocardiographic patterns, and it can reduce the serum level of creatine kinase and lactate dehydrogenase, which are regarded as diagnostic marker enzymes for altered cardiac membrane integrity and/or permeability in MI[248]. In the rat MI model induced by left anterior descending coronary artery ligation, Danshensu can alleviate myocardial ischemia injury by potentiating post-ischemia neovascularization, probably by improving endothelial progenitor cell survival against hypoxia and accelerating proangiogenic functions[249]. By using the whole-cell patch-clamp techniques, Danshensu has been observed to inhibit the L-type calcium current, leading to a recovery of the augmented myocardial contractility that responds to myocardial ischemia injury[248].

Additionally, Danshensu has been demonstrated to prevent myocardial I/R injury, which is related to its anti-apoptotic effects, by activating the PI3K/Akt and ERK1/2 signaling pathways[250], as well as its antioxidant effects by activating the Akt/ERK/Nrf2/HO-1 signaling pathways [251]. A recent study using a coexpression network-based approach by integrating gene expression profile and protein-protein interaction data suggests that the protective effect of Danshensu in coronary heart disease is associated with sodium/hydrogen exchanger 3 (SLC9A3), prostaglandin G/H synthase 2 (PTGS2), oxidized low-density lipoprotein receptor 1 (OLR1), and fibrinogen gamma chain (FGG)[252].

Protective effects of Danshensu against pathological cardiac remodeling

In pathological cardiac remodeling, Danshensu can diminish cardiac hypertrophy and cardiac fibrosis in response to spontaneous hypertension or β-adrenergic activation[253, 254]. Danshensu also inhibits aldosterone-induced cardiomyocyte apoptosis by interfering with the p53 signaling pathway, suggesting that Danshensu is protective against heart failure caused by overactivation of the renin-angiotensin-aldosterone system[255]. Moreover, Danshensu is anti-arrhythmic, as implied by observations that Danshensu reduces the incidence of ventricular tachycardia and ventricular fibrillation[253, 254].

Cardioprotective effects of Danshensu derivatives and preparations

Although Danshensu has shown promising cardioprotective effects, its poor chemical stability, poor cellular permeability and low bioavailability have limited its therapeutic applications[256]. Thus, a series of novel derivatives of Danshensu have been developed. Pharmacological investigations have shown that these derivatives prevent myocardial ischemia injury in the heart, confirming their therapeutic potential in heart diseases[256-261]. Additionally, the combination of Danshensu and other agents, such as hydroxysafflor yellow A[262], paeonol[263, 264], and puerarin[265, 266], shows synergistic cardioprotective effects, thus providing additional options for the clinical uses of Danshensu.

Salvianolic acid A

The predominant cardioprotective effects of Sal-A are to confine myocardial damage during the progression of MI and reperfusion injury. In MI models induced by either coronary artery ligation or ISO, Sal-A decreases the infarct size and improves systolic function post-MI[267-270]. One of the pos-

sible underlying mechanisms is suggested to be associated with its antioxidant properties. Sal-A is a potent free radical scavenger due to its polyphenolic structure[271]. Additionally, Sal-A improves cellular anti-oxidative defense against oxidative stress by elevating the activity of superoxide dismutase, catalase and glutathione peroxidase[269]. Moreover, Sal-A is able to maintain mitochondrial integrity and protect against mitochondrial respiratory function[269]. Considering these antioxidant properties together, Sal-A ameliorates oxidative stress-induced impairment of cellular functions and cell death in the myocardium. Another possible involved mechanism might be the ability of Sal-A to promote angiogenesis around the infarcted area[268, 272]. Sal-A enhances the expression of pro-angiogenic factors, such as VEGF and VEGFR2, and elevates the numbers and function of endothelial progenitor cells (EPCs), leading to vasculogenesis and subsequently increasing the blood flow supply in the ischemic myocardium[268]. In addition to MI, Sal-A has also been shown to protect against myocardial I/R injury[273-277]. This protection is achieved by the reduction of myocardial cell apoptosis and damage induced by oxidative stress[274, 275, 278], prevention of intracellular calcium overload by blocking L-type calcium current[276], and inhibition of platelet aggregation and inflammation[277].

Although comprehensive investigations of Sal-A in cardiac remodeling are not currently available, a study has revealed that Sal-A acts as a MMP-9 inhibitor to attenuate cardiac fibrosis in the spontaneously hypertensive rat[279], shedding new light on the cardioprotective effects of Sal-A in pathological remodeling.

Salvianolic acid B

Protective effects of Sal-B against MI and I/R injury

Similarly to Sal-A, Sal-B has demonstrated cardioprotective effects on cardiac ischemic injury[187, 280-282] and reperfusion injury[283-288].

During acute MI, Sal-B regulates multiple targets involved in cell apoptosis pathways, including the pivotal poly (ADP-ribose) polymerase-1 (PARP-1) and NF-κB signaling pathways[282]. In addition, Sal-B disrupts the interaction between p38 and TGFβ-activated protein kinase 1-binding protein 1 (TAB1), inhibiting the autophosphorylation of p38 and finally inhibiting TAB1/p38-mediated apoptosis signaling[280]. In addition to these anti-apoptotic effects, Sal-B inhibits voltage-dependent Ca^{2+} channels[289] and the Ca^{2+}-dependent cAMP and downstream PKA signaling[281], which might also contribute to its anti-MI effects. Like tanshinone IIa, treatment with Sal-B could enhance BMSC transplantation[290, 291] and suppress the apoptosis of embryonic stem cell (ESC)-derived cardiomyocytes[292], suggesting that Sal-B holds therapeutic potential in stem cell therapy for MI.

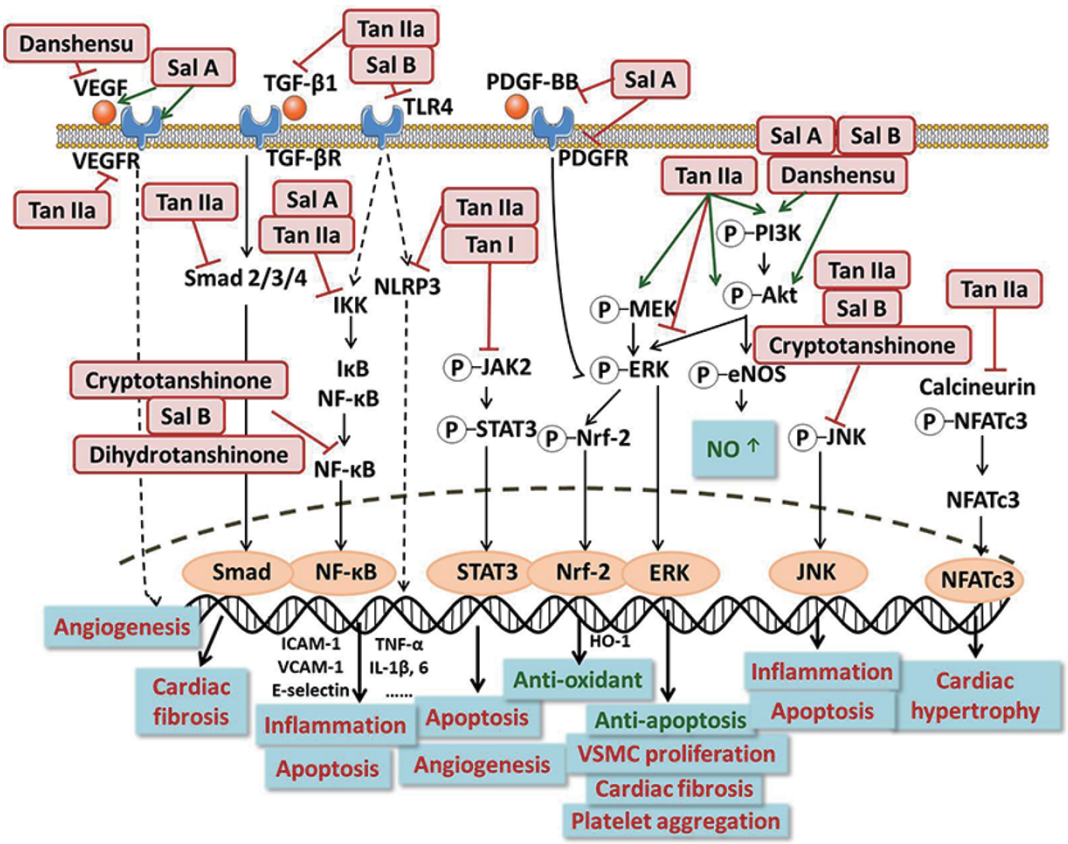

Figure 3. The major signaling pathways involved in the cardiovascular effects of Danshen components.

The predominant mechanism underlying the beneficial effect of Sal-B against myocardial I/R injury is associated with its anti-apoptotic properties[283, 287]. This anti-apoptotic effect involves the regulation of relevant signaling pathways during myocardial I/R damage, including the PI3K/Akt-dependent[287] and SAPK signaling pathways[283]. Additionally, the cardioprotective effects of Sal-B against myocardial I/R injury have also been attributed to its anti-oxidant and anti-inflammatory properties[286, 288, 293]. Moreover, Sal-B suppresses autophagy by upregulating miR-30a to improve cardiomyocyte viability during myocardial I/R damage[285, 294].

Protective effects of Sal-A against cardiac remodeling

Jiang *et al* have previously identified Sal-B as a MMP-9 inhibitor to prevent cardiac remodeling[295]. Our recent study has shown that Sal-B prevents cardiomyocyte hypertrophy by inhibiting PARP1[296]. These observations thus suggest the potential effects of Sal-B in the treatment of heart failure, which develops as an automatic response to pathological cardiac remodeling. In agreement with this notion, a recent study has demonstrated that Sal-B alleviates heart failure induced by pressure overload[297]. Therefore, Sal-B holds promise for cardioprotection against heart failure but requires confirmation in more experimental and clinical studies.

Protocatechuic aldehyde

An accumulating amount of research has shown that protocatechuic aldehyde exerts multiple biological activities, such as antioxidant, anti-inflammatory, anti-apoptosis and anti-proliferation in different tissues[298, 299]. In the heart, protocatechuic aldehyde prevents myocardial I/R injury due to its anti-inflammatory, anti-apoptosis, and anti-platelet aggregation effects[300]; prevents against cardiomyocyte apoptosis induced by hypertension[301]; and ameliorates angina by decreasing fatty acid oxidation, which is beneficial for the ischemic heart by switching the energy substrate preference from fatty acids to glucose[302]. Moreover, protocatechuic aldehyde is regarded as a promising cardioprotective complementary medicine, as determined from observations that protocatechuic aldehyde improves cardiac function in streptozotocin-induced type 1 diabetic rats[303] and prevents cardiotoxicity by exposure to the highly toxic environmental contaminant 2,3,7,8-tetracholorodibenzo-p-dioxin (TCDD)[304].

Conclusions and perspectives

Danshen is a multi-component herbal medicine that benefits the cardiac and vascular system[2]. The eminent cardiovascular actions and therapeutic potential of the lipophilic and hydrophilic components have sparked broad research interest in the past decade. Understanding the pharmacological and therapeutic profiles of these constituents may broaden the potential clinical applications of these compounds in the treatment of cardiovascular diseases, and they may promote small-molecule cardiovascular drug discovery and development through the use of these compounds as important sources of lead compounds. Based on the broad cardiovascular protective profile of these bioactive constituents, it can be recognized that both lipophilic and hydrophilic components may function in concert, targeting different tissues and signaling pathways to achieve the versatile cardiovascular actions of Danshen in experimental animals and humans. However, the differential pharmacokinetic and pharmacodynamics properties of individual compounds remain a hurdle to the systematic evaluation of the cardiovascular efficacy of Danshen. In particular, tanshinone IIa[305] and cryptotanshinone[306] have relatively low oral bio-availability. Therefore, new formulation strategies and combination therapy that might maximize the beneficial actions and reduce the potential side effects would have great therapeutic potential in this regard[307].

Although research investigating the cardiovascular effects of Danshen is expanding, many questions remain unaddressed. In the vascular system, although sodium tanshinone IIa sulfate is widely used in the clinic to treat patients with coronary artery disease, clinical studies addressing the efficacy of tanshinone IIa in patients with atherosclerosis merit further investigations. Additionally, understanding of the therapeutic basis of other bioactive components remains limited. In the cardiac system, although most of the Danshen components demonstrate promising therapeutic potential for the management of MI and myocardial I/R injury, investigations of their pharmacological actions on cardiac hypertrophy and cardiac fibrosis remain limited. The possible therapeutic role of Danshen components for the treatment of chronic heart diseases related to cardiac remodeling must be further elucidated. Future directions of cardiovascular research involving Danshen include the following: (1) use of the total synthesis of bioactive components of Danshen for the purpose of cardiovascular therapeutics as an alternative to obtaining purified compounds from the medicinal plant, such as the recently described synthesis of tanshinone I[308]; (2) use of a systems biology approach, such as RNA-sequencing[309], or network-based pharmacological research[310] to understand the gene regulation profile of each individual compound at the genome-wide level; and (3) elucidation of the therapeutic effects of Danshen components in cardiovascular aging, which is a common basis for all major cardiovascular and metabolic diseases. Overall, Danshen and its bioactive constituents represent an invaluable source for small-molecule cardiovascular drug discovery. Currently, Danshen and its preparations (such as Fufang Danshen Dripping Pill, Fufang Danshen injection, and Danhong injection, among others) have been widely used in China[1-4]. However, clinical applications of these Danshen preparations in other countries are still limited. Investigations of the cardiovascular effects and mechanisms of Danshen and its bioactive constituents may also broaden our understanding of Danshen and its preparations for therapeutic applications worldwide.

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Supplementary information

Supplementary information is available at the website of Acta Pharmacologica Sinica.

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