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POTENTIAL MEDICINAL HERB FOR CARDIOVASCULAR HEALTH: A COMPREHENSIVE REVIEW ON *Salviae miltiorrhizae*

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ABSTRACT

Cardiovascular disease (CVD) and its associated risk factors have been ranked the number 1 cause of mortality in non-communicable diseases worldwide and Malaysia. The high statistic in CVD mortality indicates gaps and limitations in current treatment strategies using long-term drug prescription therapies. Hence, an immediate quest for alternative and effective treatments is needed. Medicinal herbs, which are ethnopharmacologically used to treat a wide range of conditions, have been used as an alternative or supplementary treatment for CVDs and their associated risk factors. The roots of *Salviae miltiorrhizae* have been traditionally used for centuries to treat various diseases including neurological disorders, cancer, and even coronary heart disease. Increasing evidence demonstrated a pharmacological basis for the action of *S. miltiorrhizae* and its active compounds, suggesting its potential in treating CVD. The objectives of this review were first to summarize published literature and synthesize the new body of knowledge on the use of *S. miltiorrhizae* as the potential medicinal herb that will positively impact the cardiovascular system, and secondly to elucidate the underlying mechanisms involved in promoting cardiovascular health. It is hoped that identification of key regulatory pathways by lipophilic and hydrophilic active compounds from *S. miltiorrhizae* will aid further investigation of its safety and efficacy to promote the use of evidence-based traditional medicinal herbs in alleviating symptoms and improve the prognosis of CVDs and their associated risk factors.

Key words: Atherosclerosis, diabetes, hypercholesterolemia, hyperlipidemia, hypertension

INTRODUCTION

Non-communicable diseases (NCDs) are a major health problem worldwide. Cardiovascular diseases (CVDs) and their associated risk factors were particularly found to contribute significantly to the number of NCD cases and are the leading cause of global mortality (Laslett *et al*., 2012). According to World Health Organization (WHO) in 2017, there was an alarming number of 17.7 million deaths caused by CVDs per year. This is attributed to 31% of overall deaths globally (Sazlina *et al*., 2020). Even in Malaysia, the National Health and Morbidity Survey (NHMS) reported that in 2015, coronary artery disease was the main cause of CVD death, followed by stroke with a prevalence of 13.2%, and 6.9%, respectively (Sazlina *et al*., 2020). The prevalence of CVDs is predicted to increase up to more than 23.6 million by 2030 (Greenfield & Snowden, 2018). Consequently, deaths by CVDs have dominated the mortality rate worldwide.

CVDs include heart failure, myocardial infarction, atherosclerosis, coronary heart disease (CHD), stroke, cardiomyopathy, and peripheral artery disorders. Risk factors associated with CVDs are primarily caused by vascular dysfunction, often a result of thrombosis, atherosclerosis, obesity, diabetes, dyslipidemia, and hypertension, leading to subsequent damage of organs (Shaito *et al*., 2020). Many epidemiological studies have also indicated positive correlations between the incidence of CVDs and chronic alcohol consumption, smoking,

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psychosocial factors, physical inactivity, as well as insufficient consumption of vegetables and fruits (Rosiek & Leksowski, 2016; Sazlina *et al*., 2020). CVDs and their risk factors are commonly treated with continuous, long-term administration of aspirin, statins, beta-blockers, and angiotensin-converting enzyme (ACE) inhibitors (Rossello *et al*., 2015). Unfortunately, patient adherence to these classes of drugs has been proven poor due to direct and indirect costs of treatment, convenience, and lack of evidence for the efficacy of long-term medication intake and its effects after withdrawal (Nieuwlaat *et al*., 2013; McClellan *et al*., 2019). Inadequately treated or untreated patients due to poor medication adherence contribute to the plateau in CVD mortality trends that remain the leading cause of death worldwide (McClellan *et al*., 2019). Hence, this opens an avenue for alternative treatments other than western medicine. Besides utilizing western medicines as treatment for CVDs and their associated risk factors, medicinal herbs have been widely used as a potential alternative to treat CVDs (Pang *et al*., 2016).

To date, about 10,000 various phytochemicals have been discovered from medicinal herbs. However, there remains a wide range of unknown phytochemicals that have yet to be identified (Memariani *et al*., 2019). Since medicinal herbs possess beneficial phytochemicals that promote greater health, they are widely used in daily diet to improve the outcome of different diseases. Medicinal herbs can be prepared and consumed in various forms and ways, including ingesting whole herbs, syrup, teas, ointments, essential oils, and tablets or capsules that contain ground or powdered forms of raw herbs or even their dried extracts (Wachtel-Galor & Benzie, 2011). Over the decades, many studies have demonstrated the potential therapeutic benefits of medicinal herbs in treating CVDs and their associated risk factors. Therefore, there are attempts to enhance the research on medicinal herbs to maximize their efficacy in the treatments of CVDs.

Salviae miltiorrhizae Bunge, also known as Danshen (丹參) in Mandarin, is a popular traditional Chinese medicine used for treating various diseases including coronary heart disease, neurological disorders, and cancer (Su *et al*., 2015). In this review, we discussed the use of *S. miltiorrhizae* to treat CVDs and its associated risk factors in cell cultures, animal models, and clinical trials. It was hoped that this review would provide an overview of the beneficial effects of *S. miltiorrhizae* and promote more clinical trials on the uses of *S. miltiorrhizae* to treat CVDs and its associated risk factors.

Salviae miltiorrhizae

Salviae miltiorrhizae, is a perennial plant that belongs to the Lamiaceae family. It is predominantly found in mountainous areas, mainly in the west, southwest, and southeast regions of China as shown in Figure 1a (Li *et al*., 2013). It is a popular traditional Chinese medicinal herb that has been extensively utilized in various parts of the world, especially in Asian countries such as Mongolia, China, Korea, and Japan, for more than two millenniums.

The roots, Radix *S. miltiorrhizae* (Figure 1b), has a mild "cooling" effect on the body and has a bitter taste (Li *et al*., 2015). According to the records in "Shen Nong's Herbal Classic of Materia Medica", Radix *S. miltiorrhizae* has been significantly valued as an herb without detectable toxicity during the Dynasty of Qin and Han (Wang *et al*., 2016). In recent years, the roots of *S. miltiorrhizae* gained increasing attention from the scientific community due to its astonishing pharmacological activities. These pharmacological activities include the ability to elicit anti-oxidative, anti-cancer, anti-inflammatory, and anti-microbial effects, as well as the ability to promote blood circulation (Pang *et al*., 2016). Over the years, *S. miltiorrhizae* has been developed into over 30 medication formulations to treat CVDs, pneumonia, hyperlipidemia, and chronic nephritis (Wang, 2010).

Salviae miltiorrhizae contains more than 200 bioactive chemical compounds which can be categorized into two main groups, namely, hydrophilic phenolic compounds (water-soluble) and lipophilic diterpenoid compounds (lipid-soluble). Lipophilic compounds mostly contain tanshinone I, IIA, IIB, and cryptotanshinone (Figure 2a); whilst the main type of hydrophilic compounds are phenolic acids such as miltirone, protocatechuic acid, and various types of salvianolic acids (Figure 2b). Moreover, components such as tannin and vitamin E have been discovered in extracts of *S. miltiorrhizae*. These bioactive chemical compounds target various signaling pathways and have been tested in different cell types, animal models as well as in clinical trials (Wang *et al*., 2016).

Salviae miltiorrhizae can be administered as capsules, tablets, oral liquids, injectables, and granules (Ren *et al*., 2019). In most instances, it is prepared in the daily dosage of 9-15 g or boiled to make herbal tea or soup (Medicines Agency, 2021).

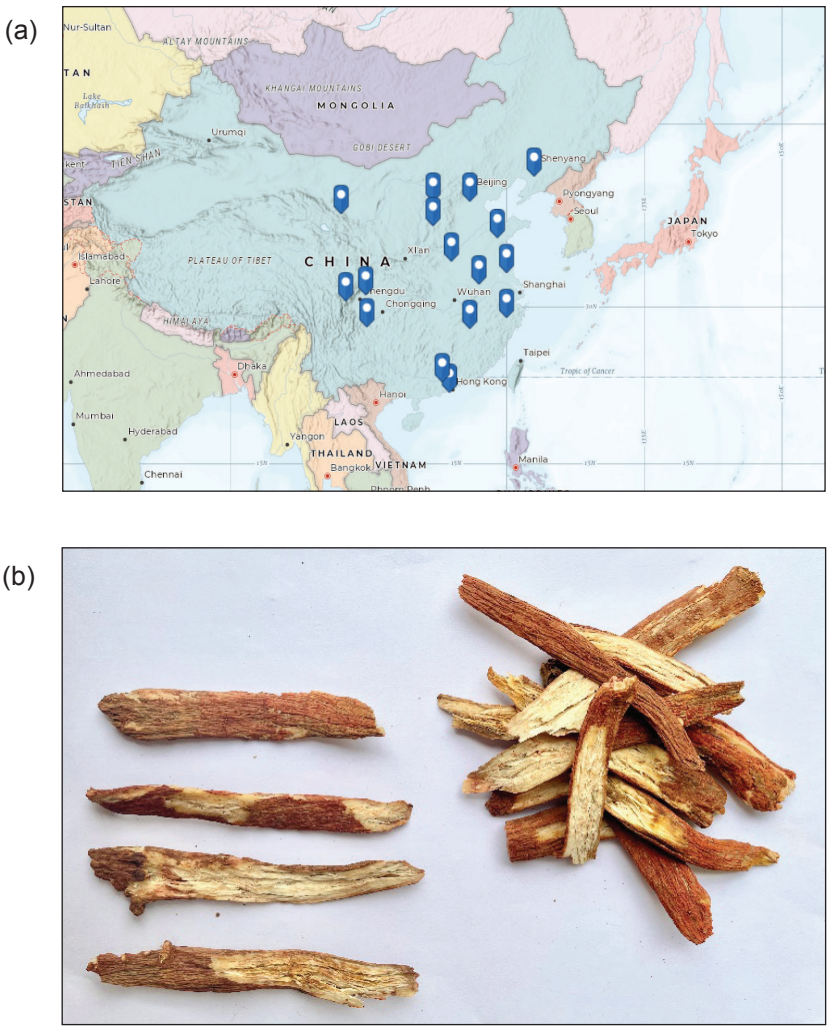

Fig. 1. (a) Wild and cultivated *Salviae miltiorrhizae* can be found in the west, southwest, and southeast regions in China (marked with blue location points). (b) The roots of *Salviae miltiorrhizae* are commonly sliced and dried for consumption.

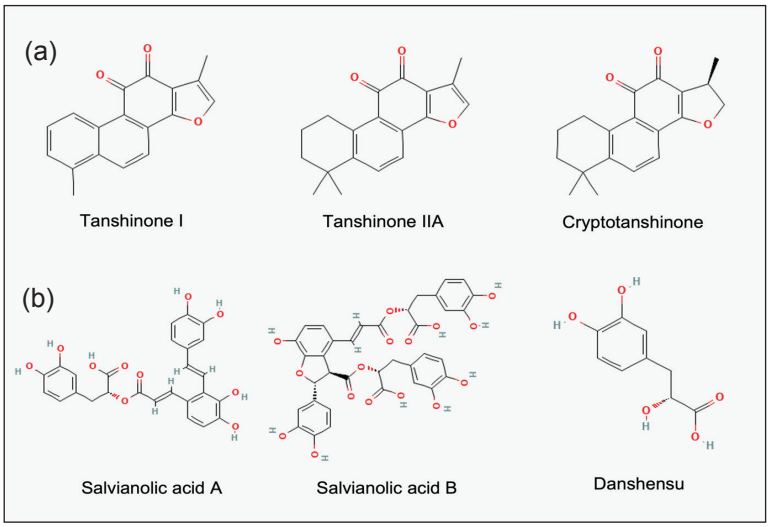

Fig. 2. (a) Lipophilic (b) hydrophilic active compounds in *Salviae miltiorrhizae* typically associated with promoting cardiovascular health

Biological properties of *Salviae miltiorrhizae* and its underlying mechanisms

Salviae miltiorrhizae and its active compounds, mainly Danshensu, tanshinone IIA, salvianolic acid B, tanshinone VI, and cryptotanshinone, were found to elicit protective effects on endothelial cells, smooth muscle cells, and cardiac myocytes. Over the last few decades, researchers thoroughly examined the preclinical pharmacological activity of *S. miltiorrhizae* related to the treatment of CVD and its associated risk factors using different animal models. The following sections reviewed the effects of *S. miltiorrizhae* in different components of the cardiovascular system and summarise its beneficial outcomes in preclinical and clinical trials as shown in Table 1 and Table 2 respectively.

Table 1. Effects of *Salviae miltiorrhizae* on hypertension, atherosclerosis, and myocardial ischemia *in vivo* models

In vivo **Models**	**Active component**	**Route of administration/ Dosage/ Duration**	**Main findings**	**References**
Hypertension				
Spontaneously hypertensive rats	Danshensu	intraperitoneal injection 10 mg/kg/day (6 weeks)	Decreased systolic and diastolic blood pressure; Increased inducible NO synthase activity and serum NO content; Lowered the incidence of ventricular fibrillation and ventricular tachycardia; Increased current density of K^+ and current density of Ca^{2+}-activated K^+ (K_{Ca}) channel in mesenteric vascular smooth muscle.	(Tang *et al.*, 2011a)
Isoproterenol induced myocardial hypertrophy rats	Danshensu	intraperitoneal injection 3 and 10 mg/kg (day 4 -7)	Reduced heart weight to body weight index and arrhythmia scores; Improved systolic and diastolic pressures of the left ventricle; Increased SOD and Cx-43 expression.	(Tang *et al.*, 2011b)
Spontaneously hypertensive rats	*Salviae miltiorrhizae*	intraperitoneal injection 1 g/kg/day (84 days)	Reduced LV mass index, sizes of cardiomyocytes, and collagen volume; circumferential area of perivascular space and the expression of TNF-α.	(Sun & Zheng, 2007)
Phenylephrine induced male SD rats	Magnesium tanshinoate B	intravenous injection 0.7-175 mg/kg (20 mins resting period after each dose or equilibration 15 min)	Reduced blood pressure (more than aqueous extract SME)	(Leung *et al.*, 2010)
ET-1 induced portal hypertension mice	Salvianolic acid B	intravenous injection 0.5 mg/mouse (3 days pre-treatment)	Lowered the average velocity of blood flow in the liver.	Tian *et al.*, 2009.
2-kidney-2-clip induced renovascular hypertension rat	Tanshinone IIA	intragastric gavage 35 and 70 mg/kg/day (6 weeks)	Attenuated the resulting interstitial fibrosis; Decreased the mRNA expressions of TIMP-1, TIMP-2, and MMP-9; improved cardiac fibrosis and improved cardiac function	(Fang *et al.*, 2010)

Table 1 continued...

Atherosclerosis				
Cholesterol-fed rabbits	*Salviae miltiorrhizae water-soluble extract*	Oral (incorporated in diet) 5% (wt/wt) (12 weeks)	Decreased endothelial injury; Improvement in the atherosclerotic area of the abdominal aorta, and cholesterol accumulation in the thoracic aorta.	(Wu *et al*., 1998)
ApoE-deficient mice	Cryptotanshinone	intragastric gavage 15 and 45 mg/kg/day (22 weeks)	Decreased atherosclerotic plaque formation and enhanced stability of plaque; reduced serum pro-inflammatory cytokines (IL-1B, IL-6, IL-7A, IFN-Ngamma, TNF-α); Reduction in LOX-1 and MMP-9.	(Liu *et al*., 2015)
HFD-induced atherosclerotic rabbits	Salvianolic acid B	Not mentioned 8 mg/kg/day (8 weeks)	Reduced triglyceride level; Elevated NO level.	(Wang *et al*., 2016)
HFD-induced atherosclerotic rabbits	Tanshinone IIA	intragastric gavage 15.0 and 37.5 mg/kg/day (2 months)	Improved SOD activity; Reduced MDA level; Decreased CD40 expression and MMP-2 activity.	(Fang *et al*., 2008)
HFD plus vitamin D3 induced atherosclerotic rats	Salvianolate	intraperitoneal injection 60, 120 or 240 mg/kg/day (12 weeks)	Reduced TC, LDL, IL-6, and CRP; Increased regulatory T cells.	(Meng et al., 2014)
Myocardial ischemia (MI)				
Closed-chest porcine model	Salvianolate	intravenous injection 10 mg/kg/day (7 days)	Improved capillary density and reduced infarct sizes; Increased activity of SOD and thioredoxin, and glutathione concentration; Decreased MDA concentration; increased Bcl-2/Bax protein expression ratio	(Han *et al*., 2011)
LAD induced MI rats	Fufang Danshen tablet	Intragastric gavage 1210 mg/kg (5 days)	Decreased arterial blood pressure and left ventricular end-diastolic pressure, Increased left ventricular pressure, and the maximum recovery rate of developed left ventricular pressure; Decreased infarct sizes; Inhibited oxidative stress	(Zhou *et al*., 2012)
	Salviae miltiorrhizae extract	Intragastric gavage 29.76 or 59.52 mg/kg (5 days)		
Ischemic reperfusion injury (IRI) induced rats	Danshensu	heart reperfusion with Krebs Heinseleit buffer 10 μmoL/L (1h)	Increased left ventricular pressure, and the maximum recovery rate of developed left ventricular pressure inhibited oxidative stress and apoptosis	(Sun *et al*., 2020)
LAD induced MI mice	Tanshinone IIA	intragastric gavage 60 mg/kg/day (1 week)	Decreased the infarct sizes and deposition of collagen as well as improved recovery in the heart; reduced MCP-I positive cells around infarct border and reduced NF-kB p65 positive nuclei	(Ren *et al*., 2010)

Table 1 continued...

LAD induced MI rats	Cryptotanshinone	intravenous (10 min before ischemia) 125 or 250* μg/kg	Inhibited NF-κB translocation; Inhibited inflammatory cytokines (TNF-α, interleukin-1 β) expression; Decreased myeloperoxidase activity. Reduced infarct size and improved ischemia and reperfusion-induced myocardial contractile dysfunction	(Jin *et al*., 2009)
LAD induced MI mice	*Salviae miltiorrhizae* extract	intraperitoneal injection 3 and 6 g/kg/day (4 weeks after LAD)	Increased hypoxia-inducible factor 1α (HIF1α) and VEGFA expression.	(Ai *et al*., 2015)
LAD induced MI rats	*Salviae miltiorrhizae* polysaccharides pre-treatment	intragastric gavage 400 and 800 mg/kg/day (7 days)	Decreased infarct sizes; Improved Na^{+}–K^{+}-ATPase and Ca^{2+}-Mg^{2+}-ATPase activities; Inhibited oxidative stress and myocardial apoptosis.	(Song *et al*., 2013)
PAH induced Sprague Dawley rats	Sodium tanshinone IIA sulfonate	intraperitoneal injection 10 mg/kg/ day (21 days)	significantly decreased right ventricular systolic pressure, right ventricular hypertrophy, peripheral pulmonary vessel thickening, increased expression of TRPC1 and TRPC6 in hypoxia	(Wang *et al*., 2013)
PAH induced Sprague Dawley rats	Tanshionone IIA	intraperitoneal injection 10 mg/kg/ day (4 weeks)	significantly attenuated hypoxia-induced pulmonary artery wall remodeling	(Zheng *et al*., 2015)

Table 2. Effects of *Salviae miltiorrhizae* in clinical trials for the treatment of cardiovascular disease

Patient Criteria	**Study Design**	**Active component**	**Dosage**	**Main Findings**	**Reference**
55 patients with uncontrolled mild to moderate hypertension	randomized, double-blinded, placebo-controlled	Formula mixture of Danshen capsules (1000 mg)	oral 500 mg capsule (twice a day; 12 weeks)	Lowered systolic blood pressure and pulse rate.	(Yang *et al*., 2012)Danshen (Salvia miltiorrhiza
60 pregnancy-induced hypertensive patients	non-blinded, randomized, and placebo-controlled trial	Tanshinone IIA (40 mg/day)	intravenous injections 40 mg/day (10 days)	Reduced blood viscosity, cholesterol, and lipoprotein.	(Wang & Zhao, 2003)
62 patients with diabetic chronic heart disease	randomized control trial	Hydrophilic extracts of *Salviae miltiorrhizae*	Oral 5 g tablet (twice per day; 60 days)	Reduced serum MDA level, sVCAM-a, oxidized LDL, and von Willebrand factor (vWF); increased the level of serum GSH, SOD, PONase, and GR activities.	(Qian *et al*., 2012a, 2012b)

Effects of *Salviae miltiorrhizae* in preclinical trials

Anti-hypertensive

Hypertension is a common medical disorder where blood pressure in the arteries appear to be consistently higher than normal. The causes of high blood pressure might be associated with high cardiac output, accelerated heart rate, increased peripheral resistance, the decline in the density or number of capillaries, elevated vasoconstriction of active arteriolar, and/or reduced peripheral venous compliance. Long-term, uncontrolled hypertension can lead to stroke, heart failure, peripheral vascular disease, coronary artery disease, and even kidney failure (Lackland & Weber, 2015).

The hypotensive effect of *S. miltiorrhizzae* was tested in animal models. Tang *et al*. (2011a) discovered that 6-weeks intraperitoneal injection of Danshensu (10 mg/kg/day), a water-soluble isolate from *S. miltiorrhizae,* decreased blood pressure of spontaneously hypertensive rats (SHR) (145±3/ 103±10 mmHg to 116±7/ 87±2 mmHg) and significantly increased serum nitric oxide (NO), and activity of NO synthase (NOS). An increase in vasodilation from NO is important in attenuating hypertension and atherosclerosis as it protects the heart by regulating blood pressure and vascular tone, suppressing platelet aggregation and adhesion of leukocytes, as well as restricting the proliferation of smooth muscle cells (Zhao *et al*., 2015). Furthermore, incidences of ventricular fibrillation and tachycardia of the SHR rats reduced from 100% to 50%, and 30%, respectively (Tang *et al*., 2011a). Additionally, Danshensu increased the current density of Ca^{2+}-activated K^+ (K_{Ca}) channels and K^+ (K_V) channels of mesenteric vascular smooth muscles that are vital in modulating vascular tone and blood pressure (Tang *et al*., 2011a; Toth *et al*., 2013). These findings showed that Danshensu protected the cardiovascular system via modulation of vascular tone in the development of hypertension.

When the isoproterenol-induced myocardial hypertrophy rats were treated with Danshensu (3 & 10 mg/kg/day, intraperitoneal injection) on the 4th to 7th day, it was found that the heart to body weight index and arrhythmia scores were reduced. The systolic and diastolic pressures of the left ventricle along with electrocardiogram parameters were improved upon the administration of Danshensu. These results were shown to be due to the regulation of antioxidant enzymes, promoting connexin 43 (Cx-43) expression in the left ventricle (Tang *et al*., 2011b).

Hypertension also has a relatively close relationship with the elevated expression of pro-inflammatory myocardial TNF-α (Bergman *et al*., 1999). *Salviae miltiorrhizae* treatment (1 g/kg for 84 days, intraperitoneal injection) was given to the SHR and the results demonstrated that *S. miltiorrhizae* had significantly reduced the mass index of the left ventricle, sizes of cardiomyocytes, collagen volume fraction, circumferential area of perivascular space respectively via decreased expression of TNF-α and hence, improve the hypertensive condition (Sun & Zheng, 2007). However, there was contradicting study indicating that the cardioprotective effect possessed by this herb was not associated with blood pressure (Sun & Zheng, 2007). Magnesium tanshinoate B (0.7-175 mg/kg) injected intravenously via the jugular vein into the high blood pressure male Sprague Dawley (SD) rats induced by phenylephrine was shown to have a hypotensive effect (Leung *et al*., 2010). Tian *et al*. (2009) revealed that *S. miltiorrhizae* (0.125 g per mouse) and salvianolic acid B (0.5 mg per mouse) reduced the average blood flow velocity in the liver of ET-1 induced portal hypertension mice. However, the mechanisms underlying its efficacy required further investigation.

Matrix metalloproteinases (MMPs) cause degradation of extracellular matrix components ultimately resulting in smooth muscle migration and proliferation and is tightly regulated by tissue inhibitors of metalloproteinases (TIMPs) which inhibit MMP activity (Galis & Khatri, 2002; Johnson, 2017). Disruption of the balance between MMPs and TIMPs results in pathophysiological conditions associated with vascular remodelling, wound healing, and inflammation such as vascular remodelling during early stages of hypertension, hypertrophy, or rupture of atherosclerotic plaques (Johnson, 2017). Proteases have been implicated in the development and progression of atherosclerosis, due to their ability to provoke focal destruction of the vascular extracellular matrix. Using renovascular hypertension rat model induced by 2-kidney-2-clip with the treatment of tanshinone IIA (70 mg/kg/day, intragastric gavage) for 6 weeks, Fang *et al*. (2010) concluded that the treatment could prevent cardiac fibrosis and hypertrophy in the left ventricle along with cardiac relaxation. Beneficial effects of tanshinone IIA were observed with the increase in the mRNA ratio of TIMP-2 to MMP-2, suggesting that tanshinone IIA exerts its effects by regulating MMPs and TIMPs at transcript levels (Fang *et al*., 2010).

Anti-atherosclerosis, anti-oxidation, and anti-inflammation

Atherosclerosis is a disorder in which the arteries become narrowed and lose elasticity due to abnormal accumulation of adhesive plaques (Aluganti Narasimhulu *et al*., 2016). Oxidative stress from an overproduction of reactive oxygen species (ROS) and inflammation is a critical contributor to atherosclerosis progression by causing several complications such as the aggravation of endothelial cells, disruption of vascular wall microenvironment, migration and adhesion of leucocytes, and increase in MMP production and degradation in collagen

(Kattoor *et al*., 2017). Therefore, selectively targeting pro-oxidant components such as NADPH oxidase and lectin-type oxidized LDL receptor 1 (LOX-1), while enhancing the activity of antioxidants such as superoxide dismutase (SOD) is vital in atherosclerosis therapy to restore balance in the oxidant-antioxidant system and to regulate inflammation (Kattoor *et al*., 2017).

Several *in vivo* studies showed that *S. miltiorrhizae* was able to reduce triglyceride and total cholesterol levels, and exhibited potent anti-oxidative and anti-inflammatory properties, thus improving atherosclerosis (Wu *et al*., 1998; Fang *et al*., 2008; Liu *et al*., 2015; Wang *et al*., 2016). A water- soluble polyphenolic antioxidant isolated from the roots of this plant, was found to scavenge 1,1-diphenyl-2-picrylhydrazyl radicals and inhibit LDL oxidation more effectively than probucol. In order to evaluate the antiatherogenic potential, New Zealand White rabbits were fed for 12 weeks a normal diet, a high cholesterol diet, a high cholesterol diet containing 1% probucol, or a high cholesterol diet containing a 5% water-soluble extract of *S. miltiorrhizae* (SM). New Zealand white rabbits fed with a high cholesterol diet comprising of a 5% water-soluble extract of *S. miltiorrhizae* for 12 weeks were found to be more resistant against copper ion (Cu^{2+})-induced oxidative stress (Wu *et al*., 1998). Endothelium disruption has been reduced by 53% ($p<0.05$) as measured at the 6th week. The atherosclerotic lesion at the abdominal aorta was reduced by 56% ($p<0.05$) and cholesterol accumulation in the thoracic aorta was reduced by 50% ($p<0.05$) with the treatment of *S. miltiorrhizae*. This study concluded that the reduction in atherosclerosis by *S. miltiorrhizae* did not solely depend on the cholesterol-lowering efficacy but also on the anti-oxidant ability in preventing endothelial damage as well as inhibiting the formation of oxidized LDL in hypercholesterolemia subjects (Wu *et al*., 1998).

Liu *et al*. (2015) demonstrated that when cryptotanshinone (15 & 45 mg/kg/day, intragastric gavage) was given to high-fat diet apolipoprotein E deficient mice for 22 weeks, the generation of ROS from NADPH oxidase 4 and the NF-κB activation was inhibited. Subsequently, LOX-1 and MMP-9 expressions were also reduced. In another study, salvianolic acid B (8 mg/kg/day) was administered to the high-fat diet-induced atherosclerotic rabbits for 8 weeks. The study revealed that the release of NO was elevated while the triglyceride level was reduced and thus, the atherogenesis was subsequently inhibited (Wang *et al*., 2016). Fang *et al*. (2008) similarly demonstrated that tanshinone IIA possessed anti-atherosclerotic properties by regulating components of the cardiovascular anti-oxidant system. When administered for 2 months to high fatty diet rabbits in different dosages (15 & 37.5 mg/kg, intragastric gavage), tanshinone IIA substantially increased superoxide dismutase (SOD) activity and caused a great reduction in pro-inflammatory malondialdehyde (MDA) levels (Fang *et al*., 2008). Moreover, the expression of pro-inflammatory molecule CD40 as well as the MMP-2 activity were both downregulated which suggested that tanshinone IIA attenuated MMP-2 via blocking CD40 inflammatory pathways (Fang *et al*., 2008). In summary, tanshinone IIA did not only possess the ability of anti-oxidation, but also anti-inflammation in alleviating atherosclerotic lesions.

Ability to reduce total cholesterol levels and reduce inflammation was also observed in hydrophilic *S. miltiorrhizae* extracts, such as salvianolate where salvianolic acid B was its main active component (85%) (Han *et al*., 2011; Meng *et al*., 2014). Salvianolate was given to a high-fat diet + vitamin D3-induced atherosclerotic rats for 12 weeks at a dosage of 60, 120, and 240 mg/kg (intraperitoneal injection) (Meng *et al*., 2014). Results demonstrated improvement of atherosclerosis development with declined levels of proinflammatory cytokines including IL-6 and C reactive protein (CRP) as well as an increase in regulatory T cells (Tregs) which possess the ability in preventing the progression of atherosclerosis through the reduction of IL-6 expression and CRP production. However, although salvianolate treatment reduced total cholesterol (TC) and LDL levels, it barely had any impact on the triglyceride and HDL levels (Poledne *et al*., 2009; He *et al*., 2010).

Prevention of myocardial ischemia

Myocardial ischemia (MI), also known as angina, is a heart disease associated with irreversible damage to the cardiac muscle as a result of the deficiency of blood supply to the heart induced by partial blockage of the coronary arteries (Buja and Vender, 2016). MI develops several threats to the myocardium, including generation of ROS, overloading of intracellular calcium, dysfunctional endothelium, apoptosis of myocardium, increased adhesion of leukocytes, and degranulation of mast cells (Mozaffari *et al*., 2013).

Studies showed that salvianolate administration (10 mg/kg/day, intravenous injection) for 7 days consecutively enhanced myocardial microvessels reflow and elevated the density of capillary as well as reduced the infarct size in a porcine model (Han *et al*., 2011). The therapeutic effect of salvianolate was potentially associated with its capability in reducing oxidative stress and cell death. The decrease in oxidative stress was mediated by the increase of SOD and thioredoxin activities and glutathione concentration, as well as a decrease in the concentration of MDA. Subsequently, this would lead to the reduction in terminal deoxynucleotide transferase-mediated dUTP nick end labeling-positive cells and increased the ratio of B-cell lymphoma-2 (Bcl-2) to Bax expression, indicating suppression of cell apoptosis signaling pathways by salvianolate (Han *et al*., 2011).

Similarly, treatment of MI rats and ischemic reperfusion injured (IRI) rats with Fufang danshen tablet (1210 mg/kg, intragastric gavage) or aqueous *S. miltiorrhizae* extract (29.76 or 59.52 mg/kg, and intragastric gavage) for 5 days, and Danshensu (10 μmol/L, heart reperfusion) for 1 h, respectively, improved recovery of cardiac function as evidenced by improved hemodynamic parameters (i.e increased in left ventricular systolic pressure, decreased in left ventricular end-diastolic pressure) and decreased infarct size (Zhou *et al*., 2012; Sun *et al*., 2020). These improvements were also observed with a reduction in serum levels of oxidative markers including lactate dehydrogenase, glutamic oxalacetic transaminase, creatine kinase, and MDA, and an increase in anti-oxidant systems (SOD and glutathione peroxidase) (Zhou *et al*., 2012; Sun *et al*., 2020). Collectively, these observations indicated that hydrophilic active components in *S. miltiorrhizae* protected against MI through inhibiting oxidative stress and apoptosis

Tanshinone IIA treatment (60 mg/kg/day, intragastric gavage) was given to the permanent left anterior descending coronary artery (LAD) ligation induced myocardial ischemia (MI) rats for 7 days. Tanshionone IIA-treated rats demonstrated a reduction in the deposition of collagen and infarct sizes, consequently resulting in an improved recovery in the heart (Ren *et al*., 2010). Immunohistochemistry staining of myocardial tissue isolated from treatment groups revealed that tanshinone IIA reduced the number of the pro-inflammatory molecule, MCP-1, containing cells around the infarct border with reduced NF-kB p65 translocation to the nucleus, suggesting that tanshinone IIA elicits anti-inflammatory effects by preventing transcription of pro-inflammatory molecules as a cardioprotective response to MI (Ren *et al*., 2010).

Jin *et al*. (2009) investigated the cryptotanshinone treatment on the modifications of hemodynamic parameters including left ventricular dp/dt_{max} end-diastolic pressure, as well as the infarct size in the LAD-induced MI rat model. The research indicated that 250 μg/kg of cryptotanshinone prevented the alterations induced by MI via modulation of the inflammatory pathway by suppressing NF-κB translocation and lowering pro-inflammatory cytokine production, as well as restricting activation of myeloperoxidase and neutrophil infiltration through the regulation of p38 MAPK/ JNK/ ERK pathways in ischemic myocardial tissues.

Cardiac angiogenesis activation is an effective therapeutic approach for achieving the increased oxygen and nutritional demands of the stressed heart (Mozid *et al*., 2014). Vascular endothelial growth factor A (VEGFA) and Hypoxia-inducible factor 1 (HIF1α) are both important in the activation of cardiac angiogenesis (Giatromanolaki *et al*., 2008). *Salviae miltiorrhizae* extract (3 & 6 g/kg/day, intraperitoneal injection) administered for 4 weeks was shown to elevate the expression of VEGF-A and HIF1α in LAD-induced MI mice, contributing to improved cardiac function and cardiac angiogenesis (Ai *et al*., 2015). Another study indicated that giving pre-treatment of 400 and 800 mg/kg by oral gavage of *S. miltiorrhizae* polysaccharides to LAD-induced MI rats respectively for 1 week improved the infarct sizes as well as enhanced the myocardial Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase activities, which were believed to be correlated to myocardial injury (Ke *et al*., 2004; Song *et al*., 2013). Though *S. miltiorrhizae* polysaccharides were found to be beneficial against MI, more investigations on the usage of polysaccharides in the treatment of CVD are needed due to the shortage of appropriate methods in accessing its contributions.

Effects of *Salviae miltiorrhizae* in clinical trials

A randomized, double-blinded, placebo-controlled, single-center clinical trial had proven that administration of *S. miltiorrhizae* could improve the hypertensive condition. A total of 55 patients having uncontrolled mild to moderate hypertension signed up for a conventional anti-hypertensive treatment were randomized into two groups receiving the Fufang Danshen extract capsules containing a mixture of 225 mg pure *S. miltiorrhizae* extract, 20 mg Rhodiola rosea extract, 100 mg Chrysanthemum extract, and 100 mg Pueraria extract (500 mg, twice a day) and placebo capsules respectively for 12 weeks (Yang *et al*., 2012). The results demonstrated that the systolic blood pressure and pulse rate of the *S. miltiorrhizae*-treated group had a significant reduction compared to the placebo group at week 12. The systolic blood pressure of the *S. miltiorrhizae*-treated group was reduced by 13.8 mmHg whilst the placebo group only decreased by 4.2 mmHg. There were no observable adverse effects between both groups. Hence, it was concluded that extract of *S. miltiorrhizae* had a high safety profile and was effective in reducing the systolic blood pressure and pulse rate of hypertensive patients (Yang *et al*., 2012). A non-blinded, randomized, and placebo-controlled clinical trial was performed to examine the efficacy of *S. miltiorrhizae* on 60 patients with pregnancy-induced hypertension (Wang & Zhao, 2003). *Salviae miltiorrhizae* injection containing tanshinone IIA (40 mg/day) was administered for 10 days. Results demonstrated that *S. miltiorrhizae* reduced blood viscosity, and both the levels of cholesterol and lipoprotein.

Another randomized controlled study was proven to soothe the symptoms of diabetic chronic heart disease. A total of 62 patients were treated with 5 g tablets containing hydrophilic extracts of *S. miltiorrhizae* for 60 days. The results demonstrated that there was a significant reduction in the serum MDA level, sVCAM-a, oxidized LDL, and von Willebrand factor (vWF) while the level of serum glutathione (GSH), SOD, paraoxonase (PONase), and glutathione reductase (GR) activities were increased (Wang *et al*., 2016).

Elucidating molecular mechanisms of *Salviae miltiorrhizae*

Increasing evidence demonstrated the advantages of *S. miltiorrhizae* in improving cardiovascular health. Consumption of the whole plant or treatment with specific bioactive compounds such as tanshinone IIA, cryptotanshinone, salvianolic acid B, and Danshensu from *S. miltiorrhizae* extracts improved the outcome of hypertension, atherosclerosis and prevent myocardial ischemia through various pharmacological actions (Table 1 & Table 2). Mechanisms of action of *S. miltiorrhizae* are discussed in this section by reviewing its effects in different *in vitro* models and summarised illustrated in Table 3 and Figure 3, respectively.

Effects of *Salviae miltiorrhizae* in endothelial cells *(in vitro)*

The vascular endothelium is the innermost layer of the blood vessel wall, located between the bloodstream and tissue. It is crucial in maintaining the integrity of the vessel wall. Endothelial cell death or damage via regulation of various vasorelaxants or vasoconstricting components and other signaling molecules can lead to the initiation of endothelial pathophysiological processes such as thrombosis, angiogenesis, and atherosclerosis.

Active components in *S. miltiorrhizae* have been shown to regulate these molecules involved in preventing endothelial injury, inflammation, and programmed cell death. Tanshinone IIA was found to reduce oxidative stress-induced endothelial apoptosis by enhancing expression of vasorelaxant nitric oxide (NO) through activation of endothelial nitric synthase (eNOS), superoxide dismutase (SOD), and activating transcription factor-3 (ATF-3), and reducing expression of vasoconstrictor endothelin-1 (ET-1) (Lin *et al*., 2006; Chan *et al*., 2012; Hong *et al*., 2012). Tanshinone IIA treatment also showed resistance against apoptosis induced by H_2O_2 through reducing the expression of pro-inflammatory CD40 in HUVECs (Lin *et al*., 2006).

SiRNA knockdown and inhibitor studies revealed that the pathway governed the release of NO which induced the expression of ATF-3, and ATF-3 in turn repressed the expression of ET-1 on top of direct NO inhibition (Hong *et al*., 2012). In the

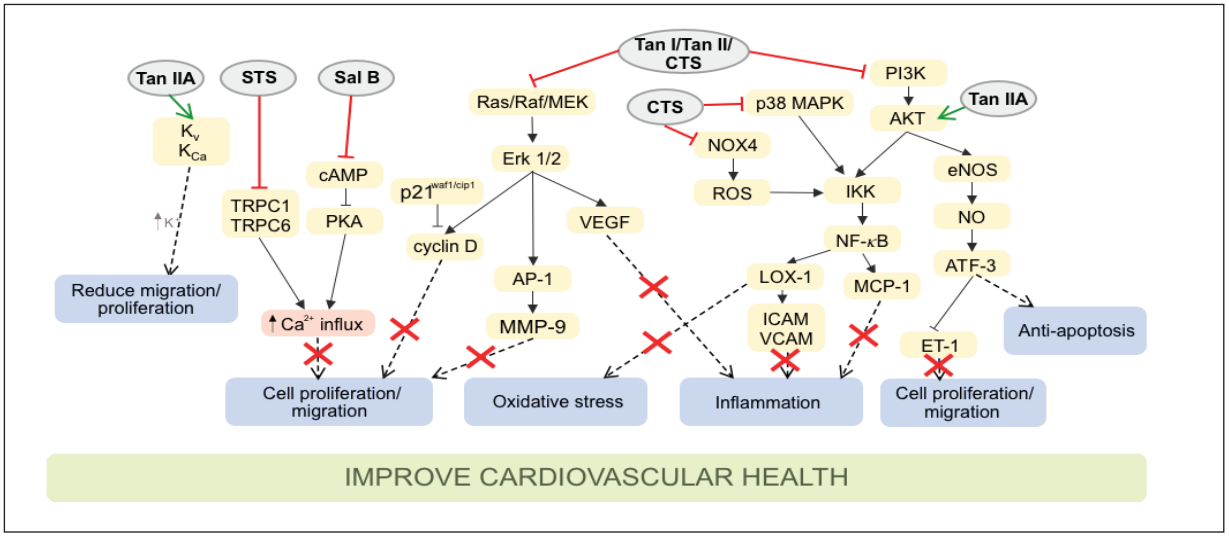

Fig. 3. Summary of the molecular mechanisms underlying the therapeutic effect of *Salviae miltiorrhizae* on cardiovascular health.

Table 3. Effects of *Salviae miltiorrhizae* on endothelial cells, vascular smooth muscle cells, cardiac myocytes, and fibroblasts *in vitro.*

***In vitro* models**	**Active Component**	**Concentration and experimental design**	**Main Finding**	**Reference**
Endothelial cells				
Human umbilical vein endothelial cells (HUVECs)	Tanshinone IIA	7.5, 15, 30 and 60 μg/mL (pre-incubation 24 h)	reduced H_2O_2-induced apoptosis and CD40 expression, increased NO and SOD activity	(Lin *et al*., 2006)
		1, 3, 10 μM (pre-incubation 24 h)	Reduced H_2O_2-induced apoptosis, p53 expression, and caspase-3 activity, induced expression of ATF3	(Chan *et al*., 2012)
		10 μmoL/L (pre-incubation 30,60 & 120 min)	reduced strain-induced ET-1 expression and increased NO by stimulating eNOS phosphorylation with subsequent increase in ATF-3 (NO dependent)	(Hong *et al*., 2012)
	Cryptotanshinone	2 and 5 μM (pre-incubation 10 min or 3 h)	decreased TNF-α induced expression of ICAM-1 and VCAM-1, reduced activation of NF-kB and expression of LOX-1, reduced production of ROS by reducing the production of NOX4	(Jin *et al*., 2009; Liu *et al*., 2015)
	Salvianolic acid B and Danshensu	1-20 μg/mL (pre-incubation 4 h)	reduced H_2O_2-induced oxidative stress injury	(Zhao *et al*., 2008)
	Salviae miltiorrhizae extract	100-400 μg/mL (pre-incubation 12 h)	Inhibited TNF-α induced endothelial permeability, decreased VEGF and ERK activation	(Ding *et al*., 2005
	Salvianolic acid B and Danshensu	10-50 μg/ML (pre-incubation 12 h)		
Vascular smooth muscle cells				
Vascular smooth muscle cells (VSMCs) of Wistar rats	a mixture of Tanshinone I, Tanshinone II, and Cryptotanshinone	0.4, 2, 10, and 50 μg/mL (pre-incubation 48 h)	reduced VSMC proliferation and cell cycle progression by reducing Erk1/2 signaling; increased p21 (waf1/cip1) and decreased the expression of cyclin D	(Wang *et al*., 2005)

Table 3 continued...

Human aortic smooth muscle cells (HASMCs)	Tanshinone IIA	15-100 μM (pre-incubation 1-2 h)	Suppressed TNF- induced Akt, ErK and c-jun phosphorylation, inhibited IB phosphorylation and p65 nuclear translocation; downregulate MMP-9 expression	(Jin *et al*., 2008)
Pulmonary artery smooth muscle cells (PASMCs) of normoxic rats	Sodium tanshinone IIA sulfonate	0 – 25 μM (pre-incubation 60 h)	blocked hypoxia-induced increase of TRPC1 and TRPC6 expression, decreased VSMC proliferation. attenuated increase of SOCE, and hindered the elevating concentration of basal intracellular $Ca^{2+,}$	(Wang *et al*., 2013)
	Tanshinone IIA	25 μg/mL (cells isolated from rats treated intraperitoneally for 4 weeks)	Recovered the hypoxia-downregulated I_{KV} currents by downregulating the expression of $K_v2.1$ and $K_v1.5$	(Zheng *et al*., 2015)
Cardiomyocytes and cardiofibroblasts				
Cardiac myocytes and fibroblasts of neonatal rats	Tanshinone VI	10 μM (pre-incubation 24 h)	Inhibited phenylephrine, ET-1, and IGF-1 induced protein synthesis; Reduced hypertrophy in cardiac fibroblasts.	(Maki *et al*., 2002)
Cardiac myocytes and fibroblasts of neonatal rats	Tanshinone IIA (2-8 μM)	2-8 μM (pre-incubation 1 h)	reduced TNF-α-induced expression of MCP-1, TGF-B, and CD68 in cardiac fibroblasts but not in cardiomyocytes	(Ren *et al*., 2010)
H9C2 cell lines of embryonic rat heart ventricle	Salvianolic acid B	0.001, 0.01 and 0.1 mg/mL (pre-incubation 2 h)	Reduced production of anoxia-induced cAMP and PKA followed by Ca^{2+} influx, leading to protective effects on MI	(Lu *et al*., 2012)
H9C2 cell lines of embryonic rat heart ventricle	Danshensu	10 μmoL/L (3 h incubation after hypoxia)	reduced apoptosis by blocking hypoxia-induced decrease of Bcl-1 and increase of Bax	(Sun *et al*., 2020)

endothelium, ATF-3 typically induces the expression of genes that result in inflammation, apoptotic responses, and oxidative stress (Aung *et al*., 2016). Specifically, in regulating apoptosis cascades, ATF-3 was found to inhibit transcription of p53 by binding to the AP-1 element in the p53 gene promoter, resulting in suppression of TNF-α induced apoptotic pathways through caspase-3 (Kawauchi *et al*., 2002). Tanshinone IIA-treated HUVECs also demonstrated a reduction in p53 expression and caspase-3 activation further confirming its role in promoting endothelial survival during oxidative damage (Chan *et al*., 2012). On the other hand, ET-1 is a vasoconstricting peptide mainly formed in the endothelium and is involved in modulating vascular tone and has been shown to mediate cell proliferation in vascular smooth muscle cells, cardiomyocytes, and cardio fibroblasts through the Ras/Raf/ERK pathway (Cheng *et al*., 2003; Marasciulo *et al*., 2006). The present study was performed to examine the role of endogenous ET-1 in ET-1 - stimulated fibroblast proliferation and to investigate the regulatory mechanism of ET-1 - induced ET-1 gene expression in cardiac fibroblasts. Both ETA receptor antagonist [(hexahydro-1 H-azepinyl. Repression of ET-1 production in the endothelium by tanshinone IIA therefore reduced subsequent migration and proliferation pathways associated with cardiac and vascular remodeling.

Cryptotanshinone, a main bioactive diterpenoid found in *S. miltiorrhizae*, also possesses anti-oxidative and anti-inflammatory properties by regulating lectin-like oxidized LDL receptor-1 (LOX-1) expression. LOX-1 is a major receptor for the ROS-producing ox-LDL in endothelial cells and plays an important role in the formation of foam cells from macrophages, endothelial dysfunction observed in hypertension, atherogenesis, and plaque instability (Kattoor *et al*., 2017). In HUVECs treated with H_2O_2, oxidized low-density lipoprotein (oxLDL) and tumor necrosis factor-α (TNF-α), cryptotanshinone treatment inhibited the corresponding LOX-1 expression and nuclear transcription factor-kappa B (NF-κB) activation (Jin *et al*., 2009; Liu *et al*., 2015). Furthermore, cryptotanshinone disrupted LOX-1-mediated adhesion of THP-1 monocytes to HUVECs by lowering the expressions of vascular cell adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1), and E-selectin in HUVECs via inhibition of NOX4/ROS/ NF-κB signaling pathway and preventing translocation of NF-κB to the nucleus to induce gene transcription (Jin *et al*., 2009; Liu *et al*., 2015. However, it is not known whether CTS can prevent experimental atherosclerosis. The present study was designed to investigate the protective effects of CTS on atherosclerosis and its molecular mechanisms of action. Higher expression and activation of VCAM-1 and ICAM-1, as well as E-selectin, are known to contribute to the binding of circulating immune cells to endothelial cells surface, subsequently initiating the progression of atherosclerosis (Ling *et al*., 2012). Further inhibition of LOX-1 mediated downregulation of eNOS, upregulation of apoptotic proteins caspase 3 and caspase 9, and production of MMP-9 remains to be validated in endothelial cells, but are likely pathways of cryptotanshinone in attenuating atherosclerosis plaque formation, and improving plaque stability as observed *in vivo* models (Liu *et al*., 2015; Kattoor *et al*., 2017).

Endothelial hyperpermeability refers to dysfunction of the endothelial barrier, allowing increased cellular leakage of various pro-inflammatory, pro-oxidants molecules which results in exacerbated inflammation, ischemic reperfusion injury, or atherosclerosis (Kumar *et al*., 2010). Tyrosine kinase receptors such as vascular endothelial growth factor (VEGF) have been shown to mediate endothelial hyperpermeability (Kumar *et al*., 2010). *Salviae miltiorrhizae* extracts along with its hydrophilic active compounds including Danshensu and salvianolic acid B demonstrated the ability to suppress VEGF expression and attenuate TNF-α-induced hyperpermeability in HUVECs (Ding *et al*., 2005). To understand its mechanism of pharmacological action, its effects on endothelial monolayer permeability were studied. The present study demonstrated that decrease in VEGF expression by Danshensu and salvianolic acid B appeared to be dependent on abolishing ERK activation and reduction of ROS levels (Ding *et al*., 2005). Additionally, salvianolic acid B and Danshensu treatment (1-20 μg/mL) prevented H_2O_2 -induced injury in HUVECs attributed to its anti-oxidant properties as evidenced by high scavenging activities against various free radicals (Zhao *et al*., 2008).

Effects of *Salviae miltiorrhizae* in vascular smooth muscle cells *(in vitro)*

VSMCs are a major cell type localized in the tunica media of the vasculature and function to mediate contraction and ECM production. VSMCs can migrate, proliferate, and differentiate into a more synthetic, less contractile phenotype in response to stress or pathological conditions, leading to VSMC dysfunction and remodeling associated with thickening of vessel walls and progression of cardiovascular disease (Guarner-Lans *et al*., 2020).

According to Wang *et al*. (2005), a combination treatment using lipohilic components tanshinone I, tanshinone II, and cryptotanshinone at the concentrations of 0.4, 2, 10, and 50 μg/mL, hindered the proliferation of the VSMCs in the Wistar rats. The reduced proliferation of VSMCs was mediated through the inhibition of extracellular signal-regulated protein kinase 1/2 (ERK 1/2) signaling and

consequently decreasing the expression of cyclin D by increasing the expression of $p21^{waf1/cip1}$. $p21^{waf1/cip1}$ is implicated to inhibit cell cycle progression from G0/G1 to S phase thus inhibiting proliferation of VSMCs (Wang *et al*., 2005). In addition, tanshinone IIA suppressed the human aortic smooth muscle cells (hASMCs) migration via downregulating MMP-9 expression through inhibition of MAPK/ERK and PI3K/Akt pathways as evidenced by Akt, ErK, and c-jun phosphorylation. Interestingly, tanshinone IIA did not inhibit activation of other MAPKs (i.e. JNK & p38) in the VSMCs. In the PI3K/Akt pathway tanshinone IIA inhibited IκBα phosphorylation and p65 nuclear translocation, subsequently preventing transcription factor NF-κB to bind to the MMP-9 gene for further transcription, indicating that tanshinone IIA regulated MMP-9 expression at transcript levels.

VSMC proliferation and contraction are also regulated by intracellular Ca^{2+} concentration and cellular membrane potential. The influx of Ca^{2+} is mediated by transient receptor potential canonical channels (TRPC) which are a group of store-operated Ca^{2+} channels (SOCE) (Cheng *et al*., 2013; Wang *et al*., 2015). Sodium tanshinone IIA sulfonate treatment (12.5 μM) altered the proliferation and migration of hypoxic and normoxic pulmonary artery smooth muscle cells (PASMCs) by decreasing SOCE and hindering the elevating concentration of basal intracellular Ca^{2+} through disruption of TRPC1 and TRPC6 expression in distal PASMCs (Wang *et al*., 2013). During chronic hypoxia, severe exposure to hypoxic conditions suppressed the activity of K_V channels in VSMCs and induced VSMC contraction and proliferation that results in pulmonary vascular remodeling typically observed in pulmonary hypertension (Wang *et al*., 2005). Danshensu therapy increased the expression of the K^+ channel stimulated by K^+ and Ca^{2+} in primary mesenteric vascular smooth muscle cells from spontaneously hypertensive rats (SHRs) when the tested potential was set at +60 mV. In another study, tanshinone IIA (25 μg/mL) therapy partially recovered the downregulated I_{KV} currents induced by severe hypoxia in PASMCs (Zheng *et al*., 2015. These results indicate that active components in *S. miltiorrhizae* can be used in therapy for pathological conditions involving hypoxia such as pulmonary hypertension.

Effects of *Salviae miltiorrhizae* in cardiac myocytes and cardiac fibroblasts *(in vitro)*

Hypertrophy or remodeling of cardiac myocytes in response to stress and injury alters the contractility of the myocardium and eventually leads to left ventricular hypertrophy commonly observed in MI (Voulgari *et al*., 2010). Monocyte chemotactic protein (MCP)-1, which stimulates invasion, activation, and cytokine production of inflammatory cells, was highly expressed in the MI animal models (Kobusiak-Prokopowicz *et al*., 2007; Kohno *et al*., 2008). In contrast, MCP-1 deficient mice showed lower macrophages recruitment in the ischemic heart, prolonged phagocytosis of damaged cardiac myocytes, reduced fibroblasts infiltration, and diminished left ventricular remodeling. Moreover, cyclic adenosine monophosphate (cAMP) stimulates the activation of protein kinase A (PKA) leading to the phosphorylation of L-type Ca^{2+} channels during myocardial ischemia, resulting in subsequent Ca^{2+} influx, and muscle contraction. Therefore, targeting MCP-1 and L-type Ca^{2+} channels would be beneficial in treating MI and its related cardiovascular diseases (Xia & Frangogiannis, 2007).

Tanshinone VI (10 μM) inhibited ET-1, insulin-like growth factor-1 (IGF-1), and phenylephrine-induced protein synthesis in neonatal rat myocardiocytes (Maki *et al*., 2002). It also reduced hypertrophy in cardiac fibroblasts induced by 5% of fetal bovine serum and 0.01 μM of IGF-1, through the reduced synthesis of collagen (Maki *et al*., 2002). Cardioprotective effects including a decrease in infarct size, decreasing collagen deposition, and improving heart recovery in tanshinone IIA-treated rats *in vivo* were attributed to a reduction in MCP-1, and TGF-β1 in cardiac fibroblasts and infiltration of macrophages (Ren *et al*., 2010). Moreover, the expression of NF-κB and its p65 subunit in the nuclei of infarcted cardiac cells decreased with the concentration of proinflammatory stimuli TNF- α (Ren *et al*., 2010). On the basis that TNF-α can induce MCP-1 activity and intensify the pro-inflammatory reactions via the p38 MAPK signaling pathways, it is conceivable that tanshinone IIA mechanistically inhibits expression of MCP-1 by blocking the MAPK/ p38/ NF-κB pathway (Lam *et al*., 2008; Ho *et al*., 2008; Takahashi *et al*., 2008). Interestingly, inhibition of MCP-1 was not observed in cardiac myocytes indicating that tanshinone IIA may have some tissue selectivity. Studies showed that salvianolic acid B treatment (0.001, 0.01, & 0.1 mg/mL) for 2 hours reduced production of cAMP, inhibited PKA and Ca^{2+} influx, in H9C2 cells originating from embryonic rat heart ventricles leading to protective effects against MI (Lu *et al*., 2012). These results demonstrate that both lipophilic and hydrophilic components in *S. miltiorrhizae* are potential therapeutics in treating MI.

Danshensu, on the other hand, significantly attenuated cardiac function by decreasing oxidant markers *in vivo* and reducing ROS-dependent apoptosis in myocardial tissues from ischemia-reperfusion injury models (Sun *et al*., 2020). *In vitro* treatment of H9C2 cell lines of embryonic rat heart ventricles demonstrated that Danshensu (10 μmoL/L) reduced apoptosis by suppressing hypoxia-induced decrease of anti-apoptotic Bcl-1 and increase of apoptotic Bax (Sun *et al*., 2020). However, specific pathways in which danshensu acts mechanistically have yet to be elucidated.

CONCLUSION

The prevalence of CVDs and their associated risk factors continues to expand, resulting in high mortality and morbidity rates. As discussed in this review, there is increasing evidence indicating that extracts from *S. miltiorrhizae* appear to reduce the risk of CVDs and its associated risk factors in cell cultures, animal models, and clinical trials through anti-hypertensive, anti-oxidant, and anti-inflammatory properties. Both lipophilic and hydrophilic compounds from *S. miltiorrhizae* modulated signaling pathways including Ras/Raf/MEK, PI3K/Akt/, p38 MAPK/ NF-κB, and NOX4/ROS/NF-κB were associated with processes vital in the progression of CVDs, such as apoptosis, oxidative stress, inflammation, and cell proliferation and migration by regulating the expression of key molecules such as cyclin D, MMP-9, LOX-1, MCP-1, and ET-1. Overall mechanisms of action elucidated from *in vitro* models demonstrated that there was a pharmacological basis for *S. miltiorrhizae* in treating CVDs and its associated risk factors as observed *in vivo* models and clinical trials. Identification of pathways and key molecules regulated by individual *S. miltiorrhizae* active compounds will aid in improving formulation and dosage and strengthen the ability in predicting possible side effects or herb-drug interactions. While certain active compounds of *S. miltiorrhizae* appear to have cell-specific actions, tissue or cell selectivity of *S. miltiorrhizae* remains elusive. It is imperative for clinical trials involving greater sample sizes to test the safety and efficacy of *S. miltiorrhizae* formulated based on specific active compounds or taken as a whole, and its interactions with commonly prescribed drug-based therapies to further validate its use as supplements or nature-based remedies for the treatment or even prevention of CVDs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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