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REVIEW ARTICLE

Salvia miltiorrhiza: A Potential Red Light to the Development of Cardiovascular Diseases

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Abstract: *Salvia miltiorrhiza* Bunge, also known as Danshen in Chinese, has been widely used to treat cardiovascular diseases (CVD) in China and other Asia countries. Here, we summarize literatures of the historical traditional Chinese medicine (TCM) interpretation of the action of *Salvia miltiorrhiza*, its use in current clinical trials, its main phytochemical constituents and its pharmacological findings by consulting Pubmed, China Knowledge Resource Integrated, China Science and Technology Journal, and the Web of Science Databases. Since 2000, 39 clinical trials have been identified that used *S. miltiorrhiza* in TCM prescriptions alone or with other herbs for the treatment of patients with CVD. More than 200 individual compounds have been isolated and characterized from *S. miltiorrhiza*, which exhibited various pharmacological activities targeting different pathways for the treatment of CVD in various animal and cell models. The isolated compounds may provide new perspectives in alternative treatment regimes and reveal novel chemical scaffolds for the development of anti-CVD drugs. Meanwhile, there are also some rising concerns of the potential side effects and drug-drug interactions of this plant. The insights gained from this study will help us to better understanding of the actions of this herb for management of cardiovascular disorders. As an herb of red root, *S. miltiorrhiza* will act as a potential red light to prevent the development of CVD.

Keywords: *Salvia miltiorrhiza*, traditional chinese medicine (TCM), clinical trials, phytochemistry, pharmacology, cardiovascular disease.

1. INTRODUCTION

Salvia miltiorrhiza Bunge, also known as red sage or Danshen (Chinese Pinyin name), is a perennial plant (Fig. **1A**) in the genus *Salvia* of the mint family, Lamiaceae [1]. Its roots are highly valued as a ''super grade herb (herbs lacking observable toxicity)'' in the *Shennong's Herbal Classic of Materia Medica* (Shennong Bencao Jing) written during the reign of the Qin and Han dynasties (221 BC to 220 AD), and has been clinically used for more than 2000 years. Following this first record, *S. miltiorrhiza* was well described in classical traditional Chinese medicine (TCM) works such as in the Compendium of Materia Medica (Bencao Gangmu, Ming dynasty, 1596 AD). In the textbooks of academic TCM, *S. miltiorrhiza* is characterized as a common drug for promoting blood circulation and removing blood stasis. The herb has been officially recorded in the Chinese pharmacopoeia since 1953. According to the Chinese pharmacopoeia [2], *S. miltiorrhiza* is the only official source of *Salvia Radix & Rhizoma* (Danshen) [3]. Phytochemical studies have shown that *S. miltiorrhiza* contained a large number of lipophilic diterpenoids (such as various tanshinone analogues), hydrophilic phenolic compounds (such as salvianolic acids), flavonoids, and triterpenoids) [4-7]. *S. miltiorrhiza* has traditionally been used in the treatment of CVD [8], such as atherosclerosis [9], thrombosis [10], and angina pectoris [11, 12]. And data about clinical information of hospitalized patients and outpatients with coronary artery disease and hypertension have demonstrated that *S. miltiorrhiza* was top-ranked (63.10% and 17.1%, respectively) among all the clinical administered drugs in Beijing, Tianjin [13] and Taiwan [14].

S. miltiorrhiza is widely distributed in the Chinese provinces of Liaoning, Hebei, Beijing, Shandong, Hubei, Hunan, Jiangsu, Jiangxi, Gansu, Henan, and Shanxi. Now, several provinces in China start to domestically plant *S. miltiorrhiza* Bunge [3]. Suitable growing conditions for this plant are found in locations with sunny, mild and wet environment where average temperature is 17.1℃ and the annual average relative humidity is 77% [15]. Currently, *S. miltiorrhiza* products are available in natural health shops almost all over the world [16].

CVD is a class of disorders that involve the heart and blood vessels, including coronary heart disease, rheumatic heart disease, peripheral vascular disease, heart failure, congenital heart disease and cardiomyopathies [17, 18]. It is becoming a global health burden and is still the number one cause of morbidity and mortality worldwide [19, 20]. Many risk factors could individually or combinedly trigger CVD, such as family history, ethnicity, age, tobacco exposure, high blood pressure, high cholesterol, obesity, physical inactivity, diabetes, unhealthy diets, and harmful use of alcohol. Therefore, multi-targeted therapeutic interventions would likely be required for effective management of CVD.

The current literature review aims to summarize the recent advances of the involvement of *S. miltiorrhiza* in cardiovascular protective effect in clinical or preclinical studies by consulting Pubmed, China Knowledge Resource Integrated, China Science and Technology Journal, and the Web of Science Databases. We also review its phytochemistry and its explanation in TCM which may help to understand pharmacological activities.

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2. THE CARDIOVASCULAR PROTECTIVE ACTIVITY OF *SALVIA MILTIORRHIZA* IN THE THEORY OF TRADITIONAL CHINESE MEDICINE

According to the Grand Compendium of Materia Medica [21], "*S. miltiorrhiza* matches the heart called Chi (Red) Shen". Thus, *S. miltiorrhiza* (Danshen) derives its name from its original color of the root (Fig. **1B**), which is usually harvested in spring or autumn every year [3]. In TCM, *S. miltiorrhiza* (Fig. **1C**) is recognized as an herb with a bitter-flavor and distribution to the heart. According to Chinese Pharmacopoeia, *Salvia Miltiorrhizae Radix & Rhizoma* exerts a beneficial action by promoting blood circulation to remove blood stasis and assuage pain, clearing heart heat to relieve restlessness, and cooling blood to remove carbuncle [22]. In TCM perspective, chest pain and heart failure are caused by obstruction of the circulation of Qi and blood. Therefore, *S. miltiorrhiza* can be used to treat CVD. For details of TCM explanations of this herb, interested readers are encouraged to consult Dr. Guo's review [23].

3. *SALVIA MILTIORRHIZA* IN CLINICAL TRIALS OF CVD

S. miltiorrhiza has been clinically used for management of CVD in China for many years. So far, there are several drugs contained Danshen as its major component which have been developed and marketed in China for the treatment of CVD, including Fufang Danshen tablets, Compound Danshen dripping pills, Danhong injection and Tongxinluo capsule, etc. From 2000 till now, we have identified 39 clinical trials comprised a total of 2431 patients where *S. miltiorr*hiza was used alone or in combination with other herbs to treat CVD. In the prescriptions of 39 clinical trials, Compound Danshen dripping pills was the most popular one (22 in 39, 56.4%), and offered potential benefits for patients with chronic heart diseases. Among 22 trials with Compound Danshen dripping pills, 9 trials used the Compound Danshen dripping pills alone to treat CVD, and 13 trials used combination treatment. 2 in 39 trials (5.1%) employed the single herb to treat CVD.

The majority of 39 trials targeted the treatment of coronary heart disease. Among them, 6 studies explicitly addressed coronary heart disease, 8 trials studied coronary heart disease combined with angina pectoris, 3 trials observed unstable angina, and 1 trial studied stable angina pectoris. Of the rest, 1 clinical trial treated ischemic cardiovascular disease, 2 trials treated congestive hearts failure, 1 trial treated chronic heart failure, 1 trial treated postmenopausal women with borderline hypercholesterolemia, 1 trial treated hyperlipidemia, 1 trial treated hyperlipidemia and blood hyperviscosity, 2 trials treated hypertension, 2 trials treated diabetes combined with silent myocardial ischemia or chronical heart disease, 1 trial treated cardiovascular neurosis, 1 trial treated cardiovascular complications in peritoneal dialysis patients, 1 trial treated children viral myocarditis, and 7 trials did not specify the disease type. The overall efficacy (with markedly and moderately improved conditions) of trials treating CVD patients was between 63.4% and 99.2% (Table **1**). The observations from the clinical trials have demonstrated that *S. miltiorrhiza* products in China are effective for the management of CVD. However, most of clinical trials are not well-designed. It should be noted that a standardized clinical trial should be randomized, double blind and multi-centered. Obviously, few trials meet the standard.

The main outcome measures were introduced to evaluate the efficacy of the TCM prescription as follows: (1) Clinical symptoms and physical signs, such as frequency of angina attacks, cardiac function, and blood pressure; (2) Biomarkers, such as antioxidant indexes, inflammation markers and blood lipids levels; (3) Improvement of electrocardiogram (ECG), such as ST segment and T wave inversion; (4) Adverse effects during the treatment. Of 39 clinical trials, 31 trials (79.5%) observed the improvement of clinical symptoms and physical signs, 20 (51.3%) trials described the improvement of ECG, 11 (28.2%) trials examined the biomarkers of CVD, 12 (30.8%) trials reported the adverse effects treatment with the prescription, in which abdominal complaints, nausea, and dyspepsia were most often appeared. And the adverse effects completely alleviated after cessation of treatment.

4. PHYTOCHEMISTRY OF *SALVIA MILTIORRHIZA*

The study on the chemical components of *S. miltiorrhiza* was initiated as early as in 1930s. Following that, a lot of researchers have focused on isolating and characterizing ingredients from this plant. Currently, more than 200 compounds have been identified from *S. miltiorrhiza* according to the Chinese Academy of Sciences Chemistry Database (www.organchem.csdb.cn) and Chinese Herbal Drug Database [63]. They can be classified into two major groups: water-soluble (hydrophilic) phenolic compounds and nonpolar (lipid-soluble) diterpenoid compounds. Salvianolic acids and diterpenoid tanshinones are two representative hydrophilic components and lipophilic components in this plant (Fig. **2**) [23, 64-66].

The basic chemical structure of the water soluble phenolic acids of *S. miltiorrhiza* is composed of C_6C_3 units. The total phenolic acids are usually isolated from this plant with water, methanol, ethanol, or aqueous actone. Most of the salvianolic acids are colorless or tan amorphous powders. As a result of the presence of α-3,4-dihydroxyphenyl in the structure, the phenolic acids are very sensitive to light and heat, and easliy oxidized in air.

Diterpenoid tanshinones are usually classified into three types, including diterpenoid tanshinone, tricyclic diterpenoid tanshinone, and royleanone tanshinone. The basic mother nucleus of diterpenoid tanshinones contain 1,2-*o*-naphthoquinone with furan or dihyrofuran rings, such as tanshinone I, dihydrotanshinone I, tanshindiol-A. The general structure of tricyclic diterpenoid tanshinone is

Fig. (1). The profiles of *S. miltiorrhiza*. (**A**) Portion above ground. (**B**) Roots for pharmaceutical use, (**C**) Medicinal slices of *S. miltiorrhiza* root. (Pictures are kindly provided by Zexin Ma from the Museum of Chinese Medicine, Beijing University of Chinese Medicine).

Table 1. Clinical cardiovascular diseases trials containing *Salvia miltiorrhiza* (2000—now).

Prescription Name	Study Design	Type Of CVD; # of Patient; Duration	Aim and Outcome Measurements	Results (# of Patients)	Refs.
Tanshinone ⅡA + Sulfonic Acid Sodium	Randomized controlled trial	Coronary heart disease 36 15 days	Significant effect: Markedly improved in clinical symptoms such as chest stuffy, palpitations, chest pain, and short of breath; Electrocardiogram (ECG) returned to normal. Effective: Frequency of clinical symptoms attacks decreased by 50%; ECG ST segment elevated by more than 0.05 mV; Amplitude of lead T wave inversion decreased by more than 25%. Ineffective: No change in ECG.	Markedly improved (23). Moderately improved (9). Ineffective (4). Overall efficacy: 88.9%. Control treatment: 75.0% using 40ml Shenmai injection + 250ml 5% glucose solution.	[24]
S. miltiorrhiza	Randomized controlled trial	Cardiovascular disease 50 4 weeks	**Clinical efficacy:** Significant effect: Clinical symptoms completely improved alleviated by ≥ 90%. Effective: 50% ≤ Clinical symptoms improvement < 90%. Ineffective: Clinical symptoms have no improvement or alleviated by < 50%. **ECG efficacy:** Significant effect: ECG completely returned to normal. Effective: ST-T wave almost returned to normal. Ineffective: No improvement in ECG.	**Clinical efficacy:** Markedly improved (33). Moderately improved (15). Ineffective (2). Overall efficacy: 96%. Control treatment: 86%, using Isosorbide Dinitrate tablet. **ECG efficacy:** Markedly improved (30). Moderately improved (17). Ineffective (3). Overall efficacy: 94%. Control treatment: 82%, using Isosorbide Dinitrate tablet.	[25]
Danshen and Gegen capsules	Randomized placebo controlled trial (double blinded)	Postmenopausal women with borderline hypercholesterolemia 85 12 months	Sitting blood pressure, resting ECG, and physical activity scale for the elderly questionnaire; Serum glucose, creatinine, low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride (TG).	**Primary efficacy:** Carotid intima-media thickness decreased. **Secondary efficacy:** LDL and total cholesterol (TC) decreased. **Quality of life:** Improvement in general health and blood pressure.	[26]
Compound Danshen dripping pills + Isosorbide Dinitrate sustained released tablets	Randomized controlled trial	Coronary heart disease 49 2 months	Significant effect: Frequency of angina attacks significantly reduced; Clinical symptoms completely disappeared. Effective: Clinical symptoms improved; Angina attacks decreased. Ineffective: No improvement in clinical symptoms.	Markedly improved (13). Moderately improved (32). Ineffective (4). Overall efficacy: 93.75%. Control treatment: 75.0%, using Isosorbide Dinitrate tablets	[27]
Compound Danshen dripping pills	Randomized controlled trial	Coronary heart disease 33 10 weeks	**Symptoms of angina pectoris:** Significant effect: Angina pectoris disappeared completely or angina pectoris attacks decreased by > 90%. Effective: Angina pectoris attacks decreased by between 50% and 90%. Ineffective: Angina pectoris attacks decreased by < 50%. **ECG efficacy:** Changes of ST-T wave, including load ECG. Effective: ST-T wave returned to normal or changed from positive to negative. Ineffective: No change in ST-T wave, load ECG test remained positive.	**Symptoms of angina pectoris:** Markedly improved (24). Moderately improved (8). Ineffective (1). Overall efficacy: 97.0%. Control treatment: 84.8%, using Isosorbide Dinitrate tablets.	[28]

(Table 1) Contd....

Prescription Name	Study Design	Type Of CVD; # of Patient; Duration	Aim and Outcome Measurements	Results (# of Patients)	Refs.
Compound Danshen dripping pills	Randomized controlled trial	Cardiovascular diseases 39 1 month	Cure: Clinical symptoms disappeared; Autonomic dysfunction disappeared; ECG and heart rate returned to normal. Significant effect: Significant improvement in clinical symptoms; Heart rate decreased; ECG significantly improved; Autonomic nerve function returned to near normal. Ineffective: No improvement or even worse in clinical symptoms.	Markedly improved (20). Moderately improved (16). Ineffective (3). Overall efficacy: 92.31%. Control treatment: 71.79% using Isosorbide Dinitrate tablets.	[29]
Compound Danshen dripping pills	Randomized controlled trial	Cardiovascular diseases 39 4 weeks	**Angina pectoris efficacy:** Significant effect: Angina pectoris disappeared completely or angina pectoris attacks decreased by > 90%. Effective: Angina pectoris attacks decreased by between 50% and 90%. Ineffective: No obvious improvement in angina pectoris symptoms; Angina attacks decreased by < 50% or even aggravated. **ECG efficacy:** Significant effect: ST segment returned to normal. Effective: ST segment almost returned to normal. Ineffective: No obvious changes in ST segment.	**Angina pectoris efficacy:** Markedly improved (23). Moderately improved (13). Ineffective (3). Overall efficacy: 92.30%. Control treatment: 46.15% using Isosorbide Dinitrate pills and Nifedipine. **ECG efficacy:** Markedly improved (21). Moderately improved (16). Ineffective (2). Overall efficacy: 94.87%. Control treatment: 76.92% using Isosorbide Dinitrate pills and Nifedipine.	[30]
Compound Danshen dripping pills	Randomized controlled trial	Cardiovascular diseases 25 4 weeks	Cardiovascular diseases symptoms, serum TC and TG, ECG.	Serum TC and TG levels returned to normal. ECG improved. Control treatment using Isosorbide Dinitrate pills and Nifedipine.	[31]
Compound Danshen dripping pills	Before- and after-control	Coronary heart disease angina pectoris 94 2 months	**Clinical efficacy:** Significant effect: (1) Exertional angina: Angina pectoris severity alleviated 2 grade; Grade 1-2 angina pectoris disappeared; Non-exertional angina pectoris: Clinical symptoms disappeared or almost disappeared; Angina attacks decreased by more than 90%; Resting ECG returned to normal; Submaximal exercise test changed from positive to negative or exercise tolerance increased by 2 levels. Effective: (1) Exertional angina: Angina pectoris severity decreased by 1 level; Grade 1 angina pectoris disappeared; (2) Non-exertional angina pectoris: Angina attacks decreased by ≥ 50%; Resting ECG back to normal, or submaximal exercise test ECG ST segment elevated by more than 0.5 mV, but did not return to normal, or amplitude of lead T wave inversion decreased more than 50%, or shape of T wave changed from flat to upright, or exercise tolerance increased by 1 level. Ineffective: No improvement in clinical symptoms, physical signs and ECG; Frequency of angina attacks decreased by < 50%.	blood viscosity and platelet aggregation rate significantly decreased. **Clinical efficacy:** Markedly improved (55). Moderately improved (34). Ineffective (5). Overall efficacy: 94%. **ECG efficacy:** Markedly improved (17). Moderately improved (22). Ineffective (55). Overall efficacy: 75%.	[32]

(Table 1) Contd....

Prescription Name	Study Design	Type Of CVD; # of Patient; Duration	Aim and Outcome Measurements	Results (# of Patients)	Refs.
Compound Danshen dripping pills	Self control	Cardiovascular diseases 439	Observe clinical symptoms and treatment efficacy. Psychological status, heart failure, myocardial infarction, arrhythmia, and general health condition scores.	Symptoms markedly improved (203), 46.2%. Partly improved (122), 27.8%. Mildly improved (78), 17.8%. Aggravate (28), 6.4%. Dead (8), 1.8%.	[33]
Compound Danshen dripping pills	Randomized controlled trial	Coronary heart disease angina pectoris 60	**Angina pectoris efficacy:** Significant effect: Clinical symptoms such as chest stuffy, short of breath disappeared; Angina or frequency of angina attacks decreased in response to the same level of exertion; ECG ischemia returned to mormal. Effective: Frequency of angina attacks decreased or chest congestion symptoms alleviated; ECG ischemia ST segment decreased; Shape of T wave changed from flat to upright. Ineffective: No change in angina attacks and ECG.	**Angina pectoris efficacy:** Markedly improved (24). Moderately improved (20). Ineffective (8). Overall efficacy: 86.7%. Control treatment 74%. **ECG efficacy:** Markedly improved (18). Moderately improved (15). Ineffective (13). Overall efficacy: 76.7%. Control treatment using Isosorbide Dinitrate tablets.	[34]
Compound Danshen dripping pills	Randomized controlled trial	Ischemic cardiovascular disease 74 1 month	Serum TC and TG levels. **ECG efficacy:** Significant effect: ST segment abnormalities disappeared. Effective: No obvious abnormalities in ST segment. Ineffective: No change in ST segment.	Serum TC and TG levels decreased. **ECG efficacy:** Markedly improved (25). Moderately improved (39). Ineffective (10). Overall efficacy: 86.5%. Control treatment: 56.8% using Isosorbide Dinitrate tablets.	[35]
Compound Danshen dripping pills	Randomized controlled trial	Diabetes combined silent myocardial ischemia 45	Levels of adiponectin and homocysteine (Hcy). **Clinical efficacy:** Significant effect: ECG ST segment abnormalities improved or disappeared during the break. Effective: ECG ST segment decreased or elevated by > 0.05 mV during resting or sports; Amplitude of T wave inverted decreased by more than 50 %, and shape of T wave appeared upright or inverted. Ineffective: No improvement in ECG, even more serious.	Markedly improved (30). Moderately improved (14). Ineffective (1). Overall efficacy: 97.8%. Control basic treatment 88.8%.	[36]
Compound Danshen dripping pills + Aspirin	Randomized controlled trial	Coronary heart disease 50	Significant effect: Clinical symptoms completely or almost disappeared; ECG completely or almost returned to normal; Blood lipid levels returned to normal. Effective: Clinical symptoms markedly improved; ECG ST segment elevated by more than 0.05mV; Myocardial ischemia attacks decreased by more than 50%; Blood lipid levels improved. Ineffective: No improvement in clinical symptoms, ECG and blood lipid levels.	LDL decreased, HDL increased. Markedly improved (19). Moderately improved (27). Ineffective (4). Overall efficacy: 92.0%. Control treatment: 76.0% using aspirin.	[37]

(Table 1) Contd....

Prescription Name	Study Design	Type Of CVD; # of Patient; Duration	Aim and Outcome Measurements	Results (# of Patients)	Refs.
Compound Danshen dripping pills + Isosorbide Mononitrate sustained release tablets	Randomized controlled trial	Elderly patients with unstable angina 40 4 weeks	Observe the clinical therapeutic effects.	Recovery (18) Markedly improved (12). Moderately improved (7). Ineffective (3). Overall efficacy: 92.5%. Control treatment: 75.0% using Simvastatin.	[38]
Compound Danshen dripping pills + low molecular weight Heparin	Randomized controlled trial	Coronary heart disease angina pectoris 80 1 month	Significant effect: Angina pectoris almost disappeared or angina attacks decreased by more than 80%; ECG returned to normal or near normal. Effective: Angina attacks decreased by between 50% and 80% or duration shorten; ECG ST segment elevated by more than 0.05 mV, but did not return to normal; Amplitude of T wave inversion decreased, or shape of T wave changed from flat to upright, or elevated ST segment decreased by more than 50%. Ineffective: No improvement in angina pectoris; Elevated ST segment decreased by less than 50%, or even worse.	Frequency and duration of angina pectoris attacks decreased. Markedly improved (42). Moderately improved (29). Ineffective (9). Overall efficacy: 88.75%. Control treatment: 76.25% using aspirin and nitroglycerin.	[39]
Compound Danshen injection + Lulutong injection	Randomized controlled trial	Cardiovascular diseases 40 3 weeks	Significant effect: Clinical symptoms disappeared; Cardiac function increased by more than 2 levels. Effective: Clinical symptoms decreased; Cardiac function increased by more than 1 level. Ineffective: No changes in symptoms and cardiac function.	Markedly improved (23). Moderately improved (15). Ineffective (2). Overall efficacy: 95.0%. Control treatment: 75.0% using basic treatment.	[40]
Compound Danshen dripping pills + Valsartan	Randomized controlled trial	Senile primary hypertension 34 6 months	Significant effect: Diastolic blood pressure decreased by $\geq$ 10 mmHg and returned to normal, or diastolic blood pressure decreased by $\geq$ 20 mmHg. Effective: Diastolic blood pressure decreased by $<$ 10 mmHg, but did not return to normal, or diastolic blood pressure decreased by between 10 and 19 mmHg, or systolic pressure decreased by more than 30 mmHg. Ineffective: No improvement in blood pressure.	Markedly improved (24). Moderately improved (7). Ineffective (3). Overall efficacy: 91.18%. Control treatment: 67.65% using Valsartan.	[41]
Compound Danshen dripping pills + Carvedilol	Randomized controlled trial	Congestive hearts failure 47 90 days	Significant effect: Clinical symptoms of heart failure and physical signs disappeared; Cardiac function improved by 2 levels. Effective: Clinical symptoms of heart failure and physical signs significantly improved; Cardiac function improved by 1 level. Ineffective: No improvement in clinical symptoms of heart failure and physical signs, or cardiac function aggregated by 1 level.	Markedly improved (15). Moderately improved (24). Ineffective (8). Overall efficacy: 83.0%. Control treatment: 73.3% using conventional treatment include angiotensin converting-enzyme inhibition, Diuretics and Digoxin.	[42]
Compound Danshen dripping pill + Simvastatin	Randomized controlled trial	Hyperlipidemia 75 12 weeks	Significant effect: TC level decreased by $\geq$ 20% or TG level decreased by $\geq$ 40%. Effective: 10% $\leq$ TC level decrease $\leq$20%; 20% $\leq$ TG level decrease $\leq$ 40%. Ineffective: No obvious improvement in blood lipids.	Basically control (28). Markedly improved (20). Moderately improved (19). Ineffective (8). Overall efficacy: 89.33%. Control treatment: 70.83% using Simvastatin.	[43]

(Table 1) Contd....

Prescription Name	Study Design	Type Of CVD; # of Patient; Duration	Aim and Outcome Measurements	Results (# of Patients)	Refs.
Compound Danshen dripping Pills	Self control	Hyperlipidemia and blood hyperviscosity 40 2 weeks	TG, TG, HDL, hematocrit, whole blood viscosity, plasma viscosity.	TG, TC, HDL decreased; Plasma viscosity, whole blood viscosity and hematocrit decreased.	[44]
Shenfu Injection	Randomized controlled trial	Chronic heart failure 129 4 weeks	Cure: Cardiac function returned to 1 level; Clinical symptoms almost disappeared; No abnormality in physical examination. Significant effect: Cardiac function improved by 2 levels, but did not reach 1 level; Significant improvement in clinical symptoms and physical examination. Effective: Cardiac function improved by 1 level; Clinical symptoms and physical examination improved. Ineffective: No improvement in clinical symptoms and physical examination, or aggravated or dead.	Cure (60). Markedly improved (43). Moderately improved (17). Ineffective (9). Overall efficacy: 93.0%. Control treatment: 69.0% using Salvia injection	[45]
Compound Danshen dripping pills + Isosorbide Dinitrate tablet	Randomized controlled trial	Coronary heart disease angina pectoris 98 2 weeks	**Angina pectoris efficacy:** Significant effect: The same level of exertion cannot induce angina, or frequency of angina attacks decreased by 80%, or nitroglycerin consumption decreased by 50%. Effective: Angina attacks or nitroglycerin consumption decreased by between 50% and 80%. Ineffective: Angina attacks or nitroglycerin consumption decreased by less than 50%. Emphasis: Angina attacks or nitroglycerin consumption increased. **ECG efficacy:** Significant effect: Rest ischemic ST segment back to normal. Effective: Ischemic ST segment improved, but did not return to normal. Ineffective: No change in ischemic ST segment.	**Angina pectoris efficacy:** Markedly improved (26). Moderately improved (62). Ineffective (10). Overall efficacy: 89.8%. Control treatment 63.2%. **ECG efficacy:** Markedly improved (32). Moderately improved (49). Ineffective (17). Overall efficacy: 82.7%. Control treatment: 54. 7% using Isosorbide Dinitrate tablet.	[46]
Compound Danshen dripping pills + Betaloc tablet	Randomized controlled trial	Stable angina pectoris 63 Unstable angina pectoris 33	Significant effect: Angina pectoris completely disappeared; Heart function improved from Ⅳ level to above Ⅲ level, or from Ⅲ level to above Ⅱ level; ST segment returned to normal. Effective: Angina pectoris improved; Pain alleviated; Frequency and duration attacks decreased; ST segment almost returned to normal. Ineffective: No improvement in Angina or angina aggravated; Cardiac function worsen and hard-to-heal; Left ventricular failure; ECG depressed or elevated; even myocardial infarction.	**Stable angina pectoris:** Markedly improved (51). Moderately improved (11). Ineffective (1). Overall efficacy: 81%. Control treatment 63.2%. **Unstable angina pectoris:** Markedly improved (26). Moderately improved (4). Ineffective (3). Overall efficacy: 79%. Control treatment: 54. 7% using basic treatment.	[47]

(Table 1) Contd....

Prescription Name	Study Design	Type Of CVD; # of Patient; Duration	Aim and Outcome Measurements	Results (# of Patients)	Refs.
Compound Danshen dripping pills	Randomized controlled trial	Coronary heart disease 30	**Angina pectoris efficacy:** Significant effect: Same level of exertion cannot induce angina, or frequency of angina attacks decreased by more than 80%. Effective: Angina attacks or nitroglycerin consumption decreased by between 50% and 80%. Ineffective: Angina attacks or nitroglycerin consumption decreased by < 50%. Aggravate: Frequency, duration and degree of angina attacks and nitroglycerin consumption increased. **ECG efficacy:** Significant effect: Resting ECG returned to normal or near normal. Effective: ECG ST segment elevated by more than 0.05 mV; Amplitude of lead T wave inversion decreased by more than 25 %, or shape of T wave changed from flat to upright. Ineffective: No improvement in resting ECG.	**Angina pectoris efficacy:** Markedly improved (15). Moderately improved (10). Ineffective (4). Aggravate: (1). Overall efficacy: 83.3%. Control treatment 50%. **ECG efficacy:** Markedly improved (10). Moderately improved (17). Ineffective (3). Aggravate: (0). Overall efficacy: 90%, Control treatment: 66.7% using Astragalus.	[48]
Compound Danshen injection + Shenmai injection	No control	Congestive heart failure 15 25 days	Ineffective: Symptoms of heart failure and physical signs markedly improved; Cardiac function improved by more than 2 levels. Effective: Symptoms of heart failure and physical signs improved; Cardiac function improved by more than 1 level. Significant effect: No improvement in symptoms of heart failure.	Markedly improved (8). Moderately improved (6). Ineffective (1). Overall efficacy: 93%. No control treatment.	[49]
Danhong Injection	Randomized controlled trial	Unstable angina pectoris 80 14 days	Blood routine examination, liver or renal functions, platelet aggregation, levels of fibrinogen and D-dimmer.	Plasma levels of fibrinogen and D-dimmer decreased; Platelet aggregation ratio decreased. Control treatment using Alprostadil lipid emulsion injection.	[50]
Gehong decoction	No control	Cardiovascular neurosis 23	Significant effect: Clinical symptoms completely disappeared. Effective: Clinical symptoms obviously improved. Ineffective: No change in clinical symptoms.	Markedly improved (21). Moderately improved (2). Ineffective (0). Overall efficacy: 100%. No Control treatment.	[51]
Tongxinluo capsule	Randomized controlled trial	Angina pectoris with coronary heart disease 48 4 weeks	**Clinical efficacy:** Significant effect: Same level of exertion cannot induce angina pectoris, or angina pectoris attacks decreased by more than 80%. Effective: Angina attacks decreased by between 50% and 80%. Ineffective: Angina attacks decreased by < 50%. **ECG efficacy:** Significant effect: Resting ECG returned to normal or/and submaximal exercise test changed from positive to negative, or exercise tolerance increased by more than 2 levels. Effective: Resting ECG returned to normal or/and submaximal exercise test ECG ischemic ST segment elevated by more than 0.05mm, but did not return to normal; Amplitude of T wave inversion decreased by more than 50%, or T wave changed from flat to upright; Exercise tolerance improved by 1 level. Ineffective: No change in ECG.	**Clinical efficacy:** Markedly improved (32). Moderately improved (12). Ineffective (4). Overall efficacy: 91.78%. Control treatment 57.14%. **ECG efficacy:** Markedly improved (12). Moderately improved (19). Ineffective (17). Overall efficacy: 64.37%. Control treatment: 35.72% using Fufang Danshen tablets	[52]

(Table 1) Contd....

Prescription name	Study Design	Type Of CVD; # of patient; Duration	Aim and Outcome measurements	Results (# of patients)	Refs.
Yindan Xinnaotong Capsule +Aspirin + β –receptor blocker + Calcium Antagonist + Nitrates	Randomized controlled trial (grouped by visiting order)	Coronary heart disease angina pectoris 50	**Angina pectoris efficacy:** Significant effect: Frequency and duration of angina pectoris attacks decreased by more than 80 %. Effective: Frequency and duration of angina pectoris attacks decreased by more than 50 %. Ineffective: Frequency and duration of angina pectoris attacks decreased by less than 50 %. **ECG efficacy:** Significant effect: ECG returned to normal. Effective: ST segment elevated by more than 0.05 mV, but did not return to normal; Amplitude of lead T wave inversion decreased by more than 25 %, or shape of T wave changed from flat to upright; Atrio- and intra- ventricular block improved. Ineffective: No change in ECG. **Blood lipid efficacy:** Significant effect: TC decrease ≥ 20%; TG decrease ≥ 40%; HDL increase ≥ 0.26 mM; (TC-HDL)/HDL decrease ≥ 20 %. Effective: 10 % ≤ TC decrease < 20%; 20% ≤ TG decrease < 40%; 0.104 mM ≤ HDL increase < 0.26 mM; 10% ≤ (TC-HDL)/HDL decrease < 20 %. Ineffective: No change in blood lipid.	**Angina pectoris efficacy:** Markedly improved (27). Moderately improved (19). Ineffective (4). Overall efficacy: 92%. Control treatment 74%. **ECG efficacy:** Markedly improved (20). Moderately improved (23). Ineffective (7). Overall efficacy: 86%. Control treatment 70%. **Blood lipid efficacy:** Markedly improved (18). Moderately improved (22). Ineffective (20). Overall efficacy: 80%. Control treatment: 62% using aspirin, β–antagonist, calcium antagonists, nitrates.	[53]
Compound Danshen dripping pills + Perindopril.	Randomized controlled trial	Hypertension complicated with diabetes 30 3 months	Significant effect: Diastolic blood pressure decreased by more than 10 mmHg and returned to normal, or decreased by ≥ 20 mmHg. Effective: Diastolic blood pressure returned to normal or decreased by between 10 and 19 mmHg, or systolic pressure decreased by 30 mmHg. Ineffective: No improvement in blood pressure.	Markedly improved (24). Moderately improved (5). Ineffective (1). Overall efficacy: 96.7%. Control treatment: 76.7% using Perindopril.	[54]
Yixinshu Capsule	Self control	Cardiovascular diseases 135 13 weeks	Significant effect: ECG returned to normal or near normal. Effective: ST segment elevated by more than 0.05 mV, but did not return to normal; Amplitude of lead T wave inversion decreased by more than 25%, or shape of T wave changed from flat to upright. Ineffective: No change in ECG.	Markedly improved (22). Moderately improved (112). Ineffective (1). Overall efficacy: 99.2%.	[55]
Guanxin Danshen dripping pills	Randomized controlled trial	Coronary heart disease angina pectoris 20 6 weeks	Serum C-reactive protein (CRP) and matrix metalloproteinases (MMP)-9. Significant effect: Angina attacks decrease ≥ 80%; Nitroglycerin consumption decrease ≥ 80%, or same level of exertion cannot induce angina pectoris ; Resting ECG returned to normal. Effective: 50% < angina attacks and nitroglycerin consumption decrease < 50%; Resting ECG ischemic ST elevation ≥ 0.1 mV; Amplitude of T wave inversion decreased by more than 25% or shape of T wave changed from flat to upright. Ineffective: Angina attacks and nitroglycerin consumption decrease < 50%. No improvement in resting ECG.	Serum CRP, MMP-9 markedly decreased Markedly improved (12). Moderately improved (7). Ineffective (1). Overall efficacy: 95.0%. Control treatment 70.0%.	[56]
Yiqi Huoxue granules	Randomized controlled trial	Cardiovascular complications with peritoneal dialysis patients 18 6 months	Left ventricular hypertrophy (LVH), cardiovascular calcification (CVC), congestive heart failure (CHF), the ratio of the early (E) to late (A) ventricular filling velocities (E/A), left ventricular ejection fraction (LVEF) evaluated by color B-ultrasound. Serum cystatin C (CysC), Hcy.	Serum levels of Hcy, CysC and tumor necrosis factor-α (TNF-α) decreased; LVEF and E/A increased; Incidence of LVH, CHF decreased; CVC increased.	[57]

(Table 1) Contd....

Prescription name	Study design	Type Of CVD; # of patient; duration	Aim and Outcome measurements	Results (# of patients)	Refs.
Compound Danshen dripping pills	Randomized controlled trial	Coronary heart disease 46 1 month	**Clinical efficacy:** Significant effect: No angina pectoris attacks or frequency of angina attacks decreased by more than 80%; No significant chest pain during angina pectoris attacks. Effective: Frequency of angina attacks decreased by between 50% and 80%; Chest pain obviously alleviated during angina pectoris attack. Ineffective: No obvious improvement in frequency of angina attacks and chest pain, or chest pain developed into acute myocardial infarction or sudden cardiac death. **ECG efficacy:** Significant effect: Resting ECG almost returned to normal. Effective: Amplitude of ST segment increased by 0.1 mV; Amplitude of T wave inversion decreased by more than 50%, or shape of T wave changed from flat to upright. Ineffective: No obvious improvement in ECG, or even appeared myocardial infarction during the attack.	**Clinical efficacy:** Markedly improved (22). Moderately improved (19). Ineffective (5). Overall efficacy: 89.1%. Control treatment 69.6%. **ECG efficacy:** Markedly improved (25). Moderately improved (19). Ineffective (2). Overall efficacy: 95.7%. Control treatment: 80.4% using Isosorbide Dinitrate Tablets	[58]
Danshen Chuanxiongqin injection + Huangqi injection	Randomized controlled trial	Viral myocarditis in children 42 30 days	Significant effect: Clinical symptoms completely disappeared; ECG returned to normal; Myocardial enzymes returned to normal. Effective: Clinical symptoms improved; ECG improved, but did not return to normal. Ineffective: No improvement in clinical symptoms, ECG and myocardial enzymes.	**Clinical efficacy** Markedly improved (26). Moderately improved (13). Ineffective (3). Overall efficacy: 93%. Control treatment: 72% using conventional treatment.	[59]
Danshen Chuanxiongqin injection	Randomized controlled trial	Coronary heart disease angina pectoris 35 14 days	Significant effect: Frequency of angina attacks decreased by≥ 80%; Resting ECG returned to normal. Effective: Frequency of angina attacks decreased by between 50% and 80%; Resting ECG improved. Ineffective: No improvement in clinical symptoms or even worse.	Frequency and duration of angina pectoris attacks, and heart rate improved. Markedly improved (26). Moderately improved (6). Ineffective (3). Overall efficacy: 93.43%. Control treatment: 77.14% using composite salvia miltiorrhiza injection.	[60]
5 g hydrophilic extracts of S. miltiorrhiza	Randomized controlled trial	Diabetes with chronic heart disease 62 60 days	Serum malondialdehyde (MDA), glutathione (GSH), superoxide dismutase (SOD), paraoxonase (PONase) and glutathione reductase (GSSG-R). Soluble vascular cell adhesion molecule-1 (sVCAM-1), von Willebrand factor (vWF) and oxidative low density lipoprotein (oxLDL)	Serum MDA level reduced; Serum GSH level increased; Serum SOD, PONase and GR activities increased; Serum levels of sVCAM-1, vWF and oxLDL decreased.	[61, 62]

Note: The ingredients of TCM prescriptions.

(1) Compound Danshen dripping pills: *Borneolum Synthcticum*, *Notoginseng Radix*, *Salvia Miltiorrhizae Radix et Rhizoma*.

(2) Danhong injection: *Salvia Miltiorrhizae Radix et Rhizoma*, *Carthami Flos*.

(3) Gehong decoction: *Puerariae Lobatae Radix* 30g, *Carthami Flos* 10g, *Cinnamomi Ramulus* 10g, *Notopterygii Rhizoma et Radix* 10g, *Angelicae Sinensis Radix* 12g, *Chuanxiong Rhizoma* 12g, *Salvia Miltiorrhizae Radix et Rhizoma* 20g.

(4) Tongxinluo capsule: *Ginseng Radix*, *Hirudo*, *Scolopendra*, *Cicadae Periostracum*，*Paeoniae Rubra Radix*, *Borneolum Synthcticum*, *Salvia Miltiorrhizae Radix et Rhizoma*.

(5) Yindan Xinnaotong soft capsule: *Ginkgo Folium*, *Salvia Miltiorrhizae Radix et Rhizoma*, *Asari Radix et Rhizoma*, *Notoginseng Radix*, *Crataegi Pinnatifidae Fructus*, *Gynostemmatis Pentaphylli Herba seu Radix*, *Allium sativum* L. (Garlic), *Borneolum Synthcticum*.

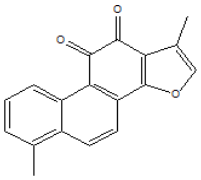
(6) Yixinshu Capsule: *Ginseng Radix*, *Ophiopogonis Radix*, *Schisandrae Chinensis Fructus*, *Salvia Miltiorrhizae Radix et Rhizoma*, *Astragali Mongolici Radix*, *Chuanxiong Rhizoma*, *Crataegi Pinnatifidae Fructus*.

(7) Guanxin Danshen dripping pills: *Salvia Miltiorrhizae Radix et Rhizoma*, *Notoginseng Radix*, *Dalbergiae Odoriferae Lignum*.

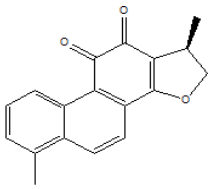
(8) Yiqi Huoxue granule: *Astragali Mongolici Radix* 20 g, *Notoginseng Radix* 3 g, *Salvia Miltiorrhizae Radix et Rhizoma* 10 g, *Allii Macrostemi Bulbus* 10 g.

Nonpolar (lipid-soluble) compounds

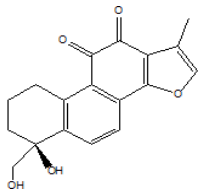
tanshinone I



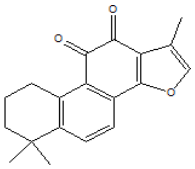
dihydrotanshinone I



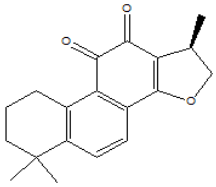
tanshindiol-A



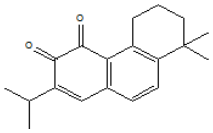
tanshinone IIA



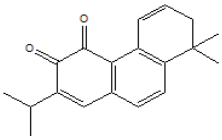
cryptotanshinone



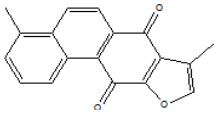
miltirone



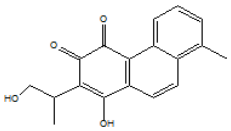
dehydro miltirone



isotanshinone I

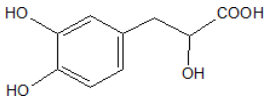


Danshenxinkun A

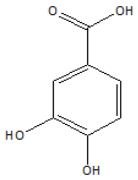


Hydrophilic phenolic compounds

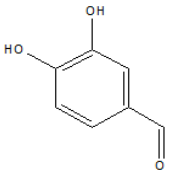
Danshensu



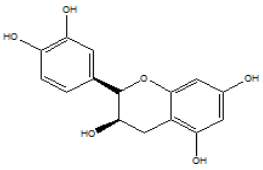
protocatechuic acid



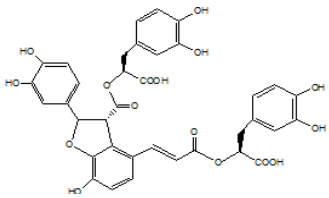
protocatechualdehyde



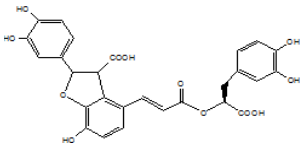
catechin



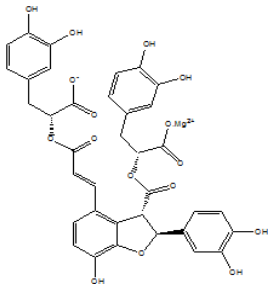
salvianolic acid B



lithospermic acid B



magnesium tanshinoate B



dimethyl lithospermate B

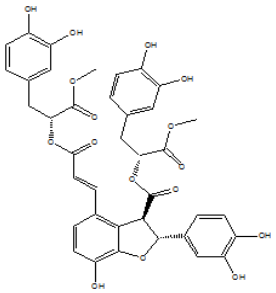


Fig. (2). Chemical structure and names of compounds isolated from *S. miltiorrhiza.*

featured as the ligation with an isopropyl group instead of a furan or dihydrofuran ring, such as miltirone, dehydro miltirone. The group of royleanone tanshinone is featured as 1,4-*p*-quinone, such as isotanshinone, Danshenxinkun A. Most compounds of the diterpenoid tanshinones are red color and stable in their solid state.

The biological actions of these compounds isolated from *S. miltiorrhiza* have been clarified over the last few years, and several mechanisms have been proposed for the cardiovascular protection effects [67] of this plant, including anti-inflammation [1], antioxidation [65, 68] anti-thrombosis [69], anti-proliferation of vascular smooth muscle cells, inhibition of the expression of adhesion molecules in vascular endothelium and leukocytes [64, 69-71], improvement of acute myocardial ischemia [72], and so on [73].

5. EFFECTS OF *S. MILTIORRHIZA* AND ITS ISOLATED COMPOUNDS ON THE DEVELOPMENT OF CVD IN ANIMAL EXPERIMENTS

The preclinical pharmacological effects of *S. miltiorrhiza* and its isolated compounds for the treatment of CVD have been extensively studied over the past few decades. The results have shown that *S. miltiorrhiza* offered therapeutic benefits on hypertension, atherosclerosis, myocardial ischemia and reperfusion injury in the animal experiments. The recent progress of *S. miltiorrhiza* in CVD animal disease models are summarized in Table **2**. In the following paragraphs, we review the recent advances of *S. miltiorrhiza* regarding cardiac protective effects *in vivo* and *in vitro* studies.

5.1. Effects of *Salvia miltiorrhiza* in the Development of Hypertension

Hypertension is a chronical medical condition in which the blood pressure in the arteries is persistently higher than it should be. Increased peripheral resistance, high cardiac output, an elevated heart rate, a reduction in the number or density of capillaries, increased active arteriolar vasoconstriction and decreased peripheral venous compliance account for the high pressure. Long term high blood pressure can cause coronary artery disease, stroke, heart failure and peripheral vascular disease [93].

It is well established that Ca^{2+} dependent and independent K^+ effluxes limit membrane depolarization and contraction and further buffer vascular resistance in arterial reactivity [94, 95]. Tanshinone IIA treatment (10 mg/kg for 4 weeks [83] or 21 days [84], i.p.) attenuated chronic intermittent hypoxia or sustained hypoxia or monocrotaline (subcutaneous injection of 50 mg/kg [84]) induced pulmonary artery wall remodeling (thickened small pulmonary artery vessel walls and deflated vessel lumina) and increased right ventricular systolic pressure (RVSP) in rats. The underlying mechanisms for these improvements may be attributed to modulate the expressions of $K_V2.1$ and $K_V1.5$ [83], and to inhibit basal intracellular Ca^{2+} concentration and store-operated Ca^{2+} entry (SOCE) via attenuating the expressions of canonical transient receptor potential (TRPC) 1 and TRPC 6 [84]. However, Tanshinone IIA did not affect rats RVSP and the mean carotid arterial pressure under normoxia exposure.

Connexins (Cxs) and endothelial nitric oxide synthase (eNOS) harmonize the adaptation of smooth muscle cells and endothelial cells. Using spontaneously hypertensive rats, Tang *et al.* found that administration of Danshensu (10 mg/kg/d for 6 weeks) decreased blood pressure and inhibited arrhythmias via increasing serum nitric oxide (NO) content and nitric oxide synthase activity [74]. Using isoproterenol (2.5 mg/kg/d for 7 days, s.c.) induced myocardial hypertrophy rats, Danshensu treatment (3 and 10 mg/kg/d from day 4 to 7 of isoproterenol treatment, i.p.) reduced heart/body weight index and arrhythmia scores as well as improved left ventricle systolic pressure and left ventricle end diastolic pressure and electrocardiogram parameters by regulating antioxidant enzymes and promoting left ventricular Cx-43 expression [85].

Matrix metalloproteinases and tissue inhibitors of metalloproteinases (MMPs/TIMPs) impact vascular relaxation/contraction via regulating ion channels in the endothelium and vascular smooth muscle during vascular remodeling [96, 97]. Fang *et al.* demonstrated that supplyment with tanshinone IIA (70 mg/kg/d for 6 weeks) prevented cardiac fibrosis and left ventricular hypertrophy as well as improved cardiac relaxation in 2-kidney-2-clip induced renovascular hypertension rats [76]. Tanshinone IIA conferred its beneficial effects by decreasing collagen volume content via decreasing mRNA levels of MMP-9, TIMP-1 and TIMP-2 and increasing the mRNA ratio of MMP-2 to TIMP-2 [76].

Angiotensin-converting enzyme (ACE) controls the fluid-electrolyte balance and blood pressure through converting the hormone angiotensin (Ang) I to the active vasoconstrictor Ang II and subsequently causing blood vessels to constrict [98, 99]. Addition of lithospermic acid B (10-1000 μg/ml) dose-dependently inhibited ACE plasma activities. Lithospermic acid B (100-400 μg/ml) treatment also attenuated Ang I induced contraction in the endothelium intact aortic rings [100].

Hypertension is associated with elevated myocardial tumor necrosis factor-α (TNF-α) production [101]. *S. miltiorrhiza* (1 g/kg for 12 weeks, i.p.) treatment decreased left ventricular mass index, cardiomyocytes sizes, collagen volume fraction, perivascular circumferential area through regulating TNF-α expression in spontaneously hypertensive rats [75]. Interestingly, the investigator claimed that the cardio protective effect of this herb was independent of blood pressure.

Further, magnesium tanshinoate B (MTB, 0.7–175 mg/kg via the jugular vein) was evidenced to exhibit hypotensive effect on phenylephrine induced elevated blood pressure in male SD rats [86]. Tian *et al* found that *S. miltiorrhiza* (0.125 g/mouse) and salvianolic acid B (0.5 mg/mouse) decreased the average blood flow velocity in liver in endothelin (ET)-1 induced portal hypertension mice evaluated by laser-Doppler flow instrument [87]. But the mechanisms remain unclear.

Taken together, *Salvia miltiorrhiza* and its ingredients, including lithospermic acid B, tanshinone IIA and Danshensu, offer therapeutic promise on hypertension through regulating expressions of TRPC/Ca^{2+}, Cx/eNOS/ET-1, MMP/TIMPs, ACE and TNF-α. However, the underlying mechanisms for their pharmacological actions of salvianolic acid B and tanshinoate B still remain unknown. Besides spontaneously hypertensive rats, a lot of measures are employed to evaluate anti-hypertensive effects of the herbs, such as hypoxia, monocrotaline, 2-kidney-2-clip, Ang I, phenylephrine and ET-1. These efforts may afford experimental evidences for clinical use of this herb.

5.2. Effects of *Salvia miltiorrhiza* in the Development of Artherosclerosis

Atherosclerosis is a condition where the arteries become narrowed and lost of elasticity of the artey walls due to an excessive build up of sticky plaques within the arterial intima [102, 103]. *S. miltiorrhiza* exihibits beneficial effects for the treatment of artherosclerosis through the following manners.

First, *S. miltiorrhiza* has the ability of inhibiting oxidative stress. Oxidative stress leads to aggravation of endothelial cells and disruption of vascular wall microenvironment as well as overexpression of adhesion molecules such as intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), which induced cardiac dysfunction [104]. By preventing low density lipoprotein (LDL) from oxidation, *S. miltiorrhiza* (5% water-soluble extract of *S. miltiorrhiza* for 12 weeks) reduced the atherosclerotic area in the abdominal aorta by 56% and cholesterol deposition in the thoracic aorta by 50% in cholesterol-fed rabbits [80]. *In vitro*, both *S. miltiorrhiza* and salvianolic acid B exhibited free radical scavenging activity in DPPH assay, and were also effective in preventing Cu^{2+} induced LDL oxidation [80]. Further,

Table 2. The efficacy of *S. miltiorrhiza* in CVD animal models.

Animal Model	Drug and Dose	Duration	Main Findings	Refs.
Spontaneously hypertensive Rats	Danshensu; 10 mg/kg/d.	6 weeks	Decrease in heart weight to body weight index and blood pressure; Decrease in ventricular tachycardia and ventricular fibrillation; Increase in serum nitric oxide content and inducible nitric oxide synthase activity.	[74]
Spontaneously hypertensive Rats	*S. miltiorrhiza;* 1 g/kg/d.	12 weeks	Decrease in left ventricular mass index, cardiomyocyte size, diameter, collagen volume fraction, perivascular circumferential area, and tumor necrosis factor-α (TNF-α) expression.	[75]
Hypertension rats	Tanshinone II-A; 70, 35 mg/kg/d.	6 weeks	Attenuatation of the attendant interstitial fibrosis; Inhition of matrix metalloproteinase (MMP)-9 and tissue inhibitors of MMP-1 expressions.	[76]
Myocardial ischemia/reperfusion injury rat	Cryptotanshinone; 125 or 250 μg/kg.	10 minitues before ischemia	Inhibition of the translocation of nuclear transcription factor-kappa B and suppressed expression of inflammatory cytokines (TNF-α, interleukin-1 β), and decreased the myeloperoxidase activity.	[77]
Porcine closed-chest model	Salvianolate; 10 mg/kg/day.	7 days	Improvement in myocardial perfusion; Increase in capillary density and decrease in infarct sizes; Elevatation of superoxide dismutase (SOD) activity, thioredoxin activity and glutathione concentration; Decrease in malondialdehyde concentration.	[78]
Myocardial ischemia rats	Salvianolic acid B; 20 mg/kg/d.	7 days	Improvement in the abnormal metabolites.	[79]
Cholesterol-fed Rabbits	5% water-soluble extract of *S. miltiorrhiza.*	12 weeks	Improvement in endothelial damage, atherosclerotic area in the abdominal aorta, and cholesterol deposition in the thoracic aorta.	[80]
LAD ligation induced MI rats	Tanshinone II A; 60 mg/kg/day.	1 week	Decrease in infarct sizes and collagen deposition; Improvement in heart recovery.	[81]
High fatty diet induced rabbit atherosclerosis	Tanshinone II A; 6.25, 15.00 and 37.50 mg/kg/day.	2 months	Increase in SOD activity; Decrease in malondialdehyde level; Decrease in cluster of differentiation (CD) 40 expression and MMP-2 activity.	[1]
Atherosclerosis rats	Salvianolate; 60, 120 or 240 mg/kg.	12 weeks	Decrease in total cholesterol, low density lipoprotein (LDL), interleukin-6 and C-reactive protein; Increase in the numbers of CD4+CD25+Foxp3+ cells.	[82]
Atherosclerosis rabbits	Salvianolic acid B; 8 mg/kg/d. Tanshinone ⅡA; 24 mg/kg/d.	8 weeks	Decrease in triglyceride level; Increase in nitric oxide level.	[9]
Hypoxia or monocrotaline rats	Tanshinone IIA; 10 mg/kg.	4 weeks or 21 days	Decrease in pulmonary artery wall remodeling (thickened small pulmonary artery vessel walls and deflated vessel lumina) and right ventricular systolic pressure.	[83, 84]
Isoproterenol induced myocardial hypertrophy rats	Danshensu; 3 and 10 mg/kg/.	from day 4 to day 7 during isoproterenol treatment	Decrease in heart/body weight index and arrhythmia scores; Improvement in left ventricle systolic pressure and left ventricle end diastolic pressure and electrocardiogram parameters; Increase in SOD and connexin 43 expression.	[85]
Phenylephrine induced male SD rats	Magnesium tanshinoate B; 0.7-175 mg/kg.	infusion of the same agent via the left femoral vein every 15 mins	Decrease in blood pressure.	[86]
Endothelin-1 induced portal hypertension mice	*S. miltiorrhiza*; 0.125 g/mouse. Salvianolic acid B; 0.5 mg/mouse.	3 days	Decrease in the average blood flow velocity in liver.	[87]
Isolated rat hearts of ischemia reperfusion (I/R)	Danshensu; 1 and 10 μM. The extract of *S. miltiorrhiza;* 29.76 or 59.52 mg/kg.	5 days	Increase in CF, heart rate, left ventricular developed pressure, and the recovery of ± dp/dtmax; Decrease in infarct sizes; Inhibition of oxidative stress through regualting Akt/extracellular signal-regulated kinase 1/2/nuclear factor erythroid-2-related factor 2 signaling pathway.	[88, 89]
Apolipoprotein E-deficient mice	Cryptotanshinone; 15 and 45 mg/kg/day.	22 weeks	Significant reduction in atherosclerotic plaque formation and enhanced plaque stability; Decrease in lectin-like oxidized LDL receptor-1 (LOX-1) and matrix metalloproteinase (MMP)-9.	[90]

(Table 2) Contd....

Animal Model	Drug and Dose	Duration	Main Findings	Refs.
Carotid artery balloon injury rats	Magnesium lithospermate B; 10 mg/kg/day.	28 days	Inhibition of neointimal formation.	[68]
LAD induced M/I mice	Danshen; 3 and 6 g/kg/day.	4 weeks	Increase in hypoxia-inducible factor 1α and vascular endothelial growth factor A expression.	[91]
LAD induced M/I rats	*S. miltiorrhiza* polysaccharides pretreatment with 400 and 800 mg/kg	one week	Decrease in the infarct sizes; Improvement of Na^+–K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase activities; Alleviatation of oxidative stress; Inhibition of myocardial apoptosis	[92]

tanshinone IIA treatment (15 and 37.5 mg/kg for 2 months by gavage) reduced malondialdehyde (MDA) level and increased superoxide dismutase (SOD) activity in high fatty diet (HFD) induced atherosclerosis rabbits [1].

Zhiping Liu *et al.* showed that treatment with cryptotanshinone (15 and 45 mg/kg/day) resulted in a significant reduction in atherosclerotic plaque formation and enhanced plaque stability in HFD insulted apolipoprotein E deficient mice by reducing the expressions of lectin-like oxidized LDL receptor-1 (LOX-1) and MMP-9 through inhibiting NADPH oxidase 4 (NOX4)-mediated ROS generation and consequent nuclear transcription factor-kappa B (NF-κB) activation [90]. Treatment with salvianolic acid B (8 m/kg/d) and tanshinone IIA (24 mg/kg/d) for 8 weeks were demonstrated to inhibit atherogenesis of HFD-fed rabbits by increasing NO release [9].

Second, *S. miltiorrhiza* is effective in inhibiting inflammation in the development of CVD. Inflammatory mediators increase local susceptibility to plaque formation which contributes to the development of atherosclerosis [105]. Using atherosclerosis rats challegened by HFD, salvianolate treatment dose-dependently (60, 120 and 240 mg/kg for 12 weeks, i.p.) alleviated the atherosclerotic process via decreasing the levels of proinflammatory cytokines (plasma interleukin-6 (IL-6) and C reactive protein (CRP)) and increasing the number of regulatory T cells (Tregs) (cluster of differentiation (CD)4+CD25+Foxp3+) [82]. Tregs is demonstrated to prevent the development of atherosclerosis by reducing IL-6 expression [106] and CRP production [107]. Interestingly, although salvianolate treatment did cause a decrease in the levels of total cholesterol and LDL, it had no effect on that of triglyceride and HDL.

Platelet CD40 stimulates activations of leukocyte and endothelial cells and further promotes atherosclerosis [108]. Meanwhile, increased MMP-2 activity potentiates inflammation insults and plaque instability in the injured vascular wall [109]. Tanshinone IIA was demonstrated to downregulate CD40 expression and decrease MMP-2 activity in atherosclerosis rabbits [1].

In a rat carotid artery balloon injury model, magnesium lithospermate B treatment (10 mg/kg/day for 28 days, i.p) prevented neointimal formation [68]. Wan *et al* studied the effect of the lipophilic fraction (tanshinone IIA and cryptotanshinone) of *S. miltiorrhiza* roots on isolated porcine coronary arteries induced by U46619 (a thromboxane A analogue). The results demonstrated that the lipophilic fraction at a concentration of 0.1 mg/mL induced complete relaxation in porcine coronary artery [110]. However, the mechanisms responsible for these effects still warrant further investigation.

In short, *S. miltiorrhiza* and its ingredients may serve as antioxidant and anti-inflammation agents to prevent the development of atherosclerosis. *S. miltiorrhiza*, salvianolic acid B, tanshinone IIA, salvianolate and cryptotanshinone are well studied in this respect. Meanwhile, HFD induced atherosclerotic rabbit and rat models are employed to evaluate the effect of this herb on atherosclerosis.

5.3. Effects of *S. miltiorrhiza* in the Improvement of Myocardial Ischemia (MI)

Myocardial ischemia (MI, also known as angina) is a heart condition caused by a lack of blood supplement to the heart, which is the result of a partial or complete blockage of coronary arteries and may consequently accelerate the deterioration of cardiac function [17]. Reperfusion therapy is the most effective therapeutic strategy for improving the prognosis of patients with acute myocardial infarction but accompanied with the potential risk of worsening tissue damage after ischemia [17, 111, 112]. MI exerts multiple insults in myocardium, frequently accompanied by reactive oxygen species (ROS) generation, intracellular calcium overload, myocardial apoptosis, endothelial dysfunction, enhanced adhesion of leukocytes and mast cell degranulation [71, 113, 114].

Using real-time myocardial contrast echocardiography and coloured microspheres techniques, Han *et al.* demonstrated that adminstration with salvianolate (10 mg/kg/day for 7 days, i.v.) improved myocardial microvascular reflow and increased capillary density as well as decreased infarct sizes in a porcine closed-chest model [78]. The beneficial effect of salvianolate was probobaly related to its ability of decreasing oxidative stress and apoptosis, which was supported by elevated SOD activity, thioredoxin activity and glutathione concentration, and reduced MDA concentration, as well as decreased terminal deoxynucleotide transferase-mediated dUTP nick end labelling-positive cells and increased ratio of B-cell lymphoma 2 to Bax expression [78].

Monocyte chemotactic protein (MCP)-1 is upregulated in the development of MI both in clincal trial [115] and animal model [116], which facilliates infiltration, activation and cytokine secretion of inflammatory cells. MCP-1 null mice exhibited decreased macrophage recruitment in the infarcted heart, delayed phagocytosis of dead cardiomyocytes, diminished fibroblast infiltration and attenuated left ventricular remodeling [117]. Meanwhile, Ang II and TNF-α stimulate MCP-1 production [118] and amplify the proinflammatory response through NF-κB and mitogen activated protein kinase (MAPK) p38 signaling pathway [119, 120]. Tanshinone IIA (60 mg/kg/day for 7 days) treatment decreased infarct sizes and collagen deposition and improved heart recovery in permanent left anterior descending coronary artery (LAD) ligation induced MI rats [81]. The cardioprotective effect of tanshinone IIA could be attributed to its abilty of inhibiting inflammatory responses by reducing expressions of MCP-1, transforming growth factor (TGF)-β1, TNF-α and NF-κB [81]. In addition, tanshinone IIA (2-8 μM) treatment also reduced MCP-1 and TGF-β1 secretion in TNF-α stimulated cardiac fibroblasts [81].

In addition, Danshensu (1 and 10 μM) [88] and the extract of *S. miltiorrhiza* (29.76 or 59.52 mg/kg for 5 days by gavage) [89] treatment contributed to the recovery of cardiac function after MI,

and the tolerance of heart against MI injury by improving coronary flow, heart rate and left ventricular developed pressure, and the recovery of ± dp/dt_{max} as well as reducing infarct sizes via inhibiting oxidative stress through regualting Akt/extracellular signal-regulated kinase (ERK) 1/2/nuclear factor erythroid-2-related factor 2 (Nrf2) signaling pathways in isolated rat hearts MI model.

Jin *et al.* observed the effect of cryptotanshinone treatment in LAD induced MI rats. They oberved the alterations of hemodynamic parameters (left ventricular end diastolic pressure and ± dp/dt_{max}) and the infarct area as well as area at risk. The results demonstrated that cryptotanshinone (250 μg/kg) reversed the MI induced alterations by modualting inflammatory pathway evidenced via inhibiting NF-κB translocation and reducing expressions of pro-inflammatory cytokines (TNF-α, IL-1β and IL-6) as well as suppressing neutrophil infiltration and myeloperoxidase activity through regualting p38 mitogen-activated protein kinase (MAPK)/ c-Jun N-terminal kinase (JNK)/ERK in ischemic myocardial tissues [77].

Activation of the cardiac angiogenesis program is a promising therapeutic strategy to match the increasing demands of oxygen and nutrients in the stressed heart [121]. The hypoxia-inducible factor 1α (HIF1α) and vascular endothelial growth factor A (VEGFA) contribute to cardiac angiogenesis [122]. Employing LAD induced MI mice, Danshen (3 and 6 g/kg/day for 4 weeks, i.p.) was proved to increase HIF1α and VEGFA expression which futher contributed to improving cardiac function and cardiac angiogenesis [91].

Song *et al* oberved the effect of *S. miltiorrhiza* polysaccharides on LAD induced MI rats. They found that pretreatment with *S. miltiorrhiza* polysaccharides (400 and 800 mg/kg for 1 week) reduced the infarct sizes and improved Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase activities by alleviating oxidative stress and inhibiting myocardial apoptosis [92]. It is known that myocardial Na^+-K^+-ATPase and Ca^{2+}-Mg^{2+}-ATPase activities are associated with myocardial damage such as ischemic cardiac dysfunction and arrhythmias [123].

Using LAD induced MI rats, Lu *et al.* [79] found that salvianolic acid B (20 mg/kg/d for 7 days) treatment was effective in resolving MI. They demonstrated that salvianolic acid B achieved its therapeutic effect by improving some of biomarkers, including 15(S)-HETE, 2',3'-cyclic adenosine monophosphate (cAMP), dihydrosphingosine, phytosphingosine, L-isoleucyl-L-proline, 2',3'-cyclic guanosine monophosphate, 1-phenylethylamine, thromboxane B2, hypoxanthine, L-homoserine, carnosine, allantoin, L-valine, L-phenylalanine, dihydrobiopterin, 2-oxoisocaproic acid, L-isoleucine, L-tryptophan and glyceraldehydes. However, the authors did not conduct further experiments to verify these alterations.

In conclusion, Danshen, the extract of *S. miltiorrhiza*, salvianolate, tanshinone IIA, Danshensu, cryptotanshinone, *S. miltiorrhiza* polysaccharides and salvianolic acid B are demonstrated to exhibit protective effect on MI through scavenging oxidative stress, reducing inflammation and improving angiogenesis via regualting p38MAPK/JNK/ERK and Akt/ERK1/2/Nrf2 pathways. Among these, *S. miltiorrhiza* polysaccharides also showed its beneficial role against MI. Given lack of effective measures to determine its contributors, there is still a long way to go for exploiting contributions of polysaccharides for the treatment of CVD.

5.4. Effects of *Salvia miltiorrhiza* on Endothelial Cells, Smooth Muscle Cells and Myocardial Cells

5.4.1. The Protective Effects of Salvia miltiorrhiza on Endothelial Cells

The vascular endothelium, positioned at the interface between blood and tissue, plays a pivotal role in maintaining the integrity of the vessel wall. The death or injury of endothelial cells may contribute to the initial endothelial pathophysiological processes, including angiogenesis, atherosclerosis, and thrombosis.

NO plays the cardioprotective role through regualting blood pressure and vascular tone, and inhibiting platelet aggregation and leukocyte adhesion as well as preventing smooth muscle cell proliferation. An impairment of NO production may result in hypertension or atherosclerosis [124]. Further, ET-1 is a vasoconstricting peptide produced primarily in the endothelium which contributes to constrict blood vessels and raise blood pressure. Activating transcription factor (ATF)-3 mediated inflammatory and apoptotic responses as well as oxidantvie stress in the endothelium [125]. NO promotes ATF-3 expression and further results in a repression of MMP-2 promoter activity [126]. Tanshinone IIA (3 and 10 μM [127]; 0-100 μM [128]) treatment inhibited ET-1 release and stimulated NO production via inducing eNOS activation and ATF-3 expression in human umbilical vein endothelial cells (HUVECs). Further, tanshinone IIA (3-10 μM) exhibited resistance to H_2O_2 induced apoptosis via decreasing CD40 expression [129] and inducing ATF-3 expression [130] in HUVECs.

Cryptotanshinone also exhibits mitigating effects against oxidative stress and inflammation insults. Using HUVECs exposed to H_2O_2, TNF-α and oxidized LDL insults [77, 90], cryptotanshinone treatment was shown to inhibit the resultant NF-κB activity and LOX-1 expression. Further, cryptotanshinone inhibited LOX-1-mediated adhesion of THP-1 monocytes to HUVECs by reducing the expression of VCAM-1, ICAM-1 and E-selectin via inhibiting NOX4/ROS/NF-κB signaling pathway in HUVECs [90, 131]. It is accepted that increased expression and activation of ICAM-1 and VCAM-1 as well as E-selectin contribute to the attachment of circulating monocytes/leukocytes to the surface of endothelial cells, which initials atherosclerosis [132].

Vascular endothelial growth factor (VEGF) regulates the endothelial hyperpermeability which resulted in inflammation and subsequent ischemic reperfusion injury or atherosclerosis. The extracts of *S. miltiorrhiza* and its active components (Danshensu and salvianolic acid B) inhibited TNF-α induced hyper-permeability by inhibiting VEGF expression [133] in HUVECs. In addition, salvianolic acid B and Danshensu (1-20 μg/ml) also protected HUVECS against hydrogen peroxide damage [65].

Danshen aqueous extract and its pure compounds (Danshensu, protocatechuic acid, catechin and protocatechualdehyde at dose of 10 μg/ml) protected HUVEC against homocysteine-induced endothelial dysfunction by tube formation assay. The efficacy was demonstrated as the following descending order: Danshen aqueous extract, Danshensu, protocatechuic acid, catechin and protocatechualdehyde [134].

5.4.2. The Protective Effects of Salvia miltiorrhiza on Smooth Muscle Cells

Vascular smooth muscle cells (VSMCs) are one of the major constituents of blood vessel walls and deeply involved in the development of CVD. Wang *et al.* demonstrated that tanshinones (a mixture of tanshinone I, tanshinone II, and cryptotanshinone at the dosages of 0.4, 2, 10 and 50 μg/ml) inhibited VSMCs proliferation by decreasing ERK1/2 signaling as well as decreasing the cyclin D expression through increasing the $p21^{waf1/cip1}$ expression, which are essential for cell cycle progression from G0/G1 phase to S Phase [70]. Tanshinone IIA (12.5 μM) treatment also inhibited hypoxia (4% O_2, 60 h) induced pulmonary artery smooth muscle cells (PASMCs) proliferation and migration, and suppressed prolonged hypoxia induced TRPC expression in PASMCs from normoxic rats [84].

TRPC proteins may act as molecualr components of store-operated Ca^{2+} channels which mediate Ca^{2+} influx [135]. Elevation of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) contributes to cell growth and contraction [136]. Administration of sodium tanshinone IIA sulfonate (10 mg/kg) reduced SOCE and inhibited elevation of

basal $[Ca^{2+}]_i$ through supressing TRPC1 and TRPC6 expression in distal PASMCs from chronical hypoxic rats [84].

Acute hypoxia inhibits K_V channel function and triggers contraction in PASMCs [137]. Tanshinone IIA (25 μg/ml) partly reversed acute hypoxia (pO_2 at about 15 mmHg for 30 min) induced downregulated I_{KV} currents in PASMCs [83].

Using primary mesenteric vascular smooth muscle cells isolated from spontaneously hypertensive rats, Danshensu treatment enhanced the K^+ and Ca^{2+} activated K^+ channel current density when the test potential was set at +60 mV [74]. Ca^{2+}-activated K^+ (K_{Ca}) channels along with K^+ (K_V) channels play an important role in regulating vascular tone and blood pressure [138].

Both phosphatidylinositide 3 kinase (PI3K)/Akt and MAPK/ERK pathways are involved in regulating smooth muscle cells [139, 140]. Tanshinone IIA was able to inhibit human aortic smooth muscle cell migration by inhibiting phosphorylation of Akt and ERK and c-jun. Meanwhile, tanshinone IIA also has the ability of reducing MMP-9 activity and NF-κB activation [141].

Following endothelial injury and excessive oxidative stress, VSMCs proliferate and migrate to the intima, leading to intima hyperplasia and development of CVD [10, 142, 143]. In an experiment performed by Hur *et al.* demonstrated that magnesium lithospermate B (10 μM) attenuated platelet-derived growth factor-BB induced VSMCs proliferation and migration via inhibiting phosphorylation of PI3K/Akt and MAPK/ERK pathways by scavenging reactive oxygen species [68].

In addition, dimethyl lithospermate B was effective in eliminating the arrhythmogenic substrate which was responsible for the Brugada syndrome by slowing I_{Na} inactivation via increased inward current during the early phase of the action potential in canine [144]. It maybe use as a pharmacological adjunct to implantable cardioverter/defibrillator usage.

5.4.3. The Protective Effects of Salvia miltiorrhiza on Myocardial Cells

The hypertrophy of myocardial cells impairs myocardial contractility and leads to LV hypertrophy [145]. Tanshinone VI (10 μM) attenuated ET-1, phenylephrine, or insulin like growth factor-1 (IGF-1) induced increases in protein synthesis in neonatal rat cardiac myocytes. Tanshinone VI (10 μM) treatment attenuated fetal bovine serum (5%) or IGF-1 (0.01 μM) induced hypertrophy via decreasing collagen synthesis in cardiac fibroblasts [146]. Thus, tanshinone VI may improve the development of cardiac remodeling under pathophysiological conditions.

In the development of MI, cAMP activates protein kinase A (PKA) which results in phosphorylation of L-type Ca^{2+} channel and consequent Ca^{2+} influx, leading to stronger muscle contraction. Salvianolic acid B treatment (0.001, 0.01 and 0.1 mg/mL for 2 h) decreased Ca^{2+} and cAMP, and inhibited PKA in H9C2 cell (a myogenic cell line derived from embryonic rat heart ventricle) [79].

In addition, *S. miltiorrhiza* is reported to be an effective inhibitor of Ang II action. However, the different fractions of the roots of *S. miltiorrhiza* exhibited different effects on Ang II treated neonatal rat cardiac cells (cardiomyocytes and non-cardiomyocytes). The ethyl acetate insoluble fraction from the methanol extract attenuated hypertrophy of cardiomyocytes. The methanol eluate fraction of the water extract treatment inhibited hyperplasia of non-cardiomyocyte [147].

To summarized *in vitro* experiments, *S. miltiorrhiza* and its active ingredients (Danshensu, salvianolic acid B, protocatechuic acid, catechin, protocatechualdehyde, tanshinone, tanshinone IIA, lithospermate B, tanshinone VI and cryptotanshinone) exhibit protective effects in CVD disease models of endothelial cell and smooth muscle cells as well as myocardial cells through mutiple targets.

Furthermore, *S. miltiorrhiza* is also synergistically cooperated with other herbs (*Radix Puerariae* Lobatae [148-150], Compound Danshen tablet [151], Fufang Xueshuantong capsule [152]), Danhong injection [153], or western drug (Atorvastatin [154]) to treatment of CVD animals. However, it is reported that tanshinones and *S. miltiorrhiza* root extracts contained potent human carboxylesterase (CE) inhibitors, while CEs hydrolyze clinically used drugs [155]. For drug interactions of this herb, interested readers are encouraged to consult Su *et al*'s review [16]. Therefore, remedies containing tanshinones should be alerted for potential drug-drug interactions when patients are taking additional western drugs.

Currently, there is a rising concern about the safety of *S. miltiorrhiza* products. And a few investigators reported potential side effects, such as abdominal discomfort [5, 156], decreased appetite, convulsions, dystonia syndromes [157], and allergy [158]. However, these side effects are relieved when patients stop taking the medications [16]. Meanwhile, these observations are not well designed. Thus, the clinical physicians still need strong and scientific evidences to make sure whether *Salvia miltiorrhiza* is suitable for long term consuming.

In summary, *S. miltiorrhiza* and its ingredients (Danshensu, salvianolic acid B, protocatechuic acid, catechin and protocatechualdehyde, tanshinone, tanshinone IIA, tanshinone VI, lithospermate B, cryptotanshinone and polysaccharides) are extensively studied in animal and cell disease models of CVD. The results reveal that *S. miltiorrhiza* plays beneficial roles in improving CVD, such as atherosclerosis, hypertension and myocardial ischemia. These pharmacological activities are associated with scavengering oxidative stress and resolving inflammation as well as improving angiogenesis via regulating TRPC/Ca^{2+}, Cx/eNOS/ET-1, MMP/TIMPs, p38MAPK/JNK/ERK, Akt/ERK/Nrf2 and Nox4/ROS/NF-κB pathways. The researchers and clinical physicians should pay attention to the potential side effects and drug-drug interactions.

CONCLUSION AND OUTLOOK

S. miltiorrhiza is one of the most frequently used herbs in formulations prescribed for the clinical treatment of CVD in China. Since 2000, there are 39 clinical trials used *S. miltiorrhiza* to treat CVD. Although most studies reported promising efficacy in improving clinical symptoms, their significance is still need to be improved through well designed clinical trials in order to provide sufficient evidence to fully demonstrate the effects of *S. miltiorrhiza* products. The investigators are also needed to pay more attention to potential adverse effects and drug-drug interactions of this herb. Currently, there have been more than 200 compounds have been identified from *S. miltiorrhiza* Bunge. Most of these compounds exhibit multipotent pharmacological activities. Various *in vitro* and *in vivo* preclinical experiments showed *S. miltiorrhiza* and its ingredients could lower hypertension, improve atherosclerosis and myocardial ischemia reperfusion. The identified active compounds, including Danshensu, salvianolic acid B, protocatechuic acid, catechin, protocatechualdehyde, tanshinone, tanshinone IIA, tanshinone VI, lithospermate B, cryptotanshinone and polysaccharides, are considered to be responsible for its cardioprotective effects through different cell signaling pathways. Fig. (**3**) briefly illustrates the different pharmacological activities of *S. miltiorrhiza* and its ingredients. The results strongly support the notion that *S. miltiorrhiza* has beneficial therapeutic properties and has a potential of being an effective alternative remedy for the management of CVD.

Taditional clinical Chinese medicine illuminates the possible indications of *S. miltiorrhiza* for patients with CVD. However, the potential pharmacological effects are still required to be studied by more strong scientific evidences. Furthermore, the holistic and dialectical approach of TCM theory suggests the scientists to probe the possible synergistic actions among multiple constituents of this herb and other co-prescribed herbs. More new drugs are expected to

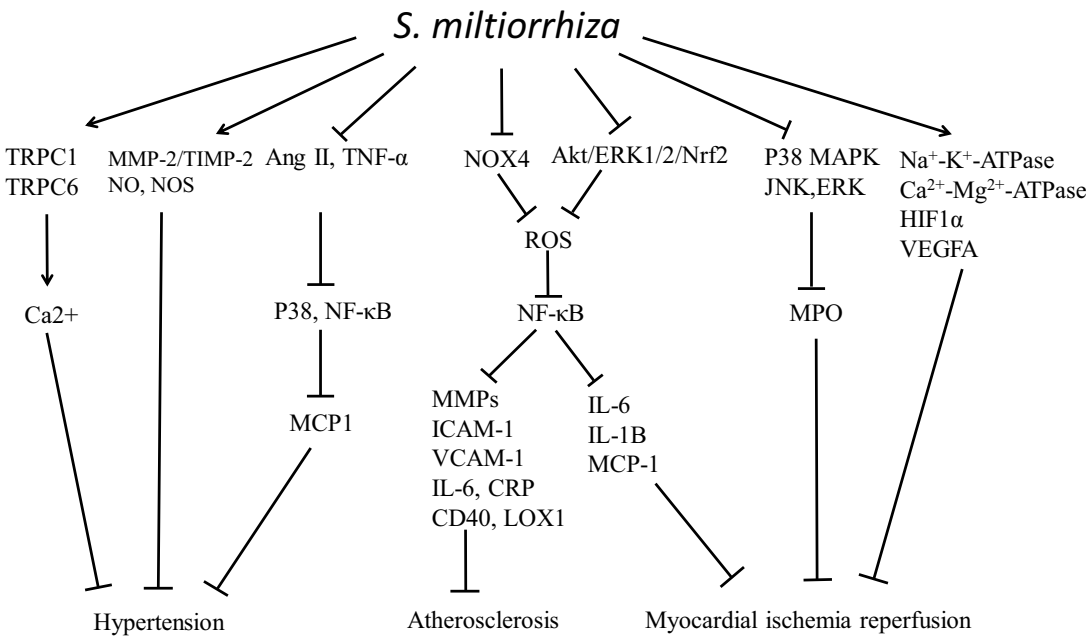


Fig. (3). The revealed pathways targeted by *S. miltiorrhiza. S. miltiorrhiza* could downregulate the levels of Nox4, ROS, NF-κB, MMPs, ICAM-1, VCAM-1, IL-6, CRP, CD40, and LOX1, which contributes to inhibition of atherosclerosis. *S. miltiorrhiza* suppresses P38MAPK/JNK/ERK pathway, and activates Na^+-K^+-ATPase, Ca^{2+}-Mg^{2+}-ATPase, HIF1α and VEGFA, which facilitates improvement of CVD. Further, *S. miltiorrhiza* upregulates TRPC1/TRPC6/Ca^{2+}, MMP-2/TIMP-2, NO and NOS expression, and inhibits Ang II, TNF-α/P38/NF-κB/MCP1 pathways, which contribute to the inhibition of hypertension.

source from this plant with better therapeutic effects and lower side effects by mining the ingredients. The existing ingredients in this plant are useful for developing potent compounds drugs, which may offer synergistic actions and exhibit better anti-CVD effects compared to the individual compound. These approaches are also useful for guiding our research to employ an integrative therapeutic approach to treat complex diseases such as CVD which could be superior to the conventional single target – single drug approach. This will shed the light on TCM researchers and patients with CVD around the world, and will also benefit for the development of TCM herbs such as *S. miltiorrhiza* in the near future.

LIST OF ABBREVIATIONS

ACE	=	Angiotensin-converting enzyme
Ang	=	Angiotensin
ATF-3	=	Activating transcription factor 3
cAMP	=	Cyclic adenosine monophosphate
CD	=	Cluster of differentiation
CE	=	Carboxylesterase
CHF	=	Congestive heart failure
CRP	=	C-reactive protein
CVC	=	Cardiovascular calcification
CVD	=	Cardiovascular disease
Cx	=	Connexin
CysC	=	Cystatin C
E/A	=	The ratio of the early (E) to late (A) ventricular filling velocities
ECG	=	Electrocardiogram
eNOS	=	Endothelial NO synthase
ERK	=	Extracellular signal-regulated kinase
ET-1	=	Endothelin-1
GSH	=	Glutathione
GR	=	Glutathione reductase
Hcy	=	Homocysteine
HDL	=	High density lipoprotein
HFD	=	High fat diet
HIF1α	=	Hypoxia-inducible factor 1α
HUVEC	=	Human umbilical vein endothelial cell
ICAM-1	=	Intracellular adhesion molecule-1
IGF-1	=	Insulin-like growth factor-1
IL-1β	=	Interleukin-1β
IL-6	=	Interleukin-6
I/R	=	Ischemia reperfusion
JNK	=	c-Jun N-terminal kinase
LAD	=	Left anterior descending coronary artery
LDL	=	Low density lipoprotein
LOX-1	=	Oxidized low-density lipoprotein receptor-1
LVDP	=	Left ventricular developed pressure
LVEDP	=	Left ventricle end diastolic pressure
LVEF	=	Left ventricular ejection fraction
LVH	=	Left ventricular hypertrophy
MAPK	=	Mitogen-activated protein kinase
MCP-1	=	Monocyte chemoattractant protein
MDA	=	Malondialdehyde
MI	=	Myocardial infarction
MMP	=	Matrix metalloproteinase
NF-κB	=	Nuclear transcription factor-kappa B
NO	=	Nitric oxide
NOX4	=	NADPH oxidase 4
Nrf2	=	Nuclear factor erythroid-2-related factor 2
oxLDL	=	Oxidized low-density lipoprotein
PASMCs	=	Pulmonary artery smooth muscle cells
PI3K	=	Phosphoinositide-3 kinase

PKA	=	Protein kinase A
PONase	=	Paraoxonase
RVSP	=	Right ventricular systolic pressure
ROS	=	Reactive oxygen species
SOCE	=	Store-operated Ca^{2+} entry
SOD	=	Superoxide dismutase
sVCAM-1	=	Soluble vascular cell adhesion molecule-1
TC	=	Total cholesterol
TCM	=	Traditional Chinese medicine
TG	=	Triglyceride
TGF	=	Transforming growth factor
TIMP	=	Tissue inhibitors of metalloproteinase
TNF-α	=	Tumor necrosis factor-α
Tregs	=	Regulatory T cells
TRPC	=	Canonical transient receptor potential
VCAM-1	=	Vascular cell adhesion molecule-1
VEGF	=	Vascular endothelial growth factor
VEGFA	=	Vascular endothelial growth factor A
VSMCs	=	Vascular smooth muscle cells
vWF	=	von Willebrand factor

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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