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Salvia miltiorrhiza and ischemic diseases

Xin-Yan JI, Benny K-H TAN, Yi-Zhun ZHU[1] (*Department of Pharmacology, Faculty of Medicine, National University of Singapore, Singapore 119260, Singapore*)

KEY WORDS *Salvia miltiorrhiza*; myocardial infarction; cardiovascular system; cerebrovascular disorders; antioxidants; free radicls; myocarodial ischemia

ABSTRACT

The demonstration of beneficial effects of *salvia miltiorrhiza* (DanShen) on ischemic diseases has revolutionized the management of angina pectoris, myocardial infarction (MI) or stroke in Chinese society. Experimental studies have shown that DanShen dilated coronary arteries, increased coronary blood flow, and scavenged free radicals in ischemic diseases, so that it reduced the cellular damage from ischemia and improved heart functions. Clinical trials also indicated that DanShen was an effective medicine for angina pectoris, MI, and stroke. This review will focus on DanShen's effects in angina pectoris, MI and stroke.

INTRODUCTION

Salvia miltiorrhiza Bunge (DanShen) belongs to the *Labiatae* family of the plant kingdom. It grows in northeastern China, Manchuria, Korea, and Japan[1]. The dried roots, which are medicinal, are available as slender, forked, brick red, wrinkled pieces. DanShen is an important natural product used in the treatment of many diseases, especially ischemic cardiovascular diseases. It is considered to possess 'slightly cold' and 'bitter' properties and enters the 'heart', 'pericardium', and 'liver' channels when used as a traditional Chinese medicine (TCM). It invigorates the blood and breaks up the blood stasis, when used in disorders of the lower abdomen such as dysmenorrhea, amenorrhea, lochioschesis, and pain due to blood stasis. It is also used for chest pain due to blood stasis, as well as for soreness in the ribs or hypochondria related to constrained Liver 'Qi' with blood stasis[2]. It clears the heat in the body and soothes irritability and is especially useful for restlessness, palpitations, and insomnia due to the entrance of into heat nutritive level. It can also be used in patterns of Heart and Kidney 'Yin' deficiency[2]. DanShen has been widely used in China, Japan, Korea, and other Chinese communities world-wide for centuries. However, the mechanisms of action of DanShen remain to be elucidated. To date, the major known ingredients in DanShen have been identified, which are: tanshinone I – VI, cryptotanshinone, isotanshinone I – II, isocryptotanshinone, miltirone, tanshinol I – II, methyl tanshinonate, hydroxytanshinone II_b, salviol, protocatechuic aldehyde, protocatechuic acid and vitamin E[3]. There is a growing interest in studying the effective elements of DanShen. However, some traditional Chinese medicine practitioners still prefer to prescribe whole extracts (eg, DanShen injection) or crude extract of the roots rather than admunister a single bioactive element. This is due to the belief that all elements in DanShen work in synergism. Experiments using modern techniques showed that DanShen is an effective platelet aggregation inhibitor[4-6]. It dilates coronary arteries, increases coronary blood flow and scavenges free radicals in ischemic diseases, thus reducing cellular damage from ischemia. Furthermore, DanShen has a significant sedative effect[2,7,8]. Clinical trials have also indicated that DanShen is an effective medicine for angina pectoris, myocardial infarction (MI) and stroke. The demonstration of the beneficial effects of DanShen on ischemic diseases has revolutionized the management of these ischemic diseases in the Chinese society. This review will focus on DanShen's effects on angina pectoris, MI, and stroke and its antioxidative effect on ischemic diseases in experimental animals and in clinical trials.

CARDIOVASCULAR EFFECTS OF DanShen

TCM practitioners describe the effect of DanShen in

[1] Correspondence to Dr Yi-Zhun ZHU, *Department of Pharmacology, Faculty of Medicine, National University of Singapore, 10 Kent Ridge Crescent, Singapore 119260.*
Phn 65-874-3676. Fax 65-773-0579.
E-mail phczhuyz@nus.edu.sg
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cardiovascular diseases as mainly "clearing heat in the 'Yin' system". Little is known from the modern pharmacological point of view about the mechanism of action of DanShen. DanShen has been reported to have multiple effective sites at the cardiovascular system. In rabbits, it has been shown that whether DanShen produces vasodilatation or vasoconstriction depends on the dose and target vessels used[9]. It induced vasodilatation of renal, mesenteric and femoral arteries at low concentration (3 g/L), while at a higher concentration (10 g/L); vasoconstriction was induced in the same vessels. However, vasodilatation of coronary arteries was induced at all concentrations (3 – 10 g/L) tested.

The study on systemic blood pressure in albino rats and rabbits showed that an aqueous extract of DanShen induced dose-related hypotension without changing the heart rate[10]. Furthermore, the hypotension was antagonized by atropine, propranolol and chlorpheniramine plus cimetidine. Akbar, *et al*[11] also showed that DanShen aqueous extract at a dose 5 – 40 mg/kg given orally produced a dose-dependent biphasic response on blood pressure in anesthetized dogs. The fall in blood pressure was blocked by atropine, resulting in a further rise in blood pressure. The hypotensive effect was not blocked by tolazoline hydrochloride (10 mg/kg).

This hypotensive effect could be due to an increased utilization of extra-cellular calcium ions[10]. Recently, Cheung and co-workers[12] showed that magnesium tanshinoate B, a compound purified from DanShen, stimulated the release of nitric oxide (NO) and its metabolites in human endothelial cells. NO is a potent vasodilator which plays an important role in regulating the vascular tone. This could be an important mechanism of DanShen's unique cardiovascular effects.

In an isolated rat heart study[13], DanShen increased the coronary blood flow significantly for 15 min and produced a positive inotropic action for 3 min after a pulse injection. During post-ischemic reperfusion, recovery of left ventricular pressure in the DanShen-treated hearts was significantly better while contracture was significantly less, compared to the untreated hearts. The results indicated that DanShen protects the heart against some of the deleterious effects of ischemia and reperfusion.

A study on the post-hypoxic recovery of cardiac contractile force showed that when the hearts were treated with tanshinone VI, during hypoxia, the beneficial recovery was accompanied by enhanced restoration of myocardial high-energy phosphates, depression of hypoxia- and reoxygenation-induced increase in tissue calcium content, and suppression of release of ATP metabolites such as adenosine, inosine, and hypoxanthine from the isolated perfused rat heart[14]. The treatment was performed by injecting 33.3 μmol/L of tansheninone at an infusion rate of 0.1 mL/min with the final concentration of tanshinone VI at 42 nmol/L. The calcium concentration was determined by an atomic absorption spectrometer. The results suggested that tanshinone VI is beneficial for the recovery of cardiac contractility after a certain period of oxygen-deficiency, possibly through mechanisms involving improvement of myocardial production upon oxygen-replenishment and/or inhibition of calcium accumulation in the myocardium. DanShen significantly increased the $+/-dp/dt_{max}$ of dog heart and reduced the necrotic sizes and malondialdehyde content in the ischemic dog myocardium[15].

Onitsuka and Fujiu[4-6] show that DanShen is an effective platelet aggregation inhibitor. The mechanisms could be that Danshensu, an active compound in DanShen, inhibits platelets to produce and release thromboxane A_2[6]. Tanshintinone II_A reduced the activity of Mg^{2+}-ATP enzyme which was stimulated by platelet actin[5]. To treat ischemic diseases by smoothing the blood flow, and improving the microcirculation is another important aspect of DanShen.

Of the 16 active compounds in DanShen, the active components conferring possibly myocardial protection against ischemia-induced injury have been reported to be tanshinone I, cryptotanshinone and tanshinone VI[16]. However, Lei and Chiou[10] showed that the effects of the aqueous extract of DanShen and tanshinones, a purified active principle of DanShen, on rat and rabbit renal, mesenteric and femoral arteries *in vitro* were very similar both qualitatively and quantitatively. This phenomenon indicated that tanshinones are the main active ingredients of DanShen and also that tanshinones' main effects are on the cardiovascular system. In a clinical trial including 108 patients with angina pectoris, Zhao, *et al*[17] showed that tanshinone II_A injection, a principle purified compound of DanShen, had similar effects as DanShen injection. These two examples suggest that an economical decoction of DanShen is as efficacious as the more expensive isolated tanshinones. However, there is research ongoing on single extracted and separated elements.

We recently studied the cardioprotective effect of DanShen in rats subjected to MI. MI was induced by the ligation of left descending coronary artery (LAD) and the rats were treated with DanShen, saline and ramipril, an

angiotensin converting enzyme (ACE) inhibitor, respectively. The treatment was started 1 week before the surgery and continued for another 2 weeks post MI. Our study showed that DanShen reduced the ratios of infarct size to the left ventricular size (Fig 1A), total heart weight (Fig 1B), left ventricular weight and right ventricular weight to body weight in Wistar rats[18] as effectively as ramipril, which is used in the clinical treatment of hypertension, angina pectoris, MI and stroke. However, the mechanism of action of DanShen in protecting the hypoxic myocardium remains to be further studied. Ramipril was taken as a positive control for studying cardioprotective effects because ACE inhibitors have become important drugs for the treatment of hypertension, congestive heart failure, post myocardial infarction, and diabetic nephropathy in Western medicine[19-21]. ACE inhibitors have been recently shown to be cardioprotective in both experimental[19,21-26] and clinical studies[27-32]. They are able to induce myocardial capillary growth, improve the metabolic status of the myocardium, prevent cardiac hypertrophy, limit MI size, and thus improve cardiac function after MI. The overwhelming therapeutic success of these drugs is related to their unique pharmacological profile involving both a reduction of plasma and tissue angiotensin II (ANG II) concentrations and a potentiation of endogenous kinins. Reduction of ANG II by ACE inhibitors can thus exert antihypertensive actions by lowering the vascular resistance as well as the intravascular volume. More recently, ANG II has increasingly been recognized as a growth promoting factor contributing to vascular media hypertrophy/hyperplasia, cardiac left ventricular hypertrophy and fibrosis, and nephrosclerosis. These ANG II-induced structural changes can also be antagonized by ACE inhibitors, in addition to the beneficial effects on blood pressure reduction. Compared to ACE inhibitors, very limited information is available for showing the mechanisms of the cardioprotective effects of DanShen. Given the parallel usage of DanShen and ACE inhibitors in MI and stroke by Chinese and Western medical practitioners, respectively, it is of interest and value to demonstrate whether DanShen has effects on renin-angiotensin system like ACE inhibitors or ANG II receptor antagonists as well as on ANG II receptor gene expression. It seems that DanShen has its unique pharmacological effect in the cardiovascular system. If this unknown mechanism of DanShen is clarified, it would lead to the future use of DanShen in conjunction with or as safer alternative to ACE inhibitors in the management of these ischemic conditions.

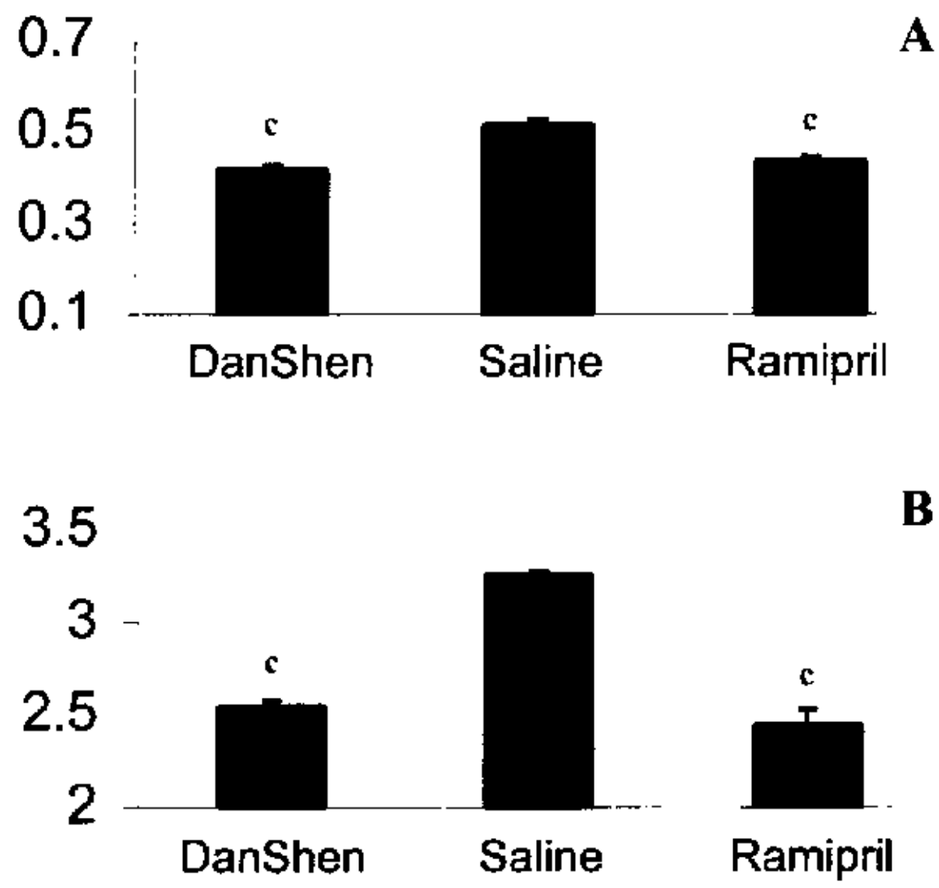

Fig 1. A) Infarct size of the left ventricle 3 weeks after LDA ligation in DanShen, saline, and ramipril treated groups. $n = 6$ rats. $\bar{x} \pm s_{\bar{x}}$. $^cP < 0.01$ *vs* saline-treated rats. B) Ratios of total heart weight to body weight 3 weeks after LDA ligation in DanShen, saline, and ramipril treated groups. $n = 6$ rats. $\bar{x} \pm s_{\bar{x}}$. $^cP < 0.01$ *vs* saline-treated rats.

In conclusion, DanShen acts on multiple sites of the cardiovascular system. The mechanisms of its two-way regulation of renal, mesenteric, and femoral arteries, and dilation of coronary arteries are still unknown. We hypothesize that DanShen has compounds that are active on the cardiovascular system. Further studies need to be done to clarify this aspect.

SCAVENGING EFFECTS OF DanShen ON FREE RADICALS

Substances isolated from DanShen have been documented to exhibit antioxidant effects and these have been well recognized recently[33]. Zhao and Wen[17] showed that DanShen Injection, an effective form used widely and successfully in hospitalized patients with myocarditis and MI, could scavenge the oxygen free radicals generated from ischemia-reperfusion injury in the myocardium as effectively as superoxide dismutase (SOD). Furthermore, in that study, the sites of action of two active compounds from DanShen, danshensu and tanshinone, were identified. Danshensu, working as a preventive antioxidant, could scavenge superoxide anions generated from the xanthine-xanthine oxidase system and protect the myocardial mitochondrial membranes from lipid peroxida-

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tion, while tanshinone, functioning as a chain-breaking antioxidant, scavenged the lipid free radicals generated from lipid peroxidation of the myocardial mitochondrial membranes. Tanshinone IIa, another active compound from DanShen, was confirmed as a new and stronger antioxidant that inhibited the association of lipid peroxidation products with DNA in the liver cells[34]. All the compounds mentioned above could inhibit the formation of thiobarbituric acid-reactive substances from hypoxia-reperfused rat myocardium and rat liver cells. In a cerebral ischemic animal model, Leung, *et al*[35] showed that the degree of lipid peroxidation could be lowered by pretreatment with a Chinese herbal preparation containing the antioxidant principle of DanShen. This mechanism was postulated to reduce the cellular damage induced by cerebral ischemia in rats.

In our recent studies using DanShen injection (0.675 g crude water extract/kg per day) for 3 weeks chronic treatment of rats starting 1 week before MI and continued for another 2 weeks after MI, we found that DanShen induced activities of hepatic antioxidant enzymes including SOD ($P < 0.001$), catalase (CAT, $P < 0.05$), glutathione perioxidase (GSH-Px, $P < 0.001$) and glutathione S-transferase (GST, $P < 0.005$) compared to placebo treated groups in Wistar rats (Tab 1)[18]. These antioxidant assays were performed after sacrificing the rats at the end of the treatment period. Ramipril-treated rats had not effect on the activities of these antioxidant enzymes. DanShen's capacity for scavenging free radicals could be one of the important mechanisms in protecting the myocardium post-MI.

Tab 1. Hepatic anti-oxidant status of DanShen-, saline-, and ramipril-treated rats. $n = 6$. $\bar{x} \pm s_{\bar{x}}$. $^cP < 0.01$ *vs* **corresponding saline-, and ramipril-treated group.** $^eP < 0.05$ *vs* **corresponding saline-treated group.**

Enzyme (U/mg protein)	DanShen	Saline	Ramipril
CAT	0.674 ± 0.016^c	0.583 ± 0.031	0.630 ± 0.019
SOD	16.24 ± 0.31^c	10.56 ± 0.31	8.94 ± 0.67
GSH-Px	0.453 ± 0.013^c	0.353 ± 0.012	0.248 ± 0.012^e
GST	5.23 ± 0.114^c	4.03 ± 0.215	2.62 ± 0.105

One unit of SOD is defined as the amount of enzyme necessary to inhibit the superoxide-dependent oxidation of 10 mmol/L pyrogallol; 1 unit of catalase (CAT) defined as mmol H_2O_2 decomposed/min; 1 unit of glutathione peroxidase (GSH-Px) is defined as 1 μmoL reduced nicotinamide adenine dinucleotide phosphate (NADPH) converted to $NADP^+$/min; One unit of glutathione *S*-transferase (GST) is defined as 1 μmoL CDNB converted to CDNB-glutathione/min. All assays were performed in duplicate at 25 ℃.

CLINICAL TRIALS OF DanShen

Many clinical trials of DanShen for treating angina pectoris, MI, and stroke have been done in China. Unfortunately, most of them were published in Chinese[36-41].

In TCM, angina pectoris is classified in three different kinds regarding its differentiation. DanShen is used for the angina pectoris due to "Blood Stasis in the Heart-vessels", which is recognized by: twinge in the chest radiating to the shoulder and back, stuffy sensation in the chest and shortness of breath, deep purple tongue with ecchymosed, taut or uneven pulse[37]. If the diagnosis is correct, DanShen treatment is efficacious.

For the treatment of acute angina pectoris without a history of MI, DanShen injection was given either intramuscularly or intravenously for 2 – 4 weeks. There were marked clinical improvements in 80 % – 90 % of patients with angina pectoris; based on ECG findings, the figures were 40 % – 66.6 % compared to placebo control[42]. In one clinical series of more than 300 patients with angina pectoris, a combination of DanShen and JiangXiang (Lignum Dalbergiae odoriferae), given either intramuscularly or intravenously, improved the symptoms in approximately 82 % and the ECGs in 50 % of the cases[2]. Normally, it is considered that a TCM formula with DanShen as a principal herb has better effect in angina pectoris than DanShen alone. There are many clinical trials supporting this statement. The reason for this is that all herbs in the formula work together to enhance the effect of the principal herb[43].

Another aspect in this area is comparing the effects of DanShen injection on angina pectoris with nitroglycerine, a well-known agent for angina pectoris. The results showed that DanShen injection or a formula containing DanShen had a better effect than nitroglycerine[42].

MI is considered as a severe ischemic disease in TCM, for which prevention is more important than treatment. DanShen is a potential herb for preventing MI after symptoms of angina pectoris have been observed. In China, DanShen is only used as a supportive agent to treat MI in combination with the Western medicine[44].

DanShen is more popularly used for stroke caused by ischemia ('blood stasis in the brain-vessels' in TCM) than in hemorrhagic stroke. "Ischemic" stroke is associated with blood clots in the brain as in Western medicine.

However, some doctors also use DanShen for stroke patients with bleeding in the subarachnoidal cavity because they believethat DanShen can reduce the blood flow in the brain under this condition and help to reduce bleeding[38,39]. Interestingly, DanShen was reported to improve the blood circulation to absorb the blood clots, scavenge free radicals to prevent further damage or even cure the damage[41]. For prevention and treatment of stroke (with and without hemorrhage), DanShen injection, given intravenously for 4 – 6 weeks, in 90 % of patients improved the symptoms[42]. In another clinical trial, 96.6 % of the 120 patients with ischemic stroke treated with DanShen injection 20 mL in 40 mL 25 % glucose intravenously improved clinically after 4 – 6 weeks[41]. In a clinical trial of 42 stroke patients with arachnoidal bleeding, DanShen injection 7 – 10 mL in 500 mL 5 % – 10 % glucose was given *iv* for 3 weeks, once daily. There was significant clinical improvement of symptoms in 95.2 % of the treated patients[40]. It is important that the proper dose be used for treating the hemorrhagic stroke. Too high a dose of DanShen may exacerbate the symptoms of stroke.

CONCLUSION

All the studies with DanShen indicate that it is an effective herb for angina pectoris, MI and stroke as it can dilate coronary vessels, increase coronary circulation, inhibit platelet aggregation, scavenge free radicals formed during hypoxic injury as well as sedate the patients. However, its use in hypertension is questionable since it induces both vasodilatation and vasoconstriction depending on the dose and the target vessels.

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