Danshen: An Overview of Its Chemistry, Pharmacology, Pharmacokinetics, and Clinical Use

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Limin Zhou, MSc, Zhong Zuo, PhD, and Moses Sing Sum Chow, PharmD

Danshen, the dried root of Salvia miltiorrhiza, *has been widely used in China and, to a lesser extent, in Japan, the United States, and other European countries for the treatment of cardiovascular and cerebrovascular diseases. In China, the specific clinical use is angina pectoris, hyperlipidemia, and acute ischemic stroke. The current review covers its traditional uses, chemical constituents, pharmacological activities, pharmacokinetics, clinical applications, and potential herb-drug interactions based on information obtained in both the English and Chinese literature. Although numerous clinical trials have demonstrated that certain Danshen products in China are effective and safe for the treatment of cardiovascular diseases, most of these lack sufficient quality. Therefore, large randomized clinical trials and further scientific research to determine its mechanism of actions will be necessary to ensure the safety, effectiveness, and better understanding of its action.*

Keywords: *Danshen;* Salvia miltiorrhiza; *danshensu; salvianolic acid B; tanshinone IIA*

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Danshen, the dried root of *Salvia miltiorrhiza* (Fam. *Labiatae*) (Figure 1), is a commonly used traditional Chinese medicine (TCM) for improving body function (eg, promoting circulation and improving blood flow). In addition, it has been used for the treatment of cardiovascular diseases such as coronary heart disease, hyperlipidemia,[1-4] and cerebrovascular disease.[5] In the United States and European countries, Danshen products can be obtained in herbal shops. In Japan, Danshen products are sold commercially for promoting circulation, improving "blood stasis" (www.goken.com/nagae/item/6104121.htm; www.est.hi-ho.ne.jp/abes/hyakkaen28/hyakkaen28-15.htm). The greatest use of Danshen is in China, which has a market that exceeded US$120 million in 2002.[6]

In China, numerous pharmaceutical dosage forms of Danshen are commercially available. These include tablets, capsules, granules, injectables, oral liquids, sprays, and dripping pills (which are made by blending the herbal extract with excipients under thermal condition followed by dripping the mixture into an insoluble cooling liquid in which the droplets are solidified to form the "dripping pill"[6]) of either Danshen or Fufang Danshen (which is a composite of *Salvia miltiorrhiza*, *Panax notoginseng*, and *Cinnamomum camphora*).[7-9] In addition, various new dosage forms such as rapid-soluble tablet,[10] liposomes,[11] and solid dispersion[12] of Danshen have been investigated. Among all the available dosage forms, the Fufang Danshen Tablet and Fufang Danshen Dripping Pill are the 2 most widely used products in China and have been officially listed in the Chinese pharmacopoeia.[13] The Fufang Danshen Dripping Pill has also been registered as a drug in several countries, including Vietnam, Russia, Cuba, the Korean Republic, and Saudi Arabia (www.tasly.com). The Fufang Danshen Dripping Pill was the first TCM product approved for phase II and III clinical trials by the Food and Drug Administration (FDA) in 1997 (IND No. 56956).[14]

In view of its large market in Asian countries as well as keen interest in the use and modernization of herbal products throughout the world, this article provides an overview of the chemistry, pharmacology, pharmacokinetics, and clinical efficacy of Danshen products.

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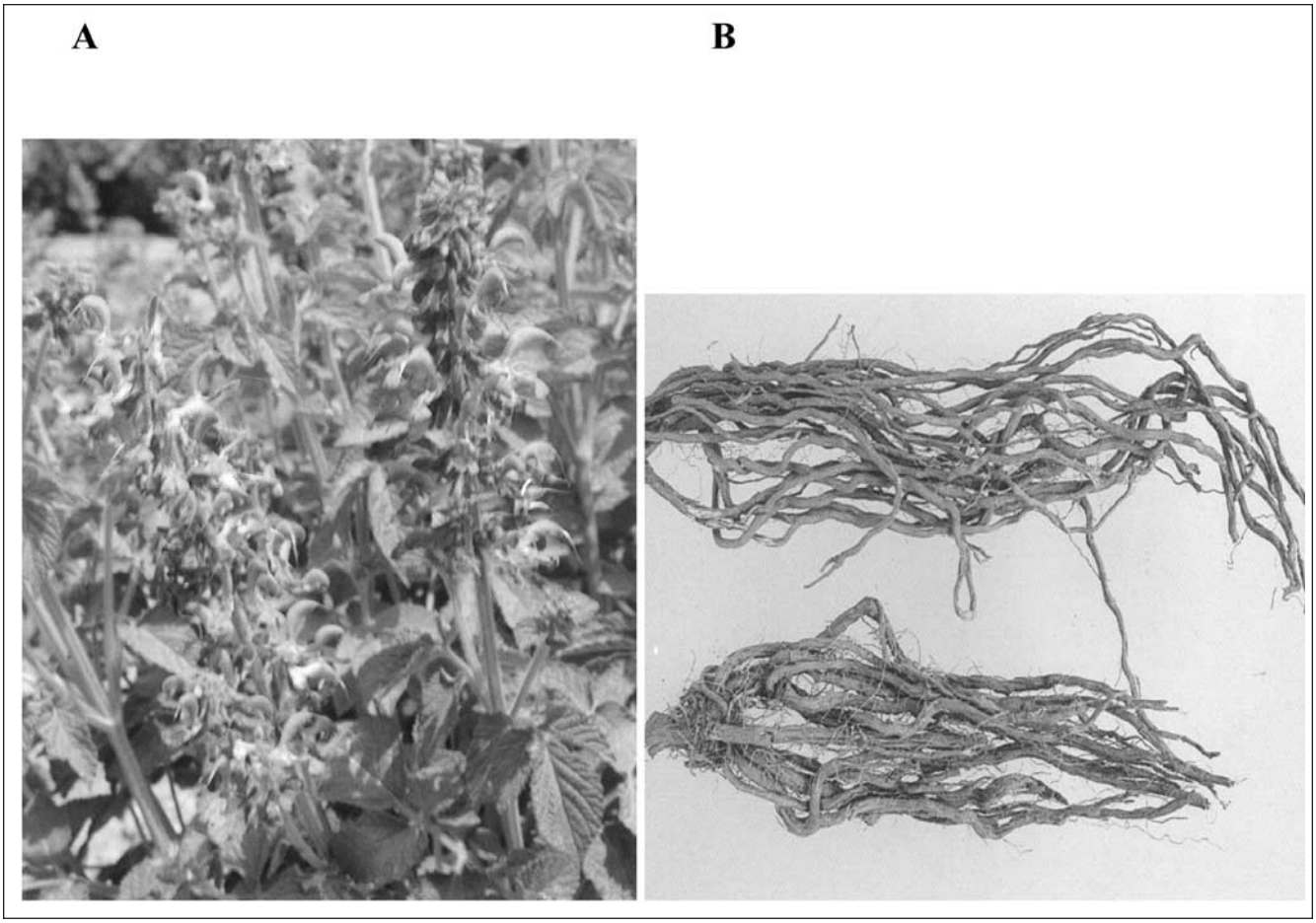

Figure 1. Photographs of Salvia miltiorrhiza *Bge. (A) and the Chinese medicine Danshen (B). Extracted from Zhonghua Renmin Gongheguo Yaodian, Zhongyao Caise Tuji, 1995.*

The following databases will be used in searching key literatures used in the present article: MEDLINE (1982 to March 2005), SCIFINDER (1982 to March 2005), and CAJVIEWER with full text of journals published in China (1994 to March 2005). We attempt to (1) summarize the key information pertaining to the above aspects and to (2) identify areas of improvement in the future pharmacokinetic and clinical studies of Danshen products.

CHEMICAL CONSTITUENTS

The chemical constituents of Danshen have been studied since the early 1930s. However, these early studies mainly focused on the lipophilic compounds. Recent studies have focused more on hydrophilic compounds, and at least 50 components have been isolated and identified from the aqueous extracts of Danshen.

Lipophilic Compounds From Danshen

More than 30 diterpene compounds have been separated and identified from Danshen. Most of them are diterpene chinone compounds of the tanshinone type, including tanshinone I, IIA, IIB; cryptotanshinone; and other related compounds (Figure 2). Among these, tanshinone IIA and cryptotanshinone are the most well studied, and their pharmacological activities have been studied.[15-17]

Hydrophilic Compounds From Danshen

Phenolic acids are the main type of hydrophilic components from Danshen. Li[18] has systematically separated and identified 15 phenolic acid compounds, including polyphenolic acids (such as various salvianolic acids) and related compounds (such as danshensu, protocatechuic aldehyde, and proto-

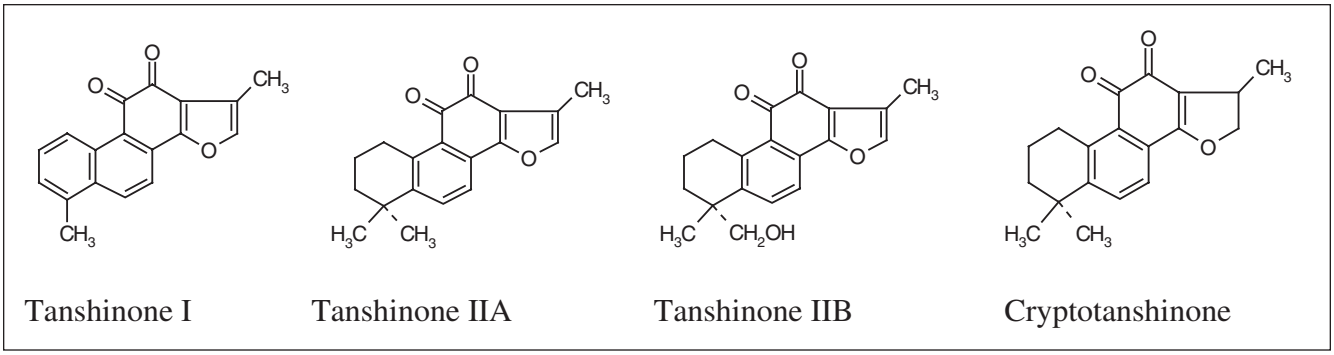

Figure 2. Chemical structures of main lipophilic compounds from Danshen.

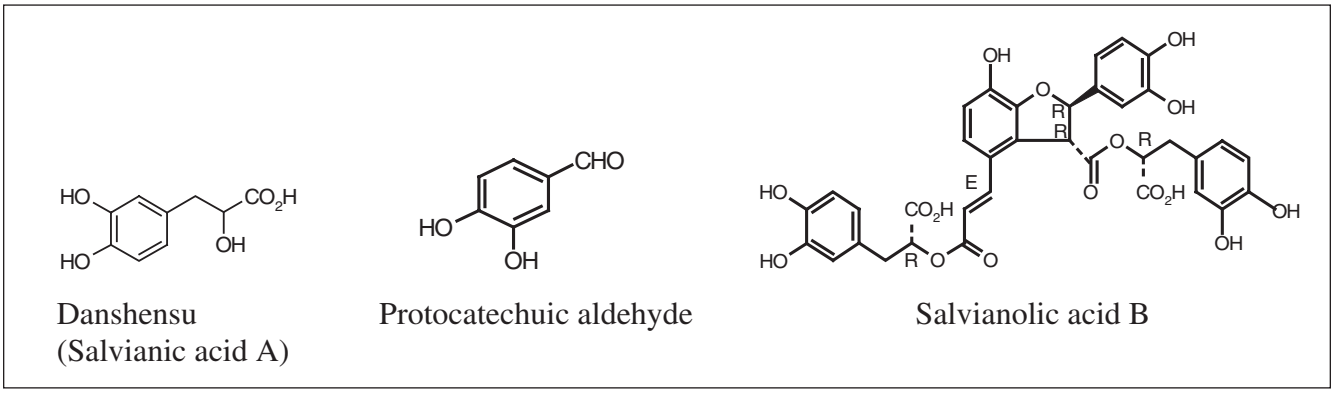

Figure 3. Chemical structures of main hydrophilic compounds from Danshen.

catechuic acid) (Figure 3). Many of these have known pharmacological activities and are present in sufficient amounts.[15-18]

Other Compounds

In addition to phenolic acids and diterpene compounds, other compounds include baicalin, β-sitosterol, ursolic acid and daucosterol isolated from alcohol extract, and 5,3′-dihydroxy-7,4′-dimethoxy flavanone isolated from ethyl acetate extract. Moreover, vitamin E and tannin have also been found in certain Danshen extracts.[15]

PHARMACOLOGICAL ACTIVITIES

Various in vitro and in vivo studies suggested that Danshen could improve microcirculation, dilate the coronary arteries, increase blood flow, and prevent myocardial ischemia. In recent years, pharmacological studies have concentrated on Danshen components such as danshensu, salvianolic acid B, and tanshinone IIA.[19-37] Because the data on other Danshen components are very limited, the main pharmacological activities of these 3 active components are summarized below. However, their clinical relevance needs to be established further.

Danshensu

In animal studies, danshensu has been shown to dilate coronary arteries,[19] inhibit platelet aggregation,[20] improve microcirculation,[21] and protect the myocardium from reperfusion injury of the ischemic heart.[22] The mechanism for some of its observed activity may be related to inhibition of Ca^{2+} aggregation in cardiac muscle cells and prevention of Ca^{2+} overload.[23] In addition, danshenshu has been found to be able to scavenge oxygen-free radicals,[24,25] inhibit myocardial cell apoptosis,[7] and protect the endothelial cells against homocysteinemia.[26]

Salvianolic Acid B

In animal studies, salvianolic acid B has been shown to protect the brain from ischemia-reperfusion injury.[27] In addition, salvianolic acid B can inhibit platelet aggregation[28] as well as oxidative modification of low-density lipoprotein (LDL), leading to the prevention of the uptake of LDL by cultured macrophages.[29,30] Other

beneficial cardiovascular effects include stimulation of nitric oxide production of the endothelial cell[31] and inhibition of angiotensin II–induced hyperplasia. Furthermore, salvianolic acid B has been shown to inhibit DNA synthesis of noncardiomyocytes[32] and inhibit stress-activated protein (SAP) kinase activity, leading to protection of ischemia-reperfusion injury.[32] In vitro studies have also found salvianolic acid B to possess superoxide radical scavenger properties and to inhibit erythrocyte hemolysis and lipid peroxide production.[34]

Tanshinone IIA

From in vivo studies, sodium tanshinone IIA sulfonate has been shown to significantly reduce myocardial infarct size.[35] One mechanism may be related to its free radical scavenger property in the myocardial mitochondrial membrane.[25] Tanshinone IIA has also been shown to inhibit LDL oxidation[36] as well as angiotensin II activity, resulting in attenuation of cardiac cell hypertrophy.[37]

PHARMACOKINETICS

Pharmacokinetic studies on the active components from the hydrophilic extracts of Danshen as well as individual components have been carried out. Tables I to V summarize various studies on danshensu, salvianolic acid B, protocatechuic aldehyde, tanshinone IIA, and cryptotanshinone.[38-56]

In animal studies for both danshensu and tanshinone IIA, the 2 major components in Danshen, they were absorbed rapidly after oral administrations of either extract formulation or individual components. On the other hand, salvianolic acid B, another major component, was found to be poorly absorbed in animal studies.[49] Only limited pharmacokinetic studies on protocatechuic aldehyde and cryptotanshinone have been conducted. Protocatechuic aldehyde was found to be absorbed orally with the appearance of a double-peak concentration.[41] Cryptotanshinone was found to be metabolized to tanshinone IIA after intravenous administration and could not be absorbed after oral administration.[55]

Danshensu is the only component that has been studied in human subjects. Based on the available human data, danshensu is absorbed quickly. The half-life for danshensu following sublingual administration is reported to be much longer than that after oral dosing. However, the actual dosage for danshensu in the sublingual dosage form was not cited in the reported study.[45-47] Therefore, the above finding needs to be confirmed by studies from pure danshensu following both sublingual and oral routes with the same dosages.

CLINICAL EFFICACY

Danshen has been widely used in China for many years. The major clinical indication of Danshen is coronary heart disease, such as angina pectoris. It has also been used for the treatment of hyperlipidemia and cerebrovascular disease.

Angina Pectoris

There are numerous clinical trials on Danshen products for the treatment of angina pectoris. Tables VI to X include a summary of the clinical studies on Danshen products for the treatment of angina and related cardiovascular diseases. The Jadad scale for the evaluation of the quality of the study is also included.[57]

Among the studies, at least 9 reports in the Chinese literature compared a Danshen product with isosorbide dinitrate (ISDN) for the treatment of stable angina pectoris or unstable angina pectoris (Table VI).[58-66] Most of these studies used clinical observation (pain control) and electrocardiograms (ECGs) to evaluate the effect after sublingual administration of either product followed by swallowing. The results generally found similar or better efficacy of the Danshen products compared to ISDN. Because of the drug resistance after ISDN, Danshen products were found to be better than ISDN for long-term use.[67]

At least 4 studies had reported clinical comparisons of a Danshen product with nitroglycerin (Table VII).[68-71] Both were administered sublingually or orally. As with the ISDN studies, clinical observation (pain control) and ECG were used to evaluate the effect. Although none of the Danshen products was found to be superior in efficacy to nitroglycerin, fewer side effects such as headache were found in the Danshen group compared to that in the nitroglycerin group.

There were at least 5 studies comparing the Danshen Dripping Pill versus the Danshen Tablet (Table VIII).[71-75] The Fufang Danshen Dripping Pill is composed of herbal ingredients extracted from *Salvia miltiorrhiza*, *Panax notoginseng*, and *Cinnamomum camphora*. This product has been shown to achieve a higher rate of effectiveness in treating patients with angina pain (10 pills sublingually 3 times daily) in comparison to the Danshen Tablet (3 tablets orally 3 times daily).

Table I Pharmacokinetics (PK) of Danshensu in Different Danshen Formulations

Species	Dose	PK Parameter	Findings	Reference
SD rat	p.o. 8 g/kg Danshen aqueous extraction (danshensu 35.7 mg/g)		Absorbable from gastrointestinal tract	38
SD rat	p.o. 0.3 mL/kg 667 g/L of Fufang Danshen Dripping Pill solution	k_α: 0.083 min^{-1} $t_{1/2\alpha}$: 11.9 min, $t_{1/2\beta}$: 196.8 min t_{max}: 30 min, C_{max}: 9.4 μg/mL	Two-compartment model; fast absorption and distribution; slow clearance	39
SD rat	p.o. 2.5 mL/100 g Fufang Danshen extract solution	t_{max}: 15 min, C_{max}: 703.6 μg/mL	Fast absorption; slow clearance (26.7 μg/mL at 6 h); unknown compound was found in serum	40
SD rat	p.o. 10 g/kg Danshen extract (4.25% danshensu)	MRT: 205.8 ± 4.2 min AUC: 23809.2 ± 1036.2 μg/mL•min	Double-peak phenomenon in the concentration-versus-time plot	41
Rabbit	i.v. 30 mg/kg danshensu	k: 0.046 ± 0.014 min^{-1} $t_{1/2}$: 16.6 ± 5.8 min	Single-compartment model	42
Rabbit	i.v. danshensu 6.25 mg/kg Danshen Injection	$t_{1/2}$: 31.7 ± 2.5 min AUC: 1996 ± 356 μg/mL•min MRT: 47.5 ± 9.6 min V_{ss}: 15 ± 23 mL/kg CL_T: 3.13 ± 0.97 mL/min/kg		43
Dog	Danshen aqueous extraction	C_{max}: 4.7 μg/mL t_{max}: 105 min	Rapid clearance (0.21 μg/mL at 5 h)	44
Human	Sublingual 250 mg Fufang Danshen Dripping Pill	k: 0.002 min^{-1}, $t_{1/2}$: 332.4 min k_α: 0.028 min^{-1}, $t_{1/2\alpha}$: 24.6 min	Single-compartment model	45, 46
Human	p.o. Fufang Danshen Granule (danshensu content: 20 mg)	k: 0.013 ± 0.002 min^{-1} $t_{1/2\beta}$: 55.2 ± 9.6 min	Absorbable from gastrointestinal tract; eliminate from kidney; no significant difference on elimination half-life of danshensu after p.o. of 2 doses	47
	p.o. Danshen decoction (danshensu content: 20 mg)	k: 0.013 ± 0.003 min^{-1} $t_{1/2\beta}$: 56.4 ± 12.6 min	Excretions of danshensu by urine after p.o. granule preparation were lower than that of decoction	
Human	p.o. Fufang Danshen Dripping Pill	Probable metabolites are danshensu sulfate and protocatechuic aldehyde glucuronide		48

AUC, area under the plasma level-time curve; CL_T, total body clearance; C_{max}, maximum concentration of drug; k, overall drug elimination rate constant (first order); k_{1e}, transfer rate constant from the central to the effect compartment; k_α, first-order absorption rate constant; MRT, mean residence time; $t_{1/2}$, half-life; $t_{1/2\alpha}$, absorption half-life; $t_{1/2\beta}$, elimination half-life; t_{max}, time of occurrence for maximum (peak) drug concentration; V_{ss}, steady-state volume of distribution.

At least 2 published studies on the Fufang Danshen Spray (Table IX)[76,77] and 3 published studies on the Fufang Danshen Injection (Table X)[78-80] have been reported. The results showed similar efficacy of the Fufang Danshen Spray compared to nitroglycerin for angina pectoris and similar or better efficacy of the Fufang Danshen Injection when compared to ISDN.

Studies using exercise ECG following the Fufang Danshen Dripping Pill were also carried out in at least 4 clinical trials.[81-84] The improvement in exercise ECG from the Fufang Danshen Dripping Pill was found to be significantly better than ISDN.

Of the published Danshen products evaluated for angina pectoris, the sublingual Fufang Danshen Dripping Pill is the most well documented. Numerous randomized controlled trials indicate that this product is at least as effective as sublingual ISDN and comparable to sublingual nitroglycerin. The reliability of the majority of these studies, however, is low due to the small number of subjects and the lack of clearly defined end

Table II Pharmacokinetics (PK) of Salvianolic Acid B (Magnesium Lithospermate B)

Species	Dose	PK Parameter	Findings	Reference
Wistar rat	i.v. 4 mg/kg magnesium lithospermate B (MLB)	AUC: 87.8 ± 10.9 μg/mL•min CL_T: 55.52 ± 7.07 mL/min/kg V_{ss}: 7.60 ± 1.03 L/kg $t_{1/2\alpha}$: 12.3 ± 2.14 min $t_{1/2\beta}$: 128 ± 4.68 min	Unchanged MLB in urine and bile was extremely low after i.v. injection	49
	i.v. 20 mg/kg MLB	AUC: 1130 ± 329 μg/mL•min CL_T: 23.5 ± 6.0 mL/min/kg V_{ss}: 3.61 ± 1.16 L/kg $t_{1/2\alpha}$: 22.7 ± 4.29 min $t_{1/2\beta}$: 176 ± 30.4 min	Nonlinear pharmacokinetics between 2 doses; suggest a saturated distribution or a saturated metabolism might occur at a high dose	
	p.o. 20 mg/kg MLB	No salvianolic acid B could be detected in plasma		
	p.o. 100 mg/kg MLB	AUC: 1.26 ± 0.36 μg/mL•min C_{max}: 0.041 ± 0.007 μg/mL t_{max}: 20 ± 5.47 min About 65% of the dose was left in the gastrointestinal tract even 4 hours after administration.	Extremely low bioavailability (0.022%); poor absorption from the rat small intestine; unchanged MLB in urine and bile was extremely low after p.o. administration.	
	In situ jejunal loop perfusion (0.1 mM, 2.5 mL MLB)	Most of the dose was retained in the loop after 20-minute infusion.	Verified the poor absorption of MLB from the small intestine	
Wistar rat	i.v. 4 mg/kg MLB p.o. 100 mg/kg MLB	Four major metabolites—namely, 3-monomethyl-(M1), 3,3‴-dimethyl-(M2), 3,3‴-dimethyl-(M4), and 3,3″,3‴-trimethyl-(M3) lithospermic acid B—were excreted into bile rapidly after i.v. and oral administration. The enzyme responsible for the biotransformation is catechol o-methyltransferase. Antioxidative activities of the metabolites were confirmed.		50
Dog	i.v. 3 mg/kg MLB	AUC: 109.3 μg/mL•min $t_{1/2\alpha}$: 2.2 min $t_{1/2\beta}$: 43 min CL_T: 28 mL/min/kg	Two-compartment model; high affinity to tissues and organs; suggest a saturated distribution and metabolism might occur at a high dose	51
	i.v. 6 mg/kg MLB	AUC: 247.9 μg/mL•min $t_{1/2\alpha}$: 2.7 min $t_{1/2\beta}$: 42 min CL_T: 26 mL/min/kg		
	i.v. 12 mg/kg MLB	AUC: 582.4 μg/mL•min $t_{1/2\alpha}$: 2.9 min $t_{1/2\beta}$: 42 min CL_T: 21 mL/min/kg		

For definitions of abbreviations, see Table I.

points. Although many studies mentioned randomization, most of them did not specify the method of randomization. Only 2 studies[58,62] had used the double-blind design, but the details of double blinding were not described. Last, only 1 study[65] described withdrawals and dropouts. Hence, all the studies included in Tables VI to X have a very low Jadad score in general.

Hyperlipidemia

The effect on cholesterol, triglyceride, and LDL and high-density lipoprotein (HDL) cholesterol levels has also been evaluated with Danshen products. In the studies by Xiang and Li,[66] a greater reduction of cholesterol and triglyceride was found following Fufang

Table III Pharmacokinetics (PK) of Protocatechuic Aldehyde in Different Danshen Formulations

Species	Dose	PK Parameter	Findings	Reference
SD rat	p.o. 8 g/kg Danshen aqueous extraction (protocatechuic aldehyde 6.19 mg/g)		Absorbable from gastrointestinal tract	38
SD rat	p.o. 2.5 mL/100 g Fufang Danshen extract solution		Not found in serum; unknown compound was found in serum	40
SD rat	p.o. 10 g/kg Danshen extract (1.58% protocatechuic aldehyde)	MRT: 258.3 ± 3.6 min AUC: 938.4 ± 39.6 μg/mL•min	Double-peak phenomenon in the concentration-versus-time plot	41

For definitions of abbreviations, see Table I.

Table IV Pharmacokinetics (PK) of Tanshinone IIA in Different Danshen Formulations

Species	Dose	PK Parameter	Findings	Reference
SD rat	p.o. 15 mg/kg tanshinone IIA	$t_{1/2\alpha}$: 33 min $t_{1/2\beta}$: 217.8 min k_α: 0.028 min^{-1} C_{max}: 5.57 μg/mL t_{max}: 51 min AUC: 1445.4 μg/mL•min	Short half-life; two-compartment model	52
Wistar rat in situ intestine perfusion	Tanshinone IIA 1008 μg/50 mL	k_α: 0.014 ± 0.010 min^{-1} $t_{1/2}$: 63.1 ± 32.6 min	The transport mechanism of tanshinone IIA perfusion is similar to active transport or facilitated diffusion.	53
	717 μg/50 mL	k_α: 0.012 ± 0.001 min^{-1} $t_{1/2}$: 58.7 ± 3.9 h		
	504 μg/50 mL	k_α: 0.017 ± 0.001 min^{-1} $t_{1/2}$: 40.7 ± 3.5 min		
Rabbit	p.o. 4 g aqueous extraction of Danshen	$t_{1/2\alpha}$: 223.8 min $t_{1/2\beta}$: 1371 min t_{max}: 51.6 min	Fast absorption; slow clearance. The absorption of tanshinone IIA is faster in Fufang dosage form.	54
	p.o. 4 g aqueous extraction of Danshen	$t_{1/2\alpha}$: 29.4 min $t_{1/2\beta}$: 1243.8 min t_{max}: 41.4 min	Two-compartment model	

For definitions of abbreviations, see Table I.

Danshen Dripping Pill treatment of angina pectoris compared to ISDN. At least 4 other studies also showed that total cholesterol, triglyceride, and LDL cholesterol levels were significantly reduced by 28.3%, 34.3%, and 29.9%, respectively, and HDL cholesterol was significantly raised by 33.2% after the Fufang Danshen Dripping Pill.[1-4] In another study comparing the Danshen injection versus the ISDN injection, the level of soluble intercellular adhesion molecule-1 and interleukin-6 was found to be lower in the Danshen injection group.[79] These data indicate the potential benefit of Danshen products for lipid control. However, it is unknown if any of the active components can produce similar effects as the composite formula used in the product.

Acute Ischemic Stroke

Wu et al[85] reported a systematic review on the clinical efficacy of Danshen agents for acute ischemic stroke.

Table V Pharmacokinetics (PK) of Cryptotanshinone

Species	Dose	PK Parameter	Findings	Reference
Pig	i.v. 10 mg/kg cryptotanshinone	For cryptotanshinone: $t_{1/2\alpha}$: 2.36 min, $t_{1/2\beta}$: 64.78 min, AUC: 23.83 μg/mL•min For tanshinone IIA: t_{max}: 4.6 min, C_{max}: 0.62 μg/mL, $t_{1/2\beta}$: 189.04 min, AUC: 22.97 μg/mL•min	Two-compartment open model; tanshinone IIA was detected as metabolite	55
	p.o. 40 mg/kg cryptotanshinone		Extremely low plasma concentration	
	i.m. 20 mg/kg cryptotanshinone		Might be biotransformed after absorption	
Rat	p.o. 350 mg/kg cryptotanshinone	Extremely low urine excretion (0.34%); 6 metabolites were obtained (tanshinone IIA, hydroxytanshinone IIA, etc)		56

For definitions of abbreviations, see Table I.

Meta-analysis of the included trials showed that Fufang Danshen had the tendency of improving the short-term effect of acute ischemic stoke patients. However, the authors indicated that a definite conclusion on the efficacy and adverse events cannot be drawn due to the limited number of trials identified, the limited duration of treatment, and the inadequate recording and reporting of adverse events. In another review by Sze et al,[86] the effect of Danshen in improving disability after acute ischemic stroke was found to be inferior in 5 trials and not significant in another 6 trials.[86]

Most of the related clinical trials from the literature included a small number of subjects and were not placebo controlled. Furthermore, the criteria for efficacy were not clearly defined. Randomized controlled trials with defined efficacy end points are needed to evaluate Danshen products for the treatment of acute ischemic stroke.

DOSAGES

There are large variations in the amount of active components in the commercially available Danshen preparations.[87] The quality control standards specified in the *Chinese Pharmacopoeia 2005* are as follows: danshensu content should not be less than 0.08 mg/pill for the Fufang Danshen Dripping Pill, tanshinone IIA content should not be less than 0.20 mg/tablet, and salvianolic acid B content should not be less than 5.0 mg for the Fufang Danshen Tablet.[13]

The most commonly used dosage forms and their doses are as follows: Fufang Danshen Dripping Pill (10 pills orally or sublingually each time, 3 times a day) and Fufang Danshen Tablet (3 tablets orally each time, 3 times a day).[13]

SIDE EFFECTS AND TOXICITY

In the study by Zhou and Xiong,[73] 3 patients (3/100) felt thirsty following the administration of the Fufang Danshen Dripping Pill (10 pills sublingually, 3 times daily). In another 3 studies, mild gastrointestinal reaction (1/40, 2/160, 3/142) was reported during administration of the Fufang Danshen Dripping Pill (10 pills sublingually, 3 times daily), and patients were willing to continue the treatment after taking other gastrointestinal drugs.[42,62,65] Two patients (2/56) reported headache during the administration of the Fufang Danshen Dripping Pill (10 pills sublingually, 3 times daily).[69] Among the studies on the Fufang Danshen Tablet (3 tablets orally, 3 times daily), upper abdominal discomfort (2/34) and bad appetite (3/34) were also reported.[72]

The acute toxicity (LD_{50}) is 25.807 g/kg in mice when a water-soluble Danshen extract (the raw material for the Fufang Danshen Dripping Pill) was administered orally. This LD_{50} value is equivalent to 3934 times the intended clinical human oral dosage (6.56 mg of

Table VI Comparison of Fufang Danshen Dripping Pill (Pill) With Isosorbide Dinitrate (ISDN) (10 mg, 3 Times/Day)

Reference	Study Design	Jadad Score[57] (Max 5)[a]	Patient Numbers	Patient Type	Danshen Dose	Duration	Clinical Efficacy, %		Electrocardiogram Efficacy, %	
							ISDN	Danshen	ISDN	Danshen
58	Randomized, double blind, controlled	2	ISDN: 52 Pill: 50	Stable angina pectoris	10 pills/time 3 times/day	2 months	90 (P >.05)	92	52 (P > .05)	64
59	Randomized, controlled	1	ISDN: 20 Pill: 40	Angina pectoris	10 pills/time 3 times/day	2 months	90 (P >.05)	95	40 (P < .01)	68
60	Randomized, controlled	1	ISDN: 30 Pill: 60	Stable and unstable angina pectoris	10 pills/time 3 times/day	6 weeks	83 (P > .05)	85	40 (P < .05)	63
61	Randomized, controlled	1	ISDN: 51 Pill: 51	Stable and unstable angina pectoris	10 pills/time 3 times/day	4 weeks	73 (P < .01)	94	37 (P < .01)	61
62	Randomized, double blind, controlled	2	ISDN: 140 Pill: 160	Stable angina pectoris	10 pills/time 3 times/day	8 weeks	89 (P > .05)	93	40 (P < .05)	63
63	Randomized, controlled	1	ISDN: 30 Pill: 56	Stable angina pectoris	10 pills/time 3 times/day	8 weeks	70 (P < .05)	96	53 (P > .05)	61
64	Randomized, controlled	1	ISDN: 35 Pill: 38	Unstable angina pectoris	10 pills/time 3 times/day	4 weeks	74 (P < .05)	92	34 (P < .05)	61
65	Randomized, controlled	2	ISDN: 142 Pill: 142	Coronary heart disease, angina pectoris	10 pills/time 3 times/day	8 weeks	83 (P > .05)	84	74 (P > .05)	77
66	Randomized, controlled	1	ISDN: 140 Pill: 160	Stable and unstable angina pectoris	10 pills/time 3 times/day	5 weeks	82 (P > .05)	86	41 (P < .05)	63

a. Jadad score ranging from 0 to 5 was used to assess the quality of clinical trials report.

Table VII Comparison of Fufang Danshen Dripping Pill (Pill) With Nitroglycerin (NTG)

Reference	Study Design	Jadad Score[57] (Max 5)[a]	Patient Numbers	Patient Type	Dose (Pill/NTG)	Observation Time	Clinical Efficacy, %		Electrocardiogram Efficacy, %	
							NTG	Danshen	NTG	Danshen
68	Randomized, controlled	1	NTG: 30 Pill: 102	Stable angina pectoris	10 pills/ 0.5 mg NTG	8 min postdosing	93 ($P > .05$)	88	40 ($P > .05$)	37
69	Randomized, controlled	1	NTG: 52 Pill: 56	Stable angina pectoris	10 pills/ 0.3 mg NTG	30 min postdosing	90 ($P > .05$)	89	60 ($P > .05$)	59
70	Randomized, controlled	1	NTG: 90 Pill: 90	Stable and unstable angina pectoris	10 pills/ 0.5 mg NTG	3-5 min postdosing	93 ($P < .05$)	70	NA	
71	Randomized, controlled	1	NTG: 20 Pill: 20	Stable and unstable angina pectoris	10 pills/time 3 times/day (ND for NTG)	After 4 weeks of dosing	95 ($P > .05$)	90	NA	

NA, not applicable; ND, not defined.
a. Jadad score ranging from 0 to 5 was used to assess the quality of clinical trials report.

Table VIII Comparison of Fufang Danshen Dripping Pill (Pill) With Fufang Danshen Tablet (Tablet)

Reference	Study Design	Jadad Score[57] (Max 5)[a]	Patient Numbers	Patient Type	Dose (Pill/Tablet)	Duration	Clinical Efficacy, %		Electrocardiogram Efficacy, %	
							Tablet	Pill	Tablet	Pill
71	Randomized, controlled	1	Tablet: 20 Pill: 20	Stable and unstable angina pectoris	10 pills/time 4 tablets/time 3 times/day	4 weeks	60 ($P < .05$)	90	NA	
72	Randomized, controlled, single blind	1	Tablet: 34 Pill: 36	Stable angina pectoris	10-15 pills/time 3 tablets/time 3 times/day	4 weeks	71 ($P < .05$)	92	47 ($P < .05$)	67
73	Randomized, controlled	1	Tablet: 100 Pill: 100	Stable and unstable angina pectoris	10 pills/time 3 tablets/time 3 times/day	4 weeks	60 ($P < .01$)	90	46 ($P < .05$)	66
74	Randomized, controlled	1	Tablet: 32 Pill: 34	Stable angina pectoris	10 pills/time 3 tablets/time 3 times/day	NA	70 ($P < .05$)	96	59 ($P > .05$)	64
75	Randomized, controlled	1	Tablet: 32 Pill: 34	Angina pectoris	10 pills/time 3 tablets/time 3 times/day	4 weeks	57 ($P < .05$)	86	50 ($P < .05$)	71

NA, not applicable.
a. Jadad score ranging from 0 to 5 was used to assess the quality of clinical trials report.

Table IX Summary of Clinical Efficacy of Fufang Danshen Spray (Spray)

Reference	Study Design	Jadad Score[57] (Max 5)[a]	Patient Numbers	Patient Type	Dose	Duration	Clinical Efficacy, %		Electrocardiogram Efficacy, %	
							Control	Spray	Control	Spray
76	Randomized, controlled	1	NTG: 30 Spray: 30	Angina pectoris	Spray: 4 sprays/time 3 times/day NTG i.v. infusion: 10 mg/day	3 weeks	74 ($P > .05$) (control: NTG)	77	43 ($P > .05$)	47
77	Randomized, controlled	1	Fufang Danshen Tablet: 30 Spray: 35	Angina pectoris	Spray: 3-5 sprays/time 3 times/day Tablet: 3 tablets/time 3 times/day	10 days	94 ($P < .05$) (control: Fufang Danshen Tablet)	97	46 ($P < .05$)	64

NTG, nitroglycerin.
a. Jadad score ranging from 0 to 5 was used to assess the quality of clinical trials report.

Table X Summary of Clinical Efficacy of Fufang Danshen Injection (Injection)

Reference	Study Design	Jadad Score[57] (Max 5)[a]	Patient Numbers	Patient Type	Dose	Duration	Clinical Efficacy, %		Electrocardiogram Efficacy, %	
							ISDN	Injection	ISDN	Injection
78	Randomized, controlled	1	ISDN: 153 Injection: 160	Angina pectoris	Injection: 30 mL/day ISDN oral: 10 mg/time, 3 times/day	3 weeks	77 ($P < .01$)	95	54 ($P < .01$)	82
79	Randomized, controlled	1	ISDN: 20 Injection: 24	Unstable angina pectoris	Injection: 30 mL/day ISDN i.v. infusion: 20 mg/day	10 days	85 (P: NA)	83	65 (P: NA)	67
80	Randomized, controlled	1	ISDN: 16 Injection: 30	Stable and unstable angina pectoris	Injection: 30 mL/day ISDN oral: 20 mg/time, 2 times/day	2 weeks	63 ($P < .05$)	90	54 ($P > .05$)	62

NA, not applicable; ISDN, isosorbide dinitrate.
a. Jadad score ranging from 0 to 5 was used to assess the quality of clinical trials report.

Danshen extract/kg). An oral dose of 2500 mg/kg Danshen extract (400 times human oral dosage) for 90 days was found to be nontoxic to rats.[14]

In summary, no serious adverse effects of Danshen have been reported so far, and wide clinical usage experience after many years in China appears to indicate that Danshen products are safe. However, similar to what we have concluded for clinical efficacy studies, better-designed studies are essential to provide sufficient evidence to prove or refute the existence of serious adverse events for Danshen products.[88]

HERB-DRUG INTERACTIONS

The effects of Danshen on the pharmacokinetics and pharmacodynamics of warfarin in rats have been reported most extensively. Lo et al[89] and Chan et al[90] reported that Danshen can increase the absorption rate constant, AUC, maximum concentration, and elimination half-life but decrease the clearance and apparent volume of distribution of both R- and S-warfarin in rats. Therefore, the anticoagulant response to warfarin could be exaggerated when coadministered with Danshen.[91] Three cases of over-anticoagulation and bleeding were reported when receiving warfarin therapy with Danshen.[92-94] Because of the risk of potential pharmacokinetic and pharmacodynamic interactions, Danshen should be avoided in patients taking warfarin. In addition to warfarin, salicylate in therapeutic concentration was reported to be able to significantly decrease free Danshen concentration as measured by free-digoxin-like activity.[95]

The primary enzymes cytochrome P450 (CYP), UDP-glucuronosyl transferase (UGT), and glutathione S-transferase (GST) are involved in the metabolism of most drugs. Deng et al[96] reported that intraperitoneal treatment with Danshen decoction could induce liver microsomal CYP content in rats. Qiao et al[97] reported the effects of the aqueous extract of Danshen on the pharmacokinetics of diazepam and liver microsomal CYP enzyme activity in rats. The results showed that Danshen aqueous extract could stimulate the metabolic activity of CYP isozymes in Danshen-pretreated rats, with a significant reduction on the maximum concentration and AUC of diazepam. Another study by Ueng et al[98] showed that tanshinone IIA induced CYP1A2 in the arylhydrocarbon-responsive C57BL/6J (B6) but not in the nonresponsive DBA/2J (D2) mice. In D2 mice, tanshinone IIA decreased CYP3A activity. Moreover, they also reported that tanshinone IIA had no effects on the activities of phase II enzymes such as UGT and GST.

SUMMARY

Danshen products have been widely reported to be useful for the treatment of cardiovascular diseases in China. Its effects of improving circulation and "removing blood stasis" have been well documented in the ancient TCM books. Various in vitro and in vivo studies in the scientific journals have demonstrated that various active components of Danshen can improve blood microcirculation, dilate the coronary arteries, increase the blood flow, and prevent myocardial ischemia. Pharmacokinetics studies of these active components in animals showed that they are absorbed orally, and various human studies on danshensu showed that it is also quickly absorbed, with an elimination half-life between 1 and 5 hours. Randomized clinical trials and clinical experience in China indicated that the Danshen products are safe, with a low side-effect profile. Although the antilipid effect of the Danshen product from a composite formula is well documented, its efficacy for cardiac and cerebrovascular ischemic heart disease needs to be further confirmed by well-designed clinical trials.

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