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Salvia miltiorrhiza: Traditional medicinal uses, chemistry, and pharmacology

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[ABSTRACT] *Salvia miltiorrhiza* Bunge (SM) is a very popular medicinal plant that has been extensively applied for many years to treat various diseases, especially coronary heart diseases and cerebrovascular diseases, either alone or in combination with other Chinese plant-based medicines. Although a large number of studies on SM have been performed, they are scattered across a variety of publications. The present review is an up-to-date summary of the published scientific information about the traditional uses, chemical constituents, pharmacological effects, side effects, and drug interactions with SM, in order to lay the foundation for further investigations and better utilization of SM. SM contains diverse chemical components including diterpenoid quinones, hydrophilic phenolic acids, and essential oils. Many pharmacological studies have been done on SM during the last 30 years, focusing on the cardiovascular and cerebrovascular effects, and the antioxidative, neuroprotective, antifibrotic, anti-inflammatory, and antineoplastic activities. The research results strongly support the notion that SM has beneficial therapeutic properties and has a potential of being an effective adaptogenic remedy.

[KEY WORDS] Danshen; Cardiovascular diseases; Antitumor; Side effect; Review

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Introduction

The dried root of *Salvia miltiorrhiza* Bunge (Lamiaceae) (SM), often referred as Danshen in China or Tanshen in Japan, is widely distributed in both China and Japan [1]. It was first recorded in the *Shennong's Classic of Materia Medica* (Shennong Bencao Jing) which was the oldest medicine monograph in China. As one of the most commonly used traditional medicines, SM has been used for the treatment of various diseases, including coronary heart disease [2], cerebrovascular disease [3], Alzheimer's disease [4], Parkinson's disease [5], renal deficiency [6], hepatocirrhosis [7-8], cancer [9], and bone loss [10]. It is an extremely popular TCM in China, either used alone or in combination with other herbs. SM is also widely used in the USA [11]. For instance, Danshen Dripping Pill (Chinese name Fufang Danshen Diwan) of Tianshili is now undergoing advanced clinical tests in the USA. Although only a small step forward, the entry of these clinical tests of TCM in western countries has promoted the development and the globalization of TCM in general. The aim of this article is to summarize and review the published literatures on the research and development of SM, including its traditional uses, chemical constituents, pharmacological activities, side effects, and interactions with other drugs. We also attempt to identify future pharmacological and clinical studies for this TCM.

Traditional Uses

The air-dried root of SM has been highly valued in TCM, as recorded in some Chinese herbal classics, such as the *Shennong's Classic of Materia Medica*, the *Compendium of*

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Materia Medica (Bencao Gangmu), and *Chinese Materia Medica* (Zhonghua Bencao). Various properties of SM, such as promoting blood circulation to remove blood stasis, clearing heart heat to relieve restlessness, and cooling blood to remove carbuncle, have been stated in *Chinese Pharmacopoeia* (2010). In ancient China, decoctions and pills were major preparations of SM, but now different preparations are developed, including tablets, capsules, granules, injections, oral liquids, sprays, and dripping pills. Occasionally, the root of the plant also can be taken as a vinum or tea. Moreover, among all the available dosage forms, the Fufang Danshen Tablet and Fufang Danshen Dripping Pill are the two most widely used products and are officially listed in *Chinese Pharmacopoeia* (2010) [12].

In Japan, SM products are sold commercially for promoting circulation and improving blood stasis [12]. In the USA and European countries, SM products are also available in natural health shops [12]. The flora of Anhui has described the medicinal usage of the SM root as an important gynecological drug for the treatment of irregular menstruation and postpartum blood stasis [13]. Furthermore, SM can also be used for the treatment of chilblain, psoriasis [14], insomnia, neurasthenia [15], and visceral pain [16].

Chemical Constituents

Representing a wide spectrum of secondary metabolite classes, 49 diterpenoid quinones (Compounds **1**–**49**), 36 hydrophilic phenolic acids (Compounds **50**–**85**), and 23 essential oil constituents (Compounds **86**–**108**), have been isolated and identified from SM. Chemical and pharmacological researches have shown that diterpenoid quinones and hydrophilic phenolic acids are the principal bioactive components in SM [17]. Diterpenoid quinones have been classified into two series, the phenanthro [1, 2-*b*] furan-10,11-dione series and the phenanthro[3,2-*b*] furan-7, 11-dione series. Hydrophilic phenolic acids are considered as the condensation derivatives of caffeic acid in different linkage forms and numbers. These two classes of active compounds are mostly isolated from the roots, whereas the essential oils are mainly extracted from flowers [18]. The compounds isolated from SM are documented in Table 1, with the main references [18-68]; some of their chemical structures are displayed in Figs. 1–3.

Pharmacological Properties

Effects on cardiovascular diseases

SM has been widely used for the treatment of vascular diseases, including atherosclerosis, hypertension, hyperlipidemia, and stroke in China, Japan, USA, and Europe [69-70]. The beneficial attributes of SM also include promotion of blood flow and resolution of blood stasis [12, 71]. Induction of heme oxygenase-1 (HO-1) expression appears to help maintain homeostasis, which has been therapeutically implicated in a number of diseases, including vascular injury and hypertension [72]. Further study has shown that SM induces HO-1 expression to reduce the intracellular production of reactive oxygen species (ROS) through the PI3K/Akt-MEK1-Nrf2 pathway [72]. After exposure of RAW264.7 cells (murine macrophages) to SM (10 and 50 $\mu g \cdot mL^{-1}$) for 18 h, the activity of HO-1 was significantly increased [73]. SM exerts its protective effect on the cardiovascular system through suppressing the circulating ROS and subsequent modulation of protein carbonylation in rat aortic smooth muscle A10 cells [74]. Treated with a low dose of the aqueous extract of SM roots (SMAE) at 0.015 $mg \cdot mL^{-1}$ for 72 h, the growth of the homocysteine was significantly inhibited (> 60%) in stimulated rat aortic smooth muscle A10 cells [74]. Stress-induced catecholamine (CA) over-secretion can be detrimental or cause direct damage to the cardiovascular system [75]. A lipophilic extract of SM (LESM) exerts antagonistic effects on nicotinic acetylcholine receptor (nAChR), as well as voltage-dependent Na^+ and Ca^{2+} channels. Pre-incubation with LESM (50 $\mu g \cdot mL^{-1}$) at 37 °C for 10 min significantly inhibited CA secretion induced by compared with acetylcholine (Ach), veratridine (Ver), and 56 $mmol \cdot L^{-1}$ K^+ in cultured bovine adrenal medullary cells *in vitro* [75]. SM injection (3 and 6 $g \cdot kg^{-1} \cdot d^{-1}$) significantly lowered cardiac iron deposition and the concentration of the lipid oxidation product malondialdehyde and improved cardiac superoxide dismutase (SOD) and glutathione (GSH) peroxidase levels in iron-overloaded mice [76].

Anti-atherogenesis

Apoptosis of vascular endothelial cells, a risk factor of atherosclerosis, results in the loss of endothelial integrity [77]. Lipopolysaccharide (LPS) induces apoptosis in human umbilical vein endothelial cells through a mechanism that involved caspase-3 [77]. Treatment with the methanol extract of SM (50–500 $\mu g \cdot mL^{-1}$) for 24 h could inhibit the tumor necrosis factor-α (TNF-α)-induced migration of human aortic smooth muscle cells (HASMC) in a dose-dependent manner (IC_{50} 65 $\mu g \cdot mL^{-1}$), compared with the control group [78]. Abnormal proliferation and migration of vascular smooth muscle cells (VSMCs) plays critical roles in the development of atherosclerosis [79]. After administration of lithospermic acid (LA) (25–100 $\mu mol \cdot L^{-1}$) for 2 h, fetal bovine serum (FBS)-induced VSMC proliferation and LPS-induced VSMC migration were inhibited [80]. By down-regulating the expression of cyclin D1 and arresting cell cycle progression at the G1 phase, LA inhibited both VSMC proliferation and DNA synthesis as induced by 5% FBS [80]. Tanshinone IIA could abolish VSMC proliferation and reduce intimal hyperplasia through inhibiting of mitogen-activated protein kinase (MAPK) signaling pathway and down-regulating *c-fos* expression [81]. After treatment of VSMCs with tanshinone IIA for 72 h, the inhibition exerted by tanshinone IIA were 0.1, 0.25, 0.5, and 1.0 $\mu g \cdot mL^{-1}$ were 10.5% ± 1.3%, 40.2% ± 8.7%, 65.5% ± 1.5%, and 91.1% ± 7.4%, respectively. After orally treatment of Sprague-Dawley (SD) rats with tanshinone IIA (120 $mg \cdot kg^{-1} \cdot d^{-1}$) for 2 weeks, the intimal area was decreased by 55.98%, compared to the controls [81]. In another study, tanshinone IIA (1–20 $\mu mol \cdot L^{-1}$) dose-dependently inhibited the adhesion of THP-1 monocytes to the TNF-α-stimulated

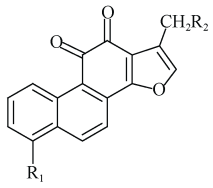
Table 1 Compounds isolated from *Salvia miltiorrhiza*

No.	Chemical component	Part of plant	References	No.	Chemical component	Part of plant	References
1	Tanshinone I	Root	[19]	58	Salviaflaside	Root	[23]
2	Tanshinol A	Root	[20]	59	Salvianolic acid D	Root and rhizoma	[50]
3	Przewaquinone B	Root	[21]	60	Prolithospermic acid	Root	[39]
4	Formyltanshinone	Rhizome	[22]	61	Salvianolic acid G	Root and rhizoma	[55]
5	Tanshinone IIA	Root	[19]	62	Salvinal	Root	[56]
6	Hydroxytanshinone IIA	Root	[23]	63	1-Hydroxy-pinoresinol-1-*O*-*β*-D-glucoside	Root	[57]
7	3-Hydroxytanshinone IIA	Root	[24]	64	Lithospermic acid	Root	[54]
8	Tanshinone IIB	Root	[25]	65	Litherospermic acid monomethyl ester	Root	[39]
9	Methyl tanshinonate	Root	[23]	66	Litherospermic acid dimethyl ester	Root	[49]
10	Tanshinaldehyde	Root	[23]	67	Ethyl lithospermate	Root	[50]
11	Tanshindiol A	Root	[24]	68	Salvianolic acid A	Root	[51]
12	Tanshindiol B	Root	[26]	69	Salvianolic acid C	Root	[58]
13	Przewaquinone A	Root	[21]	70	Methyl salvianolic acid C	Radix	[59]
14	Przewaquinone C	Root	[23]	71	Dimethyl lithospermate	Rhizome	[54]
15	Tanshindiol C	Root	[26]	72	9″-Methyl lithospermate	Root	[54]
16	Cryptotanshione	Root	[27]	73	Isosalvianolic acid C	Root	[60]
17	Methyl dihydronortanshinonate	Root	[28]	74	Salvianolic acid I	Root	[39,61]
18	1,2-Dihydortanshinquinone	Root	[29]	75	Salvianolic acid J	Root	[39,62]
19	1,2,15,16-Tetrahydrotanshiquinone	All plant	[30]	76	Salvianolic acid E	Radix	[50]
20	15,16-Dihydrotanshinone I	Root	[31]	77	Salvianolic acid B	Root	[58]
21	Dihydrotanshinone I	Root	[32]	78	Lithospermic acid B	Root	[50]
22	Tetrahydrotanshinone	Root	[33]	79	Ethyl lithospermate B	Radix	[50]
23	Methylenetanshinquinone	Root	[34]	80	Magnesium lithospermate B	Radix	[63]
24	Nortanshinone	Root	[24]	81	Ammonium-potassium lithospermate B	Root	[64]
25	3-Hydroxymethylenetanshinquinone	Radix	[35]	82	Protocatechuic acid	Radix	[23]
26	Dihydronortanshinone	Root	[36]	83	Protocatechuic aldehyde	Root	[65]
27	1,2-Didehydromiltirone	Root	[22]	84	2-(3-Methoxy-4-hydroxyphenyl)-5-(3-hydroxypropyl)-7-methoxybenzofuran-3-carbaldehyde	Root	[66]
28	Miltirone	Root	[30]	85	Ailanthoidol	Root	[66]
29	4-Methylenemiltirone	Root	[22]	86	Borneol acetate	Flower	[18]
30	Isotanshinone I	All plant	[37-38]	87	Copaene	Flower	[18]
31	Dihydroisotanshinone II	Radix	[39]	88	Bourbonene	Flower	[18]
32	Isototanshinone	Radix	[39]	89	Iso-elemene	Flower	[18]
33	Dihydroisotanshinone I	Root	[32]	90	Iso-*β*-caryophyllene	Flower	[18]
34	1-Ketoisocryptotanshinone	Root	[26]	91	Isocaryophyllene	Flower	[18]
35	Neocryptotanshinone	Root	[40]	92	*β*-Caryophyllene	Flower	[18]
36	Isotanshinone IIA	Root	[41]	93	*β*-Cubebene	Flower	[18]
37	Isotanshinone IIB	Root	[40]	94	*α*-Caryophyllene	Flower	[18]
38	Isocryptotanshione II	Root	[41]	95	Cadinadiene	Flower	[18]
39	Danshexinkun A	Root	[42]	96	Bicyclogermacrene	Flower	[18]
40	Danshexinkun B	Root	[43]	97	*α*-Farnesene	Flower	[18]
41	Danshexinkun C	Root	[42]	98	*β*-Caryophyllene oxide	Flower	[18]
42	Danshexinkun D	Root	[44]	99	Ledol	Flower	[18]
43	Ferruginol	Radix	[45]	100	*α*-Caryophyllene oxide	Flower	[18]
44	Sugiol	Radix	[46]	101	Tetradecanoic acid	Flower	[18]
45	Sibiriquinone A	Root	[47]	102	Nor-pristan-2-ol	Flower	[18]
46	Sibiriquinone B	Root	[47]	103	Hexadecanoic acid	Flower	[18]
47	Trijuganone A	Radix	[48]	104	Linoleic acid	Flower	[18]
48	Trijuganone B	Radix	[48]	105	Tricosane	Flower	[18]
49	Neo-przewaquinone A	All plant	[30]	106	Pentacosane	Flower	[18]

Continued

No.	Chemical component	Part of plant	References	No.	Chemical component	Part of plant	References
50	Caffeic acid	Radix	[49]	107	Heptacosane	Flower	[18]
51	Isoferulic acid	Root	[50]	108	Nonacosane	Flower	[18]
52	Danshensu	Root	[51]	109	Salvianonol(4-(1-hydroxy-5-methylnaphth-alen-2-yl)-2-methyl- 4-oxobutyl acetate)	Root	[67]
53	3-(3,4-Dihydroxyphenyl) lactamide	Rhizome	[52]	110	Salviamone(4,8-dimethyl-8,9-dihydro-10,12-dioxa-benzo[*a*]anthracene-7,11-dione)	Root	[67]
54	Salvianolic acid F	Root	[53]	111	2*α*-Acetoxysugiol ((3*S*,4*as*,10*as*)-1,2,3,4,4a,9,10,10a-octahydro-6-hydroxy-7-isopropyl-1,1,4a-trimethyl-9-oxophenanthren-3-yl acetate)	Root	[67]
55	Salvianic acid C	Radix	[49]	112	Palmitoyl arucadiol(1,2,3,4-tetrahydro-5-hydroxy-7- Isopropyl-1,1-dimethyl-4-oxophenanthren-6-yl palmitate)	Root	[67]
56	Rosmarinic acid	Root	[54]	113	(*E*)-4-[5-(Hydroxymethyl)furan-2-yl]but-3-en-2-one	Root	[67]
57	Methyl rosmarinate	Radix	[54]	114	Neotanshinlactone	Root	[68]

Diterpenoid quinines: 1-49, Hydrophilic Phenolic acids: 50-85, Essential Oils: 86-108, Other miscellaneous compound: 109-114



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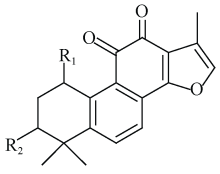

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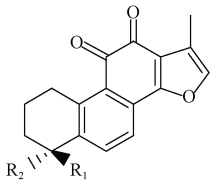
7. $R_1 = H$, $R_2 = OH$



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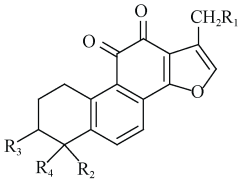

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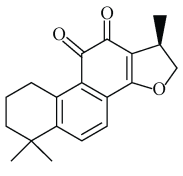

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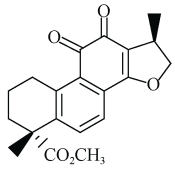

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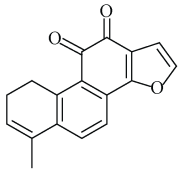

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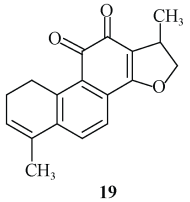

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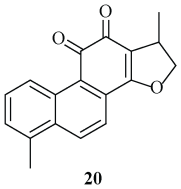

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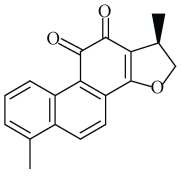

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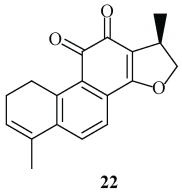

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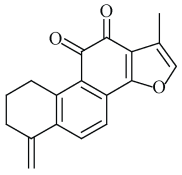

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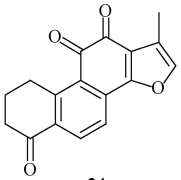

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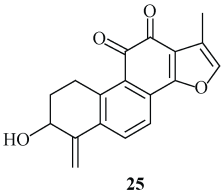

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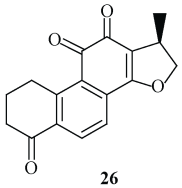

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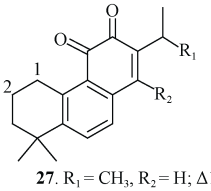

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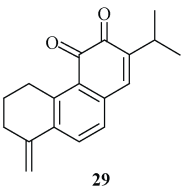
28. $R_1 = CH_3$, $R_2 = H$



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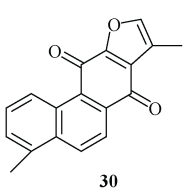

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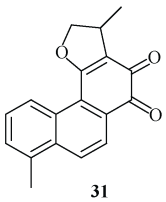

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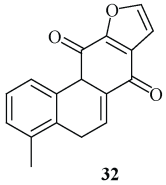

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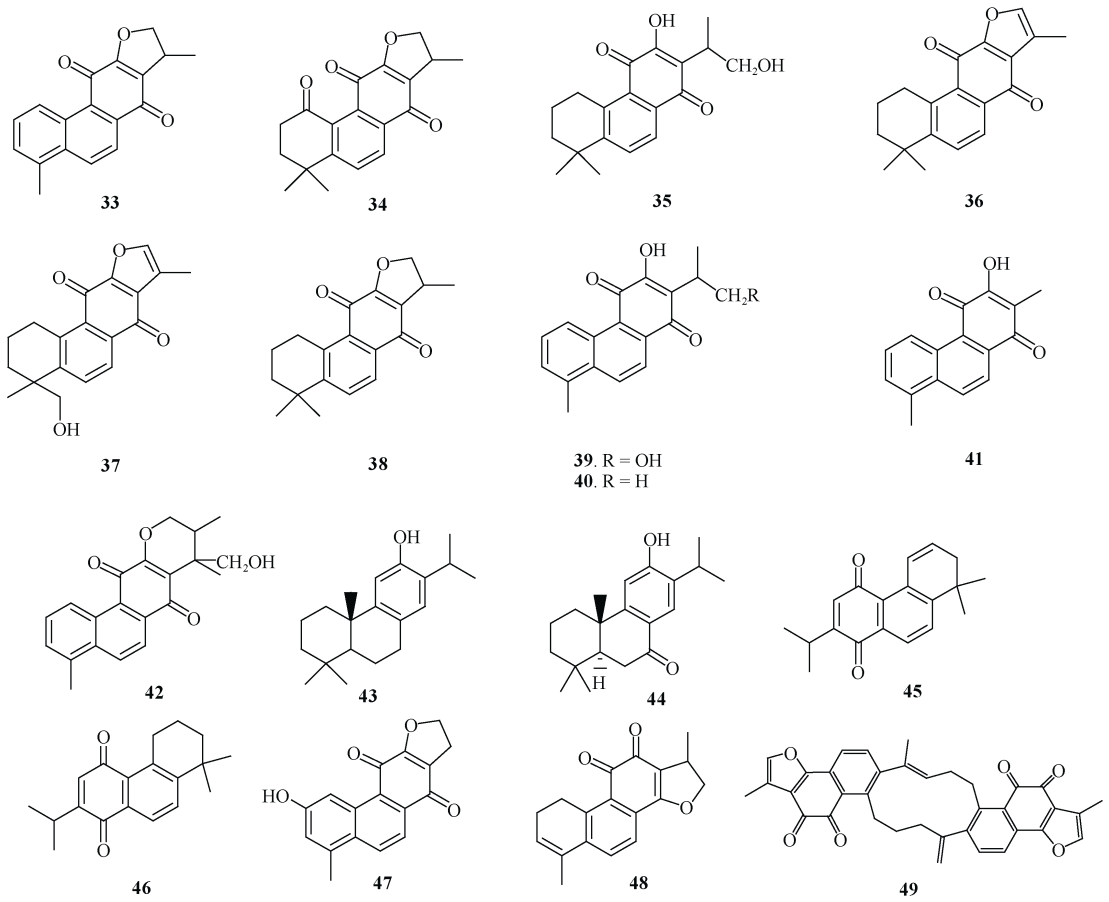
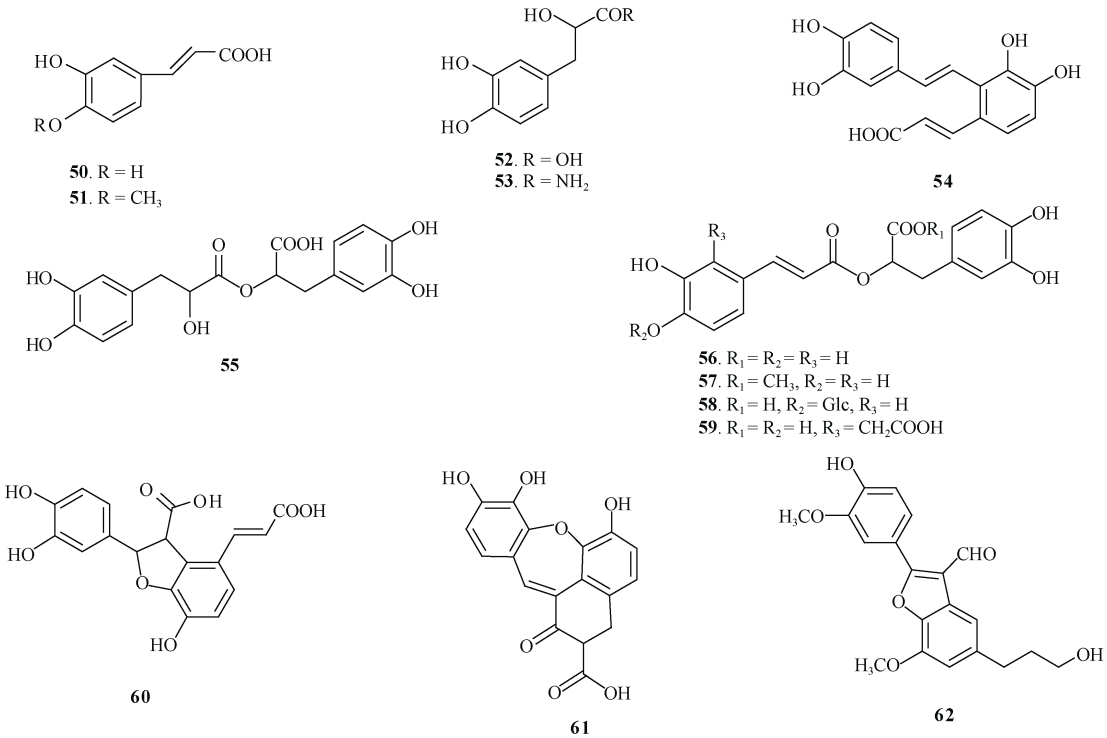
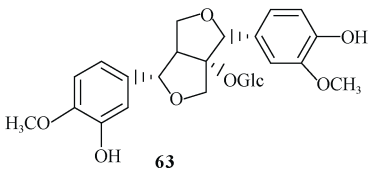


Fig. 1 Structures of diterpenoid quinines isolated from *Salvia miltiorrhiza*





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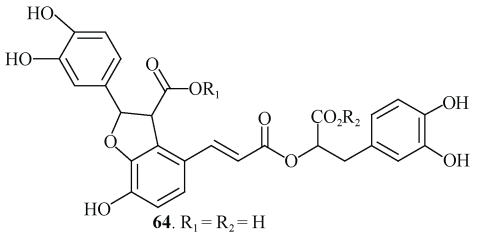
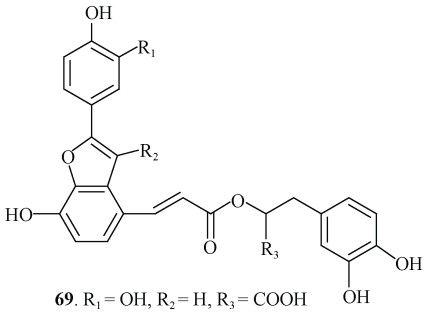
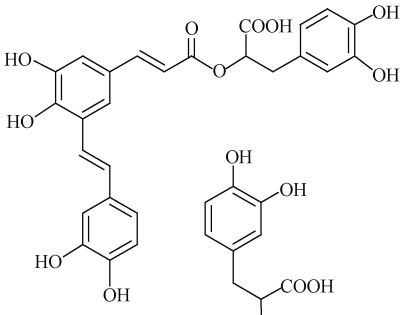


64. $R_1 = R_2 = H$
65. $R_1 = H$, $R_2 = CH_3$
66. $R_1 = R_2 = CH_3$
67. $R_1 = C_2H_5$, $R_2 = Ha$



69. $R_1 = OH$, $R_2 = H$, $R_3 = COOH$
70. $R_1 = OCH_3$, $R_2 = H$, $R_3 = COOH$
71. $R_1 = OH$, $R_2 = R_3 = COOCH_3$



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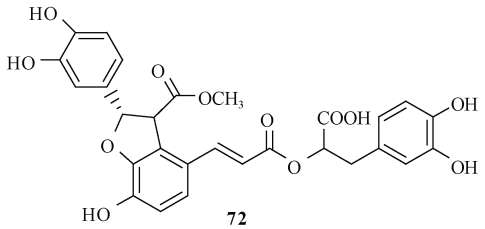

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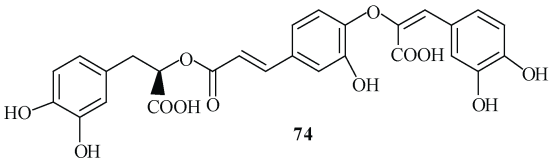

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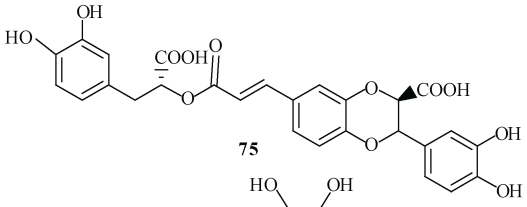

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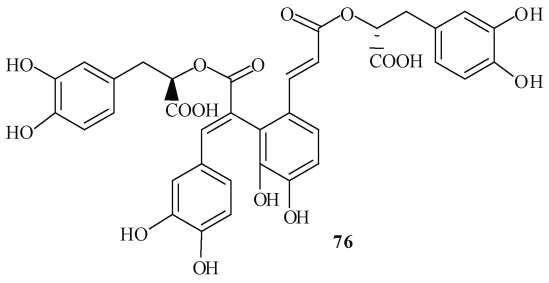

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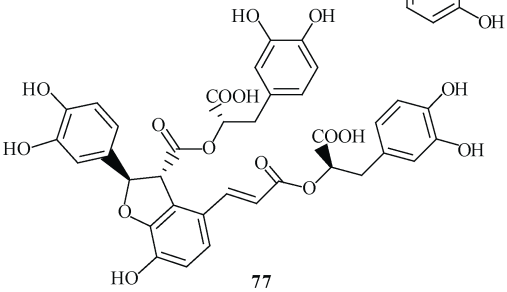

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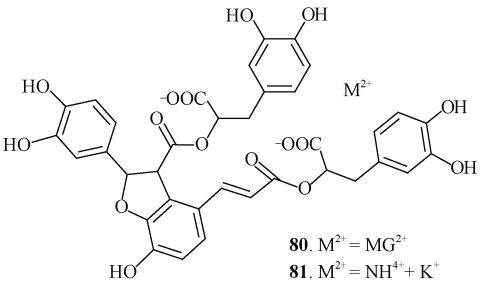
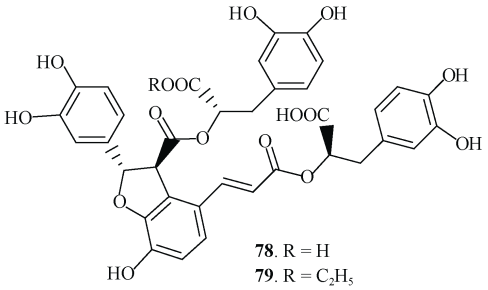


80. $M^{2+} = MG^{2+}$
81. $M^{2+} = NH^{4+} + K^{+}$



78. R = H
79. R = C_2H_5

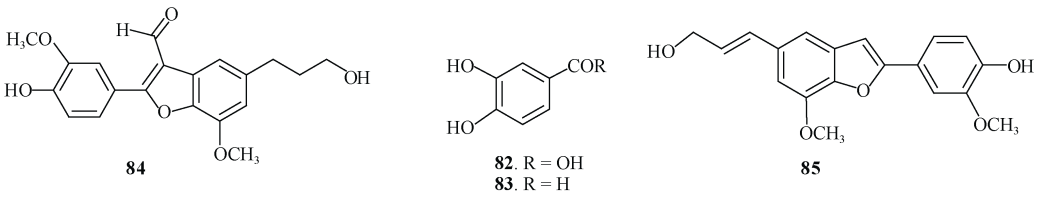


Fig. 2 Structures of hydrophilic phenolic acids isolated from *Salvia miltiorrhiza*

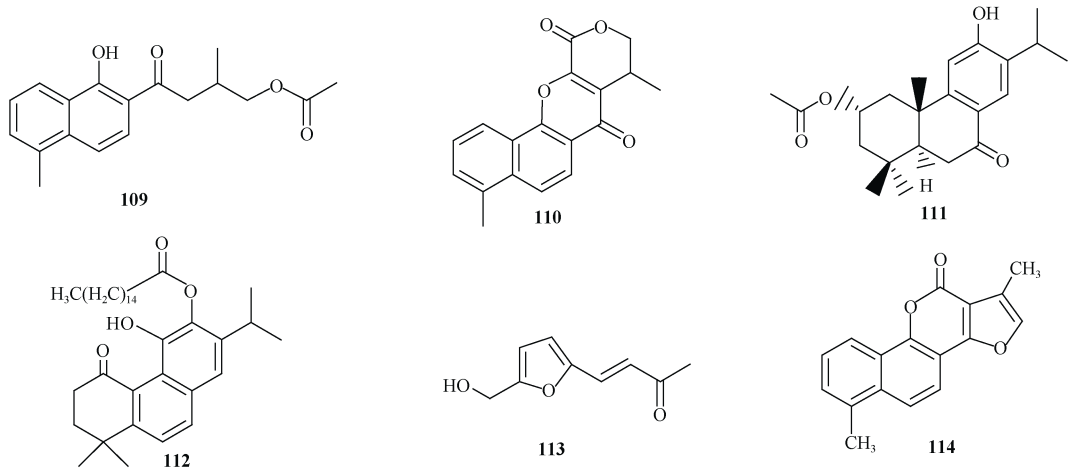


Fig. 3 Structures of miscellaneous compounds isolated from *Salvia miltiorrhiza*

human vascular endothelial cells [82]. The mRNA and protein expressions of vascular cell adhesion molecule-1 (VCAM-1) and intercellular cell adhesion molecule-1 (ICAM-1) were both significantly suppressed by tanshinone IIA in a dose-dependent manner [82]. In addition, the TNF-α-induced mRNA expression of fractalkine/CX3CL1, and the level of soluble fractalkine, were both reduced by tanshinone IIA [82]. As an intermediate product in the metabolic cycle of methionine, Homocysteine was defined as a risk factor for atherosclerosis [81]. SMAE (0.015–3 mg·mL^{-1}) could lead to a significant inhibitory effect on homocysteine-induced A10 cell proliferation [81]. SMAE itself, however, did not display a cytotoxic effect on A10 cells (IC_{50} 1.5 mg·mL^{-1}) [83]. After treatment of New Zealand white rabbits with tanshinone IIA [15 and 37.5 mg·kg^{-1}·d^{-1}, intragastric administration (i.g.)] for 2 months, the atherosclerotic lesion formation in aorta was inhibited and the protein expression and activities of matrix metalloproteinase-2 (MMP-2), MMP-9, serum vascular adhesion-molecule-1, and interleukin (IL)-1β, were down-regulated [84].

Anti-hypertension

Sodium danshensu displays a biphasic effects on vessel tension [85]. While low dosage (0.1–0.3 g·L^{-1}) of sodium danshensu produces small contractions, possibly through transient enhancement of Ca^{2+} influx, a high dosage (1–3 g·L^{-1}) produces significant vasodilation, mainly through promoting the opening of non-selective K^+ channels and small-conductance calcium-sensitive K^+ channels in VSMCs [85]. Sodium tanshinone IIA sulfonate (DS-201) activates high conductance Ca^{2+} activated K^+ channels (BKCa) in porcine coronary artery smooth muscle cells [86]. Extracellular application of DS-201 (40 and 80 μmol·L^{-1}) induced an increase in the BKCa macroscopic currents by 43.6% and 42.1%, respectively, as well as an increase in the spontaneous transient of outward K^+ currents (STOCs) by 48.7% and 47.4%, respectively. Furthermore, in inside-out patches, bath application of 20–150 μmol·L^{-1} of DS-201 activated BKCa by 5.4–173.2-fold. These results indicate that the vasodilatation by DS-201 is related to the activation of BKCa. Another study has demonstrated that pretreatment with DS-201 (10 mg·kg^{-1}·d^{-1}) for 3 weeks could reduce the increased mean pulmonary arterial pressure and right ventricle weight to left ventricle with septum weight [RV/(LV + S)] in rats with hypoxic pulmonary hypertension, but had no significant effect on normal rats [87]. In addition, in DS-201 pretreated rats, the Kv2.1 mRNA expression in pulmonary arteries is stimulated [87]. These results demonstrate that DS-201 has protective effects on hypertension through decreasing mean pulmonary arterial pressure, RV/(LV + S) and inhibiting structural remodeling in distal pulmonary arteries [87].

Anti-hyperlipidemic

The concentrations of plasma total cholesterol, low-density lipoprotein cholesterol (LDL-cholesterol) and triglycerides in rats treated with purified SM extract (PSME) (150 mg·kg^{-1}) for 4 weeks were all significantly decreased, accompanied with significantly decreased concentrations of liver total cholesterol and triglycerides [88]. As a farnesoid *X* receptor/liver *X* receptor α co-agonist, PSME largely improves the lipid profiles in the hyperlipidemic rats [88]. It has also been observed that the short heterodimer partner (SHP) mRNA level is significantly increased in PSME-treated rats, accompanied with

a decrease in the mRNA level of sterol regulatory element binding protein 1c (SREBP1c), which contributes to the decrease of liver and plasma triglycerides through a farnesoid *X* receptor-SHP-SREBP1c pathway [88]. ATP-binding cassette transporter B11 (ABCB11) and murine Mdr2 P-glycoprotein (also known as ABCB4) are significantly induced by PSME, which is responsible for biliary cholesterol solubility by proper biliary secretion of bile salts and phospholipids [88]. The SD rats treated with SMAE [600 mg·kg^{-1}·d^{-1}, per os (p.o.)] for 12 weeks had reduced body weight gain, improved serum lipid profiles, and prevented the formation of fatty liver induced by a high fat diet (HFD) [89]. In addition, SMAE could increase endothelial-dependent vasorelaxation and display vasoprotection in ovariectomized rats fed with HFD, by stimulating nitric oxide (NO) production, up-regulating the mRNA expression of endothelial NO synthase, and down-regulating the mRNA expression of TNF-α, ICAM-1, and VCAM-1 in the isolated aortas [89]. In a single-blind, placebo controlled study [90], 80 hyperlipidemic patients were randomly divided into two equal groups. One group was given PSME tablet (800 mg) three times per day for 6 weeks, while the other group was given placebo tablet. In the PSME group, the total cholesterol was decreased by 27.32 mg·dL^{-1} (12.3% reduction) and LDL-cholesterol decreased by 23.13 mg·dL^{-1} (16.8% reduction), respectively [90].

Anti-myocardial ischemia

Recent studies have demonstrated that the transplantation of bone marrow mesenchymal stem cells (BMSCs) could limit the size of a myocardial infarct and improve cardiac function [91]. After combination treatment of SD rats with tanshinone IIA (30 mg·kg^{-1}·d^{-1}, i.p.) and BMSCs for 1 week, the infarct size was significantly alleviated, compared with the naïve control group (31.46% ± 3.00% *vs* 46.95% ± 6.51%); tanshinone IIA could increase the BMSCs migration via up-regulating the SDF1/CXCR4 axis [92]. Putative endothelial progenitor cells (EPCs) could mobilize from bone-marrow to participate in neovascularization at sites of ischemia [93]. Salvianolic acids (at 3 and 30 mg·L^{-1}) could increase the number of EPCs and promote EPCs migration [93]. In addition, salvianolic acids (30 mg·L^{-1}) induced a significant increase in the number of adhered cells at 30 min, and increased tubule formation (81 ± 8 *vs* control 38 ± 8, $P < 0.001$) [93]. These results suggest that salvianolic acids might have utility for therapeutic postnatal vasculogenesis of ischemic tissue, contributing to the clinical benefit of SM therapy in patients with coronary artery disease [93]. Treatment of salvianolic acid A at doses of 10 and 5 mg·kg^{-1}·d^{-1} for 1 week resulted in dose-dependent reductions in the infarct size of 16% and 18%, respectively, in rats with myocardial infarcts. This effect could be attributed to an increased formation of vascular endothelial growth factor (VEGF), vascular endothelial growth factor receptor-2 (VEGFR-2), and MMP-9, as well as the promotion of numbers and functions of EPCs [94]. After treatment of SD rats with cryptotanshinone [125 and 250 μg·kg^{-1}, intravenous injection (i.v.)] for 10 min, ischemia and reperfusion-induced microcirculatory disturbances were attenuated through inhibition of pro-inflammatory cytokine production, reduction of neutrophil infiltration, and possibly inhibition of adhesion molecules via inhibition of NF-κB-activation during ischemia and reperfusion [95].

Anti-cerebral ischemia

Treatment of cerebral ischemia-reperfusion rats with the aqueous extract of SM (200, 400, and 600 mg·kg^{-1}·d^{-1}) dose-dependently decreased serum high-sensitivity C-reactive protein, IL-8, IL-10, TNF-α levels, and IL-10 mRNA, TNF-α mRNA expression levels, function score, infarct size, cerebral transforming growth factor β1 (TGF-β1) positive expression, and cerebral NSE levels, and increased fas-associated protein with death domain and death-associated protein positive expression levels [96]. Vasogenic edema is a major type of brain edema that is characterized by the structural and functional impairment of the blood-brain barrier (BBB) [97-98]. Administration of tanshinone IIA (30 mg·kg^{-1}, i.p.) could reduce the brain infarct area and water content in the ischemic hemisphere of SD rats [99]. Furthermore, tanshinone IIA significantly decreased BBB permeability to Evans blue, suppressed the expression of ICAM-1 and MMP-9, and inhibited the degradation of the tight junction proteins zonula occludens-1 (ZO-1) and occludin [99]. These results have demonstrated that tanshinone IIA is effective in attenuating the extent of brain edema formation in response to ischemia injury in rats, possibly due to tanshinone IIA's protective effect on the BBB. Cerebral ischemia triggered the robust phosphorylation of the cAMP response element binding protein (pCREB) and the corresponding expression of cAMP-responsive element (CRE)-targeted genes encoding neuroprotective molecules, such as the anti-apoptotic protein B cell lymphoma/leukemia-2 (Bcl-2) and the brain-derived neurotrophic factor (BDNF) in neurons [100]. Transducers of regulated CREB proteins (TORCs) including TORC1, TORC2, and TORC3, are new members of co-activators for CREB [101-103]. Treatment of SD rats with tanshinone IIA (20 mg·kg^{-1}, i.p.) could protect rat brain from pristine ischemic damage in cerebral cortex, which might be correlated with induced nuclear translocation of TORC1 and up-regulated expression of TORC1, pCREB and BDNF [104]. A study has demonstrated that after administration of salvianolic acid A (2.5 mg·L^{-1}) for 20 h, granulocyte adherence is significantly inhibited *in vitro* through decreasing the expression of ICAM-1 in brain micro-vascular endothelial cells [105]. Pretreatment of cerebral hypoxia-ischemia mice with tanshinone I (10 mg·kg^{-1}) is associated with a significant reduction in infarct volume 1 day after hypoxia-ischemia is induced [106]. In addition, tanshinone I protects against hypoxia-ischemia-induced neuronal death in the ipsilateral region [106].

Antithrombosis

For centuries, SM has been used to treat hyperviscosity syndrome or blood stasis [69, 107]. After treatment of human

umbilical vein endothelial cells (HUVECs) with salvianolic acid B (0.012 5–0.5 mg·mL^{-1}) for 2–12 h, a dose- and time-dependent decrease in plasminogen activator inhibitor (PAI) activity was observed [108]. Salvianolic acid B could increase the fibrinolytic and anticoagulant potential of cultured HUVECs by up-regulating the expression of tissue-type plasminogen activator and thrombomodulin, as well as down-regulating the expression of PAI-1 [108]. In a mouse model of arterial thrombosis, salvianolic acid A prolonged the mesenteric arterial occlusion time in wild-type mice 35 ± 2 min without salvianolic acid A and 56 ± 4 min with salvianolic acid A) [109]. Salvianolic acid A could inhibit platelet activation through inhibition of phosphoinositide 3-kinase, and attenuate arterial thrombus formation *in vivo* [109]. After treatment of SD rats with salvianolic acid A (2.5–10 mg·kg^{-1}·d^{-1}, i.v.) for 5 days, adenosine diphosphate (ADP)-induced platelet aggregation was inhibited in a dose-dependent manner [110]. Notably, coagulation parameters were not affected by salvianolic acid A [110]. *In vitro*, pretreatment with salvianolic acid A of washed rat and human platelets significantly inhibited various agonist-stimulated platelet aggregation and caused an increase in cAMP level in platelets activated by ADP [110]. Treatment of mixed-breed piglets with tanshinone IIA (10 μg·mL^{-1}) impaired the whole blood collagen-induced platelet aggregation in a dose-related manner with a maximum response [111]. Further study has demonstrated that tanshinone IIA impaired the *ex vivo* whole blood platelet aggregatory function by activating platelets *in vivo* in healthy newborn piglets. Tanshinone IIA might elicit its effects by stimulating endothelial micro-particles production and the eicosanoid metabolism pathway [111].

Anti-Alzheimer's disease

Amyloid precursor protein (APP) proteolysis is the fundamental process for the production of *β*-amyloid (A*β*) peptides implicated in Alzheimer's disease (AD) pathology [112]. After oral treatment of APP/PS1 transgenic mice with cryptotanshinone (5–30 mg·kg^{-1}·d^{-1}) for 4 months, amyloid plaque deposition was strongly attenuated [113]. In addition, cryptotanshinone is reported to promote APP metabolism towards the non-amyloidogenic products pathway in rat cortical neuronal cells [113]. With the use of thioflavin T fluorescence assay and transmission electron microscopy, the same research team has reported that cryptotanshinone could inhibit A*β*42 spontaneous aggregation. Incubation with cryptotanshinone (1.0, 2.5, and 5.0 μmol·L^{-1}) also dramatically reduced A*β*42-induced cellular apoptosis and increased the level of ROS in cultured SH-SY5Y cells [114]. The current therapeutic intervention for AD is primarily based on the inhibition of brain acetylcholinesterase to restore the brain acetylcholine level [4]. Interestingly, cryptotanshinone is reported as an inhibitor of both human acetylcholinesterase and butyrylcholinesterase [4]. Therefore, cryptotanshinone could be a potential agent to treat AD. SM ethanol extract, total tanshinones, tanshinone I, and dihydrotanshinone I have been shown to have remarkable inhibitory effects on acetylcholinesterase *in vitro* [3]. A$\beta_{25\text{-}35}$ induced cytotoxicity was revised by SM ethanol extract (1–2 mg·mL^{-1}) and total polyphenols (1–100 μg·mL^{-1}) [3]. Danshensu (200 mg·mL^{-1}) and salvianolic acid B (200 mg·mL^{-1}) could protect PC-12 cells by blocking A$\beta_{25\text{-}35}$-induced Ca^{2+}-intake, lactate dehydrogenase release, cell viability decrease and apoptosis [3]. Salvianolic acid A (1–40 μmol·L^{-1}) significantly inhibited A*β* self aggregates, disaggregated pre-formed A*β* fibrils, reduced metal-induced A*β* aggregation through chelating metal ions, and blocked the formation of ROS in SH-SY5Y cells [115].

Anti-Parkinson's disease

Parkinson's disease (PD) is characterized by a profound loss of pigmented dopaminergic neurons in the substantia nigra [116]. Several lines of evidence have strongly established that oxidative stress and mitochondrial dysfunction played major roles in the neurodegenerative process of this disease [116]. After pretreatment of SH-SY5Y cells with salvianolic acid B (0.1–10 μmol·L^{-1}) for 1 h, 6-hydroxydopamine-induced generation of ROS was significantly reduced, and an increased the level of intracellular calcium was prevented [116]. In addition, after administration of salvianolic acid B (2.5, 5.0, and 10 μmol·L^{-1}) for 24 h, the activation of extracellular signal- regulated kinase was significantly decreased, and the activation of 6-hydroxydopamine-suppressed protein kinase C was markedly stimulated [116]. 1-Methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP), one of the selective nigrostriatal dopaminergic neurotoxins, was the first conclusive demonstration of a link between environmental toxin exposure and the development of PD [117]. After pretreatment of C57BL/6J mice with protocatechuic acid (PAc) (50 and 100 mg·kg^{-1}) for 14 consecutive days, the behavior deficit induced by MPTP toxicity was significantly ameliorated (40.67 ± 4.51 s, 52.00 ± 6.24 s) [5]. Protocatechuic acid (100 mg·kg^{-1}) could inhibit the reduction of the contents of dopamine and its metabolites in striatum, as well as ameliorate the pathology in substantia nigra [5].

Anti-neuropathic pain

Neuropathic pain is a chronic disease defined as an untreatable illness by the WHO because of the unsatisfactory therapeutics in many cases [118]. Many researchers have selected the chronic constriction injury of the sciatic nerve model (CCI) to investigate neuropathic pain [119]. Recently, in the CCI model of neuropathic pain, it was shown that the oxidative-nitrosative stress, the enzymatic antioxidant SOD and reduced GSH were important determinants of neuropathological and behavioral consequences [120]. Treatment of the CCI rats with salvianolic acid B (100 mg·kg^{-1}, i.p.) and its liposomal formulation (at the same dosage of salvianolic acid B) could protect against oxidative stress as well as the antioxidant SOD and reduce activity of GSH [119]. According to these *in vivo* studies, a PEGylated formulation of salvianolic acid B could increase and prolong the antihyperalgesic activity 30 min after i.p. administration, and the effect

was still significant at 45 min [119]. In another study, it was reported that cryptotanshinone (10–20 μmol·L^{-1}) had neuroprotective effects against the sodium-nitroprusside- induced apoptosis in neuro-2a cells through regulation of the mitochondrial apoptotic cascades and anti-apoptotic cellular signaling pathways [121].

Anti-diabetes mellitus

The ethanol extract of SM (1–10 μg·mL^{-1}), tanshinone I (10 μmol·L^{-1}), tanshinone IIA (10 μmol·L^{-1}), and 15, 16-dihydrotanshinone I (DHTS, 10 μmol·L^{-1}) could enhance the activity of insulin (1 nmol·L^{-1}) on the tyrosine phosphorylation of the insulin receptor and the activation of the downstream kinases Akt, ERK1/2, and GSK3β in Chinese-hamster ovary cells [122]. Endothelial dysfunction is implicated both in the development of diabetic macrovascular and in microvascular diseases [123]. Exposure of HMEC-1 cells to 30 mmol·L^{-1} glucose resulted in significant increases in the expression of VEGF mRNA and ROS formation [124]. Treated with hydrophilic extract of SM (10 μg·mL^{-1}) for 48 h, VEGF mRNA and ROS formation were significantly decreased in 30 mmol·L^{-1} glucose conditions [124]. The SM hydrophilic extract effectively reversed induction of VEGF expression by high glucose through amelioration of mitochondrial oxidative stress [124]. Diabetic rats were treated orally with salvianolic acid A (1 mg·kg^{-1}) for 10 weeks after modeling, and were then given a high-fat diet. With salvianolic acid A treatment, the level of serum Von Willebrand factor was decreased and acetylcholine-induced relaxation, as well as KCl-induced contraction, was ameliorated in aorta rings of the diabetic rats [125]. Salvianolic acid A also could reduce the serum malondialdehyde level, the content of aortic advanced glycation end products (AGEs), the nitric oxide synthase (NOS) activity, and the expression of endothelial NOS protein in the rat aorta [125].

Anti-inflammation

Administration of ailanthoidol (20 μmol·L^{-1}), a neolignan from SM, suppresses the generation of NO and prostaglandin E2, as well as the expression of inducible NOS and cyclooxygenase-2 [126]. Similarly, ailanthoidol inhibits the production of inflammatory cytokines including IL-1β and IL-6 in RAW264.7 cells [126]. In another study, RAW264.7 cells were treated with cryptotanshinone (2.5–10 μmol·L^{-1}) over 24 h. Cryptotanshinone markedly inhibited the phosphorylation of mitogen-activated protein kinases (MAPKs), including ERK1/2, p38MAPK, and JNK, which are crucially involved in the regulation of pro-inflammatory mediator secretion [127]. Moreover, immunofluorescence and Western blot analysis indicated that cryptotanshinone completely abolished LPS-triggered nuclear factor-κB (NF-κB) activation [127]. The RAW264.7 cells were treated with the ethanol extract of SM (12.5–100 μg·mL^{-1}) for 24 h, and the results showed that the regulatory effects of the ethanol extract of SM were mediated through the suppression of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and NO, as well as the induction of anti-inflammatory cytokines including IL-4, IL-10, TGF-β, and IL-1Ra [128]. The contents of platelet activating factor (at 3 and 12 h), IL-1β (at 6 and 12 h), soluble IL-2 receptor (at 3 and 6 h), the pathological scores of thymus (at all time points), and spleen (at 3 and 12 h) in the SM-treated group were markedly lower than that in the model control group [128]. SM could also reduce the contents of serum platelet activating factor, soluble IL-2 receptor, and IL-1β, which mitigated the pathological changes in the small intestine, spleen, and thymus, as well as reduce the mortality rate of rats with severe acute pancreatitis [129]. After treatment with tanshinone IIA (5–20 μg·mL^{-1}) for 24 h, the expressions of VCAM-1 and ICAM-1 were suppressed, resulting in inhibition of TNF-α-induced adhesion of neutrophils to BMVECs in a dose-dependent manner [130]. Tanshinone IIA was established to regulate TNF-α-induced expression of VCAM-1 and ICAM-1 through inhibition of NF-κB activation and ROS generation in brain micro-vascular endothelial cells [130].

Antioxidant activity

Recent studies have indicated that treatment of two-kidney, two-clip hypertensive rats with tanshinone IIA (35 and 70 mg·kg^{-1}·d^{-1}) for 6 weeks could inhibit the increased NAD(P)H oxidase activity and expression, as well as ROS production [131]. Twenty-month-old rats were intraperitoneally injected with 5 and 10 mg·kg^{-1}·d^{-1} of dimethyl lithospermate (DML), and 6-month-old rats were used as young control animals. The results indicated that DML inhibited NO metabolites and reactive species generation, as well as reduced age-associated increases in cyclooxygenase-2 and inducible nitric oxide synthase (iNOS) expression [132]. Treatment with salvianolic acid A (0.5–50 μmol·L^{-1}) of pigment epithelial cells could activate the Nrf2/HO-1 axis, and protect against oxidative stress through activation of Akt/mTORC1 signaling [133]. The ethanol extract of SM had potent peroxy radical scavenging effect with a specific total oxyradical scavenging capacity being at least three-fold greater than that of GSH [134]. The methanol extract of the leaves of SM (ML) was evaluated by various antioxidant assays *in vitro* [135]. The total phenolic contents of ML were 54.3 ± 1.1 mg gallic acid equivalents/g extract tested. The EC_{50} of ML was 7.0 ± 0.28 μg·mL^{-1} in the DPPH radical scavenging assay and 246.5 ± 10.35 μg·mL^{-1} in the superoxide radical quenching assay. It was also found that ML had prominent effects on the inhibition of linoleic acid oxidation (93.2%), which was equivalent to the positive control, butylated hydroxytoluene (BHT), and was significantly higher than α-tocopherol (VE) [135]. The antioxidant capacity of the root of SM was better than its leaf material, and correlated with the total polyphenol and the hydroxycinnamic acid content [136].

Anticancer activity

In an *in vivo* transgenic mouse model of human vascular endothelial growth factor-A165 gene-induced pulmonary tumor, tanshinone I (1 mg·kg^{-1}) could significantly suppress

the formation of lung adenocarcinoma tumors (16.7%) [137]. After incubation with cryptotanshinone (2.5–40 μmol·L^{-1}) for 48 h, cancer cell proliferation was inhibited by arresting cells in G_1/G_0 phase of the cell cycle in human rhabdomyosarcoma cells [138]. The mechanism for the inhibition is that cryptotanshinone could inhibit expression of cyclin D1 and phosphorylation of retinoblastoma protein, and could also block the signaling pathway of the mammalian target of rapamycin, a central regulator of cell proliferation [138]. In addition, after treatment of human myeloid leukemia KBM-5 cells with cryptotanshinone (5, 10, 20, and 40 μmol·L^{-1}) for 24 h, the viability of all leukemic cells was decreased in a dose-dependent manner [139]. Cryptotanshinone could sensitize TNF-*α* induced apoptosis in human myeloid leukemia KBM-5 cells, which appeared through ROS-dependent activation of caspase-8 and p38 [139]. Tanshinone IIA (10–100 μmol·L^{-1}) caused an increase in intracellular calcium, a decrease in mitochondrial membrane potential, and induction of Bad and metallothionein 1A (MT 1A) mRNA expression in human hepatoma BEL-7402 cells [140]. Tanshinone IIA induces hepatoma cell apoptosis via activating the calcium-dependent apoptosis signaling pathways and up-regulating of MT 1A expression [140]. Tanshinone IIA could inhibit invasion and migration of HT29 and SW480 cells in a dose- and time-dependent manner. At 48 h, the average inhibition rate was increased by 55.75% compared to the control group [141]. The tumor inhibition rates, measured by the appearance of visible tumors on the liver, in the groups treated with tanshinone IIA (20 and 80 mg·kg^{-1}·d^{-1}) were 40.37% and 61.15%, respectively [141]. Tanshinone IIA inhibited invasion and metastasis of colon carcinoma cells by reducing levels of urokinase plasminogen activator (uPA), MMP-2, MMP-9, and by increasing levels of tissue inhibitor of matrix metalloproteinase protein (TIMP)-1 and TIMP-2 *in vitro* and *in vivo* [141]. Tanshinone IIA is also shown to suppress the NF-κB signal transduction pathway [141]. Salvianolic acid B has been shown to have an inhibitory effect on oral squamous cell carcinoma cell growth, and this effect could be attributed to the anti-angiogenic potential induced by a decreased expression of some key regulator genes, such as hypoxia-inducible factor (HIF)-1*α*, TNF-*α*, and MMP-9 [142]. 15, 16-dihydrotanshinone I (DHTS), at as low a concentration as 2.5 μg·mL^{-1}, significantly inhibited proliferation of human benign (SW480) and malignant (SW620) colorectal cancer cells, Activating transcription factor (ATF)-3, a basic leucine zipper-type transcription factor, was found to be predominantly up-regulated in DHTS-treated SW480 and SW620 cells [143]. For androgen-dependent LNCaP cells, a colony growth assay showed strong inhibitory potency in the following the order: tanshinone IIA ≈ cryptotanshinone > tanshinone I, being 10-30-fold higher than Casodex (racemic) [144]. It was reported that oral administration of tanshinone IIA (25 mg·kg^{-1}·d^{-1}) retarded LNCaP xenograft growth and down-regulated of tumor androgen receptor (AR) abundance in athymic nude mice [144]. In another study, tanshinones inhibited prostate cancer growth by inhibiting AR nuclear translocation, reducing protein and mRNA abundance of AR, and stimulating AR proteosomal degradation [144]. After treatment with an ethanol extract of SM (5 μg·mL^{-1}) for 3 h, the proliferation of MCF-7 breast cancer cells was inhibited through inhibition of Akt activity and up-regulation of p27 [145].

Anti-hepatocyte injury

Hepatocytes undergo cell death by apoptosis in nearly all human liver diseases and in cholestasis [146]. A standardized fraction of SM (PF2401-SF, 40 μg·mL^{-1}) which was enriched with tanshinone I (11.5%), tanshinone IIA (41.0%), and cryptotanshinone (19.1%), protected rat hepatocytes from glycochenodeoxycholic acid-induced apoptosis by inhibiting c-Jun-NH2-terminal kinase [147]. It was also reported that tanshinone I (40 μmol·L^{-1}), tanshinone IIA (40 μmol·L^{-1}), and cryptotanshinone (40 μmol·L^{-1}) inhibited lactate dehydrogenase leakage, GSH depletion, lipid peroxidation, and free radical generation in cultured rat hepatocytes. After oral treatment of acute liver injury rats with PF2401-SF (50–200 mg·kg^{-1}·d^{-1}) for 4 days, alanine aminotransferase (ALT) levels and aspartate aminotransferase (AST) levels were remarkably reduced. PF2401-SF could protect against liver toxicity due to its antioxidant effects *in vitro* and *in vivo* [148]. SM polysaccharide reduced the degree of liver injury by up-regulating the enzymes of the citric acid cycle, namely malate dehydrogenase and 2-oxoglutarate dehydrogenase complex. Immunological liver injury Kunming strain mice were treated with SM polysaccharide (360 mg·kg^{-1}·d^{-1}) for 12 days. It has been found that SM polysaccharide exerted protection against the immunological liver injury through inhibition of the NF-*κ*B activation by up-regulating of PRDX6 and the subsequent attenuation of lipid peroxidation, iNOS expression, as well as inflammation [149]. Cryptotanshinone had hepatoprotective effects in D-galactosamine (GalN)/ LPS-induced fulminant hepatic failure. The increased mortality and TNF-*α* level of male C57BL/6 mice by GalN/LPS were decreased by cryptotanshinone (20 and 40 mg·kg^{-1}) [150]. Salvianolic acid A, at doses of 15 and 25 mg·kg^{-1}, was intraperitoneally injected into the male Kunming mice 30 min before concanavalin A was used. Pretreatment with salvianolic acid A significantly reduced concanavalin A-induced elevation in serum ALT and AST activities, decreased levels of the hepatotoxic cytokines, such as interferon-gamma (IFN-*γ*) and TNF-*α*, as well as ameliorating the increases in NF-*κ*B and caspase-3. More importantly, the salvianolic acid A pretreatment significantly increased the expression of SIRT1, a NAD^+-dependent deacetylase, which is known to attenuate acute hypoxia damage and metabolic liver diseases [151].

Effects on acute lung injury

Acute lung injury (ALI) and its most severe form, acute respiratory distress syndrome (ARDS), remains a leading cause for morbidity and mortality in critically ill patients

[152-153]. Aquaporins (AQPs), a family of small (about 30 kDa monomer), hydrophobic, integral membrane proteins, play major roles in transcellular and transepithelial water movement [154-155]. Treatment with tanshinone IIA (50 mg·kg^{-1}, i.p.) could significantly reduce the elevation of AQP1 and AQP5 expression induced by seawater in SD rats, improve lung histopathologic changes and blood-gas indices, as well as reduce lung edema and vascular leakage [156].

Effects on renal injury

Treatment of iron-overloaded mice with SM injection (6 g·kg^{-1}·d^{-1}) led to significant improvements of body weight and decreased iron levels in the kidney [157]. Histopathologic examinations showed that SM injection ameliorated pathological changes and reduced iron deposition in kidneys of iron over-loaded mice [157]. The intraperitoneal administration of SM injection (0.78 mL·kg^{-1}·d^{-1}, according to the clinical dose) could ameliorate the physiological dysfunctions of increased 24 h urinary protein excretion (48.21% ± 8.04%), serum creatinine (39.4% ± 3.7%), and blood urea nitrogen (43.37% ± 6.74%), alleviate the ultrastructural abnormalities of hypertrophy, matrix expansion, and fibrosis in glomerulus, decrease TGF-β1 expression, AGEs, and lipid peroxide accumulation, as well as increase the activity of SOD and GSH- peroxidase in the kidney of diabetic rats [158]. Acute renal failure (ARF) is a syndrome defined as an acute reduction in renal function, and commonly occurs due to acute tubular necrosis with usually reversible loss of renal function incurred from ischemic or nephrotoxic insults [6]. Polyuria caused by down-regulation of renal AQP 2 in the ischemia-reperfusion induced ARF rats was partially restored by administration of lithospermic acid B (40 mg·kg^{-1}·d^{-1}, i.p.) [6]. Treatment with lithospermic acid B also restored the expression of Na, K-ATPase α1 subunit in the outer medulla of the ARF rats [6]. Chronic kidney disease (CKD) is a common cause of end-stage renal disease [159]. After CKD rats were orally-treated with tanshinone IIA (10 mg·kg^{-1}·d^{-1}) for 8 weeks, serum creatinine, angiotensin II (Ang II), TGF-β1, and collagen IV levels were significantly reduced. In addition, tanshinone IIA suppressed the increase of urinary protein excretion in CKD rats [159].

Anti-fibrotic activity

Fibrosis is the common cause of chronic failure of many organs, and has been a leading cause of morbidity and mortality worldwide [160]. Salvianolic acid B (1.75–14 μmol·L^{-1}) suppressed collagen I expression at both the mRNA and protein levels, and also variably suppressed α-smooth muscle actin expression and bromodeoxyuridine incorporation in NRK-49F cells (normal rat kidney fibroblasts) [161]. Following oral treatment of SD rats with magnesium lithospermate B (MLB) (40 mg·kg^{-1}·d^{-1}) for 8 weeks, liver fibrosis and the activation of hepatic stellate cells (HSCs) were significantly attenuated in both the early and late stages of thioacetamide-induced liver cirrhosis [162]. Administration of MLB reduced serum AST levels and ALT levels, attenuated hepatic fibrosis, as well as activated HSCs. MLB had a potent anti-fibrotic effect in thioacetamide-induced hepatic fibrosis through inhibition of NF-κB transcriptional activation and monocyte chemotactic protein 1 production, and suppression of H_2O_2-induced ROS generation, as well as inhibition of type I collagen secretion in HSCs [162]. The therapeutic goal in liver fibrosis is the reversal of fibrosis and selective clearance of activated HSCs [163]. Treatment of t-HSC/Cl-6 cells with tanshinone IIA inhibited cell viability in a dose- and time-dependent manner. Tanshinone IIA (2.5–40 μmol·L^{-1}) induced apoptosis, as demonstrated by DNA fragmentation, poly (ADP-ribose) polymerase and caspase-3 cleavage, increased Bax/Bcl-2 protein ratio, and depolarization of mitochondrial membranes to facilitate cytochrome *c* release into the cytosol [163]. Furthermore, it markedly induced S phase cell cycle arrest, and down-regulated cyclins A and E, and cdk2 [163]. Treatment of t-HSC/Cl-6 cells with PF2401-SF (20 μg·mL^{-1} for 12 h) could significantly increase caspases 3, 8, and 9, and poly (ADP-ribose) polymerase activities [164].

Anti-alcohol dependence

Alcohol abuse and dependence have held important roles in the public health because of both the medical consequences and economical costs, thus the pharmacological treatment of patients with alcohol dependence has become increasingly urgent. After treatment of male high-alcohol-preferring Wistar rats with the hydroalcoholic (1 : 1) extract of SM (150 g·kg^{-1}·d^{-1}, p.o.) for 28 consecutive days, alcohol intake was significantly lowered (23%) [165]. Following oral treatment of Sardinian alcohol-preferring (sP) rats with SM extract (200 mg·kg^{-1}·d^{-1}), standardized to contain 13% tanshinone IIA for four consecutive days, voluntary alcohol intake was significantly decreased by approximately 50% in comparison to placebo-treated sP rats [166]. Tanshinone IIA, cryptotanshinone, and miltirone were also effective in reducing voluntary alcohol intake in animal models of excessive alcohol drinking [166]. The acute administration of IDN 5082 (25, 50, and 100 mg·kg^{-1}·d^{-1}, i.g.), a standardized extract of SM, resulted in complete suppression of the extra amount of alcohol consumed during the first hour of re-access to alcohol after 7 days of deprivation in sP rats [167]. After administration of miltirone (2.5–10 mg·kg^{-1}·d^{-1}, i.g.) for 7 consecutive days, alcohol intake was reduced in alcohol-experienced rats, and the acquisition of alcohol-drinking behavior was delayed in alcohol-naive rats [168].

Other therapeutic effects

In an *in vivo* study [169], immunodeficient nu/nu male BalbC mice were randomly assigned to two groups: the SM injection group (4.5 g·kg^{-1}·d^{-1}, i.p.) and the control group (the same-volume saline injection), and the mice were periodically sacrificed on 2, 7, and 28 days after transplantation. Both healthy primordial follicle proportion and the total healthy primordial follicles pool in the SM group were significantly higher than those of the control group. In the early stages of the frozen-thawed fetal ovarian grafts, SM could facilitate graft vascularization and improve the preservation of primor-

dial follicles [169]. Pretreatment with SM injection (3 g·kg^{-1}·d^{-1} for 10 days) of adult guinea pigs decreased gentamicin-induced hearing loss, attenuated iNOS and caspase-3 expression, and decreased the number of apoptotic cells [170]. TZM-bl is a HeLa-derived cell line containing a chromatin-integrated HIV-1 long terminal repeat (LTR) [171]. Treatment with tanshinone IIA (10 μmol·L^{-1}) of TZM-bl cells could reverse Tat-induced ROS production and down-regulation of GSH levels through up-regulation of Nrf2 expression [171]. The results also indicate that Tat-induced HIV-1 LTR transactivation dependent on AMPK-nicotinamide phosphoribosyltransferase pathway is inhibited [171]. Tanshinone I and dihydrotanshinone I cause a significant increase in Nrf2 protein half-life *via* blockage of ubiquitination, ultimately resulting in up-regulated expression of cytoprotective Nrf2 target genes (*GCLC, NQO1*) with the elevation of cellular GSH levels in human dermal neonatal foreskin Hs27 fibroblasts [172]. Tanshinone I and dihydrotanshinone I pretreatment cause significant suppression of skin cell death induced by solar simulated ultraviolet radiation (UV) and riboflavin-sensitized UVA [172].

Side effects

Although numerous clinical trials have demonstrated that certain SM products in China are effective and safe for the treatment of cardiovascular diseases, most of these lack high quality [12]. In recent years, with its wide range of application, an increasing number of side effects of SM products, such as abdominal discomfort, decreased appetite [12], convulsions, dystonia syndrome [173], and allergy [174] have been reported. However, once stopping the use of SM products, these side effects are relieved [175].

In summary, better-designed studies are essential to provide sufficient evidence to prove or rule out the existence of side effects of SM products.

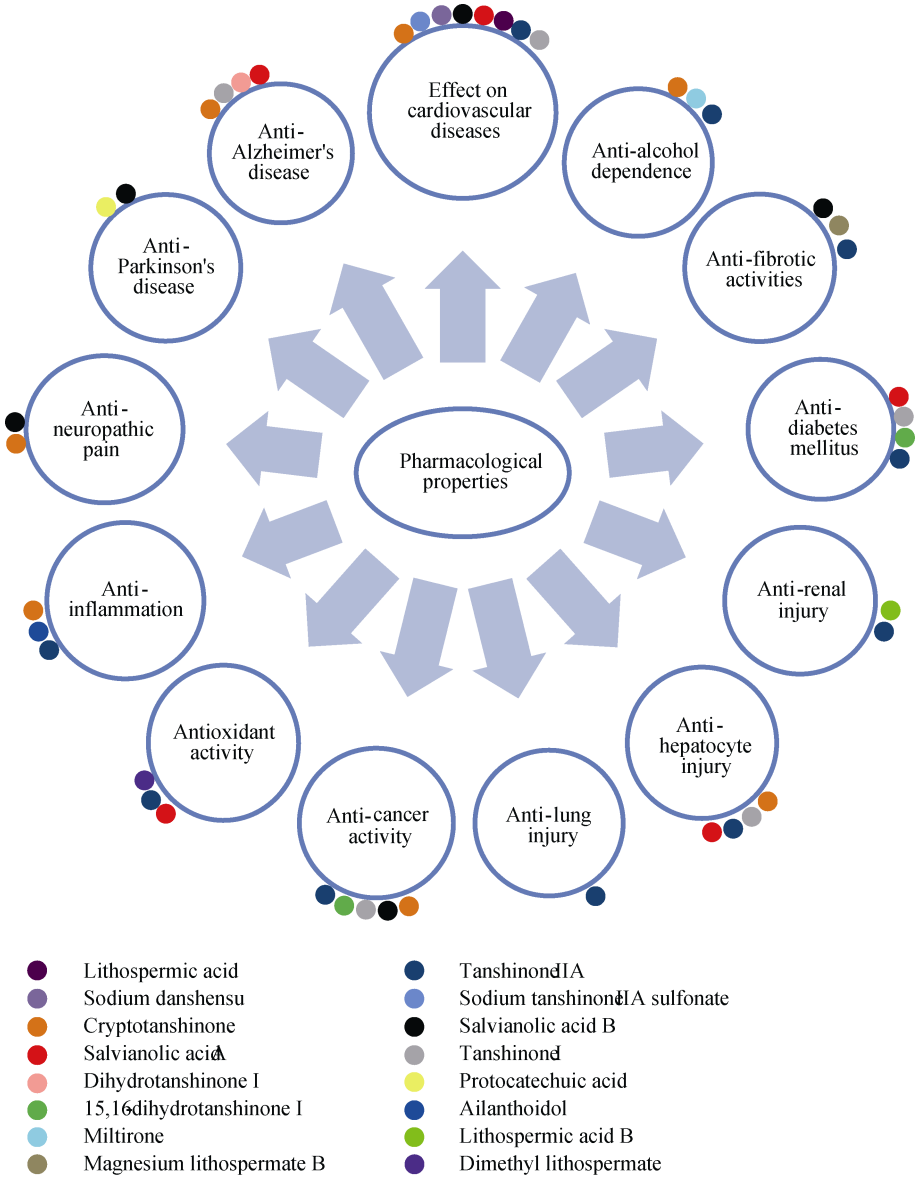


Fig. 4 The different pharmacological properties of the chemical compounds isolated from *Salvia miltiorrhiza*

Drug interactions

Suspected cases of SM-warfarin interaction have been reported in patients on warfarin therapy [176-177]. As SM is the most widely used TCM for cardiac patients, and warfarin is one of the most commonly used cardiac drugs in Western medicine, this interaction becomes a very serious patient-safety issue [173, 177]. In rat liver microsome study, the ethyl acetate extract of SM, tanshinone I, tanshinone IIA, and cryptotanshinone decreased the formation of 4′-, 6-, and 7-hydroxy-warfarin, mediated by CYP1A1, CYP2C6, and CYP2C11 activities, respectively [178]. The formation of 4′- and 7-hydroxy warfarin *in vivo* was decreased significantly after treatment of SD rats with SM (200 $mg \cdot kg^{-1} \cdot d^{-1}$) for three days [178]. In a steady state study *in vivo*, the steady state plasma warfarin concentration was increased by 23% when co-administered with SM [178]. SM extracts could increase the absorption rate constant, area under plasma concentration-time curves, maximum concentrations, and elimination half-lives, but decrease the clearances and apparent volume of distribution of both *R*- and *S*-warfarins [179].

Digoxin is a cardiac glycoside used most frequently to increase the adequacy of circulation in patients with congestive heart failure, and to slow the ventricular rate in the presence of atrial fibrillation and flutter [180]. The cardio-active pharmacologic properties of digoxin and SM are similar, and it is feasible that a patient receiving digoxin therapy may also take SM without the knowledge of the physician. In such patients, their sera may display a falsely elevated (positive interference) digoxin concentration, as measured by the fluorescence polarization immunoassay for digoxin [181]. More interestingly, serum digoxin concentrations were reported to be falsely lowered (negative interference) when measured by the microparticle enzyme immunoassay, marketed by Abbott Laboratories [181].

Conclusions

Herein, we comprehensively summarize the existing knowledge on SM, including its traditional uses, chemical constituents, biochemical and pharmacological studies, side effects, and interactions with other drugs. The importance of collecting the traditional uses of SM lies in the fact that the plant possesses wide and potent pharmacological properties, and can form a practical base for further scientific research. In recent years, SM has been proven to have various pharmacological activities, such as cardiovascular and cerebrovascular effects, antioxidative, neuroprotective, antifibrotic, anti-inflammatory, and antineoplastic activities, and its application has made significant contributions to patient care and human health. Currently, more than 114 compounds have been isolated; among them diterpenoid quinones and hydrophilic phenolic acids are the major constituents, and are also important chemotaxonomic markers. Some of these compounds have been evaluated for biological activity, and the constituents responsible for the pharmacological properties of SM have been determined. Fig. 4 briefly illustrates the different pharmacological properties of these compounds isolated from SM.

However, both experimental and clinical studies have to be encouraged to identify any side effects and possible interactions between this TCM and other drugs. Furthermore, an evaluation of the possible synergistic actions among multiple active compounds of this plant needs to be addressed. By a combination of multiple chemical ingredients, SM may elicit its beneficial effects by interacting with different cell signaling pathways and networks in a rational way, and thus achieving the same therapeutic efficacy of normal mono-ingredient agents at much lower doses of separate compounds. Well-controlled, double-blind clinical trials involving a large number of patients have to be encouraged in order to develop more new drugs from SM with good therapeutic effects and fewer side effects. In addition to these studies, more medicinal resources from SM plants, such as the endophytic fungi, need to be investigated.

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