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Chinese Journal of Natural Medicines 2019, **17**(1): 0059–0080
Chinese Journal of Natural Medicines

Danshen: a phytochemical and pharmacological overview

MEI Xiao-Dan [1△], CAO Yan-Feng [1△], CHE Yan-Yun [2], LI Jing [3], SHANG Zhan-Peng [1], ZHAO Wen-Jing [1], QIAO Yan-Jiang [1*], ZHANG Jia-Yu [4*]

[1] *School of Chinese Pharmacy, Beijing University of Chinese Medicine, Beijing 102488, China;*
[2] *College of Pharmaceutical Science, Yunnan University of Traditional Chinese Medicine, Kunming 650500, China;*
[3] *College of Basic Medicine, Jinzhou Medical University, Jinzhou 121001, China;*
[4] *Beijing Research Institute of Chinese Medicine, Beijing University of Chinese Medicine, Beijing 100029, China*

Available online 20 Jan., 2019

[ABSTRACT] Danshen, the dried root or rhizome of *Salvia miltiorrhiza* Bge., is a traditional and folk medicine in Asian countries, especially in China and Japan. In this review, we summarized the recent researches of Danshen in traditional uses and preparations, chemical constituents, pharmacological activities and side effects. A total of 201 compounds from Danshen have been reported, including lipophilic diterpenoids, water-soluble phenolic acids, and other constituents, which have showed various pharmacological activities, such as anti-inflammation, anti-oxidation, anti-tumor, anti-atherogenesis, and anti-diabetes. This article intends to provide novel insight information for further development of Danshen, which could be of great value to its improvement of utilization.

[KEY WORDS] Danshen; Traditional uses; Chemical constituents; Quality control; Pharmacological activities

[CLC Number] R965 **[Document code]** A **[Article ID]** 2095-6975(2019)01-0059-22

Introduction

Medicinal herbal products have been used for healthcare in Asia for over a millennium, and the usage has continued in modern society. Many Chinese medicinal herbal derivatives have been introduced into global market in the past decades. Among the well-known Chinese herbal medicines, Danshen, the dried root or rhizome of *Salvia miltiorrhiza* Bge., plays an important role in maintaining the well-being of Chinese population. It is commonly utilized for improving body function, such as promoting blood circulation and restoring/enhancing immunity. According to the phytochemical studies, active compounds of the processed herb are divided into two groups: diterpenoids and phenolic acids. The chemical constituents possess several therapeutic effects, such as improving microcirculation, anti-atherosclerosis, anti-inflammation, anti-tumor and alleviating diabetes.

[Received on] 17-Oct.-2018
[Research funding] This work was supported by the National Natural Science Foundation of China (No. 81430094) and Beijing Nova Program (No. Z171100001117029).
[*Corresponding author] E-mails: yjqiao@263.Net (QIAO Yan-Jiang); zhangjiayu0615@163.com (ZHANG Jia-Yu)
[△]The first two authors contributed equally to this work.
These authors have no conflict of interest to declare.

Although several literatures on the chemical constituents and biological activities of Danshen have been published, these publications are not comprehensive. More constituents of Danshen have been isolated and identified, and more information on therapeutic uses has been acquired since the publication of literatures on similar topic. Hence，this review is constructed to provide an up-to-date information on Danshen, including its chemical constituents, pharmacology, traditional uses and preparations, modern pharmaceutical products and side effects in clinic. Its quality control is also discussed. The goal is to provide a valuable and comprehensive reference for further development and utilization of Danshen.

Traditional Uses

Danshen, which is characterized by a series of functions, has been used in traditional Chinese medicine for approximately two millennia. The functions of Danshen summarized from clinical observations include promoting blood circulation to remove blood stasis, nourishing blood to tranquillize the mind, cooling blood to disperse carbuncles. The processed herb is used to treat various pains caused by blood stasis, lumps in the chest and abdomen, pyogenic infection and carbuncle of the skin, palpitation and insomnia. Danshen was originally recorded in Shennong Bencao Jing (the first Chinese Materia Medica in China during the Eastern Han Dynasty, 25 AD−220 AD). In

additional to aforementioned functions, it was used for external applications as well. Mingyi Bielu (Han Dynasty, 219 AD) has also stated that the herb could treat stiffness along the spinal column and feet numbness. Wupu Bencao (Wei and Jin Dynasties, 420 AD−589 AD) has recorded this herb for the treatment of pain in the chest and abdomen. Moreover, it has also described the medical plant in detail, including habitats, shape, eco-environment, harvest, storage and functions. Furthermore, a very clear and detailed record of the plant morphology and medicinal characters was kept in Shu Bencao (Five Dynasties and Ten States periods, 935 AD−960 AD). In addition, its functions, meridian attribution and many other aspects were documented in a comprehensive and concrete record in Bencao Gangmu (Ming Dynasty, 1578 AD). At present, the functions of Danshen, activating blood circulation to remove blood stasis, promoting menstrual discharge to relieve menalgia, clearing heart heat to relieve restlessness and cooling blood to disperse carbuncles, have been stated in official record, the *Chinese Pharmacopoeia* (2015).

In the course of Sino-foreign cultural exchanges, the medicinal uses of Danshen spread abroad, thereafter has been duly recorded locally. YI Xin-Fang (Japan, 982 AD) and Dongyi Baojian (Korea, 1611AD) included accounts on Danshen. Nowadays, products containing Danshen are sold commercially for promoting circulation and alleviating blood stasis in Japan [1]. Similar products are also available in natural health retailers in American and European countries [1].

As it is well-known, Danshen is one of the oldest and most frequently used herbal medicines in traditional preparations, which are mainly formulated as a decoction. For instance, Danshen Decoction could be used for treating chill and fever of children, Haitongpi Decoction was used to treat wind-dampness, while Qingying Decoction was indicated for the treatment of acute infectious febrile diseases. Nowadays, the preparations of Danshen have been widely used in clinic for various diseases in China. For example, Fufang Danshen tablet is used to treat chest pain caused by angina pectoris, Guanxin Danshen capsule and Fufang Danshen Dripping pill have therapeutic effects on treating chest impediment syndrome due to qi-stagnation and blood-stasis. The main traditional and modern uses of Danshen in China are listed in Table 1.

Table 1 The main traditional and modern uses of Danshen in China

Preparation Name	Compositions	Clinic uses	References
Danshen Mogao	*Salvia miltiorrhiza* Bge., *Omphalia lapidescens* Schroet.	Treating epilepsy induced by terror and fever	*Qian Jin Fang* (Tang Dynasty, AD 652)
Danshen Pill	*Salvia miltiorrhiza* Bge., *Eucommia ulmoides* Oliv., *Achyranthes bidentata* Bl., *Dipsacus asper* Wall. ex Henry, *Cinnamomum cassia* Presl, *Zingiber officinale* Rosc.	Treating pain in the loins	*Sheng Ji Zong Lu* (Song Dynasty, AD 1117)
Danshen Decoction	*Salvia miltiorrhiza* Bge., *Sophora flavescens* Ait., *Cynanchum atratum* Bge., *Cinnamomum cassia* Presl, *Acorus tatarinowii* Schott, *Omphalia lapidescens* Schroet., *Cnidium monnieri* (L.) Cuss.	Treating chill and fever of children	*Pu Ji Fang* (Ming Dynasty, AD 1390)
Danshen San	*Salvia miltiorrhiza* Bge.	Treating menstrual disorders and threatened abortion	*Fu Ren Liang Fang* (the Southern Song Dynasty, AD 1237)
Danshen Yinzi	*Salvia miltiorrhiza* Bge., *Angelica sinensis* (Oliv.) Diels, *Atractylodes macrocephala* Koidz., *Asparagus cochinchinensis* (Lour.) Merr., *Ophiopogon japonicus* (L.f) Ker-Gawl., *Fritillaria cirrhosa* D.Don, *Citrus reticulata* Blanco, *Anemarrhena asphodeloides* Bge., *Glycyrrhiza uralensis* Fisch., *Acorus tatarinowii* Schott, Coptis chinensis Franch., *Schisandra chinensis* (Turcz.) Baill.	Treating amnesia	*Gu Jin Yi Tong* (Ming Dynasty, AD 1556)
Haitongpi Decoction	*Erythrina variegata* L. var. *orientalis* (L.) Merr., *Salvia miltiorrhiza* Bge., *Stephania tetrandra* S. Moore, *Glycyrrhiza uralensis* Fisch., *Ephedra sinica* Stapf, *Asparagus cochinchinensis* (Lour.) Merr., *Aconitum carmichaelii* Debx., *Cinnamomum cassia* Presl, *Zingiber officinale* Rose.	Treating wind-dampness	*Sheng Ji Zong Lu* (Song Dynasty, AD 1117)
Tianwang Buxin Dan	*Rehmannia glutinosa* Libosch., *Panax ginseng* C. A. Mey., *Salvia miltiorrhiza* Bge., *Scrophularia ningpoensis* Hemsl., *Poria cocos* (Schw.)Wolf, *Polygala tenuifolia* Willd., *Platycodon grandiflorum* (Jacq.) A.DC., *Schisandra chinensis* (Turcz.) Baill., *Angelica sinensis* (Oliv.) Diels, *Asparagus cochinchinensis* (Lour.) Merr., *Ophiopogon japonicus* (L.f) Ker-Gawl., *Platycladus orientalis* (L.) Franco, *Ziziphus jujuba* Mill. var. *spinosa* (Bunge) Hu ex H. F. Chou	Tonifying the blood and nourishing the heart to cause tranquilization	*She Sheng Mi Pou* (Ming Dynasty, AD 1638)
Tiaojing Pill	*Salvia miltiorrhiza* Bge.	Treating irregular menstruation, dysmenorrhea, metrorrhagia and leukorrhagia due to stagnation of qi and blood	*Ji Yan Liang Fang* (Qing Dynasty, AD 1841)

Continued

Preparation Name	Compositions	Clinic uses	References
Danshen Guipi Decoction	*Salvia miltiorrhiza* Bge., *Dipsacus asper* Wall. Ex Henry, *Paeonia lactiflora* Pall., *Polygala tenuifolia* Willd., *Dioscorea opposita* Thunb., *Fritillaria cirrhosa* D.Don, *Ophiopogon japonicus* (L f) Ker-Gawl., *Poria cocos* (Schw.) Wolf, *Citrus reticulata* Blanco, *Nelumbo nucifera* Gaertn., *Cyathula officinalis* Kuan, *Rehmannia glutinosa* Libosch., *Angelica sinensis* (Oliv.) Diels, *Leonurus japonicus* Houtt., *Nelumbo nucifera* Gaertn.	Treating spitting blood	*Chuai Mo You De Ji* (Qing Dynasty, AD 1888)
Qingying Decoction	*Rehmannia glutinosa* Libosch., *Cornu Rhinoceri* Asiatici, *Salvia miltiorrhiza* Bge., *Scrophularia ningpoensis* Hemsl., *Ophiopogon japonicus* (L.f) Ker-Gawl., *Lonicera japonica* Thunb., *Forsythia suspensa* (Thunb.) Vahl, *Coptis chinensis* Franch., *Phyllostachys nigra* (Lodd.) Munro var. *henanis* (Mitf.) Stapf ex Rendle	Treating acute infectious febrile diseases	*Wen Bing Tiao Bian* (Qing Dynasty, AD 1798)
Qingliang Huagai Yin	*Salvia miltiorrhiza* Bge., *Anemarrhena asphodeloides* Bge., *Commiphora myrrha* Engl., *Glycyrrhiza uralensis* Fisch.	Treating lung abscess	*Yi Xue Zhong Zhong Can Xi Lu* (AD 1918−1934)
Huoluo Xiaoling Dan	*Salvia miltiorrhiza* Bge., *Angelica sinensis* (Oliv.) Diels, *Boswellia carterii* Birdw., *Commiphora myrrha* Engl.	Treating pain in the chest, abdomen, leg, and arm	*Yi Xue Zhong Zhong Can Xi Lu* (AD 1918−1934)
Erdan Pill	*Salvia miltiorrhiza* Bge., cinnabar, *Polygala tenuifolia* Willd., *Poria cocos* (Schw.) Wolf, *Panax ginseng* C. A. Mey., *Acorus tatarinowii* Schott, *Rehmannia glutinosa* Libosch., *Asparagus cochinchinensis* (Lour.) Merr., *Ophiopogon japonicus* (L.f) Ker-Gawl., *Glycyrrhiza uralensis* Fisch.	Treating amnesia	*Bao Ming Ji* (Jin Dynasty, AD 1188)
Qingxin Pill	*Rehmannia glutinosa* Libosch., *Salvia miltiorrhiza* Bge., *Phellodendron chinense* Schneid., *Ostrea gigas* Thunberg, *Dioscorea opposita* Thunb., *Ziziphus jujuba* Mill. var. *spinosa* (Bunge) Hu ex H. F. Chou, *Poria cocos* (Schw.) Wolf, *Ophiopogon japonicus* (L.f) Ker-Gawl., *Schisandra chinensis* (Turcz.) Baill., *Plantago asiatica* L., *Polygala tenuifolia* Willd.	Treating seminal emission	*Yi Xue Xin Wu* (Qing Dynasty, AD 1732)
Danshen Tablet	*Salvia miltiorrhiza* Bge.	Treating angina pectoris and irritability due to coronary heart disease	*Chinese Pharmacopoeia*
Fufang Danshen Tablet	*Salvia miltiorrhiza* Bge., *Panax notoginseng* (Burk.) F. H. Chen, *Cinnamomum camphora* (L.) Presl	Treating chest distress and angina pectoris	*Chinese Pharmacopoeia*
Guanxin Danshen Tablet	*Salvia miltiorrhiza* Bge., *Panax notoginseng* (Burk.) F. H. Chen, *Dalbergia odorifera* T. Chen	Treating chest distress, chest impediment syndrome, palpitation and shortness of breath due to qi stagnation, blood-stasis and coronary heart disease	*Chinese Pharmacopoeia*
Danqi Tablet	*Salvia miltiorrhiza* Bge., *Panax notoginseng* (Burk.) F. H. Chen	Treating impediment and pain of the heart and chest, vertigo, headache and dysmenorrhea due to blood-stasis and qi-stagnation	*Chinese Pharmacopoeia*
Danyi Tablet	*Salvia miltiorrhiza* Bge., *Leonurus japonicus* Houtt., *Verbena officinalis* L., *Achyranthes bidentata* Bl., *Phellodendron chinense* Schneid., *Pulsatilla chinensis* (Bge.) Regel, *Vaccaria segetalis* (Neck.) Garcke	Treating stagnation of blood stasis and downward flow of damp-heat	*Chinese Pharmacopoeia*
Danxi Granule	*Salvia miltiorrhiza* Bge., *Achyranthes bidentata* Bl., *Gastrodia elata* Bl., *Paeonia suffruticosa* Andr., *Paeonia lactiflora* Pall., *Ligusticum chuanxiong* Hort., *Rehmannia glutinosa* Libosch., *Epimedium brevicornu* Maxim., *Taxillus chinensis* (DC.) Danser, *Gardenia jasminoides* Ellis, *Cassia obtusifolia* L., *Cannabis sativa* L.	Treating obstruction of collaterals by blood stasis and deficiency of the kidney due to apoplexy	*Chinese Pharmacopoeia*
Danxiang Qingzhi Granule	*Salvia miltiorrhiza* Bge., *Ligusticum chuanxiong* Hort., *Prunus persica* (L.) Batsch, D*albergia odorifera* T. Chen, *Sparganium stoloniferum* Buch.-Ham., *Curcuma phaeocaulis* Val., *Citrus aurantium* L., *Rheum palmatum* L.	Treating qi-stagnation and blood-stasis syndrome due to hyperlipidemia	*Chinese Pharmacopoeia*
Fufang Danshen Capsule	*Salvia miltiorrhiza* Bge., *Panax notoginseng* (Burk.) F. H. Chen, Cinnamomum camphora (L.) Presl	Treating chest impediment syndrome due to qi-stagnation and blood-stasis	*Chinese Pharmacopoeia*

Continued

Preparation Name	Compositions	Clinic uses	References
Guanxin Danshen Capsule	*Salvia miltiorrhiza* Bge., *Panax notoginseng* (Burk.) F. H. Chen, *Dalbergia odorifera* T. Chen	Treating chest impediment syndrome due to qi-stagnation and blood-stasis	*Chinese Pharmacopoeia*
Danhong Huayu Oral Liquid	*Salvia miltiorrhiza* Bge., *Angelica sinensis* (Oliv.) Diels, *Ligusticum chuanxiong* Hort., *Prunus persica* (L.) Batsch, *Carthamus tinctorius* L., *Bupleurum chinense* DC., *Citrus aurantium* L.	Treating obstructive absorption period of central vein of retina attributed to qi-stagnation and blood-stasis syndrome	*Chinese Pharmacopoeia*
Fufang Danshen Dripping Pill	*Salvia miltiorrhiza* Bge., *Panax notoginseng* (Burk.) F. H. Chen, Cinnamomum camphora (L.) Presl	Treating chest impediment syndrome due to qi-stagnation and blood-stasis	*Chinese Pharmacopoeia*
Fufang Danshen Aerosol	*Salvia miltiorrhiza* Bge., *Panax notoginseng* (Burk.) F. H. Chen, Cinnamomum camphora (L.) Presl	Treating chest impediment syndrome due to qi-stagnation and blood-stasis	*Chinese Pharmacopoeia*

Chemical Constituents

A total of 201 compounds of Danshen have been summarized so far. These chemical constituents are divided into three groups based upon their structures: lipophilic diterpenoids, water-soluble phenolic acids and others. The structures of diterpenoids and phenolic acids are shown in Figs. 1−4, and the names of all the constituents are listed in Tables 2−5.

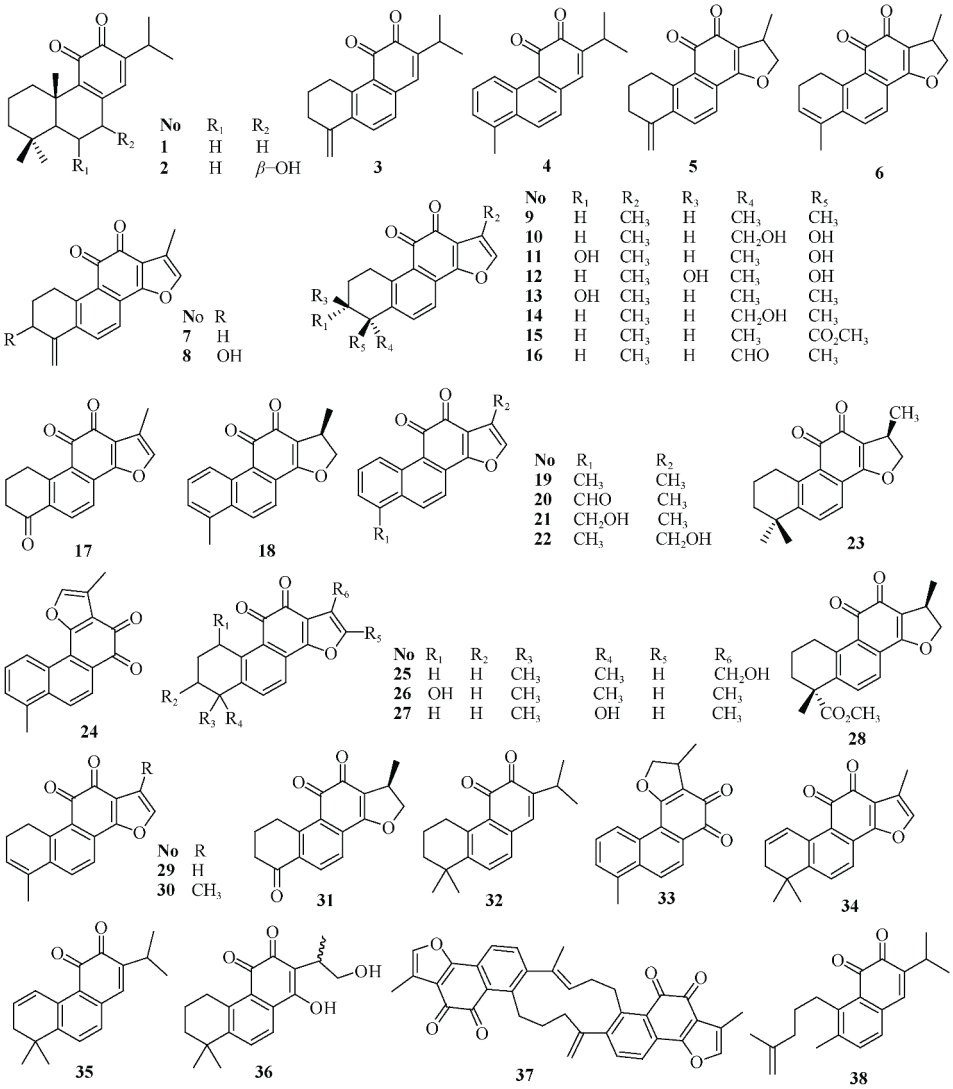

Fig. 1 Structures of tanshinones with a common ortho-naphthoquinone chromophore

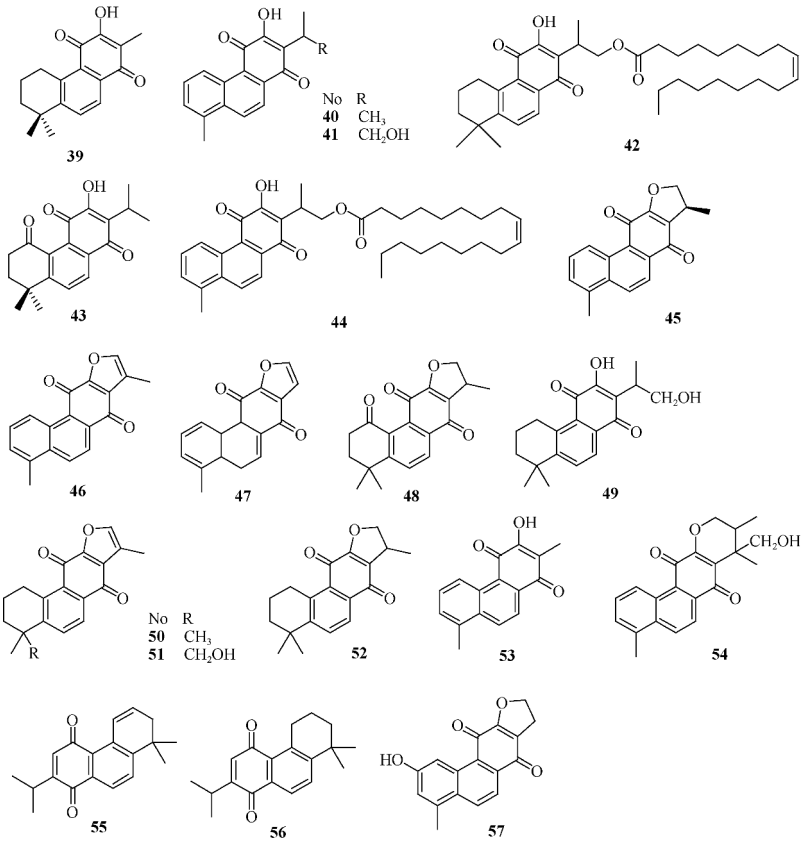

Fig. 2 Structures of abietane diterpenes with a common para-naphthoquinone chromophore

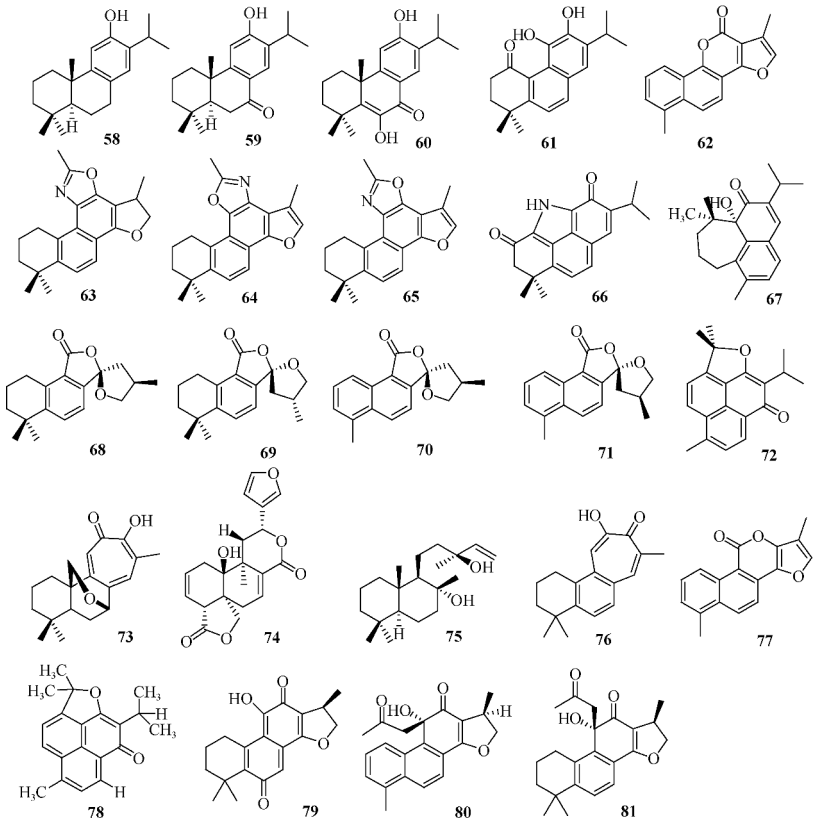

Fig. 3 Structures of the other components of diterpenoids

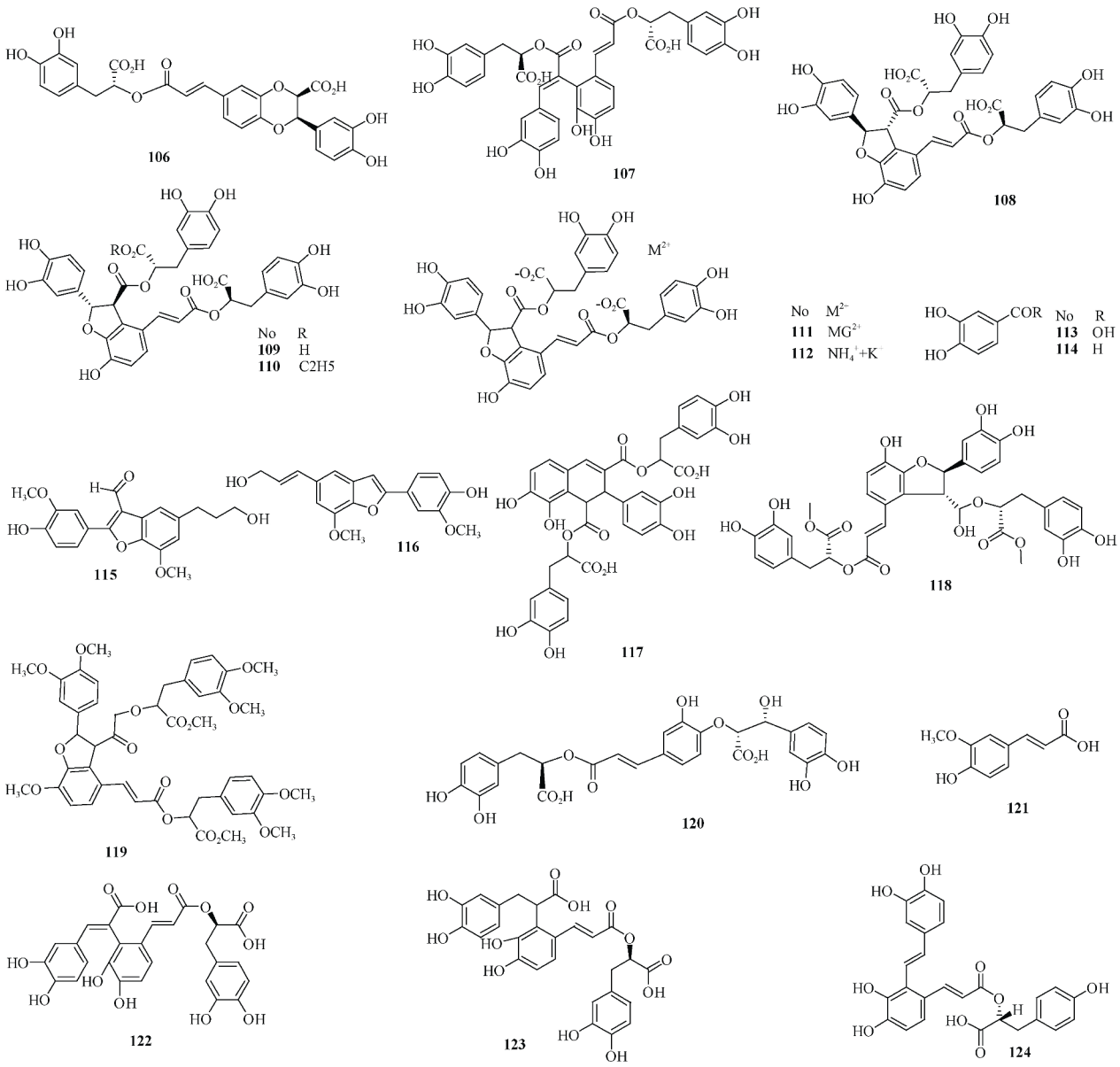

Fig. 4 Structures of phenolic acids

Strong evidence has proved that diterpenoids and phenolic acids exhibit numerous pharmacological activities, we thereby deduce that they are major representative constituents in Danshen.

Diterpenoids

Diterpenoids share a core structure of 20 carbons arranged in rings. These compounds are one group of the major bioactive components in Danshen. This group of compounds possesses a variety of pharmacological activities, such as antibacterial, anti-oxidative, anti-inflammatory, and antineoplastic [2]. At present, at least 81 diterpenoids from Danshen have been reported. According to the structural characteristics, diterpenoids in Danshen are further classified into two sub-sets. One sub-set is tanshinones which are the most abundant diterpenoids, and they contain a common ortho-naphthoquinone chromophore. The other sub-set contains royleanones, which are abietane diterpenes shared para-naphthoquinone chromophore. Moreover, diterpene chinone compounds of the two sub-sets are found exclusively in the *Salvia* genus [3]. Among all the diterpenoids, tanshinone IIA is the major constituent of the processed herb, and many studies have mainly focused on its pharmacological activities. The biosyntheses of terpenes and terpenoids were studied. It has reported that they could be synthesized through mevalonate (MVA) and methylerythritol phosphate (MEP) pathways [4-6]. The main biosynthetic pathway of tanshinones is MEP pathway, while *SmHMGR1* and *SmHMGR2* from MVA pathway are also beneficial for tanshinone biosyntheses [7-9].

Phenolic acids

The water-soluble phenolic acids have been accounted for the therapeutic effects of Danshen. Since 1980s, a lot of Chinese and Japanese researchers have paid attention to these

Table 2 Diterpenoids isolated from Danshen

No.	Name	References	No.	Name	References
1	11, 12, -dioxoabieta-8, 13-dien (= miltirone)	[188]	42	oleoyl neocryptotanshinone	[189]
2	7*β*-hydroxy-8, 13-abietadiene-11, 12-dione	[2]	43	miltionone I	[190]
3	4-methylenemiltirone	[2]	44	oleoyl danshenxinkun A	[189]
4	2-isopropyl-8-methylphenanthrene-3, 4-dione	[191]	45	dihydroisotanshinone I	[192]
5	methylenedihydrotanshinquinone	[2]	46	isotanshinone I	[193]
6	1, 2, 5, 6-tetrahydrotanshinone I	[2]	47	isototanshinone	[194]
7	methylenetanshiquinone	[195]	48	1-ketoisocryptotanshinone	[196]
8	3-hydroxymethylenetanshinquinone	[197]	49	neocryptotanshinone	[198]
9	tanshinone IIA	[192]	50	isotanshinone IIA	[199]
10	tanshindiol A	[200]	51	isotanshinone IIB	[198]
11	tanshindiol B	[200]	52	isocryptotanshione II	[199]
12	tanshindiol C	[200]	53	danshexinkun C	[201]
13	3*α*-hydroxytanshinone IIA	[200]	54	danshexinkun D	[202]
14	tanshinone IIB	[203]	55	sibiriquinone A	[204]
15	methyl tanshinonate	[205]	56	sibiriquinone B	[204]
16	tanshinaldehyde	[205]	57	trijuganone A	[206]
17	nortanshinone	[200]	58	ferruginol	[192]
18	15, 16-dihydrotanshinone I	[192]	59	sugiol	[192]
19	tanshinone I	[192]	60	6, 12-dihydroxyabieta-5, 8, 11, 13-tetraen-7-one (= montbretol)	[207]
20	formyltanshinone	[2]	61	11, 12-dihydroxy-20-nor-5(10), 6, 8, 11, 13-abietapen-taen-1-one (= arucadiol)	[2]
21	tanshinol A	[208]	62	neotanshinlactone	[209]
22	przewaquinone B	[210]	63	salvianan	[211]
23	cryptotanshinone	[192]	64	neosalvianen	[211]
24	isotanshinone II	[193]	65	salvianen	[211]
25	przewaquinone A	[210]	66	salviadione	[211]
26	hydroxytanshinone IIA	[205]	67	microstegiol	[212]
27	przewaquinone C	[205]	68	epi-cryptoacetalide	[213]
28	methyl dihydronortanshinonate	[214]	69	cryptoacetalide	[213]
29	1, 2-dihydortanshinquinone	[215]	70	epi-danshenspiroketallactone	[200]
30	1, 2-dihydrotanshinquinone	[190]	71	danshenspiroketallactone	[192]
31	dihydronortanshinone	[216]	72	9-isopropyl-2, 2, 5-trimethyl-8H-phenaleno[1, 9bc]furan-8-one (= salvilenone)	[217]
32	1, 2-didehydromiltirone	[2]	73	miltipolone	[218]
33	dihydroisotanshinone II	[194]	74	salviacoccin	[212]
34	1-dehydrotanshinone ⅡA	[207]	75	sclareol	[212]
35	1-dehydromiltirone	[2]	76	salviolone	[218]
36	tanshinone Ⅴ	[218]	77	tanshinlactone	[2]
37	neo-przewaquinone A	[219]	78	salvilenone	[217]
38	saprorthoquinone	[220]	79	miltionone II	[190]
39	neocryptotanshinone II	[207]	80	danshenol A	[200]
40	danshenxinkun B	[192]	81	danshenol B	[208]
41	(−)-danshexinkun A	[221]			

1−38 Tanshinones with a common ortho-naphthoquinone chromophore; 39−57 Abietane diterpenes with a common para-naphthoquinone chromophore; 58−81The other components of diterpenoids.

Table 3 Phenolic acids isolated from Danshen

No.	Name	References	No.	Name	References
82	caffeic acid	[16]	104	salvianolic acid N	[212]
83	isoferulic acid	[11]	105	salvianolic acid I	[222]
84	danshensu	[223]	106	salvianolic acid J	[224]
85	3-(3, 4-dihydroxyphenyl)-(2*R*)-lactamide	[225]	107	salvianolic acid E	[11]
86	salvianolic acid F	[226]	108	salvianolic acid B	[10]
87	salvianic acid C	[16]	109	lithospermic acid B	[11]
88	rosmarinic acid	[227]	110	ethyl lithospermate B	[11]
89	methyl rosmarinate	[16]	111	magnesium lithospermate B	[228]
90	salviaflaside	[229]	112	ammonium-potassium lithospermate B	[230]
91	salvianolic acid D	[11]	113	protocatechuic acid	[16]

Continued

No.	Name	References	No.	Name	References
92	prolithospermic acid	[231]	114	protocatechuic aldehyde	[16]
93	salvianolic acid G	[232]	115	2-(3-methoxy-4-hydroxyphenyl)-5-(3-hydroxypropyl)-7-methoxybenzofuran-3-carbaldehyde	[233]
94	salvinal	[234]	116	ailanthoidol	[233]
95	1-hydroxy-pinoresinol-1-*O*-*β*-D-glucoside	[234]	117	salvianolic acid L	[235]
96	lithospermic acid	[236]	118	dimethyl salvianolic acid B	[10]49
97	litherospermic acid monomethyl ester	[194]	119	dimethyl heptamethylsalvianolate B	[10]
98	litherospermic acid dimethyl ester	[16]	120	salvianolic acid K	[237]
99	ethyl lithospermate	[11]	121	ferulic acid	[11]
100	salvianolic acid C	[10]	122	salvianolic acid T	[238]
101	methyl salvianolic acid C	[239]	123	salvianolic acid U	[238]
102	dimethyl lithospermate	[236]	124	salvianolic acid A	[240]
103	9″-methyl lithospermate	[236]			

Table 4 Essential Oils isolated from Danshen

No.	Name	References	No.	Name	References
125	borneol acetate	[241]	142	hexadecanoic acid	[241]
126	copaene	[241]	143	linoleic acid	[242]
127	bourbonene	[241]	144	tricosane	[241]
128	iso-elemene	[241]	145	pentacosane	[212]
129	iso-*β*-caryophyllene	[241]	146	heptacosane	[241]
130	isocaryophyllene	[241]	147	nonacosane	[241]
131	*β*-caryophyllene	[241]	148	germacrene B	[212]
132	*β*-cubebene	[241]	149	spathulenol	[212]
133	*α*-caryophyllene	[241]	150	terpinene-4-ol	[212]
134	cadinadiene	[241]	151	*α*-Pinene	[212]
135	bicyclogermacrene	[241]	152	*α*-cadinol	[212]
136	*α*-farnesene	[241]	153	*α*-thujene	[212]
137	*β*-caryophyllene oxide	[241]	154	*β*-cadinol	[212]
138	ledol	[241]	155	*β*-chamigrene	[212]
139	*α*-caryophyllene oxide	[241]	156	*β*-phellandrene	[212]
140	tetradecanoic acid	[241]	157	*α*-elemene	[212]
141	nor-pristan-2-ol	[241]			

Table 5 The other components isolated from Danshen

No.	Name	References	No.	Name	References
158	uvaol	[212]	180	isoleucine	[243]
159	*α*-amyrin	[212]	181	phenylalanine	[243]
160	*β*-sitosterol-*β*-D-glucoside	[212]	182	valine	[243]
161	luteolin	[212]	183	threonine	[243]
162	baicalin	[212]	184	arginine	[243]
163	daucosterol	[244]	185	serine	[212]
164	*β*-sitosterol	[229]	186	tyrosine	[212]
165	shanzhiside methyl ester	[212]	187	hydrolysis amino acid	[243]
166	manool	[212]	188	calcium	[244]
167	3, 4-dihydroxyphenyl ethanol ketone	[212]	189	cobalt	[245]
168	hexadecane	[212]	190	copper	[245]
169	octadecanol	[212]	191	magnesium	[244]
170	palmitic acid	[242]	192	iron	[244]
171	fructose	[246]	193	nickel	[244]
172	saccharose	[246]	194	zinc	[244]
173	rafitrinose	[246]	195	barium	[244]
174	stachyose	[246]	196	aluminum	[244]
175	vitamin E	[247]	197	stannum	[244]
176	glutamic acid	[243]	198	cadmium	[245]
177	alanine	[243]	199	lead	[245]
178	aspartic acid	[243]	200	manganese	[245]
179	histidine	[243]	201	selenium	[244]

constituents, and more than 20 phenolic acids have been isolated [10-15]. The phenolic acids exhibit broad biological activities, such as anti-oxidative, anti-coagulation, and anti-inflammatory [16-18]. The phenolic acids in Danshen have been classified into single phenolic acids and polyphenolic acids. The single phenolic acids mainly contain a core skeleton of phenylpropanoid (C_6-C_3). This group includes danshensu, caffeic acid, protocatechuic aldehyde, protocatechuic acid and many others. Danshensu, *β*-(3, 4-dihydroxyphenyl) lactic acid, was the first compound that have been discovered among phenolic acids group. The polyphenolic acids are mainly considered as conjugate of Danshensu and derivatives or dimer of caffeic acid. Among which, salvianolic acid A−E, lithospermic acid and rosmarinic acid are depsides. The biosyntheses of phenolic acids in Danshen are involved in phenylpropanoid and tyrosine-derived pathways. It has reported that tyrosine-derived pathway might be the rate-limiting step in the biosynthetic pathways of phenolic acid, because some enzymes of tyrosine-derived pathway were related to the biosyntheses of rosmarinic and salvianolic acid B [19-20].

The other components

The other components in Danshen include essential oils, triterpenoids, flavone, amino acids, metallic elements, and many others. Among these, 33 essential oils found in Danshen have been concluded in this study, such as borneol acetate, copaene, bourbonene, iso-elemene, iso-*β*-caryophyllene, isocaryophyllene, *β*-caryophyllene, and *α*-caryophyllene. Large number of essential oil constituents have been isolated and identified from the flower of Danshen. In addition, Danshen contains several amino acids, including glutamic acid, alanine, aspartic acid, phenylalanine, serine and many others.

Quality Control

The application of analytical methods for the quality evaluation

As is known to all, the quality of Danshen is closely related to the concentrations of their active ingredients. Generally, the water-soluble salvianolic acids and liposoluble tanshinones are considered as the major bioactive components, and hence quality markers in Danshen. Some studies have been conducted to identify the characteristic components in Danshen, and the main bioactive constituents in Danshen have been determined using the three most commonly used analytical methods, including high performance liquid chromatography combined with diode array detector (HPLC-DAD), ultra-high performance liquid chromatography (UPLC), and UPLC coupled with tandem mass spectrometry (UPLC-MS/MS), respectively [21-24]. HPLC-DAD method has been established for respective or simultaneous determination of liposoluble or water-soluble characteristic constituents in Danshen. While UPLC and UPLC-MS/MS methods, which have been considered to be much more rapid and sensitive methods could be employed for the simultaneous quantification of liposoluble and water-soluble constituents in Danshen. Furthermore, some representative researches have utilized UPLC-MS/MS method for comparison and quantification of active compounds in different batches of Danshen preparations.

The chemical fingerprint analysis

The chemical fingerprint analysis of traditional Chinese medicine was proposed by the State Food and Drug Administration (SFDA) in 2000. It was accepted for the identification of authenticity, differentiation of origin, and evaluation of quality of herbal medicines and related preparations, which based on the holistic chemical profile obtained by various analytical techniques. There are some reports about fingerprint analysis of Danshen to characterize the whole chemical profile with the assays of HPLC-DAD, UPLC-DAD, and HPLC-MS/MS coupled with chemometrics including hierarchical cluster analysis (HCA), principal component analysis (PCA), and partial least squares discriminant analysis (PLS-DA) [25-26]. The HPLC-DAD and UPLC-DAD methods were developed to observe the multiple common peaks in accordance with different compounds in Danshen. The peaks/compounds in the HPLC or UPLC chromatograms were identified by their characteristic fragment ion information in LC-MS/MS analysis. Furthermore, the characteristic markers and the quality of Danshen were analyzed and evaluated with chemometrics method. And the experimental results suggested varied different bioactive components in Danshen were influenced by processing method to a great degree.

The metabolites analysis in vivo of Danshen decoction or its preparations

Preclinical researches on the absorption, distribution, metabolism and excretion (ADME) of components in Danshen decoction and its preparations are of great importance for better understanding of their biological effects and safety. Studies on determination of the phenolic constituents of Danshen in serum after intravenous administration, hypodermic administration and oral administration by LC-MS or by microdialysis coupled with HPLC have been reported [27-31].

It has reported that salvianolic acid B has extremely low systemic bioavailability in rats using high performance liquid chromatography with electrochemical detection (HPLC-ECD) method and mostly excreted rapidly into bile as methylated metabolites [32-33]. Moreover, it has indicated that the total phenolic acids or salvianolic acid B are distributed to rat tissues rapidly and the major distribution organ of the four phenolic acids in rat is kidney after oral administration [31].

Pharmacological Activities

Anti-inflammation

Inflammatory responses induced by cytokines and chemokines can cause many inflammatory vascular diseases, for which anti-inflammation is a very important therapeutic strategy. Some constituents in Danshen have been investigated for its anti-inflammatory activity [34]. Recent studies have indicated that salvianolic acid B and an aqueous ethanol extract from Danshen possessed anti-inflammatory property. They strongly inhibited tumor necrosis factor-*α*-induced (TNF-*α*-induced) nuclear factor-*κ*B (NF-*κ*B) activation in human aortic endothelial cells [35]. Another study has demonstrated

that a novel mechanism for the anti-inflammatory activity of tanshinone IIA may involve down-regulation of vascular cell adhesion molecule-1 and intracellular adhesion molecule-1 through partial blockage of TNF-α-induced NF-*κ*B activation and nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (I*κ*B-α) phosphorylation by the inhibition of I*κ*B kinase-*α* and I*κ*B kinase-*β* pathway in endothelial progenitor cells [36]. Additionally, cryptotanshinone also possessed anti-inflammatory property through various mechanisms, including inhibition of the NF-*κ*B and mitogen-activated protein kinase (MAPK) signaling pathways [37]. Moreover, some constituents isolated from Danshen, although in small quantity, had stronger anti-inflammatory activity than tanshinone IIA, for instance, tanshinone IIB, danshixinkun B, danshenol A, arucadiol, tanshindiol C, salviolone, and sugiol. And it has found that danshenol A (5 μmol·L^{-1}) had the highest inhibition ratio for the secretion of TNF-*α*, interleukin (IL)-1*β*, and interleukin (IL)-8 at 56.3%, 67.6%, and 51.7%, respectively [38]. Anti-inflammation contributes significantly in protection against many pathological conditions. Tanshinone IIA has been therapeutically used for the treatment of various diseases, such as acute lung injury, acute kidney injury, fibrosis, Alzheimer's disease (AD) and atherosclerosis, by alleviating inflammation [39-43]. Additionally, it has found that salvianolic acid B could be a potential candidate for the treatment of vascular inflammatory diseases [44-45].

Anti-oxidative activity

Oxidative stress is an underlying cause for numerous pathological disorders. Antioxidants may have protective effects against these disorders by keeping reactive species in check. Phenolic acids and tanshinones have antioxidative activity, though the activity of the former is much stronger. Salvianolic acids, especially salvianolic acid A and salvianolic acid B, have been found to have cardiovascular protective effect due to their anti-oxidative activity [46]. Additionally, it has demonstrated that tanshinone IIA contributed to the inhibition of myocardial remodeling, myocardial ischemia reperfusion injury, tanshinone IIA-induced neuroprotection from experimental ischemic stroke, and preventing cirrhosis *via* maintaining antioxidant effect [41, 47-49]. Moreover, owing to antioxidative activity, tanshinone I could provide mitochondrial protection against H_2O_2 and protect pyramidal neurons of the gerbil hippocampal CA1 region from ischemic damage induced by transient cerebral ischemia [50-51]. A study has indicated that caffeic acid and its four polymers had the activity of scavenging free radicals. Among which, lithospermic acid B and its Mg^{2+} salt displayed the strongest activity (IC_{50} of 3.87 and 4.69 μmol·L^{-1}, respectively). Lithospermic acid and rosmarinic acid also presented good activity (IC_{50} of 9.63 and 10.37 μmol·L^{-1}, respectively), while caffeic acid inhibited 1, 1-diphenyl-2-picrylhydrazyl radical weaker than its polymers, with the IC_{50} of 12.99 μmol·L^{-1} [52].

Antitumor activity

Cancer is one of the most common and fatal diseases in the world. Danshen plays an important role in the prevention of cancer. In one study, Danshen root extract exerted potential cytotoxicity, which can confer sensitivity to various resistant tumors. One possible mechanism is inducing the intrinsic apoptotic pathway [53]. Moreover, several other studies have recently indicated that tanshinones possessed potent anticancer effect both *in vitro* and *in vivo*. It has shown that they suppressed the growth and proliferation of tumor cells, induced apoptosis, inhibited invasion and metastasis, and suppressed angiogenesis *in vitro* [54]. Tanshinone IIA has been found to possess anti-neoplastic activity in the cancer cell-lines of lung, stomach, esophagus, oral cavity, and many others [55-58]. Additional studies have shown that tanshinone IIA induced apoptosis in human leukemia cell lines through the activation of caspase-3 [59] while tanshinone I also played an important role against various tumor cells, such as lung, stomach, breast, and prostate [60-63]. Cryptotanshinone, a potential anticancer agent, could inhibit the mammalian target of rapamycin complex 1 signaling through activation of adenosine monophosphate-activated protein kinase (AMPK)-uberous sclerosis complex 2 axis in cancer cells [64]. 15, 16-Dihydrotanshinone I could be an efficient therapeutic candidate for osteosarcoma treatment, which is the most common primary malignant bone tumor [65]. Moreover, the antitumor activity of phenolic acids has also been reported, such as salvianolic acid A and salvianolic acid B [66-69]. Salvianolic acid B exerted inhibitory effects on cell proliferation and tumor growth in human glioma U87 cells, which might be related with MAPK 14 p38 activation mediated reactive oxygen species (ROS) generation [70].

Effects on cardiovascular and cerebrovascular

Anti-atherogenesis

Atherosclerosis is one of the common diseases which are the leading cause of death and disability in our societies. One of the functions of Danshen is removing blood stasis, which indicates its therapeutic value on atherosclerosis treatment and prevention. Many studies have shown that tanshinone IIA had the potential for treating atherosclerosis. Several possible mechanisms have been discovered, such as interfering with receptor of advanced glycation end products and NF-*κ*B activation, inhibition of low density lipoprotein oxidation, anti-inflammation, immunomodulation and many others [43, 71-72]. Cryptotanshinone has been demonstrated to display pleiotropic effects for atherosclerosis through inhibiting lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) mediated signaling pathway, decreasing ROS level and inhibiting the NF-*κ*B pathways [73-75]. In apolipoprotein E-deficient (ApoE$^{-/-}$) mice fed with an atherogenic diet, dihydrotanshinone I (10 and 25 mg·kg^{-1}) significantly attenuated atherosclerotic plaque formation through inhibition of LOX-1 mediated by nicotinamide adenine dinucleotide phosphate-oxidase 4 (NOX4)/NF-*κ*B signaling pathways both *in vitro* and *in vivo* [76]. Moreover, water soluble Danshen extracts showed beneficial effects on atheromatous disease through inhibiting multiple pathways associated with vascular smooth muscle cells, endothelial cells, and platelets both *in vitro* and *in vivo* [77].

Anti-thrombosis

Thrombosis is hemostasis in the wrong place [78], and the function of Danshen has summarized its anti-thrombotic effect. Danshen is beneficial for the treatment of deep vein thrombosis by its antioxidative effect on vascular endothelial cells [79]. One study has indicated that Danshen exhibited an anti-thrombotic effect, and has clarified its mechanism to be inhibition of the inflammatory response [80]. Experiments have shown that salvianolic acid A reduced platelet adhesion on collagen surfaces by about 40% with an arterial shear rate of 1000 s^{-1}. Salvianolic acid A could attenuate platelet activation and arterial thrombus formation through inhibiting phosphoinositide 3-kinase (PI3K) [81]. Another study has demonstrated thatprotocatechuic aldehyde possesses the strong anti-thrombotic activity associated with suppressing the platelet aggregation, using an impedance aggregometer [82]. Moreover, rosmarinic acid could inhibit the formation of venous thrombosis and platelet aggregation by 54.8% and 46.4% at a dosage of 100 $mg \cdot kg^{-1}$ [16].

Anti-hypertension

System hypertension is an asymptomatic disorder, which poses a risk of coronary thrombosis, stroke, and renal failure [83]. Danshen has remarkable beneficiary effects on the treatment of hypertension. Experimental studies have indicated that Danshen may be useful for monocrotaline-induced pulmonary hypertension rats at low or high oral dose (4.6 or 14 $g \cdot kg^{-1}$) for 21 days [84]. Additionally, water extract of Danshen exerted anti-hypertensive effect by inhibiting the angiotensin converting enzyme activities in the renin-angiotensin system [85]. It has also demonstrated that optimal compatibility ratio of active ingredients from Danshen, including salvianolic acid A, salvianolic acid B, danshensu and protocatechuic aldehyde, exhibited a crucial anti-hypertensive effect on rats. Its mechanism is inhibiting oxidative stress and the transforming growth factor-beta (TGF-β)/Smad pathway [86]. One study has shown that sodium tanshinone IIA sulfonate had therapeutic value on pulmonary hypertension patients both alone as well as in concert with sildenafil [87]. Endothelial dysfunction could result in hypertension. It has found that salvianolic acid B had anti-hypertensive effect through reversing the impaired endothelial function and inhibiting AT_1 receptor-dependent vascular oxidative stress [88].

Anti-hyperlipidemic

Dyslipidaemia is another risk factor for atheroma and relative cardiovascular diseases and extracts of Danshen demonstrated their effects on lipid regulation in various studies [83]. It has indicated that Danhong injection could adjust lipid metabolic disorders, for example, falling serum lipid levels and suppressing formation of lipid peroxidation products [89]. Moreover, Fufang Danshen Dripping pill could decrease serum lipid levels and protect liver function, which might be associated with ameliorating of anti-oxidation and falling of inflammation [90]. Tanshinone IIA has been found to decrease the lipid deposition in liver. Additionally, it could decrease high density lipoprotein (HDL) middle subfractions levels and increase HDL large subfractions levels, which regulated intake and efflux of cholesterol [91]. It has shown that cryptotanshinone had anti-adipogenic activity through regulating signal transducer and activator of transcription 3 during early adipogenesis [92]. Moreover, salvianolic acid B and paeonol (5, 10, and 15 $mg \cdot kg^{-1}$ BW) could markedly and dose-dependently increase HDL levels [93].

Effects on ischaemic stroke

Thrombosis of a major cerebral artery is a major cause of ischemic brain damage. Danshen and its extracts provide a potential therapeutic approach for ischaemic stroke. It has demonstrated that Danshen dripping pill might be beneficial to treat stroke/transient ischemic attack recurrence *via* anti-inflammation [94]. It has indicated that salvianolic acid B had a potential effect of treating/alleviating brain injury by activating silent information regulator 1 signaling, which was related with ischaemic stroke [95]. Magnesium lithospermate B could also provide neuroprotective effect against ischemic stroke [96]. Additionally, tanshinone IIA has been found to have neuroprotection on experimental ischemic stroke, which may be associated with mechanisms of anti-inflammatory, anti-oxidative, anti-apoptosis, and inhibition of excitatory amino acid toxicity [97]. Tanshinone I and cryptotanshinone also displayed a protective effect against stroke, and the disease status could increase the brain access of cryptotanshinone [51, 98].

Effects on the heart

A recent study has indicated that Danshen plays an important role in therapeutic interventions for patients with coronary heart disease. It may decrease the risk of coronary heart disease with improved biomarkers of patients [99]. It has demonstrated that aspirin in combination with Fufang Danshen Dripping pill is much more effective than aspirin as monotherapy for treating coronary heart [100]. Myocardial ischemia-reperfusion injury (MIRI) is unavoidable during cardioplegic arrest and open-heart surgery. Danshen can protect against MIRI through various mechanisms. For example, tanshinone IIA can protect against MIRI by activating the PI3K/protein kinase B (Akt)/mTOR signaling pathway, reducing oxidative stress, decreasing HMGB1 expression, and suppressing inflammatory response [48, 101-103]. Dihydrotanshinone I possessed cardio-protective effect against MIRI through inhibiting arachidonic acid ω-hydroxylase [104]. Additionaly, Danshensu showed a cardioprotective effect on isolated heart of rats via activation of Akt/extracellular regulated protein kinases (ERK1/2)/nuclear factor erythroid-2-related factor 2 (Nrf2) signaling [105]. Tanshinone IIA can also inhibit myocardial remodeling induced by pressure overload, reduce atrial fibrillation in chronic heart failure and attenuate cardiac dysfunction in endotoxin-induced septic mice [47, 106-107].

Effects on nervous system

Sedative and analgesic activities

Danshen has been widely used for the treatment of neurasthenic insomnia in China. A number of pharmacological studies have been done on the neuroprotection of Danshen. It has demonstrated that miltirone has sedative and muscle re-

laxation activity, and it is showed to be effective in behavioral tests [108]. One study has indicated that the combination of ether extract of Danshen (300 and 600 mg·kg^{-1} body wt.) and the water extract of Suanzaoren (400 and 800 mg·kg^{-1} body wt.) have a significant sedative-hypnotic activity, which can decrease sleep latency and increase sleeping time induced by sodium pentobarbital (55 mg·kg^{-1} body wt.) in mice [109]. Experiments using extracellular microelectrode method and stereotaxic technique of brain on visceral pain discharges on the posterior nucleus of thalamus in cats have shown that Danshen exerted analgesic effect on central nervous system [110]. Evidences have demonstrated that tanshinone IIA relieved spinal nerve ligation-induced neuropathic pain *via* depressing microglial activation and immune response [111]. Moreover, it has found that tanshinone IIA sulfonate has a strong analgesic activity on spinal nerve ligation-induced neuropathic pain by suppressing astrocyterelated c-Jun N-terminal kinase phosphorylation and monocyte chemoattractant protein-1 [112].

Effects on neurodegenerative disorder

AD is a common neurodegenerative disorder that severely affects millions of elderly people and brings a great social burden. Danshen with protective effects on neurons can be used to treat AD. Tanshinone IIA has been identified to be an effective agent for AD therapy, which can suppress the proliferation of astrocytes, up-regulate the expression of Akt, and inhibit the production of NF-κB and caspase-3 in an AD model [113-114]. Moreover, tanshinone IIA can inhibit inducible nitric oxide synthase (iNOS), matrix metalloproteinase-2 production, and nuclear transcription factor kappa transcription and translation in the temporal lobes of AD rat models, thus exerting neuroprotective effects [115]. Cryptotanshinone also showed a promising potential in the treatment or prevention of AD [98, 116-119]. In one study, cryptotanshinone can inhibit human acetylcholinesterase and butyrylcholinesterase with IC_{50} of 4.09 and 6.38 μmol·L^{-1} in AD model [118]. Dihydrotanshinone has been found to have anti-cholinesterase activity, which indicated it is potential for treating AD [119]. Additionaly, phenolic acids were also accounted for the beneficial effects of Danshen in AD treatment, such as salvianolic acid A, salvianolic acid B, and danshensu [120-124]. Salvianolic acid B has been found to inhibit amyloid-β generation *via* regulating β-secretase 1 activity in SH-SY5Y-APPsw cells [123].

Parkinson's disease (PD) is a chronic progressive degenerative disorder of the central nervous system, which has the highest incidence in the elderly, especially people over 50 [125]. In one study, tanshinone I and tanshinone IIA can inhibit the aggregation of α-synuclein both *in vitro* and in a transgenic Caenorhabditis elegans PD model [126]. Another experiment has displayed that tanshinone I can prevent nigrostriatal dopaminergic neurodegeneration in a mouse PD model [127]. Oxidative stress caused by dopamine may play an important role in the PD pathogenesis. Tanshinone I can upregulate nuclear factor erythroid-2-related factor 2 to attenuate 6-hydroxydopamine-induced oxidative stress in cellular and mouse PD model [128]. Tanshinone IIA can also prevent the loss of nigrostriatal dopaminergic neurons *via* the inhibition of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and iNOS in a 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine mouse PD model [129]. Moreover, phenolic acids, especially salvianolic acid A, salvianolic acid B and danshensu, were effective in treating PD associated with oxidative stress [124, 130-131]. It has found that salvianolic acid B can protect dopaminergic neurons by an Nrf2-mediated dual action in PD models [125].

Anti-fibrotic activity

Effects on hepatic fibrosis

Danshen is used to treat hepatocyte injury and hepatic fibrosis, for it can increase the regeneration of hepatocytes and improve hepatic blood circulation. And it has found that Danshen possessed hepatoprotective effects in chronic iron-overloaded mice [132]. Immunohistochemical examinations have indicated that the hot-water extract of Danshen effectively ameliorated hepatic fibrosis induced by biliary obstruction in rats [133]. Danshen extracts can prevent dimethylnitrosamine-induced hepatic fibrosis by downregulating TGF-β1 [134]. A study has demonstrated that tanshinone IIA can suppress fibrosis and reduce liver injury in a rat model of cirrhosis *via* regulating heme oxygenase-1, Akt and phosphorylated-p38 MAPK signaling pathway [41]. Tanshinone IIA can also protect the liver from acetaminophen-induced hepatic injury through activating Nrf2 pathway [135]. Cryptotanshinone, dihydrotanshinone I and protocatechuic aldehyde also had hepatoprotective effect [136-138]. Salvianolic acid A, salvianolic acid B, magnesium lithospermate B and lithospermic acid played an important role in protecting liver [139-142].

Effects on pulmonary fibrosis

In addition to hepatic fibrosis, Danshen and its extracts are effective against fibrotic lung diseases as well. One experimental study has shown that Danshen had therapeutic potential in treating fibrotic lung diseases [143-144]. Another experimental study has demonstrated that tanshinone IIA exerted protective effect against bleomycin-induced pulmonary fibrosis in rats [145]. Salvianolic acid A was responsible for preventing pulmonary fibrosis through inhibiting proliferation, adhesion and migration of fibroblasts, and promoting apoptosis [146]. Additionally, salvianolic acid B possessed dose-dependent inhibitory effect on TGF-β1-induced proliferation and differentiation in treating pulmonary fibrosis [147]. IH764-3, a potent component isolated from Danshen, can also be considered as a potential prophylactic and therapeutic agent for fibrotic lung diseases [148-149].

Protective effects against renal injury

Danshen had protective effects on renal injury induced by myocardial infarction via restoring the renal function and preventing the oxidative stress [150]. The ethanol extracts and water extracts of Danshen had therapeutic values on treating renal injury [151-152]. Tanshinone IIA could protect against folic acid-induce kidney injury by attenuating renal tubular epithelial injury and inhibiting local inflammatory response [40]. It could prevent the progression of chronic kidney disease after acute kidney injury *via* fibrocytes recruitment in a mouse

model [153]. Tanshinone IIA could also prevent transition of acute kidney injury to chronic kidney disease by targeting glycogen synthase kinase 3β [154]. Moreover, tanshinone IIA pretreatment could attenuate ischemia/reperfusion-induced renal injury through the inhibition of myeloperoxidase, macrophage migration inhibitory factor, cleaved caspase-3 and p38 MAPK [155]. It has demonstrated that lithospermic acid B could improve ischemia/reperfusion- induced renal injury in rats at a dosage of 40 mg·kg^{-1}·day^{-1} for 4 days, the mechanism may involve scavenging of reactive oxygen species [156]. Magnesium lithospermate B with therapeutic values on ameliorating the development of age-related renal damage was isolated from the herb, and it promoted restore of renal function through NADPH oxidase-mediated reactive oxygen generation [157]. Additionally, Danshen injection was widely used to ameliorate renal damage induced by iron overload and lead exposure in mice [158-159].

Protective effects against diabetes mellitus

Diabetes mellitus, a major endocrine disorder, is an increasingly common disease in many developed and developing countries. Danshen has been showed to exert therapeutic potential against this disorder. One study has indicated that the total polyphenolic acids fraction of Danshen displayed positive effects on type 2 diabetes mellitus rat model at an oral dose (187 mg·kg^{-1}) for 28 days [160]. Salvianolic acid A could ameliorate diabetic foot problems through protecting diabetic rats from neuropathy and peripheral vascular circulation dysfunction [161]. Salvianolic acid B exhibited antidiabetic activity through many underlying mechanisms, such as attenuation of oxidative stress, prevention of apoptosis, modulation of the AMPK pathway, suppression of endothelial cell apoptosis and stimulation of endothelial nitric oxide synthase phosphorylation [162-164]. Lithospermic acid B has been reported to exert antioxidant and anti-inflammatory effects, which could treat diabetic retinopathy in rats at a dosage of 10 or 20 mg·kg^{-1}·day^{-1} for 52 weeks [165]. It has found that danshensu could produce significant protective effects in diabetes [166-167]. Additionally, pioglitazone, an extract of Danshen dripping pill, played an important role in ameliorating diabetic nephropathy [168]. Moreover, Danshen injection was also widely used to treat type 2 diabetes mellitus [169-171], in which the main active components are salvianolic acid A, salvianolic acid B, danshensu, rosmarinic acid and lithospermate B [172- 173].

Other effects

Two hydrophilic compounds isolated from Danshen, have been discovered to be effective against human immunodeficiency virus type 1 (HIV-1) integrase with no toxic side effects, which made them extremely appealing as a potential of therapeutic drugs for acquired immunodeficiency syndrome [174]. It also has demonstrated that tanshinone II A could inhibit Tat-induced HIV-1 transactivation *via* redox signaling pathway [175]. Besides, Danshen could enhance the gastric mucosal barrier and promote the gastric mucosal cell proliferation along the edge of the ulcer, which played an important role in promoting ulcer healing and preventing recurrence [176]. Salvianolic acid A exerted anti-secretory and antiulcer effects *via* inhibiting pig gastric H^+, K^+-ATPase and pNPPase with IC_{50} of 5.2×10^{-7} mol·L^{-1} and 1.7×10^{-6} mol·L^{-1} [177]. Some active components from Danshen, especially 15, 16-dihydrotanshinone Ⅰ and cryptotanshinone, have been demonstrated to have anti-allergic activity *in vitro* through inhibiting the release of β-hexosaminidase [178-179]. In addition, ethanol extract from Danshen has been found to be responsible for the beneficial effects in the treatment of allergy-related disorders [180]. Danshen has been reported to produce a protective effect against psoriasis [181]. Moreover, cryptotanshinone and dihydrotanshinone I showed antibacterial activity against a broad range of Gram positive bacteria, the mechanism may be related to the generation of superoxide radicals in Bacillus subtilis lysate [182]. Salvianolate displayed potentiating activity of multiple antibacterial agents against methicillin-resistant *Staphylococcus aureus in vitro*, which would be beneficial to combinatory therapy for fighting with this infectious pathogen [183].

Side Effects

Danshen has been successfully used in the treatment of pregnancy-induced hypertension by inhibiting the angiotensin-converting enzyme. However, many researches have demonstrated that the use of angiotensin-converting enzyme inhibitors was closely related to fetal toxicity, even stillbirths, which were caused by the chemical components from Danshen in the second and third trimesters of pregnancy [184]. It has shown that depside salt injection made from Danshen had some adverse drug events, such as headache, facial flushing, dizziness skin itching, thrombocytopenia, and abnormal liver function, which may be caused by rapid infusion rate and others. Long-term toxicity tests on beagles showed the safety dose of depside salt injection of Danshen was lower than 80 mg·kg^{-1}, and a dose at 320 mg·kg^{-1} showed toxicity [185-186]. One study has indicated that high-dose (5.76 g·kg^{-1}·day^{-1}) Danshen injection could result in peripheral vascular toxicities, for instance, the increase of vascular leakage, the rise of serum nitrate and endothelin-1, and the apoptosis of vascular endothelial cells [187]. In addition, another research has evaluated the safety of Danshen and Fufang Danshen injection with 2715 patients from 35 randomized controlled trials. Among these, five trials discovered some minor adverse drug events, such as stomach discomfort, itchy skin and local pain, which were reported to be tolerable [185].

At present, no severe adverse drug event on Danshen have been reported, and Danshen products are widely used on its recommended indications at its clinical dose. In order to conduct healthcare services safely and efficiently, more therapeutic evidence on the safety and efficacy of Danshen and its products should be collected.

Discussions and Conclusions

This review summarized the latest advancements of Danshen in traditional uses, phytochemistry, quality control, pharmacological activities, and side effects. As a Chinese herbal medicine,

Danshen has been used in therapeutic for various syndromes and preventive measures for thousands of years. Nevertheless, we proposed several suggestive points attempted to enhance the beneficial effects of Danshen in healthcare.

A total of reported 201 chemical constituents of Danshen were summarized in the present review, among which 81 were liposoluble compounds, 43 were water-soluble and 77 were catalogued as "other" constituents. The liposoluble constituents, represented by tanshinones, possessed prominent effects, such as anti-inflammation, anti-cancer, and antibacterial [2]. The water-soluble constituents, represented by phenolic acids, exhibited pharmacological activities including anti-oxidative, anti-coagulation, and anti-atherogenesis [16-18, 71]. Danshen, displaying wide-spectrum pharmacological activities, has been used to alleviate hypertension, dyslipidaemia, diabetes, and others.

As a traditional herbal medicine, Danshen has been commonly used in treating chest impediment, irregular menstruation, stroke, and so on. Among these, chest impediment is a syndrome related to cardiovascular diseases, such as atherosclerosis, thrombosis, angina and coronary heart disease. As is well known, Fufang Danshen Dripping pill, used to treat cardiovascular diseases, was the first Chinese patent traditional medicine to pass Phase II trials of the US Food and Drug Administration. Now, with the developments of medicine and clinical study, the clinical application of Danshen has broadened. As a result, it has shown that Danshen exerted protective effects against diabetes mellitus and cancer.

Diabetes is a chronic disease increasing in prevalence throughout the world. The disease, which is difficult to treat, is usually accompanied with many complications. Herbal medicines show outstanding effects in diabetic therapy. Among which, Danshen has been found to possess antidiabetic activity in clinical trials, and it can effectively be used to treating several diabetic complications in humans. Phenolic acids, such as salvianolic acid A, salvianolic acid B, lithospermic acid B, rosmarinic acid and danshensu, displayed statistically valid results in alleviating diabetes. Additionally, the preparations of Danshen, including Fufang Danshen Dripping pill and Danshen injection, have been used in ameliorating diabetes, and have shown promising outcomes.

Cancer is always one of the most common and refractory diseases that threaten people's health and life. New therapeutic strategies are required for the treatment of numerous cancers. As a widely investigated herb worldwide, the highly medicinal properties of Danshen have gotten increasing attention. Various compounds isolated from Danshen, particularly tanshinones, have been found to exert potent anticancer activity *via* promoting apoptotic cell death and cell cycle arrest and many other mechanisms in cancer cells. Moreover, salvianolic acid A and salvianolic acid B have been reported for antitumor activity.

With increasing formulated herbal products containing Danshen and an expanding global market of those remedies, the quality control of Danshen met new challenges. First of all, different resources and harvest time vary the active compounds content in Danshen. And the activity of the ingredients is greatly influenced by processing methods, formulation and manufacture processes. To ensure end-product quality, the quality of the processed herb should be strictly controlled. The summarized components could be used to enrich the chemical fingerprint data of Danshen. This review provided up-to-date information on the active components in Danshen and their corresponding pharmacological activity. Such information can be used to compose and improve the quality control standard on Danshen.

Despite that lipophilic and water-soluble constituents in Danshen have been used for the complex biological activities they displayed, the mechanism of action of those compounds remained unclear and required further inspection. A great deal of work should be carried out in order to thoroughly clarify the relationship between compounds and activities. In addition, scientists still need to improve the systematic phytochemistry researching method through analysis. With the development of modern analytical methods, UPLC-MS/MS has been widely used for detection of various constituents. And with the accumulation of analytical data, scientists will isolate new compounds more easily. It is also important to further research some constituents, which have not been tested biologically. Scientists need to work hard to make products containing Danshen be widely applied to clinical practice, whichwill be advantageous for a holistic assessment of Danshen.

In summary, Danshen, as a folk and traditional herbal medicine, has been widely used in China and other Asian countries. The traditional uses, phytochemical information, pharmacological studies and side effects should be comprehensively understood for its clinical use. Researches on the mechanisms and quality control need to be explored in order to improve its uses in the near future.

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Cite this article as: MEI Xiao-Dan, CAO Yan-Feng, CHE Yan-Yun, LI Jing, SHANG Zhan-Peng, ZHAO Wen-Jing, QIAO Yan-Jiang, ZHANG Jia-Yu. Danshen: a phytochemical and pharmacological overview [J]. *Chin J Nat Med*, 2018, **17**(1): 59-80.