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# Cistanches Herba: an overview of its chemistry, pharmacology, and pharmacokinetics property.

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**Chemical compounds studied in this article:**

Echinacoside (PubChem CID: 5281771); Acteoside (PubChem CID: 5281800); Isoacteoside (PubChem CID: 6476333); Tubuloside A (PubChem CID: 21637830); Cistanoside D (PubChem CID: 5315930); Salsosides E (PubChem CID: 102403918)

*Ethnopharmacological relevance*: Cistanches Herba is an *Orobanchaceae* parasitic plant. As a commonly used Traditional Chinese Medicine (TCM), its traditional functions include treating kidney deficiency, impotence, female infertility and senile constipation. Chemical analysis of Cistanches Herba revealed that phenylethanoid glycosides, iridoids, lignans, oligosaccharides, and polysaccharides were the main constituents. Pharmacological studies demonstrated that Cistanches Herba exhibited neuroprotective, immunomodulatory, hormonal balancing, anti-fatigue, anti-inflammatory, hepatoprotection, anti-oxidative, anti-bacterial, anti-viral, and anti-tumor effects, etc. The aim of this review is to provide updated, comprehensive and categorized information on

the phytochemistry, pharmacological research and pharmacokinetics studies of the major constituents of Cistanches Herba.

*Materials and methods:* The literature search was conducted by systematic searching multiple electronic databases including SciFinder, ISI Web of Science, PubMed, Google Scholar and CNKI. Information was also collected from journals, local magazines, books, monographs.

*Results:* To date, more than 100 compounds have been isolated from this genus, include phenylethanoid glycosides, carbohydrates, lignans, iridoids, etc. The crude extracts and isolated compounds have exhibited a wide range of *in vitro* and *in vivo* pharmacologic effects, such as neuroprotective, immunomodulatory, anti-inflammatory, hepatoprotection, anti-oxidative, anti-bacterial, and anti-tumor effects. The phenylethanoid glycosides, echinacoside and acteoside have attracted the most attention for their significantly neuropharmacology effects. Pharmacokinetic studies of echinacoside and acteoside also have also been summarized.

*Conclusion:* Phenylethanoid glycosides have demonstrated wide pharmacological actions and have great clinical value if challenges such as poor bioavailability, fast and extensive metabolism are addressed. Apart from phenylethanoid glycosides, other constituents of Cistanches Herba, their pharmacological activities and underlying mechanisms are also need to be studied further.

*Keywords:* Cistanches Herba; Phytoconstituents; Pharmacology; Echinacoside; Acteoside; Pharmacokinetics

## 1. Introduction

Cistanches Herba (Roucongrong in Chinese), is an *Orobanchaceae* parasitic plant. The genus *Cistanche* contains 27 species in the world (www.theplantlist.org), distribution mainly in arid and semi-arid habitats across Eurasia and North Africa, such as China, Iran, India, Mongolia (Piwowarczyk et al., 2016). It has been used for centuries in TCM as a yang-tonic herb. Eight species and one variation of Cistanches Herba have been recorded in China and only *Cistanche deserticola* Y. C. Ma and *Cistanche tubulosa* (Schenk) Wight are recorded in Chinese Pharmacopeia. Modern pharmacological studies have shown that

Cistanches Herba have various activities such as anti-neurodegenerative disease (Wu et al., 2014a), immunoregulatory (Dong et al., 2007), anti-inflammation (Nan et al., 2013), hepatoprotective (You et al., 2016). The broad spectrum of biological activities reported in this genus has been attributed to the complex and varied phytochemical composition. This contribution reviews the information on the traditional use, chemical composition, and pharmacology properties of the extracts. The pharmacokinetics of echinacoside and acteoside were also included.

Previous reviews on Cistanches Herba have focused on extraction, isolation and chemical analysis of constituents, neuropharmacological effects and have little information about pharmacokinetic studies (Li et al., 2016c; Gu et al., 2016; Jiang and Tu, 2009). Being aware of all this previous reviewing work, we have aimed to update the available information about the traditional uses, lists all phytochemical constituents and pharmacological activities (from 1950s to the beginning of 2017), especially pharmacokinetic studies of echinacoside and acteoside and clinical applications of Cistanches Herba to provide references for the further research and application of this genus.

## 2 Ethnobotany

### 2.1 Distribution

Cistanches Herba grows on desert and sand dune，the primary areas of cultivation of Cistanches Herba are the Mediterranean region, Asia and Africa (Shahi Shavvon and Saeidi Mehrvarz., 2010; Piwowarczyk et al., 2016). In China, eight species and one variation of *Cistanches* have been recorded, including *C. deserticola* Y. C. Ma, *C. tubulosa* (Schrenk) Wight, *C. salsa* (C.A. Mey) G. Beck, *C. sinensis* G. Beck, *C. lanzhouensis* Z. Y. Zhang, *C. ambigua* (Bge.) G. Beck, *C. fissa* (C. A. Mey) G. Beck, *C. ningxiaensis* D. Z. Ma et A. Duan and *salsa var. albiflora* P. F. Tu et Z. C. Lou, which mainly distributed in Inner Mongolia, Ningxia, Gansu, Qinghai and Xinjiang (Liu, 2004; Ma and Duan., 1993). It is called “desert ginseng” in China because of the excellent medicinal functions and nourishing effects.

### 2.2 Traditional uses

Cistanches Herba is a very important TCM that was first recorded in Shen Nong Ben Cao Jing, in approximately 100 AC, written in the Hou-Han Dynasty. Among all the tonics, Cistanches Herba is widely accepted as a "top-tier" one. 'kidney-yang deficiency syndrome' is one of the elementary syndrome patterns in TCM, which is characterized by weakness, fatigue, soreness of waist and knees, aversion to cold and in particular sexual dysfunction (Shen, 1999). Medical application of Cistanches Herba cures yang deficiency, erection dysfunction, and female with irregular menstruation, infertility and morbid leucorrhea as noted in Compendium of Materia Medica. In Chinese Pharmacopeia (2015 edition) only *C. deserticola* and *C. tubulosa* were listed, however, *C. sala* and *C. sinensis* were also used as Roucongrong in folk (Tian, 2002; Jiangsu New Medical College, 1986). Cistanches Herba is sweet and salty in taste, warm in nature, acts on kidney and large intestine channels, and has effects of invigorating the kidney and supplementing essence, moisturizes the intestine and relaxing bowels. As a commonly used TCM, its traditional functions include treating kidney deficiency, impotence, female infertility, profuse metrorrhagia and senile constipation (Jiangsu New Medical College, 1986). Chinese Pharmacopeia advocated the Cistanche at a daily dose of 6-10 g, boiled in water for oral use. In China, there are severval formulas containing Cistanches Herba used in traditional uses, such as ①Roucongrong Wan, to treat kidney deficiency and impotence: Cistanches Herba, Rehmanniae Radix praeparata, Cuscutae Semen and Schisandrae chinensis Fructus (Zhang, 1959a) ②Jingang Wan, to treat soreness of loins and knees: Cistanches Herba, Morindae officinalis Radix, Eucommiae Cortex and Dioscoreae spongiosae Rhizoma (Liu, 1959) ③Jichuan Jian, to relieve constipation: Cistanches Herba, Angelicae sinensis Radix, Achyranthis bidentatae Radix, Alismatis Rhizoma, Cimicifugae Rhizoma, and Aurantii Fructus (Zhang, 1959b). Chemical analysis reveals that phenylethanoid glycosides, iridoids, lignans, oligosaccharides, and polysaccharides are the main constituents. Pharmacological studies demonstrate that Cistanches Herba exhibits endocrine regulation, neuroprotective, immunomodulatory, anti-tumor, anti-inflammatory, hepatoprotection activities, etc. This review presents and analyzes recent developments in the chemistry, pharmacology and pharmacokinetics property of Cistanches Herba and provides a reference for further study and clinical application.

### 2.3 Economic importance

Cistanches Herba is a nature resource, with edible and pharmaceutics value. With the development of TCM and dietary cure, the demand for it has been increasing year by year. Artificial planting Cistanches Herba is necessary and advocated in China in order to protect wild resource, such as *C. deserticola*, *C. tubulosa* and *C. salsa*. The professor Pengfei Tu has made a great contribution in this field (Tu and Guo, 2015a, 2015b). *C. deserticola* lives parasitically on the roots of psammophyte *Haloxylon ammodendron* (Chenopodiaceae) and *C. tubulosa* is parasitized on the roots of *Tamarix*, which are best for precautions sand species. *C. salsa, a* plant parasite found on the roots of shrub plants, such as Chenopodiaceae, Tamaricaceae, Zygophyllaceae, which are used for improving saline land. Artificial planting has a stronger positive for climate, soil and environment, which could produce good economic, social and ecological benefits.

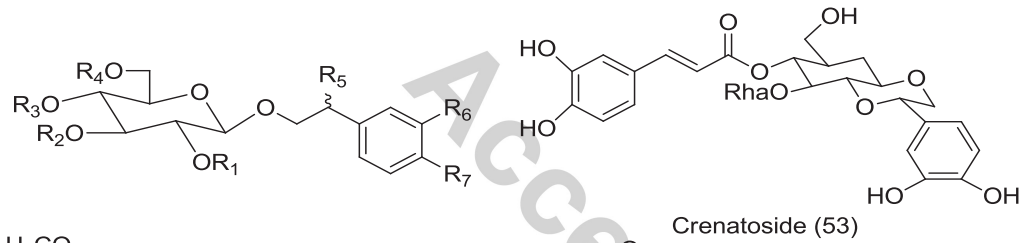
## 3 Chemical constituents

The chemical components of Cistanches Herba are variable which might be relation with species, plant origins and location. More than 100 compounds from this genus have been identified, including phenylethanoid glycosides (PhGs), carbohydrates, lignans, iridoids, essential oils and amino acids, etc. PhGs as the main consituents, up to 4%, 3% and 0.3% in *C. tubulosa*, *C. salsa*, *C. deserticola,* respectively (Wang et al. 2017). The content of total sugar content was determined to be from 26% to 46% with phenol–sulfuric method in different location of *C. deserticola* (Xue and Zhang, 1994).

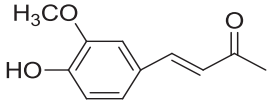
### 3.1 Phenylethanoid glycosides

PhGs are a class of polyphenolic compound distributed in many plants. To date, a total of 69 PhGs have been found by HPLC-LTQ-Orbitrap-MS in Cistanches Herba (Zhang et al. 2015b), however, as far as we know, just over fifty PhGs have been isolated, including 2 monosaccharide glycosides, 33 disaccharide glycosides and 18 trisaccharide glycosides(**1-53**, Table 1). PhGs have been reported to have various pharmacological activities, such as neuroprotective, immunomodulatory, anti-inflammatory, hepatoprotective and anti-oxidative, etc.

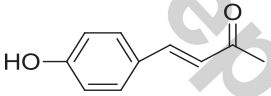
**Table 1 Phenylethanoid glycosides from *Cistanche* species**



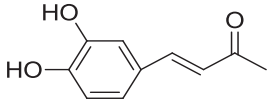

Crenatoside (53)




trans-Fer




trans-p-Cou




trans-Caf

| Compound name | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | $R_6$ | $R_7$ | Species | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| Acteoside (1) | H | Rha | Trans-Caf | H | H | OH | OH | Cd, Ct, Csa, Csi | (Xiong et al., 1998; Yoshikawa et al., 2006; Hiromi et al., 1984; Liu et al., 2013) |
| Cistanoside A (2) | H | Rha | Trans-Caf | Glu | H | OH | O $CH_3$ | Cd, Ct, Csa | ( Kobayashi et al., 1984b; Yamada et al., 2010; Xu et al., 1994) |
| Cistanoside B (3) | H | Rha | Trans-Fer | Glu | H | OH | $OCH_3$ | Cd, Csa | ( Kobayashi et al., 1984b; Xu et al., 1994) |
| Cistanoside C (4) | H | Rha | Trans-Caf | H | H | OH | $OCH_3$ | Cd, Csa | (Kobayashi, et al., 1984c; Xu et al., 1994) |
| Cistanoside D (5) | H | Rha | Trans-Fer | H | H | OH | $OCH_3$ | Cd, Csa | (Kobayashi, et al., 1984c; Liu et al., 2011) |
| Cistanoside E (6) | H | Rha | H | H | H | OH | $OCH_3$ | Csa, | (Deyama et al., 2006; Kobayashi et al., 1985b) |
| Cistanoside F (7) | Ac | Rha | Ac | H | H | OH | $OCH_3$ | Csa, Ct | (Kobayashi et al., 1985b; Tu et al., 2006) |
| Cistanoside G (8) | H | Rha | H | H | H | OH | H | Cd | ( Karasawa et al., 1986a) |
| Cistanodise H (9) | Ac | Rha | H | H | H | OH | OH | Cd, Csa | (Xu et al., 1994; Karasawa et al., 1986b) |
| Cistanoside J (10) | Ac | Rha | H | Trans-Fer | H | OH | $OCH_3$ | Cd | (Nan et al., 2013) |
| Cistanoside K (11) | Ac | Rha | H | Trans-Caf | H | OH | $OCH_3$ | Cd | (Nan et al., 2013) |
| Cistanoside L (12) | H | Rha | H | Trans-Fer | H | $OCH_3$ | $OCH_3$ | Cd | (Nan et al., 2013) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Cistanoside M (13) | H | Rha | H | Trans-p-Cou | H | OH | $OCH_3$ | Cd | (Nan et al., 2013) |
| Cistanoside N (14) | Ac | Rha | H | O-Glu | H | OH | $OCH_3$ | Cd | (Nan et al., 2013) |
| Cistantubuloside A (15) | H | Rha | Trans-Caf | Glu | H | OH | H | Ct | (Tu et al., 2006) |
| Cistantubuloside $B_1$ (16) | H | Rha | Trans-p-Cou | Glu | H | OH | OH | Ct | (Tu et al., 2006) |
| Cistantubuloside $B_2$ (17) | H | Rha | Cis-p-Cou | Glu | H | OH | OH | Ct | (Tu et al., 2006) |
| Cistansinenside A (18) | Ac | Rha | Trans-Caf | H | H | $OCH_3$ | OH | Csi, Ct | (Tu et al., 2006; Tu et al., 2007) |
| Cistansinenside B (19) | Ac | Rha | Trans-Caf | Rha | H | $OCH_3$ | OH | Csi | (Liu et al., 2013) |
| Cistantubuloside C1/C2 (20) | H | Rha | Trans-Caf | Glc | OH | OH | OH | Ct | (Tu et al., 2006) |
| Campneoside Ⅰ(21) | H | Rha | Trans-Caf | H | $OCH_3$ | OH | OH | Ct | (Tu et al., 2006) |
| Campneoside Ⅱ(22) | H | Rha | Trans-Caf | H | OH | OH | OH | Ct, Csi | (Tu et al., 2006; Liu et al., 2013) |
| Decaffeoylacteoside (23) | H | Rha | H | H | H | OH | OH | Csa, Ct | (Karasawa et al., 1986b; Song et al., 2000a) |
| Echinacoside (24) | H | Rha | Trans-Caf | Glu | H | OH | OH | Cd,Ct,Csa, Csi | (Liu et al., 2013; Kobayashi et al., 1984c; Yoshikawa et al., 2006; Morikawa et al., 2010) |
| Eutigoside A (25) | H | H | H | Trans-p-Cou | H | OH | H | Csa | (Yang et al., 2005) |
| Isocistanoside C (26) | H | Rha | H | Trans-Caf | H | OH | $OCH_3$ | Cd | (Hayashi, 2004) |
| Isoacteoside (27) | H | Rha | H | Trans-Caf | H | OH | OH | Cd, Csa, Ct, Csi | (Liu et al., 2013; Xiong et al., 1998; Lei et al., 2007; Pan, 2011) |
| Isosyringalide A 3'-α-L-rhamnopyronoside (28) | H | Rha | Trans-p-Cou | H | H | OH | OH | Ct, Cd | ( Hayashi, 2004; Yoshizawa et al., 1990) |
| Isocampneoside Ⅰ(29) | H | Rha | H | Trans-Caf | $OCH_3$ | OH | OH | Ct | (Pan et al., 2010) |
| Jionoside D (30) | H | Rha | Trans-Caf | H | H | $OCH_3$ | OH | Csi | (Tu et al., 2007) |
| Kankanoside F (31) | H | Rha | H | Glc | H | OH | OH | Ct | (Yoshikawa et al., 2006) |
| Kankanoside G (32) | H | Rha | H | Trans-Caf | H | OH | H | Ct | (Yoshikawa et al., 2006) |
| Kankanosides H1(33) | Ac | Rha | Trans-p-Cou | Glc | H | OH | OH | Ct | (Pan, 2011) |
| Kankanosides H2(34) | Ac | Rha | Cis- p-Cou | Glc | H | OH | OH | Ct | (Pan, 2011) |
| Kankanosides I (35) | H | Rha | Trans-Caf | Glc | H | H | H | Ct | (Pan, 2011) |
| Kankanosides J1/ J2 (36) | Ac | Rha | Trans-Caf | H | $OCH_3$ | OH | OH | Ct | (Pan et al., 2010) |
| Kankanosides K1/ K2 (37) | H | Rha | Trans-Caf | Glc | $OCH_3$ | OH | OH | Ct | (Pan et al., 2010) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Osmanthuside B (38) | H | Rha | Trans-p-Cou | H | H | OH | H | Cd, Csa | (Komayashi et al., 1984c; Liu et al., 2011) |
| Poliumoside (39) | H | Rha | Trans-Caf | Rha | H | OH | OH | Csi | (Liu et al., 2013; Tu et al., 2007) |
| Pheliposide (40) | Ac | Rha | Trans-Caf | Xyl | H | OH | OH | Cp | (Melek et al., 1993) |
| Salidroside (41) | H | H | H | H | H | OH | H | Csa, Ct | (Yoshikawa et al., 2006; Karasawa et al., 1986) |
| Salsosides D (42) | Ac | Rha | Trans-Caf | H | H | OH | H | Csa, Cd | (Liu et al., 2011; Lei et al., 2007) |
| Salsosides E (43) | Ac | Rha | Trans-Caf | H | H | OH | $OCH_3$ | Csa, Cd | (Liu et al., 2011; Lei et al., 2007) |
| Salsosides F (44) | Ac | Rha | H | Trans-p-Cou | H | OH | OH | Csa | (Lei et al., 2007) |
| Syringalide A 3'-α-L-rhamnopyronoside (45) | H | Rha | Trans-Caf | H | H | OH | H | Cd, Ct | (Xiong et al., 1996; Song et al., 2000) |
| Tubuloside A (46) | Ac | Rha | Trans-Caf | Glc | H | OH | OH | Cd, Ct | (Xiong et al., 1996; Kobayashi et al., 1987) |
| Tubuloside B (47) | Ac | Rha | H | Trans-Caf | H | OH | OH | Cd, Csa, Ct, Csi | (Kobayashi et al., 1987; Liu et al., 2013; Sheng et al., 2002; Nan et al., 2013) |
| Tubuloside C (48) | Ac | Ac-Rha | Trans-Caf | Glu | H | OH | OH | Ct | (Kobayashi et al., 1987) |
| Tubuloside D (49) | Ac | Ac-Rha | Trans-p-Cou | Glu | H | OH | OH | Ct | ( Kobayashi et al., 1987) |
| Tubuloside E (50) | Ac | Rha | Trans-p-Cou | H | H | OH | OH | Ct, Cd | (Liu et al., 2011; Yoshizawa et al., 1990) |
| 2'-O-acetylpoliumoside (51) | Ac | Rha | Trans-Caf | Rha | H | OH | OH | Csi | (Liu et al., 2013) |
| 2'-acetylacteoside (52) | Ac | Rha | Trans-Caf | H | H | OH | OH | Cd, Csi, Csa, Ct | (Liu et al., 2013; Xiong et al., 1998; Pan, 2011; Komayashi et al., 1985b) |
| Crenatoside (53) | | | | | | | | Ct | (Song et al., 2000b) |

Glc: β-glucopyranose. Rha: α-L-rhamnopyranose; Ac: acetyl; Cd: *C. deserticola*; Ct: *C. tubulosa*; Csa: *C. salsa*; Csi: *C. sinensis*; Cp: *C. phelypaea*.

### 3.2 Carbohydrates

Carbohydrates are another main constituents of Cistanches Herba. As important natural products, carbohydrates have drawn a lot of attention, however, the studies on the chemical composition of them are relatively less compared to PhGs. In the past few years, several saccharides structures have been found and still in progress. Galactitol, the main active component of monosaccharide, possess laxative property (Gao et al., 2015c). Most studies on polysaccharides have been focus on extraction, isolation, purification and structural analysis. Structural analysis of polysaccharides is difficult because many factors such as geographical location, environmental conditions, and extraction method can affect the monosaccharide composition, fine structure, and size. Despite all that, researchers have elucidated several polysaccharides composition or their structural backbones (Table 2). The monosaccharide composition of Cistanches Herba polysaccharides consisted of mainly mannose, galactose, glucose, xylose, and uronic acids, etc.

**Table 2. Carbohydrates from *Cistanche* species**

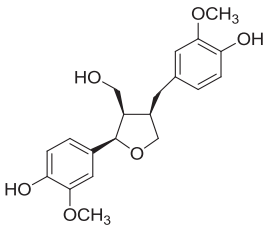
| Name | Source | Composition | Extraction method | Ref |
|---|---|---|---|---|
| ACDP-2 | Cd | 1,4-D-gal and D-glu, containing predominantly a branching point at the C6 | Cold water, hot water | (Wu et al., 2005) |
| CDA-1A<br>CDA-3B | Cd | α-(1→4)-D-glucan with α-(1→6)-linked branches attached to the O-6 of branch points, Mean Mw:$1.0\times10^4$,<br>containing a typical rhamnogalacturonan backbone and arabinogalactan or arabinan branches, Mean Mw:$8.7\times10^5$ | Cold-water | (Dong et al., 2007) |
| CDOS-1 | Cd | Sucrose | Alkali (pH=10) extraction, | (Bai et al., 2013) |
| CDOS-2 | | Sucrose, rhamnose and mannitol, with a mole ratio of 1:0.73:3.61. | ethanol precipitation, | |
| CDP-4 | Cd | 1,4-α-D-glu:1,6-α-D-glu=3:1, Mean Mw: $1.4\times10^4$ | Cold water | (Wu and Tu., 2004b) |
| CDP-6 | Cd | Backbone consisting of 1,6-α-D-glu residues and 1,6-linked mannosyl residues, substituted at O-3 of mannose, Mean Mw: $6.8\times10^4$ | Cold water | (Wu and Tu., 2004a) |
| Cistan A | Cd | Arabinose, galactose, rhamnose and galacturonic acid, with a mole ratio of 6.3:10.0:1.0:0.8, Comprised of a complex of pectic arabino-3,6-galactan type II with lowly-branched 3,5-α-L-arabinan, Mean Mw: $201\times10^3$ | Cold water | (Ebringerova et al., 2002) |
| HCP | Unknown | Containing glucose, galactose, rhamnose, arabinose and fructose. Mean Mw: 385 kDa | Hot water | (Sui et al., 2011) |
| Pectic | Cd | Galacturonic acid content varing between 30% and 80%, containing homogalacturonan and rhamnogalacturonan RG-I sequences in different proportions, mainly by a highly branched (1→3,5)-α-arabinan. | Cold water, hot water | (Ebringerova et al., 1997) |
| - | Cd | Starch-like 1,4-α-D-glucan, α-L-arabino-3,6-β-D-galactan, pectic polysaccharides and 4-O-methyl-D-glucurono-D-xylan, glucose is the main monosaccharide. | Cold water, hot water, 0.5M NaOH, 0.01M EDTA | (Naran et al., 1995) |
| - | Cd | α-(1→6)-glucan backbone, Mean Mw>$2\times10^6$, $1.5\times10^5$, $3.3\times10^4$ | 0.5 M NaOH | (Wu and Tu, 2005) |

Mw: Molecular Weight

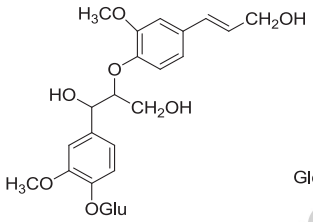
### 3.3 Other compounds

Other compounds have been isolated from Cistanches Herba, including 15 lignans (**54-68**, Table 3), 27 iridoids (**69-94**, Table 4), 3 Benzyl glycosides (Lei et al., 2007), serval monoterpenes( Yoshizawa et al., 1990; Yamaguchi et al., 1999; Morikawa et al., 2010), besides β-sitosterol, D-mannitol, succinic acid, β-sitosterol β-D-glucoside, kankanose and so on, have also been reported. HPLC-MS or GC-MS had detected the alkaloids, betaine N, N-dimethyl glycine methyl ester and essential oils in Cistanches Herba (Qin, 2012; Du et al., 1988).

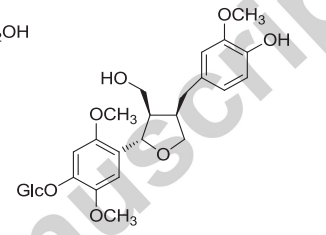
**Table 3. Lignans from *Cistanche* species**



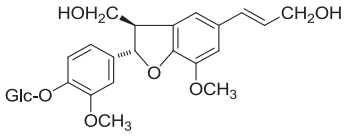

(54)



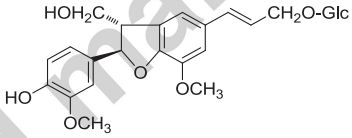

(55)



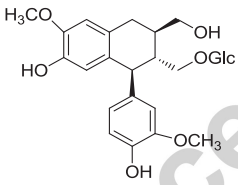

(56)



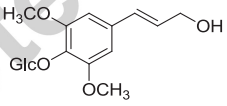

(57)



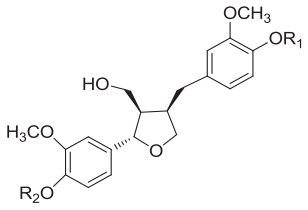

(58)



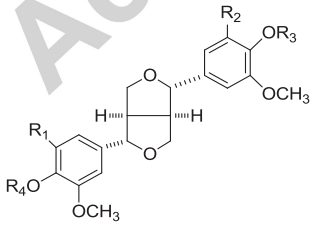

(59)




(60)



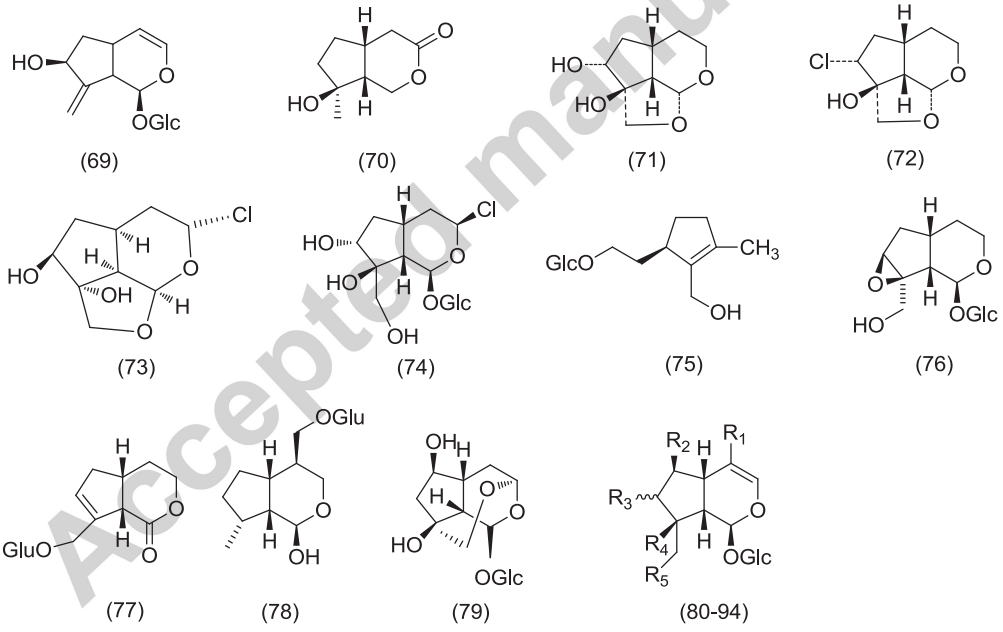

(61):$R_1$=H,$R_2$=Glc
(62):$R_1$=Glc,$R_2$=H




(63): $R_1$=$R_2$=$OCH_3$, $R_3$=H, $R_4$=Glc
(64):$R_1$=$R_2$=$R_3$=H, $R_4$= Glc
(65):$R_1$=$R_2$=$OCH_3$, $R_3$=$R_4$=Glc
(66):$R_1$=$OCH_3$, $R_2$=$R_3$=H, $R_4$=Glc
(67): $R_1$=H, $R_2$=$OCH_3$, $R_3$=H, $R_4$=Glc
(68):$R_1$=$R_2$=$R_3$= $R_4$=H

| Compounds name | Reference |
|---|---|
| Alaschanioside A (54) | (Nan et al., 2015) |
| Citrusin A (55) | (Nan et al., 2015) |
| Conicaoside (56) | (Nan et al., 2015) |
| Ddehydrodiconiferyl alcohol 4-O-β-D-glucopyranoside (57) | (Nan et al., 2015) |
| Dehydrodiconiferyl alcohol γ'-O-β-D- glucopyranoside (58) | (Liu et al., 2013) (Nan et al., 2015) |
| Isolariciresinol-9'-O-β-D-glucopyranoside (59) | (Liu et al., 2013) |
| Syringin (60) | (Yoshizawa et al., 1990) |
| Lariciresinol 4-O-β-D-glucopyranoside (61) | (Nan et al., 2015) |
| Lariciresinol 4'-O-β-D-glucopyranoside (62) | (Nan et al., 2015) |
| Syringaresinol O-β-D- glucopyranoside (63) | (Yoshizawa et al., 1990) |
| Pinoresinol O-β-D-glucopyranoside (64) | (Nan et al., 2015) |
| Liriodendrin (65) | (Nan et al., 2015) |
| Eucommin A (66) | (Nan et al., 2015) |
| Isoeucommin A (67) | (Nan et al., 2015) |
| Pinoresinol (68) | (Yoshizawa et al., 1990) |

**Table 4. Iridoids from *Cistanche* species**



| Compound name | $R_1$ | $R_2$ | $R_3$ | $R_4$ | $R_5$ | Species | Ref. |
|---|---|---|---|---|---|---|---|
| Antirrhide (69) | | | | | | Ct | (Xie et al., 2006) |
| Argyo (70) | | | | | | Ct | (Xie et al., 2006) |
| Cistanin (71) | | | | | | Csa | (Kobayashi et al., 1984a) |
| Cistachlorin (72) | | | | | | Csa | (Kobayashi et al., 1984a) |
| Kankanol (73) | | | | | | Ct | (Xie et al., 2006) |
| Kankanosides C (74) | | | | | | Ct | (Xie et al,. 2006) |
| Kankanosides D (75) | | | | | | Ct | (Xie et al., 2006) |
| Kankanosides L (76) | | | | | | Ct | (Pan, 2011) |
| Kankanosides M (77) | | | | | | Ct | (Pan, 2011) |
| Kankanosides N (78) | | | | | | Ct | (Pan, 2011) |
| Phelypaeside (79) | | | | | | | (Deyama et al., 1995) |
| Adoxosidic acid (80) | COOH | H | H | H | OH | Ct | (Song et al., 2000a) |
| Ajugol/Leomuride (81) | H | OH | H | OH | H | Csi, Csa, Ct | (Liu et al., 2013; Xie et al., 2006; Kobayashi et al., 1985a) |
| Bartsioside (82) | H | H | = | | OH | Csa, Ct | (Xie et al., 2006; Kobayashi et al., 1985a) |
| Cistadesertoside A (83) | $CH_3$ | H | OH | OH | H | Cd | (Nan et al., 2016) |
| Geniposide (84) | $COOCH_3$ | H | = | | $CH_2OH$ | Csi | (Liu et al., 2013) |
| Geniposidic acid (85) | COOH | H | = | OH | | Csa, Ct | (Xie et al., 2006; Kobayashi et al., 1985a) |
| Gluroside (86) | H | H | H | OH | H | Cd, Cp, Csa, Ct | (Xie et al., 2006; Kobayashi et al., 1985a) |
| Mussaenosidic acid (87) | COOH | H | H | OH | H | Csa, Ct | (Xie et al., 2006; Kobayashi et al., 1985a) |
| Mussaenoside (88) | $COOCH_3$ | H | H | OH | $CH_3$ | Csi | (Liu et al., 2013) |
| Kankanoside A (89) | $CH_3$ | H | H | OH | H | Ct | (Xie et al., 2006) |
| Kankanoside B (90) | H | H | e-OH | OH | OH | Ct | (Xie et al., 2006) |
| 6- Deoxycatalpol (91) | H | H | -O- | | OH | Ct, Csa | (Kobayashi et al., 1985a; Yoshizawa et al., 1990) |
| 8- Epideoxyloganic acid (92) | COOH | H | H | H | H | Csa | ( Kobayashi et al., 1985a) |
| 8-Epiloganic acid (93) | COOH | H | OH | H | H | Csi, Cd, Ct, Csa | (Yoshizawa et al., 1990; Liu et al., 2013; Yang et al., 2009) |
| 8-Epiloganin (94) | $COOCH_3$ | H | OH | H | $CH_3$ | Csi, Csa, Cd, Cp | (Liu et al., 2013; Yang et al., 2009) |

## 4 Pharmacological properties

Cistanches Herba, as an important TCM, has a wide range of applications. Echinacoside and acteoside as the main active constituents of PhGs were studied extensively, which are used as index component in quality identification. Here, we also summarized echinacoside and acteoside activities of other plants.

### 4.1 Endocrine regulation activities

Cistanches Herba was commonly used as tonic for kidney. According to TCM, *C. deserticola* decoction (1.5 g/kg, 3.0 g/kg, 6.0 g/kg, i.g.) was reported to be able to raise the weight of seminal vesicle and prostate gland of the male rat, alleviate the testicular toxicity induced by hydroxyurea, and modulate the serum sex hormones at some level (Gu et al., 2013). *C. deserticola* decoction (10 g/kg, i.g.) also could ameliorate the mice reproductive toxicity induced by Leigongteng glycoside (Li et al., 2014a), besides, the 70% ethanol extract of *C. tubulosa* (echinacoside 4.2%, acteoside 2.3%, 0.2 g/kg, i.g.) reversed bisphenol A induced testicular and sperm damage in SD rats through gonad axis up-regulated steroidogenesis enzymes, and echinacoside was one of the active compounds (Jiang et al., 2016). Wang et al. (2015c) reported that the 70% ethanol extract of *C. tubulosa* (0.4 and 0.8 g/kg for 20days, i.g.) improved SD rats sperm count, motility, as well as progesterone and testosterone level. Immunohistochemistry and western blot results showed that the cholesterol side-chain cleavage enzymes expression (CYP11A1, CYP17A1, and CYP3A4) were enhanced by the extraction. Not only in therat but also in the mice model of perimenopause, Cistanches Herba showed hormone regulation activity (Wei, 2014). Limited information suggested that water extraction of *C. deserticola* induced cytotoxicity in the male ICR mice reproductive system at three different dose (250, 500, 1000 mg/kg, p.o.) for 35 days, through the suppression of spermatogenesis and hormonal secretion, induced testicular damage (Kim et al., 2012). However, Gao et al. (2016) demonstrated that *C. deserticola* powder (polysaccharides content 13.6%) had no side effects administered at 7.8 g/kg for male and 8.0 g/kg (p.o.) for female SD rats for 90 days in viscera index and histopathology. Different sample, animal model, evaluation index and administration interval may play an important role on the results obtained. The

toxicity is important and the mechanism worthy of further investigation.

**4.2 Anti-neurodegenerative diseases activities**

Alzheimer's disease (AD) is the most common type of neurodegenerative disease, accompany by cognitive and memory impairment. In the past and present, many research groups focused their research on neuroprotective effect. Cistanches Herba water and alcohol extract all showed anti-AD effect. Aqueous extracts of *C. tubulosa* contained three phenylethanoid glycosides (100 and 200 mg/kg for 15days, i.g.), echinacoside (25.4%), acteoside (3.8%), and isoacteoside (4.1%), which repaired the rat's cognitive dysfunction caused by Aβ 1-42 *via* decreasing amyloid deposition, inhibiting cholinergic and hippocampal dopaminergic neuronal damage (Wu et al., 2014b). *C. deserticola* 95% ethanol extract (250 μg/mL) induced nerve growth factor (NGF) secretion in rat glioma C6 cells and led to neurite extension in rat pheochromocytoma PC12 cells. *In vivo*, the extract stimulated NGF production in the cortex and hippocampus, promoted neuronal cell differentiation, neurite outgrowth and synapse formation in the hippocampus at 5 and 20 mg/kg (3 days, p.o.) (Choi et al., 2011). In the vascular dementia rat model, the PhGs (10mg/kg for 14days, i.p.) have showed the protection of hippocampal neurons though decreasing tau phosphorylation and increasing the collapsin response mediator protein-2 expression level (Chen et al., 2015). Add *C. deserticola* (15 mg/kg) into the control diet for 2 months, the learning abilities of senescence-accelerated OXYS rats, was elevated in the morris water maze and anxiety was reduced in the plus-maze, cataract and retinopathy with aging were improved, however, there was no effect on open field (Stefanova et al., 2011). An open-label, nonplacebo-controlled study was conducted to investigate the neuroprotective clinical evidence of *C. tubulosa* Glycoside Capsules (Memoregain®). The total 48 weeks' study in 18 patients, administered two 300 mg capsules 3 times per day. The result showed that Memoregain® had a potential to treatment mild and moderate AD patients (Guo et al., 2013). It has been showed that PhGs (100 mg/d for 40days) can improve senescence accelerated mouse (SAMP8) mice spatial learning and memory, decrease malondialdehyde (MDA), increase superoxide dismutase (SOD) level, glutathione peroxidase (GSH-Px) activities in mice brain and survival rate of intact pyramidal cells of hippocampal region (Jia et al., 2014). Kuang used the mouse model

induced by D-gal and sodium nitrite also gave the conclusion that PhGs could improve learning and memory, and the mechanism related to increase $Na^+$-$K^+$ ATPase, GSH-Px and SOD activity and decrease nitric oxide (NO) content (Kuang, 2009).

Amyloid fibrils accumulation in cerebral can easily lead to neurodegenerative disorders. Acteoside (30 μM) has been reported to inhibit Aβ42 aggregation by activating nuclear translocation of the transcription factor NF-E2-related factor 2 (Nrf2), increasing heme oxygenase-1 (HO-1) expression in PC12 cell and in SD rat model (Wang et al., 2012). It has been shown that acteoside (30, 60, and 120mg/kg for 60days, i.g.) could decrease mouse nitric oxide synthase (NOS) activity and caspase-3 expression (Gao et al., 2015a; Peng et al., 2015). Echinacoside (100, 300 and 500μM) also showed the activity against amyloid fibril-induced PC12cell death (Zhang et al., 2015a).

Parkinson's disease (PD) is a neurodegenerative disease characterized by a progressive loss of substantia nigra neurons and depletion of the transmitter dopamine (DA), with a series of pathological features, such as bradykinesia, resting tremor, and rigidity. Numerous studies have demonstrated that the extraction of Cistanches Herba, echinacoside and acteoside significantly reduced caspase-3 and caspase-8 activation in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced apoptosis of cerebellar granule neurons (CGNs), protected dopaminergic neurons against dopamine neurotoxicity in C57BL/6 mice (Geng et al., 2004, 2007; Pu et al., 2003; Tian and Pu, 2005). Echinacoside (3.5 and 7.0mg/kg for 7 days, i.g.) showed protective activity against 6-hydroxydopamine (6-OHDA)-induced rat striatal dopaminergic neurons injury, increasing the levels of DA, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid on the striatal extracellular (Chen et al., 2007a). It was reported to be able to protect PC-12 cell from 6-OHDA or $H_2O_2$ induced apoptosis, decrease the generation of reactive oxygen species (ROS) and NO, as well as the level of $Ca^{2+}$(Wang et al., 2015d; Kuang et al., 2009, 2010). In tumor necrosis factor α (TNF-α) induced SH-SY5Y neuronal cells model, echinacoside also exhibited anti-apoptotic activity. The mechanism of it was partly dependent on antioxidant activity, regulation of mitochondria function, inhibition of caspase-3 activation and upregulation of the anti-apoptotic protein Bcl-2 expression (Deng et al. 2004a). Echinacoside inhibited rotenone induced SH-SY5Y cells apoptosis

via activating TrkA/TrkB receptors and their downstream signaling events (Zhu et al. 2013).

Besides echinacoside and acteoside, tubuloside B also has drawn lots of attention in PD disease. It showed anti-apoptosis activity in SH-SY5Y and PC12 neuronal cells. The mechanism was partially dependent on anti-oxidative stress effects, through maintaining mitochondria function, inhibiting caspase-3 activity and decreasing free intracellular calcium concentration (Deng et al. 2004b; Sheng et al. 2002).

**4.3 Immunoregulatory activities**

Polysaccharides always exhibited remarkable immune enhancing activity. Cistanches Herba contains about 26% to 46% of polysaccharides, meaning that the immunomodulation activities of Cistanches Herba might be mostly due to the immunoregulatory effects of polysaccharides. Pharmacological studies have shown that the crude polysaccharide fraction CDA-3B from Cistanches Herba exhibited immunoregulatory activity, promoted concanavalin A (ConA)-induced T- and LPS-induced B-cell proliferation of mice splenocytes *in vitro*, and CDA-1A only showed positivity on B-cell proliferation (Dong et al., 2007). Pectic polysaccharide is a common polysaccharide in Cistanches Herba. It has been reported that the ramified regions of the galacturonan core and the neutral side chains consisting of 3,6-β-D-galactan and 3,5-α-L-arabinan, which played an important role in biological activities expression. Ebringerova A. et al. (1997, 2002) isolated several pectic polysaccharides from *C. deserticola,* one of which exhibited remarkable immunomodulatory activities exceeding those of the commercial immunomodulator zymosan *in vitro* mitogenic and comitogenic rat thymocyte test. Maruyama's team had done a lot of research on *C. salsa* immunoregulatory activity. First, the extract of *C. salsa,* it was reported to be able to stimulate IgM and IgG production in human lymph node lymphocytes with the dose of 0.1%, 1% and 10% (Maruyama et al. 2008a). Secondly, the water extract of *C. salsa* was removed low molecular weight constituents (PhGs and monoterpene) with 3500Da dialysis membrane (100 μg/mL), which showed the activity of stimulating IgM production in human B cell line Ball-1 and inducing slight cell proliferation. It also promoted IgG production (50 μg/mL) in the plasma B cell line HMy-2 (Maruyama et al.,

2007, 2008c). However, the water extract showed different activities on different cell line. It inhibited the human Burkitt's lymphoma cell line Namalwa proliferation at more than 1μg/mL (Maruyama et al., 2008b, 2008c). These authors speculated that the active constitutes in the water extract were polysaccharides, the high Mw active constituent that enhanced IgM production and a middle Mw active constituent that inhibited cell proliferation (Maruyama et al., 2008d). The immunoregulatory mechanism of polysaccharides is not clear, which needs to be further studied. Most studies have focused on polysaccharide activities, however, reports on oligosaccharides are limited. Ying Bai et al. (2013) found that *C. deserticola* oligosaccharides CDOS (100 mg/kg) can significantly enhance splenocytes cell proliferation and macrophages phagocytosis of mice.

PhGs also show the immunomodulatory and antitumor activities and the benefit is largely on the basis of their anti-oxidant activity. Acteoside induced macrophage-like line J774.A1 secret IL-1, IL-6 and TNF-α at 1-100 ng/mL, however, it showed cytotoxic activity at 50 μg/mL (Inoue et al., 1998a). SAMP8 were treated with 70% ethanol extract of *C. deserticolav* (echinacoside and acteoside as the most prominent), oral administrations for 4 weeks, both naive T and natural killer cells in blood and spleen cell populations were significantly increased (Zhang et al., 2014). *C. tubulosa* PhGs (echinacoside 26.64%, acteoside 10.19% and isoacteoside 1.71%) inhibited melanoma B16-F10 cells growth *in vitro* and *in vivo* (200 and 400 mg/kg), the mechanism associated with mitochondrion-dependent signaling pathway and immunoregulatory possibly played an important role (Li et al., 2016a).

**4.4 Anti-tumor activities**

Acteoside is a natural antioxidant product unlike other anti-tumor compounds. According to a report, acteoside is a potent inhibitor of protein kinase C, with an $IC_{50}$ value of 25 μM (Herbert et al., 1991). Li et al. (1997) found that it (10 and 20μmol/L) could improve MGc80-3 cells morphology towards normalization rather than by killing tumor cells with high cytotoxicity or other side-effects. It could induce promyelocytic leukemia HL-60 DNA degradation with $IC_{50}$ value of 26.7μM (Inoue et al., 1998b). Colorectal cancer is one of the most common malignancies in the world. Acteoside (25-100 μM) promoted apoptosis by regulating HIPK2-p53 signaling in human colorectal

cancer cell line. In addition, further *in vivo* study also found that it inhibited the growth of mice tumor and the inhibition rate up to 60.99% on the concentration of 80mg/kg (Zhou et al., 2014). MTH1 is the most important enzyme for the sanitization of nucleotide pools, previous study revealed that echinacoside had the ability to inhibit MTH1 ($IC_{50}$ = 7.01μM) (Dong et al., 2015). It (20, 50, 100μM) repressed SW1990 pancreatic adenocarcinoma cell growth through promoting ROS generation, disturbing mitochondrial membrane potential and mitogen-activated protein kinase (MAPK) pathway (Wang et al., 2016).

**4.5 Anti-inflammation activities**

Inflammatory responses including NO production, phospholipase A2 activation, ROS generation, histamine release in neutrophils, macrophages and mast cells. NO plays an important role in lipopolysaccharide (LPS), TNF-α or IL-1 mediated inflammatory process. On one hand it is essential for maintaining the cellular function, on the other hand it was able to induce inflammation injury as a reactive radical. The nuclear factor κB (NFκB) and activator protein-1 (AP-1) are recognized modulator of inflammation. Several PhGs (Compound 1, 2, 24, 27, 46, 47, 52) (100 and 200 μM) from *C. deserticola* showed NO radical-scavenging activity, they inhibited LPS-induced NO production in cell line J774.1. Cistanoside K and tubuloside B inhibited LPS-induced NO production in mouse microglial cells (BV-2 cells) with $IC_{50}$ 14.94 and 14.32μM (Xiong et al., 2000; Nan et al., 2013).

Macrophages are key players in inflammation. Acteoside (50, 100 μM) was reported to have a suppressing ability on the activity of cyclooxygenase COX-2 and inhibit prostaglandin E2 ($PGE_2$), TNF-α and NO formation in LPS-stimulated mouse peritoneal macrophages (Díaz et al., 2004). Lee et al. (2005) found that acteoside (100 μM) inhibited the LPS induced NO synthase expression via block AP-1 in the RAW264.7 macrophage cell line. Several studies reported that acteoside (10, 30, 100 μM) showed a dose-dependently inhibiting β-hexosaminidase release activity, arachidonic acid and histamine release in RBL-2H3 cells stimulated by melittin. The molecular mechanisms are related to the competitive inhibition of $Ca^{2+}$-dependent phospholipase A2 and down-regulation of Ca/nuclear factor of activated T cells and JNK MAPK signaling pathways (Sim et al., 2006; Song et al., 2012; Yamada et al., 2010). As an inhibitor of

NFκB, acteoside (30 and 60 mg/kg, i.p.) decreased lung inflammatory responses in the LPS induced acute lung injury mice model (Wang et al., 2015a). It (30 mg/kg for 15days, p.o.) down-regulated the expression of intercellular adhesion molecule-1 in glomeruli and suppressed leukocytes accumulation in crescentic-type anti-glomerular basement membrane nephritis of the rats (Hayashi et al., 1994, 1996). Acteoside (200 mg/kg, i.p.) possess anti-nociceptive activity in rats subjected to chronic constriction injury for 14 days through suppressing microglia activation, anti-apoptotic and antioxidant (Amin et al., 2016).

50% ethanol of *C. deserticola* (0.1, 0.3, 1.0 g/kg) showed anti-inflammatory effect, the butanolic layers (0.1, 0.3 g/kg) with higher activity in carrageenan-induced paw edema in the SD rats. The authors speculated that kinin system but not opioid receptors and immune system were related to this process (Lin et al., 2002). When the extract of *C. tubulosa* (54 mg/kg) was used combined with fucoidan (18 mg/kg), a synergistic effect was observed. NO and PGE2 production was inhibited in carrageenan-induced air pouch inflammation mice model *in vivo* (Kyung et al., 2015). The mix was considered as a proving candidate for promoting hair growth and treating dandruff and scalp inflammation (Shin et al., 2015; Seok et al., 2015). *C. salsa* 50% ethanol extract showed anti-proliferative effect on benign prostatic hyperplasia rats, through regulating inflammatory cytokine and depressing Bcl-2/Bax ratio and activation of caspase-3 (Chung et al., 2016).

**4.6 Hepatoprotective activities**

In recent years, it is reported that PhGs, such as acteoside, echinacoside, 2'-acetylacteosid, isoacteoside, cistanoside A and tubuloside B exerted positively hepatoprotective effects through multiple mechanisms, including scavenging free radicals, blocking cytochrome P450 biotransformation, and strengthening antioxidant defense system, etc. (Xiong et al., 1998). PhGs (echinacoside 42.71%±0.42%, acteoside 14.27% ± 0.18%, $IC_{50}$=119.125 μg/mL), acteoside ($IC_{50}$=6.999 μg/mL) and echinacoside ($IC_{50}$=520.345 μg/mL) inhibited TGF-β1/smad signaling pathway in hepatic stellate cell, which showed hepatoprotective activity *in vitro*(You et al., 2016). Acteoside (30, 100 mg/kg, s.c.) showed hepatoprotective activity against $CCl_4$-induced live damage in rat

(Xiong et al., 1998), this effect maybe associated with the reduced P450 2E1 level and antioxidation (Lee et al., 2004). In this model, echinacoside (50mg/kg, i.p.) also showed hepatoprotective effects through anti-oxidant and free redical scavenging activity (Wu et al., 2007). Echinacoside significantly reduced alanine aminotransferase level in D-galactosamine plus LPS-injected mice when administered i.p. at 60 mg/kg (Li et al., 2014b). Cistanoside A alleviated alcohol-induced hepatotoxicity in mice through increasing the activities of mitochondrial antioxidant enzymes (GST, SOD and CAT) and energy metabolism enzymes (total ATPase, $Na^{+}$-$K^{+}$-ATPase, $Ca^{2+}$-$Mg^{2+}$-ATPase), as well as antioxidant defense system, besides, it inhibited apoptosis and necrosis of the primary cultured hepatocytes through upregulating Bcl-2 and downregulating c-fos expression (Luo et al., 2014, 2016). Besides PhGs, *C. deserticola* polysaccharide (0.11, 0.33, 1.00, 3.00 mg/mL, Mw=1300kDa), which contained higher proportion of galacturonic acid, can inhibit the growth and proliferation of HepG2 cell line, furthermore, it (200, 600, 1800 mg/kg) showed hepatoprotective activity against liver injury induced by alcohol in ICR mice (Guo et al., 2016).

**4.7 Cardiovascular protection**

The compounds (1, 7, 24, 31 and kankanose) were obtained from the *C. tubulosa* methanol extraction showed vasorelaxant activity in isolated rat aortic strips (Yoshikawa et al., 2006). Ko K. M. group have found that the methanol/ethanol extract from *C. deserticola* could stimulate ATP generation capacity by enhancing the oxidative phosphorylation in H9c2 cells and the rat's heart, thereby protecting against myocardial ischemia/reperfusion (I/R) injury (Leung and Ko, 2008; Wong and Ko, 2013). *C. deserticola* PhGs (content 71.7%) were considered to be an effective constituent treatment for IR-induced injury in rats. They not only significantly reduced oxidative stress in myocardial tissue, such as MDA levels and elevated the activities of GSH-Px, SOD, but also upregulated apoptosis related proteins Bcl-2/Bax and downregulated cleaved caspase-3 (Qian et al., 2016). Besides, Cistanches Herba methanol extract (0.5g/kg, 1.0g/kg for 3days, i.g.) enhanced heart ventricular tissue mitochondrial glutathione status, decreased mitochondrial $Ca^{2+}$ content, and increased mitochondrial membrane potential after I/R injury in SD rats (Siu and Ko, 2010). Statins are the common drugs used to

correct dyslipidemia, which induced myotoxicity. The water extract of Cistanches Herba (0-2000 μg/mL) exerted does-dependent protective effect by improving ATP production and via caspase-3 pathway in simvastatin treated L6 skeletal muscle cells, however, acteoside (0-160 μM) only showed weak protective effect on cells (Wat et al., 2016).

Acteoside (3-50 μmol/L) enhanced phenylephrine-induced contraction without affecting the maximum response in endothelium-intact rings, mainly through inhibition of endothelial NO synthase/release and NO-mediated tetraethylammonium-sensitive activation of $K^+$ channels (Tam et al., 2002). Besides, long-term intake of 100 mg acteoside per day in patients with cardiovascular risk significantly inhibited the platelet aggregation (Campo et al., 2012, 2015).

Echinacoside (30-300 μM) improved endothelium-dependent relaxation via NO-cGMP signal pathway in rat aortic rings (He et al., 2009). In this concentration, it also had positive effect in hypoxic pulmonary hypertension rats and the mechanism of it was closely with the NO-cGMP-PKG-$BK_{Ca}$ channels opening and intracellular $Ca^{2+}$ levels decline (Gai et al., 2015).

**4.8 Gastrointestinal tract protection activities**

Cistanches Herba was used for treating irritable bowel syndrome and constipation. Oligosaccharides and galactitol were reported as the main active component with laxative activity in ICR mice model (Gao et al., 2015c). Jia found that oral administration of *C. deserticola* water extract (0.4 g/kg/day, 2-3% PhGs, 65-70% polysaccharides, 0.6-1% protein) reduced intestinal mucosal hyperplasia and helicobacter infection in Tgfb1 Rag2 mice and the mechanism of action likely depends on immune activity (Jia et al., 2012a). After feeding *C. deserticola* water extraction (3.3 g/kg), the peristalsis of the gastrointestinal tract was increased and defecation time was shortened in mice model (Zhang et al., 2009).

Acteoside (i.p., 120, 600 μg/day) showing ameliorate activity in dextran sulfate sodium (DSS)-induced acute and chronic colitis mice model was shown to have relationship with anti-inflammatory and anti-oxidant activity (Hausmann et al., 2007). Acteoside (600 μg/day, i.g.) inhibited methotrexate induced mice mucosal layer damage, with reducing crypt depth and increasing villus height in duodenum, jejunum and ileum,

and may exert its effect through anti-inflammatory activity (Reinke et al., 2015). In farm animals, disease pressure, feed transitions, and environmental factors all can possibly disturb gut. Giancamillo et al. (2013) addedacteoside (5 mg/kg) to piglet's diet, after 166 days trial, the oxidative and nitrosative stress in the mucosal was decreased, which showed that acteoside may be useful in animal feed additive. Acteoside (40 mg/kg, i.g.) showed protective effect on ulcer induced by pyloric ligation in rat and inhibited $H^+$-$K^+$-ATPase activity *in vitro* ($IC_{50}$=60.98μg/mL, omeprazole as positive control with $IC_{50}$=30.24μg/mL ) (Singh et al., 2010)

Echinacoside (25-100 μg/mL) upregulated TGF-β1 expression, resulting in stimulating cell proliferation and preventing cell apoptosis in intestinal epithelial MODE-K cells. In DSS-induced colitis mice model, oral administration of echinacoside (20 mg/kg) extract significantly suppressed acute colitis development (Jia et al. 2014; Jia et al. 2012b).

**4.9 Anti-diabetic activities**

Quite a number of studies confirmed anti-diabetic effect of Cistanches Herba. Echinacoside and acteoside (125 and 250 mg/kg, i.g.) suppressed the increasement of postprandial blood glucose levels and improved glucose tolerance in starch-loaded mice , inhibited rat intestinal a-glucosidases, lens aldose reductase and human intestinal maltas activity *in vitro* (Morikawa et al., 2014). Male db/db mice were administered *C. tubulosa* extract (acteoside 2.66%, echinacoside 11.59%, total phenolic 66.29 ± 0.44 mg gallic acid/g and polysachcharide 10.15 ± 0.26%, 4.55, 2.73, 0.91 g/kg, i.g.), the results showed that the fasting blood glucose and postprandial blood glucose levels were decreased significantly, the insulin resistance and dyslipidemia were improved, but there was no significant effect on serum insulin levels or hepatic and muscle glycogen levels (Xiong et al., 2013). The ethanol extract of *C. tubulosa* (echinacoside 25%, acteoside 9%, 400 mg/kg for 14days, i.g.) significantly decreased serum cholesterol levels, enhanced mRNA expressions of low density lipoprotein receptor and cytochrome P450 side chain cleave in high cholesterol diet-fed mice. Acteoside was considered to be a major effective compound (Shimoda et al. 2009). Wong et al. (2014) showed that the ethanol extract of Cistanches Herba (1.5, 15, 45 mg/kg, i.g.) significantly decreased the body weight and

improved insulin sensitivity of diabetic mice, possibly through mitochondrial uncoupling and increasing energy consumption.

**4.10 Anti-osteoporosis activities**

Osteoporosis is a disease of aging characterized by low bone mass, which is most commonly seen in postmenopausal stage. Estrogen deficiency is considered as the major cause of bone loss in postmenopausal woman. A study has reported that Cistanches Herba water extract (i.g.,100 and 200 mg/kg) reversed bone loss and prevented female rats osteoporosis, which associated with enhancing bone mineral density, bone mineral content, maximum load, displacement at maximum load, stress at maximum load (Liang et al. 2011). Extensive studies have been carried to elucidate the mechanisms, including upregulation of alkaline phosphatase, bone morphogenetic proteins-2 and osteopontin mRNA expression as well as some bone metabolism related genes, e.g. Smad1, Smad5, TGF-β1 and TIEG1(Li et al., 2012a; Liang et al., 2013). Yang research group showed that echinacoside concentration from 0.01 to 10 nmol/L can significantly stimulate bone regeneration through increasing osteoprotegerin / receptor activator of NFκB ligand (OPG/RANKL) ratio in MC3T3-E1 cells (Li et al., 2012b). Authors concluded that echinacoside (30, 90, 270 mg/kg for 12 weeks, i.g.) can effectively prevent osteoporosis induced by estrogen deficiency in ovariectomized rat model (Li et al., 2013). Fang et al. (2015) found that echinacoside (0.1, 1.0 and 10 nmol/L) promoted rat osteoblast cell proliferation through extracellular regulated protein kinase (ERK)/bone morphogenetic protein-2 (BMP-2) signal pathway activation.

Chen et al. (2007b) have reported that Cistanches Herba polysaccharides (50 and 100 mg/kg, i.p.) could promote the bone marrow cell-cycle transition and hematopoietic function recovery in bone marrow-depressed anemic mice, accelerate hematogenesis in rubrum strain and macronucleus strain.

**4.11 Antioxidant activities**

The PhGs from Cistanches Herba are considered the effective ingredients for anti-oxidative activity. Due to their phenolic hydroxy structure, PhGs can act as antioxidants *via* direct combination with free radical and activating the antioxidant defense systems. These compounds' antioxidant effect increases with the number of

phenolic hydroxyl group (Xiong et al., 1996). Oxidative damage is critically involved in various pathogeneses such as inflammation, senescence, cancer, and so on. The free radicals may cause tissue injury and echinacoside (2, 10, 50, 125 mg/kg, i.p.) can protect against acute lung injury caused by oleic acid through scavenging free radicals in rats (Zhang et al., 2007). Free radical as a promoter of aging process in human, echinacoside (1, 20, 50, 100 μM) showed the anti-oxidant activity though triggering cell from G1 phase enter the S and G2 phase, effectively decreased ROS level and protected cells from DNA damage in human embryo lung fibroblastic MRC-5 cells model (Xie et al., 2009).

**4.12 Other biological activities**

*C. deserticola* extraction (acteoside 5.6%, echinacoside 33.3%, 0.25, 0.50, 1.00 g/kg) showed anti-fatigue effects, increased swimming time forced of ICR mice, significantly decreased serum creatine kinase, lactate dehydrogenase and lactic acid levels, contrarily, significantly increased hemoglobin and glucose levels (Cai et al., 2010). The fatty acids, elaidic acid and palmitic acid from *C. sala* showed a suppressing effect on SOS-induced mutagenesis activity (Shimamura et al., 1997). *C. deserticola* ethanol extract, ethyl acetate, butanolic and water fraction were reported to have sedative effect and the water fraction showed the greatest activity (Lu, 1998). Butanolic fraction of *C. tubulosa* showed anti-microbial effect on *Escherichia coli* (Adnan et al., 2014). The study reported that Cistanches Herba had obesity-suppressing activity through increasing energy consumption (Wong et al., 2015).

Acteoside can alleviate hyperuricemia in potassium oxonate-induced hyperuricemic mice model by inhibiting xanthine dehydrogenase and xanthine oxidase activity (Huang et al. 2008).Wang et al. (2015b) investigated the effects of echinacoside on hematopoietic function in 5-FU-induced bone marrow depression mice, data suggested that echinacoside may promote the recovery of hematopoietic function of the bone marrow by activation of GM-CSF/PI3K pathway. Echinacoside was reported to possess anti-senescence activity, the mechanism is associated with down-regulation of p53 expression (Zhu and Wang, 2011). The primary pharmacological actions of Cistanches Herba are summarized in Table 5.

**Table 5. Pharmacological effects of Cistanches Herba**

| Pharmacological effects | Compound name | Model | Dose range Tested | Minimal active concentration | Proposed mechanism (s) | Reference |
|---|---|---|---|---|---|---|
| Anti-AD | PhGs | Mouse | 100 mg/d, one time per day, i.g., 40d | - | Anti-oxidative, Anti-apoptotic | (Jia et al., 2014) |
| | | Mouse | 60, 120 mg/kg, i.g., 40-50d | 120mg/kg | Increasing $Na^+$-$K^+$ ATPase, GSH-Px activity, decreasing NO level | (Kuang, 2009) |
| | | Rat | 10 mg/kg/day, i.p., 14d | - | Decreasing P-tau phosphorylation, increasing the CRMP-2 expression level. | (Chen et al., 2015) |
| | Alcohol extract | Rat | 5, 20 mg/kg/day, i.g., 3d | 5 mg/kg/day | Promoting neurite outgrowth, neuronal cell differentiation, and presynaptic formation | (Choi et al., 2011) |
| | | C6 cells | 0, 10, 100, and 250 μg/mL | 250 μg/mL | Promoting neurite outgrowth, neuronal cell differentiation, and presynaptic formation | (Choi et al., 2011) |
| | | PC12 cell | 0, 10, 100, and 250 μg/mL | 250 μg/mL | Promoting neurite outgrowth, neuronal cell differentiation, and presynaptic formation | (Choi et al., 2011) |
| | Water extract | Rat | 100 and 200 mg/kg, i.g., 15d | 200 mg/kg | Decreasing Aβ deposition, reversal of neurotransmitter dysfunction, anti-oxidant, neurotrophic activities | (Wu et al., 2014b) |
| | Acteoside | Mouse | 30, 60, and 120 mg/kg/day, i.g., 60d | 30 mg/kg/day | Decreasing NOS activity and caspase-3 expression | (Gao et al., 2015a; Peng et al., 2015) |
| | | Rat | 25 mg/kg, i.p., one time | - | Upregulating HO-1 Expression | (Wang et al., 2012) |
| | | PC12 cells | 30 μM | 30 μM | Activating Nrf2-ARE pathway, upregulating HO-1 Expression | (Wang et al., 2012) |
| | Echinacoside | PC12 cells | 100, 300 and 500μM | 100 μM | Anti-oxidant | (Zhang et al., 2015a) |
| Anti-PD | PhGs | Mice | 10, 50 mg/kg, i.g., 11d | 10 mg/kg | Facilitating striatal DA release. | (Geng et al., 2004) |
| | PhGs | CGNs | 10, 20 and 40μg/mL | 10μg/mL | Inhibiting the caspase-3 and caspase-8 activation | (Tian et al., 2005) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Acteoside | CGNs | 12.5, 25 and 50μM | 25μM | Anti-apoptotic | (Pu et al., 2003) |
| | Echinacoside | Mice | 5 and 20 mg/kg, i.g., 15d | 5 mg/kg | Inhibiting the caspase-3 and caspase-8 activation | (Geng et al., 2007) |
| | | Rat | 3.5 and 7.0 mg/kg, i.g., 7d | 3.5 mg/kg | Anti-apoptosis and anti-oxidant | (Chen et al., 2007a) |
| | | SH-SY5Y cells | 1, 10, 100 μg/mL | 1 μg/mL | Anti-apoptosis and anti-oxidant | (Deng et al., 2004a) |
| | | SH-SY5Y cells | 5, 10 and 20 mg/L | 5mg/L | Activating Trk- ERK pathway | (Zhu et al., 2013) |
| | | PC-12 cells | 0.1, 1, 10 μM | 0.1μM | Attenuating mitochondrial dysfunction, reducing ROS production | (Wang et al., 2015d) |
| | | PC12 cells | 5, 10 μg/mL | 5 μg/mL | Though mitochondrial apoptotic pathway | (Kuang, 2009) |
| | | PC12 cells | 5, 10 μg/mL | 5 μg/mL | Suppression NO production | (Kuang et al., 2010) |
| | Tubuloside B | PC-12 cells | 1, 5, 10, 50, 100 μg/mL | 5 μg/mL | Antioxidant, | (Sheng et al., 2002) |
| | | SH-SY5Y cells | 1, 10, and 100 μg/mL | 1 μg/mL | Anti-apoptosis and antioxidant | (Deng et al., 2004b) |
| | Water extract | Ball-1 cells | 1, 10, and 100 μg/mL | 10 μg /mL | Stimulating B cell proliferation | (Maruyama et al. 2007), |
| | Ethanol extract | Mice | 50, 150 and 450 mg/kg, i.g., 28d | 150 mg/kg | - | (Zhang et al. 2014) |
| | | Mice | 100, 500 and 2500 mg/kg, i.g., 28d | 100 mg/kg | Increasing the naïve T cell, NK cell and spleen cell population | (Zhang et al. 2014) |
| | Polysaccharide | Spleen cells | 1, 10, and 100 μg /mL | 10μg /mL | - | (Dong et al. 2007) |
| Immunoregulatory | Arabinogalactan | Spleen cells | 10, 30 and 100μg/mL | 10μg/mL | - | (Wu et al. 2005) |
| | Pectic polysaccharides | Mitogenic and comitogenic thymocyte tests | 1, 10 and 100 μg /mL | 1μg /mL | - | (Ebringerova et al. 2002; Ebringerova et al. 1997), |
| | PhGs | B16-F10 cells | 100, 200, 300, and 400 μg/mL | 100 μg/mL | - | (Li et al., 2016a) |
| | Acteoside, | J774.A1 cells | 1-1000 ng/mL | 1 ng/mL | - | (Inoue et al., 1998a) |
| Anti-tumor | PhGs, | Mice | 200 and 400 mg/kg | 200 mg/kg | Though mitochondrion-dependent signaling pathway, immunoregulatory effects | (Li et al., 2016a) |
| | Acteoside, | MGc80-3 cells | 10, 20 μmol/L | 10 μmol/L | Reversing malignant phenotypic characteristic, induced | (Li et al., 1997) |

| | | | | | |
|---|---|---|---|---|---|
| | | | | redifferentiation | |
| | HL-60 cells | 5-100 μg/mL | $IC_{50}$ 26.7μM | Inducing apoptosis | (Inoue et al. 1998) |
| Echinacoside, | SW1990 cells | 20, 50 and 100 μM | 20 μM | Reducing ROS production, perturbing mitochondrial membrane potential, modulating MAPK activity | (Wang et al. 2016) |

## 5 Pharmacokinetics studies

Although Cistanches Herba contained many chemical constituents, pharmacokinetic studies of these compounds focused on echinacoside and acteoside due to their high content and clear pharmacological activity. PhGs are usually administered orally. Poor oral absorption was observed in Caco-2 cell monolayer model (Gao et al., 2015b). There existed different opinions on PhGs absorption. Shen reported that echinacoside was the substrate of P-glycoprotein (P-gp), verapamil and clove oil could improve echinacoside absorption. The mechanisms of which on the enhancing effect could be exocytosis of P-gp inhibition and alter the intestinal mucous membrane of lipid phase (Shen et al., 2015). Tanino et al. (2015) gave the opposite conclusion that echinacoside and acteoside transport were irrelevant to P-gp. Glucose transporter-dependent played an important role in this progress. Cistanche polysaccharides were also poorly absorbed by Caco-2 cell (Qi et al., 2010). It is important that more studies be carried out to elucidate the absorption mechanism of Cistanches Herba.

Oral administration of acteoside at 40 mg/kg produced the following pharmacokinetic parameters: $C_{max}$, 312.54 ± 44.43 ng/mL; $T_{max}$, 17.4 ± 10.2 min; $T_{1/2}$, 63 ± 13.8 min; $AUC_{0\text{-}5h}$, 364.67 ± 76.05 ng/(mL*h), respectively. The absolute bioavailability of acteoside was about 1% and the rat plasma protein binding ratio was about 60% with equilibrium dialysis method (Wen et al., 2016). The low blood drug concentration, and relatively rapid metabolism were observed. Acteoside was rapidly absorbed and widely distributed in various tissues, including intestine, stomach, lung, brain, etc. The highest concentration was detected in intestine and lung, followed by stomach, muscle and other tissues. It is worth noting that acteoside is widely distributed in all parts of the brain tissues, however, its mechanism of crossing the blood-brain barrier is unknown (Wen et al., 2016). Lei first reported that the metabolism of PhGs mainly occurred in colon but not in the stomach and intestinal. PhGs are always administered as oral formulations and unavoidably interact with gut microbiota in the intestinal. Acteoside consists of four chemical moieties: caffeic acid,

hydroxytyrosol, glucose, and rhamnose group. Under gut microbiota, acteoside metabolized to other active components *via* hydrolyzation, isomerization, hydrogenation, dehydroxylation, methylation, acetylation, hydroxylation and methoxylation. 14 metabolites were identified, among which caffeic acid and hydroxytyrosol were reported to possess biological activity, even more than acteoside (Cui et al., 2016). Qi et al. (2013) reported that 35 metabolites of acteoside in rats' urine were detected by UPLC/ESI-QTOF-MS and metabolic pathways of acteoside were proposed. Methylation occurred more easily in the metabolic process *in vivo*. Little amount of acteoside was found in urine, bile or feces, suggesting the extensive metabolism in rats (Wen et al., 2016).

Echinacoside absorption is similar to acteoside. The oral bioavailability of echinacoside was detected by HPLC-UV, single oral administration of 100 mg/kg of echinacoside got $C_{max}$, 612.2 ± 320.4 ng/mL; $T_{max}$, 15.0 min; $T_{1/2}$, 74.4 min; $AUC_{0\text{-}6h}$, 60704.9 ng min /mL and the absolute bioavailability of echinacoside was 0.83% (Jia et al. 2006). Li et al. (2015) found that echinacoside was stable in stimulated gastric juice and intestinal juice. Under human intestinal bacteria, echinacoside produced a variety of secondary metabolites, such as acteoside, HT and 3-hydroxyphenylpropionic acid, etc. It could transform into acteoside by the deglycosylation reaction in β-Glucosidase (Lei et al., 2001; Zhao et al., 2011). Fast and extensive metabolic may contribute to the low bioavailability.

## 6 Discussion and future perspectives

Cistanches Herba as a tonic herb, it is one of the most widely used 'kidney-yang' tonic herbs in China for thousand years. They have attracted growing interest in recent years owing to their significant biological activity, immunomodulatory, anti-cancer, anti-oxidant, anti-inflammatory and hepatoprotective therapeutic effect, etc., especially neuroprotective effects. Modern studies showed that damage and functional disorders of the hypothalamic-pituitary-target gland axis, including the adrenal gland, thyroid, and gonad, are the main pathological mechanisms of 'kidney-yang deficiency syndrome'. The hypothalamus is considered to be the pivot to link neuroendocrine

with immune systems (Shen, 1999). Cistanches Herba as a 'kidney-yang' tonic herb takes part in neuroendocrine-immune networks, which is related to neuroprotective and immunomodulation effects; cures yang deficiency, erection dysfunction, and female with irregular menstruation, which is related to endocrine regulation activities; cures soreness of waist and knees, which is related to anti-osteoporosis and anti-fatigue activity; moisturizes the intestine and relaxing bowels, which is related to gastrointestinal tract protection activity.

In clinical applications, Cistanches Herba showed several activities. In part 4.2, *C. tubulosa* glycoside capsules (Memoregain®) have the efficacy of treating mild and moderate AD patients (Guo et al., 2013); In part 4.5, echinacoside glycosides combined with fucoidan can prevent hair loss and scalp inflammation (Seok et al., 2015). Besides single herb, the compounds containing Cistanches Herba also be used in clinical. Bushen Huoxue Granule, Cistanches Herba as an important active composition brings improvement in people with Parkinson's disease (Li et al., 2016b). We also searched for ongoing and unpublished studies about Cistanches Herba on the International Clinical Trials Registry Platform (http://apps.who.int/trialsearch) and found that a randomized control trial about Cistanche total glycosides for amyotrophic lateral sclerosis was being carried on (Main ID: ChiCTR-IOR-15006524), further research results will be reported in the near future.

PhGs exhibit strong neuroprotective effects, based on their antioxidant activity, anti-apoptosis activity, anti-inflammation activity. PhGs may be potential candidate for treating serevaldiseases. However, its clear pharmacological characteristics such as the poor permeability, fast and extensive metabolism in the gut, is a riddle yet to be resolved by scientists. The exact mode of action of parent and metabolites are still elusive and deserved special attention in future. Polysaccharides as another active constituent are difficult to be digested by the human body. Recently, lots of reports indicate that dietary polysaccharides can be fermented into short chain fatty acids to product benefits by gut microbiota. There is no enough evidence to show the mechanism of action of *Cistanches* polysaccharides (Figure 1).

In conclusion, Cistanches Herba as a nutraceutical and functional food, as well as

potentially representing a valuable source for bioactive compounds and pharmaceutical application. The information presented in this review may form the basis of providing adequate knowledge for future studies and developments as well as commercial exploitation of Cistanches Herba. Despite that, there are still many challenges that need resolution in order to ease herbal medicine development before approval and marketed as a save pharmaceutical products.

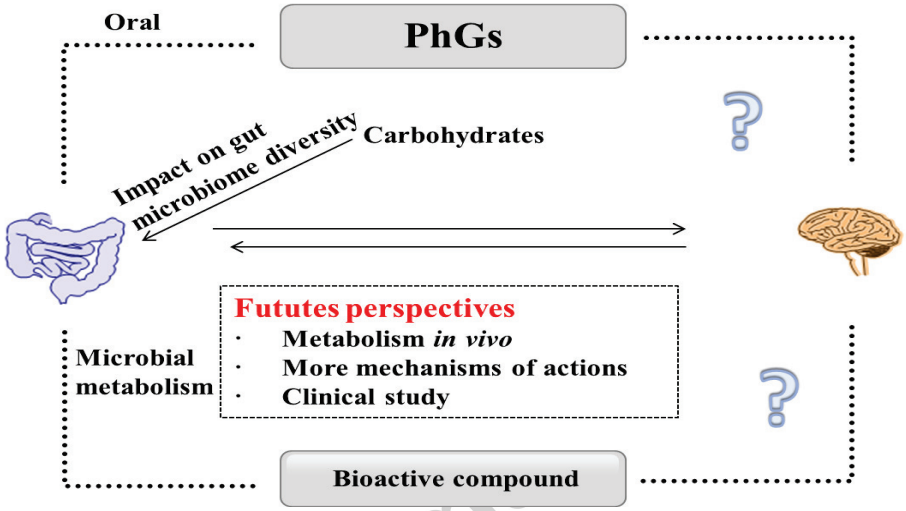



Figure 1. The future perspectives of Cistanches Herba

## Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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**References**

Adnan, M., Bibi, R., Mussarat, S., Tariq, A., Shinwari, Z., 2014. Ethnomedicinal and phytochemical review of Pakistani medicinal plants used as antibacterial agents against Escherichia coli. Ann. Clin. Microbiol. Antimicrob. 13, 40.

Amin, B., Poureshagh, E., Hosseinzadeh, H., 2016. The Effect of Verbascoside in Neuropathic Pain Induced by Chronic Constriction Injury in Rats. Phytother. Res. 30 (1), 128-135.

Bai, Y., Li, H., Chen, S., 2013. Composition Analysis and Immunological Activities of the Oligosaccharides Isolated from *Cistanche Deserticola*. 4th Int. Conf. Food Eng. Biotechnol. 157-162.

Cai, R., Yang, M., Shi, Y., Chen, J., Li, Y., Qi, Y., 2010. Antifatigue activity of phenylethanoid-rich extract from Cistanche deserticola. Phytother. Res. 24 (2), 313-315.

Campo, G., Marchesini, J., Bristot, L., Monti, M., Gambetti, S., Pavasini, R., Pollina, A., Ferrari, R., 2012. The *in vitro* effects of verbascoside on human platelet aggregation. J. Thromb. Thrombolys. 34 (3), 318-325.

Campo, G., Pavasini, R., Biscaglia, S., Ferri, A., Andrenacci, E., Tebaldi, M., Ferrari, R., 2015. Platelet aggregation values in patients with cardiovascular risk factors are reduced by verbascoside treatment. A randomized study. Pharmacol. Res. 97, 1-6.

Chen, H., Jing, F., Li, C., Tu, P., Zheng, Q., Wang, Z., 2007a. Echinacoside prevents the striatal extracellular levels of monoamine neurotransmitters from diminution in 6-hydroxydopamine lesion rats. J. Ethnopharmacol.114 (3), 285-289.

Chen, J., Zhou, S., Zhang, Y., Feng, Y., Wang, S., 2015. Glycosides of cistanche improve learning and memory in the rat model of vascular dementia. Eur. Rev. Med. Pharmacol. Sci. 19 (7), 1234-1240.

Chen, Z., Zhu, B., Yu, X., 2007b. Experiment study of desertliving Cistanche polysaccharides on regulated haematogenesis in bone marrow depressed anemia mice. Arch. Tradit. Chin. Med. 25 (7), 1473-1474.

Chinese Pharmacopoeia Committee Editing, 2005. Chinese Pharmacopoeia (part I, 2005 edition), Chemical and Industrial Publisher, 135.

Choi, J., Moon, M., Jeong, H., Kim, M., Kim, S., Oh M., 2011. Cistanches Herba enhances learning and memory by inducing nerve growth factor. Behav. Brain. Res. 216 (2), 652-658.

Chung, K., Jeon, E., An, H., 2016. Anti-proliferation effects of Cistanches salsa on the progression of benign prostatic hyperplasia. Can. J. Physiol. Pharmacol. 94 (1), 104-111.

Cui, Q., Pan, Y., Xu, X., Zhang, W., Wu, X., Qu, S., Liu, X., 2016. The metabolic profile of acteoside produced by human or rat intestinal bacteria or intestinal enzyme in vitro employed UPLC-Q-TOF-MS. Fitoterapia. 109, 67-74.

Deng, M., Zhao, J., Tu P., Jiang, Y., Li, Z., Wang, Y., 2004a. Echinacoside rescues the SHSY5Y neuronal cells from TNFα-induced apoptosis. Eur. J. Pharmacol. 505 (1-3), 11-18.

Deng, M., Zhao, J., Ju, X., Tu, P., Jiang, Y., Li, Z., 2004b. Protective effect of tubuloside B on TNFα-induced apoptosis in neuronal cells. Acta. Pharmacol. Sin. 25 (10), 1276-1284.

Deyama, T., Kobayashi, H., Nishibe, S., Tu, P., 2006. Isolation, structure elucidation and bioactivities of phenylethanoid glycosides from Cistanche, Forsythia and Plantago plants. Studi. Nat. Prod. Chem. 33, 645-674.

Deyama, T., Yahikozawa, K., Al-Easa, H., Rizk, A., 1995. Constituents of plants growing in Qatar: Part XXX. A new iridoid from Cistanche phelypaea (L) Cout. Int. J. Chem. 6(4), 107-112.

Díaz, A., Abad, M., Fernández, L., Silván, A., De, Santos., Bermejo, P., 2004. Phenylpropanoid glycosides from Scrophularia scorodonia: In vitro anti-inflammatory activity. Life Sci. 74 (20), 2515-2526.

Dong, L., Wang, H., Niu, J., Zou, M., Wu, N., Yu, D., Wang, Y., Zou, Z., 2015. Echinacoside induces apoptotic cancer cell death by inhibiting the nucleotide pool sanitizing enzyme MTH1. Oncotargets Ther. 8, 3649-3664.

Dong, Q., J. Yao, J. Fang, K. Ding. 2007. Structural characterization and immunological activity of two cold-water extractable polysaccharides from *Cistanche deserticola* Y. C. Ma. Carbohyd. Res. 342 (10), 1343-1349.

Du, N., Qu, S., Re, X., Ni, J., Zhang, H., Yan, H., 1988.Study on the composition of the essential oil

from Cistanche Salsa G. Org. Chem. 8 (6), 522-525.

Ebringerova, A., Hromadkova, Z., Machova, E., Naran, R., Hribalova, V., 1997. Isolation and characterization of mitogenic pectic polysaccharides from Cistanche deserticola YC Ma. Chem Pap. 51 (5), 289-294.

Ebringerova, A., Hromadkova, Z., Hribalova, V., Hirsch, J., 2002. An immunomodulating pectic arabinogalactan from roots of Cistanche deserticola. Chem. Pap. 56 (5), 320-325.

Fang, H., Li, J., Yao, L., Zhao, T., 2015. Echinacoside promotes cell proliferation of rat osteoblast through activating of ERK/BMP-2 signaling pathway. Med. Forum.19 (4), 435-438.

Gai, X., Wei, Y., Zhang, W., Wuren, T., Wang, Y., Li, Z., Liu, S., Ma, L., Lu, D., Zhou, Y., Ge, R., 2015. Echinacoside induces rat pulmonary artery vasorelaxation by opening the NO-cGMP-PKG-BKCa channels and reducing intracellular $Ca^{2+}$ levels. Acta Pharmacol. Sin. 36 (5), 587-596.

Gao, L., Peng, X., Huo, S., Liu, X., Yan, M., 2015a. Memory enhancement of acteoside (verbascoside) in a senescent mice model induced by a combination of d-gal and $AlCl_3$. Phytother. Res. 29 (8), 1131-1136.

Gao, Y., Zong, C., Liu, F., Fang, L., Cai, R., Shi, Y., Chen, X., Qi, Y., 2015b. Evaluation of the intestinal transport of a phenylethanoid glycoside-rich extract from *Cistanche deserticola* across the Caco-2 Cell monolayer model. Plos one, 10 (2), e116490.

Gao, Y., Qin, G., Wen, P., Wang, Y., Fu, W., He, L., Yao, S., Zhao, P., 2016. Safety assessment of powdered *Cistanche deserticola* Y. C. Ma by a 90-day feeding test in Sprague-Dawley rats. Drug Chem. Toxicol.1-7.

Gao, Y., Jiang, Y., Dai, F., Han, Z., Liu, H., Bao, Z., Zhang T., Tu, P., 2015c. Study on Laxative Constituents in Cistanche deserticola Y. C. Ma. Modern Chinese Medicine. 17(4), 307-314.

Geng, X., Song, L., Pu, X., Tu, P., 2004. Neuroprotective effects of phenylethanoid glycosides from *Cistanches salsa* against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced dopaminergic toxicity in C57 mice. Biol. Pharm. Bull. 27 (6), 797-801.

Geng, X., Tian, X., Tu, P., Pu, X., 2007. Neuroprotective effects of echinacoside in the mouse MPTP model of Parkinson's disease. Eur. J. Pharmacol. 564 (1-3), 66-74.

Giancamillo, A., Rossi, R., Vitari, F., Carollo, V., Deponti, D., Corino, C., Domeneghini, C., 2013. Changes in nitrosative stress biomarkers in swine intestine following dietary intervention with verbascoside. Histol. Histopathol. 28 (6), 715-723.

Gu, C., Yang, X., Huang, L., 2016. Cistanches Herba: A Neuropharmacology Review. Front. Pharmacol. 7.

Gu, L., Xiong, W., Wang, C., Sun, H., Li, G., Liu, X., 2013. *Cistanche deserticola* decoction alleviates the testicular toxicity induced by hydroxyurea in male mice. Asian. J. Androl. 15 (6), 838-840.

Guo, Q., Zhou, Y., Wang, C., Huang, Y., Lee, Y., Su, M., Lu, J., 2013. An open-label, nonplacebo-controlled study on cistanche tubulosa glycoside capsules (memoregain(r)) for treating moderate alzheimer's disease. Am. J. Alzheimer's Dis. Dement. 28 (4), 363-370.

Guo, Y., Cao, L., Zhao, Q., Zhang, L., Chen, J., Liu, B., Zhao, B., 2016. Preliminary characterizations, antioxidant and hepatoprotective activity of polysaccharide from *Cistanche deserticola.* Int. J. Biol. Macromol. 93 (Pt A), 678-685.

Hausmann, M., Obermeier, F., Paper, D., Balan, K., Dunger, N., Menzel, K., Falk, W., Schoelmerich, J., Herfarth, H., Rogler, G., 2007. In vivo treatment with the herbal phenylethanoid acteoside ameliorates intestinal inflammation in dextran sulphate sodium-induced colitis. Clin. Exp. Immunol.

148 (2), 373-381.

Hayashi, K., Nagamatsu, T., Ito, M., Hattori, T., Suzuki, Y., 1996. Acteoside, a Component of Stachys Sieboldii MIQ, May Be a Promising Antinephritic Agent (3): Effect of Acteoside on Expression of Intercellular Adhesion Molecule-1 in Experimental Nephritic Glomeruli in Rats and Cultured Endothelial Cells. Jpn. J. Pharmacol. 70, 157-168.

Hayashi, K., Nagamatsu, T., Ito, M., Hattori, T., Suzuki, Y., 1994. Acteoside, a Component of Stachys Sieboldii MIQ, May Be a Promising Antinephritic Agent (2): Effect of Acteoside on Leukocyte Accumulation in the Glomeruli of Nephritic Rats. Jpn. J. Pharmacol. 66 (1), 47-52.

Hayashi. K., 2004. Studies on the constituents of Cistanchis Herba. Nat. Med. 58 (6), 307-310.

He, W., Fang, T., Ma, X., Zhang, K., Ma, Z., Tu, P., 2009. Echinacoside elicits endothelium-dependent relaxation in rat aortic rings via an NO-cGMP pathway. Planta Med. 75 (13), 1400-1404.

Herbert, J., Maffrand, J., Taoubi, K., Augereau, J., Fouraste, I., Gleye, J., 1991. Verbascoside isolated from Lantana camara, an inhibitor of protein kinase C. J Nat. Prod. 54 (6), 1595-1600.

Huang, C., Shang, Y., Zhang, J., Zhang, J., Li, W., Jiao, B., 2008. Hypouricemic effects of phenylpropanoid glycosides acteoside of Scrophularia ningpoensis on serum uric acid levels in potassium oxonate-pretreated mice. Am. J. Chin. Med. 36 (1), 149-157.

Inoue, M., Ueda, M., Ogihara, Y., Saracoglu, I., 1998a. Induction of cytokines by a phenylpropanoid glycoside acteoside. Biol Pharm Bull. 21 (12), 1394-1395.

Inoue, M., Ueda, M., Ogihara, Y., Saracoglu, I., 1998b. Induction of apoptotic cell death in HL-60 cells by acteoside, a phenylpropanoid glycoside. Bio. Pharm. Bull. 21 (1), 81-83.

Jia, J., Song, W., Yan, X., Fang, X., Yang, Z., Cai, Z., Cui, C., 2014. Effect of glycosides of Cistanche on spatial learning and memory in SAMP8 mice and its mechanism. J. Baotou Med. Colg. 30 (06), 6-8.

Jia, C., Shi, H., Wu, X., Li, Y., Chen, J., Tu, P., 2006. Determination of echinacoside in rat serum by reversed-phase high-performance liquid chromatography with ultraviolet detection and its application to pharmacokinetics and bioavailability. J. Chromatogr. B. 844 (2), 308-313.

Jia, Y., Guan, Q., Guo, Y., Du, C., 2012a. Reduction of inflammatory hyperplasia in the intestine in colon cancer-prone mice by water-extract of *Cistanche deserticola*. Phytother. Res. 26 (6), 812-819.

Jia, Y., Guan, Q., Guo, Y., Du, C., 2012b. Echinacoside stimulates cell proliferation and prevents cell apoptosis in intestinal epithelial mode-k cells by up-regulation of transforming growth factor-β1 Expression. J. Pharmacol. Sci. 118 (1), 99-108.

Jia, Y., Guan, Q., Jiang, Y., Salh, B., Guo, Y., Tu, P., Du, C., 2014. Amelioration of dextran sulphate sodium-induced colitis in mice by echinacoside-enriched extract of Cistanche tubulosa. Phytother. Res. 28 (1), 110-119.

Jiangsu New Medical College. 1986. Dictionary of traditional Chinese drugs (upper volume). Shanghai Sci. Tech. Publisher, Shanghai, 1977, 895.

Jiang, Z., Wang, J., Li, X., Zhang, X., 2016. Echinacoside and *Cistanche tubulosa* (Schenk) R. wight ameliorate bisphenol A-induced testicular and sperm damage in rats through gonad axis regulated steroidogenic enzymes. J. Ethnopharmacol. 193, 321-328.

Jiang, Y., Tu, P., 2009. Analysis of chemical constituents in Cistanche species. J. Chromatogr. A. 1216 (11), 1970-1979.

Karasawa, H., Kobayashi, H., Takizawa, N., Miyase, T., Fukushima, S., 1986a. Studies on the constituents of cistanchis herba. Ⅷ. Isolation and structures of a new phenylpropanoid glycosides, cistanosides G. Yakugaku Zasshi. 106 (8), 721-724.

Karasawa, H., Kobayashi, H., Takizawa, N., Miyase, T., Fukushima, S., 1986b. Studies on the

constituents of cistanchis herba. Ⅶ. Isolation and structures of cistanosides H and I. Yakugaku Zasshi. 106(7), 562-566.

Kim, S., Yoo, S., Lee, H., Kim, K., Kim, D., Park, S., Chang, M., 2012. *Cistanches herba* induces testis cytotoxicity in male mice. Bull. Environ. Contam. Toxicol. 88 (1), 112-117.

Kobayashi, H., Karasawa, H., Miyase, T., Fukushima, S., 1984a. Studies on the constituents of cistanchis herba. II. Isolation and structures of new iridoids, cistanin and cistachlorin. Chem. Pharm. Bull. 32 (5), 1729-1734.

Kobayashi, H., Karawawa, H., Miyase, T., 1984b. Studies on the constituents of cistanchis herba. III. Isolation and structures of new phenylpropanoid glycosides, cistanosides A and B. Chem. Pharm. Bull. 32 (8), 3009-3014.

Kobayashi, H., Karasawa, H., Miyase, T., Fukushima, S., 1984c. Studies on the constituents of cistanchis herba. IV. Isolation and structures of two new phenylpropanoid glycosides, cistanosides C and D. Biol. Pharm. Bull. 32 (10), 3880-3885.

Kobayashi H., Karawawa, H, Miyase, T., Fukushima, S., 1985a. Studies on the constituents of Cistanchis herba. Ⅵ. isolation and structure of a new iridoid glycoside, 6-deoxycatalpol. Chem. Pharm. Bull. 33 (9), 3645-3650.

Kobayashi, H., Karasawa, H., Miyase, T., Fukushima, S., 1985b. Studies on the constituents of Cistanchis Herba. V. Isolation and structures of two new phenylpropanoid glycosides, cistanosides E and F. Biol. Pharm. Bull. 33 (4), 1452-1457.

Kobayashi, H., Oguchi, H., Takizawa, N., Miyase, T., Ueno, A., Usmanghani, K., Ahmad, M., 1987. New phenylethanoid glycosides from Cistanche tubulosa (SCHRENK) HOOK. f. I. Chem. Pharm. Bull. 35 (8), 3309.

Kuang, R., Sun, Y., Yuan, W., Lei, L., Zheng, X., 2009. Protective effects of echinacoside, one of the phenylethanoid glycosides, on $H_2O_2$-induced cytotoxicity in PC12 cells. Planta Med. 75 (14), 1499-1504.

Kuang, R., Sun, Y., Zheng, X., 2010. Suppression of Nitric Oxide Implicated in the Protective Effect of Echinacoside on H2O2-Induced PC12 Cell Injury. Nat. Prod. Commun. 5 (4), 571-574.

Kuang, R., 2009. Effects of Cistanche tubulosa glycosides and echinacoside on oxidative stess-induced alzheimer's disease models and mechanisms *in vivo* and *in vitro*. ZheJiang Univ.

Kyung, J., Kim, D., Park, D., Yang, Y., Choi, E., Lee, S., Kim, T., Lee, Y., Kim, Y., 2015. Synergistic anti-inflammatory effects of Laminaria japonica fucoidan and Cistanche tubulosa extract. Lab. Anim. Res. 28 (2), 91-97.

Lee, J., Woo, E., Kang, K., 2005. Inhibition of lipopolysaccharide-inducible nitric oxide synthase expression by acteoside through blocking of AP-1 activation. J. Ethnopharmacol. 97 (3), 561-566.

Lee, K. J., Woo, E., Choi, C., Shin, D., Lee, D., You, H., Jeong, H., 2004. Protective effect of acteoside on carbon tetrachloride-induced hepatotoxicity. Life Sci. 74 (8), 1051-1064.

Leung, H., Ko, K., 2008. *Herba Cistanche* extract enhances mitochondrial ATP generation in rat hearts and H9C2 cells. Pharm. Biol. 46 (6), 418-424.

Lei, L., Jiang, Y., Liu, X., Tu, P,. Wu, L., Chen, F., 2007. New Glycosides from Cistanche salsa. Helv. Chim. Acta. 90, 79-85.

Lei, L., Song, Z., Li, Y., Tu, P., Wu, L., Chen, F., 2001. Metabolic regulation of phenylethanoid glycosides from herba cistanches in dogs' gastrointestine. Acta. Pharm. Sin. 36 (06), 432-435.

Li, F., Yang, X., Yang, Y., Guo, C., Zhang, C., Yang, Z., Li, P., 2013. Antiosteoporotic activity of echinacoside in ovariectomized rats. Phytomedicine. 20 (6), 549-557.

Li, F., Yang, Y., Zhu, P., Chen, W., Qi, D., Shi, X., Zhang, C., Yang, Z., Li, P., 2012b. Echinacoside promotes bone regeneration by increasing OPG/RANKL ratio in MC3T3-E1 cells. Fitoterapia. 83 (8), 1443-1450.

Li, J., Huang, D., He, L., 2014a. Effect of Roucongrong (Herba Cistanches Deserticolae) on reproductive toxicity in mice induced by glycoside of Leigongteng (Radix et Rhizoma Tripterygii). J. Tradit. Chin. Med. 34 (3), 324-328.

Li, J., Li, J., Aipire, A., Gao, L., Huo, S., Luo, J., Zhang, F., 2016a. Phenylethanoid glycosides fromcistanche tubulosa inhibits the growth of B16-F10 cells both *in vitro* and *in vivo* by induction of apoptosis via mitochondria-dependent pathway. J. Cancer. 7 (13), 1877-1887.

Li, J., Y. Zheng, H. Zhou, Su, B., Zheng R., 1997. Differentiation of human gastric adenocarcinoma cell line MGc80-3 induced by verbascoside. Planta Med. 63 (6), 499-502.

Li, M., Yang, H., Luo, D., Chen, J., Shi, H., 2016b. Multi-dimensional analysis on Parkinson's disease questionnaire-39 in Parkinson's patients treated with Bushen Huoxue Granule: A multicenter, randomized, double-blinded and placebo controlled trial. Complement. Ther. Med. 29: 116-120.

Liu, S. Suwen Bingji Qiyi Baomingji. Beijing: people's medical publishing house, 1959, 75.

Li, T., Huang, H., Su, C., Ho, T., Wu, C., Chen, W., Fong, Y., Tang, C., 2012a. Cistanche deserticola extract increases bone formation in osteoblasts. J. Pharm. Pharmacol. 64 (6), 897-907.

Li, X., Gou, C., Yang, H., Qiu, J., Gu, T., Wen, T., 2014b. Echinacoside ameliorates D-galactosamine plus lipopolysaccharide-induced acute liver injury in mice via inhibition of apoptosis and inflammation. Scand. J. Gastroentero. 49 (8), 993-1000.

Li, Y., Zhou, G., Xing, S., Tu, P., Li, X., 2015. Identification of Echinacoside Metabolites Produced by Human Intestinal Bacteria Using Ultraperformance Liquid Chromatography–Quadrupole Time-of-Flight Mass Spectrometry. J. Agr. Food Chem. 63 (30), 6764-6771.

Li, Z., Lin, H., Gu, L., Gao, J., Tzeng, C., 2016c. Herba Cistanche (Rou Cong-Rong): One of the Best Pharmaceutical Gifts of Traditional Chinese Medicine. Front. Pharmacol. 7.

Liang, H., Yu, F., Tong, Z., Zhang, H., Liang, W., 2013. *Cistanches Herba* aqueous extract affecting serum BGP and TRAP and bone marrow Smad1 mRNA, Smad5 mRNA, TGF-β1 mRNA and TIEG1 mRNA expression levels in osteoporosis disease. Mol. Biol. Rep. 40 (2), 757-763.

Liang, H., Yu, F., Tong, Z., Huang, Z., 2011. Effect of Cistanches Herba aqueous extract on bone loss in ovariectomized rat. Int J Mol. Sci. 12 (12), 5060-5069.

Lin, L., Hsieh, M., Tsai, H., Wang, W., Wu, C., 2002. Anti-nociceptive and anti-inflammatory activity caused by Cistanche deserticola in rodents. J. Ethnopharmacol. 83 (3), 177-182.

Liu, X., Li, J., Jiang, Y., Zhao, M., Tu, P., 2013. Chemical constituents from Cistanche sinensis (Orobanchaceae). Biochem. Syst. Ecol. 47, 21-24.

Liu, G., 2004. The Technology about Planting *Cistanche Deserticola*. Beijing, China Labour and Social Security Publishing House, 10.

Liu, X., Jiang, Y., Sun, Y., Xu, X., Tu, P., 2011. Studies on the chemical constituents of *Cistanche deserticola*. Chin. Pham. J. 46 (14), 1053-1058.

Lu, M., 1998. Studies on the sedative effect of *Cistanche deserticola*. J. Ethnopharmacol. 59 (3), 161-165.

Luo, H., Zhao, F., Wang, L., Zhu, L., 2014. Protective activities of Cistanoside A on alcohol induced hepatotoxicity in mice. Lat. Am. J. Pharm. 33 (5), 778-784.

Luo, H., Cao, R., Wang, L., Zhu, L., 2016. Protective effect of Cistanchis A on ethanol-induced damage in primary cultured mouse hepatocytes. Biomed. Pharmacother. 83, 1071-1079.

Ma, De., Duan, J., 1993. A new species of the genus cistanche from ningxia. Acta Bot. Boreal. Occident. Sin. 13 (1), 75-76.

Maruyama, S., Yamada, K., Tachibana, H., 2007. Cistanche salsa extract enhanced IgM production in the human B cell line BALL-1. J. Trad. Med. 24 (6), 209-211.

Maruyama, S., Hashizume, S., Tanji, T., Yamada, K., Tachibana, H., 2008a. *Cistanche salsa* Extract Enhanced Antibody Production in Human Lymph Node Lymphocytes. Pharmacologyonline, 2, 341-348.

Maruyama, S., Yamada, K., Tachibana, H., 2008b. *Cistanche salsa* extract induced apotosis in the human burkitt's lymphoma cell line Namalva. J. Trad. Med. 25, 24-27.

Maruyama, S., Akasaka, T., Yamada, K., Tachibana, H., 2008c. Cistanche salsa extract acts similarly to protein-bound polysaccharide-K (PSK) on various types of cell lines. J. Trad. Med, 25, 166-169.

Maruyama, S., Yamada, K., Tachibana, H., 2008d. Immunomodulatory factors in Cistanche salsa. J. Trad. Med. 25, 87-89.

Melek, F., El-Shabrawy, O., El-Gindy, M., Miyase, T., Hilal, S., 1993. Pharmacological activity and composition of the ethyl acetate extract of Cistanche phelypaea. Fitoterapia. 64 (1), 11-14.

Morikawa, T., Ninomiya, K., Imamura, M., Akaki, J., Fujikura, S., Pan, Y., Yuan, D., Yoshikawa, M., Jia, X., Li, Z., Muraoka, O., 2014. Acylated phenylethanoid glycosides, echinacoside and acteoside from Cistanche tubulosa, improve glucose tolerance in mice. J. Nat. Med. 68 (3), 561-566.

Morikawa, T., Pan, Y., Ninomiya, K., Imura, K., Yuan, D., Yoshikawa, M., Hayakawa, T., Muraoka, O., 2010a. Iridoid and Acyclic Monoterpene Glycosides, Kankanosides L, M, N, O, and P from *Cistanche tubulosa*. Chem. Pharm. Bull. 58 (10), 1403-1407.

Nan, Z., Zeng, K., Shi, S., Zhao, M., Jiang Y., Tu, P., 2013. Phenylethanoid glycosides with anti-inflammatory activities from the stems of Cistanche deserticola cultured in Tarim desert. Fitoterapia. 89, 167-174.

Nan, Z., Zhao, M., Zeng, K., Tian, S., Wang, W., Jiang, Y., Tu, P., 2016. Anti-inflammatory iridoids from the stems of *Cistanche deserticola* cultured in Tarim Desert. Chinese J. Nat. Med. 14(1), 61-65.

Nan, Z., Zhao, M., Jiang, Y., Tu, P., 2015. Lignans from stems of Cistanche deserticola cultured in Tarim desert. Chin. J. Chin. Mat. Med. 40 (03), 463-468.

Naran, R., Ebringerova, A., Hromàdková, Z., Patoprsty, V., 1995. Carbohydrate polymers from underground parts of *Cistanche deserticola*. Phytochemistry. 40 (3), 709-715.

Pan Y, Morikawa T, Ninomiya K,. Imura, K., Yuan, D., Yoshikawa, M., Muraoka, O., 2010. Bioactive constituents from chinese natural medicines. XXXVI. Four new acylated phenylethanoid oligoglycosides, kankanosides J1, J2, K1, and K2, from stems of Cistanche tubulosa. Chem. Pharm. Bull. 58 (4), 575-578.

Pan, Y., 2011. Studies on the constituents and bioactivity of fresh *Cistanche Tubulosa*, Shenyang Pharm. Univ.

Peng, X., Gao, L., Huo, S., Liu X., Yan, M., 2015. The mechanism of memory enhancement of acteoside (verbascoside) in the senescent mouse model induced by a combination of d-gal and $AlCl_3$. Phytother Res., 29 (8), 1137-1144.

Piwowarczyk, R., L. Carlon, J. Kasinska, S. Tofil, P. Furmanczyk., 2016. Micromorphological intraspecific differentiation of nectar guides and landing platform for pollinators in the Iberian parasitic plant Cistanche phelypaea (Orobanchaceae). Bot. Lett. 163 (1), 47-55.

Pu, X., Song, Z., Li, Y., Tu, P., Li, H., 2003. Acteoside from Cistanche salsa inhibits apoptosis by 1-methyl-4-phenylpyridinium ion in cerebellar granule neurons. Planta Med. 69 (1), 65-66.

Qi, M., Xiong, A., Li, P., Yang, Q., Yang, L., Wang, Z., 2013. Identification of acteoside and its major metabolites in rat urine by ultra-performance liquid chromatography combined with electrospray ionization quadrupole time-of-flight tandem mass spectrometry. J. Chromatogr. B. 940, 77-85.

Qi, Y., Cai, R., Wang, X., Li, M., Li, X., Yang, M., 2010. Absorption and transportation of Cistanche deserticola polysaccharides using bioactivity assay *in vitro*. Chin. Pham. J. 45 (07), 527-530.

Qian, Y., Xin, L., Xia, C., 2016. Cardioprotective effects of phenylethanoid glycoside-rich extract from cistanche deserticola in ischemia-reperfusion-induced myocardial infarction in rats. Ann. Vasc. Surg. 34, 234-242.

Qin, J., 2012. Indentify the alkaloid constituents of the herba cistanche by HPLC-MS method. Tianjin Univ. Sci. Tech.

Qiu, Y., Chen, M. Su, M., Xie, G., Li, X., Zhou, M., Zhao, A., Jiang, J., Jia, W., 2008. Metabolic profiling reveals therapeutic effects of Herba Cistanches in an animal model of hydrocortisone-induced 'kidney-deficiency syndrome'. Chin. Med. 3 (3), 1-8.

Reinke, D., Kritas, S., Polychronopoulos, P., Skaltsounis, A., Aligiannis, N., Tran, C., 2015. Herbal substance, acteoside, alleviates intestinal mucositis in mice. Gastroent. Res. Pract. 2015, 1-9.

Seok, J., Kim, T., Kwon, H., Lee, S., Kang, M., Kim, B., Kim, M., 2015. Efficacy of *Cistanche Tubulosa* and Laminaria Japonica extracts (MK-R7) supplement in preventing patterned hair Loss and promoting scalp health. Clin. Nutr. Res. 4 (2), 124.

Shahi Shavvon, R., Saeidi Mehrvarz, S., 2010. Pollen and seed morphology of the genus *Cistanche* (Orobanchaceae) in Iran. Biologia. 65 (4), 615-620.

Shen, J., Yang, X., Yang, Z., Kou, J., Li, F., 2015. Enhancement of absorption and bioavailability of echinacoside by verapamil or clove oil. Drug Des. Devel. Ther. 9, 4685-4693.

Shen, Z., 1999. The location of deficiency syndrome of kidney Yang. Chin. Med. J. 112(11):973-975.

Sheng, G., Pu, X., Lei, L., Tu, P., Li, C., 2002. Tubuloside B from Cistanche salsa rescues the PC12 neuronal cells from 1-methyl-4-phenylpyridinium ion-induced apoptosis and oxidative stress. Planta Med. 68 (11), 966-970.

Shimamura H., Miyazawa, M., Enomoto, K., Nakamura, S., Kameoka, H., 1997. Suppression of SOS-Inducing Activity of Trp-P-1 by Fatty Acids from *Cistanche Salsa* in the Salmonella Typhimurium TA1535/pSK1002 umu Test. Nat. Prod. Lett. 10, 261-265.

Shimoda, H., Tanaka, J., Takahara, Y., Takemoto, K., Shan, S., Su, M., 2009. The Hypocholesterolemic Effects of Cistanche tubulosa Extract, a Chinese Traditional Crude Medicine, in Mice. Am. J. Chin. Med. 37 (6), 1125-1138.

Shin, K., Kim, T., Kyung, J., Kim, D., Park, D., Choi, E., Lee, S., Yang, W., Kang, M., Kim, Y., 2015. Effectiveness of the combinational treatment of Laminaria japonica and Cistanche tubulosa extracts in hair growth. Lab. Anim. Res. 31 (1):24.

Sim, S., Lee, J., Kang, H., Jeong, C., Moon, H., Whang, W., Kim, C., Sim, S., 2006. The effect of acteoside on histamine release and arachidonic acid release in RBL-2H3 mast cells. Arch. Pharm. Res. 29 (6), 508-513.

Singh, N., Shukla, N., Singh, P., Sharma, R., Rajendran, S., Maurya, R., Palit, G., 2010. Verbascoside isolated from Tectona grandis mediates gastric protection in rats via inhibiting proton pump activity. Fitoterapia. 81 (7), 755-761.

Siu, A. H., Ko, K., 2010. Herba Cistanche extract enhances mitochondrial glutathione status and respiration in rat hearts, with possible induction of uncoupling proteins. Pharm. Bio. 48 (5), 512-517.

Song, H. S., Choi, M., Ko, M., Jeong, J., Kim, Y., Jang, B., Sung, J., Kim, M., Whang, W., Sim, S.,

2012. Competitive inhibition of cytosolic $Ca^{2+}$-dependent phospholipase A2 by acteoside in RBL-2H3 cells. Arch. Pharm. Res. 35 (5), 905-910.

Song, Z., Mo, S., Chen, Y., 2000a. Studies on Chemical Constituents of Cistanche tubulosa (Schenk)R. Wight. Chin. J. Chin. Mater. Med. 25 (12), 728-730.

Song, Z., Tu, P., Zhao, Y., Zheng, J., 2000b. Phenylethanoid Glycosides from Cistanche tubulosa. Chin. Tradit. Herbal Drugs. 31(11), 10-12.

Stefanova, N., Fursova, A., Sarsenbaev, K., Kolosova, N., 2011. Effects of *Cistanche deserticola* on behavior and signs of cataract and retinopathy in senescence-accelerated OXYS rats. J. Ethnopharmacol. 138 (2), 624-632.

Sui, Z., Gu, T., Liu, B., Peng, S., Zhao, Z., Li, L., Shi, D., Yang, R., 2011. Water-soluble carbohydrate compound from the bodies of *Herba Cistanches*: Isolation and its scavenging effect on free radical in skin. Carbohyd. Polym. 85 (1), 75-79.

Tu, P., Guo, Y., 2015a. Cultivation Techniques of Cistanche tubulosa and its Host Tamarix spp. Beijing, Science Press. 05.

Tu, P., Guo, Y., 2015b. Cultivation Techniques of Cistanche deserticola and its Host Haloxylonam modendron. Beijing, Science Press. 06.

Tam, W., Chen, Z., He, Z., Yao, X., Lau, C., Huang, Y., 2002. Enhancement of contraction of rat mesenteric artery by acteoside: role of endothelial nitric oxide. J. Nat. Prod. 65 (7), 990-995.

Tanino, T., Nagai, N., Funakami, Y., 2015. Phloridzin-sensitive transport of echinacoside and acteoside and altered intestinal absorption route after application of Cistanche tubulosa extract. J. Pharm Pharmacol. 67 (10), 1457-1465.

Tian, X., Pu, X., 2005. Phenylethanoid glycosides from Cistanches salsa inhibit apoptosis induced by 1-methyl-4-phenylpyridinium ion in neurons. J. Ethnopharmacol. 97 (1), 59-63.

Tian, D., 2002. Practical dictionary of traditional Chinese Medicine (Volume One). Beijing. People's Medical Publishing House. 720-721.

Tu, P., Song, Z., Shi, H., Jiang, Y., Zhao, Y., 2006. Arylethyl (=phenylethanoid) glycosides and oligosaccharide from the stem of *Cistanche tubulosa*. Helv. Chim. Acta. 89 (5), 927-935.

Tu, P., Shi, H., Song, Z., Jiang, Y., Zhao, Y., 2007. Chemical constituents of *Cistanche sinensis*. J. Asian Nat. Prod. Res. 9 (1), 79-84.

Wang, H., Xu, Y., Zhu, C., 2012. Upregulation of Heme Oxygenase-1 by Acteoside Through ERK and PI3 K/Akt Pathway Confer Neuroprotection Against Beta-Amyloid-Induced Neurotoxicity. Neurotox. Res. 21 (4), 368-378.

Wang, J., Ma, C., Wang, S., 2015a. Effects of acteoside on lipopolysaccharide-induced inflammation in acute lung injury via regulation of NF-κB pathway *in vivo* and *in vitro*. Toxicol. Appl. Pharm. 285 (2), 128-135.

Wang, S., Zheng, G., Tian, S., Zhang, Y., Shen, L., Pak, Y., Shen, Y., Qian, J., 2015b. Echinacoside improves hematopoietic function in 5-FU-induced myelosuppression mice. Life Sci. 123, 86-92.

Wang, T., Chen, C., Yang, M., Deng, B., Kirby, G., Zhang, X., 2015c. *Cistanche tubulosa* ethanol extract mediates rat sex hormone levels by induction of testicular steroidgenic enzymes. Pharm. Biol, 1-7.

Wang, W., Luo, J., Liang, Y., Li, X., 2016. Echinacoside suppresses pancreatic adenocarcinoma cell growth by inducing apoptosis via the mitogen activated protein kinase pathway. Mol. Med. rep. 13 (3), 2613-2618.

Wang, Y., Xuan, Z., Tian, S., Du, G., 2015d. Echinacoside Protects against

6-Hydroxydopamine-induced mitochondrial dysfunction and inflammatory responses in PC12 cells via reducing ROS production. Evid. Based Complement Alternat. Med. 2015, 1-9.

Wang, Li., Cao, R., Fang, Y., Zhao, H., Ma, C., He, J., 2017. Determination of bioactive components in Cistanche Herba by UPLC-QQQMS. J. Chin. Med. Mater. 40(02), 295-300.

Wat E., Ng C., Koon, C., Wong, C., Tomlinson, B., Lau, C., 2016. The protective effect of Herba Cistanches on statin-induced myotoxicity in vitro. J. Ethnopharmacol. 190, 68-73.

Wei, Z., 2014. Intervention research of phenylethyl alcohol glycosides in *Cistanche Deserticola* on perimenopausal syndrome animal. Henan Univ. Chin. Med.

Wen, Y., Huo, S., Zhang, W., Xing, H., Qi, L., Zhao, D., Li, N., Xu, J., Yan, M., Chen, X., 2016. Pharmacokinetics, Biodistribution, Excretion and Plasma Protein Binding Studies of Acteoside in Rats. Drug Res. 66 (3), 148-153.

Wong, H., Chen, J., Leong, P., Leung, H., Chan, W., Ko, K., 2014. Cistanches Herba reduces the weight gain in high fat diet-induced obese mice possibly through mitochondrial uncoupling. J. Funct. Foods. 10, 292-304.

Wong, H., Chen, J., Leong, P., Leung, H., Chan, W., Ko, K., 2015. A Cistanches Herba fraction/β-sitosterol causes a redox-sensitive induction of mitochondrial uncoupling and activation of adenosine monophosphate-dependent protein kinase/peroxisome proliferator-activated receptor γ coactivator-1 in C2C12 myotubes: a possible mechanism underlying the weight reduction effect. Evid-based. Compl. Alt. 2015, 1-12.

Wong, H., Ko, K., 2013. Herba Cistanches stimulates cellular glutathione redox cycling by reactive oxygen species generated from mitochondrial respiration in H9c2 cardiomyocytes. Pharm. Biol. 51 (1), 64-73.

Wu, C. R., H. C. Lin, M. H. Su. 2014a. Reversal by aqueous extracts of *Cistanche tubulosa f*rom behavioral deficits in Alzheimer's disease-like rat model: relevance for amyloid deposition and central neurotransmitter function. BMC Complement Altern Med. 14, 202.

Wu, C., Lin, H., Su, M., 2014b. Reversal by aqueous extracts of *Cistanche tubulosa* from behavioral deficits in Alzheimer's disease-like rat model: relevance for amyloid deposition and central neurotransmitter function. BMC Complement. Altern. Med. 14, 202.

Wu, X., Gao, X., Tsim K., Tu. P., 2005. An arabinogalactan isolated from the stems of Cistanche deserticola induces the proliferation of cultured lymphocytes. Int. J. Biol. Macromol. 37 (5), 278-282.

Wu, X., Tu, P., 2004a. Chemical properties of a mannoglucan from Cistanche deserticola. Die. Pharmazie. 59 (10), 815-816.

Wu, X., Tu, P., 2004b. Studies on the chemical structure of polysaccharide CDP-4 isolated from *Cistanche deserticola*. J. Peking Univ. (Health Sci.). 36(01), 24-26.

Wu, X., Tu, P., 2005. Isolation and characterization of α-(1→6)-glucans from *Cistanche deserticola*. J. Asian Nat. Prod. Res. 7(6), 823.

Xie, H., Zhu, H., Cheng, C., Liang, Y., Wang, Z., 2009. Echinacoside retards cellular senescence of human fibroblastic cells MRC-5. Pharmazie. 64 (11), 752-754.

Wu, Y., Li, L., Wen, T., Li, Y., 2007. Protective effects of echinacoside on carbon tetrachloride-induced hepatotoxicity in rats. Toxicology. 232 (1-2), 50-56.

Xie, H., Morikawa, T., Matsuda, H., Nakamura, S., Muraoka, O., Yoshikawa, M., 2006. Monoterpene constituents from Cistanche tubulosa - Chemical structures of kankanosides A-E and kankanol. Chem. Pharm. Bull. 54 (5), 669-675.

Xiong, Q., Hase, K., Tezuka, Y., Tani, T., Namba, T., Kadota, S., 1998. Hepatoprotective activity of

phenylethanoids from Cistanche deserticola. Planta Med. 64 (2), 120-125.

Xiong, Q., Kadota, S., Tani, T., Namba, T., 1996. Antioxidative effects of phenylethanoids from Cistanche deserticola. Pharm. Bull. 19 (12), 1580-1585.

Xiong, Q., Tezuka, Y., Kaneko, T., Li, H., Tran, L., Hase, K., Namba, T., Kadota, S., 2000. Inhibition of nitric oxide by phenylethanoids in activated macrophages. Eur. J. Pharmacol. 400 (1):137-144.

Xiong, W., Gu, L., Wang, C., Sun, H., Liu, X., 2013. Anti-hyperglycemic and hypolipidemic effects of Cistanche tubulosa in type 2 diabetic db/db mice. J. Ethnopharmacol. 150 (3), 935-945.

Xu, W., Qiu, S., Zhao, J., Xu, Y., Yuan, K., Yan, Q., Ji, C., Qin, H., 1994. Studies on the chemical constituents of Desertliving Cistanche. Chin. Trad. Herb. Drugs. 25 (10), 509-513.

Xue, D., Zhang, M., 1994. Analysis of three Cistanche polysaccharides. J. Chin. Med. Mater. 17 (2), 36-37.

Yamada, P., Iijima, R., Han, J., Shigemori, H., Yokota, S., Isoda, H., 2010. Inhibitory Effect of Acteoside Isolated from Cistanche tubulosa on Chemical Mediator Release and Inflammatory Cytokine Production by RBL-2H3 and KU812 Cells. Planta Med. 76 (14), 1512-1518.

Yamaguchi, K., Shinohara, C., Kojima, S., Sodeoka, M., Tsuji, T., 1999. (2E,6R)-8-Hydroxy-2,6-dimethyl-2-octenoic acid, a novel anti-osteoporotic monoterpene, isolated from Cistanche salsa. Biosci. Biotech. Bioch. 63 (4), 731-735.

Yang J., Du N., Rena K., 2005. Phenylethanoid Glycosides from Cultivated Cistanche salsa. J. Chinese Pharm. Sci. 14 (04), 242-245.

Yang., J., Hu, J., Rena, K., Du, N., 2009. Studies on the iridoid glycosides of cutivated Cistanche salsa. Lishizhen Med. Mater. Med. Res. 20 (03), 522-523.

Yoshikawa, M., Matsuda, H., Morikawa, T., Xie, H., Nakamura, S., Muraoka, O., 2006. Phenylethanoid oligoglycosides and acylated oligosugars with vasorelaxant activity from Cistanche tubulosa. Bioorgan. Med. Chem. 14 (22), 7468-7475.

Yoshizawa, F., Deyama, T., Takizawa, N., Usmanghani, K., Ahmad, M., 1990. The constituents of Cistanche tubulosa (Schrenk) Hook. f. II. Isolation and structures of a new phenylethanoid glycoside and a new neolignan glycoside. Chem. Pharm. Bull. 38 (7), 1927-1930.

You, S., Ma, L., Zhao, J., Zhang, S., Liu, T., 2016. Phenylethanol Glycosides from *Cistanche tubulosa* Suppress Hepatic Stellate Cell Activation and Block the Conduction of Signaling Pathways in TGF-β1/smad as Potential Anti-Hepatic Fibrosis Agents. Molecules. 21 (1), 102.

Zhang, D., Li, H., Wang, J., 2015a. Echinacoside inhibits amyloid fibrillization of HEWL and protects against Aβ-induced neurotoxicity. Int. J. Biol. Macromol. 72, 243-253.

Zhang, J. Jingyue's Complete Works. Shanghai: Shanghai Scientific and Technical Publishers, 1959a, 1230.

Zhang, J. Jingyue's Complete Works. Shanghai: Shanghai Scientific and Technical Publishers, 1959b, 984.

Zhang, J., Li, C., Che, Y., Wu, J., Wang, Z., Cai, W., Li, Y., Ma, Z., Tu, P., 2015b. LTQ-Orbitrap-based strategy for traditional Chinese medicine targeted class discovery, identification and herbomics research: a case study on phenylethanoid glycosides in three different species of Herba Cistanches. RSC Adv. 5 (98), 80816-80828.

Zhang, Y., Xing, J., Ai, T., Wen, T., Guan, L., Zhao, J., 2007. Protection of echinacoside against acute lung injury caused by oleic acid in rats. Free Radic. Res. 41 (7), 798-805.

Zhang, T., Wei, T., Gao, Z., Zhang, J., Qin, F., 2009. Study on comparing the Runchang purge and anti-fatigue effects of *Cistanche deserticola* and the tissue culture of *Cistanche deserticola*. Sci. Tech.

Food Ind. 30(12), 155-161.

Zhang, K., Ma, X., He, W., Li, H., Han, S., Jiang, Y., Wu, H., Han, L., Ohno, T., Uotsu, N., Yamaguchi, K., Ma, Z., Tu, P., 2014. Extracts of *Cistanche deserticola* can antagonize immunosenescence and extend life span in senescence-accelerated mouse prone 8 (SAM-P8) mice. Evid-based Compl. Alt. 2014, 1-14.

Zhao, S., He, X., Jia, B., Peng, Q., Liu, X., 2011. Production of acteoside from cistanche tubulosa by β -glucosidase. Pak. J. Pharm. Sci. 24 (2), 135-141.

Zhou, L., Feng, Y., Jin, Y., Liu, X., Sui, H., Chai, N., Chen, X., Liu, N., Ji, Q., Wang, Y., Li, Q., 2014. Verbascoside promotes apoptosis by regulating HIPK2-p53 signaling in human colorectal cancer. BMC Cancer. 14, 747.

Zhu, H., Wang, Z., 2011. Echinacoside suppresses cellular senescence of human fibroblastic cells by down-regulation of p53. J. Chin. Pharm. Sci. 20 (5), 523-528.

Zhu, M., Lu, C., Li, W., 2013. Transient exposure to echinacoside is sufficient to activate Trk signaling and protect neuronal cells from rotenone. J. Neurochem. 124 (4), 571-580.

**Abbreviations:** TCM, Traditional Chinese Medicine; PhGs, phenylethanoid glycosides; HPLC-LTQ-Orbitrap-MS, high performance liquid chromatography-linear trap quadruple-Qrbitrap mass spectrometry; AD, Alzheimer's disease; NGF, nerve growth factor; MDA, malondialdehyde; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; NO, nitric oxide; PD, Parkinson's disease; DA, dopamine; DOPAC, 3,4-dihydroxyphenylacetic acid; SAMP8, Senescence accelerated mouse; ROS, reactive oxygen species; NFκB, nuclear factor κB; AP-1, activator protein-1; $H_2O_2$, hydrogen peroxide; LPS, lipopolysaccharide

## Graphical abstract