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Review

Phytochemistry and pharmacological activities of the genus *Prunella*

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ABSTRACT

Prunella is a genus of perennial herbaceous plants in the Labiatae family. There are approximately 15 species worldwide, distributed widely in the temperate regions and tropical mountains of Europe and Asia. In the genus *Prunella*, *P. vulgaris* is the most studied, following a several thousand-year history as a traditional antipyretic and antidotal Chinese herb. Furthermore, since ancient times, *P. vulgaris* has been widely used as a cool tea ingredient and consumed as a vegetable. The genus *Prunella* contains triterpenoids and their saponins, phenolic acids, sterols and associated glycosides, flavonoids, organic acids, volatile oil and saccharides. Modern pharmacological studies have revealed that *Prunella* possess antiviral, antibacterial, anti-inflammatory, immunoregulatory, anti-oxidative, anti-tumor, antihypertensive and hypoglycemic functions. The active components related to these functions are mainly triterpenoids, phenolic acids, flavonoids and polysaccharides. This review mainly summarizes recent advances in traditional usage, chemical components and pharmacological functions.

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1. Introduction

Prunella is a genus of perennial herbaceous plants in the family Labiatae. There are approximately 15 species of *Prunella* worldwide, distributed widely in the temperate regions and tropical mountains of Europe and Asia, northwestern Africa and north America. *Prunella* plants have ascending square stems, simple opposite leaves, a lipped corolla, didynamous stamens, two carpels and four nutlets. The flowering stage occurs from April to June, and the fruit stage lasts from July to October. *Prunella* plants grow mainly in woodlands, barren mountains, and ridges and on the roadside.

China has four domestic species and three variants of plants of the *Prunella* genus, including *Prunella vulgaris* L. and its two variants *P. vulgaris* L. var. leucantha SchurSec. Bailey and *P. vulgaris* L. var. lanceolata (Barton) Fernald; *Prunella asiatica* Nakai and its variant *P. asiatica* Nakaivar. albiflora (Koidz) Nakai; *Prunella hispida* Bentham, and *Prunella grandiflora* (L.) Jacq. (Wu & Li, 1977).

Currently, the most-studied *Prunella* species are *P. vulgaris* and *P. vulgaris* var. lilacina. In China, *P. vulgaris* has a concentrated distribution in the Huai River basin and the mid-lower reaches of the Yangtze River, with Jiangsu, Anhui, Zhejiang and Henan provinces having the most abundant reserves of this wild resource. The distribution of *P. vulgaris* in China is shown in Fig. 1. In addition, *P. vulgaris* is found in Korea, Japan, Ukraine and Kashmir. In contrast, *P. vulgaris* var. lilacina is mainly distributed in Korea, Japan and Europe.

Fig. 1. The producing area of *P. vulgaris* in China. The picture comes from Flora of China (http://www.eflora.cn).

Since the 1950s, researchers in Japan, the former Soviet Union and China have conducted in-depth studies on the chemical components of *Prunella* plants. To date, the compounds isolated from these plants mainly constitute triterpenoids and their saponins, phenolic acids, sterols and their glycosides, flavonoids, organic acids, volatile oil and saccharides (Xiao, 2002). Traditional Chinese medicine theory holds that *P. vulgaris* tastes bitter and acrid and is cold in nature, with functions as an antifebrile and in eyesight improvement, detumescence and lump dissipation (Chinese Pharmacopoeia, 2010). Modern pharmacological studies have revealed that *Prunella* plants possess antiviral, antibacterial, anti-inflammatory, immunoregulatory, anti-oxidative, anti-tumor, anti-hypertensive and hypoglycemic functions (Zdařilová, Svobodová, Šimánek, & Ulrichová, 2009). In the aspect of clinical practice, *P. vulgaris* is mainly applied for thyroid gland malfunction (Cao & Chen, 2009), breast hyperplasia (Wang, Xie, & Zhong, 2014; Zhao & Zhao, 2009), and ulcerative colitis (Zheng, Qiao, Yuan, & Zhao, 2004). This review aims to provide an overview of traditional usage, chemical components and the pharmacological functions present in *Prunella*. The possible trends and prospects for future study of the genus Prunella are discussed, too.

2. Traditional usage

P. vulgaris (Xia Ku Cao in Chinese, meaning "grass that withers in summer") withers when summer comes, and is how the plant received its name. *P. vulgaris* has been used in medicinal applications for more than one thousand years. Normally, the plant's half-dry tassels are collected in summer for use as medicine. But, in Europe and Taiwan, the whole plant is commonly used as medicine. *P. vulgaris* has a light body weight and is crisp, with a slight fragrant smell and little taste. Traditionally, plants that are purple-brown in colour and possess large spikes are considered good. See Fig. 2.

The first record of *P. vulgaris* in China is in the earliest Chinese pharmacy monograph "*Shennongbencaojing*." (Sun, 2006). Since then, the "*Root and Herbal*" of each Chinese dynasty have included

Fig. 2. the plant and the cluster of *P. vulgaris*. The picture comes from Baidu Gallery (http://image.baidu.com).

P. vulgaris, and the therapeutic effect of this plant alone was known to be very significant, such as *The Compendium of Materia Medica*, Tai Ping Sheng Hui Fang and Supplements of *The Compendium of Materia Medica* (Li, 1979; Wang, 1958; Zhao, 1983).

Dating from the 1963 edition of the Chinese Pharmacopoeia, every successive Chinese Pharmacopoeia has included *P. vulgaris*, clearly stipulating that the parts for use in medicinal applications are either the half-dry or mature ear of *P. vulgaris*. In addition, *P. vulgaris*, is also one of the first varieties listed as both edible and medicinal resources published by the Ministry of Health of China. In modern times, *P. vulgaris* is mainly used in compound Chinese herbal medicines, as well as in the traditional Chinese patent medicines. The traditional Chinese patent medicines only made from *P. vulgaris* that are listed in the 2010 edition of Chinese Pharmacopoeia including *P. vulgaris* Cream and *P. vulgaris* Oral Liquid. These medicines are commonly used for the treatment of headache, dizziness, scrofula, neck lump and mastitis, goiter, tuberculosis of the lymphatic system and hyperplasia of the mammary glands (Chinese Pharmacopoeia, 2010). In recent years, the numbers of traditional Chinese patent medicines and health products with P. vulgaris as the effective ingredient have grown rapidly. The most notable examples include Xiasangju particles, Xiasangju herbal tea, Wanglaoji and Jiaduobao herbal tea.

In addition to its medicinal applications, *P. vulgaris* is also consumed as a food. In China, its history as a food dates back as early as the Ming Dynasty (late 16th century), or even earlier (Li, 1979; Li & Yao, 1990). The consumption habits of *P. vulgaris* vary by region. In the Hunan province, people like to eat steamed glutinous rice cakes of *P. vulgaris*, which are made from the spring buds of *P. vulgaris.* In the Guangdong areas, people like to drink a tasty soup or cool tea made with *P. vulgaris* as the major ingredient. In addition, Europeans and Americans also consider *P. vulgaris* as a panacea, frequently using *P. vulgaris* as a vegetable to make salads, soup and tea.

3. Progress of phytochemical studies on genus *Prunella*

3.1. Background

Up to date, the chemical components (Table 1) of the plants of the *Prunella* genus mainly contain triterpenoids and their saponins, phenolic acids, sterols and their glycosides, flavonoids, coumarins, organic acids, volatile oil and saccharides. Of these compounds, triterpenoids and their saponins, phenolic acids, flavonoids and polysaccharides are the major active components.

3.2. Triterpenoids

Prunella plants contain abundant pentacyclic triterpenoids. To date, 64 of these compounds have been isolated from *Prunella* plants. Of them, 47 are triterpenoid sapogenins, and 17 are triterpenoid saponins. The above mentioned compounds include the 15 triterpenoid methyl ester compounds, which are the methylated products of *P. vulgaris* var. lilacina extracts, as reported by Kojima (Kojima & Ogura, 1986; Kojima, Tominaga, Sato, & Ogura, 1987). The basic skeleton of these compounds can be divided into three types, oleanane, ursane and lupane. Of them, the two major triterpenoid components are oleanolic acid and ursolic acid. The information of the triterpenoids are shown in Table 1.

3.3. Phenolic acids

Phenolic acid is another large category of active components in the *Prunella* genus. Phenolic acids mainly include phenylpropanoids and other phenolic acid compounds. In addition, there are *cis*- and *trans*-caffeic acids, Danshensu (salvianic acid A) and other simple phenylpropanoids (Gu, Li, Li, Qian, & Duan, 2007; Li et al., 2012; Tian, Xiao, Chen, Zhao, & Wang, 2000), the polymers that are formed through the intermolecular condensation of two phenylpropanoid derivative molecules, such as rosmarinic acid and salviaflaside (Wang, Zhao, Wang, Ai, et al., 2000), as well as the simple compounds of coumarins, esculetin, umbelliferone and scopoletin (Dmitruk, 1986). To date, 17 phenylpropanoid compounds have been isolated, with their information shown in Table 1.

3.4. Steroids

The major steroidal compounds in *Prunella* plants are β-sitosterol, stigmasterol, α-spinasterol, Δ^7-stigmasterol (stigmast-7-en-3-β-ol) and its glucoside. In addition (20E, 20S, 24S)-stigmasta-7,22-dien-3-one has been isolated from the whole plant of *P. vulgaris*, and daucosterol and α-spinaster have been isolated from the cluster of *P. vulgaris* (Kojima & Ogura, 1986; Kojima, Sato, Hatano, & Ogura, 1990; Meng & He, 1995; Xu, Liu, Yu, & Fang, 2010).

3.5. Flavonoids

Prunella plants also contain abundant flavonoids. They mainly contain quercetin, rutinoside, luteolin, kaempferol, kaempferol-3-O-glucoside, anthocyanin, delphinidin, trimethyl-delphinidin-3, 5-diglucosides and other compounds. In addition, *P. vulgaris* also contains homoorientin, wogonin, quercetin-3-O-β-D-rhamnoside, kaempferol-3-O-β-D-glucoside, hesperidin and acacetin-7-O-β-D-glucopyranoside (Sendra, 1963; Wang, Tang, Fu, He, & Fang, 2008; Wang, Zhao, Tu, Hong, & Chen, 1999; Xu, Jin, Li, & Jin, 2010; Zhang et al., 2008).

3.6. Organic acids

The organic acids in *P. vulgaris* are mainly phenolic acids and long-chain fatty acids. For phenolic acids, see Section 3.3 Phenolic acids. Long-chain fatty acids are mainly obtained through the analysis of GC/MS. Cui, Hou, and Jing (2013) analyzed the acetone extract of *P. vulgaris* with GC/MS and identified 16 compounds, which were mainly linolenic acid and unsaturated aliphatic alcohols and esters. Of them, linolenic acid was the highest fraction, accounting for approximately 53.4% of the total extract, followed by palmitic acid, which was approximately 10.2%. In addition, other researchers (Tian et al., 2000) used GC/MS to identify palmitic acid, ethyl palmitate, 6,9-octadecadienoic acid, stearic acid, 3,6,17-eicosatrienoic acid, oleic acid, arachidic acid and behenic acid from *P. vulgaris.*

3.7. Volatile oils (essential oil)

Using GC/MS analysis, roughly 30 kinds of volatile oils, which are mainly α-camphor, germacrene D, α-pinene, β-elemene and β-caryophyllene, were identified from the whole plant of *P. vulgaris* grown in Ukraine (Golembiovska, Tsurkan, & Vynogradov, 2014). Furthermore, the major components of the volatile oil of the ear of *P. vulgaris* are aliphatic compounds, such as 1,6-diene cyclodecanone, palmitic acid and hexatriacontane (Tian et al., 2000). In another specie of *Prunella* genus, *P. grandiflora*, 40 volatile oil compounds were identified. These compounds mainly contain aliphatic aldehydes and alcohols, aromatic aldehyde, and small amounts of sesquiterpenes and monoterpene hydrocarbons. Of them (E, E)-hepta-2,4-dienal and phenylacetaldehyde are the major components, with contents of 17.8% and 13.2%, respectively (Jerkovic, Marijanovic, HazlerPilepic, & Maleš, 2013).

Table 1
The secondary metabolites information.

No.	Chemical component	Source	Part of plant	Biological activities	References
	Triterpenes				
1	Oleanolic acid	a, b	The whole herb	Hepatoprotective effect, antioxidant, induce cancer cell apoptosis, anti-inflammatory, anticholinesterase activity, and inhibit glycogen phosphorylase and increase insulin-mediated glucose consumption in 3T3-L1 adipocytes	Meng and He (1995), Lee et al. (2008), Pollier and Goossens (2012), Perveen et al. (2014), Yu, Qi, Wang, Liu, and Yu (2015)
2	2α,3β-Dihydroxyolean-12-en-28-oic acid	a	Spikes	Anti-inflammatory activities, inhibit glycogen phosphorylase and increase insulin-mediated glucose consumption in 3T3-L1 adipocytes	Wang, Zhao, Wang, Li, et al. (2000), Zeng et al. (2011), Yu, Qi, et al. (2015)
3	2α,3α-Dihydroxyolean-12-en-28-oic acid	a	Spikes	Inhibit NO production with IC_{50} values of 27.7 μM	Cheng and Chen (2012), Li et al. (2014)
4	2α,3α,24-Trihydroxyolean-12-en-28-oic acid	a, b	The aerial parts	Inhibit NO production with IC_{50} values of 40.5 μM, and glycogen phosphorylase inhibitory activity	Wang, Zhao, Wang, Li, et al. (2000), Lee et al. (2008), Li et al. (2014), Yu, Qi, et al. (2015)
5	2α,3β,24-Trihydroxyolean-12-en-28-oic acid	a, b	The aerial parts	Inhibit butyrylcholinesterase activity with IC_{50} values of 9.50 μM	Qi, Hu, Liu, and Yu (2009), Perveen et al. (2014)
6	2α,3β,23-Trihydroxyolean-12-en-28-oic acid	a	Spikes	Inhibit the proliferation of HepG2 cells, with IC_{50} values of 16.13 ± 3.83 μM	Gu et al. (2007), Zhou et al. (2015)
7	3β,16α,24-Trihydroxy-olean-12-en-28-oic	a	Spikes		Gu et al. (2007)
8	3β-Hydroxyl-olean-12-en-28–al	a	The whole herb		Meng and He (1995)
9	Olean-12-en-3β,28-diol	a	The whole herb	Antimicrobial activity against *Salmonella* spp, with MIC value of 0.1-0.15 mg/mL	Meng and He (1995), Paul et al. (2014)
10	β-Amyrin	a	The whole herb	Induce angiogenesis in vascular endothelial cells by mediating Akt-eNOS signaling-dependent mechanism	He, Li, Feng, and Li (1985), Ishii, Nakahara, Ikeuchi, and Nishimura (2015)
11	β-Amyrenone	a	Spikes		Cheng and Chen (2012)
12	Uvaol	a	Spikes	Protect against DNA damage in MDA-MB-231 and MCF10A	Cheng and Chen (2012), Sánchez-Quesada, López-Biedma, and Gaforio (2015)
13	Ursolic acid	a, b	The whole herb	Induce cancer cell apoptosis, inhibit tumor growth, suppress angiogenesis, induce autophagy in TC-1 cervical cancer cells by PI3-K signaling pathways, anti-inflammatory activity by inhibiting sPLA2 enzymes, antibacterial, antioxidant, and inhibit glycogen phosphorylase	Lee et al. (2008), Leng et al. (2013), Nataraj, Raghavendra Gowda, Rajesh, and Vishwanath (2007), do Nascimento et al. (2014), Yu, Qi, et al. (2015)
14	2α,3α-Dihydroxyursa-12-en-28-oic acid	a, b	The whole herb	Induce apoptosis in Jurkat T cells, inhibit glycogen phosphorylase and anti-HSV-1 activity	Lee et al. (2008), Yu, Qi, et al. (2015), Woo et al. (2011), Ryu, Lee, Lee, Kim, and Zee (1992)
15	2α,3β-Dihydroxyursa-12-en-28-oic acid	a, b	The whole herb		Wang, Zhao, Wang, Li, et al. (2000), Lee et al. (2008)
16	2α,3α,23-Trihydroxyursa-12-en-28-oic acid	a, b	The whole herb		Qi et al. (2009), Lee et al. (2008)
17	2α,3α,24-Trihydroxyursa-12-en-28-oic acid	a	Spikes	Inhibit glycogen phosphorylase and increase insulin-mediated glucose consumption in 3T3-L1 adipocytes	Wang, Zhao, Wang, Li, et al. (2000), Yu, Qi, et al. (2015)
18	2α,3β,24-Trihydroxyursa-12-en-28-oic acid	a	The whole herb		Gai, Kong, and Wang (2010)
19	2α,3β,23-Trihydroxyursa-12-en-28-oic acid	a	Spikes	Inhibit the proliferation of HepG2 cells, with IC_{50} values of 15.97 ± 2.47 μM	Gu et al. (2007), Zhou et al. (2015)
20	2α,3α,19α-trihydroxyurs-12-en-28-oic acid	a, b	The whole herb		Gai et al. (2010), Lee et al. (2008)
21	2α,3α,19α,23-Tetrahydroxyurs-12-en-28-oic acid	b	The aerial parts		Lee et al. (2008)
22	3α,19α,24-Trihydroxy-ursa-12-en-28-oic	a	Spikes		Gu et al. (2007)
23	3β-Hydroxyl-ursa-12-en-28-al	a	The whole herb		Meng and He (1995)
24	Urs-12-en-3β,28-diol	a	The whole herb		Meng and He (1995)
25	3β,22α-Dihydroxyursa-12-en-28-oic acid	a	Spikes		Gu et al. (2007)
26	2α,3α,24-Trihydroxylursa-12,20(30)-dien-28-oic acid	a	Spikes	Glycogen phosphorylase inhibitory activity	Wang, Zhao, Wang, Li, et al. (2000), Yu, Qi, et al. (2015)
27	Betulic acid	a	The whole herb	Induce apoptosis in cancer cells via immunomodulatory activity by the release of cytokines and generation of ROS, anticholinesterase activity and anti-HSV-1 activity	Qi et al. (2009), Bhatia, Kaur, and Sekhon (2015), Perveen et al. (2014)
28	Lupeol	a	Spikes	Suppress HCC cell proliferation via BDNF inhibition and phosphorylation of GSK-3β(Ser-9), and blocking Akt/ PI3K and Wnt signaling pathway, and anti-tumour-promoting and inhibite thermal-induced protein denaturation	Cheng and Chen (2012), Zhang, Tu, He, Peng, and Qiu (2015), Rauf et al. (2015)
29	2α,3β-Dihydroxy-lup-20(29)-ene	a	Spikes		Cheng and Chen (2012)
30	Lupenone	a	Spikes	Antihyperglycemic activity	Cheng and Chen (2012), Wu, Xu, Hao, Yang, and Wang (2015)
31	Chiratenol	a	Spikes		Cheng and Chen (2012)

Table 1 (*continued*)

No.	Chemical component	Source	Part of plant	Biological activities	References
32	3β,13β-Dihydroxyolic-11-ene-28-oic acid	a	Spikes		Cheng and Chen (2012)
33	methyl oleanolate	b	Stems, leaves, roots		Kojima and Ogura (1986), Kojima et al. (1987)
34	Methyl maslinate	b	Stems, leaves, roots		Kojima and Ogura (1986), Kojima et al. (1987)
35	Methyl 3-epimaslinate	b	Stems, leaves, roots		Kojima and Ogura (1986), Kojima et al. (1987)
36	Methyl 2α,3α,23-trihydroxylolean-12-en-28-oate	b	Stems, leaves		Kojima and Ogura (1986)
37	Methyl 2α,3α,24-trihydroxylolean-12-en-28-oate	b	Stems, leaves, roots		Kojima and Ogura (1986), Kojima et al. (1987)
38	Methyl ursolate	b	Stems, leaves, roots		Kojima and Ogura (1986), Kojima et al. (1987)
39	Methyl 2α-hydroxylurs-28-oate	b	Stems, leaves, roots		Kojima and Ogura (1986), Kojima et al. (1987)
40	Methyl 2α,3α-dihydroxylurs-12-en-28-oate	b	Stems, leaves, roots		Kojima and Ogura (1986), Kojima et al. (1987)
41	Methyl 2α,3α,24-trihydroxylursa-12-en-28-oate	b	Roots		Kojima et al. (1987)
42	Methyl 2α,3α-dihydroxylursa-12,20 (30)-dien-28-oate	b	Roots		Kojima et al. (1987)
43	Methyl 2α,3α,24-trihydroxylursa-12,20 (30)-dien-28-oate	b	Roots		Kojima et al. (1987)
44	Methyl 2α,3α,24-trihydroxylolean-11,13 (18)-dien-28-oate	b	Roots		Kojima et al. (1987)
45	Methyl betulinate	b	Roots		Kojima et al. (1987)
46	Methyl (13S,14R)-2α,3α,24-trihydroxyl-13,14-cyclo-olean-11-en-28-oate	b	Roots		Kojima, Tominaga, Sato, Takayanagi, and Ogura (1988)
47	Methyl (12R,13S)-2α,3α,24-trihydroxyl-12,13-cyclo-taraxer-14-en-28-oate	b	Roots		Kojima et al. (1988)
48	Sericoside	a	Unknown		Zhang and Yang (1995)
49	Arjunglucoside I	a	Unknown		Zhang and Yang (1995)
50	Vulgarsaponin A	a	Spikes		Tian et al. (2000)
51	Vulgarsaponin B	a	Spikes		Wang et al. (1999)
52	Pruvuloside A	a	Unknown		Zhang and Yang (1995)
53	Pruvuloside B	a	Unknown		Zhang and Yang (1995)
54	Niga-ichigoside F2	a	Unknown		Zhang and Yang (1995)
55	Niga-ichigoside F1	a	Unknown		Zhang and Yang (1995)
56	2α,3β,19α,24-Tetrahydroxylurs-12-en-28-oic acid-28-β-D-glucopranoside	a	Stems, leaves		Qi et al. (2009)
57	2α,3α-24-Trihydroxyursa-12-en-28-oic acid-28-O-β-D-glucopyranosyl ester	a	Spikes	Inhibit glycogen phosphorylase and increase insulin-mediated glucose consumption in 3T3-L1 adipocytes	Yu, Qi, and Liu (2012), Yu, Qi, et al. (2015)
58	Rotundic acid 28-O-α-D-glueopyranosyl(1-6)-β-D-glueopyranoside	a	Spikes		Yu et al. (2012)
59	3β,4β,16α-17-Carboxy-16,24-dihydroxy-28-norolean-12-en3-yl 4-O-β-D-xylopyranosyl-β-D-glucopyranosiduronic acid	a	Spikes		Gu et al. (2007)
60	(3β,4β,16α)-17-carboxy-16,24-dihydroxy-28-norolean-12-en-3-yl β-D-glucopyranosiduronic acid methyl ester	a	Spikes		Gu et al. (2007)
61	(3β,4β)-24-Hydroxy-16-oxo-28-norolean-12-en-3-yl 4-O-β-D-xylopyranosyl-β-D-glucopyranosiduronic acid	a	Spikes	Inhibition activity against SMMC-7721 cells with IC_{50} values around 35 μM	Gu et al. (2007)

(*continued on next page*)

Table 1 (*continued*)

No.	Chemical component	Source	Part of plant	Biological activities	References
62	16-Oxo-17-demethyl-3β,24-dihydroxylolean-12-en-3-O-β-D-glucuronoside	a	Spikes		Zhang et al. (2008)
63	Vulgasides I	a	Spikes		Yu, Qi, et al. (2015)
64	Vulgasides II	a	Spikes		Yu, Qi, et al. (2015)
	Sterols				
65	α-Spinasterol	a, b	Stems, leaves	Anti-inflammatory effects, and TRPV1 receptor antagonist with antinociceptive effect	Kojima and Ogura (1986), Meng and He (1995), Borges et al. (2014), Trevisan et al. (2012)
66	α-Spinasterol-3-O-β-D-glucoside	b	Stems, leaves		Kojima et al. (1990)
67	Stigmasterol	a, b	Stems, leaves	Induces apoptosis in HepG2 cells via mitochondrial apoptosis signaling pathway	Kojima et al. (1990), Tian et al. (2000), Kim, Li, Kang, Ryu, and Kim (2014)
68	Stigmasterol-3-O-β-D-glucoside	b	Stems, leaves	Cytotoxic activity against P-388 murine leukemia cells with IC_{50} values of 52.09 mg/mL	Kojima et al. (1990), Harneti et al. (2014)
69	Stigmast-7-en-3β-ol	a, b	Stems, leaves		Kojima and Ogura (1986), Tian et al. (2000)
70	Stigmast-7-en-3β-ol-3-O-β-D-glucoside	b	Stems, leaves		Kojima et al. (1990)
71	β-Sitosterol	a, b	Stems, leaves	Antidiabetic and antioxidant effects, ameliorates HFD-induced colitis, and anti-tumour-promoting and inhibit thermal-induced protein denaturation	Kojima et al. (1990), Meng and He (1995), Gupta, Sharma, Dobhal, Sharma, and Gupta (2011), Kim, Lee, et al. (2014), Rauf et al. (2015)
72	Daucosterol	a, b	Stems, leaves	Promote NSC proliferation, and inhibits cancer cell proliferation by inducing ROS triggered autophagy	Kojima et al. (1990), He et al. (1985), Jiang et al. (2014), Zhao et al. (2015)
73	(20E,20S,24S)-Stigmasta-7,22-dien-3-one	a	The whole herb		Meng and He (1995)
74	α-Spinasterone	a	Spikes		Xu et al. (2010)
	Flavonoids				
75	Quercetin	a	Unknown	Acute vasodilator effects, prevent various hepatotoxicant-induced hepatotoxicity, promote apoptosis of glioma cells via inhibiting the ERK and PI3K/AKT signalling pathways, and mitigate LPS-induced NO and stimulate Nrf2 and HO-1 activity	Zhang and Yang (1995), Perez et al. (2014), Ji, Sheng, Zheng, Shi, and Wang (2015), Pan et al. (2015), Sun et al. (2015)
76	Kaempferol	a	Unknown	Induces apoptosis of HT-29 cells, and suppressive function of Treg cells through inhibiting FOXP3 expression and phosphorylation	Sendra (1963), Lee, Cho, et al. (2014), Yao et al. (2014)
77	Rutin	a, b	Unknown	Via enhancing IRK activity and insulin-signaling pathway to improve glucose uptake, and protective effect on the LPS-induced ALI via decreasing the MIP-2 expression and MMP-9 activation by inhibiting Akt phosphorylation	Sendra (1963), Lee et al. (2008), Hsu et al. (2014), Chen et al. (2014)
78	Kaempferol-3-O-rutinoside	b	Spikes	Hepatoprotective effects	Lee et al. (2008), Wang, Tang, and Zhang (2015)
79	Quercetin-3-O-β-D-glucoside	a, b	Unknown	Antioxidative activity	Zhang and Yang (1995), Agbo, Nnadi, Ukwueze, and Okoye (2014)
80	Quercitrin	a	Unknown	Apoptotic and antiproliferative effects on colon cancer cells and lung cancer cells	Yu et al. (2012), Cincin et al. (2014)
81	Quercetin-3-O-β-D-galactoside	a	Spikes		Wang et al. (1999)
82	Kaempferol-3-O-β-D-glucoside	a	Unknown		Sendra (1963), Zhang and Yang (1995)
83	Wogonin	a	Spikes		Xu et al. (2010)
84	Luteolin	a	Unknown	Inhibit invasiveness of pancreatic cancer cells by deactivation of STAT3 signaling, anticarcinogenic activity via inhibition of E6 and E7 expression, and combined therapy with paclitaxel enhances apoptosis in human breast cancer MDA-MB-231 cells via blocking STAT3	Sendra (1963), Huang et al. (2015), Ham et al. (2014), Yang et al. (2014)
85	Cinaroside	a	Unknown		Sendra (1963)
86	Homoorientin	a	Unknown		Sendra (1963)
87	Acacetin-7-O-β-D-glucopyranoside	a	Spikes		Zhang et al. (2008)
88	Hesperidin	a	Unknown	Anti-proliferative and apoptotic in NSCLC cells by modulating immune response-related pathways	Wang et al. (2008), Cincin et al. (2015)
89	Cyanidin	Unknown	Unknown	Enhance the intracellular antioxidative ability, eliminate the overproduced ROS, and attenuation cisplatin-induced cytotoxicity and apoptosis	Sendra (1963), Li et al. (2015)
90	Delphinidin	Unknown	Unknown		Sendra (1963)
91	Hirsutidin-3,5-di-O-gluciside	Unknown	Unknown		Sendra (1963)
92	Malvidin-3,5-di-O-gluciside	Unknown	Unknown		Sendra (1963)
93	Peonidin-3,5-di-O-gluciside	Unknown	Unknown		Sendra (1963)
	Phenolic acid				
94	Caffeic acid	a	Spikes	Inhibit HCV propagation, Inhibit the proliferation of influenza A virus, and antioxidative activity by chelating iron ions and minimizing the Fenton-generated hydroxyl radicals	Tian et al. (2000), Tanida et al. (2015), Genaro-Mattos, Maurício, Rettori, Alonso, and Hermes-Lima (2015), Utsunomiya et al. (2014)

Table 1 (*continued*)

No.	Chemical component	Source	Part of plant	Biological activities	References
95	Ethyl coffeate	a	Spikes	Anti-proliferative, anti-migratory and anti-invasive activities in ovarian cancer cells	Wang et al. (1999), Lee, Kim, et al. (2014)
96	Caffeic acid ethylene ester	a	Unknown		Li et al. (2012)
97	Danshensu	a, b	Spikes	Cardioprotective effect on isolated heart against ischemia reperfusion injury by activating Akt/ERK1/2/Nrf2 signaling pathways, and inhibit β-AR-mediated cardiac fibrosis by inhibiting ROS-p38 MAPK signaling	Gu et al. (2007), Lee et al. (2008), Yu, Wang, et al. (2015), Lu et al. (2014)
98	Ethyl 3,4-dihydroxy-phenyl lactate	a	The whole herb		Gai et al. (2010)
99	3,4,α-Trihydroxy-methyl phenylpropionate	a	Spikes		Wang, Zhao, Wang, Ai, and Chen (2000)
100	3,4,α-trihydroxy-butyl phenylpropionate	a	Spikes		Wang, Zhao, Wang, Li, et al. (2000)
101	p-Coumaric acid	a	Spikes	Attenuate ROS-induced cardiomyoblast damage	Wang, Zhao, Wang, Ai, et al. (2000), Chacko, Nevin, Dhanyakrishnan, and Kumar (2015)
102	p-Hydroxycinnamic acid	a	Unknown		Li et al. (2012)
103	Protocatechuic acid	a	Unknown	Prevent oxLDL-Induced Apoptosis by the activation of the JNK/Nrf2 pathway, prevent LPS-induced ALI via suppressing p38MAPK and NF-κB signal pathways, and anti-inflammatory effects on LPS-stimulated BV2 microglia by inhibiting TLR4-mediated NF-κB and MAPKs signaling pathways	Li et al. (2012), Varì et al. (2014), Zhang, Li, et al. (2015), Wang, Wang, et al. (2015)
104	Protocatechualdehyde	a	Unknown	Anticancer activity	Li et al. (2012), Choi, Jiang, Jeong, and Lee (2014)
105	Umbelliferone	a	The aerial parts		Dmitruk (1986)
106	Scopoletin	a	The aerial parts	Anti-inflammatory activity, antioxidant activities, and antibacterial and antifungal properties	Dmitruk (1986), Jamuna et al. (2015), Gnonlonfin, Sanni, and Brimer (2012)
107	Esculetin	a	The aerial parts	Anti-proliferative and apoptotic on G361 HMM cells by downregulating Sp1 protein levels	Dmitruk (1986), Jeon, Jang, Shim, Myung, and Chae (2015)
108	Rosmarinic acid	a	Spikes	Antioxidant, anti-inflammatory, anti-angiogenic activity against retinal neovascularization, prevent UVB-induced DNA damage, inhibit cell viability and migration in HNSCC cell lines, prevention and treatment of allergies and asthma, and anti-osteoporosis by promoting osteoblastic differentiation and inhibiting osteoclastic differentiation	Wang, Zhao, Wang, Ai, et al. (2000), Bulgakov, Inyushkina, and Fedoreyev (2012), Tumur et al. (2015), Stansbury (2014), Lee et al. (2015)
109	Methyl rosmarinate	a	Spikes		Wang, Zhao, Wang, Ai, et al. (2000)
110	Ethyl rosmarinate	a	Spikes	Induce vasorelaxation in rat aortic rings via endothelium-independent pathways involves open Kv channels, block extracellular Ca^{2+} influx and interactions with both VOCCs and ROCCs	Wang, Zhao, Wang, Ai, et al. (2000), Wicha et al. (2015)
111	Butyl rosmarinate	a	Spikes		Wang, Zhao, Wang, Ai, et al. (2000)
112	Salviaflaside	a	Spikes		Wang, Zhao, Wang, Ai, et al. (2000)
113	Gentisic acid 5-O-D-(6'-salicyly1)-glucopyranoside	a	Spikes		Gu, Li, Mu, and Zhang (2011)
	Anthraquinones				
114	Tanshinone I	a	Spikes		Gu et al. (2007)
115	2-Hydroxyl-3-methyanthraquinone	a	Spikes		Xu et al. (2010)
116	Rhein	a	Spikes	Anti-fibrotic and anti-tumorigenic approaches	Gu et al. (2007), Tsang and Bian (2015)
117	Chrysophanols	a	Spikes	Anti-JEV activity with IC50 values of 15.82mg/mL	Xu et al. (2010), Chang, Huang, Lin, Tsou, and Lin (2014)

a: *Prunella vulgaris* L. b: *Prunella vulgaris* L. var. lilacina

3.8. Saccharides

P. vulgaris contains free monosaccharides, disaccharides and polysaccharides. Researchers in China (Wang, Xiong, Shi, Lu, & Yuan, 2012) have conducted extensive studies on the polysaccharides of *P. vulgaris*, finding that the polysaccharides in *P. vulgaris* were mainly composed of galactose, glucose, mannose, xylose, arabinose and rhamnose, with major components of xylose and arabinose.

Furthermore, *P. vulgaris* also contains a special polysaccharide. Tabba, Chang, and Smith (1989)) isolated a sulfur-containing polysaccharide from *P. vulgaris*, with a molecular weight of approximately 10 kDa. Elemental analysis showed that this polysaccharide contained 0.14% sulfur. Acid hydrolysis results showed that the compound mainly contained glucose and galactose with small amounts of xylose and uronic acid. One study reported (Zhang et al., 2007) the isolation of a lignin and saccharide complex with a molecular weight of 8500 Da from *P. vulgaris*, containing 39% carbohydrate and 11% uronic acid. The carbohydrate moiety was found to contain mainly glucose, galactose, mannose, galacturonic acid, xylose, rhamnose and arabinose. The molar ratio of these compounds was 3.4:1.0:0.7:0.5:0.3:0.3:0.1. Elemental analysis showed that the complex contained 37.4% carbon, 3.76% hydrogen, 0.6% nitrogen and 0.92% sulfur. In addition, researchers (Xu, Lee, Lee, White, & Blay, 1999) have also isolated an anionic polysaccharide with a molecular weight of 3500 Da from *P. vulgaris*, containing 42% carbohydrate and 0.75% uronic acid. Elemental analysis showed that the anionic polysaccharide contained 30.78% carbon, 3.05% hydrogen, 0.66% nitrogen and 2.69% sulfur.

3.9. Other compounds

At present, researchers have, for the first time, isolated tanshinone I, rhein, chrysophanol and 2-hydroxyl-3-methylanthraquinone from the cluster of *P. vulgaris* (Gu et al., 2007; Xu et al., 2010). The latest studies (Lou et al., 2014) have reported that a novel diterpenoid, vulgarisin A isolated from *P. vulgaris*, exhibited weak toxicity to human lung cancer A549 cells (IC_{50} = 57.0 μM). In addition, plants of the *Prunella* genus also contain oligopeptide (Gu et al., 2007), vitamin B1, vitamin C, vitamin K, resin, amaroid, water-soluble salts (68% is KCl), alkaloids, tannins, proteins and lipids (Rasool, Ganai, Akbar, Kamili, & Masood, 2010).

4. Progress of pharmacological studies on genus *Prunella*

4.1. Background

The traditional functions of *P. vulgaris* are for antifebrile, eyesight improvement, detumescence and lump dissipation applications. According to its traditional efficacies, people have conducted a series of studies and found that the plant also possesses antiviral, antibacterial, anti-inflammatory, anti-oxidation, anti-tumor, antihypertensive and hypoglycemic functions. The accepted active components of *Prunella* plants are pentacyclic triterpenoids and phenolic acids.

4.2. Antiviral effects

P. vulgaris showed a significant anti-HIV effect, and the main effective ingredients are polysaccharides and tannins.

The anti-HIV effect of *P. vulgaris* water extract occurs mainly during the early interference and late viral binding events (Oh, Price, Brindley, et al., 2011), by inhibiting recombinant HIV-1 reverse transcriptase activity, with ID_{50} of 26.0 μg/ml (Collins, Ng, Fong, Wan, & Yeung, 1997). A sulfur-containing anionic polysaccharide-prunellin with a molecular weight of 10 kDa isolated from the water extract of *P. vulgaris* showed the ability to block HIV-1 from entering cells (Tabba et al., 1989). Some studies reported that the major anti-HIV-1 effective substance was tannins of *P. vulgaris* and that they worked by inhibiting HIV-1 integrase activity (Au, Lam, Ng, Fong, & Wan, 2001), as well as inhibiting the formation of the six-helix bundle of HIV-1 gp41 protein (Liu et al., 2002) and the recombinant HIV-1 protease activity (Lam et al., 2000). The formation of the six-helix bundle of HIV-1 gp41 protein and the recombinant HIV-1 protease activity were significantly inhibited by 50 μg/ml of the water extract of *P. vulgaris* at rates of 86.2% and 90%, respectively. But, after the water extract was purified through a polyacrylamide resin column and 60-85% of the tannin was removed, the inhibition effect of the remnant substances on HIV-1 integrase decreased by 40–80%. Purified tannin also exhibited a significant, dose-dependent inhibition effect on recombinant HIV protease.

P. vulgaris also showed significant anti-HSV-1 and anti-HSV-2 effects, and the main active constituent is polysaccharides. The mechanism may be related to the inhibition of virus-host cell binding activities, the inhibition of virus invasion (Xu et al., 1999) and the expression of viral antigens (Chi-Ming Chiu, Zhu, & Eng-ChoonOoi, 2004). *In vitro* experimental results showed that the total polysaccharide extract of *P. vulgaris* ear, and its E fraction, obtained from gel-filtration chromatography purification, can inhibit HSV-1 plaque formation in a dose-dependent manner, with an IC_{50} of 18 and 10 μg/ml, respectively. Under the same conditions, the IC_{50} values of the positive drugs heparin and acyclovir were 750 and 0.1 μg/ml, respectively. Plaque reduction tests showed that a water-soluble anionic polysaccharide isolated from the E fraction had significant inhibitory activity to HSV-1 and HSV-2 (including acyclovir-resistant strains) at the concentration of 100 μg/ml. Furthermore, the polysaccharide showed no anticoagulation or anti-cytotoxic effects (Xu et al., 1999). Another lignin-carbohydrate complex (PPS-2b), with a molecular weight of 8500 Da, obtained from the ear of *P. vulgaris* by water extraction and alcohol precipitation, can significantly inhibit HSV-1 (BW-S), HSV-2 (strain 8702) and gC-deficient HSV-1 and acyclovir-resistant viral strains activities (Zhang et al., 2007). The IC_{50} values were 18, 18, 18 and 17 μg/ml, respectively. The total polysaccharide extract of *P. vulgaris* also inhibited the expression of HSV-1 and HSV-2 antigens as well as the antigen expression of acyclovir-resistant HSV-1 strains (Chi-Ming Chiu et al., 2004).

Studies have also reported that the water extract of *P. vulgaris* exhibits anti-EIAV and anti-influenza A virus effects. The mechanisms were primarily inhibiting virus binding and early post-binding events and the inhibition of neuraminidase activity, which thereby reduced virus replication and cellular infection, respectively (Brindley et al., 2009; Tian et al., 2011).

4.3. Antibacterial effect

In recent years, studies have found that *P. vulgaris* also exhibits certain anti-pathogen effects on plant pathogens. Studies by Yoon et al. found that the methanol extract of *P. vulgaris* had a strong anti-fungal and antioomycete activity on *Phytophthora infestans*, rice blast fungus, red pepper anthracnose and wheat leaf rust fungus (Yoon et al., 2010). Among the hexane, ethyl acetate, n-butanol and water fractions of the methanol extract of *P. vulgaris*, the hexane fraction showed the strongest anti-fungal activity, with a dose-dependent correlation displayed by the anti-pathogen effect on *P. infestans*, rice blast fungus, red pepper anthracnose and wheat leaf rust. The most notable was the strong inhibitory effect of the hexane fraction on *P. infestans*: the inhibition rates were 88% and 82%, respectively, for concentrations of 250 and 125 μg/ml. In addition, both of the three-alkyne acid compounds isolated from the hexane

fraction showed a similar antifungal spectrum. The compounds displayed a strong inhibitory effect on *P. infestans*, with minimum inhibitory concentrations of 0.84 μg/ml for both. The compounds also exhibited a mild inhibitory effect on rice blast fungus, *Rhizoctonia solani*, *Fusarium oxysporum* f. sp. *raphani*, *Sclerotinia sclerotiorum* and pepper *Phytophthora capsici*, with a minimum inhibitory concentration of 7.6–200 μg/ml.

4.4. Anti-inflammatory effects

A study showed that *P. vulgaris* alcohol extracts and rosmarinic acid could not only inhibit the production of PGE2 and NO, but also reduce the secretion of TNF-α and IL-6 in LPS-stimulated RAW 264.7 mouse macrophages, but their mechanism of actions are different. P. vulgaris alcohol extract reduced the LPS-induced COX-2 and iNOS protein expression, while rosmarinic acid only inhibited COX-2 expression (Huang et al., 2009). In addition, the hexane extraction fraction of the ethanol extract of *P. vulgaris* var. lilacina also had a significant anti-inflammatory effect. By inhibiting the transcriptional factor of NF-κB activity, the extract inhibited inflammation-related iNOS and COX-2 gene expression in LPS-stimulated RAW264.7 cells. It is further believed that effective but unidentified anti-inflammation compounds might exist in the hexane extraction fraction of *P. vulgaris* var. lilacina or that palmitic acid and other compounds synergistically play a role in anti-inflammation effect (Hwang, Lee, Kim, & Hwang, 2013b).

Some studies have reported that the 70% ethanol extract of *P. vulgaris* and *P. vulgaris* var. lilacina had a significant anti-inflammatory effect. The mechanism of these extract could induce heme oxygenase-1 protein expression in RAW264.7 cells through the PI3K/Nrf2 pathway while reducing the release of HMGB1 in LPS-activated macrophage cells and CPL-induced sepsis mouse serum (Jun et al., 2012), inhibited the TNF-α-induced aortic smooth muscle inflammation response through the p38 MAPK/ERK signaling pathway (Park & Sung, 2013). Furthermore, *P. vulgaris* water extract induced the expression of heme oxygenase-1 and eNOS to inhibit the ROS / NF-κB pathway via the induction of PI3K/AKt mediated Nrf2 activity, thereby inhibiting high blood sugar-induced vascular inflammation (Hwang, Lee, et al., 2012).

4.5. Immunoregulation

A Study (Lu, Qin, Ye, & Yang, 2011) has shown that *P. vulgaris* ethanol extract significantly improved the cellular immune function of mice infected with multidrug-resistant mycobacterium tuberculosis. ELISA experimental results showed that compared with MDR-MTB-infected mice, the serum IFN-α and IL-12 contents were significantly increased in mice receiving the *P. vulgaris* alcohol extract; in addition, the IL-10 content was significantly decreased ($P < 0.05$), indicating that the extract significantly improved the cellular immune response level of the mice. RT-PCR experiments showed that *P. vulgaris* alcohol extract significantly upregulated the expression of IFN-α, IL-12 and GLSmRNA in PBMC and down-regulated the IL-10mRNA expression in a mouse model, demonstrating that the extract could enhance the cellular immune function of MDR-TB-infected mice. Furthermore, by promoting GLS mRNA expression, the extract enhanced the bactericidal capacity of the body's CTL cells.

The water extract of *P. vulgaris* can stimulate the phagocytic activity of phagocytic cells through NF-κB transcription and the activation of MAP kinase, increases NO production and TNF-α, IL-6 and IL-1β expression in macrophage RAW264.7 cells and inhibits the growth of sarcoma 180 tumor cells (Han et al., 2009). *P. vulgaris* isolates from water extraction and alcohol precipitation (0.90 g/kg) have a certain enhancing effect on mouse cellular immunity and non-specific immunity (Huang et al., 2013). Compared with the control group, 0.90 g/kg of this extract significantly increased the thickness of the mouse foot pad, in addition to increasing the activity of T lymphocytes ($CD3^+CD25^+ = 8.15 \pm 0.95\%$) and their subset Th lymphocytes ($CD3^+CD4^+CD8^-CD25^+ = 6.53 \pm 0.91\%$). LDH release assays showed that compared with a control group (0.49 ± 0.06), the concentrations of 0.15, 0.30 and 0.90 g/kg of *the extract* can all significantly increase the activity of transformed NK cells (0.54 ± 0.03, 0.57 ± 0.06 and 0.62 ± 0.07). Additionally, 0.1% and 1.0% of *P. vulgaris* ethanol extract can improve the non-specific immune response of flounder and its disease resistance to *Uronemamarinum* (Harikrishnan, Kim, Kim, Balasundaram, & Heo, 2011).

4.6. Anti-tumor effect

A study showed that the total triterpenoids and total phenolic acids purified from *P. vulgaris* can significantly inhibit the growth of SPC-A-1 cells and tumors, and the anti-lung cancer activity of the triterpenoids and phenolic acids was accomplished through the synergistic action of multiple compounds (Feng et al., 2010).

Besides ursolic acid and oleanolic acid, 2α, 3α-dihydroxyursa-12-en-28-oic acid can induce apoptosis in human acute leukemia Jurkat T cells, with IC_{50} value of 22 μg/ml (Woo et al., 2011). The compound (3β, 4β)-24-hydroxy-16-oxo-28-norolean-12-en-3-yl 4-O-β-D-xylopyranosyl-β-D-glucopyranoside uronic acid has a significant inhibitory effect on the SMMC-7721 cell line, yielding an IC_{50} value of 35 μM (Gu, Li, Li, Qian, & Zhang, 2007).

The major effective chemical component with the homologous anti-tumor mechanisms of *Prunella plants* shown in the Table 2.

4.7. Anti-oxidative effect

P. vulgaris extract enriched in phenolic acids can significantly reduce the barbital and conjugated diene content in the blood of hereditary high-triglyceride mice that are on a high-sugar diet. The phenolic enriched extract can also increase the blood GPX activity and liver GSH content (Škottová et al., 2004). *P. vulgaris* extract (containing 9% rosmarinic acid) and rosmarinic acid can reduce ROS production in cells irradiated with UVB and can reduce DNA damage. Both the extract and rosmarinic acid can reduce caspase-3 and caspase-9 activity as well as the release of IL-6. In addition, they are believed to afford a protective effect to human keratinocytes against UVA-induced oxidation (Vostálová, Zdařilová, & Svobodová, 2010).

In recent years, Liang et al. (Feng, Jia, Zhu, Chen, & Shi, 2010) used ABTS, FRAP and DPPH models to evaluate the *in vitro* anti-oxidative activity of different concentrations (95%, 60%, 30% and 0%) of *P. vulgaris* ethanol extract. The results showed that a 60% ethanol extract had the strongest anti-oxidation effect, and the total phenolic content was highly correlated with anti-oxidation activity ($R^2 = 0.9988$ in $ABTS^+$, 0.6284 in DPPH and 0.9673 in FRAP tests). Hwang, Lee, Kim, and Hwang (2013a) used DPPH, FRAP, ABTS, SOD and the generation of reactive oxygen species methods to evaluate the anti-oxidative activities of different solvent extraction fractions (70% ethanol, hexane, n-butanol, chloroform and water) of *P. vulgaris* var. lilacina; the results showed that the fractions of ethanol and water extraction had very strong anti-oxidative activity. The total phenolic content in these two fractions were 303.66 and 322.80 mg GAE/g, respectively, which were significantly higher than the values in other fractions. Another study found that the water extracts of *P. vulgaris*, *P. vulgaris* var. lilacina, *P. grandiflora* and *P. orientalis* Bornm. All had significant anti-oxidative activity. The study also indicated that the total phenolic acids was the major active substances responsible for anti-oxidative activity (Kyung-A, Yu-Jin, Dong-Sik, Jaehyun, & Ae-Son, 2011; Şahin, Ari, Demir, & Ulukaya, 2014).

Table 2
The anti-tumour information.

Composition	Anti-tumor effect	Mechanism of action	Pharmacological Models	References
Ursolic acid	Inhibit proliferation and induce apoptosis	Upregulating the expression level of caspase 3, -8, -9 and downregulating the expression level of Bcl-2	BGC-803 cells	Wang, Yin, Guo, and Xiao (2011)
	Induce apoptosis	The pathway mediated by mitochondria and downregulating the expression of XIAP	HuH7 cells	Shyu, Kao, and Yen (2010)
Oleanolic acid	Induce apoptosis	Upregulating the expression of the Bax and Bad, downregulating the expression of the Bcl-2	SPC-A-1 cells	Feng et al. (2011)
		The pathway mediated by mitochondria and downregulating the expression of XIAP	HuH7 cells	Shyu et al. (2010)
Triterpenes	Cytotoxicity	*In vitro* cytotoxicity	cancer cell line: A549, SK-OV-3, SK-MEL-2, HCT15	Lee et al. (2008)
Phenolic acid	Antioxidant activities	Increasing SOD activity, reducing the content of MAD	C57BL/6 mice	Feng et al. (2010)
		Inhibiting the production of ROS and oxidative stress induced by UVA, alleviating the DNA damage	HaCaT cells	Psotova, Svobodova, Kolarova, and Walterova (2006)
Polysaccharie	Immunomodulatory effects	Increasing the thymus and spleen index of Tumor-Bearing Mice	C57BL/6 mice	Feng, Jia, Shi, and Chen (2010)
	Inhibit proliferation and induce apoptosis	Upregulating the expression of the gene p53, p21 and Bax, downregulating the expression of the gene Bcl-2	HepG2 cells	Kyung-A et al. (2011)
Aqueous extract	Inhibit angiogenesis	Decreasing the production of total blood vessels of chick embryos, reducing the expression of VEGF-A mRNA inHT-29 and and HUVECs cell and VEGFR-2mRNA in HUVECs cell	Chick chorioallantoic membrane and HUVECs cells	Lin et al. (2011)
Alcohol extract	Inhibit invasion and metastasis	Inhibiting the expression of the NF-_B depending on MMP-9	HT-1080, B16-F1, B16-F10	Choi et al. (2010)
	Inhibit proliferation	The function target is causing the change of cell proteome	Raji and Jurkat cells	Zhang, Sun, Fu, Chen, and Ding (2009a,b)
	Inhibit proliferation and induce apoptosis	Activating the JNK signal transduction pathway and caspase pathway to cause cell apoptosis	Jurkat cells	Woo et al. (2011)
	Cytotoxicity, induce apoptosis	Cytotoxic effect *in vitro*, upregulating the expression of the p53, Bax and Fas	HepG2, HT29, A549, MKN45 and HeLa cell lines	Hwang et al. (2013)

4.8. Regulatory effect on blood pressure

Some studies have demonstrated that the ethanol extract of *P. vulgaris* can impart a significant antihypertensive effect. The working mechanism of this extract could be a direct vasodilatory effect (Sun, Yuan, Liu, & Zhang, 2006), an endothelium-dependent vasodilatory effect produced through the NO-guanylate cyclase pathway (Xu et al., 2010), or an increase in the serum NO content and reduction of the serum ET and Ang II content (Liang, Xiong, Luo, & Wang, 2011).

Recently, some studies (Xia et al., 2014) have shown that both the water extract of *P. vulgaris* and the supernatant of the alcohol precipitation of the water extract can significantly reduce the systolic pressure of spontaneous hypertensive rats. The supernatant from the alcohol precipitation of the water extract exhibited no significant difference in the strength of its efficacy compared with the water extract, but the endurance of its efficacy was more prominent. That is, the supernatant of the alcohol precipitation of the water extract worked for a longer time, and a high-dosage supernatant was also able to reduce the diastolic pressure.

4.9. Antidiabetic

Some studies (Wu, Chen, Gao, & Jiang, 2010; Wu, Zhang, Ding, Wang, & Zhuang, 2009) found that *P. vulgaris* water extract directly inhibits α-amylase, α-glucosidase and isolated intestinal α-maltase activities in a dose-dependent manner. Moreover, the studies demonstrated that the extract inhibited maltose tolerance and reduced postprandial hyperglycemia in normal ICR mice. Its working mechanism could be through the inhibition of α-glucosidase, SGLT-l,GLuT-2, Na^+-K^+-ATPase mRNA expression in Caco-2 cells to delay carbohydrate hydrolysis and thereby effecting glucose uptake (Wu, Ha, & Gao, 2010).

A recent study (Hwang, Kim, et al., 2012) also showed that the water extract of *P. vulgaris* var. lilacina significantly inhibits diabetic atherosclerosis in type II diabetic db/db mouse. After feeding type II diabetic db/db mice with 100 and 200 mg/kg/day of *P. vulgaris* var. lilacina water extract for 8 weeks, the serum urea nitrogen was reduced, and the creatinine clearance rate was increased. At the same time, the extract also reduced the plasma total cholesterol, triglycerides and low-density lipoprotein levels, while increasing the high-density lipoprotein levels. The malondialdehyde and TGF-β1 levels were also significantly decreased, and the NO level was increased.

In addition, one study (Wu et al., 2012) reported that *P. vulgaris* water extract prevented IL-1β-induced pancreatic β cell apoptosis by attenuating IL-1β-activated Fas/FasL and the JNK cellular apoptosis signal transduction pathway, and by reducing the expression of IL-1β-activated NF-κB and inflammatory cytokines. Rosmarinic acid and caffeic acid vinyl ester isolated from *P. vulgaris* L. have significant inhibitory effects on rat crystalline aldose reductase and recombinant human aldose reductase, with IC_{50} values of 2.77 ± 0.48, 3.2 ± 0.55 μM and 18.62 ± 0.40, 12.58 ± 0.32 μM, respectively. In addition, caffeic acid vinyl ester can also significantly inhibit the formation of glycosylation products, with an IC_{50} of 33.16 ± 0.54 μM. This inhibition effect was 58 times stronger than that of the positive control aminoguanidine (IC_{50} = 1944.86 ± 8.39 μM) (Li et al., 2012).

4.10. Other pharmacological effects

The flavonoid extract of *P. vulgaris* can inhibit tyrosinase activity, and it is a reversible, competitive tyrosinase inhibitor (Yan, Zhang, & Zhou, 2013). *P. vulgaris* methanol extract (0.2 mg/ml) has significant anti-lipase activity with an inhibition rate of 74.7% (Zheng, Duan, Gao, & Ruan, 2010). Various concentrations of *P. vulgaris* extract (5, 10, 25 μg/ml) and 1 μg/ml of rosmarinic

acid can inhibit the biological changes in human gingival fibrous tissue induced by LPS, including the reduction of ROS production, intracellular GSH depletion and lipid peroxidation. The extract can down-regulate IL-1β, IL-6, TNF-α and inhibit iNOS expression (Zdařilová et al., 2009). The ursolic acid and betulinic acid in *P. vulgaris* var. lilacina can inhibit ER-mediated signal transduction by inhibiting ER synthesis at the transcriptional level, which showed a significant anti-estrogen effect (Kim, Lee, Gu, Hyam, & Kim, 2014). The passive avoidance, Y-maze and Morris water maze task experiments showed that 70% ethanol flower extract of *P. vulgaris* var. Lilacina (50, 25 and 25 mg/kg, po) can improve the impairments of mouse memory induced by scopolamine. Furthermore, the passive avoidance task showed that EEPV (25 mg/kg, po) can also improve MK-801-induced mouse memory impairment. Its mechanism could be the enhancement of the cholinergic neurotransmitter system through NMDA receptor-mediated signaling (Park et al., 2010). Compounds 3β, 13β-dihydroxyolic-11-ene-28-oic acid, oleanolic acid, 2α, 3β-dihydroxyole-an-12-en-28-oic acid, 2α, 3α-dihydroxyolean-12-en-28-oic acid, ursone, 2α, 3α-dihydrox yursa-12-en-28-oic acid, 2α, 3β-dihydroxyursa-12-en-28-oic acid, 2α, 3β, 23-trihydroxy-ursa-12-en-28-oic acid have anti-complement activities for CP and AP, with CH_{50} and AP_{50} values between 0.15 and 0.37 mg/ml and between 0.29 and 0.53 mg/ml, respectively (Cheng and Chen, 2012).

5. Prospects

In summary, the chemical components of *Prunella* plants mainly include triterpenoids and their glycosides, phenolic acids (especially phenylpropanoids phenolic acid including the *Prunella*-unique rosmarinic acid and its derivatives), flavonoids and their glycosides, sterols, organic acids, essential oils and saccharides. Of them, tannins and polysaccharides exhibit very good antiviral activities. The triterpenoids showed anti-tumor activity, and the fractions enriched in phenolic acids, phenol (including phenolic acids and flavonoids) components and polysaccharides have anti-oxidation activity. Both rosmarinic acids and its derivatives showed anti-inflammatory activity.

Studies on these components and their activities provide the basis for the clinical application of *P. vulgaris* and the development of formulations. Therefore, in recent years, the application of *P. vulgaris* has expanded continuously. *P. vulgaris* capsules are used for the treatment of thyroiditis (Cao & Chen, 2009). *P. vulgaris* tablets and *P. vulgaris* oral liquid are used for the treatment of breast diseases (Wang et al., 2014; Zhao & Zhao, 2009). *P. vulgaris* injection is used for the treatment of primary liver cancer (Zhang & Zhou, 2003). In addition, *P. vulgaris* has long been used as a self-healing drug abroad, particularly for alleviating sore throat and fever and accelerating wound healing.

P. vulgaris has many effects. It is a very promising drug resource, with the potential to support new drug research and development for the treatment of diabetes, hypertension, cancer and other diseases in the future. However, due to global ecological degradation, these drug resources will become increasingly depleted over time. Studies have shown that there is a high similarity in the physiological functions and chemical components of plants between the species of *Prunella*, especially those within the same genus, indicating that the other species, such as *P. asiatica* Nakai, *P. hispida*. Benth. and *P. grandiflora* (Linn.) Jacq., may could have similar effects as that of *P. vulgaris*. Strengthening our knowledge of the other species in the *Prunella* genus not only would expand the drug resources of *P. vulgaris* but also could discover new components with significant benefit.

Currently, the chemical components of the *Prunella* genus are not studied in a systematic manner. One study on a single component is not thorough. Studies of the pharmacological effects of a given component are mainly performed at the level of the crude extract. In addition, few metabolic studies of a single compound from *Prunella* or its specific parts have been carried out. Therefore, the means, methods and ideas for the study of compounds and their pharmacology requires innovation in the future. The screening of monomeric compounds related to the pharmacological activities of the antiviral, antibacterial, anti-inflammatory, anti-oxidative and anti-tumor effects of *Prunella* and studies of the overall relationship between the chemical composition of *Prunella* and its pharmacodynamic activity should be strengthened as well. For example, the total flavonoids, total phenolic acids and total polysaccharides of *Prunella* are all effective ingredients in anti-oxidative applications, displaying strong anti-oxidative effects. However, there exists no literature regarding whether these three types of components can have a synergistic effect. If a synergistic effect does occur, then what is the compatible relationship between these compounds, or what is the proper ratio in which they should be used? In addition, metabolic studies of the monomeric compounds in the *Prunella* genus and its specific parts should be strengthened. Only after the *in vivo* existing form of each component is determined in Chinese medicine can we clarify the corresponding metabolic pathway and mechanism and define the active ingredients in with actual therapeutic effects. Meanwhile, the discovery of new metabolites can provide clues for the development of new drugs.

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