

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/331717239>

Prunella vulgaris: A Comprehensive Review of Chemical Constituents, Pharmacological Effects and Clinical Applications

Article in *Current Pharmaceutical Design* · March 2019

DOI: 10.2174/1381612825666190313121608

CITATIONS

41

READS

1,889

7 authors, including:



Khalid Rahman

Liverpool John Moores University

184 PUBLICATIONS 9,909 CITATIONS

SEE PROFILE



Hua Nian

5 PUBLICATIONS 118 CITATIONS

SEE PROFILE



Hong Zhang

Shanghai University of Traditional Chinese Medicine

131 PUBLICATIONS 4,856 CITATIONS

SEE PROFILE

Some of the authors of this publication are also working on these related projects:



Role of nutraceuticals in the prevention of chronic diseases, mainly cardiovascular disease [View project](#)



protein glycation and its possible involvement in the pathogenesis of diabetic complications [View project](#)

REVIEW ARTICLE

Prunella vulgaris: A Comprehensive Review of Chemical Constituents, Pharmacological Effects and Clinical Applications

Su-Juan Wang^{1,2†}, Xiao-He Wang^{1†}, Yuan-Yuan Dai¹, Ming-Hua Ma³, Khalid Rahman⁴, Hua Nian^{1*} and Hong Zhang⁵

¹Pharmaceutical Center of Yueyang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200437, China;

²Department of Drug Preparation, Hospital of TCM and Hui Nationality Medicine, Ningxia Medical University, Ningxia 751100, China; ³Department of Pharmacy, Yangpu Hospital, Tongji University School of Medicine, Shanghai 200090, China; ⁴School of Pharmacy and Biomolecular Sciences, Faculty of Science, Liverpool John Moores University, Liverpool L3 3AF, England, UK;

⁵Institute of Interdisciplinary Integrative Medicine Research, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China

ARTICLE HISTORY

Received: February 13, 2019
Accepted: March 8, 2019

DOI:

10.2174/1381612825666190313121608

Abstract: *Prunella vulgaris* (PV) is a perennial herb belonging to the Labiate family and is widely distributed in the northeastern Asian countries such as Korea, Japan, and China. It is reported to display diverse biological activities including anti-microbial, anti-cancer, and anti-inflammation as determined by *in vitro* or *in vivo* studies. So far, about 200 compounds have been isolated from PV plant and a majority of these have been characterized mainly as triterpenoids, sterols and flavonoids, followed by coumarins, phenylpropanoids, polysaccharides and volatile oils. This review summarizes and analyzes the current knowledge on the chemical constituents, pharmacological activities, mechanisms of action and clinical applications of the PV plant including its potential as a future medicinal plant. Although some of the chemical constituents of the PV plant and their mechanisms of action have been investigated, the biological activities of many of these remain unknown and further clinical trials are required to further enhance its reputation as a medicinal plant.

Keywords: *Prunella vulgaris*, constituent, activity, application, review, triterpenoids.

1. INTRODUCTION

In recent years, interest in the development of herbs and botanicals from plants for use as drugs has significantly increased [1]. Natural products such as microbial metabolites are a rich source for the development of new drugs as they display diverse chemical structures and biological activities [2]. *Prunella vulgaris* (PV), also known as self-heal, is a plant belonging to the Labiateae family and is traditionally used as folk medicine in the Northeastern Asian countries such as Korea, Japan, and China [3]. The Chinese name for this plant is Xia-Ku-Cao, which originates from a description that the herb is dried and withered after the summer solstice [4]. It is reported to be rich in bioactive chemicals, including polysaccharides, flavonoids, triterpenes and phenolic acids. Thus, PV has many notable pharmacological activities, such as anti-colic, anti-oxidant, anti-inflammatory, anticancer, neuroprotective [5], anti-estrogenic [6], and anti-metastatic effects [7]. In China, it is also extensively used as a health-promoting food or tea. For example, PV is a principle raw material of Guangdong Herbal Tea well known as Wanglaoji-Liang-Cha, which has been historically consumed as a healthy beverage in Southern China [8]. In Europe, this plant is also consumed widely as food or tea on a regular basis [9]. Although dietary supplement manufacturers cannot legally make disease claims without approval of a new drug application, the unsubstantiated medical uses for many botanical dietary supplements are well known and promoted in literature and news media or on the Internet although dietary supplement manufacturers cannot legally make such claims [10].

Plants have always been a very good source for research and development of new drugs and many beneficial uses of medicinal plants are extensively documented as traditional medicines in many cultures. The present review mainly focuses on the *in vitro* and *in vivo* studies involving PV. The compounds and extracts which display potential pharmacological properties are presented in Tables 1 and 2, respectively. Some of the major effective phytochemicals present in PV are listed in Table 3. It has also been reported that out of the 21 herbs screened for either estrogenic or antiestrogenic activity using the alkaline phosphatase assay only PV extract displayed the strongest biological activity [6]. Meanwhile, SKI 306X, a purified extract from a mixture of three oriental herbal medicines (*Clematis mandshurica*, *Trichosanthes kirilowii* and *Prunella vulgaris*), has been widely used for the treatment of inflammatory diseases such as lymphadenitis and arthritis in Far East Asia [11]. The current state of research regarding the medicinal use of PV is summarized in this review.

2. PHYTOCHEMISTRY

Natural products are compounds or substances produced by living organisms (or found in nature), which have pharmacological or biological activities often used for drug discovery and design [12]. These plant metabolites have noteworthy structural complexity and a variety of pharmacological and biological activities, making them effective nutritional compounds and pharmaceutical drugs. Many bioactive constituents from PV have been identified, including phenolic constituents, complex carbohydrates and hydrophobic metabolites such as triterpenes. The aqueous extract contains abundant polyphenols, rosmarinic acid and complex carbohydrates, whereas more hydrophobic metabolites, such as triterpenes and flavonoids along with some polysaccharides and polyphenols, are found in the ethanol extract [13, 14]. The abundant polysaccharides have a number of reported biological activities, such as anti-oxidant and immunomodulatory [9] whilst several of the triterpenes

*Address correspondence to these authors, Hong Zhang at Institute of Interdisciplinary Integrative Medicine Research, Shanghai University of Traditional Chinese Medicine, Shanghai 201203, China; Hua Nian at Pharmaceutical Center of Yueyang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200437, China; E-mails: hqzhang51@126.com (HZ); jackynian@126.com (HN)

[†]These authors contributed equally to this work.

display significant anti-inflammatory activity. Rosmarinic acid has also shown to be an anti-inflammatory compound due to its specific inhibition of T cell signaling and its impact on glucose metabolism [14].

2.1. Triterpenoids and Saponins

The triterpenoids isolated from PV are mainly oleanane, lupinane and ursane. At present, a total of 28 triterpenoids have been isolated: 20 triterpenoids (free state), 8 saponins (binding state); the two compounds with highest content, oleanolic acid (1) and ursolic acid (2), are mainly responsible for the pharmacological activity of PV.

Many compounds have also been isolated from methylated PV extracts such as methyl oleanolate (3), methyl ursolate (4), methyl maslinate (5) and other related compounds [15-17]. Pravuloside A (6) and Pravuloside B (7) along with two ursane-type specific triterpenoid saponins have also been isolated from PV [17, 18]. Some other compounds present in PV are vulgarsaponin A (8) [19] and vulgarsaponin B (9) [20], which is a newly identified gluco-pyranoside compound (Fig. 1).

2.2. Sterols

The main sterols present in PV include: β -sitosterol (10), stigmasterol (11), α -spinolol (12), and stigmast-7-en-3 β -ol (13) [21]. Eight sterol compounds have been isolated from the ear, stem, leaf and other parts of PV, of which four compounds are present in a free state: ducoesterol (14), α -spinasterol, β -sitosterol, stigmasterol-7-olefinic alcohol. The other four compounds are glucose glucosides: stigmast-7-enyl- β -D-gluco-pyranoside (13), (22E,20S,24S)-

stigmast-7,22-diene-3-ene (15), α -spinasterolyl- β -D-glucopyranose glucoside, and stigmasterolyl- β -D-glucopyranose glucoside [22] (Fig. 2).

2.3. Flavonoids

In addition to rutin (16) and hyperoside, three other flavonoids have been isolated and identified from PV, namely luteolin (17), homoorinetin (18) and cinaroside (19) [22]. Besides these compounds, PV also contains quercetin (20), quercetin-3-O- β -D-galactoside (21) [23], quercetin-3-O- β -D-glucoside (22), kaempferol-3-O- β -D-glucoside (23) [24] and other related components (Fig. 3).

2.4. Coumarins

PV is reported to contain only small amounts of coumarin although three coumarin compounds are isolated from it [25]. The calculation of managerial constants and infrared spectroscopy identified these as umbelliferone (24), scopoletin (25) and esculetin (26) (Fig. 4).

2.5. Phenylpropanoids

Phenylpropanoids present in PV include: *P*-cumaric acid (27), *cis*-caffeic acid and *trans*-caffeic acid (28), rosmarinic acid (29), and others such as methyl rosmarine, ethyl rosmarine, *E*-butyl rosmarine, 3,4 α -trihydroxy-methyl-phenyl propionate, 3,4 α -trihydroxy-butyl-phenyl propionate [28] (Fig. 5).

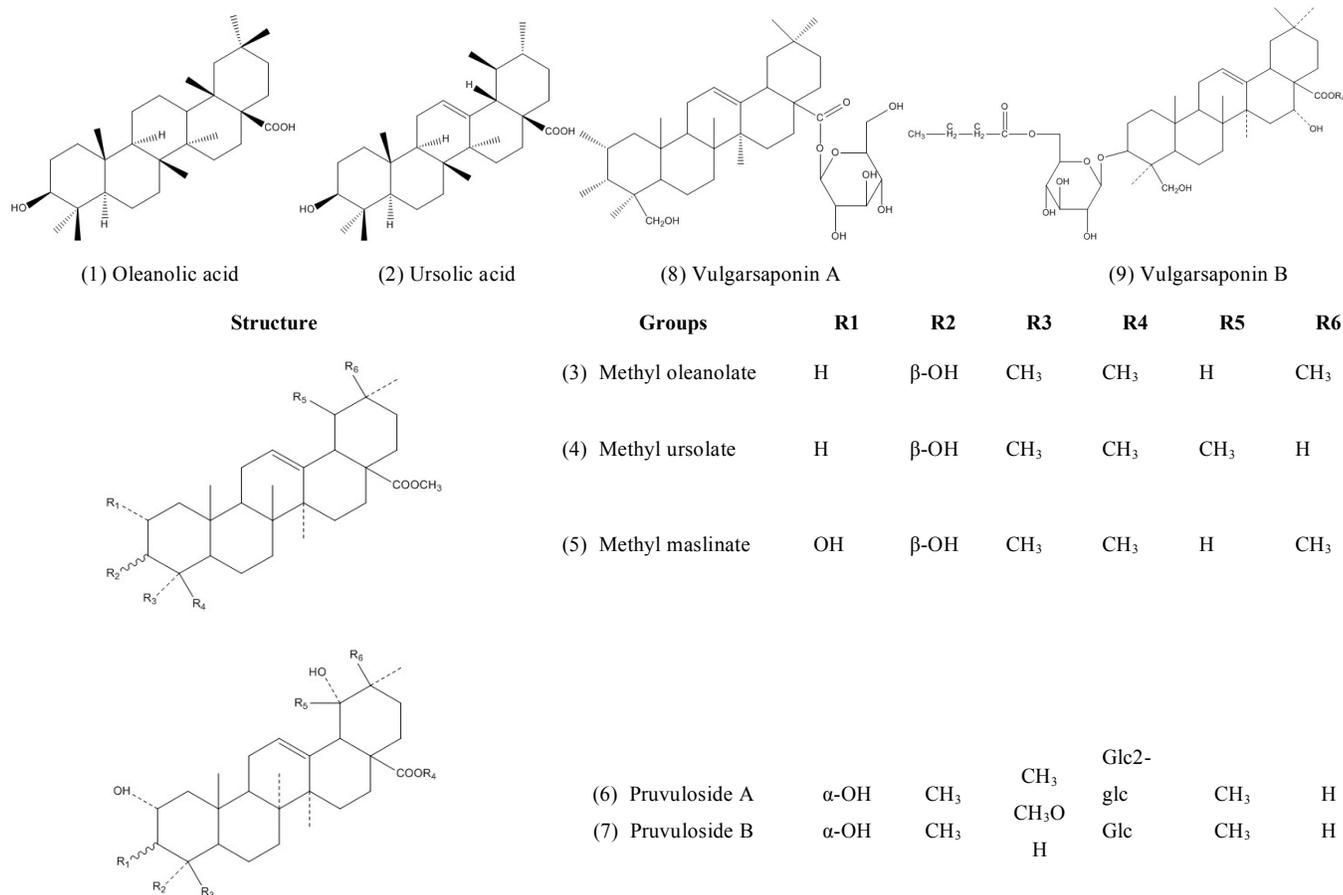


Fig. (1). Structures of triterpenes.

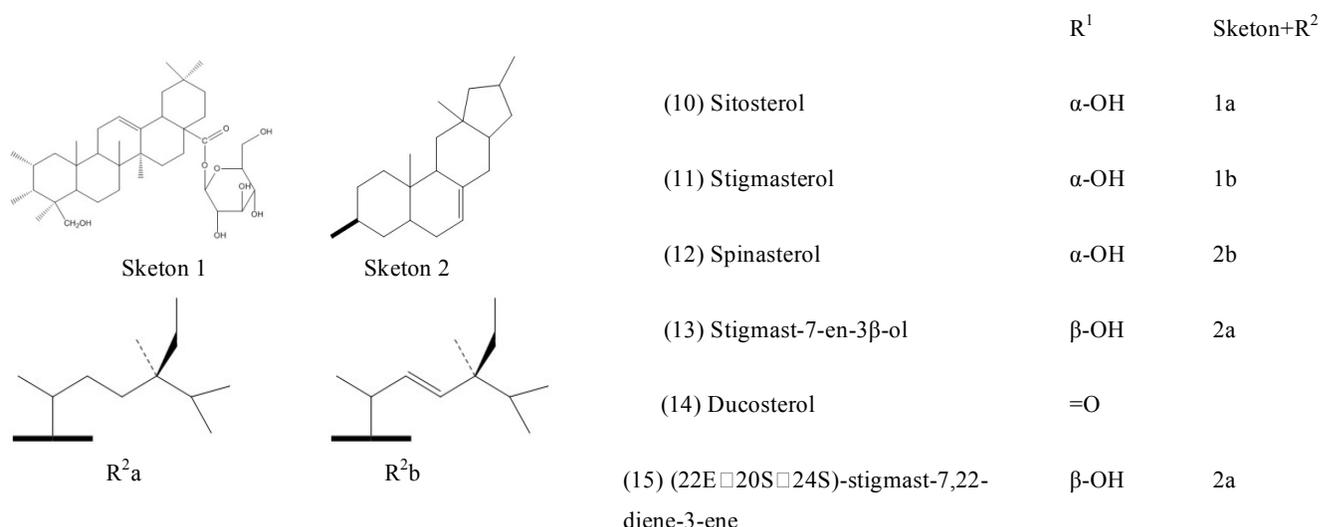


Fig. (2). Structures of steroids and derivatives.

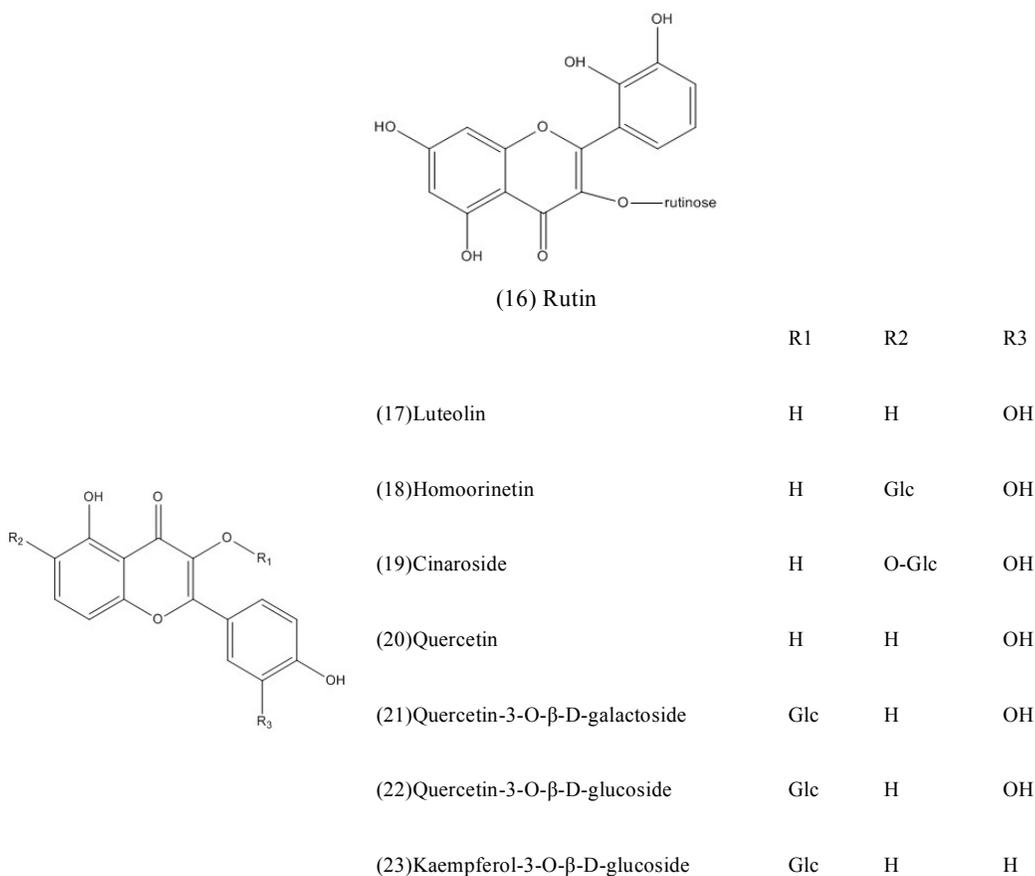


Fig. (3). Structure of steroids.

2.6. Long-chain Fatty Acids

PV contains long-chain fatty acids such as palmitic acid, ethyl palmitate, tetracosanoic acid, stearic acid, 6,9-octadecadienoic acid, 3,6,7-eicosatrienoic acid, oleic acid, peanut oleic acid, moringoic acid, lauric acid, myristic acid, linolenic acid, palmitic acid, myristic acid, and linoleic acid [22-27].

2.7. Volatile Oils

The volatile components present in PV include 1,8-eucalyptol, β-pinene, myrcene, linalylacetate, α-phellandene, linalool, 1,6-cyclononone, palmitic acid and trihexadecane. Among these, the content of 1,8-anthracene and β-pinene is the highest, and accounts for more than 60% of the total volatile oils [28].



Fig. (4). Structure of Coumarins.

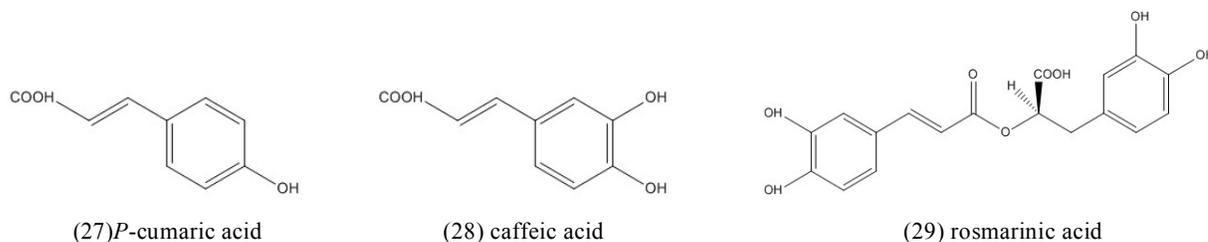


Fig. (5). Structure of Phenylpropanoids.

2.8. Sugar

PV contains free monosaccharides (mainly rhamnose, glucose, xylose, arabinose, mannose, galactose, etc.) [29], disaccharides (sucrose and fructose) and polysaccharides. In addition, a sulfur-containing polysaccharide has also been isolated from PV [30].

2.9. Other Components

Alkaloids, inorganic salts, vitamins, resins, bitter taste, tannic acid, proteins and lipids are also present in PV.

3. PHARMACOLOGY

3.1. Antitumor Activity

Anti-tumor activities of extracts and monomeric compounds from PV plant have been investigated [31]. PV inhibits metastasis and promotes the apoptosis of many different kinds of tumor cells through different pathways. Triterpene compounds 2 α -hydroxy ursolic acid and ursolic acid significantly inhibit breast cancer cells MCF-7, MDA-MB-231 and normal breast cells MCF-10A. Betulinic acid is reported to inhibit only breast cancer cells MCF-7 and MDA-MB-231, but has no effects on normal breast cells MCF-10A [33].

In addition, some studies have demonstrated that 19 α -hydroxy ursolic acid and quercetin present in PV ethanol extract can inhibit the migration of tumor cells MDA-MB-231 in a dose-dependent manner, in which quercetin reduces the proliferation of tumor cells by inhibiting the PI3k/Akt pathway. The IC₅₀ of 19 α -hydroxy ursolic acid and quercetin against MDA-MB-231 cells migration was 1.676 $\mu\text{mol} \cdot \text{L}^{-1}$ and 1.145 $\mu\text{mol} \cdot \text{L}^{-1}$, respectively [32]. The effect of prunella polysaccharide-zinc complex (P1-Zn) on HepG2 liver cancer cells has been confirmed by morphological changes, chromatin agglutination and G₀/G₁ cell cycle arrest. P1-Zn complex increases the expression of caspase-3 and -9, excessive production of reactive oxygen species and destruction of mitochondrial function to achieve effective inhibition of HepG2 cell proliferation [33]. PV also alleviated thyroid cancer symptoms through increase of Bcl-2-related protein X and caspase-3 levels by inducing apoptosis of thyroid cancer TPC-1 and FTC-133 cell lines and down-regulating B-cell lymphoma-2 expression in TC-1 and FTC-133 expression [34]. Recent studies [34, 35] have also demonstrated that PV has significant inhibitory effects on lymphoma cell Jurkat, hu-

man lung cancer cell A-549, endometrial cancer cell Ishikawa, and cholangiocarcinoma cells QBC939 and RBE.

3.2. Anti-inflammation and Immunoregulation

Inflammation is a potential risk factor in the development of many diseases and can create or exacerbate a range of diseases. Traditional Chinese medicines play a two-way immune regulatory role in the body, and the mechanisms of action are mainly related to immune organs, immune cells, immune molecules promotion, inflammatory response, and hypersensitivity [36].

Many active components of PV such as rosmarinic acid and ursolic acid have significant anti-inflammatory and immunosuppressive effects. The water extracts of PV stems and leaves markedly inhibited carrageenan-induced rat paw swelling and xylene-induced mouse auricular swelling, reducing the content of tumor necrosis factor- α [37].

3.3. Antiviral Effect

According to the lesions, the number of herpes zoster, the typical lesion score, and the expression levels of HSV-1 and HSV-2 in the lesion tissue, the guinea pig model of HSV-1 (skin) was established with HSV- Virus DNA copy number as an indicator. Prunella polysaccharide was found to not only inhibit the activity of the HSV-1 and HSV-2 *in vitro*, but also decrease HSV-1 and HSV-2 virus lesions in the guinea pig model, showing better anti-herpes simplex virus activity [38].

3.4. Anti-oxidative Effect

PV displays significant antioxidant activity [39]. High performance liquid chromatography (HPLC) and LC/MS analyses has shown that the main active compounds from 60% ethanol extract of PV (P-60) are phenols, such as caffeic acid, rosmarinic acid, rutin and quercetin. Total phenols are highly correlated with the antioxidant activity, and significantly inhibit tumor growth in C57BL/6 mice, increase superoxide dismutase (SOD) activity and decrease malondialdehyde (MDA) content in serum of tumor-bearing mice [40].

In addition, triterpenes, flavonoids and polysaccharides have the strongest antioxidant activity. The total reactive oxygen species (ROS), hydrogen peroxide (H₂O₂), and malondialdehyde (MDA) were measured in the shackle Balb/C mice model, and the activities

of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) were also analyzed, 2.50 g·kg⁻¹ of PV reduced the levels of H₂O₂, ROS, protein peroxide protein carbonyl; 1.25, 2.50, and 7.50 g·kg⁻¹ of PV decreased the content of lipid peroxidation MDA and increased the activity of SOD. Besides, the water extract of PV can reduce the pyrazole-lipopolysaccharide-induced oxidative stress in mice liver tissue by inhibiting the protein expression of CYP2E1 and CYP2A5 [41].

3.5. Anti-osteoporosis

The flavonoid extract of PV shows anti-osteoporosis effect through promoting osteoblast function in ovariectomized rats, reducing bone resorption and bone metabolism, increasing bone formation and decreasing trabecular bone loss and bone mass loss [42].

3.6. Anti-depression

The antidepressant effect of PV was investigated by use of mouse tail suspension, forced swimming and spontaneous activity tests with fluoxetine hydrochloride as a positive control drug. The water extract could increase the levels of 5-hydroxytryptamine, norepinephrine and dopamine in the hippocampus, and decrease the content of cyclooxygenase -2, prostaglandin E, interleukin-1 β , interleukin-6, indicating that the anti-depressant effect of PV aqueous extract may be achieved by increasing the content of monoamine neurotransmitter in hippocampal tissue and reducing the content of inflammatory cytokines [43].

3.7. Hypoglycemic, Hypotensive and Hypolipemic Effects

Hyperglycemia and glycosylated hemoglobin (HbA1c) are widely used as diagnostic markers for diabetes [44]. The proper management of diabetes includes blood glucose and HbA1c homeostasis, and improvement of antioxidant defenses by minimizing free radical adverse effects [45]. The indigenous hemoprotein antioxidant enzyme, catalase (CAT), directly scavenges the reactive oxygen species (ROS) and catalyzes the lessening and detoxification of hydrogen peroxides [46-48]. By using an alloxan-induced type 1 diabetes (T1D) mouse model, bio-guided fractionation, isolation, RP-HPLC, and 1H and 13C NMR identification, the active components of PV were determined: rosmarinic acid (RA), caffeic acid (CA, most active fraction) and p-coumaric acid(pCA), hence named, caffeic acid-rich fraction (CARF). CARF reduced blood glucose levels and improved in-vivo oxidative-stress. It also inhibited the carbohydrate-hydrolyzing enzymes (α -amylase and α -glucosidase) and reduced HbA1c levels more significantly than PV extract, CA or RA. In the longer time, CARF significantly increased serum-insulin, ameliorated thermal hyperalgesia and tactile allodynia more significantly than PV extract, CA or RA. Moreover, the tested compounds showed potential restoration of the lipid peroxide levels. CARF and PV extract were observed to increase serum-insulin and attenuate α -amylase and α -glucosidase, whose antioxidant potentials might be responsible for their antidiabetic and antinociceptive properties [49].

The stems, leaves, spikes, and the whole grass of PV have anti-hypertensive effect. The main active component is the total saponin. The water, 30% alcohol and ethanol - water extracts of PV exert antihypertensive effect on anesthetized animals. The water extract can reduce blood pressure by reducing the systolic pressure and diastolic pressure of SHR rats, significantly inhibit the α -amylase, α -glucosidase, and reduce the postprandial blood glucose levels of normal mice and alloxan diabetic mice, improve starch tolerance, promote liver glycogen synthesis and lower blood sugar. PV can also inhibit atherosclerosis and hyperlipidemia to some extent [50].

4. CLINICAL EFFICACY OF PRUNELLA VULGARIS PREPARATION

In recent years, a variety of PV preparations have been widely used in clinical practice. Many of the diseases treated by PV alone or in combination with other medicinal plants have received satisfactory results. Although most traditional Chinese medicines have only moderate therapeutic effects on diseases, they have few side effects compared with Western medicines. Furthermore, a large number of Chinese medicines can alleviate or eliminate the adverse reactions caused by western medicine and help the body to recover, reducing the recurrence rate. Currently PV is clinically applied for production of various preparations, such as injections, oral liquid, and ointment. Although PV is the main herb medicine, the efficacy of preparations varies with the addition of excipients, the extraction methods of medicinal substances, and the administration routes in the preparation process.

4.1. Granules

Rosmarinic acid, a major pharmacological agent of PV [78], has a number of activities, such as anti-inflammation, elimination of swelling, immune regulation and anti-thyroid, and is obtained from the water extract of PV and further processing the excipients, which are prepared as granular. Clinical research [79] founded that 356 cases of menopausal women were randomly divided into both the control group (181 cases) and the observation group (175 cases), and the control group were given cyclosporine eye drops and the observation group additional Prunella granules. After treatment, the amount of tear fluid and the time of tear film rupture in the observation group were significantly higher than those in the control group. The corneal topographic map corneal surface regular index, corneal surface irregular index, conjunctival epithelial cells TNF- α , IL-1 β , ICAM-1 significantly reduced, indicating that PV granules has a significant efficacy in the treatment of menopausal women with dry eye.

When hyperthyroidism is treated with Western drug methimazole tablets, the long period of treatment is necessary due to the slow improvement of thyroid function. However, long-term use of methimazole tablets alone will inevitably lead to many side effects. Therefore, the treatment with Western medicine alone is not considered ideal. Given the treatment with PV granules combined with methimazole tablets, the granules can enhance the function of methimazole and relieve its side responses owing to the efficacy of PV with clearing away heat and toxic material. A clinical study [80] showed that in the combination therapy group, the efficiency (91.84%) was significantly higher than that of methimazole alone (75.51%), and the difference was statistically significant ($P < 0.05$).

4.2. Tablets

PV extract is dried and pressed into tablets. The preparation has anti-tumor, antibacterial, anti-inflammatory, liver protective effects, etc. In one study for observing the clinical efficacy of PV tablets on benign prostatic hyperplasia [81], the control group was given finasteride and the observation group additional PV tablets. Prostate volume and prostate specific antigen in the observation group were improved compared to the control group, and the adverse reaction rate (5.0%) in the observation group was significantly lower than that in the control group (32.5%), these differences were statistically significant ($P < 0.05$). A recent study [82] disclosed that PV tablets had better clinical effects, fewer adverse reactions, and shorter course of treatment in the treatment of acute thyroiditis when combined with glucocorticoid. In another clinical study on acute mastitis, PV tablets combined with antibacterial penicillin could evidently improve the symptoms, restore normal breastfeeding and reduce the patient's resistance to antibacterials. PV tablets

Table 1. The compounds with pharmacological activities from PV.

Compound	Model	Observation	Dosage	Activity	Mechanism of Action	Refs.
2,3-dihydroxyurs-12-en-28-oic acid (DHURS)	human acute leukemia Jurkat T cells	<i>in vitro</i>	20–25 µg/ml	Induces apoptosis	Mitochondria-dependent activation of caspase cascades	[51]
Ursolic acid and betulinic acid	MCF7 human breast cancer cell line and LNCaP (CRL-1740) human prostate cancer cell line	<i>in vitro</i>	20,50 µM	Anti-estrogenic	Inhibited estrogen signaling by suppressing the expression of estrogen receptor α (ER α) and enhanced prostate-specific antigen promoter activity	[52]
Rosmarinic acid (RA)	UVA-induced changes in a human keratinocyte cell line (HaCaT)	<i>in vitro</i>	25–50 mg/l	Photoprotection	Suppressed UVA-induced ROS production \square reduced DNA damage \square and inhibited UVA-induced caspase-3 activation	[53]

Table 2. The extracts with pharmacological effects from PV.

Extract	Model /Cell Type	Observation	Dosage	Activity	Mechanism of Action	Refs.
Aqueous extract	Carbon tetrachloride-induced hepatic fibrosis	<i>In vivo</i>	50, 100, and 200 mg/kg	Anti-fibrosis	Inhibited the activation of hepatic stellate cells, promoted collagenolysis and regulated fibrosis-related microRNAs	[3]
60% Ethanol extract	Tumor-bearing C57BL/6 Mice	<i>In vitro</i> , and <i>in vivo</i>	5 and 10 g crude drug/kg	Antioxidant	Antioxidant and inhibition of the tumor growth	[45]
Methanol extract	Mouse Xenograft	<i>In vitro</i> , and <i>in vivo</i>	50 µg/ml	Anti-estrogen	Inhibited estrogen responses	[6]
Ethylacetate extract	Doxorubicin-induced oxidative stress	<i>In vitro</i>	0.005 to 0.05 mg/ml	Cardioprotect	Antioxidant capacity	[54]
Water extraction followed by alcohol precipitation	Female BALB/c mice	<i>in vivo</i>	0.90 g/kg	Anti-inflammation and anti-tumor	Enhanced the activity of T lymphocytes in general and its subgroup Th cells and No significant changes in B lymphocytes	[55]
Ethanol extract	LPS-activated RAW 264.7 Cells and CLP-induced Septic Mice	<i>In vitro</i> and <i>in vivo</i>	10, 50 and 100 µg/ml	Treatment of sepsis	Induced heme oxygenase-1 (HO-1) expression through PI3K/Nrf2 signal pathways and a reduction of high mobility group box 1(HMGB1)	[56]
Aqueous extract	Human T cell lymphotropic virus type 1-immortalized T cell lines MT-2 and MT-4 cells	<i>In vitro</i>	10, 50 µM	Anti-HIV activity	Inhibited syncytium formation and resultant cell death	[57]
Aqueous extract	murine macrophage RAW 264.7 cells	<i>In vitro</i>	10, 50, 100 µg/ml	Immunostimulatory and anti-tumor activity	Stimulated macrophage activation via NF- κ B transactivation and MAP kinase activation	[58]
70% Ethanol extract	The mouse macrophage cell line RAW264.7, human liver cancer cell line HepG2, human colon cancer cell line HT29, human lung cancer cell line A549, human stomach cancer cell line MKN-45 and human cervical cancer cell line HeLa	<i>In vitro</i>	10, 50, 100 µg/ml	Anti-oxidant and anti-cancer	Increased the expression of p53, Bax and Fas	[59]

(Table 2) Contd....

Extract	Model /Cell Type	Observation	Dosage	Activity	Mechanism of Action	Refs
Aqueous extract	HeLa37 cells	<i>In vitro</i>	0.1, 1, 10 µg/ml	Anti-viral	Inhibited HIV-1 infectivity	[13]
Aqueous extract	male Sprague-Dawley rats and rat peritoneal mast cells (RPMC)	<i>In vivo</i>	0.005 to 1 g/kg	Inhibition of immediate-type allergic reactions	Inhibited the passive cutaneous anaphylaxis activated by anti-dinitrophenyl (DNP) IgE antibody dose dependently and suppressed the histamine release induced by compound 48/80 or anti-DNP IgE	[60]
Aqueous extract	murine peritoneal macrophages	<i>In vitro</i>	50, 100, 200, 400 µg/ml	Immunomodulatory and antiinflammatory activities	Stimulated the proliferation of T-lymphocytes and suppressed NO production in lipopolysaccharide-stimulated macrophages	[61]
Aqueous extract	Equine dermis cells	<i>In vitro</i>	66 µg/mL or 62.4 µg/mL	Inhibition of equine infectious anemia virus (EIAV) replication	Prevented viral particles from binding to the surface of permissive cells	[14]
Ethanol extract	mdr1a-/- or wild type FVBWT mice	<i>In vivo</i>	2.4 mg/d	Anti-inflammation	Maintained mucosal homeostasis in mdr1a/ mice by regulating gene expression associated with innate inflammatory responses and attenuating the activation of the adaptive immune response	[62]
Aqueous extract	INS-1 cells	<i>In vitro</i>	100 µg/ml	Anti-inflammation	Prevented IL-1β-increased INS-1 cell death and LDH activity and attenuated IL-1β-increased caspase-3 activity	[63]
Aqueous ethanol extract (30% v/v)	lipopolysaccharide (LPS)-induced oxidative damage and inflammation in human gingival fibroblasts	<i>In vitro</i>	5, 10, 25µg/ml	Anti-inflammation	Reduced reactive oxygen species (ROS) production, intracellular glutathione (GSH) depletion as well as lipid peroxidation, inhibited LPS-induced up-regulation of interleukin 1b (IL-1b), interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), and suppressed expression of inducible nitric oxide synthase (iNOS)	[64]
80% Ethanol extract	alloxan-induced diabetic mice	<i>In vivo</i>	50, 100 and 150 µg/ml	Hypoglycemic and antinociceptive effects	Increased serum-insulin and attenuated alpha-amylase and alpha-glucosidase	[65]
50% Ethanol extract	UVB-aged normal human dermal fibroblasts	<i>In vitro</i>	10, 100 µg/mL	Protection of normal human dermal fibroblasts (NHDFs) from UVB - induced inflammatory and photo aging damage	Inhibited MAPKs, AP-1, and NF-κB signaling and promoted the TGF - β1/Smad pathway	[66]
Aqueous extract	Human umbilical vein endothelial cells (HUVEC)	<i>In vitro</i>	stock solution corresponding to 5 g raw PVL per ml	Upregulation of endothelial NO synthase (eNOS)	Increased Enos promoter activity, eNOS mRNA and protein expressions, as well as NO production.	[67]
Ethyl acetate parts of aqueous extract	scopolamine (SCOP)-induced aging rats	<i>In vitro and in vivo</i>	100 mg/kg	Anti-dementia	Attenuated SCOP-induced brain senescence in rats by improving behavioral performance and decreasing brain cell damage, reduced AChE activity and MDA level, increased SOD and GPx activities, and inhibited the expression of NF-κB and GFAP.	[68]

(Table 2) Contd....

Extract	Model /Cell Type	Observation	Dosage	Activity	Mechanism of Action	Refs.
Aqueous extract	human umbilical vein endothelial cells	<i>In vitro</i>	10, 30, 50 µg/mL	Anti-inflammation	Inhibited ROS/NF-κB pathway by inducing HO-1 and eNOS expression mediated by Nrf2	[69]
Ethanol extract	RAW 264.7 Mouse Macrophages	<i>In vitro</i>	30 µg/mL	Anti-inflammation	Inhibited lipopolysaccharide (LPS)-stimulated prostaglandin E2 (PGE2) and nitric oxide (NO) production.	[70]
Ethanol extract	normal naive mice	<i>In vivo</i>	25 or 50 mg/kg	Enhancement of cognitive performance	Increased neural cell proliferation and the number of immature neurons, enhanced ERK, Akt and GSK-3β phosphorylation levels and up-regulated adult hippocampal neurogenesis.	[71]
Aqueous extract	Human fibrosarcoma HT-1080, mouse melanoma B16-F1 and B16-F10 cells	<i>In vitro</i> and <i>In vivo</i>	10,50,100,200 µg/ml	Anti-invasion and anti-metastasis	Suppressed MMP-9 expression by the inhibition of NF-κB via ERK1/2 signaling pathway as well as MMP-9 activity	[7]
Ethanol extract	Male ICR mice	<i>In vivo</i>	25 or 50 mg/kg	Anti-amnesia	Ameliorated scopolamine-induced cognitive impairments.	[72]
Aqueous extract	Human liver carcinoma HepG2, Huh-7 and Hep3B cells	<i>In vitro</i>	1, 5 and 10 mg/ml	Anti-invasion and anti-metastasis	Inhibited activities of metalloproteases, MMP-2 and MMP-9, without affecting cell viabilities, and suppressed migration through attenuation of enzymatic activities of MMP-9 and MMP-2 at transcriptional levels	[73]

Table 3. The phytochemicals categories with pharmacological properties from PV.

Effective Phytochemicals	Model /Cell Type	Dosage	Observation	Activity	Mechanism of Action	Refs.
Polysaccharides	Murine macrophage RAW 264.7 cells	125, 250, 500, 1000 µg/mL	<i>In vitro</i>	Antioxidation and immunomodulation	Stimulated the production of pro-inflammatory cytokines, including nitric oxide (NO), tumor necrosis factor- (TNF-), and interleukin-6 (IL-6)	[9]
Lignin-polysaccharide complex	BALB/c mice	10,20,30,40,50 µg/mL	<i>In vivo</i>	Anti-herpes	Inhibited viral binding and penetration into host cells	[74]
Polysaccharide	HSV-1 and HSV-2	100 µg/mL	<i>In vitro</i>	Anti-HSV	Inhibited HSV by competing for cell receptors	[32]
Phenolics-rich	Hereditary hypertriglyceridemic rats or high-sucrose diet (HSD, 70 cal% of sucrose) for two weeks	1% w/w	<i>In vivo</i>	Antioxidation	Suppressed a high-sucrose diet induced oxidative stress and positively modified lipoprotein cholesterol profile in plasma of hereditary hypertriglyceridemic insulin-resistant rats	[75]
Polysaccharide-zinc	HepG2 cells	500 µg/mL	<i>In vitro</i>	Antiproliferation	Activated caspase-3 and -9, reactive oxygen species (ROS) overproduction and mitochondrial dysfunction	[76]
Polysaccharide	Human breast carcinoma-associated fibroblasts	5 µg/mL, 8 µg/mL	<i>In vitro</i>	Anti-migration and anti-apoptosis	Inhibited basic fibroblast growth factor (bFGF) expression, and suppressed the growth of breast cancer SKBr-3 cells.	[77]

combined with adapalene gel also showed a significant clinical effect in the treatment of acne vulgaris [83].

4.3. Ointment

PV ointment is composed of PV, licorice, Scrophulariaceae and 14 other herbs. These herbs are decocted with water, concentrated

into a clear paste, and appropriate amount of refined honey or sucrose is added and heated, which turns this into a concentrated dark brown semi-fluid formulations. PV ointment also has the efficacy of clearing fire, loosing knot and eliminating swelling. For 50 cases with thyroid nodules [84], the total effective rate was 76.00% when treated with PV ointment combined with thyroxine tablets, while the total effective rate was only 42.00% in the patients treated with thyroid hormone tablets alone. The difference was statistically significant ($P < 0.05$). Therefore, the combination therapy has more obvious treatment effect, and can be widely used in clinic.

4.4. Oral solution

The preparation of PV oral solution is obtained by decoction with water, filtration, and concentration, followed by addition of sodium benzoate and sucrose which is then dissolved by heating the mixture. PV oral solution possesses several effects, such as anti-bacteria, anti-inflammation, dissipating binds and dispersing swelling, clearing heat and purging fire. The effect of PV oral liquid combined with betamethasone in the treatment of patients with subacute thyroiditis was more significant than that of betamethasone alone. The total effective rate (81.40%) was significantly higher in the combination group than in the betamethasone alone group (81.40%) [85]. A clinical study [86] showed that the total effective rate was 75.68% and the recurrence rate in one year was 36.84% when the chronic breast cancer patients were treated with the combination of PV with oral antibiotics (cefdinir dispersible tablets). The rates were significantly lower than those of patients treated with antibiotics alone.

4.5. Capsules

PV capsules are made by concentration of PV water extract plus brown sugar filled in empty capsules or soft capsules. The preparation possesses anti-tumor, immune regulative and anti-inflammatory analgesic effects. In a clinical study on Hashimoto's thyroiditis, PV capsules combined with levothyroxine sodium tablets apparently enhanced thyroid hormone levels in patients when compared with patients given L-thyroxine alone. The levels of thyroid peroxidase antibody and thyroglobulin antibody were significantly lower in the combination administration group than in the group given levothyroxine alone. This indicates that PV capsules have a significant effect on improving Hashimoto's thyroid function, lowering thyroid antibody levels, etc. [87].

CONCLUSION AND PROSPECTS

In summary, PV is a widely distributed plant and is a very popular and commonly used traditional medicine for the treatment of clinical disorders. It is a widely investigated plant worldwide due to its promising therapeutic properties. In China, this plant has been used historically as a healthy food and traditional Chinese medicine (TCM) for the treatment of jaundice, hepatitis, gonorrhoea, tuberculosis and diabetes mellitus [88]. *In vivo* and *in vitro* studies have provided the evidence of its various ethnomedical and potential pharmacological activities, indicating its effectiveness against many diseases. PV plant has rich chemical composition, and the major chemical components include triterpenoids and their glycosides, flavonoids, phenolic acids and their glycosides, organic acids, sterols, essential oils and saccharides. Of these, tannins and polysaccharides exhibit very good antiviral activities. The triterpenoids show anti-tumor activity, and the fractions enriched in phenolic acids, phenol components and polysaccharides have antioxidant activity whilst both rosmarinic acids and its derivatives possess anti-inflammatory activity. Polysaccharides, the main compounds isolated from *Prunella vulgaris*, are considered as biological response modifiers (BRMs) for their antioxidant, anticancer, and immune-modulating activities. These biological activities are affected by the unique structural characteristics of polysaccharides. The antioxidant activities are related to their compositions of pro-

teins and uronic acid and structural features of molecular weights, monosaccharide composition and types of glycosidic.

In recent years, some investigations on biological activities of PV have been carried out on animal and at cellular levels. PV single formulations and compound prescriptions have been used in clinical practice with encouraging results. PV preparations can be used alone in clinic or be combined with western medicines for the treatment of thyroiditis, breast hyperplasia, cancer and other diseases. Owing to the efficacy for clearing away liver-fire, dissipating binding depression and so on, the "edible" PV gradually integrates with the "Chinese medicine" boom, and a series of PV life products are available for health protection, such as herbal tea (withered tea), ingredients (cold Prunella, Prunella porridge), and daily necessities (dried tangerine peel).

However, further research is needed to clarify the targets of the active compounds from PV, understand the mechanisms involved, and characterize the metabolites responsible for these activities. In addition, these promising compounds or their class should be extracted and purified by using more advanced technologies to treat increasing health issues including cancer, diabetes, tuberculosis and other diseases. Furthermore, the relationship between the biological properties and traditional uses should be clearly verified through valid studies. In conclusion, PV is a medicinal resource with great potential for development and should be further studied in all aspects, so as to extract, purify and synthesize active compounds under the premise of quality standard determination, and provide series of daily necessities ingredients and medicinal substances with highly effective and low toxic properties.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

This work was supported by Shanghai University of Traditional Chinese Medicine - Gaofeng Clinical Medicine Grant and Outstanding Leaders Training Program of Pudong Health Bureau of Shanghai (PWR12015-05).

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

- [1] Chen ST, Dou J, Temple R, Agarwal R, Wu KM, Walker S. New therapies from old medicines. *Nat Biotechnol* 2008; 26(10): 1077-83.
- [2] Kakeya H. Natural products-prompted chemical biology: phenotypic screening and a new platform for target identification. *Nat Prod Rep* 2016; 33(5): 648-54.
- [3] Hu YX, Yu CH, Wu F, et al. Antihepatofibrotic effects of aqueous extract of *Prunella vulgaris* on carbon tetrachloride-induced hepatic fibrosis in rats. *Planta Med* 2016; 82(1-2): 97-105.
- [4] Huang R, Zhao M, Yang X, et al. Effects of *Prunella vulgaris* on the mice immune function. *PLoS One* 2013; 8(10): e77355.
- [5] Ru M, Wang K, Bai Z, et al. A tyrosine aminotransferase involved in rosmarinic acid biosynthesis in *Prunella vulgaris* L. *Sci Rep* 2017; 7(1): 4892.
- [6] Collins NH, Lessey EC, DuSell CD, et al. Characterization of anti-estrogenic activity of the Chinese herb, *Prunella vulgaris*, using *in vitro* and *in vivo* (Mouse Xenograft) models. *Biol Reprod* 2009; 80(2): 375-83.
- [7] Choi JH, Han EH, Hwang YP, et al. Suppression of PMA-induced tumor cell invasion and metastasis by aqueous extract isolated from *Prunella vulgaris* via the inhibition of NF-kappaB-dependent MMP-9 expression. *Food Chem Toxicol* 2010; 48(2): 564-71.

- [8] Qu Z, Zhang J, Yang H, *et al.* *Prunella vulgaris* L., an Edible and Medicinal Plant, Attenuates Scopolamine-Induced Memory Impairment in Rats. *J Agric Food Chem* 2017; 65(2): 291-300.
- [9] Li C, Huang Q, Fu X, Yue XJ, Liu RH, You LJ. Characterization, antioxidant and immunomodulatory activities of polysaccharides from *Prunella vulgaris* Linn. *Int J Biol Macromol* 2015; 75: 298-305.
- [10] Chen ST, Dou J, Temple R, Agarwal R, Wu KM, Walker S. New therapies from old medicines. *Nat Biotechnol* 2008; 26(10): 1077-83.
- [11] Jung YB, Roh KJ, Jung JA, *et al.* Effect of SKI 306X, a new herbal anti-arthritis agent, in patients with osteoarthritis of the knee: a double-blind placebo controlled study. *Am J Chin Med* 2001; 29(3-4): 485-91.
- [12] Yue R, Shan L, Yang X, Zhang W. Approaches to target profiling of natural products. *Curr Med Chem* 2012; 19(22): 3841-55.
- [13] Oh C, Price J, Brindley MA, *et al.* Inhibition of HIV-1 infection by aqueous extracts of *Prunella vulgaris* L. *Virology* 2011; 8: 188.
- [14] Brindley MA, Widrlechner MP, McCoy JA, *et al.* Inhibition of lentivirus replication by aqueous extracts of *Prunella vulgaris*. *Virology* 2009; 6: 8.
- [15] Kajima H, Ogura H. Triterpenoids from *Prunella vulgaris*. *Phytochemistry* 1986; 25: 729-33.
- [16] Kajima H, Tominga H, Sato S. Pentacyclic triterpenoids from *Prunella vulgaris*. *Phytochemistry* 1987; 26: 1107-11.
- [17] Zhang YJ, Yang CR. Two New Ursane Glycosides from *Prunella Vulgaris* in France. *Yunnan Institute of Botany* 1995; 17: 468-72.
- [18] Meng G, Zhang KJ, Zhang MZ. Study on chemical constituents and anticancer activity of *Prunella vulgaris* L. *J Northwest Pharm Univ* 2007; 22: 211-3.
- [19] Gu XJ, Li YB, Li P, Qian SH, Duan JA. Studies on chemical constituents of *Prunella vulgaris*. *Zhongguo Zhongyao Zazhi* 2007; 32(10): 923-6.
- [20] Wang ZJ, Zhao YY, Tu GZ. Studies on the chemical constituents from *Prunella vulgaris*. *Yao Xue Xue Bao* 1999; 34: 679-81.
- [21] Tian J, Xiao ZY, Chen YY. Structure Identification of Vulgarsaponin A. *Yao Xue Xue Bao* 2000; 35: 29-31.
- [22] Kojima H, Sato N, Hatano A. Sterol glucosides from *Prunella vulgaris*. *Phytochemistry* 1990; 29: 2351-5.
- [23] Dmitruk SI, Dmitruk SE, Berezovskaya TP. Flavonoids of *Prunella vulgaris*. *Khim Prirod Soedin* 1987; 23: 449-50.
- [24] Meng ZM, He LW. Studies on constituents of *Prunella vulgaris* L. *Zhongguo Yaoke Daxue Xuebao* 1995; 26: 329-31.
- [25] Kajima H, Tominga H, Sato S. Two novel hexacyclic triterpenoids from *Prunella vulgaris*. *Phytochemistry* 1988; 27: 2921-5.
- [26] Dmitruk SI. Coumarins of *Prunella vulgaris*. *Chem Nat Compd* 1986; 22: 480.
- [27] Wang ZJ, Zhao YY, Wang B. Depsides from *Prunella vulgaris*. *China Acad J Elect Publ House* 2001; 17: 157-61.
- [28] Jain M, Saxena VK. Chemical examination of the fat from the leaves of *Brunella vulgaris*. *J Inst Chem (India)* 1984; 56: 133.
- [29] Qin R, Lu J. Advances in studies on chemical constituents and pharmacological effects of *Prunella vulgaris*. *Guide China Med* 2012; 10: 435-6.
- [30] Xu HX, Lee SH, Lee SF, White RL, Blay J. Isolation and characterization of an anti-HSV polysaccharide from *Prunella vulgaris*. *Antiviral Res* 1999; 44(1): 43-54.
- [31] Bai Y, Xia B, Xie W, *et al.* Phytochemistry and pharmacological activities of the genus *Prunella*. *Food Chem* 2016; 204: 483-96.
- [32] Xu HY, Jin Y. Study on anti-tumor constituents of *Spica Prunellae* and their anti-tumor activity. *Tradit Chin Drug Res Clin Pharmacol* 2015; 26: 351-5.
- [33] Chao L, Qiang H, Jie X, *et al.* Preparation of *Prunella vulgaris* polysaccharide-zinc complex and its antiproliferative activity in HepG2 cells. *Int J Biol Macromol* 2016; 91: 671-9.
- [34] Yin DT, Lei M, Xu J, *et al.* The Chinese herb *Prunella vulgaris* promotes apoptosis in human well-differentiated thyroid carcinoma cells via the B-cell lymphoma-2/Bcl-2-associated X protein/caspase-3 signaling pathway. *Oncol Lett* 2017; 14(2): 1309-14.
- [35] Shen YF, Ding QX, Song LB. Experimental study on inhibition of *Prunella vulgaris* l. for three kinds of tumor cells. *J N Chin Med* 2015; 47: 273-5.
- [36] Wu XM, Xu YP. Effect of *Prunella vulgaris* L. on proliferation and apoptosis of cholangiocarcinoma cells. *Zhejiang Zhong Yi Yao Dai Za Zhi* 2017; 52: 227-8.
- [37] Zhou YF, Fan PH. Research Progress of Immunomodulatory Effect of Traditional Chinese Medicine. *Lishizhen Medicine and Materia Medica Research* 2017; 28: 204-7.
- [38] Yan D, Xie JC, Zhou YM. Substitutability of *Prunella vulgaris* L Stem Leaf and Ear Based on HPLC-ESI-MSn Analysis and Anti-Inflammatory and Antioxidant Activity. *China Pharm J* 2016; 51: 792-7.
- [39] Cai S P, Yang Y, Wu R. Pharmacodynamics of *Prunella vulgaris* and Gel against Herpes Simplex Virus. *World Science and Technology/Modernization of Traditional Chinese Medicine and Materia Medica* 2017; 19: 247-53.
- [40] Tan JB, Zhao M, Yang XF. Protective Effect of *Prunella Spica* on Oxidative Stress Injury. *Zhongguo Shiyang Fangjixue Zazhi* 2016; 22: 89-94.
- [41] Feng L, Jia X, Zhu MM, Chen Y, Shi F. Antioxidant activities of total phenols of *Prunella vulgaris* L. *in vitro* and in tumor-bearing mice. *Molecules* 2010; 15(12): 9145-56.
- [42] Shaiy-Buzhati M, Chen C, Wang M, Wang J, Zhang XY. Protection of pyrazole-lipopolysaccharide induced liver injury in mice by *Prunella vulgaris* L. *Shipin Anquan Zhiliang Jiancexuebao* 2016; 7: 2334-6.
- [43] Liu H, Zhong YJ, Wu D. Inhibitory Effect of *Prunella vulgaris* L. Flavonoids on Osteoporosis in Ovariectomized Rats. *Xiandai Shipin Keji* 2014; 30(8): 6-11.
- [44] Liu YM, Ni YC, Li HB. Antidepressant Effect of the Water Extracts from *Prunella vulgaris* L. *Zhongyao Xinyao Yu Linchuang Yaoli* 2017; 440-4.
- [45] Kwon SS, Kwon JY, Park YW, Kim YH, Lim JB. HbA1c for diagnosis and prognosis of gestational diabetes mellitus. *Diabetes Res Clin Pract* 2015; 110(1): 38-43.
- [46] Rajanandh MG, Kosey S, Prathiksha G. Assessment of antioxidant supplementation on the neuropathic pain score and quality of life in diabetic neuropathy patients - a randomized controlled study. *Pharmacol Rep* 2014; 66(1): 44-8.
- [47] Arulselvan P, Subramanian SP. Beneficial effects of *Murraya koenigii* leaves on antioxidant defense system and ultra structural changes of pancreatic beta-cells in experimental diabetes in rats. *Chem Biol Interact* 2007; 165(2): 155-64.
- [48] Punitha IS, Rajendran K, Shirwaikar A, Shirwaikar A. Alcoholic stem extract of *Coscinium fenestratum* regulates carbohydrate metabolism and improves antioxidant status in streptozotocin-nicotinamide induced diabetic rats. *Evid Based Complement Alternat Med* 2005; 2(3): 375-81.
- [49] Manonmani G, Bhavapriya V, Kalpana S, Govindasamy S, Apparanantham T. Antioxidant activity of *Cassia fistula* (Linn.) flowers in alloxan induced diabetic rats. *J Ethnopharmacol* 2005; 97(1): 39-42.
- [50] Raafat K, Wurglics M, Schubert-Zsilavecz M. *Prunella vulgaris* L. active components and their hypoglycemic and antinociceptive effects in alloxan-induced diabetic mice. *Biomed Pharmacother* 2016; 84: 1008-18.
- [51] Li YL. Study on Antihypertensive Effect of *Prunella vulgaris* Extract on Spontaneously Hypertensive Rats. *Chinese and Foreign Medical Research* 2012; 180: 147.
- [52] Kim HI, Quan FS, Kim JE, *et al.* Inhibition of estrogen signaling through depletion of estrogen receptor alpha by ursolic acid and betulinic acid from *Prunella vulgaris* var. *lilacina*. *Biochem Biophys Res Commun* 2014; 451(2): 282-7.
- [53] Psotova J, Svobodova A, Kolarova H, Walterova D. Photoprotective properties of *Prunella vulgaris* and rosmarinic acid on human keratinocytes. *J Photochem Photobiol B* 2006; 84(3): 167-74.
- [54] Psotová J, Chlopčíková S, Míketová P, Šimánek V. Cytoprotectivity of *Prunella vulgaris* on doxorubicin-treated rat cardiomyocytes. *Fitoterapia* 2005; 76(6): 556-61.
- [55] Huang R, Zhao M, Yang X, *et al.* Effects of *Prunella vulgaris* on the mice immune function. *PLoS One* 2013; 8(10): e77355.
- [56] Jun MS, Kim HS, Kim YM, *et al.* Ethanol extract of *Prunella vulgaris* var. *lilacina* inhibits HMGB1 release by induction of heme oxygenase-1 in LPS-activated RAW 264.7 cells and CLP-induced septic mice. *Phytother Res* 2012; 26(4): 605-12.
- [57] Kageyama S, Kurokawa M, Shiraki K. Extract of *Prunella vulgaris* spikes inhibits HIV replication at reverse transcription *in vitro* and can be absorbed from intestine *in vivo*. *Antivir Chem Chemother* 2000; 11(2): 157-64.

- [58] Han EH, Choi JH, Hwang YP, *et al.* Immunostimulatory activity of aqueous extract isolated from *Prunella vulgaris*. *Food Chem Toxicol* 2009; 47(1): 62-9.
- [59] Hwang YJ, Lee EJ, Kim HR, Hwang KA. *In vitro* antioxidant and anticancer effects of solvent fractions from *Prunella vulgaris* var. lilacina. *BMC Complement Altern Med* 2013; 13: 310.
- [60] Shin TY, Kim YK, Kim HM. Inhibition of immediate-type allergic reactions by *Prunella vulgaris* in a murine model. *Immunopharmacol Immunotoxicol* 2001; 23(3): 423-35.
- [61] Harput US, Saracoglu I, Ogihara Y. Effects of two *Prunella* species on lymphocyte proliferation and nitric oxide production. *Phytother Res* 2006; 20(2): 157-9.
- [62] Haarberg KM, Wymore Brand MJ, Overstreet AM, *et al.* Orally administered extract from *Prunella vulgaris* attenuates spontaneous colitis in mdrla(-/-) mice. *World J Gastrointest Pharmacol Ther* 2015; 6(4): 223-37.
- [63] Wu H, Gao M, Ha T, Kelley J, Young A, Breuel K. *Prunella vulgaris* aqueous extract attenuates IL-1 β -induced apoptosis and NF- κ B activation in INS-1 cells. *Exp Ther Med* 2012; 3(6): 919-24.
- [64] Zdarilová A, Svobodová A, Simánek V, Ulrichová J. *Prunella vulgaris* extract and rosmarinic acid suppress lipopolysaccharide-induced alteration in human gingival fibroblasts. *Toxicol In Vitro* 2009; 23(3): 386-92.
- [65] Raafat K, Wurglics M, Schubert-Zsilavec M. *Prunella vulgaris* L. active components and their hypoglycemic and antinociceptive effects in alloxan-induced diabetic mice. *Biomed Pharmacother* 2016; 84: 1008-18.
- [66] Zhang M, Hwang E, Lin P, Gao W, Ngo HTT, Yi TH. *Prunella vulgaris* L. Exerts a Protective Effect Against Extrinsic Aging Through NF- κ B, MAPKs, AP-1, and TGF- β /Smad Signaling Pathways in UVB-Aged Normal Human Dermal Fibroblasts. *Rejuvenation Res* 2018; 21(4): 313-22.
- [67] Xia N, Bollinger L, Steinkamp-Fenske K, Förstermann U, Li H. *Prunella vulgaris* L. Upregulates eNOS expression in human endothelial cells. *Am J Chin Med* 2010; 38(3): 599-611.
- [68] Qu Z, Zhang J, Yang H, *et al.* *Prunella vulgaris* L., an Edible and Medicinal Plant, Attenuates Scopalamine-Induced Memory Impairment in Rats. *J Agric Food Chem* 2017; 65(2): 291-300.
- [69] Hwang SM, Lee YJ, Yoon JJ, *et al.* *Prunella vulgaris* suppresses HG-induced vascular inflammation via Nrf2/HO-1/eNOS activation. *Int J Mol Sci* 2012; 13(1): 1258-68.
- [70] Huang N, Hauck C, Yum MY, *et al.* Rosmarinic acid in *Prunella vulgaris* ethanol extract inhibits lipopolysaccharide-induced prostaglandin E2 and nitric oxide in RAW 264.7 mouse macrophages. *J Agric Food Chem* 2009; 57(22): 10579-89.
- [71] Park SJ, Ahn YJ, Lee HE, Hong E, Ryu JH. Standardized *Prunella vulgaris* var. lilacina Extract Enhances Cognitive Performance in Normal Naive Mice. *Phytother Res* 2015; 29(11): 1814-21.
- [72] Park SJ, Kim DH, Lee IK, *et al.* The ameliorating effect of the extract of the flower of *Prunella vulgaris* var. lilacina on drug-induced memory impairments in mice. *Food Chem Toxicol* 2010; 48(6): 1671-6.
- [73] Kim SH, Huang CY, Tsai CY, Lu SY, Chiu CC, Fang K. The aqueous extract of *Prunella vulgaris* suppresses cell invasion and migration in human liver cancer cells by attenuating matrix metalloproteinases. *Am J Chin Med* 2012; 40(3): 643-56.
- [74] Zhang Y, But PP, Ooi VE, *et al.* Chemical properties, mode of action, and *in vivo* anti-herpes activities of a lignin-carbohydrate complex from *Prunella vulgaris*. *Antiviral Res* 2007; 75(3): 242-9.
- [75] Skottová N, Kazdová L, Oliyamyk O, Vecera R, Sobolová L, Ulrichová J. Phenolics-rich extracts from *Silybum marianum* and *Prunella vulgaris* reduce a high-sucrose diet induced oxidative stress in hereditary hypertriglyceridemic rats. *Pharmacol Res* 2004; 50(2): 123-30.
- [76] Li C, Huang Q, Xiao J, Fu X, You L, Liu RH. Preparation of *Prunella vulgaris* polysaccharide-zinc complex and its antiproliferative activity in HepG2 cells. *Int J Biol Macromol* 2016; 91: 671-9.
- [77] Hao J, Ding XL, Yang X, Wu XZ. *Prunella vulgaris* polysaccharide inhibits growth and migration of breast carcinoma-associated fibroblasts by suppressing expression of basic fibroblast growth factor. *Chin J Integr Med* 2016; doi: 10.1007/s11655-016-2.
- [78] Huang MX, Zou K, He K. The improvement of quality standard about *prunellae spica* granule. *Ningxia Med J* 2016; 38: 329-31.
- [79] Yuan JS, Wang PY, Wang J. Curative effect of selfheal granules in treatment of xerophthalmia in menopausal women and its effect on expressions of IL-1 β , TNF- α , and ICAM-1 in conjunctiva. *Zhongguo Fuyou Baojian* 2017; 32: 2675-8.
- [80] Ying ZY. Clinical observation of Xiakucao Granules combined with Thiamazole Tablets in treatment of diffuse goiter with hyperthyroidism. *Drugs & Clinic* 2016; 31: 70-4.
- [81] Gong XJ, Liu WG, Zhong H. *Prunella* tablets treatment of benign prostatic hyperplasia in 40 cases. *J Pract Tradit Chin Med* 2014; 30: 964-5.
- [82] Mo YT, Liu P. Clinical study of *prunella* combined with glucocorticoids on subacute thyroiditis. *Asia-Pacific Traditional Medicine* 2015; 11: 119-20.
- [83] Hu Y, Dai XY, Han YY. Effect of *Prunella vulgaris* Tablets and Adapalene Gel on Acne Vulgaris. *Asia-Pacific Traditional Medicine* 2014; 10: 108-9.
- [84] Zhong RY. *Prunella* cream adjuvant treatment of thyroid nodules. *Aerosp Med* 2014; 368-9.
- [85] Li DJ, Wang Y, Zhao T. Clinical study on Xiakucao Oral Liquid combined with compound betamethasone in treatment of subacute thyroiditis. *Drugs & Clinic* 2017; 32: 1714-7.
- [86] Li X, Liu W, Niu B. Clinical observation of *prunella* oral liquid and cefdinir dispersible tablets in treating chronic mastitis. *Pharmacol Clin Tradit Chin Med* 2017; 33: 190-2.
- [87] Fan ZY, Zhang LL, Mi R. Effect of Xiakucao capsule on Hashimoto thyroiditis and the ultrasonic diagnosis of thyroid morphology before and after treatment. *J Hebei Med Univ* 2017; 38: 446-9.
- [88] Cheung HY, Zhang QF. Enhanced analysis of triterpenes, flavonoids and phenolic compounds in *Prunella vulgaris* L. by capillary zone electrophoresis with the addition of running buffer modifiers. *J Chromatogr A* 2008; 1213(2): 231-8.