

# Research Progress on the Chemistry and Pharmacology of *Prunella vulgaris* Species

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Received 9 April 2014; revised 13 May 2014; accepted 21 June 2014

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## Abstract

An exhaustive literature survey on the secondary metabolites of widely distributed *Prunella vulgaris* L. species has been carried out. Triterpenoids, sterols, phenylpropanoids, flavonoids, coumarins, fatty acids, volatile oils and carbohydrates along with some other compounds, have been reported from this species. Many of these compounds have been found to possess significant biological properties, including antihypertensive activity, anticancer activity, anti-lipidemic activity, antibacterial and antiviral activities, anti-inflammatory activities, hypoglycemic effects, hepatoprotective effects, antineoplastic activities, etc. *P. vulgaris* might offer a rich natural source with relative cheap price for developing new anti-neoplastic drugs.

## Keywords

Biological Properties, *P. vulgaris* L., Triterpenoids, Sterols, Phenylpropanoids, Flavonoid, Coumarins, Fatty Acids, Volatile Oil, Carbohydrates

**Subject Areas:** Medicinal Chemistry Phytochemistry

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## 1. Introduction

As a commonly used Chinese native medicine, dried ears of *P. vulgaris* are used as medicine for the treatment of many kinds of disease (**Figure 1**). *P. vulgaris* was first literally recorded as one kind of medical grass in Volume 3 of “Shennong Bencao Jing (or Shennong’s Classic of Chinese *Materia Medica*)” during the Qin-Han dynasty in ancient China. It was recorded as one of 365 kinds of Chinese *Materia Medica*. In China, this plant got its Chinese name “Xiakucao” for drying after summer solstice. In Europe, it got another name “self-heal or

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#Inquires about this paper are preferred to be sent to Ge Meng.



**Figure 1.** *Prunella vulgaris* and its matured dried ears.

self-heal spike” for its medicinal usage. The medicine made from *P. vulgaris* is also known by other names, such as Square-stem, Prunella Spike, Spica Prunellae, and Common Selfheal Fruit-Spike. *P. vulgaris* bursts into flower during April and June and produces fruits from July to October. *P. vulgaris* often grows wildly on the barren mountain areas, the grasslands, the roadside and the moist ground nearby rivers and other areas.

There are fifteen kinds of plant variation in the *P. vulgaris* species all over the world. They are widely distributed in places such as the warm regions of Europe and Asia, northwest region of Africa and northern region of America. Four kinds of species and three kinds of varieties are produced in China, including *P. vulgaris* and its two varieties, such as *P. vulgaris* L. var. *leucantha* Schur sec. Bailey and *P. vulgaris* L. var. *lanceolata* (Barton) Fernald, *P. asiatica* Nakai and its variations *P. asiatica* Nakai var. *albiflora* (Koidz.) Nakai, *P. hispida* Benth and *P. grandiflora* (Linn.) Jacq.

*P. vulgaris* tastes bitter and has a pungent aroma. It could be absorbed by human body by going through the liver and the gallbladder organ according to Traditional Chinese Medicine. It has many medical effects such as anti-inflammation, clearing vision, relief of congestion and detumescence. It is often used in the treatment of headache, dizziness, swollen eyes, scrofula, cecidium, swollen and painful mastitis, breast cancer, goiter, tuberculosis [1] [2].

It has long been used as a folk medicine for alleviating sore throat and reducing fever by Europeans and Chinese. It was also used as a material to manufacture functional beverages. Modern pharmacological studies reveal that the methanol or water extracts of this herb could show many biological activities including systemic anaphylaxis inhibition, antihyperglycemic activity, UV radiation photo protection [3], immune modulation, anti-oxidative action, anti-viral and anti-bacterial effects [4].

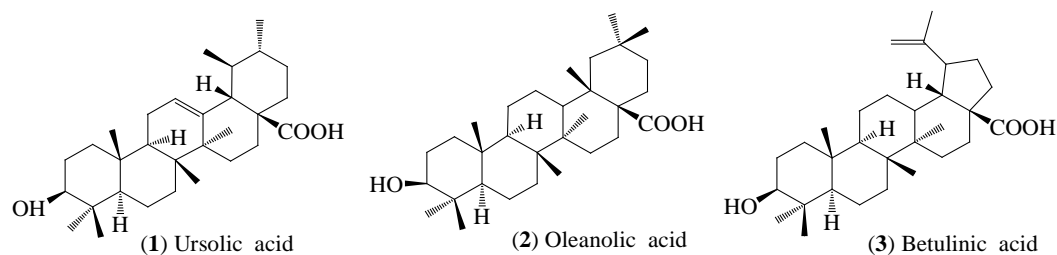
As a result of its important medicinal value and widespread pharmacological action, *P. vulgaris* has received more and more attention in the world [5]. For many years, pharmaceutical scholars have conducted comprehensive research toward both chemistry and pharmacology aspects of *P. vulgaris*. In view of the medicinal properties attributed to this species, this paper presents a comprehensive review of the chemical constituents and the pharmacological activities of *P. vulgaris*.

## 2. Chemical Substance

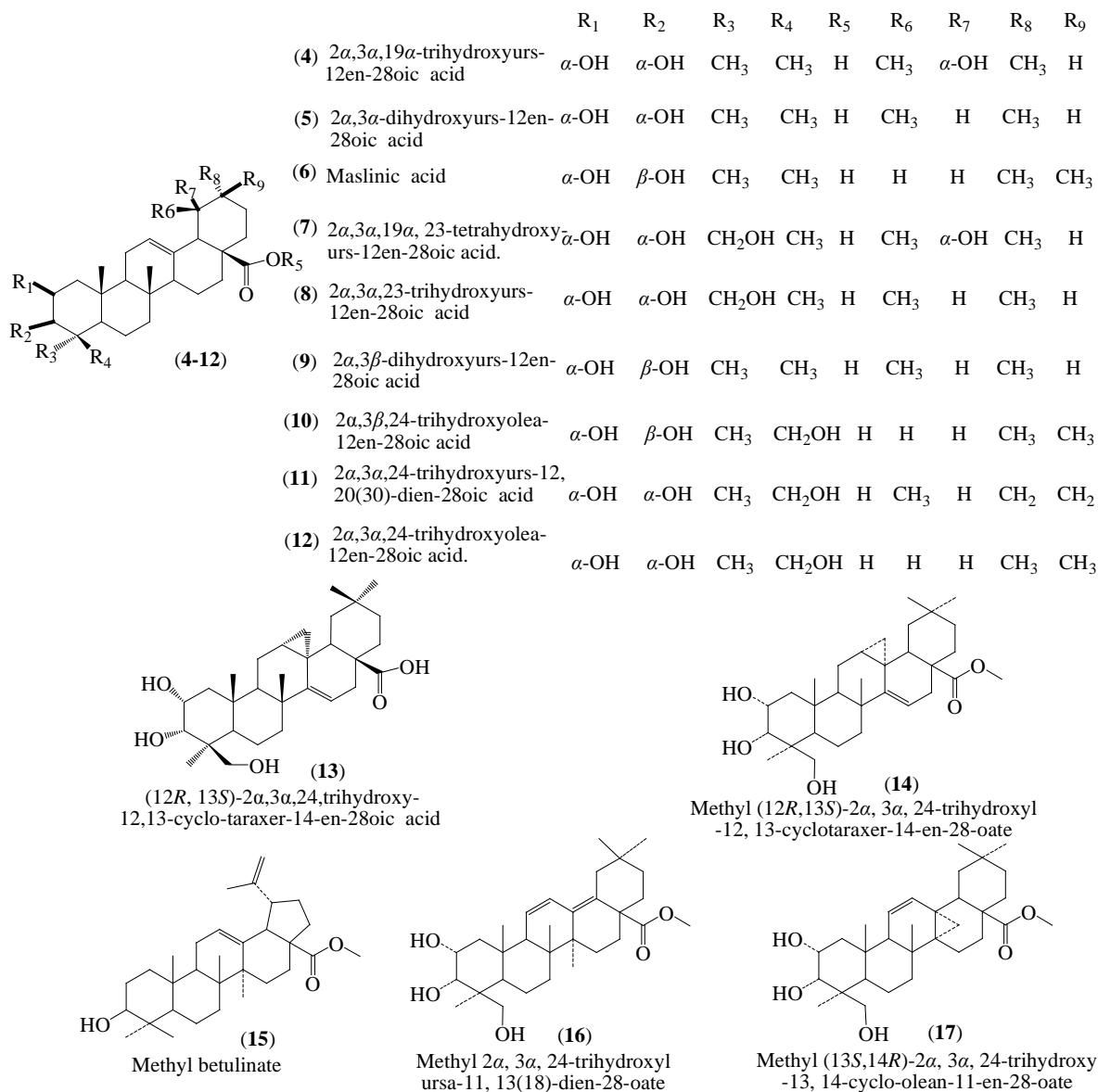
### 2.1. Triterpenoids

There are many kinds of triterpenoid compounds existing in *P. vulgaris*, including oleanane, ursane and lupinane type triterpenoids [6] (Figure 2). The contents of ursolic acid **1** and oleanolic acid **2** in the *P. vulgaris* are much higher than those of other triterpenoids [7] [8], which are obviously correlated with the pharmacological action of the plant [9]-[11].

The activity-guided fractionation of the extract of the herb of *P. vulgaris* (Labiatae) led to the isolation of five triterpenes, including **1**, **2**, betulinic acid (**3**),  $2\alpha$ ,  $3\alpha$ -dihydroxyurs-12-en-28-oic acid (**5**) and 2-hydroxyursolic acid. Compound **5** demonstrated significant inhibition on the release of  $\beta$ -hexosaminidase from cultured RBL-2H3 cells in a dose-dependent manner. When the isolated compounds were tested for their effects on the production of nitric oxide from cultured murine macrophages, RAW 264.7 cells, **1** and 2-hydroxyursolic acid exhibited strong inhibitory activities (Figure 3) [12].



**Figure 2.** Structures of ursolic acid, oleanolic acid and betulinic acid.



**Figure 3.** Structures of triterpenes isolated from *P. vulgaris*—Part I.

Until now, forty-two triterpenoids have been separated and identified from this species altogether, of which thirty three compounds are triterpenoid sapogenins, and eight exist in the state of saponins [13] [14]. The sugar chain of saponins are usually connected at the 28-position of the triterpenoids skeleton, few of them are connected

in the 3-position or other position of the triterpenoid skeleton. Furthermore, the sugar chains at the 28-position are composed only of one or two monosaccharides. The  $^{13}\text{C}$  NMR spectrum for different triterpenoids shows their distinct features correlated with the skeleton type, substituted positions and configurations [6] [15] (Figure 3, Figure 4).

Pruvuloside A **33** and Pruvuloside B **34** along with triterpenoid saponins **35** - **38** have been isolated from *P. vulgaris* species grown in France (Figure 5, Figure 6), although the properties of both compounds are quite similar [16].

Other compounds were also obtained from the dried ears of *P. vulgaris* by chromatograph and identified as the following:  $3\beta$ ,  $16\alpha$ ,  $24$ -trihydroxyl-olean- $12$ -ene- $28$ -acid- $32$ - $O$ -( $6$ -butyryl)- $\beta$ - $D$ -glucopyranose ester glucoside (Vulgar saponin B **40**) (Figure 6),  $2\alpha,3\alpha$ -dihydroxyl-ursolic- $12$ -ene- $28$ -acid [17], respectively.

## 2.2. Sterols

Apart from pentacyclic triterpenoids, sterols including sitosterol **41**, stigmasterol **42**, spinasterol **43** and stigmast- $7$ -en- $3\beta$ -ol **44** have been isolated from *P. vulgaris* and identified by Kojima. Furthermore, four  $\beta$ - $D$ -glucopyranosides of the sterols have also been isolated from *P. vulgaris* and were identified by analysis of  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, HOMCOR and HETCOR spectrum [18] (Figure 7).

Eight sterols have been isolated from the ears, stem and leaves of *P. vulgaris*, of which four compounds,  $\beta$ -sitosterol,  $\alpha$ -spinasterol, stigmasterol- $7$ -olefinic alcohol and ducosterol **46**, assume a free state, another four

	$\text{R}^1$	$\text{R}^2$	$\text{R}^3$	$\text{R}^4$	$\text{R}^5$	$\text{R}^6$
(18) Methyl oleanolate	H	$\beta$ -OH	Me	Me	H	Me
(19) Methyl ursolate	H	$\beta$ -OH	Me	Me	Me	H
(20) Methyl maslinate	OH	$\beta$ -OH	Me	Me	H	Me
(21) Methyl 3-epimaslinate	OH	$\alpha$ -OH	Me	Me	H	Me
(22) Methyl $2\alpha$ , $3\alpha$ , $23$ -trihydroxylolean- $12$ -en- $28$ -oate	OH	$\alpha$ -OH	$\text{CH}_2\text{OH}$	Me	H	Me
(23) Methyl $2\alpha$ , $3\alpha$ , $24$ -trihydroxyl- $12$ -en- $28$ -oate	OH	$\alpha$ -OH	Me	$\text{CH}_2\text{OH}$	H	Me
(24) Methyl $2\alpha$ , $3\alpha$ , dihydroxylurs- $12$ -en- $28$ -oate	OH	$\alpha$ -OH	Me	Me	Me	H
(25) Methyl $2\alpha$ -hydroxylurs- $28$ -oate	OH	$\beta$ -OH	Me	Me	H	Me
(26) Methyl $2\alpha$ , $3\alpha$ , $24$ -trihydroxylursa- $12$ -en- $28$ -oate	OH	$\beta$ -OH	Me	Me	Me	H
(27) Methyl $2\alpha$ , $3\alpha$ , dihydroxylursa- $12$ , $20(30)$ -dien- $28$ -oate	H	Me				
(28) Methyl $2\alpha$ , $3\alpha$ , $24$ -trihydroxylursa- $12$ , $20(30)$ -dien- $28$ -oate	H	$\text{CH}_2\text{OH}$				
(29) $3\beta$ -hydroxyl-olean- $12$ -en- $28$ -al	CHO	H	Me			
(30) $3\beta$ -hydroxyl-urs- $12$ -en- $28$ -al	CHO	Me	H			
(31) Olean- $12$ -en- $3\beta$ , $28$ -diol	OH	H	Me			
(32) Urs- $12$ -en- $3\beta$ , $28$ -diol	OH	Me	H			

Figure 4. Structures of triterpenes isolated from *P. vulgaris*—Part II.

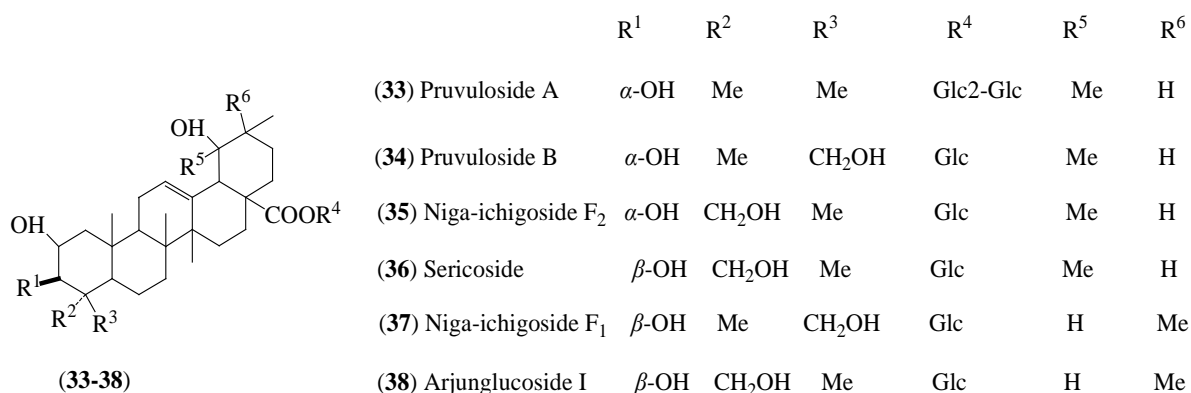


Figure 5. Structure of the triterpenoid saponins from *P. vulgaris*.

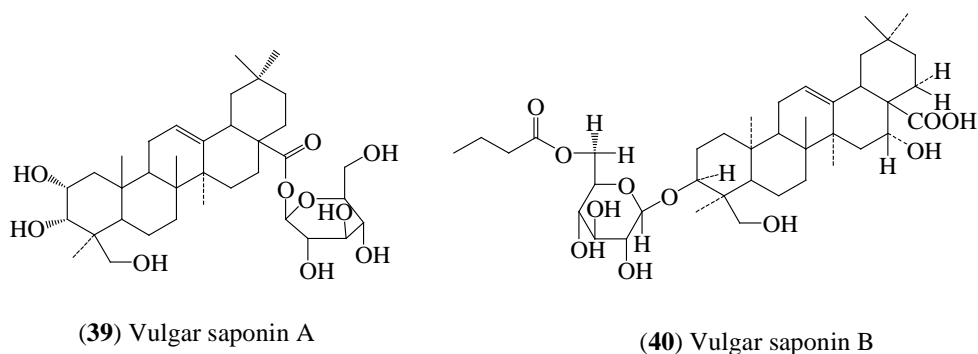


Figure 6. Structure of Vulgar saponin A and Vulgar saponin B.

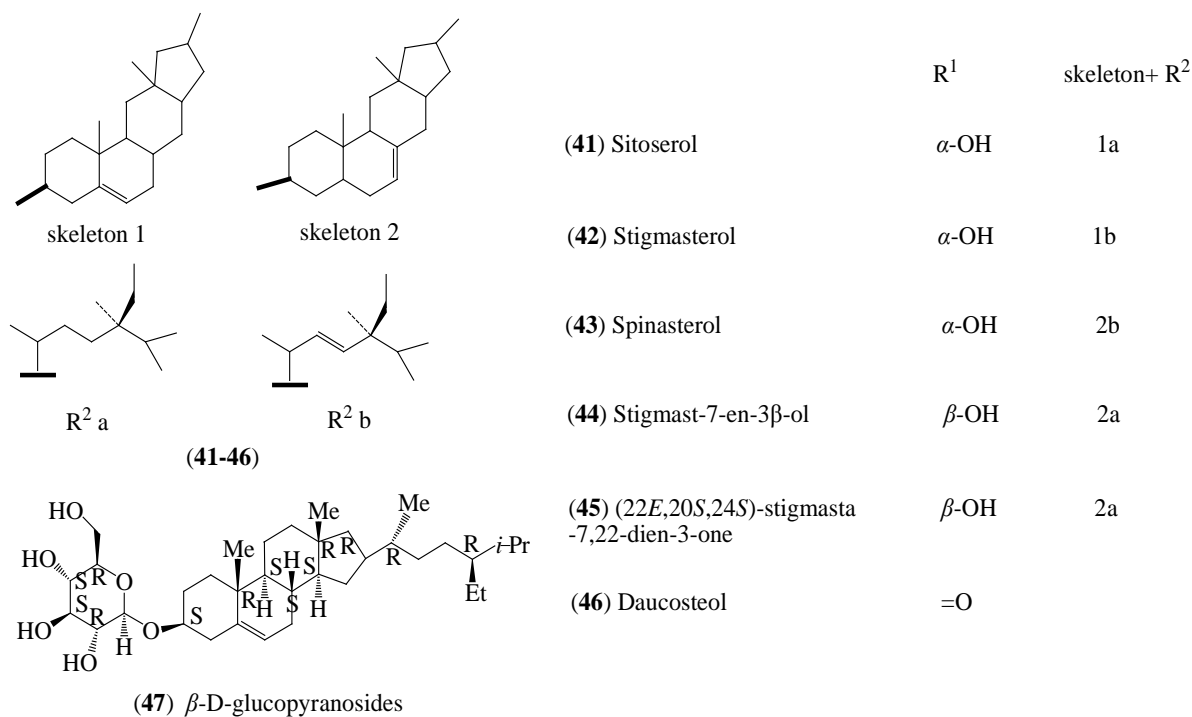


Figure 7. Structure of steroids from *P. vulgaris* L.

are the glucose glucosides, such as  $\alpha$ -spinasteroyl- $\beta$ -D-glucopyranose glucoside, stigmasteroyl- $\beta$ -D-glucopyranose glucoside, stigmast-7-enyl- $\beta$ -D-glucopyranoside **44** and (22*E*, 20*S*, 24*S*)-stigmasta-7,22-diene-3-one **45** [19].

Anti-neoplastic cyasterone has been isolated from *P. vulgaris* L. var. *leucantha* Schur sec. Bailey. The content of cyasterone in *P. vulgaris* was also determined at the same time [20].

Six compounds have been isolated from the ears of *P. vulgaris* by modern chromatography methods. These sterols are  $\beta$ -amyrin **49** (Viminalol) (Figure 8),  $\alpha$ -spinasterol, stigmasterol, stigmasterol-7-ene-23 $\beta$ -ol and 2 $\alpha$ , 3 $\alpha$ , 24-trihydroxyl-olean-12-ene-28-acid-28- $\beta$ -D-glucopyranose ester glucoside (Vulgar saponin A **39**) (Figure 6) [21]. Cholesterol was also found in this plant.

### 2.3. Phenylpropanoids

The antioxidant potential of *P. vulgaris* was found *in vitro* and *in vivo* and is probably associated with phenolic acid content, mainly rosmarinic acid (RA) **51** (Figure 9), which is known for its wide ranging antioxidative, anti-inflammatory, antimutagenic, antibacterial, antiviral and immunosuppressive biological activities [22].

Apart from phenolic acids such as *P*-coumaric acid **50**, rosmarinic acid **51** *cis*-caffeic acid and *trans*-caffeic acid **52**, several other compounds have also been separated from *P. vulgaris* by Chinese researchers, such as methyl rosmarine, ethyl rosmarine, *E*-butyl rosmarine, *Z*-butyl rosmarine, ethyl caffeate, 3, 4 $\alpha$ -trihydroxyl-methyl-phenyl propionate, 3,4 $\alpha$ -trihydroxyl-butyl-phenyl propionate [23], Danshensu **53** and its ethyl acetate 3,4-dihydroxyphenyl lactate [13] (Figure 9).

Quercetin and quercetin-3-*O*- $\beta$ -D-galactoside were also obtained from the dried ears of *P. vulgaris* by chromatograph [17].

### 2.4. Flavonoids

Seventeen flavonoids have been isolated and identified from *P. vulgaris*, including 5-hydroxyl flavanone, luteolin **54**, kaemferol, kaemferol-3-*O*-glucoside **60**, rutin **61** [24], isoquercitrin, 5-hydroxyl flavanone-3-*O*-galactoside, anthocyanins, delphinidin, hirsutidin-3,5-diglucoside, malvidin-3,5-diglucoside, hyperin, luteoloside, peonidin-3,5-diglucoside [25], homoorientin **55**, cinaroside **56**, quercetin **57**, quercetin-3-*O*- $\beta$ -D-galactoside **58** and quercetin-3-*O*- $\beta$ -D-glucoside **59** [26].

Beside the above compounds, *P. vulgaris* also contained flavonoid glycosides (galactoside), such as hyperoside(2-(3,4-dihydroxyphenyl)-3-( $\beta$ -D-galactopyranosyloxy)-5,7-dihydroxy-4*H*-1-benzo-pyran-4-one) (Figure 10) and acacetin-7-*O*- $\beta$ -D-glucopyranoside [14].

Anthocyanidins, such as delphinidin **62** and cyanidin **63**, also existed in the blossom clusters of *P. vulgaris* (Figure 11). As the flavonoid analogues, anthocyanidin is one kind of chromene derivatives usually existing in the ion form.

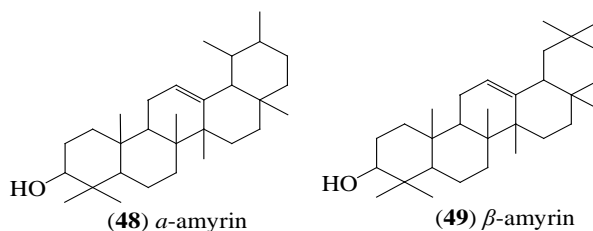


Figure 8. Structure of  $\alpha$ -amyrin and  $\beta$ -amyrin.

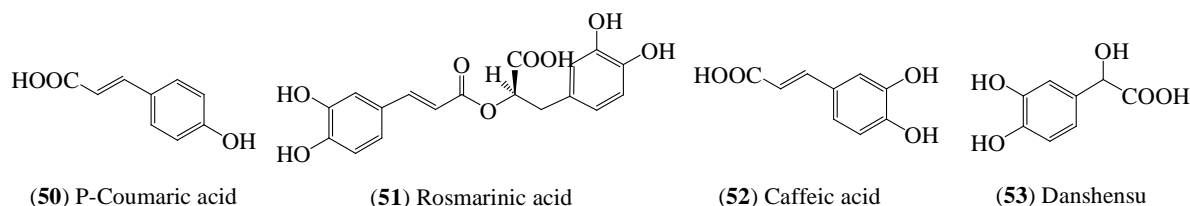
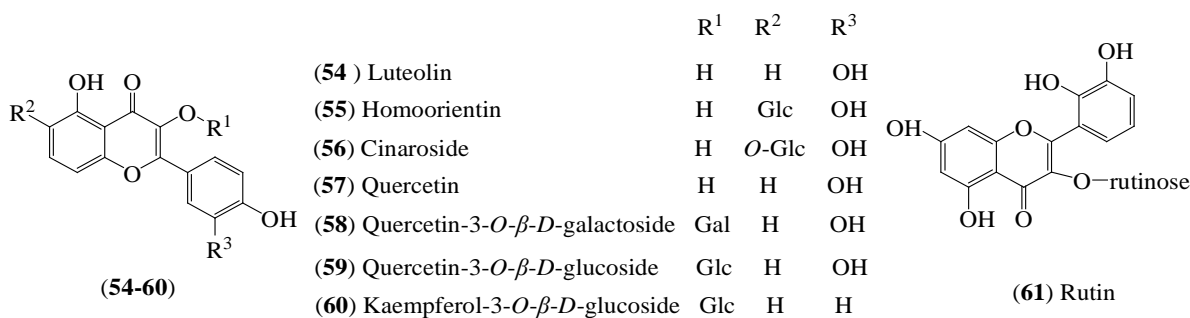
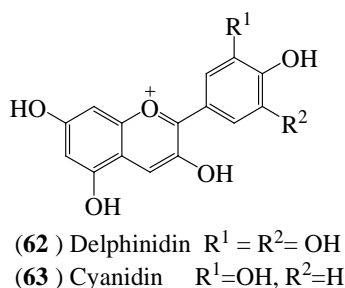


Figure 9. Structure of P-coumaric acid, rosmarinic acid, caffeic acid and danshensu.



**Figure 10.** Structure of flavonoids in *P. vulgaris*.



**Figure 11.** Structure of delphinidin and cyaniding.

The structural feature of most of these compounds, including flavonoids, flavonols, anthocyanins and their glycosides, is that the sugar groups are often attached at the 3-position of the main skeleton. Ethyl coffee acid ester was also isolated and identified from the dried ears of *P. vulgaris* [17].

## 2.5. Coumarins

Until recently, only three coumarins have been isolated from *P. vulgaris* by Russian scholars Dmitruk. Umbelliferone **64** [24], scopoletin **65** and esculetin **66** [24] have been identified by both spectral analysis and chemical and physical properties [27] (Figure 12).

## 2.6. Fatty Acids

Fatty acids are carboxylic acids often with a long unbranched aliphatic chain, which is either saturated or unsaturated. The fatty acids in *P. vulgaris* are isolated and reported as oleic acid, linoleic acid, lauric acid, palmitic acid (cetylic acid), myristic acid, stearic acid and tetracosanoic acid. Beside, another five fatty acid derivatives have been identified as ethyl palmitate, 6,9-octadecadienoic acid, 3,6,7-eicosatrienoic acid, archidic acid and behemic acid with GC-MS [21].

## 2.7. Volatile Oils

The studies on volatile ingredients in *P. vulgaris* showed that the volatile oil has been obtained at a rate of 0.31%. By using GC-FT-IR methods, twenty three known components have been isolated from *P. vulgaris*. The principal constituents are 1,8-eucalyptol, β-pinene, myrcene, linalylacetate **67**, α-phellandrene **68** and linalool **69** (Figure 13). The content of 1, 8-eucalyptol and β-pinene constitutes more than 60% of the total volatile oil [28].

Another fourteen compounds have also been identified in the ears *P. vulgaris* by Wang, the content of the main constituents, such as 1,6-cyclodecanone-diene, hexadecanoic acid and hexatriacontane are 17.16%, 10.94% and 4.04% respectively [29].

The results of contents of volatile oil are different, which may be related with the different parts dryness and collecting period of *P. vulgaris*.



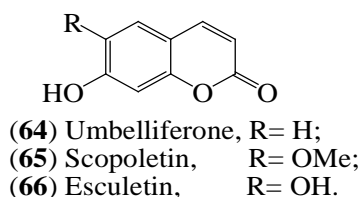


Figure 12. Structure of umbelliferone, scopoletin and esculetin.

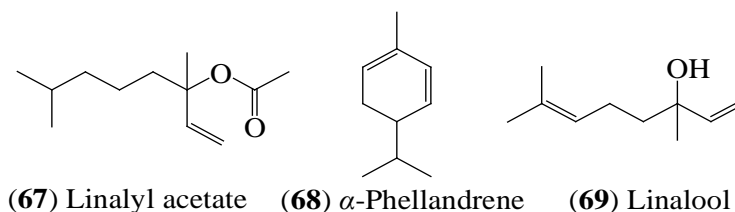


Figure 13. Active components in volatile oils.

## 2.8. Carbohydrates

*P. vulgaris* contains dissoluble monosaccharides, disaccharides and polysaccharides. Dissociated glucose, galactose, fructose and sucrose have also been isolated and obtained from *P. vulgaris* [30]. A sulfur-containing polysaccharide (Prunellin) has also been isolated from the water soluble extraction of *P. vulgaris*, the molecular weight of which has been identified to be around 10,000 [31].

Sucrose, mannose, glucose and fructose have been detected from the ethanol extract of *P. vulgaris*, *P. vulgaris* L. var. *leucantha* Schur sec. Bailey. The glycosides of mannose, glucose, arabinose, xylose and rhamnose have also been obtained from both water and ethanol extractions of these above two speices. Fructose was also found in *P. vulgaris* L. var. *lanceolata* (Barton) [32].

DEAE-Sepharose FF chromatography was used by Chinese scholars to purify polysaccharides from *P. vulgaris* L. Their structures were characterized through chemical and spectral methods. Five polysaccharides were obtained from the water extract and three which were named XKC00, XKC02-A and XKC02-B were homogeneous, molecular weights estimated by HPGPC to be 26,000, 136,000, 5600. XKC00 is a neutral heteropoly-saccharide obtained for the first time from this herb [33].

## 2.9. Other Components

Vitamin A, vitamin C, vitamin K, vitamin B1, vitamin PP (niacin), carotene, daucosterol, bicyclic monoterpenoids (*d*-camphor, *d*-fenchone), tannic acid, resin, bitter substance, fatty oil, alkaloid (1120 mg%), proteins (441.6 mg%) and lipids (2403.8 mg%) are contained in *P. vulgaris*. Apart from these above compounds, *P. vulgaris* also contains 3.5% water-soluble inorganic salts, in which potassium chloride constitutes 68% [34].

## 3. Biological Activities

### 3.1. Antihypertensive Activity

Clinical treatments of hypertension with the compound preparations from *P. vulgaris* have achieved good results [35] [36]. Pharmacology experiments have proved that both water extract and ethanol-water (30%) extract from *P. vulgaris* could reduce the blood pressures of anesthetic animals. The stems, leaves, ears and whole grass of *P. vulgaris* have antihypertensive effects, while the function of the ears is relatively less than that of other parts. Potassium salts in *P. vulgaris* have been suggested to be the active ingredients for antihypertensive activity. Biological activity screening had shown that both methylene chloride extract and methanol extract show activity against  $\alpha$ -adrenalin receptor, dopamine receptor, cephalin receptor, enkephalin receptor and diazepam receptor. The principal constituents **1** and **2** have been isolated from the methylene chloride extract of *P. vulgaris*. The total saponins, in which both **1** and **2** are constituted as the main sapogenins, have also been separated from the methanol extract of *P. vulgaris*. The pharmacological experiment had shown that both the sapogenins (**1**, **2**) and



their total saponins have antihypertensive activity [37].

The antihypertensive activities of Sancaojiangyang, which has been prepared from *P. vulgaris*, *Leonurus sibiricus* and *Rough gentian*, have been studied on normal domestic rabbits, Wislar rats and acute experimental renal hypertension rats (RHR). This compound preparation showed positive antihypertensive activity on normal domestic rabbits and displayed a positive quantity-activity relationship ( $P < 0.01$ ). The antihypertensive activities have remarkable statistical significance ( $P < 0.01$ ) by comparing the changes of blood pressures of Wislar rat before and after using this preparation. This prescription could obviously suppress the increase of blood pressure of RHR with statistical significance ( $P < 0.05$  or  $P < 0.01$ ) using physiological saline as the control group. Other reports also had shown that *P. vulgaris* could assume double functions on blood pressure, which means that a small amount of decoction has the expansion function on blood vessels, while a large amount has the weak expansion affects, and even may have vasoconstriction effects instead [38]. Total saponins from *P. vulgaris* (PVS) have been isolated and obtained by Wang. The diastolic blood pressure and the systolic blood pressure of the anesthetic rat could be decreased by using a dosage of 2.5 mg/kg of PVS. There are relationships between the diastolic/systolic blood pressures and the logarithm of the dosage of PVS [39].

The antihypertensive activity on spontaneous hypertensive rat (SHR) of Sanwujiangyang prepared from *P. vulgaris* leucantha schur sec. bailey, *Cassia tora* Linn. and toasted *Eucommia ulmoides*, as well as the effects on the killing cells (LAK cells) activated by the lymph factors have been observed by Feng *et al.* [40]. The positive antihypertensive activity of this preparation had shown with statistical significance ( $P < 0.05$ ) based on the blood pressures before and after dosing SHR rats. While contrasting with physiological saline control group, the results were also statistical significant ( $P < 0.05$ ). After being treated with Sanwujiangyang, the systolic pressures of patients were decreased significantly, while the multiplication and the vitality of LAK cells, radical-eliminating effects and the expression quantity of super oxidase (SOD)-like substances were increased significantly. The correlation between the increasing pressures and the decreasing SOD are remarkable [40].

Thoracic aortic rings of rats cultivated by the LAK cells (from the spontaneous hypertensive rats being treated with Sanwujiangyang) have been increased to some extent by the diastolic function of acetylcholine. Recent studies have shown that the reasons for the significant decreasing of endothelium-dependent vasodilatation effects might not be due to the damages of any links in the L-arginine/nitrogen monoxide pathway and not due to the defects in M-acceptors on the endothelial cells [41], but due to the inactivation of nitrogen monoxide by excessive superoxide anion free radicals owing to the decreasing of the SOD in hypertensive patients [42]. Sanwujiangyang could increase the SOD-like substances so significantly that blood pressures of the patients could be reduced, which have indicated that Sanwujiangyang could offer the new effective ways for both treatment of hypertension and regulation of immune functionality.

### 3.2. Promoting Blood Circulation and Removing Blood Stasis

By injecting adrenalin to the white rats subjected to an ice-bath, Chen had created the acute blood stasis model of stagnation of cold and *qi*. The effects of *P. vulgaris* on the prothrombin time (PT), the blood plasma euglobulin lysis time (ELT) and the hemorheology of the model rats had been observed and researched. The results had indicated that *P. vulgaris* could obviously extend PT of model rats, reduce ELT ( $P < 0.01, 0.05$ ) and improve some of the indexes of the hemorheology. Based on these results, *P. vulgaris* is thought to have the activities of anticoagulation and enhancement of fibrinolytic function [43].

Taking *P. vulgaris* as the main medicine, Liu had prepared capsules from *P. vulgaris*, *Fritillaria thunbergii* Miq., *Dioscorea bulbifera* L, *Draconis Resina*, *Salivae Miltiorrhizae Radix*, *Carapax trionycis*, *Semen coicis* and others [44]. This preparation, with the effects of activating the blood circulation, reducing phlegm, softening and resolving hard mass, was used for the treatment of the experimental endometriosis model of domestic rabbits. The results showed that the whole blood viscosity, the blood plasma viscosity, the blood cells pressure, the erythrocyte sedimentation rate and the weight of implantation could be decreased significantly compared with the control group.

The results of histopathology observation had also shown that the implanted endometriosis tissues might show signs of atrophy, which indicated that the abnormal hemorheology of domestic rabbits could be improved significantly and the abnormal proliferation of endometriosis could also be inhibited. It should be noted that *P. vulgaris* has the function of improving blood circulation and removing blood stasis, as well as the action of softening and resolving hard mass. Clinical reports have also shown that *P. vulgaris* compound prescription could

be used to treat the ischemic vascular disease [45].

The total *P. vulgaris* saponins (PVS) have been extracted from *P. vulgaris*. Four hours after ligation on the coronary artery and then being injected with 20 mg/kg of PVS into the abdominal cavity, the myocardial infarction scope of the anesthetic rats could be shrunken, compared with the control group. The results showed that *P. vulgaris* extraction could expand the heart coronary artery by activating blood circulation [39].

### 3.3. Antilipidemic Activity

The observation of the influential effect on the metabolism of blood lipids of Sian capsules (*P. vulgaris*, *Hirudo nipponia* Whitman, *Coptidis Rhizoma* and so on) has shown that Sian capsules could adjust the proportion of blood lipids of many kinds of animals by decreasing the indexes of TG, VLDL and blood lipid ( $P < 0.05$  or  $P < 0.01$ ), obviously decreasing the level of TCH, LDL and APOB of diabetic model rabbits ( $P < 0.05$  or  $P < 0.01$ ), increasing the level of HDL in young white rats ( $P < 0.05$ ) and decreasing the level of ox LDL and Lp(a) of atherosclerosis model rabbits [46].

### 3.4. Antibacterial and Antivirus Activities

*P. vulgaris* shows a good antimicrobial effect to *influenza*, *streptococcus*, *Kata bacteria*, *Staphylococcus aureus*, *Pneumococcus*, *Pseudomonas aeruginosa* and *Escherichia coli*. The water decoctum of *P. vulgaris* has a broad spectrum of antibacterial activities. *In vitro* experiments indicated that *P. vulgaris* decoctum had strong inhibitory activity against Gram-negative bacilli, such as *Dysentery bacillus*, *Typhoid bacillus*, *Paratyphoid bacillus*, *Cholera vi-brio*, *E. coli*, *Pseudomonas aeruginosa*, *Proteus*, *Yersinia pestis*, *Bacillus anth*, and Gram-positive bacilli, such as  $\alpha$ - or  $\beta$ -*Hemolytic streptococcus*, *Diphtheria bacteria*, *Streptococcus pneumoniae*, and *Human-type Mycobacterium tuberculosis* (H37) [47]. The water decoctum (1:4) showed inhibitory action at different level on *Leather Ashland's rubrum*, *Odua Ang's small Bacillus yellow rubrum* and other pathogenic dermal fungi *in vitro* [48]. *P. vulgaris* could alleviate symptoms of the lungs of mouse with experimental tuberculosis [1].

A sulfur containing polysaccharide (prunellin) isolated from *P. vulgaris* showed inhibitory action on Human Immunodeficiency Virus (HIV) [48]. The crude extract from *P. vulgaris* could obviously suppress HIV with low cell toxicity. Zheng has researched on the anti-herpes simplex virus (HSV) type I effects of *P. vulgaris* extract using human embryonic skin muscle monolayer cell culture technology, demonstrating the obvious anti-viral activity of *P. vulgaris* extraction [49] [50]. The observation on the anti-inflammatory and analgesic effects of the oral liquid and paste from *P. vulgaris* had shown that the oral liquid from *P. vulgaris* could obviously inhibit mouse ear edema induced by croton oil, reduce the increasing permeability of the capillary vessel caused by acetic acid, inhibit both paw oedema and granulation hyperplasia of rats induced by carrageenan or egg white, and show the effective analgesic function against pain caused by acetic acid [51] [52]. The sensitivity test against resistant *Staphylococcus aureus* by the cylinder-plate method showed that *P. vulgaris* had better activity against the resistant *Staphylococcus aureus* than vancomycin hydrochloride [53]. Inhibition of the monkey immunodeficiency virus *in vitro* by the Chinese native medicine compound prescription Aikeqing (containing *Viola philippica* Car, *P. vulgaris*, *Scutellariae baicalensis* and *Salvia Miltorrhiza*) was observed [54] and showed that the inhibition rate on antigen-cells by Aikeqing is 69.6% at sub-cytotoxic concentration (1:32) with the remarkable decreasing in viral duplication. The inhibition percentage of the SIV-1P<sup>27</sup> antigen expression was 94.67%, showing the similar curative effect to AZT, which is an efficient anti-HIV-1 agent.

The polysaccharides isolated from *P. vulgaris* have marked immune-stimulatory effects, which may bring about the anti-microbial effects [55] and has specific activity against HSV [49]. The mode of action appears to be different from other anionic carbohydrates, such as heparin [56]. The aqueous and methanol extractions of *P. vulgaris* used as anti-fever remedies in China were screened for their *in vitro* inhibition on human immunodeficiency virus type-1 protease (HIV-1 PR) [57]. It has been reported that extracts of the spike of *P. vulgaris* exhibit anti-HIV activity at the adsorption and reverse transcription stages [58]. The anti-HIV-1 activity of aromatic herbs in Labiatae was evaluated *in vitro*, *P. vulgaris* aqueous extracts inhibited giant cell formation in co-culture of Molt-4 cells with and without HIV-1 infection and showed inhibitory activity against HIV-1 reverse transcriptase (RT) [59] [60]. Prunellin, an anti-HIV compound isolated from aqueous extractions of *P. vulgaris*, is a partially sulfated polysaccharide with the molecular weight of approximately 10,000.

The aqueous and methanol extracts of *P. vulgaris* have also shown anti-HIV-1 integrase activity in a non-radioactive ELISA-based HIV-1 integrase (IN) assay [61]. With the aid of the ELISA system this schema

represented a laboratory approach to the recognition of anti-HBsAg capability by using *P. vulgaris* herbal extracts [62].

### 3.5. Anti-Inflammatory Activities

*P. vulgaris* has been used therapeutically for inflammation-related conditions for centuries, but systematic studies of its anti-inflammatory activity are lacking and no specific active components have been identified. Recently, extracts from different accessions of *P. vulgaris* were screened for anti-inflammatory activity to identify accessions with the greatest activity. Recently, the antihyperglycemic activity of *P. vulgaris* L. in streptozotocin-induced diabetic mice has been reported [63]. Rosmarinic acid (RA) content in *P. vulgaris* was found to independently inhibit inflammatory response, but it only partially explained the extract's activity. LPS-induced cyclooxygenase-2 (COX-2) and nitric oxide synthase (*i*-NOS) protein expression were both attenuated by *P. vulgaris* ethanol extract, whereas RA inhibited only COX-2 expression [64] [65] had tested the effects of *P. vulgaris* L. extract and its component rosmarinic acid on LPS-induced oxidative damage and inflammation in human gingival fibroblasts. PVE and RA reduced reactive oxygen species (ROS) production, intracellular glutathione (GSH) depletion as well as lipid peroxidation in LPS-treated cells. The results indicated that PVE and RA were able to suppress LPS-induced biological changes in gingival fibroblasts. The effects of PVE and RA are presumably linked to their anti-inflammatory activities and thus use of PVE and RA may be relevant in modulating the inflammation process and including periodontal disease.

SKI 306X is a purified extract from a mixture of three oriental herbal medicines (*Clematis mandshurica*, *Trichosanthes kirilowii* and *P. vulgaris*) that have been widely used for the treatment of inflammatory diseases such as lymphadenitis and arthritis in Far East Asia [66]. Protective effects of SKI 306X, on articular cartilage was examined and compared with other osteoarthritis (OA) drugs using *in vitro* and *in vivo* models. This strongly suggests that SKI 306X can be a good OA agent with some cartilage protection activity [67].

Hypodermic injection with *P. vulgaris* inoculation fluid might obviously cause the atrophy of the thymus and the spleens of experimental animals, an increase of the adrenal gland and an increase of blood plasma cortisol level after the abdominal cavity administration [68], which indicated that *P. vulgaris* might act as a possible immunity inhibitor in the latent treatment of pathology damage caused by the immunity process. The results of animal experimentation indicated that *P. vulgaris* could show remarkable inhibitory activity on the early inflammatory reaction, which might be closely related to the synthesis and the enhancing of secretion of the sugar cortical hormone in adrenal cortex glucocorticoid. As for the effect on the immune organs, *P. vulgaris* could inhibit both the non-specific immune function of the inflammatory response and specific immune functions [69] [70].

### 3.6. Hypoglycemic Effect

50 mg/kg dosage of the effective component of *P. vulgaris* (hypoglycemic hormone) could obviously suppress elevated blood glucose in mice caused by alloxan, with the effect of 100 mg of hypoglycemic hormone being equal to that of 22.6  $\mu$ g of insulin. The lowest effective dose without toxicity is 15 mg/kg [71]. The level of the blood glucose level of the normal mouse and the diabetes model mouse induced by alloxan could be reduced by being treated with the alcohol extract from *P. vulgaris* (0.5 g/kg, IP). Treatment with this extract (0.5 - 0.25 g/kg  $\times$  3d, IP) could inhibit elevated blood glucose by adrenaline, improve glucose tolerance, and increase the synthesis of hepatic glycogen. The mechanism might be connected with the ability to repair the  $\beta$ -cells, normalize the secretion of insulin, or increase the conversion and utilization of glucose *in vivo*, which had been verified by clinical cases [72]. The alcoholic extract of *P. vulgaris* (AEP) was found to prevent and control renal diseases of experimental diabetic rats by obviously reducing urinary protein in diabetic rats. 100mg/kg of AEP could be used to reduce the concentrations of serum urea nitrogen and creatinine. The mechanism might be reducing the loss of inositol and the accumulation of sorbitol caused by sustaining high-sugar levels and maintaining the normal physiological function of cells and tissues by inhibiting the activity of kidney aldose reductase (AR), which might be the synergetic effect of these basic chemical constituents, including triterpenoid glycosides, flavonoids and coumarins [73].

### 3.7. Effect of Protecting the Hepatobiliary System

The result of animal experiments indicated that *P. vulgaris* mixture (*P. vulgaris*, *Scutellaria baicalensis*, *Artemisia*

capillaries, etc.) could obviously protect against chemical-induced liver injury caused by  $\text{CCl}_4$ , D-galactosamine and lipopolysaccharide (LPS) and immunological liver injury caused by *Bacillus Calmette-guerin* (BCG) vaccine and LPS [74]. The compound prescription of *P. vulgaris* could significantly decrease the fibrosis indexes including the procollagen type-IV, the hyaluric acid and the laminin ( $P < 0.01$ ). The treatment effects with *P. vulgaris* were obviously better than the treatment without *P. vulgaris* on the latter two indexes, such as the hyaluric acid and the laminin [75]. The mechanism of the anti-fibrosis activity of *P. vulgaris* is worthwhile to be researched furthermore.

### 3.8. Antineoplastic Activities

*P. vulgaris* has been used in the treatment of malignant cancer for many years [76]. The anti-colon cancer activity of *P. vulgaris* was reported recently by Liu [77]. Pharmacological research had indicated that the water extract, the water-soluble portion of ethanol extract and the residue obtained after extraction from *P. vulgaris* could inhibit U 14 tumor in mice with the rate of 42.2%, 34.1% and 36.2%, respectively. Water extract from *P. vulgaris* could inhibit both sarcoma-180 ( $S_{180}$ ) in mice with a rate of 5.5% and Ehrlich's ascites carcinoma in mice. Experimental research on the apoptosis of cancer cells *in vitro* indicated that *P. vulgaris* could induce the apoptosis of SGC-7910 cancer cells and block the cell cycle between the G1 and G2 [78]. The experiment on the anti-tumor *in vivo* also showed that ursolic acid and its derivatives in *P. vulgaris* might show remarkable cytotoxic activity on P388, L1210 and human lung tumor cells A-549 [79]. By injecting rabbits with *P. vulgaris* with hydrothorax, Xu observed that the pleural surfaces of the experimental rabbits were rough, reddish and congested with adhesive tendency, which was verified by microscopic examination showing the obvious fibrotic thickening between the splanchnic layer pleurae in the thoracic cavity of the experimental rabbits adhered by large amount of lymphocytes. The result demonstrated that *P. vulgaris* injection could not only show significant anti-neoplastic activity but also promote fibrotic overgrowth, which resulted in the therapeutic adhesion of pleurae [80]. *P. vulgaris* injection was used in the treatment of 78 cases of patients with bronchitic lung cancer by intrapleural injections, with more effective treatment results ( $P < 0.01$ ) and less side-effects ( $P < 0.05$ ) than both  $\beta$ -elemene and *cis*-platin/VP16 in chemotherapy group [81].

Studies of apoptosis of cancer cells *in vivo* and *in vitro* indicated that *P. vulgaris* L could induce apoptosis of EL-4 cells by researching on the proliferation of the Jurkat human lymphoma cell line [82]. The effective parts of *P. vulgaris* could significantly inhibit the proliferation of Raji cells, Jurkat cells K562 cells and 4355 cells *in vitro*. *P. vulgaris* could inhibit Dutch T lymphoma EL-4 cells in mice *in vivo* by prolonging the survival period with positive anti-tumor effects and relatively lower toxicity [83]. *P. vulgaris* contains anti-mutagenic factors against both picrolonic acid and benzo[ $\alpha$ ]pyrene-induced mutation [84]. *P. vulgaris* have also shown significant antioxidative activities, by free radical scavenger effect on DPPH, compared with those of *Rosmarinus officinalis* L. and *Salvia officinalis* L. extracts [85].

Although there are many chemical compositions in *P. vulgaris*, it is still not very clear which ingredient or groups of ingredients elicit anti-tumor activities. By now, the active components reported to have the anti-tumor effects are ursolic acid and flavonoids, which shall be discussed in the following context respectively.

Ursolic acid, a triterpenoid which is distributed widely in the medicinal plants, is also the dominant compound in *P. vulgaris* with many bioactivities including hepatoprotection and anti-cancer [86]. The content of ursolic acid is used as the referential criteria of controlling the quality of *P. vulgaris* by Chinese Pharmacopoeia. The contents of ursolic acids in *P. vulgaris* flowers, stems and leaves harvested in June are 0.5110%, 0.3046% and 0.9364%, respectively. But in July, the content ursolic acids in *P. vulgaris* cob, stems and leaves changed to 0.7800%, 0.4356% and 0.6788%, respectively [87]. Ursolic acid has been listed as one of the most promising cancer chemoprevention drugs in 1990 [88]. In recent years, studies indicated that ursolic acid might prevent mutations induced by carcinogens, such as benzopyrene[B( $\alpha$ )P] and aflatoxin B [89] [90], inhibit tumor promotion of phorbol ester (TPA) in mouse skin cancer induced by 2-methyl-benzo onion (DMBA) [91]. Apart from anti-mutation and anti-tumor promotion activities, the initial anti-mutation and anti-tumorpromotin activities of ursolic acid might act through its anti-oxidative effect, in which both the carcinogen-inducing and cancer promoting stages are connected with active oxygen. The carcinogens could have been activated as an extremely reactive electrophilic compounds or free radicals before carcinogenesis occurred, which could damage the target molecules by the interaction with them and then result in the expression of cancer gene [92]. Ursolic acid could capture  $\text{O}_2^-$  and show strong inhibition to lipid peroxidations in the liver microsomes and the  $\text{P}_{450}$



monoamine oxidase system [93]. Ursolic acid could inhibit the activity of cyclooxygenase-2 (COX-2) ( $IC_{50} = 130 \mu\text{M}$ ) so strongly that it could be used as antioxidant, protecting DNA molecules from being oxidative attack [94] [95]. Cytotoxicity tests against six kinds of cancer cell lines with ursolic acid had shown that it has obvious cytotoxicity against P388, leukemia cells (L1210 and L1810) and human adenocarcinoma cells lung cancer A549 ( $ED_{50} < 4 \text{ mg/L}$ ) as well as S180 cell [96]. The anti-neoplastic activity of ursolic acid might be associated with the induction of cancer cell differentiation [97] [98]. Neovascularization is an important step in the growth and metastasis of tumors [99], ursolic acid is a strong inhibitor of angiogenesis [92] [100] [101]. The proliferation of genomic DNA induced by ursolic acid indicated that the mechanism for inducing death of the cells should be apoptosis [102]. Ursolic acid could inhibit the proliferation and induce apoptosis of human acute promyelocytic leukemia cells (HL-60) [103]. In summary, anti-mutagenic, anti-carcinogenic, anti-proliferative, anti-angiogenic and anti-oxidative effects have made ursolic acid the focus for developing a new clinical anti-cancer agent.

Flavonoids, a group of natural polyphenolic compounds, have been researched for their anti-oxidative and anti-neoplastic activity ever since the 1970's [104] [105]. The anti-cancer activity of flavonoids might be connected with the following five aspects:

1) Flavonoids could inhibit proliferation of cells mainly by stopping cell cycle with cytotoxic effect to cancer cells [106]-[108] and without toxicity or mutagenic effects to normal cells [109]. Flavonoids also showed anti-oxidative activity [110] [111] and positive immune regulation function [112].

2) Flavonoids could promote the apoptosis of tumor cells. The cell viability test had confirmed that Licochalcone-A could not only inhibit the growth of both human breast cancer cells MCF-7 and human leukemia cells HL-60, but also strengthen the effect of *vincristine* by inducing the apoptosis of the above two cell lines through down-regulation of the expression of anti-apoptotic protein bcl-2 and the ratio of bcl-2/bax complex [113]. The above apoptosis-inducing properties of flavonoids have been confirmed by other research [114]-[117].

3) Flavonoids could inhibit the activity of tyrosine protein kinase (TPK), protein kinase C, and phosphatidylinositol 3-kinase (PI3) during the process of cell signal transduction [118]-[121]. Sharing structural similarity and weak estrogen-like effect with estrogens, flavonoids are also known as phytoestrogens, which have been confirmed as inhibitors of TPK with cytotoxic and inhibitory effect against a variety of hormone-dependent neoplasms [122].

4) Flavonoids could promote the expression of anti-oncogenes and inhibit the expression of oncogenes [123].

5) Flavonoids could also prevent tumor growth by inhibiting the formation of new blood vessel in solid tumors and irreversibly inhibiting the blood supply of tumor [124].

There are many kinds of anti-neoplastic chemical compositions in *P. vulgaris*, including ursolic acid and flavonoids, polysaccharides and coumarins, that it is quite worthwhile to research this herb further and develop new anti-cancer drugs.

### 3.9. Other Biological Functions

The pharmacological research showed that *P. vulgaris* decoction at 1:100, 1:50 and 1:25 dilutions could strengthen the intestinal peristalsis of isolated rabbits. *P. vulgaris* decoction at 1:200, 1:100 and 1:50 might cause the tetanic contraction of the isolated uterine of the domestic rabbits. *P. vulgaris* decoction at 50% and 100% could obviously show vasodilative effect in the perfusion experiment on the lower limbs of toads [1].

The immediate-type anti-allergic activity of aqueous extract of *P. vulgaris* (Labiatae) (PVAE) was reported [125] [126]. In this report, *P. vulgaris* increased lymphocytes and leucocytes and inhibited the release of allergic media to have an anti-histamine effect. The protection against myocardial ischemia-reperfusion by *P. vulgaris* extract composition was also reported [125]. The anti-phage and anti-tussive activities of *P. vulgaris* are often used in the treatment of cough with chest pain and hemoptysis, combined with other traditional Chinese medicine, such as *Pyrrosia lingus*, *Peucedanum praeruptorum* and *Taraxacum officinale* Dandelion. Besides, *P. vulgaris* has been reported to treat headache, irritability, moss yellow and pulse string in Chinese traditional medicine.

## 4. Conclusion

As a summary, *P. vulgaris* is widely distributed all over the world, with rich sources and relative cheap price. It has so many kinds of active constituents that researching and developing this species for further potential medical

usage are worthwhile and fruitful. It is quite important to mention that the anti-neoplastic activity of this species has become the focus of research. The mechanism for its anti-neoplastic activity has been researched and discussed deeply at the molecular level, which includes from the anti-neoplastic spectrum of *P. vulgaris in vitro*, the isolation and identification of anti-cancer active constituents, toxicology research and the establishment of the targets and dosage of drugs for cancer treatment. Hopefully, *P. vulgaris will continue to be a source for developing new anti-neoplastic drugs.*

## Acknowledgements

The authors would like to thank the Chinese Medicinal Burro in Shaan Xi Province of China for financial funding with the title of Antineoplastic active chemical substance in *P. vulgaris* L. (Registration number is 2009zy54), the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry, China (2011), the Shaanxi Province Science and Technology Research and Development Program of China, International Cooperation (2013KW31-04) and the National Natural Science Foundation of China (Grants 81172957) for the financial support.

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