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CANCER CHEMOPREVENTION (R AGARWAL, SECTION EDITOR)

Anti-tumor Properties of *Prunella vulgaris*

Mofei Huang[1,2] · **Yian Wang**[2] · **Ling Xu**[1] · **Ming You**[2]

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Abstract Cancer is one of the most serious threats to public health around the world. Efforts in developing new therapies and prevention strategies are clearly insufficient in the face of a dramatically rising disease burden worldwide. New evaluation of alternate strategies, including those based on traditional medicine, is increasingly needed. These therapeutic or prevention approaches could prove complementary to current medical practice or could potentially aid in the development of new classes of pharmaceutical drugs with anti-cancer properties. *Prunella vulgaris*, a perennial herb, is a representative Chinese herb that has been put into practice to treat various types of diseases, including cancer. The triterpenoid, flavonoids, and phenylpropanoids in *P. vulgaris* have shown a collective therapeutic effect against cancer mediated through multiple pathways. This review discusses the chemical constituents of *P. vulgaris*, summarizes all of the known formulas that contain *P. vulgaris*, and also discusses in vitro, in vivo, and clinical studies on the anti-tumor properties of *P. vulgaris*. The aim is to bring better insights regarding *P. vulgaris* as an effective complementary method for treating cancer. Highlighted throughout this review is the necessity for additional prospective clinical trials on anti-tumor properties of *P. vulgaris*.

Keywords *Prunella vulgaris* · Chinese herbs · Cancer · Chemoprevention

Abbreviations

PV	*Prunella vulgaris*
HUVEC	Human umbilical vein endothelial cell
PVAE	Aqueous extract isolated from *Prunella vulgaris*
EESP	Ethanol extract of *Spica prunella*
RA	Rosmarinic acid
ROS	Reactive oxygen species
OA	Oleanolic acid
UA	Ursolic acid
MAPK/ERK	Mitogen-activated protein kinases/extracellular signal-regulated kinase
NSCLC	Non-small cell lung cancer
TRAIL	Tumor necrosis factor-related apoptosis-inducing ligand
FASN	Fatty acid synthase
EPVL	Extract of *Prunella vulgaris* L
IR	Inhibitory rate
DMH	1,2-Dimethylhydrazine
ACF	Aberrant crypt foci
FLT	Flourothymidine
P 60	60 % ethanol extract of PV
CTX	Cyclophosphamide
GR	Gastrointestinal reaction
BMS	Bone marrow suppression
ALT	Alanine aminotransferase
4NQO	4-nitroquinoline-1-oxide
ATB	Anti-tumor B

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✉ Ming You
myou@mcw.edu

[1] Longhua Hospital, Shanghai University of Traditional Chinese Medicine, 725 South Wanping Rd., Shanghai 200032, China

[2] Medical College of Wisconsin Cancer Center and Department of Pharmacology and Toxicology, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226, USA

Introduction

Traditional Chinese medicine (TCM) is often considered as complementary to Western medicine in treating various types of cancer. It is a major part of the use of botanical medicine that is widespread in all regions of developing world and is consistently growing in popularity in industrialized countries, especially among patients diagnosed with cancer [1]. *Prunella vulgaris*, a perennial herb, grows natively across East Asia throughout China, Japan, Korea, and Europe. It is commonly used as a dietary supplement [2]. As a folk medicine used for thousands of years in China, it has been mainly used as an antipyretic remedy for alleviating sore throat, reducing fever, and accelerating wound healing [3, 4•]. Its major bioactive ingredients consist of triterpenoids, steroids, flavonoids, coumarins, organic acid, volatile oil, phenylpropanoids, and carbohydrate [5]. Most of these substances have been shown a wide spectrum of biological properties including anti-viral [6, 7], anti-oxidant [8, 9], anti-microbial [10, 11], anti-inflammatory [12, 13], anti-diabetic [14, 15], anti-estrogenic [16], anti-allergic [17], immune modulatory [18, 19], and anti-cancer [20, 21] effects. In China, this well-known traditional herb is used as the key ingredient in many Chinese herbal mixtures in the forms of decoction, capsule, granule, or infusion for treatment of cancer, primarily as an adjuvant/complementary treatment in the majority of patients (see Table 1).

Of these formulas containing *P. vulgaris*, anti-tumor-B (ATB) have shown strong cancer chemopreventive activities both preclinically and in clinical trials. In a clinical study [56], a total of 449 patients with esophageal epithelial hyperplasia were randomly divided into an anti-tumor B treatment (n=300) and a placebo control group (n=149). After 6 months of oral administration, the response rate of the ATB group was 64.4 vs 22.8 % compared to placebo group (p<0.001) and the frequency of progression was 3.3 and 24.8 % (p<0.001), respectively. In a 4-nitroquinoline-1-oxide (4NQO) induced oral squamous cell carcinoma model in A/J mice [55], ATB inhibited tumor development by 59.2 %. ATB treatment resulted in a significant reduction in multiplicity and tumor load in a A/J mutant lung adenocarcinoma model [57]. ATB inhibited the incidence of bladder cancer by 90.7 % (p<0.01) in a rat bladder cancer model treated with N-butyl-(4-hydroxybutyl) nitrosamide (BBN) [58]. In general, ATB has been shown to be a potent cancer chemopreventive agent. However, it is still not clear if *P. vulgaris* is responsible for the observed chemopreventive efficacy of ATB or in any other Chinese herbal mixtures containing *P. vulgaris*. Future studies should focus on the role *P. vulgaris* in ATB's efficacy as well as its chemopreventive effects as a single agent.

Chemical Constituents of *P. vulgaris*

P. vulgaris contains nine categories of chemical compounds isolated by various methods (listed in Tables 2 and 3). Four of the nine structural categories, namely, triterpenoid, flavonoid, phenylpropanoids, and steroids are found to have strong anti-tumor properties. Among these, triterpenoids have been the most widely investigated probably due to its high content in *P. vulgaris*. Kyun Lee et al. [94] isolated fifteen triterpenoids through the method of methanol extraction of *P. vulgaris*. Of the extracted triterpenoids, ursolic acid and oleanic acid are the two key constituents [59] that have shown anti-cancer properties (Tables 2 and 3). Ursolic acid [95] has anti-cancer effects against gallbladder cancer through suppression of proliferation, cell cycle arrest, and increased tumor cell apoptosis. Two new triterpenoids, pentacyclic triterpenoid [96] glycosides Vulgasides I and II have recently been isolated from *P. vulgaris*. The amount of flavonoid [97] was 2.2–10.3 % in *P. vulgaris*. Other phytochemicals, such as rutin, quercetin, and hyperoside, are found to have anti-cancer properties, including anti-proliferation, immune-enhancing, anti-oxidant, pro-apoptosis, cell cycle arrest in in vivo or in vitro studies. Phenolic acids consisting of rosmarinic acid and caffeic acid may also play a role in the anti-tumor properties of *P. vulgaris* through the mechanism of anti-angiogenesis, anti-proliferation, and induction on apoptosis. In the 7,12-dimethylbenz[a]anthracene (DMBA) induced skin tumor model using Swiss albino mice [88], oral administration of rosmarinic acid completely prevented the formation of skin tumors. Finally, five additional categories of chemical compounds are steroid, coumarins, organic oils, carbohydrates, and volatile oils. Steroid category [59] extracts include β-sitosterol, stigmasterol, and α-spinasterol.

In Vitro Anti-cancer Activity (Table 3)

Anti-proliferation

Several studies [67, 71, 98–109] revealed that *P. vulgaris* inhibits the proliferation of human cancer cell lines (Table 3), including human esophageal cancer cell line Eca 109 [110, 111], liver cancer cell line $HepG_2$, cervical cancer Hela cell, and stomach cancer MKN 45 cell line [8]. Possible mechanisms suggested include the inhibition of the c-Jun N-terminal kinase (JNK) pathway [1, 2] and the Akt pathway [2, 3]. Ethanol extract of *P. vulgaris* was found to inhibit colon cancer cell line HT-29 by arresting the cell cycle at the G1/S checkpoint and reducing the expression of pro-proliferative cyclin D1 and cyclin-dependent kinase 4 (CDK4) at the transcriptional and translational level [108]. *P. vulgaris* has also been shown to have combinatorial effects with other agents. For example, *P. vulgaris* extracts enhanced the effects of

Table 1 Chinese herbal formula containing *Prunella vulgaris*

Formula	Cancer type	Key constituents	References
Gong Ai Duo Ming Decoction	Lymphoma	*Seaweed* (Haizao 海藻), *Licorice* (Gancao 甘草), *Momordica cochinchinensis* (Mubiezi 木鳖子), *Turtle shell* (Biejia 鳖甲), *Diffusa* (Baihuasheshecao 白花蛇舌草), *Prunella vulgaris* (Xiakucao 夏枯草), *Paris polyphylla* (Zaoxiu 蚤休), *Sea Clam Shell* (Haigeke 海蛤壳), *Airpotato Yam* (Huangyaozi 黄药子), *Raw Pinellia Ternata* (Shengbanxia 生半夏), *Ginseng* (Shengjiang 生姜), *Scrophularia* (Yuanshen 元参), *Oyster shell* (Muli 牡蛎), *Fritillariae Thunbergii* (Dabei 大贝), *Lphigenia* (Shancigu 山慈菇), *Radix Sophorae Tonkinensis* (Shandougen 山豆根), *Scorpion* (Quanxie 全蝎), *Centipede* (Wugong 蜈蚣), *Realgar* (Xionghuang 雄黄)	Sun QX [22]
Basic Gong Ai Ma Xin Decoction	Cerebroma, spinal cord glioma, osteolytic sarcoma	*Seaweed* (Haizao 海藻), *Licorice* (Gancao 甘草), *Momordica cochinchinensis* (Mubiezi 木鳖子), *Prunella Vulgaris* (Xiakucao 夏枯草), *Raw Pinellia ternata* (Shengbanxia 生半夏), *Ginseng* (Shengjiang 生姜), *Scrophularia* (Yuanshen 元参), *Oyster shell* (Muli 牡蛎), *Fritillariae Thunbergii* (Dabei 大贝), *Semen Brassicae* (Baijiezi 白芥子), *Scorpion* (Quanxie 全蝎), *Centipede* (Wugong 蜈蚣), *Ephedra sinica Stapf* (Mahuang 麻黄), *Radix Aconite Lateralis Preparata* (Zhifuzi 制附子), *Asarum* (Xixin 细辛)	Sun QX [22]
Shu GanKui Jian Decoction	Nasopharyngeal carcinoma	*Prunella vulgaris* (Xiakucao 夏枯草), *Bombyx Batryticatus* (Jiangchan 僵蚕), *Cyperus Rotundus* (Xiangfuzi 香附子), *Concha Haliotidis* (Shijueming 石决明), *Angelica Sinensis* (Danggui 当归), *Radix Paeoniae Alba* (Baishao 白芍), *Dried Tangerine peel* (Chenpi 陈皮), *Bupleurum* (Chaihu 柴胡), *Ligusticum Wallichii* (Fuxiong 抚芎), *Pangolin* (Chuanshanjia 穿山甲), *Safflower* (Honghua 红花), *Rhizoma Curcumae Longae* (Jianghuang 姜黄), *Licorice root* (Shenggancao 生甘草)	Lin H et al. [23]
Xiao Liu Decoction	Thyroid neoplasms	*Bupleurum* (Chaihu 柴胡), *Oyster shell* (Shengmuli 牡蛎), *Radix Paeoniae Alba* (Baishao 白芍), *Turtle shell* (Biejia 鳖甲), *Prunella vulgaris* (Xiakucao 夏枯草), *Seaweed* (Haizao 海藻), *Kelp* (Kunbu 昆布), *Figwort* (Xuanshen 玄参), *Rhizoma Sparganii* (Sanleng 三棱), *Peach kernel* (Taoren 桃仁), *Thunberg Fritillary Bulb* (Zhebeimu 浙贝母), *Pangolin* (Chuanshanjia 穿山甲), *Licorice* (Gancao 甘草)	He XM [24]
Chai Xia Xiao Yin Decoction	Thyroid neoplasms	*Bupleurum* (Chaihu 柴胡), *Prunella vulgaris* (Xiakucao 夏枯草), *Curcuma aromatica* (Yujin 郁金), *Semen Brassicae* (Baijiezi 白芥子), *Seaweed* (Haizao 海藻), *Oyster shell* (Muli 牡蛎), *Airpotato Yam* (Huangyaozi 黄药子), *Pangolin* (Chuanshanjia 穿山甲), *Curcuma zedoaria* (Ezhu 莪术), *Radix Paeoniae Rubra* (Chishao 赤芍), *Gleditsia Thorn* (Zaoci 皂刺), *Lphigenia* (Shancigu 山慈菇)	Zhang YY et al. [162]
ErBei Mu Capsule	Breast carcinoma	*Thunberg Fritillary Bulb (Zhebeimu* 浙贝母), *Bolbostemma* (Tubeimu 土贝母), *Lphigenia* (Shancigu 山慈菇), *Prunella vulgaris* (Xiakucao 夏枯草), *Dandelion* (Pugongying 蒲公英), *Forsythia* (Lianqiao 连翘)	Shi JG et al. [163]
Jie Du Xiao Zhen Decoction	Gastrointestinal tumors	*Diffusa* (Baihuasheshecao 白花蛇舌草), *Prunella vulgaris* (Xiakucao 夏枯草), *Sophora flavescens* (Kushen 苦参), *Lphigenia* (Shancigu 山慈菇)	Cao ZY et al. [25]
Fu Zheng Qing Jie Decoction	Gastrointestinal tumors	*Astragalus membranaceus* (Huangqi 黄芪), *Ligustrum lucidum* (Nvzhenzi 女贞子), *Lucid Ganoderma* (Lingzhi 灵芝), *Chinese yam* (Shanyao 山药), *Prunella vulgaris* (Xiakucao 夏枯草), *Diffusa* (Baihuasheshecao 白花蛇舌草)	Cao ZY et al. [25]
Ruan Jian Hua Tan Decoction	Non-small cell lung cancer with brain metastasis	*Araceae* (Tiannanxing 天南星), *Pinellia ternata* (Banxia 半夏), *Kelp* (Kunbu 昆布), *Seaweed* (Haizao 海藻), *Fritillaria cirrhosa* (Chuanbeimu 川贝母), *Prunella vulgaris* (Xiakucao 夏枯草), *Peach kernel* (Taoren 桃仁), *Radix Paeoniae Rubra* (Chishao 赤芍), *Oyster shell* (Muli 牡蛎), *Diffusa* (Baihuasheshecao 白花蛇舌草), *Salvia chinensis* (Shijianchuan 石见穿), *Hive* (Fengfang 蜂房)	Gui HT et al. [26]
Fu Zheng Yi Liu Decoction	Gastrointestinal tumors	*Astragalus Membranaceus* (Huangqi 黄芪), *Ligustrum Lucidum* (Nvzhenzi 女贞子), *Lucid Ganoderma* (Lingzhi 灵芝), *Chinese Yam* (Shanyao 山药), *Prunella Vulgaris* (Xiakucao 夏枯草), *Diffusa* (Baihuasheshecao 白花蛇舌草)	Lan L et al. [27]

Table 1 (continued)

Formula	Cancer type	Key constituents	References
Fu Zheng Yi Liu Ointment	Rectal carcinoma	*American Ginseng* (Xiyangshen 西洋参), *Astragalus Membranaceus* (Huangqi 黄芪), *Chinese Yam* (Shanyao 山药), *Poria* (Fuling 茯苓), *Ganoderma lucidum* (Lingzhi 灵芝), *Chinese Wolfberry* (Gouqi 枸杞), *Dodder* (Tusizi 菟丝子), *Ligustrum Lucidum* (Nvzhenzi 女贞子), *Prunella vulgaris* (Xiakucao 夏枯草), *Diffusa* (Baihuasheshecao 白花蛇舌草), *Licorice* (Gancao 甘草), *Hawthorn* (Shanzha 山楂)	Lv Y et al. [28]
Anti-cancer Yi Shen Decoction	Gastrointestinal tumors	*Astragalus Membranaceus* (Huangqi 黄芪), *Pericarpium Citri Reticulatae Viride* (Qingpi 青皮), *Radix Aucklandiae* (Muxiang 木香), *Agalloch Eaglewood* (Chenxiang 沉香), *Syzygium Aromaticum* (Dingxiang 丁香), *Curcuma zedoaria* (Ezhu 莪术), *Rhizoma Sparganii* (Sanleng 三棱), *Ligusticum Wallichii* (Chuanxiong 川芎), *Raw Pinellia Ternata* (Banxia 半夏), *Semen Brassicae* (Baijiezi 白芥子), *Euphorbia Helioscopia* (Zeqi 泽漆), *Scutellaria Barbata* (Banzhilian 半枝莲), *Lobelia Chinensis Lour* (Banbianlian 半边莲), *Diffusa* (Baihuasheshecao 白花蛇舌草), *Prunella Vulgaris* (Xiakucao 夏枯草), *Eupolyphaga* (Tubiechong 土鳖虫), *Leech* (Shuizhi 水蛭), *Gadfly* (Mengchong虻虫)	Xiao GS et al. [29]
Luo Li Ointmint	Lymphnoditis, lymphoma	*Prunella vulgaris* (Xiakucao 夏枯草), *Figwort* (Xuanshen 玄参), *Seaweed* (Haizao 海藻), *Oyster Shell* (Muli 牡蛎), *Kelp* (Kunbu 昆布), *Dried tangerine peel* (Chenpi 陈皮), *Tangerine seed* (Juhe 橘核)	Chen PY et al. [30]
Qing Liu Liang Hou Recipe	Hypopharyngeal carcinoma	*Radix Pseudostellariae* (Taizishen 太子参), *Codonopsis pilosula* (Dangshen 党参), *Dendrobium* (Shihu 石斛), *Adenophora* (Shashen 沙参), *Ophiopogon Japonicus* (Maidong 麦冬), *Hawthorn* (Shanzha 山楂), *Endothelium Corneum Gigeriae galli* (Jineijin 鸡内金), *Amomum Villosum* (Sharen 砂仁), *Prunella Vulgaris* (Xiakucao 夏枯草), *Diffusa* (Baihuasheshecao 白花蛇舌草), *Gleditsia Thorn* (Zaoci 皂刺), *Perrin* (Peilan 佩兰), *Patchouli* (Huoxiang 藿香), *Cortex Moutan* (Mudanpi 牡丹皮), *Belamcanda Chinensis* (Shegan 射干), *Acorus Gramineus Soland* (Shichangpu 石菖蒲), *Tortoise Shell* (Guiban 龟板), *Trichosanthin* (Huafen 花粉)	Chen WJ et al. [31]
No 1 Brain Tumor Decoction	Neuroepithelial tumors	*Konjak* (Sheliugu 蛇六谷), *Diffusa* (Baihuasheshecao 白花蛇舌草), *Scutellaria Barbata* (Banzhilian 半枝莲), *Lobelia Chinensis Lour* (Banbianlian 半边莲), *Prunella Vulgaris* (Xiakucao 夏枯草), *Radix Semiaquilegiae* (Tiankuizi 天葵子), *Paris Polyphylla* (Chonglou 重楼), *Cyrtomium Fortunei* (Guanzhong 贯众), *Smilax China* (Baqia 菝葜)	Wu YQ et al. [32]
Hua Tan Decoction	Hypophysoma	*Araceae* (Tiannanxing 天南星), *Pinellia Ternata* (Banxia 半夏), *Prunella Vulgaris* (Xiakucao 夏枯草), *Oyster shell* (Muli 牡蛎), *Centipede* (Wugong 蜈蚣), *Gecko* (Shougong 守宫), *Polyporus Umbellatus* (Zhuling 猪苓), *Acorus Gramineus Soland* (Shichangpu 石菖蒲), *Bombyx Batryticatus* (Jiangchan 僵蚕), *Salvia Chinensis* (Shijianchuan 石见穿)	Wu YQ et al. [32]
Hua Yu Xi Feng Decoction	Nervous system neoplasms	*Araceae* (Tiannanxing 天南星), *PinelliaTernata* (Banxia 半夏), *Prunella Vulgaris* (Xiakucao 夏枯草), *Acorus Gramineus Soland* (Shichangpu 石菖蒲), *Bombyx Batryticatus* (Jiangchan 僵蚕), *Oyster Shell* (Muli 牡蛎), *Beretima, Centipede* (Wugong 蜈蚣), *Polyporus Umbellatus* (Zhuling 猪苓), *Cinobufagin Venom Toad, Eupolyphaga sinensis*	Wu YQ et al. [32]
Liver Cancer Pain Removal Ointment	Liver cancer pain	*Diffusa* (Baihuasheshecao 白花蛇舌草), *Prunella Vulgaris* (Xiakucao 夏枯草), *Salvia Miltiorrhiza* (Danshen 丹参), *Corydalis Ambigua* (Yanhusuo 延胡索), *Nightshade* (Longkui 龙葵), *Paris Polyphylla* (Chonglou 重楼), *Rhizoma Sparganii* (Sanleng 三棱)	Wang YS et al. [33]
Ping Liu Kang Capsule	Glioma	*Konjak* (Sheliugu 蛇六谷), *Prunella Vulgaris* (Xiakucao 夏枯草), *Kelp* (Kunbu 昆布), *Lphigenia* (Shancigu 山慈菇), *Angelica Dahurica* (Baizhi 白芷), *Scorpion* (Quanxie 全蝎)	Liu HY et al. [34]
Gui Jiu Shi Cao Decoction	Terminal cancer	*Podophyllotoxin Grass* (Guijiu 鬼臼), *Prunella Vulgaris* (Xiakucao 夏枯草), *Eclipta Alba* (Hanliancao 旱莲草), *Radix Gentianae* (Longdancao 龙胆草), *Houttuynia Cordata* (Yuxingcao 鱼腥草)	Jin CS [35]

Table 1 (continued)

Formula	Cancer type	Key constituents	References
Decoction of Esophageal Cancer	Esophagus cancer	*Radix Sophorae Tonkinensis* (Shandougen 山豆根), *Fructus Trichosanthis* (Quangualou 全瓜蒌), *Prunella vulgaris* (Xiakucao 夏枯草), *Nightshade* (Longkui 龙葵), *Citron* (Xiangyuan 香橼)	Yang ZJ et al. [36]
Shan Jia Long Kui Decoction	Pancreatic carcinoma	*Pangolin* (Chuanshanjia 穿山甲), *Nightshade* (Longkui 龙葵), *Chinaberry fruit* (Chuanlianzi 川楝子), *Curcuma Aromatica* (Yujin 郁金), *Salvia Chinensis* (石见穿), *Prunella vulgaris* (Xiakucao 夏枯草), *Sargentgloryvine Stem* (Hongteng 红藤), *Five-leaf Akebia fruit* (Bayuezha 八月札)	Cao HT et al. [37]
Huang Yao Hai Kun Decoction	Thyroid adenoma	*Airpotato Yam* (Huangyaozi 黄药子), *Kelp* (Kunbu 昆布), *Seaweed* (Haizao 海藻), *Oyster Shell* (Muli 牡蛎), *Prunella Vulgaris* (Xiakucao 夏枯草), *Rhizoma Sparganii* (Sanleng 三棱), *Zedoary* (Ezhu 莪术), *Semen Brassicae* (Baijiezi 白芥子)	Hao YX et al. [38]
Anti-cancer Yi Capsule	Esophageal precancerous lesions	*Airpotato Yam* (Huangyaozi 黄药子), *Polygonum Bistorta* (Quanshen 拳参), *Radix Sophorae Tonkinensis* (Shandougen 山豆根), *Prunella vulgaris* (Xiakucao 夏枯草), *Patrinia* (Baijiangcao 败酱草), *Cortex Dictamni* (Baixianpi 白鲜皮)	Hao YX et al. [38]
Xiao Yan Decoction	Malignant tumor	*Astragalus Membranaceus* (Huangqi 黄芪), *Oyster Shell* (Muli 牡蛎), *Radix Pseudostellariae* (Taizishen 太子参), *Prunella Vulgaris* (Xiakucao 夏枯草), *Hive* (Fengfang 蜂房), *Rhizoma Curcumae Longae* (Jianghuang 姜黄)	Li XJ et al. [39]
Wei Chan An Decoction	Gastrointestinal tumor	*Radix Pseudostellariae* (Taizishen 太子参), *Atractylodes* (Baizhu 白术), *Poria* (Fuling 茯苓), *Dolichos lablab L* (Baibiandou 白扁豆), *Sargentgloryvine Stem* (Hongteng 红藤), *Oyster Shell* (Muli 牡蛎), *Prunella Vulgaris* (Xiakucao 夏枯草)	Hu RJ [40]
Yi Qi Xiao Zhen Decoction	Advanced tumor	*Radix Pseudostellariae* (Taizishen 太子参), *Atractylodes* (Baizhu 白术), *Chinese angelica* (Danggui 当归), *Rhizome of Chuanxiong* (Chuanxiong 川芎), *Earthworm* (Dilong 地龙), *Zedoary* (Ezhu 莪术), *Prunella Vulgaris* (Xiakucao 夏枯草), *Seaweed* (Zicao 紫草)	Li PP et al. [41]
Pu Ji Jian Decoction	Nasopharyngeal carcinoma	*Fructus Arctii* (Niubangzi 牛蒡子), *Ligustrum Lucidum* (Nvzhenzi 女贞子), *Prunella Vulgaris* (Xiakucao 夏枯草), *Baikal Skullcap* (Huangqin 黄芩), *Forsythia* (Lianqiao 连翘), *Bupleurum* (Chaihu 柴胡), *Radix Isatidis* (Banlangen 板蓝根)	Su XC et al. [42]
Bi Yan Qing Du Granule	Nasopharyngeal carcinoma	*Chrysanthemum* (Juhua 菊花), *Paris Polyphylla* (Chonglou 重楼), *Radix Zanthoxyli* (Liangmianzhen 两面针), *Prunella Vulgaris* (Xiakucao 夏枯草), *Radix Gentianae* (Longdancao 龙胆草), *Fructus Xanthii* (Cangerzi 苍耳子)	Han H et al. [43]
Yi Qi Jie Du Decoction	Colon cancer	*Astragalus Membranaceus* (Renshen 人参), *Hairyvein Agrimony* (Xianhecao 仙鹤草), *Atractylodes* (Baizhu 白术), *Poria Cocos* (Fuling 茯苓), *Pinellia ternata* (Banxia 半夏), *Dried Tangerine peel* (Chenpi 陈皮), *Prunella Vulgaris* (Xiakucao 夏枯草), *Diffusa* (Baihuasheshecao 白花蛇舌草), *Scutellaria Barbata* (Banzhilian 半枝莲), *Duchesnea Indica* (Shemei 蛇莓)	Shu JH et al. [44]
Yi Qi Jie Du Qu Yu Decoction	Advanced non-small cell lung cancer	*Astragalus Membranaceus* (Huangqi 黄芪), *Radix Pseudostellariae* (Taizishen 太子参), *Rhizoma Curcumae Longae* (Yujin 郁金), *Curcuma aromatica* (Jianghuang 姜黄), *Prunella Vulgaris* (Xiakucao 夏枯草), *Diffusa* (Baihuasheshecao 白花蛇舌草)	Zhao C et al. [45]
Yi Ai San Jie Decoction	Pancreatic carcinoma	*Iphigenia Indica* (Shancigu 山慈菇), *Five-leaf Akebia fruit* (Bayuezha 八月札), *Ranunculus ternatus Thunb* (Maozhuacao 猫爪草), *Diffusa* (Baihuasheshecao 白花蛇舌草), Chinese Rhubarb (Dahuang 大黄), *pseudo-ginseng* (Tianqi 田七), *Prunella vulgaris* (Xiakucao 夏枯草), *seaweed* (Haizao 海藻), *kelp* (Kunbu 昆布), *Scorpion* (Quanxie 全蝎), *Centipede* (Wugong 蜈蚣), *Platycladus Orientalis Leaf* (Ceboye 侧柏叶), *Chinese Yam* (Shanyao 山药), *Atractylodes* (Baizhu 白术)	Chen LZ et al. [46]
Yan Shu Injection	Liver cancer	*Astragalus Membranaceus* (Huangqi 黄芪), *Radix Pseudostellariae* (Taizishen 太子参), *Atractylodes* (Baizhu 白术), *Poria* (Fuling 茯苓), *Grifola* (Zhuling 猪苓), *Radix Rhapontici* (Loulu 漏芦), *Paris Polyphylla* (Chonglou 重楼), *Prunella Vulgaris* (Xiakucao 夏枯草), *Curcuma Zedoaria* (Ezhu 莪术), *Cortex Moutan* (Mudanpi 牡丹皮), *Oyster Shell* (Muli 牡蛎), *Dried Tangerine peel* (Chenpi 陈皮), *Fructus Oryzae Germinatus* (Guya 谷芽), *Hordeum Vulgare* L (Maiya 麦芽)	Gu XX et al. [47]

Table 1 (continued)

Formula	Cancer type	Key constituents	References
Xiao Ling Capsule	Lung cancer	*Rhizoma Sparganii* (Sanleng 三棱), *Zedoary* (Ezhu 莪术), *Kelp* (Kunbu 昆布), *Lphigenia* (Shancigu 山慈菇), *Prunella Vulgaris* (Xiakucao 夏枯草), *Thunberg Fritillary Bulb* (Zhebeimu 浙贝母), *Curcuma Aromatica* (Jianghuang 姜黄), *Pinellia Ternata* (Banxia 半夏), *Rhizome of ChuanXiong* (Chuanxiong 川芎), *Codonopsis Pilosula* (Dangshen 党参), *Astragalus Membranaceus* (Huangqi 黄芪)	He JF et al. [48]
Jie Du San Jie Xiao Zhen Decoction	Gastrointestinal tumor	*Polygonum Cuspidatum* (Huzhang 虎杖), *Oriental Wormwood* (Yinchen 茵陈), *Gardenia* (Zhizihua, 枝子花), *Prunella Vulgaris* (Xiakucao 夏枯草), *Turtle shell* (Biejia 鳖甲), *Pangolin* (Chuanshanjia 穿山甲), *Lphigenia* (Shancigu 山慈菇), *Nightshade* (Longkui 龙葵), *Scutellaria Barbata* (Banzhilian 半枝莲), *Astragalus Membranaceus* (Huangqi 黄芪), *Codonopsis Pilosula* (Dangshen 党参), *Poria* (Fuling 茯苓), *Atractylodes* (Baizhu 白术)	Ma JW et al. [49]
San Cao Decoction	Lung cancer	*Prunella vulgaris* (Xiakucao 夏枯草), *Diffusa* (Baihuasheshecao 白花蛇舌草), *Hairyvein Agrimony* (Xianhecao 仙鹤草), *Eclipta prostrata* (Mohanlian 墨旱莲), *Cornus Officinalis* (Shanzhuyu 山茱萸)	Jia XB et al. [50]
Anti-tumor Decoction	Malignancy	*Astragalus Membranaceus* (Huangqi 黄芪), *Red Ginseng* (Hongshen 红参), *Radices Trichosanthis* (Tianhuafen 天花粉), *Fructus Aurantii* (Zhike 枳壳), *Prunella Vulgaris* (Xiakucao 夏枯草), *Chinese Angelica* (Danggui 当归)	Song CS et al. [51]
Fu Zheng Xiao Liu Mixture	Malignancy	*Astragalus Membranaceus* (Huangqi 黄芪), *Codonopsis Pilosula* (Dangshen 党参), *Atractylodes* (Baizhu 白术), *Alvia Miltiorrhiza* (Danshen 丹参), *Curcuma aromatica* (Yujin 郁金), *Rhizoma Sparganii* (Sanleng 三棱), *zedoary* (Ezhu 莪术), *Prunella Vulgaris* (Xiakucao 夏枯草), *Diffusa* (Baihuasheshecao 白花蛇舌草), *Paris Polyphylla* (Chonglou 重楼)	Li YH et al. [52]
Fu Zheng Xiao Ji Decoction	Middle-late stage lung cancer	*Diffusa* (Baihuasheshecao 白花蛇舌草), *Astragalus Membranaceus* (Huangqi 黄芪), *Prunella vulgaris* (Xiakucao 夏枯草), *Semen Coicis* (Yiyiren 薏苡仁), *Panax ginseng* (Renshen 人参), *Pericarpium Citri Reticulatae Viride* (Qingpi 青皮), *Glehnia Littoralis* (Beishashen 北沙参), *Kelp* (Kunbu 昆布), *Pinellia ternata* (Banxia 半夏), *Asparagus* (Tiandong 天冬), *Ophiopogon japonicus* (Maidong 麦冬), *vinegar turtle shell* (Biejia 鳖甲), *Araceae* (Tiannanxing 天南星)	Shen D et al. [53]
GuJin Kang Ai Decoction	Lung cancer	*Dried Human Placenta* (Ziheche 紫河车), *Mongolian Snakegourd* (Gualou 栝楼), *Dried* Tangerine Peel (Chenpi 陈皮), *Semen Coicis* (Yiyiren 薏苡仁), *Zedoary* (Ezhu 莪术), *Prunella Vulgaris* (Xiakucao 夏枯草), *Radix Sophorae Tonkinensis* (Shandougen 山豆根), *Lilium brownie* (Baihe 百合)	Cai GR et al. [54]
Anti-tumor B		*Sophora Tonkinensis* (Shandougen 山豆根), *Polygonum Bistorta* (Quanshen 拳参), *Prunella Vulgaris* (Xiakucao 夏枯草), *Sonchus Brachyotus* (北败酱), *Dictamnus dasycarpus* (Baixianpi, 白鲜皮), *Dioscorea Bulbifera* (Airpotato yam or Huangyaozi黄药子)	Wang Y [55]

Table 2 Key ingredients contained in *Prunella vulgaris*

Types	Nutrient ingredients	References
Triterpenoid	28 kinds of triterpenoid with ursolic acid and oleanic acid highest in quantity	[5, 59, 60]
Steroids	B-sitosterol, stigmasterol, α-spinasterol, stigmast-7-en-3β-ol,(22E,20S,24S)-stigmastra-7, 22-dien-3-one,daucosteol	
Flavonoids	Rutin, lutiolin, homoorientin, cinaroside, quercetin, quercetin-3-O-β-D-galatoside, quercetin-3-O-β-D-glucoside, kaempferol-3-O- β-D-glucoside	
Coumarins	Umbelliferone, scopoletin, esculetin	
Organic acid	*cis*- and *trans*-caffeic acid, palmitic acid, stearic acid, 6,9-otodecadienoic acid, 3,6,17-eicosatrienoic acid, oleic acid, arachidic acid, behemic acid, lauric acid, myristic acid, linoleinic acid	
Carbohydrate	Monosaccharide, disaccharide, polysaccharide	
Volatile oil	1,8-Eucalyptol, pinene, myrcene, linalyl acetate, α-phellandrene, linalool	
Phenylpropanoids	*cis*-and-*trans*-caffeic acid, rosmarinic acid, methyl rosemarinicine, ethyl rosemarinicine, 3, 4, α-3 hydroxyl-methyl-phenyl propionate	
Others	*d*-camphor, *d*-fenchone, carotene, vitamin B, vitamin C, vitamin K, resin, tannin, alkaloid, water soluble salt	

paclitaxel (TAX) and adriamycin (ADM) on inhibiting cell growth of cancer cells [105]. A combination of *P. vulgaris* and *Cremastra appendiculata* exhibited an enhanced effects in inhibiting the growth of thyroid cancer cell line [112, 113], along with down-regulation of the c-myc expression.

In addition to *P. vulgaris* extracts, some of its ingredients have also been examined for anti-cancer activities (Table 3). Triterpenoicacids, a component of *P. vulgaris* [94, 106, 107], exhibited strong cytotoxic activity against human lung cancer cell line A459. Triterpenoic acid [94] isolated from *P. vulgaris* has been shown to inhibit cell growths of various human cancer cell lines, namely, A549 cell lines, SK-OV-3 (ovarian cancer cell), SK-MEL-2 (skin melanoma), and HCT 15 (colon cancer cell). Ursolic acid [67], one of the most abundant triterpenoic acids in *P. vulgaris*, showed inhibitory effect on colon cancer cell lines HCT-15 and DLD-1. The mechanism [67] underlying ursolic acid-mediated anti-proliferation against human colon cancer cell lines is believed to be related to the N-terminal phosphorylation and subsequent proteasomal degradation of β-catenin. Ursolic acid also reduced proliferation in many other tumor cell lines, like human leukemic cell line HL-60 [114], mouse melanoma cell line B16 [115], human breast MCF7 [116]. Oleanic acid, an active component of *P. vulgaris* [71], inhibited the proliferation of HT-29 cells in dose-dependent manner through the mechanism of G0/G1 checkpoint arrest. Oleanolic acid [70] also exhibited strong anti-proliferation activity against human lung SPC-A-1 cells. Interestingly, an endophytic fungus CPCC 480171 [117] isolated from *P. vulgaris* was found to have cytotoxic effects on multiple human cell line, A549 (lung cancer), LOVO cells (colon cancer), CEM cells (T cell leukemia), and HL-60 (leukemia). Caffeic acid, a major phenolic compound in *P. vulgaris* [93], was observed to inhibit cancer cell proliferation, especially at a high concentration (over 30 μg/ml). Table 4 summarized in vitro efficacy of *P. vulgaris* and its extracts or components against cancer cell lines.

Regulation of Cell Cycle Progression and Cell Cycle Arrest

P. vulgaris has been shown to induce cell cycle arrest at various checkpoints in cancer cells. After thyroid carcinoma cell line SW579 [109] was treated with *P. vulgaris*, the proportion of cells in the S phase was observed to be reduced, while those in the G0/G1 phase was significantly increased when compared to the control group. In another study [108], the ethanol extract of *P. vulgaris* arrested cells at the G1/S checkpoint in human colon carcinoma cells and inhibited the expression of both cyclin D1 and CDK4. Rutin [83], one of the flavonoids from *P. vulgaris*, showed anti-tumor effect against human neuroblastoma LAN-5 cells by inducing G2/M cell cycle arrest and apoptosis. Ursolic acid, another component of *P. vulgaris*, was shown to block B16 mouse melanoma cell line in G1 phase [115]. These reports suggest that *P. vulgaris* is capable of inducing cell cycle arrest in various cancer cell lines.

Induction of Apoptosis

Apoptosis [143–148] has been shown to be induced by many anti-tumor regimens [145–148] such as chemotherapy, radiation as well as Chinese herbs such as *P. vulgaris. P. vulgaris* and its components have been shown to induce apoptosis in a variety of cancer cell lines (including Raji cells [1, 4•], SGC-7901 [119], SW 579 [109, 112], Eca 109 [111], EL-4 [121], Jurket cells [103, 104], PANC-1 [122], T24 [136], HepG2, HT29, A549, MKN-45, and Hela cells [8]). Several phytochemicals from *P. vulgaris* including oleanic acid [70], ursolic acid [65], rosmarinic acid [126], and caffeic acid [93] have also been shown to either induce or promote apoptosis in cancer cells. Mechanisms suggested by several studies are both the up-regulation of the expression of p53 [65], Bax [8, 64, 70, 101, 104, 111, 122], Fas [136], Bad [70], caspase 3

Table 3 Chemical structures of the major anti-cancer chemical compounds in *Prunella vulgaris*

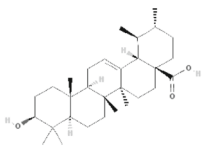
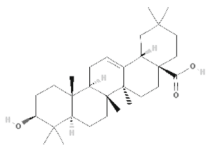
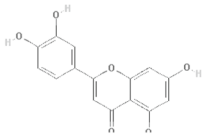
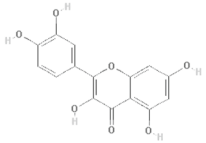
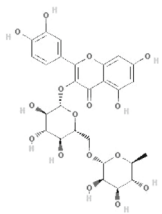
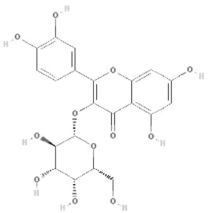
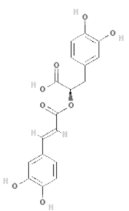
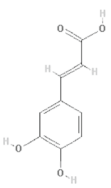
Classification	Compound	Molecular formula	Chemical structure	MW	Effect and references
Triterpenoid	Ursolic acid	$C_{30}H_{48}O_3$		456.70	Anti-oxidant [61], cell cycle arrest [62], immune-enhancing [63], induction on apoptosis [64,65] and differentiation [66], anti-proliferation [67]
	Oleanic acid	$C_{30}H_{48}O_3$		456.70	Anti-oxidant [68], cell cycle arrest [69], induction on apoptosis [70], anti-proliferation [71], and suppression on migration and metastasis [72]
Flavonoid	Luteolin	$C_{15}H_{10}O_6$		286.24	Enhancing sensitivity of chemotherapy [73], cell cycle arrest [74], apoptosis [75,76]
	Quercetin	$C_{15}H_{10}O_7$		302.24	Anti-oxidant [77], cell cycle arrest [78], induction on apoptosis [79], anti-proliferation [80],
	Rutin	$C_{27}H_{30}O_{16}$		610.52	cytotoxic effect [81], immune-enhancing [82], anti-proliferation [83], Anti-oxidant [84]
	Hyperoside	$C_{21}H_{20}O_{12}$		464.38	Anti-proliferation [85], apoptosis [86], Anti-oxidant [87
Phenylpropanoid	Rosmarinic acid	$C_{18}H_{16}O_8$		360.31	Induction on apoptosis [88], anti-angiogenesis [89], anti-proliferation [90, 91], and chemoprevention [92]
	Caffeic acid	$C_9H_8O_4$		180.16	Anti-proliferation [73], and induction on apoptosis [93]

Table 4 In vitro anti-cancer activities

Mechanism	Compound	Models	Cancer type	Outcome	Description	References
Anti-proliferation	PV	Raji cell	Lymphoma	PV shows a strong inhibitory effect upon the growth of lymphoma cell line compared to other groups ($p \leq 0.05$)	Activation of JNK pathway and caspase channel	Liu XK et al. [118]
	PV	Eca 109 cells	Esophageal cancer	PV can dramatically inhibit the Eca 109 cell from proliferation		Ma LP et al. [110]
	Injection of PV	SGC-7901 cells	Gastric adenocarcinoma	Cell line growth were inhibited dramatically	Morphologic feature of apoptosis were also seen	Wang K et al. [119]
	Crude of PV	MCF-7/S cells and MCF-7/R cells	Breast cancer	Inhibition the cell line in a dose/time-dependent manner	Increase the expression of P53	Wei MJ et al. [120]
	PVor combination of PV with *Cremastra appendiculata*	SW 579	Thyroid cancer	PV can anti-proliferate the growth of SW 579 with a IC_{50} of 21 mg/l	Down-regulated the expression of the protein of c-myc	Meng WW et al. [112]
	Extract of PV	Raji cell	Lymphoma	Inhibition on the proliferation of Raji cells in a dose-dependent manner	Expression of Bcl-2 down-regulated and Bax up-regulated	Chen CY et al. [101]
	Extract of PV	Jurket cells	Leukemia	Remarkable effect on anti-proliferation of cell line with a IC_{50} of 53.59±3.10 mg/l	Expression of Bcl-2 down-regulated and Bax up-regulated	Fu XR et al. [103]
	PVE combined with chemotherapeutic agents	Raji cell	Lymphoma	PVE can enhance the sensitivity of Raji cell line to TAX and ADM agents	Up-regulated the expression of protein caspase-3 and down-regulated the survivin	Zhang MZ et al. [105]
	PV	Raji cell	Lymphoma	The proliferation rate of PV was lower than control group ($p \leq 0.05$)	Probably through anti-activation of Akt pathway	Shi XQ et al. [100]
	An endophytic fungus CPCC 480171 isolated from *Prunella vulgaris*	LOVO, A549, CEM, HL-60 cell line	Multiple cancer	All the three compounds showed inhibitory effect against LOVO, A549, CEM, HL-60 cell lines		Liu M et al. [117]
	Two triterpenoids in *Prunella vulgaris* L	A549	Lung cancer	Compound I and II both have inhibitory effect against A459 cells compared to control group ($p < 0.05$)		Pei H et al. [107]
	Triterpenoic acids of *Prunella vulgaris*	A549, SK-OV-3, SK-MEL-2, HCT15	Adenocarcinoma lung cancer, ovarian cancer, skin melanoma, and colon cancer	Only compound 3 ursolic acid exhibited moderate cytotoxic activity against cell line		Lee, I. K et al. [94]
	Caffeic acid	HT-1080	Fibrosarcoma	Decrease cell proliferation, enhances lipid peroxidative markers and ROS levels	Involvement of oxidative mechanism	Rajendra Prasad, N et al. [93]
	Oleanolic acid	HT-29	Colon cancer	Oleanolic acid inhibited the proliferation of HT-29 cells in dose-dependent manner	Via G0 /G1 checkpoint control and DNA replication control	Juan, M. E [71]
	Ursolic acid	HEK293, HCT-15, DLD-1, and Wnt3a-secreting L cells	Colon cancer	Performed anti-proliferation in colon cancer cells	By promoting the N-terminal phosphorylation and subsequent proteasomal degradation of beta-catenin	Kim, J. H et al. [67]
	Ursolic acid	HL60	Leukemia	Inhibited cell growth (IC50=0.85 microM) and their DNA synthesis (IC50=1 microM)		Simon, A et al. [114]
	Ursolic acid	B16	Melanoma	Ursolic acid acted a potent inhibitor of B16 cell growth	Via redistribution of cell cycle phase	Es-saady, D et al. [115]
Apoptosis	Extract of PV	EL-4 cell	Lymphoma	200 kg per day EPVL ranked the highest inhibition rate and the apoptosis band was in 200 kg and 400 per day group		Yao ZH et al. [121]
	Extract of PV	Jurket cells	Leukemia	Induce apoptosis on cell line and typical DNA ladder was showed	Expression of Bcl-2 down-regulated and Bax up-regulated	Fu XR et al. [103]
	Crude of PV	MCF-7/S cells and MCF-7/R cells	Breast cancer	Induction on the MCF-7/S cells and MCF-7/R cells apoptosis	Increase the expression of P53	Wei MJ et al. [120]
	Injection of PV	PANC-1	Pancreas cancer	IPV has an effect on apoptosis of PANC-1 and this effect has a positive relation with the concentration	Up-regulated the expression of bax and down-regulated the expression of bal-2	Song W et al. [122]
	PWE of PV	A549 and SMMC-7721	Lung cancer and liver cancer	Effect of apoptosis on A549 correlates with concentration		Li D et al. [123]

Table 4 (continued)

Mechanism	Compound	Models	Cancer type	Outcome	Description	References
	Oleanolic acid	SPC-A-1	Adenocarcinoma lung cancer	OA significantly promoted cell apoptosis and show strong anti-prohibition on cell line	Down-regulated the expression of BCL-2 and up-regulated the expression of Bad and Bax	Feng, L [70]
	Ethanol extract of PV	HT-29	Colon carcinoma	Induction on the pro-apoptosis of HT-29 cell line	Suppression on the activation of STAT3 signaling	Lin W et al. [124]
	2,3-Dihydroxyurs-12-ene-28-oic acid from *Prunella vulgaris* var. lilacina	Jurkat T cell	Leukemia	Induceapoptotic DNA fragmentation of human acute leukemia Jurkat cell	Mediated by Deltapsim loss, mitochondrial cytochrome c release, and activation of caspase-9 and caspase-3 before activation of caspase-7 and caspase-8	Woo, H. J [125]
	Rosmarinic acid	HCT15, CO115	Colon-rectal cancer	Induced apoptosis in a dose-dependent manner in both HCT 15 cells and C0115 cells lines	Due in part to the inhibition of MAPK/ERK pathway	Xavier, C. P [126]
	Rosmarinic acid	U937	Leukemia	Significantly sensitizes TNF-a-induced apoptosis in human leukemia U937 cells	Through the suppression NF-κB and ROS	Moon, D. O et al. [127]
	Quercetin	H460, A549, H2009, H1299	NSCLC	Quercetin sensitized TRAIL-induced cytotoxicity	Through induction of DR5 and suppression of survivin expression	Chen, W et al. [128]
	Quercetin	HepG2	Liver cancer	Induce apoptosis of HepG2 cells	Via overexpression of FASN	Zhao, P et al. [79]
	Ursolic acid	PC-3, LNCaP, DU145	Prostate cancer	Enhance ethidium homodimer stained cells, apoptotic bodies, sub-G1 apoptotic accumulation in PC-3 cells	Via inhibition of the Wnt5/β-catenin pathway and activation of caspase	Park, J. H et al. [64]
	Prunella vulgaris L extract	Jurkat T cell	Lymphoma	Apoptosis rate increased in a concentration-dependent manner	By down-regulating Bcl-2 protein and up-regulating Bax protein	Chen CY [104]
	Rosmarinic acid	Jurkat T cell	Lymphoma	Induced apoptosis in a dose-dependent manner	Through the mitochondrial pathway	Kolettas, E et al. [129]
Anti-oxidant	Ethanol extract and water fraction of PV	Macrophage, HepG2, HT29, A549, MKN-45, and Hela cells	Liver cancer, colon cancer, lung cancer, stomach cancer, and cervical cancer	Strong correlation coefficients were seen between anti-oxidant activity and its phenolic content	Apoptosis was induced through elevation the expression of P53, Bax, and Fas	Hwang, Y. J et al. [8]
	60 % ethanol extract of PV			Exhibited high free radical scavenging activity		Feng, L et al9
	Prunella vulgaris extract and rosmarinic acid	Gingival fibroblasts cell		Reduced ROS production, intracellular glutathione (GSH) depletion as well as lipid peroxidation		Zdarilova, A et al11
	Rosmarinic acid	Jurkat T cells	Leukemia	Protect Jurkat cells from oxidative stress caused by hydrogen peroxide	Enhancement of anti-oxidant enzymes and the release of anti-inflammatory signaling molecules	Chkhikvishvili, I et al. [130]
	Hyperoside	Fibroblast cell		Decrease the intracellular ROS as well as increase anti-oxidant enzyme activity	Act as a free radical scavenger or activate anti-oxidant enzyme activity	Piao, M. J et al. [131]
	Oleanolic acid and ursolic acid	PC12		OA or UA significantly reversed H(2)O(2)- and MPP(+)-induced impairment	Through sparing GSH, raising the activity of SOD and catalase, reducing the release of IL-6 and TNF-α	Tsai, S. J et al. [68]
	Rutin	PC-12	Pheochromocytoma	Inhibited 6-OHDA-induced neurotoxicity	By improving anti-oxidant enzyme levels and inhibiting lipid peroxidation	Magalingam, K. B et al. [84]
Anti-angiogenesis	Alcohol extract of PV	HUVEC		Angiogenetic ability of HUVEC was also inhibited and the expression of mRNA and protein of VEGF and VEGRR were significantly decreased		Fang F et al. [132]
	Rosmarinic acid	HUVEC		Inhibit several important steps of angiogenesis in a dose-dependent manner	Anti-angiogenic potential of RA might be related to its anti-oxidative activity	Huang, S. S et al. [89]

Table 4 (continued)

Mechanism	Compound	Models	Cancer type	Outcome	Description	References
	UA and OA			Inhibited angiogenesis in a dose-dependent manner		Sohn, K. H et al. [133]
Impairment on cell cycle progression	PV	Eca 109 cells	Esophageal cancer	Dramatically decrease on the number of Eca 109 cell in the stage of G0/G1 and the percentage of cells in stage of S cycle surges from 8.41 to 14.64 %		Ma LP et al. [110]
	PV	SW579	Thyroid cancer	Retard the proliferation of SW579 cell at G0/G1 phase, decreased the cell ratio at S phase		Zhang J et al. [134]
	EESP	HT-29	Colon cancer	EESP prevents G1/S progression of HT-29 cells	The expression of mRNA and protein of cyclin D1 and CD k4 were reduced	Lin, W et al. [108]
	Rutin	LAN-5	Neuroblastoma	Inhibited the growth of LAN-5 cells by inducing G2/M arrest in the cell cycle progression		Chen, H et al. [83]
Others	PV	SW 480	Colon cancer	Up-regulate functional Fal-L mRNA expression of SW480	Indication of increase of invasive ability	Chen CH et al. [135]
	PV	T24	Bladder cancer	Up-regulate functional Fal-L mRNA expression of T24	Indication of increase of invasive ability	Zhang J et al. [136]
	PVAE	HT-1080	Fibrosarcoma	PVAE reduced PMA-induced activation of MMP-9 and further inhibited cell invasion and migration	Through suppression of NF-κB activation and phosphorylation of ERK1/2	Jae H. C et al. [137•]
	PVAE	RAW 264.7 cells		Stimulated macrophage phagocytic activity, NO production and augment cytokines such as TNF-α,IL-1 and IL-6	Anti-tumor activity was firmly associated with macrophage activation via NF-κB transactivation and MAPK activation	Han, E. H et al. [138]
	Rosmarinic acid	MDA-MB-231BO, ST-2	Breast cancer	RA could inhibit the migration of MDA-MB-231BO human bone-homing breast cancer cells dose-dependently	Via the pathway of RANKL/RANK/OPG and by suppressing the expression of IL-8 at the same time	Xu, Y et al. [139]
	Rosmarinic acid	Ls174-T	Colon carcinoma	Inhibit migration, adhesion, and invasion dose-dependently	Via the pathway of extracellular signal-regulated kinase	Xu, Y et al. [140]
	Aqueous extract of *Prunella vulgaris*	HepG2, Huh-7, and Hep3B	Liver cancer	Inhibit migration and invasion of human liver carcinoma cells in a dose- and time-dependent manner	Attenuation of MMP-9 and MMP-2 protein expression and the corresponding enzymatic activities	Kim, S. H et al. [141]
	Hyperoside	U2OS,,MG63	Osteosarcoma	Osteopontin and runt-related transcription factor 2 protein levels and osteocalcin activation were up-regulated profoundly	Induction differentiation involves the TGF-beta signaling pathway	Zhang, N et al. [142]
	Oleanolic acid	U-87 MG	Glioma	OA significantly decreased the ability of glioma cells to migrate and invade	Inhibition on. MAPK/ERK pathway	Guo, G et al. [72]
	Ursolic acid	U937	Leukemia	Induced U937 cells differentiation	Thorough PI3K/Akt pathway activation	Deng, L et al. [66]
	Ursolic acid	Daudi cells	Lymphoma	Increased intracellular Ca2+ levels and triggered apoptosis		Lauthier, F et al. [65]

[64, 118], and caspase 9 [64] as well as down-regulation of the expression of c-myc [119], Bcl-2 [64, 70, 101, 104, 121, 122, 149], Mcl [64], and Bcl-xl [64]. Other mechanisms have been suggested are the inhibition of mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway [126], the mitochondrial pathway [150, 151], the nuclear transcription factor NF-κB [127] pathway, and the intracellular generation of reactive oxygen species (ROS) [61, 68, 77, 130, 131, 152, 153].

Anti-angiogenesis

P. vulgaris extracts [154] and rosmarinic acid [89] exhibited a dose-dependent inhibition of in vitro angiogenic properties of endothelial cells, including proliferation, metastasis, adhesion, and tube formation. Inhibition of ROS production was implicated as a potential mechanism for the decreased VEGF expression and decreased interleukin 8 (IL-8) release in response to rosmarinic acid treatment [89]. Triterpene acids [133], ursolic acid, and oleanolic acid, have been shown to inhibit angiogenesis in a dose-dependent manner in the chick chorioallantoic membrane (CAM) assay. Both ursolic acid and oleanic acid inhibited the proliferation of bovine arotic endothelial cells [133]. Jae HC et al. [137•] found that aqueous extract of *P. vulgaris* inhibited tumor angiogenesis and metastasis through suppression of NF-κB activation and phosphorylation of ERK1/2 by reducing the expression matrix metalloproteinase 9 (MMP-9). Aqueous extract of *P. vulgaris*, called PVAE [141], inhibited the migration and metastasis of human liver cancer cell lines by inhibiting the enzymatic activity and protein expression of MMP-2 and MMP-9.

In Vivo Anti-cancer Activity (Table 5)

P. vulgaris has been characterized for its in vivo anti-cancer effects in multiple animal models (Table 5). Using Lewis lung carcinoma model, *P. vulgaris* [155•] has shown a significant anti-tumor effect when compared with control group. Using a human colon carcinoma HT-90 cell xenograft athymic nude mouse model [124], ethanol extract of *P. vulgaris* (also called EESP) significantly reduced tumor load when compared to control group without any signs of toxicity. In a T cell lymphoma EL-4 cell transplanted C57BL/6 mice model [20], ethanol extract of *P. vulgaris* inhibited tumor growth. In a benzo(a)pyrene intraperitoneal (i.p) injected A/J mice model [21], ethanol extract of *P. vulgaris* inhibited lung tumor multiplicity by more than 90 %; rosmarinic acid, a key component of *P. vulgaris*, has been shown to inhibit skin and colon carcinogenesis in a DMBA-induced skin carcinogenesis Swiss albino mice model [140] and in a rat model of colon carcinogenesis [92], respectively.

Clinical Studies (Table 6)

Table 6 summarized clinical studies reported for *P. vulgaris*. Zhang et al. [157••] reported a randomized clinical trial (RCT) in which 101 patients with non-Hodgkin's lymphoma were divided into three groups: EPVL (extract of *P. vulgaris*), CHOP (combined chemotherapy regimen), and EPVL+CHOP. CHOP consists of (C)yclophosphamide, (H)ydroxydaunorubicin, (O)ncovin (vincristine), and (P)rednisone or (P)rednisolone. A 70 % curative efficacy were observed in the combination group (EPVL+CHOP) comparing with 52.6 % in the chemotherapy group (CHOP) and 10.5 % in *P. vulgaris* alone (EPVL) group, indicating that *P. vulgaris* may serve as an effective adjuvant treatment with chemotherapy for non-Hodgkin's lymphoma [157••]. Zhou RY [158] reported another randomized clinical trial of 23 late stage liver cancer patients into two groups: treatment group in which *P. vulgaris* (EESP-ethanol extract of *Spica prunella*) and a formulated injectable mixture called "anti-inflammation injection formulation #1" were perfused through liver artery; and control group with cisplatin (DDP), hydroxycamptothecin (HCPT), and 5-fluorouracil (5-FUu) perfused. Although there was no significant difference in the 1-year survival rates between the two groups, there is a significant difference of clinical symptoms with a higher Karnofsky Performance Scale (KPS) index (a higher KPS score indicates less functional impairment) was seen in the *P. vulgaris* group ($p<0.01$). A similar observation was also seen in another study [159] in which *P. vulgaris* injection showed better results in controlling cancer-associated symptoms and higher KPS scores in patients with late stage gastrointestinal cancer. Zhou et al. [161••] reported the randomization of a group of 52 bronchopulmonary carcinoma patients with moderate or severe hydrothorax into two groups: one group received tube closed drainage along with intrapleural injection of *P. vulgaris*, and the control group received chemotherapy alone. The curative effect rate, average remission period, adverse reaction rate between *P. vulgaris* group, and chemotherapy alone group were 85 vs 46 %, 7 vs 1.5 months, and 0~12 % vs 4~35 %, respectively ($p\leq0.05$). This observation is confirmed by another study [160] on using *P. vulgaris* injection to treat hydrothorax in 78 patients as compared with the chemotherapy alone group. These results suggest that *P. vulgaris* is a potentially non-toxic therapeutic agent for the treatment of hydrothorax caused bronchopulmonary carcinoma.

Conclusion

P. vulgaris has been extensively used in China both independently and as a part of a multi-modal approach to treat cancer patients with standard chemotherapy. *P. vulgaris* appears to

Table 5 In vivo anti-cancer activities

Models	Treatment and dosage	Administration	Main findings	References
A/J mice received B[a]P in corn oil (100 mg/kg) by intraperitoneal injection	0.4 ml P-60 (10.0 g/kg)	Oral feeding everyday for 24 weeks	The number of tumors in back side and front side was lower than untreated group (31.2±5.66 vs 3.0±2.16, $p \leq 0.01$). Treatment with P-60 decreased the tumor multiplicity by 90.3 %	Feng, L et al. [21]
C57BL/6 mouse with subcutaneous injection of 106 Lewis cells in 200 μL PBS in the right anterior limb	Aqueous extract of PV high dose: 10 g crude drug/kg; low dose: 5 g crude drug/kg	Intragastrically administered every day for 14 consecutive days	P32 group and Prunella extract high-dose group show significant anti-tumor effect involving tumor control rate and tumor weight when compared with control group ($p \leq 0.05$)	Jia, X. B et al. [155•]
CRC mouse received subcutaneous injection of human colon carcinoma HT-29 cells	6 g/kg of EESP	Intragastric administration for 5 days a week for 16 days	EESP treatment significantly reduced both tumor volume and tumor weight, as compared to control ($p<0.01$) with no change of body weight	Lin, W et al. [124]
C57BL/6 mice were subcutaneously inoculated with EL-4 cells in the right axilla	*Spica prunellae* high, medium, and low doses were 600 mg crude drug/Kg, 400 mg crude drug/Kg, and 200 mg crude drug/Kg, respectively	Not illustrated	Tumor weight in both high dose and medium group were significantly different compared with model group ($p \leq 0.05$) and the tumor inhibition rates of the two groups were both greater than 30 %	Mao, X et al. [20]
Fifty BALB/C mice were intraperitoneally injected with T-lymphoma cells EL-4	The mice in the EPVL 400, 200, and 100 mg/kg groups were injected with 400, 200, and 100 mg/kg per day EPVL, respectively	For 8 consecutive days	The IR in the three doses of EPVL groups and the CTX group was obviously higher than that of the negative control group ($p<0.05$), as well as the survival time was obviously longer compared to negative control group ($p<0.05$)	Yao, Z. H et al. [121]
Mice received human neuroendocrine xenografts (H727)	Received 0.25 ml of an extract of *Prunella vulgaris* in ethanol once or twice daily	p.o by gastric tube feeding for 10 days	No effect on tumor volume measured by CT or uptake of FLT was observed in neuroendocrine tumors in mice gavaged with PV	Camilla B. J et al. [156]
The Wistar rat received subcutaneous injection of 40 mg/kg or 80 mg/kg weekly for 2 weeks of DMH for evaluation of DNA damage and ACF formation	Received RA at the doses of 4, 8, and 16 mg/kg body weight/day	Gavage	A significant reduction in the extent of DNA damage and in the frequency of ACF were observed after gavaged with RA when compared with administrated with DMH alone	Furtado, R. A et al. [92]
The Wistar rats were subjected to a two-phase model of hepatocarcinogenesis (initiated-promoted group)	Initiated-promoted animals also received quercetin 10 and 20 mg/kg body weight (IPQ10 and IPQ20 groups, respectively)	Gavage 2 h before administration with hepatocarcinogenesis for each duration	Only IPQ20 group showed a reduction in number volume of preneoplastic lesions and proliferative index and enhancement of apoptosis as well as redistribution of cell cycle	María Laura Casella et al. [78]
Male C57BL/6 mice implanted with the Lewis lung carcinoma (LLC) cells	Treated with RA at the dosage of 1, 2, and 4 mg/kg	Celiac injection for 20 days	Inhibition ratios were 55.40, 56.83, and 29.98 % and inhibitory rates of the formation of metastasis nodules reached 33.11, 59.53, and 25.75 % in the case of administration with 1, 2, and 4 mg/kg of RA relatively and not loss body weight was seen	Yichun Xu, et al. [140]
Male C57BL/6 mice were subcutaneously injected in the right anterior limb of 0.2 ml cell suspension (106 Lewis cells)	Mice in the P-60 group were orally given P-60 (high dose: 10 g/kg/day, low-dose: 5 g/kg/day)	By intragastric administration	Tumor volumes in the P-60 and CTX groups were visibly smaller than in the 0.9 % NaCl group ($p<0.05$) tumor weights were significantly decrease in P-60 group compare with negative group ($p<0.05$)	Liang F et al. [9]

Table 6 Clinical studies

Type of study	Type of cancer	No of patients	Outcome	Administration method	Adverse reaction	References
RCT	Indolent lymphoma	*N*=101 Txn=44 CtrAn=19 CtrnBn=38	Therapeautic effect Tx:CR:16/44, PR:17/44, NC:6/44, PD:11/44 CtrA:CR:1/19, PR:6/19, NC:11/19, PD:7/19 CtrB:CR:9/38,PR:11/38, NC:7/38, PD:4/38 ($p<0.05$)	CtrA:PV 20/d po 30 days*3 CtrB:CHOP (CTX 750 mg/m2 d1, VCR 14 mg/m2 d1,d8,VCR40 mg/m2 d1) iv every 21 days*2 Tx:PV+CHOP	Tx:mild diarrhea (3) I GR (20) II GR (7),III~IV BMS (8), ALT (5) CtrA:diarrhea (1) CtrB:I GR (18), II~IIIGR (6) III~IV BMS (7), ALT (5)	Zhang MZ et al. (2009) [157••]
RCT	Late primary liver cancer	*N*=23 Txn=12 Ctrn=11	Syndrome score:Tx before 9.45±2.62 after 8.64±2.61 Ctr before 10.58±3.34 after 6.08±2.39 ($p<0.05$) Therapeautic effect: Tx:PR:1/12, NC:9/12, PD:2/12 rate of relief 8.33 % Ctr: PR:1/11, NC:6/11, PD:4/11 9.09 % ($p>0.05$)	Tx: injection of 60 ml/m2 of PV and No.1 Anti-inflammation 60 ml by liver artery perfusion Ctr: chemotherapy (DDP 60 mg+5-FU 750 mg+HCPT 20 mg) by liver artery perfusion	Tx: fever (1), pain (1) Ctr: ALT, TBil, Cr ↑($p<0.05$)	Zhang HB et al. (2003) [158]
RCT	Late stage gastrointestinal cancer	*N*=50 Txn=30 Ctrn=20	KPS score:Tx before 54.87±2.42 after610.13±6.66 Ctr before 55.12±3. after 57.01±4.02 ($p<0.05$) Therapeutic effect: Tx:MR:3/30, SD:24/30, PD:3/30 Ctr: SD:16/20, PD:4/20	Tx: injection of PV 80 ml+5%GS or 0.9%NS 500 ml iv 30 days Ctr: Ping Xiao Capsule po Tid 30 days	Tx: mild dizzy (6) Ctr:no	Wang HW et al. (2003) [159]
RCT	Lung cancer with hydrothorax	*N*=78 Txn=26 CtrAn=26 CtrnBn=26	Therapeutic effect Tx:CR:9/26, PR:13/26, SD:2/26, PD:2/26 CtrA:CR:8/26 PR:12/26, SD:1/26, PD:5/26 CtrB:CR:5/26,PR:7/26, SD:8/26, PD:4/26 ($p<0.01$) Remission period: Tx:3~19 months average 7 months CtrA:3~12 months average 5 months CtrB:1~5 months average 2 months ($p<0.05$)	Tx:30~50 ml of PV injection into chest after drainage everyday and 60~80 ml of PV before last drainage CtrA:20~40 ml of elemene injection into chest after drainage twice a week CtrB: injection of DDP 80~100 mg+VP16 200 mg+5-Fu 1000 mg after last drainage	Tx: chest pain (3) CtrA: chest pain (6) CtrB: WBC↓ (5), GR (9), chest pain (9), lost of hair (4), abnormity of liver function (1), abnormity of kidney function (1)	Zhou RY et al. (2001) [160]

target multiple signaling pathways and has a complex mechanism of action. The complexity of the herb may be a key element of its therapeutic or preventive effectiveness. However, the pleiotropic effects that it causes make determining definitive targets for future pharmaceutical development more challenging. Based on its strong efficay in both pre-clincial model systems and in a number of clinical trials with limited toxicity or adverse effects, further studies should focus on characterizing *P. vulgaris* as a promising cancer chemopreventive agent.

Compliance with Ethics Guidelines

Conflict of Interest Mofei Huang, Yian Wang, Ling Xu, and Ming You declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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