REVIEW ARTICLE

A systematic review on multi-nutritional and phytopharmacological importance of *Perilla frutescens*

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Abstract

Perilla frutescens (L.) Britt, a worldwide distributed plant, is an important economic crop and with a long cultivation history in China as well as some other countries in Asia. The plant species were the main parts of folk medicine practiced by the ancient peoples in different parts of the world. *P. frutescens* (L.) is an annual short-day plant belonging to the family Labiatae which is used by ancient people in different parts of the world. *P. frutescens* have been used as an important traditional herbal medicine for treating various diseases including depression, anxiety, tumor, cough, antioxidant, allergy, intoxication, and some intestinal disorders. Perilla seeds contain considerably high levels (approx. 60%) of α-linolenic acid, which can be expected to possess various biological activities. The leaves are said to be helpful for asthma, colds, and different types of flu's. The current review has been written after gone through several literature of review on *P. frutescens* and a great effort have been given to enhance the pharmacological contents in the current review from different literature of review. The current review included many bioactive metabolites present in *P. frutescens* and their nutritional as well as pharmacological importance.

Key words: *Perilla frutescens*, phytochemistry, phytomedicine, antioxidant activity

INTRODUCTION

Perilla frutescens (Shiso) (also called Zisu in China), is an annual herb of the Mint family (Lamiaceae) native to East Asia. It is an edible medicinal plant and a traditional crop of China, India, Japan, Korea, Thailand, and other Asian countries, and USA.[1,2] In India, it is found in Northern hillsides of Lohagat, Champawat, and Tanakpur. The entire plant is very nutritious, containing vitamins and minerals. There are many scientifically proven medicinal uses for Perilla. It has been used as an antiasthmatic,[3] antibacterial, antidote,[4] antipyretic, antiseptic, antispasmodic, antitussive, emollient, expectorant, antioxidant,[5-7] anti-inflammatory,[8] analgesic, and antiallergic,[4,9-11] Perilla has been reported to have cardioprotective, antithrombotic, antihypertensive,[12-14] anticancer,[15] insecticidal, tonic, and heat-protecting properties.[1]

The seed of *P. frutescens*is the important source of Perilla oil and the fresh plant of *P. frutescens* is a spicy vegetable in East Asia. In China, people get used to deal with fish and crab poisoning with *P. frutescens* based on ancient Chinese medicine. In Japan and Korea, people get used *P. frutescens* to be representative flavors in Japanese food and make pickles as well as packages with roast meat, respectively.[16] Except for the edible usages, *P. frutescens* is also widely used as traditional Chinese medicines (TCM) for various diseases, such as cold due to wind-cold, headache, cough, abdominal fullness and distention, poisoning from fish, and crabs.[17]

Moreover, *P. frutescens* also plays an important role and involved in various TCM-based prescriptions to enhance the therapeutic effect of individual herb in clinical applications. Various compounds from this plant have been isolated and

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identified, including flavonoids, volatile oils, fatty acids, triterpenes, phenolic compounds, and others.[18]

TRADITIONAL USE OF *P. FRUTESCENS*

The traditional uses of *P. frutescens* include two aspects: edible and medicinal. In edible, *P. frutescens* has been used as a common flavor for fish and crab cooking with the purposes of detoxification in China for more than 2000 years.[13] The tender leaf of *P. frutescens*is a favorite vegetable and with high nutritional values. In addition, *P. frutescens* is also a representative flavor in Japan and a spicy vegetable in Korea. Moreover, the *P. frutescens* seed is the important source of Perilla oil internationally because it is rich in omega-3 fatty acids.[19]

In medicinal, the herb of *P. frutescens* has long been used as a source of medicinal materials. *P. frutescens* leaf and *P. frutescens* seed are commonly used separately in Chinese medicine, as well as the *P. frutescens* stem is commonly used with the leaves. Leaves of Perilla are a major constituent of traditional Chinese herbal medicine "Banxia Houpu Decoction" and SYJN which is used to treat depression.[10] In Japan, dried leaves and stems of Perilla are used in the preparation of herbal medicine "saibokuto," which is used in the treatment of asthma and morning sickness. Perilla is also used in skin creams, soaps, and medicinal preparations because of its antioxidant and anti-allergic properties. Perilla is also a major constituent of herb Houttuyniacor data Thunb (HC), which is used in the treatment of alopecia. As a medicinal plant, Perilla is used as a treatment for cold, cough, vomiting, abdominal pain, and constipation. Volatile oil from Perilla leaves used to prepare microcapsules, and these capsules are used as a food preservative agent.[5] Perilla leaves are also used in the preparation of herbal tea for cold and fever. Juice from Perilla leaves applied to wounds and cuts because of its anti-bacterial properties 34. A chewable tablet is prepared using Perilla leaf powder and extract, a good source of Vitamin and minerals, especially calcium. It can also be used as a treatment for cold, cough, vomiting, abdominal pain, and constipation.[6,8]

In Japan and China, perilla is the main ingredient of antidepressant herbal formulas such as Suyu-Jiaonang, Banxia Houpu decoction, and Hange-kouboku-to.[20] When taken together, perilla leaf and seed deliver luteolin, omega-3 fatty acids, and rosmarinic acid, which reportedly impart significant neuroprotective and anti-depressive benefits.

NUTRIENTS AND PHYTOCHEMICALS

Fresh Perilla leaves are a good source of folic acid, β-carotene, and minerals including iron, calcium, zinc, magnesium, and phosphorus. Perilla leaves also contain carotenoids, polyphenols (including anthocyanins), alpha-tocopherols, and phytosterols.[21] The anthocyaninsshisonin, malonylshisonin, and other acylatedcyanidin-derivatives impart red pigmentation to perilla leaves. When the antioxidant levels of green/red perilla leaves were compared with green perilla leaves, the green/red cultivar was found to contain higher levels of beta-carotene, lutein, alpha-tocopherol, and beta-sitosterol.[22]

DIFFERENT TYPES OF PHYTOCHEMICALS

Phenolic Compounds

Rosmarinic acid, caffeic acid, ferulic acid, caffeic acid-3-Oglucoside, and rosmarinic acid-3-O-glucoside were identified in the leaf, stem, and seed of *P. frutescens* among them, rosmarinic acid has been demonstrated to be one of the main phenolic compounds in *P. frutescens* leaves and highly concentrated during the period from flowering to seeding.[24,25]

Flavonoids and Triterpenes

Flavonoids were mainly detected in the leaves and seeds of *P. frutescens*. The identified flavonoids included apigenin, luteolin, and (þ)-catechin, etc.[25,26] Moreover, trace triterpenes including tormentic acid, oleanolic acid, and ursolic acid were determined in *P. frutescens* by HPLC analysis.[27]

Volatile Compounds (Essential Oils)

Volatile compounds (essential oils) are mainly distributed in the leaves, flowers, and stems of *P. frutescens* plant. The contents of essential oils have been reported to be 0.821% in leaves, 0.269% in flowers, 0.022% in stems, and 0.011% in seeds.[28]

Fatty Acids

The seeds of *P. frutescens* are rich in fatty acids. The major constituents of the fatty acid comprise palmitic acid (C17:0), stearic acid (C18:0), oleic acid (C18:1), linoleic acid (C18:2), and linolenic acid (C18:3).[29,30] As a good source of polyunsaturated fatty acids, only the seed oil of *P. frutescens* contains a-linolenic acid, a considerable proportion of omega-3 fatty acids, at 54–64% while comparing to other plant oils. In addition, the omega-6 (linoleic acid) compound is usually around 14% and omega-9 (Oleic acid) is also present in *P. frutescens* oil.[16]

Policosanols

Similar to the structure of fatty acid, policosanols are a mixture of long-chain alcohols. Based on gas chromatography,

policosanolsin the *P. frutescens* seed were determined to be 67–68% octacosanol, 16–17% hexacosanol, 6–9% triacontanol of the total policosanols composition.[31] In depth, another research group demonstrated that *P. frutescens* seed was found to be abundant source of policosanols, containing 427.83 mg PCs/kg oil, ranking the highest in the investigated vegetable oils.[32]

Tocopherols and Phytosterols

Four types of tocopherols (α-, β-, γ- and δ-tocopherol) has been determined in *P. frutescens*. Phytosterols were also determined in this plant and the contents of β-sitosterol and γ-tocopherol were demonstrated to definitely correlate to the content of linolenic acid by the metabolite profiling and multivariate statistical analysis.[33]

Pharmacological Profile of *P. frutescens*

Antioxidant properties of Perilla leaf and seed extracts, as well as individual chemical constituents, have been extensively studied with limited therapeutic applications evaluated.

Anti-Inflammatory and Antiallergic Effects

In vitro modeling has been used to describe anti-inflammatory properties of perilla. A marked influx of neutrophils and formation of leukotriene B4, along with changes in thromboxane B2 levels, was demonstrated in one experiment. In another, large increases in prostaglandin levels were seen. In a contact dermatitis model, perilla induced hypersensitivity mediated by leukotrienes, prostaglandins, histamine, inflammatory cytokines, and immunoglobulin E (IgE).[34] Extracts of perilla have also been shown to suppress the overproduction of tumor necrosis factor-alpha, a cytokine important in immunologic and inflammatory reactions. Several anti-inflammatory components of perilla leaf have been identified, including luteolin and tormentic acid. *In vitro* and *in vivo* immunoenhancing effects have been described for a crude polysaccharide extract isolated from the leaves of perilla.[35]

Antimicrobial

Luteolin, extracted from perilla seed oil, showed marked antimicrobial activity against bacteria commonly associated with dental caries oral pathogenic bacteria (Oral Streptococci and strains of Porphyromonasgingivalis). Activity of perilla oil against toxins produced by Staphylococcus aureus has been demonstrated.[36]

Antioxidant Activity

Gu *et al*. (2009)[37] for the 1st time isolated four antioxidant compounds from fruit of *P. frutescens*var *acuta.* They determined the antioxidant activity of fruit of *P. frutescens* using 1, 1-diphenyl-2-picryl-hydrazyl radical (DPPH). These compounds were identified as rosmarinic acid, luteolin, apigenin, and chrysoeriol. Rosmarinic acid and luteolin showed significant DPPH_ scavenging capacities, with IC_{50} values of 8.61and 7.50 mM, respectively. Lee *et al*. (2013)[38] investigate phenolic compound profiles and antioxidant properties in the seeds of various perilla (*P. frutescens*) cultivars. The 80% methanol extract (50 lg/ml) of this species showed potent antioxidant activities against 2, 2-diphenyl-1-picrylhydrazyl (DPPH) and 2, 20- azino-bis (3-ethylbenzthiazoline-6-sulphonic acid) (ABTS) radicals. Perilla seeds were reported to have a higher antioxidant activity than chia seeds and flax seeds, measured using ABTS, DPPH, and FRAP assays. *In vitro* experiments demonstrated that red perilla exhibited stronger antioxidant activity than green perilla and that perilla upregulated superoxide dismutase and catalase.[39]

Antibacterial Effect

The antimicrobial activity of *P. frutescens* essential oils on bacteria and fungi has been widely investigated by many researchers. In addition, *P. frutescens* oil also dose-dependently decreased the production of α-toxin, enterotoxins A and B (the major staphylococcal enterotoxins), and toxic shock syndrome toxin 1 (TSST-1) in Staphylococcus aureus suggesting *P. frutescens* oil may be useful for the treatment of *S. aureus* infections when used in combination with β-lactam antibiotics.[36]

Antidepressant Effect

Perilla is an important constituent of antidepression medicines such as Hange-koubokuto, Saiboku-to, SYJN, and Banxia Houpu. In various studies, the extracts and/or purified compounds of *P. frutescens* have been demonstrated to present antidepressant-like effects. Fed with *P. frutescens* seed oil-rich diet was found to improve the depressant-like behaviors in rats through modulating fatty acid profiles and BDNF expression in the brain[38] and inhalation of perillaldehyde was found to exhibit antidepressant-like activity through the olfactory nervous function in mice[40] during the force swimming test (FST). Apigenin and 2,4,5 trimethoxycinnamic acid rosmarinic acid and it metabolites caffeic acid also showed decent antidepressant-like effects in different animal models.

Anti-asthmatic

In China, Perilla is a major constituent in various folk medicines used for the treatment of Asthma, because of the flavone luteolin present in Perilla, which gives relaxant action to the smooth muscles of the trachea.[41] Dietary treatment plays a key role in decreasing the Asthmatic allergies, serum OVA-specific immunoglobulin1 level, and total immunoglobulin

A antibodies, hence a diet with Perilla oil supplementation helps in treating Asthma. The effect of Perilla seed oil and Corn oil on Asthma patients was compared, and the results revealed that Perilla seed oil rich in á- linolenic acid (omega-3) inhibits the generation of leukotriene LB4 and LC4 more efficiently than corn oil rich in linoleic acid (omega-6).[42]

Anti-diabetic

The supplementation of Perilla seed (100, 300, and 1000 mg/kg of body weight) sprouts decreased body weight and serum triacylglyceride level; improved hyperglycemia, glucose tolerance, and insulin resistance; induced AMP-activated protein kinase activation and regulated gluconeogenesis.[43] Chlorogenic acid and rosmarinic acid are identified as Aldose reductase enzyme inhibitor in an ethyl acetate soluble fraction of methanol extract of Perilla, which reduces the diabetic complications. It was found that Perilla oil supplementation significantly reduced the microfora *blautia,* which is a gram-positive anaerobe bacterium and responsible for glucose metabolism disturbances and increased the microfora *Lactobacillus,* which considered to be a beneficial bacteria as it converts sugars to lactic acid.[28]

Anti-cancer

Perilla leaves and its seed oil showed anti-cancerous properties. In an experiment it was reported that a treatment of 12% fat diet with Perilla and safflower oil in the proportion of 1:3, 1:1, and Perilla oil alone, showed protection against

Table 1: Chinese Herbal Formulas that Contain Perilla[19]

Chinese Herbal Formula	Description	Perilla Plant Part	Indications for Use
BanxiaHou Pu Tang	*Pinellia* (*Pinellia ternata*, *Araceae*) and *Magnolia* (*Magnolia officinalis*, *Magnoliaceae*) Combination	Leaf	Nausea and vomiting associated with pregnancy, threat of miscarriage, sore throats, generalized anxiety
Shen Su Yin	Ginseng (*Panax ginseng*, *Araliaceae*) and Perilla Combination	Leaf	Common cold with lung complications
San He San	Aquilaria (*Aquilaria* spp., *Thymelaeaceae*) and Perilla Formula	Leaf	Stagnation of qi with abdominal fullness
Fen Xinqi Yin	Citrus (*Citrus aurantium*, *Rutaceae*) and Perilla Combination	Leaf	Stagnation of qi with stomach deficiency
Su ZiJiangqi Tang	Perilla Seed Combination	Seed	Asthmatic breathing with weakness in the lower body

Table 2: Phytochemicals in *Perilla frutescens* var. *crispa*[23]

Phytonutrient	Type of Compound	Plant Part	Associated Properties
Perillaldehyde	Monoterpene	Leaf and seed	Antibacterial, antifungal
Shisonin	Anthocyanin	Leaf, stem	Antioxidant; natural colorant
Malonylshisonin	Anthocyanin	Leaf	Antioxidant; natural colorant
Rosmarinic acid	Polyphenol	Stem, leaf, and seed	Antioxidant, neuroprotective, hepatoprotective
Caffeic acid	Phenylpropane	Leaf and seed	Hepatoprotective
Scutellarein	Flavonoid	Leaf	Anxiolytic
Catechin	Flavonoid	Leaf and seed	Antioxidant, anti-inflammatory
Luteolin	Flavonoid	Leaf and seed	Smooth muscle relaxant (trachea), antioxidant, neuroprotective, reduces cholesterol
Octacosanol, Hexacosanol, Triacontanol	Long-chain fatty alcohol	Seed	Reduces cholesterol, neuroprotective

MNU- induced colon tumors as compared with safflower oil alone in female F3344 rats.[15] Further synergistic effect of Perilla oil with â- carotene in the prevention of colon cancer was also proved, the supplementation of Perilla oil with olive oil and b carotene reduced colonic aberrant crypt foci induced by azoxymethane in F344 male rates. The Perilla seed main active polyphenol rosmarinic acid is reported to inhibited apoptosis in H9C2 cardiac muscle cells induced by Adriamycin (ADR) by inhibiting reactive oxygen species and the activations of c-Jun N-terminal kinase and extracellular signal-regulated kinase.[44]

Cardioprotective

Recently, the effect of Perilla seeds oil or palm oil was studied on serum cholesterol, hepatic lipid accumulation, and hepatic expression of proteins regulating lipid metabolism in high-fat diet (HFD) fed mice for 90 days.[45] Perilla seed oil when fed to the mice for the period of 8 weeks showed cardio-protective effect, as it increases the plasma concentration of docosapentaenoic acid and eicosapentaenoic acid Replacement of Soybean with Perilla oil in cooking for 10 months resulted in increased serum level of n-3 fatty acid in elderly subjects, which showed cardio-protective activity without causing any side effect In an another investigation, Apigenin isolated from Perilla seed shows the anti-obesity effect by increasing pro-opiomelanocortin (POMC) and "cocaine and amphetamine-related transcript (CART) anorexigenic neuropeptides in neuronal cells which further reduced food intake in mice.[13]

Effect on Gastrointestinal System

Gastrointestinal discomfort is caused because of ileum contraction and its risk factors are daily stress, food sensitivity and allergies, infections, and genetic preposition. The effect of Perilla seed oil on gastrointestinal motility was investigated and it was found that Perilla seed oil supplementation (5 ml/kg, 7.5 ml/kg, and 10 ml/kg) increased the motility and produced a laxative effect in constipated albino rats, constipation in rats was induced by loperamide73.[29] Similarly, the intraperitoneal administration of Perilla seed oil (1, 2, and 3 ml/kg) in wister strain albino rats provides significant protection against reflux esophagitis by inhibiting esophagitis index, reducing the volume of gastric juice, and increasing gastric pH.[46]

Neuroprotective

The active component of Perilla seed containing certain fatty acid (á- linolenic acid) showed anti-apoptosis and anti-inflammatory effects in the brain cells of mice during atherogenic diet, thus showed neuroprotective effect. More recently the safety and feasibility of Perilla seed oil as an antioxidative therapy has been proved in patients with mild-to-moderate dementia Cold pressed seed oil of Perilla showed protective effect against beta-amyloid induced neurotoxicity in PC12 rat pheochromocytoma cells and could be used as a functional food in Alzheimer disease.[47]

Managed Joint Pain and Inflammation

Fatty acids present in Perilla are helpful most especially for people who are regularly bugged by achy and swollen joints.[48] Its for the fact that those beneficial fats support the joints, keeping them from becoming painful and inflamed. Supplementing with Perilla may help those who are prone to arthritis as they can be saved from the need to regularly pop NSAIDs in their mouths, which are drugs known to carry all sorts of side effects and risks.[8]

CONCLUSION

P. frutescens has extensive traditional uses, nutritional, phytochemistry, and Pharmacological analysis Perilla seeds and its oil. It is found that leaves, seeds, and oil are used in various regions of the world such as China, Japan, Korea, and India in the preparations of spices, condiments, sauces, tea, leafy vegetables, and herbal medicines. In Japan and China, this plant is also used as a major constituent of anti-depressant and anti-asthmatic herbs such as SYJN, Banxia Houpu, Hange-kouboku-to, and Saiboku-to. Components of this plant are potential in curing diseases such as food poisoning, asthma, diabetes, cancer, and heart diseases. Medicinal investigation showed that the plant has potential antiviral, antioxidant, anti-inflammatory, anti-allergic, anti-aging, and anti-tumor activities. The major phytochemical compounds reported in this species are phenols, flavonoids, phytosterols, tocopherols, Policosanols, and fatty acids. Perilla seed oil is also a rich source of essential fatty acids. The details of some noted Chinese Herbal Formulas that Contain Perilla and Phytochemicals which are present in Perilla frutescens are illustrated in Tables 1 and 2 respectively. Despite its numerous benefits and uses, this plant is still unknown to the common population.

ETHICS APPROVAL AND CONSENT

This study has nothing to do with human and animal testing.

CONSENT FOR PUBLICATION

All the authors gave their consent to publish the current manuscript.

COMPETING INTEREST

The authors declare that they have no conflict of interest.

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