ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 15, Issue 8, 2022

Online - 2455-3891
Print - 0974-2441

Review Article

PERILLA FRUTESCENS – A REVIEW ON PHARMACOLOGICAL ACTIVITIES, EXTRACTION PROCEDURE AND APPLICATIONS

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Received: 20 April 2022, Revised and Accepted: 30 May 2022

ABSTRACT

Perilla frutescens, a member of the mint family Lamiaceae, is a medicinal, aromatic, edible, and beautiful plant. The source of perilla lies into East Asian countries (China, Japan, Korea, Taiwan, Vietnam, and India), in which it is been used as an important root of culinary and conventional medicinal uses. Perilla plant's leaves, seeds, and stems are utilized in community medicine for a variety of ailments[1]. Recently, Perilla plant is gaining extra interest due to its medicinal advantages and phytochemical contents. The fundamental phytochemical compounds found in this species are phenolic compounds (Rosmarinic acid, caffeic acid, and ferulic acid), flavonoids (luteolin and apigenin), Phytosterols, Tocopherols, Policosanols, and Fatty acid. Perilla seed oil too is a wealthy supply of vital fatty acid which includes α-linolenic acid (54–64%) and linoleic acid (14%) [2]. Perilla has shown different biologicalactions for example, antioxidant, antimicrobial, anti-allergic, antidepressant, anti-inflammatory, anticancer, and neuroprotective actions. Perilla seed oil consists of omega-3-fatty acid, and alpha-linolenic acid (ALA). In comparison to other plant oils, perilla seed oil has one of the highest percentages of omega-3 (ALA) fatty acids, at 54–64%. The omega-6 (linoleic acid) is around 14% and omega-9 (Oleic acid) too is found in perilla oil. These polyunsaturated fatty acids are very useful to human wellbeing and in prevention of various illnesses such as cardiovascular disorders, cancer, inflammatory, and rheumatoid arthritis [3].

Keywords: Perilla, Rosmarinic acid, α-Linolenic acid, Neuroprotective.

 DOI: http://dx.doi.org/10.22159/ajpcr.2022v15i8.44982. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

Perilla frutescens is a member of the family Lamiaceae/Labiatae and is usually known as perilla. The crop is annual and is local to India and China. China, India, Japan, Korea, Thailand, and other East Asian countries are major perilla cultivator nations. It is an edible plant, grown in gardens. It is fragrant with a sturdy mint-like smell. Another variety of this plant, *P. frutescens* var. *crispa* called "shiso," is extensively grown in Japan. Perilla is an annual plant found in China, Korea, Japan and the Himalayan regions of India and Nepal. Because of its growing economic relevance, western countries such as Russia, Europe, and the United States of America are also cultivating it [4]. In India, it is found in Uttarakhand, Kashmir, Himachal Pradesh, Sikkim, Manipur, Mizoram, and Meghalaya states. Perilla plant contains important phytochemicals such as Rosmarinic acid, Luteolin, Quercetin, Catechin, Caffeic acid, and Ferulic acid. Occurrence of Phytosterols, Tocopherols, Squalene, and Polyunsaturated fatty acid has also been reported from Perilla seed. It is consumed as a functional food in various parts of the world but in some parts, there is no proper cultivation of this crop, and it is still an underutilized plant despite having numerous benefits and uses. Biological analysis of Perilla plant revealed that this plant showed antimicrobial, anti-allergic, anti-cancer, anti-tumor, anti-depression, anti-viral, anti-asthmatic, and antioxidant activities [2]. The Chinese Pharmacopeia 2010 has record of the dried components of P. frutescens, including stems Perillae Caulis (PCa), leaves Perillae Folium (PFo), and ripe fruits Perillae Fructus (PFr) which are used for different therapeutic benefits. It has been used as a natural, herbal, medicinal drug to recover from different symptoms, such as depression-related disease, asthma, anxiety, tumors, coughs, allergies, intoxication, cold, fever, chills, headache, stuffy nose, and few intestinal disorders. Perilla is a vital herb that has been documented in Chinese medical texts since around 500 A.D., particularly in documents titled "Ming Yi Bie Lu." ("Renowned Physicians' Extra Records," and others in which the herb is noted as a drug named "su," which means "body comforting" and "blood circulation promotor." It is also used in salads, sushi, and soups, as well as a spice, garnish, or food colorant. The seed oil has long been used to flavor meals. Perilla also has market importance in cosmetics, being processed in skin creams, soaps, and dermatological medicinal preparations, because of its biological activities [5]. Nowadays, many investigations associated with the phytochemistry and pharmacology for *P. frutescens* has been carried out by many researchers. Various compounds from this plant are now isolated and identified, together with flavonoids, volatile oils, fatty acids, triterpenes, phenolic compounds, and others. The capabilities of *P. frutescens*-derived compounds encompass anti-allergy, anti-inflammation, antioxidant, anticancer, antibacterial, antidepressant, and so on [6].

METHODS

This review article is a compilation of information available on multiple online databases such as Google scholar, PubMed, Wikipedia, Science direct, and international science journals which include information as recent as 2019. Published information from these databases is authentic and well known, and only frequently reviewed articles are included. The pharmacological activities of perilla plant found are based on scientific experiments which included proper controls in experiments.

Description

Perilla is an annual plant growing about 25–35 in tall, with hairy square stalks. The leaves are opposite, with a broad oval shape, pointy ends, serrated (saw-toothed) margins, and long leafstalks. The leaves are green with slight touches of purple on the underside [4].

The flowers bloom along the axis (raceme) at the end of branches and the main stalk in late summer. The calyx is 3–4 mm long, consist of upper three sepals and the hairy lower two. The corolla is 4–5 mm long with its lower lip longer than the upper. There are four stamens of which two are elongated. The fruit is a schizocarp with a reticulate pattern on the outside and a diameter of 2 mm. Perilla seeds can be gentle or hard, being white, grey, brown, and darkish brown in shade and globular in shape [7]. Perilla seed's lipid content is about 38–45% [8].

The seeds are sown in summer in the month of May and harvesting period is around September–October, which varies and depending on

geographic area. It is grown in mixed cropping; the crop needs moisture absorbent soil but not necessarily very fertile soil.

Taxonomical classification [2]

Kingdom	Plantae
Subkingdom–	Tracheobionta
Division	Spermatophyta
Super division	Magnoliophyte
Class	Magnoliopsida
Subclass	Asteridae
Order	Lamiales
Family	Lamiaceae – Mint Family
Genera	Perilla

Vernacular names of perilla

Perilla has a variety of local names that vary by region. It is locally called as Zisu in China, shiso in Japan [9], Deulkkae in Korea [10], and Silam in Nepal. In India, it has several names across the states, such as Bhanjeer or Banjiraa in Uttarakhand, Hanshi or thoiding in Manipur, and chhawhchhi in Mizoram [11].

Methods of extraction

Perilla seed oil is extracted in a variety of ways, the most common of which is cold pressing. Other methods such as ultrasound-assisted aqueous enzymatic extraction (UAAEE), Soxhlet extraction at 90°C using n-hexane as solvent can be also used [12]. Comparing above three methods, Soxhlet extraction gives the best yield among the other methods. The Soxhlet extraction is carried out at 90°C for 7 h. Then, the solvent is removed at 50°C using rotary evaporator. The oil samples are then stored at 4°C.

Powdered seeds are treated with water at 300°C for 30 min on an ultrasonic machine in the ultrasound-assisted aqueous enzymatic extraction process. Then an enzyme cocktail is added (cellulase, proteinase, and pectinase) and the mixture is kept in a water bath at 50°C for 2–3 h with constant stirring. The pH is adjusted to 7. The mixture then is centrifuged at 8000 g for 20 min at room temperature. The upper layer of oil is then removed carefully and stored.

Fatty acid composition evaluation of all three extracts shows that extract obtained by using Soxhlet method and UAAEE has higher iodine values which indicate these two extracts have higher levels of fatty acids than cold pressed extraction. These extracts include palmitic acid, stearic acid which are saturated fatty acids, oleic acid which is monounsaturated fatty acid (MUFA), and linoleic acid and α-linoleic acid (ALA) which are two main polyunsaturated fatty acids (PUFA). MUFA and PUFA make up over 90% of the total fatty acids in perilla seed oil.

Perilla seed oil contains tocopherols and phenolic compounds, which are essential antioxidants in addition to fatty acids. Soxhlet extracted oil has higher levels of tocopherol and phenolic components than UAAEE. Evidence shows a co-relation among higher tocopherol content and high PUFA content.

Phytochemicals

In perilla seeds, stems, and leaves, there are currently 271 distinct phytochemical substances that have been isolated and reported. On the basis of their chemical properties, those active compounds in perilla may be categorized either as hydrophilic (phenolic acids, flavonoids, and anthocyanins) or hydrophobic (lipophilic) (volatile compounds, triterpenes, phytosterols, fatty acids, and tocopherols).

Phenolic compounds

Rosmarinic acid, caffeic acid, ferulic acid, caffeic acid-3-Oglucoside, and rosmarinic acid-3-O-glucoside were found in leaf, stem, and seed of *P. frutescens* [13]. Among them, rosmarinic acid has been verified to be one of the foremost phenolic compounds in *P. frutescens* leaves and is present in high concentrations in the period from flowering to seeding. With the aid of UV–vis spectroscopy, NMR spectroscopy and electrospray ionization mass spectrometry (ESI-MS), Gu *et al*. [14] recognized rosmarinic acid, luteolin, apigenin, and chrysoeriol from the fruit of *P. frutescens* var. acuta. Meng *et al*. [9] identified different polyphenols from various perilla varieties (var. crispa and var. frutescens) Britt., which consisted of cinnamic acid derivatives (coumaroyl tartaric acid, caffeic acid, and rosmarinic acid), flavonoids (apigenin 7-O-caffeoylglucoside, scutellarein 7-O-diglucuronide, luteolin 7-O-diglucuronide, apigenin 7-O-diglucuronide, luteolin 7-O-glucuronide, scutellarein 7-O-glucuronide), and anthocyanins (especially cis-shisonin, shisonin, malonylshisonin and cyanidin 3-O-(E)-caffeoylglucoside-5-O-

Fig. 1: Flower of *Perilla frutescens*

Fig. 2: Leaves of *Perilla frutescens*

Fig. 3: Seeds of *Perilla frutescens*

malonylglucoside). It has been indicated that the red color of leaves is due to the presence of a chief anthocyanin, malonylshisonin, 3-O-(6-O-(E)-p-coumaryl-β-d-glucopyranosyl)-5-O-(6-O-malonyl-β-d-glucopyranosyl)-cyanidin, and different associated anthocyanin compounds that acquire with inside the epidermal cells of stems and leaves of the red-leaf chemotype.

Volatile compounds

Volatile compounds (crucial oils) are principally found in the leaves, flowers and stems of *P. frutescens* plant. The contents of volatile oils have been documented to be 0.821% in leaves, 0.269% in flowers, 0.022% in stems, and 0.011% in seeds [15]. Chemically, those compounds may be in addition divided into seven chemotypes [16-18]. The reprehensive compounds of every chemotype encompass perillaldehyde and limonene for perillaldehyde type (PA); perillaketone, isoegomaketone, and egomaketone for perillaketone type (PK); for elsholtzoaketone type (EK) elsholtziaketone and naginataketone; perillene for perillene type (PL); myristicin, elemicin, and dillapiol for phenylpropanoid type (PP); citral for citral type (C); and rosefuran containing type (R). Tian *et al*. [19] recognized 119 compounds from the volatile oil of perilla from 11 different areas of plant, of which the primary compounds have been 2-acetylfuran (max. 82.17%), perillaldehyde (max. 53.41%), caryophyllene (approx. 38.34%), laurolene (up to 40.6%), 2-hexanoylfuran (up to33.03%), 2-butylamine (22.22%), α-asarone (up to 11.85%), farnesene (9.25%), α-caryophyllene (up to 9.16%), and (Z,E)-farnesene (up to 7.14%).

Terpenoids

Carotenoids are tetraterpenoids that are extensively distributed in nature and accumulate in chloroplasts. Perilla has shown better carotenoid content, even as compared to β-carotene-rich (carrots and spinach) or lutein-rich (spinach, broccoli, and lettuce) crops, where the content material of carotenoids in perilla is as much as five-fold better [20]. Moreover, triterpenes, such as tormentic acid, oleanolic acid, and ursolic acid, have been detected in perilla by use of high-performance liquid chromatography (HPLC) analysis [21]. There also are few phytosterol compounds (ampesterol, stigmasterol, β-sitosterol, β-amyrin, oxalic acid, and triacylglycerols) which have been observed in perilla seeds.

Fatty acids and lipids

Perilla oil constitutes approximately 40% of the seed weight, and seeds of perilla are a great source of fatty acid composition together with palmitic acid (C17:0), (C18:0) stearic acid, (C18:1) oleic acid, linoleic acid (C18:2), and linolenic acid (C18:3). Furthermore, the unsaturated fatty acid content of perilla seed oils is typically greater than 90%, and it contains significantly higher levels of α-linolenic acid (ω-3 fatty acid) (α–LNA) levels from 52.58% to 61.98%. Furthermore, the ω-6 (linoleic acid) about 14% and ω-9 (oleic acid) too is found in perilla oil. These polyunsaturated fatty acids are predicted to own different benefits for human health which include decreasing the cholesterol and triglyceride levels in serum, decreasing the threat of colon cancer, and stopping the immoderate growth of visceral adipose tissue [3,22,23]. Neutral lipids accounted for approximately 91.2– 93.9%, glycolipids (3.9–5.8%) and phospholipids (2–3%). Recently in United States, in association with the National Institutes of Health's Office of Dietary Supplements and the FDA's Centre for Drug Evaluation and Research, the National Institute of Standards and Technology (NIST) evolved Standard Reference Material (SRM) 3274 Botanical Oils Containing Omega-3 and Omega-6 Fatty Acids, which included Perilla (*P. frutescens*), which paved a way for this plant being evolved for nutritional supplements [24].

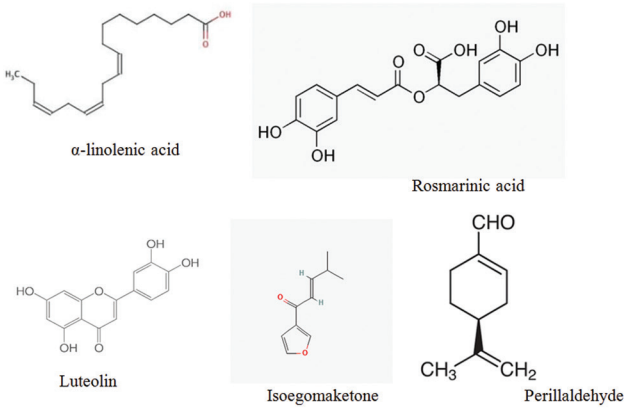
Policosanols

Policosanols are long chain alcohols similar to fatty acids. Based on gas chromatography, 67–68% of policosanols are octacosanols, 16–17% are hexacosanols, and 6–9% are triacontanols [25]. According to another study, *P. frutescens* seeds contain the highest quantity of policosanols, containing 427.83 mg PCs/kg oil out of all examined vegetable oils [26].

Nutrients

There is also good nutritional value in perilla seed, such as ash content 2.2%, crude fiber 23.28%, crude protein 5.12%, carbohydrate 18.53%, and minerals such as calcium 0.238, magnesium 0.325, potassium 0.5004, and phosphorus 0.2124 (mg/g), as well as a good fatty acid composition [27]. Researchers investigated the protein quality of perilla seeds and found that the protein had an excellent amino acid profile [23].

Active constituents of perilla



Pharmacological properties

Antioxidant property

Epidemiological, clinical, and dietary research displays that intake of "functional foods" and nutraceuticals can be related to a reduced risk of cancer, cardiovascular diseases, and metabolic disorders [29]. These advantages are regularly attributed to the increased antioxidant ability of the drug, and specifically to the content material of phenolic acids, flavonoids, and carotenoids. It has been discovered that extracts from perilla seeds and leaves showcase concentration-based antioxidant activity, primarily based on the DPPH radical assay, and 2,2′-azino-bis (3-ethylbenzothiazoline-6 sulfonic acid) (ABTS) radical cation assay. Perilla seeds reported to exhibit a higher antioxidant activity than chia seeds and flax seeds. Perilla seed has greater average tocopherol content (152.1 mg/kg) than other seed oil crops such as linseed (83.0 mg/kg), mustard (69.0 mg/kg), and sesame (100.0 mg/kg) [30]. Rosmarinic acid, luteolin, apigenin, and chrysoeriol are four antioxidant compounds isolated from Perilla extract [31]. Tian *et al*. [19] demonstrated that the antioxidant activity of perilla essential oil may vary depending on where it is grown. Drug extracts from various regions demonstrated varying degrees of scavenging ability at 10 mg/mL concentrations, with an inhibition percentage of 94.80±0.03%. The 80% methanol extract of perilla seeds demonstrated significant antioxidant activity [32]. *In vivo*, the protecting ability of Rosmarinic acid from *P. frutescens* leaf (PFL) was performed on Lipopolysaccharide (LPS)-induced liver injury of d-GalN-sensitized mice due to the scavenging or lowering activities of superoxide or peroxynitrite as opposed to inhibition of tumor necrosis factor (TNF)-α production [33].

The flavonoid luteolin, which is found in perilla seeds, appears to have substantial antioxidant action in medicines and extracts. In primary cultured cortical neurons, this chemical effectively reversed hydrogen peroxide-induced cytotoxicity. Luteolin significantly reduced the generation of reactive oxygen species (ROS) and avoided the decline in mitochondrial, catalase, and glutathione activities in ROS-stimulated primary neurons, which could help to prevent neurodegenerative disorders [31].

Anti-allergic

In the year 2002, Ueda *et al*. [34] extracted the active components luteolin, rosmarinic acid, and caffeic acid from perilla leaf extract. Only luteolin exhibited *in vivo* action among the separated chemicals.

Table 1: Analysis of fatty acid (as a percentage of total oil)

Compound	Perilla seed oil
C16:0 Palmitic	5.94±0.12
C18:0 Stearic	2.20±0.14
C20:0 Arachidic	0.20±0.01
C22:0 Behenic	0.03±0.01
C24:0 Lignoceric	0.01±0.00
C16:1 Palmitolic	0.12±0.02
C18:1 oleic acid	16.21±0.07
C18:2 linoleic acid	14.72±0.08
C18:3 linolenic acid	60.93±0.10
C20:1	0.17±0.02
C20:2	0.05±0.01
SFA	7.58±0.05
MUFA	16.57±0.11
PUFA	75.85±0.17
Ratio of n-6/n-3	0.22
Lipid %	40.0±1.6

Source – Ciftci *et al*., 2012. [28]

Perilla leaf extract (PLE) reduces inflammation, allergic reaction, and tumor necrosis factor-a production in rats when given orally. Another study looked at the anti-allergic impact of perilla aqueous extract on mice and found that perilla and rosmarinic acid are potentially promising agents for treating allergic illnesses [35]. Heo *et al*. (2011) [36] investigated the anti-allergic effects of PFAE on DNFB-induced (2,4-dinitrofluorobenzene) atopic dermatitis in C57BL/6 mice. According to the findings, PFAE (100 mg/mL) significantly inhibited DNFB-induced atopic inflammation by decreasing the expression of MMP-9 and IL-31 and increasing T-bet activity. Another study found that PFAE effectively suppressed mast cell-mediated immediate-type allergic reactions *in vivo* and *in vitro*. In addition to crude extracts, individual molecules have also been examined as a potential physiologically active drug against allergies. It was discovered that a new glycoprotein fraction derived from perilla hot water extract considerably reduced mast cell degranulation and hyaluronidase activities (IC50 = 0.42 mg/mL) in a dose-dependent manner [37]. An ethanol extract of PF, rather than an aqueous extract, suppressed allergen specific Th2 responses. Furthermore, in an ovalbumin-sensitized murine model of asthma, airway inflammation and hyperreactivity were reduced. As a result, perilla may be a promising phytotherapeutic tool for immunomodulation. Another study looked at the effects of perilla seed extracts on allergic symptoms as sneezing, nasal blockage, and itchy skin and eyes in volunteers. For 2–4 weeks, 20 volunteers were administered perilla seed extracts, and their symptoms were assessed. Sneezing (almost 40% improvement), clogged nose (over 60% improvement), and itchy eyes (50% improvement) were all substantial improvements in all 20 patients [38].

Neuroprotective effects

The active component of Perilla seed, which contains a specific fatty acid (α- linolenic acid), demonstrated anti-apoptosis, and anti-inflammatory effects in mouse brain cells during an atherogenic diet, indicating a neuroprotective effect [39]. Perilla seed oil, which is high in α- linolenic acid, may be a viable alternative to fish oil for neuroprotective and mitochondrial functions in the brain [40]. Perilla seed oil has recently been shown to be safe and effective as an antioxidative therapy in patients with mild to moderate dementia [41]. Perilla cold-pressed seed oil protected against beta-amyloid-induced neurotoxicity in PC12 rat pheochromocytoma cells and could be used as a functional food in Alzheimer's disease [42]. In a 6-month randomized, placebo-controlled trial, supplementation of Perilla seed oil with brain training improved plasma and erythrocyte plasma membrane α-linolenic acid levels; and improved cognitive function as measured by Frontal Assessment Battery (FAB) score in elderly with mild cognitive impairment [43]. A seed oil-rich diet during a forced swim test in adult male rats changed fatty acid profiles and brain-derived neurotrophic factor (BDNF) expression in the brain [44], suggesting that the oil from PF seeds may have anti-depressant properties. Furthermore, ω-3 fatty acid-rich perilla seed oil boosted rats' cognitive function by producing new hippocampal neural membrane structures and triggering particular protein production [45].

Anti-cancer

Perilla leaves and seed oil were found to have anti-cancer properties. In one study, a 12% fat diet supplemented with Perilla and safflower oil in the ratios of 1:3, 1:1, and Perilla oil alone protected female f3344 rats from MNU-induced colon tumors when compared to safflower oil alone [46]. The supplementation of Perilla oil with olive oil and β carotene reduced colonic aberrant crypt foci induced by azoxymethane in F344 male rats, demonstrating a further synergistic effect of Perilla oil and β- carotene combination in the prevention of colon cancer [47]. The active polyphenol rosmarinic acid from Perilla seed has been shown to inhibit apoptosis in H9C2 cardiac muscle cells induced by Adriamycin (ADR) by inhibiting reactive oxygen species and activating c-Jun N-terminal kinase and extracellular signal-regulated kinase [48]. Lin *et al*. [49] (2007) used a cell proliferation assay, flow cytometry, and cDNA microarrays to investigate the effects of *P. frutescens* leaf extract (PLE) on proliferation and apoptosis induction in human hepatoma HepG2 cells. The results show that *P. frutescens* extract has a growth inhibitory and apoptosis inducing effect on human hepatoma HepG2 cells. There are numerous studies that support *P. frutescens*' anti-cancer activity [3]. In another study, ethanol extract of PFL triggered apoptosis in human leukemia HL-60 cells by a combination of death receptor-mediated, mitochondrial, and endoplasmic reticulum stress-induced mechanisms, and significantly inhibited cell growth through p21-mediated G1 phase arrest [50]. Another possible anti-cancer agent was discovered to be isoegomaketone (IK), an essential oil component of PF. In human colon adenocarcinoma DLD-1 cells, IK promotes apoptosis through caspase-dependent and caspase-independent mechanisms [51].

Anti-inflammatory

Luteolin was extracted from PFL ethanol extracts and shown to reduce the production of inducible nitric oxide synthase (iNOS) in BV-2 microglial cells, resulting in favorable effects on neuro-inflammatory illnesses in a dose-dependent manner (IC50=6.9 μM) [52]. The seed oil from PF displayed an exceptional protecting effect to reflux esophagitis and this can be attributed to the antisecretory (anticholinergic and antihistaminic), antioxidant, and lipoxygenase inhibitory activities because of the presence of α-Linolenic acid (ALA) (18:3, n-3) [53]. Furthermore, RA isolated from PFL inhibited the release of the high mobility group box 1 protein (HMGB1) and down-regulated HMGB1-dependent inflammatory responses in human endothelial cells, HMGB1-mediated hyperpermeability, and leukocyte migration in mice, as well as reduced CLP-induced (cecal ligation and puncture) HMGB1 release and sepsis-related mortality. Through suppression of the HMGB1 signaling pathway, this could be a viable treatment for numerous vascular inflammatory disorders such as sepsis and septic shock [54]. Lipophilic triterpene acids derived from the ethanol extracts of red and green PFL were found to have potent anti-inflammatory activity against 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced inflammation in mice (ID50: 0.09–0.3 mg/ear) and against Epstein–Barr virus early antigen (EBV-EA) activation (91–93% inhibition at 1 × 103 mol ratio/TPA) [55]. The total flavonoid content of *P. frutescens* was found to have substantial anti-inflammatory characteristics, such as lowering vascular inflammation, permeability, reducing the synthesis of inflammatory mediators, increasing oxygen free radical scavenging, and anti-lipid role peroxidation function. Furthermore, the fatty acids in *P. frutescens* seed have anti-inflammatory effect, most likely through suppressing inflammatory lipid mediators, platelet activating factor (PAF), and leukotrienes (LTs).

Other pharmacological activities

The principal phenolic components (rosmarinic acid and caffeic acid) contained in cold-pressed Perilla frutescence seed flour (CP-PFSF) following oil extraction were examined *in vivo* and *in vitro* for their hepatoprotective effects. *In vitro*, administration of RA-rich extract reduced

H_2O_2-induced cytotoxicity, while *in vivo*, RA-rich extract dramatically reduced aspartate aminotransferase and alanine aminotransferase levels, as well as hepatocyte degeneration and neutrophilic infiltration caused by tert-butyl hydroperoxide [56].

P. frutescens upregulates endometrial receptivity by increasing the cytokine LIF (leukemia inhibitory factor). The improvement of endometrial receptivity is necessary for proper implantation of the embryo; hence, Perilla can help women with defective implantation [56].

Ileum contraction causes gastrointestinal discomfort and risk factors include everyday stress, food sensitivities and allergies, infections, and genetic predisposition. The effect of Perilla seed oil on gastrointestinal motility was studied, and it was discovered that supplementing with Perilla seed oil (5 ml/kg, 7.5 ml/kg, and 10 ml/kg) increased motility and caused a laxative effect in constipated albino rats [57].

Recently, the effect of Perilla seed oil or palm oil on blood cholesterol, hepatic lipid accumulation, and hepatic expression of proteins regulating lipid metabolism in high fat diet (HFD) fed mice was examined for 90 days. Furthermore, Perilla oil treatment significantly reduced blood cholesterol and hepatic triglyceride levels in HFD-fed mice compared to palm oil treatment, and Perilla seed oil treatment lowered lipid build-up in the thoracic aorta and liver compared to palm oil treatment [58].

In one investigation, an aqueous extract of *P. frutescens* showed strong anti-HIV-1 activity. The active ingredients in the extract samples were discovered to be water-soluble polar compounds. In co-cultures of Molt-4 cells with and without HIV-1 infection, the aqueous extract of *P. frutescens* suppressed giant cell development and expressed inhibitory activity to HIV-1 reverse transcriptase [59].

A study found out that the ethyl acetate extract of Perilla seeds, as well as polyphenols derived from ethyl acetate extract (luteolin), were beneficial against oral pathogenic microorganisms (Oral Streptococci and strains of Porphyromonas gingivalis). Perilla seed oil, when combined with Nisin, has bactericidal properties against L. monocytogenes and *S. aureus* [60].

Uses of perilla

Perilla seed oil is the third highest with respect to the % of omega-3 content which is about 58%, more than flax seed oil. It is an edible plant; leaves are eaten as such and perilla seed oil is used as cooking oil in some parts of the world. In India, the seeds are pounded and mixed with various spices to make chutney like dish [5]. To thicken and flavor the soup, perilla seed powder is added. Rice porridge made with Perilla seed and "rayu" (Pepper oil sauce), a traditional condiment made with Perilla seed oil, are popular in Korea and Japan. Perilla leaves are treated as a vegetable [61] and used as a spice to give color and flavor in many dishes. The leaves are used as garnish in cuisine or are eaten by deep frying in a batter. In Korea, perilla seeds are used in powdered form as seasoning and oil as salad dressing. Perilla leaves tea is consumed for cold and cough. In China, it is recognized as food and a medicine as well. Perilla leaves are used in traditional Chinese herbal medicine "Banxia Houpu Decoction" which is used in treatment of depression [2]. In Japan, dried stems and leaves are used in herbal medicine "saiboku-to" used in treating asthma and morning sickness. The fresh leaves are cooked with seafood to prevent food poisoning [35].

It is primarily used by indigenous communities in Northeast Asia for its edible seeds, which are a less expensive source of fat and protein. In Manipur, a salad called "Singju" is made using ground roasted seeds. As a medicinally active plant, perilla is used in treatment of many diseases such as cough, cold, abdominal pain, constipation, and vomiting microcapsules are prepared from its volatile oil and are used as food preservative agent. Perilla seeds contain about 50% of a drying oil, same as linseed oil. It forms a hard protective surface when it becomes dry. Perilla oil has been used as a drying oil in paints, varnishes, printing ink, lacquers, etc., and for protective waterproof coatings on cloth [62]. Oil cake left after cold pressing can be fed to cattle.

Its raw flower buds are eatable, and the young shoots are used to make soup [63,64]. In Japan, a volatile oil is distilled from the dried vegetation of perilla [65,66]. One of the aldehydes present in perilla is 2000 times sweet as sugar; it is used as a tobacco sweetener [62]. Perilla alcohol is used in perfume industry as a fragrance. Leaf juice of perilla is used to expel out intestinal worms in Nepal [67]. Perilla oil is used to massage twice a day for arthritis [68]. Because of its antioxidant and anti-allergic characteristics, perilla is often used in skin lotions, soaps, and medical preparations [69]. Perilla is also found in large amounts in the herb Houttuynia cordata Thunb (HC), which is used to treat alopecia [70].

Toxicity

Perilla is often avoided by cattle; however, it has been linked to cattle poisoning in the past. Plants are most poisonous when cut and dried for hay late in the summer, when seed production is at its peak. In several animal species, except pigs and dogs, perilla ketone induces pulmonary edema (fluid in the lung cavity) [71]. In Japan, 20–50% of long-term perilla workers get dermatitis on their hands because of exposure to perillaldehyde [72]. Brenner [62] reviewed the toxicity of perilla in the year 1993. Inhaling smoke from roasting perilla seeds led to occupational asthma through an IgE-mediated mechanism [73]. A single instance of anaphylaxis due to perilla seed has also been documented [74].

CONCLUSION

The present review paper compiles information about current and possible uses of perilla, its chemical composition, possible biological effects of various parts of perilla plant including seeds and seed oil. *P. frutescens* L. cultivars have a long history of use in many Asian nations and are currently used all around the world. The plant has been cultivated for a variety of purposes, including treating depression-related disease, asthma, anxiety, tumors, coughs, allergies, intoxication, cold, fever, chills, headache, stuffy nose, and various digestive ailments, as well as acting as an antioxidant. Because of genetic variations, it has been used as a decorative plant in gardens. The leaves and seeds have significant nutritional value because the leaf is high in carotenoids and the seed is high in fatty acid oils, and both have potential applications as functional dietary supplements in the food industry. The pharmacological activities resulting from its consumption presented in this review indicate that *P. frutescens* has a higher therapeutic value. The presence of various phytochemicals, active constituents and its pharmacological activities prove that this plant has the potency to be used in development of new high efficiency formulations in the coming future.

ACKNOWLEDGMENT

We the authors are pleasured to thank the Management of Oriental College of Pharmacy, Sanpada, Navi Mumbai- 400705, our Guide Dr. Mrs Vanita G. Kanase and Principal Dr. Mrs. Sudha Rathod.

AUTHORS' CONTRIBUTIONS

Megh Thosar and Shivam Dubey carried out the literature review and collected the information. Mrs. Vanita Kanse contributed to preparing the manuscript and revision. All the authors have read and approved the final manuscript.

CONFLICT OF INTEREST

There are no conflicts of interest among any of the authors of this paper.

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