A Phytopharmacological Overview on Perilla frutescens

R. K. Bachheti1*, Archana Joshi2, Tofik Ahmed1
1Department of Chemistry, College Natural and Computational Science, Haramaya University, Ethiopia.
2Department of Biology, College Natural and Computational Science, Haramaya University, Ethiopia.
*Corresponding author’s E-mail: rkbfr@rediffmail.com

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ABSTRACT

Since the dawn of civilization, human beings are dependent on higher plant species for their foods, clothing, shelter and health care needs. The plant species were the main parts of folk medicine practiced by the ancient peoples in different parts of the world. Perilla 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. The 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. However, the best diagnostic features of Perilla are the net-patterned testa of the nutlets as well as the typical minty odor of the crushed foliage.

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INTRODUCTION

Lamiaceae, also called Labiatae, the mint family of flowering plants, with 236 genera and more than 7,000 species, the largest family of the order Lamiales. It is important to humans for herbal plants useful for flavour, fragrance, or medicinal properties. Most members of the family have square stems; paired, opposite, simple leaves; and two-lipped, open-mouthed, tubular corollas (united petals), with five-lobed, bell-like calyces (united sepals).

The 40 to 50 species of the genus Lamium are known as dead nettles; they are low weedy plants that are sometimes cultivated. There are about 350 species in the genus Thymus, all Eurasian. Wild thyme (T. serpyllum), with scented leaves, is a creeping plant that is native in Europe but naturalized in eastern North America. Its foliage and flower heads resemble those of garden thyme (T. vulgaris), the source of the kitchen herb.

Perilla is cultivated as one commercial oilseed crop in other countries like Japan, Korea and northern India. Now, it has also been introduced to Europe, Russia and USA as an oilseed crop.

Botanical Description

Perilla frutescens, commonly called beefsteak plant, is an upright, bushy annual that is native from the Himalayas to Southeast Asia. It is related to coleus and basil. It has become a very popular foliage annual and salad herb plant. It grows to 1-3’ (less frequently to 4’) tall, wrinkled, serrate, broad ovate, medium green leaves (to 4” long) are sometimes tinged with purple leaves. Several analyses have reported that this characteristic odor is due to the various essential oil components which affect their nutritional and medical function and toxicity.

Edible young leaves of perilla are cooked as vegetable. Older leaves are used as a garnish or flavouring, the leaves can also be dried for later use. The juice of the leaves is applied to cuts and wounds. Seed oil is used as edible oil for centuries by local people of northern India and also used by local women of the region for massaging new born infants. The seeds are used as spice and also roasted to prepare a very delicious sauce (chutney), one of the famous traditional dishes of Uttarakhand, India.
This plant is commonly known as "Dlggae" in Korea and the leaves are widely used in sushi and herb salad and as a spice, garnish, and food colorant. Perilla seeds are a traditional source of oils produced in Korea. A perilla line from Bangladesh is a potential commercial source of rosefuran, a compound of interest in flavoring and perfumery. Asian herbalists prescribe perilla for cough and lung afflictions, influenza prevention, restless fetus, seafood poisoning, incorrect energy balance, etc. Perilla alcohol prepared from perilla aldehyde, is used in fragrances, and has legal food status in the United States and Europe.

The leaves of Perilla frutescens Britton are one of the most popular garnishes in Japan, used as an antidote for fish and crab meat allergy or as a food colorant. Leaves of the plants are used in traditional, Japanese herbal medicine (Kampo medicine). The quality of Perilla plants used for Kampo medicine is determined by the concentrations of essential oil components in leaves and the appearance such as redness of leaves attributed to anthocyanin. Recently, Kampo medicine has become popular worldwide as an alternative therapy.

Phytochemical

In one study the glycosidic constituents of two varieties of Perilla frutescens have been compared. A new phenylpropanoid glucoside named perilloside E has been isolated from the fresh leaves of the purple type plant. Besides 7-(2-O-β-D-glucuronyl-β-D-glucuronylxylo)-5,3',4'-trihydroxyflavone, scutellarin, rosmarinic acid and caffeic acid, two cyanogenic glycosides have been isolated from the dried leaves of Perilla frutescens var. acuta. One of them is prunasin and the other is (R)-2-(2-O-β-D-glucopyranosyl-β-D-glucopyranosyloxy)-phenylacetonitrile, a new isomer of amygdalin.

Perilla seeds are a good source of linolenic acid, linoleic acid, oleic acid, stearic acid, and palmitic acid. Major fatty acids of the oil are unsaturated fatty acids (USFAs) like - linolenic acid (54-64%), oleic acid (14-23%), linoleic acid (11-16%) and the saturated fatty acids (SFAs) (6.7-7.6%). The Perilla seeds are small and weight about 4 gms/1000 seeds. A new monoterpene glucoside named perilloside A has been isolated from the fresh leaves of Perilla frutescens. Its structure has been characterized on the basis of spectral and chemical evidence. Three new monoterpene glucosides have been isolated from the fresh leaves of Perilla frutescens. The structures were determined on the basis of spectral and chemical evidence. In a study Perilla seed collected from five provinces in China were analyzed to determine their fatty acid composition. Result shows that oil from seeds obtained in regions with lower average growth temperature has relatively higher percentage of unsaturated fatty acids.

Active Components of Perilla seed extract

Perilla seed extract is rich in polyphenols such as luteolin, chrysoeriol and apigenin as aglycons. Luteolin and so on are main polyphenols and main active ingredients in Perilla seed extract to shown anti-dental caries and antiperiodontal disease effect.

Another study in the year 2009 Gu, et al Fig. 2 four antioxidant compounds from fruit of Perilla frutescens were isolated. These compounds were identified as rosmarinic acid (1), luteolin (2), apigenin (3), and chrysoeriol (4) (Figure 1 by means of UV, NMR, and ESI MS).

Figure 1: Chemical structures of compounds (1–4) isolated from fruit of Perilla frutescens var. acuta; Source: Gu et al.
Lee et al.\(^3^4\) in year 2013 investigate phenolic compound in the seeds of various perilla (\textit{Perilla frutescens}) cultivars. Phenolic compounds were characterized by nuclear magnetic resonance (NMR) spectroscopy, and ultra performance liquid chromatography with photodiode array detector and electrospray ionisation/mass (UPLC-PDA-ESI/MS) analysis. Nine compounds were elucidated as caffeic acid-3-O-glucoside (1), caffeic acid (2), luteolin-7-O-glucoside (3), apigenin-7-O-glucoside (4), rosmarinic acid-3-O-glucoside (5), rosmarinic acid (6), luteolin (7), apigenin (8), and chrysoeriol (9) Fig. 2. The individual and total phenolic contents were remarkably different.

Six flavonoids (apigenin 7-O-cafeoylglucoside, scutellarein 7-O-diglucuronide, luteolin 7-O-diglucuronide, apigenin 7-O-diglucuronide, luteolin 7-O-glucuronide, and scutellarein 7-O-glucuronide) were isolated from leaves of \textit{Perilla frutescens}\(^3^5\) as shown in figure 3.

A study characterises the metabolites of \textit{Perilla frutescens} var. crispa leaf and flower for by NMR. Results showed higher metabolite content in leaves compared to flowers, showing the presence of amino acids, organic acids, saccharides and large amounts of aromatic compounds, mainly in the form of rosmarinic acid. Cultivated Perilla...
has also been confirmed to be a good bee plant for both nectar and pollen.

Antioxidant activity of fruit

Gu et al. for the first time isolated four antioxidant compounds from fruit of P. frutescens var. acuta. They determined the antioxidant activity of fruit of Perilla 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 8.61 and 7.50 mM, respectively.

Lee et al. investigate phenolic compound profiles and antioxidant properties in the seeds of various perilla (Perilla 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. Another study demonstrated that 2’,3’,5’-trihydroxy-4’,6’-dimethoxychalcone (DDC) contained in green perilla enhanced cellular resistance to oxidative damage through activation of the Nrf2-antioxidant response element (ARE) pathway. One study was conducted to investigate the profiles of phenolic phytochemicals in the leaves of Korean purple perilla using reversed-phase C18 column chromatography and HPLC with DAD-ESI/MS analysis. Changes in their contents were also the first reported through eight different harvest times during two months. In another study the of Perilla frutescens shows antioxidant activities against LDL oxidation in vitro and in vivo.

In one study, investigation on the hepatoprotective effects of P. frutescens leaves grown in different concentrations of sucrose was done. Result shows that sucrose-treated perilla leaves, which had better antioxidant activities than untreated leaves, can be used as a potential dietary source.

Antidepressant-like Effect of l-Perillaldehyde

l-Perillaldehyde (PAH) is a major component in the essential oil containing in Perillae leaf and its antidepressant activity was studies in 2011 on mice. Results suggest that the inhalation of l-Perillaldehyde shows antidepressant-like activity through the olfactory nervous function.

Anti-allergic and Anti-inflammatory Activity

Ueda et al. in year 2002 isolated luteolin, rosmarinic acid and caffeic acid as active components from the perilla leaf extract. Among the isolated compounds, only luteolin showed in vivo activity. Oral administration of the perilla leaf extract (PLE) to mice inhibits inflammation, allergic response, and tumor necrosis factor-a production. Another study was conducted to evaluate its anti-allergic effect of perilla aqueous extract on mice which shows that perilla and rosmarinic acid are potentially promising agents for the treatment of allergic diseases.

Another study observed the effects of perilla seed extracts in volunteers with allergic symptoms such as sneezing, nasal obstruction, and itchy skin and eyes. 20 participants were given perilla seed extracts for 2-4 weeks, and their change in symptoms was evaluated. Symptoms were improved in all 20 patients, with significant improvements in sneezing (almost 40%), stuffy nose (over 60%) and itchy eyes (50%). one study shows that isoeugenol isolated from perilla frutescens shows the anti-inflammatory activity.

Anti-HIV-1 activity

In one study the aqueous extract of Perilla frutescens showed potent anti-HIV-1 activity. The active components in the extract samples were found to be water-soluble polar substances. The aqueous extract of Perilla frutescens inhibited giant cell formation in co-culture of Molt-4 cells with and without HIV-1 infection and showed inhibitory activity against HIV-1 reverse transcriptase.

Antitumor activity

Lin et al. evaluated the effects of Perilla frutescens leaf extract (PLE) on proliferation and apoptosis inducing in human hepatoma HepG2 cells using a cell proliferation assay, flow cytometry, and cDNA microarrays. Result shows that growth inhibitory and apoptosis inducing effect of Perilla frutescens extract on human hepatoma HepG2 cells. There are many reports which support the anti-cancer activity of Perilla frutescens. Rosmarinic acid, frequently found as a secondary metabolite in herbs and medicinal plants, has exhibited antioxidative and anti-inflammatory activities. Rosmarinic acid inhibited Jurkat cell proliferation by altering the expression of cyclins and cyclin-dependent kinase inhibitors and induced apoptosis most likely acting through the mitochondrial pathway and possessed no anti-oxidant properties.

Antibacterial activity

In one study Perrilla seed extract was examined for its antibacterial activity against oral cariogenic streptococci and periodontopathic porphyromonas gingivalis. The ethanolic extract of defatted perilla seed weakly inhibited the growth of the oral pathogenic bacterial strain. The ethyl acetate extract exhibits strong antibacterial activity against oral streptococci and varies strain porphyromonas gingivalis. Luteolin and quercetin showed marked antibacterial activity against oral bacterial tested. This study is also support by another study in which poly phenol from Perilla seed extract show anti-dental caries and antiperiodontal disease effect.

Miscellaneous use

Perilla oil has its many other benefits. In animal experiments, perilla oil proved superior to either soyabean or safflower oil in inhibiting mammary, colon and kidney cancers. In one study, the preparation and

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trophic characterization of perilla chewable tablet were investigated. Results from nutrient analysis showed that perilla chewable tablet was rich in essential vitamins and mineral substances, which are good for human health. In another study has been conducted to study the effects of increasing levels of *Perilla frutescens* L. seed (PFS) in the diet on the performance, meat quality traits, lipid oxidation and fatty acid profile of rabbit fat and meat. These results shown that the use of a diet supplemented with PFS is effective in reducing the saturation, atherogenic and thrombogenic indexes in the rabbit tissues. In another study rosmarinic acid, a major polyphenolic component of *Perilla frutescens*, reduces lipopolysaccharide (LPS)-induced liver injury in d-galactosamine (D-galn)-sensitized mice.

**Toxicity**

Perilla is ordinarily avoided by cattle but has been implicated in cattle poisoning. Plants are most toxic if cut and dried for hay late in the summer, during seed production. Perilla ketone causes pulmonary edema (fluid in the lung cavity) in many animal species, although not in pigs or dogs. In Japan 20 to 50% of long term workers in the perilla industry develop dermatitis on their hands due to contact with perillaldehyde (http://www.hort.purdue.edu). Perilla toxicity is reviewed by Brenner (http://www.hort.purdue.edu). Perilla toxicity is reviewed by Brenner in 1993. One report available on determination of toxic perilla ketone from five *Perilla frutescens*.

**CONCLUSION**

The use of medicinal plants for the treatment of various diseases has been dated from ancient times in various parts of world. Recent trends have shown a drastic rise among people in developed nations in the use of herbal medicines for the cure of several disorders as they provide better therapeutic efficacy with lesser side effects. *Perilla frutescens* is a widely traditionally used and potent medicinal plant amongst all the thousands of medicinal plants. The pharmacological activities reported in the present review confirm that the therapeutic value of *Perilla frutescens* is much more. The presence of phytochemical constituents and pharmacological activities proved that the plant has a leading capacity for the development of new good efficacy drugs in future.

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