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BIOLOGICAL ACTIVITIES AND THERAPEUTIC POTENTIAL OF *PERILLA FRUTESCENS* (PURPLE MINT): A REVIEW

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ABSTRACT: *Perilla frutescens* (Linn.) is an annual herbal medicinal, aromatic, vitamins-rich food and ornamental plant that belongs to the mint family, Lamiaceae. It is distributed throughout India, extending to China, Japan, Korea, Taiwan, Vietnam, and other Asian countries. *Perilla frutescens* seeds, leaves and stems contain fixed oil which is useful edible oil. It is an alternative source of polyunsaturated fatty acids (linolenic acid (54%-64%), i.e., omega-3-fatty acids), phenolic compounds (rosmarinic acids, luteolin, chrysoeriol, quercetin, catechin, protocatechuic acid, and apigenin), natural antioxidants, vitamins and minerals. Recent advances prove that compounds purified from *Perilla frutescens* have been proven to be biologically active against several major diseases to treat depression-related diseases, anxiety, asthma, chest stuffiness, vomiting, coughs, colds, flu, phlegm, tumors, allergies, intoxication, fever, headache, stuffy nose, constipation, abdominal pain, and indigestion. It also acts as an analgesic, anti-abortive agent, sedative such as an antioxidant, antimicrobial, anti-allergic, antidepressant, anti-inflammatory, anticancer and neuroprotective activities. This present review deals with the update of biological activities of isolated bioactive chemical constituents of *Perilla frutescens* and explores pharmacological actions and therapeutic applications.

INTRODUCTION: *Perilla frutescens* L. belongs to the family Lamiaceae or Labiatae, also called as Shisho plant or purple mint plant. It consists 235 genera and about 7000 species. *P. frutescens* is an annual herb found in China, Korea, Japan, and the Himalayan region of India and Nepal.

In China, *Perilla* is distributed in south-eastern and southwestern parts. In India, it founds in Uttarakhand, Kashmir, Himachal Pradesh, Sikkim, Manipur, Mizoram, and Meghalaya¹. Some reviews show that it has commonly been used as traditional medicine and a functional food throughout Asian countries.

Some crude extract also shows the aromatic property of *Perilla*, and its aromatic property shows antidepressant activity. Many bioactive compounds have been isolated from *Perilla* leaves and seeds. *Perilla* plant contains a rich amount of omega-3-fatty acids such as alpha-linoleic acid (ALA),

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linolenic acids, rosmarinic acid, luteolin, chrysoeriol, quercetin, catechin, caffeic acid and ferulic acid². The presence of phytosterols, tocopherols, and polyunsaturated fatty acid (PUFA) has also been reported from *Perilla* seeds⁶. Due to the evidence of the above components *Perilla* shows anti-microbial, anti-allergic, anti-cancer, anti-tumor, anti-depression, anti-viral, antiasthmatic and anti-oxidant activities³. Life without natural products is unimaginable. It has provided mankind with oxygen, water, fire, food, clothing, shelter and medicine. Its public health impact is considerably high, especially in the form of traditional medicines and nature-based modern drugs. Traditional medicines, despite their limitations, are addressing the health needs of millions of people worldwide. It is estimated that about 65-85% of the world population uses traditional medicines for their primary health care. As there are many diseases that cannot be cured by the existing drugs and as there are increasing cases of drug resistance, there is an urgent need for drugs that are effective against non-curable pathogens. Probably, traditional medicines could provide a solution in fighting them both as a health care delivery mechanism and as a means of chemotherapeutic pool.

Amongst several factors contributing towards the potential use of herbal drugs, holistic approach to the health problems, safety, lack of adverse reactions, and side effects have been mostly found to particularly influence the use of such medicines in the developed countries. Interestingly, there are not many comprehensive scientific reviews to cover all aspects of information about *perilla*⁴. Therefore, the purpose of this study is to provide an updated summary in relation to the botanical, biological, physiochemical properties and traditional uses with new perspectives of *Perilla frutescens* and to provide an overview for future research on this plant.

Biological Properties of *Perilla*: *Perilla* plants have green-leafed and purple-leafed varieties, which are generally recognized as separate species by botanists. Its essential oils provide for a strong taste whose intensity might be compared to that of mint or fennel. It is considered rich in vitamins and has anti-inflammatory properties⁵. *Perilla* oil is obtained by cold pressing the seeds of *perilla*, which contain 35 to 45% oil. In parts of Asia,

perilla oil used as edible oil is valued more for its medicinal benefit than its flavor. *Perilla* oil is a very rich source of omega-3 fatty acid, e.g., alpha-linolenic acid. It may be an excellent alternative to fish oil supplementation. *Perilla* oil has been used for paints, varnishes, linoleum, printing ink, lacquers, and for protective waterproof coatings on cloth. The oxime of perillaldehyde (perillartin) is used as an artificial sweetener in Japan, as it is about 2,000 times sweeter than sucrose⁶. Omega fatty acids are necessary for normal immune function and clotting. Due to the high content of ALA (alpha-linolenic acid) present in *perilla* seed oil, the oil decreases serum cholesterol and triglyceride levels.

According to the University of Maryland Medical Centre, preliminary research suggests that ALA may also help to prevent and treat depression, reduce menstrual pain, reduce the risk for fatal heart attacks, prevent breast cancer, and treat autoimmune diseases such as lupus and rheumatoid arthritis. *Perilla frutescens* seeds are a good source of polyunsaturated fatty acids (PUFAs). The seeds of *Perilla* contain approximately 35-45% oil. In comparison to other plant oils, *perilla* seed oil consistently contains one of the highest proportions of omega-3 (ALA) fatty acids, at 54-64%. These polyunsaturated fatty acids are most beneficial to human health and in the prevention of different diseases like cardiovascular disorders, cancer, inflammatory, rheumatoid arthritis, etc. *Perilla* oil is also used for the reduction in asthma symptoms and seasonal allergies.

In Asia, it is also used as a traditional treatment for lung health and coughs, cold, and flu⁷. *Perilla* oil suppresses the production of chemical mediator in allergy and inflammatory reactions. These essential fatty acids have been associated with benefits in a wide range of inflammatory conditions, heart diseases, colitis/Crohn's disease, asthma, allergies, antimicrobial, anticancer etc. *Perilla* seed oil is used against Gastroesophageal reflux diseases recently as it has a rich source of omega 3 fatty acid & especially 58% of ALA, which are associated with improved cardiovascular health, i.e., included with heartburn disorder⁸. *Perilla* is also used for nausea, sunstroke, to induce sweating, and as an antispasmodic. *In-vivo* metabolism of polyunsaturated omega-3 fatty acids, it mainly

exists in the form of DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid). These two specific omega-3 fatty acids metabolites are inserted in cell membranes throughout the body, where cellular machinery converts them into substances that prevent abnormal clotting, reduce inflammation and relax blood vessels and improved ventilatory parameters⁹.

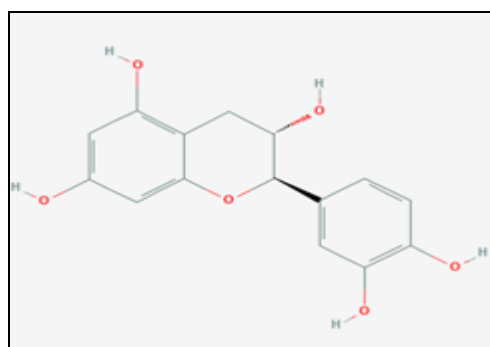
Chemical Constituents of *Perilla Frutescens*::

Perilla frutescens seeds contain 35 to 45% oil which is obtained by pressing *Perilla* seeds. The seeds can be used as high energy with rich vitamins; high protein feedstuffs as well as an excellent source of dietary linolenic acid for modifying plasma and tissue lipids. The fatty acid chemical composition of total glycolipids and its components are determined by GLC showed linolenic acid, linoleic acid, and oleic acid as the major fatty acids. Components of *Perilla* seed are Alpha-linolenic acid (ALA), unsaturated fatty acids

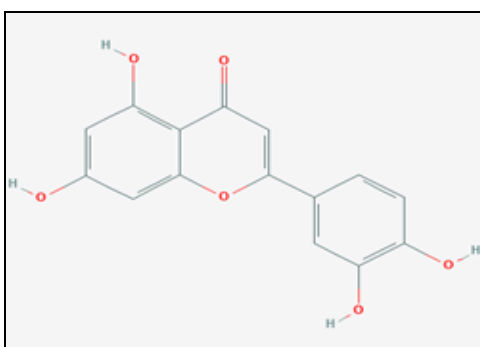
(linolenic acid (35-67%), linoleic acid (8-29%), oleic acid (12-30%), apigenin, ascorbic acid, beta carotene, caffeic acid, citralquarsetine, Rosmarinic acid, luteolin, flavonoid & anthocyanin, chrysoleriol, catechin, Rosmarinic and tormentic acids and luteolin, agents identified as having anti-inflammatory properties have also been isolated from *Perilla*¹⁰. Major photochemical of *Perilla* seed are given in **Fig. 1**. *Perilla* oil is a polyunsaturated fatty acid (PUFA). ALA is found in *perilla* oil as a triglyceride. It is a very rich source of omega-3 polyunsaturated fatty acid which contains 18 carbon atoms and 3 double bonds (ALA 18: 3n). The functional compounds of perilla include luteolin, apigenin, chrysoleriol, rosmarinic acid, caffeic acid, monoterpene alkaloids, ascorbic-acid, beta-carotene, citral, limonene, myristicin, protocatechuic acid, perillaldehyde¹¹. Major saturated and unsaturated fatty acids are given in **Table 1**.

TABLE I: MAJOR SATURATED AND UNSATURATED FATTY ACIDS

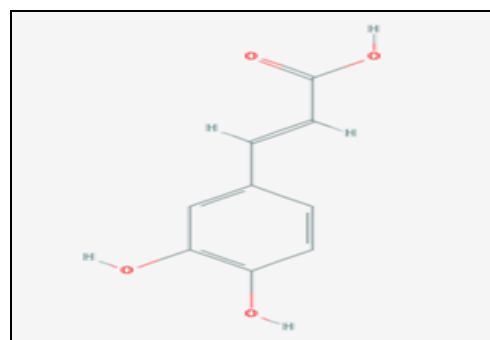
Saturated fatty acids	Molecular formula
Palmitic acid	CH ₃ (CH ₂) ₁₄ COOH
Stearic acid	CH ₃ (CH ₂) ₁₆ COOH
Unsaturated fatty acids	Molecular formula
Oleic acid	CH ₃ (CH ₂) ₇ CH=CH(CH ₂) ₇ COOH
Linoleic acid	CH ₃ (CH ₂) ₄ CH=CHCH ₂ CH=CH(CH ₂) ₇ COOH
Linolenic acid	CH ₃ CH ₂ CH=CHCH ₂ CH=CHCH ₂ CH=CH(CH ₂) ₇ COOH



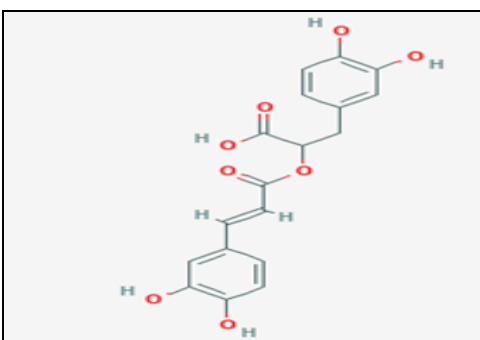
CATECHIN



LUTEOLIN



CAFFEIC ACID



ROSMARINIC ACID

FIG. 1: ACTIVE CONSTITUENT OF PERILLA

Linoleic Acid (LA): is an unsaturated n-6 fatty acid. It is a colorless liquid at room temperature. In physiological literature, it has a lipid number of 18:2 (n-6). Chemically, linoleic acid is a carboxylic acid with an 18-carbon chain and two cis double bonds; the first double bond is located at the sixth carbon from the methyl end. Linoleic acid belongs to one of the two families of essential fatty acids that humans and animals must ingest for good health, because the body requires them for various biological processes, but cannot synthesize them from other food components. Linoleic acid is used in making quick-drying oils, which are useful in oil paints and varnishes¹². Linoleic acid has become increasingly popular in the beauty products industry because of its beneficial properties on the skin. Research points to linoleic acid's anti-inflammatory, acne reductive and moisture retentive properties when applied topically on the skin. Linoleic acid can be used to show the antioxidant effect of natural phenols.

Luteolin: is a yellow crystalline compound. It is a flavonoid to be specific; it is one of the more common flavones¹³. From preliminary research, it is thought to play a role in the human body possibly as an antioxidant, free radical scavenger, a promoter of carbohydrate metabolism, or an immune system modulator. If applicable to the human condition, these characteristics may inhibit cancer mechanisms. Basic research results indicate luteolin as an anti-inflammatory agent with other potential effects on septic shock. It has been suggested for multiple sclerosis on the basis of in vitro work, is a PDE4 inhibitor and a general phosphodiesterase inhibitor, and an Interleukin 6 inhibitor.¹⁴

Rosmarinic Acid: is an ester of caffeic acid and 3, 4-dihydroxyphenyllactic acid. It is commonly found in the Lamiaceae family. Rosmarinic acid has a number of interesting biological activities, for example, astringent, ant oxidative, ant mutagen, antibacterial, and antiviral effects. The anti-inflammatory properties of rosmarinic acid are thought to be based on the inhibition of lipoxygenase and cyclooxygenase and on the interference of rosmarinic acid with the complement cascade and the inhibition of expression of inflammatory cytokines; recently, extracts of *perilla* have undergone study as a

treatment for allergic rhinitis (hay fever). *Perilla* contains high levels of the substance rosmarinic acid (also found in the herb rosemary and many other plants). Rosmarinic acid appears to have anti-inflammatory and anti-allergic actions. Animal studies hint that *perilla* might also be useful for a different type of allergy: the severe, rapid reaction known as anaphylaxis, commonly associated with shellfish, peanut and bee-sting allergies. Very weak evidence suggests that rosmarinic acid may have anti-cancer effects and might also have benefits for rheumatoid arthritis and other autoimmune diseases as well as depression¹⁵. Apigenin, one of the most common flavonoids, has been shown to possess anti-inflammatory, ant carcinogenic and free radical-scavenging properties.

Pharmacological Properties with Potential Therapeutic Values of *Perilla Frutescens*:

Utilizing the biological properties for prevention and treatment of various ailments has been evaluated by a number of researchers. Some of the clinical uses have been found to be scientifically well established. Some of the roles of extracts from various parts of these plants are as follows.

Cardiovascular Effects: Heart disease is one of the most common diseases now a day due to current lifestyle and eating habits. Certain population studies have shown that a diet high in omega-3 fatty acids, specifically EPA and DHA found in fish oil, or metabolized product of ALA (perilla oil) can help to prevent heart disease. Omega-3 fatty acid (ALA), through the body's metabolic pathway, can be converted into EPA and DHA at a rate of roughly 7–10%. The research proved that when using omega-3 rich perilla oil instead of soybean oil, the subjects increased omega-3 levels in their blood, which may lead to the prevention of coronary heart disease and decrease blood clotting¹⁶.

Anti-Inflammatory and Rheumatoid Arthritis

Actions: *Perilla* oil is rich in omega-3 fatty acids, on metabolism gives eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which can displace arachidonic acid (AA) from cell membranes. These omega-3 fatty acids are also released with AA by phospholipases and act as substrate inhibitors of conversion of AA by cyclooxygenase (COX) and pro-inflammatory

oxygenated inflammatory mediators known as eicosanoids. EPA is structurally identical to AA with the exception of its additional n-3 double bond and can be converted to eicosanoids that resemble eicosanoids. *Perilla* oils have been shown to reduce the production of the inflammatory cytokines IL-1 β and TNF- α by monocytes stimulated *in-vitro*. These cytokines are important effector molecules in inflammatory responses, and TNF α blocking agents are now used widely to treat rheumatoid disease¹⁷.

Antidepressant Actions: Some researchers reported that the bioactive constituent of *Perilla frutescens*, such as rosmarinic acid and apigenin has an anti-depression effect. The intraperitoneal administration of Rosmarinic acid (2 mg/kg.) and caffeic acid (4 mg/kg) each significantly reduced the duration of immobility in the forced swimming test in mice. PUFAs plus multivitamins and minerals supplementation in children treated learning and behavioral problem. Omega-3 exerts neuroprotective action in Parkinson's disease, exhibits a protective effect¹⁸.

Antiasthmatic Actions: *Perilla* seed oil increases lung function and it may be beneficial to asthma sufferers. A four-week placebo-controlled study published in the June 2000 edition of "International Archives of Allergy and Immunology" examined the effects of *perilla* seed oil on asthma sufferers. At the end of the four weeks, the patients taking the oil experienced a notable increase in lung capacity and enhanced air-flow capabilities. The exact mechanism of action is unknown, but researchers suspect that *perilla* seed oil benefits asthma sufferers because the ALA in it suppresses the production of leukotrienes, which is an inflammatory substance¹⁹.

Antimicrobial Activity: Ethyl acetate extract of *Perilla* seeds and active fatty acid is isolated from ethyl acetate extract (luteolin) was effective against oral pathogenic bacteria (Oral Streptococci and strains of *Porphyromonas gingivalis*)²⁰.

Immunomodulator Actions: *Perilla* seed has laxative effects arising from increased volume and consequent irritation of intestinal peristalsis from stimulation of stretch receptors. It stimulates immune function.

Fatty acid has been associated with benefits to treat heart disease, colitis, asthma, and support lungs, protecting them from colds and flu. *Perilla* oil has its own benefits. In animal experiments, *perilla* oil proved superior to soya bean oil in inhibiting mammary, colon, and kidney cancers. *Perilla* assists in the management and relief of the symptoms of allergy/atopy and associated inflammation, respiratory, and skin manifestations resulting from an increase in aspects of the immune system that drive allergies.

Perilla supports the immune function to help reduce the duration and symptoms of hay fever and allergy (Th2 dominant conditions) and enhances antimicrobial activity (Th1 immune cells). The natural antioxidants in *Perilla* also act to decrease the risk of cell damage attributable to free radicals caused by allergies and asthma²¹.

Antihistaminic Actions: *Perilla* seed flavonoids (such as luteolin) have been found to inhibit histamine release from mast cells stronger than the potent anti-histamine drug sodium cromoglycate. Inhibitory activities of additional *Perilla* constituent's rosmarinic acid and caffeic acid against histamine release were slightly more potent than sodium cromoglycate²².

Antioxidant Activity: Phenolic and steroid compounds of the leaves of *Perilla* like β -sitosterol, shisonin, kaempferol 3-O-rutinoside, rosmarinic acid, rosmarinic acid methyl ester, 4-glucopyranosyl cinnamic acid, and caffeic acid methyl ester revealed remarkable superoxide scavenging activity. Rosmarinic acid has antioxidative and anti-inflammatory activity.

The antioxidant properties of *Perilla* seed, leaf, and stalk extract investigated by DPPH, superoxide radical scavenging activity, reducing power, and metal chelating ability and reported that 50% of methanol leaf extract could be used as a new functional food^{23, 24, 25}. *Perilla* seeds were reported to have a higher antioxidant activity than chia seeds and flax seeds, measured using ABTS, DPPH, and FRAP assays. The average tocopherol content in *Perilla* seed (152.1 mg/kg) is higher than that in various other seed oil crops, such as linseed (83.0 mg/kg), mustard (69.0 mg/kg), and sesame (100.0 mg/kg).

Four antioxidant compounds were isolated from *Perilla* extract and identified as rosmarinic acid, luteolin, apigenin, and chrysoeriol^{26, 27}.

Antidiabetic Actions: A study carried out on the anti-diabetic effect of *Perilla* seed type 2 diabetes mice model. The supplementation of *Perilla* seed sprouts decreased body weight and serum triacylglyceride level; improved hyperglycemia, glucose tolerance, and insulin resistance; induced AMP-activated protein kinase (AMPK) activation and regulated gluconeogenesis^{28, 29}. In another study, chlorogenic acid and rosmarinic acid are identified as Aldose reductase enzyme inhibitors in an ethyl acetate soluble fraction of methanol extract of *Perilla*, which reduces the diabetic complications⁴⁸.

Additionally the effect of *Perilla* oil supplementation on gut microbiota was studied in diabetic KKAY mice for 12 weeks. 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^{30, 31}.

Anticancer Activity: The seeds of *perilla* have show the suppressing effect on azoxymethane induced foci of colonic aberrant crypts in rats even in small amounts, and a possible preventive agent in the early stage of colon cancer. Alpha-linolenic acid has an inhibitory action on the growth and metabolism of breast cancer. Inhibitory effects of *Perilla* and its phenolic constituents on cytokine-induced proliferation of murine cultured mesangial cells were investigated. *Perilla* extract inhibited DNA synthesis of mesangial cells stimulated by platelet-derived growth factor or tumor necrosis factor (TNF)^{32, 33}. *Perilla* leaf extract on proliferation and apoptosis-inducing in human hepatoma HepG2 cells using a cell proliferation assay, flow cytometry, and cDNA microarrays. In the PLE-treated HepG2 cells, anti-proliferative activity was observed. The extract of *Perilla* showed a marked reduction in tumorigenesis in a murine, two-stage skin carcinogenesis model. Topical application of a *perilla*-derived fraction caused significant inhibition of tumorigenesis.

Perilla oil proved superior to either soyabean or safflower oil in inhibiting mammary, colon, and kidney cancers. Similarly, ω -3 fatty acids suppress cancer formation. Oleic acid and SFAs have not been found to have any specific effects on carcinogenesis. Conjugated linoleic acids (CLA), appear to be unique among fatty acids because low levels in the diet produce significant cancer protection.

Accumulating evidence suggests that diets rich in antioxidant may help reduce the risk of some cancers. Vitamin E is an antioxidant vitamin found principally in vegetable oil products. A group of isomers of the essential fatty acid linoleic acid, CLA, appear to have both anticarcinogenic and antiatherogenic properties. The CLA reduces the incidence of tumors induced by carcinogens^{34, 35}.

Neuroprotective Activity: *Perilla* seed contains certain fatty acid (α - linolenic acid) shows anti-apoptosis and anti-inflammatory effect in the brain cells of mice during atherogenic diet, thus showed neuroprotective effect^{36, 37}. *Perilla* seed oil rich source of α - linolenic acid, offers a novel substitute to fish oil for neuroprotective and mitochondrial functions in the brain. More recently, the safety and feasibility of *Perilla* seed oil as an anti-oxidative therapy has been proved in patients with mild to moderate dementia. The cold-pressed seed oil of *Perilla* showed a protective effect against beta-amyloid-induced neurotoxicity in PC1₂ rat pheochromocytoma cells and could be used as a functional food in Alzheimer's disease^{38, 39}.

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 loperamide⁴⁰. Similarly, the intraperitoneal administration of *Perilla* seed oil (1, 2, and 3 ml/kg) in Wistar strain albino rats provides significant protection against reflux esophagitis by inhibiting esophagitis index reducing the volume of gastric juice and increasing gastric pH^{41, 42}.

Anti-abortion Activity: *Perilla frutescens* increases cytokine LIF (leukemia inhibitory factor), which regulates endometrial receptivity. Proper implantation of the embryo depends upon the enhancement of endometrial receptivity; thus, *Perilla* can be beneficial for women suffering from faulty implantation⁴³.

Other Pharmacological Activity: Hepatoprotective activity -Rosmarinic acid and caffeic acid are present in cold-pressed *Perilla frutescens* seed flour after oil extraction was studied *in-vivo* and *in-vitro*. *In-vitro* treatment with RA-rich extract reduced H₂O₂-induced cytotoxicity, and in *In-vivo*, oral administration of RA-rich extract significantly reduced the levels of aspartate aminotransferase and alanine aminotransferase, and hepatocyte degeneration and neutrophilic infiltration induced by tert-butyl hydroperoxide⁴⁴. It has proved that *Perilla* oil exerts the same properties as fish oil in the reduction of the hepatic level of pro-inflammatory cytokines, the levels of TNF and IL-5 and IL-6 found significantly lower in fish oil and *Perilla* oil supplemented to high-fat diet mice; also *Perilla* oil and fish oil supplementation showed a reduction in Gram-negative *Prevotella*, which might be considered as a cause in the development of nonalcoholic fatty liver disease⁴⁵.

CONCLUSION: It is quite evident that *Perilla* contains several important bioactive compounds, and some have already shown their therapeutic potential. Medicinal investigation showed that the plant has potential antioxidant, anti-inflammatory, anti-allergic, anti-diabetic, and anti-tumor activities. The major physicochemical compounds reported in this species are phenols, flavonoids, phytosterols, tocopherols, and fatty acid. *P. frutescens* has been reported to possess a wide variety of activities. Various phytoconstituents of *perilla* confirm its uses in alternative medicines. This plant is useful in curing many diseases and disorders. *Perilla* oil is potentially effective in reducing allergic hypersensitivity in humans and may be helpful for the treatment of asthma and improving lung function. Researches show that PUFAs of *perilla* seeds oil effectively prevent cardiac, cancer, inflammation, colitis, asthma, cancer allergy, and support lungs, protecting them from colds and flu. Its general benefits include

protecting the heart, anticoagulant, blood thinner, analgesic, anti-inflammatory, and immune-modulator. It is naturally highly unsaturated oil, containing ALA 52-64%. Hence, extensive research is required to find out the mechanisms of action and bioactivity of other compounds in crude extracts and to exploit their therapeutic potential to combat various diseases. A drug development program can be developed through extensive investigation of the bioactivity of various compounds, their mechanism of action, pharmacotherapeutics, toxicity, standardization, and clinical trials. Thus in the near future, *Perilla* may play a vital role in the modern system of medicine.

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