PERILLA

Perilla frutescens (L.) Britton

Family

Lamiaceae, the mint family.

Parts Used

Leaf.

Description

Perilla is an upright, bushy, herbaceous annual that is native to the Himalayas through to Southeast Asia. It is related to coleus *(Coleus forskohlii)* and basil *(Ocimum basilicum)*. It has become a very popular foliage and salad herb plant. It grows 30cm to one metre (less frequently to 1.2m) with wrinkled, serrate, broad ovate, medium green leaves (to 10cm long) which are sometimes tinged with purple. Perilla plants have distinctive square stems and four stamens as with most species in the Lamiaceae family. However the best diagnostic features of perilla are the net-patterned testa of the nutlets as well as the typical minty odour of the crushed foliage. Perilla has 20 synonyms including *Ocimum frutescens* L. Other common names include zisu (Chinese), beefsteak plant, wild coleus (English) and shiso (Japanese).

Among the common varieties of *Perilla frutescens* three are widely used which are generally known as var. *frutescens*, var. *crispa* and var. *acuta*.[1,2,3,4]

Traditional Use

Perilla has been used as a traditional herbal medicine for treating various diseases including depression, anxiety, tumours, cough, allergy, intoxication and some intestinal disorders. In northern India the stem of the plant is traditionally used as an analgesic and to prevent threatened

miscarriage. The leaves are said to be helpful for asthma, colds and flu, and to regulate stomach function. Seed oil was used as an 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 a spice and also roasted to prepare a chutney, one of the famous traditional dishes of Uttarakhand, India.[5]

Perilla leaves are frequently served with seafood in Asian countries because the leaves are believed to protect the digestive tract from inflammatory diseases. The juice of the leaves is applied to cuts and wounds. Asian herbalists prescribe perilla for cough and lung afflictions, influenza prevention, restless foetus, seafood poisoning and incorrect energy balance. Edible young leaves of perilla are cooked as a vegetable. Older leaves are used as a garnish or flavouring and the leaves can also be dried for later use. Perilla is commonly known as 'deulkkae' 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.[6]

Perilla leaves are one of the most common herbs, and a popular garnish in Japan and are used as an antidote for fish and crab meat allergy or as a food colorant. For example the purple form is used to dye umeboshi (pickled plums). In the summer of 2009 Pepsi Japan released a new seasonal flavoured beverage, Pepsi Shiso. Leaves of the plants are used in traditional Japanese herbal medicine, Kampo medicine. Perilla is listed in the Chinese Pharmacopoeia and has been used for centuries there in traditional Chinese medicine (TCM) as a medicinal plant for asthma, influenza, cough, chronic bronchitis and vomiting. According to Chinese classics it was used to treat fish and crab poisoning symptoms. Perilla is included in Kampo medicines such as Hangekobokuto (Chinese name: Banxia Houpu), Kososan (Chinese name: Xiang-Su-San) and Saibokuto (Chinese name: Chai-Pu-Tang) for the treatment of cough, bronchial asthma and other Type I hypersensitivity reactions and stress symptoms. Perilla is also found in the Chinese Suyu-Jiaonang which is used to treat mental conditions. Perilla alcohol, prepared from perilla aldehyde, is used in fragrances and has legal food status in the United States and Europe.[7,8,9,10,11]

According to TCM the property of perilla is warm and the flavour is pungent. The meridian tropism is lung and spleen meridians. The actions are to release the exterior and dissipate cold, move qi and harmonise the stomach. Indications are the common cold caused by wind-cold, cough, vomiting and nausea, morning sickness and fishery product poisoning.[12]

Constituents

A variety of constituents have been isolated from perilla including monoterpenes, triterpenes, flavonoids, phenylpropanoids and phenolic compounds. Perilla contains several essential oils including (–)-perillaldehyde, which contributes to the aroma, (–)-perillylalcohol, (+)-limonene, alpha-pinene and trans-shisool. The red or purple form contains the purple pigments shisonin and cyanin. Several compounds such as rosmarinic acid, scutellarin, luteolin, apigenin, adenine, arginine, ferulic acid, (+)-catechin, caffeic acid, chrysoeriol and isoegomaketone have been identified. A new phenylpropanoid glucoside named perilloside E has been isolated from the fresh leaves of the purple type plant. A new monoterpene glucoside named perilloside A has been isolated from the fresh leaves.[13,14,15,16]

Actions

Antiallergic, anti-inflammatory, anticancer, antioxidant, hepatoprotective, antidepressant, antidiabetic.

Pharmacological Activity

There are very few studies of perilla on humans but there are many *in vivo* and *in vitro* investigations of its biological properties. Whereas dietary effects of perilla leaf remain unknown, perilla oil is considered a high quality oil in nutritional sciences concerned with lifestyle-related diseases. According to numerous *in vivo* and *in vitro* studies perilla and its constituents have anticancer, antiallergy and antidepressant properties, and the biological activities of perilla and its constituents are increasingly well characterised. Although there are several *in vitro* studies demonstrating anticancer properties, studies conducted *in vivo* are very few.

Hence, further research is required to examine the effects of using perilla as a food and medicine in daily life.[17]

Antiallergic Activity

The results of a 2015 clinical study showed a clear efficacy for the food supplement Lertal (containing perilla, quercetin and Vitamin D3 formulated in a double layer fast-slow release tablet) in reducing nasal and/or eye symptoms. This activity was objectively confirmed by the reduction in the consumption of antiallergic drugs used to relieve symptoms. Seasonal allergic rhinitis is characterised by runny nose, congestion, sneezing and sinus pressure. Twenty-three subjects enrolled in the open clinical study had at least one year history of allergic rhinitis and positive skin prick test or radioallergosorbent test to *Parietaria officinalis* pollen. At baseline the subjects had symptoms of nasal and/or ocular seasonal allergic rhinitis. The activity of the food supplement was evaluated using the Total Symptoms Score at first (baseline) and second (final) visit, after one month of supplementation. The consumption of antiallergic drugs was also evaluated. The comparison of the scores obtained in the two visits (baseline and final) showed a highly significant reduction of the overall symptoms: approximately 70% for symptom scores and 73% in use of antiallergic drugs. Sneezing, rhinorrhea, nasal obstruction, ocular itching, lacrimation and congestion of the conjunctiva all showed a highly significant reduction.[18]

Perilla can be an effective intervention for mild seasonal allergic rhinoconjunctivitis (SAR) a 21-day, randomised, double-blind, age-matched, placebo-controlled parallel group study found. The results show that the mechanism is at least partly through inhibition of polymorphonuclear leukocytes (PMNL) infiltration into the nostrils. Perilla enriched with rosmarinic acid, a polyphenolic phytochemical, suppresses allergic immunoglobulin responses and inflammation caused by PMNL in mice. However few placebo-controlled clinical trials have examined the efficacy and safety of polyphenolic phytochemicals for treatment of allergic inflammatory diseases in humans. The study determined whether oral supplementation with rosmarinic acid is an effective intervention for patients with SAR. Patients with mild SAR were treated daily with perilla enriched with rosmarinic acid (200mg [n=10] or 50mg [n=9]) or placebo (n=10). Patients recorded symptoms daily in a diary. As compared with placebo supplementation, supplementation with perilla enriched with rosmarinic acid resulted in a significant increase in responder rates for itchy nose, watery eyes, itchy eyes and total symptoms. Active treatment significantly decreased the numbers of neutrophils and eosinophils in nasal lavage fluids.[19]

Ethanol extracts, rather than water extracts, of perilla leaves could significantly suppress Th2 responses and airway inflammation in the allergic murine model of asthma. A 2015 study investigated the effects of different fractions of perilla leaves extracted by water or ethanol on asthma. The results demonstrated that perilla, especially the ethanol extracts, decrease Th2 cytokines production, serum IgE level, cells infiltration, allergic mediator secretions and airway hyperresponsiveness. According to the dose translation from animal to human it corresponds to 1.5 to 6g (5 to 20 pieces) of fresh perilla leaves daily for a 60kg adult and 0.7 to 3g (2.5 to 10 pieces) for a 20kg child, respectively. In conclusion, ethanol extracts of perilla could downregulate Th2 activities to secrete less IL-5 and IL-13 and thus lower serum IgE level when counting allergen challenge. The cell infiltration, particularly eosinophils, and proinflammatory mediators such as histamine and eotaxin in bronchoalveolar lavage fluid were significantly suppressed. As a result, airway hyperresponsiveness is alleviated by perilla suggesting it is a potential herbal medicine for immunomodulation.[20]

The findings of a 2013 study suggest that perilla should be beneficial in alleviating both allergic and inflammatory responses on airway epithelium in response to aeroallergens. The study aimed to investigate the effects of perilla on expression of pro-allergic and pro-inflammatory cytokines in airway epithelial cells exposed to mite major allergen Der p2 (DP2) and the underlying mechanisms. Investigations revealed that perilla dose-dependently diminished mRNA expression of pro-allergic cytokine IL-4, IL-5, IL-13 and GM-CSF, as well as pro-inflammatory cytokine IL-6, IL-8 and MCP-1 in test cells. These findings

revealed that perilla significantly diminished both mRNA expression and protein levels of pro-allergic and pro-inflammatory cytokines inf response to DP2 through inhibition of P38/JNK and NK-κB activation.[21]

Antiallergic effects of perilla decoctions have been demonstrated in mice. In these studies perilla decoctions partly controlled immunoglobulin A (IgA) nephropathy (the most common form of chronic kidney inflammation) and type I hypersensitivity. Perilla decoction significantly suppressed the animal model allergic reaction and the inhibition percentage at the dose of 500mg/kg was 43%. In addition perilla decoctions demonstrated suppressive effects on mesangioproliferative glomerulonephritis in rats. In mice with IgA renal damage perilla decoctions alleviated IgA nephropathy through adjustments of the mucous membrane. The total number of glomerular cells, proliferating cell nuclear antigen positive cells and macrophage/monocyte antigen-positive cells in the glomerulus was significantly decreased in perilla-treated rats. A significantly lower level of proliferation was induced by the serum of the perilla-treated rats than by that of the controls. These results suggest that perilla decoction suppresses the proliferation of mesangial cells *in vivo* by an inhibition of the glomerular infiltration of macrophage/monocytes and of the production of circulating growth factors. The study shows that the oral administration of a decoction of perilla leaves results in antiproliferative effects on glomerular cells in rat mesangioproliferative glomerulonephritis. Taken together with the previous *in vitro* study showing that a perilla decoction can inhibit the proliferation of cultured murine mesangial cells it is suggested that perilla is a promising agent for preventing mesangioproliferative glomerulonephritis.[22,23,24,25]

A 2011 *in vivo* and *in vitro* study indicates that perilla and rosmarinic acid ameliorate allergic inflammatory reactions such as allergic rhinitis and allergic rhinoconjunctivitis. Blood levels of IgE and histamine were reduced by perilla and rosmarinic acid administration.[26]

Oral administration of perilla *in vivo* inhibits inflammation, allergic response and tumor necrosis factor-alpha production. Researchers also found that perilla suppressed the tumour necrosis factor-alpha (TNF-alpha) production *in vitro*. They searched the active constituents from perilla and isolated luteolin, rosmarinic acid and caffeic acid as active components. Among the isolated compounds, only luteolin showed *in vivo* activity. These results suggest that luteolin is a genuinely active constituent which is accountable for the oral effects of perilla.[27]

In vivo data suggests that perilla down-regulates Th2-type cytokine production and prevents the Th1/Th2 balance from polarising toward Th2-type immune responses. In this study the effect of perilla on antigen-specific antibody and on cytokine production was examined.[28]

In vivo and *in vitro* results indicate that perilla inhibits mast cell-mediated immediate-type allergic reactions. South Korean researchers investigated the effect of aqueous extract of perilla on the mast cell-mediated immediate-type allergic reactions. Perilla dose-dependently inhibited systemic allergic reaction. It also significantly inhibited local allergic reaction. The plasma histamine levels were reduced in a dose-dependent manner. The level of cyclic adenosine monophosphate (AMP) transiently and significantly increased about 4-fold compared with that of basal cells. Perilla had a significant inhibitory effect on antiDNP IgE-induced tumour necrosis factor-alpha production.[29]

Perilla may inhibit the symptoms of atopic dermatitis a 2016 *in vivo* study has shown. The assessment scores of the skin lesions and total serum IgE levels of perilla-treated mice were significantly lower than the control group. Hyperplasia of the epidermal and dermal layers and infiltration of inflammatory cells (cell infiltration in corium tissues) were suppressed by perilla.[30]

Perilla has potential for mitigation of induced atopic dermatitis-like symptoms induced *in vivo*. The results of the 2011 study revealed that perilla exhibited strong antiatopic dermatitis activity, interceding drastic reduction of the immune response, and resulting in decreased eosinophil levels in adjacent skin tissues.[31]

Oral administration of perilla-derived rosmarinic acid was an effective intervention in an *in vivo* study for allergic asthma, possibly through the amelioration of increases in cytokines, chemokines, and allergen-specific antibody.[32]

Anti-inflammatory, Antitumour and Antioxidant Activity

The demonstrated effects of perilla to improve gastrointestinal complaints in a 2014 clinical study offer very promising results. Especially taking into consideration the challenging set up of a nutritional human study with healthy subjects in the area of digestive health which is known for high placebo effects. Gastrointestinal discomfort (GI), e.g. bloating or rumbling, is a common symptom in otherwise healthy adults. Approximately 20% of the population, particularly women, suffer from gastrointestinal discomfort and this affects quality of life. Recent studies discovered a link between the body and mind, called the gut-brain axis. Psychosocial factors, such as e.g. daily stress may cause altered gut physiology leading to ileum contractions and consequently gastrointestinal symptoms. *In vitro* and ex vivo studies clearly showed that perilla combines prokinetic (helps control acid reflux), antispasmodic and anti-inflammatory effects. The aim of the intervention was to investigate the effects of perilla on GI discomfort in healthy subjects with gastrointestinal discomfort and reduced bowel movements in comparison to a placebo product. The pilot study was performed according to a double-blind, randomised, placebo-controlled parallel design. Fifty healthy subjects with gastrointestinal discomfort and reduced bowel movements, 30 to 70 years, documented their GI symptoms, stool frequency and consistency daily during a two week run-in phase and a four week intervention phase with perilla or placebo. GI symptoms were assessed on a 5-point scale daily and average scores over 14 day intervals were calculated. All GI symptoms were significantly improved over time by perilla during the intervention phase, whereas in the placebo group only abdominal discomfort was significantly improved. In the subgroup of women, results were strengthened and a subscore out of bloating and abdominal discomfort was significantly improved against placebo.[33]

In 2016 an *in vitro* study found perilla exerts anticancer activities against colon and lung cancers. Further studies are needed in order to determine whether similar effects are reproduced *in vivo*. The aim of the study was to investigate the inhibitory effects of ethanol extract of perilla leaf against important characteristics of cancer cells, including unrestricted growth, resisted apoptosis and activated metastasis, using human cancer cells. Treatment of cell lines with perilla resulted in dose-dependent inhibition of growth by 52 to 92% and completely abolished the colony formation in soft agar. It also resulted in a change of the nucleus morphology and significantly increased sub-G1 cell population in both cells, indicating its apoptosis-inducing activity. Perilla inhibited growth, anchorage-independent colony formation, and adhesion in both human colon and lung cancer cells as well as migration in human lung cancer cells, indicating the anticancer activities of perilla *in vitro*. Whether or not similar inhibitory effects of perilla can be reproduced in relevant animal models and finally humans still needs to be determined. More studies are needed in order to better understand the detailed mechanism of the inhibitory action of perilla against colon and lung cancers.[34]

Perilla might be useful in the treatment and prevention of induced colitis concluded a 2015 *in vivo* study. The researchers said the individual compounds found in perilla may additionally, or synergistically, work to regulate colitis due to not only suppression of proinflammatory cytokines but also promotion of anti-inflammatory cytokines at certain stages of disease which suggests the efficacy of perilla for prevention and in the mucosal wound-healing stage in inflammatory bowel disease. The serum cytokine profile demonstrated that TNF-α, IL-17A, and IL-10 were significantly lower in the perilla group than in the control group. In the therapeutic protocol, mice in the perilla group showed significantly higher body weight and lower histological colitis scores compared with mice in the control group on day 15. The serum cytokine profile demonstrated that TGF-β was significantly higher in the perilla group than in the control group. *In vitro* analyses of biologically active ingredients, such as luteolin, apigenin, and rosmarinic acid, in perilla were performed. Luteolin suppressed production of proinflammatory cytokines, such as TNF-α, IL-1β, IL-6, and IL-17A. Apigenin also suppressed secretion of IL-17A and increased the anti-inflammatory cytokine IL-10. Rosmarinic acid increased the regulatory T cell population.[35]

A 2015 study indicated that perilla effectively regulated the inflammatory activities of human neutrophils. The anti-inflammatory effects of perilla

on activated human neutrophils were mediated through two independent signalling pathways involving Src family kinases (Src and Lyn (Tyr396)) and mobilisation of intracellular Ca(2+). Perilla inhibited superoxide anion production, elastase release, reactive oxygen species formation, CD11b expression and cell migration in activated human neutrophils in dose-dependent manners.[36]

A 2014 study demonstrated for the first time that perilla possess inhibitory activity against lung inflammation. And the constituents such as elemicin, myristicin and rosmarinic acid showed similar activity, suggesting their contribution to the *in vivo* activity of perilla. In the preliminary screening procedure, the 70% ethanol extract of perilla was found to clearly inhibit tumour necrosis factor-α (TNF-α) production in the lung at 100mg/kg, after intranasal lipopolysaccharide treatment of mice. Since TNF-α is one of the most prominent inflammatory cytokines to produce an inflammatory response in the lung, the inhibitory effect on TNF-α generation in the bronchoalveolar lavage fluid strongly supports the scientific rationale of the clinical use of perilla in lung inflammatory disorders in traditional medicine.[37]

South Korean scientists examined the possibility that cancer cell growth is reduced through treatment with perilla using human leukaemia cells and then investigated the mechanism of the growth inhibition. They found that perilla treatment suppressed cell viability in a dose-dependent manner. It was concluded that perilla induced apoptosis through the combinations of mitochondrial, death receptor-mediated, and endoplasmic reticulum pathways, and suppressed the cell proliferation via p21-mediated G1 phase arrest in human leukaemia cells.[38]

Perilla significantly decreases the mRNA expression and protein production of pro-inflammatory mediators a 2014 study found, It does this via the inhibition of extracellular-signal-regulated kinase (ERK)1/2, c-Jun N-terminal kinase (JNK), p38, as well as NF-κB signalling *in vitro*. This study aimed to investigate the anti-inflammatory effects of perilla and the underlying mechanisms. Perilla slightly affects cell viability but alleviates induced activation of cells *in vitro* and it significantly reduced the induced mRNA expression of the interleukin (IL)-6, IL-8, tumour necrosis factor-α (TNF-α), cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) genes in a dose-dependent manner. In addition perilla reduced nitric oxide and prostaglandin E2 secretion.[39]

Perilla has traditionally been used to treat tumours but the antitumourigenesis mechanism is unclear. In a recent study perilla extract increased restraint and induced cell death in human hepatoma HepG2 cells. Researchers evaluated the effects of perilla on proliferation and apoptosis inducing in human hepatoma HepG2 cells. Gene expression and apoptosis were also assessed in HepG2 cells treated with a major constituent of perilla, rosmarinic acid. In the perilla treated HepG2 cells, antiproliferative activity was observed. Compared with perilla, rosmarinic acid was less effective in increasing the expression of apoptosis-related genes and apoptosis inducing in HepG2 cells. Thus, additional perilla constituents may influence apoptosis in HepG2 cells. The results of the study suggest that perilla should be further investigated as a promising treatment for hepatocellular carcinoma. Flow cytometry and DNA microarray experiments in these studies revealed significant apoptosis and time-dependent regulation of apoptotic genes, respectively, in cells treated with perilla leaf extracts. However the experiment was conducted *in vitro* with a high dose of the perilla extract therefore it is unclear if perilla extract is effective *in vivo*.[40,41]

Perilla showed marked reduction of tumourigenesis in an *in vivo* study. Topical application of perilla resulted in significant inhibition of tumourigenesis. The efficacy of each fraction was correlated with rosmarinic acid and luteolin concentration. Topical application of perilla that contained 68% rosmarinic acid or an equivalent amount of commercially available rosmarinic acid showed nearly identical anti-inflammatory activity. Application of luteolin had less anti-inflammatory activity. The researchers concluded that part of the anticarcinogenic effects of perilla is due to rosmarinic acid via two independent mechanisms: inhibition of the inflammatory response and scavenging of reactive oxygen radicals.[42]

Various cultivars of perilla (var. crispa and var. frutescens) were investigated for their antioxidant activity and their polyphenolic compounds compared. Among them, 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, and scutellarein 7-O-glucuronide) and anthocyanins (mainly cis-shisonin, shisonin, malonylshisonin and cyanidin 3-O-(E)-caffeoylglucoside-5-O-malonylglucoside) were quantified. The mean amount of total phenolics of the water extracts confirmed the high antioxidant activity of these leaf water extracts.[43]

Polyphenols present in perilla have various structural varieties with a large diversity of biological activities. It has a direct influence on the quality of the perilla plant and its potential functions. Some of these products have been studied and proven to be an effective source of phenolic antioxidants. The aqueous extract contains phenolic compounds such as phenolic acids, cinnamic acid derivatives, flavonoids, and lignans. Gallic acid, hydroxytyrosol (3,4-DHPEA), cinnamic acid derivatives (coumaroyl tartaric acid, caffeic acid and rosmarinic acid), flavonoids, scutellarein 7-O-diglucuronide, luteolin 7-O-diglucuronide, apigenin 7-O-diglucuronide, luteolin 7-O-glucuronide, and scutellarein 7-O-glucuronide), and anthocyanins (mainly cis-shisonin, shisonin, malonylshisonin and cyanidin 3-O-(E)-caffeoylglucoside-5-O-malonylglucoside) are present.[44]

Hepatoprotective Activity

Perilla has the potential to protect the liver against hepatic damage an *in vivo* study found. The object of the study was to evaluate the protective effects of an aqueous extract of perilla leaves on the tert-butyl hydroperoxide (t-BHP)-induced oxidative injury observed in rat livers. The treatment of the hepatocytes with the perilla leaf extract significantly reversed the t-BHP-induced cell cytotoxicity and lipid peroxidation. In addition, perilla exhibited ferric-reducing antioxidant power and 2,2-diphenyl-1-picrylhydrazyl free radical scavenging activities. The study showed that the pretreatment with perilla (1000 or 3000mg/kg) for five days before a single dose of t-BHP significantly lowered the serum levels of aspartate aminotransferase and alanine aminotransferase, reduced the indicators of oxidative stress in the liver, such as the glutathione disulfide content and lipid peroxidation level in a dose-dependent manner, and remarkably increased the activity of hepatic gamma-glutamylcysteine synthetase.[45]

Neuroprotective Activity

A 2016 study suggests that perilla, and its major compound rosmarinic acid, have beneficial effects on cognitive improvement and may help prevent Alzheimer's disease induced by amyloid-β (Aβ). The accumulation of Aβ in the brain is a hallmark of Alzheimer's disease and plays a key role in cognitive dysfunction. Perilla and rosmarinic acid have shown antioxidant and anti-inflammatory activities. The *in vivo* study investigated whether administration of perilla and rosmarinic acid contributes to cognitive improvement in a mouse model. The study demonstrated that perilla and rosmarinic acid administration significantly enhanced cognition function and object discrimination. Perilla and rosmarinic acid significantly decreased the levels of nitric oxide (NO) and malondialdehyde (MDA) in the brain, kidney and liver. In particular, perilla markedly attenuated oxidative stress by inhibiting production of NO and MDA in the mouse brain.[46]

In another 2016 study the same researchers found perilla could prevent the progression of neurodegenerative diseases through attenuation of neuronal oxidative stress. Neurodegenerative diseases are often associated with oxidative damage in neuronal cells. The *in vitro* study was conducted to investigate the neuro-protective effect of methanolic extract of perilla and rosmarinic acid under oxidative stress. The perilla and rosmarinic acid prevented oxidative stress by increasing cell viability and inhibiting cellular lipid peroxidation. Perilla and rosmarinic acid also reduced H2O2-induced expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) at the transcriptional level. Moreover, iNOS and COX-2 protein expression was down-regulated.[47]

One of the critical features of Alzheimer's disease is cognitive dysfunction, which is, in part, due to decreases in acetylcholine (ACh). The ethanol extract of perilla was selected for isolating the acetylcholinesterase (AChE) inhibitor based on preliminary screening. *In vivo* behavioural tests were performed to examine the effects of perilla on trimethyltin chloride-induced impairment of learning and memory in mice. The AChE inhibitor was identified as rosmarinic acid.[48]

Antidepressant Activity

Perilla may be an antidepressive substance. The aim of a recent study was to identify the bioactive component in perilla that possesses antidepressive activity. The results suggest that rosmarinic acid may be the main component involved in the antidepressive effect.[49]

Antidiabetic Activity

In 2013 researchers investigated the inhibitory effect of perilla on aldose reductase (AR) to evaluate its potential in treating diabetic complications. The goal of this study was to identify the active constituents of perilla by enzyme assay-guided HPLC microfractionation and to improve the understanding of how the active compound of perilla acts against retinoic acid receptor. The ethyl acetate soluble fraction of methanol extracts of perilla inhibits aldose reductase AR, the key enzyme in the polyol pathway (a two-step metabolic pathway in which glucose is reduced to sorbitol, which is then converted to fructose). The main AR inhibiting compounds were tentatively identified as chlorogenic acid and rosmarinic acid.[50]

Female Reproductive Activity

Perilla may be used for improving endometrial receptivity, and therefore successful pregnancy rates, following the results of a 2016 *in vitro* study. The leaves and stems of perilla have been used to prevent threatened abortion in traditional medicine in East Asian countries. Because reduced receptivity of endometrium is a cause of abortion researchers analysed the action of perilla on the endometrial receptivity. Perilla increased the level of leukaemia inhibitory factor (LIF), a major cytokine regulating endometrial receptivity, and LIF receptor in human endometrial Ishikawa cells. The results suggest that perilla enhanced the adhesion between Ishikawa cells and JAr cells by increasing the expression of integrin β3 and β5 via an LIF-dependent pathway.[51]

Immunostimulant Activity

In a non-specific cell-mediated immunity study of Perilla it was found that the natural substances in perilla increase the activity of phagocytes *in vivo* and *in vitro* and stimulate phagocytosis.[52]

A polysaccharide from perilla may be an immunopotentiator after demonstrating phagocytic ability both *in vitro* and *in vivo*.[53]

Antibacterial Activity

A 2011 study evaluated the ideal condition for determining the antibacterial activity of perilla against *Staphylococcus aureus* using evolutionary operation factorial design technique. The ideal antibacterial activity was obtained at 75°C extraction temperature, 24 hour extraction time and 45% ethanol concentration. The scanning electron microscopic study showed a potential detrimental effect of the *Perilla frutescens* var. *acuta* leaf extract on the morphology of *Staphylococcus aureus*. These morphological features in bacterial cells might be due to the lysis of outer membrane and the transformation by weak peptidoglycan followed by the loss of cellular electron dense material on the surface of the treated cells, resulting in the release of inner cell materials. These results support the possible use of perilla extracts in the food industry, where pathogenic bacteria causes severe destruction by hampering the quality of food and consumer demand. Perilla might be a suitable candidate to serve as a natural preservative to control food-borne pathogens.[54]

Antiobesity Activity

A South Korean study evaluated the antiobesity effect of perilla in animal models of high fat diet-induced obesity. The perilla supplementation significantly decreased body weight gain, food efficiency ratio and relative liver and epididymal fat mass compared with those of the high fat diet group. Also, triglyceride, total cholesterol and LDL levels in the plasma were significantly reduced by perilla supplementation compared with the high fat diet group. These results suggest that the perilla supplement suppressed body weight gain and improved the blood lipid profiling, in part by down-regulating adipogenic transcription factor and other specific target genes.[55]

Cardiovascular Activity

Perilla could be useful for the prevention of vascular diseases such as arteriosclerosis. In cultured murine vascular smooth muscle cells perilla water extract has been shown to induce nitric oxide production.[56]

Indications

- Hay fever (allergic rhinitis), asthma, bronchitis, sinusitis, allergies associated with excessive mucous
- Eczema, dermatitis

Energetics

Warming, pungent.

Use in Pregnancy

Traditionally it has been used for morning sickness and to prevent threatened miscarriage. Limited information is available to determine whether perilla is safe, or unsafe, during pregnancy therefore it should be used under supervision.[57,58,59]

Contraindications

None known.

Drug Interactions

Caution with antihistamines.

Administration and Dosage

Liquid Extract:	1:2
Alcohol:	35%
Weekly Dosage:[60]	30 to 70mL

References

1. Jin CH, So YK, Han SN, Kim JB. Isoegomaketone Upregulates Heme Oxygenase-1 in RAW264.7 Cells via ROS/p38 MAPK/ Nrf2 Pathway. Biomol Ther (Seoul). 2016 Sep 1;24(5):510-6. doi: 10.4062/biomolther.2015.194.
2. Bachheti RK, Joshi A, Ahmed T. A Phytopharmacological Overview on Perilla frutescens. Int. J. Pharm. Sci. Rev. Res. 2014 Jun;26(2):55-61.
3. The Plant List. [Internet]. Kew and Missouri: Royal Botanic Gardens, Kew and Missouri Botanical Garden; c2013 Version 1.1 [accessed 2016 Oct 11] Available from http://www.theplantlist.org/tpl1.1/record/kew-150299
4. He YK, Yao YY, Chang YN. Characterization of Anthocyanins in Perilla frutescens var. acuta Extract by Advanced UPLC-ESI-IT-TOF-MSn Method and Their Anticancer Bioactivity. Molecules. 2015 May 19;20(5):9155-69. doi: 10.3390/molecules20059155.
5. Bachheti RK, Joshi A, Ahmed T. A Phytopharmacological Overview on Perilla frutescens. Int. J. Pharm. Sci. Rev. Res. 2014 Jun;26(2):55-61.
6. Bachheti RK, Joshi A, Ahmed T. A Phytopharmacological Overview on Perilla frutescens. Int. J. Pharm. Sci. Rev. Res. 2014 Jun;26(2):55-61.
7. Moghadamtousi SZ, Fadaeinasab M, Nikzad S, Mohan G, Ali HM, Kadir HA. Annona muricata (Annonaceae): A Review of Its Traditional Uses, Isolated Acetogenins and Biological Activities. Int J Mol Sci. 2015 Jul 10;16(7):15625-58. doi: 10.3390/ijms160715625.
8. Igarashi M, Miyazaki Y. A review on bioactivities of perilla: progress in research on the functions of perilla as medicine and food. Evid Based Complement Alternat Med. 2013;2013:925342. doi: 10.1155/2013/925342. Epub 2013 Nov 11.
9. Makino T, Ono T, Matsuyama K, Nogaki F, Miyawaki S, Honda G, et al. Suppressive effects of Perilla frutescens on IgA nephropathy in HIGA mice. Nephrol Dial Transplant. 2003 Mar;18(3):484-90.
10. Bachheti RK, Joshi A, Ahmed T. A Phytopharmacological Overview on Perilla frutescens. Int. J. Pharm. Sci. Rev. Res. 2014 Jun;26(2):55-61.
11. Nishiyori T, Tsuchiya H, Inagaki N, Nagai H, Koda A. [Effect of Saiboku-to, a blended Chinese traditional medicine, on Type I hypersensitivity reactions, particularly on experimentally-caused asthma]. [Article in Japanese] Nihon Yakurigaku Zasshi. 1985 Jan;85(1):7-16.
12. Pharmacopoeia of the People's Republic of China; English Edition; China Medical Science Press; 2010 Edition; Volume 1; Page 314
13. Jin CH, So YK, Han SN, Kim JB. Isoegomaketone Upregulates Heme Oxygenase-1 in RAW264.7 Cells via ROS/p38 MAPK/ Nrf2 Pathway. Biomol Ther (Seoul). 2016 Sep 1;24(5):510-6. doi: 10.4062/biomolther.2015.194.
14. Igarashi M, Miyazaki Y. A review on bioactivities of perilla: progress in research on the functions of perilla as medicine and food. Evid Based Complement Alternat Med. 2013;2013:925342. doi: 10.1155/2013/925342. Epub 2013 Nov 11.
15. Bachheti RK, Joshi A, Ahmed T. A Phytopharmacological Overview on Perilla frutescens. Int. J. Pharm. Sci. Rev. Res. 2014 Jun;26(2):55-61.
16. Huo LN, Wang W, Zhang CY, Shi HB, Liu Y, Liu XH, et al. Bioassay-Guided Isolation and Identification of Xanthine Oxidase Inhibitory Constituents from the Leaves of Perilla frutescens. Molecules. 2015 Sep 25;20(10):17848-59. doi: 10.3390/molecules201017848.
17. Igarashi M, Miyazaki Y. A review on bioactivities of perilla: progress in research on the functions of perilla as medicine and food. Evid Based Complement Alternat Med. 2013;2013:925342. doi: 10.1155/2013/925342. Epub 2013 Nov 11.
18. Ariano R. Efficacy of a novel food supplement in the relief of the signs and symptoms of seasonal allergic rhinitis and in the reduction of the consumption of anti-allergic drugs. Acta Biomed. 2015 Apr 27;86(1):53-8.
19. Takano H, Osakabe N, Sanbongi C, Yanagisawa R, Inoue K, Yasuda A, et al. Extract of Perilla frutescens enriched for rosmarinic acid, a polyphenolic phytochemical, inhibits seasonal allergic rhinoconjunctivitis in humans. Exp Biol Med (Maywood). 2004 Mar;229(3):247-54.
20. Chen ML, Wu CH, Hung LS, Lin BF. Ethanol Extract of Perilla frutescens Suppresses Allergen-Specific Th2 Responses and Alleviates Airway Inflammation and Hyperreactivity in Ovalbumin-Sensitized Murine Model of Asthma. Evid Based Complement Alternat Med. 2015;2015:324265. doi: 10.1155/2015/324265. Epub 2015 Apr 20.
21. Liu JY, Chen YC, Lin CH, Kao SH. Perilla frutescens leaf extract inhibits mite major allergen Der p 2-induced gene expression of pro-allergic and pro-inflammatory cytokines in human bronchial epithelial cell BEAS-2B. PLoS One. 2013 Oct 18;8(10):e77458. doi: 10.1371/journal.pone.0077458. eCollection 2013.
22. Makino T, Furuta A, Fujii H, Nakagawa T, Wakushima H, Saito K, et al. Effect of oral treatment of Perilla frutescens and its constituents on type-I allergy in mice. Biol Pharm Bull. 2001 Oct;24(10):1206-9
23. Makino T, Ono T, Matsuyama K, Nogaki F, Miyawaki S, Honda G, et al. Suppressive effects of Perilla frutescens on IgA nephropathy in HIGA mice. Nephrol Dial Transplant. 2003 Mar;18(3):484-90.
24. Makino T, Nakamura T, Ono T, Muso E, Honda G. Suppressive effects of Perilla frutescens on mesangioproliferative glomerulonephritis in rats. Biol Pharm Bull. 2001 Feb;24(2):172-5.
25. Makino T, Furuta Y, Wakushima H, Fujii H, Saito K, Kano Y. Anti-allergic effect of Perilla frutescens and its active constituents. Phytother Res. 2003 Mar;17(3):240-3.
26. Oh HA, Park CS, Ahn HJ, Park YS, Kim HM. Effect of Perilla frutescens var. acuta Kudo and rosmarinic acid on allergic inflammatory reactions. Exp Biol Med (Maywood). 2011 Jan;236(1):99-106. doi: 10.1258/ebm.2010.010252.
27. Ueda H, Yamazaki C, Yamazaki M. Luteolin as an anti-inflammatory and anti-allergic constituent of Perilla frutescens. Biol Pharm Bull. 2002 Sep;25(9):1197-202.
28. Ishihara T, Okamoto I, Masaki N, Kohno K, Tanimoto T, Ikegami H, et al. [Inhibition of antigen-specific T helper type 2 responses by Perilla frutescens extract]. [Article in Japanese] Arerugi. 1999 Apr;48(4):443-50.
29. Shin TY, Kim SH, Kim SH, Kim YK, Park HJ, Chae BS, et al. Inhibitory effect of mast cell-mediated immediate-type allergic reactions in rats by Perilla frutescens. Immunopharmacol Immunotoxicol. 2000 Aug;22(3):489-500.
30. Komatsu KI, Takanari J, Maeda T, Kitadate K, Sato T, Mihara Y, et al. Perilla leaf extract prevents atopic dermatitis induced by an extract of Dermatophagoides farinae in NC/Nga mice. Asian Pac J Allergy Immunol. 2016 Mar 20. doi: 10.12932/AP0717. [Epub ahead of print]
31. Heo JC, Nam DY, Seo MS, Lee SH. Alleviation of atopic dermatitis-related symptoms by Perilla frutescens Britton. Int J Mol Med. 2011 Nov;28(5):733-7. doi: 10.3892/ijmm.2011.763. Epub 2011 Aug 2.
32. Sanbongi C, Takano H, Osakabe N, Sasa N, Natsume M, Yanagisawa R, et al. Rosmarinic acid in perilla extract inhibits allergic inflammation induced by mite allergen, in a mouse model. Clin Exp Allergy. 2004 Jun;34(6):971-7.
33. Buchwald-Werner S, Fujii H, Reule C, Schoen C. Perilla extract improves gastrointestinal discomfort in a randomized placebo controlled double blind human pilot study. BMC Complement Altern Med. 2014 May 27;14:173. doi: 10.1186/1472-6882-14-173.
34. Kwak Y, Ju J. Inhibitory activities of Perilla frutescens britton leaf extract against the growth, migration, and adhesion of human cancer cells. Nutr Res Pract. 2015 Feb;9(1):11-6. doi: 10.4162/nrp.2015.9.1.11. Epub 2015 Jan 28.

35. Urushima H, Nishimura J, Mizushima T, Hayashi N, Maeda K, Ito T. Perilla frutescens extract ameliorates DSS-induced colitis by suppressing proinflammatory cytokines and inducing anti-inflammatory cytokines. Am J Physiol Gastrointest Liver Physiol. 2015 Jan 1;308(1):G32-41. doi: 10.1152/ajpgi.00294.2014. Epub 2014 Oct 30.
36. Chen CY, Leu YL, Fang Y, Lin CF, Kuo LM, Sung WC, et al. Anti-inflammatory effects of Perilla frutescens in activated human neutrophils through two independent pathways: Src family kinases and Calcium. Sci Rep. 2015 Dec 14;5:18204. doi: 10.1038/srep18204.
37. Lim HJ, Woo KW, Lee KR, Lee SK, Kim HP. Inhibition of Proinflammatory Cytokine Generation in Lung Inflammation by the Leaves of Perilla frutescens and Its Constituents. Biomol Ther (Seoul). 2014 Jan;22(1):62-7. doi: 10.4062/biomolther.2013.088.
38. Kwak CS, Yeo EJ, Moon SC, Kim YW, Ahn HJ, Park SC. Perilla leaf, Perilla frutescens, induces apoptosis and G1 phase arrest in human leukemia HL-60 cells through the combinations of death receptor-mediated, mitochondrial, and endoplasmic reticulum stress-induced pathways. J Med Food. 2009 Jun;12(3):508-17. doi: 10.1089/jmf.2008.1103.
39. Huang BP, Lin CH, Chen YC, Kao SH. Anti-inflammatory effects of Perilla frutescens leaf extract on lipopolysaccharide-stimulated RAW264.7 cells. Mol Med Rep. 2014 Aug;10(2):1077-83. doi: 10.3892/mmr.2014.2298. Epub 2014 Jun 5.
40. Igarashi M, Miyazaki Y. A review on bioactivities of perilla: progress in research on the functions of perilla as medicine and food. Evid Based Complement Alternat Med. 2013;2013:925342. doi: 10.1155/2013/925342. Epub 2013 Nov 11.
41. Lin CS, Kuo CL, Wang JP, Cheng JS, Huang ZW, Chen CF. Growth inhibitory and apoptosis inducing effect of Perilla frutescens extract on human hepatoma HepG2 cells. J Ethnopharmacol. 2007 Jul 25;112(3):557-67. Epub 2007 May 10.
42. Osakabe N, Yasuda A, Natsume M, Yoshikawa T. Rosmarinic acid inhibits epidermal inflammatory responses: anticarcinogenic effect of Perilla frutescens extract in the murine two-stage skin model. Carcinogenesis. 2004 Apr;25(4):549-57. Epub 2004 Jan 16.
43. Meng L, Lozano YF, Gaydou EM, Li B. Antioxidant activities of polyphenols extracted from Perilla frutescens varieties. Molecules. 2008 Dec 31;14(1):133-40. doi: 10.3390/molecules14010133.
44. Asif M. Phytochemical study of polyphenols in Perilla frutescens as an antioxidant. Avicenna J Phytomed. 2012 Fall;2(4):169-78.
45. Kim MK, Lee HS, Kim EJ, Won NH, Chi YM, Kim BC, et al. Protective effect of aqueous extract of Perilla frutescens on tert-butyl hydroperoxide-induced oxidative hepatotoxicity in rats. Food Chem Toxicol. 2007 Sep;45(9):1738-44. Epub 2007 Mar 18.
46. Lee AY, Hwang BR, Lee MH, Lee S, Cho EJ. Perilla frutescens var. japonica and rosmarinic acid improve amyloid-β25-35 induced impairment of cognition and memory function. Nutr Res Pract. 2016 Jun;10(3):274-81. doi: 10.4162/nrp.2016.10.3.274. Epub 2016 Apr 1.
47. Lee AY, Wu TT, Hwang BR, Lee J, Lee MH, Lee S, et al. The Neuro-Protective Effect of the Methanolic Extract of Perilla frutescens var. japonica and Rosmarinic Acid against H2O2-Induced Oxidative Stress in C6 Glial Cells. Biomol Ther (Seoul). 2016 May 1;24(3):338-45. doi: 10.4062/biomolther.2015.135.
48. Choi SJ, Oh SS, Kim CR, Kwon YK, Suh SH, Kim JK, et al. Perilla frutescens Extract Ameliorates Acetylcholinesterase and Trimethyltin Chloride-Induced Neurotoxicity. J Med Food. 2016 Mar;19(3):281-9. doi: 10.1089/jmf.2015.3540. Epub 2015 Oct 27.
49. Takeda H, Tsuji M, Matsumiya T, Kubo M. Identification of rosmarinic acid as a novel antidepressive substance in the leaves of Perilla frutescens Britton var. acuta Kudo (Perillae Herba). Nihon Shinkei Seishin Yakurigaku Zasshi. 2002 Feb;22(1):15-22.
50. Paek JH, Shin KH, Kang YH, Lee JY, Lim SS. Rapid identification of aldose reductase inhibitory compounds from Perilla frutescens. Biomed Res Int. 2013;2013:679463. doi: 10.1155/2013/679463. Epub 2013 Nov 6.
51. Kim EY, Choi HJ, Chung TW, Choi JY, Kim HS, Jung YS, et al. Water-extracted Perilla frutescens increases endometrial receptivity though leukemia inhibitory factor-dependent expression of integrins. J Pharmacol Sci. 2016 Aug;131(4):259-66. doi: 10.1016/j.jphs.2016.07.004. Epub 2016 Jul 25
52. Simoniene G, Jurkstiene V, Jankauskiene K, Gailys V, Kevelaitis E, Venskutonis PR. [The influence of common perilla (Perilla frutescens (L.) Britton) on non-specific cell-mediated immunity--phagocytosis activity]. [Article in Lithuanian] Medicina (Kaunas). 2005;41(12):1042-7.
53. Kwon KH, Kim KI, Jun WJ, Shin DH, Cho HY, Hong BS. *In vitro* and *in vivo* effects of macrophage-stimulatory polysaccharide from leaves of Perilla frutescens var. crispa. Biol Pharm Bull. 2002 Mar;25(3):367-71.
54. Kim DH, Kim YC, Choi UK. Optimization of antibacterial activity of Perilla frutescens var. acuta leaf against Staphylococcus aureus using evolutionary operation factorial design technique. Int J Mol Sci. 2011;12(4):2395-407. doi: 10.3390/ijms12042395. Epub 2011 Apr 6.
55. Kim MJ, Kim HK. Perilla leaf extract ameliorates obesity and dyslipidemia induced by high-fat diet. Phytother Res. 2009 Dec;23(12):1685-90. doi: 10.1002/ptr.2811.
56. Makino T, Ono T, Muso E, Honda G. Effect of Perilla frutescens on nitric oxide production and DNA synthesis in cultured murine vascular smooth muscle cells. Phytother Res. 2002 Mar;16 Suppl 1:S19-23.
57. Braun L, Cohen M. Herbs and Natural Supplements.4th ed: Volume 2. Sydney:Churchill Livingstone Elsevier, 2015. p. 753.
58. Bachheti RK, Joshi A, Ahmed T. A Phytopharmacological Overview on Perilla frutescens. Int. J. Pharm. Sci. Rev. Res. 2014 Jun;26(2):55-61.
59. Kim EY, Choi HJ, Chung TW, Choi JY, Kim HS, Jung YS, et al. Water-extracted Perilla frutescens increases endometrial receptivity though leukemia inhibitory factor-dependent expression of integrins. J Pharmacol Sci. 2016 Aug;131(4):259-66. doi: 10.1016/j.jphs.2016.07.004. Epub 2016 Jul 25
60. Pharmacopoeia of the People's Republic of China; English Edition; China Medical Science Press; 2010 Edition; Volume 1; Page 314