

Perilla

An Allergy Fighting Herb

Perilla frutescens is a plant whose leaves are commonly used as a garnish with raw fish in Japan. It is also used in Chinese herbal medicine¹, and its leaves are used medicinally as a sedative, for indigestion, and for food poisoning treatment.² The functional components of perilla are flavonoid aglycones such as luteolin, apigenin, and rosmarinic acid. These substances have been studied for their anti-allergic and anti-inflammatory potential.

Perilla's Mechanisms at all 3 Levels of Study

In cell studies, perilla effectively inhibits mast cells from "degranulating" and releasing histamine, which is one of the principle mechanisms behind allergic symptoms. One study found that perilla not only dose-dependently inhibited the release of histamine from mast cells, but also significantly inhibited the production of a main pro-inflammatory cytokine.³ Perilla also selectively blocks the activity of 5-lipoxygenase, a key enzyme in one of the pathways of inflammation.⁴



Figure 1. Inhibitory effect of Perilla on histamine release

The effects of perilla extracts have also been tested in animal models of allergy. In rats, *Perilla frutescens* extract inhibited mast cell-mediated allergic reactions. It dose-dependently decreased plasma levels of histamine and inhibited systemic and local allergic reactions.³ In another study, a perilla extract containing luteolin, scutellarin, apigenin and rosmarinic acid significantly suppressed cutaneous anaphylaxis, a severe allergic reaction, in mice. This type of reaction is related to the second and third stages of common allergic responses, when mast cells are activated to release mediators such as histamine, serotonin and leukotrienes, and when these mediators cause inflammatory reactions such as enhancing vascular permeability and causing smooth muscle to constrict.² This then leads to allergic symptoms such as swelling and redness. A second trial confirmed the ability of perilla extracts to suppress cutaneous anaphylaxis.⁵

Other studies have indicated that perilla extracts may inhibit the production of immunoglobulin E (IgE).⁶ IgE is the antibody that is responsible for recognizing "allergens", which are proteins from substances such as food, plant pollens, latex, animal hair, etc. and priming the immune system for an allergic reaction. Total serum levels of IgE have been roughly correlated with the severity of allergic disease.⁷ Blocking IgE production is therefore an effective way to block an allergic reaction at the first step.

In humans, perilla has been found to reduce the severity of asthma. One trial compared the clinical features of patients with asthma who had been given perilla seed oil for 4 weeks to those of asthmatics who had not been given perilla extracts. In the group given perilla seed oil, pro-inflammatory leukotriene synthesis was significantly decreased, whereas it increased significantly in the control group. Perilla seed oil also significantly increased breathing measurements such as peak expiratory flow, forced vital capacity and forced expiratory volume in one second.⁸ 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%), stuffed nose (over 60%) and itchy eyes (50%). Two of the patients had blood samples taken to determine the effect of the extract on IgE concentrations. IgE levels were significantly lower in both patients, without any change in other antibody levels.⁹

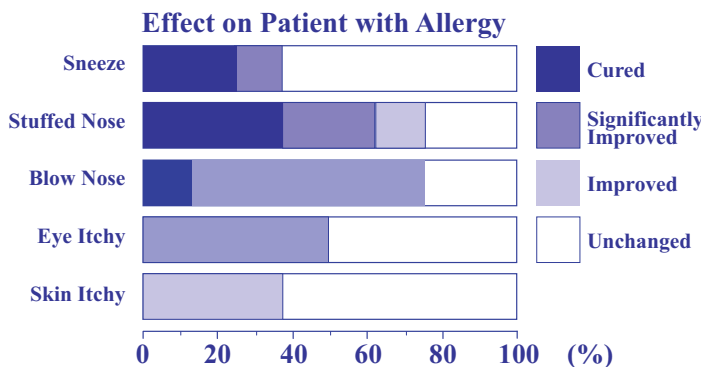


Figure 2. Effect of *Perilla* seed extract on a patient with allergy

Luteolin

Luteolin is considered by many scientists to be the major active constituent in *Perilla frutescens*. Studies of this component have found that it exerts antimutagenic and anti-inflammatory-allergic effects. It is also recognized as an antioxidant scavenger of damaging free radicals, and as an inhibitor of protein kinase C, which is a key regulator in the initiation of inflammatory events such as smooth muscle constriction.⁹ Luteolin has been shown to be a potent inhibitor of human mast cell activation.^{10,11} One study compared the effects of luteolin, baicalein and quercetin on the inhibition of the release

of histamine, leukotrienes, cytokines and other inflammatory factors from human mast cells, and found that luteolin was the most effective at inhibiting the release of these components.¹⁰ Another study found that luteolin could completely block the stimulation of mast cells, inhibiting the IgE-mediated release of histamine and pro-inflammatory cytokines.¹¹

Luteolin is effective at preventing the production of proinflammatory cytokines.^{3,12} Some of the cytokines that are primarily responsible for allergic diseases include interleukin (IL)-4 and IL-5. IL-4 is one of the most important cytokines in the production of IgE and allergic inflammation.¹² IL-5 is responsible for recruiting eosinophils.¹³ Eosinophils are immune cells that assist in priming the immune system for an allergic response. When they infiltrate the inflamed tissue, eosinophils become activated and release mediators such as histamines, cytokines, leukotrienes and other pro-inflammatory mediators.¹⁴ Eosinophil accumulation is a distinctive feature of allergic inflammation.¹⁴ One study compared the anti-inflammatory activities of 37 flavonoids and related compounds, and found that luteolin and compounds with a similar structure were the strongest inhibitors of

interleukin-4 production by basophils.¹² Other studies have found that luteolin reduces levels of IL-5.¹⁵

Luteolin's effects hold up in animal studies as well. Mice that were orally given luteolin had a significantly inhibited production of the cytokine tumour necrosis factor alpha. Luteolin also inhibited ear swelling in mice that was induced by pro-inflammatory molecules.¹

Luteolin has shown benefits in models of asthma. Asthma is an inflammatory disease of the airways which is characterized by difficulty in breathing due to inflammation which causes smooth muscles in the bronchi to constrict. It is also characterized by elevated levels of IgE in the blood, and infiltration of eosinophils into the airways.¹⁵ The development of asthma is mediated by the cytokines IL-4 and IL-5, IgE, eosinophils and other mediators such as leukotrienes. On the other hand, the cytokine interferon gamma (IFN- γ) blocks the process. In a mouse model of airway hyperactivity which mimics

some of the characteristic features of asthma, orally administered luteolin significantly decreased airway hyperreactivity and blood levels of IgE. It also reduced levels of IL-4 and IL-5 in the bronchoalveolar lavage fluid while increasing levels of IFN- γ .¹⁵

Rosmarinic Relief

Like rosemary, one of perilla's active constituents is rosmarinic acid. This compound's antioxidant and anti-inflammatory properties have been shown to help with allergic disease in several studies. One study observed a mouse model in which an allergic reaction was induced using a dust mite allergen. Mice that were given rosmarinic acid in a perilla extract had strongly inhibited recruitment of inflammatory cells. Rosmarinic acid also decreased the numbers of mucus-containing airway cells and significantly prevented the intensity of infiltration of eosinophils and other inflammatory cells into tissues, and it prevented the allergy-induced increase in the production of IL-4 and IL-5. Furthermore, rosmarinic acid reduced the production of antibodies that react to allergens. All of these results indicate that rosmarinic acid is capable of strongly blocking allergic inflammation¹⁴.

Rosmarinic acid has also proved its worth in helping with human allergies. In one randomized, double-blind, age-matched placebo-controlled parallel group study, 30 patients with seasonal allergic rhinoconjunctivitis (SAR) were given either a low or high dose of *Perilla frutescens* extract enriched with

rosmarinic acid or a placebo for 21 days. Their symptoms were recorded, and their levels of infiltrating inflammatory cells and histamine in the nasal lavage fluid were measured. Serum levels of IgE were also measured. At the end of the trial period, there was a significant increase in responder rates for itchy nose, watery eyes, itchy eyes and total symptoms. 55.6% of patients given a lower dose of the extract and 70% of patients given the higher dose reported global symptom relief, compared to only 30% of the placebo group. The extract also significantly decreased the number of eosinophils and other inflammatory cells in the nasal lavage fluid at both doses. These results were suggested to be due to the inhibition of immune cells from infiltrating into the nostrils. Since there were no adverse effects or significant abnormalities in blood tests, the study concluded that rosmarinic acid from perilla extract is an effective intervention for SAR.¹⁶

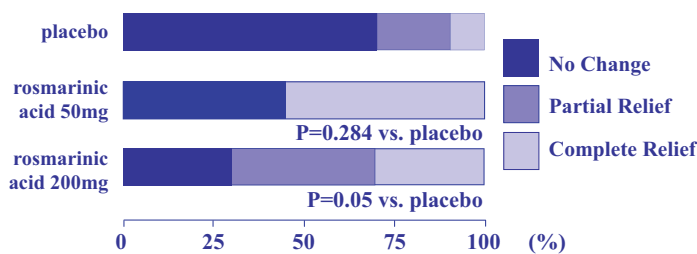


Figure 3. Patients' evaluations of global symptoms using the health-related quality of life questionnaire. Patients' assessments of global symptoms at study endpoint relative to prestudy levels are shown for each group.¹⁶

Apigenin vs IgE

Apigenin is another flavonoid constituent of perilla with anti-allergic activity. Studies have found that it blocks the expression of the receptor on basophil cells that IgE antibodies bind to, thereby preventing IgE from stimulating these cells to release pro-inflammatory mediators.¹⁷ Dietary apigenin also decreases serum levels of IgE in mice.¹⁸ Another study found that mice fed apigenin for 3 weeks and sensitized to develop an allergic reaction had suppressed levels of IgE, while other antibody levels were unaffected. Apigenin also blocked the production of IL-4.¹⁹

An Effective Way to Scratch the Allergy Itch

Overall, *Perilla frutescens* is full of anti-allergic potential. By blocking the production and release of pro-inflammatory mediators, reducing levels of IgE, and reducing the infiltration of inflammatory cells, luteolin, rosmarinic acid and apigenin help prevent the misery of a full-blown allergic reaction.

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