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REPORT**Rosmarinic Acid Provides Natural Allergy Relief**

By John Colman



The latter part of the twentieth century has seen an explosion in the incidence of airborne allergies. A growing portion of the world's population now suffers from the sneezing and coughing associated with allergies. Although increased air pollution, weakened immune systems, sick building syndrome, and other theories have sought to explain the growing number of allergy sufferers, epidemiological studies have failed to make a compelling connection to any specific new allergens in the environment. One thing, however, is certain: the increase in allergy sufferers has accelerated, especially in the last 20 years.

Understanding Upper-Airway Allergies

Upper-airway allergies (allergic rhinitis) are a symptom complex of hay fever with seasonal or perennial sneezing, and may include nasal congestion, conjunctivitis (inflammation of the eye), or pruritis (itching).^{1,2} This complex can be divided into hay fever, an acute seasonal form, and perennial rhinitis, whose symptoms last throughout the year. Seasonal allergic rhinitis is usually

caused by allergens such as tree pollens in the spring, grass pollens in the summer, and weed pollens in the fall. Perennial rhinitis is typically caused by allergens such as house dust mites, feathers, animal dander, and fungi.³

The annual costs of allergy treatment worldwide have been estimated to be approximately \$7 billion. While traditional drug treatments have steadily improved, alternative herbal products and vitamins have grown in popularity and now account for about one sixth of the total allergy medication market. Although natural remedies have been used for centuries to treat allergies, controlled human studies of their effects in treating allergic rhinitis have been virtually nonexistent.⁴

Allergic rhinitis is characterized by immune responder cell proliferation in the bloodstream and nasal fluids. Neutrophils, polymorphonuclear leukocytes, eosino-phils, and T cells are all activated in allergies and proliferate rapidly in the blood and nasal fluids due to the action of the inflammatory cytokines interleukin (IL)-1 beta, IL-2, IL-4, IL-5, and IL-8. During bouts of allergy and asthma, higher levels of chemoattractants such as histamine and eotaxin draw eosinophils and other immune cells into the airways and nasal passages.⁵ The primary cause of discomfort in allergies is the congestion, fluid outpouring, and swelling in the upper airways caused by this massive inflow of responder cells to such a small area of the body, which shuts off the free flow of air to the lungs.

The traditional method of treating allergic rhinitis with antihistamines works to reduce some of the more intrusive symptoms of allergic reactions but does not reduce T cell and neutrophil activation or proliferation. Anti-histamines either prevent the release of histamine from mast cells or block histamine receptor sites, but do not address the toxic effects of already proliferated neutrophils and T cells.⁶

**Herbal Alternatives to Shots and Pills**

Now there is an herbal alternative to painful allergy shots and pills. Rosmarinic acid is a plant polyphenol found in the Lamiaceae genus of plants, which includes basil, sage, mint, rosemary, and perilla leaf.⁷ Oral supplementation with perilla leaves or extracts of rosmarinic acid has been shown to suppress allergic reactions in mice and, more recently, in humans.^{8,9} Rosmarinic acid relieves allergy symptoms by preventing the activation of immune responder cells and by inducing apoptosis, or cellular suicide, in already activated immune responder cells.¹⁰ Natural flavonoids like rosmarinic acid only kill off excess allergy-activated immune cells, while leaving the vast bulk of responder cells to fight off bacteria and other foreign invaders.

Rosmarinic acid has been shown to kill allergy-activated T cells and neutrophils during allergic reactions without affecting the T cells or neutrophils in their resting state.¹¹ Using traditional antihistamines in allergic reactions, on the other hand, is somewhat analogous to turning off a fire alarm without putting out the fire. Antihistamines do nothing to lower the number of excess immune

cells once they are formed.⁶ High levels of immune cells in their active form can lead to other dangers, such as free radical damage to normal tissues and to circulating proteins like HDL.

One theory of cardiovascular disease taken from epidemiological data states that the number of infections such as colds and flus experienced over a lifetime is an important risk factor for developing heart disease. Another theory has drawn a link between the number and type of allergies suffered over a lifetime and the risk of cardiovascular disease.

Rosmarinic acid was first shown to reduce allergic reactions in mice using the mouse ear-passive cutaneous anaphylaxis reaction.¹² Perilla leaf extract and rosmarinic acid were found to be nearly equal at inhibiting the allergic response when given orally. Perilla leaf contains significant amounts of luteolin, which also has an anti-allergic effect. A follow-up study confirmed that oral administration of perilla leaf extract inhibits production of tumor necrosis factor-alpha and attenuates the allergic response and inflammation in mice caused by arachidonic acid-induced ear edema and allergic edema.¹³

In response to these favorable reports, scientists began to take a deeper look at the exact mechanisms responsible for the anti-allergic effects of rosmarinic acid. One study showed that rosmarinic acid inhibited IL-2 promoter activation of T cells in a large-scale screening of plant extracts.¹⁴ Another study showed that rosmarinic acid had potent immunosuppressive effects when combined with rapamycin, an anti-rejection drug.¹⁵ That study's most important discovery was that rosmarinic acid acted in two ways, inhibiting both the activation and proliferation of T cells.

In another study, researchers showed that rosmarinic acid inhibited lung injury from diesel exhaust particles, and outlined the exact steps by which rosmarinic acid brings about the cell death of activated T cells. The study also showed that the accumulation of neutrophils in human lung disease is directly related to the localized elevation of the cytokine IL-8, which supports the theory that IL-8 plays a central role in the pathogenesis of acute lung injury. Daily pretreatment with rosmarinic acid at 2 mg per kilogram of body weight taken orally strongly inhibited the increased expression of IL-8, IL-1 beta, and nitric oxide, thereby completely protecting the mice against lung damage.¹¹

In another, more recent study, rosmarinic acid was shown to dispose of excess activated T cells by inducing cellular suicide through an Lck-dependent apoptosis, a form of cellular suicide that is unique among plant phenols. Neither curcumin nor resveratrol, among other plant phenols, has been shown to do this. The rosmarinic acid-induced killing of excess immune cells is a longer process, taking at least 24 hours rather than the normal killing time of just two minutes.¹⁴



Sage (*Salvia officinalis*)

Earlier this year, researchers demonstrated that daily treatment with 1.5 mg of rosmarinic acid in perilla leaf extract given orally to mice prevented allergic asthma caused by house dust mite allergen. Rosmarinic acid significantly prevented increases in IL-4, IL-5, and eotaxin in the bronchoalveolar lavage fluids and murine airways. The study concluded that oral administration of perilla-derived rosmarinic acid may be an effective treatment for allergic asthma by limiting cytokines and allergy-specific antibody.¹⁶

In a landmark original research article, extract of perilla leaf enriched with rosmarinic acid was shown to be an effective treatment for humans suffering from seasonal allergic rhinoconjunctivitis. In this 21-day, double-blind, placebo-controlled, randomized, age-matched parallel group study, patients with seasonal allergic rhinoconjunctivitis were given a total daily dose of either 50 mg or 200 mg of rosmarinic acid and kept a daily diary of their symptoms.

Nasal lavage fluids were measured for IL-1 beta, IL-8, eotaxin, and histamine on days 3 and 21.⁹

The study results showed that by day 3, both the 50-mg and 200-mg doses of rosmarinic acid significantly lowered the numbers of polymorphonuclear leukocytes and neutrophils in nasal lavage fluid compared to the control group. Levels of eotaxin, IL-1 beta, and histamine in the nasal fluid were not significantly different in the groups studied. This study was the first to demonstrate the alleviation of allergic symptoms in humans suffering from seasonal allergic rhinitis with polyphenolic phytochemicals.⁹

The authors concluded that relief from seasonal allergies is caused at least in part by inhibiting polymorphonuclear leukocyte infiltration into the nostrils. Rosmarinic acid particularly inhibited the eye-related symptoms associated with seasonal allergies. No side effects were noted and extensive blood cell counts and hepatic and renal function tests showed rosmarinic acid to be a safe, effective, and less expensive alternative to prescription drugs in the treatment of seasonal allergies in humans.^{9,17}



Anterior rhinoscopy showing allergic rhinitis.

Anti-Allergic Effects of Luteolin

Like rosmarinic acid, luteolin is another natural plant flavonoid that has been shown to have potent anti-allergic properties. It is found along with rosmarinic acid in various species of the perilla plant but at lower concentrations. For centuries, the Japanese have used luteolin from perilla extracts in ancient Kampo herbal formulations to treat bronchial asthma.¹⁸



In present-day Japan, 210 medicinal preparations based on the ancient Kampo herbal formulas are available at pharmacies. According to a survey by the National Asthma Campaign, herbal formulas for asthma have been used by 60% of moderate asthma sufferers and 70% of severe asthma sufferers.¹⁹ Many of the anti-allergy preparations in traditional Kampo medicine contain both luteolin and rosmarinic acid.

In a study of Kampo herbs at the Osaka University Medical School, luteolin was shown to be the most potent inhibitor of IL-4 production in human basophils and T cells. IL-4 and IL-5 are the two most prevalent allergic stimulants in blood.²⁰ Okayama University tested six flavonoid glycosides and found that luteolin glycosides were the most potent inhibitors of histamine release from mast cells. Both free luteolin and luteolin glycosides are found in perilla extracts.²¹ This study confirms earlier work showing that luteolin is the most potent inhibitor of histamine and cytokine release from human mast cells. Oral administration of perilla leaf extract inhibited inflammation, allergic

response, and tumor necrosis factor in whole mice. Of the active compounds tested in this study, only luteolin showed in-vivo (whole animal) activity.¹³

Luteolin is active orally as an anti-allergy compound at very low doses. IL-5 promotes the growth and survival of eosinophils, one particular type of leukocyte, or immune responder cell, that is activated during allergies. Luteolin inhibited 95% of IL-5 activity at a concentration of 30 micromoles, achieved 79% inhibition at 15 micromoles, 54% inhibition at 3.8 micromoles, and 29% inhibition at 1.9 micromoles. The latter two doses are easily achievable by humans taking perilla leaf extract in supplemental form.²²

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Asthma and Allergies

Asthma historically has been considered a lower-airway disease, while allergic rhinitis is considered an upper-airway disorder. New associations are being found between asthma and allergies, and a new integrated theory called the “united airway” theory has been proposed.²³ Allergies of the upper airway are now considered a risk factor for asthma development, and it is now clear that high eosinophil count in the nasal mucous is one common link between the two disorders.²⁴ Many people suffer from both seasonal allergies and asthma, and nasal eosinophils can be regarded as the most important predictor of upper- and lower-airway functions in patients with both seasonal allergic rhinitis and asthma, as demonstrated in a June 2004 study.²⁵



Asthma

In fact, the toughening and thickening of lung tissue seen in the lower airway in asthmatics has been connected with repeated bouts of allergies in the upper airways. The tissue changes are probably due to free radical scarring caused by the responder cells—neutrophils, T cells, and other leukocytes drawn to the inflamed site by histamines and other chemoattractants.²⁶

In February 2004, researchers duplicated the characteristic smooth muscle thickening in asthmatic airways by repeatedly exposing rats to allergens and noting the changes in lung architecture. T cells, macrophages, eosinophils, lymphocytes, and neutrophils in lung fluid increased dramatically, resulting in the characteristic changes seen in the airway walls of asthmatics.²⁶ New studies such as this reinforce the importance of controlling seasonal and year-round allergies; failure to control these conditions presents the very real danger of causing permanent structural changes to lung tissue.

Conclusion

Among natural compounds, rosmarinic acid and luteolin are the best choices for treating seasonal allergies, perennial allergies, and asthma. Rosmarinic acid is the only nutraceutical shown to be effective in treating seasonal rhinitis in humans. In numerous animal and human cell studies, luteolin has been shown to be effective in suppressing allergic inflammation. At least one natural source—perilla leaf extract—contains significant amounts of both compounds. This holds great promise for allergy sufferers around the world, as these products have been demonstrated to act as antihistamines while killing off excess allergy-activated responder cells, the real root cause of suffering in allergic conditions.

References

1. Umetsu DT, McIntire JJ, Akbari O, Macaubas C. Asthma: an epidemic of dysregulated immunity. *Nat Immunol.* 2002 Aug;3(8):715-20.
2. Kosunen TU, Hook-Nikanne J, Salomaa H, Dekruff RH. Increase of allergen-specific immunoglobulin E antibodies from 1973 to 1994 in a Finnish population and a possible relationship to *Helicobacter pylori* infections. *Clin Exp Allergy.* 2002 Mar;32(3):373-8.
3. Berkow R. *The Merck Manual*, 16th ed. Merck Research Laboratories;1995.
4. Ziment I, Tashkin LP. Alternative medicine for allergy and asthma. *J Allergy Clin Immunol.* 2000 Oct;106(4):603-14.
5. Costa JJ, Welker PF, Galli SJ. The cells of the allergic response: mast cells, basophils, and eosinophils. *JAMA.* 1997 Dec 10;278(22):1815-22.
6. Wong BR, Grossbard EB, Payan DG, Masuda ES. Targeting Syk as a treatment for allergic and autoimmune disorders. *Expert Opin Investig Drugs.* 2004 Jul;13(7):743-62.
7. al Sereiti MR, Abu-Amer KM, Sen P. Pharmacology of rosemary and its therapeutic potentials. *Indian J Exp Biol.* 1999 Feb;37(2):124-0.
8. Makino T, Furuta A, Fujii H, et al. Effect of oral treatment of *Perilla frutescens* and its constituents on type-I allergy in mice.

9. Takano H, Osakabe N, Sanbongi C, et al. Extract of *Perilla frutescens* enriched for rosmarinic acid inhibits seasonal allergic rhinoconjunctivitis in humans. *Exp Biol Med*. 2004 Mar;229(3):247-54.
10. Hur YG, Yun Y, Won J. Rosmarinic acid induces p56lck-dependent apoptosis in jurkat and peripheral T cells via mitochondrial pathway independent from fas/fas ligand interaction. *J Immunol*. 2004 Jan 1;172(1):79-87.
11. Sanbongi C, Takano H, Osakabe N. Rosmarinic acid inhibits lung injury induced by diesel exhaust particles. *Free Radic Biol Med*. 2003 Apr 15;34(8):1060-9.
12. 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.
13. Ueda H, Yamazaki C. Luteolin as an antiinflammatory and anti-allergic constituent of *Perilla frutescens*. *Biol Pharm Bull*. 2002 Sep;25(9):1197-202.
14. Won J, Hur YG, Hur EM, et al. Rosmarinic acid inhibits TCR-induced T cell activation and proliferation in an Lck-dependent manner. *Eur J Immunol*. 2003 Apr;33(4):870-9.
15. Yun SY, Hur YG, Kang MA, Lee J, Ahn C, Won J. Synergistic immunosuppressive effects of rosmarinic acid and rapamycin in vitro and in vivo. *Transplantation*. 2003 May 27;75(10):1758-60.
16. Sanbongi C, Takano H, Osakabe N, et al. Rosmarinic acid in perilla leaf extract inhibits allergic inflammation induced by mite allergen, in a mouse model. *Clin Exp Allergy*. 2004 Jun;34(6):971-7.
17. Hu G, Walls RS, Bass D, et al. The Chinese herbal formulation Biminne in management of perennial allergic rhinitis: a randomized, double-blind, placebo-controlled, 12-week clinical trial. *Ann Allergy Asthma Immunol*. 2002 May;88(5):478-87.
18. Borchers AT, Sakai S, Henderson GL, et al. Shosaiko-to and other Kampo[Japanese herbal] medicines: a review of their immunomodulatory activities. *J Ethnopharmacol*. 2000 Nov;73(1-2):1-13.
19. Huntley A, Ernst E. Herbal medicines for asthma: a systematic review. *Thorax*. 2000 Nov;55(11):925-9.
20. Hirano T, Higa S, Arimitsu J, et al. Flavonoids such as luteolin, fisetin and apigenin are inhibitors of interleukin-4 and interleukin-13 production by activated human basophils. *Int Arch Allergy Immunol*. 2004 Jun;134(2):135-40.
21. Inoue T, Sugimoto Y, Masuda H, Kamei C. Antiallergic effect of flavonoid glycosides obtained from *Mentha piperita* L. *Biol Pharm Bull*. 2002 Feb;25(2):256-9.
22. Park KY, Lee SH, Min BK, et al. Inhibitory effect of luteolin 4'-O-glucoside from *Kummerowia striata* and other flavonoids on interleukin-5 bioactivity. *Planta Med*. 1999 Jun;65(5):457-9.
23. Gonzalez HJ, Gomez VJ, Orea SM, Flores SG, Rios NR, de la Torre F. Airway hyper-reactivity in patients with allergic and non-allergic rhinitis. *Rev Alerg Mex*. 2003 May- Jun;50(3):86-90.
24. Baybeck S, Demirel YS, Ereku S, Kalayctoglu O, Beder S, Misirligil Z, Gurbuz L. The mechanism of bronchial hyperactivity in allergic rhinitis patients. *Allergol Immunopathol[Madr]*. 1996 Mar- Apr;24(2):45-53.
25. Ciprandi G, Cirilli I, Vizzaccaro A, Milanese M, Tosca MA. Airway function and nasal inflammation in seasonal allergic rhinitis and asthma. *Clin Exp Allergy*. 2004 Jun;34(6):891-6.
26. Leung SY, Eynott P, Noble A, Nath P, Chung KF. Resolution of allergic airways inflammation but persistence of airway smooth muscle proliferation after repeated allergen exposures. *Clin Exp Allergy*. 2004 Feb;34(2):213-20.

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