Rosmarinic Acid

Derivation

Rosmarinus officinalis, *Perilla frutescens*, *Prunella vulgaris*, *Melissa officinalis*, *Salvia*, *Borago officinalis*, *Lithosperma*, *Lycopus virginicus*, *Thymus vulgaris*, *Mentha piperita*.

Indications

Autoimmune disease, inflammation, and allergies (e.g., food and respiratory, including asthma).

Mechanism of Action

Rosmarinic acid has many complex actions on inflammatory cascades including inhibition of cytokine release from activated T cells and prevention of T-cell activation in the first place. Rosmarinic acid's mechanisms of action are becoming increasingly intricate, technical, and complex as the field of immunology and research techniques advance. Without detailing all of the molecular actions, rosmarinic acid limits the production of proinflammatory mediators[1,2,3,4] while promoting anti-inflammatory mediators[5]; protecting the lungs,[6,7] vasculature,[8] and skin[9]; reducing mortality in animal models of sepsis[10,11]; reducing pain through antinociceptive effects[12]; and displaying anticancer and chemopreventative effects.[13] In short, T cells are up-regulated or down-regulated in response to various chemical, infectious, oxidative, toxic, and other influences, and rosmarinic acid may both improve immune responses in cases of cancer or infection and decrease immune hyper-reactivity in allergic and autoimmune situations.[14]

In general, in allergic situations such as asthma, dermatitis, and chemical reactivity involve activation of T cells and mast cells and their release of proinflammatory interferon and interleukins. Nuclear factor-κB (NF-κB) and tumor necrosis factor (TNF)-α are several agents at the top of the inflammatory cascade that activate T cells, including CD4 and CD8 cells, and rosmarinic acid inhibits their expression.[15,16] Rosmarinic acid's inhibition of TNF-α and NF-κB activation may protect the kidneys from nephrotoxins,[16] the liver from fibrosis,[17,18] and tissues from ischemic cytotoxicity.[19]

T-Cell Activation: Nuclear DNA possesses a multitude of binding sites, and one in particular, the Src Homology 2 (SH2) domain, directs T-cell activities in the body and thus plays role in cancer, autoimmune diseases, and inflammatory diseases. Rosmarinic acid has been shown to act as an agonist to the SH2 domain and reduce T-cell activation via several common T-cell antigens and inflammatory mediators. Furthermore, rosmarinic acid has been shown to reduce the ability of activated T cells to promote interleukin production and release.[20]

Protein Kinase Signal Transduction: Another mechanism of T-cell inhibition may involve protein kinase enzymes. There are numerous protein kinases that play important roles in translating signals from cellular receptors and the outside of cells to the interior and ultimately act on the cellular DNA to direct the activity of that cell. This process is called signal transduction, and protein kinases are one type of enzymes on the interior of the cell membrane that are involved with signal transduction.

One group of protein kinases are a family of tyrosine-based kinases, and one in particular, named Lck, is specific to T-cell signal transduction. Rosmarinic acid has been shown to inhibit activity between these tyrosine kinase enzymes and downstream peptides, thereby reducing signal transduction in T cells.[21] Researchers report that T-cell apoptosis is promoted when Lck pathways are interfered with and that the apoptosis is restricted to actively proliferating cell and does not affect cells at rest.[22] This is extremely significant as it suggests that rosmarinic acid may reduce hyperactive immune response and yet not impair healthy T cells or appropriate lymphocyte functioning, as do the immunosuppressive drugs.

T-Cell Receptors: T-cell antigen receptors are located on the T-lymphocyte cell surface, enabling the cell to recognize and respond to outside influences, microbes, and a wide a variety of antigens. Binding of an antigen or other activator to these receptors promotes several reactive processes inside the cell. The molecules involved with transducing the signal to the nuclear DNA are called transcription factors, and one such molecule is the nuclear factor of activated T cells. Another is simply called activating protein. A domino effect of molecular activation can ultimately lead to T-cell activation, the release of interleukins from T cells, and the promotion of inflammatory and immune responses. Rosmarinic acid has been found to inhibit nuclear factor of activated T cells, but not activating protein.[23] Because the nuclear factor of activated T cells is mediated by calcium ions and the activating protein is not, researchers feel that rosmarinic acid may inhibit pathways involving calcium signaling. Rosmarinic acid also has direct effect on antigen receptors on T cells by blocking signal transduction at the membrane including blockade of nuclear factors and kinase enzymes and tyrosine phosphorylation.[23]

Autoimmune Disease: One group of researchers showed that rosmarinic acid was able to induce apoptosis of T cells taken from rheumatoid arthritis patients.[24] The mechanism seems to be that rosmarinic acid induces the release of cytochrome *c* from mitochondria that, in turn, plays a role in inducing apoptosis of the aberrant T cells.[22]

An animal model of collagen-induced arthritis has shown rosmarinic acid to reduce inflammation by several mechanisms. Animals treated with rosmarinic acid displayed “remarkably reduced” synovial inflammatory markers, such as cyclooxygenase according to researchers, compared with the control animals.[25]

Rosmarinic acid is also being explored as a medicine to reduce transplant rejection. Animal research revealed that rosmarinic acid may reduce antibodies from attacking the transplanted tissue. One group of researchers investigated the ability of rosmarinic acid alone and in combination with the immunosuppressive drugs cyclosporine, prednisone, or rapamycin to inhibit proliferation of splenic T cells in animals having undergone skin graft procedures as a model of graft versus host disease. The study showed that rosmarinic acid worked synergistically with immunosuppressive drugs and increased their ability to reduce transplant rejection.[26] This might mean that a lower dose of the harsh immunosuppressant would be required if used in tandem with rosmarinic acid.

Antivenom, Collagen, and Tissue-Protecting Effects: Rosmarinic acid inhibits the classical complement pathway that may be induced my venom, bacterial infection, and other toxins and prevents sepsis,

hemolysis, and tissue destruction,[27] in part by preventing connective tissue destruction and supporting cell survival. Rosmarinic acid exerts antiaging effects on the skin, protecting against tyrosinase-, hyaluronidase-, elastase-, and collagenase-induced breakdown of the connective tissue support tissue.[28]

Rosmarinic acid shows potential as an antidote to toxic snake bites by neutralizing venom-induced hemorrhage and breakdown of collagen.[29,30,31] Rosmarinic acid prevents the venom's hemorrhagic effects by inhibiting the breakdown in fibrinogen and collagen.[29] Phospholipases A_2 are the most abundant muscle-damaging components of snake venom, and rosmarinic acid drastically reduces both the muscle damage and the neuromuscular blockade exerted by phospholipase activation.[32]

Although not all clinicians will have the need for snake bite remedies, the ability of rosmarinic acid to protect against connective tissue destruction may also offer protection in collagen vascular and autoimmune conditions. For example, rosmarinic acid exerts a hepatoprotective effect[17]; supports periodontal gingival tissue[15]; and inhibits the migration, adhesion, and invasion of tumor cells[33] via stabilizing effects on T cells and limiting cytokines-driven breakdown of connective tissues.[34]

Rosmarinic acid may protect glomerular function in diabetes by reducing activation of fibronectin, collagen, and fibrin that contributes to expansion and fibrosis of the glomerular matrix,[35,36] protect against the proliferation of mesangial cells in animal models of glomerulonephritis,[36] and protect against cisplatin-induced nephrotoxicity.[16] Connective tissue growth factor plays a pathogenic role in diabetic nephropathy, and rosmarinic acid inhibits connective tissue growth factor stimulated by hyperglycemia, helping protect proximal tubular epithelial cells of the kidneys in animal models of nephropathy.[37,38]

Transplanting functional pancreatic islets is being explored as a therapeutic option in type I diabetes, but the transplants are often rejected because of the background inflammatory state of the pancreas. Pharmaceutical immunosuppressants have debilitating side effects, and rosmarinic acid is suggested to be an effective adjuvant to monoclonal antibodies, reducing cytokine expression and T-cell infiltration and preventing apoptosis in transplanted cells.[39]

Evidence-Based Research

Rosmarinic acid's effects on T cells and the release of inflammatory cytokines are shown to benefit chronic inflammatory disease, acute and chronic allergic phenomena, and autoimmune diseases. Rosmarinic acid has antimicrobial,[40] antioxidant,[41] and anti-inflammatory activity[11,42,43,44,45] that contributes to its effects in medical conditions as varied as hayfever[4] to organ rejection in transplant patients[39,46,47] to acute snake bite[30,31] because of its significant ability to limit inflammatory and toxic processes. Rosmarinic acid attenuates inflammation as a result of chemical irritants[48] and allergic disorders[4,6]; protects neurons in situations of oxidative and ischemic stress[19]; slows the development of Alzheimer's disease[18,49,50]; protects dopaminergic cells in animal models of Parkinson's disease[51]; and may reduce inflammation in rheumatoid arthritis, allergic airway disease, atopic conditions, and chronic inflammation, such as diabetes.

Rosmarinic acid reduces oxidative stress and the resultant release of inflammatory compounds,[52] limits the activation of complement pathways,[53] reduces allergic immunoglobulin and cytokine responses, and attenuates the release of proinflammatory cytokines from activated T cells. T cells are among the most prominent lymphocytes involved in both allergic and autoimmune diseases. Rosmarinic acid may offer a safer alternative to inhibiting T cells than immunosuppressive drugs for allergy and autoimmune disease patients and help control pathologic progression in chronic inflammatory diseases such glomerulonephritis. Autoimmune diseases involve aberrant T-cell activity. For example, T cells play a

large role in initiating and perpetuating rheumatoid arthritis[54] commonly managed with immunosuppressive drugs as a means of controlling pain, symptoms, and skin, tissue, and joint destruction. Research is emerging showing that rosmarinic acid can induce T-cell apoptosis[24] and reduce autoinflammatory activity in a similar manner, but without the risks and long-term side effects of the immunosuppressive drugs.

Allergic Airway Diseases: Airborne pollutants, such as diesel exhaust particles, are believed to contribute to the increasing rates of allergies, asthma, and lung diseases in the general public.[55] Animal models of lung disease have shown intratracheal instillation of diesel exhaust particles to generate reactive oxygen species. One study showed rosmarinic acid to prevent lung inflammation when animals were supplemented orally with rosmarinic acid and then exposed to diesel exhaust.[6] The increases in interleukins and several inflammatory proteins normally elevated by diesel particle inhalation were all inhibited by rosmarinic acid, as was the infiltration of neutrophils in the lung tissue and local interstitial edema.

One mouse model of allergic asthma sensitized tracheal tissue with dust mite exposure, inducing eosinophilic inflammation, and then measured interleukins and eotaxin. Eotaxin is a cytokine that activates eosinophils, the type of white blood cell most commonly elevated in allergic conditions. Pretreatment with a high rosmarinic acid *Perilla* showed that it was able to prevent the eosinophilic inflammatory response.[3] The researchers also reported that interleukins and eotaxin elevations were inhibited by rosmarinic acid. Similar effects are seen in animal models of atopic dermatitis.[14]

Human Clinical Trials on Asthma: One human trial on allergic rhinoconjunctivitis investigated the effects of rosmarinic acid-enriched *Perilla* extract. The 21-day study administered either the *Perilla*–rosmarinic acid combo at a dose of 200 mg in 10 subjects and 50 mg in nine additional subjects or a placebo and evaluated logs of patient's symptoms as well as evaluated nasal lavage samples for inflammatory cells. At the end of the 3 weeks, the group receiving the rosmarinic acid reported fewer symptoms (including itchy nose, itchy eyes, and watery eyes) compared with the group receiving the placebo. Furthermore, the nasal lavage contained significantly fewer neutrophils and eosinophils.[56]

Another nearly identical study by the same researchers administered rosmarinic acid to seasonal allergic rhinitis sufferers and examined nasal lavage–obtained cells and cytokine concentration in dosed patients compared with placebo-treated controls. Rosmarinic acid supplementation was shown to decrease the numbers of neutrophils and eosinophils in nasal lavage fluid.[57]

The results of these animal and human investigations suggest that rosmarinic acid ameliorates increases in cytokines, chemokines, and allergen-specific antibodies in allergic airway diseases.[3]

Safety in Pregnancy and Breastfeeding

There have been no investigations on the use rosmarinic acid in pregnancy and lactation to date. Animal investigations in milk goats have found rosemary consumption to have no deleterious effects on milk quantity or quantity.[58] Because of the historical use of rosemary and related herbs that contain rosmarinic acid as culinary spices, it is generally assumed that moderate consumption of rosemary and *Perilla* is safe during pregnancy and lactation, but less can be assumed for isolated and concentrated rosmarinic acid.

General Safety

Rosmarinic acid is considered safe and well tolerated. One clinical study that investigated rosmarinic acid in allergic rhinitis patients reported no adverse events, and no significant abnormalities were detected in routine blood tests.[56]

Dosage

Animal studies have dosed 1–5 mg/kg.[59]

Rosmarinic acid is generally considered safe; typical formulas use 12–100 mg per capsule.

Traditional Uses

Rosmarinic acid is a caffeic acid derivative that occurs in occurs in several plants in addition to rosemary (*Rosmarinus*), including *Perilla*, *Prunella*, *Melissa*, *Salvia, Borago*, and *Lithosperma.* Many of these plants have been used traditionally for upper respiratory symptoms and occasionally allergic phenomena. Rosmarinic acid may now be produced in plant cell cultures. Rosmarinic acid is one of the most abundant caffeic esters occurring in plants. It seems to be most active in humans when it becomes auto-oxidized.[60]

Rosmarinic acid is reportedly fairly well absorbed from the gastrointestinal tract and may have some capacity for dermal absorption as well. It seems to be readily assimilated by all of the major organs, with the highest concentrations seen in the lungs. This may explain why plants high in rosmarinic acid are traditionally used to treat asthma and respiratory allergies.

Studies on each of these individual herbs noted to be high in rosmarinic acid include numerous reports of antiinflammatory actions. *Rosmarinus*,[61] *Salvia*,[62,63] and *Perilla*[64] have powerful antioxidant actions, much of which is now being credited to immune-modulating effects or rosmarinic acid. *Perilla frutescens* is a popular culinary garnish and part of the Asian herbal medicine tradition used for allergies[41,65] and as an antidote for allergic reactivity to fish and crab ingestion, and for bronchial asthma.

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