Rosmarinic Acid as a Novel Agent in the Treatment of Autoimmune Disease

Jill Stansbury, ND[a]
Paul Saunders, PhD[b]
David Winston, RH(AHG)[c]
Eugene R. Zampieron, ND[d]

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ABSTRACT

Rosmarinic acid has been shown to selectively induce T cell apoptosis in aberrant lymphocytes, but not normal/quiescent T cells. Rosmarinic acid also reduces gamma interferon driven T cell responses and reduces interleukin production following T cell stimulation. Furthermore, rosmarinic acid affects signal transduction inside T cells by affecting specific tyrosine kinase enzymes inside the cell. By direct effects on T cells as well as other anti-inflammatory and antioxidant effects, rosmarinic acid may be a safe and valuable tool for reducing autoimmune inflammation. It may also be safe and advantageous to use in tandem with pharmaceutical treatment of autoimmune diseases.

Keywords: Rosmarinic acid, Autoimmune diseases, Inflammation, T cell apoptosis

CLINICAL IMPLICATIONS

Autoimmune diseases are among the most challenging to treat. Conventional medical therapies are immunosuppressive agents that suppress symptoms, but also have undesirable side effects. An effective alternative therapy without these side effects would be extremely valuable. Rosmarinic acid, which has been used in multiple sclerosis and thyroid autoimmune disease, may be such an alternative therapy.

PRIMARY INDICATION

Autoimmune diseases, allergies and inflammation

ADJUNCTIVE OR STAND ALONE TREATMENT

Adjunctive

BIOACTIVE CONSTITUENTS

150-500 mg bid

TIME TO CLINICAL IMPROVEMENT

Changes in lab tests or symptomatology can occur within four weeks.

LAB TEST TO ASSESS EFFICACY

Tests specific to the condition being treated

SYNERGISTIC COMBINATION

Unknown

SIDE EFFECTS

Consume with food and water to prevent possible gastric irritation

PROVEN DRUG INTERACTION

None documented

[a] Corresponding author: Battle Ground Healing Arts, 408 E Main Street , Battle Ground, WA 98604, USA
[b] Dundas Naturopathic Centre, Dundas L9H 1V6, Canada
[c] David Winston's Center for Herbal Studies, Broadway, NJ 08808, USA
[d] 413 Grassy Hill, Woodbury, CT 06798, USA

DISCUSSION

Rosmarinic acid is a caffeic acid derivative found in the *Nepetoideae* branch of the *Lamiaceae* (Mint) family including *Rosmarinus officinalis*,[1] *Prunella vulgaris*,[2] *Melissa officinalis*,[3] *Coleus spp*.,[4] and *Salvia officinalis,*[5] and several members of the *Boraginaceae* family including the genus *Lithospermum*.[6] Rosmarinic acid is synthesized in plants from the amino acids phenylalanine and tyrosine involving at least eight enzymatic steps. Botanical research has identified several specific genes involved with the synthesis of rosmarinic acid.

ROSMARINIC ACID AND IMMUNE FUNCTION

Early animal and molecular studies found rosmarinic acid had antimicrobial, antioxidant,[7] and anti-inflammatory benefits.[6] These anti-inflammatory actions may be particularly useful in the treatment of autoimmune diseases. Additionally, rosmarinic acid is being studied as an anti-rejection agent for transplant patients.[8] The herb may also possess the ability to modulate neuroendocrine function.[9]

T CELLS, APOPTOSIS AND AUTOIMMUNE DISEASE

T cells are lymphocytes largely responsible for the destructive processes that occur in both autoimmune diseases and organ transplant rejection. Inhibiting T cells with immunosuppressive agents is the primary therapy for autoimmune disease and transplant patients. Once started, these immunosuppressants typically must be used by the transplant patient for life. Many of the immunosuppressive drugs used for autoimmune diseases suppress white blood cell activity and induce apoptosis in T cells, NK cells and other lymphocytes as a means of controlling pain, reducing symptoms, and slowing or preventing skin, tissue, and joint destruction. Research results reveal that rosmarinic acid can induce T cell apoptosis (programmed cell death)[10] and reduce auto-inflammatory activity in a similar manner but apparently without the risks and long-term side effects of immunosuppressive therapy.

ROSMARINIC ACID AND T CELL ACTIVATION

A region on the nuclear DNA of lymphocytes, called the SH2 domain, appears to be involved in directing T cell activities and thus playing a role in cancer, autoimmune, and inflammatory diseases. Rosmarinic acid has been shown to act as an agonist at the SH2 domain and inhibit T cell activity *in vitro.*[11] *Rosmarinic acid has also been shown to reduce the ability of activated T cells to promote pro-inflammatory interleukin production and release.*[12]

ROSMARINIC ACID AND PROTEIN KINASE SIGNAL TRANSDUCTION

One mechanism of T cell inhibition may involve protein kinase enzymes. There are numerous protein kinases that play important roles in translat-

Rosmarinus officinalis of the Labitae family

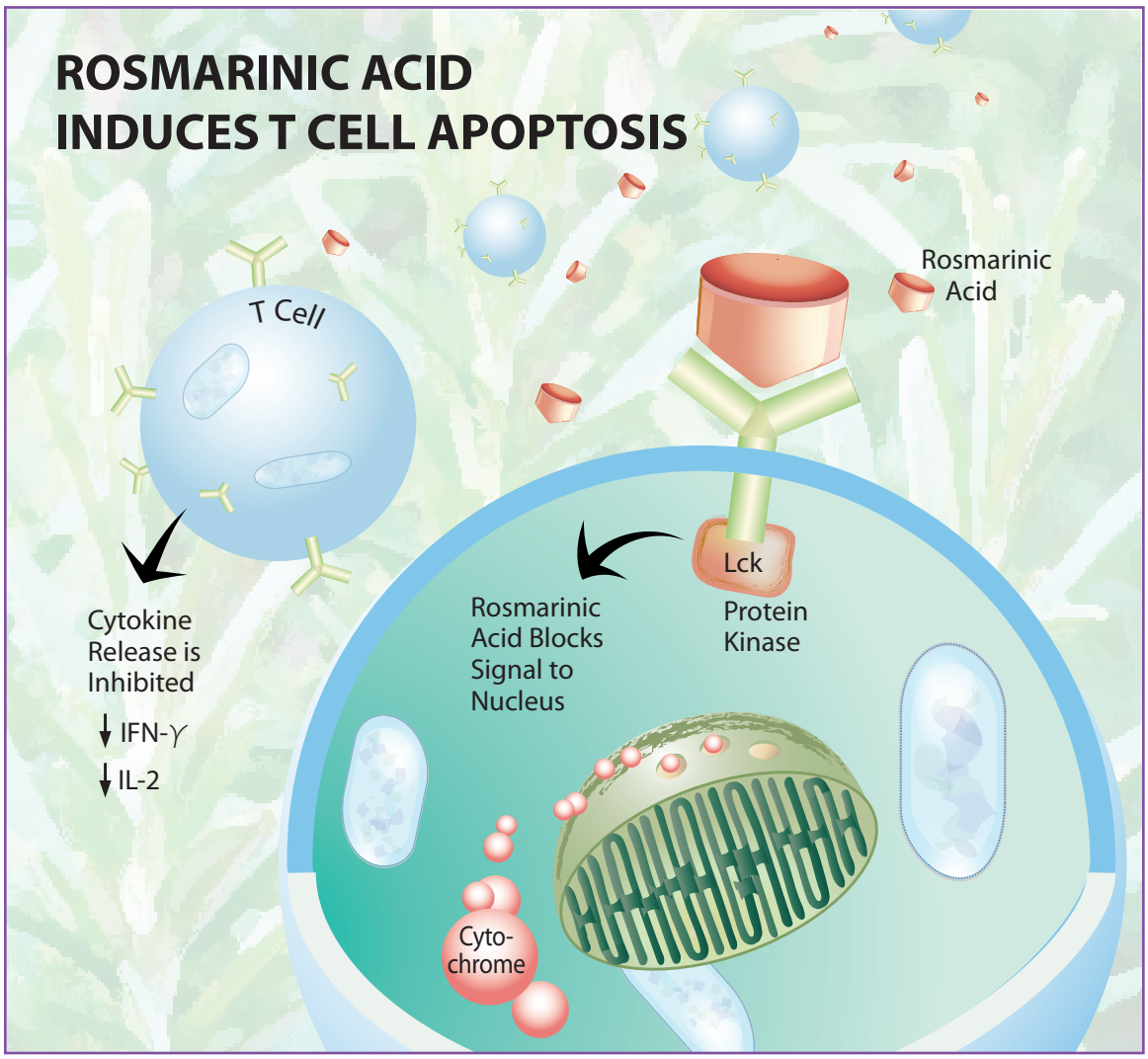

Figure 1

ing signals from cellular receptors to the interior of cells to ultimately act on the cellular DNA This process, called signal transduction, directs certain cellular activities. Lck, a tyrosine protein kinase, is specific to T cell signal transduction. Rosmarinic acid has been shown to inhibit activity between the Lck tyrosine kinase and a downstream peptide, thereby reducing signal transduction in T cells.[13] Importantly, disrupted Lck signal transduction promotes apoptosis only in T cells that are actively proliferating, not T cells at rest.[14] This is extremely significant since it suggests that rosmarinic acid may reduce a hyperactive immune response while preserving appropriate lymphocyte function.

T CELL RECEPTORS AND ROSMARINIC ACID

T cell antigen receptors are located on T lymphocytes and enable the cell to recognize and respond to outside influences, microbes, and a wide variety of antigens. Binding of an antigen or other activator to these receptors promotes a number of reactive processes inside the cell (**Fig 1**). The molecules involved with transducing the signal to the nuclear DNA are called transcription factors. Two such factors are the nuclear factor of activated T cells and activating protein. A domino effect of molecular activation can ultimately lead to T cell activation, the

release of interleukins from T cells, and promotion of inflammatory and immune responses. Rosmarinic acid has been found to inhibit nuclear factor of activated T cells, but not activating protein.[12] This mechanism is shared by non-steroidal anti-inflammatory drugs.[15]

Rosmarinic acid was able to induce apoptosis in activated T cells taken from patients with rheumatoid arthritis.[10] In this study, rosmarinic acid appeared to induce the release of cytochrome C from mitochondria which in turn induced apoptosis in *ex vivo* human T cells.

In addition, rosmarinic acid reduced inflammation in an animal model of collagen-induced arthritis. Animals treated with rosmarinic acid displayed markedly reduced levels of synovial inflammatory markers (e.g. cyclooxygenase) compared to control animals.[16]

ROSMARINIC ACID AND TRANSPLANT MEDICINE

Rosmarinic acid is also being explored as a medicine to reduce transplant rejection. Animal research revealed that rosmarinic acid reduces the antibody attack on 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 that had undergone skin grafts as a model of graft versus host disease. The study showed that rosmarinic acid worked synergistically with the immunosuppressive drugs and decreased the transplant rejection response.[17] Since anti-rejection drugs have a number of undesirable side effects that increase with dose, co-administration of rosmarinic acid could reduce the total required dose of immunosuppressant medication.

SUMMARY

Rosmarinic acid has been shown to selectively induce T cell apoptosis in aberrant lymphocytes, but not normal/quiescent T cells. Rosmarinic acid also reduces gamma interferon driven T cell responses and reduces interleukin production following T cell stimulation. Furthermore, rosmarinic acid affects signal transduction inside T cells by affecting specific tyrosine kinase enzymes inside the cell. By direct effects on T cells as well as other anti-inflammatory and antioxidant effects, rosmarinic acid may be a safe and valuable tool for reducing autoimmune inflammation. It may also be safe and advantageous to use in tandem with pharmaceutical treatment of autoimmune diseases.

DISCLOSURE OF INTERESTS

Dr. Saunders reports personal fees related to employment or seeing patients from CCNM, the Dundas Naturopathic Centre, and from Beaumont Health Systems, Troy Hospital, MI, outside the submitted work. Dr. Winston reports personal fees from Herbalist & Alchemist, Inc, outside the submitted work. Dr. Zampieron reports royalties from a product he has developed for Restorative Formulations with rosmarinic acid as one of its therapeutic ingredients, outside the submitted work. Dr. Stansbury has nothing to disclose.

REVIEW ESSAY

Many nutrients and herbs that have not been the subject of randomized controlled studies are used regularly by clinicians. They have also been used traditionally for hundreds, sometimes thousands of years. Review Essays contain the opinions of professionals and experts in the fields of nutritional and botanical medicine on how to most effectively use herbs and nutrients in clinical practice. The dosages recommended are based on clinical experience. Side effects that are described in "Unsubstantiated Theoretical Concerns" have not been seen in clinical practice or clinical studies but are speculative based on, for example, possible mechanisms of action.

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