Natural Support for Autoimmune Rheumatic Conditions

Liz Sutherland, ND

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Overview

The prevalence of organ-specific and systemic autoimmune conditions is increasing worldwide.[1] This rise is not attributable to improvements in diagnosis, but more likely to increasing exposure to a growing array of unavoidable environmental risk factors.

Because autoimmune rheumatic disorders manifest in a diverse array of signs and symptoms, they can be extremely challenging to manage. Goals of treatment are manifold and include modulating immune activity, reducing or preventing organ damage and comorbidities, and alleviating pain and fatigue.[2]

With regard to immune activity in autoimmune disorders, aberrant autoreactivity of $CD4^+$ T helper cells leads, among other outcomes, to Th1 cells producing interferon gamma (IFN?), and Th17 cells producing IL-17. IFN? is considered central to the pathogenesis and clinical course of systemic lupus erythematosus (SLE),[3] and IL-17 to the pathogenesis and clinical course of rheumatoid arthritis (RA).[4] Drugs that modulate or suppress immune function, the core of conventional treatment for autoimmune disorders, have limited benefit and serious side effects. With the rising global prevalence of autoimmune diseases, it is all the more important to identify potentially effective and non-toxic options to support a holistic therapeutic approach.

Certain phytoconstituents appear to exert downstream immunoregulatory and anti-inflammatory effects via their ability to modulate intracellular signaling. Among other mechanisms, these phytoconstituents are able to regulate expression of cell-cycle proteins and other protein kinases involved in transcription of autoantibodies and inflammatory cytokines, both of which are implicated in the onset and worsening of autoimmune pathophysiology.[5,6,7,8]

Phytoconstituents with Immunomodulatory Properties

Berberine

Pre-clinical and cell culture studies suggest that the isoquinoline alkaloid berberine impedes cell signaling pathways that promote the differentiation and function of pro-inflammatory Th1 and Th17 cells. It may also inhibit the biosynthesis of interferons that trigger the apoptosis cascade in SLE.[9] Berberine has been shown to redress the imbalance of the Treg to Th17 cell ratio, which is a hallmark of autoreactivity, both directly, by inducing differentiation of Treg cells, and indirectly, by selectively influencing gut microbiome composition to promote Treg development.[10]

In addition, berberine has been found to mitigate autoreactivity by decreasing the expression of M1 macrophages, which produce pro-inflammatory cytokines, and promoting the M2 phenotype, which produces anti-inflammatory factors and supports tissue repair.[11] In an animal model of RA, berberine considerably improved clinical signs, such as joint destruction, and downregulated several pro-inflammatory factors, including IL-1?, IL-6, and IL-17.[12,13]

Cordyceps sinensis

Cordyceps sinensis is a fungus with a long history of therapeutic use in Chinese medicine as an adaptogenic agent in a multitude of complex health conditions.[14] In an animal model of SLE, oral administration of *C. sinensis* at 2.4 mg/g/day mitigated disease severity, increased survival, lowered proteinuria, and decreased antibodies to anti-double-stranded DNA, potentially through its ability to modulate the ratio of CD4 to CD8 T lymphocytes.[15] A bioactive constituent of Cordyceps, cordycepin, was found to modulate inflammation by inhibiting IL-1?-induced chemokine production in synovial fibroblasts, suggesting it might help attenuate connective tissue damage in RA and related autoimmune disorders.[16]

Rehmannia glutinosa

Rehmannia glutinosa is another adaptogenic botanical with a long history of use in Chinese medicine. Its mechanisms of action are not yet fully elucidated, but studies that highlight its potential neuroprotective effects suggest it has powerful antioxidant and anti-inflammatory properties.[17] In addition, recent evidence shows that the polysaccharide constituents of *Rehmannia glutinosa* may favorably influence Th1/Th2 balance, suggesting it has potential as an immune modulator.[18]

Rosmarinic acid

Rosmarinic acid is a polyphenolic compound found in plants such as R*osmarinus officinalis*. Multiple in vitro and in vivo studies have corroborated its extensive anti-oxidative, anti-apoptotic, and anti-inflammatory effects.[19,20,21]Rosmarinic acid was found to limit intracellular production of IFN by inhibiting the expression of IFN-stimulated genes. This is significant because a deranged response to self-nucleic acids results in the sustained production of type 1 IFN, which is a hallmark of autoimmune reactivity.[22]

Rosmarinic acid has been shown to inhibit the signal transduction of lymphocyte-specific protein tyrosine kinase (Lck), which regulates many cellular processes including T-cell development and homeostasis. Interestingly, the net effect of this inhibition triggered apoptosis only in active, proliferating T cells, preventing the expression of pro-inflammatory cytokines such as IL-2 and IFN?.[23] It is possible, therefore, that rosmarinic acid could play a role in re-establishing immune homeostasis under autoreactive conditions. In an in vivo study of RA, rosmarinic acid was found to induce apoptosis in activated T cell subsets far more than in naïve T cells and did so in a dose-dependent manner via the mitochondrial pathway of apoptosis. T cells in particular contribute to the onset and clinical progression of RA, and so the potentially preferential apoptosis of pathogenic T cells, is an important consideration.[24]

In two studies using animal models of RA, rosmarinic acid was found to substantially lower levels of inflammatory markers, such as COX-2, in synovial tissue, with associated improvements in the arthritis index and clinical signs of treated animals.[25,26]

A Word on the Microbiome

Evidence for the fundamental contribution of gastrointestinal health and, in particular, the gut microbiome, to

immune function and dysfunction is irrefutable and growing.[27] As a consequence, any Restorative Medicine approach to autoimmune disorders must also focus on gut health. The ability of berberine to shift microbiome composition toward Treg development has already been mentioned.[10] In addition, *Lactobacillus* has been shown to have many immunomodulatory effects, including reducing the population of pro-inflammatory ILC3 and Th17 cells, inhibiting IL-17 production, shifting the Treg/Th17 balance toward the Treg phenotype, and stimulating production of IL-10, which protects against hyper-immune reactivity.[28,29] In pre-clinical studies of RA, *Lactobacillus casei* was found to decrease joint swelling, arthritis scores, and serum inflammatory cytokine levels.[30,31]

MicroRNAs (MiRNAs) are known to play an extensive regulatory role in immune cell function. Studies have shown an association between dysregulated expression of some miRNAs, such as miR-155 and miR-181a, and the pathogenesis and clinical severity of SLE.

Interestingly, an in vivo study found that *Lactobacillus rhamnosus* and *Lactobacillus delbrueckii* attenuated the activity of miR-155 and miR-181a in SLE patients.[32]

Key Takeaways

- Certain phytoconstituents may be helpful as part of a therapeutic protocol for autoimmune rheumatic conditions, as they have been shown to have immunoregulatory effects in experimental and pre-clinical studies.
- By modulating intracellular signaling pathways, they downregulate or upregulate downstream immune and inflammatory factors to re-establish immune balance.
- The mechanisms of action are complex and can involve impeding or promoting gene expression at the level of transcription.
- Important phytoconstituents and plants with immunomodulatory properties via intracellular signaling pathways include berberine, *Cordyceps sinensis*, *Rehmannia glutinosa*, and rosmarinic acid.
- Berberine exerts some of its immunomodulatory effects by shifting microbiome composition in a favorable direction for immune balance. Certain *Lactobacillus sp*. have also been shown to be significant regulators of systemic immune function.

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27 State Street, Suite 5 | Montpelier, VT 05602 | 866-962-2276