Natural Support for Autoimmune and Inflammatory Disease

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ABSTRACT

Autoimmune diseases such as rheumatoid arthritis (RA), ankylosing spondylitis, and systemic lupus erythematosus (SLE), involve destruction of healthy cells by the body's own defensive mechanism. If the immune system's *faux pas* is not corrected, the attack can progress to the heart, lungs, and other vital organs. The mechanisms that cause the deregulation of the immune response are not entirely understood. It can be assumed that heavy metal toxicity, leaky gut syndrome, infectious bacteria and parasites, and nutritional imbalances can overburden the body's immune system, thus deregulating immune signals and responses. Ongoing research investigates the mechanism by which these factors cause the immune system to attack the body's own tissues. In this paper, we discuss natural therapies that can help regulate the immune system's aggressive behavior without suppressing or altering its necessary defenses.

KEY WORDS

Inflammation, botanicals, natural therapies, autoimmune, arthritis, rheumatology, nuclear factor kappa beta (NFkB), cytokines

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THE FUNCTIONAL IMMUNE RESPONSE

The immune system constantly surveys the body for foreign ("non-self") substances, such as cancerous cells, bacteria, viruses, parasites, foreign proteins and chemical insults. During a normal immune response, leukotrienes and prostaglandins dilate blood vessels so that immune components can quickly travel to the area that needs protection.[1] Increased blood flow causes swelling, redness, and heat. Another wave of pro-inflammatory compounds, chemotactic factors (also known as cytokines), activate the white blood cells to begin attacking damaged cells and pathogens. As pathogens are destroyed, their cell walls and internal components leak out, triggering still another phase of immune defense. B cells produce antibodies specific to the pathogen or cell under attack, and also alert macrophages that invaders are present. The oxidizing chemicals released by white blood cells to destroy pathogens can inadvertently affect normal cells. The healthy cells surrounding an inflammatory response attempt to protect themselves by secreting anti-inflammatory prostaglandins, antioxidants, anti-chemotactic chemicals, and enzymes. All of these chemicals counter the destructive substances released by white blood cells, protecting against 'collateral damage' to healthy tissue. When the body is functioning normally, pro-inflammatory cytokines are soon suppressed by the anti-inflammatory cytokines secreted by neighboring cells. The inflammatory response subsides; suppressor T cells stop the production of antibodies, blood vessels return to their normal size, and the repair process begins to mend damaged tissue.

AUTOIMMUNE DE-REGULATORS – WHEN THE IMMUNE SYSTEM RUNS AMOK

In autoimmune diseases, the immune response continues unabated even if there is no foreign invader to attack. The exact sequence of events that lead the immune system to turn against the body, has yet to be determined. However, Nuclear factor kappa beta (NFkB) regulators, pro-inflammatory prostaglandins, auto-antibodies, and defective suppressor T cells have been identified as suspects in deregulating the immune response.

High levels of inflammatory agents spur the immune system into constant activity. Initially, the immune system raises its defenses against foreign substances only. With prolonged inflammatory stress however, the immune system will turn against its host and attack the body's own tissues, thus establishing a classical autoimmune disease.[2] Herbs that reduce inflammation may help down-regulate the autoimmune response. Several herbs that have been traditionally used for this purpose also have been investigated scientifically to determine their mechanism(s) of action. These herbs include: Hops, Artemisia, Sarsaparilla, Reishi Mushroom, Ashwagandha, Nettle, Rehmannia, and Chinese Skullcap (Scute). Other important herbs that may have a role in decreasing both inflammation and the overzealous auto immune response include Boswellia serrata, Green Tea, Ginger, Turmeric, White Willow, Stephania and Chinese Thunder God Vine.

IMMUNE MODULATING HERBS

Hops (*Humulus lupus*)

Hops is a rambling vine and member of the *Cannabinacea* family, which has traditionally been used in herbal medicine as a nervine and sedative. It also is a plant of economic importance in the production of beer. Recent research into the plant shows it has excellent potential for the management of pain and inflammation associated with rheumatologic issues. In one clinical trial, Hops exhibited Cox-2 inhibition over 9 hours, equivalent to ibuprofen 400 mg but had significant Cox-1 sparing activity relative to ibuprofen. The authors of this article concluded that Hops extracts may represent a safe alternative to ibuprofen for non-prescription anti-inflammation.[3]

A combination of hops—standardized to iso-alpha acids—with oleanolic acids (a powerful anti-inflammatory triterpenoid saponin), and rosmarinic acid, has been the subject of a clinical trial on pain management in patients with rheumatic disease. (Rosmarinic acid is a natural caffeic acid deriva-

tive, classified as a polyphenol antioxidant, and found in many herbs in the mint family.) Patients with diagnosed osteoarthritis (OA), rheumatoid arthritis (RA) and fibromyalgia were given this botanical combination, 440 mg three times per day for 4 weeks, and then increased to 880 mg twice per day for the subsequent 4 weeks. Pain and condition-specific systems were assessed from 40% to 50% and a reduction in C-reactive protein were noted in the arthritic, but not fibromyalgia patients.[4] Other studies have also investigated possible mechanisms of action by which hops reduced inflammation through inhibition of multiple kinases involved in the NFkB pathway, and conclude that hops may have potential as a safe anti-inflammatory therapeutic.[5,6,7]

Artemisia (*Artemisia annua*) Qinghao

Although many Westerners might recognize this plant by the name Sweet Annie or Sweet Wormwood, Qinghao was described in 2737 BC by the Blazing Emperor Shen Nong, in one of the oldest herbal books known.[8] In traditional Chinese medicine, *Artemisia annua* has been widely used to treat autoimmune diseases such as Systemic Lupus Erythematoses (SLE) and RA.[9] It was traditionally prescribed for "summer heat' or inflammatory conditions which worsen in the hot summer months. Even its name 'wormwood' was most likely chosen for its observed ability to destroy parasites.

With the isolation of a novel compound named artemesinin, as well as its derivatives (artesunate and artemether), Qinghao has gained attention for its ability to treat drug resistant malarial strains,[10] and it has been embraced by the World Health Organization as a breakthrough in preventing this deadly scourge. Since 1979, both Qinghao and artemesinin have been used in the treatment of SLE, with claimed positive effects in recent clinical trials.[11] The dose of artemesinin that has been used clinically for SLE has ranged from 0.2-0.6 grams per day; this corresponds to a dose of qinghao of about 2030 grams, the same as used to treat malaria. Treatment time is typically about 3 months. Qinghao has also been applied in treatment of discoid lupus and was deemed to be a useful therapy.[12-13] Modulatory effects of *Artemisia annua* extracts on human complement, neutrophile oxidative burst and proliferation of T lymphocytes may explain its effect on autoimmune disease. Research suggests that Qinghao extracts could modulate both cellular and humoral response.[14] Artemisia may be useful in the treatment of autoimmune diseases via an immune-modulatory effect.[15] In addition, many healthcare practitioners are using Qinghao as adjunctive care for borelliosis due to the spirochete that is linked to the development of Lyme disease, and the several co-infections accompanying Lyme and other tick-borne illnesses.

Sarsaparilla *(Smilax spp.)*

Sarsaparilla grows throughout the world, with the tropical varieties found in the Caribbean, South America, Mexico, and Central America being most prized for their medicinal value. Sarsaparilla is particularly useful for illness caused by spirochetes, such as syphilis,[16,17] leptospirosis and Lyme disease. In fact, it was included in the United States Pharmacopoeia as a treatment for secondary syphilis.[18] Sarsaparilla contains plant steroids like sarsasapogenin, smilagenin, sitosterol, stigmasterol, and pollinastanol, and saponins including sarsasaponin, smilasaponin, sarsaparilloside, and sitosterol glucoside.[19,20] The majority of sarsaparilla's pharmacological properties and actions have been attributed to these steroids and saponins.

In China, the herb has been used in combination with other botanicals for syphilis and leptospirosis.[21] Zampieron *et al* have experienced excellent clinical success using sarsaparilla for patients with Lyme disease.[22] A protocol developed by Zampieron and Kamhi combines Jamaican or Honduras sarsaparilla (4:1 solid extract), tetracyclic oxidonle alkaloid (TOA), free cat's claw (*Uncaria tomentosa*), standardized olive leaf extract, Qinghao, and a combination of Chinese botanicals (including *Lonicera Japonica*, *Glycyrrhiza uralenisi*, *Dictamnus dasycarpi*, *Portulacae oleraceae*, *Taraxacum mongoli,* and *Dipsacus japonica*). These herbs are used as part of a comprehensive holistic protocol to address the ravages of Lyme disease.[23]

Saponins (found in sarsaparilla) emulsify and bind to endotoxins in the gastrointestinal tract, aiding in their elimination.[24] Many illnesses, including RA,[25]

psoriasis,[26] gout, and acne have been associated with increased levels of endotoxins.[27,28] The anti-inflammatory mechanism of action of sarsaparilla for arthritis is linked to its ability to inhibit TNF-alpha-induced NFkB activation.[29,30]

Indian Sarsaparilla Vine (*Hemidesmus indicus*)

Indian sarsaparilla vine is not a true sarsaparilla, but is actually a close family member of American Milkweed and European Pleurisy Root. It is traditionally used for snakebites, chronic skin diseases, and autoimmune illnesses such as RA.[31,32] The active chemical constituents of this plant include coumarins and triterpenoid saponins, which act as oxygen radical scavengers[33] and immune modulators[34] while protecting kidney[33] and liver function.[35] *Hemidesmus* down-regulates the activity of pro-inflammatory agents (interferons, interleukins, prostaglandins) and other immune cells (T and B cells, antibodies, cytokines) involved in the inflammatory process, and acts as a powerful tissue protective anti-oxidant.[33,36]

Ashwagandha (Withania somnifera)

Reishi Mushroom (*Ganoderma spp.*)

Reishi mushroom has been called the "mushroom of immortality." A member of the *Polyporacae* family, it is commonly found growing in a shelf-like form on decaying trees. Ancient Chinese medical texts list it as an immune regulator, with calming, pain relieving action, which "tonifies the blood".[37] In traditional Chinese medicine, the main function of blood is to nourish the body, moisten the body tissues and "anchor the mind". If the blood is "deficient", it cannot provide physiologically adequate nutrition, which manifests in generalized fatigue, paleness, dry skin, anxiety and mental restlessness. These symptoms are treated by "tonifying" the blood (*i.e.,* by boosting the nutritive capacity of the blood).[38]

While illnesses such as cancer and viral infections may require an increase in immune function, allergic reactions and autoimmune disease call for a down-regulation of the immune system. Reishi mushroom is a true "amphoteric" herb, which can up regulate or down regulate the immune system as needed.[39] Reishi mushroom is rich in polysaccharides, immune-modulating proteins, and steroidal saponin glycosides that influence the adrenal-hypothalamic-pituitary axis feedback loop, which regulates inflammation. An amphoteric protein isolated from *Ganoderma* (called Ling Zhi-8) was shown to be both mutagenic (causing white blood cells to multiply) and immunosuppressive (reducing TNF-alpha and the formation of antibodies) in autoimmune disease.[39] In another study, *Ganoderma* showed significant effects on modulating the pro-inflammatory cytokine IL-18 after 24 weeks. This may exert a beneficial immune-modulatory effect in patients with RA.[40]

Ashwagandha (*Withania somnifera*)

Ashwagandha is widely used in Ayurvedic medicine, the traditional medical system of India.[41] Ashwagandha is akin to Ginseng in other parts of the Orient. Both herbs are touted for their longevity-enhancing and sexual stimulant properties; however, Ashwagandha is considered to be milder than Ginseng. It is an ingredient in many formulations prescribed for a variety of musculoskeletal conditions (*e.g.,* arthritis and rheumatism), and as a

general adaptogen used to increase energy, improve overall health, and balance pathological states.[41] It is credited to enhance longevity, prevent adrenal exhaustion, balance hormones in men with andropause, and prevent convalescence in the elderly.[42] Ashwagandha has been comprehensively analyzed, and a plethora of chemical components have been identified. Some of the biologically active chemical constituents are alkaloids (isopelletierineanaferine), steroidal lactones (withanolides, withaferins), saponins (sitoindoside VII and VIII) and withanolides, as well as a generous amount of iron, calcium, and other elements.[42]

Ashwagandha can be applied externally as a topical analgesic. Cyclooxygenase (COX) inhibition is one of the mechanisms for the herb's antiarthritic properties.[43] In animal studies, Ashwagandha's anti-inflammatory effects were comparable to those of hydrocortisone.[44] *In vitro* studies suggest that Ashwagandha has anti-inflammatory properties that may protect against cartilage damage in OA.[45] Human clinical trials on OA patients using a combination herbal formula inclusive of Ashwagandha, report positive effects.[46] Although human clinical trials on RA study subjects are sparse in the literature, *in vitro* studies illustrate that the effect of an Ashwagandha tincture (crude ethanol extract) exhibited ant-inflammatory effects on peripheral blood mononuclear cells and synovial fluid mononuclear cells of RA patients. In one study, the extract was shown to significantly suppress lipopolysaccharide-induced production of proinflammatory cytokines TNF-alpha, IL-1beta and IL-12p40, but had no effect on IL-6 production at the protein and transcript level[47] *Withania somnifera* is an immune amphoteric, both stimulating immune response in low immune states[48] and exerting an immunosuppressive action on B and T cell activity in hyper-immune/autoimmune states.[49]

Nettle (*Urtica dioica)*

Nettle is often called Stinging Nettle with good reason—as anyone who comes in contact with it will attest! The leaves of *Urtica dioica* have been used as a medicine and food since ancient times.[50] "Nettle" originated from the Anglo-Saxon word 'netel' or 'noedl', meaning 'needle'.[50] It refers to the tiny needle-like hairs of the plant. These hairs are coated with formic acid, histamine, serotonin, and acetylcholine, and cause a localized swelling and rash when touched. The history of nettles in treating the pain and swelling of arthritic conditions focused on its topical use.[51,52] Patients would rub the stingers of the plant directly over the painful joint and experience an analgesic (pain relieving) effect. Scientific studies have replicated this ancient practice with significant success. In a randomized controlled double-blind, crossover study, patients with osteoarthritic pain in the thumb or index finger applied stinging nettle leaf to the painful area daily for one week. The effect of this treatment was compared with that of the placebo, dead nettle leaf and a non-stinging nettle variety. After one week's treatment with stinging nettle, score reductions on both pain and disability were significantly greater than with placebo.[53]

Stinging nettle is also useful for arthritis when taken orally.[54] This action may be due to nettle leaf's ability to lower the level of the inflammatory compound TNF-alpha in the body.[54] Nettle leaf alters the genetic transcription of nuclear factor kappa beta (NFkB), thereby decreasing inflammation of synovial tissue in the joints.[55] Nettle leaf extract also had a suppressive effect on the development of dendritic cells that stimulate T-cells to release inflammatory chemicals. This may contribute to the therapeutic effect of nettle leaf extract on T cell mediated inflammatory diseases like RA.[56] There are various preparations of nettle "leaf" extracts on the market. These are not to be confused with the standardized Nettle "root" extracts used in the treatment of benign prostatic hyperplasia (BPH).

Rehmannia (*Rehmannia glutinosa)*

A popular Chinese root, *Rehmannia glutinosa* has shown promise in bringing balance to aggressive autoimmune states.[57] It is referred to in Chinese medical literature as Shen or Shu Di Huang, which is used as blood and kidney (adrenal) yin tonic.[58] Studies have shown that this herb possesses both immune-enhancing and immune-suppressant effects.[59] This dual activity may render *Rehmannia*

glutinosa superior to Disease Modifying Anti-Rheumatic Drugs (DMARDs), which can suppress the immune system so much so that they increase susceptibility to opportunistic infections.[60,61]

Modern pharmacological research has isolated various components in *Rehmannia*, which may be responsible for its adrenal tonifying, immune-modulatory, and anti-inflammatory effects.[62,63] *Rehmannia* also reduces allergic reactions by decreasing histamine release caused by TNF-alpha activity on mast cells.[64] *Rehmannia*, like most TCM herbs, is almost always used in a time-honored formulation with other items from the TCM pharmacopoeia. One classic TCM formula ("Ren Shen Yang-Rong Tang") contains *Rehmannia*, ginseng, dong quai, atractylodes, hoelen, licorice, astragalus, cinnamon, schizandra, citrus, and polygala. This formulation has been shown in mice to regulate the Th1 and Th2 imbalance often seen in autoimmune diseases.[65]

Chinese skullcap *(Scutellaria baicalensis)*

Scutellaria baicalensis or Chinese skullcap (often referred to as Scute) is also known as Huang Qin in the traditional Chinese *Materia Medica*.[66] It is one of the most widely used herbs in oriental medicine.[67] It has an expansive range of therapeutic effects (including anti-inflammatory, anti-cancer, anti-viral, anti-bacterial and amphoteric effects) on the immune response.[67,68] The active ingredients found in *Scutellaria baicalensis* include natural anti-inflammatory flavonoids and flavones. The flavonoids baicalin, baicalein and wogonin, have potent anti-oxidant properties.[69]

Scutellaria baicalensis displays anti-inflammatory effects by reducing the expression of nitric oxide (NO), inducible NOS (iNOS), Cyclooxygenase2 (COX-2), Prostaglandin E2 (PGE2), NFkB and I-kappaB-alpha as well as inflammatory cytokines, such as IL-1beta, IL-2, IL-6, IL-12 and TNF-alpha.[67] This is achieved through the down-regulation of I-KK-alpha-beta, I-kappaB-alpha, NFkB activation. Other studies have illustrated this herb's effect on the inhibition of the 5-LO pathway of arachidonic acid metabolism.[70]

Research has illustrated the effectiveness of *Scutellaria baicalensis* in treating gout (urate-crystal induced arthropathy) and inflammation in animal models. Chinese skullcap diminished MSU crystal-induced inflammation by reducing neutrophil recruitment and expression of pro-inflammatory factors and increasing the level of the potentially anti-inflammatory prostaglandin D2.[71] In a double-blind human study, a proprietary mixture of baicalin from Chinese skullcap and catechins, two anti-inflammatory flavonoids, was tested against a traditional nonsteroidal anti-inflammatory drug (NSAID), naproxen, for the management of the signs and symptoms of moderate OA in humans. In this double-blind study, 103 subjects were randomly assigned to receive either the proprietary mixture of flavonoid molecules (baicalin and catechin, referred to as flavocoxid), 500 mg twice per day or naproxen 500 mg twice per day in a 1-month onset of action trial. In this short-term study, flavocoxid was found to be as effective as naproxen in controlling the signs and symptoms of OA of the knee and that it may present a safe and effective option for those individuals on conventional nonsteroidal anti-inflammatory drugs or COX-2 inhibitors.[72] At a therapeutic dose of 2-6 grams per day, *Scutellaria baicalensis* has little known toxicity. In fact, Flavonoid, given 250 mg twice per day combined with a catechu extract known as flavocoxid given 250 mg twice per day for 12 weeks did not cause side effects more frequently than placebo.[73] However, one report has linked Baikal skullcap to pneumonitis;[74] if administered intramuscularly, Baikal skullcap has been linked to fever and a sudden drop in the leukocyte count.[75]

Boswellia *(Boswellia serrata)*

Boswellia serrata is a tree gum extract that has been shown to inhibit Th1 cytokines and promotes Th2 cytokines, which helps to reverse the imbalance of Th1 and Th2 that increases inflammation.[76]

Green tea (*Camellia sinensis*)

Among its many healing attributes in both traditional folklore and scientific literature, *Camellia sinensis* has also been shown to inhibit IL-1.[77]

Ginger (*Zingiber officinale*)

Zingiber officinale has been shown to inhibit cyclooxygenase (COX) and lipoxygenase pathways.[78] Ginger's high concentration of proteolytic enzymes (zingibain) are partially responsible for its ability to subdue pain and inflammation. Proteolytic enzymes block the action of several inflammatory substances, including prostaglandins and leukotrienes. Ginger has been shown to decrease pain in arthritis.[79,80]

Turmeric *(Curcuma longa*)

Curcuma longa is a bright yellow herb used in preparing curry. It has powerful anti-inflammatory properties, which are credited to a chemical component, curcumin. Research suggests that Turmeric suppresses NFkB and interleukin-8, while enhancing glutathione biosynthesis.[81] Turmeric also inhibits NFkB activation.

White Willow *(Salix alba)*

Salix alba is used in anti-inflammatory formulas, and has been found to inhibit lipoxygenase.[82]

Stephania *(Stephania tetrandra)*

Stephania tetrandra (called "Han-Gang-Ji in Chinese medicine") has an extensive record of medicinal use for inflammation, inflamed and swollen joints, and a variety of disorders involving the kidneys and cardiovascular system.[83,84] By relaxing both the smooth and skeletal muscle, and inhibiting fibrosis (painful scar tissue deposition in muscles), *Stephania* relieves the pain and stiffness associated with rheumatic ailments,[85] and fibrotic and inflammatory conditions (*e.g.,* fibromyalgia).[83] The active component, tetrandrine, has been used to treat patients with silicosis (an autoimmune disease of the lungs triggered by silicone dust), RA, and hypertension. Tetrandrine has a wide variety of immune-modulating effects, including inhibiting TNF alpha, as well as the formation of anti-Type 2-collagen antibodies, which are directly responsible for the destruction of cartilage and tissue destruction in autoimmune arthritis.[86,87]

Chinese Thunder God *(Tripterygium Wilfordii Hook F)*

In remote areas of southern China, the *Tripterygium wilfordii* (TW) vine grows wild; it has been used for 2000 years in traditional Chinese medicine.[88] Clinical trials have found that TW is effective in treating autoimmune diseases including RA[89] ankylosing spondylitis,[90] and other types of arthritis.[91] TW contains glycosides, which have immune-suppressing, anti-inflammatory, and analgesic properties. This herb has been found to have a wide array of immunosuppressive chemical constituents[89] which accounts for the many mechanisms of action that are effective against arthritis and inflammation. These include inhibiting the production of inflammatory cytokines, and blocking TNF-alpha, COX-2, and NFkB activities.[91]

While the results are promising, the use of TW also entail side effects. Adverse reactions include skin rashes, dry mouth, poor appetite, menstrual disturbances in women and hormonal disturbances in men. Researchers have also found that TW causes a temporary reduction of sperm count and have begun to develop a male contraceptive drug from the plant's active ingredients.[92] Importantly, fertility is restored upon cessation of use.[93] The side effects of TW are reduced when administered in combination with other Chinese herbs, or when the outer bark of the roots are extracted without the inner wood of the roots. Because of the possibility of serious side effects, TW should be used only under the care of a licensed health-care professional. [92]

CONCLUSION

Natural health practitioners often feel that disease is due to lack of balance within the body systems. Establishing proper balance by employing the above botanicals, therapies, and lifestyle modifications may thus offer a safe and effective alternative to conventional treatment and bring new hope to patients suffering from autoimmune disease.

DISCLOSURE OF INTERESTS

Dr. Zampieron reports commissions on formulas with some of the herbs mentioned in the article for Restorative Formulations, outside the submitted work.

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