



Immune Enhancement By Nature December 2010



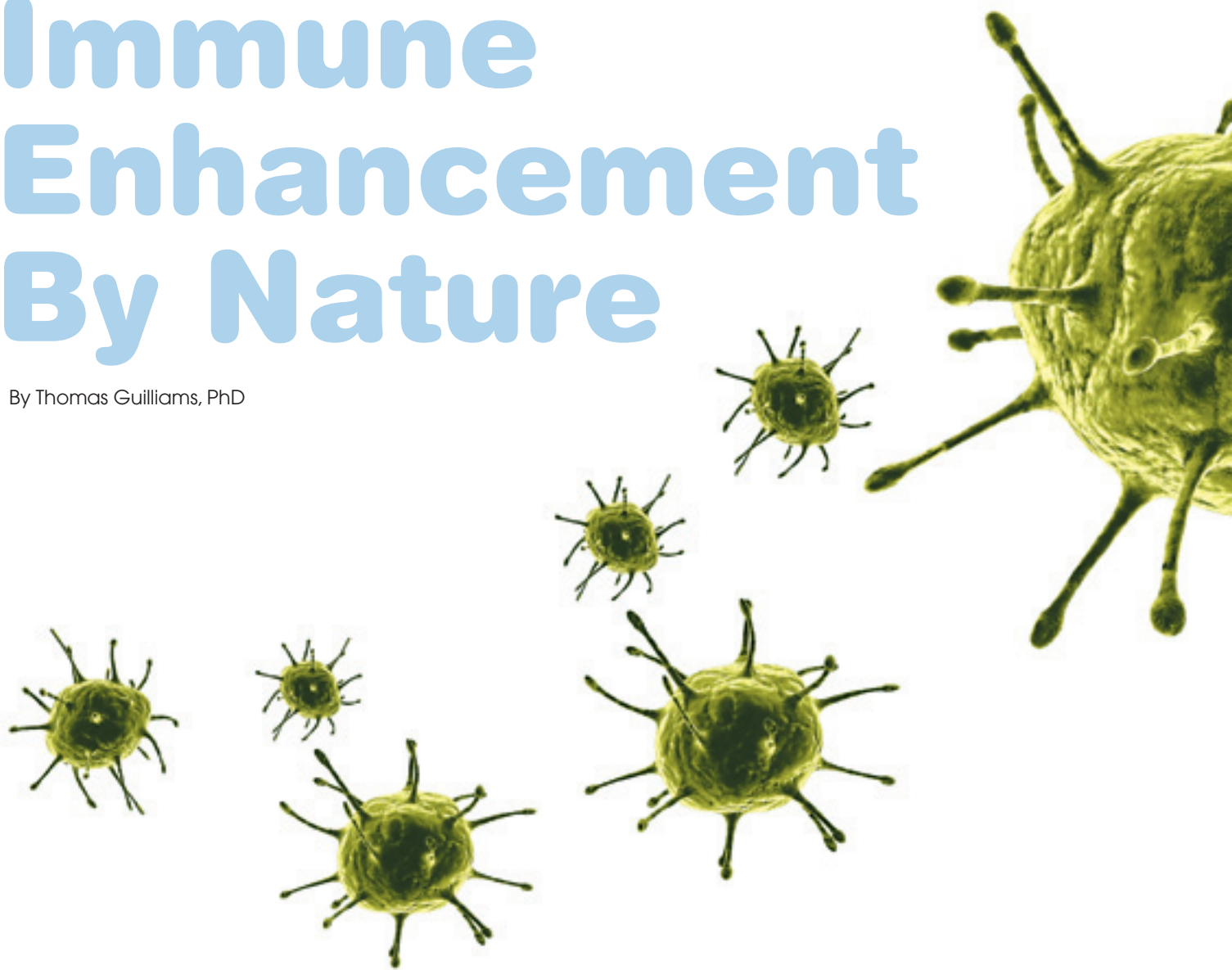
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Immune Enhancement By Nature

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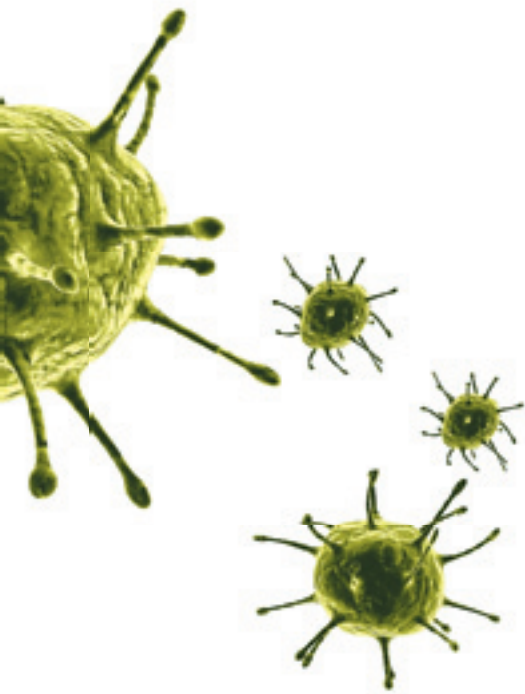


The immune system is a complex network that is divided into the innate and adaptive immune systems. The innate immune system is the first-line of defense, and involves non-specific mechanical barriers, chemical barriers, secretory barriers and inflammatory processes, as well as cells that prevent pathogens from invading sensitive tissues. In contrast, the adaptive immune system “adapts” to invading organisms over time with T and B lymphocytes, which recognize invading organisms with high specificity using T-cell

receptors and immunoglobulin (antibody) proteins. The adaptive immune cells have “memory,” allowing a second invasion of the same (or cross-reactive) antigen to stimulate a quicker response.

The maturation and specificity of the adaptive immune response is partially centered on the differentiation of a specific set of CD4+ T-lymphocytes called T-helper cells (Th) which coordinate how the rest of the adaptive immune system will respond to the antigen and determine which portions of the immune system will mount a response. Many factors can

influence a shift in the Th1/Th2 ratio, including maternal diet and immune challenges during fetal development, early childhood exposure to antigens and allergens, diet, gut microflora and immunizations.¹ Both immune systems are candidates for improvement with proper diet, exercise and nutritional supplementation. This overview will discuss the most widely researched botanicals and nutraceutical immunomodulators, with a focus on published clinical trials and potential mechanisms from in vitro and animal research.



Macronutrients and Micronutrients

Macronutrient ratio imbalances along with metabolic insufficiencies (or frank deficiencies) of many micronutrients can contribute to immune suppression. Protein is particularly important as the immune system requires high levels of energy and amino acids for cell division and protein synthesis.² An elevated intake of refined carbohydrates is often considered harmful to the immune system, and fatty acids, particularly the essential fatty acids linolenic acid and linoleic acid and the long-chain polyunsaturated fatty acids from fish oil (EPA and DHA), are also vital for proper immune function^{3,4} Dietary fibers benefit the immune system directly by stimulating cells in the gut-associated lymphoid tissue (GALT), or indirectly by increasing the number of probiotic organisms (prebiotic activity) or by moving toxins from the body, limiting the stress placed upon the immune system. In addition to the macronutrients, immune cell function is often compromised in individuals with deficiencies in any critical micronutrient, as well.^{5,3}

Vitamin A

Vitamin A deficiency is widespread throughout the developing world, leaving millions susceptible to a variety of infectious diseases. Vitamin A and the pre-vitamin carotenes are vital

to many specific immune functions including the maintenance of epithelial and mucosal barriers, lymphocyte differentiation, natural killer cell activity, improved secretory IgA response, lactoferrin secretion, improved antibody responses and improved cytokine secretion.^{5,3,6,7} Most clinical trials involve children in developing countries with severe vitamin A deficiencies taking periodic large-doses of vitamin A, while most clinical trials in the West provide vitamin A with other micronutrients.

Vitamin C

It has long been believed that increased vitamin C intake will lower an individual's risk for different infections or limit their duration or severity. Deficiencies of vitamin C are known to cause immune system suppression and increase the risk for a variety of infectious diseases, while high oral doses improve immune activities.^{8,9} Antioxidants such as vitamin C quench free radicals,¹⁰ boost T-cell activity, modulate pro-inflammatory cytokines and up-regulate natural killer (NK) cells.³ High doses (1 gram or more) are regularly recommended for improved immune function and for treatment and prevention of upper respiratory infections. In general, vitamin C is more effective in children than adults and even higher doses (>2 g/day) may be needed to see these effects in some individuals.¹¹

Zinc

Zinc is a vital trace mineral involved in over 100 different enzymatic reactions in humans. Deficiencies are linked to specific immune susceptibilities and increased risk of pathogenic infections^{12,13} and they can suppress thymic function, T-lymphocyte development, T-cell dependent B-cell function and macrophage activity.¹⁴ Some reviews suggest that lozenges and nasal gels can directly inhibit rhinovirus attachment; although these studies have not always shown statistically significant results^{15,16}. Supplementation of zinc alone is often inadequate to alter measurable clinical outcomes in otherwise healthy patients. However, when zinc status is compromised in the elderly,^{17,18} or in individuals with immune-related diseases,^{19,20} zinc supplementation has a more profound clinical effect.

Other Antioxidants

Most micronutrients with immunomodulatory activity have antioxidant capacity and many other vitamins, minerals and nutrients have documented impact on immune system improvement, as well. Vitamin E significantly reduces the rates of common colds in an elderly population^{21,22} improves immune markers, and decreases oxidative stress in healthy individuals.²³ **Selenium** is also vital for proper immune function^{3,24,25,26,27,28,29,30} and nutrient

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antioxidants such as **lipoic acid** and glutathione-inducers (e.g. **N-acetyl cysteine**), as well as **carnitine**, **acetyl-carnitine** and **coenzyme Q-10**, improve immune function and reduce risk of infection in individuals with stressed immune systems.^{31, 32} Oral supplementation of N-acetyl cysteine,^{33,34} whey protein,^{35,36} and silymarin,^{37,38} also show a measurable increase in total cellular glutathione levels.³⁹

HERBS & BOTANICAL EXTRACTS

Echinacea

Various preparations and components of *E. purpurea* have been shown to stimulate macrophage activation, as well as NK cell activity in both human and animal models.^{40,41,42,43,44} Clinical trials involving preparations of Echinacea^{45,46,47,48} have been shown to reduce the frequency, severity and/or duration of common cold symptoms in several trials; particularly in children^{49,48} yet other studies with various preparations showed no statistical differences compared with placebo.^{50,51} Multi-herb/nutrient formulas containing Echinacea⁵² appear the preferable method of use, yet additional research is needed to confirm combinations, doses and patient conditions. Echinacea is generally regarded as safe for pregnant and nursing women when used at suggested doses.⁵³

Andrographis

The leaves of *Andrographis paniculata* have become more popular in Europe for the treatment and prevention of upper-respiratory tract infections (URTI) and sinusitis. Systematic reviews show a consistent and clinically relevant effect when used as a single herb or in combination with other herbal preparations.^{54,55,56} Constituents within *Andrographis* possess anti-inflammatory, immune-stimulating, anti-pyretic, anti-cancer and anti-viral activities.^{57,58,59,60,61,62} Few reports of adverse events are associated with *Andrographis* and it is generally assumed safe when consumed at the recommended dose.⁵⁴

Arabinogalactan

Arabinogalactan is a polysaccharide fiber and one of the active components

of immunomodulating plants such as Echinacea and several mushroom species. As a prebiotic fiber, arabinogalactan can stimulate the growth of healthy bacterial growth in the GI tract, indirectly aiding the immune system and the unique shape of this polysaccharide directly stimulates immune cell function.⁶³ Arabinogalactan is perhaps most well known for its up-regulation and mobilization of natural killer (NK) cells.^{64,65,66} More research is still needed to define how much is ideal to stimulate the immune system for specific conditions and end-points, but commercially available arabinogalactan is safe and has GRAS status by the U.S. FDA.

Mushroom Extracts

The mushrooms most commonly used as dietary supplements in the US are Shiitake (*Lentinus edodes*), Reishi (*Ganoderma lucida*), Maitake (*Grifola frondosa*), and *Agaricus blazei*; although others are becoming more popular. Numerous immunomodulating constituents have been described from mushroom extracts, although the most studied are the branched polysaccharides (primarily b-D glucans) and polysaccharide proteins⁶⁷ which bind to pattern-recognition receptors on immune system cells and trigger the activation of these cells.^{68,69,70} Macrophages, natural killer (NK) cells, neutrophils, and dendritic cells, as well as cytokines specific to these innate immune cells are activated by various mushroom extracts⁶⁷ which have also been shown to modulate T-helper responses (usually toward TH1 subtype) and activate both B and T cells; although some studies show a suppression in antibody production with certain isolated components.^{71,72,73,74,75} Because of the diversity of clinical uses and the relatively few published clinical trials available, specific dosing recommendations should be provided by the manufacturer.

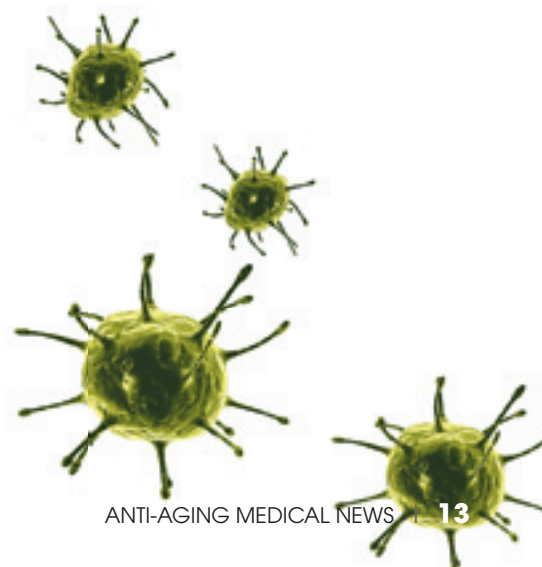
Astragalus

Astragalus membranaceus root is generally considered to have immunomodulatory, anti-inflammatory and adaptogenic (stress-relieving) properties.⁷⁶ Its traditional and modern usage is primarily for frequent infections

or malignancies.⁷⁷ *Astragalus* extracts and constituents have been shown to enhance the activity of NK cells and lymphocyte activated killing of tumors; as well as stimulate the activity of other immune cells such as macrophages and B-cells.^{77,78} Much of the research on this herb is published in Chinese and its usage is most often combined with several other herbal preparations making specific dosing recommendations difficult. *Astragalus* is generally considered safe, with few reported adverse events.

Probiotics

Probiotics or the beneficial bacteria or yeast in human gut flora, have proven their efficacy in numerous conditions such as antibiotic associated diarrhea,^{79,80} irritable bowel diseases,^{81,82} and general gut health, and researchers are now beginning to investigate the immune system effects of some probiotic bacteria in humans.^{83,84} Probiotics enhance mechanical barriers, decreasing gut permeability to pathogenic bacteria and viruses and some species of *Lactobacillus* and *Bifidobacterium* increase the innate immune response directly, increasing NK cell, polymorphonuclear cell, and macrophage activity in humans and animals.^{85,86,87,83,88} Supplementation with *Lactobacillus* and *Bifidobacterium* have also increased IgA, IgM, and IgG secreting cells.^{89,90,91} and enhance the cellular immune response, increasing the number of beneficial cytokines and modulating the Th1/Th2 response.^{83,84,85} Further research and human clinical trials are needed to better understand how these microorganisms benefit certain disease states.





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Bovine Colostrum

Colostrum is the “early” milk produced by cows during the first days after parturition and it is richer than later milk in growth factors, immunoglobulins, immune-stimulating cytokines, as well as enzymes and proteins which protect the young animal and promotes healthy growth.^{92,93} Due to colostrum’s high immunoglobulin content, it has been used to treat bacterial-induced diarrhea⁹⁴ and showed positive benefits with harmful organisms such as *Cryptosporidium* (in immune-compromised individuals), *Shigella*, *Clostridium* and *E.coli*^{95,96,97,98,99} using doses from 10 grams per day and higher. Studies have not established an appropriate dose for immune enhancement in other populations. High doses of colostrum have led to GI complaints in some, but most studies show colostrum is well-tolerated. Those who do not tolerate or are allergic to dairy should avoid colostrum use.

Lactoferrin

Lactoferrin is an iron-binding glycoprotein secreted in many biological fluids especially milk and colostrum.¹⁰⁰ Lactoferrin is considered vital to the mucosal immune system- aiding the host defense against microbial infections and has direct antimicrobial activity, and the ability to recruit and activate cells within both the innate and adaptive immune system.^{101,102,103,104} Most published clinical trials using lactoferrin are for the treatment of hepatitis C and *H. pylori* (mostly

with other agents), and show mixed results.^{105,106,107,107,108,109,110} Research is also being conducted on the anti-inflammatory and anti-cancer potential of lactoferrin use.^{111,112,113,104,114,115,116,117} Additional clinical trials will need to be conducted to confirm uses and make specific clinical recommendations.

Antimicrobial or Anti-Viral Agents

Numerous plants, plant extracts and constituents have been identified as having anti-microbial, antiviral or antifungal activities¹¹⁸ and are often considered “immune enhancing” even when no specific immune system function is measured because of their use during infection or combination with other immune-modulating herbs. Some of the most common are olive leaf extract,¹¹⁹ berberine-containing plants (e.g. goldenseal, Oregon grape root, barberry),^{120,121} Elderberry (*Sambucus nigra*),^{122,123} garlic,¹²⁴ Pau d’arco,¹²⁵ St. John’s wort,¹²⁶ propolis (bee-product from tree resin),^{127,128} green and black tea,¹²⁹ tea tree oil,¹³⁰ and nearly every popular spice.¹³¹

Caution with Immune-Stimulating Therapies

Only a general precaution can be given that aggressive use of ingredients that stimulate the adaptive immune system may not be advisable in patients with auto-immune diseases, since there are little more than a few case reports of potential autoimmune exacerbations.¹³² Herbal traditions recommend using immune-stimulating therapies

for short periods of time, followed by a removal of the therapy for weeks or months before starting the therapy again. In general, it is most effective to use immune-stimulating protocols with a memory-stimulating antigen, when a patient is infected or during the season or environment where they have a higher likelihood of contacting pathogens.

Conclusion

There are many ways to support and enhance immune function, from macro and micronutrient support for optimal energy production to antioxidant support to protect immune cells requiring higher metabolic energy. The numerous dietary supplements give the practitioner of evidence-based medicine a wider formulary in dealing with immune-related disorders and continued research into these remedies and others, will provide more options in the future, allowing for even greater outcomes. ♦

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EDITOR’S NOTE: Due to the amount of research discussed in this article, an exhaustive reference list is not included. Additional references are available online at www.pointinstitute.org

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