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Strategies for Immune Enhancement

Our immune system acts to protect us from a myriad of potentially harmful organisms, often with an efficiency that goes unnoticed. If the invading organisms get the upper hand, however, we notice immediately. These challenges to the immune system result in the vast majority of hospital and physician visits- often resulting in a prescription antibiotic or analgesic. One constant throughout every culture and historical time period is the use of remedies to treat and prevent recurrent ailments that overwhelm the immune system (colds, flu, gastrointestinal disturbances etc.). Some of these treatments have been scrutinized by modern scientific research methods, although most have not. While the diversity of remedies and research modalities make it difficult to capture all the historical and emerging clinical approaches, 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.

Immune System Overview:

The immune system is a complex network of cells and glands that interact through a multitude of cytokines and cell receptors. In general, the immune system is divided into two sub-systems: the innate immune system and the adaptive immune system. Both are vital for protecting our bodies from invading organisms.

The innate immune system is considered the first-line of defense and is generally non-specific. This system involves mechanical barriers to pathogens (skin, mucous etc.), chemical barriers (stomach acid), secretory barriers (enzymes, immunoglobulin (sIgA)) and the inflammatory processes. Within the innate immune system are cells such as neutrophils, macrophages and natural killer (NK) cells which are non-antigen specific and have no "memory." These barriers and cells often prevent pathogens from getting a foothold within sensitive tissues, limiting the need for the adaptive immune system.

In contrast to the innate immune system, the adaptive immune system "adapts" to invading organisms over time. The primary cells involved in this system are the T and B lymphocytes, which recognize invading organisms with a high degree of specificity using T-cell receptors and immunoglobulin (antibody) proteins. The adaptive immune cells also have "memory" allowing a second invasion of the same (or cross-reactive) antigen to stimulate a quicker and more potent response.

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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). The two most well understood are the Th1 and Th2 subsets, but newer research has defined a Th17 subset (named for its expression of IL-17) as well.[1,2] The interaction of a naïve T-helper cell (Th0) with an antigen (in the context of an antigen presenting cell) causes the permanent differentiation to one of these T-helper cell subsets. Since T-helper cells coordinate how the rest of the adaptive immune system will respond to the antigen, their differentiation determines which portions of the immune system will mount a response. In general, Th1 cells secrete interferon-gamma and TNF-β, stimulating a cellular response against viruses, bacterially-infected macrophages and cancer. Th2 cells, on the other hand, secrete cytokines that up-regulate antibody production (e.g. the IgE allergic response) and protection against parasites. Th17 cells may be involved in stimulating a portion of the inflammatory response while activating neutrophils.

Many factors can influence a shift in immune system Th1/Th2 ratio, including maternal diet and immune challenges during fetal development, early childhood exposure to antigens and allergens, diet, gut microflora and immunizations. The so-called "hygiene hypothesis" suggests that children with more exposure to pathogens earlier in life will preferentially develop a Th1 profile which results in less allergic susceptibility. The inverse relationship between atopic diseases and exposure to childhood pathogens seems to confirm the hygiene hypothesis, although the relationship is far from scientific agreement. Other factors that have been shown to be associated with increasing

allergic potential are urban living, exposure to diesel exhaust, use of antibiotics, fewer siblings and vaccination programs.[3]

Both the adaptive and innate immune systems need to be working properly in order to maintain protection against infectious agents and malignant cells. Both systems are vulnerable to nutritional deficiencies and stress; however, they are both candidates for improvement with proper diet, exercise and nutritional supplementation. When reviewing the agents one could use to improve immune function, it is important to understand that there is no one single end-point or surrogate marker for measuring immune function; certainly not an end-point that can be used in every patient and in all circumstances.[4] For instance, in HIV positive patients, measuring CD4+ T-cells is a fairly good measure of immune health; however, in most other individuals, this measurement is less predictive of overall immune strength. Likewise, measuring the number of various immune cells, cell activity or the concentration of various cytokines or antibodies needs to be tailored to each condition. There are laboratories that have developed various immunology panels, which include test such as lymphocyte subpopulation analysis (including Th1/Th2 ratios), immunoglobulin levels (including secretory IgA), lymphocyte immune function, natural killer cytotoxicity activity, interferon production and many others. These tests can be valuable for diagnostic and follow-up analysis in patients with recurrent infections or immune system challenges (chronic fatigue, fibromyalgia, cancer etc.) but are not yet widely used in the clinical setting.

While immunology tests can add to our understanding of immune function in the individual, the prevention of recurrent infections (colds, flus, UTIs etc.) is a clinical end-point which most consider to be a good functional marker for immune health. Every generation and every culture has remedies for preventing or limiting these sorts of recurrent illnesses (chicken soup, salt water gargles, herbal teas etc.). In the past several decades, many of these traditional remedies have been scrutinized at the clinical level (do they really prevent disease in a controlled trial?) and the basic science level (can we explain how these remedies might affect immune cell function?). What is emerging is very promising, but often times contradictory, due to the complexity of the research process, the individuals being studied and the immune system itself.

Macronutrients

Immune system inadequacies are common among malnourished populations, related both to macronutrient energy restriction and select micronutrient deficiencies. When combined with the lack of sanitation among malnourished populations, these immune deficiencies lead to rampant infections and life-threatening illnesses in a large part of the under-developed world. While these conditions may not exist widely in the U.S., macronutrient ratio imbalances along with metabolic insufficiencies (or frank deficiencies) of many micronutrients contribute to immune suppression in many patients. Individuals with certain gastrointestinal disorders, anorexia or bulimia and those who are obese are vulnerable to these deficiencies.[5] Protein levels are particularly important as the immune system requires high levels of energy and amino acids for cell division and protein synthesis. Protein-energy malnutrion (PEM) is commonly connected with immune depression and infectious diseases among malnourished populations, especially children.[6]

Elevated intake of refined carbohydrates is often considered to be harmful to the immune system. This idea stems mostly from a study done in 1973 where neutrophil phagocytic activity was nearly cut in half for more than 5 hours following the intake of 100 grams of various sugars including glucose, fructose, sucrose, honey or orange juice.[7] Starch intake did not cause a significant decline in neutrophil activity. Some studies suggest that changes in insulin levels as well as vitamin C depletion may be driving this carbohydrate-induced diminution of neutrophil activity.[8] Whether these same immune-suppressing changes would be detected at different carbohydrate doses and/or when combined with other macronutrients and micronutrients is not yet known.

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 vital for proper immune cell function. Fatty acids are potent modulators of lymphocyte and macrophage function and also act as precursors to many lipid-derived mediators in the eicosanoid pathways.[9,10] Clinical trials are mixed as to the appropriate dose and types of fatty acids that will preferentially up-regulate the immune system and more research needs to be conducted before making specific recommendations.

Dietary fibers are known to benefit the immune system either directly by stimulating cells in the gut-associated lymphoid tissue (GALT) or indirectly by increasing the number of probiotic organisms (prebiotic activity). This activity will be mentioned briefly below in the section discussing the immunomodulatory activities of probiotics. Fiber is also considered to be vital in moving toxins from the body, limiting the stress these toxins place upon the immune system.

Micronutrients

The role of vitamins, minerals and other micronutrients for proper cellular function cannot be underestimated. In fact, immune cell function is often compromised in individuals with deficiencies in any critical micronutrient.[11,9]

Vitamin A

Vitamin A deficiency is widespread throughout the developing world, leaving millions of individuals susceptible to a wide variety of infectious diseases. Distribution of vitamin A capsules in these countries ranks with vaccinations and oral rehydration in importance as public health measures. Vitamin A and the pre-vitamin carotenes are vital to many specific immune functions including the maintanance of epithelial and mucosal barriers, lymphocyte differentiation, natural killer cell activity, improved secretory IgA response, lactoferrin secretion, improved antibody responses and improved cytokine secretion.[11,9,12,13]

Vitamin C

While vitamin A may be more widely recognized globally for its immune stimulating effects, vitamin C is by far the most popular vitamin for immune enhancement in the United States. It has long been believed that increased vitamin C intake will lower an individual's risk for different infections, especially upper respiratory tract infections, or limit the duration or severity of these infection.

Vitamin C is highly concentrated in immune cells and reduced amounts of this vitamin are directly related to lower immune function.[14,15] Vitamin C deficiencies are known to cause immune system suppression and increases the risk for a variety of infectious diseases, while high oral doses of ascorbic acid are known to improve immune cell activities.[16,17] Immune cells are sensitive to oxidative stress and antioxidants such as vitamin C are beneficial for quenching free radicals before they cause DNA damage or trigger apoptosis.[18] Other potential mechanisms include boosting T-cell activity, modulation of pro-inflammatory cytokines and up-regulation of natural killer (NK) cells.[9]

High doses (1 gram or more) are regularly recommended for improved immune function and for the treatment and prevention of upper respiratory infections. A recent review of vitamin C supplementation for respiratory infections in military personnel and similar settings showed a consistent reduction in the incidence and severity of respiratory infections.[19] The doses and end-points differed in each setting, so one specific recommendation is difficult to make using the current published literature. 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.[20]

Zinc

Zinc is a vital trace mineral involved in over 100 different enzymatic reactions in humans. Zinc deficiencies are linked to specific immune susceptibilities and increased risk of pathogenic infections.[21,22] The mechanisms related to zinc's immune enhancement are multi-dimensional through the improvement of immune cell function and enzyme activity. Zinc deficiency suppresses thymic function, T-lymphocyte development, T-cell dependent B-cell function and macrophage activity.[23] Since there is no body store for zinc, constant intake through diet and supplementation is required to maintain adequate zinc levels.

Results from clinical trials using various doses and forms of zinc for the reduction of colds or related symptoms have been mixed.[24,25] Some reviews have suggested that lozenges and nasal gels are able to directly inhibit rhinovirus attachment, although these studies have not always shown statistically significant results. As with other nutrients studied, supplementation of zinc alone is often inadequate to alter measurable clinical outcomes in otherwise healthy patients. However, when zinc status is compromised (inflammatory bowel disorders, anorexia nervosa, obesity), in the elderly[26,27] or in individuals with immune-related diseases such as HIV or chronic fatigue syndrome[28,29] zinc supplementation has a more profound clinical effect.

Other Antioxidants

One of the similarities of most micronutrients with immunomodulatory activity is their antioxidant capacity. Indeed, like vitamin C, zinc and carotenoids, many other antioxidant vitamins, minerals and nutrients have documented impact on immune system improvement.

Vitamin E, one of the most important lipid-soluble antioxidants, is also very essential for optimal immune function.[30] As little as 200 IU/day of supplemental vitamin E significantly reduced the incident rates of common colds in an elderly population over a year.[31] Vitamin E supplementation improves CD4/CD8 ratios, T-cell proliferation and decreases oxidative stress in healthy individuals.[32] The antioxidant mineral selenium, which works synergistically with vitamin E, is also vital for proper immune function.[9,33] Selenium supplementation has been shown in both humans and animals to improve immune cell function and activity.[34,35,36,37,38] Selenium supplementation (200 mcg/day for 9 months) statistically reduced HIV viral load, helping to improve CD4+ cell counts in HIV positive patients.[39]

Nutrient antioxidants such as lipoic acid and glutathione-inducers (e.g. N-acetyl cysteine), as well as nutrients which protect mitochondria from excessive oxidation such as carnitine, acetyl-carnitine and coenzyme Q-10, have been shown to improve immune cell function and reduce risk of infection in individuals with stressed immune systems. In fact, improved mitochondrial function is predicted to be one of the underlying mechanisms that strengthen immune function, as immune cell energy needs are dramatically increased to fight off infections.[40] This was shown in AIDS patients given a cocktail of vitamins and minerals with a significant dose of mitochondrial antioxidants (400 mg lipoic acid, 1000 mg acetyl-carnitine, 1200 mg NAC per day) over a 12-week period.[41] While these patients' CD4 cells had stabilized on standard anti-viral medications, the antioxidant therapy increased CD4 cell count by 24% over the duration of the treatment.

Glutathione, a tri-peptide made from cysteine, glutamic acid and glycine, is critical to many antioxidant and detoxification processes throughout the body. Research suggests that supplemental glutathione, taken orally, does little to increase serum or cellular glutathione levels.[42] However, oral supplementation of N-acetyl cysteine,[43,44] whey protein[45,46] and silymarin[47,48] show a measurable increase in total glutathione levels; while nearly any antioxidant will improve the ratio of reduced to oxidized glutathione levels (esp. lipoic acid).[49]

Multivitamin/Minerals

The most common way to consume the micronutrients listed above is through multivitamin/mineral supplements. We have shown in the above section that one combination of vitamins, minerals and antioxidant nutrients had a positive affect on CD4 cell counts in HIV positive patients; however, in other populations it is more difficult

to measure specific immune responses. A recent systematic review of clinical trials using multivitamin/mineral supplementation showed no consistent statistical benefits in reducing infections, except in certain elderly populations or in patients supplemented longer than 6 months.[50] Yet other recent studies have shown that daily multivitamin consumption has been shown to reduce the rate of infection in elderly diabetic patients,[51] and that multivitamin preparations with probiotics reduced upper-respiratory infections in healthy non-vaccinated adults.[52]

Unfortunately, most of the studies reviewed used supplements that varied greatly in the amount of each component and used different patient populations and different end-points. It should also be noted that the role of multivitamin/mineral therapies is to ensure that a patient is replete with all of the necessary cofactors for proper metabolism and that most commercially-available products (used in the studies) do not represent therapeutic doses of any the key antioxidant nutrients mentioned above. The clear link between nutrient deficiencies and the risk for infection warrants the use of a comprehensive multivitamin/mineral supplement in patients being treated for conditions in which an optimized immune system is vital.

Exercise

The relationship between physical activity or exercise and the immune system is complex. In general, intense and prolonged training seems to stress the immune system, particularly the mucosal immunity (as measured by secretory IgA) and results in increased frequency of upper respiratory infections in athletes. In contrast, moderate exercise (especially in the elderly) seems to support and strengthen many immune system functions. There are several theories for how strenuous exercise reduces immune function including increased oxidative load-depleting antioxidant stores, increased adrenal stress and cortisol output and decrease in muscle glutamine.[53,54]

Several clinical trials have attempted to show how specific nutrients may prevent exercise-induced immune system suppression.[55] Vitamin C intake above 1000 mg/day was associated with a statistical decrease in several parameters of exercise-induced immune suppression, although glutamine (avg. 5 grams/day) did not. Fish oil supplementation may inhibit the exercise-induced inflammatory response in some athletes.[56] The flavonoid quercetin has been shown to positively modulate post-exercise immune system functions and reduce upper respiratory tract infections after intense cycling in trained athletes (1000mg/day).[57,58] One study showed that *Echinacea purpurea* attenuated the mucosal-immunity suppression caused by exercise as measured by secretory IgA (sIgA).[59]

Herbs & Botanical Extracts

The use of herbs and botanical extracts for immune enhancement has ancient roots in nearly every culture across the globe. For some cultures, this is still the primary medicinal choice for prevention and treatment of common illnesses. Even in the West, where pharmaceutical drugs have dominated the medical landscape, the use of herbal therapies is still quite popular. Many of these herbs and botanical extracts have been studied using modern research techniques; methods which are not always suitable to describe the historical benefits seen with these compounds. Even so, we have learned surprising things about the mechanisms and clinical efficacy of many traditional herbal preparations even if some clinical trials have had less-than-favorable outcomes.[60,61]

Echinacea

Products containing various forms of Echinacea are among the top-selling herbal preparations every year in the United States. These products are consumed most often to prevent or treat common illnesses, especially cold and flu prevention. The general term Echinacea describes preparations of three species of purple coneflowers; *E. purpurea, E. angustifolia* and *E. pallida*. The roots and rhizomes of each species are used for medicinal purposes, while the whole plant (flowers and leaves) is also used in the case of *E. purpurea*. Dried roots, liquid extracts, tinctures, dried extracts and standardized extracts are available as single-ingredient preparations or mixed with other herbs, vitamins or nutrients.

The constituents with potential immunomodulatory activity within Echinacea species are many; including arabanogalactan polysaccharides, alkamides, caffeic acid esters, echinacoside (not in *E. purpurea*), volatile oils, polyacetylenes and flavonoids. Rather than a single active component, most researchers consider Echinacea's activities to be derived from a combination of these constituents.[62] Various preparations and components of *E. purpurea* have been shown to stimulate macrophage activation, a key initiator of the immune response, as well as NK cell activity in both human and animal models.[63,64,65,66,67] These activities, in many cases, are linked directly to increased cytokine expression.[68,61] Echinacea preparations also show limited antiviral,[69] antifungal[70,71] and antibacterial activities.[72]

Clinical trials involving preparations of Echinacea have been frequently performed and numerous reviews are available.[73,74,75,62] Comparing these trials is difficult because most study designs differ in the type and dose and method of delivery of the Echinacea preparations, the length of the study and the primary outcome (prophylaxis vs. treatment). The most common studies are for the prevention or treatment of upper respiratory tract infections where Echinacea preparations have been shown to reduce the frequency, severity and/or duration of common cold symptoms in several trials; particularly in children.[76,62] Other studies with various preparations; however, showed no statistical differences when compared with a placebo.[77,78] One study showed that Echinacea purpurea attenuated the mucosal-immunity suppression caused by exercise as measured by secretory IgA (sIgA).[59]

Many trials have been conducted on multi-herb/nutrient formulas containing Echinacea preparations.[79,80] One such trial showed that children aged 1 to 5, given a liquid herbal blend (containing

E. angustifolia and *E. purpurea* , propolis, and vitamin C) had 50% fewer upper respiratory tract infections, 68% fewer incidents of otitis media, and 66% fewer incidence of pneumonia compared to children given a placebo syrup over a 12-week winter season. When children did get an illness episode, the children taking the herbal preparation had a 45% shorter duration compared to those taking a placebo. Additionally, children were prescribed 50% fewer antibiotics and 53% fewer antipyretics when taking the herbal preparation.[81]

Echicacea preparations have been well studied and relied upon for centuries for their immune enhancing effects. Modern clinical research suggests that by themselves, these preparations may not always prove beneficial or be limited by dose or patient profile. Combination therapies, more typical of Echinacea's historical use, seem to be the preferable method of use. Additional research is needed to confirm which combinations, doses and patient conditions result in consistent positive clinical outcomes. Echinacea is generally regarded as safe for pregnant and nursing women when used at suggested doses,[82] although allergic reactions to any botanical are possible and have been reported for Echinacea

Andrographis

The leaves of *Andrographis paniculata* have been used in traditional Eastern medicine systems for centuries and have recently 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 (typically with Echinacea or Eleuthero/Siberian Ginseng).[83,84,85]

Constituents within Andrographis have been shown to possess anti-inflammatory, immune-stimulating, anti-pyretic, anti-cancer and anti-viral activities.[86,87,88,89,90,91] While many of these activities have not been confirmed in human clinical trials, these mechanisms will help researchers find extracts and doses which may confirm the traditional use of Andrographis for these other related activities. Few reports of adverse events are associated with Andrographis use and it is generally assumed to be safe when consumed at the recommended dose.[83]

Arabinogalactan

Arabinogalactan is a polysaccharide fiber composed of galactose and arabinose linked polymers. It is known to be one of the active components of immunomodulating plants such as Echinacea and several mushroom species (see below). For most commercial dietary supplement use, arabinogalactan is derived from the Eastern and Western Larch tree (*Larix spp.*). As a prebiotic fiber, arabanogalactan can stimulate the growth of healthy bacterial growth in the GI tract, indirectly aiding the immune system. The unique shape of this polysaccharide directly stimulates immune cell function as well.[92]

Arabinogalactan is known to stimulate immune cell function and cytokine production, but is perhaps most well known for its up-regulation and mobilization of natural killer (NK) cells.[93,94,95] More research is still needed to define how much purified arabinogalactan is ideal to stimulate the immune system for specific conditions and end-points, but commercially-available arabinogalactan is safe and has been given GRAS status by the U.S. FDA.

Mushroom Extracts

Like plants, fungi have been used for centuries as medicinal agents. The complexities of mushrooms (fruiting body) and their extracts have only recently been investigated. The mushrooms most commonly used as dietary supplements in the US are Shiitake (*Lentinus edodes*), Reishi (*Ganoderma lucida*), Maitake (*Grifola frondosa*), and A*garicus 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 β-D glucans) and polysaccharide proteins.[96] These polysaccharides (similar to arabanogalactans) bind to pattern-recognition receptors on immune system cells which triggers the activation of these cells.[97] Different linkages between the fungal glucans (1,3 and 1,6) differentially stimulate immune cells (primarily neutrophils, macrophages and natural killer cells) giving different patterns of immune stimulation.[98,99]

Mushroom extracts and isolated constituents affect both the innate immune system and the adaptive immune system. Studies have shown that macrophages, natural killer (NK) cells, neutrophils and dendritic cells, as well as cytokines specific to these innate immune cells, are activated by various mushroom extracts.[96] While there is less data in the area of the adaptive immune system, mushroom extracts have been shown to modulate T-helper responses (usually toward Th1 sub-type) and activate both B and T cells; although some studies show a suppression in antibody production with certain isolated components.[100,101,102,103,104]

The diverse stimulation of the innate immune system, along with a characteristic increased activity of natural killer (NK) cells and cytotoxic T-lymphocytes, has also lead many researchers to study the anti-cancer effects of mushroom extracts, including several clinical trials.[105,106,107,108] While there is much more to learn about how mushroom extracts and their isolated constituents affect tumorogenesis and cancer-related immune function, the data has shown a promising line of investigation. Because of the diversity of clinical uses and the relatively few published clinical trials available, specific dosing recommendations cannot be made. Information should be provided by the manufacturer that allows for clinically-appropriate doses.

Astragalus

Astragalus membranaceus root has a long tradition in Chinese medicine. It is generally considered to have immunomodulatory, anti-inflammatory and adaptogenic (stress-relieving) properties.[109] Its traditional and modern usage is primarily for immune-related complaints (frequent

infections) or malignancies.[110] 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.[110,111] 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. Astagalus is generally considered safe with few reported adverse events.

Probiotics

Probiotic is the general term for the group of beneficial bacteria or yeast (*Saccromyces boulardii* is often used in similar ways as classic probiotics) that are found among the gut flora in humans. *Bifidobacterium* and *Lactobacillus* are two of the most well-recognized and researched groups of probiotic bacteria. Probiotics have proven their efficacy in numerous conditions such as antibiotic associated diarrhea,[112,113] irritable bowel diseases[114,115] and general gut health. More recently they have found their way into conventional foods and compose a large portion of the dietary supplement market. Researchers are now beginning to investigate the immune system affects that some probiotic bacteria exert in humans.[116,117]

There are a number of core mechanisms by which different probiotic microorganisms enhance the immune system. One of the most well-known mechanisms is that probiotics enhance mechanical barriers, thereby decreasing gut permeability. This prevents certain pathogenic bacteria and viruses from penetrating into the gut, taking up residence and causing illness. Some species of *Lactobacillus* and *Bifidobacterium* also increase the innate immune response directly. After ingestion of specific probiotic species, increased NK cell, polymorphonuclear cell and macrophage activity have been reported in humans and animals.[118,119,120,116,121] Likewise, probiotics support the immune system by increasing antibody response.[122,123,124] Supplementation with species of *Lactobacillus* and *Bifidobacterium* have increased IgA, IgM, and IgG secreting cells. This may be especially helpful in the case of newborns or those with allergies or atopic skin conditions. Lastly, probiotic bacteria have been found to enhance the cellular immune response, increasing the number of beneficial cytokines and modulating the Th1/Th2 response.[116,117,118] In cases of allergies and some health conditions such as autoimmune diseases and diabetes, modulating the Th1/Th2 response could potentially play a key role in managing the condition.

The relationship between probiotic microorganisms and humans is very intricate and complex. Further research and human clinical trials are needed in order to get a better understanding of how these microorganisms function and their potential benefits in certain disease states and conditions.

Bovine Colostrum

Colostrum is the "early" milk produced by cows during the first several days after parturition. Colostrum is considerably different in nutrient profile when compared to the milk produced days later. For example, colostrum is very rich in growth factors, immunoglobulins and immune-stimulating cytokines, as well as enzymes and proteins which protect the young animal and promote healthy growth.[125,126] This nutrient-dense material has been concentrated and used to promote immune benefits in other animals and in humans.[127]

Due to colostrum's high immunoglobulin content, it has been used to treat bacterial-induced diarrhea and related complaints.[128] Most of these trials were relatively small and uncontrolled, but showed positive benefits using colostrum on a variety of harmful organisms such as Cryptospridium (in immune-compromised individuals), Shigella, Clostridium and E.coli.[129,130,131,132,133] Since these trials used colostrum for preventing or treating infectious diseases or immune compromised individuals, the doses ranged from 10 grams per day and higher. Studies have not established a dose which would be appropriate for general immune enhancement in other populations.

Colostrum products should be collected within the first 24 hours to ensure the highest concentration of proteins (esp. immunolglobulins) and are often standardized for protein or Ig content as well as for specific proteins such as lactoferrin (see below). High doses of colostrum have lead to GI complaints in some patients, but most studies show that 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.[134] Along with its role in iron homeostasis, lactoferrin is considered vital to the mucosal immune system- aiding the host defense against microbial infections. Lactoferrin has direct antimicrobial activity, as well as the ability to recruit and activate cells within both the innate and adaptive immune system.[135,136,137,138]

The most frequent published clinical trials using lactoferrin are for the treatment of hepatitis C and H. pylori (mostly as an adjunct with other agents), with mixed results.[139,140,141,141,142,143,144] Research is also being conducted on the anti-inflammatory and anti-cancer potential of lactoferrin use, most of which is still in the cell-culture and animal-model stages of research.[145,146,147,138,148,149,150,151] Additional clinical trials will need to be conducted to confirm these uses and to make specific clinical recommendations.

Antimicrobial/viral agents

Numerous plants, plant extracts and constituents have been identified as having anti-microbial, antiviral or antifungal activities.[152] These activities are often considered "immune enhancing," even when no specific immune system function is measured, because of their use during infection or combination with other immunomodulating herbs. Some of the most common are olive leaf extract,[153] berberine-containing plants (e.g. goldenseal, Oregon grape root, barberry),[154,155]

Elderberry (*Sambucus nigra*),[156,157] garlic,[158] Pau d'arco,[159] St. John's wort,[160] propolis (bee-product from tree resin),[161,162] green and black tea,[163] tea tree oil,[164] and nearly every popular spice.[165]

Caution with Immune-Stimulating Therapies

There is a general precaution within the medical community that anything that stimulates the immune system could possibly trigger or exacerbate auto-immune conditions, aggravate inflammatory conditions or intensify IgE-related allergic reactions. The published scientific literature is almost silent on these issues, however. With little more than a few case reports of potential autoimmune exacerbations,[166] 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.

Many herbal traditions also recommended using immune-stimulating therapies for short periods of time (weeks or months depending on the tradition), followed by a removal of the therapy for weeks or months before starting the therapy again. Once more, the scientific literature is mostly silent on this approach. In general, it is most effective to stimulate the immune system when there is a "live" target. This is especially true of the adaptive immune system that is best up-regulated in the presence of a memory-stimulating antigen. The use of immune enhancing protocols is therefore advised when a patient is infected, or during the season or situation (indoors, daycare, nursing home, confined travel etc.) where they have a higher likelihood of contacting pathogens.

Conclusion:

The immune system is versatile and complex, able to handle new and old pathogens with remarkable efficiency. Even while there are many vulnerabilities within the system, there are also many ways to support and enhance immune function. Proper macro and micronutrient support that allows for optimal energy productions is vital to immune cell function. Providing antioxidant support during energy production is also necessary to protect immune cells requiring higher metabolic energy. Numerous dietary supplements have been studied for immune enhancement, giving the modern practitioner of evidence-based medicine a wider formulary in dealing with immune-related disorders. Continued research into these remedies, and others, will provide even more options in the near future, allowing for even greater patient outcomes.

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