Optimizing Immune Function Naturally

Clinically proven natural alternatives for boosting immune function and preventing infection

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Evidence-Based Use of Supplements

ABSTRACT

The importance of preventing infection is becoming increasingly clear in the United States and around the globe as we face the challenge of the COVID-19 pandemic. While our immune systems have evolved sophisticated mechanisms for preventing illness, their activity can be compromised, allowing dangerous invaders to adversely affect our health. While treatments for specific diseases or infections may be effective, prevention via a strong immune system can reduce suffering and improve outcomes. Research shows that a healthy lifestyle and consumption of substances that boost immune health can improve the integrity of the immune system and our overall health and well-being. Here, we provide an overview of the functioning of the immune system and data that highlight the benefits of specific practices and supplemental ingredients.

Our bodies have a highly sophisticated biological defense system that, when working properly, can protect us from a wide range of threatening invaders.1 Our immune systems have evolved to identify and eliminate potentially harmful substances by relying on an ability to distinguish self from non-self. This capability depends on both innate and adaptive immunity mechanisms. These systems work by detecting structural features of toxins or pathogens that signal that these substances are foreign and allow bodies to specifically attack those potentially harmful substances without attacking our own tissues.

Without the ability to distinguish self from non-self – a phenomenon referred to as self-tolerance – auto-immune disease occurs. Even with an intact ability to distinguish self from non-self, our immune systems fail to function properly if the mechanisms involved in the attack of foreign invaders are compromised. Given that maintaining the integrity of the immune system is vital for our health and our survival, there are significant research efforts to uncover the best ways to protect and bolster this critical system.

Innate and Adaptive Immunity Work Synergistically to Protect Our Bodies

Innate Immunity

Innate - or non-specific - immune responses are our first line of defense against pathogens. These responses are hard-wired and encoded by our genes to identify common molecular patterns that are found in several microbes and toxins, with the goal of providing an immediate mode of protection that prevents the spread or foreign matter within our bodies.1 Our innate immunity enables the rapid identification and attack of invaders and acts on a broad range of cells.2

Innate immunity begins with physical barriers against invaders like hair and skin layers with tight cell-to-cell contacts as well as mucus layers over the epithelium of respiratory, gastrointestinal, and integumentary tracts.3 The epithelial cilia that clear these mucus layers also play vital roles in restoring the integrity of these layers following contamination to ensure that they continue to prevent the invasion of threatening molecules.1

Adaptive Immunity

Our adaptive immune response – also referred to as specific immune response or acquired immune response - acts as a second line of defense and is slower and more specialized to an individual pathogen, toxin, or allergen.1 For our adaptive immunity to work, we must first be exposed to the potentially harmful substance, and our adaptive immunity must then initiate a proliferation of cells that can mount an effective attack on this newly encountered substance.

Adaptive immunity relies on encoded information that enables our immune systems to rearrange and assemble molecules that can find antigens with a high level of specificity.3 Adaptive immunity is antigen-dependent and generally occurs starting 4 days or later after the initial invader has entered the body.

Humoral immunity and cell-mediated immunity are the mechanisms by which adaptive immunity protects us.4,5 While humoral immunity relies on the secretion of antibodies that defend against pathogens that exist in the extracellular spaces of our bodies, cell-mediated immunity involves the attack on infected cells, transplant tissues, and cancer cells. Whereas humoral immunity involves B cell activity and acts through plasma cells and memory B cells, cell-mediated immunity works through memory T cells and active T cells. Both types of adaptive immunity, however, are initiated through helper T cells.

The Immune System Depends on the Proper Functioning of Several Cell Types

Though innate and adaptive immunity are often discussed in isolation, synergy between them is crucial for an effective, productive immune response.1 These branches of the immune system therefore interact and cooperate to optimize our defense against invaders, but different cell types constitute each system and contribute to the distinct types of activities associated with innate versus adaptive immunity.

While innate immunity is responsible for immediate protective

responses like coughing and sneezing, adaptive immunity underlies reactions that arise later, such as swelling, redness, pus, and pain. Both systems are regulated in part by leukocyte-released cytokines, or white blood cells.6

The leukocytes that underlie innate immunity are granulocytes, which can be further subcategorized into neutrophils, eosinophils, and basophils, as well as monocytes. Innate immunity, which relies on antigen-independent mechanisms, also involves the release of antimicrobial peptides at the surfaces of epithelium.6 These peptides work to disrupt membranes on microbial pathogens. At the same time, toll-like receptors that are located on epithelial cells and leukocytes identify molecular patterns on microbes and initiate appropriate responses via intracellular signaling.

Adaptive immunity, on the other hand, is characterized by the clonal expansion of T and B lymphocytes, which involves the rapid increase in abundance of these cells from few to millions.3 Clonal expansion enables millions of cells to carry the same antigen receptor so that these cells can launch a coordinated attack on the same pathogen.

How to Prevent the Immune System from Being Compromised

While the very pathogens that our immune systems are built to protect us against can jeopardize the integrity of our immune systems, by, for instance, damaging our cells through the release of toxins that can cause pores in our cells, there are several things we also do that can compromise the functioning of our immune systems.7 Indeed, though our immune systems are highly sophisticated, they are also commonly dysregulated.2

Several of our choices and habits have serious implications for the health of our immune systems and of our bodies. These behavioral factors include:

· *What we ea*t. Nutrition is commonly associated with health, but it is less frequently recognized for its importance in our immune functioning.8 Nonetheless, what we eat has been implicated in our immune response to even acute insults such as viral infections like colds and flus, with researchers highlighting that communication dysfunction between the immune system and gut microbiota could contribute to complex disease.9

There appear to be two main reasons that the food we eat influences our immune systems. One is that what we eat affects our weight, and obesity and weight-related diseases like diabetes negatively affect our immune systems, even in terms of their ability to fight off seasonal viruses.10–12 The other is that what we eat determines if we get nutrients that are critical to the proper functioning of our immune cells.8 Malnutrition is the leading cause of immunodeficiency.13 Cell-mediated immunity, cytokine production, phagocyte functioning, and secretory immunoglobulin A antibody concentrations, for instance, are impaired as a result of protein-energy malnutrition.

While failing to consume enough nutrients can prevent our immune systems from functioning optimally, too much of certain substances can be equally detrimental. One particularly dangerous culprit from the perspective of our diets is sugar.

The problem with sugar. Simple sugars have adverse effects on our health and immunity by, for instance, reducing phagocytosis by white blood cells and potentially enhancing inflammation.14,15 The subclinical inflammation associated with dietary sugar intake has been demonstrated through measurements of C-reactive protein (CRP), an inflammatory marker.16 Unfortunately, in Western diets, these kinds of sugars have largely replaced the healthier, complex sugars found in fruits and vegetables, which can reduce inflammation.17–21

As with fat, when sugar enters our blood following a meal, our immune systems react, which impacts the homeostasis of our immunity.22 Given that glucose fuels immune cells, changes in blood sugar levels influence immune activity. For instance, glucose activates lymphocytes and affects lymphocyte proliferation and secretion.23–26 Macrophages and neutrophils too are activated by glucose.27,28 In cases where we accumulate excess adipose tissue – often due to excessive sugar consumption - macrophages accumulate and demonstrate dysfunctional activity.22

Perhaps even more troubling is the glycation that occurs when excess sugar is present in our bodies. While detrimental to several bodily systems, glycation of elements of the immune system can significantly compromise our immunity. Immunoglobulins are particularly affected by glycation, which has been shown to impair, for instance, Fc fragment function in immunoglobulin G, rendering it less effective in performing its immune functions.29 This mechanism has been suggested as a means by which diabetic patients become immunosuppressed and more susceptible to infections.

Another problematic outcome associated with the glycation occurring when too much sugar is present is the immune response to glycated proteins. When the compositions of proteins are modified by glycation, the immune system will produce antibodies to attack the unfamiliar proteins. This type of process has been implicated in rheumatoid arthritis.30,31

The formation of advanced glycation end products (AGEs) that occur in the presence of high levels of glucose are thought to contribute to diabetic complications.32 Methylglyoxal (MGO) is an AGE considered particularly relevant in diabetes. Beyond diabetes, however, AGEs are problematic for immunity, as they interact with receptors and activate signaling cascades that promote immune responses and inflammation.33 Sugar thus negatively impacts the immune system through several mechanisms and can be especially problematic in those suffering from sugar metabolism abnormalities.

· *How active we are*. As with diet, exercise is widely acknowledged as critical to our health but also tends to be overlooked in the context of proper immune functioning.8 Nonetheless, regular, moderate exercise benefits the immune system and reduces the likelihood of infection.8 For example, adults who live an active lifestyle experience fewer upper respiratory tract infections.34,35

Exercise is impactful on the immune system even in older people and people who may be otherwise unhealthy. For instance, research has shown that compared to those who are sedentary, older people and obese people who participate in 12 weeks of exercise that included moderate activity 5 days each week, for 30 to 45 minutes each day, have fewer upper respiratory tract infections and that these infections last for a shorter time when they do occur.36,37

· *How much we sleep*. Consistent with the intuitive notion

that sleep is restorative, getting adequate levels of sleep has been shown to protect the immune system and enhance the ability to fight off viruses.38 At the same time, sleep loss adversely affects critical immune system cells and activities.39 For instance, loss of sleep impacts the nocturnal secretion of cytokines.

Critically, suboptimal sleep is associated with both acute and chronic inflammation as well as with chronic disease.40 One reason for these associations may be the role of sleep in immunological memory formation, which may occur through sleep's effects on the migration, proliferation, and distribution of leukocytes, its impact on cytokine production or antibody levels, its influence of immune-related genes, or some combination of these activities.41 Regardless of the specific mechanisms, sleep disturbances affect disease risk and are associated with the dysregulation of immune cell counts, inflammatory markers, and cellular aging markers.

There is indeed a strong correlation between chronic disease and suboptimal sleep.

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· *The toxins to which we expose ourselves.* Cigarette smoke and alcohol are two common substances that compromise our immune systems.42–44 While alcohol has been shown to affect activity in several immune system cell types, cigarette smoke is associated with immunosuppression, and research has helped to elucidate the mechanisms by which cigarettes can compromise the immune system.43–45 Both innate and adaptive immunity are affected by smoking.45 Chronic exposure to nicotine has been shown in preclinical research to inhibit the antibody-forming cell response and to cause T-cell specific dysfunction.42

· *The stress we endure*. Psychological stress is associated with dysregulation of the autonomic system, which can affect the immune system. One study showed, for instance, that when people with consistently higher levels of worry are exposed to a phobic stimulus, they do not experience the normal rise in natural killer cells in peripheral blood.46 Acute stress is also impactful on our ability to stay healthy, as stress during cold and flu seasons has been shown to increase the likelihood of getting sick.47

· *Our hand hygiene*. Unwanted invaders often enter our bodies through our mouths and noses after our hands are contaminated and we touch our faces. Using soap and water to wash hands for 15 to 20 seconds is recommended for removing viruses and other pathogens from the hands.48–50 Though less effective, hand sanitizers are also recommended in cases where soap and water are not available.51,52

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When the Immune System is Overwhelmed: Conventional Treatments

In the case that we get acutely ill, there are conventional treatments that tend to address the symptoms of our illness but not the underlying cause. There is no cure for common viral illnesses like colds and flus.

Pharmacological treatments

· *Paracetamol.* A go-to over-the-counter medication, also known as acetaminophen, paracetamol is used during acute illness in adults and children to treat fever, reduce pain, and mitigate other symptoms associated with viruses like colds and flus.53,54 Though abundantly used, there is some research that suggests that this medication may not be as effective as was once thought and is likely overprescribed.54 Also problematic, paracetamol is associated with liver toxicity even at low doses and can compromise immunity.

· *Ibuprofen*. Adults and children also use ibuprofen, another over-the-counter drug.53 While some research points to ibuprofen as being slightly more effective than paracetamol in combatting fevers, healthcare providers also often recommend that these two medications be alternated during the duration of a relevant illness.55

· *Acetylsalicylic acid.* More commonly known as Aspirin, acetylsalicylic acid is often used to reduce fevers and relieve symptoms associated with infections in adults. However, its use in children and adolescents is not indicated because it can lead to the dangerous condition known as Reye's syndrome.53 In adults, acetylsalicylic acid is also associated with some unwanted side effects such as indigestion.56,57 Regular use is also associated with internal bleeding.58

· *Antiviral drugs*. There are some prescription antiviral drugs that may be prescribed in cases like the flu, particularly in those at risk for complications, such as people who are over the age of 65, suffer from chronic health diseases, are immunocompromised, are morbidly obese, or who are pregnant or recently pregnant.59 Perhaps the most well-known of these antiviral drugs is Tamiflu, which may be able to reduce duration of a flu virus for up to a day.60 However, this drug is also associated with nausea and vomiting and does not affect the course of illness if taken 2 days following symptom onset or beyond.

Non-pharmacological treatments

The non-pharmacological treatments for common viruses, such as colds and flus, are measures that address the issues that compromise the immune system, discussed above. With no cure for these viruses, mitigating the symptoms and attempting to boost immunity are the goals of treatment. The non-pharmacological means for pursuing these goals include rest, hydration, and body cooling.38,53,59,61–65

In addition to these conventional approaches to treating and preventing infection, proper nutrition can help to boost mmunity. Research aimed at understanding how specific foods and supplements may influence immune function has helped to uncover specific ingredients, the consumption of which, may provide immune benefits. Below is a description of some of these ingredients whose clinical relevance is supported in the medical literature.

Andrographis Extract

Andrographis Paniculata (*A. Paniculata*) has been used for centuries in Indian and Chinese cultures as an herbal medicine, and its use has extended to several countries.66–68 It has been relied on for colds and flus and specifically for coughs, sore throats, and fevers, suggesting that the substance may play a role in respiratory tract infections.69,70

Combats viral symptoms

According to a recently conducted systematic review of the impact of *A. Paniculata*, this substance appears both effective and safe in relieving symptoms of acute respiratory infections and in reducing the time it takes to resolve symptoms.69 Other systematic reviews have also pointed to the potential value of *A. Paniculata* in combatting uncomplicated upper respiratory tract infections (URTIs) compared with placebo.70,71

There are also data that point to the specific symptoms that have been relieved with the help of A. Paniculata. For instance, a

a randomized double-blind placebo controlled study involving 223 patients that compared the success of 200 milligrams (mg) per day of an *A. paniculata* extract versus placebo in addressing symptoms of URTIs found that, while the extract significantly reduced overall symptom scores more than the placebo, it was particularly effective in reducing earache relative to placebo.72 Another study that found that an *A. paniculata* extract was more effective than placebo in improving URTI symptoms also showed that the extract was most effective in resolving throat symptoms.73

A study on the use of an herbal combination containing A. *paniculata* as an adjuvant treatment for children with uncomplicated common colds showed that the combination was particularly successful in treating nasal congestion and that it reduced the use of standard medication compared to other treatment regimens. It was also not associated with any adverse side effects.74

May reduce virus prevalence and intensity
In a randomized placebo-controlled double-blind study, it was found that after 3 months of consumption of a dried extract of A. paniculata during the winter season, cold incidence was lower than in a placebo group, suggesting that this extract may provide protective prophylactic benefits.75 Another randomized double-blind study on the impact of 1200 mg of *A. paniculata* extract on common cold symptoms in 158 adults over a 5 day period showed that this dose was associated with a reduction in both the prevalence and intensity of symptoms.76

Acts through andrographolide lactones
The active ingredients of this substance are lactones known as andrographolides, which have been shown to stimulate the immune system and have antiviral, anti-allergic, anti-diarrheal, hypoglycemic, and anti-inflammatory effects.70,77–79 Research shows that andrographolides are comparable to paracetamol in terms of their analgesic and antipyretic capabilities.80

A role of andrographolides in combating viral activity has been observed beyond common cold and flu viruses. Andrographolides have been implicated, for instance, in the treatment of a wide array of viruses. Research into their potential role shows that they may inhibit virus-induced cell death or block viral hemagglutinin from binding to cells.81,82 Chikungunya virus (CHIKV), Epstein-Barr virus (EBV), Hepatitis C virus (HCV), Herpes simplex virus 1 (HSV1), human immunodeficiency virus (HIV), and human papillomavirus (HPV) are all impacted by andrographolides.83

The potential of andrographolides to fight viruses appears to derive from immunomodulatory effects including the stimulation of phagocytosis and antibody-dependent cell-mediated cytotoxicity and the enhancement of both cytotoxic T cells and NK cells.83,84 Andrographolides are able to efficiently block T-cell activation both *in vitro* and *in vivo*, which may help to interfere with detrimental T-cell responses.85 One study demonstrated that *A. paniculata* extract can also stimulate the production of cytotoxic T lymphocytes, which appears to occur via increased secretion of IL-2 and IFN-gamma by T cells.86

Andrographolides are able to suppress pro-inflammatory protein expression, such as the expression of cyclooxygenase 2, and to combat platelet-activating factor mediated inflammatory responses.87–89 Mechanistic research points to andrographolide-induced changes in signaling pathways in human bronchial epithelial cells that have improved cell mortality in cases of H1N1 flu and may help account for observations that andrographolides effectively combat H9N2 and H5N1 flu viruses *in vitro*.82

Achieves immunomodulatory effects in non-viral conditions
It is worth noting that the data on the immunomodulatory properties of *A. paniculata* point to the value of this supplement as extending beyond its antiviral effects. For example, A. paniculata extract can enhance IgG antibodies against specific pathogenic bacteria and has been shown to possess anti-tumor and anti-metastatic properties.90,91

Eleutherococcus Senticosis

Eleutherococcus senticosus, more commonly known as Siberian ginseng, is a medicinal plant that has been shown to modify immune responses and is mainly used for its immune-stimulant and anti-cancer activities.92,93 Research has shown that when the substance is prepared and stored as an extract, its antiviral activities remain intact. Its antiviral effects have been studied in several viruses. Siberian ginseng has been shown to inhibit the successful replication of multiple RNA type viruses, including human rhinovirus (HRV), respiratory syncytial virus (RSV), and influenza A.94

Increases T lymphocyte numbers
A placebo-controlled study investigating the effects of Siberian ginseng on healthy volunteers found that compared to a placebo, those taking a 10 mL ethanolic Siberian ginseng preparation 3 times each day over a 4-week period had significantly more immunocompetent cells.95 The increase in absolute numbers of T lymphocytes was particularly prominent. While most of these T lymphocytes were helper cells or inducer cells, cytotoxic and natural killer cells increased as well. In addition to the change in numbers, the activation state of these cells was also enhanced.

Reduces swelling and inflammation
One result of the enhanced immune potential conferred by Siberian ginseng is reduced inflammation. The anti-inflammatory properties of Siberian ginseng include a tendency to promote anti-inflammatory phenotypes in human macrophages.96 Siberian ginseng has also been shown to induce lymphatic endothelial cell migration and cord formation. This influence on the lymphatic system is thought to underlie the ability of Siberian ginseng to combat edema.97

Works in combination with andrographis
Multiple studies looking at the effects of combining Siberian ginseng with *A. Paniculata* through Kan Jang, a fixed combination containing both substances, has showed that the combination eads to a significantly better symptom improvement in those with URTIs when compared to placebo, as well as when compared to standard treatments.73,74,98 Recovery with this combination has been shown to be faster and particularly pronounced for headache, nasal secretion, nasal congestion, and throat symptoms. Interestingly, the combination therapy has also been shown to have beneficial effects on male sterility.99

Elderberry Extract

Elderberry (*Sambucus nigra*) is one of the most commonly used medicinal plants in the world, known especially for its antiviral and antimicrobial properties.100 While the mechanisms underlying the therapeutic effects of elderberry extract are not completely understood, there is a significant amount of data that helps to clarify how this extract affects us.

Reduces flu symptoms and illness duration
Elderberry has demonstrated an antiviral effect in several flu strains. According to a meta-analysis of data on elderberry supplementation in those with upper respiratory symptoms, elderberry is an effective way to substantially reduce these problematic symptoms. The authors of this meta-analysis suggest that elderberry may present a valuable alternative to prescription drugs that are often used to fight common colds and flus as well as a way to avoid the misuse of antibiotics in these

cases.101

The effects of an oral elderberry syrup were recently tested on 60 adult patients with influenza A and influenza B infections who had had symptoms for up to 48 hours. The patients received 5 milliliters (mL) of the elderberry treatment or a placebo 4 times each day for 5 days. Those receiving the elderberry experienced resolution of their symptoms on average 4 days faster than those in the placebo group. In addition, those taking the elderberry were less likely to use other rescue medications during their illness. Based on their observations, the authors of this study concluded that elderberry extract is likely a safe, cost-effective, and efficient treatment for influenza.102

A placebo-controlled, double blind study conducted in response to a 1993 flu outbreak showed that those who were treated with elderberry extract recovered from their symptoms within 2 days on average, whereas those in the control group did not recover for 6 days. Upon observing their results, the authors of this study suggested that the elderberry extract be considered as a treatment for influenza A and influenza B, given its efficacy, low cost, and lack of association with side effects.103

There is also research that compares the effects of elderberry extract versus medications used to fight the flu. These data show that elderberry extract has favorable anti-flu activity relative to Oseltamivir, more commonly known as Tamiflu, and Amantadine at doses of 0.32 microliters (mM) and 27 mM, respectively.104

Combats cold viruses
Elderberry's impact on common viruses encompasses not only flu viruses but also cold viruses. A study investigating how elderberry extract may provide value for intercontinental air travelers observed the effect of the extract on 312 economy class passengers flying from Australia to overseas destinations and found that the extract produced beneficial effects, particularly for respiratory health and mental health. Specifically, those who took the extract were found to have less severe colds and shorter cold durations than those who took placebo.105

May fight coronaviruses
Elderberry has been implicated in coronaviruses. A species of elderberry has been shown to have strong anti-viral effects against one of the most common circulating human coronaviruses, HcoV-NL63.106 Elderberry has also been shown to significantly reduce virus titers in infectious bronchitis virus (IBV), a pathogenic chicken coronavirus.107

Provides protection through several mechanisms
Data suggest that at least some of the antiviral effects of elderberry are achieved through the stimulation of immune responses.108 For example, it has been observed that the extract enhances certain types of immune activity in dendritic cells, consistent with antiviral activity.109 Its impact includes inhibiting the replication of H1N1 and H3N2 viruses and reducing hemagglutination.103 Electron microscopy analysis also points to a mechanism in which elderberry extract may damage the envelopes surrounding virions, thereby compromising the integrity of the viral structure.109

In addition to its effects on immune cells, there is evidence that elderberry flavonoids may act directly on virions. Research into the mechanism whereby elderberry extract exhibits anti-flu virus activities has shown, for example, that flavonoids from the extract bind to H1N1 virions, thus preventing the virus from infecting host cells.104

Antiviral properties are not the only value elderberry brings to immunity. For instance, elderberry also displays antimicrobial activity, including activity against both Gram-positive and Gram-negative bacteria.110 Elderberry extract also has antioxidant effects, inhibiting the production of IFNγ-induced ROS and the expression of p-ERK1/2, leading to lower levels of reactive oxygen species.111,112

Vitamin A

Vitamin A has been established as a vitamin that is critical to both the development and the maintenance of the human immune system.113 The vitamin has been recognized for nearly a century for its ability to enhance anti-inflammatory responses.114,115 Since the initial observations of the benefits of vitamin A, its anti-inflammatory capabilities have been corroborated, and more has been revealed about how vitamin A can boost immunity.113,115–118

Improves infectious disease outcomes
Vitamin A has an established role in the spread of infectious disease. For example, vitamin A deficiency is thought to underlie the spread of diseases in children via respiratory and digestive systems.119–121 Investigations into its role in specific infectious diseases has shown its ability to relieve symptoms of pneumonia and to enhance antiviral activity in cases of hand, foot, and mouth disease.122,123 It has also been shown to reduce mortality in measles and diarrhea and morbidity in diarrhea, and alaria.124–128 It is also thought to be beneficial in cases of Acquired Immune Deficiency Syndrome (AIDS), likely owing to its anti-oxidant properties.113

Supports epithelial and mucous layer integrity
Vitamin A affects innate immunity through its role in maintaining the integrity mucous layers and epithelial tissues.129 It enhances antigen non-specific immunity in mucous layers of the respiratory tract and intestine by promoting the secretion of mucin.130,131 Vitamin A also contributes to the formation of the epithelium – aiding in the differentiation of epithelial cells as well as their functional maturation.130

Epithelial cells shrink in cases of vitamin A deficiency, which is accompanied by a variety of symptoms including coughing, diarrhea, and dry skin and eyes.113 On the other hand, vitamin A supplementation improves intestinal integrity in children with severe infections as well as in those who are malnourished.115

Acts through several mechanisms
It is thought that vitamin A supplementation may enhance T-cell counts in children.115 Vitamin A also plays a role in the synthesis of antibodies to antigens that are T-cell-dependent - leading to lower levels of these antibodies in cases of vitamin A deficiency - and is also required for normal macrophage development.115,132 Clinical trials have shown that vitamin A supplementation could reduce the amount of proinflammatory cytokines that macrophages secrete and that it may provide benefits for mmunosuppressed children through its effects on natural killer cells.115,133,134

Vitamin C

Vitamin C - also known as ascorbate - is critical to the human diet and plays a critical role in immunity. It is particularly relevant for functional cells of the immune system.135 It is often observed that very ill patients have severely depleted plasma levels of vitamin C, or below 20 micro milliliters.136

Unfortunately, vitamin C deficiency is the fourth most common nutrient deficiency, and humans cannot synthesize vitamin C.137,138 The suggested daily intake of vitamin C is 100-200 mg/day for adults, which is up to 100 fold higher than for other vitamins.139

May improve infectious disease symptoms
Vitamin C supplements have been shown to improve infectious conditions. Studies have consistently shown that impaired eukocyte chemotaxis can be reversed with vitamin C upplementation in patients with recurrent infections.140–143 Similarly, 400 mg/day supplementation for neonates suspected to be suffering from sepsis has been shown to significantly improve neutrophil chemotaxis.144

Affects critical activities in a variety of immune cells
A well-known antioxidant with immune-modulating effects, vitamin C aids in immune defense via effects on both the innate and adaptive immune systems.139,145 In terms of innate immunity, vitamin C contributes to the ability of the epithelial barrier to prevent pathogens from entering the body and enhances the ability of the skin to scavenge oxidants. Vitamin C can improve the integrity of epithelial barriers through several different mechanisms. For instance, vitamin C promotes the synthesis and stabilization of collagen, increases the proliferation and migration of fibroblasts as well as the synthesis of lipids and differentiation of keratinocytes, and hastens wound healing.146–163

Vitamin C also affects adaptive immunity at several levels, affecting inflammatory mediators and modulating the production of cytokines and reducing histamine levels.164–181 Vitamin C is implicated in B lymphocyte and T lymphocyte activity. For xample, vitamin C increases antibody levels as well as B ymphocyte and T lymphocyte differentiation and proliferation.165,182–192 It may also play a role in T cell differentiation.193 Perhaps unsurprisingly, both plasma and cellular levels and vitamin C appear to be depressed during active inflammation.194–196

Vitamin C deficiency helps to highlight several key functions for vitamin C in immune responses. For instance, severe vitamin C deficiency is associated with impaired bactericidal ability ineutrophils and also impacts the ability of phagocytes to migrate to infection sites.197,198 The effects of vitamin C deficiency on phagocyte function has also led to the revelation that vitamin C can increase phagocytes' motility and chemotaxis, improve their ability to kill microbes, enhance their clearance potential, and reduce necrosis.140,143,173,185,197–202

Vitamin D

Before effective antibiotics were invented, vitamin D served as a treatment for infection. We have since learned that vitamin D plays a critical role in innate immunity and the innate immune system's anti-microbial response.203–205 For example, vitamin D has been shown to improve physical barrier functioning of epithelial cells and to enhance immune cells' capacity for phagocytosis.206,207

Contributes to immune functioning
The idea that vitamin D contributes to human immune function has in part been born out of observations of differences in disease occurrence based on geographic location.208 For instance, autoimmune disease has been associated with lower past sun exposure or lower vitamin D status than what is observed in healthy controls.209,210

Several studies involving thousands of patients have corroborated the association between vitamin D levels and infection. Research has shown that even when controlling for variables such as age, sex, race, and body mass index (BMI), people with vitamin D levels below 30 nanograms per milliliter (ng/mL) are more likely than those with higher vitamin D levels to report having recently suffered from an upper respiratory tract infection.211 Additionally, vitamin D administration has been shown to significantly decrease flu infection incidence.212

Modulates B cell and T cell activity
Vitamin D modulates the activity of B cells and T cells in those with autoimmune diseases, pointing to potential mechanisms underlying the ability for vitamin D to confer its benefits to the immune system. Indeed, in all people, vitamin D has important implications for B cell and T cell functions. For instance, vitamin D blocks B cell differentiation and inhibits B cell proliferation.213,214 It also suppresses proliferation of T cells and promotes T cell phenotypes that are anti-inflammatory rather than proinflammatory.215–224

Biotin

Biotin, also known as vitamin B7, has been deemed by medical experts as indispensable in human health.225 It has several roles in normal immune functioning.

Influences adaptive immunity
Much of the research on the relationship of biotin and immunity has revealed the effects that biotin has on adaptive immunity, including contributing to cytotoxic T lymphocyte generation, the normal functioning of human natural killer lymphocytes, and the maturation as well as the responsiveness of immune cells.226–229

Improves blood glucose management
Glycemic management has been shown to be improved when biotin is used as an adjuvant to insulin in patients whose type 1 diabetes is poorly controlled.230 Preclinical work has shown that biotin is able to reduce blood sugar and improve insulin resistance, perhaps by lowering gluconeogenesis and enhancing glycogen synthesis.231,232 The role of biotin in mitigating the impact of sugar may help to combat the detrimental effects of sugar on the immune system.

Critical for normal immune cell makeup
Biotin deficiency is associated with higher levels of proinflammatory cytokines.233,234 Patients with multiple carboxylase deficiency, which is associated with biotin eficiency, have been reported to suffer from defects in immunity related to T cell and B cell function.235 Children who have hereditary biotin metabolism abnormalities have been reported to suffer from abnormal percentages of T lymphocytes in their peripheral blood, as well as IgA deficiency.235

Affects immune cell expression
Immune cell secretion of cytokines may rely to some extent on biotin status. Research has shown that supplementation with biotin influences human immune cell gene expression and likely affects the ability of immune cells to respond to antigens.236

Chromium

Chromium is known to be critical to health, and deficiencies in chromium are linked to health defects ranging from coronary artery disease to metabolic disturbances.237 Chromium is especially implicated in obesity and obesity-related disorders. Given that obesity has a well-established negative impact on immune health,238 chromium may offer an opportunity to prevent immune deficits, through - in part - a healthy metabolic system.

While it is recommended that adults consume between 20 and 45 micrograms (mg) of chromium per day, depending on their age, sex, and whether they are pregnant or lactating, there is some debate about the prevalence of chromium deficiency.239 Nonetheless, there is evidence to suggest that older people are more likely to suffer from chromium deficiency.

In North America, chromium deficiency is thought to occur

because people tend not to consume enough chromium in their diets. Also contributing to chromium deficiency is the body's tendency to lose chromium stores through urine in response to things like strenuous exercise, diets that are high in sugar, physical trauma, and emotional stress.240 Though the body only needs trace amounts of chromium, it can be difficult to get chromium through the diet. While many vitamins can be obtained through fruits and vegetables, experts point to less appetizing foods like calf liver as a recommended source of chromium.241

I*mpacts immune cell production*
While the heavy metal occurs in meats and vegetables, it is also often used in salt form as a micronutrient because supplementation with this type of chromium has been shown to provide health benefits.242 Chromium has clear effects on several aspects of the immune system. It influences both the stimulatory and suppressive activities of the immune system by altering the production of several immune cells including T lymphocytes, B lymphocytes, macrophages, cytokines.243

Helps to regulate blood glucose
Research has shown that chromium supplementation in elderly patients with diabetes is beneficial with respect to glucose intolerance.244 One study showed that fasting blood glucose and hemoglobin A1c (HbA1c) improved in those taking 200 mg of chromium twice each day for 3 weeks.245 A recent comprehensive meta-analysis on the effects of chromium supplementation on indices of glycemic control in type 2 diabetes patients found that supplementation could help this group of patients control their sugar.246 Because sugar can harm the immune system, the ability of chromium to lower the amount of sugar in the blood could impart benefits on immunity.

Zinc

Zinc plays a role in both innate and adaptive immunity. It is an important cofactor that helps with the stabilization of cell membranes, which makes it critical for the integrity of skin tissues and other parts of the body that are regularly exposed to pathogens, such as the lungs and intestines.247

Zinc is an antioxidant that can improve even localized oxidative injuries and is considered an essential micronutrient. It also shows capabilities for improving glycemic control, which is known to be important for healthy immunity.248,249 According to the U.S. Food and Nutrition Board, men and women should consume 11 mg and 8 mg of zinc per day, respectively.247,250

Implicated in several infectious diseases
Zinc deficiency – especially mild and moderate deficiency - is common and linked to infectious diseases like pneumonia, tuberculosis, malaria, measles, and HIV.247,251,252 The deficiency has been also been reported to account for 16% of respiratory tract infections.247 Almost 30% of older adults suffer from zinc deficiency.253

In cases where sepsis occurs, zinc deficiency is associated with heightened risk for excessive inflammation and poor outcomes.247,254,255 Interestingly, zinc supplementation has been shown to be valuable when used prophylactically but not in esponse to sepsis.256 On the other hand, there is evidence that zinc supplements may be helpful even after the onset of symptoms associated with some common viruses. For example, supplements at doses of 75 mg per day or higher have been shown to reduce the length of common cold symptoms in healthy patients.257 Research into how zinc supplements may afford these benefits has revealed that supplementation can improve abnormal activities in immune cells responsible for adaptive immunity.247

Affects immune cell functioning
Zinc is implicated in the proper functioning of several immune cell types, including monocytes, polymorphonuclear cells, natural killer cells, T-cells, and B-cells.258 Zinc deficiency affects the proper functioning of immune cells by impacting the progression of the cell cycle as well as immune cell maturation, proliferation, function, and survival.258–260 Zinc upplementation has been shown to improve some of these impairments, such as increasing natural killer cell differentiation.247,261

Helps eliminate pathogens
Zinc appears to be involved in danger signaling for immune cells, with immune system sequestration of zinc helping to fight off invading pathogens.253,254 Zinc has, for instance, been shown to be essential for parts of the pathogen-eliminating signal transduction pathways that lead to the formation of neutrophil extracellular traps.247,262,263

Contributes to anti-inflammatory responses
Acute zinc deficiency inhibits both innate and adaptive immunity, while chronic zinc deficiency leads to enhanced inflammation through increased production of in proinflammatory cytokines.258 Zinc targets the transcription factor nuclear factor kappa b (NF-kB), which is the master regulator of proinflammatory responses, thereby modulating proinflammatory responses.247 During sepsis, zinc signals serve an anti-inflammatory role.247

The importance of zinc for combatting inflammation is also highlighted by activities that occur in zinc deficiency. For xample, low zinc levels are associated with elevated nflammatory responses that can damage host tissue.247 Additionally, the immune changes that accompany zinc deficiency involve imbalanced immune responses, such as changes in the ratio of Th1 to Th2 cells, which are conducive to autoimmune disease and allergies.260,264

Conclusion

Our immune systems are our key to wellness. To fight off threatening invaders while also protecting our own tissues, the immune system is necessarily complex. Though this complexity affords it impressive functions, it also makes it susceptible to dysfunction. The best ways to maintain the integrity of our immune systems and boost our overall immune health are not perfectly understood. However, there is a plethora of research on the impacts of various substances on the cells of the immune system and how substance-induced changes to these cells alter overall immune functioning. This research offers insight into how we can meaningfully change what we consume to promote healthy immunity and how to best formulate supplements that can support these efforts.

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