

## Review Article

# Nutrients Interaction with the Immune System

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### Abstract

This study described the interactions of different nutritional components with the immune system. A detailed search was carried out on Google Scholar and PubMed databases to find out the relevant research studies using different keywords, such as "Nutrients", "Micronutrients", and "Immune system and micronutrients". Only those papers that discussed the interactions between nutrients and the components of the immune system were included in the study. This research outlined the impact of different vitamins, trace elements or metals, amino acids, and fatty acids on different immune system components. It was found that vitamins, such as vitamin A, D, and C, tend to help immune cell differentiation and enhance the expression of different cytokines. Vitamins also contribute to the proliferation of T and B cells and impact the production of white blood cells. Similarly, trace elements or metals act as enzyme cofactors and control different immune response cycles by controlling the expression of cytokines, chemokines, and other signaling molecules. Moreover, different essential and non-essential amino acids play important roles in immune system development as they are primarily involved in protein synthesis. Amino acids, such as arginine, glutamine, and alanine, modulate the expression of cytokines and also control the migration and transmigration capabilities of macrophages. They also enhance the phagocytic properties of macrophages and neutrophils. In a similar way, fatty acids act as anti-inflammatory agents since they can decrease the expression of major histocompatibility complex class I (MHC-I) and MHC-II. Furthermore, they inhibit the secretion of different inflammatory cytokines. In conclusion, all the components of our daily diet are associated with the development of the immune system, and understanding their interactions is important for future immune therapies and drug development.

**Keywords:** Nutrients, Immune system, Vitamins, T cells, B cells

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### 1. Context

Our bodies are highly dependent on the environment for proper development. We share our environment with several other organisms, of which some are pathogenic to our bodies if they somehow manage to cross the physical barriers and reach our bodies. The immune system protects our body from external pathogens and invaders. The immune system tackles pathogens through physical and biochemical barriers, immune cells, and antibodies formed by the immune cells (1). This system is usually divided into innate and

adaptive categories. The innate immune system comprises different myeloid and lymphoid cells that can rapidly work against any foreign pathogen. On the other hand, the adaptive immune system relies on T and B cells that identify the antigens and produce antibodies against them (2). When a pathogen manages to cross physical and biochemical barriers, the innate immune system cells, phagocytes, and natural cytotoxic cells suppress the pathogen (3). Neutrophils and macrophages are involved in boosting the protective ability of phagocytes. At the same time, antigen-

presenting cells present the antigens recognized by the lymphocytes, which produce antibodies against those antigens.

The human body comes across several pathogens throughout life, and therefore, the immune needs to be boosted and developed to protect the body against foreign invaders. Nutrients play an essential role in the proper development of the immune system. Adequate nutrition is necessary for all cells to perform their functions at optimal levels (4). The nutritional requirement rises further during infection as immune cells use direct and indirect approaches to fight those pathogens. For instance, lymphocytes rapidly multiply and produce antibodies rapidly, thereby increasing the body's energy and nutritional requirements. Moreover, in the absence of some nutrients, phagocytes involved in innate immunity tend to lose their effectiveness (5). Nutritional imbalance is prevalent across the world. It has been reported that 1.9 billion people are overweight, while 462 million people are suffering from malnutrition (6). These perturbations result in different diseases. Different dietary micro and macro-nutrients are also known to affect the leukocyte structure. Furthermore, some humans are severely allergic to some foods. For instance, 16 protein-based allergens present in peanuts induce immunoglobulin E antibodies in predisposed humans (7). Therefore, it is necessary to understand how different nutrients impact the immune system to develop therapies that strengthen the immune system.

Nutrients play key roles against different viral diseases. They can either directly interact with the viral pathogen or activate immune cells as part of the adaptive immune system (8). Dietary components, such as vitamins, have been found to enhance body development and repair mechanisms resulting in increased immunity (9). Therefore, the consumption of vitamin-rich foods, such as citrus, carrots, nuts, milk, oils, and dairy products, has been observed to increase an individual's overall immunity and health. Similarly, metals or metallic ions and their derived proteins are also important components of the diet that can help

develop effective immune responses. Amino acids are also involved in developing and boosting the immune system. For example, different branched-chain amino acids are essential for nutrition and intestinal health and immunity (10).

Considering the importance of nutrients in the development of the immune system, this review discussed the role of nutritional components in the functioning and development of the immune system. It also discussed how different nutrient intake perturbations could impact immunity and how to tackle the problem. It would systematically discuss different vitamins, metal ions, fatty, and amino acids and their role in developing the immune system.

## 2. Evidence Acquisition

The basic objective of this article was to explore the interaction between different nutrients, including vitamins, minerals, trace elements, amino acids, and fatty acids, and the immune components and system. In this regard, a detailed search was carried out on Google Scholar and PubMed databases to find out the relevant research studies. The search process was performed using the following keywords: "Nutrients", "Micronutrients", "Immune system and micronutrients", "Vitamins and immunity", "Minerals and immunity", "Trace elements and immune system", "Immunity and amino acids", "Fatty acids and immune system", and "Nutrients and immune microenvironment".

To retrieve those studies containing subcategories of the above-mentioned micronutrients, the names of those micronutrients were used to find out the relevant articles. Inclusion and exclusion criteria were employed to shortlist only those studies that discussed the immune system's interaction with nutrients and the role of micronutrients on the immune microenvironment. Other studies were excluded as they did not meet the inclusion criteria of this study. Other than the direct search, cross-referencing was also employed from the already reviewed and included studies to broaden the search to more relevant articles. Only published studies

were included in this review, and all other articles and studies were excluded.

### 3. Results

#### 3.1. Vitamins and Immune System

The word 'Vitamin' was formerly known as a slightly different term in 1911: 'Vitamine', which was derived from two different words (i.e., Vital+Amine); however, later, this term was changed to 'Vitamin'. Various members of this family have proven roles against various diseases, such as rickets, xerophthalmia, pellagra, and beriberi, which makes them an interesting candidate to study their interaction with the immune system. They are a vital part of our diet, and that is why they have been known to influence the immune system (11).

##### 3.1.1. Vitamin A

Vitamin A is considered an essential component of diet as immune components need a constant supply of Vit A to work properly. It is available in the diet in the form of retinyl esters, all-trans-retinol, and  $\beta$ -carotene (11). Retinol plays a vital role in mediating immune responses, such as innate and cell-mediated immunity. It also influences the responses of the humoral antibodies produced by the immune system. Retinoid acid, another derivative of Vit A, also has regulatory roles towards innate immunity and has a major influence on the development, differentiation, and proper functionality of the various immune components of innate immunity. Macrophages and various neutrophils constitute the innate immune cells that, upon pathogen invasion, further activate the natural killer (NK) cells. The deficiency of Vit A can lead to the affected immune responses against pathogens (12). In another research, it has been demonstrated that Vit A acts as a vital nutritional component for the optimal development and function of CD169, which is an important component of the immune system (13).

##### 3.1.2. Vitamin D

Vitamin D is available in different forms, and the most effective form of Vit D is Vitamin D<sub>3</sub> (14).

Consuming Vit D in the form of supplements and diet can maintain the requirement of Vit D in the human body. Sunlight exposure, along with dietary intake, is also a good source of Vit D and to overcome its deficiency. Proper intake of Vit D in any form can prevent the body from serious viral infections. It has a crucial role in enhancing the physical barrier by mediating the protein synthesis for tight junctions (15), gap junctions (16), and adherent junctions (17) as they were the first barrier that gets destroyed in case of microbial infection, specifically viral infection (18).

Deficiency of Vit D increases the susceptibility of the body to various diseases and infections. Its deficiency also leads the body towards various autoimmune diseases, while, when taken in adequate amounts, it can act as a potential immunosuppressant for preventing the body from autoimmune diseases (19, 20).

##### 3.1.3. Vitamin C

Vitamin C has numerous beneficial immune properties to enhance the functionality of the immune system. It is a reducing agent; that is why it acts as the best antioxidant or a cofactor of an enzyme. It is also widely known as a leukocyte stimulant/enhancer as it stimulates the efficient working of white blood cells and neutrophils. In case of recurring infections, the overall consumption of Vit C increases as white blood cells increase their Vit C uptake from the body to fight against those infections. Intake of Vit C supplements can boost the proliferation rate of T lymphocytes by enhancing the overall production of cytokines and immunoglobulins against infections (20). Treatment with Vit C in case of viral infections also has proven roles. The results of various clinical trials have represented that adequate intake of Vit C as supplements and in the form of diet works as an effective treatment against the common cold and flu. Deficiency of Vit C can increase the susceptibility of the body against pathogenic infections and increases weakness of the immune system (21).

## 3.2. Trace Elements and Immune System

Among micronutrients, trace elements constitute one of the important categories. Not only do they have a crucial role in various physiological processes of the body but they are also critically important for the proper functioning of the immune system (22). Deficiencies and elevated levels of the trace elements negatively impact the immune system by affecting the activity of the immune components, such as NK cells, by modulating the antibody responses against antigens, and also affect the innate and cell-mediated immune responses (23).

### 3.2.1. Iron

Iron (Fe) is known as the most important trace element for host-pathogen interactions because of its beneficial properties. It is an essential component for the proper functioning of the living system; therefore, whether it is a host or the invading microbe, it requires an adequate amount of Fe to sustain its functionality. Nutritional immunity is the hot term widely used these days by researchers. It is a strategy in which the host cell uses the nutritional components, such as Fe, of the invading pathogens and deprives them of their essential nutrients, which will eventually make them non-pathogenic (24). Iron has a vital role in the differentiation and proliferation of T-cells and helps in the regulation of the optimum ratio between the T-helper cells and T-cytotoxic cells in the immune microenvironment. Furthermore, it has a notable role in the production of interferon gamma (INF- $\gamma$ ) (25).

### 3.2.2. Zinc

After iron, zinc (Zn) is another most crucial trace element which is also naturally present in the human body. The naturally occurring amount of Zn in the human body is 2 g. About 0.1% of the total zinc content naturally exists in the blood plasma, which is vital for regulating body homeostasis. It is also widely known for its promising properties for modulating host defense mechanisms, specifically in the case of viral diseases. This trace element is known to be able to enhance the virus-fighting properties of various mammalian cells by boosting the natural immune

system (26). Zinc is considered an important structural component of numerous enzymes; therefore, the intake of Zn supplements can even help in preventing humans from infection by severe acute respiratory syndrome coronavirus 2 (27). Zinc, along with its several zinc-based proteins, has a promising role in combating viral infections by stimulating the functionality of the immune cell present in the respiratory tract of individuals. The findings of various pieces of research have shown that when taken along with hydroxychloroquine, Zn can cause a notable decrease in the death rate caused by corona virus disease 2019 (28).

### 3.2.3. Selenium

Selenium (Se) is also one of the important trace elements with beneficial properties, and one of them is antioxidant property. It prevents the cell from oxidative stresses as it resides on the active sites of the enzymes. Selenium is often unified with the protein structure, and such compounds are known as selenoproteins. These selenoproteins enhance the host defense system by acting as antioxidants, thus stimulating the functionality of NK cells and leukocytes against infectious pathogens (28). Selenium plays a vital role in regulating the balance of the effective functioning of the immune components. In a recent study, the findings suggested that Se has an inverse relationship with the mortality rate of COVID-19 patients. Patients who were declining and those who passed away had extremely low concentrations of the Se, compared to those of the survivors and healthy individuals (29). It is also known to stimulate the production of INF- $\gamma$  and T-helper cells, both of which are important components of the immune system. It strengthens the immune system by regulating antibody production (30).

## 3.3. Amino Acids and Immune System

Amino acids are important components of our diet that can be broadly divided into two categories, namely essential and non-essential amino acids. Essential amino acids are the ones that cannot be synthesized by our body, while non-essential amino acids can be synthesized. Therefore, individuals entirely depend on

external sources (31) for non-essential amino acids. Amino acids support immunity as they are part of nucleotide synthesis, adenosine triphosphate production, redox balance, and cellular activation (32).

### 3.3.1. Arginine

Arginine is a non-essential amino acid; however, it is a crucial immunity booster. Arginine can stimulate the secretion of different hormones, growth factors, insulin, and glucagon. Arginine is an important nutrient for both innate and adaptive arms of immunity. Arginine has been found to enhance body defense against gastric carcinoma as it can stimulate the production of immunoglobulin M (IgM) and immunoglobulin A antibodies (33). Moreover, arginine boosts the levels of hydroxyproline, which can improve the reaction of lymphocytes against antigens. Similarly, arginine-derived compounds and arginine-rich peptide-based messenger ribonucleic acid nanoparticles have been successfully used to enhance cytotoxic T cells immunity (34). Arginine has also been observed to regulate signal transduction pathways in immunocytes. The findings of different studies on T cell culturing indicate that the lack of arginine leads to the downregulation of the CD3 $\zeta$  subunit, thereby impacting the T cell receptor complex assembly. The decrease in the expression of this subunit suppresses the proliferation of T cells (31). Furthermore, the lack of arginine impacts the glycolytic functions of T cells. Therefore, arginine guides the energy metabolism functions of T cells (35).

### 3.3.2. Glutamine

Glutamine is a non-essential amino acid, which is majorly synthesized in muscles. It is involved in hematopoiesis, immune responses, and endocrine and nervous system regulation. Glutamine has important functions in intestinal integrity and naïve immune system development as it is an important substrate of different immune cells, such as lymphocytes and macrophages (36). Glutamine plays an essential role in cell-mediated immunity. During different diseases and metabolic stresses, such as surgery, trauma, transplant,

sepsis, chemo, and radiotherapy, the glutamine reserves are highly depleted (37). Consequently, glutamine supplements help restore the gut barrier and improve immunity levels in patients. Glutamine helps boost the immune system by reducing inflammatory responses. The results of a study conducted on porcine circovirus type 2 (PCV2) infected mice indicated that glutamine supplementation could increase the amount of interleukin 2 (IL-2) in the serum. Moreover, glutamine also positively affects the cytokine profile of the mice infected with PCV2. Furthermore, glutamine is an essential source of energy for enterocytes or the intestinal epithelial cells, as it can also help reduce intestinal atrophy and mucosal repair (38).

### 3.3.3. Alanine

Alanine is another non-essential amino acid that plays different roles in gluconeogenesis, cellular activation, and immunity. It also helps in nitrogen balance, protein synthesis, and immune responses in living organisms. The immunomodulatory roles of alanine have not been well explored. Most of the available studies have tried to explore the impact of alanine supplementation on IL-6, IL-8, and tumor necrosis factor alpha (TNF- $\alpha$ ). In a study, alanine has been found to upregulate IL-6 expression in cells treated with polysaccharides (39). Alanine performs an opposite function to arginine, as it enhances the production of IL-6. However, it plays a similar role as arginine as it can also enhance the production of TNF- $\alpha$  in septic monocytes. Nevertheless, alanine, exactly as arginine, could not impact the expression of IL-8 in immune cells. Extracellular alanine has been found to be responsible for T cell activation. Alanine helps T cells to exit quiescence and protein synthesis in T cells. Therefore, the human immune deficiency virus tends to target sodium-dependent amino acid transporter 1 to cut off the supply of alanine (40).

### 3.4. Fatty Acids and Immune System

Fatty acids are a major component of our diet. Like vitamins, metallic ions, and amino acids, fatty acids also have an important role in immunity. Fatty acids act

as modulators of immune response and inflammation with anti-inflammatory properties (41). There have been a number of studies to understand the role of fatty acids in immunity, most of which have explored the roles of different polyunsaturated fatty acids (PUFAs).

#### **3.4.1. Omega-3**

Omega-3 PUFAs have long been known to reduce cardiac arrhythmias risks in patients suffering from coronary heart disease. Apart from this, omega-3 also has several impacts on different cells of the immune system. It can impact macrophages in three different aspects. Firstly, omega-3 enhances the phagocytic properties of macrophages, probably by altering the membrane structure. Secondly, omega-3 can reduce inflammation by downregulating the expression and secretion of interleukins, cytokines, and chemokines. Thirdly, omega-3 can also decrease M1 polarization and increase M2 polarization in macrophages, helpful in reducing brain injury after a stroke (42). Similarly, omega-3 affects the properties of neutrophils in different ways. First, it can inhibit the migration and transmigration capabilities of neutrophils by inducing epithelial cells to produce prostaglandin D<sub>3</sub> rather than prostaglandin D<sub>2</sub> (43). Prostaglandin D<sub>2</sub> increases their migration while prostaglandin D<sub>3</sub> decreases it. Second, the results of a study have shown that omega-3 can enhance the phagocytic activity of neutrophils by 35% (44). Third, omega-3 also improves the number of neutrophils in the bone marrow, as a diet rich in omega-3 increases neutrophils and CD117+ precursor cells.

#### **3.4.2. Eicosapentaenoic Acid**

Eicosapentaenoic acid (EPA) is another important PUFA and a subtype of omega-3 fatty acids with a crucial role in the immune system. It is usually found in cold-water fish and fish oil supplements. It has been found that EPA is effective in different autoimmune disorders, which occur due to aberrations in the immune system. It can also help control inflammation and immunologic disorders by inhibiting cytokine and leukotriene production (45). Moreover, EPA has been reported to impact the T cells and be able to inhibit the

differentiation of Th17 cells by preventing the effects of etanercept. Therefore, it can be used as an anti-TNF therapeutic agent (46). In addition, EPA contributes CD4+ and CD25+ cells to convert into regulatory T cells (Tregs) (42). Tregs regulate different functions of the immune system. Similarly, EPA also enhances the number and differentiation of both transitional type 1 and type 2 B cells. Furthermore, it influences B cells to increase the amount of IgM antibodies in both mice and humans by increasing the number of antibody producer cells (42).

#### **3.4.3. Docosahexaenoic Acid**

Docosahexaenoic acid (DHA) is also a PUFA, like EPA, and a subtype of omega-3 fatty acids. Docosahexaenoic acid is mostly found in fish oil supplements and can also be synthesized from  $\alpha$ -linolenic acid. Most of the time, DHA has similar, however, non-identical effects as EPA on the immune system. Eicosapentaenoic acid usually regulates cell cycle pathways, and DHA tends to regulate immune response pathways. Docosahexaenoic acid can enhance reactive oxygen species (ROS) production by neutrophils (44). These ROS have a key role in antimicrobial defense and inflammation as they can enhance transcriptional signaling and cellular apoptosis. Docosahexaenoic acid treatment can decrease the major histocompatibility complex class I (MHC-I) expression and conjugation in lymphoblasts, leading to a decreased lysis of lymphoblasts by alloreactive CD8 cells (47). Similarly, DHA has been found to inhibit MHC-II expression of dendritic cells in both mice and humans. Moreover, DHA increases splenic NK cells activation as it was found to increase the expression of IL-1 $\beta$ , IL-2, IFN- $\gamma$ , and TNF- $\alpha$  in immunosuppressed mice (48). Furthermore, DHA has also been reported to have inhibitory effects on eosinophils and basophils.

#### **3.5. Other Nutrients and Their Interaction with the Immune System**

Table 1 presents several other micronutrients and their interaction and impact on the immune components and overall immune responses.

**Table 1.** Micronutrients and their impact upon the immune system

Micronutrients	Impact on the immune system	References
<b>Vitamins</b>	Vitamin E	Stimulates T-cell differentiation in the thymus and prevents the cell membrane from radical damage. (48, 49)
	Vitamin B12	Acts as an immune modulator and cofactor for various metabolic processes. (50)
	Vitamin B9	Maintains the efficient activity of immune cells. (51)
<b>Trace Elements</b>	Copper	Essential micronutrient for optimum immune response and host defense mechanism and stimulates the functionality of natural killer cells. (52, 53)
	Manganese	Boosts the immune system by stimulating nutritional immunity. (13, 54)
	Magnesium	Stimulates the activation of leukocytes and maintain apoptosis (55)
<b>Amino Acids</b>	Leucine	Regulates the immune responses of various immune components. (56)
<b>Fatty Acids</b>	Proline	Stimulates the proliferation of lymphocytes in the immune microenvironment. (42, 57)
	Lysine	Protects the cells against viral infections. (42)
	Tyrosine	Acts as a neurotransmitter and has a role in the regulation of immune responses. (13, 58)
	Tryptophan	Acts as a neurotransmitter and an inhibitor against inflammatory cytokines. (58)
	Glutamate	Inhibits the inflammatory responses of T-cells. (53, 58)

#### 4. Conclusions

This review study gathered evidence supporting the role of different dietary or nutritional components in the development and modulation of the immune system. This article discussed the role of different vitamins, metallic ions, amino acids, and fatty acids in immunity. A detailed search was carried out on Google Scholar and PubMed databases using different keywords, such as "Nutrients", "Micronutrients", and "Immune system and micronutrients". Only those studies that discussed the interaction between nutrients and the immune system were included in this study.

Vitamins are important for the development and maturation of the immune system. Vitamin A helps

discriminate different cells of the immune system as it helps in the development of CD169 cells. The deficiency of Vit A can affect the immune response. Similarly, Vit D has been found to be effective against viral infections and helps enhance the physical barrier by developing tight, gap, and adherent junctions. Due to leukocyte stimulating properties, Vit C improves the working efficiency of neutrophils and other white blood cells.

Different trace elements or metal ions affect the functioning of our immune system. Iron is well known for its role in the differentiation and proliferation of T cells. It also helps regulate the ratio of cytotoxic and helper T cells. Moreover, iron enhances the production

of INF- $\gamma$ . Similarly, zinc can modulate host defense mechanisms. It also improves immune system functionality in the respiratory tract of individuals. Selenium, along with its antioxidant properties, can stimulate the production of IFN- $\gamma$  and T-helper cells. Moreover, it regulates antibody production as it is an important component of several key enzymes.

Numerous amino acids have different immune system modulating properties. For instance, arginine can improve gut barrier and immunity and has positive effects on the cytokine profile. Likewise, glutamine is important to intestinal integrity and naïve immune system development. Alanine can affect the production of IL-2, IL-6, and TNF- $\alpha$ . It also activates T cells by helping them to exit quiescence. The role of different PUFAs, omega-3, EPA, and DHA indicate that fatty acids are quite critical in the development and maturation of the immune system. These fatty acids affect immune cells and modulate their maturity, migration, and secretions. In the light of the studies discussed in this review, it is possible to assert the importance of different nutritional components in immune system development.

### Authors' Contribution

Study concept and design: G. A.

Acquisition of data: G. A.

Analysis and interpretation of data: S. P.

Drafting of the manuscript: S. N.

Critical revision of the manuscript for important intellectual content: G. A.

Administrative, technical, and material support: S. P.

### Conflict of Interest

The authors declare that they have no conflict of interest.

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