



## **Coronavirus and Nutrition: An Approach for Boosting Immune System-A Review**

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### **Authors' contributions**

*This work was carried out in collaboration among all authors. Author LMF designed the study and wrote the first draft of the manuscript. Author WBN managed the literature searches. Authors BMV and MM reviewed the paper. Author ISTDC designed the study and approved the final draft before submission. All authors read and approved the final manuscript.*

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### **ABSTRACT**

The global health crisis as a result of covid-19 demands fast and efficient response from global health care system. The evidence of nutrition-based interventions for viral diseases from past clinical trials, and its importance for optimizing the host immune response was reviewed in this paper. The immune system has involved in the protection of the host from pathogenic organisms, communicating molecules and functional responses. It is a known factor that nutrition plays key

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role in supporting the immune system as the role of nutrients feature prominently in a number of scientific literatures. Several clinical data showed that micronutrients like vitamins, including vitamins A, B<sub>6</sub>, B<sub>12</sub>, C, D, E and folic acid; trace elements including, zinc, iron, selenium, magnesium, copper and the omega-3 fatty acids like EPA & DHA play a major role in supporting the immune system. Inadequate intake of these nutrients is widespread resulting to a decreasing in resistance to infections and an increasing in diseases burden. Regarding the COVID-19 pandemic, the roles of nutrition for strengthening immune system for the patients to have strong resistant against the virus is also considered in this paper. It is believed that COVID-19 increases its severity or a host is susceptible to infectious disease once the immune system does not function optimally.

*Keywords: Nutrition; micronutrient; immune system; coronavirus.*

## 1. INTRODUCTION

Different types of coronaviruses have been around for many years as pathogens to animals and humans [1]. However, a novel coronavirus named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) causing the COVID-19 has first been reported in Wuhan (Hubei, China) and has been declared a global pandemic, the COVID-19 [2,3]. Whereas common cold and fatigue constitute mild COVID-19 symptoms that may appear within two weeks of exposure to the virus, severe diseases may include, pneumonia, haemoptysis, dyspnoea, lymphopenia and severe acute respiratory distress syndrome leading to even death [4]. As the covid-19 clinical symptoms range from mild to severity [2], this severity seems to correlate with age (from around 70 years) and affect more patients with comorbid conditions such as obesity, diabetes, chronic obstructive pulmonary disease, hypertension [5].

From what is known so far, organs that the SARS-CoV-2 targets include the lungs, the heart, the renal system and the gastrointestinal tract [6]. However, Tang [7] reported the abnormal coagulation in patient with COVID-19 which was associated with poor prognosis.

The impact of diet on human health has long been a topic of research as foods are capable of boosting both innate and acquired immunity [8]. It is established that malnourished people have reduced immune functions to provide defense against pathogenic organisms [9]. Immuno-nutrition may be necessary though not sufficient in the fight against potentially lethal viruses such as SARS-CoV-2. Immuno-nutrition can be understood as the adoption of a diet rich in immuno-nutrients or nutrient that enhances the immune system [10]. This review paper provides updated information about nutrients that have effect on the immune system in relation to the

COVID-19. In addition, the paper puts the evidence of nutrition-based interventions for control of viral diseases based on selected clinical trials to optimize the host immune response.

## 2. NUTRITION AND IMMUNE SYSTEM

The immune system is a host defence system within the organism that protects from invading pathogens, such as viruses or bacteria. Though the system functions endlessly, it is the presence of pathogens that activates immune cells. There are two main subsystems, different from their properties and defence mechanisms: the innate and the adaptive (acquired or specific) immune systems. The innate immune system is faster but with limited specificity. It is made of cells of structural barriers (such the skin and mucous membranes) and physiological barriers (such as pH and O<sub>2</sub> levels). These cells are macrophages, neutrophils, eosinophils, basophils, mast cells, natural killer cells (NK) and dendritic cells [11,12]. The adaptive immune system is more specific but with delayed activation. It is made of B-cells (humoral immunity) and T-cells (mediated immunity) and synthesises antibodies, acts as memory, and kills pathogens. The presence of surface immunoglobulin characterises B-cells that mostly carry major histocompatibility complex (MHC) class II antigens. T-cells are made of helper T-cells (CD4+), which recognize their specific antigens in association with major histocompatibility complex (MHC) class II molecules and cytotoxic and T-cells (CD8+), which recognize antigens in association with MHC class I molecules [11]. Immunity is impaired when it becomes overwhelmed and heralds serious infection, disease and may lead to death [13]. Such immunodeficiency occurs with ageing and environmental factors, especially malnutrition. In a study of nutritional status and nutrient supplements on immune responses and incidence of infection in older individuals,

Chandra [14] reported that immunodeficiency is noticeable as early as 35-40 years old. The study observed potential immunodeficiency mechanisms such as: Thymic involution and subsequent reduced output of naïve T-cells leading to a declining of T-cell function, the poor micronutrient status, ageing associated inflammation, a bidirectional relationship between infection/immunity and nutrition whereby changes in one of these components can impact the other [15]. The infection stimulates the activity of the immune system which increases the rate of metabolism, requiring sources of energy, a substrate for biosynthesis and regulatory molecules found in food. It is therefore important to provide an adequate range of nutrients to support the immune system for optimal functioning [16]. Evidence demonstrates that both humoral and cell-mediated immune function are impaired by a nutritional depletion in human body. Even for a moderate energy restriction experienced by overweight individuals weight lost diet, interferes with the immune function [17]. Therefore, healthy nutrition should feature among the objectives of protecting people against the potential lethal consequences of COVID-19 [18].

The progression to respiratory failure and mechanical ventilation had been predicted by low prealbumin levels in clinical spectrum of COVID-19 disease [19]. Various immunonutrients essential for immunocompetence may include micronutrient such as vitamins A, C, D, E, B6, Biotin, B12, folic acid, trace minerals like iron, selenium, copper, zinc and macronutrients including omega 3 fatty acids and bioactive components as polyphenols [13,20]. Cognisant of this and in the wake of the COVID-19, recommendations are now coming for evaluation of nutritional status in all infected patients at hospital admission [21], Call is being made to those who are not at risk of malnutrition to maintain daily healthy food intake (1.5 g/kg/d and 25-30 Kcal/kg/j for protein and calory respectively) [22].

## 2.1 Immune Boosting Nutrients

### 2.1.1 Proteins and amino acids

The activation of immune cells discussed earlier augments the need in the immune system for energy yielding substrates such as glucose, fatty acids and amino acids. Amino acids are necessary because this activation causes the production of different types of protein such as

immunoglobulins, chemokines, cytokines, cytokine receptors, adhesion molecules and acute-phase proteins [16].

Furthermore, some proteins are directly involved in the enhancement of the immune function. In a study of immunomodulatory effects of dietary whey proteins in mice, Wong and Watson [23] have detected in bovine milk proteins (casein and whey) most activities of immunomodulatory. Whey protein and  $\alpha$ -lactalbumin has been found to enhance lymphocyte function when included mice diet and the responsiveness of spleen derived lymphocytes to T-cell mitogens [23]. Lymphocyte function are also improved by lactoferrin and K-casein derived caseinoglycopeptides [24].

**Arginine:** Arginine is a nonessential amino acid with multiple biological effects in depressed immunodeficiency and other situations including trauma, tumors, infections. A study found that arginine supplementation increases blood lymphocyte proliferation and suppressor T-cell numbers in healthy people [25], while boosting phagocytic activity of alveolar macrophages in rats with tumor transplants. It has also been found that arginine being the sole precursor of nitric oxide, is important in microbicidal molecule that appears to be involved in macrophage killer function and in regulating interactions between macrophages and lymphocyte adhesion and activation [26]. Moreover, the synthesis of polyamine which have roles in regulation of the DNA replication and cell division require arginine availability for its proper function [13]. Increasing arginine rich food consumption or arginine supplementation for patients with COVID-19 could play important role to increase the blood lymphocyte proliferation, T-cell numbers and boosting alveolar macrophage activity which is important to cope against this virus.

**Glutamine:** Glutamine appears to have numerous important functions within the body. In the liver, it plays an important role in gluconeogenesis, amino acid synthesis, and the production of urea and glutathione; in the kidneys, it functions to promote ammonia excretion and thus neutralize acid loads; and in cells such as intestinal enterocytes, colonocytes, lymphocytes, and macrophages, it functions as a major source of carbohydrate skeletons for fuel and promotes cell proliferation [26]. In addition, glutamine assist in intestinal mucosal growth and integrity and enhances intestinal functions in

affected patients. The administration of glutamine provokes quick recovery to previously immune-suppressed bone marrow transplant patients as it reduces clinical infections [27]. The enhancement of food rich in glutamine may also help COVID-19 patients to fatty recover due to its reduction in infections.

### 3. VITAMINS AND IMMUNE SYSTEM

In general, micronutrients play a key role as cofactors in the metabolic machinery involved in energy generation and biosynthesis needed in immune response [28] as discussed earlier. With regards to vitamins, those that play direct role in immune system and may play a role in the prevention of COVID-19 are discussed below.

**Vitamin B<sub>6</sub> (pyridoxine):** Key in physiological functions [13], deficiency in vitamin B<sub>6</sub> impairs lymphocyte maturation, growth and proliferation, and antibody production. In addition, this deficiency eliminates the production of Th<sub>1</sub> cytokines and, thus, promotes Th<sub>2</sub> responses [16]. In a study of Vitamin B<sub>6</sub> supplementation in critically ill patients, Cheng et al. [29] found that low vitamin B<sub>6</sub> affects the interleukin - 2 (IL-2) production and responses to T and B-cell mitogens in old people but short term supplementation with 50 mg/day improved the immune function [29]. Vitamin B<sub>6</sub> as well as vitamin B<sub>12</sub> and folic acid support the natural killer cells and CD8+ cytotoxic T-lymphocytes effects which would be important in antiviral defense [30]. Therefore, during this pandemic period, a daily consumption food rich in vitamin B<sub>6</sub> like fruit, vegetables, eggs, fish has to be encouraged.

**Vitamin B<sub>12</sub> (cobalamin):** It is a water-soluble vitamin which must be taken in every day. It was stated that cobalamin affects the ability of pathogens to establish infection and influence disease progression [31]. The immunoglobulin synthesis of B-cells by pokeweed mitogen and T-cell proliferative responses to concanavalin A are enhanced by vitamin B<sub>12</sub>. Rutten et al. [32] reported a suppression of protective immune responses to viruses and bacteria in animal with vitamin B<sub>12</sub> deficiency. However, in adult patients, reduction in bactericidal activity with megaloblastic anemia and serum low vitamin B<sub>12</sub> were observed and in children, neutropenia, leukopenia and related white blood abnormalities were observed [15]. The vitamin B<sub>12</sub>, as it affects pathogens ability of causing infection as well as

disease progression, it may help COVID-19 patients not to easily threatened by the virus.

**Vitamin B<sub>9</sub> (Folic acid):** Folic acid, water-soluble compound is precursor of a coenzyme tetrahydrofolate and involved in synthesis of nucleic bases, purines and pyrimidines, constituting the nucleic acids of genetic material. In animal model, folic acid deficiency has caused thymus and spleen atrophy and decreased circulating T-lymphocyte numbers. Likewise individuals with low folate levels have impairments in neutrophil function that can be corrected by improved nutrient status [16]. Moreover, folic acid is involved in intestinal immune regulation and maintains or enhances NK cell cytotoxic activity [33], which may improve the ability of body to fighting against this SARS-CoV-2.

**Biotin (Vitamin B<sub>7</sub>):** A water soluble vitamin, biotin in human body serves as coenzyme for five carboxylases, and covalently attached to distinct lysine residues in histones, affecting chromatin structure and mediating gene regulation [34]. Biotin deficiency has adverse effects on cellular and humoral immune functions. It was reported by Baez & Ortega [35] that in rodents, biotin deficiency decreased antibody synthesis, the number of spleen cell and the percentage of B-lymphocytes and impairs thymocyte maturation.

**Vitamin C:** It is water soluble vitamin, which was proposed by physicians that could be beneficial in the treatment of pneumonia. Vitamin C is vital for maintaining epithelial integrity and is required for collagen biosynthesis [36]. This nutrient supports cellular functions of adaptive and innate immune systems, and protects them against oxidative stress [9]. Bactericidal activity and locomotion of neutrophils and macrophages decrease with vitamin C deficiency as consequence, increasing of susceptibility to microbial infection [14,37]. The modulation of prostaglandin (PG) synthesis, protection of 5'-lipoxygenase, enhancement of cytokine production, modulation of intracellular cyclic nucleotide level, antagonism of immunosuppressive interactions of histamine and leukocytes and neutralization of phagocyte derived autoreactive and immune-suppressive oxidants are among the proposed mechanisms of vitamin C immune-stimulation [36].

Some reactive oxygen species which are oxidizing agents are produced by activated

phagocytes in a typical infection. Vitamin C is a renowned antioxidant which can counteract these effects [38]. Jacob et al. [39] showed that, a diet deficient in vitamin C in healthy young human adults decreased mononuclear cell vitamin C content by 50% and the T-lymphocyte-mediated immune responses to recall antigens. Moreover, the role of vitamin C supplementation in decreasing the duration and severity of upper respiratory tract infections like common cold, especially in subject under physical stress, has been reported [16]. Vitamin C may play an important role in boosting immune system to protect the body from easily invaded by novel coronavirus. Since vitamin C widely found in fruits and vegetables, increasing daily consumption of these food product are very helpful during this pandemic period for booting the immune system.

**Vitamin A:** vitamin A is among the fat-soluble group of vitamins including vitamin D, vitamin E and vitamin K. It is involved in physiological functions, epithelial tissue differentiation and immune cells maturation. The alteration of immune response, increase in susceptibility to range of infections and impairment in barrier function is caused by the deficiency of vitamin A [26]. Vitamin A enhances T and B-lymphocyte proliferative responses, stimulate effector T-cell functions, promote cytokine production and increase macrophage, cytotoxic T-cell and natural killer cell tumoricidal capacity. Additionally, it can protect phagocytic cells from auto-oxidation [40]. Mora et al. [41] stated that the deficiency of vitamin A has an important influence on immune response in human. Vitamin A and its metabolites modulate same aspect of innate immunity in addition to barrier function such as control of neutrophil maturation. In vitamin A deficiency, blood neutrophil numbers are increased but they have impaired phagocytic function [16]. It was also reported that vitamin A supplementation in humans reduce morbidity and mortality in different infectious diseases, such as measles, diarrheal disease, measles related to pneumonia, malaria and HIV/AIDS infections [18].

**Vitamin D:** It is a fat-soluble vitamin which has important in calcium metabolism and bone homeostasis in the human body. Apart from that, vitamin D is involved in innate and adaptative immune responses [42]. Vitamin D increase phagocytosis, superoxide production and bacterial killing by innate immune cells. It also promotes differentiation of monocytes and

antigen processing by dendritic cells [43]. It is also involved in pulmonary resistance; various respiratory infections have been linked to vitamin D deficiency that affects both cytokine and immunoglobulin production [44]. Vitamin D protects against adipose tissue inflammation [45], enhance epithelial integrity and induces antimicrobial peptide synthesis in epithelial cells and macrophages [43]. An inverse linear relationship between blood vitamin D concentration and respiratory tract infections was found in a cross-sectional study of 6,789 British adults and showed that 10 nmol/l increase in 25 (OH) D resulted in a 7 % lower risk of respiratory tract infection [46]. Moreover, the survey from the US third National Health and Nutrition Examination which included 18,883 adults, showed that an independence inverse association between serum 25(OH)-vitamin D and recent upper respiratory tract infection [47]. Low vitamin D status was reported to increase individual susceptibility to number of different viral diseases including influenza [48], human immunodeficiency virus (HIV) and hepatitis C [18]. In calves, decreased vitamin D levels have been reported to enhance risk for bovine coronavirus infection [49]. Given that SARS-CoV-2 is among respiratory tract infection viruses, vitamin D could also play vital role in the prevention and recovery from Covid-19. The importance of vitamin D has led the national academia of medicine of France to recommend this vitamin as adjuvant in all treatments of COVID-19.

**Vitamin E:** The lipid soluble, vitamin E is the most important antioxidant in biologic membranes of all cells. The high risk for oxidative damage of immune cells require vitamin E to protect them against oxygenizing agent then to strengthen their physiologic function [50]. According to Meydani et al. [51] vitamin E supplementation has been associated with a boost of immune functions that may modulate host defense against infectious pathogens. Pae et al. [52] and Pallast et al. [53] stated that vitamin E may decrease the immunosuppressive factors such as prostaglandin PGE<sub>2</sub> and hydrogen peroxide by activated macrophages, the latter depresses lymphocyte proliferation. Additionally, High [54], showed that vitamin E could alter cytokine generation from T-cells or macrophages. It was also reported that Vitamin E has been investigated as a privative measure for many human conditions, including heart disease and cancer [55-57]. Chandra [14], report that just a

modest dose, around 40 mg as food supplement provides the best immunological benefit. Therefore, an adequate intake of vitamin-E rich diet may help patients contracted Covid-19 to maintain immune system.

**Minerals and immunity:** Minerals are inorganic elements required by humans to conduct functions necessary for life, and they cannot be synthesized by humans as most of the minerals in human diets derive from animal and plant sources and drinking water [58]. These micronutrients also play a vital role in supporting immune cells and tissues with regard to COVID-19 [16]. Mineral are used perform different functions in human body such as, transmitting nerve impulses and building strong bones, make hormones or maintain a normal heartbeat. However, some minerals like zinc, magnesium, selenium, iron, and copper play an important role in immune system [59].

**Selenium (Se):** The specific, nonspecific and cell mediate immune response involve selenium incorporation in cytosolic glutathione peroxidase bio-membranes [60]. The cellular immune response increase with selenium supplementation through an increase of interferon  $\gamma$  (IF  $\gamma$ ) and other cytokines, T-cell proliferation, and increase in T-helper cells. In humans, selenium deficiency has been linked with diminished natural killer cells activity and increased mycobacterial disease. It was reported by Beck [61] that selenium deficiency adversely affects several components of innate and acquired immunity, including T and B-lymphocyte function, antibody production and increases susceptibility to infections in animal laboratory. The mutation and increasing virulence of certain virus such as coxsackievirus, polio and murine influenza viruses were observed to be caused by selenium deficiency [62]. Various aspects of immune function have been improved when 100 to 300  $\mu\text{g}$  of selenium were daily supplemented to humans [63]. The study conducted in China by Dinh et al. [64] showed that an endemic cardiomyopathy disease identified as coxsackievirus B3, was observed in patient with selenium deficiency, and after Se supplementation, the incidence of that disease decreased dramatically. Selenium and selenoproteins have been involved in multiple cellular and viral mechanisms which could influence viral pathogenicity including virally encoded selenium dependent glutathione peroxidases. Such viral mechanisms could contribute to the well documented oxidative

stress associated with many RNA virus infections [65]. Recently, a research conducted on cure rates in mean regional or city hair Se concentration in Chine showed an association between the reported cure rates for COVID-19 and selenium status [66]. Increasing daily consumption of food rich Se appears to be important during this period because, Se is among on the most important trace element which was found to exert effect on RNA virus including SARS-CoV-2.

**Zinc (Zn):** Zinc is an indispensable trace element which is crucial to numerous functions in cellular process. Many consequences have been described in case of zinc deficiency with a marked impact on bone marrow including, decrease immune precursor cell numbers, with reduction of naïve B-lymphocytes output and thymic atrophy. Also many aspect of innate immunity are impaired such as phagocytosis and natural killer cell activity [67]. Zinc supports the release of neutrophil extracellular traps that capture microbes. It is probably involved in stimulation of NADPH oxidase through its role as a cofactor for phospho-lipase A2 or phospholipase C. Zinc may stabilize arachidonic acid against oxidation by iron complexes [68]. In contrast, excess zinc intake interferes with iron and copper absorption. Both lymphocyte functions and phagocyte functions are impaired with an excessive intake of zinc. On the other hand, iron supplementation may lead to subclinical zinc deficiency [14]. Daily supplementation of zinc (20 mg) plus selenium (100 mg) had shown a decrease in infection rates [54]. In RNA viruses like coronavirus, zinc inhibits the RNA polymerase replication [69], suggesting that zinc may play a key role in host defense against RNA viruses. In vitro replication of the influenza virus was inhibited by the zinc ionophore pyrrolidine dithiocarbamate [70], and there are indications that zinc may inhibit SARS-CoV-2 replication [71]. Moderate or mild zinc deficiency in humans result in decreased natural killer cell activity, T-lymphocyte proliferation, IL-2 production and cell mediated immune responses which can all be corrected by zinc repletion [72]. Lower respiratory tract diseases and diarrhea are part of the health consequences associated with zinc deficiency [16]. Since the COVID-19 disease affect respiratory tracts, the intake of dietary sources of Zn is advisable to strengthen the immune system. It appears to be important to inform population the important source of this micronutrient so as to help them benefited.

**Copper (Cu):** Cu is a trace mineral which is involved in the maintenance of bone health and homeostasis as well as immune functions. Its deficiency was found to cause a number of degenerative diseases [11]. Neutrophil function including travelling to the site of infection, adhering to the endothelium and transmigration across the endothelium for phagocytosis and killing foreign invaders by activation of the respiratory burst, involve copper blood status [73]. In animal model, Cu deficiency caused neutropenia [11] and in humans studies, a low copper diet have decreased lymphocyte proliferation and IL-2 production that was corrected by copper supplementation [74].

**Magnesium (Mg):** Cellular metabolism, including immune system cells require magnesium for its essential function [75]. Magnesium is involved in the protein synthesis of resistance factors; therefore, serum antibody concentration could provide a sensitive index to deficiency or suboptimal status of Mg. It is also required for participation of properdin in the alternate complement pathway [76]. In cell,  $Mg^{2+}$  acts as an essential cofactor and it bound to DNA, to RNA, to cellular energy carrier ATP or enzymes. T-cells recognize and respond to foreign antigens via T-cell receptors (TCRs) on their surface. However, in patients deficient in the magnesium ion transporter (MAGT1), T-cells cannot effectively increase their intracellular levels of free  $Mg^{2+}$  in response to TCR stimulation which decrease resistance to infection and increase the susceptibility to coronavirus because the body's defense is weakened. Fortunately, Mg is very prevalent in food and a balanced diet covers the recommended daily allowance [77].

**Iron (Fe):** Iron is an essential micronutrient in humans, and its deficiency induces atrophy of the thymus, which reduces the production of naïve T-lymphocytes and has multiple effects on immune function including an alteration of the activity of natural killer cells, T-lymphocyte proliferation and cytokine production as well altered respiratory function [16]. Diets rich in Fe are important to keep people from the COVID-19 by strengthening the immune system. It was found that T-lymphocyte proliferation was iron deficient at 50% to 60% lower in older Canadian women [78]. In the tropics, iron above a certain threshold has been associated with an increased risk of malaria and other infections, including pneumonia, in children of all ages. Thus, the intervention of iron in areas endemic for malaria

is not recommended, especially at high doses in young people [79].

**Essential fatty acid (EFA):** Essential fatty acid has been named vitamin F because the human body cannot synthesize the amount required for its daily physiologic function and therefore must be supplied by alimentation. It plays an important role for organism protection, and EFA deficiency result in lymphoid atrophy and depressed antibody responses [44]. Small dietary amounts of linoleic acid, n-6 fatty acid is required for the normal propagation and maturation of cell mediated immune response. Additionally, it acts as a substrate for prostaglandin (PG) and leukotriene synthesis. Adequate intake of essential fatty acids is important to help mediated immune response cells function well especially during the pandemic disease outbreak. High intakes of n-6 polyunsaturated fatty acids (n-6 PUFA) like linoleic and/or arachidonic acid, increase the synthesis of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) by macrophages [80].

Omega-3 fatty acid has capacity to reduce inflammation processes and effect related disorders. Despite of using omega -3 fatty acids as treatment decreases the polarization of macrophages, alpha linoleic acid (ALA), Docosapentaenoic acid (DHA) and Eicosapentaenoic acid (EPA) can increase the phagocytic capacity of macrophages [79]. This omega-3 fatty acid-mediated increase in phagocytic capacity has been demonstrated for engulfment of zymosan particles, an effect which may be related to changes in the composition and structure of the cell membrane caused by the incorporation of omega-3 fatty acids [80,81]. The activation of splenic NK cells by dietary DHA in mice was also reported [82].

**Probiotics:** Probiotics maybe defined as microorganism which are beneficial to the host [83]. They strengthen intestinal immunity and eradicate microbial pathogens, prevent infection and eliminate toxins in intestine [84,85]. These bacteria were reported to exert effects on immune modulation by increasing macrophage phagocytosis and increasing NK activity and numbers. Age-related decline in lymphoid cell activity increase the risk of infectious and noninfectious diseases on elderly patients. Dietary supplementation with probiotic lactic bacteria (LAB) was stated by Gill et al. [86] to enhance NK activity and therefore to improve the immune system. The gut microbiota is strongly influenced by habitual diet [87], in addition, aging

and the presence or absence of disease significantly influence the composition of the microbiota [88]. For instance, with aging, the sufficiency and diversity of bifidobacteria decreases, while bacteria such as streptococci, staphylococci, enterococci, and enterobacteria rise in number [89]. Importantly, Xu et al. [5] found that an intestinal dysbiosis with low number of lactobacilli and bifidobacteria on some Chinese patient with COVID-19. Nonetheless, observations suggest administration of probiotics may have clinical relevance in patients with COVID-19 [16]. Probiotics can directly inhibit the growth of pathogens by producing antibacterial substances, including bacteriocins and different acids (acetic, lactic, and propionic acid). It appears thus important for people chiefly elderly, to consume a diet rich probiotic like yogurt, curd for boosting the health of intestinal tract which could protect against COVID-19.

**Prebiotics:** Prebiotics are nondigestible, but fermentable in large intestine, food stuffs such as fiber and oligosaccharides which enter the colon and are metabolized by probiotics [13]. Dietary fibers such as oligosaccharides constitute the majority of prebiotics but other molecular exist. The main effect of prebiotics is linked to the metabolism of the microbiota, and upon fermentation, prebiotics generates short chain fatty acids (SCFAs), such as acetate, propionate or butyrate, which are a potential fuel for epithelial tissues [90]. It was observed from research conducted by Luying et al. [91] that, in enterocyte models, butyrate improved the intestinal barrier by regulating the assembly of tight-junction proteins. Thought-provoking results have shown that a diet high in fiber not only changes the gut microbiota, but can also affect the lung microbiota, indicating the influence of nutrition on lung immunity [92]. This could be important to consider importance of prebiotics for the health of respiratory system particularly of lung. This can in turn help people by reducing the possibility of being vulnerable to be infected by COVID-19 through strengthening immunity of respiratory system. Butyrate is produced by the genera *Clostridium*, *Eubacterium* and *Ruminococcus*, while other SCFAs, such as acetate or propionate, are produced by lactic acid bacteria of the genera *Bifidobacterium* and *Lactobacillus*. prebiotics stimulate lactic acid bacteria activity much more than butyrate producing bacteria [93].

**Quercetin:** Quercetin could be a flavonoid compound found in assortment of nourishment counting apples, berries, Brassica vegetables, capers, grapes, onions, shallots, tea and tomatoes, as well as many seeds, nuts, flowers, barks and leaves [94]. The potential benefits of quercetin for general well-being and resistance to illness incorporate anti-carcinogenic, anti-inflammatory, antiviral, antioxidant, and psychostimulant activities, as well as the capacity to restrain lipid peroxidation, platelet conglomeration, and capillary porousness [95]. Quercetin has been appeared to apply a defensive impact against high initiated aggravation in mice by expanding cytokine discharge [96]. Literature abounds in showing that quercetin helps human body reaction against bacteria and viruses including herpes simplex viruses (HSV-1 and HSV-2), adenoviruses, parainfluenza virus type 3, and severe acute respiratory syndrome (SARS) [94,97]. The precise mechanisms of this effect are not known. However, it has been shown that for several respiratory viruses, quercetin can block viral replication at an early stage of multiplication by inhibiting proteases by molecular anchoring, suppressing virulence enzymes such as DNA gyrase and cellular lipase, and by binding to viral capsid proteins [98]. Therefore, increasing rich food quercetin consumption during this pandemic period may be helpful for human body fighting against this dangerous SARS-CoV-2.

**Ajoene:** It is stated that ajoene, as the dynamic compound allicin of the garlic, applies an antiviral action on herpes simplex virus (HSV) types 1 and 2, cytomegalovirus (CMV), the flu infections, type 2 rhinovirus responsible for colds [99]. An in vitro study also showed the inhibitory activity of ajoene, the condensation item of allicin, on the replication of the human immunodeficiency virus type 1 (HIV-1). Ajoene appeared to strengthen the CD4 T-lymphocytes action guaranteeing the disposal of pathogens [100]. In addition, its activity appears mainly due to ajoene compound which would responds with the viral envelope [101]. The ajoene antiviral action has been detailed in literature and it can be accommodating to incorporate garlic in daily nourishment amid this widespread COVID-19 since it may boost the immune system. To give more information for consumers, the food sources with respective nutrients is presented in Table 1.

**Table 1. Important dietary sources of nutrients that support the immune system**

<b>Nutrient</b>	<b>Good dietary sources</b>
<b>Vitamin A (or equivalents)</b>	Milk and cheese, eggs, oils fish, fortified cereals, liver, green vegetables or dark orange (carrots, sweet potatoes, pumpkin, spinach, broccoli), orange fruits (e.g., peaches, papaya, mango, cantaloupe melon), tomato juice
<b>Vitamin B12</b>	Fish, meat, eggs, some shellfish, milk and cheese, yeast extract, fortified cereals
<b>Vitamin B6</b>	Poultry, fish, eggs, meat, whole grain cereals, fortified cereals, many vegetables (green leafy) and fruits, soya beans, tofu, yeast extract.
<b>Folate</b>	Widely spread in green leafy vegetables (spinach, cabbage, kale, broccoli); others sources include peas, chick peas, fortified cereals.
<b>Vitamin C</b>	Orange juice, red and green peppers, strawberries, blackcurrants, kiwi, broccoli, potatoes, citrus fruits, guava, pineapple, tomato
<b>Vitamin D</b>	The main source is sunlight, others are, oily fish (salmon, sardines), liver, eggs, fortified foods spreads and some breakfast cereals, mushrooms.
<b>Vitamin E</b>	Many vegetable oils, nuts and seeds, wheat germ (in cereals), sunflower oil, peanuts, eggs, tuna, salmon
<b>Zinc</b>	Shellfish, meat, cheese, some grains and seeds, cereals, seeded or wholegrain bread
<b>Selenium</b>	Fish, shellfish, meat, eggs, some nuts, milk, sunflower seeds, tofu, whole grain cereals
<b>Iron</b>	Meat, liver, beans, nuts, dried fruits (e.g. apricots), wholegrains (e.g. brown rice), fortified cereals, most dark green leafy vegetables (spinach, cassava leaf, kale)
<b>Copper</b>	Shellfish, nuts, liver, some vegetables, oysters, organ meats, wheat-bran cereals, whole grain products, seeds and nuts.
<b>Magnesium</b>	Salmon, chicken, beef, green leafy vegetables, legumes, nuts, seeds and whole grain
<b>Quercetin and ajoene</b>	Garlic, oily fish, cranberry juices, broccoli sprouts, onion
<b>Probiotics</b>	Yogurt, curd
<b>Amino acids</b>	Meat, poultry, fish, eggs, milk and cheese, soya, nut, seeds, pulses
<b>Essential fatty acids</b>	Many seeds, nuts and vegetable oils, fish

Sources: Calder et al.[16] and Jayawardena et al. [102]

#### 4. CONCLUSION

Immune system exerts always main role for disease management. However, viral disease treatments remain a big challenge because of the virus genetic material which are so easily rearrange themselves to produce new specific antigens which have the ability to evade the host organism. For a viral disease like, COVID-19, where no pharmacological strategies for prevention or treatment are presently available and the exact time of the ending of the alarming situation is unknown, nutritional strategies for enhancing immunity is to be explored. Immuno-nutrition plays an important role in modulation either of the activity of the immune system, or modulation of the consequences of the activation of the immune system,

by specific nutrients or foods. Therefore, to cope with potentially lethal viruses such SARS-CoV-2, immuno-nutrition and lifestyle adjustment are very important. In this review, we have highlighted the potential preventive and therapeutic application of few vitamins, trace elements and probiotics. Through experimental research and studies of people with deficiencies, number of vitamins (A, B<sub>6</sub>, B<sub>12</sub>, C, D,E, biotin and folic acid) and trace elements ( zinc, copper, magnesium, selenium, iron) have been demonstrated to have key roles in supporting the human immune system and reducing risk of infections. Achieving recommended amounts of calories and micronutrient will be a challenge. Selective micronutrient supplementations may be beneficial especially for vulnerable populations such as the elderly.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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