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COVID-19: A Review of Immune-enhancing Nutrients and Supplements

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Abstract

In the era of COVID-19 infection, there is an urgent need to use immune-enhancing nutrients. The frequency of COVID-19 infection is largely affected by an individual's nutritional status. This review summarizes the available nutrients and supplements that help enhance the immune system against infections especially COVID-19. They have antiviral activities, especially against SARS-CoV-2, or even can ameliorate the undesired consequences of COVID-19 by their anti-inflammatory and antioxidant properties. It mentions many nutrients and supplements that aid in fighting or protecting from this pandemic infection such as probiotics, milk including breastfeeding, camel's milk, and supplements including vitamins and minerals. It discusses their role as an antiviral, immunostimulant, or even their role as antioxidant and anti-inflammatory COVID-19 protection. Until our time, the pieces of evidence determining the use of dietary supplements in COVID-19 protection and treatment are insufficient and restricted. So, the use of dietary supplements cannot be used alone to treat COVID-19 but to support the current management of COVID-19.

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Highlights:

- Prompt hydration and a balanced diet are needed to enhance immunity and protect from infectious diseases
- Breastfeeding during COVID-19 infection is recommended after performing the required precautions.
- Probiotics have antiviral and immunomodulatory actions alongside a role in decreasing the cytokine storm with current antiviral therapy.
- Several supplements of vitamins and minerals have an antiviral, antioxidant, anti-inflammatory, and immune-modulatory function.

1. Introduction:

Since the present epidemic of the COVID-19 keeps increasing. Now the serious choice is to improve the ability of the immune system to fight against covid-19.

The severity of COVID-19 depends on different factors such as smoking habits, co-existing medical conditions, and the most important factor is the nutritional status which affects immunity. There are a lot of nutrients that help to enhance the immune system [1].

2. Nutrition during COVID-19 outbreak:

World health organization (WHO) recommends prompt hydration and eating a balanced diet to fulfill the body's needs of vitamins, minerals, protein, fibers, antioxidants to raise the immune system and shield the body from contagious and chronic illnesses. WHO recommends eating fresh, unprocessed foods and unsaturated fats found in fish, nuts, olive oil, and avocado? WHO warns against eating foods high in salts or sugars and recognizes the need for therapeutic assistance to support the mental health of persons at high risk of COVID-19 infection [2].

2.1 Breast milk as the best immunity-enhancing source:

Breast milk is one of the most effective sources for enhancing the immunity of newborns against environmental pathogens. There are major antibodies in breast milk, such as (IgA, IgG, and IgM), transforming growth factor β2 (TGF-β2), the soluble cluster of differentiation 14 (sCD14), and antibacterial enzymes such as lysozyme that play significant immune protection role in infant's health [2].
There are about 10-fold higher leukocytes in first milk for humans more than mature milk (5 M/ ml). Ten percent of them are NK cells, B cells, and T cells. Neutrophils and macrophages are the main remaining leukocytes, and their numbers decrease with time [3]. It also contains massive numbers of innate lymphoid cells that are divided into 1,2,3 lymphoid cells [4, 5]. These immune cells in a newborn's body destroy pathogens and have a role in shaping an infant's gut microbiota [6].
60 days of drinking camels' milk with peginterferon and ribavirin confers regulation of immunomodulators,

As breastfeeding is a critical and indispensable step in infant life, the WHO and UNICEF are playing an important role in inspiring women to breastfeed during COVID-19 disease - SARS-CoV-2 is unlikely to be passed through breastmilk. Breastfeeding can relieve the possible dangers of COVID-19. Centers for disease control and prevention (CDC) support breastfeeding during COVID-19 infection after performing the required precautions. The precautions to avoid the extent of SARS-CoV-2 infection include handwashing before touching the baby and his tools along with wearing a cloth face covering. If the mother is isolated from her baby, she could express her milk eight to ten times a day using a dedicated pump [3].

2.2 Camels' milk as nutritive and therapeutic application

While camels are expected to be a MERS-COV source. The camel's milk can be used as a food of high nutritious and medicinal use. It has excessive therapeutic uses compared with that of other species such as goat, cow, and buffalo milk. It contains large amounts of essential amino acids (e.g. leucine and phenylalanine), vitamins (e.g., vitamin C and niacin), unsaturated fatty acids, antioxidants, and antimicrobial factors (e.g., lactoperoxidase, lactoferrin, lysozyme, and immunoglobulin G)and secretory immunoglobulin A [7, 8].
Those immunoglobulins cause high antibody titers against rotavirus in an old study [9]. Other studies suggest that camels' milk has antiviral activity as that of Saltanat and his colleagues who found that camels' milk inhibits the replication of hepatitis B virus and support the response of cellular immunity via correcting the imbalance of Th1/Th2 cytokine and regulating the expression of these cytokines [10].
Another Egyptian study confirmed that

3. Supplementations:

inflammatory mediators, antioxidants, antiapoptotic factors for Hepatitis C (HCV) virus infection in patients [11].

2.3 Probiotic diets and supplements:

Although cytokine refereed special effects that are an essential part of the infection response, extreme production of pro-inflammatory cytokines, or wrong biological context of cytokines, raise the danger of an extensive range of diseases, such as COVID-19.

Inflammation, such as pro-inflammatory and anti-inflammatory cytokines, has a significant role in COVID-19 pathogenesis. Probiotics supplementation can restore innate and adaptive immunity, also modify intestinal microbiota variations which are responsible for immune homeostasis, and the equilibrium balance between Th17 cells and regulatory T-cells (Tregs). It is important to know that probiotics consumption can help to quench the cytokine storm when recombined with suitable antiviral treatments [12].

Oral probiotics can protect against the systemic and intestinal effects of SARS-CoV-2 infection. Inhaled probiotic provides a direct effect on respiratory immune cells and respiratory epithelium. It can enhance virus clearance and decrease the inflammation caused by this virus. There is an ongoing clinical trial on Lactobacillus coryniformis K8 consumption for COVID-19 patients [13].

2.4 Nutrients and virus-host immunologic responses

From the initial virus-host encounter, innate immune activation, to adaptive immune responses, micronutrients play a role in the host immune response to the virus, as summarized in Fig. 1.

3.1 Omega 3 fatty acids:

Seafood (especially fatty fish) is a rich source of docosahexaenoic acid (DHA), omega-3 (n-3) fatty acids, and eicosatetraenoic acid (EPA). They are also found in many supplements and concentrated pharmaceutical formulations [15]. Their anti-inflammatory effect was evidenced, especially EPA and docosahexaenoic acid (DHA). The potential effects of n-3 fatty acid supplements are co-therapy for patients afflicted with SARS-CoV-2, including less inflammatory eicosanoids (PG3, TXs, LTs5), non-inflammatory cytokines (TNF-a, Ll-1β), advanced pro-resolving mediators such as proteins. It has anti-inflammatory, antiplatelet, and potential antiviral effects. The detrimental effects of EPA and DHA are also vulnerable to non-enzymatic oxidation by reactive oxygen species (ROS), possibly toxic oxidation products (MDA,4- HNE, 4HHE, IsoPs), oxidative stress, and delayed virus clearness [16].

3.2 Vitamins and Minerals:

Supplementation of minerals and multivitamins including water-soluble and non-water-soluble vitamins that reduce morbidity and mortality rates of severe COVID-19 infection [17, 18].

3.2.1 Vitamins:

3.2.1.1 Vitamin A:

Retinoid supplementation is important for human health. It is largely found in fish oils, animal and fish livers, and fish oil. It is also present in milk and milk products, seafood, shellfish, meats, and poultry, as well as in other food sources such as dark leafy plants, algae, red, yellow vegetables, and tubers [19].

Vitamin A ensures epithelial tissue barrier stability and normal separation. Retinoid has

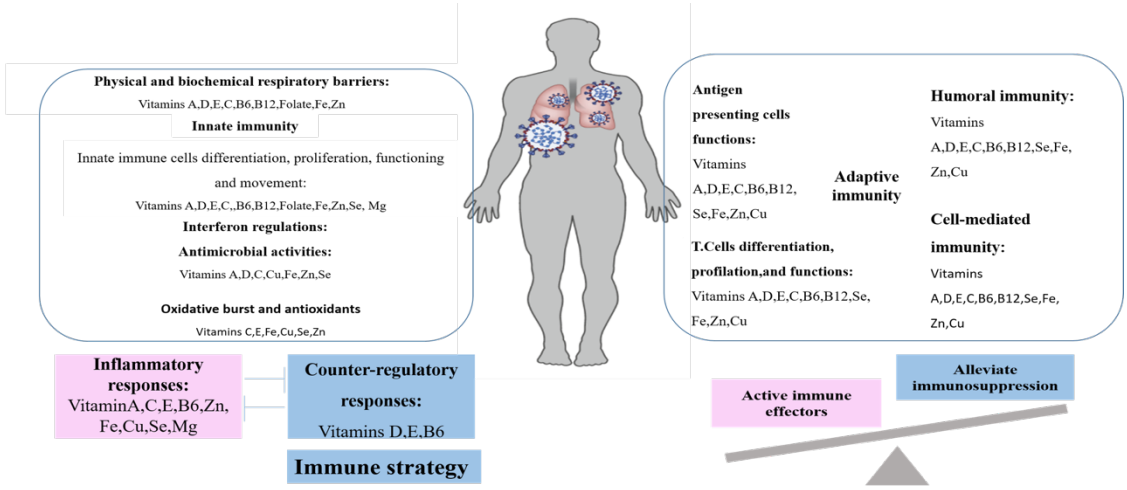

Fig.1. The immunomodulatory activity of different dietary substances in different stages of the host immune response to the virus [14]

a role in immune function by regulating NK cells and encouraging the phagocytic oxidative burst activities of macrophages [20, 21], development, and differentiation of the Th1/Th2 [22]. A recent study indicates that vitamin A is used in the treatment of COVID-19 depending on bioinformatics analysis, they confirmed that vitamin A enriches the immune reactions and has an anti-inflammatory function and decreases reductive oxygen species. They also identified IL10, MAPK1, EGFR, MAPK14, ICAM1, CAT, and PRKCB as the main targets against COVID-19 [23].

3.2.1.2 Vitamin B6:

Nature is full of hundreds of carotenoids but there are few amounts found in human tissues. Beta-carotene is a pro-vitamin A in the diet. Almost 50 carotenoids have pro-vitamin A activity, but beta-carotene is the most powerful and widely distributed carotenoid in plant species.

Diet and nutrition such as milk and soya beans have a positive impact on immunity, especially against COVID-19. It is documented that pyridoxine (the active form of vitamin B6) is depleted gradually during inflammation. As COVID-19 causes many inflammatory reactions, it may be recommended to administer vitamin B6 [24].

3.2.1.3 Vitamin C:

Vitamin C can't be produced in the human body. It motivates absorption of non-heme iron from the intestine and moderates transport and storage of iron that helps in anemia prevention [25]. It has an essential role in epithelial barrier integrity [26] and immune cell activities including the production of antibodies, T- cells proliferation, and differentiation [27].

It supports the production of antimicrobial agents such as IFN γ and increases serum complement proteins [28]. It's an antioxidant that keeps the intracellular reductive-oxidative homeostasis [29]. The increased oxidative stress in COVID-19 patients caused by free radicals and cytokine's rapid release during a cytokine storm makes an urgent need to add antioxidants in the treatment protocols for COVID-19, vitamin C is the most suggested antioxidant [30].

Some clinical trials were done to determine the impact of using high doses of vitamin C (oral or intravenous administration). Staying in the intensive care unit (ICU) decreased by 7.8% after 200 mg/kg body weight/day consumption [31]. Some studies have shown that oral vitamin C decreases the risk of infection with viruses [30]. Analysis of 17 COVID-19 patients found that the use of high-dose I.V. Vitamin C can be used in patients with moderate-severe illnesses [31].

In the last trial to assess the use of high-dose of vitamin C (intravenous) for COVID-19; they found that vitamin C may be useful for oxygenation of severe COVID-19. They revealed that intravenous vitamin C in high doses does not affect patients who need invasive mechanical ventilation [32]. Thomas and her colleagues reported that the use of high-dose of vitamin C, zinc gluconate, or a combination of them have an insignificant decrease in the duration of symptoms [33]. Assessing the COVID-19 patients for their vitamins and minerals deficiencies is an indispensable step in the correct management of COVID-19 [34].

3.2.1.4 Vitamin D:

Vitamin D supplementation is an important source for the prevention of cancer, osteoarthritis progression, multiple sclerosis, and hypertension [35]. Milk and dairy products are the best vitamin D sources. The general actions and metabolism of vitamin D are well recognized. Vitamin D3 is formed by the effects of UVB radiation on 7-dehydrocholesterol, followed by a thermal reaction in the skin. It helps to increase immune barrier integrity [35], antimicrobial peptides production [36] and it supports macrophages, monocytes, and dendritic cell functions [37].
It regulates oxidative burst potential [38] and IFN γ inhibition [39]. Vitamin D is confirmed to improve innate immunity by activating toll-like receptors (TLRs) or the number of β-defensins and cathelicidins. Vitamin D's immunostimulant effect is not limited to intrinsic immunity, it affects adaptive immunity, and it modulates the function of T cells. Supplementation with vitamin D could help in combating the SARS-CoV-2 infection [40].

3.2.1.5 Vitamin E:

It is a vital antioxidant, that prevents oxidative damage to the cell membranes and rises respiratory epithelial barriers stability [41]. It may increase the cytotoxic activity of NK cells and macrophages, decrease the production of prostaglandin E2, and change IFN-γ and interleukin 2 development [42].

It helps T-cells lymphocytes proliferation and mediates optimize Th1 response, supports Th2 response suppression, encourages effective immune synapses of vitamin E protection including Th cells and helps to increase the amount of antigen-experienced T-cell memory [43]. Almonds and peanuts are vitamin E sources.

3.2.2 Minerals:

3.2.2.1 Zinc:

Zinc (Zn) is a significant micronutrient for human beings. Cereals including wheat are good sources of it [44]. Zinc deficiency is a predisposing factor for the progression of COVID-19 infection, as its deficiency is correlated with reduced breathing epithelial integrity, increased viral entry, and imbalanced immune and redox system [12]. It modifies the biological and physiological roles of approximately 2,000 enzymes and 750 transcription factors involved in the development of immunity [45].

Zn can increase the anticancer bioactivity, promote the production and differentiation of essential immune cells [46]. It is correlated with the activities of complement proteins, the IFN γ creation, T- cells, and antibody production essentially the immunoglobulin G [29]. It also has a direct antiviral property that

prevents the RNA-dependent RNA polymerase enzyme [29]. So, it is strongly recommended to add zinc in the treatment protocols of COVID-19 either alone or combined with other strategies [47]. There is a recent study that mentioned that adding zinc to the treatment protocol of COVID- 19 containing low doses of hydroxychloroquine is associated with significantly lower hospitalization [48].

3.2.2.2. Selenium:

Selenium is an important micronutrient in the living systems [49]. It plays a necessary role in enhancing antioxidant defense capacity, improve immunity, metabolism of thyroid hormone, and function reproduction [50]. So, it is relevant to develop new food sources of selenium [50]. A recent study reported that COVID-19 mortality is increased with selenium deficiency [51]. It helps in the formation of killer cells, T-cells, and the production of antibodies [52]. Cereals and dairy products are selenium sources.

3.2.2.3 Magnesium:

Cereals and vegetables are healthy sources of magnesium, while milk and dairy products are considered better sources [53]. It is incorporated in the synthesis of nucleic acid, transcription of DNA, encouragement of leukocytes, macrophage antigen binding, and apoptotic directive [39]. It influences cell-mediated immunity as well as humoral adaptive immunity [21]. It keeps DNA from oxidative damage and inhibits the production of superoxide anions at high concentrations [52].

3.2.2.4 Copper:

For humans, copper (Cu) is an important ingredient. It is present in different grains as wheat [54]. During viral infection, copper (Cu) is a vital micronutrient. Cu improves the function of extreme immune cells, including T helper cells, B cells, NK neutrophils, and macrophages. These blood cells are responsible for infectious microbes being killed. Cu-deficient humans play a significant benefit in infections because of the reduced number and function of these blood cells. In addition, Cu is capable of successfully destroying various viruses, such as SARS-CoV-2. [55]. Table 1 shows the mechanism of fighting COVID-19 by different dietary supplements.

4. Additional potential immunomodulatory agents for COVID- 19 management:

4.1 N-acetylcysteine (NAC):

NAC can treat Glucose 6-phosphate dehydrogenase (G6PD) deficiency and prevent glutathione depletion caused by COVID-19 infection. A recent study is conducted on a patient with G6PD deficiency with COVID-19 infection, they demonstrated that intravenous (IV) NAC prevents hemolysis, the elevation of C-reactive protein (CRP), liver enzymes, and ferritin. Intravenous NAC facilitates full retrieval of G6PD deficient COVID-19 patients. NAC may be involved in viral infection blockage and cytokine storm alleviation [56]. NAC is a pioneer of decreased glutathione. Due to its acceptability, this pleiotropic drug has been suggested not only as a mucolytic agent but also as a defensive/ therapeutic agent in a diversity of patients relating to reduction and oxidative stress. The oral administration of N- Acetyl-L- cysteine is probable reducing the risk of COVID-19 emerges. Furthermore, high-dose intravenous N-Acetyl-L-cysteine can play an important role in COVID-19 cases treatment [57].

5. The use of dietary supplements in light of the levels of evidence-based medicine:

It is worth saying that the evidence which determines the use of food supplements in

Table 1: Beneficial dietary supplements in COVID-19 protection and treatment:

Dietary supplements	Role of dietary supplement in fighting COVID-19
Omega 3 FAs	▪ It has anti-inflammatory and antiviral activity [16]
Vitamin A	▪ It ensures epithelial tissue barrier stability [20, 21]. ▪ It stimulates innate and adaptive immunity [21, 22]. ▪ It has anti-inflammatory activity [23]
Vitamin B6	▪ Vitamin B6 is recommended during COVID-19 to compensate for the pyridoxine depletion which happens during inflammation [24].
Vitamin C	▪ It increases epithelial barrier integrity [27]. ▪ Stimulate innate and adaptive immune responses [27]. ▪ It has potent antioxidant activity [29]. ▪ It supports the production of IFN γ and serum complement proteins [28].
Vitamin D	▪ It increases immune barrier integrity [35]. ▪ It increases antimicrobial peptide production [35]. ▪ It supports innate and adaptive immune responses [40].
Vitamin E	▪ It has antioxidant activity [41]. ▪ It supports adaptive immune responses [43].
Zinc	▪ Zn promotes the production and differentiation of essential immune cells [46] and increases the activity of complement proteins, T- cells, and antibody production [29]. ▪ It has a direct antiviral property [29].
Selenium	▪ It has antioxidant activity [50]. ▪ It improves immunity, the formation of killer cells, T-cells, and the production of antibodies [50], [52].
Magnesium	▪ It supports cell-mediated and humoral adaptive immunity [21]. ▪ It has antioxidant activity [52].
Copper	▪ Cu improves the function of extreme immune cells, including T helper cells, B cells, NK neutrophils, and macrophages. ▪ Cu can destroy various viruses, such as SARS-CoV-2 [55].

COVID-19 protection and treatment is insufficient and restricted [58] to do well-designed systematic reviews and meta-analysis from randomized controlled trials and reach accurate advice. For example, vitamin D, one of the most studied vitamins regarding its deficiency with the severity of COVID-19, there are only 13 registered clinical trials, only 4 of them are completed [59]. Most studies discuss the use of supplements through their previous data regarding protection from respiratory viral infections and opposing the mechanism of SARS-CoV-2 pathogenesis. By the time, studies that are especially targeting COVID-19 are increasing facilitating the accessibility to accurate information.

In a large study which is based on an application survey among UK people and included 372720 persons to know the correlation between dietary supplements administration and being positive to SARS-CoV-2, they found that vitamin D, probiotics, omega-3 fatty acids, and multivitamins which include vitamin A, D, E, zinc, and selenium decrease the risk

of SARS-CoV-2 infection in females only. They found that vitamin C, zinc, and garlic have no protective effect from SARS-CoV-2 infection. A large number of randomized controlled trials of dietary supplements are needed [60].

6. Conclusion:

There is an urgent need to find different strategies to control the highly virulent SARS-CoV-2 virus which affects most humans' organs [61]. Nutrients can show an effective role in the prevention of SARS-CoV-2 infection. Camel's milk, breastfeeding, probiotics, and supplements (i.e. vitamin D, vitamin C, vitamin A, zinc, selenium, magnesium, and copper) have an obvious role in immune modulation and help to fight this pandemic infection. Some supplements may have antiviral properties such as zinc, vitamin C, vitamin D, and probiotics. Vitamin C and zinc increase respiratory epithelial integrity. Vitamin C, selenium, and magnesium have strong antioxidant activities which protect from the effect of SARS- CoV-2 on the human being. Fatal cytokine storm can be reduced by the anti-inflammatory actions of omega-3, probiotics, vitamin A and vitamin B6 with the available antivirals. The general recommendation is to consume dietary supplements (i.e. vitamins C and D, zinc, and selenium) that should be administered to individuals with or at risk of respiratory viral infections or in whom deficiency is detected.

List of abbreviations:

CDC: Centers for Disease Control

COVID-19: Coronavirus Disease 2019

Cu: Copper

DHA: Docosahexaenoic Acid

EPA: Eicosapentaenoic Acid

Fe: Iron

G6PD: Glucose 6-Phosphate Dehydrogenase

HCV: Hepatitis C Virus

ICU: The Intensive Care Unit IV: Intravenous

M: Million

NAC: N-acetylcysteine

NK: Natural Killer

n-3: omega-3

ROS: Reactive Oxygen Species

Scd14: Soluble Cluster of Differentiation 14

TGF-β2: Transforming Growth Factor β2
TLRs: Toll-like Receptors

WHO: World health organization
Zn: Zinc

Conflict of interest

The authors declare that they have no conflict of interest regarding this study.
Author contribution
All authors have contributed in writing the manuscript. HFF & OKR participated in conceptualization. OKR was responsible for revising and editing the manuscript.

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