World Health Organization (WHO) declared a global public health emergency due to the recent spread of COVID-19 throughout the world. Millions of people are affected daily and thousands died. Almost all countries are now paying attention to control this pandemic outbreak. Therefore, researchers are trying to identify the pathophysiology of the disease, appropriate prognosis, effective management and prevention of COVID-19. Based on current published evidence, this review article specifies the role of different nutrients in the possible prevention and management of COVID-19 and viral infections. Balanced nutrition including adequate vitamin C, vitamin A, vitamin D, magnesium, selenium, zinc and phytoneutrients have shown promising immune-boosting roles in COVID-19 and other respiratory infections due to their potential anti-inflammatory and antioxidants properties. These micronutrients act against COVID-19 infections both individually and synergistically.
Introduction

Recently, a highly transmissible respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), commonly known as COVID-19, has been proclaimed a worldwide public health emergency by the World Health Organization (WHO) after an unprecedented outbreak in Wuhan City, China in December, 2019. To date (June 30, 2021, 19:05 GMT), COVID-19 was affecting 219 countries and territories, with 182,794,034 confirmed cases and death reported 3,957,208 globally. The incubation period from infection to symptoms manifestation is estimated 5.2 days, with a range of 1-14 days. The broad spectrum of COVID-19 ranges from asymptomatic infection to mild upper respiratory tract infection, fever, cold-cough, difficult breathing, dyspnea, pneumonia with respiratory problems and multiple organ dysfunction.

A number of factors have been identified leading to the progression of COVID-19. Individuals with poor nutritional status and pre-existing various comorbidities such as diabetes, hypertension, cardiovascular diseases (CVD), liver and kidney disease, or cancer are prone to severe COVID-19 infections due to the patient immunocompromised or lessened systemic immunity and increased deaths are being reported with very short time. There is no particular prevention or treatment folio for COVID-19 yet, most of the cases are concerned with symptomatic therapeutic strategy and supportive management. Therefore, it is essential to improve self-resistance and elevate the body’s immunity. Diversified and adequate nutrients intake with healthy lifestyle are recommended approaches to boost-up an individual’s immunity and also to treat severe and critical COVID-19 patients.

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Food or diet, nutrition, infection, and immunity are interlinked. The risk along with the severity of infections are often determined by the nutrients from various foods effecting the immune competence, hence nutrition is the core of human health well-being. Balanced nutrition is indispensable to prevent and manage viral infections by maintaining immunity. Many macronutrients, micronutrients and phytoneutrients in foods and diet usually promote healthy immune responses of individuals. Various polyphenolic phytoneutrients and micronutrients including β-carotene, vitamin C, vitamin E mainly function as antioxidants and anti-inflammatory agents, which modulate the immune functions and thereby suggest the upkeep of host macro- and micronutrient status for COVID-19 preventive measure. The immune responses have been shown to be deteriorated due to poor nutrition in COVID-19 affected patients.

However, a number of scientific notions have been published concentrating on the role of specific nutrients or diet in the immune boosting and/or respiratory tract infections, but data regarding total nutritional supports in COVID-19 infection are not meticulous yet. Therefore, this article presents an overview of the synergistic role of various nutrients in COVID-19 pandemic management.

Materials and Methods

The methodology used while constructing this review involved several search hubs, mainly Google Scholar, Pub Med/Medline, HINARI, Database of Open Access Journal and Science Direct search links were used for getting journal articles into relevant data and information.

The Synergistic Role of Nutrients of Against Covid-19 Infection

Nutrition is a vital element in modulating immune homeostasis in the individual. Balanced nutrition comes from diversified food sources and provides sufficient micronutrients and phytoneutrients for maintaining immunity to withstand short duration of weakness. Protein energy malnutrition or even single micronutrient deficiency at subclinical level may weaken one’s immune responses substantially. A recent study of COVID-19 management showed that a proper nutritional recommendation is to decrease indemnities to the lungs due to corona virus as well as other lung infections. The significance of optimal nutritional status to shield against viral contagions has also been emphasized in another study. The macronutrients, micronutrients and phytoneutrients in diet, mainly the sufficient meat, fish, egg, milk, green leafy vegetable and colorful fruits and vegetable, largely promote healthy immune responses and balanced nutrition. Since no effective medicine (neither preventive nor curative) is available yet to protect against COVID-19, balanced nutrition with a robust immune system is one of the most vital strategies.
The individuals with lower level of multiple vitamins and minerals are more susceptible for the development of various infections. Vitamin C plays a major role in immune system functioning along with others especially vitamin A, D, E, niacin (B3), pantothenic acid (B5) and pyridoxine (B6). In the modulation of the innate and adaptive immunity, Zinc has been shown to be a critical micronutrient. It is eminent that geriatric nutrition is essential for senior citizens as getting old can pave the way to fading of the innate immunity, which may result in the progression of severe COVID-19 and consequently the over activation of the adaptive immune responses producing an elevated level of cytokines.

**Role of Macronutrients**
Macronutrients encompasses carbohydrates, lipids and proteins, and found in diversified food groups. Discrepancy in diets such as high amount of saturated fats, refined carbohydrates and sugars may contribute to the occurrence of obesity and type 2 diabetes, subsequently increasing the risk for severe COVID-19 complications and mortality. Carbohydrates
Carbohydrates are primarily considered as the main source of calories that should consistently be covered with balanced natural sugars, starch, dietary fiber or complex carbohydrates. The effect of simple sugars and unhealthy carbohydrate craving diet could proliferates the risk of obesity development, which is often complicated by cardiac disease, lung ailment and diabetes mellitus types co-morbidity during COVID-19 pandemic situation.

**Fatty Acids**
Some evidence on protective role of polyunsaturated fatty acids are summarized in Table-1. Inflammation and adaptive immune system have been demonstrated to be mediated by long-chain polyunsaturated fatty acids. Omega-3 and omega-6 polyunsaturated fatty acids largely stimulate the anti-inflammatory or pro-inflammatory reactions in the body. A study showed that lipid mediator derived from omega-3 PUFA significantly mitigate the replication of influenza virus. Several PUFAs have also been found to have anti-hepatitis C virus activities. Hence, PUFAs might serve as a prospective dietary ingredients to fight against novel corona virus.

**Vitamin C: Main Immune-Boosters**
As an antioxidant and enzymatic co-factor, vitamin C acts on many physiological responses including biosynthesis of essential collagen, carnitine, and neurotransmitters, production of hormones and as an immune-boosting agent. Vitamin C supports the epithelial barrier function against pathogens, helps in conducting cellular functions concerning adaptive and innate immune responses, and defends against oxidative stress. The association of vitamin C deficiency with pneumonia and immune-modulating effects in respiratory infections at risk populations are well-documented. Moreover, several studies showed that mega doses administration of vitamin C lessen the flu-symptoms and regular...
supplementation showed significant effects on common cold duration. Some trials found a statistically significant decline in the incidence of pneumonia in groups treated with vitamin C. In a study during World War II, an additional 50 – 300 mg vitamin C per day were given to their snacks and observed a probable part in the prevention of pneumonia. Again, supplemented with 0.3 g vitamin C on a daily basis in military recruits who were infected with influenza type A, found a potential adjunctive role. It was also seen that administered with high dosages (2 g/day) to US Marine recruits for two months showed a reduced incidence of pneumonia with no adverse effects. Therefore, therapeutic use of supplementation with vitamin C might be rational for pneumonia patients. Again, a respiratory syncytial virus decline the antioxidant enzymes activity and thereby enhanced oxidative damages consequently. Vitamin C is a prominent antioxidant which can counteract these effects.

A human controlled trial stated that there was a significant deduction of incidence of pneumonia in those who were supplemented with vitamin C, signifying that this vitamin might avert the vulnerability to lower respiratory tract infections. It was seen that high-dose of oral vitamin C could provide a certain defense in contrast to viral infection without posing any substantial side effect. Since patients affected with corona virus COVID-19 cause severe infection in lower respiratory tract, supplementation with vitamin C could be a suitable option to treat the infection and to boost the immune system who are susceptible to COVID-19.

Very recently, it was informed that various high-dose intravenous vitamin C infusions shortened the intensive care unit and reduction in the mortality rate. High dose oral vitamin C (6 g per day) have shown the capacity to lessen the risk of viral infection or to recover symptoms. High-dose intravenous vitamin C (10-20g per day, given over a period of 8–10 h) has also been effectively used to treat some COVID-19 patients in China and it was found the all of them were cured. Dietary antioxidants (rich in vitamin C) have been shown to reduce acute inflammatory lung damage in patients who were on mechanical ventilation. Thus, vitamin C supplement (intravenous or oral) should be incorporated in the management of COVID-19 and can be utilized as a precautionary measure for at risk populations such as healthcare workers.

**Vitamin D**

Vitamin D is a fat soluble vitamin, acts like hormone and stimulates the maturation of immune cells. It possess a positive impact on immune responses against flu and coronaviruses attacks. In the winter of 2019, the COVID-19 was first recognized and it was observed that affected adults (middle-aged to older adults) had the unsatisfactory level of vitamin D. Low vitamin D is associated with morbidity in children and adults. An interventional study of vitamin D supplementation in children showed that the incidence of influenza and other acute respiratory infections was reduced. It has been shown that when vitamin D is supplemented and restored to normal levels, infected patients might improve their retrieval during ART, inflammation is reduced and immunity is increased against pathogens. Therefore, vitamin D can be a suitable nutritional supports for the management of novel corona virus.

Vitamin D prevents inflammation by inhibiting maturation of dendritic cells, reducing the pro-inflammatory cytokines production (IFN-γ, IL-1β and TNF-α), and enhancing anti-inflammatory IL-10. An interventional study suggested that individuals who are at risk of developing influenza and/or COVID-19 might consider taking vitamin D3 (10,000 IU/d) for a few weeks to promptly increase the concentration of 25(OH) D. Vitamin D boosts innate immunity partially through the induction of peptides (antimicrobial). Again, vitamin D improves cellular immunity by decreasing the cytokine production which is prompted by the innate immune responses. Due to viral infections and bacterial infections, pro-inflammatory and anti-inflammatory cytokines are produced by the innate immune responses. Vitamin D can also shrink the production of pro-inflammatory Th1 cytokines like interferon γ and tumor necrosis factor α. The lower levels of 7-dehydrocholesterol in the skin of elderly people and less time spent in the sun exposure causes case-fatality rates higher in elderly COVID19 patients as an increase with age reduce vitamin D production. Adequate vitamin D
levels could be suitable candidate for reducing the severity of multisystem inflammatory syndrome in certain circumstances by raising serum [25(OH)D] concentrations.68 Again, vitamin D supplementation enhances the expression of glutathione reductase and glutamate–cysteine ligase modifier subunit genes related to anti-oxidation.69 Therefore, augmented production of glutathione standbys the usage of vitamin D, which possesses antimicrobial activities and has been suggested in the special management of COVID-19 patients.43, 69

**Vitamin E**

Vitamin E is a strong antioxidant, plays a vital part in the process of oxidative stress reduction and also modulates the host immune functions.55, 70 A pilot study of randomized controlled trial showed that supplementation of vitamin E helped to normalize the liver enzymes and in the negativization of HBV-DNA of patients with chronic hepatitis B virus. Analogous results have also been reported in a controlled trial where treatment with vitamin E caused an increase in virological response and anti-HBe seroconversion.71 A study in animal model reported that reduced levels of vitamin D and vitamin E in calves trigger the bovine coronavirus infection.54 Therefore, adequate supplementation of both vitamins E and D together may increase the resistance to COVID-19 infections.

**Vitamin A**

The immune boosting functions of vitamin A consists of the elevation of keratins and mucins, antibody production, apoptosis, expression of cytokine, lymphopoiesis, and the enhanced roles of neutrophils, monocytes or macrophages, natural killer cells, B cells and T cells.72, 73 Vitamin A deficit people are more susceptible to the weakened immunity towards viral infections, including the influenza, measles, and respiratory syncytial virus.73, 74 After vitamins D and A supplementation, immune response has been shown to be enhanced due to influenza virus vaccination in children who were vitamin D and A deficit at baseline.74 Hence, vitamin A might be a favorable option to treat this novel coronavirus and to prevent lung infection.

**Minerals and Trace Elements**

**Magnesium (Mg)**

Magnesium has some vital roles to play in regulating immune system by exercising a noticeable impact on immunoglobulin production, adherence to immune cells, cytolyis (antibody-dependent), binding with Immunoglobulin M (IgM) lymphocyte, T helper-B cell adherence and macrophage response to lymphokines.75 Several in-vivo and in-vitro studies showed that magnesium is likely to have a function in the immune reactions against viral infections.76, 77 In healthy young individuals, the Mg-supplementation caused a significant increase in adrenocorticotropic hormone (ACTH) concentrations leading to the reduction of IL-6 and cortisol levels, which may contribute to the protection against SARS-CoV-2-related pneumonia.78, 79 Moreover, some studies have demonstrated that Mg-supplementation was able to correct vitamin D deficiency owing to its role as a co-factor for vitamin D-binding protein 80 and thus helps to increase vitamin D in its active forms. A very recent study identified the positive effects on the COVID-19-related mental health problems in healthcare workers by Mg supplementation along with vitamins B.81 Similarly, a co-supplementation of Mg+2 (300 mg) with vitamins B (30 mg) was evaluated in 264 healthy persons with depression, anxiety, and stress symptoms. After 8 weeks, a significant 48% decrease was observed in subjects with severe stress.82

**Selenium (Se)**

Selenium is an essential trace element that has a wide range of pleiotropic effects including protection against viral infection through its redox signaling, antioxidant, redox homeostatic contributions and anti-inflammatory characteristics.83, 84 Lower level of selenium has been found to be associated with reduced immune responses, cognitive weakening and an augmented risk of mortality, while a higher concentration of selenium or supplementation with selenium has displayed antiviral effects.83-85 Dietary deficiency of selenium may cause oxidative stress in the host and modify a viral genome so that a generally benign or mildly pathogenic strain can convert into an extremely virulent in the selenium deficit host.86 A three months controlled trial revealed that selenium supplementation increases selenoprotein W (SEPW1) mRNA, while after an influenza vaccination, a dose dependent increase in selenoprotein S (SEPS1) gene expression was observed.87 Plasma level of selenium, cytosolic glutathione peroxidase and lymphocyte phospholipid activities, cellular immunity, proliferation of T-cells,
and a rise in T-helper cells were observed due to selenium supplementation.  

A significant clinical benefits of selenium supplementation have also been observed in other viral infections including HIV-1 virus. Selenium appear relevant to a number of evolutionarily distinct viruses, via potential immunomodulatory effects that are fully consistent with the many essential roles of selenium in the immune system. Therefore, a treatment of selenium supplementation in conjunction with other micronutrients could be an effective intervention for the COVID-19 affected patients.

Zinc (Zn)
Zinc is an essential ‘gatekeeper’ of immune function and crucial role for most enzymatic activities and the regulation of transcription in the human body. Zinc plays a part in the control of intracellular signaling pathways in innate and adaptive immunity. Zinc deficiency is usually associated with enhanced risk of human coronaviruses infections, impaired immunity, and altered the homeostasis of at least 16 minerals such as magnesium, selenium, copper, potassium and iron. The zinc deficiency also modifies the progression of acquired immunity by limiting both certain and outgrowth functions of T lymphocytes, including the production and activation of Th1 cytokine. The function of macrophage also is diversely affected by the zinc deficiency through the phagocytosis, dysregulation of cytokine production and intracellular killing.

Few RCTs have assessed the outcome of zinc supplementation on the immunity. A study among 103 children with pneumonia displayed a statistically significant clinical improvement in the group with zinc supplementation compared to the placebo. Another RCT on oral supplementation of high-dose zinc (150 mg/day) after transplantation of stem cell, proved that it develops the thymic function and the output of new CD4+ naïve T cells, helping to avert the reactivation of TTV. Promising anti-inflammatory effects were observed in Zn supplementation which upregulated the zinc transcription factor A20 able to inhibit the NF-κB signaling and therefore reduce cytokines release. The intake of up to 50 mg zinc per day might provide a defensive role against the COVID-19 infection as it has antiviral properties by improving immunity and quashes viral replication. Some COVID-19 related symptoms such as diarrhea and lower respiratory tract infection might be improved by Zinc supplementation.

Role of other Micronutrients and Phytonutrients
The addition and supplementation of different nutrients and nutraceuticals have beneficial effects on the immune response and can prevent or ameliorate viral infections. Vitamin B complex has been shown to play critical roles to prevent, improve or even treat mental health disorders such as anxiety, stress, or depression. Vitamin B supplementation was significantly associated with reduced stress symptoms. It has been shown that treatment with Vitamin B3 had a strong anti-inflammatory effect, inhibiting neutrophil infiltration into the lungs throughout the ventilator-induced lung damage. Vitamin B6 is required for protein metabolism and it contributes in varieties of reactions and performs significant role in our immune system. Moreover, co-supplementation of Mg (200mg) and vitamin B6 (50mg) for one month synergistically relieved anxiety. Since lack of B vitamins might abate the host immunity, they ought to be provided to the patients infected with virus to boost their immunity. Hence, B complex vitamins might be used as a rudimentary option for the management of COVID-19 patients. Polyphenols include phenolic acids, flavonoids, and stilbenoids, which are universally found in plants and occur either as free aglycones or as glycosides. They may be used to control immune responses in intestinal mucosa, allergic diseases, and antitumour immunity.

Lactoferrin, curcumin, cinnamaldehyde, probiotics and quercetin have a proven ability to boost the immune system, inhibit virus spread, and impede the disease progression to severe stage against COVID-19 infection.

Lactoferrin is a glycoprotein, also a nutritional supplement which has well-known in vitro anti-viral properties to fight against a wide array of virus including SARS-CoV, a closely linked corona virus to SARS-CoV-2. Moreover, lactoferrin possesses unique anti-inflammatory and immunomodulatory effects that might be related to the pathophysiology
of severe COVID-19 cases. It has been found to experimentally impede the entry of viruses via binding with host cell surface HSPGs in murine coronavirus and human coronaviruses hCOV-NL63 and pseudotyped SARS-CoV).

Melatonin retains highly antioxidant characteristics and it may bind up to ten free radicals in each molecule, whereas other antioxidants like vitamins E and C can one. Besides, melatonin has the quality to penetrate placenta and blood-brain barrier, and also have high bioavailability. Indirectly, melatonin’s antioxidant properties are actually connected to an augmented action of reductase, superoxide dismutase, catalase and glutathione peroxidase. The usage of melatonin may partially lessen the age-related comorbidities aggravating the SARS-CoV-2 infection and enhancing the risk.

Table 1: Potential role of nutrients against Covid-19 and other respiratory infections

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>Evidence on potential roles</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyunsaturated fatty acids</td>
<td>a) Stimulate the anti-inflammatory or pro-inflammatory reactions.</td>
<td>28</td>
</tr>
<tr>
<td>Protein</td>
<td>b) Mitigate the replication of influenza virus (Omega-3).</td>
<td>30,32</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>a) Play significant role in deduction of incidence of pneumonia and might avert the vulnerability to lower respiratory tract infections.</td>
<td>35,36</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>a) It potentially suppresses the production of cytokine by improving the innate immune responses to instantly react to viral load.</td>
<td>53,54,56</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>a) Reduced level of vitamin D and vitamin E in calves triggered in the bovine coronavirus infection.</td>
<td>54</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>a) Vitamin A deficit people are more susceptible to the weakened immunity towards viral infections, including the influenza, measles, and respiratory syncytial virus</td>
<td>73</td>
</tr>
<tr>
<td>Magnesium</td>
<td>a) Supplementation of Mg2+ oxide (500mg/day/8 weeks) resulted in insomnia improvement and a significant reduction of stress levels in healthy individuals</td>
<td>81</td>
</tr>
<tr>
<td>Selenium</td>
<td>a) Higher concentration of selenium or supplementation with selenium has displayed antiviral effects.</td>
<td>84</td>
</tr>
<tr>
<td>Zinc</td>
<td>a) A study among the 103 children with pneumonia displayed a statistically significant clinical improvement in the group with zinc supplementation compared to the placebo.</td>
<td>93,94</td>
</tr>
<tr>
<td>Vitamin B-complex</td>
<td>a) It contributes in a variety of reactions and performs significant roles in immune system.</td>
<td>96</td>
</tr>
<tr>
<td>Melatonin</td>
<td>a) Melatonin may partially lessen the age-related comorbidities aggravating the SARS-CoV-2 infection and enhancing the risk.</td>
<td>102</td>
</tr>
</tbody>
</table>
Suggested Nutritional Guidelines for Covid-19 Infected Patients

The current COVID-19 pandemic is still devastating in nature and no appropriate treatment regime is confirmed yet. Therefore, it is suggested that people might follow the following nutritional guidelines, summarized in Table 1 and Figure 1 which may help resisting against COVID-19 infections via boosting the immune response.

- Adequate and balanced macronutrients intake: People should consume a diversified diet containing high quality protein, moderate amount of complex carbohydrate and good amount of healthy fats.
- Diet diversification: Consumption of food containing dark color vegetables and fruits, organ meat, red and white meat, fish, milk, butter, eggs, nuts and seeds will ensure delivery of key nutrients such as Vitamin A, C, D, zinc, magnesium, selenium and omega 3 fatty acids.
- Special Attention: Ensure sufficient amounts of vitamin C consumption daily either by rich foods sources like citrus fruits, peppers, gooseberry, guava etc. or vitamin C supplements as it plays the major role for immune boosting.
- Emphasize the other micronutrients: Along with vitamin C, regular consumption of other micronutrients should be emphasized specially vitamin D, magnesium, zinc and selenium.
- Consider phytonutrients: Increase the consumption of phytonutrients like melatonin enriched fruits and vegetables considerably.
- Berries, banana, pineapple, orange, oats, spirulina, sunflower seeds, pumpkin seeds, sesame seeds etc. may help increasing melatonin production.
- Avoid: Foods high in refined carbohydrates, sugars, salt, junk foods, sweetened beverages and trans-fats are highly recommended to be avoided.
- Encourage: It should be encouraged to drink plenty of healthy drinks specially masala tea, herbal tea, broth and soup etc. Also encourage to take at least 6-7 hours rest daily.
- Special medical care: Patients with comorbidities (ex. diabetes, cardiovascular disease, chronic kidney disease) should take extra special medical care.
- Non-nutritional factor: Patients in quarantine should continue regular home-based physical activity at least 30 min regularly while taking precautions. Daily exposure to sunlight (minimum 15-20 minutes) at morning is suggested for natural vitamin D synthesis in the body.
Conclusions
Healthy balanced diet and adequate amount of micro- and phytonutrients from diversified food sources enhance the immune boost up and self-resistance. Vitamin C along with other vitamins (vitamin A, D, E) and minerals (magnesium, zinc, selenium) synergistically improve the immune responses from individuals at with COVID19 infections and help preventing adverse effects of co-morbidities. In global lockdown context, it is challenging to achieve a well-balanced dietary intake. Therefore, the general suggestion is to consume fresh fruits, vegetables, whole grains, low-fat dairy sources, and Omega 3 PUFAs and to avoid intakes of junk processed foods. Besides, dietary supplements of micronutrients should be administered to individuals who are at risk or deficient of certain micronutrients.

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Conflict of Interest
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