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REVIEW

Fat-Soluble Vitamins and the Current Global Pandemic of COVID-19: Evidence-Based Efficacy from Literature Review

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Abstract: The outbreak of pneumonia caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), later named COVID-19 by the World Health Organization (WHO), was initiated at Wuhan, Hubei, China, and there was a rapid spread of novel SARS-CoV-2 and the disease COVID-19 in late 2019. The entire world is now experiencing the challenge of COVID-19 infection. However, still very few evidence-based treatment options are available for the prevention and treatment of COVID-19 disease. The present review aims to summarize the publicly available information to give a comprehensive yet balanced scientific overview of all the fat-soluble vitamins concerning their role in SARS-CoV-2 virus infection. The roles of different fat-soluble vitamins and micronutrients in combating SARS-CoV-2 infection have been recently explored in several studies. There are various hypotheses to suggest their use to minimize the severity of COVID-19 infection. These vitamins are pivotal in the maintenance and modulation of innate and cell-mediated, and antibody-mediated immune responses. The data reported in recent literature demonstrate that deficiency in one or more of these vitamins compromises the patients' immune response and makes them more vulnerable to viral infections and perhaps worse disease prognosis. Vitamins A, D, E, and K boost the body's defense mechanism against COVID-19 infection and specifically prevent its complications such as cytokine storm and other inflammatory processes, leading to increased morbidity and mortality overemphasis. However, more detailed randomized double-blind clinical pieces of evidence are required to define the use of these supplements in preventing or reducing the severity of the COVID-19 infection.

Keywords: SARS-CoV-2, COVID-19, fat-soluble vitamins, micronutrients, immune response

Introduction

A strong and well-built immune system is of absolute necessity for every individual. Immune physiology is strongly correlated with adequate intakes of vitamins and trace elements.[1] Healthy dieting, including regular intake of vitamins and trace elements, is responsible for the immune system's proper function. Henceforth, a sufficient amount of vitamins should be present in our daily meals due to their capacity to influence and strengthen the immune system.[2] A recent report demonstrated that the benefits of vitamins to the human body could not be overemphasized. Vitamin supplementation, especially vitamin D, is crucial, especially when vitamins are deficient or insufficient.[3] It has been well established that high-quality nutrition is vital in modulating immune homeostasis. Any subclinical deficiency of

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micronutrients or even protein-energy malnutrition may impair one's immune responses.[4]

Enhancement of body innate immunity using vitamin supplements in patients suffering from viral infections has shown positive impacts. A typical example is vitamin A and D supplementation, which increases pediatric patients' humoral immunity following influenza vaccination.[5–7] A review by Calder et al[8] suggested that one of the primary ways to protect a person against viral infections is to maintain a well-balanced nutritional status.[4] Furthermore, balanced nutrition and a varied diet have been proven to complement vitamin deficit and minimize frequent and unnecessary consumption of marketed vitamin supplements.[9] A recent study by Wu suggested nutritional recommendations that could improve the body's immune system and significantly limit lung damage from COVID-19 and other lung infections.[10] In addition to proper dietary intake, lifestyle modification is necessary to prevent and treat viral diseases like the current COVID-19. To complement such efforts, regular fundamental hygienic practices should be maintained, and every individual is urged to comply with rules laid down by the government and the health authorities.[11] The typical healthy eating practice encourages everybody to take a minimum of five servings of different (at least 05) fruits since one fruit is not enough to meet and combat the current global pandemic of COVID-19 situation and vegetables each day and the main meal that should contain more carbohydrates. Other components of a healthy diet include a few segments of meat or protein for vegetarians. A reasonable amount of protein-rich foods should be incorporated into daily meals.[11] Unfortunately, during the lockdown period, the achievement of a well-balanced diet appeared tedious due to logistics, economic troubles, and movement restrictions, however taking a multivitamin–mineral (MVM) supplement for a limited time is very helpful, especially among the elderly populations who are more vulnerable to COVID-19 infection (Figure 1).[12]

Currently, malnutrition increases the burden of morbidity and mortality due to infectious diseases, which significantly affects the health care systems from an economic standpoint and the nutrition care of any country.[13] A higher predisposition to morbidity and mortality caused by protein-energy malnutrition from inadequate dietary intake has been attributed to an increased rate of infections and delayed recovery, leading to a higher demand for several nutrients.[14–18] Furthermore, malnourished patients or patients at risk of malnutrition are expected to take extra

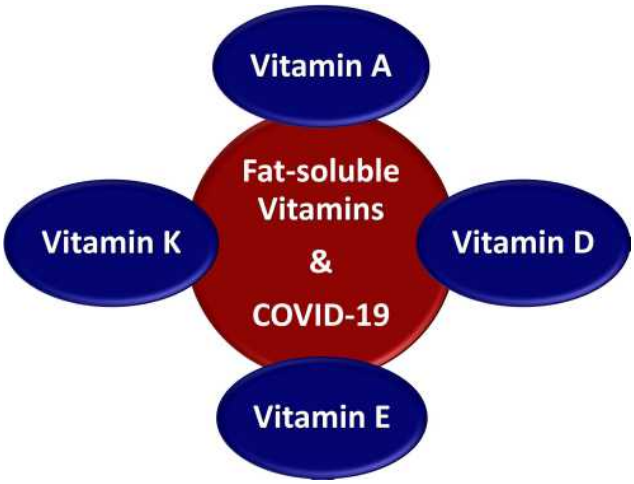

Figure 1 Fat-soluble vitamins crucial in COVID-19.

supplements to improve their energy, protein, and micronutrient levels.[4] Notably, for a viral infection like COVID-19 with minimal therapeutic approaches available for prevention and treatment, nutritional strategies for enhancing immunity remain an avenue to be explored.

Furthermore, medical nutrition therapy (MNT) performs an essential responsibility in the averting and management of malnutrition.[19,20] The COVID-19 pandemic is predictable to escalate the risk of all types of malnutrition.[21,22] Moreover, movement control policy, popularly known as lockdowns, messed up the overall healthcare services that deterred maternal and child health, increasing mortality.[23,24] Researchers anticipated child stunting, micronutrient malnutrition, and maternal nutrition to intensify because of the disruption of national and international economies and the food supply chain.[25–27] Additionally, 3.9 million children of South Asia have a higher possibility of developing muscle-wasting.[27] Thereafter, registered dietitian nutritionists (RDNs) should be motivated and energetically take the initiative to create and implement appropriate nutrition policy planning to evaluate, avert, and manage malnutrition through a multidisciplinary team-based approach for ongoing COVID-19-infected patients or patients at risk.[22,28,29]

A most critical warning sign of the vitamin C deficiency ailment is known as scurvy. Scurvy has been frequently correlated with increased susceptibility to infections, predominantly of the respiratory tract, pneumonia, and pulmonary tuberculosis, and remains the primary cause of death.[30–32]A classic example is the consumption of vitamin C, which plays a prophylactic role due to its ability to facilitate the favorable immune response required for the growth and repair of body tissues.[33] It

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also reduces the susceptibility of the lower respiratory tract to infections.[34–36] It has been reported that patients with acute respiratory infections when receiving intravenous vitamin C followed by serum level increase positively correlate to minimizing the respiratory symptoms.[37,38] Multiple studies reported that vitamin C possesses significant anti-inflammatory, immunomodulation, antioxidant, antithrombotic, and antiviral activities.[39–41] Vitamin C positively impacts both innate and adaptive immune systems and exhibits through virucidal activity.[33,42–45] Additionally, vitamin C promotes T-lymphocytes' growth and maturation process and works shoulder to shoulder in improving leukocytes physiology performance regarding the phagocytic and chemotactic process.[33,46,47] Moreover, vitamin C, with its antioxidant action, improves the phagocytic property; in this manner, it leads to increased formation of reduced vitamin C (ascorbic acid) from oxidized vitamin C (dehydroascorbic acid).[48]

Furthermore, vitamin E is a potent antioxidant and can modulate the host's immune functions. On the other hand, several studies demonstrated the harmful effects of vitamin E intake on the immune response. The same view has also been backed up by researchers who discouraged vitamin E supplementation in cardiovascular disease and cancer prevention.[5] It was also speculated that a high dosage of vitamin E supplementation might increase all-cause mortality. Taken together, there is a need to investigate the prospects of these vitamins as an effective measure in the treatment of COVID-19.

Objectives of the Study

This review aims and scopes to highlight 1) role of vitamin A, D, E, and K in COVID-19, 2) antiviral effects of vitamin E on COVID-19, 3) immune-boosting effects of vitamin E relevant to combat COVID-19, and 4) to conclude and give prescribers and policymakers direction.

Materials and Methods

Even though the literature investigation is an obligatory segment for systematic review and meta-analysis several critical studies about narrative review encouraged integrating a section about search strategies. In that way, this manuscript comprises the section of materials and methods. The literature search was not systematic but was based on the four core bibliographic databases (Google Scholar, PubMed, Scopus, and China National Knowledge Infrastructure). We are conscious of the specialty and strength of the web of science; nevertheless, we could not embrace it because of monetary constraints as the current paper did not obtain any fiscal support. The authors depend predominantly on open access journals and access to journals fixed by the Universiti Pertahanan Nasional Malaysia (UPNM), the National Defence University of Malaysia (UPNM), Kuala Lumpur, Malaysia, and North South University, Dhaka-1219, Bangladesh. Articles those not available in full-text or not written in English were excluded. The only non-English papers utilized refer to the historical purpose. The study was conducted between early June 2020 and mid-February 2021. The search terms used include "Coronavirus Disease 2019 Virus, Wuhan Seafood Market Pneumonia Virus, Novel Coronavirus 2019, SARS-CoV-2 Virus, COVID-19 Virus, Wuhan Coronavirus, SARS Coronavirus 2, Severe Acute Respiratory Syndrome Coronavirus 2, Vitamin A, Vitamin D, Vitamin E, Vitamin K, Trace Element, Biometals, Immune Processes, Humoral Immunity, Acquired Immunity, Adaptive Immune Response". This was trailed by the snowballing of references cited by essential manuscripts. We had included all types of peer-reviewed articles published in English. Further references were dappled through labor-intensive exploration through the selected references after the first-round search. As this paper is of a narrative nature review, both recent and older publications with historical significance were incorporated.

Role of Vitamin A in COVID-19

Vitamin A plays a vital role in metabolism and immune response. Its pleiotropic influences have been established, ranging from a diverse physiological task in maintaining the required biological need of our system, including well-known fact in improving the eyesight.[49] In recent reviews, vitamin A acts by boosting all-trans-retinoic acid (ATRA), and it is also pivotal in the maintenance of innate cell-mediated and antibody-mediated responses.[50] In another study on vitamin A, Field et al ascertained vitamin A's capacity to resist infection.[51] A report by Mora et al proposed a decline in vitamin A uptake has a critical influence on the immune response.[52] This was also further testified in the work of Cunningham-Rundles et al, who stated that HIV-infected pregnant women should be encouraged to eat food rich in vitamin A. This is because the decrease in vitamin A could predispose her to an increased risk of congenital HIV and AIDs.[53] Food substances rich in vitamin A are primarily vegetables such as carrots, spinach, and sweet potato. These vegetables also constitute a group of fat-soluble compounds such as retinol, retinoic acid, and β-carotene that play a vital role in regulating immune

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responses and reducing susceptibility to infections.[54–58] The mechanism adopted by vitamin A to reduce infection is often through modifying epithelial cell integrity and function, improving specific and non-specific immunity of the host, and lymphoid mass use.[59–61]

The three primary active forms of vitamin A include retinol, retinoic acid, and retinol. Hence, they are regarded as "anti-infectives as many of the body"s defense mechanisms against infections depend on their constant supply. Semba et al believed that adequate vitamin A supplementation helped reduce morbidity and mortality resulting from different infectious diseases.[62] Examples of such conditions include diarrhea, measles, HIV infections, measles-related pneumonia, and malaria. In furtherance to this, vitamin A remains of significant importance as it offers some protection against life-threatening complications and infections such as malaria, HIV, and lung diseases.[63–65] Often, they are made refractory to infection during subsequent rounds of viral replication. Nevertheless, Jee et al[66] believed that diets low in vitamin A supplements are likely to reduce inactivated bovine coronavirus vaccines' effectiveness, increasing the calves' vulnerability to infectious diseases.[54,66,67] Another significant link of vitamin A to COVID-19 infection was more pronounced in its activity against the infectious bronchitis virus (IBV), a kind of coronavirus that was found more in chickens fed with a diet deficient vitamin A as opposed to those provided with adequate proportions of vitamin A. Lastly, vitamin A is envisaged to be a promising option in treating the COVID-19 pandemic by preventing lung infection (Figure 2). The method by which vitamin A and retinoids prevent measles replication is through the up-regulation of mineral elements and the innate immune response in bystander cells free of infections.[68]

Multiple earlier studies have reported that type 1 interferons (IFN-I) possess antiviral effects in two closely related coronaviruses, SARS-CoV and MERS-CoV, either administered single-handedly or in mish-mash with other

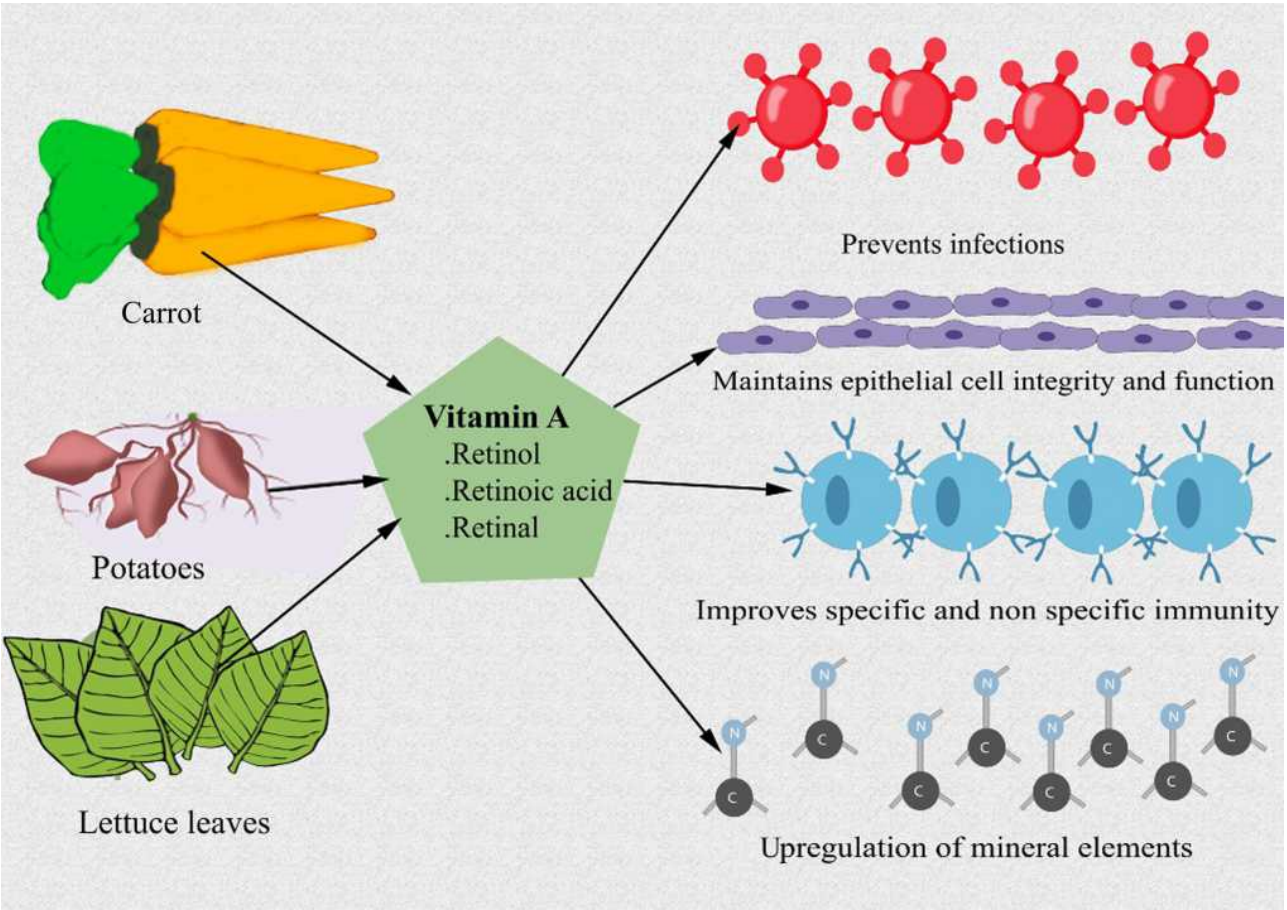

Figure 2 Role of vitamin A in COVID-19.

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antiviral medication.[69–71] Additionally, retinoids are closely interconnected molecules associated with vitamin A that have robust immune-modulating chattels, together with the capability to escalate and heighten the efficacy of IFN-I.[72,73] Moreover, retinoids and their related compounds have been well documented as a safe therapeutic option for over 60 years.[74,75] In that way, multiple studies have reported that retinoids possess potential possibilities in the management of COVID-19.[73,76,77] Recently, seven core targets of vitamin A against COVID-19 were recognized. Those are MAPK1 (mitogen-activated protein kinase 1), IL-10 (interleukin 10), EGFR (epidermal growth factor receptor), ICAM1 (intercellular adhesion molecule 1), MAPK14 (mitogen-activated protein kinase 14), CAT (catalase), and PRKCB (protein kinase C β).[78,79] Thereby, several studies reported that vitamin A and related compounds have a potentially beneficial role in the management of COVID-19.[77,80–82] Moreover, it has been reported that vitamin A can minimize COVID-19-induced adverse effects on the angiotensin system and minimize medication-related adverse effects.[83] On top of these novel beneficial effects, vitamin A, is well known for the positive role in promoting innate and adaptive immunity.[2] By this means, vitamin A prevents or diminishes primary and secondary infections.[84,85] In consequence, it improves respiratory health by curtailing inflammation and fibrosis.[86–88] Furthermore, COVID-19 has been found to persuade inflammatory response/cytokine storms, especially involving liver, lung, and kidney, which further increases the risk of depletion of vitamin A stores that demand supplementation and has the prospect to restore the acceptable status and combat the grave life-threatening disease.[88,89]

Role of Vitamin D in COVID-19

Numerous physiological, hereditary, and environmental factors account for the emerging disparity and fluctuations in the number of confirmed COVID-19 cases, morbidity, and mortality across different nations. Movement restrictions (lockdown) to reduce the exposure to COVID-19-infective cases to ensure social distancing. This measure to control COVID-19 is probably one of the best instruments policymakers incorporated throughout the globe to save their countrymen. Thereafter, COVID-19 risk somewhat minimizes; nevertheless, people are less exposed to sunlight, which has enhanced vitamin D deficiency risk. Vitamin D functions in various ways, including interaction with the nonspecific defense mechanisms, activation of Toll-like receptors, and/or increment in the levels of cathelicidins and β-defensins.[90] This influences the acquired immunity by lowering immunoglobulin released by plasma cells and pro-inflammatory cytokines production to modulate T cell function.[90] Promising results further described vitamin D nutrients as an essential supplement in treating respiratory tract infections, autoimmune diseases, and pulmonary fibrosis.[91] An increase in serum 25(OH)D is associated with increased beneficial bacteria and lowered pathogenic bacteria in the body.[92]

A classic example is that of three hospitals of Southern Asian origins that conducted a retrospective multicentre study of 212 cases with laboratory-confirmed infection of COVID-19, with a depicted data related to clinical features and serum 25(OH)D levels.[93] The results suggested that an increased serum 25(OH)D level in the body could either improve clinical outcomes or mitigate severe to critical outcomes. However, a decreased serum 25(OH)D level in the body could lead to a detrimental consequence.[93]

The defensive effect of vitamin D against SARS-CoV-2 infection can be linked to its previous effect on other respiratory infections.[94] This notion was further supported by a meta-analysis that conclusively affirmed that vitamin D intake is beneficial in acute respiratory tract infections.[94] After having millions of the confirmed COVID-19 cases, evidence continually depicts the older populace and malnourished individuals as the most vulnerable groups in this disease condition. Univariate analysis in an Indonesian retrospective cohort study consisting of 780 confirmed cases of COVID-19 depicted that older patients, males sufferers with a pre-existing medical condition, and those with lower vitamin D levels were associated with an increased odds ratio of mortality. When controlling independent variables during epidemiology such as age, sex, and comorbidity, low vitamin D status is strongly associated with increasing cases of COVID-19 mortality.[95] Seneca et al demonstrated that older people have an average serum vitamin D level of 26 nmol/L in Spain, 28 nmol/L in Italy, and 45 nmol/L in the Nordic countries. In Switzerland, the intermediate vitamin D level is 23 nmol/L in nursing homes; and data from Italy indicated that 76% of women over 70 years of age have vitamin D levels below 30 nmol/L.[96] These estimates of low vitamin D levels among the elderly across Europe showed that the aging population represents the group with the highest risk of morbidity and mortality with SARS-CoV-2 infection.[97]

The recommended dietary allowances (RDA) for Vitamin D are 10 μg/day and 15–20 μg/day for infants and adults, respectively. Additionally, the sources to supply Vitamin D

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accounts for a limited number of nutritional sources such as cod liver oil, catfish, mushrooms, etc. The content of most of the milk supplies in the US is added with 400 IU vitamin D per quart, and the same applies to the vegetative alternatives (soy milk, almond milk, oat milk, etc.).[98] Currently, the majority of breakfast, including bowls of cereal and some orange juice brands, yogurt, margarine, and soy beverages, are fortified with vitamin D. This vitamin is usually added in two different forms that are vitamin D2 (ergocalciferol) and D3 (cholecalciferol) that collectively increase vitamin D in the blood.[99] Based on previous studies, patients with respiratory disease, to rapid and safe increase serum 25(OH)D levels, and patients with low circulating levels (below 50 nmol/L) can be offered vitamin D supplementation of 50,000 IU twice a week.[100,101] Overall, doses above 6000 IU/d are needed to achieve serum 25(OH)D concentrations above 100 nmol/L, and intakes of vitamin D up to 15,000 IU/d (Figure 3) were found to be safe.[101,102]

The effectiveness of vitamin D in reducing infections that may require hospitalization cannot be overemphasized, especially with the rising incidences of COVID-19. Consequently, frontline warriors working in hospitals treating COVID-19 patients linked with increased risk of COVID-19 infection require vitamin D supplementation. This was further justified by a report in which 40 out of 138 admitted COVID-19 cases in Wuhan in the Zhongnan Hospital from 1 to 28 January were healthcare workers.[103] It was announced that COVID-19 infected more than 1700 Chinese health workers, out of which 6 already died by 14 February 2020.[104] Another study revealed that 152,888 confirmed cases and 1413 deaths among healthcare workers around the globe.[105] Medscape reported on 11 March 2021, that over 3000 healthcare workers passed away in the last year because of COVID-19.[106] Aljazeera reported on 5 March 2021 that according to Amnesty International, at least 17,000 health workers have died globally from the current global pandemic COVID-19.[107] A dose of at least 40–50 ng/mL (100–125 nmol/L) of vitamin D is recommended for individuals as prophylaxis based on observational studies.[108–111] During the COVID-19 pandemic, it is crucial that all people in the hospital, including the patients

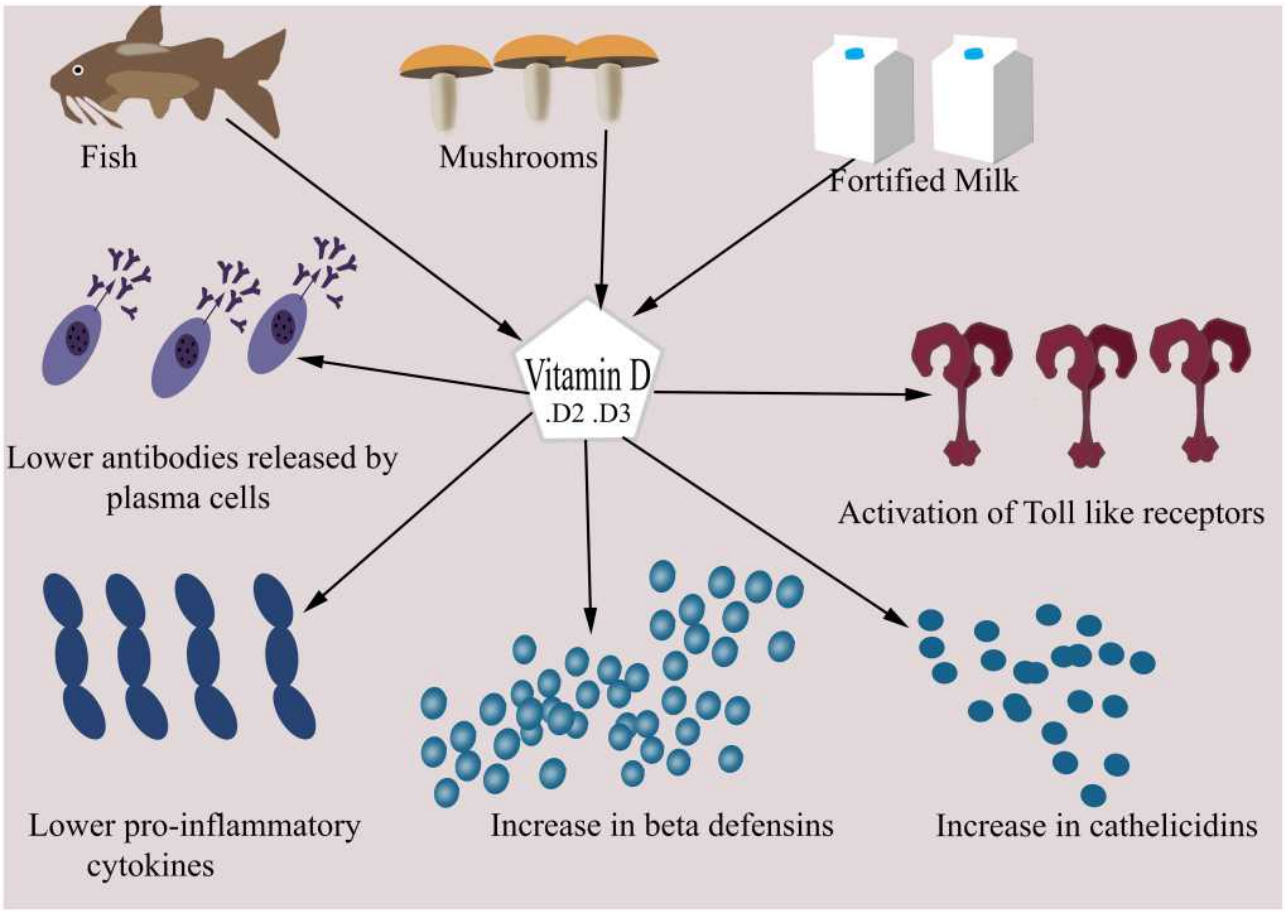

Figure 3 Role of vitamin D in COVID-19.

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and staff, take vitamin D supplements to raise 25(OH)D concentrations as an essential step in preventing infection spread.[112]

Before recommending vitamin D to a particular population, initial testing of their vitamin D level at an interval is advocated to determine the dosing levels required. Moreover, there should be followed up to determine whether vitamin D is adequate until vitamin D status is optimal. This is important because once vitamin D deficiency is corrected, giving more vitamin D supplementation may not provide additional benefits.[113] The dosing should be done continuously, even without the occurrence of respiratory tract infection. Amid this pandemic, there is difficulty in routine maintenance of vitamin D supplements ranging from its preparation to storage, distribution, and quality control.[109,114] With proper blinding, randomized controlled trials with a higher number of subjects from representative populations should be conducted to evaluate these recommendations.

Role of Vitamin E in COVID-19

Antiviral Effects of Vitamin E on COVID-19

Coronaviruses are a family of common RNA viruses. They are potential causes of severe lower respiratory tract infections, followed by pneumonia, which is generally associated with cytokine storm production, inflammation, cell death, and other pathophysiological processes involving redox imbalance or oxidative stress.[115] COVID-19 patients are at a higher risk of developing inflammatory responses associated with fatal respiratory distress. Although limited clinical data is available to establish a link between oxidative stress and viral infection due to SARS-CoV-2, many lines of evidence still suggested that overproduction of reactive oxygen species (ROS) and deprived antioxidant system play a significant role in the pathogenesis and severity of SARS-CoV-2 viral infection.[116] Reactive oxygen and nitrogen species (RONS) and other free radicals resulting from oxidative stress are potential causes of cell membrane damage by lipid peroxidation, oxidation, and protein denaturation. According to a few studies, it is often suggested that the onset of severe lung injury in COVID-19 patients is based on the activation of the oxidative stress mechanism coupled with an innate immune response that activates the transcription factor NF-kB resulting in an exacerbated pro-inflammatory host response associated with the pathophysiology of the virus.[116–120] In like manner, another study suggests an upregulation of mitochondrial genes and genes responding to oxidative stress in peripheral blood mononuclear cells (PBMC) of convalescent SARS-CoV-2 patients. Stress response protein DNAJB1, differentiation-associated gene IFRD1, cytokine IL-1B, and other genes were overexpressed in the PBMC of these patients. These results support the association between oxidative stress, inflammation, and pathogenesis of SARS-CoV-2 infection.[121]

Vitamin E is a fat-soluble antioxidant that can protect the polyunsaturated fatty acids (PUFAs) in a membrane from oxidation, regulate RONS production, and modulate signal transduction.[122] It facilitates the inhibition of protein kinase C activity by enhancing PKC-alpha dephosphorylation via activation of protein phosphatase 2A by vitamin E has been demonstrated in different cells, and the suppression of platelet aggregation, reduced proliferation of macrophages, and decreased superoxide production in neutrophils and macrophages.[123] The high concentration of vitamin E present in immune cells of COVID-19 patients defends them from oxidative damage because of its high metabolic activity and PUFA contents in age-associated dysregulation of the immune system.[124–129] Vitamin E donates hydrogen to reactive free radicals, becomes oxidized, and quenches the reactive species produced from oxidative stresses.[130–132] Vitamin E antioxidant therapeutic potential can be exploited to prevent oxidative damages associated with the SARS-CoV-2 pathogenesis due to its scavenging effects.[133–135]

Immune-Boosting Effects of Vitamin E That Can Help Combat COVID-19

The novel coronavirus pandemic has affected millions of people all over the world. SARS-CoV-2 enters the cell via the viral trimeric spike protein binding with the host's angiotensin-converting enzyme-2 (ACE2) receptor and mainly affects the lower respiratory tract. It also binds to ACE2 on the alveolar epithelial cells after infecting the human body.[136] Immediately after binding, it creates a successive immune response through inflammation-related manifestations and recruitment of antigen-presenting cells (APC), which results in an infection of innate and adaptive immunity within the cells.[137–139] SARS-CoV-2 inhibits the rapid expression of interferon type-1 (IFN-1), which is known as "initial alarm."[140] IFN-1, upon encounter with the virus, influences the immune cells to the "antiviral state."[140]

Consequently, the compromised function of IFN-1 would favor immune evasion. On the other hand, antigen

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presentation via MHC class 1/2 may be compromised by infected APC, leading to an impaired T-cell response.[141] T helper cells produce proinflammatory cytokines and chemokines, which in turn recruit lymphocytes, monocytes, and neutrophils, followed by the secretion of vast amounts of cytokines from all these immune cells, an increase in the inflammatory processes. This uncontrolled and massive release of proinflammatory cytokines such as IL-6 and tumor necrosis factor (TNF-alpha) is termed the "cytokine storm," leading to T-cell suppression.[142]

Vitamin E, a fat-soluble natural antioxidant, has very little evidence of antiviral actions; instead, it reduces inflammatory cytokine production and improves T cell proliferation by directly impacting membrane integrity, signal transduction, and T cell differentiation. Vitamin E supplementation enhances leukocyte phagocytic activity and functions of neutrophils and natural killer (NK) cells.[143] Vitamin E is known to affect inflammatory responses in different tissues, including the lungs, via direct scavenging oxidative stress and modulation of oxidative eicosanoid pathways and prostaglandin synthesis; it also influences inhibition of inflammatory mediators and control of apoptotic lipid signaling.[144] Different cell-based animal and human studies have shown evidence of the mechanism involved in vitamin E's immunomodulatory effects of vitamin E. These studies have demonstrated that vitamin E has direct and indirect effects on immune cells, especially on the T cells.[145] The immunoregulatory function of vitamin E has clinical relevance as it affects a host's susceptibility to viral infection, thereby reducing the risk of respiratory diseases.[3,146] In the absence of any known effective treatment for COVID-19, nutrients and food supplements that exert anti-inflammatory and immunomodulatory effects can lay significant protective function. In this light, uptake of vitamin E as a nutrient can be categorized as a vital prospect in treating the SARS-CoV-2 virus (Figure 4).

Preliminary Results of Vitamin E Treatment in COVID-19

Investigations of antioxidant vitamins' effectiveness, especially vitamin E, are still ongoing as a potential treatment for COVID-19 patients. Nevertheless, several studies showed immunoregulatory functions and preventive functions from the oxidative disruption caused by vitamin E. This act has contributed to its recognition as potential agents while treating patients infected with COVID-19. Vitamin E, vitamin C, and selenium have been demonstrated in various studies to have beneficial effects that reduce oxidative stress in patients with this

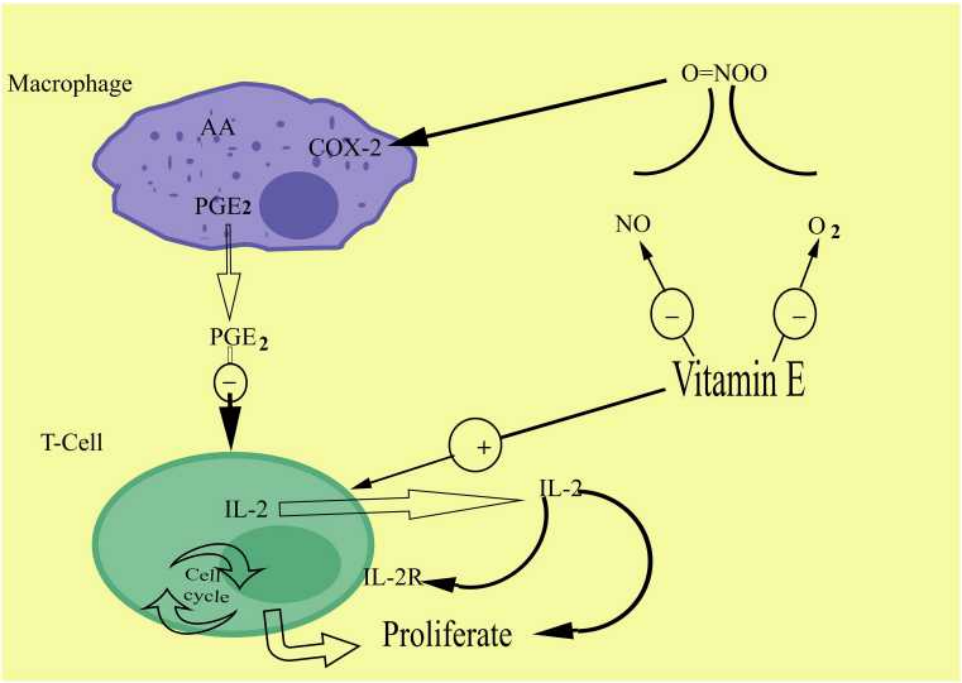

Figure 4 The immunomodulatory function of antioxidant vitamin E.

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infection[147] including COVID-19.[35,148–150] Despite its possible prospects, a lot still needs to be considered as the use of this nutrient will require a long route in its achievement as a successful therapeutic measure for COVID-19 patients.

Prospects of Vitamin E as Adjuvant Therapy in COVID-19

Researchers have often claimed that the effect of COVID-19 infection is particularly detrimental to the health of vulnerable populations such as the elderly and pregnant women.[151–156] Older people with severe diabetes, cardiovascular diseases, cancer, etc., are predisposed to COVID-19 infection due to immunosenescence.[157–159] Vitamin E administration among elderly patients is likely to help the immune function, which increases the chances of infection resistance and decreases mortality that could be triggered by infection.[160–163] Multiple studies regarding vitamin E's potential benefits to COVID-19 patients indicated that vitamin E and C in combination could be a beneficial antioxidant therapy for cardiac implications of COVID-19.[1,164–168] Despite these facts, there is limited evidence that suggests the use of vitamin E as adjuvant therapy for COVID-19.[145,169]

Sources of Vitamin E

Numerous food sources provide vitamin E, such as nuts, seeds, and vegetable oils, a vital alpha-tocopherol source with significant amounts in green leafy vegetables and fortified cereals. Other selected food sources include wheat germ oil, sunflower seeds, dry roasted almonds, sunflower and safflower oils, hazelnuts, peanut butter, corn oil, spinach, broccoli, kiwi fruit, mango, yams, sweet potatoes, soybean oil, etc.[170]

Daily Recommended Dose of Vitamin E in COVID-19 Patients

Even though vitamin E is a potential beneficial nutrient against COVID-19, there is no recommended dosage estimate. However, the recommended daily intake of vitamin E is 15 mg per day for healthy individuals.[171]

Future Needs for Vitamin E and Its Limitations

Concerning the limited evidence available on vitamin E prospects, scientists are investigating whether, by free radical scavenging mechanisms, immune function, or other possible potential effects of vitamin E, they can prevent or delay the severity of the SARS-CoV-2 virus and its associated complications.[77,172] Vitamin E supplements more than RDA showed no additional impact; instead, studies reported that very high intake might cause several body complications.[173] Moreover, a significant vitamin E limitation can be recommended for their antioxidant actions and immunoprotective functions.[147] However, there is still little progress in using them as therapeutic agents for chronic diseases and severely ill patients.

Role of Vitamin K in COVID-19

Vitamin K, one of the fat-soluble vitamins, is essential for synthesizing several proteins – factor II (prothrombin), factors VII, IX, and X involved in regulating blood clotting (coagulation).[174] Natural vitamin K is found in two different forms: K1 (phylloquinone), an effective form of dietary vitamin K and mainly found in green leafy vegetables, and K2 (menaquinones).[175] They are primarily of microbial origin, and sources are especially from fermented foods like cheese, curds, and animal livers. It is noteworthy to understand that these menaquinones are synthesized by human intestinal microbiota.[176–178] The third form of vitamin K is K3 (menadione), which is synthetically or artificially produced.[179] The dietary reference intake of vitamin K recommended by Food and Nutrition Board (FNB) at the Institute of Medicine of the National Academies is 120 mcg for adult males and 90 mcg for adult females.[180] Research has revealed the role of vitamin K beyond blood coagulation.[181] Vitamin K's consumption, combined with anticoagulant drugs such as warfarin, can threaten individuals who take them. Vitamin K and vitamin K-dependent proteins are vital for calcification (maintaining bone and cardiovascular health), energy metabolism, and inflammation.[175,181] To lower the risk of vascular deformation, an adequate intake of vitamin K2 is found to be effective. This is because it activates matrix Gla protein (MGP), inhibiting calcium deposition in the vessel walls.[182] Another importance of this vitamin K is its ability to act as a potent antioxidant reducing the lipid peroxidation in the cell by producing vitamin K-hydroquinone, a robust radical scavenging species.[183,184] Vitamin K has been found to have an anti-inflammatory activity, which would probably modulate through NF-KB signaling [Figure 5].[185]

Typically, the risks for vitamin K deficiency in adults include high consumption of vitamin K antagonists like warfarin (which blocks the vitamin K-dependent pathway,

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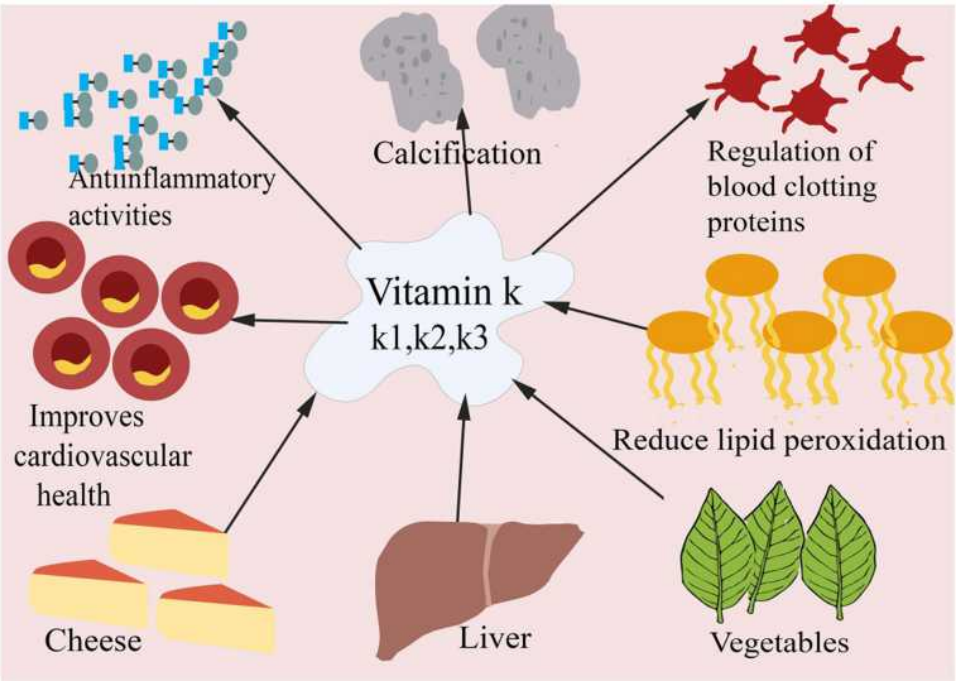

Figure 5 Role of vitamin K in maintaining health.

reducing the body's ability to produce blood-clotting proteins) and individuals with liver diseases and disorders.[186] Mothers who are on anticonvulsant medications (to prevent seizure) could act as a risk factor for infants and can lead to a bleeding disorder known as vitamin K deficiency bleeding (VKDB) of the newborn.[187] Excessive intakes of K1 and K2 forms of vitamin K are not related to abnormal coagulation, and no known associated toxicity has been reported yet.[188,189] Nevertheless, in Menadione's case, it can interfere with glutathione activity (antioxidant), resulting in oxidative damage to the cell membrane. Menadione has also been reported to induce hepatic toxicity, jaundice, and hemolytic anemia.[188,189]

Consequently, menadione is no longer suggested for vitamin K deficiency treatment.[186] Vitamin K deficiency can contribute to excessive bleeding, poor bone development, increased risk of osteoporosis and fractures, as well as several cardiovascular diseases involving vascular calcification and atherosclerotic plaques.[179,190] Reduced vitamin K levels have also been reported in COVID-19 patients.[191] Several factors may contribute decreased dietary intake,[192] high alcohol consumption,[193] and excessive use of medications containing anticoagulants like warfarin[194] during the lockdown.

Recently researchers observed the link between individuals with vitamin K status and COVID-19 outcomes. Coagulopathy is one of the primary features of poor outcomes in patients who develop sepsis from an infection. Similarly, coagulopathy has been observed in severe COVID-19 patients and is associated with poor prognosis, as observed by Tang et al in 183 consecutive patients.[195] One of the most common laboratory findings in COVID-19 patients is the elevation of D-dimers.[196] Coagulopathy and disseminated intravascular coagulation (DIC) appear to be associated with high mortality rates. Among the parameters, the D-dimer peak was a strong predictor of COVID-19 mortality.[197] The other laboratory markers recommended by the International Society of Thrombosis and Hemostasis (ISTH) for monitoring DIC formation are fibrinogen, prothrombin time, and platelet count.[198]

Patients in the Intensive Care Unit (ICU) are at risk of vitamin K deficiency with elevated D-dimer protein levels. This deficiency reduces the functional levels of coagulation factors II, VII, IX, and X, predisposing them to develop coagulopathy, increasing hemorrhage risk,[199,200] and DIC formation. DIC is well recognized for its function in contributing to multi-organ system failure due to the accumulation of thrombus in the microvasculature.[201] (86). Also, low vitamin K level appears to be associated with increased elastin degradation,[191,202] preferably degrading the lung tissue, resulting in breathing difficulty in COVID-19 patients. Since COVID-19 patients with severe disease are associated with co-morbidities such as cardiovascular diseases, type II diabetes, or hypertension, which are linked to reduced vitamin K

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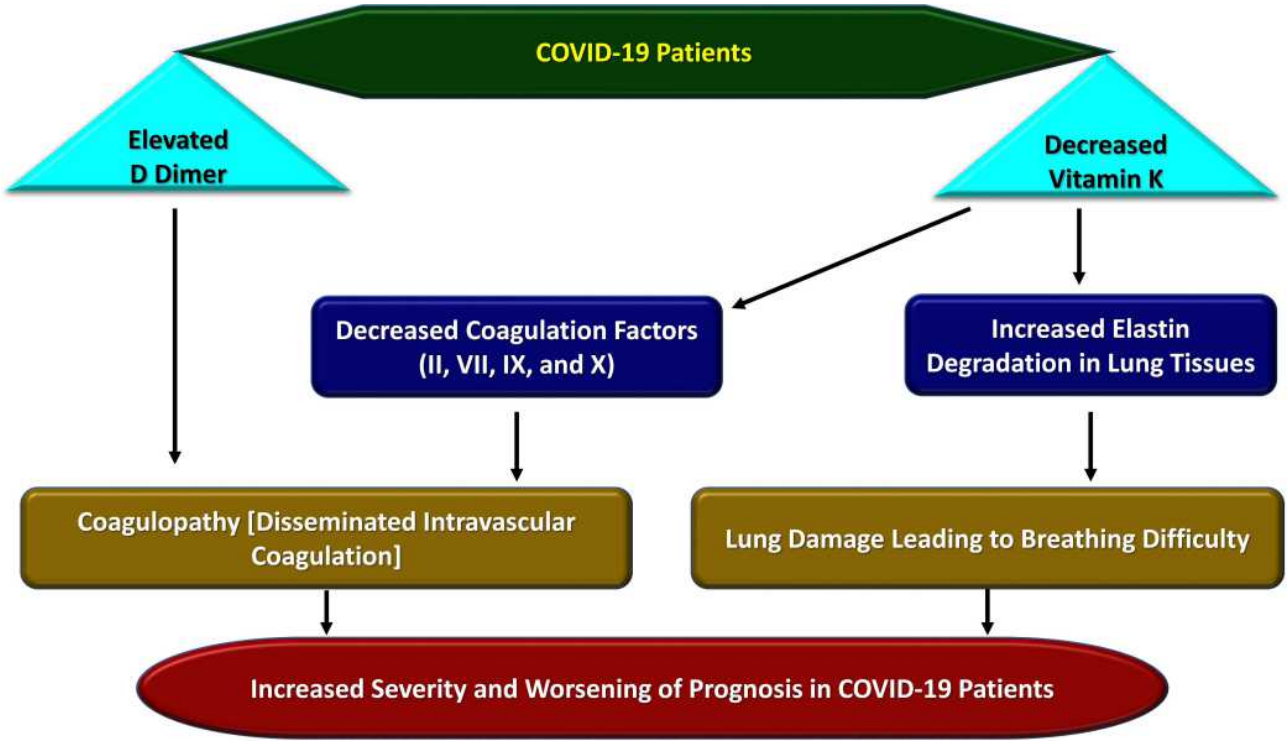

Figure 6 Importance of vitamin K in COVID-19 patients.

levels, it is hypothesized that low vitamin K levels might be associated with severity in COVID-19.[203–205] Furthermore, a study conducted by Dofferhoff et al measuring the level of desphospho-uncarboxylated matrix Gla protein (DP-ucMGP, inversely related to vitamin K status) and comparing between 123 COVID-19 patients and 184 controls concluded that reduction of vitamin K levels in COVID-19 patients than the controls and is related to poor prognosis (Figure 6).[191]

For the treatment of COVID-19 induced coagulopathy, the use of an anticoagulant is recommended. A study concluded that the use of unfractionated heparin (UFH) might be a better choice of anticoagulant for treating coagulopathy in COVID-19 patients when compared to low molecular weight heparin (LMWH).[198] However, the correct dose needs to be established. Simultaneously, the use of recombinant activated factor VIIa (rVIIa) is not recommended for COVID-19 patients.[206] Likewise, Thachil et al[207] suggested the need to switch the patient receiving vitamin K antagonist (VKA) to direct oral anticoagulants (DOAC) for coagulation therapy to reduce laboratory testing frequency monitoring during this pandemic.

Nevertheless, it is not applicable for patients with mechanical heart valves or anti-phospholipid syndrome.[207] Since there is a risk of vitamin K deficiency in patients admitted to ICU, administering vitamin K supplements to patients during admission to ICU might help reduce the risk of vitamin K deficiency and further complications.[200] However, other studies are still needed to verify the results. Notably, the prescription of anti-vitamin K anticoagulants is not recommended for pregnant or lactating women. It may place the newborn at an increased risk of vitamin K deficiency.[208]

Furthermore, prolonged use of broad-spectrum antibiotics like cephalosporins can interfere with vitamin K synthesis by intestinal flora and lower vitamin K absorption level by altering gastrointestinal functioning, which should be considered during the infection.-[209] These studies illustrate that poor vitamin K status is linked to poor prognosis and worse outcomes. Thus, maintained vitamin K2 level is essential for better health, including cardiovascular, bone, and lung health. However, further studies are required to assess whether vitamin K administration improves the severity of COVID-19 patients.

Limitations of the Study

1. Hence, the study is a narrative review that does not follow the PRISMA methodology for Preferred

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Reporting Items for Systematic Reviews and Meta-analyses, Protocols 2015 (PRISMA-P 2015).

2. There are limited data from randomized, double-blind controlled clinical trials to support the efficacy of fat-soluble vitamins in managing COVID-19 infection.
3. Pre-print publications were also used during the review because research in COVID-19 disease is novel and incessantly developing field of study.
4. Also, we did not authenticate the quality of the articles used in this study using scales such as the Newcastle–Ottawa scale due to the presence of pre-print articles.
5. The research has no supporting fund to enable the purchase of articles that are not open to access.

Conclusion

The big data presented by various previous studies depict the efficacy of fat-soluble vitamins such as vitamin A, D, E, and K in immune-modulation and lowering the severity of disease in patients with COVID-19 infection. These vitamins are pivotal in the maintenance and modulation of innate and cell-mediated, and antibody-mediated immune responses. The fat-soluble vitamins are functional in various ways, including increasing the levels of cathelicidins and β-defensins, regulating RONS production, and influencing the acquired immune system by reducing immunoglobulin secretion by plasma cells and pro-inflammatory cytokines production to modulate T cells function, etc. Vitamin A, D, E, and K boost the body's defense mechanism against COVID-19 infection and specifically prevent its complications such as cytokine storm and other inflammatory processes, leading to increased morbidity and mortality overemphasis. However, more detailed randomized double-blind clinical pieces of evidence are required to define the use of these supplements in preventing or reducing the severity of the COVID-19 infection.

Recommendations

Based on the supportive evidence, it is crucial to take vitamins like vitamin A, D, E, and K in recommended portion to maintain a healthy immune system and physiology. Future studies are highly advocated to determine pharmacokinetics and pharmacodynamics with adverse drug reaction profile and cost. Apart from these fat-soluble vitamins, other micronutrients and minerals are also essential in maintaining adequate immunity. Eating vegetables and fruits containing the above vitamins daily is recommended to maintain a balanced diet. Supplementation of vitamin D can prove a crucial step to help prevent a worse prognosis in COVID-19.

Article Highlights

- Micronutrients and vitamins are crucial in maintaining the normal health of an individual.
- Fat-soluble vitamins like vitamin A, D, E, and K have shown some promise in the therapy of COVID-19.
- Vitamin A, with its immunomodulation effects and maintaining epithelial integrity, can prove crucial in SARS-CoV-2 infection.
- Many trials and retrospective studies have supported evidence of the usefulness of vitamin D in COVID-19 patients.
- Vitamin E acts as an immunomodulator and reduces the reactive oxygen species, which help minimize the inflammation-induced damage, yet appropriate dosage and usefulness in COVID-19 are yet to be decided.
- Vitamin K deficiency is associated with various diseases, increasing the severity and mortality in COVID-19 patients with associated co-morbidities.

Professional Annotation

In the light of limited therapeutic strategies for the treatment of viral diseases like COVID-19, research suggests that the exploration of nutritional standards capable of enhancing immune system function at this time is of very high value. Considering this fact, authors have held that a healthy immune system and its ability to function correctly are critical assets for any individual. It is undoubtedly linked to the uptake of several vitamins and trace elements.[1,2] The importance of adequate nutrition remains vital in regulating the body's homeostasis as any sub-clinical deficiency of even a micronutrient could disrupt normal immune functions.[4] In support of this view, vitamin supplementations and well-balanced diets have been recognized to influence immune system functions, particularly in viral infections positively.[4–7] In preventing and treating respiratory viral diseases like COVID-19 cases, proper dietary intake, healthy lifestyle changes, and maintaining acceptable hygienic practices are unique requirements. However, there are difficulties in obtaining a well-balanced diet in many nations due to the various restriction measures set out to curb this virus.

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Notwithstanding this, the uptake of multivitamin–mineral (MVM) supplements in the meantime have been found helpful, particularly for the vulnerable groups.[12] Conversely, malnutrition poses a substantial threat to healthcare systems as it increases mortality and morbidity in many nations across the globe.[13] A possible explanation for this trend has been linked to a higher rate of infectious transmission and delayed recovery, which in no small measure leads to demand for several nutrients.[14]

On a positive note, various vitamins remain beneficial in alleviating viral infections and other respiratory conditions. A classic example is vitamin A, a promising option in treating the COVID-19 pandemic and preventing lung infection. It plays a vital role in body metabolism, regulating immune responses from minute details like the eyesight to functional body organs and reducing diseases' susceptibility.[49,54] In support of its role, Semba et al[62] stated that an adequate uptake of vitamin A supplements reduces morbidity and mortality resulting from infectious diseases such as diarrhea, measles, HIV infections, measles-related pneumonia malaria. Taking a glance at vitamin D, it can be suggested that numerous physiological, hereditary, and environmental factors account for the emerging disparity and fluctuations in the number of confirmed SARS COVID-19 cases and mortality rates globally. This is exemplary in movement restrictions to reduce the exposure of many individuals to COVID-19, which has enhanced their risk of being deficient in vitamin D. Promising results have extensively described vitamin D nutrients as an essential supplement in treating respiratory tract infections, autoimmune diseases, and even pulmonary fibrosis.[91] Next in this category is vitamin E, a beneficial antioxidant therapy in oxidative damages associated with the SARS-CoV-2 virus's viral pathogenesis due to its scavenging effects. Researchers have opined that the impact of COVID-19 is particularly detrimental to the health of vulnerable populations such as the elderly, pregnant women, and children. Older people with severe diabetes, cardiovascular diseases, cancer, etc., are even more susceptible to COVID-19 infection. The uptake of vitamin E by these patients is likely to help the immune function, which increases their chances of infection resistance and decreases mortality that could be triggered by infection. Nevertheless, several studies showed immunoregulatory functions and preventive functions from the oxidative disruption caused by vitamin E. This act has contributed to its recognition as potential agents while treating patients infected with COVID-19. The immunoregulatory process of vitamin E has clinical relevance as it affects a host's susceptibility to viral infection, thereby reducing the risk of respiratory infections.[146] Multiple studies regarding the potential benefits of vitamin E to COVID-19 patients indicated that vitamin E and C in combination could be a beneficial antioxidant therapy for cardiac implications of COVID-19.[1,164–166] In the absence of any known effective treatment for COVID-19, nutrients and food supplements that exert anti-inflammatory and immunomodulatory effects can lay significant protective function.

Despite its possible prospects, a lot still needs to be considered as the use of this nutrient will require a long route in its achievement as a successful therapeutic measure for COVID-19 patients. Recently, researchers started to observe the link between individuals with vitamin K status and COVID-19 outcomes. Coagulopathy is one of the primary features of poor outcomes in patients who develop sepsis from an infection. In the same vein, low vitamin K level appears to be associated with increased elastin degradation,[191,202] preferably degrading the lung tissue, resulting in breathing difficulty in COVID-19 patients. Since COVID-19 patients with severity are associated with co-morbidities such as cardiovascular diseases, type II diabetes, or hypertension, which are linked to reduced vitamin K levels, it is hypothesized that low vitamin K levels might be associated with severity in COVID-19.[203–205]

Finally, an exit strategy for a path back to normalcy is required. It should involve a collective effort towards research and development of new treatments and successful vaccine that stems from vitamins and nutrients that can influence viral infections and protect human health. Therefore, it is crucial to develop more effective and practical approaches to investigate the relevance of fat-soluble vitamins as an adjunct therapy for the COVID-19 pandemic.

Five- to Ten-Year Expectation

Globally, the rapid outbreak of the COVID-19 pandemic is a public health concern as this experience disrupts everyday life activity. Notwithstanding its invasion, minimal evidence-based treatment options are currently available for this infection. Meanwhile, many studies are beginning to recognize the role of different fat-soluble vitamins and micronutrients in combating coronavirus infection. Research has proven their capacity to minimize the severity of this infection. Recent surveys have expatiated that the deficiency of one or more of these vitamins compromises immune response and could cause detrimental effects to the patient.

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However, studies have stated that nutritional strategies for enhancing immunity against viral diseases like COVID-19 have been underexplored, and using these patterns as a therapeutic measure should not be ignored. For instance, the uptake of vitamin C with its prophylactic effect and its ability to exert immune response for growth and repair of body tissues and its ability to reduce lower respiratory tract infection susceptibility is highly beneficial.[33,34] Several evidence support the view that COVID-19 disease is particularly detrimental to the health of vulnerable populations like the elderly, pregnant women, and children. Furthermore, older people with long-term chronic conditions of diabetes, cardiovascular diseases, cancer, etc., are well predisposed to COVID-19 infection. The uptake of vitamin E by these patients is likely to help their immune function, increasing infection resistance, thus decreasing mortality. One more study investigated the potential benefits of vitamin E to COVID-19 patients.[1] Additionally, it was reported that vitamin C regenerates the antioxidant potential of vitamin E,[2,3] and, when administered in combination (vitamin E and C) among critically ill patients, found to be beneficial including COVID-19-infected cases.[1,210–215] Despite these facts, there is limited evidence that suggests the use of vitamin E as adjuvant therapy for COVID-19. Therefore, a clear need to investigate these vitamins' prospects as an effective measure in the treatment of COVID-19 is vital. Although investigations into the effect of vitamin K still seem vague, studies have stated that patients admitted into ICU are potentially at risk of having low levels of this vitamin. Also, there is a need to verify these claims as records have shown that administering vitamin K supplements to patients during ICU admissions might reduce the risk of vitamin K deficiency and further health complications.[200]

Finally, even though big data have been presented in prior studies regarding the efficacy of fat-soluble vitamins in immunomodulation and lowering the severity of disease in patients with COVID-19, more detailed clinical pieces of evidence are required to define the use of these supplements in prevention, prophylaxis or reduction of severity in COVID-19 cases. We hope that in the next 5–10 years, clearer, well-established, and substantial evidence to support the prevention and treatment of diseases like coronavirus and other future epidemics will be obtainable.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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