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Current Perspective on Vitamins and SARS-CoV-2 Disease (COVID-19)

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a highly pathogenic and transmissible coronavirus, has resulted in a pandemic named coronavirus disease 2019 (COVID-19). It has taken over the world in no time causing nearly 5 million deaths and almost 500 million people being affected as of June 2022 causing an extensive burden on healthcare facilities globally. Though the disease onset is via respiratory tract, but it affects almost all organs of the body and due to induction of mutations in the virus, combating with the disease is extremely difficult. The major damage associated with disease is driven through inflammatory pathways in tissues with accompanying cytokine storm mediated mainly by macrophages. Building a strong immune system requires maintenance of a healthy diet along with keeping vitamin and coenzyme deficiencies away. The review focuses on the importance of the vitamins for maintaining a good immune system to reduce the susceptibility to SARS-CoV-2 infection, to fight the infection efficiently, and to reduce the impact of the disease. Vitamins play an essential role in modulating the immune responses to infection via altering the signaling pathways, which can act as potential weapons against the disease. Various water- and fat-soluble vitamins like vitamin B, C, D, and E have crucial roles in mediating primary interferon response, improving innate as well as adaptive functions of immunity and antioxidant properties. The current understanding about the supplementation of various vitamins as an adjunct therapeutic strategy to fight COVID-19 disease has also been discussed.

Keywords
- COVID-19
- vitamins
- vitamin D
- micronutrients
- inflammation
- cytokine storm

Introduction

Coronavirus disease or COVID-19 is an extremely widespread infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus, member of the *Coronaviridae* family with positive-sense single-stranded RNA genome. Previously, human coronaviruses were known to be linked to mild respiratory tract problems, causing 15 to 25% of all "common colds," until the outbreak of SARS in 2002 and Middle East respiratory syndrome (MERS) in 2012.[1] The first case of novel coronavirus was reported in December, 2019 in Wuhan, China, which has now rapidly spread to other countries across the world due to its high mutation rate and rapid evolution, thus developing a severe pandemic. Despite tremendous efforts and vaccination drive as of April 2021, more than 149 million

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cases of COVID-19 have been recorded worldwide along with 3 million deaths as reported to the World Health Organization (WHO).[2]

COVID-19 is predominantly acquired orally with a wide range of clinical manifestations from asymptomatic forms to mild symptoms like dry cough, fever, fatigue, and severe cases including acute respiratory distress syndrome (ARDS) and multiorgan dysfunction.[3] Although the exact pathophysiology of SARS-CoV-2 still needs to be explored, it is already known that the virus uses angiotensin-converting enzyme 2 (ACE-2) as receptor via the spike protein for access to the host cells in the respiratory tract and ultimately lead to ARDS and pulmonary edema.[4] Patients infected with SARS-CoV-2 also show increased circulating levels of proinflammatory cytokines, the so-called "cytokine storm," leading to a hyperinflammatory state.[5]

Till date, some vaccines and treatments have been approved for the disease but none of the above are entirely effective against it, making it necessary to maintain optimum levels of personal hygiene and good immunity for its prevention. One of the major preventive factors is maintaining a diet rich in essential proteins, vitamins, and minerals. Healthy diet is the best way to strengthen the immune system and to reduce the susceptibility to viral infections including COVID-19.[6] With existing knowledge regarding the vitamins playing pivotal roles in supporting both innate and acquired immune responses, the vitamins supplementations have gained much attention during the current pandemic. Also, anti-inflammatory properties of several vitamins are well elucidated.[7] Notably, uncontrolled inflammation is a key component in COVID-19 pathogenesis, and in the absence of any specific treatment strategy, vitamin supplementation can act as an important weapon against COVID-19. This review aims to investigate the current findings on identifying the potential value of vitamin supplementation in the fight against COVID-19.

Potential Role of Vitamins Supplementation against COVID-19

The contribution of vitamin supplementation in enhancing the immunity and exhibiting their anti-inflammatory role has long been known. Vitamin A and vitamin B complex are already known for regulating the production of proinflammatory cytokines. Not only this, vitamin D also promotes the synthesis of anti-inflammatory cytokines and antimicrobial peptides that help in inhibiting cytokine storm.

Evidences suggest that different vitamins like vitamin C, vitamin K, and vitamin D and members of vitamin B mediate anti-inflammatory actions by inhibiting NF-κB, an important member of inflammatory cascade.[8,9] Moreover, vitamin C is gaining attention of many researchers due to the fact that antioxidant properties of vitamin C can be used against cytokine storm-mediated oxidative stress in ARDS.[10]

Notably, vitamin deficiencies can lead to weakened immune system and can decrease resistance to infections. Epidemiological studies have confirmed the link between vitamin D deficiency and increased susceptibility to respiratory viral infections.[11] Thus, exploring the role of each vitamin in context to COVID-19 will be of great use.

Vitamin A

Vitamin A, a fat-soluble vitamin, enhances the immune related functions and plays a regulatory part in cellular and humoral immunity. Retinoids stimulate natural killer (NK) cells, dendritic and innate lymphoid cells.[12] It plays a crucial role in maintaining morphology and functional maturation of the epithelium thus enhancing antiviral properties. Thus, reduced vitamin A status has been correlated with improper functioning of neutrophils, macrophages, T-and B-cells and an increased risk of acquiring viral infections. Also, the subjects with deficit vitamin A levels showed morphological changes in pulmonary epithelial and parenchymal lining, causing respiratory dysfunction, as reviewed by Iddir et al.[13] This information is relevant while considering the COVID-19 effects on lung function. Yuan et al depicted that an agonist for retinoic acid (RA) receptor α (Am580) serves as an effective inhibitor of SARS-CoV by disrupting sterol regulatory element binding protein-mediated lipogenic pathways.[12] Another study suggested vitamin A as a treatment of coronavirus infection.[14] A scientific report proved that dietary supplementation with vitamin A increased antibody generation in response to the vaccine in calves. Moreover, lower vitamin A with viral infestations led to an increased damage to epithelium in chickens. These observations also correlate with clinical reports, which stated an increased susceptibility to SARS-CoV with reduced vitamin A amounts in various diseased models. Vitamin A oral supplementation is currently being tested as COVID-19 therapeutics.[7] Vitamin A supplementation to deficient subgroups reduces infection with *Mycoplasma pneumoniae*, a secondary infection seen associated with COVID-19.[15] With bioinformatics-based tools, several potential targets of vitamin A against COVID-19 like "*MAPK1, IL10, EGFR, ICAM1, MAPK14, CAT* and *PRKCB*" have been identified.[16] Also a literature report suggested a possibility of vitamin A usage for rectifying olfactory dysfunction in COVID-19 infection that might help in regenerating olfactory neurons.[17]

However, some other observations from pooled analysis suggested no effect on symptoms or incidences of lower acute respiratory tract infection (RTI) after vitamin A administration. Also, in old age individuals, poor association was found between circulatory carotene and retinal levels with immune response to vaccine, signifying that the immune function was not appreciably influenced upon varying these dietary micronutrients in elderly population. Even in children, vitamin A administration had no influence upon risk assessment of the lower respiratory diseases. Similar results were revealed by a meta-analysis study, where acute RTI incidence did not corelate with the supplemented subset in developing nations as reviewed by Iddir et al.[13] Taking above observations into consideration the role of vitamin A is protective against respiratory tract infections and hence must be considered for its therapeutic value against COVID-19.

Vitamin B Complex

SARS-CoV-2 infection results in increased proinflammatory cytokines mediating its effect on both innate and adaptive immune response. Vitamin B is important for the activation of both innate and adaptive immune responses and it also assists in maintaining endothelial integrity, reducing proinflammatory cytokine levels, preventing hypercoagulability; therefore, it is imperative to unveil the effects of vitamin B complex in reference to inflammatory pathways and COVID-19.[18]

Vitamin B1

Thiamine or thiamine pyrophosphate is an essential water-soluble vitamin crucial for regulating cellular metabolism. Vitamin B1 exhibits an anti-inflammatory role by influencing proapoptotic proteins, cytochrome C release, and MAPK activity.[9] It has also been reported that vitamin B1 deficiency induces cytokine storm by producing high amounts of proinflammatory cytokines like IL-1, tumor necrosis factor-alpha (TNF-α), and IL-6 indicating that adequate amount of thiamine is essential during COVID-19 infection.[19]

Vitamin B2

Vitamin B2 or riboflavin is an important precursor of coenzymes needed for flavoprotein enzymatic reactions. According to Lindsay et al, pathogen reduction with riboflavin-ultraviolet (UV) decreases the infectivity of CoV-2 in whole blood and plasma, thus suggesting that vitamin B2 infusion can be helpful against COVID-19. Not only this, riboflavin insufficiency can induce the intensification of proinflammatory activity of adipocytes that leads the way to chronic inflammation.[20]

Vitamin B3

The immense demand for vitamin B3 or niacin is due to its pivotal role in oxidation–reduction reactions. One of the clinical studies suggests that niacin is a strong agent to decrease proinflammatory cytokines interleukin-1 (IL-1), IL-6, and TNF-α.[21] Besides this, niacin also inhibits the enzymatic activity of M^{pro} protease by binding to its catalytic pocket.[22] On molecular levels as a part of the innate response, PARPs (poly ADP ribose polymerase) get activated due to DNA damage and are required for the inhibition of viral replication.[23] Continued activation of PARP will lead to their depletion at one time. Previous data indicated that nicotinamide adenine dinucleotide (NAD) infusion may restore PARPs' function for inhibition of viral replication and thus support in innate response towards COVID-19.[24] Furthermore, studies indicated that supplementation of NAD precursors like nicotinamide ribose helps combat COVID-19 infection by increasing activity of Sirtuins, reducing oxidative stress and are therefore considered as potential therapeutics for reducing hyperinflammation.[25]

Vitamin B5

Vitamin B5 usually known as pantothenic acid is used for the synthesis of acetyl CoA required in the metabolic pathway of proteins, carbohydrates, and fats. Apart from this, it also plays an important role in decreasing inflammation, improves mental health, and is an important regulator of innate and adaptive response. However, vitamin B5 or the mechanisms of its action in context to COVID-19 has not been studied yet.

Vitamin B6

Pyridoxine is a water-soluble vitamin; its active form pyridoxal phosphate (PLP) has a supporting role in inflammation, metabolism, and immunomodulation. In this context, PLP supplementation has been proposed to decrease proinflammatory cytokines, prevent hypercoagulability, and support endothelial integrity which tends to diminish COVID-19 symptoms.[26] Insufficient levels of PLP have also been observed in type-2 diabetes patients, persons with long suffering cardiovascular disease, and in the elderly, the groups who are at an increased risk of poor COVID-19 outcomes.[27] According to Qian et al, pyridoxine deficiency decreased the lymphocyte number and interleukins production that are an important part of adaptive response during COVID-19 infection.

Vitamin B9

Vitamin B9/ folate is a water-soluble vitamin involved in one carbon metabolism and is essential for DNA and protein synthesis. It has been studied that folic acid inhibits furin protease and $3Cl^{pro}$ (coronavirus main proteinases).[28] Hence, folic acid decreases the rate of replication in these two ways. Folic acid supplementation reverses the uncoupling of epithelial nitric oxide synthase (eNOS) restoring nitric oxide production along with an affect on endothelial function therefore, showing an anti-inflammatory and antioxidant activity.[29] Moreover, the expression of nuclear factor kappa B (NF-κB; proinflammatory molecules) and cyclooxygenase-2 is also under the control of eNOS. As NF-κB is a regulatory factor for proinflammatory cytokines, folic acid is known to reduce homocysteine induced NF-κB.[30]

Vitamin B12

Vitamin B12 is necessary for the synthesis and division of red blood cells and white blood cells. Vitamin B12 deficiency gives rise to hyperhomocysteinemia further leading to increased inflammation, reactive oxygen species (ROS), and endothelial dysfunction. Patients with COVID-19 show the symptoms like elevated homocysteine, hypercoagulopathy, and increased oxidative stress that are parallel to that of vitamin B12 deficiency.[31] Romain et al showed that vitamin B12 also exhibits anti-inflammatory effects similar to folate by regulating NF-κB. Interestingly, a recent study manifested that methylcobalamin supplementations tends to decrease COVID-19-related symptoms and organ damage.[32] Various roles of vitamin B have been compiled in ►**Table 1**.

Vitamin C

Vitamin C is a water-soluble vitamin known for its antioxidant role. COVID-19 patients show increased number of neutrophils but are lymphopenic. Researchers also reported that vitamin C suppresses antiviral T cells through

Table 1 Role of different vitamins of B complex

Vitamin	Physiological role	Role in COVID-19	Recommended (per day)
B1 (Thiamine)	• Important cofactor for enzymes involved in carbohydrate and amino acid metabolism[68] • Antioxidant role	• Anti-inflammatory (inhibits NF-κB pathway)[9] • Antioxidant role[19]	• 1.1 mg
B2 (Riboflavin)	• Precursor of enzymes needed for reactions of flavoproteins[69]	• Riboflavin-UV in combination reduces the infectivity of CoV-2 in whole blood and plasma[70]	1.1mg
B3 (Niacin)	• Cofactor in oxidation reduction reactions[71] • Reduction in pro-inflammatory cytokines[21]	• Potent inhibitor of M^{pro} protease (needed for viral replication)[2263,64] • Increase sirtuins activity[72] • Relieves oxidative stress	14 mg
B5 (Pantothenic acid)	• Synthesis of coenzyme A (essential for carbohydrate, fatty acid, proteins metabolism)[73] • Wound healing[74]	• Not studied yet	5 mg
B6 (Pyridoxine)	• Red blood cell synthesis[75] • Vital for metabolic pathway of fats, carbohydrates and proteins	• Prevents hypercoagulability • Inhibits release of proinflammatory cytokines.[26]	1.3 mg
B9 (Folate)	• DNA and protein synthesis • Transfers one carbon units in metabolic pathways (one carbon metabolism)[76]	• Inhibits furin protease (viral entry)[28] • Inactivates protease $3Cl^{pro}$ (virus replication)[77] • Anti-inflammatory (regulate NF-κB) and antioxidant activity[78]	400 μg
B12 (Methylcobalamin)	• Important for synthesis of DNA • Red blood cells' and white blood cells' division	• Exhibits anti-inflammatory effects by regulating NF-κB[79] • Methylcobalamin supplements tends to decrease COVID-19 related symptoms[32]	2.4 μg

Abbreviations: COVID-19, coronavirus disease 2019; NF-κB, nuclear factor-kappa beta; UV, ultraviolet.

augmentation of interferon (IFN) production and thus it is helpful in maintaining normal neutrophils to lymphocytes ratio.[33]

Neutrophils bind to platelets that induce them to form neutrophil extracellular traps (NETs).[34] NETs play both protective and detrimental roles during viral infections. Small pathogen like viruses gets entrapped inside NETs as found during influenza and syncytial respiratory virus infection.[35] On the other hand, NET-associated antimicrobial factors may have toxic effects for the host and their increased production may cause tissue damage.[36] Additionally, vitamin C has a prime role in clearance of dead neutrophils from the site of infection; vitamin C also weakens NET formation in healthy people.[37] Furthermore, it counteracts oxidative stress, thus preventing NF-κB-driven cytokine storm too. However, vitamin C treatment must be started before the requirement of intensive care unit to maintain normal neutrophil to lymphocytes ratio that may prevent SARS-CoV-2 patients to worsen toward ARDS.[38] Vitamin C may also help in decreased alveolar epithelial damage by preventing excess activation and aggregation of neutrophils.[7] In addition, SARS-CoV downregulates ACE-2 receptor via its spike protein that contributes to multiple organ injury in COVID-19. Moreover, SIRT-1 is expressed next to the promoter region of ACE-2 gene; hence, ACE-2 transcript is under the epigenetic control of SIRT-1. Vitamin C is known to upregulate SIRT-1 consequently leading to increased expression of ACE-2.[39] Therefore, vitamin C is a potential rescue therapy for COVID-19.

Vitamin D

In context to COVID-19 pandemic, vitamin D is one of the most extensively studied vitamins due to its crucial role in immune response against viral diseases. The potential roles of vitamin D with respect to its structure and other cellular and immune related functions has been summarized in the ►**Table 2**. Scientific literature has discovered that 91% of indoor workers possessed suboptimal vitamin D status.[40] Its role as immune modulator in viral acute RTIs came from a study involving patients possessing mutated vitamin D receptors.[15] Jain et al illustrated that administration of vitamin D with L-cysteine decreased oxidative stress in vitamin D deficient mouse model.[41] In a rat model of ARDS, calcitriol upregulated ACE-2 and downregulated renin and angiotensin-II indicating vitamin D hinders the advancement of infection induced ARDS. Furthermore, a meta-analysis demonstrated a 12% shielding effect of vitamin D supplementation and risk of acute RTIs that raised up to 19% either through a daily or weekly treatment relative to a monthly bolus. Although, 70% of the protective effect was observed when the deficiency was corrected.[7] A current analysis including 11,000 subjects depicted a protective role of vitamin D administration in acute RTIs in 25 random control

Table 2 Potential roles of vitamin D

	Roles	References
Structural-related functions	-Maintenance of lung structure, size, volume, and functions -Upregulation of ACE-1, ACE-2	7,40
Cellular functions	-Induction of autophagy -Stimulation of apoptosis	41,47
Immune-related functions	Differentiation and killing potential of monocytes	14
	Supports antigen presentation	14
	Augmentation of natural protective barriers	7
	Downregulates NF-κB that led to increased anti-inflammatory, reduced proinflammatory factors (IL-6, IL-8, IL-12, COX-2, GM-CSF, IL-4, IL-5, VCAM-1, ICAM-1, E-selectin)	80
	Affects the production of enzymes, i.e., iNOS, PLA2	81
	Generation of antimicrobial peptides like cathelicidins (LL-37), defensins	45,81
	Immunosuppression by activating T-regulatory cells	45
	Antioxidant functions	41

Abbreviations: ACE-1, angiotensin-converting enzyme 1; Cox2, cyclooxygenase-2; GM-CSF, granulocyte-macrophage colony-stimulating factor; ICAM-1, Intercellular adhesion molecule-1; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; NF-κB, nuclear factor-kappa beta; PLA2, Phospholipase A2; VCAM-1, Vascular cell adhesion molecule-1.

trials.[42] Similarly in one more clinical trial, a 100,000IU intake of vitamin D once in a month declined acute RTIs in older patients, with respect to a standard dose of 12,000IU/month.[43]

The cocooning or indoor confinement might be the main cause of vitamin D deficiency that was aggravated during COVID-19 lockdown. The prevalent vitamin D deficiency in Northern Hemisphere has been linked to inflammation suppressive role of vitamin D as evident in severe COVID-19 subjects.[40] The correction of vitamin D deficient levels in COVID-19 individuals represses an adhesion-related molecule (CD26/DPP4) via which the COVID-MERS viruses are thought to access a host cell. The interaction of spike protein with ACE-2 translocates the virus inside the host cell, thereby diminishing ACE-2 and probably improving the pathogenesis of respiratory infections. Also, a negative association was revealed between vitamin D levels and COVID-19 mortality in many European countries as reviewed in ref.[7] Similarly, SARS-CoV-2 patients in Switzerland had significantly lower vitamin D status (11.1 ng/mL) relative to the negative cases (24.6 ng/mL).[42] Overall, the usage of multivitamins including vitamin D might decrease inflammation in SARS-CoV-2 infection and can serve as an adjunct in COVID-19 therapeutics. Vitamin D is known to affect the risks, severity, morbidity, and mortality of numerous pulmonary diseases and may also have similar effects in case of COVID-19. However, Rhodes et al suggested that a few nations have low mortality, which signifies the role of vitamin D in determining outcomes from COVID-19.[44] Also, the circulatory 25(OH)D declines with age, which parallels the mechanism of increased COVID-19 fatality with increasing age.[45] In relation to COVID-19, khoramipour considered that 1000 to 2000 IU/d of vitamin D was sufficient to enhance respiratory immunity.[46] Moozhipurath et al depicted an inverse connection of UV-B exposure, which is related to vitamin D production thus showing inverse correlation of vitamin D production with COVID-19 mortality. There is 17.3% risk of COVID-19 among individuals with severe vitamin-D deficiency; however, it was 14.6% in individuals having vitamin D within normal limits. Vitamin D diminishes proinflammatory cytokines that are involved in COVID-19 manifestation, shifts cell population from Th1 to Th2 type, thus preventing cytokine storm. The data from studies worldwide correlates severe 25(OH)D deficiency with COVID-19 that caused coagulopathies, disrupted immune activity, thrombocytopenia, and raised prothrombin time, suggesting vitamin D supplementation as a potential therapeutic regime as reviewed by Vyas et al.[41]

Adding to the advantages of vitamin D, recent findings showed raised number of white blood cells after vitamin D ingestion in COVID-19 cases.[47] Further as treatment to COVID-19, the combination of vitamin D with melatonin and a triple therapy comprising of quercetin, calcitriol and estradiol is advised.[48] A trial conducted by University of Granada involving 200 subjects proposed a dosage of 25,000 IU of calcitriol in preventing and curing COVID-19.[49]

Surprisingly, contrasting evidences to the above-mentioned information do exist, as investigations of UK biobank and The Royal Society revealed no clue to conclude vitamin D as a solution in COVID-19 infections. However, they discerned that COVID-19 disproportionately affects Black and minority ethnic subsets irrespective of vitamin D levels.[42] Studies on RTIs detected nonsignificant differences between the high-dose (2000IU/d) versus standard-dose (400IU/d) except in the severe deficient cases.[43] "Scientific Advisory Committee on Nutrition" verified that the present evidences do not support calcitriol administration to avert acute RTIs in the individuals.[40] Moreover, calcitriol deficiency has also been linked with numerous disorders such as diabetes, hypertension, cognitive dysfunctions, and cardiac illness, making one more prone to COVID-19. The reason for

complicated role of vitamin D might be due to its different doses, course of therapy, study settings, study subjects and interval, definitions, and verification of the outcomes.[40]

Thus, the existing studies suggest a preventive role of vitamin D supplementation against COVID-19; however, exceeding supplementation causing hypervitaminosis must also be taken into consideration as a consequence.

Vitamin E

Vitamin E is a fat-soluble vitamin with an antioxidant activity along with important immunomodulatory effects. Excessive ROS production and lipid peroxidation have been observed in ARDS as well as in vitamin E deficiency.[50] Vitamin E supplementation improves the immune function by T cell activation, enhancing NK cell activity by modulating NO levels, increasing macrophage phagocytic activity along with the decreased IL-12 production and regulating function of dendritic cells.[51] In analysis of male Finnish smokers, vitamin E infusion was found to reduce the risk of pneumonia in older subjects (>60 years) but no significant effect was found on respiratory infection in another study of Dutch older adults.[52] A study in year 2020 showed the mitigating effect on cardiac injuries in COVID-19 patients with combined supplementation of vitamin C and E. However, another group of researchers found that risk of pneumonia was increased in 50 to 69 years old smokers due to vitamin E administration.[52]

A randomized double-blind trial reported that vitamin E supplementation (200IU/d) for 1 year decreased the risk of upper respiratory tract infections.[53] Therefore, it can be speculated that vitamin E might be helpful in prevention of COVID-19 infection. Not only this, one study had already indicated that vitamin E administration is more helpful in reducing elevated oxidative stress than vitamin C in influenza patients, but both vitamin C and E in combination even reduce lipid peroxidation.[54] Study by Dewald in 2021 indicated the greater number of COVID-19 patients (36%) were linked with high dose of vitamin E (>15.5mg/mL) that is attributed to vitamin E supplementation. Patients with intracranial hemorrhages also have the vitamin E levels ranged between 23 and 46.7 mg/mL and the deceased patients show even higher levels of vitamin E (111.7mg/mL). Altogether, this suggests that although vitamin E has protective effects in context to COVID-19, it is necessary to evaluate the necessary supplement intake and patients' needs in order to avoid overdosing and thus toxicity.

Vitamin K

Vitamin K is another fat-soluble vitamin recognized for its crucial role in coagulation via prothrombin (clotting factor II). Vitamin K also activates anticoagulant protein S, required for thrombosis prevention. These pleiotropic roles of vitamin K in blood clotting could be very important in the context of severe COVID-19 where coagulopathy has been well known. The key mediators behind this hypercoagulable state are the increased levels of proinflammatory cytokines, the cytokine storm observed during COVID-19 infection. Therefore, special attention should be paid to vitamin K levels in COVID-19 patients with heart-related comorbidities especially those taking vitamin K antagonists.[55]

Apart from this, vitamin K is also essential for carboxylation and activation of many proteins including osteocalcin in bone and matrix Gla protein (MGP) that protect against vascular calcification.[56] Increased circulating levels of inactive MGP (desphospho-uncarboxylated MGP) in COVID-19 patients exhibiting elastic fiber pathologies indicate the link between vitamin K deficiency and COVID-19.[57]

Other than its role as cofactor for different enzymes, vitamin K also shows significant anti-inflammatory effects. One mechanism for such effects is the inhibition of IL-6, a major cytokine in NF-κB signaling. Taking into consideration the anti-inflammatory actions of vitamin K, another study suggested that vitamin K deficiency can cause activation of the Th2 storm with increased production of IL-6 and thus suggesting its link with cytokine storm in COVID-19 patients.[58] However, further investigations are required to understand the interrelationship between vitamin K and COVID-19.

Discussion

COVID-19 had caused drastic health crisis worldwide. Although a few vaccines and treatments have been approved for COVID-19, due to the lot of people being infected in the COVID-19 scenario, clinical preventive measures are required to reduce the catastrophic effects of COVID-19. One such approach is maintaining optimum vitamin levels and a balanced diet to strengthen the immune system. In this review, we have highlighted the potential role of vitamin supplementation in the fight against COVID-19 taking into consideration the pleiotropic roles played by vitamins that are required for a healthy immune system (summarized in ►**Fig. 1**). Retinoids (vitamin A) perform various immune functions by regulating multiple processes like actions of IFN-I, phagocytic and oxidative activity of macrophages, function of immune cells, production of IL-2, TNF-α, and differentiation of Th1 and Th2 cells.[12,59] In relation to coronavirus it has been known that retinoid signaling inhibits coronavirus and RA receptor α (Am580) serves as a potential SARS-CoV inhibitor.[60] Also, vitamin A ingestion via diet raised the antibody production in response to inactivated bovine coronaviruses.[61] Apart from this, there are existing reports that suggested either negative or no associations of vitamin A supplementation with risk of reducing COVID-19 infections. However, as contradictory studies exist in the present literature, it is difficult to say whether vitamin A intake is fully advantageous against COVID-19.

Evidences from literature also demonstrated anti-inflammatory, antioxidative, as well as anticoagulopathic function of vitamins that have been proven to be beneficial in fighting disease. Vitamin C, D, K, and B have a peculiar regulatory function in mediating the innate immunity via regulation of pro- and anti-inflammatory pathways. These vitamins either inhibit the production of proinflammatory cytokines like IL-1, IL-6, and TNF-α or promote their anti-inflammatory

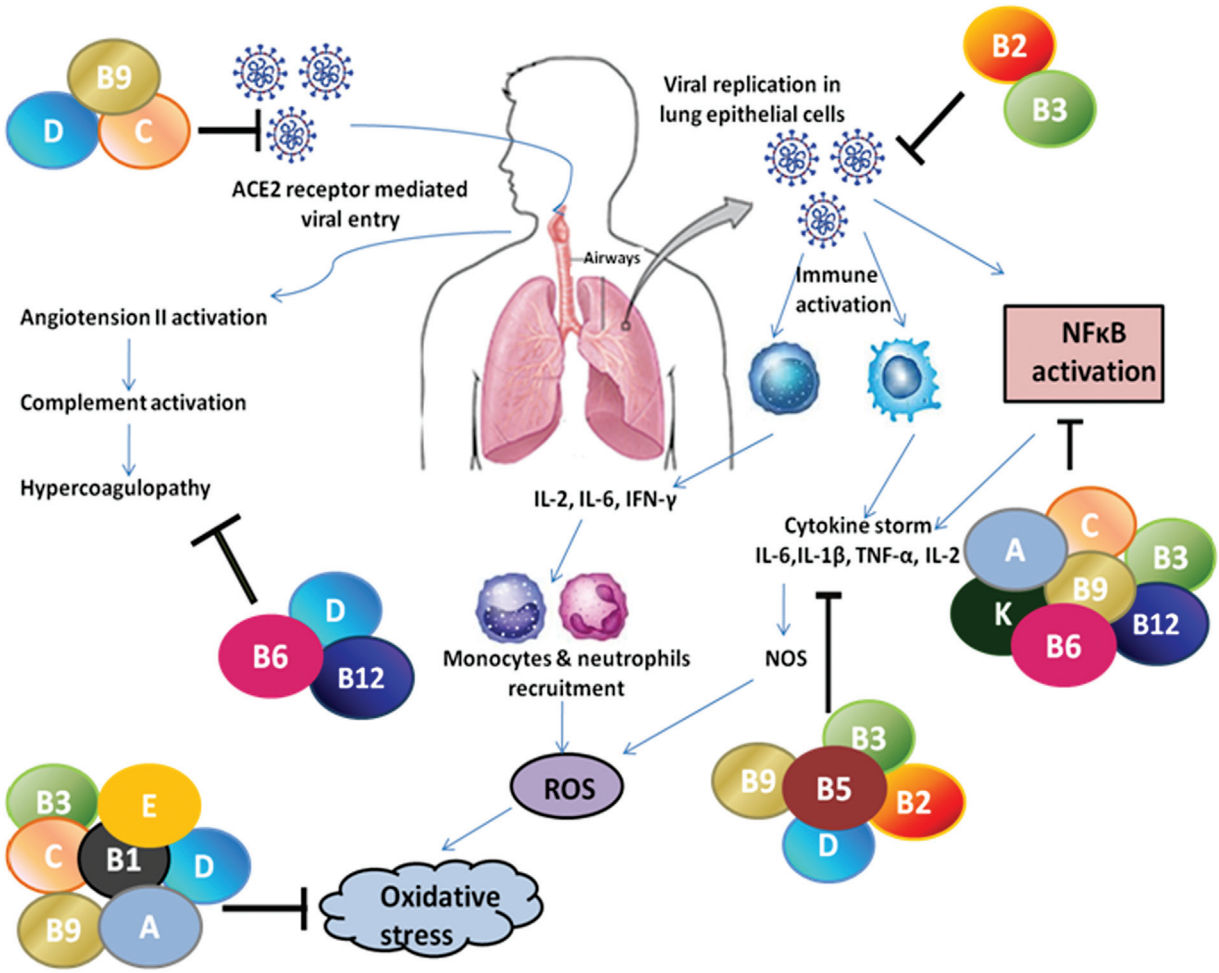

Fig. 1 Potential role of various vitamins against the pathogenesis of coronavirus disease 2019 (COVID-19). ACE-2, angiotensin-converting enzyme 2; IFN-γ, interferon γ; IL-2, interleukin-2; NOS, nitric oxide synthase; NF-κB, nuclear factor-kappa beta; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α. Vitamins are depicted by the alphabets and numbers.

effects by inhibiting NF-Kb.[9,26] Moreover, both vitamin E and B9 modulate NO production that add to their anti-inflammatory activities.[29,62] In addition to their anti-inflammatory role, vitamin B family is found to be beneficial in respiratory tract infections like COVID-19 because of their role as antioxidants. As inflammation is also accompanied by increased ROS production and lipid peroxidation in COVID 19, vitamin E, C, B1, B9, and B12 mediate their vital functions by acting as strong antioxidant agents.

Some of the vitamin B complex are also known to inhibit the activity of the enzymes essential for SARS-CoV-2, like folate inhibits the furin protease and niacin blocks M^{pro} protease.[63,64] Moreover, vitamin C is a potential rescue therapy for COVID-19 because its supplementation opposes oxidative stress-induced cytokine storm by preventing NF-κB activation and neutrophil sequestration.[10] Furthermore, combined treatment of vitamin C and E reduces oxidative stress and lipid peroxidation.[54] Vitamin D has a versatile impact in combating lung diseases by functions such as monocyte differentiation to macrophages, inflammatory cytokine production, antigen presentation, maintenance of cell-to-cell junctions, and production of antimicrobial peptides like cathelicidins and defensins. Moreover, the sufficient consumption of vitamin D might help to reduce the prevalence, symptom severity, death, and recovery rate of COVID-19 patients.[15] Further as therapeutics or prevention strategies to COVID-19, a few combination therapies have been suggested including quercetin or estradiol.[65]

Besides this, it has been noted that severe 25(OH)D deficient environment with coronavirus infection can cause disruption in coagulation profile namely reduced platelet count and raised prothrombin time that might be rectified after 25(OH)D supplementation.[41] Vitamin B6 and B12 are also known to prevent hypercoagulopathic state and thus sum up to be beneficial in COVID-19 infection. Apart from this, vitamin K also has a pleiotropic role in blood clotting.

Till scientific evidence come forward, excessive doses of vitamins should be avoided. Excessive vitamin D intake could result in hypercalcemia and renal stones.[66] Also, vitamins can act as epigenetic modulators and can alter transcriptional and translational switch of diverse inflammation related markers.[67] All these evidences suggest that adequate vitamin consumption is essential for precise body functioning in the COVID-19 scenario.

Data Availability Statement
As this is a review article, thus the data added in has been taken from the available literature.

Authors' Contributions
J.K. supported the conceptualization and the objective of the article. D.R., H.G., R.S. carried out the writing of the article. D.L. contributed by editing the article so as to make it a crisp read. J.K. also contributed by conceptually revising the article on a critical level.

Conflicts of Interest
None declared.

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