Immunol Genet J, Vol. 6, No. 1, March 2023, pp.6-20 DOI: https://doi.org/10.18502/igj.v6i1.16339

Review Article

Vitamins in COVID-19: Probable Mechanisms and Efficacy

Soroush Najdaghi[1,2], Sepideh Razi[1,3], Amene Saghazadeh[3,4,5*]

[1] *Cancer Immunology Project (CIP), Universal Scientific Education and Research Network (USERN), Tehran, Iran*
[2] *Isfahan Neurosciences Research Center, Isfahan University of Medical Sciences, Isfahan, Iran*
[3] *Research Center for Immunodeficiencies, Children's Medical Center, Tehran University of Medical Sciences, Tehran, Iran*
[4] *Systematic Review and Meta-analysis Expert Group (SRMEG), Universal Scientific Education and Research Network (USERN), Tehran, Iran*
[5] *Dietitians and Nutrition Experts Team (DiNET), Universal Scientific Education and Research Network (USERN), Tehran, Iran*

Received: 07 January 2023; Accepted: 28 February 2023

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), also known as coronavirus disease 2019 (COVID-19), is a pandemic crisis. Little is known about the treatment of this disease, and supportive care is the only therapy for patients with COVID-19. It has been shown that mineral vitamins have an important role in improving the health status of patients, and several studies have investigated their effects on patients affected with other coronaviruses. In this review, the probable mechanisms of action of each vitamin against COVID-19 infection, the benefits of co-therapy of vitamins with other supplements, and the recommended daily intake of each nutrient are discussed.

Keywords: COVID-19; Cytokine Storm; Nutrients; SARS-CoV-2; Severe Acute Respiratory Syndrome Coronavirus 2, Vitamins

***Corresponding Author:** Amene Saghazadeh, MD
Systematic Review and Meta-analysis Expert Group (SRMEG), Universal Scientific Education and Research Network (USERN), Tehran, Iran
E-mail: amene.saghazadeh@gmail.com

How to cite this article
Najdaghi S, Razi S, Saghazadeh A. Vitamins in COVID-19: Probable Mechanisms and Efficacy. Immunology and Genetics Journal, 2023; 6(1): 6-20. DOI: https://doi.org/10.18502/igj.v6i1.16339

Introduction

Coronaviruses are a species in the Coronaviridae family. They include human coronavirus 229E (HCoV-229E), HCoV-OC43, severe acute respiratory syndrome (SARS)-associated coronavirus (SARS-CoV), Middle East Respiratory Syndrome-CoV (MERS-CoV), and HCoV-NL63 detected in humans. A new coronavirus isolated from humans is recognized as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), due to its similarities to SARS-CoV (1-3). SARS-CoV-2 emerged in December 2019 in Wuhan (China), and it soon became widespread so that World Health Organization (WHO) declared the outbreak of SARS-CoV-2 as a pandemic crisis (4, 5). SARS-CoV-2 causes multisystem complications involving the central nervous system, cardiovascular system, endocrine system, and the skin, collectively referred to as coronavirus disease 2019 (COVID-19) (4, 6-11). Few publications have discussed the difference between SARS-CoV and SARS-CoV-2 in pathogenesis. However, ex-vi

vo experiments on human lungs highlighted that SARS-CoV-2 could induce more amount of pro-inflammatory mediators along with decreased anti-viral immunity and therefore cause a more severe phenotype of the disease (12, 13). Although primary immunodeficiency appears to be not a risk factor for COVID-19 and related outcomes (14, 15), genetic background, hyper-inflammatory shock, and cytokine storm, a phenomenon characterized by fulminant hyper-cytokinemia, are associated with multi-organ failure and increased mortality rate in patients with COVID-19 (4, 14, 16-18).

Of note, SARS-CoV-2 and SARS-CoV overlap at the point of cell entry. Both these hCoVs have been shown to engage the angiotensin-converting enzyme 2 (ACE2) receptor for cell entry (19). ACE2 engagement by the virus would affect the function of the renin-angiotensin system (RAS), which involves ACE2, angiotensin II (Ang II), and angiotensin receptor 1 (AT1), and this might contribute to creating an inflammatory environment in lung tissue providing the way for the viral invasion in alveolar type 2 (AT2) cells (20, 21).

Mineral vitamins are categorized into water (vitamins B and C) and fat-soluble (vitamins A, D, E, and K) nutrients. They take many crucial actions to improve the health status of the patients. Vitamin supplements have the potential to revive either susceptible or afflicted patients with COVID-19 by helping with the release of specific immunoglobulins from immune cells (22), provoking immunoregulatory cells, modulating inflammatory responses (23, 24), and regulating reactive oxygen species (ROS) generation (25) and RAS function (26). Also, they can restore the balance between prothrombotic and antithrombotic pathways directly or even with their serum-transporting proteins (27, 28). No specific therapeutic agent is available for COVID-19, and supportive care is the only treatment for infected patients. The present review addresses what vitamins can potentially bring to the practice in the COVID-19 pandemic condition. It discusses the molecular mechanisms of action for each vitamin, followed by evaluating the plausible efficacy of each vitamin as an add-on therapy for COVID-19.

Vitamin A

Vitamin A, a fat-soluble vitamin, has a potential role in fetal organ development, proliferation of cellular and humoral immunity, and may increase the immunity accomplished by vaccination properly (29). Studies imply that the burden of a significant portion of respiratory tract infections may hasten among patients with low dietary vitamin A intake (30). This may be due to the role of vitamin A in maintaining the normal pulmonary epithelial lining structure in the parenchyma that protects the respiratory system against viral and bacterial invasion (31). In the first trimester of 2020, ENTUK (British Association of Otorhinolaryngology-Head and Neck Surgery) declared that a notable portion of COVID-19 patients have degrees of either anosmia or hyposmia (32). These symptoms may be initialized 2-14 days after the viral attack (33). ACE2 receptor and transmembrane serine protease 2 (TMPRSS2) are expressed at the surface of respiratory epithelium, neuronal olfactory epithelium, olfactory mucosa, and olfactory bulb neurons. They play a role in supporting cells, stem cells, and perivascular cells in the respiratory tissue (34). TMPRSS2 mediates virus entrances via the ACE2 receptor into respiratory system lining cells, and thus, smell loss following viral infection is expected (11, 35). Based on available surveys, the benefits of administrating nasal corticosteroid spray in COVID-19 patients with post-infectious olfactory dysfunction have not been proven or recommended. However, studies support the advantage of using systemic and topical corticosteroids in patients with post-infectious anosmia/hyposmia (36). Despite the results of the Reden et al. study, which showed no difference between the use of vitamin A and placebo in patients with postviral olfactory dysfunction (37), Hummel et al. (38) declared that the daily administration of the intranasal form of this supplement in 10,000 IU dose followed by two months would be a beneficial regimen in patients with post-infectious olfactory loss. Nevertheless, more trials are needed to prove this fact in patients with SARS-CoV SARS-CoV-2.

West et al. (1991) found a significant correlation between the severity of disease and the level of vitamin A in the serum of chickens infected with infectious bronchitis virus (IBV), a subfamily of coronaviridae. This research explained that a low level of vitamin A in plasma was due to an increased rate of consumption of this vitamin by

invaded tissues (39).

In 2013, Jee et al. (22) conducted a trial and observed the antibody response coming after bovine coronavirus (BCoV) vaccination in 40 feedlot calves with high (3,300 U/kg) and low (1,100 U/kg) levels of vitamin A dietary intake. Specific serum titers of Immunoglobulins (Ig) were assessed in terms of the immunological response to vaccination. They showed that although the exact mechanism of how vitamin A affects antibody responses to the vaccine is mysterious, a low level of vitamin A intake could suppress IgG1 responses against the BcoV vaccine. Therefore, a low level of vitamin A could affect the efficacy of viral vaccines. To our knowledge, there is no published data that shows the efficacy of vitamin A on COVID-19 prognosis and mortality yet. However, a trial is in progress by Beigmohammadi et al., which aims to investigate the impact of mineral vitamin intake on the improvement of intensive care unit (ICU) admitted patients with COVID-19 (40).

Vitamin D

Historically, several trials have detected low serum levels of vitamin D in respiratory diseases such as acute respiratory tract infection and pneumonia. Also, vitamin D deficiency is related to increased susceptibility to seasonal influenza and mortality of patients with respiratory diseases (41-43).

1,25 (OH)2D3 induces alveolar macrophages to produce antimicrobial peptides named defensin and cathelicidin (e.g., LL-37) (44). Also, cellular immunity is regulated by the active metabolites of vitamin D. More clearly, it can attenuate cytokine storm in COVID-19 infection by the production of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) inhibitory protein (IκB α), which can inhibit the expression of the pro-inflammatory cytokine, tumor necrosis factor-alpha (TNFα), on T helper (Th1)-1 cells (45, 46). 1,25 (OH)2D3 also represses the secretion of Th1 cytokines such as interleukin (IL)-2 and interferon-gamma (IFN-γ). Vitamin D can support T helper-2 cytokine secretion, an alternative way to inhibit the cytokine storm formed in the pathogenesis of COVID-19 (46). Also, free radical damages exerted by inflammatory cytokines and enzymes (e.g., Inducible nitric oxide synthase (iNOS) and cyclo-oxygenase (COX)-2 may be diminished by the positive effect of vitamin D on genes related to the expression of antioxidant molecules (45, 46).

Vitamin D seems to help anti-viral immunity by inducing IFN-α secretion. Additionally, unbounded vitamin D receptor (VDR) can sequester signal transducer and activator of transcription 1 (STAT1), a transcription factor involved in the IFN signaling pathway. Therefore, vitamin D deficiency related to the increased level of unbounded VDR could lead to less anti-viral activity. Both vitamin D and IFN up-regulate ACE2 via their exertion on ACE2/Ang (1–7)/MasR axis and hold a crucial role in COVID-19 infection. Hence, adequate consumption of vitamin D has an important effect on IFN anti-viral action (26).

Vitamin D binding protein (DBP) is a complex protein that belongs to α_2–globulin family and can act as a multifunctional protein that binds to actin protein (47). Also, disseminated intravascular coagulopathy (DIC) has been reported in patients with COVID-19 due to the polymerization of actin proteins mediated by the coagulation factor Va. DBP affinity to actin compartment increases the accumulation of DBP and mediates the formation of actin complex, which may raise its inclination to cell injury and a new opportunity for coronavirus invasion (28, 48). Thus, low levels of active metabolites of vitamin D correspond with increased serum DBP, which might worsen the outcome of viral infection.

The protective role of vitamin D in COVID-19 is plausible (49). Older adults, who are the most vulnerable population to the disease, suffer from vitamin D deficiency because of (a) minor exposure to sunshine, (b) less biological capability to produce cholecalciferol, (c) notable variations in dietary intake which may be inadequate in supplements, (d) reduced vitamin D absorption in the intestine, (e) interference with consuming medications, and (e) renal filtration insufficiency (50). It has been reported that during the COVID-19 pandemic, populations residing in countries that lie below 35 degrees north latitude have shown a lower mortality rate compared with those of other countries. It supports the view that a high concentration of vitamin D produced in the summer in those countries might serve a protective role (51). This finding led authors to conduct studies

to investigate the correlation between serum vitamin D levels and susceptibility to SARS-CoV-2 infection and its outcomes. However, Ilie et al. (47) found vitamin D profile correlated with neither the number of afflicted patients nor the morbidity rate in each country.

To the best of our knowledge, no study has been performed to recommend the optimal range of vitamin D supplement intake in patients with COVID-19. Evidence is not conclusive; there is no dietary plan approved that may be clinically optimal to protect against respiratory viral infections. However, studies mostly suggest a baseline profile of vitamin D to determine the amount of vitamin D intake. McCartney et al. (52) reported that the essential daily intake of 25-50 micrograms of vitamin D in those who have a baseline serum level of 50 nmol/l might increase 25(OH) D serum level over 50nmol/l, and this is optimal to eliminate the risk of respiratory infection by viruses. Also, Ebadi et al. (53) affirmed that the amount of vitamin D intake needs to be determined by the baseline status of serum concentration and its increment rate during treatment. The authors recommended 50,000 IU vitamin D two times a week in those with a low level of baseline circulating vitamin D (below 50nmol/L). A maximum level of 15,000 IU daily consumption seems to be safe, and serum 25(OH)D concentrations above 100 nmol/L are need for 6000 IU daily intake efficiently. An initial dose of 100.000 IU followed by 50,000 IU per week for three weeks is an option for other patients.

Irrespective of the type of either daily or weekly prescription, studies show that the effect of vitamin D intake on the improvement of respiratory disease complications in patients with lower baseline calcifediol levels (below 25nmol/L) is more significant compared to patients with higher levels of baseline calcifediol (54). Nevertheless, no evidence proves the optimal dose and daily intake of vitamin D (55). Clinical studies are required to investigate the correlation between administered vitamin D, the baseline level of its circulating type, and the pattern of infection progression besides immune responses.

The combination of vitamin D and melatonin

From the molecular perspective, the signaling pathway of vitamin D resembles that of melatonin, a neuropeptide that regulates the sleep-wake cycle (56). Here we explain the anti-inflammatory effect of melatonin briefly.

Melatonin can interfere with NF-κB signaling thereby preventing T cell-mediated adverse response significantly. However, the great concern is that a high dose of melatonin prescription or administration in immunosuppressed patients is contradictory when it may provoke the secretion of pro-inflammatory cytokines (56). Studies report increased levels of inflammatory cytokines in patients with COVID-19, in particular, IL-6 (57-59). Moreover, melatonin could decrease levels of inflammatory cytokines (60).

From another point of view, COVID-19 initializes its invasion by ACE2 receptors (ACE2r) and RAS (19, 21, 61). Meanwhile, the degeneration of Ang II-mediated by ACE2/Ang I-7/Mas signaling by the action of ACE2 is in apposition with the neural RAS axis (62). It is an innate biological defense against COVID-19 viral action, which may preserve Ang II against the provocation of respiratory inflammatory response interestingly. A neural RAS is well-appreciated to regulate the secretion of melatonin. Surprisingly, Ang II interacts with the AT1 receptor located in the pineal gland, which indirectly mediates melatonin secretion (62, 63). Increased serum level of melatonin confronts the RAS axis and reduce the concentration of Ang I that the former may justify Ang II to inhibit its adverse actions during the inflammatory response. Firing up antioxidant gene replication (e.g., superoxide dismutase) besides its role in suppressing pro-oxidant agents (e.g., NO) and its direct interaction with free radicals defines another role for melatonin (64). Vitamin D and its interaction with melatonin modulated via the ACE2/Ang (1-7)/MasR pathway hold this hypothesis that probable co-therapy should be considered in further trials to investigate the accuracy of this mechanism shared here. Moreover, pretreatment with melatonin combined with quercetin (65) (well explained in the vitamin C part) will reduce the plasma level of inflammatory cytokines. Hence, these double (vitamin D + melatonin), triad (vitamin D + melatonin + quercetin), and tetrad (vitamin D + vitamin C + melatonin + quercetin) hypothesized medications should be considered in future trials.

Vitamin E

There is no human investigation that shows the relationship between the serum level of vitamin E and susceptibility to COVID-19. Vitamin E is of plant origin that interferes with biological purposes in the body. Notably, it affects the function of the immune system, using a direct effect on immune mediators and hormonal patterns (66). Among the two available biomolecule forms of vitamin E, only α-tocopherol is considered for human requisites (67). Moreover, it can exert an antioxidant role by protecting polyunsaturated fatty acids (PUFAs) on cell membranes' surface from oxidative reactions during cytokine storm (67).

COVID-19 mediates a cytokine storm, a process through which high levels of pro-inflammatory cytokines IL-1β and IL-6 advance the pathogenicity of the disease in the context of low levels of the anti-viral factors interferons (IFNs) (13, 57, 68-70). In this way, the virus attacks AT2 thereby releasing pro-inflammatory cytokines that, in turn, increase the accumulation and activity of alveolar macrophages (AMs) (71). NF-κB substantially mediates the release of these inflammatory cytokines. Studies imply high levels of Vitamin E (250 mg) in serum may inhibit the NF-κB signaling pathway and hence, modify the pro-inflammatory role of AMs in the pathogenesis of respiratory infections (72).

These findings contrast with animal experiments that have evaluated the effect of supplementary vitamin E on the state of immunity to Coronaviridea subfamily vaccination. In 2001, Leshchinsky et al. (66) figured a dose-dependent correlation between serum level of vitamin E and immune response in chickens receiving the vaccination against the coronaviridae subfamily. Results showed that moderate administration of vitamin E (25 to 50 IU/kg) had the most immunoregulatory role, and the high level of vitamin E was less effective. In another trial, Rostami et al. investigated the effect of co-administration of vitamin E and rosemary (Rosmarinus officinalis L.) powder (RP) in chickens vaccinated with coronaviridae subfamily antigen and found its significant effect in strengthening humoral immunity. However, it failed to increase the specific antibody titer (73). To be added, it has been reported that co-therapy of vitamin E with vitamin C could have a therapeutic effect in eliminating cardiac complications in COVID-19 patients (74). This is important because the cardiovascular system is highly affected by COVID-19 (75).

Vitamin K

Patients afflicted with COVID-19 are divided into mild, moderate, and severe based on their clinical symptoms (76, 77). Notable respiratory failures, including asthma (78), pneumonia (79), and ARDS (80), are the manifestations that happen to patients with severe COVID-19 (7) and are associated with poor prognosis. Coagulopathy and venous thromboembolism are other such manifestations associated with COVID-19 (81, 82). Coagulation is a state of blood hemodynamics between processing and inhibiting clot formation, which is integrated by vitamin K-dependent coagulation factors (83). Hepatic proteins (e.g., coagulation factor II, VII, IX, X, protein-C, and protein-S) and extra-hepatic proteins (e.g., a portion of protein-S and matrix Gla protein (MGP)) are functionally related to vitamin K concentration for γ-carboxylation (83-85). However, a low blood level of vitamin K can deviate the coagulation equilibration of carboxylation toward extra-hepatic proteins and enhance the state of thrombogenicity as a result (27, 86). MGP is expressed in different tissues such as cartilage, lungs, and arterial walls and plays a role in inhibiting the calcification of elastic extracellular fibers in these matrices (85).

SARS-CoV-2 invasion of AT2 cells induces the synthesis of pro-inflammatory cytokines that activate macrophages and induce matrix metalloproteinases (MMPs). MMPs, in turn, enhance the modification of lung elastic fibers and desmosine (DES) release from them (71). The elevated level of DES is associated with chronic obstructive pulmonary disease (COPD) severity and its clinical outcome (87). Moreover, degenerated elastic fibers may undergo polar changes that raise their affinity to calcium. Further, the up-regulation of MGP prevents lung wall calcification that the former proceeds the stimulation of vitamin K. Hence, the circulating levels of vitamin K will drop down, and coagulation equilibration of carboxylation goes to extra-hepatic coagulation and thrombogenesis (71).

Lower blood levels of vitamin K reported in

patients with COVID-19 are associated with low dietary intake, small bowel involvement in COVID-19 patients, stockpiling that decreases the chance of gaining fresh green leafy vegetables, increased alcohol and paracetamol consumption (88), and psychological effects of social distancing among people which may have an important impact on adherence to medical prescriptions (71). According to these complications, increased intake of dietary vitamin K and vitamin K antagonist (VKA) has been suggested in this situation. However, regular visits to control the international normalized ratio (INR) at the hospital may predispose vulnerable patients to COVID-19 due to the airborne transmission of the virus and close contact with other individuals (89-91). Therefore, it has been suggested to shift to novel oral anticoagulants (NOACs) to decrease the need to check INR regularly. Also, self-testing for checking INR in patients receiving VKA should be considered to decrease the false positive correlation between low levels of vitamin K, high INR, and susceptibility to COVID-19 infection (89).

Dofferhoff et al. (71) considered three blood markers, Desphospho-uncarboxylated (dp-uc) MGP, Protein induced by vitamin K absence (PIVKA)-II, and DES to evaluate the accuracy of each factor in the assessment of COVID-19 patients compared to that of computerized tomography (CT) scan. The study showed: i, the association of high level of dp-ucMGP with poor prognosis; ii, normal levels of PIVAK-II in the majority of patients; and iii, high levels of PIVAK-II in all patients using VKA; and iv, no significant relationship between vitamin K status and the severity of pneumonia.

Vitamin B6

Vitamin B6 plays a role in enzymatic reactions (92). The depletion of vitamin B6 has been reported in inflammatory conditions (93). However, its actual mechanism in the downregulation of inflammatory cytokines is still under research. There is still no study that surveys the potential effects of vitamin B status in patients with COVID-19. Ling et al. reported that the level of C-reactive protein (CRP), an inflammatory biomarker, is positively related to the severity of the disease in COVID-19 patients (94). In 2009, Shen et al. (95) examined the association between vitamin B6 active plasma form named phosphate ester derivative pyridoxal 5-phosphate (PLP) and CRP. The results showed that the increased level of PLP is associated with a lower level of CRP. Therefore, based on these results, we suggest that the low level of vitamin B6 could be associated with more severe disease in patients with COVID-19. However, more studies are needed.

Wu et al. (96) reported that hypertension has a hazardous ratio of 1.70 and 1.82 for death and ARSD in COVID-19 patients, respectively. In another study, Dakshinamurti et al. (97) reported a positive correlation between vitamin B6 deficiency and high blood pressure in rat models. A probable explanation for this result is that the sympathetic center is stimulated, followed by decreased brain serotonergic activity due to vitamin B6 deficiency. Additionally, vitamin B6 interactions with RAS have not been discussed extensively. Despoint et al. (98) and Delorme et al. (99) independently demonstrated that vitamin B6 could increase the sensitivity of rats to renin effects, and vitamin B6-deficient rat models develop hypertension.

Vitamin C

Vitamin C is a water-soluble nutrient required for the proper performance of immune defense (100). There are four main mechanisms that vitamin C utilizes to inhibit infection and support anti-viral activity (25). First, it can function as an immunoregulatory nutrient by i, increasing the activity of phagocytes; ii, activation of T lymphocytes; iii, secretion of cytokines such as IFN, TNF-α, and IL-6; iv, inhibition of NF-κB activation and granulocyte-macrophage colony-stimulating factor (GM-CSF) signaling pathway; v, prevention of neutrophils extracellular trap (NET) generation; and vi, activation of the humoral and cell-mediated immune responses (25, 101, 102). Second, vitamin C can repair damaged alveolar tissues during ROS production in the inflammatory state by its anti-oxidative action (25). Thirdly, vitamin C can control alveolar fluid clearance, and it could increase the function of the lung epithelial layer by increasing the transcription of protein channels (25). Fourth is the role of vitamin C in restoring mitochondrial function (103). Clinical investigations demonstrated that 1 g/day consumption of vitamin C could not prevent upper respiratory tract infections (URTIs). However, it has been shown that vitamin C can shorten the duration of URTIs (104, 105). Also, studies revealed that vitamin C inactivates and prevents the replication of viruses (100). Hiedra et al. (106) reported that administrating a high dose of vitamin C in patients with COVID-19 decreased mortality rate, inflammatory markers, and the number of patients requiring intubation and mechanical ventilation. Following this information, more trials are in progress worldwide to evaluate the efficacy of vitamin C in patients with COVID-19.

A challenge in the use of vitamin C is which route of its administration is more useful for treating patients. Some studies suggested that dietary intake of vitamin C could be useful in the treatment of patients under mechanical ventilation (107), decreasing the risk of viral infections (108), and relieving the symptoms of viral infections (109). Another study suggested that the low oral dose (1-2 g/d) of vitamin C could be used as prophylaxis for COVID-19, and HIVC may be useful for treating patients with severe COVID-19 (110). It has been reported that a high dose of intravenous (IV) vitamin C (HIVC) is beneficial for reducing the respiratory symptoms of patients with COVID-19 (25, 111). Also, the oxygenation index was improved in patients with moderate to severe COVID-19 infection who received HIVC (112). However, there are many concerns about the adverse effects of a high dose of this supplement on organs since reports indicated that hemolysis, acute kidney injury (AKI), and nephropathy occur in patients with COVID-19 (25). These findings may draw attention toward precautions when administrating HIVC, including a controlled rate of infusion, patients' well hydration, and proper dilution of the vitamin (25).

Some studies recommended adjuvant therapy of vitamin C and bioactive components to decrease the side effects of vitamin C. Li et al. (113) investigated the effect of vitamin C in combination with glycyrrhizic acid (GA), an ingredient used to reduce the inflammatory state in pneumonia, for the treatment of COVID-19. The results showed that treatment with this compound is related to increased immunity and reduced inflammatory state. In another study by Colunga Biancatelli et al. (103), the co-administration of vitamin C and quercetin has been suggested for prophylaxis and early treatment of COVID-19 patients. Quercetin is a vegetable-derived component that can exert immunoregulatory and anti-viral effects through inhibiting virus entry, interfering with RNA and DNA polymerases, inhibiting reverse transcriptase and proteases, and preventing virus assembly. Co-administration of quercetin and vitamin C could result in synergistic anti-viral activity (103, 114-116). **Figure 1** explains the pathogenicity of COVID-19 and the probable mechanism of action of each vitamin as well. **Table 1** summarizes the probable mechanisms of action of each vitamin, suggested co-therapy, and recommended daily consumption dose.

Conclusion

The COVID-19 pandemic has brought concerns among the professions and people in society, in both elderly and young groups, and both men's and women's groups worldwide (117-119). The accuracy of diagnostic tests is far from what it should be, and this would cause delayed diagnosis of patients (120), which is a real threat to treating patients with COVID-19, especially patients with co-morbid immune-mediated disorders (121) when there is a high risk of infection and re-infection (122), no proven drug or vaccine, and supportive care is the only therapy for the patients. However, universal efforts (123-125) occur in regenerative medicine, immunotherapy, medical biotechnology and microtechnology, telemedicine, and computational drug discovery (13, 126-134). It has been shown that mineral vitamins could be effective in treating patients with COVID-19 and several studies investigated the efficacy of mineral vitamins, their optimal dose, and the mechanism of action in viral respiratory infections. Trials reported a significant correlation between the serum level of vitamin A and the severity of respiratory tract infections. Vitamin A can inhibit the IgG1 response. Also, it has an important role in maintaining the normal structure of the epithelial layer in the respiratory system. Low serum levels of vitamin D have also been demonstrated in patients with acute respiratory tract infections and pneumonia. It can attenuate the cytokine storm in COVID-19 patients by supporting Th-2 cytokine secretion and inhibiting the expression of pro-inflammatory cytokines. Additionally, it has antioxidant and anti-viral activity. A low level of active metabolites of vitamin D is correlated with increased serum levels of DBP that might worsen the infection. Inhibi-

Table 1. Summary of different type of vitamins, mechanisms of action, suggested co-therapy, and recommended daily consumption

Main nutrient	Probable mechanisms of action in COVID-19	Supplements	Recommended daily consumption
Vitamin A	Preserving normal structure of the respiratory epithelial layer (31) Increase the concentration of T-helper 2 inducing B-cells IgG1 (22)	N/A	Adult: 10,000 IU/day (38) Infants: 12,500 – 25,000 IU/day (135)
Vitamin D	Secretion of defending and cathelicidin peptide from alveolar macrophages (44) Regulation of the production of Cell immunity cytokines (46) Expression of antioxidant genes (46) Interaction with RAS (136)	Melatonin ± flavonoid quercetin (65, 136)	Baseline VD (≤ 50nmol/ L): 100,000 IU/week Baseline VD (≥ 50nmol/ L): initial 100,000 IU + 50,000 IU/week (53)
Vitamin E	Antioxidant role via PUFAs (67) Modifying alveolar macrophages pro-inflammatory action by inhibition of NF-κB signaling pathway (72)	Rosemary (Rosmarinus officinalis L.) powder (RP) (60) Vitamin C (74)	0-25 IU/Kg/day (66)
Vitamin K	Balancing the coagulation state of blood circuits and preventing thrombogenicity complications during viral infections (27)	N/A	N/A
Vitamin B	Modification in T helper-1 activity (24)	N/A	N/A
Vitamin C	Immunoregulatory action on cellular and humoral immunity (25) Repairing damaged tissues (25) Increase respiratory clearance (25) Anti-oxidative role in inflammation (107)	Glycyrrhizic acid (GA) (113) Flavonoid quercetin (103) Hydrocortisone and thiamin (137) Vitamin E (74)	1 HIVC (10-20g daily) in moderate to severe cases + bolus doses in complicated cases (112)

N/A, Not Available; VD, Vitamin D; RAS, Renin-Angiotensin System; HIVC, High-Dose Intravenous Vitamin C; PUFAs, Polyunsaturated Fatty Acids

tion of NF-κB signaling and antioxidant activity are two main ways that vitamin E may assist immune response against virus infection. It has been shown that low blood levels of vitamin K could increase the state of thrombogenicity. Vitamin B6 is a water-soluble nutrient its low level is correlated with a higher level of CRP and probably more severe disease in patients with COVID-19. However, more studies are needed. Vitamin C inhibits infection and supports anti-viral activity by its immunoregulatory functions, antioxidant activity, controlling the alveolar fluid clearance, and restoring mitochondrial function. Also, studies demonstrated that administrating a high dose of vitamin C results in a decrease in mortality rate, inflammatory markers, and the need for intubation and mechanical ventilation in patients with COVID-19. Also, the co-therapy of vitamins with other supplements could increase their potential to protect against COVID-19. As summarized in Table 1, there is a collection of prescriptions related to other viral infections and coronaviruses derived from animal studies. However, the amount of recommended daily consumption of each vitamin depends on different factors, and more trials are needed to determine the exact dose in humans.

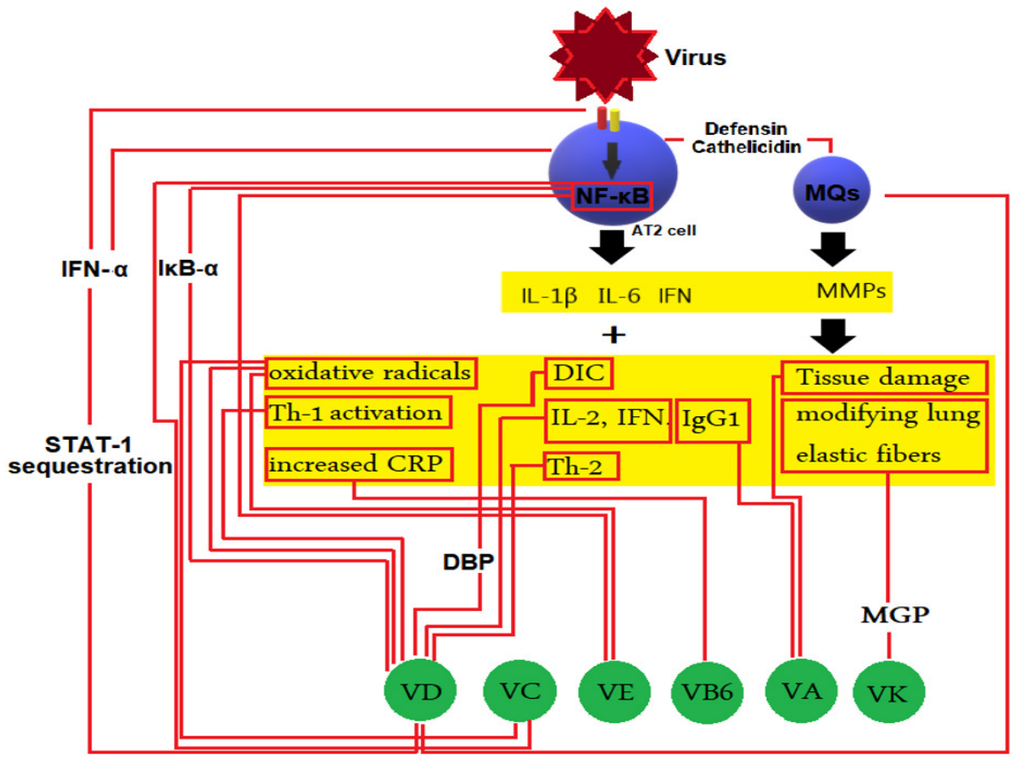

Figure 1. The probable role and mechanism of actions of vitamins in the pathogenesis of COVID-19
AT2 cell, alveolar type 2 cell; MQs, macrophages; IL, interleukin; IFN, interferon; Ig, immunoglobulin; MMPs, matrix metalloproteinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IκB α, NF-κB inhibitory protein; Th, T helper; DIC, disseminated intravascular coagulopathy; DBP, vitamin D binding protein; VA, vitamin A; VD, vitamin D; VE, vitamin E; VK, vitamin K; VB6, vitamin B6; VC, vitamin C

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med. 2012;367(19):1814-20.
2. van der Hoek L, Pyrc K, Jebbink MF, Vermeulen-Oost W, Berkhout RJ, Wolthers KC, et al. Identification of a new human coronavirus. Nat Med. 2004;10(4):368-73.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
4. Coperchini F, Chiovato L, Croce L, Magri F, Rotondi M. The cytokine storm in COVID-19: An overview of the involvement of the chemokine/chemokine-receptor system. Cytokine Growth Factor Rev. 2020;53:25-32.
5. Hanaei S, Rezaei N. COVID-19: Developing from an Outbreak to A Pandemic. Arch Med Res. 2020;51(6):582-84.
6. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708-20.
7. Lotfi M, Rezaei N. SARS-CoV-2: A comprehensive review from pathogenicity of the virus to clinical consequences. J Med Virol. 2020;92(10):1864-74.
8. Heidarpour M, Vakhshoori M, Abbasi S, Shafie D, Rezaei N. Adrenal insufficiency in coronavirus disease 2019: a case report. J Med

Case Rep. 2020;14(1):134.
9. Goudarzi S, Dehghani Firouzabadi F, Dehghani Firouzabadi M, Rezaei N. Cutaneous lesions and COVID-19: Cystic painful lesion in a case with positive SARS-CoV-2. Dermatol Ther. 2020;33(6):e14266.
10. Jahanshahlu L, Rezaei N. Central Nervous System Involvement in COVID-19. Arch Med Res. 2020;51(7):721-22.
11. Saleki K, Banazadeh M, Saghazadeh A, Rezaei N. The involvement of the central nervous system in patients with COVID-19. Rev Neurosci. 2020;31(4):453-56.
12. Chu H, Chan JF, Wang Y, Yuen TT, Chai Y, Hou Y, et al. Comparative Replication and Immune Activation Profiles of SARS-CoV-2 and SARS-CoV in Human Lungs: An Ex Vivo Study With Implications for the Pathogenesis of COVID-19. Clin Infect Dis. 2020;71(6):1400-09.
13. Fathi N, Rezaei N. Lymphopenia in COVID-19: Therapeutic opportunities. Cell Biol Int. 2020;44(9):1792-97.
14. Babaha F, Rezaei N. Primary Immunodeficiency Diseases in COVID-19 Pandemic: A Predisposing or Protective Factor? Am J Med Sci. 2020;360(6):740-41.
15. Ahanchian H, Moazzen N, Sezavar M, Khalighi N, Khoshkhui M, Aelami MH, et al. COVID-19 in a child with primary antibody deficiency. Clin Case Rep. 2021;9(2):755-58.
16. Bahrami A, Vafapour M, Moazzami B, Rezaei N. Hyperinflammatory shock related to COVID-19 in a patient presenting with multisystem inflammatory syndrome in children: First case from Iran. J Paediatr Child Health. 2021;57(6):922-25.
17. Yousefzadegan S, Rezaei N. Case Report: Death due to COVID-19 in Three Brothers. Am J Trop Med Hyg. 2020;102(6):1203-04.
18. Darbeheshti F, Rezaei N. Genetic predisposition models to COVID-19 infection. Med Hypotheses. 2020;142:109818.
19. Rezaei N. COVID-19 and Medical Biotechnology. Avicenna J Med Biotechnol. 2020;12(3):139.
20. Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, et al. Association of Inpatient Use of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers With Mortality Among Patients With Hypertension Hospitalized With COVID-19. Circ Res. 2020;126(12):1671-81.
21. Sharifkashani S, Bafrani MA, Khaboushan AS, Pirzadeh M, Kheirandish A, Yavarpour Bali H, et al. Angiotensin-converting enzyme 2 (ACE2) receptor and SARS-CoV-2: Potential therapeutic targeting. Eur J Pharmacol. 2020;884:173455.
22. Jee J, Hoet AE, Azevedo MP, Vlasova AN, Loerch SC, Pickworth CL, et al. Effects of dietary vitamin A content on antibody responses of feedlot calves inoculated intramuscularly with an inactivated bovine coronavirus vaccine. Am J Vet Res. 2013;74(10):1353-62.
23. Paul L, Ueland PM, Selhub J. Mechanistic perspective on the relationship between pyridoxal 5'-phosphate and inflammation. Nutr Rev. 2013;71(4):239-44.
24. Ulvik A, Midttun O, Pedersen ER, Eussen SJ, Nygard O, Ueland PM. Evidence for increased catabolism of vitamin B-6 during systemic inflammation. Am J Clin Nutr. 2014;100(1):250-5.
25. Liu F, Zhu Y, Zhang J, Li Y, Peng Z. Intravenous high-dose vitamin C for the treatment of severe COVID-19: study protocol for a multicentre randomised controlled trial. BMJ Open. 2020;10(7):e039519.
26. Gauzzi MC, Fantuzzi L. Reply to Jakovac: COVID-19, vitamin D, and type I interferon. Am J Physiol Endocrinol Metab. 2020;319(2):E245-E46.
27. Booth SL, Martini L, Peterson JW, Saltzman E, Dallal GE, Wood RJ. Dietary phylloquinone depletion and repletion in older women. J Nutr. 2003;133(8):2565-9.
28. Speeckaert MM, Delanghe JR. Association between low vitamin D and COVID-19: don't forget the vitamin D binding protein. Aging Clin Exp Res. 2020;32(7):1207-08.
29. Jayawardena R, Sooriyaarachchi P, Chourdakis M, Jeewandara C, Ranasinghe P. Enhancing immunity in viral infections, with special emphasis on COVID-19: A review. Diabetes Metab Syndr. 2020;14(4):367-82.
30. Hurwitz JL, Jones BG, Penkert RR, Gansebom S, Sun Y, Tang L, et al. Low Retinol-Binding Protein and Vitamin D Levels Are Associated with Severe Outcomes in Children Hospitalized with Lower Respiratory Tract Infection and Respiratory Syncytial Virus or Human Metapneumovirus Detection. J Pediatr. 2017;187:323-27.
31. Timoneda J, Rodriguez-Fernandez L, Zaragoza R, Marin MP, Cabezuelo MT, Torres L, et al. Vitamin A Deficiency and the Lung. Nutrients. 2018;10(9):1132.

32. British Association of Otorhinolaryngology - Head and Neck Surgery. Loss of sense of smell as marker of COVID-19 infection ENTUK: ENTUK; [Available from: https://www.entuk.org/loss-sense-smell-marker-covid-19-infection/default.aspx.
33. Symptoms of COVID-19 Centers for Disease control and Prevention2022 [updated 2024. Available from: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html.
34. Kanjanaumporn J, Aeumjaturapat S, Snidvongs K, Seresirikachorn K, Chusakul S. Smell and taste dysfunction in patients with SARS-CoV-2 infection: A review of epidemiology, pathogenesis, prognosis, and treatment options. Asian Pac J Allergy Immunol. 2020;38(2):69-77.
35. Yazdanpanah N, Saghazadeh A, Rezaei N. Anosmia: a missing link in the neuroimmunology of coronavirus disease 2019 (COVID-19). Rev Neurosci. 2020;31(7):691-701.
36. Scangas GA, Bleier BS. Anosmia: Differential diagnosis, evaluation, and management. Am J Rhinol Allergy. 2017;31(1):3-7.
37. Reden J, Lill K, Zahnert T, Haehner A, Hummel T. Olfactory function in patients with postinfectious and posttraumatic smell disorders before and after treatment with vitamin A: a double-blind, placebo-controlled, randomized clinical trial. Laryngoscope. 2012;122(9):1906-9.
38. Hummel T, Whitcroft KL, Rueter G, Haehner A. Intranasal vitamin A is beneficial in post-infectious olfactory loss. Eur Arch Otorhinolaryngol. 2017;274(7):2819-25.
39. West CE, Sijtsma SR, Kouwenhoven B, Rombout JH, van der Zijpp AJ. Epithelia-damaging virus infections affect vitamin A status in chickens. J Nutr. 1992;122(2):333-9.
40. Beigmohammadi MT, Bitarafan S, Hoseindokht A, Abdollahi A, Amoozadeh L, Mahmoodi Ali Abadi M, et al. Impact of vitamins A, B, C, D, and E supplementation on improvement and mortality rate in ICU patients with coronavirus-19: a structured summary of a study protocol for a randomized controlled trial. Trials. 2020;21(1):614.
41. Ginde AA, Mansbach JM, Camargo CA, Jr. Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. Arch Intern Med. 2009;169(4):384-90.
42. Zhou YF, Luo BA, Qin LL. The association between vitamin D deficiency and community-acquired pneumonia: A meta-analysis of observational studies. Medicine (Baltimore). 2019;98(38):e17252.
43. Jolliffe DA, Griffiths CJ, Martineau AR. Vitamin D in the prevention of acute respiratory infection: systematic review of clinical studies. J Steroid Biochem Mol Biol. 2013;136:321-9.
44. Tripathi S, Tecle T, Verma A, Crouch E, White M, Hartshorn KL. The human cathelicidin LL-37 inhibits influenza A viruses through a mechanism distinct from that of surfactant protein D or defensins. J Gen Virol. 2013;94(Pt 1):40-49.
45. Infusino F, Marazzato M, Mancone M, Fedele F, Mastroianni CM, Severino P, et al. Diet Supplementation, Probiotics, and Nutraceuticals in SARS-CoV-2 Infection: A Scoping Review. Nutrients. 2020;12(6):1718.
46. Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, et al. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients. 2020;12(4).
47. Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality. Aging Clin Exp Res. 2020;32(7):1195-98.
48. Al-Samkari H, Karp Leaf RS, Dzik WH, Carlson JCT, Fogerty AE, Waheed A, et al. COVID-19 and coagulation: bleeding and thrombotic manifestations of SARS-CoV-2 infection. Blood. 2020;136(4):489-500.
49. Shojaeefar E, Malih N, Rezaei N. The possible double-edged sword effects of vitamin D on COVID-19: A hypothesis. Cell Biol Int. 2021;45(1):54-57.
50. Saraiva GL, Cendoroglo MS, Ramos LR, Araujo LM, Vieira JG, Maeda SS, et al. [Prevalence of vitamin D deficiency, insufficiency and secondary hyperparathyroidism in the elderly inpatients and living in the community of the city of Sao Paulo, Brazil]. Arq Bras Endocrinol Metabol. 2007;51(3):437-42.
51. Rhodes JM, Subramanian S, Laird E, Kenny RA. Editorial: low population mortality from COVID-19 in countries south of latitude 35 degrees North supports vitamin D as a factor determining severity. Aliment Pharmacol Ther. 2020;51(12):1434-37.
52. McCartney DM, Byrne DG. Optimisation of Vitamin D Status for Enhanced Immuno-protection Against Covid-19. Ir Med J.

2020;113(4):58.
53. Ebadi M, Montano-Loza AJ. Perspective: improving vitamin D status in the management of COVID-19. Eur J Clin Nutr. 2020;74(6):856-59.
54. Martineau AR, Jolliffe DA, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G, et al. Vitamin D supplementation to prevent acute respiratory infections: individual participant data meta-analysis. Health Technol Assess. 2019;23(2):1-44.
55. Kow CS, Hadi MA, Hasan SS. Vitamin D Supplementation in Influenza and COVID-19 Infections Comment on: "Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths" Nutrients 2020, 12(4), 988. Nutrients. 2020;12(6).
56. Zhang R, Wang X, Ni L, Di X, Ma B, Niu S, et al. COVID-19: Melatonin as a potential adjuvant treatment. Life Sci. 2020;250:117583.
57. Rokni M, Hamblin MR, Rezaei N. Cytokines and COVID-19: friends or foes? Hum Vaccin Immunother. 2020;16(10):2363-65.
58. Saghazadeh A, Rezaei N. Immune-epidemiological parameters of the novel coronavirus - a perspective. Expert Rev Clin Immunol. 2020;16(5):465-70.
59. Saghazadeh A, Rezaei N. Towards treatment planning of COVID-19: Rationale and hypothesis for the use of multiple immunosuppressive agents: Anti-antibodies, immunoglobulins, and corticosteroids. Int Immunopharmacol. 2020;84:106560.
60. Zarezadeh M, Khorshidi M, Emami M, Janmohammadi P, Kord-Varkaneh H, Mousavi SM, et al. Melatonin supplementation and pro-inflammatory mediators: a systematic review and meta-analysis of clinical trials. Eur J Nutr. 2020;59(5):1803-13.
61. Patel AB, Verma A. COVID-19 and Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers: What Is the Evidence? JAMA. 2020;323(18):1769-70.
62. Campos LA, Cipolla-Neto J, Amaral FG, Michelini LC, Bader M, Baltatu OC. The Angiotensin-melatonin axis. Int J Hypertens. 2013;2013:521783.
63. Ishigaki S, Ohashi N, Matsuyama T, Isobe S, Tsuji N, Iwakura T, et al. Melatonin ameliorates intrarenal renin-angiotensin system in a 5/6 nephrectomy rat model. Clin Exp Nephrol. 2018;22(3):539-49.
64. Wu X, Ji H, Wang Y, Gu C, Gu W, Hu L, et al. Melatonin Alleviates Radiation-Induced Lung Injury via Regulation of miR-30e/NLRP3 Axis. Oxid Med Cell Longev. 2019;2019:4087298.
65. Al-Rasheed NM, Fadda L, Attia HA, Sharaf IA, Mohamed AM, Al-Rasheed NM. Original research paper. Pulmonary prophylactic impact of melatonin and/or quercetin: A novel therapy for inflammatory hypoxic stress in rats. Acta Pharm. 2017;67(1):125-35.
66. Leshchinsky TV, Klasing KC. Relationship between the level of dietary vitamin E and the immune response of broiler chickens. Poult Sci. 2001;80(11):1590-9.
67. Zabetakis I, Lordan R, Norton C, Tsoupras A. COVID-19: The Inflammation Link and the Role of Nutrition in Potential Mitigation. Nutrients. 2020;12(5).
68. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the ;Cytokine Storm' in COVID-19. J Infect. 2020;80(6):607-13.
69. Nasab MG, Saghazadeh A, Rezaei N. SARS-CoV-2-A Tough Opponent for the Immune System. Arch Med Res. 2020;51(6):589-92.
70. Yazdanpanah F, Hamblin MR, Rezaei N. The immune system and COVID-19: Friend or foe? Life Sci. 2020;256:117900.
71. Dofferhoff ASM, Piscaer I, Schurgers LJ, Visser MPJ, van den Ouweland JMW, de Jong PA, et al. Reduced Vitamin K Status as a Potentially Modifiable Risk Factor of Severe Coronavirus Disease 2019. Clin Infect Dis. 2021;73(11):e4039-e46.
72. Khanduja KL, Avti PK, Kumar S, Pathania V, Pathak CM. Inhibitory effect of vitamin E on proinflammatory cytokines-and endotoxin-induced nitric oxide release in alveolar macrophages. Life Sci. 2005;76(23):2669-80.
73. Rostami H, Seidavi A, Dadashbeiki M, Asadpour Y, Simoes J, Shah AA, et al. Supplementing dietary rosemary (Rosmarinus officinalis L.) powder and vitamin E in broiler chickens: evaluation of humoral immune response, lymphoid organs, and blood proteins. Environ Sci Pollut Res Int. 2018;25(9):8836-42.
74. Wang JZ, Zhang RY, Bai J. An anti-oxidative therapy for ameliorating cardiac injuries of critically ill COVID-19-infected patients. Int J Cardiol. 2020;312:137-38.
75. Nejadghaderi SA, Heidari A, Shakerian N, Saghazadeh A, Rezaei N. Cardiovascular system is at higher risk of affecting by COVID-19. Acta Biomed. 2020;91(3):e2020018.
76. Gandhi RT, Lynch JB, Del Rio C. Mild or Moderate Covid-19. N Engl J Med. 2020;383(18):1757-66.
77. Bar-On YM, Flamholz A, Phillips R, Milo R. SARS-CoV-2 (COVID-19) by the numbers. Elife. 2020;9:e57309.
78. Butler MW, O'Reilly A, Dunican EM, Mallon P, Feeney ER, Keane MP, et al. Prevalence of comorbid asthma in COVID-19 patients. J Allergy Clin Immunol. 2020;146(2):334-35.
79. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med. 2020;8(5):475-81.
80. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020;146(1):110-18.
81. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-47.
82. Jenab Y, Rezaei N, Hedayat B, Naderian M, Shirani S, Hosseini K. Occurrence of acute coronary syndrome, pulmonary thromboembolism, and cerebrovascular event in COVID-19. Clin Case Rep. 2020;8(12):2414-17.
83. Brenner B, Kuperman AA, Watzka M, Oldenburg J. Vitamin K-dependent coagulation factors deficiency. Semin Thromb Hemost. 2009;35(4):439-46.
84. Fair DS, Marlar RA, Levin EG. Human endothelial cells synthesize protein S. Blood. 1986;67(4):1168-71.
85. Fodor D, Albu A, Poanta L, Porojan M. Vitamin K and vascular calcifications. Acta Physiol Hung. 2010;97(3):256-66.
86. Nigwekar SU, Thadhani R, Brandenburg VM. Calciphylaxis. N Engl J Med. 2018;378(18):1704-14.
87. Luisetti M, Stolk J, Iadarola P. Desmosine, a biomarker for COPD: old and in the way. Eur Respir J. 2012;39(4):797-8.
88. Speed V, Patel RK, Byrne R, Roberts LN, Arya R. A perfect storm: Root cause analysis of supra-therapeutic anticoagulation with vitamin K antagonists during the COVID-19 pandemic. Thromb Res. 2020;192:73-74.
89. Doganci S, Yildirim AK. Problems related with anticoagulant usage during COVID-19 outbreak. J Vasc Surg Venous Lymphat Disord. 2020;8(4):695-96.
90. Lotfi M, Hamblin MR, Rezaei N. COVID-19: Transmission, prevention, and potential therapeutic opportunities. Clin Chim Acta. 2020;508:254-66.
91. Mohamed K, Rezaei N, Rodriguez-Roman E, Rahmani F, Zhang H, Ivanovska M, et al. International Efforts to Save Healthcare Personnel during COVID-19. Acta Biomed. 2020;91(3):e2020044.
92. Hellmann H, Mooney S. Vitamin B6: a molecule for human health? Molecules. 2010;15(1):442-59.
93. Bates CJ, Pentieva KD, Prentice A, Mansoor MA, Finch S. Plasma pyridoxal phosphate and pyridoxic acid and their relationship to plasma homocysteine in a representative sample of British men and women aged 65 years and over. Br J Nutr. 1999;81(3):191-201.
94. Wang L. C-reactive protein levels in the early stage of COVID-19. Med Mal Infect. 2020;50(4):332-34.
95. Shen J, Lai CQ, Mattei J, Ordovas JM, Tucker KL. Association of vitamin B-6 status with inflammation, oxidative stress, and chronic inflammatory conditions: the Boston Puerto Rican Health Study. Am J Clin Nutr. 2010;91(2):337-42.
96. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934-43.
97. Dakshinamurti K, Paulose CS, Viswanathan M, Siow YL, Sharma SK, Bolster B. Neurobiology of pyridoxine. Ann N Y Acad Sci. 1990;585:128-44.
98. Despoint R, Lupien P. Inhibition of renin response in pyridoxine-treated pregnant and non-pregnant rats. Can Med Assoc J 1968 Vol. 98, No. 2:109.
99. DeLorme CB, Lupien PJ, Despointes RH. Influence of vitamin B-6 on the renin--angiotensin system in rats. J Nutr. 1975;105(9):1192-8.
100. Mousavi S, Bereswill S, Heimesaat MM. Immunomodulatory and Antimicrobial Effects of Vitamin C. Eur J Microbiol Immunol (Bp). 2019;9(3):73-79.
101. Carr AC, Maggini S. Vitamin C and Immune Function. Nutrients. 2017;9(11):1211.
102. Barnes BJ, Adrover JM, Baxter-Stoltzfus A, Borczuk A, Cools-Lartigue J, Crawford JM, et al. Targeting potential drivers of COVID-19: Neutrophil extracellular traps. J Exp Med.

2020;217(6).
103. Colunga Biancatelli RML, Berrill M, Catravas JD, Marik PE. Quercetin and Vitamin C: An Experimental, Synergistic Therapy for the Prevention and Treatment of SARS-CoV-2 Related Disease (COVID-19). Front Immunol. 2020;11(1451):1451.
104. Hemila H, Chalker E. Vitamin C as a Possible Therapy for COVID-19. Infect Chemother. 2020;52(2):222-23.
105. Hemila H, Chalker E. Vitamin C for preventing and treating the common cold. Cochrane Database Syst Rev. 2013;2013(1):CD000980.
106. Hiedra R, Lo KB, Elbashabsheh M, Gul F, Wright RM, Albano J, et al. The use of IV vitamin C for patients with COVID-19: a case series. Expert Rev Anti Infect Ther. 2020;18(12):1259-61.
107. Patel V, Dial K, Wu J, Gauthier AG, Wu W, Lin M, et al. Dietary Antioxidants Significantly Attenuate Hyperoxia-Induced Acute Inflammatory Lung Injury by Enhancing Macrophage Function via Reducing the Accumulation of Airway HMGB1. Int J Mol Sci. 2020;21(3):977.
108. Kim TK, Lim HR, Byun JS. Vitamin C supplementation reduces the odds of developing a common cold in Republic of Korea Army recruits: randomised controlled trial. BMJ Mil Health. 2022;168(2):117-23.
109. Gorton HC, Jarvis K. The effectiveness of vitamin C in preventing and relieving the symptoms of virus-induced respiratory infections. J Manipulative Physiol Ther. 1999;22(8):530-3.
110. Feyaerts AF, Luyten W. Vitamin C as prophylaxis and adjunctive medical treatment for COVID-19? Nutrition. 2020;79-80:110948.
111. Carr AC. A new clinical trial to test high-dose vitamin C in patients with COVID-19. Crit Care. 2020;24(1):133.
112. Cheng RZ. Can early and high intravenous dose of vitamin C prevent and treat coronavirus disease 2019 (COVID-19)? Med Drug Discov. 2020;5:100028.
113. Li R, Wu K, Li Y, Liang X, Lai KP, Chen J. Integrative pharmacological mechanism of vitamin C combined with glycyrrhizic acid against COVID-19: findings of bioinformatics analyses. Brief Bioinform. 2021;22(2):1161-74.
114. Robaszkiewicz A, Balcerczyk A, Bartosz G. Antioxidative and prooxidative effects of quercetin on A549 cells. Cell Biol Int. 2007;31(10):1245-50.
115. Uchide N, Toyoda H. Antioxidant therapy as a potential approach to severe influenza-associated complications. Molecules. 2011;16(3):2032-52.
116. Nair MP, Kandaswami C, Mahajan S, Chadha KC, Chawda R, Nair H, et al. The flavonoid, quercetin, differentially regulates Th-1 (IFN-gamma) and Th-2 (IL4) cytokine gene expression by normal peripheral blood mononuclear cells. Biochim Biophys Acta. 2002;1593(1):29-36.
117. Momtazmanesh S, Ochs HD, Uddin LQ, Perc M, Routes JM, Vieira DN, et al. All together to Fight COVID-19. Am J Trop Med Hyg. 2020;102(6):1181-83.
118. Rezaei N. COVID-19 affects healthy pediatricians more than pediatric patients. Infect Control Hosp Epidemiol. 2020;41(9):1106-07.
119. Mirbeyk M, Rezaei N. The impact of COVID-19 on pregnancy and neonatal health: a systematic review. Europe PMC. 2020.
120. Basiri A, Heidari A, Nadi MF, Fallahy MTP, Nezamabadi SS, Sedighi M, et al. Microfluidic devices for detection of RNA viruses. Rev Med Virol. 2021;31(1):1-11.
121. Sahu KK, Siddiqui AD, Rezaei N, Cerny J. Challenges for management of immune thrombocytopenia during COVID-19 pandemic. J Med Virol. 2020;92(11):2277-82.
122. Jabbari P, Rezaei N. With Risk of Reinfection, Is COVID-19 Here to Stay? Disaster Med Public Health Prep. 2020;14(4):e33.
123. Mohamed K, Rodriguez-Roman E, Rahmani F, Zhang H, Ivanovska M, Makka SA, et al. Borderless collaboration is needed for COVID-19-A disease that knows no borders. Infect Control Hosp Epidemiol. 2020;41(10):1245-46.
124. Moradian N, Ochs HD, Sedikies C, Hamblin MR, Camargo CA, Jr., Martinez JA, et al. The urgent need for integrated science to fight COVID-19 pandemic and beyond. J Transl Med. 2020;18(1):205.
125. Rzymski P, Nowicki M, Mullin GE, Abraham A, Rodríguez-Román E, Petzold MB, et al. Quantity does not equal quality: scientific principles cannot be sacrificed. Int Immunopharmacol 2020;86:106711.
126. Basiri A, Pazhouhnia Z, Beheshtizadeh N, Hoseinpour M, Saghazadeh A, Rezaei N. Regenerative Medicine in COVID-19 Treatment: Real Opportunities and Range of Promises. Stem Cell Rev Rep. 2021;17(1):163-75.
127. Jahanshahlu L, Rezaei N. Monoclonal antibody as a potential anti-COVID-19. Biomed Pharmacother. 2020;129:110337.
128. Mansourabadi AH, Sadeghalvad M, Mohammadi-Motlagh HR, Rezaei N. The immune system as a target for therapy of SARS-CoV-2: A systematic review of the current immunotherapies for COVID-19. Life Sci. 2020;258:118185.
129. Pashaei M, Rezaei N. Immunotherapy for SARS-CoV-2: potential opportunities. Expert Opin Biol Ther. 2020;20(10):1111-16.
130. Seyedpour S, Khodaei B, Loghman AH, Seyedpour N, Kisomi MF, Balibegloo M, et al. Targeted therapy strategies against SARS-CoV-2 cell entry mechanisms: A systematic review of in vitro and in vivo studies. J Cell Physiol. 2021;236(4):2364-92.
131. Pourahmad R, Moazzami B, Rezaei N. E ficacy of Plasmapheresis and Immunoglobulin Replacement Therapy (IVIG) on Patients with COVID-19. SN Compr Clin Med. 2020;2(9):1407-11.
132. Moazzami B, Razavi-Khorasani N, Dooghaie Moghadam A, Farokhi E, Rezaei N. COVID-19 and telemedicine: Immediate action required for maintaining healthcare providers well-being. J Clin Virol. 2020;126:104345.
133. Mohamed K, Yazdanpanah N, Saghazadeh A, Rezaei N. Computational drug discovery and repurposing for the treatment of COVID-19: A systematic review. Bioorg Chem. 2021;106:104490.
134. Rabiee N, Rabiee M, Bagherzadeh M, Rezaei N. COVID-19 and picotechnology: Potential opportunities. Med Hypotheses. 2020;144:109917.
135. Neuzil KM, Gruber WC, Chytil F, Stahlman MT, Graham BS. Safety and pharmacokinetics of vitamin A therapy for infants with respiratory syncytial virus infections. Antimicrob Agents Chemother. 1995;39(5):1191-3.
136. Martin Gimenez VM, Inserra F, Tajer CD, Mariani J, Ferder L, Reiter RJ, et al. Lungs as target of COVID-19 infection: Protective common molecular mechanisms of vitamin D and melatonin as a new potential synergistic treatment. Life Sci. 2020;254:117808.
137. Marik PE, Khangoora V, Rivera R, Hooper MH, Catravas J. Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock: A Retrospective Before-After Study. Chest. 2017;151(6):1229-38.