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The prophylaxis and treatment potential of supplements for COVID-19

Adeleh Sahebnasagh^{a,*,**}, Fatemeh Saghafi^b, Razieh Avan^c, Amirhosein Khoshi^d,
Masoud Khataminia^e, Mohammadreza Safdari^f, Solomon Habtemariam^g,
Hassan Rezai Ghaleno^h, Seyed Mohammad Nabavi^{i,j,*}

^a Clinical Research Center, Department of Internal Medicine, North Khorasan University of Medical Sciences, Bojnurd, Iran

^b Department of Clinical Pharmacy, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

^c Department of Clinical Pharmacy, Medical Toxicology and Drug Abuse Research Center (MTDRC), Faculty of Pharmacy, Birjand University of Medical Sciences, Birjand, Iran

^d Department of Clinical Biochemistry, School of Medicine, North Khorasan University of Medical Sciences, Bojnurd, Iran

^e Student Research Committee, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

^f Department of Orthopedic Surgery, Faculty of Medicine, North Khorasan University of Medical Sciences, Bojnurd, Iran

^g Pharmacognosy Research Laboratories and Herbal Analysis Services UK, University of Greenwich, Central Avenue, Chatham-Maritime, Kent, ME4 4TB, United Kingdom

^h Department of Surgery, Faculty of Medicine, Lorestan University of Medical Sciences, Khorramabad, Iran

ⁱ Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran

^j Division of Translational Medicine, Baqiyatallah Hospital, Baqiyatallah University of Medical Sciences, Tehran, Iran

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ABSTRACT

The global impact of the new coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), infection that caused COVID-19 has been evident in the last few months from the unprecedented socioeconomic disruption to more than 600,000 deaths. The lack of vaccine and effective therapeutic agents for the disease prompted world-wide effort to test those antiviral therapeutics already in use for other diseases. Another interesting approach has been based on the pathological sequel of the disease that involve severe inflammatory reaction (or the cytokine storm) associated with pneumonia in critically ill patients. This article outlines the prophylaxis therapeutic potential of supplements vitamins and micronutrients in COVID-19. By ameliorating the inflammatory and oxidative stress associated with the disease and some direct antiviral effects, the application of these agents as adjuvants and other alternative approaches are discussed. Available clinical trials including those currently registered on these supplements are scrutinized.

1. Introduction

The new coronavirus disease (COVID-19) rapidly spread to 216 countries in the world and is currently a pandemic (Kashouris et al., 2020). With a characteristic feature of severe acute respiratory syndrome (SARS), COVID-19, according to the World Health Organization (WHO) report, caused more than 640,016 deaths, while the number of global confirmed cases has been over 15, 785, 641 (updated on July 27, 2020). The virus that causes COVID-19 has been named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in view of its

similarity with the previously known coronavirus (SARS-CoV) outbreak in China in 2002/3.

Regarding the alterations of the immune system during COVID-19 infection, most of the patients experience lymphopenia with or without reduced leukocyte counts and they also display significantly increased profile of pro-inflammatory factors (Lin et al.; Wang et al., 2020). Moreover, the life-threatening acute respiratory distress syndrome (ARDS) due to the cytokine storm is associated with increased mortality rate in the patients (Ren et al., 2020).

An explosive level of inflammatory cytokines and reactive oxygen

* Corresponding author. Division of Translational Medicine, Baqiyatallah Hospital and Applied Biotechnology Research Center, Baqiyatallah University of Medical Sciences, P.O. Box 19945-546, Tehran, Iran.

** Corresponding author. Clinical Research Center, Department of Internal Medicine, North Khorasan University of Medical Sciences, Bojnurd, Iran.

E-mail addresses: masoomehsahebnaasagh@gmail.com (A. Sahebnasagh), saghafi.fa@gmail.com (F. Saghafi), avanr91@gmail.com (R. Avan), ahkh83@gmail.com (A. Khoshi), masoodkhataminia@yahoo.com (M. Khataminia), safdari57@yahoo.com (M. Safdari), s.habtemariam@herbalanalysis.co.uk (S. Habtemariam), Hassan.Rezai2020@yahoo.com (H.R. Ghaleno), Nabavi208@gmail.com (S.M. Nabavi).

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species (ROS) occur during the pneumonia episode of coronavirus infection. The inflammasome activity or inflammation in the lungs and programmed cell death and fibrosis are also common complications associated with SARS-CoV-2 infection (Shneider et al., 2020).

Since there is no vaccine or specific antiviral therapy against COVID-19, current treatment approaches mainly focus on trial of previous therapeutic experiences with other viral infections. Some potential therapies on the basis of direct effect on the virus replication cycle, interference with the mechanisms of viral pathogenesis and also effect on the human immune system have already been identified (Ge et al., 2013; Sanders et al., 2019). The most often used antiviral treatments so far include the followings: nucleotide analogues for inhibition of RNA-dependent-RNA polymerase, such as ribavirin (Elfiky, 2020) and remdesivir (Ko et al., 2020), combination of the antiviral drugs lopinavir/ritonavir (LPV/r) (Lim et al., 2020), anti-malarial drug hydroxychloroquine (Colson et al., 2020), glucocorticoids (Zhou et al., 2020), and sometimes antibiotic combination therapy (Gautret et al., 2020).

Dietary or drug supplements containing vitamins and micronutrients that boost the immune system are a low-cost and effective adjuvant approach to fight against acute respiratory tract complication of COVID-19 (Wang et al., 2020a). Inflammatory response in the airways due to over-activity of immune cells can induce oxidative stress and tissue damage. Indeed, inflammatory reactions in the airways via pro-inflammatory cytokines would enhance ROS production (Xu et al., 2020). The role of vitamins in both innate and adaptive immune responses has been confirmed. Some vitamins such as vitamins E and C and some members of the vitamin B family have antioxidant and various other effects in the immune system. Moreover, vitamins A and D as immunomodulatory compounds play critical roles in the immune system (Mora et al., 2008). Furthermore, some supplements, such as melatonin (Shneider et al.), reduce the level of oxidative stress, and inflammatory reactions. Some supplements may also improve the efficacy of antiviral therapies and decrease dose-dependent toxicity.

Currently, there are no proven prophylactic or therapeutic intervention for management COVID-19. Some therapeutic agents are used off-label, alone or in combination, but we need further experimental data and validation to achieve gold-standard therapeutic regimen with the highest possible efficacy and low side effects. In this review, the effects of different supplemental agents against pneumonia associated with COVID-19 are assessed and are summarized in Table 1. Furthermore, an overview of several clinical trials which have been recruited along with current antiviral treatments in management of COVID-19 are presented (Table 2).

2. Potential of supplements for COVID-19

2.1. Vitamin C

Vitamin C or ascorbic acid is a water-soluble vitamin that is present in substantial amounts in a variety of fruits and vegetables. It is an important nutrient which is involved in various enzymatic processes in the immune system and has also other physiological function in the human body (Kashiouris et al., 2020). Several formulations containing vitamin C are available for oral administration. However, when higher doses of vitamin C are needed, parenteral administration should be considered (Alan Rossetti et al., 2020). The most well-known functions of vitamin C is in the synthesis of collagen in connective tissues and as a small molecular weight antioxidant (Zhang and Liu, 2020). Vitamin C also has a basic role in the regulation of DNA and histone methylation by acting as an epigenetic cofactor for enzymatic hydroxylation (Alemdar, 2020). Moreover, this vitamin is categorized as an immunomodulator agent for its stimulating effects on interferon formation, lymphocyte proliferation support, and boosting the phagocytic ability of neutrophils (Zhang et al., 2020b). Hence, it may have a role in attenuating lung inflammation caused by coronavirus infection (Hernández et al., 2020).

Numerous animal studies revealed that vitamin C is able to control or

Table 1
The supplements mechanism of action.

Supplement Name	Functions
Vitamin C	<ol style="list-style-type: none"> 1. Synthesis of collagen in connective tissue 2. Antioxidant activity 3. Regulation of DNA synthesis and histone methylation 4. Immunomodulation by: <ul style="list-style-type: none"> - stimulating effect on the formation of IFN, - supporting of lymphocyte proliferation, - boosting of neutrophil phagocytic ability 5. Enhances innate immunity of alveolar epithelial type II via inhibition of lactate secretion
Vitamin D	<ol style="list-style-type: none"> 1. Immunomodulation by downregulation of pro-inflammatory cytokines 2. Reduce of acute lung injury by inhibitory effects on the angiotensin-2-Tie-2 and renin-angiotensin signaling pathways 3. Modulation of innate immune system 4. Modulation of adaptive immune system by: <ul style="list-style-type: none"> - suppressing Th1 responses - accelerating the induction of T regulatory cells 4. Local "respiratory homeostasis" by induction of the release of some antimicrobial peptides 5. Preserve of cell junctions 6. Consolidation of cellular immunity 7. Reduce of cytokine storm by effects on the releasing of TNF-α and IFN-γ
Melatonin	<ol style="list-style-type: none"> 1. Antioxidant activity by: <ul style="list-style-type: none"> - intracellular scavenging of hydroxyl and peroxy radicals, - indirect enhancement of antioxidant enzyme activities (including glutathione peroxidase, glutathione reductase, superoxide dismutase, and catalase) 2. Anti-inflammatory effect by preventing of the release of pro-inflammatory cytokines 3. Probable role in suppression of initial cytokine storm 4. Effect on immune system and respiratory cells via modulating of the calcium signaling pathways 5. Effect on angiogenesis via inflammatory signaling pathways 6. Anti-vascular endothelial growth factor (anti-VEGF) properties 7. Inhibition of pyroptosis
Selenium	<ol style="list-style-type: none"> 1. Antioxidant activity through incorporation into the selenoproteins 2. Affects multiple types of immune responses including the expression of inflammatory protein and cytokines 3. Effect on virus-host cell attachment interaction 4. Inhibition of angiotensin converting enzyme 5. Anti-inflammatory activity 6. Anti-clotting properties
N-acetyl cysteine	<ol style="list-style-type: none"> 1. Potential antioxidant, as a rate-limiting substrate for glutathione synthesis 2. Role in increasing the number of immune cells
Zinc	<ol style="list-style-type: none"> 1. Maintenance of adaptive and innate immunity 2. Important cofactor for several enzymes involved in the function of immune system 3. Role in proliferation, differentiation, and maturation of lymphocytes and other leukocytes 4. Regulation and formation of inflammatory responses 5. Effect on viral biological processes including replication and the translation of viral proteins 6. Antiviral activity by the stimulation of interferon-α secretion

prevent infections caused by different bacteria, viruses, and protozoa (Alemdar, 2020). Vitamin C has also shown to reduce the duration and symptoms of the common cold (Nnolim, 2020). High-dose of intravenous (IV) vitamin C infusions (e.g. 200 mg/kg/day, divided into 4 doses) could decrease the intensive care unit (ICU) length of stay by 7.8% (Hemilä and Chalker, 2019), along with a significant decrease in the mortality rate by 31.9% (Marik et al., 2017). The findings of a meta-analysis study have further shown that high-dose IV administration of vitamin C was beneficial in better management of sepsis and septic shock (Amini et al., 2020; Lin et al., 2018a). Its beneficial effect is possibly due to its immune system booster activity. High-dose vitamin C has pro-oxidant property for immune cells, while it serves as an

antioxidant for the lung epithelial cells. Furthermore, it enhances innate immunity of alveolar epithelial type II (ATII) via inhibition of lactate secretion, which is generated by over-activated immune cells (Erol, 2020; Kashiouris et al., 2020). In the largest randomized study performed so far, CITRIS-ALI, the effect of 96-h infusion of vitamin C in 167 patients with sepsis and ARDS, this supplement could not improve organ failure or biomarkers for inflammation and vascular injury. However, it significantly decreased mortality rate by 16.5% (Truwit et al., 2019). Furthermore, trial of vitamin C combination with hydrocortisone and thiamine revealed a significantly lower hospital mortality rate in comparison to control group in patients with severe pneumonia (17% vs. 39%; $P = 0.04$) (Kim et al., 2018). Several studies have also reported that vitamin C may prevent lower respiratory tract infection under some conditions. Since COVID-19 could affect the lower respiratory tract, moderate doses of vitamin C supplementation may be considered to prevent/treat the disease (Wang et al., 2020a).

In one of the first clinical trials scheduled for evaluating the effect of IV vitamin C on COVID-19, 140 patients are to be recruited to receive high dose (24 g per day) for 7 days. The need for mechanical ventilation, vasopressor therapy, organ failure scores, ICU length of stay and 28-day mortality will be assessed. The findings of this trial, which is expected by September 2020, will provide valuable information about the efficacy of vitamin C (Carr, 2020). High doses of vitamin C in COVID-19 patients have been shown to induce immunosuppression in hyper-activated immune effector cells which led to lung damage (Erol, 2020). High-dose IV vitamin C at different dosages between 10 g and 20 g daily during 8–10 h had been successfully used for the treatment of moderate to severe cases of COVID-19 in China. In critically ill patients, additional bolus doses of vitamin C were needed. Notably, in one case of severely ill patient who received 50,000 mg vitamin C infusion over 4 h, a dramatic improvement was reported. Finally, all the enrolled patients were successfully managed and discharged from hospital. Moreover, no serious side effects were reported with high doses of vitamin C in this study (Downing and Schuitemaker, 2020). In another study, three children with COVID-19 received interferon nebulizer, vitamin C, and oral Chinese medicine therapy. After receiving treatment, all three patients had improved outcomes and showed negative throat swab nucleic acid, and were discharged from hospital (Zhang et al., 2020c). The real contribution of vitamin C in this case is however not known.

A recent National Institutes of Health (NIH) expert panel document announced that a high dose of 1.5 g/kg vitamin C is safe and without main adverse effects. Intravenous and oral high-dose vitamin C have no known significant adverse effects. Thus, vitamin C could be suggested for the treatment and prevention of COVID-19 (Cheng, 2020). It must be kept in mind that high-dose vitamin C may cause osmotic death of immune cells, but not apoptosis. This could develop a local inflammation in alveolar medium. So, IV glucocorticoid therapy might be considered to alleviate the likely inflammatory consequences of high-dose vitamin C (Erol, 2020). One treatment protocol was developed to investigate the efficacy of available pharmaceuticals and nutrition such as vitamin C (20 mg/10 ml) enriched multivitamin nutraceutical syrup to inhibit the spread of SARS-CoV-2 infection to other individuals during its incubation period. The patients along with other medicines and nutrition, received 10 ml of multivitamin nutraceutical syrup orally twice a day for 4 days, then they received a single dose of 10 ml on days 5, 6 and 7. This treatment protocol successfully managed SARS-CoV-2 infection at the incubation period. Unfortunately, COVID-19 patients with underlying respiratory diseases such as diabetes, cardiovascular diseases, immunocompromised or any severe conditions; especially lower respiratory tract infection and dyspnea could not benefit from this protocol (Banerjee, 2020).

In a narrative review by BASE Medicine Task Force, 3,000 mg once daily vitamin C was recommended for COVID-19 patients (Force, 2020). In a recent review, in addition to the vitamins A, D, and B, other vitamins such as vitamin C, omega-3 polyunsaturated fatty acids, and also minerals including selenium, zinc and iron should be evaluated in nutrient

status in patients with COVID-19 (Zhang and Liu, 2020). In one case report of COVID-19, a female patient received empirical antibiotic therapy along with hydroxychloroquine. After one day of receiving therapy, the respiratory symptoms of the patient were worsened and she was intubated. Then, a high dose of IV vitamin C (6 g twice daily) and 220 mg of zinc sulfate per day by orogastric tube was initiated and added to the antiviral therapy. In spite of aggressive therapy, she experienced severe ARDS and received other treatment strategies such as higher mechanical ventilation settings, vasopressor, tocilizumab, and venovenous extracorporeal membrane oxygenation (VV-ECMO). However, four days after starting VV-ECMO, the patient died (Douedi et al., 2020). Several clinical trials were registered to evaluate the efficacy of vitamin C infusion for the treatment of COVID-19 pneumonia which are summarized in Table 2.

2.2. Vitamin D

Vitamin D, a group of lipid-soluble micronutrients, is obtained either by conversion of 7 dehydrocholesterol in our skin through exposure to UVB radiation or from some food sources (Ghavideldarestani et al., 2020). By downregulating pro-inflammatory cytokines, vitamin D exerts its immuno-modulatory activity. It reduces acute lung injury related to lipopolysaccharide in mice through inhibitory effects on the angiotensin (Ang)-2-Tie-2 and renin-angiotensin signaling pathways (Panarese and Shahini, 2020). It could also modulate innate and adaptive immune systems. Vitamin D deficiency may be present due to enhanced autoimmunity and susceptibility to infection. It is suggested that vitamin D could induce the release of antimicrobial peptides such as cathelicidins and defensins to reduce SARS-CoV-2 replication and pro-inflammatory cytokines (Zhang et al., 2020b). Other mechanisms by which vitamin D exerts its action include the following: preserving cell junctions, modulating adaptive immunity, and consolidation of cellular immunity. Vitamin D reduces cytokine storm through its effects on tumor necrosis factor α (TNF- α) and interferon- γ (INF- γ). Its modulatory effects on adaptive immunity takes place by suppressing T helper cell type 1 (Th1) responses and accelerating the induction of T regulatory cells. It can also enhance the levels of CD4⁺ T cell in HIV disease (Tian and Rong, 2020). In vitro studies have shown that vitamin D may play a basic role in local “respiratory homeostasis” by accelerating the expression of antimicrobial peptides or directly influencing the replication of respiratory viruses (Fabbri et al., 2020). The results of a meta-analysis study showed that oral vitamin D2/D3 use (up to 2000 IU daily without additional bolus) is safe and could protect against acute respiratory tract infection, especially in individuals with vitamin D deficiency (Martineau et al., 2017). It has been revealed that the infection rates reduces by increasing UV exposure and serum level of vitamin D in the body (Grant and Giovannucci, 2009). Several clinical studies also stated that lower serum vitamin D levels were significantly associated with respiratory tract infectious diseases such as influenza. Hence, vitamin D deficiency is considered as a risk factor for COVID-19 severity (Fabbri et al., 2020). The protective effect of vitamin D against COVID-19 depends on its inhibitory effect on cytokine storm and reduction in severity/risk of ARDS (Panarese and Shahini, 2020).

Vitamin D deficiency is more common in housebound, those who work at night, and elderly because of low exposure to sunlight (Zhang and Liu, 2020). One of the proposed theories for vitamin D deficiency in COVID-19 arises from breakthrough of this disease in winter of 2019. Reduction in vitamin D levels in calves increased the risk for bovine coronavirus infection (Barazzoni et al., 2020). Furthermore, vitamin D deficiency is involved in different diseases such as ARDS, tuberculosis, cardiovascular and autoimmune diseases, and some types of cancers (Li et al., 2020a). Vitamin D deficiency is the most common risk factor for ARDS, heart failure, and sepsis, as well as critically ill COVID-19 patients (Tian and Rong, 2020). It is also commonly seen in patients with hypertension, diabetes, and obesity which are all associated with increased risk for developing the severe features of COVID-19 (Rhodes et al.,

2020). Hypovitaminosis D could accelerate the renin-angiotensin system (RAS) and lead to cardiovascular disease and diminished lung function. Other characteristic of severe COVID-19 is coagulopathy. Vitamin D deficiency has been related to increased risk of thrombosis (Tian and Rong, 2020). Several studies have stated the likely relationship between COVID-19 mortality and vitamin D deficiency (Alipio, 2020a). The results of a retrospective multicenter study concluded that vitamin D status is significantly associated with clinical outcomes of patients with COVID-19 (Alipio, 2020b). It is also suggested that vitamin D could reduce the risk of COVID-19 disease and mortality (Grant et al., 2020). Furthermore, a cross-sectional analysis reported a significant relationship between the average vitamin D levels and the number of COVID positive cases ($P = 0.004274$), and also the rate of COVID-19 mortality ($P < 0.00001$) (Ilie et al., 2020). Supplementation and restoration to normal range of vitamin D in patients with COVID-19 also decreased inflammation levels and improved immunologic state during antiretroviral treatment (Caccialanza et al., 2020).

Several observational studies and clinical trials indicated that supplementation with vitamin D, with an oral dose of 50,000 IU, may reduce the risk of influenza (Grant et al., 2020). Furthermore, vitamin D helps reduce the severity of pneumonia related to coronavirus infections. More than 30 ng/mL (75 nmol/L) of 25(OH)D is suggested, preferably more than 40 ng/mL (100 nmol/L) along with adequate amount of other micronutrients and antioxidants such as zinc and selenium (Wimalawansa, 2020).

Acute lung injury (ALI) and ARDS are the most common causes of severe lung injury and respiratory failure in patients with COVID-19. Being considered as a favorable factor (Ghavideldarestani et al., 2020), vitamin D exerts its notable activities in COVID-19 infection by binding to the angiotensin-converting enzyme 2 (ACE2) receptor. This receptor is believed to be related to acute lung injury in host cells. According to experimental studies, the use of calcitriol as the active form of vitamin D, showed protective effects on lung injury by modulating components of the RAS (Kouhpayeh et al., 2020).

Regarding the protective effects of vitamin D in ALI, supplementation in deficient individuals may boost the immune system against COVID-19 and decrease its severity, especially when other comorbidities exist (Ghavideldarestani et al., 2020).

The outcome of COVID-19 patients seems to be improved by nutritional support. If the patient is undernourished, enteral feeding may be needed. In cases of inadequate gastrointestinal tolerance, parenteral nutrition might be considered (Puig-Domingo et al., 2020). Administration of calcium and vitamin D supplements and regular monitoring for serum calcium concentration have been suggested in holistic care of severe COVID-19 patients (Members et al., 2020). Administration of vitamin D3 along with thiamine and selenium were recommended in a treatment protocol for ARDS patients with COVID-19 (Jamaati et al., 2020).

It is suggested that in individuals at higher risk for influenza or COVID-19, consumption of 10,000 IU daily of vitamin D3 for a few weeks may enhance 25(OH)D levels. To achieve the goal of treatment, 25(OH)D levels should be increased above 40–60 ng/mL (100–150 nmol/L). However, in patients with COVID-19, higher doses of vitamin D3 might be considered. Thus, several large randomized clinical trials (RCT) should be carried out to assess the efficacy of these recommendations. In a recent review, consumption of oral doses of vitamin D, 200,000–300,000 IU, was suggested to decrease the risk and severity of COVID-19. All the positive COVID-19 cases as well as those with long hospital stay should consume vitamin D supplements to enhance 25(OH)D levels to prevent infection and its spread. This hypothesis however needs to be confirmed in larger group of patients with COVID-19 (Grant et al., 2020). Several RCTs of vitamin D in patients with COVID-19 have been ongoing and they are summarized in Table 2.

A growing body of news media and governmental public news updates indicate that people who are overweight or obese and of Asian, Black, and mixed ethnicity could be at a greater risk from COVID-19.

While this needs further research, speculative arguments on the link between these confounding factors and vitamin D level have been made. For example, about 25% lower level of vitamin D in overweight and over 50% less in black and Asian ethnic as compared to white have been widely reported in news media. This could account to the relatively higher number of COVID-19 death reported for the people of colour in countries such as the UK.

2.3. Melatonin

Melatonin, the classical night-time hormone which is released by the pineal gland, is derived from tryptophan (Anderson and Reiter, 2020). The powerful antioxidant and anti-inflammatory activities of melatonin have been shown in different studies. The regulation of immune system is driven by the circadian rhythm which is modulated by pineal melatonin. Thus, some conditions such as increased age or fatal viral infections, which are associated with decreased pineal melatonin, might attenuate the host's immunity (Anderson, 2019; Reiter et al., 2019). There are some evidence indicating that the initial cytokine storm due to severe viral infections may suppress the production of pineal melatonin (Pontes et al., 2007).

There are only very few reports on mortality from SARS-CoV-2 pneumonia in patients younger than 20 years old. On the other hand, older individuals have an excessively higher mortality rate. It could be hypothesized that the reduced level of melatonin in this group of patients makes them susceptible to SARS-CoV-2 infection (Scheer et al., 2004; Zisapel, 2018). Some evidence indicated the zoonotic transmission of coronavirus from bats to humans (Calisher et al., 2006; Wang et al., 2006; Wong et al., 2019). Considering that bats live in dark places during the day-time and also staying awake at night, a higher levels of melatonin are present in this group of animal (Haldar and Yadav, 2006; Heideman et al., 1996). Thus, there may be some protection against severe pneumonia due to coronavirus in bats (Shneider et al.).

It has been shown that in viral respiratory infections, such as SARS-CoV-2, the oxidative stress, which is characterized by imbalance between the levels of ROS and antioxidants, is significantly high (Khomich et al.). Unlike classical antioxidant agents such as vitamins E and C, which bind to one oxygen free radical, melatonin is able to bind with up to ten free radicals (Emerit et al., 2004; Tan et al., 2007). It appears that melatonin is capable of protecting cells against oxidative damage via intracellular scavenging of hydroxyl and peroxyl radicals (Reiter et al., 1995; Reiter et al., 1994). Moreover, melatonin can indirectly enhance the antioxidant activities of glutathione peroxidase, glutathione reductase, superoxide dismutase, and catalase (Emerit et al., 2004; Reiter et al., 1997; Reiter, 1997, 2000). Indeed, melatonin play its role as antioxidant in human cells only at its pharmacological concentrations (Reiter et al., 1994). The reduction in the activity of antioxidant enzymes due to the long-term sleep deprivation leads to the development of oxidative stress (Ramanathan et al., 2002; Teixeira et al., 2019) and consequently deterioration of immune functions. Because of significant impairment in melatonin production in people with chronic insomnia, taking melatonin may restore the normal sleep pattern and decrease anxiety during COVID-19 crisis (Shneider et al.). One of the most important complications in SARS-CoV-2 infection is pulmonary fibrosis which may also be caused by mechanical ventilation-induced oxidative stress (Cabrera-Benítez et al., 2016; Lionetti et al., 2005). Melatonin through its potent antioxidant effects and inhibition of oxidative stress may prevent pulmonary fibrosis (Shneider et al.).

It has been shown that melatonin modulates the calcium signaling pathways by binding to calmodulin (Romero et al., 1998). This signaling pathway has a broad spectrum of roles in cellular activities and apoptosis. Hence, melatonin may affect the immune system and respiratory cells via regulating this pathway during COVID-19 infection. Moreover, it has been revealed that melatonin influences angiogenesis through inflammatory signaling pathways (Mirza-Aghazadeh-Attari et al., 2020).

Development of ARDS during COVID-19 infection is accompanied by increased pulmonary vascular permeability and alveolar injury. In this process, the vascular endothelial cell growth factor (VEGF) can increase vascular permeability. Hence, the VEGF has potential role in the pathogenesis of ARDS (Medford and Millar, 2006). The anti-VEGF properties of melatonin on angiogenesis has also been stated in different studies (Alvarez-García et al., 2013a, 2013b; Alvarez-García et al., 2013a, 2013b; Carbajo-Pescador et al., 2013; Mirza-Aghazadeh-Attari et al., 2020). Thereby, melatonin may influence pulmonary vessels permeability during COVID-19.

Molecular studies have shown that melatonin could inhibit pyroptosis, a highly inflammatory form of programmed cell death (Cookson and Brennan, 2001; Yang, 2020). Moreover, melatonin prevents the release of pro-inflammatory cytokines (Panesar, 2003; Shi et al.) via inhibition of NLRP3 (nucleotide-binding domain leucine-rich repeat and pyrin domain containing receptor 3) inflammasome during the severe lung injury by SARS-CoV (Kouhpayeh et al., 2020; Man et al., 2017; Zahid et al., 2019).

In the cases of melatonin combination therapy with antiviral and immunomodulatory agents, there have been several satisfactory reports. Treatment of rats with lopinavir/ritonavir (LPV/r) combination with melatonin resulted in a significantly decreased level of oxidative stress and kidney damage (Adikwu et al., 2019). In order to alleviate the side effects associated with LPV/r, it is recommended to use melatonin as an adjuvant modality (Shneider et al.). Additional benefits of nucleotide analogues, such as ribavirin and remdesivir, in combination with melatonin have also been observed (Han et al., 2007; Law et al., 1986). Moreover, the adverse effects of chloroquine and hydroxychloroquine for treatments of COVID-19 may be alleviated with melatonin combination therapy (Michaelides et al., 2011; Shneider et al., 2020). An even higher efficacy for prednisolone administration would be expected in COVID-19 patients when it is combined with melatonin (Shneider et al.).

Melatonin has a high bioavailability and can penetrate the blood-brain barrier and placenta (Reppert et al., 1979). Evidences have shown that acute toxicity due to melatonin administration is very rare (Malhotra et al., 2004; Nordlund and Lerner, 1977; Papavasiliou et al., 1972). Because of the naturally high level of melatonin synthesis in children, adolescents, and young adults, it is recommended to cautiously administer this agent in this group of population.

However, the potential effectiveness of melatonin supplementation in COVID-19 patients should be confirmed in clinical trials. In a multi-center randomized controlled trial on 450 Spanish participants among healthcare workers (NCT04353128), the prophylactic effect of melatonin is being investigated with 12 weeks therapy regimen (Members et al., 2020). Moreover, a randomized, single-center clinical trial on 20 Iranian patients is registered for investigating the efficacy of supplementation with melatonin, vitamin C and zinc in combination with standard protocol medications (Jamaati et al., 2020). Furthermore, the effects of melatonin combination therapy with standard treatment is being evaluated in an ongoing clinical trial in COVID-19 patients and their effects on patients' outcomes and the quality of sleep will be evaluated (2020). In another randomized, double blinded clinical trial, the effects of melatonin on duration of clinical recovery, improvement of laboratory parameters and radiographic imaging are being evaluated in patients with COVID-19 (Amini et al., 2020). A recently published algorithm suggested high doses of melatonin (40 mg per day) for prevention of COVID-19 in elderly, health care providers and patients with comorbidities (Reiter et al., 2020). The possible effects of melatonin on clinical outcomes in these trials have not been reported yet. Their results could clarify the exact role of melatonin in the prevention and treatment of COVID-19.

2.4. Selenium (Se)

Selenium (Se) is an essential trace element and a potent nutritional antioxidant that affects different types of immune responses (Hoffmann

and Berry, 2008; Zhang and Liu, 2020). Se induces its biological effects through incorporation into selenoproteins which play critical roles in reducing oxidative stress in human. Modest Se deficiency and selenoproteins polymorphisms are associated with immune system dysfunction. Twenty five selenoproteins genes are expressed in human immune cells with the highest level of expression being observed in T helper-1 lymphocytes and macrophages (Fairweather-Tait et al., 2011; Hoffmann and Berry, 2008). Furthermore, the mRNA expression of macrophage inflammatory protein and mRNA levels of cytokine were modified in Se-deficient mice. Interleukin (IL)-4, IL-5, IL-10, and IL-13 were boosted, whereas INF- γ and IL-2 were decreased, which suggested that Se differentially affects multiple types of immune responses (Gasmi et al., 2020). This substantiates that Se supplementation is necessary in viral infections. Previous evidence also suggested that correcting Se levels in Se-deficient individuals improves immunity when compared to Se-normal individuals (Hoffmann and Berry, 2008).

Micronutrients deficiencies, especially the essential trace element Se, is associated with several viral and bacterial infections. Dietary Se has improved several clinical and lifestyle variables in patients co-infected with viral and bacterial infections (Steinbrenner et al., 2015). In the 1990s, Beck laboratory published a set of studies indicating that Se deficiency increased the pathogenicity of some RNA viruses (Zhang et al., 2020a).

Moreover, Se-deficiency influences several aspects of RNA viruses such as mutations, replication and virulence. Various mechanisms by which Se might be effective include the following: virus-host cell attachment interaction, host antioxidant capacity amendment, potential inhibition of ACE, anti-inflammatory and anti-clotting properties. Therefore, Se has a potential role in the management of COVID-19 patients. However, its potential benefit versus risk is not so obvious (Hiffler, 2020; Wilgers, 2020). It has been shown that critically ill patients suffering from viral diseases had a rapid drop in Se level and also worse outcomes in comparison to individuals with adequate levels of Se. Since then, the focus on Se-deficiency as a main risk factor for poor outcomes in viral diseases has increased (Wilgers, 2020). Although numerous micronutrients, such as Se, zinc and iron are essential in host defense against infectious diseases, dietary intake alone might not be sufficient in certain conditions (Gasmi et al., 2020; Zhang and Liu, 2020).

Many of typical manifestations of sepsis or septic shock, including hypotension, cold extremities, metabolic acidosis, weak peripheral pulses and even multiple organ failure developed in many critically ill COVID-19 patients (Li et al., 2020b). The effects of high doses of Se in patients with severe septic shock were evaluated in different studies. In a prospective, multi-center placebo-controlled, randomized, double-blind clinical trial, patients in the intervention group received 4000 mg Se on the first day, and 1000 mg per day on the following nine days. In the second group, patients received placebo as IV infusion. The results of this study indicated that the rates of adverse effects were similar in both groups and there was no significant difference in mortality rates between groups. However, the use of bolus high-dose Se in patients with hemorrhagic fever with renal syndrome, caused by Hantaan virus, has been associated with reduced mortality rate (Forceville, 2007). The possible role of Se in septic shock needs to be explored through further studies.

In order to determine the role of Se deficiency in influenza virus infection, two infected Se-deficient and Se-adequate infected mice groups were evaluated. Interstitial pneumonitis was more severe in Se-deficient group. It is believed that this complication was related to significant alterations in mRNA levels for cytokines and chemokines involved in pro-inflammatory responses. The Se is the most important nutrient for immune system to fight viral infections and its deficiency leads to a weak immune system so that a mild viral infection can change to dangerous infection. Thus, adequate nutrition containing Se, is essential for protection against viral infection (Beck et al., 2001;).

In order to evaluate the efficacy of Se in COVID-19 patients, a double-blind, randomized, placebo-controlled, phase IV study was registered on

May 2020 in Saudi Arabia (NCT04323228). A total of thirty SARS-CoV-2 positive participants are enrolled into two study groups; intervention group (n = 15) and placebo group (n = 15). The intervention group receive oral nutrition supplement (ONS) enriched in eicosapentaenoic acid (EPA), γ -linolenic acid and antioxidants daily. The composition of 8 fluid ounce of the ONS group includes the following: 14.8 g protein, 22.2 g fat, 25 g carbohydrate, 355 kcal, 1.1 g EPA, 450 mg DHA, 950 mg GLA, 2840 IU vitamin A as 1.2 mg β -carotene, 205 mg vitamin C, 75 IU vitamin E, 18 ug Se and 5.7 mg zinc. The composition of the control group has the same macronutrient composition, calorie density, and normal concentrations of vitamin A, C, E, Se and zinc. All patients are to be assessed at the baseline and reassessed again after 7 and 14 day-period. Nutritional screening by Nutritional risk screening 2002 (NRS-2002), anthropometric measurements, clinical assessment, and biochemical data will be used for assessment. Change from baseline score of NRS-2002, ferritin level, IL-6, C-reactive protein (CRP), TNF- α , and monocyte chemoattractant protein 1 (MCP-1) are to be measured as primary outcome. This trial is expected to conclude by the end of October 2020 (Marik et al., 2017).

2.5. N-acetylcysteine

In the 1960s, N-acetylcysteine (NAC), a derivative of the natural amino acid cysteine, was presented as a safe mucolytic drug for respiratory diseases. It has other indications in hospital setting including acute bronchopulmonary diseases, paracetamol antidote and is also a potent antioxidant. NAC breaks disulphide bridges between macromolecules leading to mucus viscosity reduction (Medici and Radjelovic, 1979; Van Hecke and Lee, 2020).

NAC is used as a rate-limiting substrate for glutathione (GSH) synthesis. GSH serves as an antioxidant in the body and decreases the production of proinflammatory cytokines. At the dose of ≥ 1200 mg daily, NAC acts as a potential antioxidant that can combat COVID-19 which has a strong oxidative stress component in its pathology (Teskey et al., 2018; Van Hecke and Lee, 2020).

ARDS is one of the main reasons for fatality in COVID-19 patients. As explained in the preceding sections, this is due to cytokine storm syndrome, a systemic inflammatory response arising from increased oxidative stress due to rapid release of free radicals and cytokines, which leads to cellular injury, organ failure and death. Early use of large doses of compounds with antioxidant properties, including NAC, may become an effective strategy in treating these patients (Cheng, 2020). Previous studies showed that NAC has anti-viral activity against influenza A (H3N2 and H5N1) (Ghezzi and Ungheri, 2004). Enhancement of GSH levels could diminish viral load by inhibiting viral replication. NAC can also help combat COVID-19 by increasing the number of immune cells that fights viral infections. This improvement in immunity may help the COVID-19 patients to be discharged from critical care unit (ICU) or go off a ventilation support (Van Hecke and Lee, 2020).

At the present time, there is no approved drug or vaccine for the management of COVID-19. A therapeutic protocol suggested in April 2020 contained an IV cocktail of 1 mg/kg reduced methylene blue, 1–2 gram (g) vitamin C, 0.5–1 g NAC and 10–20 g Urea (optional) in 100 ml of dextrose water (5%). Hyperinflammation and oxidative stress are common in the pathophysiology of COVID-19 and reduced methylene blue can prevent inflammation and diffusion of RNA-viruses. In this connection, NAC and Vitamin C are two commonly used medications in the management of lung injury. NAC has also anti-inflammatory effects and has been used to improve the penetration of other medications into the tissues (Celleno, 2018; Hamidi Alamdari et al., 2020).

Heretofore, three phase I and II clinical trials were conducted to evaluate the efficacy of NAC in positive cases with severe COVID-19 infections. The first non-randomized, phase II trial was started on May 1, 2020 and estimated to be completed on May 2021. Eighty-six severe or critically ill participants with refractory COVID-19 infection in both arms, A and B, will be enrolled. In Arm A, the included cases were

mechanically ventilated patients who are managed in a critical-care. In Arm B, the patients would be non-mechanically ventilated, non-critical-care. Both arms of the study will receive 6 g/day intra-venous NAC in addition to COVID-19 supportive therapy at the discretion of treating physicians. The outcome of the study in Arm A will be discharge from critical-care unit, extubation, toxicity, and death. In Arm B, discharge from hospital, admission to a critical-care unit, intubation, toxicity, and death will be evaluated and recorded [Time Frame: 1 year] (Erol, 2020).

In a double-blind randomized placebo-controlled clinical trial, NAC at dosage of 600 mg twice daily dramatically attenuated influenza when compared with placebo in a population of 262 frail older adults. In the intervention group, participants showed less clinical illness and the influenza episodes were much less severe. In addition, cell-mediated immunity in the NAC group improved significantly when compared to the placebo group (De Flora et al., 1997; Millea, 2009). The clinical effectiveness of intravenous NAC for the management of sepsis or septic shock was also evaluated. However, NAC showed no significant effect on the average length of stay in a hospital, mechanical ventilation duration, and organ failure. Early and late application of NAC did not affect the oxidato-inflammatory responses (Szakmany et al., 2012).

By April 19, 2020 another phase I randomized study was registered to evaluate the efficacy of combination of methylene blue, vitamin C, and NAC in COVID-19 patients (NCT04370288). The control group received standard medical therapy (supportive therapy), while the intervention group was treated with the combination containing NAC. Ventilator-free days, mortality rate, Pao₂/Fio₂ ratio, average length of stay in hospital and ICU, days free from dialysis, serum CRP level, and WBC count are primary and secondary outcomes of the study. The final results of the trial is expected to be released by September 2020 (Truwit et al., 2019).

For the therapeutic management of pulmonary fibrosis due to COVID-19 pneumonia, a clinical trial consisting of 136 participants is being conducted in two intervention and control groups. Patients in the intervention group are to receive one capsule of NAC and four Fuzheng Huayu tablets three times a day for 24 weeks and subjects in control group are administered placebo instead of Fuzheng Huayu tablet. High-resolution computed tomography (HRCT) score and lung function improvement are the primary outcomes, while acute exacerbation time, 6-min walking test, dyspnea scores, and composite physiological index are secondary outcomes that will be measured at week 24. Details of all ongoing trials are summarized in Table 2 (Kim et al., 2018).

2.6. Zinc

Zinc is a metal which is crucial for many biological processes such as metabolism of lipids and carbohydrates. It helps maintain the proper function of the nervous and the cardiovascular systems. Zinc exerts its functions as a signaling molecule and cofactor as well as a structural element (Escobedo Monge et al., 2019). In the human body, there is almost 2–3 g of zinc which is stored in nucleus, cytosol, and cell membrane (Chasapis et al., 2012). It is estimated that about 2 billion people around the world suffer from zinc deficiency. The deficiency of this essential metal dramatically affect population health (Skalny and Rudakov, 2004). The adverse effects of zinc deficiency on elderly and infants are considered to be higher. Therefore, more attention should be paid to these groups of people to take supplemental zinc (Yasuda, 2017).

It should be mentioned that an excessive amount of zinc may cause impairment of the immune system, so both excessive amount of zinc intake and zinc deficiency are considered to be harmful to the body (Molina-López et al., 2016). Proteins responsible for zinc transportation are needed to maintain cytosolic and intracellular concentrations of Zn. Homeostasis of cellular zinc includes the following mechanisms: the first mechanism is modulated by a group of proteins called ZIP-family importers (Zrt-, Irt-like proteins, or SLC39), which transport zinc into the cytosol. The second mechanism is exporting zinc out the cytosol with the help of ZnT-family (ZnT or SLC30) and the last one is performed by

proteins maintaining the homeostasis of Zn ions (Bafaro et al., 2017; Molina-López et al., 2016). Zinc homeostasis has a critical role in the maintenance of adaptive and innate immunity. Zinc as an essential nutrient and a metal cofactor is needed by several enzymes for proper function of the immune system (Park et al., 2004). Indeed, one of the critical mechanisms for protecting the human body against pathogens or even overreaction of the body's immune system is balancing the homeostasis of zinc (Wessels et al., 2017). The transportation of Zn in the blood is through binding to transferrin, α -2-macroglobulin, albumin, and amino acid. One of the principal control area for the regulation of Zn serum level is the gastrointestinal tract. The small intestine is where zinc absorption takes place. Zinc homeostasis is also being regulated by Zip 4 transporters that aid zinc absorption into intestinal cells (Myers et al., 2017; Pascual et al., 2012).

Zinc plays a critical role in proliferation, differentiation, and maturation of lymphocytes and leukocytes. Additionally, this essential element is involved in the regulation and formation of immune system and inflammatory responses. Hence, a significant role for zinc in the immune system function is undeniable (Maywald and Rink, 2019; Wessels et al., 2017).

Zinc acts against viral infection targeting the respiratory system by affecting biological processes including replication and the translation of viral proteins (Ishida; Phillips et al., 2017). Some studies have shown that the increase in the production of INF- α by leukocytes takes place in response to viral infection (Nagamine et al., 2000; Takagi et al., 2001). It has been suggested that zinc stimulates the antiviral activity of INF- α by upregulating enzymes with antiviral effects and through mediating downstream signaling of Janus kinase1-signal transducer and activator of transcription 1 (JAK1-STAT1). These antiviral enzymes inhibit the viral RNA translation and involve in degradation of viral RNA (Lin and Young, 2014).

Zinc, with its potential antiviral properties, may be considered as an adjuvant therapeutic approach in COVID-19 management. An in vitro experimental study has shown that chloroquine has antiviral activity against SARS-CoV-2. However, the exact mechanisms of its antiviral function is unclear and is in need further investigations (Wang et al., 2020b). Chloroquine, as ionophore of zinc, increase in zinc flux into the cells. It is also hypothesized that zinc supplementation does not have chloroquine-related side effects (Guastalegname and Vallone, 2020; Xue et al., 2014). Another zinc ionophore, quercetin, could be used instead of chloroquine. This agent has lower adverse effects, however, more experimental studies are required to support this hypothesis (Dabagh-Bazarbachi et al., 2014).

The release of zinc from papain-like protease by using disulfiram would result in destabilization of this protein. Therefore, this antiviral supplement is considered as a potential treatment strategy for SARS-CoV-2 (Lin et al., 2018b). SARS-CoV-2 needs ACE2 for entrance into the host cells and hence modulation of ACE2 receptor has been considered for COVID-19 therapy (Hoffmann et al., 2020; Lan et al., 2020). The reduction in the activity of recombinant human ACE2 has been observed in rat lungs after exposure to 100 μ M of zinc. This amount is nearly the same as the total recourses of zinc in human body. Therefore, to better understand the efficient concentration of zinc for SARS-CoV-2 and ACE2 interaction, more experiments should be done (Chilvers et al., 2001).

It is hypothesized that zinc might have a role in amelioration of the dysfunction of mucociliary clearance induced by COVID-19. Respiratory epithelium requires zinc for its anti-inflammatory and antioxidant properties. Zinc also helps in increasing the barrier function of tight junction protein ZO-1 and Claudin-1 (Roscioli et al., 2017). The combination of zinc and pyrithione has been reported to inhibit SARS coronavirus replication at low concentrations (Te Velthuis et al., 2010).

One of the key factors in the pathogenesis of COVID-19 is local and systemic inflammation, hence an agent with anti-inflammatory properties is crucial in the management of this viral infection (Mehta et al., 2020). There are several reports of interstitial pulmonary fibrosis in

patients with COVID 19. Notably, extracellular matrix inflammatory changes of the lung, which may lead to fibrosis, is also associated with zinc deficiency. Therefore, zinc supplementation may play a critical role in the treatment of COVID-19 (Luo et al., 2020).

Several RCTs are currently underway to evaluate the impact of zinc on patients with COVID-19 (Table 2).

3. Conclusion

The morbidity and death caused by COVID-19 are highly dependent on the severity of the immune reaction to SARS-CoV-2 infection. The pathological cascades from the requirement of oxygen supply to severe cases of pneumonia and ARDS involve hyperinflammatory reaction with prevalent cytokine storm and oxidative stress. Since no known therapeutic approach is available to treat COVID-19, different agents with previously known antiviral properties are being evaluated and trying out to lower the viral burden. This article outlines the therapeutic and prophylaxis potential of some selected supplements in COVID-19. The indicated vitamins (e.g., vitamin C and D) and micronutrients (e.g., Se) have been shown to have antiviral potential in the various experimental models and clinical trials. The results of these undergoing clinical trials would determine the exact role of these supplements as adjuvants and potential alternatives for better management of SARS-CoV-2 infection.

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

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