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Review Article

A Recent Update on the Role of Nutraceuticals in COVID-19 Infection

Adil Farooq[1], Muddasir Hassan Abbasi[1,*], Muhammad Babar Khawar[2,*], Nadeem Sheikh[3,*]

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[1]*Department of Zoology, University of Okara, Renal Khurd, 56300, Pakistan*

[2]*Applied Molecular Biology and Biomedicine Lab, Department of Zoology, University of Narowal, Narowal, Pakistan*

[3]*Cell and Molecular Biology Lab, Institute of Zoology, University of the Punjab, Lahore-Pakistan*

Correspondence

Muddasir Hassan Abbasi, Department of Zoology, University of Okara, Renal Khurd, 56300, Pakistan

Email: dr.muddasir@uo.edu.pk

Correspondence

Muhammad Babar Khawar, Applied Molecular Biology and Biomedicine Lab, Department of Zoology, University of Narowal, Narowal, Pakistan

Email: babar.khawar@uon.edu..pk

Correspondence

Nadeem Sheikh, Cell and Molecular Biology Lab, Institute of Zoology, University of the Punjab, Lahore-Pakistan

Email: nadeem.zool@pu.edu.pk

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ABSTRACT

The viral infection (SARS-CoV-2) COVID-19 has played havoc on the health of the human population globally. In late December 2019, the first case of COVID-19 was reported in Wuhan city, China. Its destructive effects like acute respiratory distress syndrome then began to be globally reported. Many treatment options such as remdesvir and dexamethasone were used to treat and reduce the hospitalization rate among COVID-19 patients. Numerous scientific studies have reported the use of nutraceuticals as a therapy for COVID-19 patients to enhance immunity. Differently formulated multivitamins that are water and fat-soluble (A, B complex, D, and C) and minerals like Mg and Zn minimize the virulence of COVID-19, oxidative stress, C-reactive protein, as well as boost the immunity.

Key words: SARS-CoV-2, COVID-19, water and fat-soluble multivitamins, acute respiratory distress syndrome

INTRODUCTION

Tyrell and Bynoe worked initially on coronaviruses in 1966 by isolating the infections from individuals with ordinary colds. COVID-19 viruses are contained, large RNA viruses with a single-stranded RNA strand that is positive in the human population [1]. In late December 2019, in Wuhan, China, a new type of coronavirus called the novel coronavirus (2019-nCoV, or COVID-19) was identified. It then spread rapidly throughout the whole of China and then worldwide [2]. SARS-CoV-2 (enclosed virus with a 32kb genomic size) also affects the respiratory tract due to infection and the alveolar epithelium tissue of the inner lungs via receptor-mediated engulfing with the help of angiotensin-converting enzyme II (ACE2) serving as a door receptor [3] **(Figure 1).**

Chan *et al.* reported that the initial diagnostic symptom of SARS-CoV-2 was pneumonia linked to infection with COVID-19. The present study reveals that in infants, it causes gastrointestinal infection and asymptomatic infections [4]. SARS-CoV-2 is a beta coronavirus of the B lineage that is usually correlated to SARS-CoV [5,6].

According to the innumerable amount of research, COVID-19 is propagated by an inflammatory process produced by immune system hyperactivity in an attempt to destroy the virus. Persistent inflammation can lead to lung tissue loss, pulmonary-edema fluid exudation, dyspnea, and pulmonary disease [7].

Coronavirus causes a decrease in the alveolar lacunar sac spaces of the patients' lungs and ultimately, apoptosis (cell death) [8]. COVID-19 decreases the number of lymphocytes in the peripheral blood while elevating the inflammatory cytokine concentration in the serum. In an intense condition of COVID-19, the patient's respiratory tract inflammation cause significant pulmonary function impairment and the cytokines responsible are generated by inflammatory monocytes [9]. Scientists have discovered a cure for such patients. This quick endeavor resulted in the discovery of certain potential pharmacological medicines for hospitalized patients, including remdesivir and dexamethasone [10,11].

During the pandemic, the consumption of nutraceutical products was greater and showed a double-digit percentage of growth worldwide because they provide prophylactic and therapeutically effects against disease prevention [12–15]. It is also considered that fat and water-soluble vitamins like vitamin B complex, C, and D along with trace minerals Zinc (Zn), Magnesium (Mg), and Iron (Fe) have a significant role in the treatment of COVID-19. They transfer a synergistic effect to the patient by promoting the antioxidant activity in the body and also competing with the energy level.

FAT-SOLUBLE VITAMIN

Covid-19 and Vitamin D

Martineau *et al.* reported that the intake of vitamin D is an efficacious supplement used for the prevention

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of COVID-19 infection [16]. The link between vitamin D and COVID-19 is obvious enough because vitamin D kills renin, and less so angiotensin I (the precursor to angiotensin II) is created [17,18]. Straight inhibition can be used in the construction of angiotensinogen II as well as ACE by vitamin D [6,19]. Regarding respiratory disorders, vitamin D also has an established control over the immuno-pathological inflammatory responses [16]. According to a study published in March 2020, the regular intake of vitamin D is the link between age, the prevention of comorbidities, and vulnerability. It can reduce the risk of chronic diseases such as COVID-19 infection [20].

Murdaca *et al.* reported that supplements with energy boosters were more effective in patients suffering from viral infections due to COVID-19 [21]. Vitamin D affected the mortality of the microbes in three respective way: it affected the corporeal barriers, sometimes affected the cellular normal immunity, and also affected the adaptive immunity [22]. COVID-19 individually affects the natural immune system response like when it is infected by other microorganisms, producing both pro-inflammatory and inflammatory cytokines at the same time [23]. Antipsychotics, antineoplastic, anti-infective, and anti-inflammatory treatments, as well as antihypertensive, antiretroviral, endocrine pharmaceuticals, and some herbal medicines can reduce the level of vitamin D in the bloodstream by activating the transmitter [24]. Vitamin D supplementation also has a significant role in antioxidation activity [25] **(Figure 2)**.

Deficiency in vitamin D levels was also an interconnected reason for the amplified risk of COVID-19 infection in the research done in Israel [26]. Comparative studies reveal that the risk of COVID-19 was greater in the vitamin D deficient group compared to a vitamin D-rich group according to a retrospective cohort study conducted at the University of Chicago [27]. Danesh *et al.* observed that addressing the severe vitamin D insufficiency ultimately diminishes the probability of elevated CRP levels [28]. CRP is a surrogate marker for cytokine storm which is predicted to be increased in severe COVID-19 patients [29]. The supplementation of vitamin D is highly constructive when it comes to the reduction of circulating highly sensitive CRP [30].

Water-Soluble Vitamins

Vitamin C

One of the trace micronutrients — vitamin C — has been proven to have a critical role in the treatment of COVID-19, especially during the very first phase of infection when it was observed that the vitamin C levels in both serum and leukocytes are low [5]. COVID-19 infection leads to an increase in reactive oxygen species production and an increase in the production of proinflammatory cytokines, leading to cytokine storm, both of which cause serious lung difficulties and contribute to the formation of adult respiratory failure syndrome (ARDS) [31,32]. Vitamin C may have an antiviral effect according to the findings from in vitro investigations and clinical trials. A loaded dose of vitamin C is thought to have virucidal properties since it inhibited viral growth [5].

Vitamin C may aid in the enhancement of innate immunity as well as cellular and humoral immune responses. The inadequate ingestion of micronutrients like vitamin C has been found to lower infection resistance [33] and it is the initial line of defense against foreign pathogens like viral infections [34]. Vitamin C appears to accumulate intracellularly in the neutrophils, implying that it plays a role in maintaining leukocyte activity and that it may have an anti-apoptotic effect on the neutrophils under the peripheral circulation [5,35]. Vitamin C vitally inhibits the cohort of proinflammatory cytokines which may help to mitigate the cytokine storm caused by COVID-19 infection, resulting in less inflammatory-induced tissue damage [36]. Abobaker *et al.* reported that Vitamin C may also decrease the negative immunological effects of SARS-CoV-2 contamination, allowing it to be a viable therapy option for COVID-19 (5). Vitamin C lowers the level of immune reactivity and OS, as well as immunological dysfunction, both of which are important pathophysiological processes in sepsis [37]. Gao *et al.* reported in their study that Vitamin C reduced the T regulatory cells' negative immunoregulatory function, promoting a T cell-mediated cellular immune response and ameliorating sepsis-induced multi-organ failure illness [38].

COVID-19 reduces the development of cytokine storm when the late stage of COVID-19 infection is reached [39]. Severe SARS-CoV-2 virus causes endothelial destruction and malfunctioning which ultimately increases the likelihood of extensive microscale and macrovascular thrombosis and multi-organ failure [40]. Vitamin C has the capability to maintain the dysfunction of the endothelial tissues in Covid-19 and it may also contribute to reducing lung inflammation and damage [41]. Cheng *et al.* reported the remarkable result following a loaded dose of vitamin C in the treatment of Covid-19 pneumonia [42]. A deficiency in vitamin C can be controlled by environmental factors such as air quality and the prevalence of diseases, including type 2 diabetes [34].

Table 1: Clinical trials of nutraceuticals against COVID-19 (htps://www.clinicaltrials.gov/)

Serial No.	NCT No.	Disease Target	Intervention	No. of Subjects	Phase
1.	NCT05126602	COVID-19	Vit-D	60	NA
2.	NCT04449718	COVID-19	Vit-D	240	NA
3.	NCT04483635	Prevention of COVID-19	Vit-D	34	III
4.	NCT05221983	COVID-19	Vit-D	168	NA
5.	NCT04334005	Severity of COVID-19	Vit-D	200	NA
6.	NCT04628000	COVID-19 Disease severity	Vit-D	50	NA
7.	NCT04411446	COVID-19 patients	Vit-D	218	IV
8.	NCT04579640	COVID-19 and Other Acute Respiratory Infections	Vit-D	6200	III
9.	NCT04710329	critically Ill COVID-19 patients	Vit-C	78	NA
10.	NCT04323514	COVID-19	Vit-C	500	NA
11.	NCT04344184	Novel Coronavirus, Acute Lung Injury	Vit-C	48	II
12.	NCT04335084	COVID-19 Preventing Infection	Vitamin C, D, Zn+	600	II

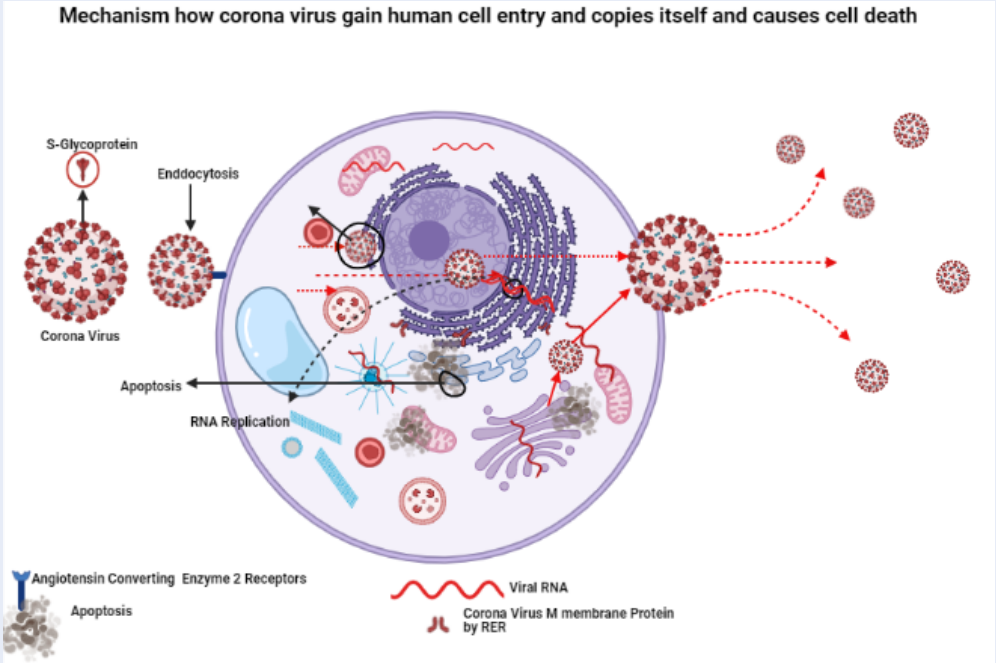

Figure 1: Mechanism of coronavirus penetration in the cell. The Angiotensin-converting enzyme-2 aid Coronavirus penetrate the cell and then replication of its RNA and destruction of the cell along with its organelles. This figure was drawn originally by the authors using the Biorender.com platform.

One of the respiratory disorders, ARDS pulmonary edema, is due to the prevalence of liquid and protein in the structural unit of the lung alveoli. Cell surface disruption in the lung tissue such as in the endothelium leads to an increase in the penetration of fluids, neutrophils, and erythrocytes which results in an overabundance of these components in the alveolar spaces, making the passage narrow[43]. During acute lung damage, neutrophils in the intravascular and extravascular areas are typically linked with platelets, producing a combined cause of oxidative stress due to their inflammatory thrombogenic function[44]. In patients with ARDS, a higher concentration of vitamin C is connected to a range of positive outcomes including reduced inflammatory functions, the prevention of organ damage, lower pathogenic infections and virulence, and an improved immune system[45]. Vitamin C has potent antioxidant and anti-inflammatory capabilities, reducing the risk of oxidative cellular harm and inhibiting cytokine storm, an excessive inflammatory response. By increasing interferon generation and stimulating cell multiplication, vitamin C improves the swarm's antiviral immune response[5].

Supplementation of B complex and COVID-19

B1

Multi-functioned vitamin B1 overcomes the diabetic threat, prevents cardiovascular disease, improves mental health, reduces the risk of cancer, and improves immune activity[46]. Its deficiency also causes multiple malfunctions in the body such as neuronal inflammation and abnormal antibody responses[47]. Critically, T-cells are necessary to eradicate the SARS-CoV-2 virus and a thiamine deficiency can lead to a decrease in antibody levels. The use of appropriate thiamine reduces the symptoms of SARS-CoV-2 infection and the associated inflammatory processes. Additionally, the signs of coronavirus are strikingly similar to those of elevation sickness, including the high risk of pulmonary edema[48]. An increase in thiamine given to persons with COVID-19 in the early stages may help to prevent hypoxia and nosocomial infections[46].

B2

The combination of riboflavin and ultraviolet light damages DNA and RNA and prevents viral replication in the body. Furthermore, riboflavin-UV was fond to decrease the infectious frequency of SARS-CoV-2 in the blood plasma underneath the finding threshold[49].

B3

Nicotinamide is a type of cofactor that turns into a constructive block (NAD and NADP). It plays an active role in chronic general infection[50]. NAD+ is a molecule with immunomodulatory characteristics that is produced during the early stages of inflammation. IL-1, 6, & TNF-α are examples of pro-inflammatory mediators that can be reduced[51]. Viral nucleotides replication is compacted by nicotinamide and it provides strength to the body's immune system[1,52]. Furthermore, B3 individually lowers neutrophil infiltration and has an anti-inflammatory impact on the breathing mechanism of the lungs, as well as Niacin. Nicotinamide protects the lung tissue[46].

B9

B9 (Folic Acid) is a necessary cofactor in the replication of hereditary material and protein synthesis via polypeptide chain synthesis, and it also works as an inflammatory reaction. Furin is a pathogenesis-related enzyme in bacteria that can be a promising infection treatment target. Furin, which prevents the SARS-CoV-2 spike protein from sticking to the host cell, is reduced by folic acid, blocking the cell entrance and virus turnover. As a result, folic acid has been proposed as a potential treatment for COVID-19-related respiratory illness in its early stages[53]. Kumar *et al.* reported that the molecular modeling of folic acid with its analogs tetrahydrofolic acid and 5-methyl tetrahydrofolic acid exhibit substantial then consistent binding with SARS-CoV-2. Thus, folic acid can be used as a treatment line for COVID-19[54].

B12

Red blood cell creation by B12 supplies energy directly to the brain system and allows for rapid DNA production. Cobalamin is an essential nutrient for human health. The vigorous formulation of vitamin B12 involves hydroxo-adenosyl- and methyl-cobalamin[51].

In contrast, SARS-CoV-2 may interfere with vitamin B12 metabolism, restricting microbial proliferation in the intestine. Vitamin B12 deficiency may incur similar risks to COVID-19 infection including increased OS and lactate dehydrogenase, hyperhomocysteinemia, thickening flow activation, blood vessel constriction with rising pressure, and renal and bronchial vasculopathy[46]. A B12 insufficient intake can also cause disorders in the respiratory, digestive, and neurological systems[55]. According to Dos Santos *et al.*, B12 can reduce COVID-19-related organ failure and its effects[56].

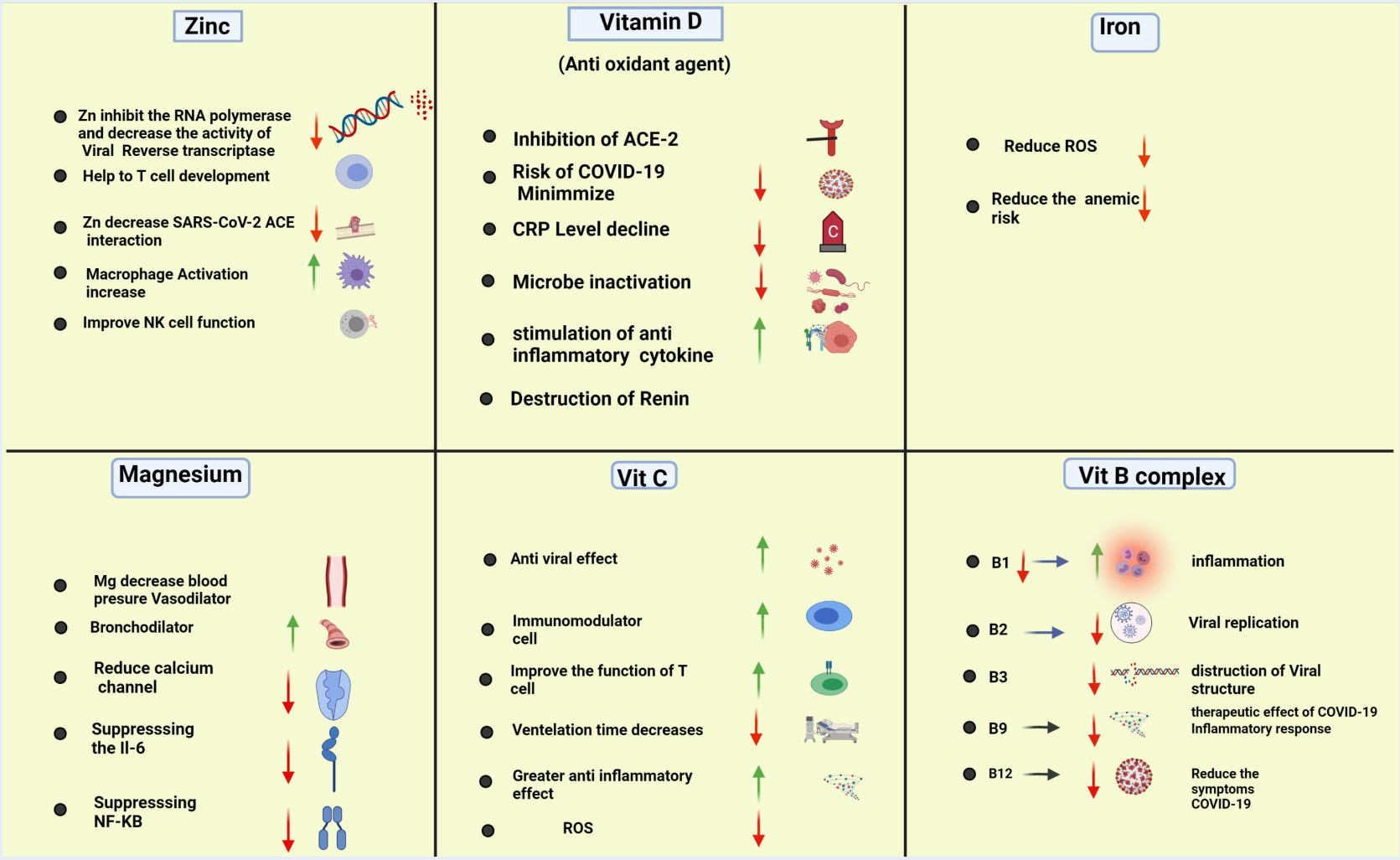

Figure 2: Role of major dietary supplements in COVID-19. Vit-D plays a significant role as an antioxidant agent, Fe reduces oxidative stress, Zn^{+} increases the function of NK cells, Vitamin C with antiviral effect and reduces oxidative stress, Mg act as a vasodilator, Fe^{+} reduces the anemic & and ROS stress. This figure was drawn originally by the authors using the Biorender.com platform.

Trace Minerals

Zinc (Zn)

Zn is a trace metal present in humans predominantly and it has efficacious roles in various aspects. Its functions involve a variety of cellular processes, especially in connection to neurotransmitted immunological health[57]. Some clinical evidence has reported that a deficiency of Zinc (Zn) causes gonadal growth retardation, the degeneration of the thymus, immune dysfunction, and lymphopenia which decreases the number of B cells. Zn+ also has a potential and significant role in antiviral immunity[57–59].

An in vitro study revealed that the deficiency of Zn+ reciprocal induces a higher level of IL6 and IL1-β production[60]. Many studies support the use of Zinc as an antiviral treatment and immunity modulator[58,59] and it is a vital component of thymulin hormone which is intricately involved in the development and distinction of T cells, It also arouses the macrophages, causing them to yield the IL-12, causing the destruction of various pathogens[61]. Zn+ has been found to be identified as strong RNA virus inhibitor due to forming a bond with pyrithione (PT)[62].

Furthermore, targeting RNA viruses i.e. SARS-RNA-dependent CoV-2's RNA polymerase (RdRps), is better for antiviral medication expansion since RdRp activity is entirely virus-specific. In addition, it can be stopped if there is a lack of compromising important cellular activities. Zn ions have a vital role in different kinds of cellular functions. This includes the appropriate breakdown and activation of cellular enzymes. In some disciplines, Zn metal also works in transcription factors. Furthermore, Zn^{2+} is likely to be a key cofactor for a variety of viral proteins (enzymes). Overdosages of Zn^{2+} can act as an intracellular second messenger that causes the apoptosis program by reducing protein synthesis[63]. Cao *et al.* reported that ACE-2 expression may be affected by zinc regulation inhibiting the prevalence of COVID-19 inside the cell[63]. Finzi *et al.* reported that treating four COVID-19 cases with a greater dosage of zinc reduced the disease symptoms within 24 hours (i) in a 63-year-old male patient given a high dose for 10 days, (ii) in a 57-year-old female patient given a high dose for 10 days, (iii) in a 41-year-old female patient given a high dose for 9 days, and (iv) in a young female patient who was 26-year-old who was given a high dose for 14 days. All four case studies showed a reduction in their COVID-19 symptoms and the patients moved toward recovery[64].

Magnesium (Mg)

Magnesium supplementation has a vital role including decreasing blood pressure, reducing the risk of cardiovascular disease, and stopping smooth muscle contractions[65]. Magnesium is a vasodilator and has sympatholytic properties which may help in the regulation of blood pressure[66]. Moreover, a deficiency of Mg exacerbates the inflammatory response that directly affects cytokine storms leading to the ARDs in COVID-19 Patients[67]. Pneumonia alternatively shows the form of COVID-19 infection which includes a cough, chest infection, COPD, hemoptysis, runny nose, dyspnea, and chest tightness[68]. Magnesium sulfate has been used instead of calcium to overcome smooth muscle contractions, causing bronchodilation and decreasing the inflammatory response and oxidative stress, as well as controlling pulmonary symptoms in COVID-19[66,69].

Mg protects against viral infections like SARS-CoV-2. The viral protein binds to the ACE-2 receptors for the penetration of the virus inside the cell, followed by destruction[70]. The preliminary findings indicate that magnesium treatment increases the methylation of the TMPRSS2 promoter, thereby inhibiting transcription and, as a result, inhibiting the activation of the enzyme expression[71].

Iron (Fe)

COVID-19 patients face a severe deficiency of iron in terms of their hemoglobin levels which ultimately results in anemia (limited oxygen delivery to tissues) which seems pathological in which there is a higher ferritin level. This causes interference in terms of cell functioning in infected patients[70,72]. A heavy intake of ferritin in COVID-19 patients indicates a severe inflammatory response and it allows the virus to enter the human body. This situation impacts the Fe^{+} metabolic processes[73].

Anemia potentially leads to multi-organ failure. It's critical to understand the relationship between anemia, iron metabolism, and the evolution of COVID-19, as well as how the relationships change according to age, gender, and any current chronic conditions[72]. Fe+ chelation acts as antiviral and immunomodulatory, and it also controls the nucleotide replication and pro-inflammatory pathways in COVID-19 patients[74,75]. Dalamaga *et al.* reported that Fe+ chelation (Deferoxamine, Deferiprone, and Deferasirox) controlled different mechanisms of SARS-CoV-2 multiplication including viral replication inhibition, and B-Cell regulation, as well as the upgrading of the neutralizing anti-viral antibody, endothelial inflammation inhibition, and the anticipation of pulmonary fibrosis[75].

CONCLUSIONS

The current study reported using clinical trials to reveal that nutraceutical supplementation such as water and fat-soluble vitamins along with trace minerals is the best choice as an immunity booster with management to reduce the symptoms of COVID-19.

ABBREVIATIONS

TMPRSS2: transmembrane protease serine 2
CRP: C-reactive Protein
PT: pyrithione
ARDS: Acute respiratory distress syndrome
ACE2: Angiotensin-converting enzyme II
TNF-α: Tumor necrosis factor alpha
IL: Interleukin

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All authors in this current article sufficiently contributed to the conceptualization, design of the manuscript, editing, and revision Moreover, each author declares that this or comparable content has not been submitted to or published in any other publication.
All authors read and approved the final manuscript.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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