Role of Vitamins and Minerals as Immuno-boosters in COVID-19

51

Aatikah Shehzadi[1], Shamshad Fareed[1], Ali Hassan[1], Hizqeel Ahmed Muzaffar[1], Muhammad Zoraiz[1], Muhammad Rizwan Saeed[1], Muhammad Usman[2], Qaiser Akram[3], Muhammad Ahsan Naeem[4*] and Sidra Altaf[5*]

ABSTRACT

Vitamins and minerals are receiving a lot of attention for their potential to boost the immune system, particularly in relation to the COVID-19 pandemic. Although these nutrients do not act as a cure or preventative measure for the virus, their role in boosting the immune system is essential for fighting infections such as respiratory illnesses, including COVID-19. Vitamin C is recognized for its ability to act as an antioxidant, stimulating the development of white blood cells and antibodies, which strengthens the body's ability to defend itself. Likewise, vitamin D is crucial for the functioning of the immune system, and a lack of it has been associated with a higher risk of getting sick. Vitamin A helps maintain the health of skin and mucous membrane cells, acting as a protective shield against harmful pathogens. Zinc and selenium are necessary for the proper operation of immune cells, while vitamin E serves as an antioxidant, shielding cells from harm. Although it is ideal to have a well-rounded diet that is high in these nutrients, it is important to recognize that excessive supplementing may not provide any extra advantages and may even be harmful. The focus should be on getting a variety of nutrients from a wide range of foods such as fruits, vegetables, nuts, seeds, and lean meats. Amid the COVID-19 pandemic, it is crucial to prioritize compliance with public health precautions including vaccination, hygiene protocols, and maintaining physical distance. It is recommended to seek guidance from medical professionals before making any dietary changes or starting on any supplements, especially for those with pre-existing health issues. Recognizing the importance of vitamins and minerals in supporting the immune system contributes to a comprehensive approach to staying healthy during difficult times.

Keyword: COVID-19 pandemic; Vitamins and minerals; Immuno-boosters; antioxidant; immune system

CITATION

Shehzadi A, Fareed S, Hassan A, Muzaffar HA, Zoraiz M, Saeed MR, Usman M, Akram Q, Naeem MA and Altaf S, 2023. Role of Vitamins and Minerals as Immuno-boosters in COVID-19. In: Aguilar-Marcelino L, Zafar MA, Abbas RZ and Khan A (eds), Zoonosis, Unique Scientific Publishers, Faisalabad, Pakistan, Vol 3: 651-665. https://doi.org/10.47278/book.zoon/2023.131

CHAPTER HISTORY Received: 12-May-2023 Revised: 21-June-2023 Accepted: 17-July-2023

[1]University of Veterinary and Animal Sciences, Lahore (Narowal Campus) Narowal 51600, Pakistan
[2]Department of Basic Sciences (Histology), University of Veterinary and Animal Sciences, Lahore (Narowal Campus) Narowal 51600, Pakistan
[3]Department of Pathobiology (Pathology), University of Veterinary and Animal Sciences, Lahore (Narowal Campus) Narowal 51600, Pakistan

[4]Department of Basic Sciences (Pharmacology), University of Veterinary and Animal Sciences, Lahore (Narowal Campus) Narowal 51600, Pakistan
[5]Department of Pharmacy, University of Agriculture, Faisalabad 38040, Pakistan
*Corresponding Author: sidra.altaf@uaf.edu.pk; ahsan.naeem@uvas.edu.pk

1. INTRODUCTION

The World Health Organization (WHO) declared COVID-19 a global pandemic due to its potential to endanger public health worldwide. The focus has switched to techniques that might boost the immune system against COVID-19 due to the lack of expedient therapeutics in the developing countries. Pharmaceutical firms are striving to manufacture-cum-launch anti-COVID-19 vaccines and therapeutic agents because of significant viral influence on the immune system in the form of cytokines storm. A well-balanced diet rich in essential vitamins (A, B, C, D, E, and K) and minerals (sodium, potassium, phosphorus, calcium, magnesium, zinc, selenium, sulfur, etc.) has been shown to be highly beneficial in enhancing immune function and in the prevention and management of COVID-19 (Silver 2020).

Coronavirus is responsible for the spread of COVID-19. Previous outbreaks such as; the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) modeled serious health-threats to the entire world (Rothan et al. 2020). Both of these illnesses were zoonotic and originated from bats to the whole mankind (Derbyshire and Delange 2020). It is believed that COVID-19 was disseminated to the exposed persons from routinely traded animals of the Wuhan (China) market. Still, a search for reservoir/intermediate host remained a big mystery and challenge. However, aside from mammals and birds, there hasn't been any conclusive proof of the existence of its additional reservoirs (Bassetti et al. 2020). In December 2019, the first instance of COVID-19 was recorded (Du Toit 2020) that primarily affects the human respiratory system (Lu et al. 2020).

A cluster of epidemiologically connected individuals from Wuhan (Hubei Province, China) were identified with an early symptom of idiopathic pneumonia. Along with respiratory symptoms, vomiting, diarrhea, dry cough, dyspnea, sore throat, headaches and disorientation were also noted (Shakoor et al. 2021). The outbreak incidence was typically higher in people > 60 or with diabetes, heart or lung co-morbidities. Males exceeded females despite the absence of a clearly defined dominant gender because of their inclination for drinking and smoking (Yuki et al. 2020). Since the COVID-19 epidemic started, fear and despair have spread around the globe. The immune system of an individual is compromised by this virus (Michienzi and Badowski 2020). Although the immune system is continuously monitoring itself, it becomes more active when a person is in a diseased state. Increased activity leads to a faster metabolism, requiring the consumption of energy sources, biosynthetic substrates, and regulatory molecules, all of which are derived from food. Many essential vitamins and trace minerals (such as zinc, copper, selenium, and iron) play a vital role in enhancing the body's immune response and lowering the likelihood of infection (Calder 2020). Alternatively, inadequate nutrition hindered the immune system's ability to work properly. Poor nutrition results in decreased natural and acquired immunity, increasing the likelihood of infections (Calder 2020). By rectifying the shortage, it is possible to enhance both immune function and resistance to infection, demonstrating a direct correlation between the presence of certain nutrients and the body's ability to fight off pathogens. This chapter specifically delves into how different vitamins and minerals can boost immunity against COVID-19.

2. NUTRITION, IMMUNITY, AND COVID-19

The European Food Safety Authority has authorized vitamins A, B6, B12, C, D, and folate (vitamin B9) as well as the trace elements zinc, iron, selenium, and copper to make claims related to the maintenance of the immune system functions." (Calder 2020). Upon admission to the hospital, it is important to assess the nutritional status of all patients with COVID-19. Those at risk of malnutrition should be prioritized for nutritional support, including increased protein intake through oral supplements (Jin et al. 2020). Pattern recognition receptors (PRRs) like the retinoic acid-inducible gene I-like receptors play a role in the innate immune system by identifying the viral genetic material when it enters the host cell (Li et al. 2020; Yi et al. 2020). The Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2's) attachment to macrophages triggers the inflammatory cascade by presenting its antigens to the CD4 T cells, which then activated and differentiated into Th17 cells. Production of MCP-1, TNFα and IL (1, 6, 8, and 21) cytokines mobilize the adaptive IR. According to Li et al. (2020), these mediators cause T cells to activate NK and CD8 T cells. By activating B cells, TCD4 cells are in charge of causing specific antibodies to be produced against SARS-CoV-2 (Li et al. 2020; Yi et al. 2020). SARS-CoV-2 spike glycoprotein (S-protein) bound to the DPP4 receptor and encouraged protein-receptor adhesion that instigated the release of viral DNA. The key responder protein MyD88 is essential for the production of pro-inflammatory cytokines (IFN-1, TNFα, NF-kB activation, IL-1, and IL-6) and was dependent on S-protein (Li et al. 2020). Viral RNA binding to the TLR-3 receptor stimulated interferon regulatory factors (IRF) to activate inflammatory pathways. As a result, it causes the synthesis of TNFα, IL-1, IL-6, and IFN-1. The activation of IRF and NF-kB by the viral RNA's binding to TLR-7 and/or TLR-9 was also demonstrated as these cytokines caused lymphocytes and leukocytes to migrate to the infected cell to cope the infection (Li et al. 2020). It is important to underline IFN-1's role in preventing viral transmission. IFN-1 also triggered dendritic and NK cells and in response enhancing macrophages' phagocytosis of viral antigens (Li et al. 2020; Yi et al. 2020). Vitamins and minerals are necessary for the entire procedure. SARS is especially dangerous to the cardiovascular system, kidneys, stomach, lungs, brain, and other organs that express the angiotensin-converting enzyme 2 (ACE 2) (Guo et al. 2020; Shi et al. 2020). This is particularly true if the immune system was struggling and the virus was allowed to propagate unconstrained. Recent studies have shown that the respiratory epithelium must display ACE 2 for the virus to enter and start replicating (Cheng et al. 2020). Then the virus was introduced to lymphocytes, triggering the inflammatory cascade that caused the injured cells to produce pro-inflammatory cytokines. The primary symptom of COVID-19's most severe stage was respiratory which are brought on by IR and pro-inflammatory granulocytes and macrophages (Shi et al. 2020; Xu et al. 2020). High levels of pro-inflammatory cytokines, including IL-1, IL-6, and TNFα are present in the lungs of the infected patient which may serve as a catalyst for the creation of pulmonary mucus and the stimulation of the immune system (Guo et al. 2020). Because of this, medications that allowed for the inhibition or limitation of those pro-inflammatory cytokines' actions might be expedient for advanced stage COVID-19 patients (Shi et al. 2020).

3. VITAMINS AS IMMUNITY BOOSTERS IN COVID-19

It is commonly recognized that when a person was exposed to diseases due to dietary deficiencies, their immune system could become weakened. Recent studies have underlined the importance of feed additives, and they might be helpful in lowering viral loads and therapy rates for COVID-19 patients if taken in more than the prescribed daily doses. Vitamins were crucial nutritional components because of their capacity to regulate the immune system and function as defenders. There wasn't yet an approved COVID-19 drug or vaccination. To maintain a healthy body and a strong immune system until they were available, one must eat a well-balanced, nutrient-rich diet. Micronutrients like vitamin C and vitamin D have drawn a lot of interest because of their capacity to lower inflammation and strengthen the immune system. Vitamin D and C deficiencies weakened and degraded the immune system, causing pancytopenia and bleeding disorders. There was evidence that people with COVID-19 who have low vitamin D concentrations die more frequently. Additionally, giving vitamin C to COVID-19 patients increased their oxygenation level (Shakoor et al. 2021). Vitamin B was important because it was required for optimal immune system function, energy metabolism, and cell function. In a manner similar to this, a vitamin B shortage could lead to hyper-homocysteinemia, which in turn could lead to poor immunological and cell function as well as inflammation (Mikkelsen and Apostolopoulos 2019). Vitamin B facilitated the appropriate induction of innate and adaptive immune responses. Hospitalizations were reduced, respiratory function was improved, endothelium integrity was protected, pro-inflammatory cytokine levels were reduced and vascular consistency was upgraded (Zhang and Liu 2020).

Table 1.1: Impact analysis of minerals and vitamins supplementation on COVID-19 patients (Nimer et al. 2022).

Supplement taken before COVID-19	Total number of users	Severity			Hospitalization		
		P	OR	95%CI	P	OR	95%CI
Vitamin C	651	0.18	0.81	0.59-1.11	0.08	0.73	0.51-1.04
Vitamin A	144	0.36	0.77	0.43-1.36	0.40	0.77	0.42-1.41
Vitamin D	796	0.01	0.68	0.50-0.92	0.001	0.64	0.45-0.89
Omega 3	356	0.43	1.15	0.81-1.65	0.30	1.23	0.83-1.80
Folic acid	213	0.16	0.69	0.40-1.17	0.23	0.70	0.39-1.26
Vitamin B complex	190	0.69	1.10	0.70-1.74	0.40	1.23	0.76-2.00
Vitamin B12	395	0.06	0.70	0.48-1.02	0.15	0.74	0.49-1.11
Zinc	326	0.46	1.15	0.79-168	0.21	1.29	0.86-1.93
Calcium	245	0.76	0.94	0.61-1.43	0.40	1.21	0.78-1.88
Magnesium	143	0.73	1.09	0.66-1.81	0.24	1.36	0.81-2.29
Iron	371	0.83	1.04	0.70-1.55	0.37	1.22	0.79-1.88
Selenium	57	0.80	1.10	0.54-2.26	0.48	1.30	0.62-2.71
Aspirin	427	0.28	1.20	0.86-1.66	0.08	0.96	0.67-1.37

Age, gender, BMI, status as a smoker, and the number of comorbidities were all taken into account while adjusting each independent variable. **$p<0.01$; *$p<0.05$.

4. ROLE OF VARIOUS VITAMINS AS IMMUNITY BOOSTERS

To combat COVID-19 and SARS-CoV-2, pharmaceutical companies are developing specific drugs and vaccines since COVID-19 infection has a serious adverse effect on the immune system by causing a variety of allergic reactions. To maintain overall health and avoid serious viral diseases, a balanced, healthy diet may be required. All fat- and water-soluble vitamins should be included in a balanced diet (Kumar et al. 2021). Some of them control immune cells' genetic makeup and promote their proliferation and differentiation. The antioxidant powers of vitamins C and E help fight free radicals. The body depletes these nutrients, vitamins, and minerals when combating infections because of the energy requirements for immune activation, a hectic lifestyle, viral infection, diabetes, and obesity all of which have a direct impact on nutrient status (Gombart et al. 2020).

4.1. ROLE OF VITAMIN A

The process by which vitamin A imposes its effects is through the conversion of vitamin A into retinoic acid, which binds to nuclear receptors in target cells, especially the retinoic acid receptors (RARs) and retinoid X receptors (RXRs). To control the transcription of particular genes involved in cellular differentiation, proliferation, and death, these receptors attach to retinoic acid response elements (RAREs) on DNA. Following ligand interaction, the RARs and RXRs heterodimerize, and the resultant complex attract coactivator or corepressor proteins to the gene promoter region, therefore either activating or suppressing gene expression. In the end, this process results in the preservation of sound immunological, bone, and eyesight development.

According to Raverdeau and Mills (2014), RA, also known as vitamin A and made from retinyl esters, controls a number of genes involved in both innate and adaptive immune responses. Numerous studies (Angulo et al. 1998; Trottier et al. 2008; Lee and Han 2018; Li et al. 2018) have demonstrated the protective effects of synthetic as well as natural retinoids against a variety of viruses, including viruses such as hepatitis B (HBV), influenza, norovirus, MeV, and cytomegalovirus (CMV). It affects MERS-CoV and SARS-CoV by blocking SREBP-controlled lipogenic pathways (Yuan et al. 2019).

4.2. ROLE OF VITAMIN B

The B vitamins, which are soluble in water, support a number of cellular and metabolic functions. Although each B vitamin has a different mode of action, they all serve as cofactors or coenzymes in activities that are catalyzed by enzymes. In the metabolism of carbohydrates, vitamin B_1 (thiamin) functions as a coenzyme, whereas vitamin B_6 (pyridoxine) is required for the metabolism of amino acids. Cobalamin, a form of vitamin B_{12}, is necessary for the synthesis of DNA and the production of red blood cells. It works with folate to help the body maintain homocysteine levels. Deficits in B vitamins, which are often obtained through diet, can cause a variety of health issues. Red blood cell (RBC) synthesis is known to be aided by the naturally occurring chemical vitamin B. For organisms to operate normally, all of the B complex vitamins are required (Zhang et al. 2018). The human body utilizes nutrients such as proteins, lipids, and carbohydrates to sustain the functional integrity of skin, brain cells, and other bodily tissues by furnishing energy. The inclusion of Vitamin B facilitates and contributes to the aforementioned process. Thiamine (vitamin B_1), riboflavin (vitamin B_2), niacin (vitamin B_3), pantothenic acid (vitamin B_5), pyridoxine (vitamin B_6), biotin (vitamin B_7), folate (folic acid), and cyanocobalamin (vitamin B_{12}) are the eight vitamins that make up the vitamin B complex. It is essential for maintaining the integrity of the intestinal barrier and managing the immune system of the colon (Lindschinger et al. 2019).

4.2.1. ROLE OF VITAMIN B_1

Vitamin B1 (Thiamine) functions as a vital coenzyme in facilitating the energy production process within the human body, regulates body temperature, is involved in fat formation, and is required for the proper operation of the nervous and immunological systems (Kraft and Angert 2017). Thiamine deficiency exerts a notable influence on the immune system through various pathogenic mechanisms, including heightened inflammatory response and augmented oxidative stress and other factors. Additionally, aberrant antibodies are produced as a result of metabolic abnormalities (Mikkelsen and Apostolopoulos 2019). Thiamine has been shown to significantly help with SARS-CoV-2 virus eradication by inducing humoral and cell-mediated immunity. The development of immunity against SARS-CoV-2 patients is thus supported by proper thiamine levels (Shakoor et al. 2021).

4.2.2. ROLE OF VITAMIN B_2

A lack of vitamin B_2, a neuroactive chemical with immune-modulating properties, causes the expression of genes that promote inflammation. Riboflavin demonstrated a conspicuous protective effect in experimental animal models when exposed to carbon tetrachloride (CCL4)-induced liver damage. The subsequent mitigation by TNF further indicates its potential use as a medication for hepatoprotection (Yoshii et al. 2019). Nucleic acids are permanently damaged when riboflavin is exposed to UV radiation, which stops bacteria from multiplying. It can be used to lower infections in COVID-19 patient blood plasma in order to lessen the chance of COVID-19 transmission by transfusion.

4.2.3. ROLE OF VITAMIN B_3

Niacin affects inflammatory mediator synthesis as well as immune cell migration in a variety of ways. Therefore, it has an anti-inflammatory impact even if its whole spectrum of actions is unclear. Targeting IL-6 in COVID-19 patients, according to recent studies, may assist to lessen inflammation (Liu et al. 2020). Niacin's anti-inflammatory properties help patients with ventilator-induced lung damage by reducing neutrophil infiltration (Jones et al. 2015). According to the most recent scientific research, nicotinamide reduced viral infection and strengthened defensive mechanisms. Niacin may be added to other medications for COVID-19 patients because of its therapeutic advantages (Mehmel et al. 2020).

4.2.4. ROLE OF VITAMIN B_6

Vitamin B_6 affects immune cell activity, proliferation, and innate/adaptive immunity (Ueland et al. 2017). The suppression of cytokine/chemokine release was used to identify individuals with vitamin B_6 deficiencies. According to studies, vitamin B_6 activates IFNɣ, which mediates the cellular immunological response (Parra et al. 2018). A recent study revealed that pyridoxine supplementation has an impact on vascular, pro-inflammatory cytokine, and immunological responses. Integrity, hypercoagulability, and other factors all help to lessen COVID-19 symptoms.

4.2.5. ROLE OF VITAMIN B_9

The vitamin folate is essential for the adaptive immune system and is required for the synthesis of DNA and proteins. A recent study found that folic acid inhibits the binding of the SARS-CoV-2 spike protein as well as the furin enzyme, which promotes bacterial and viral infections. Folic acid might thus aid in the early treatment of respiratory illnesses linked to COVID-19 (Sheybani et al. 2020). Tetrahydrofolate and its derivatives, 5-methyl tetrahydrofolate and folic acid, exhibit a significant affinity for SARS-CoV-2, according to a recent study (Kumar et al. 2021).

4.2.6. ROLE OF VITAMIN B_{12}

The generation of chemokines and cytokines as well as the interaction of immune cells in pathogenic pathways may be regulated by vitamin B. It is therefore suggested that it may provide defense against a number of bacterial and viral illnesses. Probiotics like bifidobacteria and lactic acids may be essential for defense against the COVID-19 pathogen and revealed a significant role in colonic immune regulation (Calder et al. 2020). These probiotics have been shown in studies to be able to modulate immune responses and protect against infections such as respiratory tract infections. This is the process by which dendritic cells (DCs) transform vitamin A from the diet into retinoic acid (RA). The molecules CCR9 and 47 integrins are expressed by dendritic cells, which then activate B and T cells in the presence of retinoic acid. Moreover, RA encourages the development of regulatory T (Treg) cells from inexperienced T cells. Upon transformation into Treg cells, T-cells begin to display the folate receptor 4 (FR4), a receptor for vitamin B9. The interaction between vitamin B9 and FR4 is crucial for T cell survival. Vitamin D stimulates the production of antimicrobial peptides (AMPs) in macrophages and epithelial cells, promoting their ability to fight off pathogens. Additionally, it prevents DCs from maturing and promotes the migration of the IEL population within the epithelium (Kumar et al. 2021).

4.3. ROLE OF VITAMIN C

In general, the mode of action of vitamin C is critical for preserving the health and functionality of different body tissues and preventing oxidative damage. In terms of its metabolic pathway, vitamin C is absorbed in the small intestine and then transferred to tissues throughout the body. Once ingested, it can undergo enzymatic and non-enzymatic processes that will either cause it to oxidoxidizeo dehydroascorbic acid (DHA) or reduce it back to ascorbic acid. Through the action of certain transporters, DHA can also be converted back into ascorbic acid. When the body has more vitamin C than it requires, it is expelled in the urine**.** Vitamin C possesses antiviral attributes that encompass the amelioration of endothelial dysfunction, elevation of interferon-alpha production, regulation of cytokines, mitigation of inflammation, and restoration of mitochondrial function (Carr and Maggini 2017; Dey and Bishayi 2018). Numerous investigations have shown that vitamin C has viricidal effects (Furuya et al. 2008). Vitamin C facilitates the enhancement of the immune system's ability to combat bacterial and viral infections. The process of eliminating dead cells and introducing new cells offers advantageous outcomes. Vitamin C's antioxidant properties protect against the damaging consequences of oxidative stress (Carr and Maggini 2017; Ekert and Vaux 1997). Numerous studies have shown that taking vitamin C supplements lowers the chance of developing upper respiratory tract infections (Carr and Maggini 2017). Children and adults experienced fewer common cold symptoms (Hemilä and Chalker 2013). The use of intravenous vitamin C has been shown to significantly decrease the risk of developing severe infections like sepsis and acute respiratory distress syndrome (ARDS) (Kashiouris et al. 2020). Several pieces of indirect and direct evidence support the utilization of vitamin C for the management of COVID-19 patients. According to a systematic review conducted by Cochrane and a randomized controlled trial, the administration of 0. 2 g/day of oral vitamin C demonstrated a significant reduction in both clinical manifestations and subjective symptoms of the common cold. In a controlled experiment, adult patients were subjected to the administration of two varying doses of vitamin C. The outcomes of this trial revealed a direct correlation between the dosage of vitamin C and the duration of pneumonia, as a reduction in the length of the illness was observed in a manner corresponding to the administered dose (Baladia et al. 2020). Therefore, it is crucial to conduct research on the function of vitamin C (Carr 2020).

4.4. ROLE OF VITAMIN D

The body can synthesize Vitamin D through sun exposure or by consuming it in food. The body undergoes two stages of hydroxylation. The main type of vitamin D found in the body is 25-hydroxyvitamin D [25(OH) D], which is produced through initial hydroxylation in the liver. The kidneys are responsible for the majority of the second hydroxylation process that creates 1, 25-dihydroxy vitamin D [1, 25(OH)2D]. This dynamic form engages with the vitamin D receptor (VDR) in specific body tissues such as the intestines, bones, and immune cells, to kickstart a sequence of biochemical reactions that control calcium and phosphate levels, bone formation, and immune system performance. A secosteroid with antioxidant and anti-inflammatory effects is vitamin D. It supports the metabolism of calcium and phosphorus. Additionally, it influences how the immune system reacts to autoimmune and viral disorders. The skin absorbs ultraviolet B light from the sun, which changes 7-dehydrocholesterol into cholecalciferol (Sajadi et al. 2020).

Because food sources did not supply enough vitamin D. As a result, oral supplementation is frequently in need of fortification. According to the latest research, COVID-19-affected cities have similar latitudes and temperatures to the worst-affected regions. This is crucial since people in high-latitude nations have low vitamin D concentrations (Cannell et al. 2006). Patients residing in regions categorized as high-alert areas have previously been subject to suspicion regarding their potential vitamin D deficiency. Moreover, the prevalence of vitamin D deficiency exhibits substantial variation among distinct geographical areas within each nation, thus rendering the task of summarizing findings considerably challenging. Respiratory tract infections can be brought on by vitamin D insufficiency, according to published research (Lemire 1992). Extensive research has been conducted to explore the therapeutic efficacy of vitamin D in the treatment of acute respiratory tract infections (ARTIs). Calcitriol, a vitamin D agonist, has been found to play a role as a pathogenic factor in COVID-19. It exerts its effect by modulating the expression of angiotensin-converting enzyme 2 (ACE2) in lung tissue, thereby mitigating the risk of acute lung injury (Xu et al. 2017). Observed substantial findings from studies using large doses of vitamin D between 250,000 and 500,000 IU, including shorter hospital stays, higher hemoglobin levels, and better blood oxygenation (Han et al. 2016). Vitamin D supplementation lowered the likelihood of getting acute respiratory tract infections in comparison to individuals with low baseline vitamin D levels (25 nmol/L) (Martineau et al. 2017). Based on empirical evidence, scholarly studies indicate that the administration of vitamin D exerts a multi-faceted impact on microbial infections and mortality, yielding notable decreases in both. The assessment divided the effectiveness of vitamin D in fighting the common cold into three specific areas: physical defenses, natural cellular immunity, and adaptive immunity (Rondanelli et al. 2018). Vitamin D improves the body's natural ability to fight off infections by helping to produce antimicrobial peptides such as cathelicidin and defensins (Laaksi 2012). Due to its ability to increase glutathione production and enhance cellular immunity, vitamin D has been suggested as a potential preventive and therapeutic measure for COVID-19 (Wimalawansa 2020).

4.5. ROLE OF VITAMIN E

By giving its electrons to free radicals, unstable chemicals that can harm cells, vitamin E functions as an antioxidant. This procedure aids in scavenging free radicals and stopping their ability to harm cells. In addition, vitamin E interacts with proteins and enzymes that are important in cellular signaling and gene expression, which may have health advantages. Vitamin E has also been demonstrated to block the action of some enzymes linked to inflammation, which may aid in reducing inflammation in the body**.** As a strong antioxidant, vitamin E is essential for controlling and sustaining immune system activity (Jayawardena et al. 2020). Vitamin E reduces oxidative stress, prevents unshared electron free radicals, highly energetic damaged cells, and all of the above, in addition to acting as a free radical scavenger. Oxygen and unused electrons readily combine to generate reactive oxygen species (ROS) (Di Credico et al. 2015). In addition to its involvement in immunity, vitamin E has anti-inflammatory and antioxidant properties. Alpha-tocopherol prevents smooth muscle cells, monocytes, and platelets from proliferating, differentiating, and activating protein kinase C. By preventing the metabolism of arachidonic acid, which dilates blood arteries and prevents platelet aggregation, vitamin E raises prostacyclin levels (vitamin E-Health Professional Fact Sheet). According to one study, maintaining immunological function benefits older people more than younger people when vitamin E intake is higher (Meydani et al. 2018).

4.6. ROLE OF VITAMIN K

A vitamin K-dependent enzyme called glutamyl carboxylase converts glutamyl residues in these proteins into carboxy glutamyl (Gla) residues, which is the basic mechanism of action of vitamin K. To create vitamin K epoxide, which is then transformed back into vitamin K hydroquinone by the enzyme vitamin K reductase, vitamin K hydroquinone, the reduced form of vitamin K, is needed as a cofactor in this process. Because of carboxylation, clotting factors can bind calcium ions and participate in the coagulation cascade. Along with aiding in blood clotting, vitamin K also supports bone health by regulating the activity of osteocalcin, a protein essential in bone development. Vitamin K is offered as a food additive in two different forms: K1 (phylloquinone) and K2 (which is made up of numerous MKs, or menaquinones) (Walther et al. 2013). Vitamin K plays a crucial role in facilitating the synthesis of proteins and other fundamental physiological processes. Additionally, it acts as a co-factor and co-enzyme during hemostasis (Janssen and Walk 2020). The pulmonary extracellular matrix is guarded against degeneration brought on by inflammation in SARS-CoV-2 patients by producing more matrix Gla protein (MGP) in the lungs. Utilizing vitamin K from extrahepatic stores is encouraged by the MGP. The occurrence of venous and arterial thromboembolic disease can be influenced by the severe inflammation, hypoxia, immobilization, and diffuse intravascular coagulation (DIC) associated with COVID-19.On top of that, blood clotting and lung elastic fiber degradation are potential side effects. By inducing hepatic coagulation factors in COVID-19 patients, vitamin K1 reduces thrombosis (Klok et al. 2020).

5. ROLE OF VARIOUS MINERALS AS IMMUNITY BOOSTERS

The COVID-19 pandemic has increased our understanding of the immune system's significance. The immune system may be boosted by a healthy diet, vitamin and mineral consumption, and appropriate cleanliness habits. There are distinct anti-infection defensive mechanisms in the immune system. The COVID-19 pandemic, characterized by its rapid and extensive dissemination, has emerged as a worldwide health concern, eliciting severe respiratory tract infections in affected individuals. The defense mechanism and its influential determinants presently constitute the primary challenges associated with the COVID-19 pandemic. "Cow's milk is highly abundant in an array of micronutrients which possess the capacity to enhance and sustain the immune system as is widely recognized. Research has shown that these nutrients are particularly good for preventing COVID-19, and those who are lacking in any of them may be less able to fight the infection. These nutrients have demonstrated efficacy in mitigating COVID-19, with the absence of any of them diminishing the body's immune response against the virus. Given that cow's milk is readily available to the general population, individuals who possess a transient immunity against the SARS-CoV-2 virus may potentially benefit from consuming colostrum, raw milk, or micro-filtered milk obtained from vaccinated cows. The COVID-19 pandemic has emerged as a significant global health crisis due to its exponential rate of transmission and consequential manifestation of severe respiratory tract infections among individuals. The primary challenges associated with COVID-19 involve the defense system and the various influential factors affecting its functioning. The nutritional composition of cow's milk includes a plethora of micronutrients which are known to enhance and sustain the functionality of the immune system, a widely acknowledged assertion within the academic community (Dhok et al. 2020).

5.1. ROLE OF MACRO-MINERALS

A robust immune system constitutes a formidable defense mechanism against the adverse consequences of COVID-19 infection, particularly in the absence of suitable therapeutic interventions. According to research by Jayawardena et al. (2020), mineral supplements have also been proven to boost resistance to viral infections. Inorganic substances called minerals are needed by the body to support biological function. Minerals have an impact on a variety of physiological functions, including bone growth, blood synthesis, hormone production, and cardiac modulation (Rondanelli et al. 2018). Numerous epidemiological studies have shown that dietary deficiencies in essential minerals are essential for avoiding and minimizing CVS and CSF problems, which may speed the onset of corona infections (Zabetakis et al. 2020).

5.1.1. ROLE OF SODIUM

In SARS-CoV-2, salt has a substantial effect on both the change in electrolytic balance and the expression of ACE2 (Luo et al. 2020). Furthermore, a study discovered that when disease severity grows, salt levels decrease (Lippi et al. 2020). A meta-analysis revealed that COVID-19 patients' sodium concentration considerably drops (Habib et al. 2020). Hyponatremia of this type could be a biomarker for COVID-19 infection and be linked to the virus.

5.1.2. ROLE OF POTASSIUM

The most frequent side effects of COVID-19 are thought to be ARDS and acute cardiac damage, both of which are considerably increased by hypokalemia. Angiotensin-II levels rise as a result of COVID-19 binding to ACE2 and inhibiting its synthesis, which ultimately results in hypokalemia (Alwaqfi et al. 2020). Potassium content was found to be significantly lower in COVID-19 patients with severe disease compared to non-severe patients and to be less variable than salt (Lippi et al. 2020). According to SARS-CoV animal models, higher plasma angiotensin-II concentrations in COVID-19 patients may be the cause of acute lung damage (Zemlin et al. 2020).

5.1.3. ROLE OF PHOSPHOROUS

Phosphorus plays a crucial role in the stimulation of protein synthesis, which is essential for the growth, maintenance, and repair of cells and tissues (Vance 2011). Monitoring the blood phosphorus level in COVID-19 patients who are severely or seriously ill has been shown to be helpful for prognosis. According to research, hypophosphatemia and the severity of the illness are directly associated (Xue et al. 2020). The innate immune system works overtime to combat infection when a virus enters the body through ACE-2 receptors. However, due to the dearth of accessible minerals, phosphorus has a substantial impact on immunological responses, impairing their ability to repair damaged cells and tissues and fostering the development of illness. This clarifies how phosphorus could play a part in the transmission of illness (Ni et al. 2020).

5.1.4. ROLE OF CALCIUM

In addition to helping to strengthen our bones, calcium also helps to fight against viruses by flushing them out of the cells. Thus, calcium ions offer protection against the common cold. The severity of the disease is negatively correlated with the calcium level in the patient's serum, with critical COVID-19 patients having lower calcium concentrations than patients with less severe disease (Rodriguez-Morales et al. 2020), according to a combined analysis. Hypocalcaemia, low salt and potassium levels, and SARS-CoV-2 infection severity are all indicators.

5.1.5. ROLE OF MAGNESIUM

Magnesium is frequently underestimated. The stress brought on by the pandemic and the resulting PTSD that would affect COVID-19 survivors, medical personnel, and the general public may both be greatly reduced by magnesium supplementation. Moreover, it plays a crucial part in enhancing the immune system by controlling a range of functions, such as immune cell adhesion, production of immunoglobulins, attachment of IgM lymphocytes, antibody-dependent cell breakdown, and adjustment of macrophage reaction to lymphokines (Ni et al. 2020). Research conducted both in laboratory settings and in living organisms has shown that magnesium is essential for the immune system to effectively combat viral infections (Jayawardena et al. 2020). A study in Singapore showed that older individuals with COVID-19 experienced a slower progression of the disease when they took a combination of vitamin D, magnesium, and vitamin B12 (DMB). Taking 150 mg of magnesium and 1000 IU of vitamin B12 can reduce inflammation and protect against respiratory infections. We suggest conducting a double-blind experiment using random selection (Tan et al. 2020).

5.2. ROLE OF MICRO-MINERALS

In general, medical experts and scientists advised preventive measures during this COVID-19 pandemic emphasize the significance of immunity as a potential COVID-19 defense (Calder 2020). Since there is now know WHO-approved treatment for the illness, the only line of defense against this viral infection is a strong, functioning immune system (Cascella et al. 2022). In fact, trace elements are important micronutrients that have a big impact on immunity. Trace elements including Cu, Zn, Se, and others exhibit antiviral activity in addition to their immunomodulatory effects by preventing the replication of viruses in host cells. Small elements' antioxidant properties have an impact on the viral DNA and alter the immune response. Through a variety of immunomodulatory routes, trace elements strengthen the body's immune system (Calder 2020).

5.2.1. ROLE OF ZINC

Zinc (Zn) is a vital component of dietary immunity and has several functions in the biological system. This mineral is considered to be in charge of the circulatory, reproductive, and neurological systems in addition to its active participation in lipid metabolism and glucose management (Collins 2016). The immune system's fight against H1N1 is said to depend heavily on zinc (Sandstead and Prasad 2010). The etiology of COVID-19 (SARS-CoV-2) centers around the angiotensin-converting enzyme 2 (ACE2), through which the virus gains entry into the host cell, akin to COVID-19 (SARS-CoV). Therefore, angiotensin-converting enzyme 2 (ACE2) emerges as the most optimal candidate for therapeutical intervention in the management of this pandemic (Zhang et al. 2020). The findings from in vitro experiments revealed that the Zn2+ cation effectively impeded the replication process of the virus RNA polymerase, thereby inhibiting its activity (Te Velthuis et al. 2010). The idea that using zinc in a complement treatment regimen might help treat COVID-19 is substantially supported by each of these justifications and pieces of evidence (Zhang et al. 2018).

5.2.2. ROLE OF SELENIUM

Considering its antiviral and anti-inflammatory qualities, she is regarded as the most trustworthy trace element. Several sets of seleno-proteins generally regulate the immune system, which is made up of seleno-cysteine. Selenium deficiency dramatically raises the risk of viral infections (Guillin et al. 2019). Basal selenium levels in the body are associated with COVID-19 patient cure rates, according to data from China (Zhang and Liu 2020). The cytosolic selenoenzyme that Se activates and is in charge of the enzyme's antiviral activity is glutathione peroxidase 1 (GPX1). The severity of oxidative stress induced-inflammation brought on by SARS-CoV-2 has been balanced by sialoproteins (GPX1) (Seale et al. 2020). Hence, a substantial intake of selenium with high nutritional value may potentially exert a notable influence on the infection caused by SARS-CoV-2. This information proposed that selenium-based mechanisms are crucial for SARS-CoV-2. Fig. 1 shows the proposed technique by which SARS-COV-2's life cycle and mutation towards virulence may be inhibited.

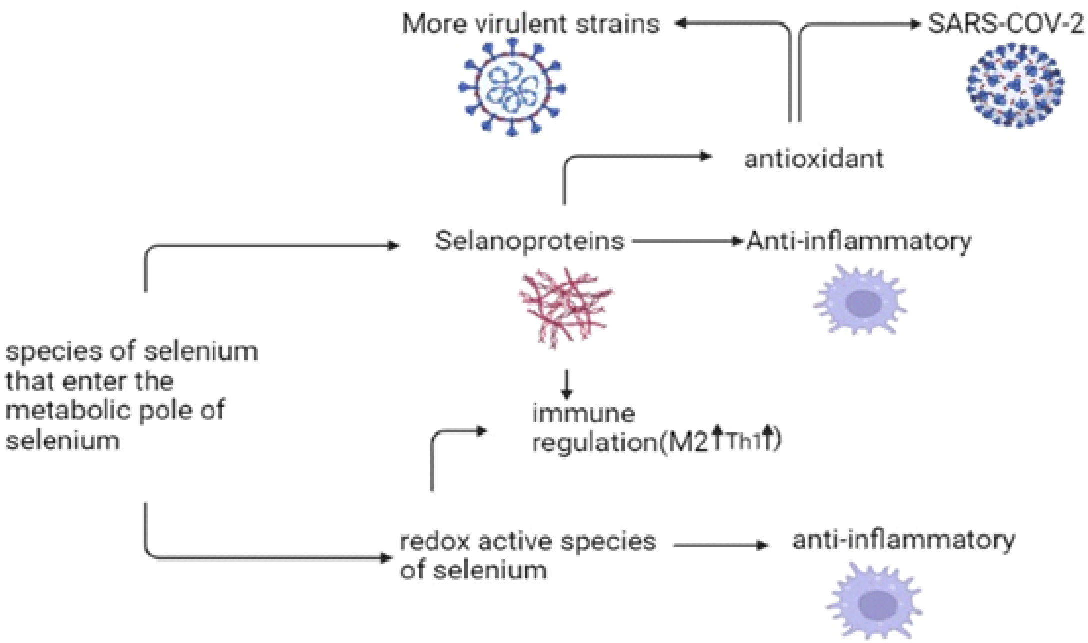

Fig. 1: Proposed technique by which SARS-COV-2's life cycle and mutation towards virulence may be inhibited while the virus's effects on organ damage, oxidative stress, and cytokine storm were reduced.

5.2.3. ROLE OF SULFUR

In addition to other physiological activities including transport across cell membranes, immunological responses, and blood coagulation, cysteine, and methionine- two significant amino acids produced by sulfur- are essential for bio-catalytic reactions (Dutta et al. 2009). According to studies on COVID-19, sodium is a sulfate-based molecule that has therapeutic potential for the lungs and respiratory illnesses. Additionally, clinical evidence shows that sodium thiosulfate ($Na_2S_2O_3$) is a successful therapy for pneumonia and lung damage in both adults and children. Sulfur may be protective against COVID-19 because of its numerous medicinal uses and connection to the respiratory system (Evgen'ev and Frenkel 2020).

6. CONCLUSION

Numerous successful vaccinations have been created in response to the current situation and work is being done on pharmaceutical therapies that are particularly customized; nevertheless, they are very expensive and challenging procedures with a limited range of focused activity. On the other hand, when supported by strong clinical trials, supplementing with vitamins and minerals is a relatively simple and cost-effective method that may have broad-spectrum of activity and long-term health effects. It is probably reasonable with very little risk to eat vitamins and minerals when assessing the risk-to-benefit ratio. On the other hand, certain new medications and vaccinations come with some risks. As a result, nutritional supplementation appears to be an effective way to treat SARS-CoV illness.

REFERENCES

Alwaqfi NR and Ibrahim KS, 2020. COVID-19: an update and cardiac involvement. Journal of Cardiothoracic Surgery 15(1): 1-6.

Angulo A et al., 1998. Ligand induction of retinoic acid receptors alters an acute infection by murine cytomegalovirus. Journal of virology 72(6): 4589-4600.

Baladia E et al., 2020. Vitamin C for COVID-19: A living systematic review. Medwave 20(6): e7978.

Bassetti M et al., 2020. The novel Chinese coronavirus (2019-nCoV) infections: Challenges for fighting the storm. Wiley Online Library 2020: e13209.

Calder PC et al., 2020. Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections. Nutrients 12(4): 1181.

Calder PC, 2020. Nutrition, immunity and COVID-19. BMJ Nutrition, Prevention & Health 3(1): 74.

Cannell J et al., 2006. Epidemic influenza and vitamin D. Epidemiology & Infection 134(6): 1129-1140.

Carr AC and Maggini S, 2017. Vitamin C and immune function. Nutrients 9(11): 1211.

Carr AC, 2020. A new clinical trial to test high-dose vitamin C in patients with COVID-19. Critical care 24(1): 1-2.

Cascella M et al., 2022. Features, evaluation, and treatment of coronavirus (COVID-19). Statpearls [internet] 2022.

Cheng H et al., 2020. Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. Journal of medical virology 92(7): 726-730.

Collins JF, 2016. Molecular, genetic, and nutritional aspects of major and trace minerals. Academic Press.

Derbyshire E and Delange J, 2020. COVID-19: is there a role for immunonutrition, particularly in the over 65s? BMJ Nutrition, Prevention & Health 3(1): 100.

Dey S and Bishayi B, 2018. Killing of S. aureus in murine peritoneal macrophages by ascorbic acid along with antibiotics chloramphenicol or ofloxacin: correlation with inflammation. Microbial pathogenesis 115: 239-250.

Dhok A et al., 2020. Role of vitamins and minerals in improving immunity during Covid-19 pandemic-A review. Journal of Evolution of Medical and Dental Sciences 9(32): 2296-301.

Di Credico B et al., 2015. Efficacy of the reactive oxygen species generated by immobilized TiO2 in the photocatalytic degradation of diclofenac. International Journal of Photoenergy 2015.

Du Toit A, 2020. Outbreak of a novel coronavirus. Nature Reviews Microbiology 18(3): 123-123.

Dutta P et al., 2009. Perspectives for chitosan based antimicrobial films in food applications. Food chemistry 114(4): 1173-1182.

Ekert PG and Vaux DL, 1997. Apoptosis and the immune system. British medical bulletin 53(3): 591-603.

Evgen'ev MB and Frenkel A, 2020. Possible application of H2S-producing compounds in therapy of coronavirus (COVID-19) infection and pneumonia. Cell Stress and Chaperones 25(5): 713-715.

Furuya A et al., 2008. Antiviral effects of ascorbic and dehydroascorbic acids in vitro. International journal of molecular medicine 22(4): 541-545.

Gombart AF et al., 2020. A review of micronutrients and the immune system–working in harmony to reduce the risk of infection. Nutrients 12(1): 236.

Guillin OM et al., 2019. Selenium, selenoproteins and viral infection. Nutrients 11(9): 2101.

Guo W et al., 2020. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes/metabolism research and reviews 36(7): e3319.

Habib MB et al., 2020. Acute symptomatic hyponatremia in setting of SIADH as an isolated presentation of COVID-19. IDCases 21: e00859.

Han JE et al., 2016. High dose vitamin D administration in ventilated intensive care unit patients: a pilot double blind randomized controlled trial. Journal of clinical & translational endocrinology 4: 59-65.

Hemilä H and Chalker E, 2013. Vitamin C for preventing and treating the common cold. Cochrane database of systematic reviews 2013(1).

Janssen R and Walk J, 2020. Vitamin K epoxide reductase complex subunit 1 (VKORC1) gene polymorphism as determinant of differences in Covid-19-related disease severity. Medical Hypotheses 144: 110218.

Jayawardena R et al., 2020. Enhancing immunity in viral infections, with special emphasis on COVID-19: A review. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 14(4): 367-382.

Jin YH et al., 2020. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). Military medical research 7(1): 1-23.

Jones HD et al., 2015. Nicotinamide exacerbates hypoxemia in ventilator-induced lung injury independent of neutrophil infiltration. PloS one 10(4): e0123460.

Kashiouris MG et al., 2020. The emerging role of vitamin C as a treatment for sepsis. Nutrients 12(2): 292.

Klok F et al., 2020. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thrombosis research 191: 145-147.

Kraft CE and Angert ER, 2017. Competition for vitamin B1 (thiamin) structures numerous ecological interactions. The Quarterly Review of Biology 92(2): 151-168.

Kumar P et al., 2021. Role of vitamins and minerals as immunity boosters in COVID-19. Inflammopharmacology 29(4): 1001-1016.

Kumar V et al., 2021. In silico virtual screening-based study of nutraceuticals predicts the therapeutic potentials of folic acid and its derivatives against COVID-19. Virus Disease 32(1): 29-37.

Laaksi I, 2012. Vitamin D and respiratory infection in adults. Proceedings of the Nutrition Society 71(1): 90-97.

Lee GY and Han SN, 1992. The role of vitamin E in immunity. Nutrients 10(11): 1614.

Lemire JM, 1992. Immunomodulatory role of 1, 25-dihydroxyvitamin D3. Journal of cellular biochemistry 49(1): 26-31.

Li B et al., 2018. Identification of retinoic acid receptor agonists as potent hepatitis B virus inhibitors via a drug repurposing screen. Antimicrobial Agents and Chemotherapy 62(12): e00465-18.

Li G et al., 2020. Coronavirus infections and immune responses. Journal of medical virology 92(4): 424-432.

Lindschinger M et al., 2019. A randomized pilot trial to evaluate the bioavailability of natural versus synthetic vitamin B complexes in healthy humans and their effects on homocysteine, oxidative stress, and antioxidant levels. Oxidative medicine and cellular longevity 2019.

Lippi G et al., 2020. Electrolyte imbalances in patients with severe coronavirus disease 2019 (COVID-19). Annals of clinical biochemistry 57(3): 262-265.

Liu B et al., 2020. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? Journal of autoimmunity 111: 102452.

Lu H et al., 2020. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. Journal of medical virology 92(4): 401.

Luo Y et al., 2020. Low blood sodium increases risk and severity of COVID-19: a systematic review, meta-analysis and retrospective cohort study. medRxiv 2020: 2020.05. 18.20102509.

Martineau AR et al., 2017. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. bmj 356.

Mehmel M et al., 2020. Nicotinamide riboside—the current state of research and therapeutic uses. Nutrients 12(6): 1616.

Meydani SN et al., 2018. Perspective: should vitamin E recommendations for older adults be increased? Advances in Nutrition 9(5): 533-543.

Michienzi SM and Badowski ME, 2020. Can vitamins and/or supplements provide hope against coronavirus? Drugs in context 9.

Mikkelsen K and Apostolopoulos V, 2019. Vitamin B1, B2, B3, B5, and B6 and the Immune System. Nutrition and immunity 2019: 115-125.

Ni W et al., 2020. Role of angiotensin-converting enzyme 2 (ACE2) in COVID-19. Critical Care 24(1): 1-10.

Nimer RM et al., 2022. The impact of vitamin and mineral supplements usage prior to COVID-19 infection on disease severity and hospitalization. Biomolecules and Biomedicine 2022.

Parra M et al., 2018. Vitamin B6 and its role in cell metabolism and physiology. Cells 7(7): 84.

Raverdeau M and Mills KH, 2014. Modulation of T cell and innate immune responses by retinoic acid. The Journal of Immunology 192(7): 2953-2958.

Rodriguez-Morales AJ et al., 2020. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel medicine and infectious disease 34: 101623.

Rondanelli M et al., 2018. Self-care for common colds: the pivotal role of vitamin D, vitamin C, zinc, and echinacea in three main immune interactive clusters (physical barriers, innate and adaptive immunity) involved during an episode of common colds—practical advice on dosages and on the time to take these nutrients/botanicals in order to prevent or treat common colds. Evidence-Based Complementary and Alternative Medicine 2018.

Rothan HA and Byrareddy SN, 2020. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of Autoimmunity 109: 102433.

Sajadi MM et al., 2020. Temperature, humidity, and latitude analysis to predict potential spread and seasonality for COVID-19. Social Science Research Network 2020.

Sandstead HH and Prasad AS, 2010. Zinc intake and resistance to H1N1 influenza. American journal of public health 100(6): 970-971.

Seale LA et al., 2020. A role for selenium-dependent GPX1 in SARS-CoV-2 virulence. The American Journal of Clinical Nutrition 112(2): 447-448.

Shakoor H et al., 2021. Be well: A potential role for vitamin B in COVID-19. Maturitas 144: 108-111.

Shakoor H et al., 2021. Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19? Maturitas 143: 1-9.

Sheybani Z et al., 2020. The role of folic acid in the management of respiratory disease caused by COVID-19.

Shi Y et al., 2020. COVID-19 infection: the perspectives on immune responses. 2020, Nature Publishing Group 2020: 1451-1454.

Silver JK, 2020. Prehabilitation could save lives in a pandemic. bmj 369.

Tan CW et al., 2020. A cohort study to evaluate the effect of combination Vitamin D, Magnesium and Vitamin B12 (DMB) on progression to severe outcome in older COVID-19 patients. MedRxiv 2020: 20112334.

Te Velthuis AJ et al., 2010. Zn2+ inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS pathogens 6(11): e1001176.

Trottier C et al., 2008. Retinoids inhibit measles virus in vitro via nuclear retinoid receptor signaling pathways. Antiviral research 80(1): 45-53.

Ueland PM et al., 2017. Inflammation, vitamin B6 and related pathways. Molecular aspects of medicine 53: 10-27.

Vance CP, 2011. Phosphorus as a critical macronutrient. The molecular and physiological basis of nutrient use efficiency in crops 2011: 227-264.

Walther B et al., 2013. Menaquinones, bacteria, and the food supply: the relevance of dairy and fermented food products to vitamin K requirements. Advances in nutrition 4(4): 463-473.

Wimalawansa SJ, 2020. Global epidemic of coronavirus—Covid-19: what can we do to minimize risks. European Journal of Biomedical Research 7(3): 432-8.

Xu J et al., 2017. Vitamin D alleviates lipopolysaccharideinduced acute lung injury via regulation of the reninangiotensin system. Molecular medicine reports 16(5): 7432-7438.

Xu Z et al., 2020. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet respiratory medicine 8(4): 420-422.

Xue X et al., 2020. Correlation between hypophosphatemia and the severity of Corona Virus Disease 2019 patients. MedRxiv 2020: 20040816.

Yi Y et al., 2020. COVID-19: what has been learned and to be learned about the novel coronavirus disease. International journal of biological sciences 16(10): 1753.

Yoshii K et al., 2019. Metabolism of dietary and microbial vitamin B family in the regulation of host immunity. Frontiers in nutrition 6: 48.

Yuan S et al., 2019. SREBP-dependent lipidomic reprogramming as a broad-spectrum antiviral target. Nature communications 10(1): 120.

Yuki K et al., 2020. COVID-19 pathophysiology: A review. Clinical immunology 215: 108427.

Zabetakis I et al., 2020. COVID-19: the inflammation link and the role of nutrition in potential mitigation. Nutrients 12(5): 1466.

Zemlin AE and Wiese OJ, 2020. Coronavirus disease 2019 (COVID-19) and the renin-angiotensin system: A closer look at angiotensin-converting enzyme 2 (ACE2). Annals of clinical biochemistry 57(5): 339-350.

Zhang L and Liu Y, 2020. Potential interventions for novel coronavirus in China: A systematic review. Journal of medical virology 92(5): 479-490.

Zhang Y et al., 2018. A review of the extraction and determination methods of thirteen essential vitamins to the human body: An update from 2010. Molecules 23(6): 1484.