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Roles of Nutritional factors against COVID-19

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Acknowledgements

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2. ABSTRACT

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus, also known as the coronavirus disease (COVID-19), was discovered in Wuhan, China, in December 2019. On March 11, 2020, it was determined that there was a pandemic all over the world. As the world struggles with COVID-19 and an inability of clinically relevant medicines, attention has shifted to modalities that may aid in immune system bolstering. Pharmaceutical companies are working to develop targeted treatments and vaccines for the SARS-CoV-2 COVID-19 virus. This is due to the COVID-19 virus's significant impact on the immune system, which manifests itself in a variety of inflammatory reactions. A diet that provides a healthy balance of calories, nutrients, and other macronutrients could significantly aid in the prevention and management of chronic infectious illnesses. A healthy diet rich in vitamins A, C, D, and E, and certain micronutrients and zinc, selenium, copper, iron, and omega-3 fatty acids, may help with a variety of infectious disorders.

The goal of this study was to investigate and report on the latest discoveries regarding the use of vitamins and minerals in the treatment of COVID-19. A review of past research is conducted to identify the conclusions reached by other experts considering the beneficial effects of dietary components. Insufficiency of these minerals and nutrients in plasma concentration may result in a decrease in the immune system's excellent functioning, which is one of the ingredients that contribute to a bad immunological condition. Also, This is one of the elements that contribute to a weakened immune system. This paper provides a review of the literature on the characteristics of COVID-19, and data on the use of minerals and vitamins as preventative measures to reduce morbidity and mortality in COVID-19 patients.

3. INTRODUCTION

The recent epidemic of coronavirus disease 2019 (COVID-19), which was caused by a novel zoonotic severe acute respiratory syndrome coronavirus (SARS-CoV-2), poses a significant danger to the general population's health in every region of the world (Lai et al., 2020). Over 165 million individuals throughout the world have been infected with variations of the coronavirus SARS-CoV-2 as of the 19th of April, 2020, and this has led to 3.42 million fatalities(Ahmad et al., 2020). The limitations and lockdown procedures that are required to manage the COVID-19 outbreak have emerged in response to a worldwide social and economic crisis. These measures have a significant impact on the overall well-being, psychological health, as well as social support of the people.While some individuals are asymptomatic or have only minor upper respiratory tract symptoms, other people have severe pneumonia that is characterized by cough, fever, dyspnea, bilateral lung infiltrates, or even acute respiratory damage that requires ventilation(Wang et al., 2021). An infection with SARS-CoV-2 affects not only the respiratory system, but also the kidneys, the gastrointestinal tract, the testis, the heart, and the brain. Overall, the impact on these target organs may have substantial and far-reaching repercussions for the lethality of COVID-19 and recovery(Chen et al., 2020). It is critical to maintaining one's emotional wellbeing, and level of fitness, to keep one's immune system stable and resilient and to make sure that it is capable of mounting an adequate response to SARS-CoV-2.

Along with the worldwide effort to create a vaccine, there has been a surge in interest in the epidemiological variables that underpin COVID-19 vulnerability and development. This is being done to find the most effective preventative and therapeutic strategies that are currently available(Park et al., 2020). A great deal of research has been conducted on the possible correlations between a people's dietary state and their immune function. As the epidemic measures spread such as lockdown, it exacerbates the factors that endanger malnutrition including unhealthy diets(Akseer et al., 2020). Food price increases are caused by disruptions in agricultural production, market links, and seasonal labor migrations. Meanwhile, worldwide panic shopping increased waste and lowered diet quality as individuals seek to get fresh food(Torero, 2020). Lockdown initiatives in many countries have increased high calorie consumption, creating an environment that encourages the development of obesity in many people as look for instant food(Muscogiuri et al., 2020).

Obesity is associated with endocrine disruption, metabolic dysfunction, dysfunctional adipose tissue, decreased immunological function, and low-grade (sub) chronic inflammation (Kawai et al., 2021). Moreover, obesity is the leading cause metabolic syndrome, which is linked to increased angiotensin-converting enzyme 2 (ACE2) expression in adipose tissue(Landecho et al., 2021).

The increased prevalence of these risk factors is strongly linked to dietary patterns, which include increased consumption of refined carbohydrates, increased amounts of saturated fat (high-fat diet), and low levels of fiber and antioxidants(Manna et al., 2015). A balanced diet has the potential to play a significant role in maintaining immunological system and resistance to disease, which would include infections with bacterial and viral pathogenic organisms(Aman et al., 2020). Malnutrition has long-term effects on both mental and physical well-being due to its influence on gene expression and cell activation, as well as its interference with the signalling molecules that form and modify the immune response(Alwarawrah et al., 2018). As a result, a lack of proper nutrition and an improper diet can significantly affect one's immune system, increasing one's chances of acquiring communicable diseases like influenza and SARS-CoV-2(Chaari et al., 2020).

Ethnic background influences nutrition and obesity, and there is a direct link between these disparities and severe COVID-19-related consequences. Malnutrition may be blamed for higher hospitalization rates for COVID-19 positive participants among Native Americans and Latin Americans compared to White Americans in the United States(Acosta et al., 2021). Another example of the impact of a country's cultural history and socioeconomic standing on the severity of COVID-19 can be found in Islamic countries with insufficient healthcare systems and a scarcity of facilities, particularly during Ramadan, which is traditionally indicated by fasting. Many Muslims find it difficult to maintain their normal exercise routines during the holy month of Ramadan, which may have a detrimental effect on their immune system. On the other hand, studies on the effects of Ramadan fasting on health have found that reducing the number of times you eat each day and cutting back on calories can have a beneficial affect on insulin sensitivity, as well as a reduction in oxidative stress and inflammation(Moghadam et al., 2021).

Diet and obesity play a significant role in both the outcome of viral infectiousness and the health of the people during this particular disease outbreak. In this review, we provide a summary of recent data addressing the impact of diet on the variation in COVID-19 illness severity, as well as its potential implications for COVID-19 management in the midst of the present crisis. Understanding the dietary pattern that is detrimental to COVID-19 survival may allow for the development of public health initiatives aimed at reducing the spread of COVID-19 and developing novel methods for its management and, possibly, treatment.

It is therefore critical to understand the relationship between one's nutritional status and the risk of contracting COVID-19 to formulate evidence-based suggestions. Nutritional interventions may be able to reduce an individual's vulnerability to infections, the rate at which symptoms develop, and the risk of developing a serious disease. However, nutrition incorrect information has been widely circulated to the general population for a long time (Kininmonth et al., 2017), and nutrition-related misconceptions about COVID-19 treatment and prevention are widely spread in this epidemic. To achieve this goal, a comprehensive systematic review of academic journals, preprints, and clinical trial data was conducted in this study to establish a strong evidence foundation of what is presently known regarding the significance of nutritional variables in the fight against COVID-19.

4. PATHOPHYSIOLOGY OF COVID-19

The SARS-CoV-2 is a new beta-coronavirus that caused the coronavirus illness in 2019. (also known as COVID-19). As of the 15th of June, 2020, the number of confirmed cases worldwide had surpassed 8 million, with over 400,000 deaths documented (George, 2020). Because of the unprecedented pathogenicity and global impact of this pandemic, the scientific community has jumped right into critical research. According to preliminary reports from the Chinese Center for Disease Control and Prevention, the great majority of SARS-CoV-2 cases reported are mild. The majority of accidents are gentle, with 14% showing symptoms related with pneumonia and 5% developing acute respiratory distress syndrome (ARDS), sepsis, and/or multisystem organ failure (Wu et al., 2020). The vast majority of patients are capable of eliciting an appropriate immune response(Nielsen et al., 2021), a significant proportion of people have shown clinical symptoms such as cough, fever, and dyspnea(Goyal et al., 2020).

Coronavirus subgroups are denoted by the letters alpha, beta, gamma, and delta. The letters S, E, M, and N represent the four major structural glycoproteins that comprise the Coronavirus(Mohamadian et al., 2021). S protein, in particular, is the only one of these four proteins capable of connecting to the virus and allowing it to enter the host cell, which is one of the most critical stages in the viral replication process (Bohn et al., 2020). S protein is made up of two distinct subunits known as S1 and S2. The receptor-binding domain is found in S1, while S2 is in charge of fusion and other functions (Li et al., 2003).

The respiratory system is the major target of the SARS-CoV-2 virus's damaging impacts; however, other organ systems are also affected(Zhang et al., 2020). Patients in the original case series from Wuhan, China, observed symptoms related to lower respiratory tract infections(Huang et al., 2020). People also experience headaches, dizziness, generalized weakness, vomiting, and diarrhea(Mao et al., 2020).

Despite the fact that COVID-19 is primarily a respiratory illness, the gastrointestinal tract has the capability to act as a reservoir for SARS-CoV-2(Pal et al., 2020). Furthermore, neurological symptoms have been observed in the vast majority of COVID-19 patients who have been hospitalized (Mao et al., 2020).

The respiratory symptoms of COVID-19 are now well known to be quite diverse, ranging from no symptoms at all to significant hypoxia, which is respiratory failure. This is something that the vast majority of people now recognize. According to preliminary reports from Wuhan, the time between the onset of symptoms and the onset of ARDS was as short as eight days(Li et al., 2020). The SARS-CoV has been discovered to have a functional receptor in ACE2(Li et al., 2003). An investigation of the structure and function of the SARS-CoV-2 spike protein revealed that it interacts with the ACE2 receptor(Ortega et al., 2020). The lung, heart, ileum, kidney, and bladder all have high levels of ACE2 expression (Xu et al., 2020). More specifically, the ACE2 receptor is highly expressed on the apical surface of lung epithelial cells in the alveolar space(Yao et al., 2020).

The host's response to infectious diseases, where inborn immune system defects are frequently important, can be greatly influenced by genetic vulnerability, which can be a key component (Dutta et al., 2021). Variations in genetic susceptibility may also be to blame for COVID-19's varying clinical outcomes. Advanced age, gender, and the presence of comorbidities such as cardiovascular disease, respiratory illness, hypertension, and diabetes are all potential risk factors. These factors are strongly related to illness intensity but also the fatality rate. Although the vast majority of infected individuals recover completely, even patients who are incredibly young and otherwise healthy may die as a result of this disease due to environmental factors including social distancing, lack of education(Rashedi et al., 2020). Many questions remain unanswered about the susceptibility and result outcomes associated with SARS-CoV-2 infection.

It is necessary to have a healthy immune system to mount an effective defense against invading germs. However, because COVD-19 is known to have immunological flaws, there is a slim chance that a defence against SARS-CoV-2 can be established. The vast cytokines and chemokines production observed during a COVID-19 infection(Chi et al., 2020). This phenomenon is known as a "cytokine storm." It causes extensive and uncontrollable tissue damage(Ragab et al., 2020).

When it comes to COVID-19, men are far more likely than women to experience severe symptoms and develop more serious complications(Conti et al., 2020). People with prostate cancer who received androgen-deprivation therapy, a medication that limits the production of androgens that feed the growth of prostate cancer cells, had a significantly lower risk of SARS-CoV-2(*Science*, 2020). The precise cause of this disparity is unknown; however, Inhibiting testosterone production in males, according to this scientific proof, protects against SARS-CoV-2 infection because decreased testosterone levels are linked to diseases and pro-inflammatory cytokine expression(Azevedo et al., 2021). There is also evidence that males and females have different activities of receptors that detect infections or act as an entry point for SARS-CoV-2. This is supported by the fact that the disease has a gender difference in prevalence(Salah et al., 2021). Although there is no definitive evidence in men versus females which affecting on covid-19, this contribute to think difference in the covid infection(Bienvenu et al., 2020).

5. VITAMINS

5.1 Vitamin A

Vitamin A(VA) is a lipid-soluble compound composed of a conjugated system of double bonds in a trans-configuration (Jovic et al., 2020), which is a member of the retinyl-ester family and also known by its chemical name, retinoic acid (RA) (Kumar et al, 2021). This vitamin, which has several derivatives such as retinal, retinol, and retinoic acid, is known as an "anti-infective" vitamin (Semba, 1998). Carotenoids, a type of provitamin A, are commonly obtained from dairy products, rich in fish and vegetables (Carazo et al., 2021).

This VA shows a wide range of biological functions, including antioxidant activity, gene transcription regulation, vision maintenance, cell proliferation and epithelial barrier formation. Especially, VA plays an important role in the activation of both innate and adaptive immune responses, which can be referred to as defending action(Jovic et al., 2020). In immune system, VA is linked to a wide range of immune cells, including T-lymphocytes, B-lymphocytes, macrophages, and granulocytes(Chang et al., 2015).

For example, Natural killer(NK) cells, which play a role in the body`s immune response against cancer, can be found in blood, liver, and spleen. In case of deficiency of VA, the numbers of NK cells in the body decrease and their cytolytic functions are impaired.

Macrophages and monocytes are responsible for the activation of high levels of tumor necrosis factor-A, which can then perform a variety of functions, including initiating the production of T and B lymphocytes and activating cell adhesion molecules.

According to the findings of various studies, retinoids have the ability to influence not only the total number of macrophages but also their level of activity. All-trans RA increased phagocytosis in murine macrophages twofold and resulted in a high level of transforming growth factor-p activation in human monocytes and myelomonocytic cells. These effects were observed in both murine and human cells (Semba, 1998).Furthermore, VA has a direct effect on the activity of both neutrophils and macrophages. In the Lack of VA, these cells` phagocytic and antibacterial functions are inhibited, resulting in reduced resistance ability against certain infections (Stephensen et al., 2021). Interleukin-1 has a similar function to tumor necrosis factor(TNF)-a, which stimulates the production of T and B lymphocytes and regulates inflammatory mediators. This Interleukin-1 production can be enhanced by retinoic acid. T lymphocytes, which include T helper and T cytotoxic lymphocytes, are responsible for the regulation of the immune system. A shortage of VA has resulted in the impairment of cytotoxic T lymphocytes (Semba, 1998). Furthermore, It ensures that B lymphocytes function normally, which is required for the production of antibody responses to antigens(Di Renzo et al., 2020).

Several studies have shown that retinoids can inhibit the replication of certain viruses, including cytomegalovirus, hepatitis B virus, norovirus, and influenza (Li et al. 2020).

Therefore, RA may have a wide range of effects on the immune system`s cells(Semba, 1998). A lack of VA exacerbates the disease to worsen by causing tissue damage and hyperinflammatory responses. On the other hand, a sufficient supply of VA has benefits for tissue impairment and infection control (Stephensen et al., 2021).

As a result, VA should be regarded as an essential component in the maintenance of immunological balance in COVID-19 infections. Reduced VA levels in the plasma may contribute to immune dysregulation and disruption of antiviral T-cell responses in patients with COVID-19 diseases(Tepasse et al., 2021).

5.2 Vitamin C

Vitamin C is water-soluble, and cannot be synthesized in the human body. The primary sources of vitamin C in the diet come from fruits and vegetables. Potatoes, and sugar-sweetened beverages, such as soda and fruit juice, also contribute significantly(Doseděl et al., 2021).

Vitamin C may have antiviral properties, as shown by several research conducted in vitro, on animals, and in humans (Abobaker et al., 2020). Furthermore, when taken in sufficient quantities, it is known to defence against flu-like diseases(Shakoor et al., 2021). Vitamin C deficiency is common in hospitalized patients who are under physiological stress from factors such as illness, infection, trauma, and surgery(Holford et al., 2020).

Vitamin C boosts the immune system's ability to fight respiratory and systemic infections. It aids in the production of antibody(Carr et al., 2017).

Based on evidence from in vitro studies, animal testing, and clinical trials, a high dose of vitamin C has been suggested to have virucidal effects due to the decrease in viral replication(Abobaker et al., 2020). In one the clinical trials, for example, vitamin C supplementation alleviated a patient`s flu-like symptoms. In the meta-analysis, it has been shown that overdosing on vitamin C may help improve flu-like symptoms such as fever and chills when taken during the common cold. Vitamin C supplementation has been shown to significantly improve the resistance to viral infections in animal research(Bae et al., 2020). Vitamin C is also beneficial for helping to strengthen the humoral and cell-mediated immune systems(Pecora et al., 2020). This is necessary for the proliferation and proper function of neutrophils, monocytes, phagocytes, and lymphocytes, which eventually result in the production of antibodies(Di Renzo et al., 2020).

Preliminary studies have shown that vitamin C can lower the levels of pro-inflammatory cytokines like TNF-α while increasing the levels of anti-inflammatory ones like interleukin-2 (IL-2). It has been demonstrated that increasing one`s daily vitamin C consumption to 1g can increase the amount of IL-10 released by peripheral blood mononuclear cells(Shakoor et al., 2021). According to recent studies, it has been found that vitamin C supplementation can reduce the production of IL-6, and IL-1(Pecora et al., 2020). In COVID-19, IL-10 acts as a negative feedback mechanism to IL-6, which is an important component in the regulation of inflammation(Shakoor et al., 2021). An Elevated IL-6 in many tissues is related to aging, which eventually leads to multiple organ failure. According to a randomized placebo-controlled study, Patients with hypertension and/or diabetes obesity were given 500 mg of vitamin C twice daily, which resulted in a reduction in IL-6 and C-reactive protein. On the Basis of these findings, Vitamin C may be beneficial in the treatment of patients with severe COVID-19(Feyaerts et al., 2020). A decreased status of vit c is shown commonly among people with COVID-19(Lordan et al., 2021).

According to a previous study, Vitamin C treatment has been linked to lower a risk of pneumonia and low respiratory tract infections, as well as boost the immune system in patients with low levels of vitamin C (Akhtar et al., 2021). Vitamin C delivered intravenously has been shown to greatly lessen the severity of severe illnesses, including septic shock and ARDS (Kashiouris et al. 2020). Also, upper respiratory infections could be prevented by consuming 1 to 2 g of vitamin C per day(Di Renzo et al., 2020).In general, most patients with pneumonia or ARDS typically have vitamin C levels that are lower than normal. Elderly patients who are taking vitamin c treatment showed decreased mortality and severity of pneumonia, due to benefit of vitamin C(Pecora et al., 2020).

In an animal study, mice suffering ARDS with vitamin C supplementation resulted in a decrease in the expression of proinflammatory genes and an improvement in epithelial barrier function(Hemilä et al., 2021). Furthermore, vitamin C administration reduced the effects of the influenza A virus on lung inflammation and the production of proinflammatory cytokines in Gulo knockout mice. Endothelial dysfunction and damage caused by Covid-19, both of which can contribute to multi-organ failure Because of its ability to restore endothelial function, vitamin C may be able to aid in the prevention of this damage if it is administered early in the Covid-19 study (Abobaker et al., 2020). According to the studies cited above, it is expected to be effective as a preventative measure and treatment for respiratory, systemic, and COVID-19 infections by boosting immunity(Pecora et al., 2020).

However, there is still limited evidence that vitamin C can treat covid-19, thus, more clear studies and evidence are needed to recommend vitamin C treatment against Covid-19(Cerullo et al., 2020).

5.3 Vitamin D

Vitamin D(Vit D) can be obtained by taking vitamin supplements or found in the diet such as fish-liver oils, especially cod-liver oil which are excellent sources of Vit D. However, it is synthesized by the thermal reaction from 7-dihydrocholesterol in the skin as the primary source. UV-B rays cause the breakdown of 7-dehydrocholesterol in the skin, which leads to the production of vitamin D3. There are enzymes in the liver, which are known as CYP2R1 and CYP27A1 that hydroxylate vitamin D3 to 25-hydroxyvitamin D3 (25(OHD3)). Once more, the enzyme CYP27B1 is responsible for converting the inactive compound 25(OH)D3 into the physiologically active hormone 1,25(OH)2D3, which is commonly referred to as calcitriol(Chen et al., 2018).

Vit D endocrine and autocrine processes are responsible for carrying out the functions of Vit D in the body. Calcium absorption and osteoclastic activity are both increased by the action of these endocrine mechanisms. Vit D is required for healthy bone mass, density, and strength. Inadequate Vit D levels can have the opposite effect. Due to these functions, a lack of Vit D can cause an increase in bone turnover, which increases the risk of bone injury. The second route of action for Vit D is the autocrine route.

Because the majority of the most important metabolic functions occur along this pathway, this vitamin is required in its modulator role for protein synthesis, immune response, cell proliferation, and differentiation (De la Puente Yagüe et al., 2020).

The relationship between a lack of Vit D and increased disease activity in the immune system is critical for determining whether or not immune cells are capable of responding appropriately to Vit D. Vit D's immunomodulatory properties affect immune cells such as B cells, T cells, monocytes, and dendritic cells. These immune cells have a different response to Vit D.

For example, Vit D has been shown to have a direct relationship with the suppression of B cell proliferation and differentiation, which leads to a decrease in immunoglobulin mediated by T cells. Furthermore, Vit D has an effect on T cells, which plays an important role in the Vit D's immunomodulatory effects. This vitamin can inhibit not only B cell proliferation and differentiation, but also T cell proliferation and differentiation. It is critical to acknowledge the critical roles that these controls play in immune diseases(Prietl et al., 2013).

In addition, Vit D affects monocytes and dendritic cells in the body. It brings downregulation of a number of proinflammatory cytokines such as IL-1, IL-6, IL-8, and IL-12, as well as TNFα which are produced by monocytes while increasing the levels of anti-inflammatory cytokines(Aranow, 2011).

There appears to be a correlation between a low level of Vit D and an increased risk of COVID-19 infection. A wide range of COVID-19 risk factors is strongly associated with

Vit D levels. Vit D deficiency is linked to many factors, including overweight and obesity, hypertension, and climates that provide less sun exposure.

Furthermore, Patients with severe COVID-19 symptoms and vit D insufficiency showed high levels of C-reactive protein (CRP), which is a marker of inflammation(Shakoor et al., 2021).

High mortality increase with age and with chronic disease comorbidity in patients with ARDS. This means that both are associated with lower 25(OH)D3 concentrations(Alkhatib, 2020). As we are getting older, the production of 7-dihydrocholesterol in the skin is decreased, resulting in lower levels of active Vit D. Due to this reason, It Is hypothesized that the elderly have high mortality of COVID-19 (Shakoor et al., 2021).

Xu et al. conducted a study that found calcitriol (a vitamin D agonist) to be protective against acute lung damage. This protection was achieved by controlling the expression of ACE2 in lung tissue (Xu et al. 2017). One of the pathogenic factors in COVID-19 is high levels of ACE2.

According to several studies, individuals with Vit D levels greater than 95 nmol/L have a significantly lower risk of developing acute viral respiratory tract infections than those with levels less than 95 nmol/L. (Ebadi et al., 2020). A recent meta-analysis found that Vit D supplementation reduced the incidence of acute respiratory tract infections when compared to those with low baseline Vit D levels (25 nmol/L) (Martineau et al. 2017).

Previous researches have demonstrated that taking a Vit D supplement can aid in the prevention of acute infections of the upper respiratory tract as well as a low level of vitamin D status (Shakoor et al., 2021).

Furthermore, on March 23, 2020, Dr. Tom Frieden, former director of the Centers for Disease Control and Prevention, suggested taking vit D to combat COVID-19(Maha et al., 2021)

Despite the fact that conclusive evidence against COVID-19 has yet to be discovered (Shakoor et al., 2021), however, Taking vit D to maintain an adequate serum level in the COVID-19 patients may be able to play a potential role in the prevention or treatment of COVID-19 in order to strengthen the immune system and reduce the risk of mortality based on the previously published studies(Ebrahimzadeh-Attari et al., 2021).

5.4 Vitamin E

Vitamin E is a lipid-soluble vitamin that is classified into two groups: tocopherols and tocotrienols, each containing four isomers (alpha, beta, gamma, and delta). Not only vitamin E is well-known for its antioxidant properties, but this vitamin also possesses anti-inflammatory properties(Mohd et al., 2020).

Different forms of vitamin E are found in foods. The amount of vitamin E in food depends on how it is stored, processed, and prepared. The major dietary sources are plant oils and nuts. Especially Fats and oils, vegetables, meat, and seafood are the primary sources. The predominant form of vitamin E found in oils derived from wheat germ, sunflower, safflower, canola, and olives is alpha-tocopherol, whereas gamma-tocopherol is found primarily in oils derived from corn, soybean, sesame, and peanuts. (Meydani et al., 2005).

Vitamin E, as a potent antioxidant, is essential for the regulation and maintenance of healthy immune system function (Jayawardena et al. 2020). Vitamin E acts as a free radical scavenger, lowering oxidative stress(Vitamin E, 2022). It also prevents free radicals from producing highly energized and damaged cells(Lobo et al.,2010).

Vitamin E is beneficial to the immune system for more than just its ability to fight free radicals production(Rizvi et al., 2014). Alpha-tocopherol inhibits protein kinase C, which inhibits cell proliferation and differentiation in smooth muscle cell, and platelets. (Boscoboinik et al., 1991).

A lack of vitamin E can harm the immune system and cause inflammation by altering membrane integrity and signal transmission, as well as modulating inflammatory mediators and the cell cycle, all of which are included in regulatory activities. Vitamin E influences the host's susceptibility to bacterial and viral infections(Lewis et al., 2019).

Fetal resorption, necrotizing muscle illness, nerve deterioration in central and periperal, red blood cell hemolysis and immunodeficiency are all symptoms of vitamin E deficiency, which can be seen in animals.

Under normal circumstances, vitamin E deficiency in humans is unusual; however, vitamin E deficiency can be attributed to a variety of factors, including a genetic problem in the α- tocopherol-transfer protein, a condition known as fat malabsorption disorder, or a problem with lipoprotein production. A lack of vitamin E in the diet can cause a variety of health issues in humans, including peripheral neuropathy, skeletal myopathy, a shorter Red blood cell half-life, and immunological dysfunctions (Meydani, et al., 2005).

Dendritic cells, which play an important role in both the innate and adaptive immune systems, have been shown to be affected by vitamin E, which influences both their development and activities(Di Renzo, et al., 2020).

According to the findings of a study, an increased intake of vitamin E is more beneficial in maintaining immune function in people in their senior years than in people in their younger years (Rizvi et al., 2014).

Treatment with vitamin E promotes humoral B cells and antibody responses in both animals and humans, in addition to increasing NK cell activity by regulating NO levels. Vitamin E has been shown to activate T-cell activation signals in naive T-cells as well as promote the development of immunological synapses in those T-cells (Iddir et al., 2020).

It stimulates lymphocyte proliferation as well as T cell-mediated activities; additionally, it enhances and perfects the Th1 response while inhibiting the Th2 response (Di Renzo et al., 2020).

Recent research on adults in Malaysia who were given either tocopherol or tocotrienol as a supplement discovered that the expression of a variety of immune-related genes was increased (Iddir et al., 2020).

As a result, taking a vitamin E supplement may reduce the number of superoxides produced, which may re-balance the system in favor of antioxidants, and help the COVID-19 therapy process(Lai et al., 2021).

6. MINERALS

6.1 Zinc

Zinc is a micronutrient that is essential for the proper functioning of physiological systems, including the immune system. It is nutritionally necessary for the biological function of many enzymes and proteins, as well as cell proliferation and the integrity of genomic material (Mocchegiani et al., 2013).

Zinc is found in a variety of food groups, each with its own concentration and level of bioavailability. Red meat, certain types of seafood, beans, fortified cereals, and whole grains have the highest zinc concentrations. Zinc derived from animal sources is more readily available for cellular uptake than zinc derived from plant sources. People who eat little red meat, vegetarians, or live in developing countries and eat mostly plant-based meals are more likely to develop zinc deficiency as a result of not getting enough zinc in their diet(Gammoh et al., 2017).

People who eat a lot of meat and seafood, as opposed to vegetarians, may have healthier immune systems and are less likely to be zinc deficient. This contrasts with the fact that vegetarians are more likely to be zinc deficient (Joachimiak, 2021).

Because zinc is present throughout the human body, including in its tissues, organs, and fluids, a zinc deficiency is detrimental to human health (Jarosz et al., 2017).

Insufficiency in zinc can have a negative impact on different organs, particularly the immune system, which is particularly sensitive to changes in zinc levels.

The immune system of the body is divided into two categories: innate immunity and adaptive immunity. Invading pathogens are initially recognized and eliminated by innate immune system cells. These cells, specifically macrophages, NK cells, and polymorphonuclear (PMN) cells, are critical in this process. Zinc deficiency is linked to decreased PMN chemotaxis and phagocytosis, whereas zinc supplementation increases activity in these processes. Pathogens are eliminated after phagocytosis by the action of nicotinamide adenine dinucleotide phosphate oxidases, which can be inhibited by zinc deficiency or excess.

In addition, zinc increases monocyte adhesion to endothelial cells in vitro.

Zinc deficiency affects the production of proinflammatory cytokines such as interleukins IL-1, IL-6, and TNF- α, as well as the recognition of major histocompatibility complex class I by NK cells and their lytic activity. In terms of the adaptive immune response, Zinc deficiency causes thymic atrophy, which leads to T-cell lymphopenia, as well as a decrease in the number of B cells, which results in a decrease in the number of antibodies produced (Gammoh et al., 2017).

It has been demonstrated that zinc possesses potent antiviral activity against a wide variety of viruses, such as herpes simplex virus(HSV) types 1 and 2, rhinovirus, influenza, coronaviruses, human immunodeficiency virus, and some other pathogenic viruses. Zinc has been shown to reduce the pathogenicity of HSV1 and HSV2 by influencing viral polymerase activity, protein synthesis, and virus inactivation. Furthermore, zinc can inhibit HSV replication by interfering with the pathway by which proteins become ubiquitinated. Furthermore, a mouse study discovered that intravaginal zinc inoculation significantly reduced HSV2 infection, whereas topical zinc treatment significantly reduced the frequency of HSV1 and HSV2 infections as well as the length of time they lasted (Oyagbemi et al., 2021).

As a result, zinc is required for a wide range of cellular processes. It also has direct and indirect antiviral activities, such as cell membrane stabilization to prevent virus entry and viral replication inhibition via a variety of mechanisms, including viral genome transcription, protein translation, polyprotein processing, viral attachment, and uncoating. (Kumar et al., 2020).

Zinc supplementation in the diet has been shown to reduce the production of inflammatory cytokines by T helper cells and macrophages. This is most likely accomplished by lowering IL-1 and TNF- α gene expression (Oyagbemi et al., 2021).

In these kinds of circumstances, taking zinc supplements in adequate therapeutic dosages has the potential to either restore or improve the normal activity of immune cells.

Therefore, zinc supplementation may have a role to play in the prevention and therapy of covid-19 in patients who are zinc deficient (Kumar et al., 2020).

6.2 Selenium

Selenium is an essential micronutrient for all living things, including humans and animals. Animals, and humans consume it in greater quantities than plants, in the form of vegetables, meats, and nutritional supplements (Hariharan et al., 2020).

High levels of selenium were found in protein-rich meals, whereas vegetables with low levels of protein were found to have low levels. Selenium is found in cereals, meat and dairy products, fish, seafood, milk, and nuts. Furthermore, sea salt, eggs, yeast (yeasts containing selenium), bread, mushrooms, garlic, and asparagus all contain high levels of selenium. Selenium is found in relatively low concentrations in foods like fruits and vegetables. Plants and vegetables with a low protein content are a poor source of selenium because it is found primarily in the protein fraction of these plants and vegetables (Kieliszek, 2019).

Dietary selenium has a significant function in inflammation and immunity. Adequate levels of selenium consumption are required for the initiation of immunity, as well as in the control of overactive immunological responses and chronic inflammation(Huang et al., 2012).

As a result, a selenium deficiency can be hazardous because it makes the immune system more vulnerable to infections and even cancer. This is one of the reasons why a lack of selenium is dangerous.

There is some evidence that selenium can control the pathophysiology associated with chronic inflammatory illnesses in the gut and liver, as well as malignancies related to inflammation. In several tissues, such as the digestive tract, the uterus, and the mammary glands, as well as in other organ systems, having a lower status of selenium and selenoprotein has been linked to higher levels of inflammatory cytokines. (Avery et al., 2018).

For instance, selenium deficiency in experimental animals impairs various components of innate and acquired immunity, including T and B cell functions such as antibody formation, and increases susceptibility to infections. This occurs because selenium is required for the formation of antibodies. In humans, low selenium concentrations have been linked to decreased NK cell function. This association was found through various studies (Calder, 2020).

Furthermore, when selenium deficiency persists for an extended period of time, significant illnesses can develop in the human body. According to research, a lack of this nutrient is associated with an increased risk of cardiovascular disease, including myocardial infarction. It is linked to two endemic diseases known as Keshan and Kashin-Beck, which were discovered for the first time in women of reproductive age and children in a region of China with very low levels of selenium in the soil and crops. Both of these diseases were discovered in the same location. Keshan disease is distinguished by heart muscle degeneration. Osteoarthritis is known in Kashin-Beck to cause cartilage degeneration in the joints of the arms or legs, which can result in increased pain and decreased mobility (Kieliszek, 2019).

Researchers discovered elevated levels of the cytokines IL-6, IL-1, and TNF- α in selenium-deficient patients with Kashin-Beck illness (Zhang et al., 2020).

Some epidemiological studies have found that a lack of dietary selenium can contribute to a decrease in immunity, which can lead to an increased risk of disease (Kieliszek, 2019).

Selenium is an element found in glutathione peroxidase's active site. This enzyme contains four selenium atoms and is responsible for antioxidant activity, which protects body cells from oxidation and reduces the hazardous chemicals produced by oxidative stress(Freitas et al., 2014).

The activity of reduced glutathione peroxidase is what causes a more severe case of coxackie virus infection and Keshan disease in both mice and humans when selenium levels are low(Weeks et al., 2012). According to these findings, selenium deficiency may lead to the development of more pathogenic virus strains, which raises both the risks and costs associated with viral infection(Calder, 2020). Aside from that, it has been demonstrated that taking a selenium supplement can increase antibody production in addition to the activity of helper T cells, cytotoxic T cells, and NK cells (Mehdi et al., 2013).

However, it is important to note that this is dependent on the individual's baseline selenium status, and it is possible that the greatest effects will be seen when supplementation raises the level of selenium from an inadequate to a sufficient level. It has been demonstrated that selenium-rich foods can activate the leukocytes found in human blood. Similarly, selenium supplementation was shown to improve respiratory function in people suffering from respiratory distress syndrome. This was accomplished by restoring the lung's antioxidant capacity, which reduced inflammatory responses such as IL-1 and IL-6 levels while also improving respiratory mechanics (Avery et al., 2018).

Because selenium has many different functions in the human body, such as antioxidant, anti-inflammatory, anti-mutagenic, anti-carcinogenic, and antiviral properties(Hariharan et al., 2020), selenium supplementation may be helpful in the prevention or treatment of many different types of viruses, including the COVID-19 virus (Ebrahimzadeh-Attari et al., 2021).

6.3 Copper

Copper is a trace metal that is essential for the proper function of immune system components such as T cells, B cells, neutrophils, natural killer cells, and macrophage activities. Copper is required for these components to function effectively (Galmés et al., 2020).

Copper is a mineral that can be found in a variety of foods, including chocolate, meat, seafood, seeds, legumes, nuts, grains, and potatoes (Arrieta, et al., 2021). Copper-deficient diets made the animal more prone to infection, prolonged the duration of illness, and increased the likelihood of death (Djoko et al., 2015). Despite the fact that severe copper deficiency is extremely rare in humans, inadequate copper intake through diet has been linked to both innate and adaptive immunity (Raha et al., 2020).

Copper deficiency in humans can cause immune system dysfunction as well as a decrease in the body's ability to fight pathogens, which is more noticeable in infants and the elderly. Copper deficiency can also increase the risk of infection (Fooladi et al., 2020).

A lack of copper can cause neutrophils to become overactive and accumulate in the liver, leading to inflammation (Raha et al., 2020). In conditions that cause inflammation, the mean serum copper content tends to be higher when the disease activity is higher as well. In addition, rats with adjuvant-induced arthritis had elevated levels of copper in their livers during the inflammatory phase of the disease. According to the findings of another study, increased levels of IL-6 led to increased levels of the protein ceruloplasmin, which is the primary copper-carrying protein in the blood. As a consequence of this, an increase in copper levels may be related to the physiological response that the body has to inflammation (Andreou, et al., 2020).

In addition, copper oxide nanoparticles and ions (Cu^{+2}) have antiviral properties, which have an impact on the inhibition of viral entrance and replication, as well as the degradation of viral capsid protein and mRNA, which all contribute to the viral life cycle (Raha et al., 2020).

Copper supplementation has been shown to play an important role in the control of IL2, which is essential for T helper cell proliferation, the balance of Th1 and Th2 cells, and NK cell cytotoxicity, all of which are important in patients suffering covid-19(Fooladi et al., 2020).

Since the battle against the covid-19 virus requires a strong immune system and Copper is required by the immune system for a range of functions(Govind, et al., 2021), dietary supplementation and deficiency correction may be beneficial for patients with covid-19(Fooladi et al., 2020), and reduce the severity of the viral infection(Raha et al., 2020).

6.4 Iron

Iron is a micronutrient that is required by all living cells because it is essential to the proper functioning of a wide variety of metabolic processes, including the production of energy, the transport and storage of oxygen, the detoxification of drugs, the synthesis, repair, and transcription of DNA(Habib, et al., 2021). Grain and cereal products (like whole-wheat bread, cereal bars, biscuits, and cakes), red meat, and poultry are all good sources of iron to incorporate into your diet (Lim et al., 2013).

Heme iron and non-heme iron are the two forms that can be found in foods. The primary sources of heme iron in humans are found in their hemoglobin and myoglobin. Non-heme iron can be found in foods that have been fortified as well as in dietary supplements.

Iron deficiency can be caused by several factors, including abnormalities in iron absorption, inadequate intake of iron-containing foods, increased menstrual bleeding, and gastrointestinal disorders (Geissler et al., 2011).

Iron deficiency is the most common type of micronutrient deficiency found around the world; furthermore, it has been linked to immunological dysfunction. Iron deficiency, either from a lack of it in the diet or from a functional deficit that already existed, has also been linked to dysfunction in the immune system (James et al., 2021).

Iron deficiency has been shown by researchers to result in a decrease in the number of naive T-helper cells as well as T-cytotoxic cells in the immune system. Iron is required for the regeneration of new CD4+ T cells as well as the maintenance of cytolytic activities in T cells. It has also been proposed that the balance between pro- and anti-inflammatory cytokines may also be affected by iron. According to a recent study, The iron levels in the Covid-19 patients' serum were shown to be low. It was found that an iron deficiency in the serum was associated with a poor prognosis (hospitalization in an intensive care unit, intubation, and death) (Domingo et al., 2021).

On the other hand, having iron levels that are higher than the recommended maximum has been associated with an increased risk of malaria as well as other illnesses like pneumonia. In addition, excessive iron weakens the immune system and enhances the toxic effects of inflammation. Pathogens need iron because they rely on iron for their growth and reproduction (Di Renzo et al., 2020).

The tissue location where iron accumulates and the pathological effects caused by an excess of iron have a direct correlation. Iron deposits in the skin can result in hyperpigmentation, ferritin deposition in the pancreas can result in diabetes, ferritin deposition in the pituitary can result in hypogonadism, and ferritin deposition in the liver can result in liver disease that can progress to cirrhosis, and so on(Raju et al., 2018). Recent research has linked iron accumulation to cancer, aging, and the progression of chronic neurological disorders such as Alzheimer's and Parkinson's disease(Carota et al., 2021).

However, several COVID-19 symptoms (inflammatory response, hypercoagulation, hyperferritinemia, and immunodeficiency) are similar to those of iron overload. In the context of the disease's etiology, this would lend credence to the theory that an excess of iron may have contributed to the progression of COVID-19 (Domingo et al., 2021).

As a result, given the evidence presented above, an adequate intake is critical for maintaining a healthy immune response and lowering the risk of iron toxicity caused by an excess of the element due to its ability to accumulate in the body (Ebrahimzadeh-Attari et al., 2021)

6.5 Omega-3 fatty acid

Omega-3 fatty acids(FA) are a kind of polyunsaturated fatty acids(PUFAs)(Pecora et al., 2020). The omega-3 fatty acid family includes linolenic acid (LNA) and its derivatives such as alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Many cells and organs, including the immune system and inflammation, are known to require omega-3 for proper function.

According to the research findings, the human body is unable to produce omega-3, which means that they can only be obtained through the consumption of specific foods (Hathaway et al., 2020).

They are especially rich in fish and seafood. Among the fish having the greatest omega-3 FA, the primary sources are salmon, herring, mackerel, sardines and anchovies. Also, tilefish, albacore tuna, pollock, halibut, and trout can be sourced(Mendivil, 2021). Other than marine foods, non-marine foods containing trace amounts of omega-3 include cereals, seeds, nuts, and even some fruits and vegetables (Hathaway et al., 2020).

Metabolites of omega-3 FA derived from fish and other seafood have been found to stimulate the body's natural anti-inflammatory responses (Di Renzo et al., 2020).

One study discovered that people who ate salmon or took EPA and DHA supplements had lower levels of several cytokines, as well as the inflammatory marker CRP (Djuricic et al., 2021).

Omega-3 FA and their metabolites are mentioned as specialized proresolving mediators including prostaglandins, leukotrienes, thromboxanes, maresins, protectins and resolvins. All of these molecules have an impact on inflammation resistance. They are thought to be crucial in the maintenance of healthy immune function, particularly in the regulation of inflammatory responses, phagocytosis, and neutrophil differentiation.

Protectin D1, a lipid mediator derived from omega-3 FA, is one example of a substance that can significantly inhibit influenza virus replication. Furthermore, Morita and colleagues discovered an inverse relationship between the pathogenicity of the influenza virus and the levels of the protein protectin D1 (Akhtar et al, 2021).

Both EPA and DHA have numerous anti-inflammatory properties. According to previous research, high EPA and DHA consumption leads to higher concentrations of EPA and DHA in cell membranes, which is active in inflammation as well as many other cell types. Another study discovered that increasing the concentration of omega-3 FA reduced the levels of other inflammatory markers such as adhesion molecules, chemokines, and cytokines. CRP, IL-6, and adhesion molecules, which are indicators of inflammation in the blood, have been shown to have an inverse relationship with EPA and DHA status (Djuricic et al., 2021).

As a result, low levels of EPA and DHA can result in either too slow or insufficient inflammation resolution (Di Renzo et al., 2020). This has been associated with severe COVID-19 cases as well as ARDS (Calder et al., 2020).

Patients with pneumonia or COVID-19 may benefit from omega-3 FA administration to reduce inflammatory responses and restore lung function (Saeed et al., 2021). According to research conducted by Pontes-Arruda and colleagues, EPA and DHA treatment resulted in a significant reduction in organ failures, hospitalization periods in the ICU, and mortality rates in ARDS patients (Rogero et al., 2020).

By boosting immune function, dietary supplementation with omega-3 FA can be an effective part of treatment for patients with COVID-19 and its complications, including ARDS. This is supported by evidence that omega-3 fatty acids have anti-inflammatory properties (Hathaway et al., 2020).

7. CONCLUSION

Based on newly available data, the potential therapeutic benefits of vitamins A, C, D, and E via immunomodulation in COVID-19 patients have been assessed and analyzed. Micronutrients are essential, and some examples include zinc, selenium, copper, iron, and omega-3 fatty acids. Antiviral and antioxidant abilities participate in a wide range of immunomodulatory pathways, boosting the body's defense system in a variety of ways. Taking vitamin and mineral supplements, along with other micronutrients, may help to speed up the healing process for COVID-19 infection. However, there is a scarcity of research on the role of vitamins and minerals in the treatment of COVID-19 in both preclinical and clinical settings. Multiple clinical trials are currently underway to investigate the possibility of vitamins and minerals having a beneficial effect on COVID-19 patients. After reviewing the findings of various studies, one may conclude that proper vitamin and mineral supplementation should be addressed to improve the outcomes of SARS-CoV infection. The current situation has resulted in the development of some extremely effective vaccinations, as well as work on developing a targeted pharmacological therapy; both of these methods are very expensive and sophisticated, with a limited spectrum of focused activity. When supported by rigorous clinical trials, vitamin and micronutrient supplementation, on the other hand, has the potential for both broad-spectrum action and potential long-term health benefits; it is also a technique that is very simple and straightforward to implement. When the potential health benefits are weighed against the potential risks, the use of vitamins and micronutrients is undeniably reasonable, despite the minor risks involved. In contrast, the risk associated with the use of novel medications and some vaccinations are presented here. As a result, nutritional supplementation appears to be a promising method for combating SARS-CoV infection.

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9. LIST OF ABBREVIATIONS

Abbreviation	
SARS-CoV-2	*Severe acute respiratory syndrome coronavirus-2*
ACE2	*Angiotensin-converting enzyme 2*
ARDS	*Acute respiratory distress syndrome ARDS*
VA	*Vitamin A*
NK	*Natural killer*
TNF -α	*Tumor necrosis factor -α*

IL	*Interleukin*
Vit D	*Vitamin D*
CRP	*C-reactive protein*
PMN	*polymorphonuclear*
HSV	*herpes simplex virus*
PUFAs	*Polyunsaturated Fatty acids*
FA	*Fatty acids*
LNA	Linolenic acid
ALA	α -linolenic acid
EPA	*Eicosapentaenoic acid*
DHA	*Docosahexaenoic acid*