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VITAMINS, MINERALS AND COVID-19: COMPREHENSIVE REVIEW FOR STATE OF BEING IMMUNE

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ABSTRACT

Mankind is at global threat today due to COVID-19 disease caused by a virus known as SARS-CoV-2. WHO has reported this virus as pandemic to be a global public health emergency. As of now, there is no vaccine or curative medicine to stop this COVID-19 virus. Consequently, it is essential for individuals to boost their immunity to fight against the virus. Nutrition enriched diet can help in maintaining immunity, strengthens immune system and to prevent viral infections. In the present review attempts were made to explain the different branches of immune system with the classification tree and to evaluate the evidences that have been trailed clinically from the past that analyzed nutrition-based medications to handle and treat viral diseases. Review summarized possible advantages and immune boosting properties of essential nutrients of human system such as vitamins, trace elements, nutraceuticals, and some healthy practices that enhance immunity against particularly viral infections.

KEYWORDS: COVID-19, Coronavirus, Immunity, Vitamins, Minerals.

INTRODUCTION

The expression of the current pandemic goes back to late December 2019, when an instance of unidentified pneumonia was accounted for in Wuhan, Hubei Province, People's Republic of China. Its clinical qualities are somewhat similar to those of pneumonia. After investigation on respiratory examples, China's Centre for Disease Control (CDC) specialists proclaimed that the pneumonia to be novel coronavirus pneumonia, which was brought about by novel coronavirus. To fight against different dangerous infections it is necessary to have a strong immune system. Immunity cannot build in a day or a week, but taking a well-balanced diet to keep our body in good physical and mental health builds our immune system automatically stronger. Immune system is a network of special cells, tissues, proteins and organs. Immunity is the state of protection against infectious disease conferred either through an immune response generated by immunization or previous infection or by other non-immunological factors. Good nutrition is crucial for health, particularly in times when the immune system mightneed to fight back. Limited access to fresh foods may compromise opportunities to continue eating a healthy and varied diet. It can also potentially lead to an increased consumption of highly processed foods, which tend to be high in fats, sugars and salt. Nonetheless, even with few and limited ingredients, one can continue eating a diet that supports good health. This article review describes the various immunity booster and mechanism of the immune system in the human body. Main objective of this review is to provide information about all type immunity boosters and Nutrients available in nature and market.

SARS caused by SARS coronavirus -1. Primarily, it was identified in the province of Guangdong, South China in 2003. It was thought to be an animal virus from an as yet uncertain animal reservoir. According to some research it was a laboratory incident but according to another, it was transferred from animal to human, possibly bats. SARS-CoV-1 lethality rate was observed at approximately 10%. SARS-CoV-1 was identified in more than 26 countries and causes 8000 cases all over the world, that's why WHO declared SARS-CoV- 1 as an epidemic. A disruption of atypical pneumonia, referred to as severe acute respiratory syndrome and first identified in Guangdong Province, China, has spread to several countries. The severity of this disease is such that the lethality rate appears to be 3 to 6 %, although a recent report suggests this rate can be as high as 43 to 55 % in people older than 60 years.[10] An outbreak of COVID-19 caused by the 2019 novel coronavirus (SARS-CoV-2) began in Wuhan, Hubei Province, China in December 2019; SARS-CoV-2 is caused by a single stranded RNA virus.

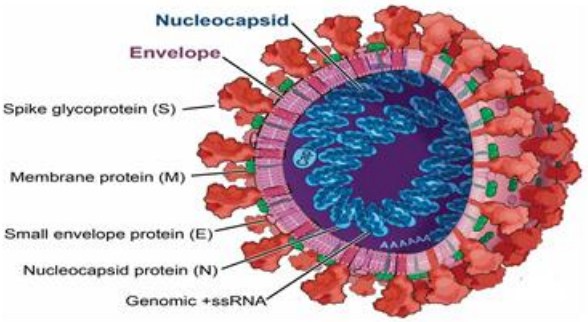

Fig.1. Structure of Coronavirus.

METHODOLOGY

The term immunity in a biologic context has historically referred to resistance to pathogens; however, reactions to some noninfectious substances including harmless environmental molecules, tumors, and even unaltered host components are also considered forms of immunity (Allergy, tumor immunity, and autoimmunity, respectively). The collection of cells, tissues, and molecules that mediate these reactions is called the immune system, and the coordinated response of these cells and molecules to pathogens and other substances comprises an immune response. The most important physiologic function of the immune system is to prevent or eradicate infections.

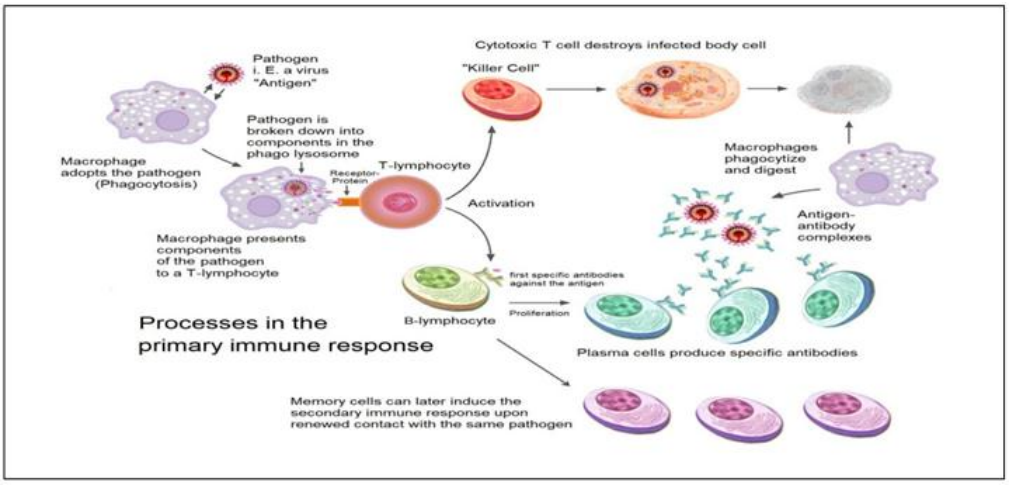

Fig.2. Response of Immune Syste.

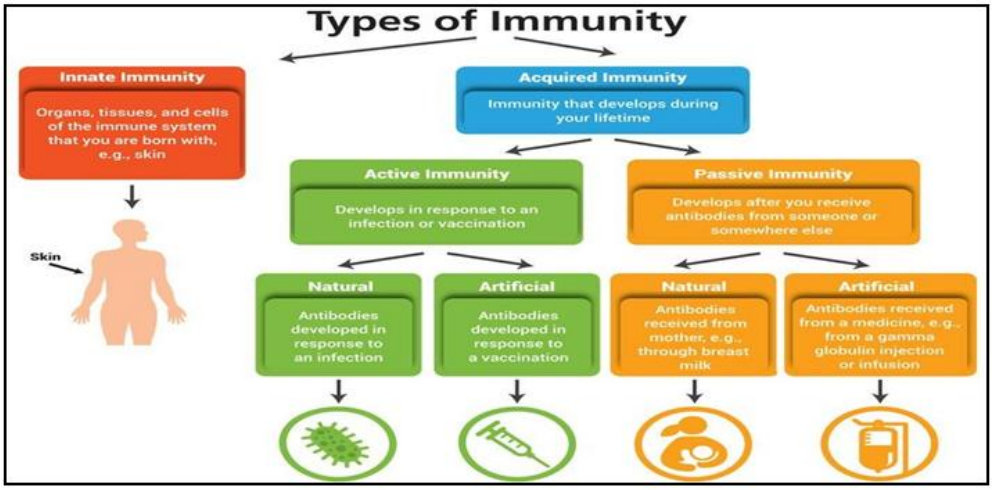

Fig.3. Types of Immunity.

Innate Immune Response

In an infectious process, the most common host response is to generate inflammation. Viruses in the absence of cytopathologic damage at early stages of infection inhibit

the induction of acute phase protein response because early monocytes are not activated. By contrast, the participation of natural killer cells against the virus play an important role in the host's defense, they recognize cells infected by viruses in an antigen independent manner, exert cytotoxic activities and rapidly produce large amounts of interferon-γ that participate in the activation of the adaptive immune cell.

Acquired Immune Response

Acquired immunity relies on the capacity of immune cells to distinguish between the body's own cells and unwanted invaders. The host's cells express "self" antigens. These antigens are different from those on the surface of bacteria or on the surface of virus-infected host cells ("non-self" or "foreign" antigens). Microorganisms that overcome or circumvent the innate non-specific defense mechanisms or are administered deliberately (active immunization) come up against the host's second line of defense: acquired immunity.

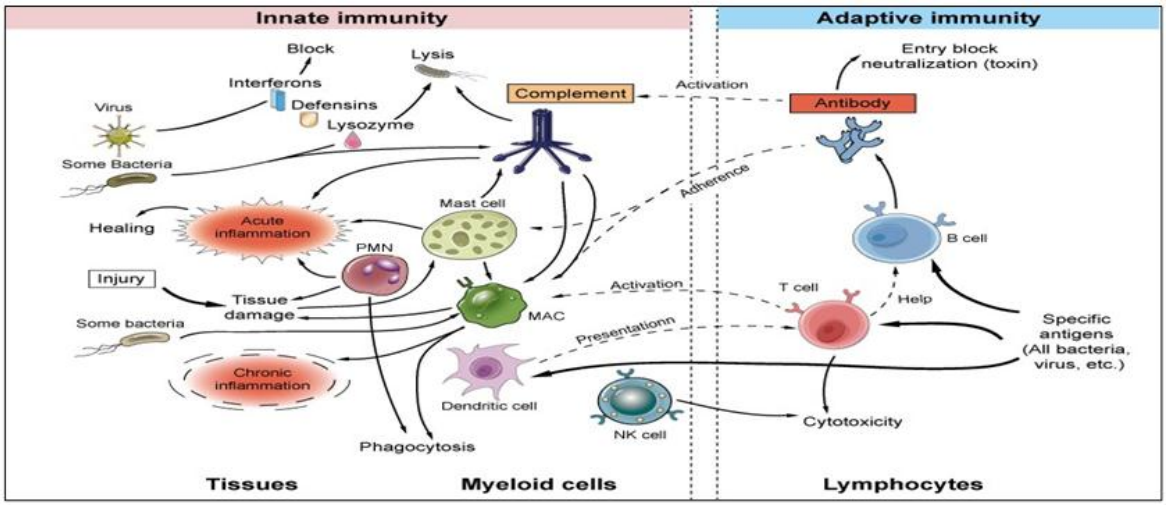

Fig.6. Mechanisms of Innate Immunity and Adaptive Immunity.

Mechanism of Immunity

The immune mechanism can be produced when the infection agents attack our body or go through vaccination. However, the same immune mechanism (Antibodies and cytotoxic T- cells) which were discussed earlier, in certain situations can cause the destruction to the cells or tissues in our body Macrophage captures engulfs and digests an antigen. Macrophage presents a fragment of the antigen on its surface and then interaction between proteins on the macrophage and helper T cell occur, activating the helper T cell proliferates into either TH 1 or TH 2 cells, which secrete different types of cytokines. Cytokines secreted by the TH 1 cell activate a cytotoxic T cell to kill the infected target cell.

Immunity Booster

The immune system is responsible for fighting foreign invaders in the body, like pathogenic bacteria and viruses and also destroying cells within the body when they become cancerous. Studies show that immune function often decreases with age and recent research suggests this decrease is also related to nutrition and may be slowed or even stopped by maintaining healthy nutrition. Certain foods may be helpful for boosting the immune system and preventing colds and the flu. Here's a look at five types of nutrients that your immune system needs to perform and which foods to find them in. To boost immunity means intake or consumption of certain food that provides additional benefits to the body.

Role of Vitamins as an Immunity Booster

It is well established that nutritional deficiency can impair and adversely affect one's immune system by infections. Recent evidence has highlighted the role of nutritional supplementation and if administered in higher than recommended daily doses, it might be beneficial in potentially reducing viral load and hospitalization for COVID-19 patients. Vitamins are essential dietary components because of their antioxidant properties and immunomodulatory effects (Shakoor et al. 2020b). Some of them regulate gene expression in immune cells and support the maturation and differentiation of immune cells.

Role of Vitamin A in COVID

Vitamin A belongs to the family of retinyl-esters and is also known as retinoic acid, which controls the various genes involved in innate and adaptive immune responses. Vitamin A acts as T-cell effectors, facilitating adaptive and innate immunity (Raverdeau and Mills 2014). Retinoid directly stimulates the expression of Interferon stimulated genes (ISGs), including retinoic acid-inducible gene I (RIG-I) and IFN regulatory factor 1 (IRF-1) (Matikainen et al.1996; Luo and Ross 2006).

Role of Vitamin B in COVID-19

Vitamin B is a naturally occurring component and is

known to be involved in Red blood cells (RBC) production. All the vitamins under the B complex category are important for the body cells' normal physiological functioning (Zhang et al. 2018). Vitamin B supports the body to use energy-yielding nutrients (such as carbohydrates, fat, and protein) for sustaining healthy skin and brain cells and some other tissues.

Vitamin B1 (Thiamine)

Thiamine is a coenzyme aids in the generation of energy for the body, maintains a constant temperature, and is implicated in fat synthesis, and is necessary for the nervous and immune system functioning (Kraft and Angert 2017). It has been reported that vitamin B1 has a potential anti-inflammatory effect while acting on macrophages, and it suppresses oxidative stress evoked NF-kappa B activation (Spinas et al. 2015). Thiamine deficiency affects the immune system due to various pathological initiations like increased inflammation, oxidative stress, metabolic disturbances, which further leads to the production of aberrant antibodies (Mikkelsen and Apostolopoulos 2019). It was documented that thiamine plays a significant role in eliminating the SARS-CoV-2 virus by triggering humoral and cell-mediated immunity. Hence, sufficient levels of thiamine help in building immunity against SARS- CoV-2 patients (Shakoor et al. 2020).

Vitamin B2 (Riboflavin)

Vitamin B2 is a neuroactive compound with immunomodulatory impressions, and its insufficiency provides a pro inflammatory gene expression pattern. It has been found that riboflavin provides a shielding effect versus liver damage induced through CCL4, arbitrated by TNF, in experimental animal models, intimating that it can be employed as a hepatoprotective agent (Yoshii et al. 2019). Riboflavin with UV light causes irreversible damage to nucleic acids leading to inhibition of replication of pathogens. Hence, it can be used to reduce pathogens in the blood plasma of COVID-19 patients to reduce the risk of transfusion transmission of COVID-19.

Vitamin B3 [Niacin (Nicotinic Acid, Pantothenic Acid)]

Niacin has extensive modulatory effects on the generation of inflammatory mediators and the immune cell movement. Hence, it has an anti-inflammatory impact, though its effects have not been thoroughly explained. It restrains CXC chemokine, CXCL-8/IL-8 induction, neutrophil migration induced by lipid mediator leukotriene (LT) B4 (in mice), and adherence (Shibata et al. 2017). It has been found to decrease IL-6, IL-1β, and TNF-α in stimulated alveolar macrophages. Recent data indicate that targeting IL-6 could reduce inflammation in COVID-19 patients (Liu et al. 2020).

Vitamin B6 (Pyridoxine)

Vitamin B6 influences innate/adaptive immunity, function and proliferation of immune cells (Ueland et al. 2017). Persons with vitamin B6 deficiency were found with the inhibition of cytokine/chemokine release. Studies suggest that vitamin B6 mediates the cellular immune response by activating the IFN-gamma (Parra et al. 2018).

Vitamin B9 (Folic Acid, Folate)

Folate is an essential vitamin for DNA and protein synthesis and also plays an important role in the adaptive immune response. A recent study determined that folic acid inhibits the furin, an enzyme responsible for bacterial and viral infections, and blocks the binding of SARS- CoV-2 spike protein. Therefore in the early stages, folic acid could be useful for controlling COVID-19-associated respiratory disease (Sheybani et al. 2020). A recent study reported that folic acid and its derivatives, 5-methyl tetrahydrofolic acid, and tetrahydrofolic acid have a strong affinity against the SARS-CoV-2 (Kumar and Jena 2020).

Vitamin B12 (Cyanocobalamin)

Vitamin B may regulate chemokine/cytokine formation and arbitrate the intercommunication with immune cells implicated in pathophysiological pathways. Thus, it is recommended that it can protect against various bacterial and viral infections (Calder et al. 2020).

Role of Vitamin C in COVID-19

Vitamin C is well known for its antiviral properties, such as increasing the interferon-alpha production, modulating cytokines, reducing inflammation, improving endothelial dysfunction, and restoring mitochondrial function (Dey and Bishayi 2018). In the early 30s and 70s, Linus Pauling (Nobel Prize winner) stated the beneficial effect of vitamin C in the common cold (Heikkinen and Järvinen 2003). Vitamin C supports the immune system to fight against bacterial and viral infections. It helps to eliminate the dead cells and replace them with new cells (Carr and Maggini 2017).

Role of Vitamin D in COVID-19

Vitamin D is a secosteroid with anti-inflammatory and antioxidant properties. It helps to maintain the calcium phosphorus metabolism. A number of studies suggested that vitamin D inhibits the overexpression of inflammatory cytokines such as IL-1α, IL-1β, tumor necrosis factor-α (Hughes and Norton 2009). It is also involved in the modulation of the immune response in infectious and autoimmune diseases. Literature has demonstrated that vitamin D insufficiency can lead to respiratory tract infection (Lemire 1992). Therefore, vitamin D has been widely investigated as a therapeutic agent for acute respiratory tract infections (ARTIs). A study conducted by Xu et al. reported the protective effect of calcitriol (vitamin D agonist) against acute lung injury by modulating the expression of ACE2 in lung tissue (Xu et al. 2017), which is one of the pathogenic factorsin COVID-19.

Role of Vitamin E in COVID-19

Vitamin E plays a crucial role in regulating and

supporting immune system function as a potent antioxidant (Jayawardena et al. 2020). Vitamin E acts as a free radical scavenger, reduces oxidative stress, and prevents free radicals containing unshared electrons and highly energetic and damaged cells. Unshared electrons form reactive oxygen species (ROS) with rapidly reacting with oxygen. (Verhagen et al. 2006). Other than antioxidant and anti- inflammatory properties, vitamin E also has a function in immunity.

Role of Vitamin K in COVID-19

Vitamin K is a fat-soluble vitamin, belongs to the family of 2-methyl-1, 4-naphthoquinone (Booth 2012). It is naturally present in some foods and also available as a dietary supplement in two forms: K1 (phylloquinone) and K2 (including different menaquinones, MKs) (Hubicka et al. 2020). Vitamin K is a co-factor and functions as a co-enzyme involved in hemostasis by synthesizing protein and other physiological functions (Janssen and Walk 2020).

Role of Macro and Micro Minerals

Considering the outcomes of COVID-19 infection, in the absence of effective treatment, a strong immune system is one of the most effective defense mechanisms. Moreover, supplementation of minerals has positively impacted immunity in viral infections (Jayawardena et al. 2020). Minerals are inorganic substances required by the body to support body functions. In early COVID-19 studies ACE-2 receptors are the coronavirus' main targets for its entry into the respiratory system and badly affect this system (Ivanov et al. 2020). The low availability of the minerals affects our immune system, which triggers various pathogenic infections. Further disclosure about each mineral may help us approach stronger immunity, thus preventing the body from such infections (Gombart et al. 2020).

Sodium: Sodium plays a significant role in the regulation of electrolytic balance and the expression of ACE2 in SARS-CoV-2 (Luo et al. 2020). In a meta-analysis, it was found that sodium concentration significantly decreases in COVID-19 patients. A study in the US reported the serum sodium concentration of COVID-19 patients as 136.0 mmol/L, which was less than the normal level, i.e., 138.0 mmol/L (Habib et al. 2020). Another study has also reported that sodium level decreases with the increase in severity of disease (Lippi et al. 2020).

Potassium: Hypokalemia can increase ARDS and acute cardiac injury risk, which is considered the most commonly occurring complication in COVID-19. The literature demonstrated that SARS- CoV-2 binds to ACE2 and reduces its expression; consequently, angiotensin-II increases, which subsequently leads to hypokalemia (Alwaqf and Ibrahim 2020). COVID-19 patients showed increased concentration of plasma angiotensin-II, possibly responsible for acute lung injury and as confirmed in SARS-CoV animal models (Zemlin and Wiese 2020).

Calcium: Calcium plays an essential role in making our bones stronger, but it also works against invading viruses by eliminating them out from the cells. Hence, calcium ion protects from the common cold. A joint analysis reported a lower calcium concentration in critical COVID-19 patients than those with less severe disease and concludes that serum calcium level in patients is inversely proportional to the severity of the disease (Rodriguez-Morales et al. 2020). As with low sodium and potassium, hypocalcemia may serve as a marker of the severity of a SARS-CoV-2 infection.

Phosphorus: Phosphorus is involved in making protein for the growth, maintenance, and repair of cells and tissues (Vance 2011). A retrospective study of the clinical data of the coronavirus 2019 showed decreased phosphorus levels in COVID-19 patients. This study suggests that hypophosphatemia is directly proportional to the severity of COVID-19; monitoring the serum phosphorus level in COVID-19's severe/critical patients is proved to be beneficial for prognosis (Xue et al. 2020). Further, there is a need to understand the pathological mechanisms involved in hypophosphatemia related to COVID-19 infections (Ni et al.2020). Magnesium (Mg): Magnesium is the forgotten cation. Mg supplementation might reveal very useful in managing the stress triggered by the pandemic and the post-traumatic stress disorder that will plague COVID-19's survivors, health professionals, and common people. However, some in vitro and in vivo studies suggest that magnesium plays a vital role in the immune response against viral infections (Jayawardena et al. 2020).

Role of Micro Minerals in COVID-19

During this pandemic COVID-19, preventive measures suggested by medical practitioners and scientists generally underline the significant role of immunity as a potential weapon against COVID-19. Till now, no WHO-approved treatment is available to cure the disease; hence an efficient and healthy immune system is the only defense against this viral infection (Ashour et al. 2020; Cascella et al. 2020). Indeed, trace elements are the essential micronutrients having a significant role in immunity.

Zinc (Zn): Biological function Zinc is an important element of nutritional immunity and plays a versatilerole in the biological system. Various pieces of evidence reveal that zinc shows antiviral property and plays an essential role in immunity. Zinc was reported as an active agent for immunity against H1N1 influenza (Sandstead and Prasad 2010).

Iron (Fe): Biological function Iron plays a versatile role in the biological system. Despite being an oxidant, iron plays a significant role in hemoglobin and red blood cell production. Role in COVID-19 Recent evidence reveals that apart from pulmonary involvement and elevation in

IL-6, COVID-19 patients display a broader spectrum of hyper inflammatory syndromesdistinguished by cytokine release syndrome (CRS), such as secondary haemophagocyticlymphohistiocytosis (sHLH).

Copper (Cu): Biological function Copper is enlisted as the essential micro nutrient for humans against viral infections. After absorption in the small intestine, dietary Cu enters the systemic circulation and involves many biological processes to maintain the body's average ionic balance (Osredkar and Sustar 2011). Role in COVID-19 Cu is involved in B cells' normal functioning, T helper cells, macrophages, and natural killer (NK) cells, also involved in cell- mediated immunity, encounter infamous microbes, and produce antibodies against the pathogen (Raha et al. 2020).

Selenium (Se): Biological function for multiple reasons, Se is considered the most reliable trace element due to its antiviral and anti-inflammatory properties. Distinct sets of selenoproteins regulate the normal functioning of the immune system comprised of selenocysteine. Deficiency of Se established severe risk factors for viral infections (Guillin et al. 2019). Role in COVID-19 Data from China link the cured rate of COVID-19 patients in association with the body's basal selenium status (Zhang and Liu 2020).

Manganese (Mn): Biological function being an essential trace element, nutritional manganese has various effects on the biological system. Mn possesses antioxidant activity and responsible energy production by the amino acid breakdown (Sigel 2000). Role in COVID-19 In an emerging approach towards the treatment of COVID-19, various shreds of evidence reveal Mn's immunomodulatory and antiviral action.

Iodine (I): Biological function Iodine is a widely used trace element, especially for therapeutic purposes. Biologically, iodine is a mineral responsible for producing thyroid hormones and plays a significant metabolic role in the body. Iodine also plays an important role in neurodevelopment during pregnancy (Venturi et al. 2000). Role in COVID-19 According to previous reports, iodine-based products like povidone-iodine (PVP-I) are highlighted as potent chemical agents against SARS-CoV. Evidence reveals that such iodine-based compounds are equally efficient to 70% ethanol.

Cobalt (Co): Biological function biologically, vitamin B12 is a cobaloxime responsible for maintaining the nervous system and producing red blood cells (RBC). Nutritional Co is an essential mineral responsible for blood formation (Chaturvedi et al. 2004). Role in COVID-19 Study reveals that cobalt (III), upon complex with a tetra-azamacrocyle chelator, hydrolyzes phosphodiester bonds in viral DNA and RNA. Furthermore, its high affinity towards RNA template inhibits the RNA translation and is responsible for therapeuticeffects against several viral infections such as hepatitis virus, sindbis virus, herpes simplex virus, and Epstein–Barr virus (Chang et al. 2010).

Sulfur (S): Biological function Sulfur is responsible for producing essential amino acids such as cysteine and methionine, which plays a significant role in bio catalytic processes and other events like transport across cell membranes, immune functions, and blood clotting (Dutta et al. 2009).

CONCLUSION

The possible therapeutic benefits of vitamins A, B, C, D, E, and K via immunomodulation in COVID-19 patients have been evaluated and analyzed based on available evidence. Trace elements such as zinc, selenium, manganese, and copper, are essential micronutrients. Antiviral and antioxidant properties are involved in multiple immune-modulatory pathways and improve the body's defense system by different mechanisms. Supplementation of vitamins and micronutrients may have a positive impact on the recovery of COVID-19 infection. However, there is a lack of preclinical and clinical studies associated with vitamins and micronutrients in the management of COVID-19. To explore the possible beneficial role of vitamins and micronutrients in COVID-19 patients, various clinical studies are being carried out. By reviewing various studies, it can be concluded that adequate supplementation of vitamins and micronutrients should be considered to improve SARS- Co-V2 infection outcomes. The current situation has resulted in several highly effective vaccines, and work is being conducted for targeted drug therapy; these are very expensive and complicated processes with a narrow spectrum targeted activity. In contrast, vitamin and micronutrient supplementation is a relatively cost efficient and easy approach when supported by robust clinical studies, and has possible broad-spectrum activity and potentially long-term health benefits. Therefore, nutrient supplementations seem to be a promising approach towards SARS-CoV-2 infection.

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