Annals of Phytomedicine, Volume 11, Special Issue 3 (COVID-19): S18-S29, 2022

DOI: http://dx.doi.org/10.54085/ap.covid19.2022.11.3.4

Annals of Phytomedicine: An International Journal

http://www.ukaazpublications.com/publications/index.php

Print ISSN : 2278-9839 Online ISSN : 2393-9885

Review Article : Open Access

Special Issue 3 (COVID-19)

Protective effect of nutrition and supplements on COVID-19 management

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Article Info

Article history

Received 25 March 2022

Revised 13 May 2022

Accepted 14 May 2022

Published Online 30 June 2022

Keywords

COVID-19

Proximate principles

Vitamins

Nutritional supplements

Protective effects

Abstract

In March 2020, an infection caused by SARS-CoV-2 termed COVID-19, was declared by WHO, as a world pandemic having affected 54.1 crores individuals across 230 countries to date (23rd June 2022). The infection is caused due to a fast-mutating virus that can best be controlled through one's immune system and strengthening the same is a challenge currently. Enriching immunity has persistently been a matter of study and conclusive results depict that nutritional status has a tremendous impact on strengthening immunity.

Both macro-and micronutrients play a significant role in developing a strong immune response. Most of the mediators of immune response like cytokines, interferons, and antibodies along with surface markers such as MHC, toll-like receptors, membrane transporters, *etc*., are all proteinaceous, and hence an adequate protein intake is vital for ideal immune response. The fermentation of dietary fiber by the microflora in the gut leads to the generation of short-chain fatty acids known to be anti-inflammatory. Poor status of nutrients such as vitamin A and zinc have been reported to be related to not only the increased rate of infection risk but also higher levels of oxidative stress as well as inflammation. Both these factors down regulate the immunity and thereby lower the recovery rate. These nutrients mediate the immune signalling pathways including the transcription of factors as NF-kB and Nrf-2 and reduce the generation of cytokines as IL-6 which are associated with reducing inflammation. Nutrients like vitamin D besides working on immunity also play a substantial contribution in preventing infection as they modulate the surface receptors, thereby hindering the entry of viruses into the host cells. This article is aimed at emphasising the vital significance of nutritional status in enhancing the immune system and preventing infection during the current pandemic.

1. Introduction

With no slowing down of the COVID-19 pandemic as indicated by 538,321,874 confirmed cases including 6,320,599 deaths world wide as of 5:40 pm CEST, 22 June 2022 (https://covid19.who.int/), researchers are inquest of ways to potentially protect people from the SARS-CoV-2 or to alleviate its effects. According to NASDAQ's 2021 report, the global immunity booster supplement market is expected to grow from USD 8,054.68 million in 2020 to USD 12,718.10 million by the end of 2025. The advent of the COVID-19 pandemic is further expected to add to this growing market as so far, no effective anti-COVID therapy has been established. The need of the hour is a supportive or prophylactic treatment that involves supplementation with macro-and micronutrients. This approach has been found to be pivotal in the management of COVID-19 (Abobaker *et al.*, 2020).

COVID-19 is an unprecedented global public health emergency that has reached pandemic proportions. The novel coronavirus, SARS-CoV-2, predominantly affects the respiratory system. Although, COVID-19 affects individuals of all age groups, the severity and mortality of the disease has been found to be disproportionately higher in the elderly and in certain ethnic communities like Latinos and blacks/African Americans as well as in those with pre-existing comorbidities. The major underlying comorbidities are hypertension, obesity and type 2 diabetes (Dharmasena *et al.*, 2016; Dietzand Santos-Burgoa, 2020).

The reason for these risk factors driving the surge of COVID-19 can be largely attributed to the consumption of a diet rich in saturated fats and processed carbohydrates and deficient in fibres, antioxidants, and essential fatty acids (Cordain *et al.*, 2005). Also, with the lockdowns and restrictions in place in many countries globally, limiting the number of people in a store at a given time resulted in decreased reach to fresh food and people adapting to convenient, easy-to-cook packaged foods with a longer shelf-life. This resulted in an increase in body weight. Also, psychological stress enhanced oxidative stress leading to increased susceptibility to various debilitating conditions (Mattioli *et al.*, 2020).

According to the study of Moynihan *et al.* (2015), quarantine has been associated with disruption of the normal work schedule, leading to boredom. Boredom in turn has been linked with greater consumption of 'comfort foods' which are primarily foods having a higher content of carbohydrates. Many people reported quarantine-related stress that led to sleep disturbances, which further

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on led to increased consumption of sugar-rich foods, thus leading to a vicious cycle (Muscogiuri *et al.*, 2021). Sleep disturbances were mostly attributed to decreased serotonin/melatonin levels. Peuhkuri *et al.* (2012) suggested consuming foods like almonds, oats, cherries and bananas that promote the synthesis of serotonin and melatonin. The amino acid tryptophan is the precursor of serotonin. The inclusion of foods rich in tryptophan like milk and dairy products is known to regulate calorie intake and promote a feeling of fullness and induce sleep.

The pandemic was largely controlled using antiviral available in the market, like remdesvir while prevention from infection was mediated with the use of vaccines. However, a large number of people resorted to the use of medicinal aromatic plants (MAPs) to avoid infection and mitigate symptoms associated with infection. MAPs are a rich source of phytoconstituents having immense potential in preventing infection as well as holding immunomodulatory activities (Russo *et al.*, 2020; Solnier and Fladerer, 2020). Besides these phytoconstituents, the role of proximate principles along with the micro-and macronutrients too has immense importance in the control of diseases like COVID-19 (Mortaz *et al.*, 2021).

It has been suggested through various studies that an interlink exists between the functionality of the immune system and nutritional status (Keusch, 2003; Bhaskaram, 2002). It is critically important to gain insight into the relationship between the current pandemic and nutritional status (Bourbour *et al.*, 2020). With this understanding, use of nutritional interventions can be made to lower vulnerability to infection, its progression and the likelihood of fatality.

The current review is aimed at exploring the nutritional status and COVID-19 infection. Published literature has been compiled to put forward the idea of the significant role played by the proximate principles, *viz.*, carbohydrates, proteins and lipids, along with the important role of vitamins A, C, D, E, folic acid and minerals, namely; zinc and selenium in combating the pandemic.

2. Macro-and micronutrients

2.1 Proteins

Amongst the macronutrients, proteins play a substantial role in cell organization and metabolism. Deficiency results if the estimated average requirement (EAR) is below 0.8 g/kg body weight. Rodríguez *et al.* (2011) have suggested that low protein intake increases infection rate and can even be fatal. The major mediators of the body's immune system, both innate as well as adaptive are mainly proteins and glycoproteins. Amaral *et al.* (2006) reported that a decrease in protein concentration results in a negative nitrogen pool that affects the production of functional immunoglobulins along with the activity of gut-associated lymphoid tissue (GALT), thereby reducing the defense mechanism against infections. These effects are observed not only in the case of low protein intake, but also by proteins present in many foods containing saturated fats (Jakulj *et al.*, 2007), and those high in calories such as cheese, processed meats, *etc*. These are known to exacerbate post-prandial effects, thereby increasing lipogenesis as well as inflammation (O'Keefe *et al.*, 2007). On the other hand, high biological value protein intake, *viz.*, eggs, lean meat, fish and whey protein, has been associated with lowering of post-prandial lipogenesis as well as inflammation (Arora and McFarlane, 2005), and so an anti-inflammatory diet should contain high-quality protein (O'Keefe *et al.*, 2008). Hruby and Jacques (2019) compared proteins from plant and animal sources and found the former to be pro-inflammatory and latter as inflammatory. Meat-rich diets were found to increase colonic monocytes, in presence of saturated fats (Kostovcikova*et al.*, 2019).

Amino acids are known to modulate the immune response (Li *et al.*, 2007) (Figure 1). Ren *et al.* (2015) suggested that enhanced intestinal immunoglobulin levels lead to improve gut immunity in presence of branched-chain amino acids. Arginine supplementation in comparison to the control group suggested improved T-helper cell numbers and response of T-lymphocytes (Kim *et al.*, 2018). For the expression of many genes associated with the immune system, glutamine is a prerequisite (Cruzat *et al.*, 2018). Mills *et al.* (2017) hypothesized that glutamine is required by macrophages, neutrophils, and lymphocytes, for the identification of pathogens as it propagates immune cell proliferation and tissue repair, and also is an energy substrate. It also activates signal transduction mediated by JNK and ERK kinases (Cruzat *et al.*, 2018), expression of major lymphocyte cell surface markers, and the secretion of cytokines as IL-6, IFN-γ, and TNF-α (Curi *et al.*, 2016).

Taylor *et al.* (2013) studied in mice the effect of protein-energy malnutrition on recovery rate from influenza infection. They found that the severity of influenza infection was higher as the humoral immunity was low due to a reduction in antibody concentration, leading to prolonged virus presence in the lungs, hyper-inflammation as well as increased mortality. Thus, low protein diets hinder the body's immune response to infections. Increased susceptibility to viruses such as influenza and Zika were observed under protein malnutrition conditions as it adversely affects cell-mediated immune responses, functionality of neutrophils, complement system activation as well as antibody response (Ah, 2016).

In COVID-19 patients hospitalized in the ICU whey protein in the diet reduced the time the patients were on mechanical ventilation, with a decline of cytokine storm and inflammatory response there, by increasing the rate of survival (Scarcella *et al.*, 2022).

A retrospective study by Cobre *et al.* (2021) was conducted and consumption of various foods was associated with recovery from COVID-19 in 170 countries, with help of Kaggle the database, employing multivariate analysis built on a generalized linear model. The study showed that a diet comprising of protein-rich eggs, fish and seafood, meat and milk, increased recovery rates.

L-glutamine was tested on 30 COVID-19 patients and a similar number without L-glutamine. It was observed that the duration of hospitalization for the test group vs control was 10.4 and 8.9 days, respectively and none required ICU care in case of test with 4 in the control group. It was postulated that L-glutamine boosts the immune system by inhibiting inflammatory responses (Cengiz *et al.*, 2020). Hawryłkowic *et al.* (2021) further suggested that the daily calorie intake should ideally be in the range of 1500-2000 with an ideal protein intake of 75-100 g, for faster recovery from SARS-COV 2 infection.

2.2 Lipids

Lipids are polymers of fatty acids (FA) a major nutrient and the basic molecule present in the bi-phospholipid layer of the plasma membrane. Amongst the types of fatty acids, major contributors

are polyunsaturated fatty acids (PUFAs), *viz*,. omega-3 and 6 fatty acids. α-linolenic acid (ALA), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are major omega-3 FAs, while arachidonic acid, a pro-inflammatory agent, is omega-6 FA, leading to the synthesis of mediators as eicosanoids, prostaglandins and leukotrienes (Gutierrez *et al.*, 2019; Gabbs *et al.*, 2015).

Homeostasis and functionality of immune cells as macrophages, neutrophils, and lymphocytes are correlated (Radzikowska *et al.*, 2019). Clarke *et al.* (2009) and Calder (2010) reported that in presence of increased consumption of saturated FA, an increase in high-sensitivity C-reactive protein (hs-CRP), and fibrinogen is observed, whereas with PUFA, hs-CRP levels were reduced, thus suggestive of possessing anti-inflammatory capability. Further analysis suggested that processed foods as chips possessing trans-fatty acids are associated with elevated levels of hs-CRP as well as cytokines like TNF-α and IL-6, which are pro-inflammatory (Lennie *et al.*, 2005).

Omega-6 FAs metabolite-eicosanoid signalling and cytokine signalling, bear similarities as both are affected by phospholipase A2 activity that controls the various phases of the inflammatory response as well as the conversion of pro-inflammatory response to anti-inflammatory. Omega-3-derived oxylipins facilitate bacterial clearance along with the down regulation of pro-inflammatory cytokines (Gabbs *et al.*, 2015). Both the omega FAs can compete for the same enzymes, wherein higher omega-6 concentrations will have an adverse reaction on the metabolism of omega-3 FA. The recommended ratio of these two FA in the diet is considered 1:1 to 4:1 (Simopoulos, 2011), though most diets have this ratio skewed, with a higher amount of omega-6 FA. This is suggestive of a disparity between the omega-6 and 3 FAs, which can alter immune system homeostasis, setting in metabolic and allergic conditions or even autoimmunity (Magnusson *et al.*, 2015; Scaioli *et al.*, 2017). Akbar *et al.* (2017) suggested that for patients characterized by chronic inflammation due to rheumatic diseases omega-3 fatty acid supplementation resulted in eicosanoid synthesis, reducing pro-inflammatory cytokine concentration (Figure 1). In randomized control trials, omega-3 FA supplementation showed downregulation of IL-6 production, the cytokine leading to hastened inflammatory responses (Kiecolt-Glaser *et al.*, 2011). Thus, increased consumption of omega-3 FA is likely to decrease the efficiency of viral entry and stimulate an efficient immune response with a decrease in the severity of COVID-19 (Hathaway *et al.*, 2020).

Further, other lipid classes such as phospholipids, sphingolipids, or glycolipids are also present in fish and its oil, one of the richest sources of omega-3 FA. These are potent blockers of platelet-activating factor (PAF) and its receptor, which exhibits an anti-inflammatory, effect and thus is advantageous during COVID-19 infection (Lordan *et al.*, 2020). Another complication of COVID-19 is platelet activation which is blocked with fish being incorporated in the diet, thereby preventing thrombotic complications (Zabetakis *et al.*, 2020).

It has been suggested that angiotensin-converting enzyme 2 (ACE2) and the transmembrane serine protease 2 (TMPRSS) are a part of lipids rafts and PUFA governs the formation of the same, in the phospho-bilayer (Messina *et al.*, 2020). Entry into the host cell for the SARS family of viruses is mediated via lipid rafts (Lu *et al.*, 2008), and the modulation of these membrane structures can control infection (Glende *et al.*, 2008).

2.3 Carbohydrates and fibers

The fuel or energy generation *via* metabolism is mediated mainly by carbohydrates while dietary fiber is essential for gut health. An increase in carbohydrates especially ones with higher glycemic indexes like processed foods, is likely to lead to intense hyperglycemia and insulin response, thereby leading to an increase in mitochondrial activity cascading to higher free radical generation (O'Keefe *et al.*, 2008).

Monnier *et al.* (2006), reported that a high glycemic diet leads to an increase in inflammatory cytokines, as IL-6 and TNF-α as well as CRP. Bullo *et al.* (2013) further added that iso-calorific diets with higher glycemic index also leads to higher levels of inflammatory cytokines. An inverse relation has been found between dietary fiber consumption and fatality due to infectious and respiratory disorders (Park and Subar, 2011). In the case of chronic obstructive pulmonary disease (COPD), the risk of severe infection has been limited, in presence of dietary fiber intake (Weaver *et al.*, 2013). The importance of both prebiotics and probiotics for infection risk prevention has just recently been highlighted (Yang *et al.*, 2020). Through randomized control trials, probiotic treatment has brought about a reduction of respiratory infections (Araujo *et al.*, 2015). Yang *et al.* (2020) suggested that the mechanism of action of dietary fiber and pre and probiotics are similar as both enrich gut microbiota, so effect of dietary fibres on COVID-19 infection, will be at par with the effect of probiotics.

Intense inflammatory response is the most fatal consequence of COVID-19 infection, and thus a diet with restricted carbohydrate intake will prove beneficial.

Another approach is the transition to a diet with high fat but low-carbohydrate content or a ketogenic diet (KD). KDs are classified into 2 categories based on calorie intake and protein content. As reported by Watanabe *et al.* (2022), ketogenic diets differ mainly in calorie intake and protein content. In high-fat ketogenic diets (HFKD), components of diet include < 50 g per day of carbohydrates with fat, and protein content in the range of 0.8-1.2 g per day. In the case of very-low-calorie ketogenic diets (VLCKD), the content of carbohydrates and proteins is similar, though it contains significantly reduced fat. These diets prevent aerobic glycolysis, seen in immune cells activated due to inflammatory response and production of β-hydroxybutyrate and are known to inhibit activation of NLRP3 inflammasome (Trompette *et al.*, 2018).

Fiber plays a significant role in the body's metabolic functioning as well as the immune system. An intake in the range of 25-35 g/day is known to facilitate the reduction of inflammation as the inflammatory cytokines are lowered (Iddir *et al.*, 2020).

Dietary fiber undergoes fermentation by microbiota in the gut and produces short chain fatty acids (SCFAs) (Tungland *et al.*, 2018). SCFAs thus produced lead to the activation of signalling cascades involved in anti-inflammatory responses, through G-protein-coupled receptors (GPRs) (Thorburn *et al.*, 2014), leading to an inhibition of IL-12 along with activation of IL-10 production (Saemann *et al.*, 2000), repressing release of IL-1, TNFα, and NO, and reduced expression of NF-kB expression (Figure 1) (Ni *et al.*, 2010).

The presence of dietary fiber promotes gut flora as species of *Lactobaccillus* and *Bifidobacterium* species, inhibit species that are detrimental to the well-being (Carlson *et al.*, 2018). Beneficial gut flora has been shown to reduce inflammation, hs-CRP and IL-6 (van den Munckh of *et al.*, 2018). Desai *et al.* (2016) have suggested that dietary fiber increases the thickness of mucosa in GIT and prevents invasion of *Citrobacter rodentium*, a mucosal pathogen as well as degradation of this preventive barrier. A good microbiota is an effective arm of the immune system as it not only prevents internalization of the virus but also binds to the virion destabilizing its morphology, as well as suppressing viral replication (Bandoro *et al.*, 2017; Chen *et al.*, 2016). COVID-19 affects both the gut as well as nasal microbiota, as both respiratory and GIT can be affected and this also increases the risk of secondary infection (Ferrey *et al.*, 2020). Fiber-rich food such as whole-grain products, vegetable products, vegetable oil, and fruits in the diet of COVID-19 patients helped in faster recovery (Cobre *et al.*, 2021).

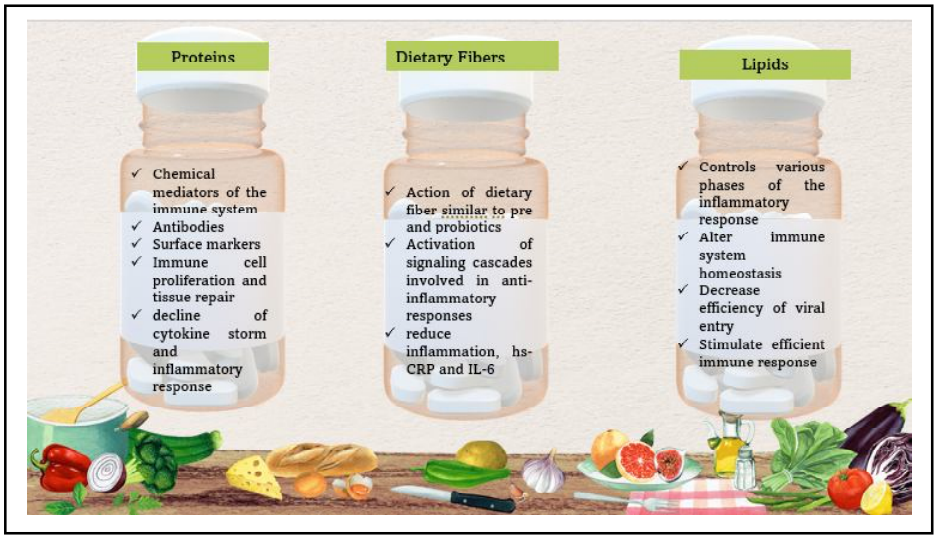

Figure 1: Immunomodulatory effects of proteins, dietary fibers, and lipids.

2.4 Vitamin A

Vitamin A is an important fat-soluble vitamin, extensively involved in maintaining vision. It exists in three biologically active forms-retinal, retinoic acid, and retinol. Of the three, retinoic acids exhibit the highest biological activity. Not only this, vitamin A supplementation has also been credited with robust immune function and delayed immunosenescence (Samad *et al.*, 2021). It plays an important role in maintaining cell-mediated and humoral immunity (Hall *et al.*, 2011). As a result of its immunomodulatory role, vitamin A provides resistance against a number of infections. Individuals with compromised immune system, such as HIV-infected pregnant women are recommended to consume a diet rich in vitamin A (Samad *et al.*, 2021). Vitamin A works by improving epithelial cell integrity, thus improving specific and non-specific immunity (Huang *et al.*, 2018). A deficiency of vitamin A is thus associated with epithelial damage and impaired recovery (Stephensen and Lietz, 2021). Vitamin A and its derivatives play important role in activating IFN-1 which is an important molecule involved in the immune system (Trasino, 2020). According to the research conducted by Oliveira *et al.* (2018), it was observed that vitamin A supplementation resulted in reduced production of IL-12 and TNF- α and increased production of IL-10 (Figure 2).

According to Gröber and Holick (2021), vitamin A elicits its effect on the immune system by acting on PRKCB (protein kinase C β), ICAM1 (intercellular adhesion molecule 1), APK1 (mitogen-activated protein kinase 1), IL-10 (interleukin 10), MAPK14 (mitogen-activated protein kinase 14), EGFR (epidermal growth factor receptor) and CAT (catalase). According to the study of Yang *et al.* (2015), vitamin A supplementation along with the antilipemic drug-simvastatin, exhibited an anti-inflammatory effect on patients suffering from acute respiratory distress syndrome, exacerbated by COVID-19. Low plasma vitamin A levels are associated with an increased vulnerability to COVID-19 related ARDS (Tepasse *et al.*, 2021). It has been elucidated that immune response to COVID-19 is defective in conditions of vitamin A deficiency, especially the mucosal IgA response. Also, the CD^{8+} T cytotoxic response was also affected (Stephensen and Lietz, 2021). As per the molecular docking study of Belhassan *et al.* (2022), 9-cis-retinol and all-trans-retinal demonstrate binding energy of -6.4 and -6.3 kcal/mol against SARS-CoV-2 main protease.

2.5 Vitamin C

Vitamin C is known to exhibit numerous beneficial physiological effects, as it is a potent antioxidant as well as possesses immune-modulatory effects (Milani *et al.* 2021; Boretti and Banik, 2020). Researchers have suggested a potential role of vitamin C in the management of COVID-19 (Abobaker *et al.*, 2020). According to the study by Earar *et al.* (2020), it was observed that levels of vitamin C in the serum and leukocytes decreased significantly during severe COVID-19 infection. Vitamin C supplementation has been attributed to improving the body's defense mechanism, and thus can serve as an effective remedy for the same (Figure 2). As suggested by Bauer *et al.* (2020), clinical studies have researched that high dose supplementation of vitamin C ameliorated the effects of respiratory tract infections. The pathogenesis of SARS-CoV-2 is

largely mediated by extensive immune response and the release of highly reactive free radicals. Vitamin C being an antioxidant, exhibits ameliorative effects (Boretti and Banik, 2020). Studies have claimed that *in vitro* vitamin C exhibits virucidal properties (Colunga Biancatelli *et al*., 2020). According to the *in vitro* study of Jariwalla *et al*. (2007), a dose-dependent reduction in the synthesis of influenza surface proteins was observed by a combination of nutrients that include vitamin C. Many randomised clinical trials have also been conducted to elucidate the pathophysiological effects of Vitamin C. Almost six of them conducted on 642 soldiers, skiers and athletes who participated in marathons, exhibited a 50% reduction in the incidence of common cold when supplemented with vitamin C (Wintergerst *et al.*, 2006). The immune response enhancing effect of vitamin C could be mediated by improving innate immunity as vitamin C supplementation was found to strengthen the stability and integrity of the epithelial layer as well as enhanced the activity of natural killer cells that are involved in the primary immune response against pathogens (Carr and Maggini, 2017). According to the research conducted by Liugan and Carr (2019), vitamin C was found to be involved in the proper functioning of leukocytes as it was found to be present inside neutrophils. Mousavi *et al*. (2019) through experimental studies have reported that insufficiency of vitamin C has led to the weakening of cellular and humoral immunity. This is also associated with age-dependent decrease in immunity due to low levels of circulating IgG and IgM (Figure 2). One of the hallmarks in the pathogenesis of SARS-CoV-2 infection is the 'cytokine storm'. According to Stipp (2020), vitamin C supplementation significantly mitigated the same, thus preventing damage to respiratory tissue and helping maintain the redox integrity of the tissue (Wintergerst *et al*. 2006). In a study reported from China, intravenous administration of vitamin C for therapeutic management of COVID-19 has shown encouraging results and improved the clinical outcome of the patients, and reduced their hospitalization duration by 3-5 days (Boretti and Banik, 2020). Administration of 1500 mg vitamin C intravenously 4 times a day significantly improved the health of hospitalised COVID-19 patients (Simonson, 2020). A number of clinical trials are currently ongoing to evaluate the effectiveness of high dose vitamin C against COVID-19. As per the *in silico* assay of Kumar *et al*. (2021), magnesium ascorbate, a buffered (non-acidic) form of vitamin C (ascorbic acid), was found to be the top lead compound among 106 nutraceuticals analysed by them with a binding energy of 8.1 kcal/mol.

Thus, vitamin C supplementation is a potential modality for the treatment of pneumonia in patients suffering from COVID-19, thus preventing acute respiratory distress syndrome (Abobaker *et al*., 2020).

2.6 Vitamin D

Vitamin D supplementation has been associated with reduced severity of COVID-19 as well as a reduction in the mortality rate (Tian and Rong, 2020). In general, vitamin D deficiency usually occurs due to a decrease in ultra violet-B (UVB) exposure and/or insufficient sunlight exposure. Globally, it is estimated that more than 1 billion people suffer from vitamin D deficiency/insufficiency (Alam *et al.*, 2021). The deficiency becomes more critical during the colder months. According to *in vivo* and *in vitro* study by Ianevski *et al*. (2019), there was a positive correlation between low temperature and low UV light exposure with elevated incidence of influenza infection.

A recent review by Nurshad (2020) also supported the possible role of vitamin D in decreasing the risk of COVID-19 infections and mortality. Randomized clinical trials, like the one undertaken by Grant *et al*. (2020) have supported the same. Vitamin D is able to elicit its protective effect by conserving gap and cell junction, abating cytokine storm by affecting the release of INF γ and TNF α. Vitamin D regulates the adaptive immune response by inducing T cells (Cantorna *et al.*, 2015) and has even been associated with acute respiratory distress syndrome leading to heart failure (Grant *et al*., 2020)

In the research done by Alvarez *et al*. (2019), supplementing a diet with vitamin D increased CD^{4+} T cell number in people infected with HIV (Figure 2). In a study on interstitial pneumonitis on both mouse models and human cell lines, vitamin D supplementation was found to exert a protective effect (Tsujino *et al.*, 2019). Zdrenghea *et al*. (2017) conducted *in vitro* studies wherein vitamin D was shown to exhibit a homeostatic effect on the respiratory system by promoting the display of antimicrobial peptides and by directly interfering with respiratory virus replication. Individuals suffering from hypertension, and cardiovascular diseases are attributed to suffering from severe COVID-19 as vitamin D insufficiency may stimulate the renin-angiotensin-aldosterone system, which is said to lead to reduced lung function (Shi *et al.* 2017)

In a study involving randomized clinical trials by Rejnmark *et al.* (2017), it was observed that the incorporation of vitamin D ameliorated the incidence of respiratory infections. A similar result was observed in another trial involving 5660 subjects (Bergman *et al.*, 2013). Another study included 25 randomized controlled trials, with 10,933 participants in total from 14 different countries indicating the beneficial effects of vitamin D supplementation in reducing the risk of at least one acute respiratory tract infection (Martineau *et al.*, 2017). According to a study undertaken in Singapore by Tan *et al*. (2020), it was observed that patients treated with combined vitamin D, Mg, and vitamin B_{12} showed significant protective effects against clinical deterioration ($p = 0.041$) even after adjusting for age, gender and comorbidities.

Thus, extensive research data recommends supplementation of up to 250 µg/day for a month of vitamin D which is needed to increase the serum levels of 25(OH)D to the optimal range between 75 and 125 nmol/l (Nurshad, 2020). Currently, in biological and pharmaceutical research *in silico* assays are being extensively performed to elucidate the ideal drug candidate against COVID-19. According to the molecular docking study of Shalayel *et al*. (2020), vitamin D exhibited a higher binding affinity of – 8.01 kcal/mol when compared with chloroquine and hydroxychloroquine. Vitamin D exhibited the strongest interaction against the putative binding sites of the Nsp 15 of COVID-19 with respect to other compounds.

2.7 Vitamin E

The active form of vitamin E, alpha-tocopherol, is a fat-soluble vitamin that is known for its antioxidant properties. It is actively involved in neutralizing peroxide radicals, generated due to oxidation of membrane lipids, and thus helps maintain the integrity of cellular membranes (Hakamifard *et al.*, 2021). Supplementation with

vitamin E provides the body with disease-fighting ability by activating T and NK cells (Darbar *et al.*, 2021) as well as macrophages and dendritic cells (Lee and Han, 2018). The mechanism behind vitamin E's immunomodulatory effects involves a reduction in the production of prostaglandin E2, which is caused due to inhibition of the cyclooxygenase activity (Lee and Han, 2018). Wu and Meydani (2014) have suggested that vitamin E stimulates T lymphocyte-mediated immune function in response to mitogens and IL-2, but also neutrophil and natural killer function, the decline of which is seen with increasing age (Figure 2). Vitamin E has been known to promote dephosphorylation by activating protein phosphatases, thus leading to the inhibition of the protein kinase C activity. It also has been reported to suppress platelet aggregation and propagation of macrophages (Freedman and Keaney, 2001).

According to the study of Hakimford *et al.* (2021), vitamin E levels were found to be low in patients suffering from acute respiratory distress syndrome. This can even be considered an important criterion in patients suffering from SARS COVID-19. However, so far, no direct correlation has been established between vitamin E levels and COVID-19. According to the study by Galabov *et al.* (2015), it was suggested that supplementation with vitamin E ameliorated influenza virus infection. Also, in a clinical trial conducted by Meydani *et al.* (2004), individuals administered 200 IU of vitamin E daily reported fewer instances of common cold. Vitamin E supplementation has been found to increase vaccine efficacy that has been observed by enhanced antibody titers as observed against tetanus (Meydani *et al.*, 2004). Decreased levels of vitamin E in animal models are associated with mutations leading to a greater level of virulence of other negative-strand RNA viruses, such as influenza virus (Calder *et al.*, 2020).

Ferroptosis, a recently discovered cell death mechanism involves excessive accumulation of iron, along with lipid peroxidation. This ultimately leads to multiorgan failure. Tavakol and Seifalian (2021) suggested that vitamin E supplementation at a dose of 500 mg/kg can be used as a potential treatment to inhibit ferroptosis in COVID-19 patients. In a clinical trial undertaken on 33 geriatric males and females with compromised immune function, Vitamin E supplementation was found to improve immune function (De la Fuente *et al.*, 2008). The susceptibility and severity of COVID-19 are directly proportional to age as increasing age is also associated with a weakened immune system (Jovic *et al.*, 2020). The COVID-19 pathophysiology is mediated by the production of free radicals. The production of free radicals generates oxidative stress that leads to lipid peroxidation and membrane damage. This results in pulmonary edema which is the hallmark clinical manifestation of COVID-19 severity. Vitamin E supplementation is associated with reduced production of superoxides.

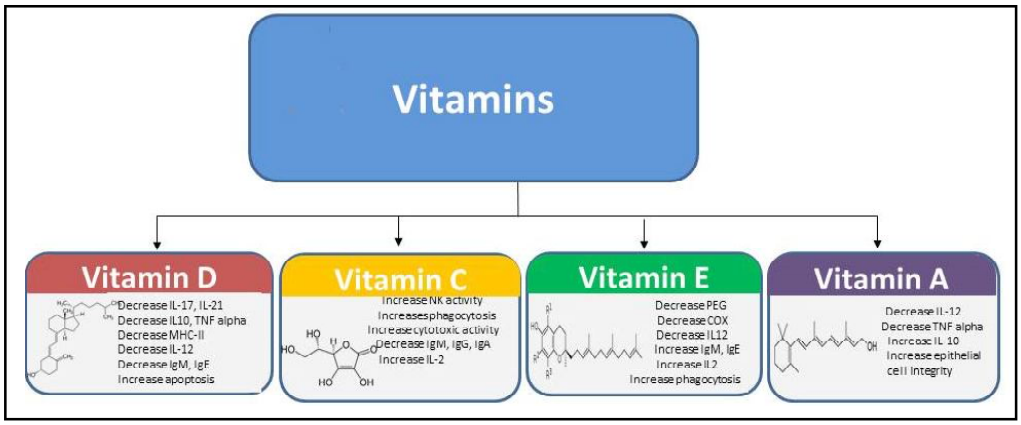

Figure 2: Immunomodulatory effect of vitamins in the physiological system.

2.8 Folic acid

One of the important B group vitamins is folic acid. Although, the requirement for folic acid is low, still many individuals suffer from its deficiency largely due to a diet comprising of corn, rice and potatoes that lack folic acid (Gorelova *et al.*, 2017). This further leads to megaloblastic anaemia, defects in cognitive functions, weak bones, and even certain cancers (Acosta-Elias and Espinosa-Tanguma, 2020). Serine is an important constituent for antibody synthesis and lack of serine can interfere with the synthesis of T cells. Folic acid is required for the conversion of glycine to serine. Thus, a deficiency of folic acid impacts the immune system (Jayawardena *et al.*, 2020). Folic acid also plays a significant role in DNA replication. In scenarios of folate deficiency, DNA replication gets adversely affected. This has a compounding effect on other cellular pathways as well which causes impairment in cytokine production, unregulated immune response and dysfunctional immune system (Childs *et al.*, 2019). According to a clinical study performed on 23-month-old mice, folate supplementation was found to increase the T cell distribution to the levels found in 12-month-old mice. There was also a concurrent increase in the number of CD4+ cells. The study highlighted that folate supplementation can help overcome immunosenescence (Sharma, 2020) (Figure 3).

It has been suggested by the study of Acosta-Elias and Espinosa-Tanguma (2020) that folic acid in a dose of 5 mg or more is a potential therapeutic modality for patients suffering from severe COVID-19. This supplemental treatment is favoured due to less adverse effects.

According to the computer simulation study of Sheybani *et al.* (2020), it was elucidated that folic acid can inhibit viral replication by inactivating the protease enzyme furin which is essential for virus entry into the host cell. Also, folic acid inactivates the essential SARS-CoV-2 protein, 3 CLpro (Serseg *et al.*, 2020). The same has

also been confirmed by the molecular docking studies of Kumar *et al.* (2021) wherein it was observed that three compounds-hispidin, lepidine E, and folic acid-bound tightly to the main protease of coronavirus by establishing some hydrogen bonds of bond length varying from 1.69-1.80Å. Computational studies suggested that folic acid and its derivatives can be a potential therapeutic modality against COVID-19 (Wiltshire *et al.*, 2020).

2.9 Selenium

The trace element, selenium plays important physiological functions largely due to its presence as selenoproteins (Zhang *et al.*, 2020). Research has suggested that there are close to 25 genes in the human genome that code for selenoproteins. These selenium-containing proteins have been largely associated to their function as an antioxidant and anti-inflammatory agents (Labunskyy *et al.*, 2014). According to the 2012 study by Rayman on HIV, there was observed an inverse relationship between selenium levels in the human body and mortality rate. Similar findings were also observed for liver cancer caused due to hepatitis B infection as well as hantavirus (Zhang *et al.*, 2020). Administration of selenium salts led to a reduction in mortality by close to 80%. Experimental studies have suggested a correlation between selenium status and the pathophysiological response to viruses, especially pertaining to SARS-COVID-19 (Bermano *et al.*, 2021; Huang *et al.*, 2020; Guillemn *et al.*, 2019). The importance of selenium for the pathophysiological system can be understood by the selenium deficiency disease, Keshan, which is reported to be prevalent in the Chinese province of Heilongjiang. Keshan disease is associated with muscle weakness leading to heart failure and death (Loscalzo, 2014). Selenium is known to be an important constituent of antioxidant enzymes glutathione peroxidase and thioredoxin reductase (Tapiero *et al.*, 2003). Its antioxidant characteristics have been studied extensively and have been reported to reduce oxidative stress, even in clinical trials of patients suffering from acute respiratory distress syndrome caused due to COVID-19 (Tomo *et al.*, 2021). Huang *et al.* (2019) have reported that selenium also plays an immunomodulatory role, wherein it strengthens the innate immune system by stimulating T-cell proliferation (Figure 3). This was further experimentally supported by administering 200 µg/day of sodium selenite for 56 days which resulted in an enhancement in the number of Tc and NK cells (Huang *et al.*, 2019). IL-6 has been reported to be primarily responsible for the cytokine storm associated with the pathogenicity of COVID-19. One of the functions attributed to selenium is its ability to down-regulate IL-6 response. Thus, low selenium levels in the elderly are associated with higher levels of IL-6, promoting cytokine storm (Hoffmann and Berry, 2008). For *in silico* studies conducted to develop suitable therapeutic targets against COVID-19, Ebselen, an organoselenium compound designed as a GPX1 mimic, was found to have the strongest inhibitory activity (Jin *et al.*, 2020). It was reported to inhibit the activity of SARS-CoV-2 PLpro by the formation of sulfhydryl bonds.

2.10 Zinc

During the COVID-19 pandemic, zinc supplementation showed positive results as both prophylactic and therapeutic modality (Pal *et al.*, 2021). Zinc insufficiency has been associated with cognitive dysfunction as well as immune deregulation (Fukada *et al.*, 2019) by interfering with important cellular functions such as phagocytosis. Zinc supplementation has been associated with improved antiviral immunity as well as its antioxidant activity is responsible for maintaining membrane integrity and protecting against the inflammatory process characteristic of COVID-19 infection (Read *et al.*, 2019).

The role of zinc in maintaining immune health is largely attributed to the fact that zinc is a component of the hormone, thymulin. This thymus hormone is accredited with the maturation and differentiation of T cells as well as stimulates macrophages to produce IL-12 which in turn promotes natural killer and T cytotoxic cells (Prasad, 2008). Several preclinical studies have suggested that zinc insufficiency affects both helper and cytotoxic CD8+ T cell responses (Prasad, 2008). Thus, deficiency of Zn causes the immune system to function ineffectively due to thymus degeneration leading to dysfunctional lymphocyte response. Both IFN-γ and IL-12 play a crucial role in the destruction of various pathogens (Figure 3). Pyrithione, the zinc ionophore is said to be a potential inhibitor of RNA-containing viruses, possibly mediated by its ability to inhibit RNA virus RdRp (teVelthuis *et al.*, 2010). Also at enhanced concentrations, zinc can stimulate apoptosis of the virus. In a clinical trial, administration of high-dose zinc lozenges to four COVID-19 patients led to a reduction in the symptoms associated with the disease (Finzi, 2020). However, at high concentrations, zinc is said to function as a proxidant as well. The benefits associated with zinc supplementation outweigh its harmful effects (Pal *et al.*, 2021). As per the study of Read *et al.* (2019), zinc antiviral efficacy is attributed to its ability to inhibit the viral lifecycle by preventing the fusion of the virus with the host cell membrane, restricting the activity of the virus's polymerase enzyme, affecting protein processing and inhibiting the release of virus particles.

With an aim to identify novel drugs against COVID-19, zinc oxide nanoparticles were developed by Hamdi *et al.* (2021). These nanoparticles are known to have superior potency and have been found to be effective against COVID-19. These nanoparticles interfere with viral replication by inhibiting the DNA polymerase activity. Binding energy of zinc nanoparticles against the major SARS-COVID-19 proteins-ACE2, COVID-19 RdRp, and COVID-19 Mpro was found to be 5.7, 5.4 and – 4.5 kcal/mol, respectively.

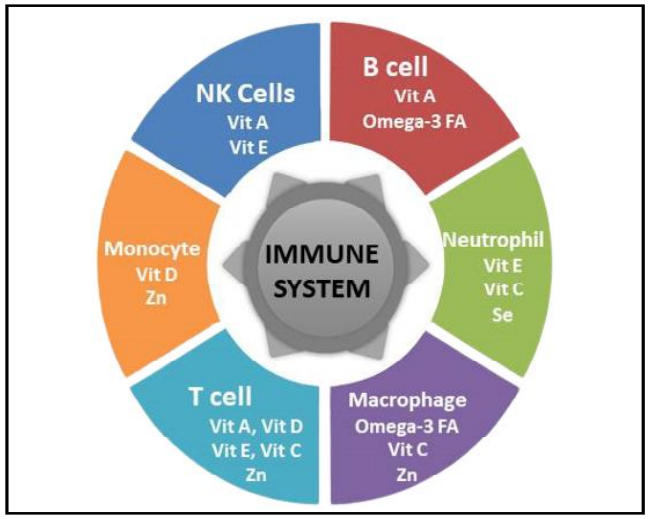

Figure 3: Effect of micronutrients on cells of the immune system.

3. Conclusion

COVID-19 pandemic started in March 2020 and since then has seen the virus mutate several times leading to more than 16 variants of the disease. The current literature review presents an array of observational data to emphasize the role that nutrition can play as an alternative to therapy for viral diseases. Published literature presented depicts the connections between nutrition and control of other viral diseases and the same can be extended for SARS-CoV-2. The data relating to the consumption of micronutrients being potent in preventing infection and helping recovery in relation to COVID-19 is still not established, though it is known that nutritional status is important for immune function. Thus, we propose that emphasis should be laid on promoting holistic wellbeing through the consumption of a balanced diet to reduce pathogenic load (Akhtar *et al.*, 2021). In the case of nutritional status in relation to COVID-19, results of clinical trials to support the hypothesis are just pouring in and literature-supported assumptions need to be verified.

Acknowledgments

Financial and infrastructural support to the Department of Biochemistry from Shri Vile Parle Kelavani Mandal (SVKM) is gratefully acknowledged.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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Citation **Sara Anees Khan and Nupur Mehrotra (2022). Protective effect of nutrition and supplements on COVID-19 management. Ann. Phytomed., Volume 11, Special Issue 3 (COVID-19): S18-S29. http://dx.doi.org/10.54085/ap.covid19.2022.11.3.4.**