



Deciphering the immunoboosting potential of macro and micronutrients in COVID support therapy

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Abstract

The immune system protects human health from the effects of pathogenic organisms; however, its activity is affected when individuals become infected. These activities require a series of molecules, substrates, and energy sources that are derived from diets. The consumed nutrients from diets help to enhance the immunity of infected individuals as it relates to COVID-19 patients. This study aims to review and highlight requirement and role of macro- and micronutrients of COVID-19 patients in enhancing their immune systems. Series of studies were found to have demonstrated the enhancing potentials of macronutrients (carbohydrates, proteins, and fats) and micronutrients (vitamins, copper, zinc, iron, calcium, magnesium, and selenium) in supporting the immune system's fight against respiratory infections. Each of these nutrients performs a vital role as an antiviral defense in COVID-19 patients. Appropriate consumption or intake of dietary sources that yield these nutrients will help provide the daily requirement to support the immune system in its fight against pathogenic viruses such as COVID-19.

Keywords Macronutrients · Micronutrients · COVID-19 · Vitamin D · Vitamin C · Immune-enhancing

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Introduction

Compounds in foods that affect a recognizable change in an organism's immune system are referred to as immune-enhancing nutrients. Glutamine, arginine, omega-3 fatty acids (FAs), and several others are nutrients that have been proven to express regulatory effects on immune function. Hence, they are assumed as immuno-nutrients or immune regulators (Schloerb 2001). It is well established that diet influences immune levels, and poor diet is the most rampant culprit in cases of weakened immunity worldwide (WHO 2020a, b). Micronutrients such as folic acid, Zn, Mg, Mn, Se, Fe, Cu, B-vitamins, and water-soluble vitamins all function to improve the human body defense mechanism activity against many disease-causing organisms as shown in Table 1 (Rytter et al. 2020). The lack of these essential micronutrients could cause an altered immune response (Gleeson 2013). Therefore, a healthy immune system resulting from a good and balanced consumption of nutrients needed in the body is essential (Agovino et al. 2018).

A healthy immune system is a major defense against disease with no known drugs, an example of such disease being the current COVID-19 pandemic. Several vital nutrients are required for enhancing the body's innate and adaptive

Table 1 Immunoboosting potential of vitamin A, B, C, D, E, zinc, iron, and selenium via innate and adaptive immunity

Name of nutrient	Immune function	Innate immunity	Adaptive immunity
Vitamin A	Differentiation of epithelial tissue, imprinting T, and B cells with gut-homing specificity and array T cells and IgA ⁺ cells into intestinal tissues, supporting the gut barrier	Regulation of differentiation, maturation, and function of macrophages and neutrophils	Regulation of proliferation of B- and T-cell differentiation and interaction and induction of T cell migration
Vitamin B	Regulation of intestinal immune	Stimulation of cell proliferation, differentiation, function, and movement	Proliferation, differentiation, function of T-cell, balance of Th1 and Th2, required for production and metabolism of antibodies
Vitamin C	Synthesis of collagen that helps in stabilization of epithelial barriers	Stimulation of leukocyte functions, neutrophil and monocyte movement, offers protection against ROS-induced damage by neutrophils, enhance chemotaxis, increase killing and phagocytosis, increments in the production of interferon	Regulation of proliferation of B- and T-cell differentiation and interaction
Vitamin D	Proliferation/maturation of keratinocyte, repairs mucosal junction integrity, helps in development of permeability barrier in the skin, maintains renal epithelial barrier function, and enhances corneal epithelial barrier function	Helps in improving chemotaxis and phagocytic capabilities, production of antimicrobial proteins (defensin β 2, cathelicidin, LL-37), modulation of cytokine, induction of regulatory T cells	Regulation of proliferation of B- and T-cell differentiation and interaction
Vitamin E	Helps in synthesis of collagen that provides stabilization and integrity of epithelial barriers, protects cell membranes from damage caused by free radicals	Stimulation of leukocytes, protection of neutrophils against ROS-induced damage especially of neutrophil and monocyte movement, enhance killing and phagocytosis, enhances production of interferon	Regulation of proliferation of B- and T-cell differentiation and interaction, balance of Th1 and Th2
Zinc	Helps in maintaining integrity of skin and mucosal membrane	Enhance phagocytosis of macrophages and neutrophils, activate IgG, generate the oxidative burst, activate complement, modulate cytokine	Regulation of proliferation of stem cells, B- and T-cell differentiation and interaction, balance of Th1 and Th2
Iron	Essential for differentiation and growth of epithelial tissue	Involved in regulation of cytokine production and action, required for the generation of pathogen-killing ROS by neutrophils during oxidative burst	Helps in differentiation and proliferation of T cells, regulate ratio between T helper cells and cytotoxic T cells
Selenium	Required for impairment of oxidative damages	Helps to maintain antibody levels	Helps in differentiation and proliferation of T cells, improve Th cell counts

defense mechanisms (Purohit et al. 2020b). Poor micronutrients negatively affect immune function and reduce the body's ability to resist infections (Carr and Maggini 2017; Gombart et al. 2014). Apart from magnesium and vitamin E, micronutrients have therapeutic effects in the European Union for being a key player in normal immune function (EU 2020). Omega-3 FAs are another nutrient group that helps in the regulation of the immune system, mainly by modulating inflammatory responses (Calder 2020). Nutritional status can greatly impact a person's total well-being, decrease non-communicable diseases, and reduce vulnerability to growing infections (Agovino et al. 2018). Currently, there is no permanent or proven pill, vaccine or treatment, food, or herb for confirmed prevention of COVID-19 infection based on the information from WHO (WHO 2020a). Poor nutritional status can increase a patient's susceptibility to contracting lethal COVID-19 (Purohit et al. 2020a). Many nutrients play a vital role in the immune system's functioning, and an adequately managed balanced diet will enhance the effectiveness of the immune system. Also, for an effective immune response, it is required that zinc, iron, selenium, copper, magnesium, and vitamins be present in consumed diets (Calder 2013; Smith et al. 2018). Nutrients like vitamins and minerals influence health and upregulation responses of the immune system to harmful agents as well as laboratory antigens (Jose et al. 2017; Pan et al. 2018; El-Senousey et al. 2018). Prior to admission, COVID-19 patients should be checked for nutrient deficiencies using standard screening tools to determine effective treatment and dietary regimens (Reber et al. 2019; Lomax and Calder 2009; Yaqoob 2017).

In review aims to discuss the immunoboosting potential of macro and micronutrients in COVID support therapy. This review intends to provide basic insight and understanding of synergetic mechanisms of vitamin A, B, C, D, E, zinc, iron, and selenium on the immune system. Later, we elaborate the immune functions of micro- and macronutrients in COVID support therapy with recently published data. Various micro- and macronutrients are highlighted in this review for the management of COVID-19.

Immune functions of nutrients

Macronutrients (carbohydrates, fats, and proteins)

Carbohydrates also known as sugars are the primary energy source that should be obtained frequently from food intake. Research has also shown that certain protein monomers such as arginine, glutamine, taurine, methionine, and cysteine possess immunomodulatory activities (Li et al. 2007). Meat is a highly digestible (about 94% digested) protein source as compared to beans (78%) and whole wheat (86%) (Bhutta

1999). Meat is a good origin of all the eight essential amino acids and lacks in non-essential amino acids. The use of a scoring method known as protein digestibility–corrected amino acid score to rate how viable a protein is uses a maximum score of 1.0. Most plant foods have values of 0.5–0.7 while animal proteins like beef have a value of 0.9 (Schaafsma 2000). Glutamic acid/glutamine is the highest amino acid in meats (16.5%), followed by aspartate, alanine, and arginine. Taurine is a free amino acid that is primarily present in all tissues, with its presence higher in blood, heart, and retina (Wójcik et al. 2010). Taurine mainly helps in bile acid conjugation and other biological functions. Also, taurine is implicated in several physiological processes including osmotic regulation, modulation of the immune responses, and membrane integrity. It plays a vital role in nervous system coordination and the eyes (HuxTable 1992). Due to the limited nature of the endogenous synthesis of taurine, it is often considered a conditional essential nutrient, and it is majorly obtained from foods. Aquatic animals are mostly a preferred taurine source than their terrestrial animal counterparts (Bouckennooghe et al. 2006; Dragnes et al. 2009; Spitze et al. 2003). High taurine levels have been reported in some marine invertebrates, compared to terrestrial plants with a low taurine content (Kataoka and Ohnishi 1986). Taurine is also present in considerable amounts in meats (77 mg/100 g in beef and 110 mg/100 g in lamb) (Purchas et al. 2004).

Furthermore, some polyunsaturated fatty acids (PUFA), as well as their metabolic products, modulate cell functions, particularly omega (ω)-3 fatty acids (DHA and EPA) that affect immune cell activities (Gleeson 2013). However, most positive effects are caused by n-3 PUFA, particularly DHA and EPA. These FAs have been shown to possess pleiotropic effects, consequently influencing the production of the inflammatory components via in vivo, membrane functionality, and blood flow properties and studies have shown the preventive properties of n-3 PUFA in several ailments (Riediger et al. 2009). Beef from animals fed with pasture is a preferred source of ω -3 fats than those fed with grains, and this clarifies why Australian meats have a preferred fatty acid ratio compared with that in the USA, where grains are the major source of food for the animals (Sinclair and O'Dea 1987; Marmer et al. 1984). Studies have shown that meats from fowls and pigs possess lower ω -3 PUFA than beef and lambs though fish remain the most preferred source of omega-3 PUFA. Moreover, ω -3 and ω -6 PUFAs mostly modulate inflammatory effects, being a starting material for leukotrienes or prostaglandins and resolvins or protectins (both are derivatives of omega-3 FA that helps inflamed tissues to return to normal once the inflammatory response is over) respectively. Protectin D is an omega-3 serving as a newly discovered antiviral drug that shows a promising role in interventions of the novel virus COVID-19 (Purohit et al.

2020a). Recently, 160 mg and 90 mg daily consumption of omega-3 fats (EPA and DHA) was recommended for males and females, respectively, as the Nutrient Reference Values for Australians, with an upper consumption range of 610 mg for control and 430 mg for prevention of lingering chronic ailments (National Health and Medical Research Council 2006). Australian beef is a good source of omega-3 FA with 135 g of red meat yielding more significant than 30 mg (Food Standards Australia New Zealand 2002). Also, mutton muscle meat yields a good level of long-chain omega-3 PUFA. Among Australians, fish and red meat serve as the first and second-largest sources of omega-3 long-chain PUFA (Howe et al. 2006).

Endogenous negative-feedback mechanisms help resolve inflammation quickly after an immune response. In achieving this, EPA and DHA localized at the inflammatory region are transformed into cell signaling molecules known as specialized pro-resolving lipid mediators (SPMs), namely maresins, protectins, and resolvins. They work together to quench inflammation and ensure the process of healing in tissues with respiratory system inclusive (Calder 2012; Basil and Levy 2016). Sea animals are rich in protein with lower calories, and high levels of omega-3 long-chain PUFAs compared to terrestrial animals (Tacon and Metian 2013). It has been found that the absence of PUFAs can cause a slow removal of inflammation (Mehta et al. 2020). This will be crucial to the so-known cytokine storm observed amid severe COVID-19 with the presentation of unsuppressed inflammation (Pedersen and Ho 2020; Gao et al. 2017). SPMs derived from DHA and EPA protect against acute lung injury and acute respiratory distress syndrome (ARDS) (Zhang et al. 2019).

Antioxidants rich in DHA and EPA have been employed in several trials involving ARDS patients. A recent review on these trials noted an undeniable betterment in oxygen flow in the circulatory system and a considerable amount of decrease in the need for ventilators, new organ breakdown, time spent in the intensive care unit (ICU), and mortality (Dushianthan et al. 2019). Eicosanoids derived from n-3 PUFA possess the ability to downregulate immune response (Calder 2001). Eicosanoids derived from n-6 PUFA possess pro-inflammatory properties and enhanced immune responses such as pyrexia and agony. In the past four decades, research has shown the importance of EPA and DHA for protection against several diseases (Calder 2006). α -linolenic acid, an omega-3 FA usually found in seeds and oils, can be used as a substrate for DHA and EPA biosynthesis. Although, its synthesis may be inadequate in old people and babies (Brenna 2002). Altering the fatty acid (FA) content in the diet helps to enrich meat from chicken with n-3 PUFA (Ribeiro et al. 2013; Konieczka et al. 2017). Meat from rabbits contains 60% unsaturated FA and 32.5% PUFA, this is higher than what is obtained from other meats

including farm birds, and it may serve as an important diet in humans (Wood et al. 2008). DHA and EPA are the most bioactive n-3 PUFA; lower activity observed in α -linolenic acid is due to its biotransformation to the bioactive EPA which is usually lacking in man (17:1); enhancement of DHA and EPA in rabbits can be done by animal feeding (Decker and Park 2010).

Micronutrients (vitamins and minerals)

Deficiencies of trace elements result in immune disorder. A nutritious and balanced meal has the potential to boost and regulate immune cells against COVID as demonstrated in Fig. 1. A viable immunity is the most potent tool to combat a disease like COVID-19, with no established treatment or drug. The increased risk of death due to poor nutrition is due to increased severity of infection coupled with slowed recuperation.

In addition, an increase in more nutrient demands results from infection (WHO 2020a, b). A recent study reported that optimum nutritional status helps protect the body against infections with viruses (Maggini et al. 2018; Calder 2020). Also, another study provided nutritional advice to help curtail lung damages caused by infections with coronavirus and other lung issues (Wu and Zha 2020). Studies have reported that deficiency in individual nutrient or combo of nutrients affects the immune system by activating immune cells, modifying the production of signaling molecules, and expression of genes (Valdés-Ramos et al. 2010). Also, depression of immune function and higher vulnerability to infection may occur. Proper intake of the required amount of nutrients is crucial in the strong maintenance of immune response (Gleeson et al. 2004; Fernández-Quintela et al. 2020).

Vitamin A

Studies have shown that consumption of vitamin A-deficient diets hampers the potency of attenuated vaccines in bovine coronavirus and thereby increases vulnerability of calves to infections. Vitamin A also demonstrates a prospective headway towards discovering a coronavirus treatment and preventing lung problems (Jee et al. 2013). Vitamin A and folate are abundant in the liver, but the levels in lean meat are low (Table 1). Vitamin levels are often higher in older animals; hence, beef has more vitamins than mutton meat or veal (Williams et al. 2007). Chicken meat is the only meat with a useful amount of β -carotenes which can serve as a precursor for vitamin A which can be enhanced by food fortification (Decker and Park 2010).

Vitamin A and folic acid are often largely present in offal meats (Biesalski 2005). Vitamin A is important for adequate development. A study recommended the liver as a good vitamin A source with 100 g yielding more than

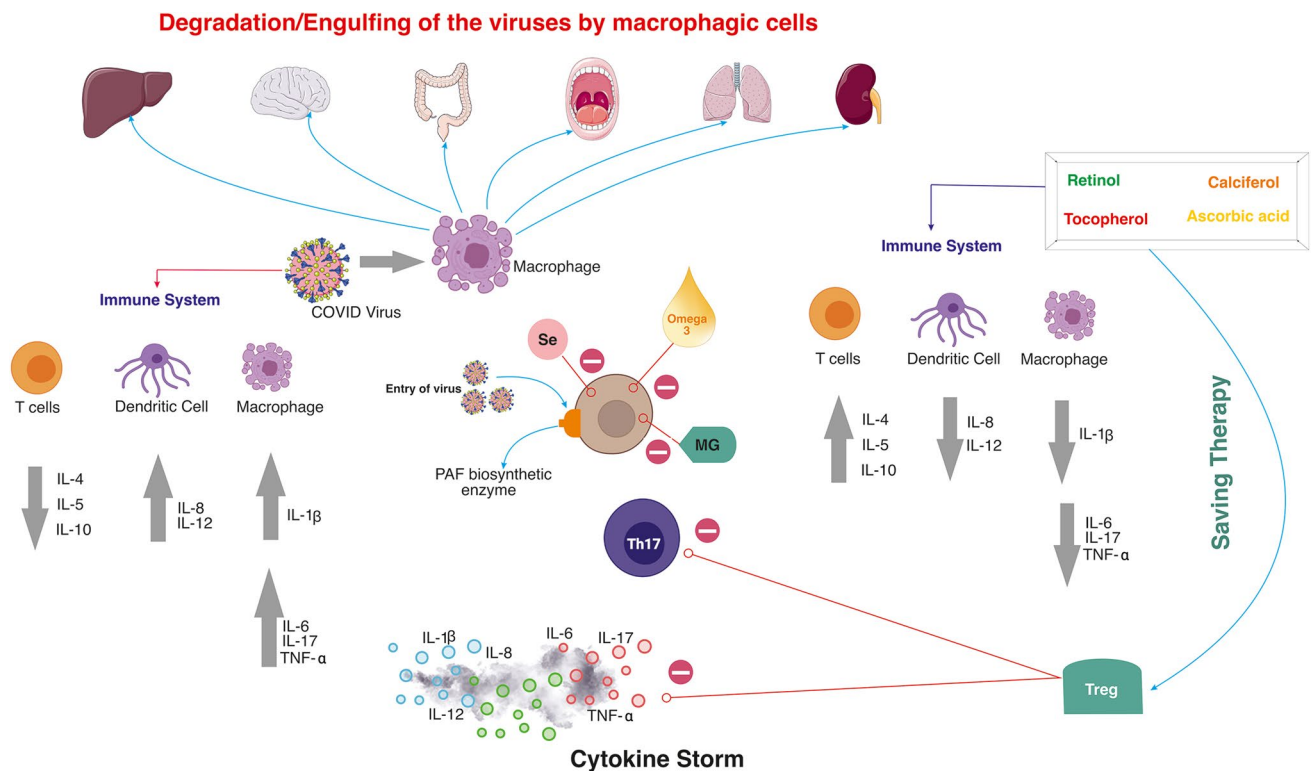


Fig. 1 Role of macrophagic cells and micronutrients against COVID infection

the recommended dietary value (USDA 2011). Mucin production in the respiratory tract is sustained by vitamin A. Mucin serves as a barrier that protects the respiratory tract from pathogenic infections (Fan et al. 2015). Vitamin A is very crucial in the production of antibodies. It helps in the movement of T lymphocytes to infection or inflammation site, enabling cells of the mucous membrane involved in IgA production to develop an appropriate immune response (Mora and Andrian 2006).

A randomized, single-blinded, and two-arm clinical trial of 7 days was executed to evaluate severity and mortality rate in ICU patients suffering from COVID-19 that were supplemented with vitamin A, B, C, D, and E (Beigmohammadi et al. 2020).

Vitamin B

Another wise approach could be to supplement the COVID-19 patient with vitamin B. Over two-thirds of the daily required vitamin B can be obtained from 100 g serving of red meat as they serve as the most bioavailable source of vitamin B (Sinclair et al. 1999; Williams et al. 2007). A 100 g intake of red meat can yield 25% of the everyday required amount of other B vitamins such as vitamin B₂, B₃, pyridoxine, and pantothenic acid (Williams 2007a, b). Seafood such as herring, oysters, clams,

anchovies, pilchard, and sardines contain high levels of vitamin B₁₂. Mussels, clam, and oysters have a B₁₂ content of 15.71, 87.0, and 46.3 mg per 100 g respectively. B₁₂ content in sardine, salmon, and tuna ranges from 3.8 to 8.9 mg per 100 g. Clams and mollusks have B₁₂ content of 98 mg per 100 g (Watanabe et al. 2001).

The combination of C and E vitamins serves as a potential antioxidant treatment for COVID-19 cardiac complications (Wang et al. 2020). More so, there is no adequate fact on vitamin E use as an agent for prevention or treatment against COVID-19. It is suitable to maintain nutritional habits, alongside a healthy nutritious diet containing enough minerals, antioxidants, and vitamins. Bio-available vitamin B can be obtained from meat. However, its concentrations vary considerably in meats from different animal species. High temperatures during meat processing lower the levels of vitamin B (Lombardi-Boccia et al. 2005). The daily recommended amount of vitamin B₁₂ for an adult is 22 µg, and this can be obtained through the consumption of 100 g of beef (LARN 1996). Studies have revealed that 100 g consumption of rabbit meat can yield triple the vitamin B₁₂ daily requirement (DR), comprising about 8% vitamin B₂, 21% vitamin B₆, 12% vitamin B₅, and 77% vitamin B₃ (Hernández and Dalle Zotte 2010). However, pork yields 37% of the RDI for vitamins B₁, B₂, B₆, and B₁₂ (Esteve et al. 2002).

For niacin, a consumption of 100 g of chicken breast will yield 56% of the DR and 27% DR of B₆ vitamin, while a consumption of 100 g of turkey breast will provide 31% DR of niacin and 29% DR of vitamin B₆ (USDA 2011). Regulatory T cells (T_{reg}) are known for their high expression of vitamin B₉ receptors; vitamin B₉ (folic acid) is a survival factor, and it helps in preventing excessive immune response (Hernández and Dalle Zotte 2010; Sakaguchi et al. 2009). Inadequate vitamin B₉ may result in a low population of T_{reg} cells, thereby resulting in upregulation in the susceptibility of the organism to sudden inflammation outburst, as observed during the fatal stage in patients with COVID-19 (Kinoshita et al. 2012).

Vitamin C

It is a water soluble micronutrient that acts as an antioxidant. Vitamin C cannot synthesize in the body because of the absence of the enzyme that is a key factor for its de novo biosynthesis. It blocks oxidative stresses via reduction or prevention of generation of reactive oxygen and nitrogen species (Xu et al. 2021; Aldwihi et al. 2021). Vitamin C provides support to the immune system, protecting it against the coronavirus. Vitamin C can be used as an alternative treatment in COVID-19 cases. Reports from some controlled trials showed that sometimes, patients administered with vitamin C showed a reduced occurrence of pneumonia. However, high-dose administration in patients is yet to be approved (Hemila 1997).

Vitamin C influences various aspects of immunity such as development and function of adaptive and innate immune cells, aiding activities of the epithelial barrier, translocation of white blood cells to infection sites, phagocytosis, killing of microbes, and producing antibodies. The deficiency of vitamin C results in susceptibility to worse respiratory infections (Hemila 2017).

A study reported a reduced risk of pneumonia due to intake of vitamin C supplements (Hemilä and Chalker 2013). The mortality risk is reduced in aged people by adding vitamin C to foods (Hemila and Louhiala 2013). Vitamin C intake decreases the virulence period of infections associated with the upper region of the respiratory tract and decreased significantly the risk of infection when administered as a preventative measure to people who undergo enhanced physical stress (Hemilä and Chalker 2013). The intake of vitamin C-deficient foods by a healthy young adult (humans) results in reducing vitamin C content in mononuclear cells by half and reduced ability of the T lymphocyte-mediated immune responses in recalling antigens (Jacob et al. 1991).

Recently, investigations to validate its effect in severe COVID-19 treatment have begun (Carr 2020). Vitamin C may possess effects on viral infections of the respiratory tract especially when specific therapy for COVID-19 is

absent. It is noteworthy that vitamin C increases the resistance to coronavirus and under certain conditions reduce the risk of infections of the lower respiratory tract (Hemilä 2003; Hemilä and Douglas 1999).

For severe conditions of COVID-19 which require ICU, its high-dose intravenous administration is highly valuable for such patients. Numerous trials of its high-dose i/v administration have demonstrated varied outcomes regarding laboratory and clinical results for acute lung injury and acute respiratory suffering disease (Hemilä and Chalker 2020).

Its combination with glycyrrhizic acid was proposed for COVID-19 treatment by bioinformatical network pharmacology. In another case, its co-administration with quercetin was also suggested. But, further investigations did not provide a strong indication for the utility of its high dose or its combination with zinc for the treatment. At present, pilot-scale studies are ongoing such as in Canada (LOVIT-COVID) and Italy (NCT04323514) for proving its utility for improving the condition of COVID-19 patients (Clemente-Suárez et al. 2021).

In a single case report, a 74-year-old female suffering from COVID-19 ARDS was supplemented with vitamin C (1 g bis in die upto six days orally) and after that, 11 g/day for 10 days as a continuous infusion. Her clinical status was improved within 5 days of treatment and she was capable of halting mechanical ventilation (Waqas Khan et al. 2020).

Seventeen patients (age 64 ± 14 yrs, M:F = 10:7) of the USA suffering from SARS-CoV-2 were administered intravenously with vitamin C (1 g *ter in die* for 3 days). It was observed that there was a significant decline in ferritin and D-dimer intensities and a fraction of FiO₂ that helps in inspiration of oxygen (Hiedra et al. 2020).

In China, 34-year-old subject (male) with COVID-19-associated symptoms (dry cough, fatigue, reduced hunger, and subjective fever) was given vitamin C (3 g per day) in combination with antiviral and antimicrobial cures. After 14 days of this ailment, it improved her SpO₂ levels that assured her improved clinical condition (Chen et al. 2021).

A female patient (66 years old) from China suffering from COVID-19-associated shortness of inhalation and continuous fever received orally (200 mg *ter in die*) of vitamin C with diammonium glycyrrhizinate. After 7 days of the following treatment, her condition was improved and she was completely healthy (Ding et al. 2020).

For twelve Chinese patients with severe ($n=6$, 56 years old) or critical ($n=6$; 63 years old) COVID-19 pneumonia, a high dose of vitamin C (162.7 and 178.6 mg/kg/day) was administered intravenously. There was a significant decline in counts of C-reactive protein, lymphocyte, and CD⁴⁺ T cells, as well as an enhancement of organ failure score, which was improved in the severe group in contrast to the critical group (Zhao et al. 2020).

Twelve trials with 1766 subjects of ICU conditions showed that its administration shortened the stay in ICU by 8%. Another 8 trials demonstrated that its administration declined the period of mechanical ventilation in patients who needed the longest ventilation (Hemilä and Chalker 2019).

Vitamin D

Vitamin D fights against acute infections of the respiratory tract. Recent studies reported a reduced risk of infections with COVID-19 on increased intake of vitamin D as shown in Fig. 2. It plays a critical role by affecting the maturation of immune cells (Grant et al. 2020). Studies reported a reduced level of vitamin D in healthy individuals particularly at the end of winter season, this coincides with COVID-19 discovery in winter of 2019 (Arabi et al. 2020). Vulnerable patients are advised to increase their vitamin D intake. Due to the stay-at-home order, there is reduced exposure of people to sunlight. Therefore, it is very important to increase the consumption of dietary sources rich in vitamin D (Zabetakis et al. 2020). Vitamin D-rich foods include oily fish and cod liver oil, among others (Larsen et al. 2011). The lack of vitamin D in cold weather periods is connected to viral outbreaks. The proper vitamin D level prevents the risk of chronic conditions like high blood pressure, cancer, heart diseases, stroke, diabetes, and hypertension in people with respiratory infections (Muscogiuri et al. 2017).

Vitamin D performs a series of function in the body, such as protection of the respiratory tract, tight junction preservation, and elimination of encapsulated viruses via cathelicidin and defensin activation, and decreases pro-inflammatory cytokine production by the innate immune system; thus, the

risk of cytokine storm development is reduced, which will consequently lead to pneumonia. Considering that going outside is not very feasible and the exposure to sunlight is limited, foods now serve as the best alternative source of vitamin D. Fish, egg yolk, liver, yogurt, and milk are known foods that contain vitamin D. Several body defense cells possess vitamin D receptors which enhance efficacy after bonding to ligands, and therefore, vitamin D greatly impacts on immunity. Vitamin D promotes monocyte differentiation into macrophages, thereby increasing their killing capacity, affecting cytokines release, and promoting antigen presentation. Additionally, metabolites of vitamin D help in regulating the release of proteins with antimicrobial properties that destroy pathogens and therefore reduce infections of the lungs (Gombart 2009; Greiller and Martineau 2015). Research has shown that vitamin D is present in meat (Ovesen et al. 2003). Cholecalciferol (vitamin D3), which is obtained through skin exposure to sunlight, has greater potency than ergocalciferol (vitamin D2) found in mushrooms (Holick 2008; Norman 2008). Vulnerability to respiratory tract infection has been reported in some studies in people with low vitamin D in the blood (Cannell et al. 2006; Jollie et al. 2013). Also, several meta-analyses reported that the addition of vitamin D to food decreases the risk of respiratory tract infections in humans (Charan et al. 2012; Autier et al. 2017). Its lack impedes the functions of the immune system due to its immunomodulatory role, thereby increasing inborn immunity by antiviral peptide production, which helps in the improvement of mucosal defenses (Gombart et al. 2005; Wang et al. 2010).

Recently, some reviews propounded that low vitamin D in the blood results in compromised immune functions

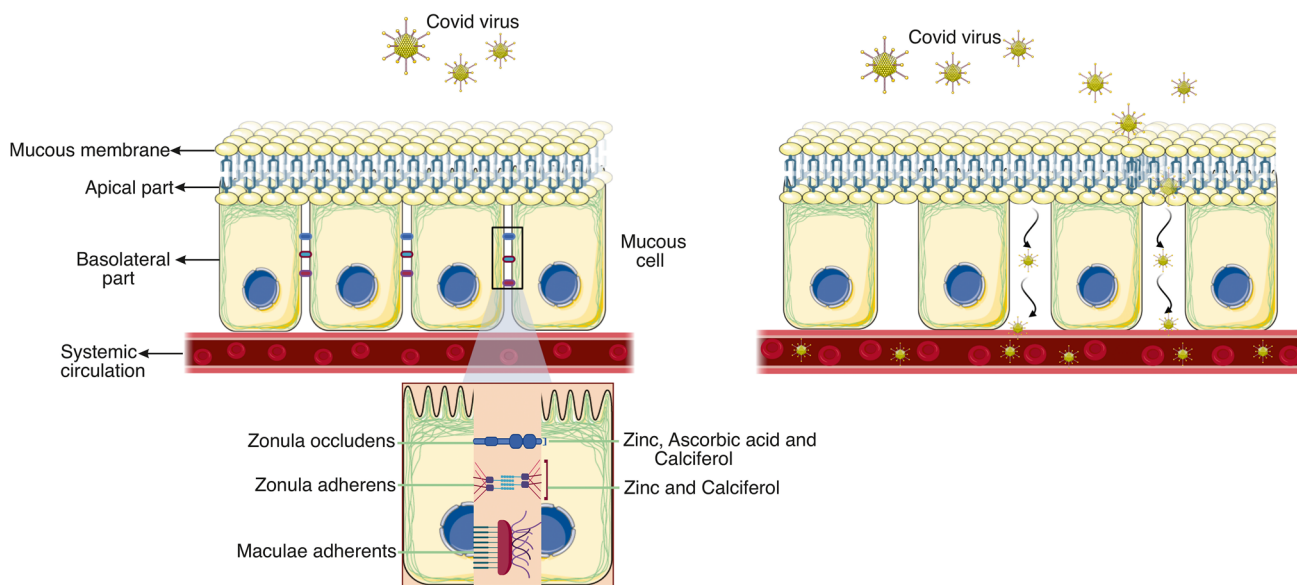


Fig. 2 Mechanistic illustration of vitamin C, vitamin D and zinc against COVID virus infection

in the respiratory tracts; thus, severity as well as mortality increases in patients with COVID-19. Also, its antiviral effects inhibit directly viral replication, have been reported in recent data, and are also effective in immunomodulatory and anti-inflammatory away (Teymoori-Rad et al. 2019). Poultry products are good sources of riboflavin, pyridoxine, and vitamin B₃ (Borenstein 1981). Unlike the riboflavin content, the thiamine content of muscles is drastically reduced when muscles are cooked (Al-Khalifa and Dawood 1993). For patients with COVID-19, an Italian research group suggested a dietary protocol that is involving vitamin D supplementation for those who are deficient (Caccialanza et al. 2020).

Various data based on clinical trials revealed its varying results on respiratory tract infections. Thirty-nine types of research (14 clinical trials, 8 case–control, 4 cross-sectional, and 13 cohort studies) indicated a significant impact of low level of vitamin D and more threat of both upper and lower respiratory tract infections from observational investigations. However, inconsistent outcomes were reported from RCTs (Jollie et al. 2013).

Twenty-five randomized controlled investigations (meta-analysis) revealed that its supplementation interconnected with low threat of acute respiratory infections ($OR = 0.88$ and $p < 0.001$). Its positive effect was even more pronounced in subjects with vitamin D deficiency at the start of intervention (Martineau et al. 2017).

Some research suggests a link between vitamin D insufficiency and liability to COVID infection and disease severity. Ilie et al. conducted a study in 20 European countries and observed a negative correlation between its mean serum levels and COVID-19 belongings and mortality rate. Rigorously, its lower level has been recognized in geriatric patients, particularly in Spain, Italy, and Switzerland (Ilie et al. 2020).

Seven retrospective investigations (1368 subjects with COVID-19) found its mean serum level of 22.9 nmol/l. Its lower serum levels were linked with subjects with poor disease forecasting in contrast to those with good results, demonstrating a standardized mean difference of -5.12 ($p = 0.012$). It was summarized that its deficiency shows an independent fundamental role in COVID-19 severity (Munshi et al. 2020).

A consequent study with an Israeli cohort of 7807 patients recognized its low level among those who confirmed positive for COVID-19 contrasted to negative. Its lower level was measured as an independent threat factor for COVID-19 ($p < 0.001$) and hospitalization ($p < 0.05$) (Merzon et al. 2020).

Vitamin E

Tocopherol (vitamin E) is an effective immune-enhancing nutrient. It protects PUFA which usually enriches immune cells from oxidation. Marine fish are known for their expression of vitamin E. Salmon and shellfish can yield about 15% of vitamin E DR Coquette et al. 1986). Chicken meat also contains vitamin E. Twelve milligrams is a DR of vitamin E according to EFSA NDA Panel (Holland et al. 1993). Fortified meat and dietary supplements with α -tocopheryl acetate can also serve as vitamin E sources; this possesses high anti-inflammatory properties. Vitamin E in muscle cell membranes helps to reduce lipid oxidation and could help prevent protein oxidation. Meats supplemented with vitamin E have a long shelf life and an improved color, flavor, and texture (EFSA NDA Panel 2015). It also plays a significant role in enhancing of immune reactions by inactivating and inhibiting free radicals (Zhang et al. 2010). Oral intake of vitamin E helps in the improvement of response by T cell and macrophage activities against infective agents and it reduces vulnerability to upper respiratory tract infections in older patients (Maggini et al. 2007; Meydani et al. 2005, 2004; Pae et al. 2012).

Vitamins C and E had been considerably authenticated to diminish lung infection in animals, and similar outcomes were obtained in geriatric patients. While, they had no advantage in children suffering from pneumonia (Murni et al. 2021).

Minerals

Selenium supplementation displays potential for COVID-19 treatment. Red meat supplies more than 20% RDI per 100 g served, although selenium levels in meat are likely to be greatly influenced by the location where animals were fed as well as the season (Williams 2007a, b). Zinc supplementation helps lower symptoms of COVID-19 such as stooling and reduces infections of the respiratory tract. The increasing risk in the development of acute infections of the respiratory tracts results due to low iron levels in the body (Guillin et al. 2019; Wu et al. 2019). Zinc, a trace element, plays a significant role in immune cell development and is known for its crucial role as a cofactor for many enzymes (Prasad 2008). An inadequate amount of zinc can lead to defective immunity resulting in increased vulnerability to pneumonia (Walker and Black 2004; Hess et al. 2009). Increasing zinc intakes help against infections with COVID-19 due to reduced replication of the virus; it also reduces gastrointestinal effects and decreases respiratory symptoms (Zheng et al. 2020).

Studies have shown that an average intake of 40 mg of zinc per day may help in controlling RNA-viruses such as coronaviruses and influenza (McCarty and DiNicolantonio

2020). Research has shown that a man's zinc status is among the vital factors determining immunity to infections with virus, stating that low intake of zinc in a population increases the risk of contracting infections such as HIV (Read et al. 2019). Best sources of iron and zinc include beef and lamb meats, with 100 g of meat providing a portion of the daily adult requirements. Heme iron, which is mainly found in meat, is well absorbed; meat protein promotes iron absorption from meat. The rate of absorption of iron from meat is higher than that from plants (heme iron); an example is the absorption of folic acid which is tenfold higher compared to vegetables (Biesalski 2005). In addition, the absorption of zinc from animal protein diet is higher than plant foods; therefore, vegetarians should increase their zinc intake by 50% higher (National Health and Medical Research Council 2006). Studies on human subjects reported that people on a low-copper diet have reduced lymphocyte proliferation and decreased IL-2 production, and copper administration reverses these effects (Hopkins and Failla 1997). Raw lean cuts from beef and veal have a copper content ranging from 0.055 to 0.190 mg per 100 g, while the copper content from 100 g of lamb and mutton ranges from 0.090 to 0.140 mg and 0.190 to 0.240 mg respectively. The consumption of 100 g meat or liver daily can yield half of the daily required micronutrients such as iron, selenium, zinc, and vitamins (Chan et al. 1995). Nutritional status maintenance is very crucial in combating COVID-19 (Williams 2007a, b).

Iron

Iron is basically found in a series of foods as heme and non-heme irons. Heme iron can be found only in the flesh of animals with its origin from hemoglobin and myoglobin, readily bioavailable and easily absorbed as an intact molecule by the intestinal lumen (Hallberg and Hulthen 2000; Simpson and McKie 2009). Heme iron can be obtained by consuming foods such as lamb, beef, and mutton. The benefit of heme iron in meat is that it is more biologically available with red meat having 72 to 87% and rabbit and pork meat having 56 to 62% (Lombardi-Boccia et al. 2002). Non-heme iron can be obtained from animal flesh when animals eat plant foods containing non-heme iron and also from fortified foods. Non-heme iron can also be obtained from the consumption of spinach, beans, breakfast fortified with cereals and lentils, and enriched breads.

Iron is the most abundant transitional metal that is present in the body. It is a crucial constituent for all alive cells since it plays a key role in metabolic processes such as energy production, transportation, and storage of oxygen, drug detoxification and synthesis, and repairing and transcription of DNA (Habib et al. 2021). It mainly bounds to macromolecules such as hemoglobin, transferrin, ferritin, and other iron-containing proteins. Unbounded iron (labile or

catalytic iron) is considered a transitional pool of extracellular and cellular iron. Moreover, iron status and nutrition are modifiable modulators of the immunologic response to SARS-Cov-2 mRNA vaccines (Gozzi-Silva et al. 2021).

It is proposed that SARS-CoV-2 may need iron for replication and other roles, offering a prospective mechanism for greater pathogenicity in the existence of high SCI. Chakurkar et al. 2021 reported the role of ferrotoxicity in COVID-19 and the concept that SCI is a sign of poor results in COVID-19. Tissue injury either from a direct cytopathic effect can result in rise in their level or inflammation or ischemia leads to a burst release of intracellular iron stores (Chakurkar et al. 2021).

Iron chelation therapy is beneficial in COVID-19 because it is well known that SARS-CoV-2 requires iron for viral replication (Liu et al. 2020). So, this therapy can be a novel approach to COVID-19 treatment. This therapy signifies a pillar in the treatment of iron overload due to a wide spectrum of diseases and multiple chelating agents are currently registered and usually employed in clinical practice (Perricone et al. 2020). Bipyridyl and desferoxamine (iron chelators) are under clinical trial for COVID-19 patients (NCT04333550) (Romeo et al. 2001).

Banchini et al. suggested that iron helps in exploring both endogenous (insulin, heparin, and erythropoietin) and exogenous options (vitamins D and C, tocilizumab, carvedilol), relating to hepcidin control in the setting of COVID-19 (Banchini et al. 2020). Abbas et al. also suggested the use of iron chelators to reduce disease severity in COVID-19 infection (Abbas and Mostafa 2020).

Zinc

Zinc is an essential nutrient that must continuously be added to diets since it cannot be synthesized and stored in the body (Maggini et al. 2010). The lack of zinc, even in a low grade, leads to acquired and innate immune system disorder (Shankar and Prasad 1998). Zinc supplementation is effective and cost-effective intervention method used to treat and prevent respiratory tract infections and diarrhea, especially in children living in poor areas (Baqui et al. 2003; Brooks et al. 2005). Apart from iron, beef, and lamb meat, pork meat can also be considered a rich dietary zinc source (Wyness et al. 2011). A total of 100 g of beef meat can yield 26% of zinc.

Zinc is considered to fortify the body's antiviral machinery and its ions (Zn^{2+}) play significant roles in the growth, replication, differentiation, and immune cell functions. Physical processes such as virus binding, infection, and uncoating, as well as inhibition of polymerase enzymatic processes and viral protease, connote the antiviral properties of Zn against different viruses (Overbeck et al. 2008; Haddad et al. 1999). Phytates make zinc from plant sources

less bioavailable than animal sources like meat (Mocchegiani et al. 2000). Zinc deficiency in old people is associated with age-related immune response dysregulation (Prasad et al. 1993). Its supplementation in diets has been reported to improve immunity in old people (Mocchegiani et al. 1999). Its deficiency in the elderly is considered a risk factor resulting in susceptibility to infection. Zinc supplementation plays a crucial role in the prevention of infectious diseases (Kajachumpol et al. 1995).

At lower concentrations, a combination of zinc ions (Zn^{2+}) and zinc ionophores prevents replication of SARS-CoV, via inhibiting elongation of RdRP and reducing binding of RNA template. Resemblances among RdRP of SARS-CoV and SARS-CoV-2 may be responsible for inhibition of replication of SARS-CoV-2 in cell culture. According to one hypothesis, oral or i/v administration of zinc ascorbate could be beneficial in prevention and ailment of COVID-19, because of the higher intracellular Zn^{2+} concentration that inhibits SARS-CoV-2 replication (Lee et al. 2009).

Various clinical trials are presently ongoing for analyzing the effect of zinc in different forms for COVID-19 (Cingolani 2021).

Forty-eight subjects (randomized double-blind study) suffering from cold got zinc acetate lozenges (80 mg/day) or placebo within 24 h once the symptoms begin. In contrast to placebo, there was a significant short in cold symptoms and total severity score of all symptoms (p value < 0.002) in zinc supplementation (Prasad et al. 2000).

Four patients suffering from COVID-19 received a high dose of zinc (207 mg/day) orally that resulted in better oxygenation and fast resolution of quickness of inhalation later after 1 day of ailment (Yao et al. 2020).

Sometimes, zinc has been recommended for improving common cold symptoms. A total of 100 subjects (randomized, double-blind, placebo-controlled study) with common cold received 13.3 mg zinc. In contrast to placebo, it considerably declined period of symptoms of common cold, from 7.6 to 4.4 days. In the case study, it was observed that the combination of azithromycin (500) + naproxen (500) + vitamin C (1000) + zinc + vitamin D₃ (1000) resulted in significant outcomes in course of COVID-19 treatment (Khodavirdipour 2021).

Selenium

Selenium plays a role in the regulation of several physiological functions and is also an integral part of selenoproteins; they form part of the body's antioxidant defense system (e.g., glutathione peroxidase). The recommended intake of selenium for females and male adults is 60 and 70 μ g per day in the UK and 55 and 70 μ g per day in the USA respectively (Reilly 1998). This requirement often cannot be achieved

because the selenium concentration in foods is different for different regions and countries.

Among red meats, lamb and beef meats have high selenium levels, followed by mutton and veal. Among white meats, reasonable selenium level is found in chicken (Bou et al. 2005). Low selenium level in the body leads to decrease in immune system function, cognitive decline, and mortality. Antiviral effects were observed under the higher intake of selenium or supplementation (Rayman 2012). Studies have shown an increase in selenium levels of beef from animals given dietary supplementation of selenium (Juniper et al. 2008; Dokoupilová et al. 2007). Seafood is also a good dietary source of selenium; they ranked 17th according to selenium level by the USDA National Nutrient Database (Ralston 2008). Selenium obtained from fish is bioavailable and higher in amount than yeast (Fox et al. 2004).

Copper

Copper (Cu) is crucial at ensuring strong immunity; it plays a vital role in the normal functioning of helper T cells, neutrophils, natural killer cells, macrophages, and B cells that help in the destruction of infectious microorganisms and production of specific antibodies and cell-mediated immunity. The lack of copper in humans causes white blood cells to decrease, immune reactions, and abnormalities in bone and connective tissue (Percival 1998). Cu^{2+} also plays a crucial role by its active participation in immune cell growth and differentiation (Li et al. 2019). Cu^{2+} is found in foods such as crustaceans, mollusks, fish, and land meats; its deficiency affects innate and adaptive immunity (Munoz et al. 2007). Its supplementation helps in restoring the secretion and activity of Inter-leukin-2, which is very helpful for cytotoxicity of NK cell and T helper cell proliferation. A recent study reported the sensitivity of new coronavirus strains (SARS-CoV-2) to a copper surface (Van Doremalen et al. 2020). Other studies have revealed blockage of papain-like protease-2 by Cu^{2+} , a protein required for replication by SARS-CoV-1; therefore, the need for high demand of copper supplementation is essential (Baez-Santos et al. 2015; Han et al. 2005). Due to the high competition in the absorption of Cu and Zn in the jejunum through metallothionein, high doses of zinc (greater than 150 mg per day) can lead to deficiency of Cu in healthy individuals. Therefore, it is possible that people taking Zn supplement regularly could be susceptible to contacting SARS-CoV-2.

Low Cu^{2+} levels can lead to stress responses by pathogens; hence, an optimal Cu^{2+} level is required. Presently, there is limited understanding of the effect of medicinal use of Cu^{2+} as related to COVID-19. The intake of Cu affects the immune function of a host as well as micronutrients metabolism which helps prevent virulence. Hence, Cu^{2+} intake is beneficial in patients with COVID-19 (Rahaa et al. 2020).

Magnesium

Magnesium plays a pivotal role in immune system function regulation by strongly affecting immunoglobulin production, immunoglobulin M (IgM) lymphocyte binding, immune cell adhesion, T helper-B cell adherence, antibody-dependent cytotoxicity, and response of macrophages to lymphokines (Liang et al. 2012). Its role in an immune response against viral infections has been reported (Chaigne-Delalande et al. 2013). Magnesium plays a key role both in physiology and pathology. Newly, it has been hypothesized that its low level may favor the transition from mild to critical clinical manifestations of COVID-19. Decreased NK and T-cell cytotoxicity because of magnesium deficiency may illuminate the vulnerability of elder, hypertensive, obese, and diabetic patients to SARS-CoV-2 infection (Faa et al. 2021). Furthermore, its deficiency upregulates pro-inflammatory cytokine creation in monocytes and raises NFκB expression (Fanni et al. 2020).

Despite the nonexistence of controlled trials, magnesium supplementation for supportive treatment in COVID-19-suffering patients should be encouraged. This may be valuable in all phases of the COVID-19. It is very well known that magnesium is involved in over 600 enzymatic reactions in human cells. Its level may explain an increased risk of severe COVID-19 (Fanni et al. 2020).

A combined oral treatment of older COVID-19 patients with magnesium, vitamin D, and vitamin B₁₂ reduced the percentage of patients needing oxygen and ICU support (Tan et al. 2020a, b).

An observational cohort study was executed for evaluating the combined effect of vitamin D, magnesium, and vitamin B₁₂ in older subjects (≥ 50 years) with COVID-19. Eighteen subjects received DMB already onset of primary outcome and 26 subjects did not. Fewer treated subjects than controls needed beginning of oxygen therapy amid hospitalization (17.6 vs 61.5%, $p=0.006$) (Tan et al. 2020a, b).

Conclusion

It is well established that diet influences immune levels, and poor diet is the most rampant culprit in cases of weakened immunity worldwide. Nutritional status can greatly impact a person's total well-being, decrease non-communicable diseases, and reduce vulnerability to growing infections. The immune system protects the body from pathogenic organisms such as SARS-COV-2 by its surveillance activities. Its activity is affected when individuals become infected with microorganisms that cause diseases, leading to an increased rate of metabolism that demands substrates, molecules, and energy sources such as micronutrients (folic acid, Zn, Mg, Mn, Se, Fe, Cu, B-vitamins, vitamin E, vitamin D, vitamin

C) and macronutrients (carbohydrates, fats, and proteins) that can only be derived from dietary sources by the consumption of foods. The lack of any of these important micronutrients could cause an altered immune response. These nutrients provide the immune system with vital supporting roles in its fight against pathogens and thereby reducing the risk associated with infections. Prior to admission, COVID-19 patients should be checked for nutrient deficiencies using standard screening tools to determine effective treatment and dietary regimens.

A series of studies was found to have demonstrated the enhancing potentials of macronutrients (carbohydrates, proteins, and fats) and micronutrients (vitamins, copper, zinc, iron, calcium, magnesium, and selenium) in supporting the immune system's fight against respiratory infections. Each of these nutrients performs a vital role as an antiviral defense in COVID-19 patients. As the exploration for the effective cure for COVID-19 continues, particular micro- and macro nutrients may effect the severity of infection, symptoms, and outcomes related to the diseases.

Abbreviations ARDS: Acute respiratory distress syndrome; COVID-19: Coronavirus disease 2019; Cu: Copper; DR: Daily requirement; Fe: Iron; ICU: Intensive care unit; Mg: Magnesium; Mn: Manganese; PUFA: Polyunsaturated fatty acids; Se: Selenium; SPMs: Specialized pro-resolving mediators; Treg: Regulatory T cells; Zn: Zinc

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Data availability The data sets in this study are available from the corresponding author on reasonable request.

Declarations

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