

SUPPORTIVE THERAPY: AN OPTION TO ENHANCE HOST IMMUNITY AGAINST COVID-19

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ABSTRACT

The threat posed by COVID 19 outbreak, which is considered to be a global pandemic, is immeasurably affecting all the communities worldwide. COVID-19 is a zoonotic disease, which can affect birds, humans and, other animals. The emergence of this pandemic has been creating a tragic situation worldwide by affecting more people through human-human transmission. The burden (both healthwise and economic) placed by the disease is so huge that any measures to improve the current situation, to fasten up the recovery of already affected patients and, to reduce the risk of death and health deterioration should be considered. Vaccination, being the hope in the scenario, helps in preventing the condition to an extent, but in the absence of availability of a proper drug regimen to fight off COVID 19, the requirement of the need to find a system to control the severity of the infection is a necessity. Nutritional supplementation helps in boosting up the immune system especially, vitamins like vitamin C, Vitamin D, Zinc, Omega 3 fatty acids, etc. They also exhibit established immunomodulatory, antiviral as well as anti-inflammatory effects. Pieces of evidence have also highlighted the importance of supportive therapy using nutrient supplements in covid patients as it helps in prominent decreasing of SARS CoV2 load of the virus and also significantly reduces the hospitalization period. Hence the nutritional levels of each of the infected person must be assessed before initiating the anti-viral therapy. The search criteria used were PubMed, Medscape, google scholar, etc. The keywords used to search were COVID 19 Supportive therapy, Vitamin D, Vitamin C, Nutrient supplementation, Host immunity, etc. The range of years is between 1978 and 2021.

Keywords: COVID 19 supportive therapy, Vitamin D, Vitamin C, Nutrient supplementation, Host immunity

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INTRODUCTION

Towards the end of 2019, the novel coronavirus was identified as 2019-nCoV at Wuhan, China, and WHO named it Corona Viral Infectious Disease 2019 or COVID-19. This is the third coronavirus outbreak that we have been witnessing. The first two were Severe Acute Respiratory Syndrome Corona Virus (SARS-CoV) in 2002 and Middle East Respiratory Syndrome (MERS-CoV) in 2012 [1]. Coronavirus came up in 2003 in China was an epidemic that consequently resulted in SARS and subsequently, in 2012 in Saudi Arabia, it led to Middle East Respiratory Syndrome (MERS). While comparing the current pandemic with the SARS-CoV in 2002, the present SARS CoV-2 is highly pestilent as well as virulent and affected the whole world [2]. Interpersonal transmission of SARS-CoV-2 take place mainly through droplet infection developed as a result of coughing, sneezing, etc. and this is highly comparable with the outspread of influenza. Transmission can, *yet al.* so occur when a person is purulent with or without the sign of infection is near a normal person [3].

Structure of COVID-19 virus

These viruses are usually spherical or pleomorphic [4, 5]. The rounded envelope of the virion consists of Membrane glycoprotein, small envelope glycoprotein, and protruding crown-like spike glycoproteins. The name corona (means 'crown' in Latin) was obtained from these spike glycoproteins and it will help to ease the entry of the virus into the host cell. Membrane and small envelope proteins mediate the viral assembly and as well as maintain the structural shape of the envelope. Some coronaviruses also encode for another type of glycoproteins called haemagglutinin-acetyltransferase glycol proteins on their envelope [6]. Inside, it has a large genome with positive-stranded Ribo Nucleic Acid (RNA) covered by helical capsids made up of nucleocapsid phosphoproteins; together they form the ribonucleoprotein core. Other than virus entry, the spike proteins play a critical role in determining the viral host range and tissue tropism and are also involved in mediating the host immune response. These spike proteins are clove like structures made up of two subunits S1 and S2. S1 is the head of the spike and is involved in binding to the receptor present on the host cell surface for viral attachment and S2

which forms the stem of the spike and is responsible for the fusing of virus membrane with host cell membrane followed by injecting the viral genome into the host cells. Species-specific interactions between these glycoproteins are facilitating the localization of viral assembly at the intermediate compartment between the endoplasmic reticulum and Golgi apparatus [7, 8].

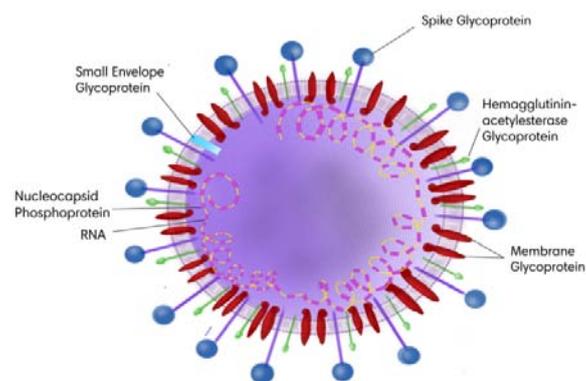


Fig. 1: Structure of COVID-19 viruses [9]

Mode of transmission

The virus can spread mainly via droplets released when the infected person cough or sneezes. The major problem is that these droplets can travel at a distance of 1-2 meters and they may get deposited on different surfaces. Anyone who inhales the droplets or touching the surface which contains these droplets, and then touching the eyes, nose, and mouth afterward may get infected. This virus can survive for several hours on the surfaces unless it is destroyed immediately by disinfectants such as sodium hypochlorite, hydrogen peroxide, etc. [10]. Both symptomatic and asymptomatic patients can transmit the disease to other people. Studies have shown that the viral loads for both asymptomatic and symptomatic patients are the same [11].

Based on some scientific evidence, on 9th July 2020 WHO has announced that COVID-19 maybe get transmitted through the air. It may usually happen in the case of specific settings or circumstances where aerosols are generated from the supportive treatment. However, the latest data reveals that the virus also has the potential to spread through the air, fomite, fecal-oral, blood, mother to child, and animal to human. Still WHO continues to recommend precautions for airborne transmission since it is a major source of transmission [12].

Pathophysiology

The virus will enter into the host cell through endocytosis and the process is mediated by the spike glycoproteins. Then it will undergo membrane fusion with the help of membrane glycoproteins. After uncoating, the virion will release its RNA. Once it is released, it will go to the nucleus and undergo replication, followed by transcription and translation for the biosynthesis of viral proteins. Afterward, the viral assembly will occur at the endoplasmic reticulum Golgi intermediate compartment. Finally, the new virions are made and released [13]. Coming to the pathophysiology, the SARS-CoV has a good affinity for Angiotensin Converting Enzyme-2 (ACE2) receptors, and some studies have shown that SARS-CoV-2 (nCoV-19) also binds to the same [14, 15]. ACE2 receptors are distributed in the lungs, kidney, heart, ileum, and bladder. But it is more expressed in lung epithelium [16]. The person who got infected with SARS-CoV-2 shows a wide range of symptoms from a mild cold to severe respiratory failure with multiple organ impairments. Innate immunity of the lungs is regulated by the epithelial cells, alveolar macrophages, and dendritic cells. Lung injury observed in many patients with SARS-CoV-2 can be matched with the binding of SARS-CoV-2 with the ACE2 receptors located in the lungs [17]. Occupying these receptors by the spikes of the virus results in ACE2 downregulation, which will further amplify the production of angiotensin due to the decreased conversion of angiotensin to vascular heptapeptide angiotensin 1-7 and can cause lung injury later [18]. Based on the reports from the immunological studies, the infected person with SARS-CoV-2 shows a remarkable reduction in the lymphocyte, especially in peripheral T cells. In the case of patients with severe Novel Coronavirus Pneumonia (NCP), their T cell count will become half of the lower limit of the normal range. Likewise, this irregular expression of T cell-associated mRNA can initiate Venous Thromboembolism (VTE). Thus, elder patients with the same disease were more possible to have poor immunity and which make them more prone to develop VTE. This viral infection can also cause the release of inflammatory cytokines such as Interleukin (IL)-6, IL-8, TNF-alpha, etc. [19, 20]. Production of inflammatory cytokines in patients with severe NCP can also boost the development of VTE and this irregular blood clotting and thrombosis in turn results in a poor prognosis of the disease [21]. Infected people can also develop an acute myocardial injury. Blood Pressure and cardiac biomarkers levels will be high for patients admitted to the Intensive Care Units (ICU) than other patients. It might be related to the ACE2 receptors present in the heart. This myocardial injury can also result from the release of different inflammatory cytokines, respiratory depression, and decreased levels of oxygen in the blood due to SARS-CoV-2. COVID-19 patients with severe cardiovascular disease may result in an adverse prognosis [22]. The presence of ACE2 receptors in the stratified epithelium of the upper esophagus and enterocytes of the ileum

might be the reasons behind the early gastrointestinal symptoms like diarrhea, nausea, vomiting, etc during COVID-19 infection [23]. The detailed pathogenesis of the coronavirus is as shown in fig. 2.

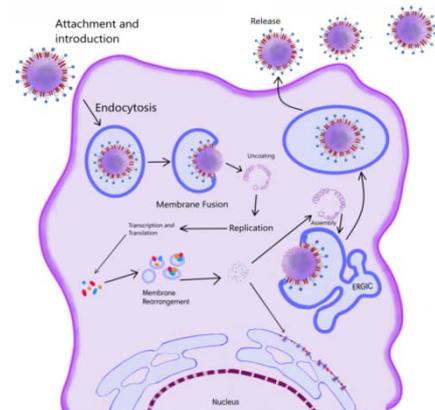


Fig. 2: Pathogenesis of SARS CoV2 infection [24]

Epidemiology

nCoV-19 has emerged in Wuhan, China, towards the end of December 2019. The geriatric population having an age group above 65 y and the children below 8 y were more prone to get infected. The increased death rate was also found in the case of older people, and the major reasons were multiple organ failures like respiratory failure, shock, and acute respiratory distress symptoms due to SARS-CoV-2. A study conducted in two hospitals of Wuhan has taken the risk factors like older age, higher Sequential Organ Failure Assessment (SOFA) score, and the d-dimer value above 1mcg/ml at the time of admission as part of the multivariable analysis. Cardiovascular disease, hypertension, and diabetes are considered for univariable analysis. From China, the disease has been spreading all over the world. According to the WHO statistics at the beginning of July 2021 more than 18.3 crore cases were reported worldwide, among them, nearly 2.95 crores were confirmed in India.

Clinical features

Persons who do not exhibit any symptoms and no variations in the radiographic images like Computed Tomography (CT) scans even though he/she is tested positive for the nucleic acid of nCoV-19 by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) is referred to as asymptomatic infections. Due to the absence of clinical symptoms and the lack of awareness, most asymptomatic people might not seek any medical support which can lead to quick transmission of the disease. People who have been infected with nCoV-19 show a wide variety of symptoms ranging from mild fever to severe illness like respiratory failure. These symptoms may develop after 2-14 d of exposure. The severity of COVID-19 mainly depends upon various factors like age, body condition, and immune response of the patient and it can vary from person to person. The major symptoms of the coronavirus are categorized into four types, namely, mild, moderate, severe, and critical cases as shown in table 1.

Table 1: Symptoms associated with SARS CoV 2 infection

Stages	Characteristics	References
Mild	<ul style="list-style-type: none"> • Fever/chills • Cough, Loss of appetite • Malaise • Fatigue • Sore throat 	[25]
Moderate	<ul style="list-style-type: none"> • Mild to moderate symptoms • Chest images may show mild pneumonia 	[26]
Severe	<ul style="list-style-type: none"> • Suspected respiratory infection symptoms with either shortness of breath or decreased respiratory rate • Significant lesions can be seen in chest images 	[27]
Critical stage	<ul style="list-style-type: none"> • Severe respiratory illness like ARDS, shock, etc. along with multiple organ impairment (requires mechanical ventilation) 	[28]

Diagnosis, treatment, and prevention

The extensive method used for the diagnosis of COVID-19 is RT-PCR (Reverse Transcriptase-Polymerase Chain Reaction). It involves the detection of SARS-Cov-2 RNA from the samples collected from the nasopharynx [29]. The mechanism behind the test is the reverse transcription of the viral RNA to the complementary Deoxyribo Nucleic Acid (cDNA), and afterward, the amplification of few sections of the cDNA [30]. The test sensitivity depends on the time of testing respective to the virus exposure. Sometimes the test can give false-negative results, and it may be due to inadequate sample, specimen used for the sample collection, and the time of testing after exposure [31]. Mutations in the viral genome, sample collection technique, and samples with low viral load (mostly seen in the case of asymptomatic or people with mild signs and symptoms) can also result in false-negative results. The samples collected from the lower respiratory tract like bronchoalveolar fluid, are more sensitive than the samples collected from the upper respiratory tract (e. g.: oropharyngeal swabs). Other specimens are sputum, nasopharyngeal and nasal swabs. The presence of viral genetic material in the sample taken from the respiratory tract cannot be used to confirm the viability of the virus; hence RT-PCR is not that much efficient to predict if the person with the viral genetic material (RT-PCR positive) can transmit the virus to others. Saliva can also be employed as a specimen, only after validation due to its lower sensitivity. The presence of the virus has also been detected in feces in certain cases but it is rare [32]. There are different types of serological tests to detect the humoral response to the SARS-CoV-2. Enzyme-Linked ImmunoSorbent Assay and chemical luminescence immunoassays (CLIA) are used to detect the antibodies of IgA, IgM, and IgG isotypes specific to different viral proteins in which the latter one has the highest sensitivity. The technique used for testing, immunity of the patient, tenure of symptoms, and antibody specificity are the factors that determine the sensitivity and specificity of the serological tests. The support laboratory tests like elevation in CRP, thrombocytopenia, high procalcitonin levels, etc., and abnormalities in imaging tests like chest x-rays and CT scans may show features of COVID-19, but they lack specificity when compared to other tests [33]. Treatment methods available for COVID-19 are antiviral therapy using remdesivir, ritonavir, danoprevir, favipiravir, and nefamostat, etc [34, 35]. Antimalarial drugs like chloroquine or hydroxychloroquine along with the antibacterial drug azithromycin, can decrease the severity of symptoms. Interferons, monoclonal antibodies, and anti-inflammatory drugs such as steroids can also be included in the treatment of COVID-19 [36]. Patients with mild to moderate symptoms only need supportive therapy to maintain the homeostasis and fluid-electrolyte balance etc. Mechanical ventilation and extracorporeal membrane oxygenation are used in the case of patients with serious symptoms to improve the condition [37]. The available preventive measures are proper hand washing, maintaining social distance, double masking, and vaccination. As of 2021 February, about seven vaccines have been enrolled in various countries and about 200 vaccine candidates are in the process of development. Vaccines are crucial tools in fighting against COVID 19. Safe and effective vaccines may change the situation; however, in the foreseeable future, should continue to wear masks, follow physical-social distancing, and must avoid crowds.

Supporting the antiviral therapy in covid patients with supplemental nutrient supply has highlighted advantages. COVID 19 high-risk category patients have been noticed with significant dietary deficiency of nutrient supplements [38]. It is also noted that elderly people are more liable to be nutrient lacking and immunosenescent, thereby more likely experiencing the risks of COVID 19 [39]. Therefore ensuring the adequacy of nutrients is equally important. The immunomodulatory as well as antioxidant properties of these nutrients like vitamin C, vitamin D, zinc, etc. helps in a prominent reduction in the viral load [40].

The supportive role of nutrient supplementation in immune-boosting

Once entered into the human system, the SARS CoV 2 virus initially binds to the epithelial cells of the alveoli, thereby activating the

immune systems (innate as well as adaptive). The resulting cytokine release syndrome impairs the immune response of the host system and causes acute respiratory distress syndrome [41]. The condition is mainly relevant in the elderly group of people who are more prone to developing cytokine storms. The major inflammatory markers that are highly elevated in covid patients are interleukin 6 (associated with high mortality rates), interleukin 2, IL 7, tumor necrotic factor (TNF), etc., which can aggravate inflammation [42]. SARS, as well as MERS, are also associated with the over-activation of cytotoxic T cells, irregularities in histocompatibility complex 2, and thereby prominent decline in natural killer cells, T lymphocytes, B lymphocytes, etc. [43, 44]. The prominent nutrients that can offer immune-boosting effects include vitamins like vitamin A, vitamin B, vitamin C, vitamin D, and other nutrients like zinc, selenium, magnesium, omega 3 fatty acids, etc.

Vitamin A

Vitamin A is found to be the first recognized fat-soluble vitamin. It is essential for maintaining healthy vision, cellular growth and also plays a major role in enhancing the body's natural defense mechanism; hence it is called an anti-infective vitamin. Retinoic acid, retinol, and retinal are the three active versions of vitamin A. Immune responses are primarily dependent on the availability of essential nutrients in the body. Pieces of evidence suggest that supplementation of vitamin A is associated with a reduction in morbidity and mortality in case of certain diseases like malaria, measles, Human Immunodeficiency Virus (HIV) infection, etc. [45]. A Diet low in vitamin A can render calves more susceptible to infections because the deficiency has resulted in reduced effectiveness of the bovine coronavirus vaccine [46]. Among children below the age of five, one of the leading reasons for mortality includes lower respiratory tract infections like bronchiolitis, pneumonia, etc. [47]. The majority of these deaths are due to malnutrition, poverty, and lack of resources. Vitamin A, otherwise retinol is engaged in the manufacture, development, and differentiation of cells in the lymph node, red blood cells, antibodies, as well as maintaining the integrity of epithelial cells. Due to the proven potency in safeguarding against measles-associated pneumonia [48], vitamin A supplementation has been examined as an accomplishable intervention in decreasing the severity as well as prevention against further episodes of acute lower respiratory tract infections [49-53]. In children with sufficient stores of vitamin A, an increased dose of vitamin A supplementation may result in transient malfunction in the regulation of immunomodulatory functions. This may further lead to a raised susceptibility to infectious diseases [54]. A study involving a systematic review about the function of vitamin A supplementation in the interference of respiratory tract infections among children have terminated their result as that supplements must only be provided to children having impaired nutritional status [55]. The mechanism by which vitamin A controls replication of measles is by upregulation of innate immune response in non-infected bystander cells and devising them unresponsive to fertile infection during later rounds of viral replication [56]. Hence vitamin A can be considered as a promising supportive option for the management of novel coronavirus and thereby hindering lung infection [57].

Vitamin B

B vitamins are water-soluble and each of the B vitamins has specific functions. Vitamin B1 or thiamine is involved in glucose metabolism and is essential for the proper functioning of the nerve, heart, etc. B vitamins are involved in a wide range of functions, including activating innate adaptive immune responses, maintaining the integrity of endothelial cell layers, preventing hypercoagulation, enhancing respiratory functions as well as reducing proinflammatory cytokines [58]. The various B vitamins involved in immune-boosting effects include vitamin B1 (thiamine), vitamin B2 (riboflavin), vitamin B3 (nicotinamide), vitamin B5 (pantothenic acid), vitamin B6 (pyridoxal-5-phosphate and pyridoxine), vitamin B9 (folic acid), and vitamin B 12 (cyanocobalamin) [59].

Vitamin C

Otherwise called ascorbic acid, Vitamin C is also a water-soluble vitamin. Being soluble in water requires daily intake. It is also a

relevant cofactor that plays a main role in cartilage and blood vessel formation. Vitamin C also has antioxidant properties which enable the protection of cells from the damage caused by free radicals. It also inhibits reactive oxygen species and helps in the cytokinin remodeling as well as safeguarding the essential biomolecules like lipids, proteins, etc. from oxidative damages [60]. Large doses of Vitamin C play a major role in wound healing and in enhancing immunity by aiding in the production and maturation of natural killer cells and T lymphocytes, engaged in antiviral responding. The daily recommended dose of vitamin C is 90 mg for adult males and 75 mg for adult females. Smokers require an additional dose of 35 mg daily [61]. A study in the culture of a tracheal organ of the chick embryo has shown increased resistance to the infection of the avian coronavirus after getting administered with vitamin C [62]. The regular use of vitamin C has been shown to reduce the duration of a common cold. Under certain circumstances, vitamin C prevents susceptibility to lower respiratory tract infections also [63]. Vitamin C sometimes also functions as a weak antihistaminic agent and decreases the signs and symptoms related to flu-like sinus swelling, running nose, etc. and these antiviral properties of vitamin C have paved the way for its use in fighting COVID 19 [64]. COVID 19 associated pneumonia has a higher rate of morbidity and mortality

[65]. Vitamin C is mainly effective in fighting Acute Respiratory Distress Syndrome associated with COVID 19. The antioxidant properties of vitamin C are effective in reducing oxidative stress. About 1.5 mg/kg vitamin C has been considered safe and was in use for decades. It is also reported that the use of vitamin C has significantly reduced the length of stay in the intensive care unit in novel coronavirus detected patients [66]. Also, the administration of 1.5 g vitamin C intravenously every 6 h showed a statistically significant reduction by about 30 percentages in the mortality rate of acute respiratory disease syndrome in patients with the condition of sepsis [67]. A clinical trial started in china is now in phase two to identify the effect of high dose vitamin C in ICU patients having covid associated severe pneumonia. About 2-10 g vitamin C per day IV infusion over 8-10 h was given to about 50 moderate to severe covid 19 infected patients in China and it was found that there was a relevant improvement in oxygen index in all the patients and all the patients significantly improved and got discharged [68]. The levels of vitamin C in the body of corona virus-infected patients significantly drop once sepsis develops. Hence it is so important to maintain vitamin C levels in the patient's body [69]. Vitamin C has proven viricidal, immunomodulatory as well as antioxidant properties as summarized in table 2.

Table 2: Properties of vitamin C

Immunomodulatory effects	Enhance proliferation, maturation, and differentiation of T lymphocytes Anti-apoptotic activity on peripheral blood neutrophils Raised immunoglobulin production Enhance the integrity of barriers of epithelial cells, which is the preliminary step in defencing outside pathogens Accumulate in neutrophils and enabling normal leukocyte functioning Improve the activity of phagocytes, natural killer cells, and chemotaxis of neutrophils	[70-73]
Anti Inflammatory effect	Decrease cytokine storm	[74]
Effect in critically ill patients	Reduce the length of mechanical ventilation Reduce hospital and ICU stay Vasopressin requirements are reduced [69]	[75]

Vitamin D

Vitamin D is a prohormone and is generated in the skin on exposure to sunlight, ultraviolet B (UVB) rays of 290-315 nanometer. Also, a small quantity is obtained via food. In the case of people in areas lying in middle to high latitude, there will be an elevation in solar light during the winter season and hence sufficient production of vitamin D is not possible due to the lack of UV B rays [76]. There is a huge global prevalence of lack of vitamin D levels among various populations and for most people, dietary supplementation may not be sufficient to provide adequate vitamin D levels [77]. Vitamin D plays a major role in preventing inflammatory responses in the pulmonary system and also enhances the innate defense pathways against the pathogens present in the respiratory system [78, 79]. There are reports that in a cross-sectional study conducted among the US population, there is evidence of an association between lower levels of vitamin D and the occurrence of upper respiratory tract infections. The relation was more profound in the case of diseases like chronic obstructive pulmonary disease and asthma [80]. Also, there was evident relation between lower vitamin D levels and the development of acute respiratory tract infection [81]. The alarming spread of COVID 19 disease caused by the novel SARS CoV 2 virus has raised the need to administer vitamin D supplements as a supporting therapy [82]. The use of vitamin D as a nutritional supplement in COVID 19 disease is based on presumed mechanisms. The first one is the use of Calcitriol, which is an active vitamin D hormone, has been highlighted in potentially treating avian influenza virus, (AVH5N1 virus) using accurate cell lines and mice upon screening certain repurposed drugs [83]. The second mechanism is based on the analysis made to relate vitamin D and viral infection [84]. Adaptive, natural cellular immunity and physical barrier mechanisms offered by vitamin D contribute to decreasing microbial-induced infections and death [85]. By taking into consideration, the facts that this covid outbreak occurred in the Winter season, the time when vitamin D levels are low, and that the deficiency can contribute to acute respiratory distress syndrome, which is related to the deficiency

of 1,25(OH)2D concentration. Hence it is sensible to hypothesize that the use of vitamin D may enhance the immune responses in the host on the major organ systems [86].

Zinc

Zinc is an essential micronutrient and plays a major role in cellular metabolism, growth, synthesis of DNA. It is also involved in the formation, maintenance, and maturation of immune cells associated with innate as well as adaptive immunity. Deficiency in levels of zinc has been associated with the dysfunction of both humoral mediated and cell-mediated immunity [87]. Therefore zinc can be provided in combination with other nutrients as supplements in covid 19 infected patients. There are reports that zinc supplementation can importantly reduce the morbidity and mortality associated with lower respiratory tract infections. A lower concentration combination of zinc and pyridine (zinc ionophore) can prevent SARS COV replication and hence can provide symptomatic relief in covid infected patients [88]. Studies have also shown that supplementation of zinc may reduce covid symptoms like respiratory tract infection and it might be due to blocking of uncoating, binding, and replication process of the virus. A case series involving 4 covid 19 positive patients who were provided with zinc supplementation in high doses had shown symptomatic improvement [89].

Selenium

Selenium, an essential trace element, can also be given as a general supportive treatment in fighting COVID 19. When the host is having an infectious disease, selenium deficiency can have an impact on both the host immune system as well as the pathogenic virus [90]. There are reports that the oxidative stress developed as a result of selenium deficiency can cause genomic changes in the virus and may sometimes result in a highly virulent virus in place of a normal mild or benign disease-causing virus [91]. RNA virus benign variants can also undergo fast mutations to highly virulent viruses [92]. Selenium and vitamin E combinations can be used to prevent the formation of

free radicals and can thus reduce oxidative stress in cells and tissues. Selenium and saponins of ginseng stem leaf were found to have synergistic effects to generate immune responses to a live vaccine of

bronchitis corona in chicken [93]. Various ongoing clinical trials aimed at demonstrating the protective role of vitamin C, vitamin D, zinc, and selenium are summarised in table 3.

Table 3: Ongoing clinical trials to demonstrate the protective role of vitamin C, vitamin D, zinc, and selenium

Clinical trial number	Started date	Sponsor	Study participants	Study design	Intervention	Primary outcome	Ref
NCT04335084	Jun 2020	USA	Age 18 y and older male/female healthy volunteers	The randomized, interventional, double-blind study focuses on medical workers who are at elevated risk of COVID-19	Drug Hydroxychloroquine (Plaquenil) with dietary supplements such as Vit C, Vit D, and Zinc for the prophylactic treatment of COVID-19	Prevention of COVID-19	[94]
NCT04334512	Jun 2020	USA	18 y and older with COVID-19	Randomized, double-blind, placebo-controlled phase 2 interventional study	Quintuple therapy with Hydroxychloroquine (Plaquenil) and drug azithromycin with dietary supplements such as Vit C, Vit D, and Zinc	Rate of recovery of mild to moderate patients	[95]
NCT04344041	Apr 2020	France	Age 65 y and older with COVID-19	Randomized, controlled open-label, parallel study	Vit D 400,000 IU in a single oral dose	Number of death of any cause	[96]
NCT04449718	Jun 2020	University of Sao Paulo Brazil	240 subjects Age: 18 y and older with the diagnosis of flu syndrome	A randomized, double-blind, placebo-controlled study	200,000 IU of vitamin D3 on admission	There is no significant reduction in the length of hospitalization in patients who received a single high dose of vitamin D3	[97]
NCT04682574	Nov 2020	University of Lahore, Pakistan	Critically ill patients admitted to ICU	A randomized, parallel, open-label study	Vit C 30g per day(10g TDS) for 2 d	The partial pressure of oxygen in arterial blood to the fraction of inspired oxygen	[98]
NCT04357782	Apr 2020	Hunter Holmes McGuire Veteran Affairs medical center USA	20 participants: age 18 to 99 y, hospitalized with COVID-19	Non-randomized, open-label. Parallel study	L-ascorbic acid 50 mg/kg infusion given every 6 to 4 h for 4 d	Incidence of adverse events	[99]
NCT04636086	Nov 2020	University of Liege China	Male and female 18 y and older with COVID-19	A randomized, double-blind, controlled study	One ampoule (25,000 IU/ml)cholecalciferol given on day1,2,3,4,8,15,22,29 and 36	Length of hospital stay	[100]
NCT04459247	Jun 2020	PG Institute of Medical Education and Research, India	Asymptomatic or mildly symptomatic SARS-CoV-2 RNA positive with Vit D deficiency	The randomized, placebo-controlled short term study	60000 IU cholecalciferol for 7 d	Participants turned to be SARS-CoV-2 RNA negative, followed by the administration of Vit D.	[101]
NCT04334005	Apr 2020	Universidad de Granada,	200 subjects within the age limit of 40-70 y, both male and female with mild symptoms such as cough, fever, nasal congestion, etc.	Randomized, parallel, double-blinded study	Single-dose of 25000 UI of Vit D	Total no of death for any cause	[102]
NCT04264533	Feb 2020	Zhi Yong Pang, China	140 ICU patients, Age 18years and older male or female diagnosed with COVID-19	Randomized, parallel, Triple blinded study	12g Vit c IV infusion twice daily for 7 d.	Ventilation free days	[103]
NCT04323514	Mar 2020	University of Palermo,	500 subjects of any ages	Uncontrolled longitudinal,	10g Vit C IV in addition to conventional therapy	In-hospital mortality	[104]

NCT03680274	Nov 2018	Italy Universite de Sherbrooke, Canada	hospitalized with COVID-19 pneumonia 800 ICU patients, age 18 y and older, either male or female diagnosed with COVID-19 and receiving continuous IV infusion vasopressors	Open-label, single-group study Randomized, parallel, quadruple blinded study	Vit C 200 mg/kg/day IV	Decreased dependency for mechanical ventilation and mortality	[105]
NCT04386850	Apr 2020	Tehran University of Medical Science, Iran	1500 CoVID-19 positive patients	Randomized, parallel, multicentre, double-blinded study	25 mcg Vit D daily at bedtime for 2 mo	Rate, severity, and duration of COVID	[106]
NCT04411446	Aug 2020	Vit D study group, Argentina	1265 COVSD-19 positive subjects, Age 18 y and older either male or female	Randomized, parallel, quadruple blinded study	5 capsules of 100,000 IU of Vit D	Organ failure assessment and need for mechanical ventilation	[107]
NCT04363840	May 2020	Louisiana State University Health Science Center in New Orleans, USA	1080 subjects, 18 y an older male or female newly diagnosed with COVID-19	Randomized, parallel, open-label assessment	Vit D 50,000 IU once weekly along with Aspirin 81 mg once daily for 2 w	Length of hospitalization and severity of symptoms	[108]

Iron

Iron deficiency can lead to an increased risk of continual acute respiratory tract infection [109]. At the same time, iron overload can result in oxidative stress, which can ultimately result in dangerous mutations in the virus [110]. Hence iron in recommended doses can be given to deficient patients.

Omega-3 polyunsaturated fatty acids

Polyunsaturated fatty acids with long chains like omega 3, omega 6 polyunsaturated fatty acids play a major role in promoting anti-inflammatory, proinflammatory as well as adaptive immune responses.

They are as well as precursors of protectins, prostaglandins, leukotrienes, etc. One of the major sources of omega 3 polyunsaturated fatty acid is fish oil. Some study reports studying plasma lipid levels in AIDS patients have shown a significant reduction of long-chain omega polyunsaturated fatty acids [111]. Also, studies showed that the use of a lipid derivative of omega 3 polyunsaturated fatty acid, called protectin D1, may inhibit the replication of viral particles by RNA export mechanism. Also, they exhibit activity against the hepatitis C virus [112]. Thus these antiviral properties of omega polyunsaturated fatty acids may show a protective role in covid patients as well [113]. Apart from the nutrient supplements, some corona virus-specific treatments are mentioned in table 4 [114, 115].

Table 4: Coronavirus specific treatments

Chymotrypsin like (3C) inhibitors, Flavonoids like Herbacelin, Pectolarin, etc-inhibits 3C like protease Antioxidant action, Herbacetin, Isobavachalcone etc can inhibit MERS-COV/3CL Pro	[116]
Papain-like protease inhibitors Diarylheptanoids-Obtained from the bark of Alnusjaponica Can inhibit papain-like protease of SARS-COVID along with other natural components like cinanserin	[117]
Spike (S) protein angiotensin-converting enzyme 2 blockers ACE 2 receptor is a major active receptor of SARS-CoV. S protein mediates the viral entry as well as the fusion of viral-host cells Blocking the interaction of ACE2 receptor and spike protein is therefore important	[118, 119]

CONCLUSION

The possible effects of various nutrient supplements like vitamin A, B, C, D, E, trace elements like zinc, selenium, and others like omega fatty acids on the immune system and the benefits in covid patients have been looked into. The established antiviral, immunomodulatory as well as anti-inflammatory effects of these nutrient supplements may help in reducing the complications associated. The benefits can be especially noted in the vulnerable population like the elderly and geriatrics who were presented with disproportionate morbidity as well as mortality rate.

FUTURE PERSPECTIVES

All the supportive nutrient supplies which are mentioned above may demonstrate a protective role in the management of COVID-19

patients. However, clinical trials are ongoing to determine the benefits and effectiveness of supplementing the supportive therapy with nutrients in COVID patients. Hopefully, these studies may reveal and confirm the supportive role of nutrients in COVID 19 patients.

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AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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