Role of vitamins and minerals as immunity boosters in COVID-19

Puneet Kumar1 · Mandeep Kumar2 · Onkar Bedi3 · Manisha Gupta3 · Sachin Kumar4 · Gagandeep Jaiswal4 · Vikrant Rahi4 · Narhari Gangaram Yedke4 · Anjali Bijalwan1 · Shubham Sharma1 · Sumit Jamwal5

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Abstract
Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) known as coronavirus disease (COVID-19), emerged in Wuhan, China, in December 2019. On March 11, 2020, it was declared a global pandemic. As the world grapples with COVID-19 and the paucity of clinically meaningful therapies, attention has been shifted to modalities that may aid in immune system strengthening. Taking into consideration that the COVID-19 infection strongly affects the immune system via multiple inflammatory responses, pharmaceutical companies are working to develop targeted drugs and vaccines against SARS-CoV-2 COVID-19. A balanced nutritional diet may play an essential role in maintaining general wellbeing by controlling chronic infectious diseases. A balanced diet including vitamin A, B, C, D, E, and K, and some micronutrients such as zinc, sodium, potassium, calcium, chloride, and phosphorus may be beneficial in various infectious diseases. This study aimed to discuss and present recent data regarding the role of vitamins and minerals in the treatment of COVID-19. A deficiency of these vitamins and minerals in the plasma concentration may lead to a reduction in the good performance of the immune system, which is one of the constituents that lead to a poor immune state. This is a narrative review concerning the features of the COVID-19 and data related to the usage of vitamins and minerals as preventive measures to decrease the morbidity and mortality rate in patients with COVID-19.

Keywords COVID-19 · Corona virus · Minerals · Therapy · Vitamin

Introduction
Coronavirus is the cause of newly discovered infectious diseases known as COVID-19. The clinical features of COVID-19 are similar to previous outbreaks reported in the 21st century, the Middle East respiratory syndrome (MERS) and Severe acute respiratory syndrome (SARS) (Rothan and Byrareddy 2020). Both SARS and MERS were said to emerge in bats and transmit to humans (Derbyshire and Delange 2020; Tay et al. 2020). On December 31, 2019, the World Health Organization (WHO) announced that SARS-CoV-2 is responsible for COVID-19 and on March 11, 2020, it was declared a global pandemic. The primary site of action of COVID-19 is the human respiratory system (Rothan and Byrareddy, 2020), although other organ systems are also involved. An initial sign of pneumonia of an unknown etiology was diagnosed in a clump of epidemiologically linked patients to Wuhan, Hubei Province, China. Other symptoms include fever, dry cough, dyspnoea, sore throat, headache, dizziness, generalized weakness, vomiting and diarrhea were observed (Shakoor et al. 2020a). It is now well recognized that COVID-19 has complex respiratory symptoms ranging from minimal signs to hypoxia with acute respiratory distress syndrome (ARDS) (Rothan and Byrareddy, 2020). Angiotensin-converting enzyme2 (ACE2) receptor is utilized to invade SARS-CoV-2 into human cells (Yazdanpanah and Hamblin 2020; Zabetakis et al. 2020).
Epidemiology data of COVID-19 show that the outbreak rate is often more severe among above 60 years older people or who have health conditions like lung or heart disease, diabetes. Children below the age of 10 are affected but not at high rates as the percentage is very low. Although no gender was predominantly seen, males outnumbered females due to smoking and drinking habits (Yuki et al. 2020). The daily report shows the steep elevation in new cases from different regions/countries (Tay et al. 2020). There is no registered treatment for COVID-19 due to a lack of in-depth knowledge about the pathogen to host response (Shakoor et al. 2020b; Tay et al. 2020). Remdesivir is the only FDA-approved treatment in the US for COVID-19 patients and in a highly selected group. It is now used for hospitalized patients of every age group with severe conditions (Michienzi and Badowski 2020). Two important steps in battling COVID-19 infection are proper nutrition and activation of the immune system to fight against the disease (Derbyshire and Delange 2020). Scientists are working around the clock to find a suitable cure, and till then, it is our prime duty to be safe and not compromise our health and increase the risk of COVID-19. Several vitamins and trace elements may play critical functions in strengthening the immune system and decreasing infections.

The primary goal of this review is to highlight the potential therapeutic role of vitamins A, B, C, D, E and K, along with micronutrients as an immunity booster in COVID-19 patients.

### Immunity and COVID-19

COVID-19 is omnipresent; since the onset of the COVID-19 outbreak, fear and panic have traveled globally. This virus plays with an individual’s immunity, i.e., the severity of the infection depends on one’s immuno-competence; every individual has a different kind of immune system, with their daily activity significantly impacting the immune system’s strength (Michienzi and Badowski 2020).

The SARS-CoV-2 virus can bind to ACE2 expressing cells present in orals tissues, especially in alveolar lung cells, bronchial epithelium, and vascular endothelial cells. In the lungs, the infection cause downregulation of ACE2 receptors and RAS dysfunction, causing acute lung injury (Tay et al. 2020) (Ni et al. 2020). RAS dysfunctions trigger the release of various Proinflammatory mediators such as interleukins and cytokines (Yuki et al. 2020). This elevation leads to dysregulation of the host immune system (Shakoor et al. 2020a, b). People with a robust immune system can fight back the infection. However, the reasons behind the decline in immunity were proposed to be inflammation, improper functions of T cells, due to dietary imbalance lack of micro and macro nutrients (Derbyshire and Delange 2020).

### Introduction to vitamin as an immunity booster

It is well established that nutritional deficiency can impair and adversely affect one’s immune system by infections. Recent evidence has highlighted the role of nutritional supplementation, and if administered in higher than recommended daily doses, it might be beneficial in potentially reducing viral load and hospitalization for COVID-19 patients. Vitamins are essential dietary components because of their antioxidant properties and immunomodulatory effects (Shakoor et al. 2020b). Some of them regulate gene expression in immune cells and support the maturation and differentiation of immune cells. The vitamins C and E act as powerful antioxidants in combatting free radical species (Gombart et al. 2020). It was scientifically documented that body may be deprived of these nutrients, vitamins, and minerals while fighting against infections due to the demand for activation energy for the immune stimulation, by a stressful lifestyle, diseases like viral infection, diabetes, obesity, which directly affects the nutrients status (Gombart et al. 2020). Clinical trials and associated interventions for vitamins are shown in Table 1.

### Role of vitamin A in COVID-19

Vitamin A belongs to the family of retinyl-esters and is also known as retinoic acid (RA) (Gudas 2012), which controls the various genes involved in innate and adaptive immune responses (Raverdeau and Mills 2014). Vitamin A acts as T-cell effectors, facilitating adaptive and innate immunity (Raverdeau and Mills 2014). Retinoid directly stimulates the expression of Interferon stimulated genes (ISGs), including retinoic acid-inducible gene I (RIG-I) and IFN regulatory factor 1 (IRF-1) (Matikainen et al. 1996; Lindner et al. 1997; Luo and Ross 2006).

Several studies showed the protective effect of natural and synthetic retinoids on some viruses such as hepatitis B virus (HBV), influenza, norovirus, MeV, and cytomegalovirus (Angulo et al. 1998; Trottier et al. 2008; Lee and Han 2016; Li et al. 2018). A study conducted by Yuan et al showed the significant effect of Am580. It is an agonist of RAR-α against, it acts on MERS-CoV and SARS-CoV through interruption of lipogenic pathways mediated by SREBP (Yuan et al. 2019). It was determined that coronavirus SARS-CoV and MERS-CoV could stop the antiviral responses mediated by IFN-I and probably delay treatments (Spiegel et al. 2005; Frieman et al. 2007; Yang et al. 2015; Hu et al. 2017). A study revealed that IFN-I signaling significantly increases by retinoids (Gudas 2012).
which permits the pre-clinical testing of retinoids and IFN-I combination in both in vivo and in vitro models.

### Role of vitamin B in COVID-19

Vitamin B is a naturally occurring component and is known to be involved in Red blood cells (RBC) production. All the vitamins under the B complex category are important for the body cells’ normal physiological functioning (Zhang et al. 2018). Vitamin B supports the body to use energy-yielding nutrients (such as carbohydrates, fat, and protein) for sustaining healthy skin and brain cells and some other tissues. Vitamin B complex comprises a total of 8 vitamins, i.e., thiamine [B1], riboflavin [B2], niacin [B3], pantothenic acid [B5], pyridoxine [B6], biotin [B7], folate, or folic acid [B9], cyanocobalamin [B12]. It plays an essential role in colonic immune regulation and contributes to intestinal barrier function. (Lindschinger et al. 2019).

#### Vitamin B1 (thiamine)

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

#### Vitamin B2 (riboflavin)

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

#### Vitamin B3 [niacin (nicotinic acid, pantothenic acid)]

Niacin has extensive modulatory effects on the generation of inflammatory mediators and the immune cell movement. Hence, it has an anti-inflammatory impact, though its effects have not been thoroughly explained. It restrains CXC chemokine, CXCL-8/IL-8 induction, neutrophil migration induced by lipid mediator leukotriene (LT) B4 (in mice), and adherence (Shibata et al. 2017). It has been found to decrease IL-6, IL-1β, and TNF-α in stimulated alveolar macrophages. Recent data indicate that targeting IL-6 could reduce inflammation in COVID-19 patients (Liu et al. 2020). Furthermore, niacin acts as an anti-inflammatory agent; it reduces neutrophil infiltration in patients with ventilator-induced lung injury (Nagai et al. 1994). The other scientific report described that nicotinamide reduces viral infection and stimulates defense mechanisms. Considering the therapeutic features of niacin, it can be used as an adjunct in the therapy of COVID-19 patients (Mehmel et al. 2020).

#### Vitamin B6 (pyridoxine)

Vitamin B6 influences innate/adaptive immunity, function, and proliferation of immune cells (Ueland et al. 2017). Persons with vitamin B6 deficiency were found with the inhibition of cytokine/chemokine release. Studies suggest that vitamin B6 deficiency mediates the cellular immune response by activating the IFN-gamma (Parra et al. 2018). A recent study revealed that pyridoxine supplement helps to relieve COVID-19 symptoms by improving immune responses, reducing pro-inflammatory cytokines, supporting endothelial integrity, and preventing hypercoagulability.

#### Vitamin B9 (folic acid, folate)

Folate is an essential vitamin for DNA and protein synthesis and also plays an important role in the adaptive immune response. A recent study determined that folic acid inhibits the furin, an enzyme responsible for bacterial and viral infections, and blocks the binding of SARS-CoV-2 spike protein. Therefore in the early stages, folic acid could be useful for controlling COVID-19-associated respiratory disease (Sheybani et al. 2020). A recent study reported that folic acid and its derivatives, 5-methyl tetrahydrofolic acid, and tetrahydrofolic acid have a strong affinity against the SARS-CoV-2 (Kumar and Jena 2020).
Vitamin B12 (cobalamin/cyanocobalamin)

Vitamin B may regulate chemokine/cytokine formation and arbitrate the intercommunication with immune cells implicated in pathophysiological pathways. Thus, it is recommended that it can protect against various bacterial and viral infections. Furthermore, as it also plays an essential role in colonic immune regulation and contributes to intestinal barrier function, it might play a crucial role in the immunity and protection against coronavirus (COVID-19) as there is proof that probiotics such as bifidobacterial and lactobacilli can modulate the immune response and protect against infections, including respiratory tract infections (Calder et al. 2020).

Role of vitamin C in COVID-19

Vitamin C is well known for its antiviral properties, such as increasing the interferon-alpha production, modulating cytokines, reducing inflammation, improving endothelial dysfunction, and restoring mitochondrial function (Carr and Maggini 2017; Dey and Bishayi 2018). In the early 30s and 70s, Linus Pauling (Nobel Prize winner) stated the beneficial effect of vitamin C in the common cold (Heikkinen and Järvinen 2003). There is also some evidence that showed the viricidal property of vitamin C (Furuya et al. 2008). Vitamin C supports the immune system to fight against bacterial and viral infections. It helps to eliminate the dead cells and replace them with new cells (Ekert and Vaux 1997; Carr and Maggini 2017). The antioxidant property of vitamin C protects the damage induced by oxidative stress.

Several studies showed that vitamin C supplementation reduces the risk associated with upper respiratory tract infections (Carr and Maggini 2017). A review published by Hemila et al. confirmed that daily 1–2 g of vitamin C reduced the symptoms of common cold both in adults and in children (Hemilä and Chalker 2013). Intravenous administration of vitamin C significantly reduces severe infections, such as sepsis and acute respiratory distress syndrome (ARDS) (Kashiouris et al. 2020). There is some indirect and direct evidence that reveals vitamin C’s effectiveness in treating patients with COVID-19. One Cochrane review and a randomized controlled trial showed a significant reduction in the common cold symptoms by oral administration of 0.2 g/day vitamin C. One trial on adult patients showed a dose-dependent decrease in the duration of pneumonia with two vitamin C doses (Baladia et al. 2020). Therefore, research addressing vitamin C’s role specifically for COVID-19 would add helpful information (Carr 2020).

Role of vitamin D in COVID-19

Vitamin D is a secosteroid with anti-inflammatory and antioxidant properties. It helps to maintain the calcium–phosphorus metabolism. A number of studies suggested that vitamin D inhibits the overexpression of inflammatory cytokines such as IL-1α, IL-1β, tumor necrosis factor-α (Hughes and Norton 2009). It is also involved in the modulation of the immune response in infectious and autoimmune diseases. The sunlight emits ultraviolet B radiation, which is absorbed in the skin and leads to the conversion of 7-dehydrocholesterol into cholecalciferol. As dietary sources did not provide a sufficient amount of vitamin D, Therefore, fortification of oral supplementation is often necessary. The new investigation revealed that the cities’ temperature and latitude affected by COVID-19 are similar to those of the most affected areas (Sajadi et al. 2020). This is an essential factor because people have a low vitamin D concentration in high-latitude countries (Cannell et al. 2006). Previously, vitamin D insufficiency was reported in patients from high alert areas. Furthermore, the prevalence of vitamin D deficiency varies among several geographical regions of each country, limiting our ability to simplify the results.

Vitamin D for respiratory tract infections

Literature has demonstrated that vitamin D insufficiency can lead to respiratory tract infection (Lemire 1992). Therefore, vitamin D has been widely investigated as a therapeutic agent for acute respiratory tract infections (ARTIs). A study conducted by Xu et al. reported the protective effect of calcitriol (vitamin D agonist) against acute lung injury by modulating the expression of ACE2 in lung tissue (Xu et al. 2017), which is one of the pathogenic factors in COVID-19. Some studies showed significant results with a high dose of 250,000–500,000 IU.

Vitamin D is associated with a decreased hospital stay, improved blood oxygen level, and increased hemoglobin levels (Han et al. 2016). Studies reported that persons with a vitamin D level of more than 95 nmol/L have a low risk of acute viral respiratory tract infections as compared with the patients with lower than 95 nmol/L (Sabetta et al. 2010). A recent meta-analysis demonstrated that supplementation of vitamin D decreased the risk of acute respiratory tract infections as compared to those with low levels of vitamin D at baseline (< 25 nmol/L) (Martineau et al. 2017).

Vitamin D for microbial infections

Several mechanisms are reported to be involved through which vitamin D helps reduce microbial infections and
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Role of vitamin E in COVID-19

Vitamin E plays a crucial role in regulating and supporting immune system function as a potent antioxidant (Jayawardena et al. 2020). Vitamin E acts as a free radical scavenger, reduces oxidative stress, and prevents free radicals containing unshared electrons and highly energetic and damaged cells. Unshared electrons form reactive oxygen species (ROS) with rapidly reacting with oxygen. (Verhagen et al. 2006). Other than antioxidant and anti-inflammatory properties, vitamin E also has a function in immunity. Alpha-tocopherol is an inhibitor of protein kinase C, cell proliferation and differentiation in smooth muscle cells, monocytes and platelets. Vitamin E also increases the level of prostacyclin by inhibiting the metabolism of arachidonic acid which results in dilation of blood vessels and inhibition of platelet aggregation (vitamin E—Health Professional Fact Sheet). A study reported that increased intake of vitamin E is more beneficial in maintaining immunity function in elderly individuals as compared to younger individuals (Hemila 2016; Meydani et al. 2018).

Role of vitamin K in COVID-19

Vitamin K is a co-factor and functions as a co-enzyme involved in hemostasis by synthesizing protein and other physiological functions (Janssen and Walk 2020). At times of insufficiency of vitamin K hepatic factor, coagulation factors over extrahepatic ones are predominant. Matrix Gla protein (MGP), a vitamin K-dependent protein, is soft tissue mineralization and elastic fiber degradation inhibitor. To protect the pulmonary extracellular matrix from degradation induced by inflammation, there is an increase in the synthesis of Matrix Gla protein (MGP) in the lungs of SARS-CoV-2 patients, which promotes the utilization of vitamin K from extrahepatic vitamin K stores (Mccann and Ames 2020). COVID-19 may affect venous and arterial thromboembolic disease due to extreme inflammation, hypoxia, immobilization, and diffuse intravascular coagulation (DIC). It can also cause blood clotting and leads to the degradation of elastic fibers in the lungs. As vitamin K1 is responsible for the activation of hepatic coagulation factors, thus it helps combat thrombotic complications in COVID-19 patients (Klok et al. 2020).

Role of minerals as immunity boosters in COVID-19

Role of macrominerals in COVID-19

Considering the outcomes of COVID-19 infection, In the absence of effective treatment, a strong immune system is one of the most effective defense mechanisms. Moreover, supplementation of minerals has positively impacted immunity in viral infections (Jayawardena et al. 2020). Minerals are inorganic substances required by the body to support body functions. Minerals are involved in various physiological processes such as bone development, blood formation, hormone synthesis, and regulation of heartbeat. The role of macro minerals are described individually in Table 2 (Romita and O’Brien 2018). Many epidemiological studies have demonstrated that low intake of essential minerals in diet plays a crucial role in preventing and reducing cardiovascular and cerebrovascular diseases, which may be involved in the progression of corona infections (Zabetakis et al. 2020).

In early COVID-19 studies, some data have been given that show how the presence and absence of minerals in the body are considered essential in regulating the expression of angiotensin-converting enzyme-2 (ACE2) in boosting the immune system. ACE-2 receptors are the coronavirus’ main targets for its entry into the respiratory system and badly affect this system (Ivanov et al. 2020). Also, an animal study showed that mineral deficiency could increase the expression of ACE2 through the activation of RAAS. Therefore, we could consider that the long-term mineral deficiency may increase the level of ACE2 in lower respiratory tract cells,
| S.no | Study title                                                                 | No. of subjects | Intervention/ treatment                                                                 | Recruitment status | Study type                        | Primary outcome measures                                                                 | Secondary outcome measures                                                                 | Clinical trials. gov identifier |
|------|------------------------------------------------------------------------------|-----------------|-----------------------------------------------------------------------------------------|--------------------|-----------------------------------|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|--------------------------------|
| 1    | The effect of melatonin and vitamin C on COVID-19                           | 150             | Vitamin C and melatonin                                                                  | Recruiting         | Interventional (Clinical Trial)    | Symptom severity [time frame: 14 days] Symptom severity will be tracked electronically  | Symptom progression [time frame: 14 days] Determine symptom course of those with moderate or severe symptoms | NCT04530539                     |
| 2    | Administration of Intravenous vitamin C in Novel Coronavirus Infection (COVID-19) and Decreased Oxygenation (avocado) | 20              | L-Ascorbic acid                                                                          | Completed (Phase-1&2) | Interventional (Clinical Trial)    | Incidence of serious adverse reactions [Time Frame: Days 1–4] Occurrence of serious adverse events during study drug infusion | Ventilator-free days, Documented days free of mechanical ventilation the first 28 days post-enrollment ICU-free days, Documented days free of ICU admission the first 28 days post-enrollment | NCT04357782                     |
| 3    | Efficacy and safety of high-dose vitamin C combined with Chinese medicine against coronavirus pneumonia (COVID-19) | 60              | Chinese medicine formula combined with high-dose vitamin C treatment                      | Active but not recruiting | Interventional (Clinical Trial)    | Recovery time [Time Frame: From date of randomization until the date of discharge, assessed up to 6 months] | Respiratory rate [Time Frame: 1–14 days after treatment], PaO2 and PaCO2 [Time Frame: 1–14 days after treatment] in kPa with blood gas analysis | NCT04664010                     |
| 4    | N-terminal Pro B-type natriuretic peptide and vitamin D Levels as Prognostic Markers in COVID-19 Pneumonia | 100             | Vitamin D                                                                                | Recruiting         | Observational                     | NT-pro-BNP and vitamin D [Time Frame: 6 month]                                           | Assessment of any possible correlation between NT-pro-BNP and Vitamin D and the need for mechanical ventilation or mortality in COVID-19 infection [Time Frame: 6 month] | NCT04487951                     |
| 5    | Impact of vitamin D level and supplement on SLE patients during COVID-19 pandemic | 38              | Vitamin D                                                                                | Completed          | Observational                     | Level of serum vitamin D in SLE infected with COVID-19 [Time Frame: 6 months]            | Vitamin D level with COVID-19 severity [Time Frame: 6 months]                              | NCT04709744                     |
| S.no | Study title                                                                 | No. of subjects | Intervention/treatment | Recruitment status | Study type                              | Primary outcome measures                                                                                                                                                                                                                                                                                                                                                                                                  | Secondary outcome measures                                                                                                                                                                                                                                                                  | Clinical trails.gov identifier |
|------|------------------------------------------------------------------------------|----------------|-----------------------|------------------|----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 6    | Vitamin D and COVID-19 Trial (VIVID)                                        | 2700           | Vitamin D             | Recruiting       | Interventional (Clinical Trial)        | Rate of seeking healthcare visits for symptoms or concerns related to COVID-19 or deaths in participants newly diagnosed with COVID-19 (index cases)  
Time Frame: 4 weeks  
Severity: 1 = no COVID-19 illness; 2 = COVID-19 illness with no hospitalization; 3 = COVID-19 illness with hospitalization; or 4 = death | Self-reported disease severity in index cases  
Time Frame: 4 weeks  
Severity: 1 = no COVID-19 illness; 2 = COVID-19 illness with no hospitalization; 3 = COVID-19 illness with hospitalization; or 4 = death | NCT04536298  |
| 7    | Vitamin D supplementation in patients with COVID-19                         | 240            | Vitamin D             | Completed        | Interventional (Clinical Trial)        | Length of hospitalization  
Time Frame: From date of randomization until the date of hospital discharge or death, which is usually less than 1 month  
total number of days that patient remained hospitalized | Mortality  
Time Frame: From date of randomization until the date of hospital discharge or death, which is usually less than 1 month  
number of patients that died | NCT04449718  |
| 8    | Low vs. moderate to high-dose vitamin D for prevention of COVID-19           | 2000           | Vitamin D3            | Recruiting       | Interventional (Clinical Trial)        | SARS-CoV-2 infection as measured by patient report of clinically confirmed COVID-19 (or viral PCR when available)  
Time Frame: 9 months | SARS-CoV-2 antibody seroconversion confirmed by a COVID-19 antibody test  
Time Frame: 9 months | NCT04868903  |
| 9    | Vitamin D3 levels in COVID-19 outpatients from Western Mexico               | 42             | Vitamin D3            | Completed        | Interventional (Clinical Trial)        | Correlation between D-dimer and vitamin D serum levels in COVID-19 patients  
Time Frame: At baseline | – | NCT04793243  |
| 10   | A Phase 2, double blind, randomized, placebo-controlled clinical trial to investigate the safety and effects of oral vitamin K2 supplementation in COVID-19 | 40             | Vitamin K2 in the form of Menaquinone-7 (MK-7) | Recruiting (Phase-2) | Interventional (Clinical Trial)        | Plasma desmosine levels and dp-acMGP levels before and during vitamin K supplementation in intervention versus control patients.  
Time Frame: Day 1 until day 28 or until discharge if this is earlier. | Serum PIVKA-II levels before and during vitamin K supplementation in intervention versus control patients.  
Time Frame: Day 1 until day 28 or until discharge if this is earlier. | NCT04770740  |
| Sr no | Study title                                                                 | No. of subject | Intervention/treatment                                                                 | Recruitment status | Phase      | Primary outcome measure                                                                 | Secondary outcome measure                                                                 | Clinical trial gov identifier |
|-------|------------------------------------------------------------------------------|----------------|----------------------------------------------------------------------------------------|--------------------|------------|-----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|------------------------------|
| 1     | The study of quadruple therapy zinc, quercetin, bromelain and vitamin C on the clinical outcomes of patients infected with COVID-19 | 60             | Drug: Zinc  
 Drug: vitamin C  
 Drug: Quercetin  
 Dietary Supplement: bromelain | Recruiting         | Phase 4     | Speed the days of recovery and discharge from hospital                                  | The level of serum zinc is very important especially at chronic diseases                  | NCT04468139                   |
| 2     | The effect of COVID-19 patients' serum phosphate level on mortality in ICU     | 160            | Diagnostic Test: 4C mortality score                                                      | Recruiting         | –          | 4C Mortality Scores of the patients will be calculated, according to age, gender, number of comorbidities, respiratory rate, SpO2, GCS, urea, and CRP parameters | –                                                                                         | NCT04800770                   |
| 3     | Evaluation of the daily intake of 0.5 L of water saturated with molecular hydrogen for 21 days in COVID-19 patients treated in ambulatory care (HYDRO COVID) | 450            | Dietary Supplement: MOLECULAR HYDROGEN  
 Dietary Supplement: PLACEBO MAGNESIUM | Recruiting         | –          | Decreases the incidence rate of the appearance of clinical worsening in patients within 12 to 14 days following a COVID-19+ diagnosis with outpatient care | Assessment of tolerance  
 Assessment of compliance  
 Assessment of medium-long-term fatigue symptoms  
 Assessment of risk factors etc | NCT04716985                   |
| 4     | COVID-19 primary care platform for early treatment and recovery (COPPER) Study | 17             | Drug: Dexamethasone                                                                    | Terminated         | Phase 4     | Time to first hospital admission or death                                               | To assess the effectiveness of early treatment with dexamethasone in reducing time to recovery in COVID19 patients | NCT04746430                   |
| 5     | Povidone iodine mouthwash, gargle, and nasal spray to reduce nasopharyngeal viral load in patients with COVID-19 | 24             | Drug: Povidone-Iodine                                                                  | Completed          | Phase 2     | Change from baseline naso-pharyngeal viral load quantified by RT-PCR at Day7           | Delay between inclusion and negativation of SARS-CoV-2 nasopharyngeal carriage            | NCT04371965                   |
| Sr no | Study title                                      | No. of subject | Intervention/treatment                                      | Recruitment status | Phase     | Primary outcome measure                                      | Secondary outcome measure                                                                 | Clinical trial gov identifier |
|-------|-------------------------------------------------|----------------|------------------------------------------------------------|--------------------|-----------|-------------------------------------------------------------|-------------------------------------------------------------------------------------------|-------------------------------|
| 6     | Virucidal effect of povidone iodine on COVID-19 in vivo | 200            | Drug: Povidone-Iodine 0.4% NI Drug: Povidone-Iodine 0.5% NI Drug: Povidone-Iodine 0.6% NI Drug: Povidone-Iodine 0.5% NS Drug: Povidone-Iodine 0.6% NS Other: Placebo comparator: DW-NI Other: Placebo comparator: DW-NS | Recruiting         | Phase 2   | Proportion of COVID-19 positive cases following intervention in all groups | Any adverse event following administration of both intervention and placebo agent          | NCT04549376                  |
| 7     | Efficacy of iodine complex against COVID-19 patients | 200            | Drug: Iodine Complex Drug: Placebo Drug: Iodine Complex     | Recruiting         | Phase 1/Phase 2 | qRTPCR- Time taken for viral load clearance HRCT chest- Time taken for radiological improvement | Severity of Symptoms- Time taken for symptomatic response in patients | NCT04473261                  |
| 8     | Selenium as a potential treatment for COVID-19 patients | 100            | Drug: Selenium (as Selenious Acid) Other: Placebo          | Not recruiting     | Phase 2   | Rate of hospital discharges or deaths- Rate of patient discharge to home or other long-term care facilities, or death | Clinical status using ordinal scale Mean change in the ordinal scale Duration of hospitalization Duration of new oxygen use Etc | NCT04869579                  |
which would increase the sensitivity and pathogenicity of SARS-CoV-2 infection (Cole-Jeffrey et al. 2015; Gheblawi et al. 2020). The low availability of the minerals affects our immune system, which triggers various pathogenic infections. Further disclosure about each mineral may help us approach stronger immunity, thus preventing the body from such infections (Gombart et al. 2020).

**Sodium**

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

**Potassium**

Hypokalemia can increase ARDS and acute cardiac injury risk, which is considered the most commonly occurring complication in COVID-19. The literature demonstrated that SARS-CoV-2 binds to ACE2 and reduces its expression; consequently, angiotensin-II increases, which subsequently leads to hypokalemia. (Alwaqfi and Ibrahim 2020). COVID-19 patients showed increased concentration of plasma angiotensin-II, possibly responsible for acute lung injury and as confirmed in SARS-CoV animal models (Zemlin and Wiese 2020). A pooled analysis reported that potassium concentration is significantly lower in severe COVID-19 patients than non-severe patients with substantially less heterogeneity than observed for sodium. (Lippi et al. 2020). As with low sodium, reduced plasma potassium levels may be a marker of SARS-CoV-2 infection.

**Calcium**

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

**Phosphorus**

Phosphorus is involved in making protein for the growth, maintenance, and repair of cells and tissues (Vance 2011). A retrospective study of the clinical data of the coronavirus 2019 showed decreased phosphorus levels in COVID-19 patients. This study suggests that hypophosphatemia is directly proportional to the severity of COVID-19; monitoring the serum phosphorus level in COVID-19’s severe/critical patients is proved to be beneficial for prognosis (Xue et al. 2020). During coronavirus entry into the body, the decreased phosphorus level increases the risk of proneness to the infections. This virus, when it enters the body through ACE-2 receptors, our body activates innate immune responses against the viral infection. But due to the low availability of minerals, phosphorus mainly weakens immune responses and thus cannot recover the damage to the cells and tissues, leading to disease progression. This gives insight into the possible role of phosphorus in the prevention of COVID-19 causalities. Further, there is a need to understand the pathological mechanisms involved in hypophosphatemia related to COVID-19 infections (Ni et al. 2020). A clinical study may be needed to show the benefit of restoring low phosphate levels in SARS-CoV-2 patients.

**Magnesium (Mg)**

Magnesium is the forgotten cation. Mg supplementation might reveal very useful in managing the stress triggered by the pandemic and the post-traumatic stress disorder that will plague COVID-19’s survivors, health professionals, and common people. It also plays a significant role in immune function by regulating various functions such as immune cell adherence, immunoglobulin synthesis, binding of Immunoglobulin M (IgM) lymphocyte, antibody-dependent cytolysis, and macrophage response towards lymphokines (Ni et al. 2020). However, some in vitro and in vivo studies suggest that magnesium plays a vital role in the immune response against viral infections (Jayawardena et al. 2020). In Singapore, a cohort study reported that the combination of vitamin D, magnesium, and vitamin B12 (DMB) could reduce the progression rate in older patients with COVID-19. Vitamin B12 (1000 IU) and magnesium (150 mg) have a protective effect against respiratory tract infection and reduce proinflammatory cytokines. A double-blind, randomized trial is suggested. (Tan et al. 2020).
Role of vitamins and minerals as immunity boosters in COVID-19

During this pandemic COVID-19, preventive measures suggested by medical practitioners and scientists generally underline the significant role of immunity as a potential weapon against COVID-19. Till now, no WHO-approved treatment is available to cure the disease; hence an efficient and healthy immune system is the only defense against this viral infection (Ashour et al. 2020; Cascella et al. 2020). Indeed, trace elements are the essential micronutrients having a significant role in immunity. Apart from immunomodulatory action, trace elements such as copper, zinc, manganese, selenium, etc., show antiviral activity by inhibiting virus replication in host cells. The antioxidant properties of trace elements improve the immune response and make alterations in the viral genome. Trace elements are involved in multiple immunomodulatory pathways and improve the defense system of the body by a different mechanism (Calder 2020; Zabetakis et al. 2020).

Zinc (Zn)

**Biological function** Zinc is an important element of nutritional immunity and plays a versatile role in the biological system. Apart from its active involvement in lipid metabolism and carbohydrate regulation, Zn is responsible for the cardiovascular, reproductive, and nervous systems (Collins 2016).

Various pieces of evidence reveal that zinc shows antiviral property and plays an essential role in immunity. Zinc was reported as an active agent for immunity against H1N1 influenza. (Sandstead and Prasad 2010). Mechanistically, like SARS-CoV, the pathogenesis of SARS-CoV-2 is also based upon angiotensin-converting enzyme 2 (ACE2), which allows virus entry into the host’s cell. Therefore, ACE2 is considered the most promising therapeutic target for the treatment of COVID-19 (Zhang et al. 2020a, b). Evidence reveals the decline in the activity of ACE2 in rat lungs after Zn2+ treatment (Chilvers et al. 2001). Furthermore, in vitro data demonstrate that Zn2+ cation allows the inhibition of SARS-coronavirus RNA polymerase by suppressing its replication (Te Velthuis et al. 2010), hence show antiviral activity. All these pieces of evidence and arguments strongly favor that zinc supplementation might support adjuvant therapy in COVID-19 treatment (Zhang et al. 2018). A randomized, double-blind study is suggested.

Iron (Fe)

**Biological function** Iron plays a versatile role in the biological system. Despite being an oxidant, iron plays a significant role in hemoglobin and red blood cell production.

Role in COVID-19 Recent evidence reveals that apart from pulmonary involvement and elevation in IL-6, COVID-19 patients display a broader spectrum of hyperinflammatory syndromes distinguished by cytokine release syndrome (CRS), such as secondary hemophagocytic lymphohistiocytosis (sHLH). Hyperferritinemia is the primary feature of these syndromes, which plays a significant role in inflammation. These findings support the theory that the acute phase of SARS-CoV-2 infection induces ferritin production associated with the rapid onset of inflammation. Hence, ferritin’s immunomodulatory effects contribute to the formation of reactive oxygen species (ROS) and lead to tissue damage. With this contrast, iron chelation therapy is represented as the novel approach against COVID-19. Iron chelation therapy is the most effective approach in a wide spectrum of diseases associated with iron overload. Therefore, iron chelation therapy is considered an appropriate approach to improve survival in COVID-19 patients. A randomized, double-blind clinical trial should be considered.

Copper (Cu)

**Biological function** Copper is enlisted as the essential micronutrient for humans against viral infections. After absorption in the small intestine, dietary Cu enters the systemic circulation and involves many biological processes to maintain the body’s average ionic balance (Osrđekar and Sustar 2011).

**Role in COVID-19** Cu is involved in B cells’ normal functioning, T helper cells, macrophages, and natural killer (NK) cells, also involved in cell-mediated immunity, encounter infamous microbes, and produce antibodies against the pathogen (Raha et al. 2020). Studies reveal that Cu’s exposure to coronavirus 229E damage the viral genome and impact viral morphology irreversibly (Warnes et al. 2015). Furthermore, Cu processes the potential to neutralize infectious viruses such as poliovirus, bronchitis virus, human immunodeficiency virus type 1(HIV-1), and boost immunity. These studies reflect the sensitivity of viral infection towards Cu; hence, copper supplement may be a better treatment approach for COVID-19 patients (Raha et al. 2020).

Selenium (Se)

**Biological function** For multiple reasons, Se is considered the most reliable trace element due to its antiviral and anti-inflammatory properties. Distinct sets of selenoproteins regulate the normal functioning of the immune system comprised of selenocysteine. Deficiency of Se established severe risk factors for viral infections (Guillin et al. 2019).

**Role in COVID-19** Data from China link the cured rate of COVID-19 patients in association with the body’s basal
selenium status (Zhang and Liu 2020). Studies reveal that glutathione peroxidase 1 (GPX1) is the cytosolic selenoenzyme activated by Se and responsible for the antiviral property. Data reveal that multiple sets of selenoproteins like GPX1 potentially counterbalance the oxidative stress level and inflammation induced by SARS-CoV-2 (Seale et al. 2020). This evidence suggests the crucial role of Se-based mechanisms in SARS-CoV-2; hence it can be concluded that a high intake of nutritional selenium has a significant impact on SARS-CoV-2 infection.

Manganese (Mn)

*Biological function* Being an essential trace element, nutritional manganese has various effects on the biological system. Mn possesses antioxidant activity and responsible energy production by the amino acid breakdown (Sigel 2000).

*Role in COVID-19* In an emerging approach towards the treatment of COVID-19, various sherds of evidence reveal Mn’s immunomodulatory and antiviral action. The experimental data indicate that the hepatitis-B virus’ protein priming depends upon the concentration of manganese ion; hence, it acts as a potent antiviral agent (Yao et al. 2009). Evidence also suggests impaired antibody production as a response to Mn deficiency, highlighting its crucial role in promoting immunity (Haase 2018). All this evidence indicates the supportive role of nutritional Mn in COVID-19 treatment.

Iodine (I)

*Biological function* Iodine is a widely used trace element, especially for therapeutic purposes. Biologically, iodine is a mineral responsible for producing thyroid hormones and plays a significant metabolic role in the body. Iodine also plays an important role in neurodevelopment during pregnancy (Venturi et al. 2000).

*Role in COVID-19* According to previous reports, iodine-based products like povidone-iodine (PVP-I) are highlighted as potent chemical agents against SARS-CoV. Evidence reveals that such iodine-based compounds are equally efficient to 70% ethanol. Hence, it can be used as a disinfectant against SARS-CoV-2, used for handwashing, disinfecting medical instruments, gargling, spraying the throat, and other external uses (Kariwa et al. 2006). In in vivo systems, iodine also plays an essential role as antiviral in respiratory mucosa, saliva, and airways. Evidence reveals the augmentation of innate antiviral immunity upon iodine delivery to airway mucosa (Fischer et al. 2011). Furthermore, a high dose of iodide supplement reduces the risk of severity in the respiratory syncytial virus and improves mucosal oxidative defenses (Turkia 2020). Iodine’s external and internal applications make it a feasible candidate to be used as supportive therapy in SARS-CoV-2 infection.

Cobalt (Co)

*Biological function* Biologically, vitamin B12 is a cobaloxime responsible for maintaining the nervous system and producing red blood cells (RBC). Nutritional Co is an essential mineral responsible for blood formation. (Chaturvedi et al. 2004).

*Role in COVID-19* Study reveals that cobalt (III), upon complex with a tetra-azamacrocyle chelator, hydrolyzes phosphodiester bonds in viral DNA and RNA. Furthermore, its high affinity towards RNA template inhibits the RNA translation and is responsible for therapeutic effects against several viral infections such as hepatitis virus, sindbis virus, herpes simplex virus, and Epstein–Barr virus (Chang et al. 2010). Their therapeutic activities against a wide range of viral infections indicate its role as supportive therapy in COVID-19 treatment and a double-blind placebo-controlled study may be warranted.

Sulfur (S)

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

*Role in COVID-19* Evidence reveals that the sulfate-based compound like sodium thiosulfate possesses therapeutic efficacy for lungs and respiratory infection. Furthermore, clinical data demonstrate that sodium thiosulfate successfully ameliorates pneumonia and lung injury in adults and children. Based on multiple therapeutic roles and the respiratory system’s involvement, sulfur might show a protective effect against COVID-19 (Evgen’ev et al. 2020).

Lay summary and conclusion

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

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Declarations

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References

Alwaqfi NR, Ibrahim KS (2020) COVID-19: an update and cardiac involvement. J Cardiothorac Surg 15(1):1–6. https://doi.org/10.1186/s13019-020-01299-5
Angulo A, Chandraratna RA, LeBlanc JF, Ghazal P (1998) Ligand induction of retinoic acid receptors alters an acute infection by murine cytomegalovirus. J Virol 72(6):4589–4600. https://doi.org/10.1128/JVI.72.6.4589-4600.1998
Ashour HM, Elkhattab WF, Rahman M, Elshabrawy HA (2020) Insights into the recent 2019 novel coronavirus (SARS-CoV-2) in light of past human coronavirus outbreaks. Pathogens 9(3):186. https://doi.org/10.3390/pathogens9030186
Baladia E, Pizarro AB, Rada G (2020) Vitamin C for the treatment of COVID-19: a living systematic review. medRxiv. https://doi.org/10.1101/2020.04.28.20083360
Calder PC (2020) Nutrition, immunity, and Covid-19. BMJ Nutr Prev Heal Bmjnph. https://doi.org/10.1136/bmjnph-2020-000085
Calder PC et al (2020) Optimal nutritional status for a well-functioning immune system is an important factor to protect against viral infections. Nutrients. https://doi.org/10.3390/nu12041181
Cannell JJ, Vieth R, Umhau JC, Holick MF, Grant WB, Madronich S, Garland CF, Giovannucci E (2006) Epidemic influenza and vitamin D. Epidemiol Infect 134(6):1129–1140. https://doi.org/10.1017/S0950268806007175
Carr AC (2020) A new clinical trial to test high-dose vitamin C in patients with COVID-19. Crit Care 24(1):1–2. https://doi.org/10.1186/s13054-020-02851-4
Carr AC, Maggini S (2017) Vitamin C, and immune function. Nutrients 9(11):1211. https://doi.org/10.3390/nu9111211
Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R (2020) Features, evaluation and treatment coronavirus (COVID-19). In: Statpearls [internet]. StatPearls Publishing
Chang EL, Simmers C, Knight DA (2010) Cobalt complexes as anti-viral and antibacterial agents. Pharmaceuticals 3(6):1711–1728. https://doi.org/10.3390/ph3061711
Chaturvedi UC, Shrivastava R, Upeti RK, 2004. Viral infections and trace elements: a complex interaction. Curr Sci 1536–54. https://www.jstor.org/stable/24109032
Cole-Jeffrey CT, Liu M, Katovich MJ, Raizada MK, Shenoy V (2015) ACE2, and microbiota: emerging targets for cardiopulmonary disease therapy. J Cardiovasc Pharmacol 66(6):540
Collins JF (2016) Molecular, genetic, and nutritional aspects of major and trace minerals. Academic Press
Colunga Bancatelli RML, Berrill M, Marik PE (2020) The antiviral properties of vitamin C, Taylor & Francis. https://doi.org/10.1080/14787210.2020.1706483
Derbyshire E, Delange J (2020) COVID-19: is there a role for immune-nutrition, particularly in the over 65s? BMJ Nutrition, Prevention & Health 3(1):100–105. https://doi.org/10.1136/bmjnph-2020-000071
Dey S, Bishayi B (2018) Killing of S. aureus in murine peritoneal macrophages by ascorbic acid along with antibiotics chloramphenicol or ofloxacin: correlation with inflammation. Microb Pathog 115:239–250. https://doi.org/10.1016/j.micpath.2017.12.048
Dutta PK, Keller J, Yuan Z, Rozendal RA, Rabaey K (2009) Role of sulfur during acetate oxidation in biological anodes. Environ Sci Technol 43(10):3839–3845. https://doi.org/10.1021/es900394j
Ekert PG, Vaux DL (1997) Apoptosis and the immune system. Br Med Bull 53(3):591–603. https://doi.org/10.1093/oxfordjournals.bmb.a011632
Evgen’ev MB, Frenkel A (2020) Possible application of H2S-producing bacteria in treatment of patients with COVID-19. Leukemia & Lymphoma. https://doi.org/10.1080/10428194.2020.1757668
Fischer AJ, Linnemann NJ, Krishnamurthy S, Pócza P, Durairaj L, Evgen’ev MB, Frenkel A (2020) Possible application of H2S-producing bacteria in treatment of patients with COVID-19. Leukemia & Lymphoma. https://doi.org/10.1080/10428194.2020.1757668
Fischer AJ, Linnemann NJ, Krishnamurthy S, Pócza P, Durairaj L, Evgen’ev MB, Frenkel A (2020) Possible application of H2S-producing bacteria in treatment of patients with COVID-19. Leukemia & Lymphoma. https://doi.org/10.1080/10428194.2020.1757668
Fisher AJ, Linnemann NJ, Krishnamurthy S, Pócza P, Durairaj L, Launspach JL et al (2011) Enhancement of respiratory mucosal antiviral defenses by the oxidation of iodide. Am J Respir Cell Mol Biol 45(4):874–881
Frieman M, Yount B, Heise M, Kopecky-Bromberg SA, Palese P, Baric RS (2007) Severe acute respiratory syndrome coronavirus ORF6 antagonizes the STAT1 function by sequestering nuclear import factors on the rough endoplasmic reticulum/Golgi membrane. J Virol 81(18):9812–9824. https://doi.org/10.1128/JVI.101012-07
Furuya A, Uozaki M, Yamasaki H, Arakawa T, Arita M, Koyama AH (2008) Antiviral effects of ascorbic and dehydroascorbic acids in vitro. Int J Mol Med 22(4):541–545. https://doi.org/10.3892/ijmm.0000053
Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong J-C, Turner AJ et al (2020) Angiotensin-converting enzyme 2: SARS-CoV-2 receptor and regulator of the renin-angiotensin system: celebrating the 20th anniversary of the discovery of ACE2. Circ Res

Role of vitamins and minerals as immunity boosters in COVID-19

1013
Hemila H (2016) Vitamin E administration may decrease the incidence of pneumonia in elderly males. Clin Interv Aging 11:1379–1385. https://doi.org/10.2147/CIA.S114515

Kashiouris MG, L’Heureux M, Cable CA, Fisher BJ, Leichtle SW (2020) The emerging role of vitamin C as a treatment for sepsis. Nutrients 12(2):292. https://doi.org/10.3390/nu12020292

Klok FA, Kruip MJHA, van der Meer NJM, Arbous MS, Gommers DAMPJ, Kämmerer C, Bonten M, van der Veer DN et al (2020) Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 191:145. https://doi.org/10.1016/j.thromres.2020.04.013

Kraft CE, Angert ER (2017) Competition for vitamin B1 (thiamin) structures numerous ecological interactions. Q Rev Biol 92(2):151–168. https://doi.org/10.1002/qjcb.201600160

Kumar V, Jena M (2020) In silico virtual screening-based study of nutraceuticals predicts the therapeutic potentials of folic acid and its derivatives against COVID-19. https://doi.org/10.1007/s13337-020-00643-6

Laaksi I (2012) Vitamin D and respiratory infection in adults. Proc Nutr Soc 71(1):90–97

Lee GY, Han SN (2018) The role of vitamin E in immunity. Nutrients. MDPI AG. https://doi.org/10.5281/zenodo.3990659

Lemire JM (1992) Immunomodulatory role of 1, 25-dihydroxyvitamin D3. J Cell Biochem (1):26–31. https://doi.org/10.1002/jcb.2880120104

Lindner DJ, Borden EC, Kalvakolanu DV (1997) Synergistic antitumor effects of a combination of interferons and retinoic acid on human tumor cells in vitro and in vivo. Clin Cancer Res 3(6):931–937

Lindschinger M, Tatzber F, Schimetta W, Schmid I, Lindschinger B, Cvitan G, Stanger O, Lamont E, Wonisch W (2019) A randomized pilot trial to evaluate the bioavailability of natural versus synthetic Vitamin B complexes in healthy humans and their effects on homocysteine, oxidative stress, and antioxidant levels. Oxid Med Cell Longev. https://doi.org/10.1155/2019/6082613

Lippi G, South AM, Henry BM (2020) Electrolyte imbalances in patients with severe coronavirus disease 2019 (COVID-19). Ann Clin Biochem 57(3):262–265

Liu B, Li M, Zhou Z, Guan X, Yang Y (2020) Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? J Autoimmunity. https://doi.org/10.1016/j.jaut.2020.102452

Luo XM, Ross AC (2006) Retinoic acid exerts dual regulatory actions on the expression and nuclear localization of interferon regulatory factor-1. Exp Biol Med 231(5):619–31. https://doi.org/10.1772/F15337020623100517

Luo Y, Li Y, Dai J, 2020. Low blood sodium increases risk and severity of COVID-19: a systematic review, meta-analysis and retrospective cohort study. medRxiv. https://doi.org/10.1101/2020.05.18.20102509

Martineau AR, Jolliffe DA, Hooper RL, Greenberg L, Aloia JF, Bergman P, Dubnov-Raz G, Esposito S, Ganaswa D, Ginde AA, Goodall EC (2017) Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. BMJ. https://doi.org/10.1136/bmj.i6583

Gombart AF, Pierre A, Maggini S (2020) A review of micronutrients and the immune system—working in harmony to reduce the risk of infection. Nutrients. https://doi.org/10.3390/nu12010236

Guillim OM, Vindry C, Ohlmann T, Chavatte L (2019) Selenium, selenium-protoporphyrin and viral infection. Nutrients 11(9):2101. https://doi.org/10.3390/nu11092101

Haase H (2018) Innate immune cells speak manganese. Immunity 1014 P. K Kumar et al.

Herr C, Shaykhiev R, Bals R (2007) The role of cathelicidin and RIG-I ubiquitination. J Virol. https://doi.org/10.3390/v13010047

Han JE, Jones JL, Tangpricha V, Brown MA, Hao L, Hebbar G et al (2016) High dose vitamin D administration in ventilated intensive care unit patients: a pilot double blind randomized controlled trial. J Clin Transl Endocrinol 4:59–65. https://doi.org/10.1016/j.jcte.2016.04.004

Heikkinen T, Järvinen A (2003) The common cold. Lancet 361(9351):51–59. https://doi.org/10.1016/S0140-6736(03)60225-6

Hemila H (2016) Vitamin E administration may decrease the incidence of pneumonia in elderly males. Clin Interv Aging 11:1379–1385. https://doi.org/10.2147/CIA.S114515

Hemila H, Chalker E (2013) Vitamin C for preventing and treating the common cold. Cochrane database Syst Rev. https://doi.org/10.1002/14651858.CD000980.pub4

Hemila H, Chalker E (2019) Vitamin C can shorten the length of stay in the ICU: a meta-analysis. Nutrients 11(4):708. https://doi.org/10.3390/nu11040708

Herr C, Shaykhiev R, Bals R (2007) The role of cathelicidin and defensins in pulmonary inflammatory diseases. Expert Opin Biol Ther 7(9):1449–1461. https://doi.org/10.3331/nu1040708

Hu Y, Li W, Gao T, Cui Y, Jin Y, Li P et al (2017) The severe acute respiratory syndrome coronavirus nucleocapsid inhibits type I interferon production by interfering with TRIM25-mediated RIG-I ubiquitination. J Virol. https://doi.org/10.3399/vj.13010047

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y et al (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan. China Lancet 395(10223):497–506. https://doi.org/10.1016/S0140-6736(20)30183-5

Hubicka U, Padiasek A, Żuromska-Witek B, Szlósarczyk M (2020) Determination of Vitaminamins K1, K2 MK-4, MK-7, MK-9 and D3 in pharmaceutical products and dietary supplements by TLC-Densitometry. Processes 8(7):870. https://doi.org/10.3390/ijfs20194z

Hughes DA, Norton R (2009) Vitamin D and respiratory health. Clin Exp Immunol 158(1):20–25. https://doi.org/10.1111/j.1365-2249.2009.04001.x

Ivanov V, Ivanova S, Niedzwiecki A, Rath M, Niedzwiecki A (2020) Effective and safe global public health strategy to fight the COVID-19 pandemic: Specific micronutrient composition inhibits Coronavirus cell-entry receptor (ACE2) expression. https://doi.org/10.1056/NEJMoa2015432

Janssen R, Walk J (2020) Vitamin K epoxide reductase complex subunit 1 (VKORC1) gene polymorphism as determinant of differences in Covid-19-related disease severity. Med Hypotheses 144:110218. https://doi.org/10.1016/j.mehy.2020.110218

Jayawardena R, Sooriyacharachchi P, Chourdakis M, Jeewandara C, Ranasinghe P (2020) Enhancing immunity in viral infections, with special emphasis on COVID-19: A review. Diabetes MetabSyndr Clin Res Rev. https://doi.org/10.1016/j.dsx.2020.04.015

Kariwa H, Fujiy N, Takashima I (2006) Inactivation of SARS coronavirus by means of povidone-iodine, physical conditions and chemical reagents. Dermatology 212(Suppl. 1):119–123. https://doi.org/10.1159/000089211
Role of vitamins and minerals as immunity boosters in COVID-19

Martínez-Moreno J, Hernandez JC, Urcuqui-Inchima S (2020) Effect of high doses of vitamin D supplementation on dengue virus replication, Toll-like receptor expression, and cytokine profiles on dendritic cells. Mol Cell Biochem.464(1–2):169–180. https://doi.org/10.1007/s11010-019-03658-w

Matikainen S, Ronni T, Hurme M, Pine R, Julkunen I (1996) Retinoic acid activates interferon regulatory factor-1 gene expression in myeloid cells

Mccann JC, Ames BN (2020) Vitamin K, an example of triage theory: is micronutrient inadequacy linked to diseases of aging? 1–3. https://doi.org/10.3945/ajcn.2009.27930

Mehmel M, Jovanovic N, Spitz U (2020) Nicotinamide riboside—the current state of research and therapeutic uses. Nutrients 12(6):1616. https://doi.org/10.3390/nu12061616

Meydani SN, Lewis ED, Wu D (2018) Perspective: Should vitamin D, magnesium and omega-3 fatty acids: could they help against COVID-19? Maturitas. https://doi.org/10.1016/j.maturitas.2020.08.003

Shakoor H, Feehan J, Mikkelsen K, Al Dhaheri AS, Ali HI, Platat C, Ismail LC et al (2020a) Immune-enhancing role of vitamin D, C, E, zinc, selenium and omega-3 fatty acids: could they help against COVID-19? Maturitas. https://doi.org/10.1016/j.maturitas.2020.08.003

Shakoor H, Feehan J, Mikkelsen K, Al Dhaheri AS, Ali HI, Platat C, Ismail LC, Stojanovska L, Apostolopoulos V (2020b) Be well: a potential role for vitamin D in COVID-19. Maturitas. https://doi.org/10.1016/j.maturitas.2020.08.007

Shafiri A, Vahedi H, Nedjat S, Rafiei H, Hosseinzadeh-Attar MJ (2019) Effect of single-dose injection of vitamin D on immune cytokines in ulcerative colitis patients: a randomized placebo-controlled trial. APMIS 127(10):681–687. https://doi.org/10.1111/apm.12982

Sheybani Z, Dokoozlian MH, Negahdarpour M, Dehdashti M, Zolghadr H, Moghadami M, Masoompour SM, Zolghadr AR (2020) The role of folic acid in the management of respiratory disease caused by COVID-19

Shibata N, Kuniwasa J, Kiyono H (2017) Dietary and microbial metabolites in the regulation of host immunity. Front Microbiol 8:2171. https://doi.org/10.3389/fmicb.2017.02171

Sigel H (2000) Metal ions in biological systems: manganese and its role in biological processes, vol 37. CRC press

Spiegel M, Pichlmair A, Martínez-Sobrido L, Cros J, García-Sastre A, Haller O et al (2005) Inhibition of beta interferon induction by severe acute respiratory syndrome coronavirus suggests a two-step model for activation of interferon regulatory factor 3. J Virol 79(4):2079–2086. https://doi.org/10.1128/JVI.79.4.2079-2086.2005

Spinas E, Saggini A, Kritas SK, Cerulli G, Caraffa A, Antinolfi P (2015) Crossstalk between vitamin B and immunity. J Biol Regul Homeost Agents 29(2):283–288

Tan CW, Ho LP, Kalimuddin S, Cherng BPZ, Teh YE, Thienn Y et al (2020) A cohort study to evaluate the effect of combination Vitamin D, Magnesium and Vitamin B12 on progression to severe outcome in older COVID-19 patients. Nutrition. https://doi.org/10.1016/j.nut.2020.06.011

Tay MZ et al (2020) Inflammation and intervention, pp 363–374

Te Velthuis AJW, van den Worm SHE, Sims AC, Baric RS, Snijder EJ, van Hemert MJ (2010) Zn2+ inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathog 6(11):e1001176. https://doi.org/10.1371/journal.ppat.1001176

Trottier C, Chabot S, Mann KK, Colombo M, Chatterjee A, Miller WH Jr et al (2008) Retinoic acid inhibits measles virus in vitro via nuclear retinoic receptor signaling pathways. Antiviral Res 80(1):45–53. https://doi.org/10.1016/j.antiviral.2008.04.003

Turkia M (2020) COVID-19 and iodide. Available at SSRN 3585989

Ueland PM, McCann A, Midttun Ø, Ulvik A (2017) Inflammation, cytokines in ulcerative colitis patients: a randomized placebo-controlled trial. APMIS 127(10):681–687. https://doi.org/10.1111/apm.12982

Venturi S, Donati FM, Venturi M, Venturi A, Grossi L, Guidi A (2000) Role of iodine in evolution and carcinogenesis of thyroid, breast and stomach. Adv Clin Pathol 4:11–18
Verhagen H, Buijsse B, Jansen E, Bueno-De-Mesquita B (2006) The state of antioxidant affairs. Nutrition Today 4:244–252
Booth LS, Vitamin K: food composition and dietary intakes, 2012. Food & nutrition research. 56(5):5505. https://doi.org/10.3402/fnr.v56i0.5505
Warnes SL, Little ZR, Keevil CW (2015) Human coronavirus 229E remains infectious on common touch surface materials. MBio. https://doi.org/10.1128/mBio.01697-15
Yuan S, Chu H, Chan JF-W, Ye Z-W, Wen L, Yan B et al (2019) SREBP-dependent lipidomic reprogramming as a broad-spectrum antiviral target. Nat Commun 10(1):1–15. https://doi.org/10.1038/s41467-018-08015-x
Yuki K, Fujiogi M, Koutsogiannaki S (2020) COVID-19 pathophysiology: a review. In: Clinical immunology. Academic Press Inc., pp 108427. https://doi.org/10.1016/j.clim.2020.108427.
Zabetakis I, Lordan R, Norton C, Tsoupras A (2020) COVID-19: the inflammation link and the role of nutrition in potential mitigation. Nutrients 12(5):1466. https://doi.org/10.3390/nu12051466
Zemlin AE, Wiese OJ (2020) ANNALS EXPRESS: Coronavirus disease 2019 (COVID-19) and the renin-angiotensin system: a closer look at angiotensin-converting enzyme 2 (ACE2). Ann Clin Biochem 0004563220928361
Zhang L, Liu Y (2020) Potential interventions for novel coronavirus in China: a systematic review. J Med Virol 92(5):479–490. https://doi.org/10.1002/jmv.25707
Zhang Y, Zhou W, Yan J, Liu M, Zhou Y, Shen X et al (2018) A review of the extraction and determination methods of thirteen essential vitamins to the human body: an update from 2010. Molecules 23(6):1484. https://doi.org/10.3390/molecules23061484
Zhang H, Penninger JM, Li Y, Zhong N, Slutsky AS (2020a) Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: molecular mechanisms and potential therapeutic target. Intensive Care Med 46(4):586–590. https://doi.org/10.1007/s00134-020-05985-9
Zhang J, Taylor EW, Bennett K, Saad R, Rayman MP (2020b) Association between regional selenium status and reported outcome of COVID-19 cases in China. Am J Clin Nutr 111(6):1297–1299. https://doi.org/10.1093/ajcn/nqaa095

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