

Review

# Prevention is always better than Cure: Immunity Boosting to Fight Infections

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**Abstract:** Since the first outbreak of SARS-CoV2, Severe Acute Respiratory Syndrome Coronavirus-2 in Wuhan, China in the December 2019, the world continues to be in state of fear, uncertainty, tension and anxiety till date and this state might continue because of emerging mutants. The vaccination drive all over the world is continuing, still the new variants are cause of concern, with the aim to prevent the spread of the virus, focus should be on techniques and processes which helps in strengthening our defense mechanism, the immune system. It has becoming clear from several studies that the immune system is greatly impacted by the COVID-19 infection through several inflammatory reactions. The role of balanced diet full of nutrients cannot be overlooked in controlling infectious diseases. A balanced diet which should include plant foods, vitamins and micronutrients and this review wants to emphasize on the preventive role played by the plant foods, vitamins and minerals in COVID-19 infections, to reduce the mortality rate as well as the morbidity in patients who are infected.

**Keywords:** Immune response, plant food, vitamins, minerals, COVID-19, variants

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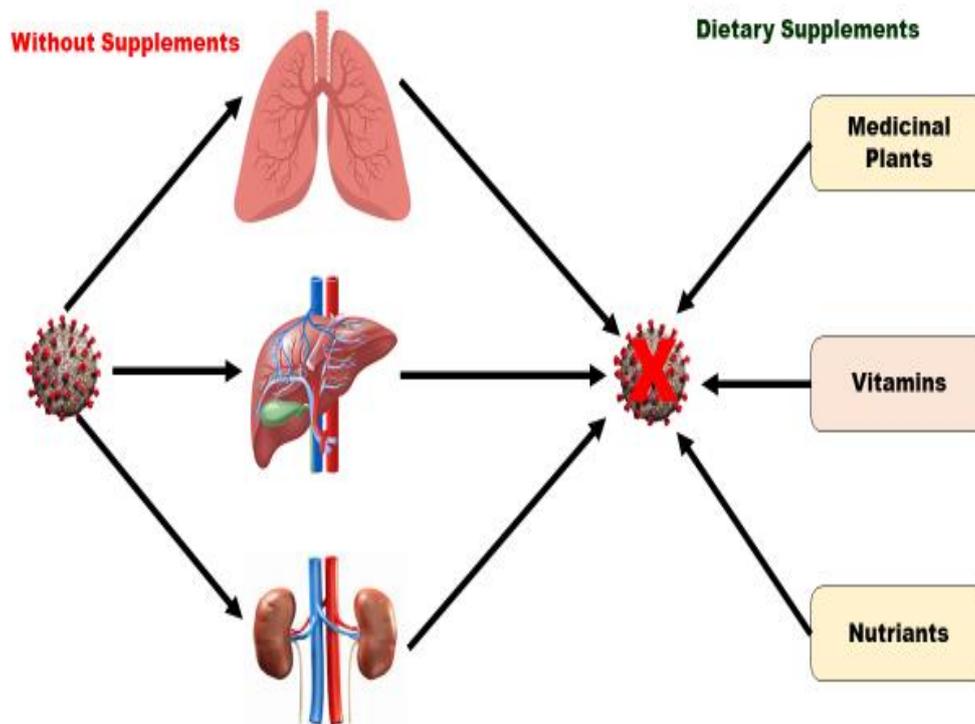
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## 1. Introduction

The world is not free of COVID-19 yet and with emerging strains corona the virus is surviving, and this is keeping most of us under lockdown across the globe. The impact has not only been on physical and mental well-being [1] but also on the world economy. Despite vaccination drives being taken in all the countries, the fear of the virus is still looming large as no vaccine can give 100% protection against the mutated strain [2]. Many studies have focused attention on enhancing immunity as the immunocompromised people are easy target of emerging infections and other diseases which have become rampant in today's changing lifestyle [3]. Treating viral diseases is challenging because of resistance, emergence of new strains, adaptability of the virus and the inadequacy of antibiotics [4]. To continue fighting with the SARS-CoV2 we need to concentrate on plant-based food, vitamins, food supplements and micronutrients which would enhance the immunity, and impact the overall health and well-being (Figure 1). Enhanced immune power gives the controlling power to the host and prevent various pathogens from causing infection [5]. It was observed by researchers from the SARS autopsies, that the T-lymphocytes and macrophages found in blood, lungs, spleen and lymph nodes and were infected [6,7] and concentrations of immune cells were also reduced. Both T-lymphocytes and monocytes/macrophages are implicated in adaptive and innate immunity and the immune system gets weakened when an infection happens in these cells. These evidences suggest a strong correlation between the spread of viral infection to the weakened immune system.



**Figure 1.** Role of Dietary supplements to inhibit the COVID-19 infection

The aim of the present review is to document easily accessible immunity boosters which includes food plants, vitamins and micronutrients (micro & macro) that can modulate the immune system and give the ability to fight primary and secondary infections. Most of the patients who died of Covid-19 were suffering from other health issues [8], which is an indication that for minimizing the associated risk factors related to Covid-19, the overall health and the immune system have a major role to play.

## 2. Role of Plants

Mostly all cultures have been using plants in traditional medicines in curing several chronic infections which also included viral diseases [9-11]) and presently researchers are trying to validate the health benefits of nutraceuticals [12-14]. Various parts of the plant contain components which include flavonoids, alkaloids, terpenoids and polysaccharides, are mainly responsible for immunomodulatory properties [15,16].

Both garlic and liquorice can be used to improve the immune responses, have antiviral and other biological properties. The bioactive compound containing sulphur and polyphenols in garlic are responsible for immunodulation [17,18]. The saponin glycyrrhizin in the root of liquorice is causing the enhancement-of immunity and other responses [19]. Curcumin obtained from *C. longa* is responsible for enhancing body's defense. Black and green tea have immunostimulatory effect because of epigallocatechin gallate, gallic acid and quercetin [20,21]. Some of the medicinal plants and food supplements to boost immune power are presented in Figure 2.



**Figure 2.** Medicinal plants and food supplements boost immune power to fight against COVID infection

Mushrooms contain antioxidants that regulate immunity and are beneficial in reducing inflammation. Bitter greens augment liver health and help in production of natural killer cells and proper functioning of T-cell [41]. Flax seeds also aid in immune health being good source of omega-3 fatty acids. The vegetables and fruits which are brighter due to anti-inflammatory and anti-oxidant phytochemicals like polyphenols, flavonoids, carotenes and anthocyanidins are immunity boosting and are integral part of well-balanced diet.

### 3. Role of vitamins

Many studies have demonstrated the role of vitamins like A, B, C, D, E and K in boosting immunity [42], the nutritional supplements can help in reducing the viral load and also rates of hospitalization in COVID-19 patients. Vitamins show immunodulatory and antioxidative responses, they modulate the expression of genes in immune cells and also help in differentiation and maturity of immune cells.

#### Vitamin A

Vitamin A or retinoic acid [43], regulates number of genes in both adaptive and innate responses [44]. Vitamin A facilitates innate and adaptive immunity by acting as T-cell effectors. Retinoid stimulates the expression of number of genes which includes Interferon stimulated genes, retinoic acid-inducible gene I and IFN regulatory factor 1 [45-47]. Table 1 shows the recommended doses of vitamin A for all.

**Table 1.** Recommended doses of vitamin A in different ages including Pregnant and lactating woman

Sl. No.	Age	Recommended dose	
		Male	Female
1.	0 to 6 months	400 mcg (16000 IU)	400 mcg (16000 IU)
2.	7 to 12 months	500 mcg (20000IU)	500 mcg (20000IU)
3.	1 years to 3 years	300 mcg (12000 IU)	300 mcg (12000 IU)
4.	4 years to 8 years	400 mcg (16000 IU)	400 mcg (16000 IU)
5.	9 years to 13 years	600 mcg (24000 IU)	600 mcg (24000 IU)
6.	14 years to 18 years	900 mcg (36000 IU)	700 mcg (28000 IU)
7.	Above 19 years	900 mcg (36000 IU)	700 mcg (28000 IU)
8.	Pregnant woman		770 mcg (30800 IU)
9.	Lactating woman		1300 mcg (52000 IU)

### Vitamin B

Vitamin B complex includes 8 vitamins namely vitamin B1, vitamin B2, vitamin B3, vitamin B5, vitamin B6, vitamin B7, vitamin B8 and vitamin B12, it is essential in normal physiological functioning [48], regulating the immune response of the colon and also involved in barrier function of the intestine [49]. The deficiency of B1 or thiamine effects the immune system causing oxidative stress and elevated inflammation. Thiamine triggers humoral and cell mediated immunity and thus helps in eliminating SARS-CoV-2 virus. Vitamin B2 or riboflavin can reduce the risk of transfusion-transmission in COVID-19 patients by reducing pathogens in blood. Recent studies in patients with COVID-19 and vitamin B3 or niacin showed reduction in inflammation and thus vitamin B3 can be used in adjunct therapy [50,51]. Vitamin B6 or pyridoxine also contributes to immune response as well as plays role in propagation of immune cells [52]. Studies have shown that supplements with pyridoxine helps in reducing pro-inflammatory cytokines in COVID-19 patients thereby preventing hypercoagulation and bettering the immune responses. Vitamin B9 or folate is essential in adaptive immune response and can block the spike protein binding by inhibiting the enzyme, furin responsible for viral and bacterial infection. It can be used as preventive measure to control the respiratory diseases due to SARS-CoV-2 [53]. It has been reported by researchers that folic acid, tetrahydrofolic acid and 5-methyl tetrahydrofolic acid can prevent the interaction of S protein with ACE-2 receptor [54] and thus could be helpful in combating the COVID-19 infection. Vitamin B12 or cobalamin/cyanocobalamin can modulate the cytokine formation, may regulate chemokine/cytokine formation and mediate in the pathophysiological pathways through the immune cells due to which they can protect against pathogens. Studies on the role of probiotics have been undertaken and they suggest that they can regulate immune responses and provide protection against infections. [55]. Table 2-4 shows the recommended doses of vitamin B12, B7 and folic acid respectively for all.

**Table 2.** Recommended doses of vitamin B12 in different ages including Pregnant and lactating woman

Sl. No.	Age	Recommended dose	
		Male	Female
1.	0 to 6 months	0.4 mcg (16IU)	0.4 mcg (16IU)
2.	7 to 12 months	0.5 mcg (20 IU)	0.5 mcg (20 IU)
3.	1 years to 3 years	0.9 mcg (36IU)	0.9 mcg (36IU)
4.	4 years to 8 years	1.2 mcg (48IU)	1.2 mcg (48IU)
5.	9 years to 13 years	1.8 mcg (72IU)	1.8 mcg (72IU)
6.	Above 14 years	2.4 mcg (96IU)	2.4 mcg (96IU)
7.	Pregnant woman	-	2.6 mcg (104IU)
8.	Lactating woman	-	2.8 mcg (112IU)

**Table 3.** Recommended doses of Biotin (vitamin B7) in different ages including Pregnant and lactating woman

Sl. No.	Age	Recommended dose	
		Male	Female
1.	0 to 6 months	5 mcg (200 IU)	5 mcg (200 IU)
2.	7 to 12 months	6 mcg (240 IU)	6 mcg (240 IU)
3.	1 years to 3 years	8 mcg (320 IU)	8 mcg (320 IU)
4.	4 years to 8 years	12 mcg (480 IU)	12 mcg (480 IU)
5.	9 years to 13 years	20 mcg (800 IU)	20 mcg (800 IU)
6.	14 years to 18 years	25 mcg (1000 IU)	25 mcg (1000 IU)
7.	Above 19 years	30 mcg (1200 IU)	30 mcg (1200 IU)
8.	Pregnant woman		30 mcg (1200 IU)
9.	Lactating woman		35 mcg (1400 IU)

**Table 4.** Recommended doses of Folic acid in different ages including Pregnant and lactating woman

Sl. No.	Age	Recommended dose	
		Male	Female
1.	0 to 6 months	65 mcg (2600 IU)	65 mcg (2600 IU)
2.	7 to 12 months	80 mcg (3200IU)	80 mcg (3200IU)
3.	1 years to 3 years	150 mcg (6000 IU)	150 mcg (6000 IU)
4.	4 years to 8 years	200 mcg (8000 IU)	200 mcg (8000 IU)
5.	9 years to 13 years	300 mcg (12000 IU)	300 mcg (12000 IU)
6.	14 years to 18 years	400 mcg (16000 IU)	400 mcg (16000 IU)
7.	Above 19 years	400 mcg (16000 IU)	400 mcg (16000 IU)
8.	Pregnant woman		600 mcg (24000 IU)
9.	Lactating woman		500 mcg (20000 IU)

### Vitamin C

Linus Pauling advocated about the conducive effect of vitamin C in common cold though his book “Vitamin C and the Common Cold” in 1970 and some researchers have also documented about the viricidal feature of vitamin C [56]. It gives support to immune system, has antioxidant property, and helps in eliminating dead cells and replacing them with newer ones [57]. It has been documented by Kashiouris et.al. that the infections like acute respiratory distress syndrome and sepsis was significantly reduced by administering vitamin C injection [58]. The efficiency of vitamin C in treating COVID-19 has been proven both directly and indirectly. Data from trial on patients suffering from pneumonia showed the efficacy of two vitamin C dose regime in reducing the duration of pneumonia [59]. Hence it is very pertinent in this pandemic to get substantial research data addressing the effectiveness of vitamin C in treatment and prevention of COVID-19 [60]. Table 5 shows the recommended doses of vitamin C for all.

**Table 5.** Recommended doses of vitamin C in different ages including Pregnant and lactating woman

Sl. No.	Age	Recommended dose	
		Male	Female
1.	0 to 6 months	40 mg (800IU)	40 mg (800IU)
2.	7 to 12 months	50 mg (1000IU)	50 mg (1000IU)
3.	1 years to 3 years	15 mg (300IU)	15 mg (300IU)
4.	4 years to 8 years	25 mg (500IU)	25 mg (500IU)
5.	9 years to 13 years	45 mg (900IU)	45 mg (900IU)
6.	14 years to 18 years	75 mg (1500IU)	65 mg (1300IU)
7.	Above 19 years	90 mg (1800IU)	75 mg (1500IU)
8.	Pregnant woman	-	80 mg (1600IU)
9.	Lactating woman	-	85 mg (1700IU)
10.	Smokers		35 mg (700 IU)

### Vitamin D

It has been reported by researchers in many countries of the world that average vitamin D levels has strong link with the number of COVID-19 infections as well as with the associated death due to the infections [61]. In order to reduce the cases of COVID-19 infection, criticality and mortality from COVID-19 the vitamin D supplementation are recommended [62] Table 6 shows the recommended doses of vitamin D for all.

**Table 6.** Recommended doses of vitamin D in different ages including Pregnant and lactating woman

Sl. No.	Age	Recommended dose
1.	0 to 12 months	10 mcg (400IU)
2.	1 years to 13 years	15 mcg (600IU)
3.	14 years to 18 years	15 mcg (600IU)
4.	19 years to 70 years	15 mcg (600IU)
5.	Above 71 years	20 mcg (800IU)
6.	Pregnant and lactating woman	15 mcg (600IU)

The data from retrospective cohort study by Demir et.al. also found that the deficiency of vitamin D was associated with greater infection probability by coronavirus. The patients who were found to be COVID-19 positive having adequate levels of vitamin D

showed remarkably lesser D-dimer levels in blood also lower CRP level, which is the inflammatory marker, decreased recurrence of ground-glass opacity in CT scan of chest region and brief hospital stay [63].

#### Vitamin E

Vitamin E acts as regulator of immune response, supports in functioning of the immune system as well is a free radical scavenger [64,65]. It inhibits the metabolism of arachidonic acid by increasing the level of prostacyclin thereby causing dilation of blood vessels and inhibiting the aggregation of platelets (vitamin E—Health Professional Fact Sheet). Few studies documented that vitamin E plays more important role in maintenance of immune response in elderly than in younger individuals [66,67]. Table 7 shows the recommended doses of vitamin E for all.

**Table 7.** Recommended doses of vitamin E in different ages including Pregnant and lactating woman

Sl. No.	Age	Recommended dose	
		Male	Female
1.	0 to 6 months	4 mg (6IU)	4 mg (6IU)
2.	7 to 12 months	5 mg (7.5IU)	5 mg (7.5IU)
3.	1 years to 3 years	6 mg (9IU)	6 mg (9IU)
4.	4 years to 8 years	7 mg (10.4IU)	7 mg (10.4IU)
5.	9 years to 13 years	11 mg (16.4IU)	11 mg (16.4IU)
6.	Above 14 years	15 mg (22.4IU)	15 mg (22.4IU)
7.	Pregnant woman	-	15 mg (22.4IU)
8.	Lactating woman	-	19 mg (28.4IU)

#### Vitamin K

Vitamin K is natural content present in some food, it functions as a co-enzyme, synthesizes proteins and also involved in various biological functions. The dietary supplements of vitamin K are K1 and K2 [68].

In case of inflammation in the body due to SARS-CoV-2 infection, synthesis of Matrix Gla protein in the lungs increases to safeguard the extracellular matrix of the lungs from degradation. The synthesis of Matrix Gla protein is dependent on the vitamin K thereby during this type of infection utilization of vitamin K is also increased [69]. The thrombotic complications which are seen in COVID-19 patients can be combated by vitamin K1, which is required in activation of hepatic coagulation factors. [70]. Table 8 shows the recommended doses of vitamin K for all.

**Table 8.** Recommended doses of vitamin K in different ages including Pregnant and lactating woman

Sl. No.	Age	Recommended dose	
		Male	Female
1.	0 to 6 months	2.0 mcg (80 IU)	2.0 mcg (80 IU)
2.	7 to 12 months	2.5 mcg (100IU)	2.5 mcg (100IU)
3.	1 years to 3 years	30 mcg (1200 IU)	30 mcg (1200 IU)
4.	4 years to 8 years	55 mcg (2200 IU)	55 mcg (2200 IU)
5.	9 years to 13 years	60 mcg (2400 IU)	60 mcg (2400 IU)
6.	14 years to 18 years	75 mcg (3000 IU)	75 mcg (3000 IU)
7.	19 years to 50 years	120 mcg (4800 IU)	90 mcg (3600 IU)
	50 years to 70 years	120 mcg (4800 IU)	90 mcg (3600 IU)
	Above 70 years	120 mcg (4800 IU)	90 mcg (3600 IU)
8.	Pregnant woman		75mcg (3000 IU)
9.	Lactating woman		90 mcg (3600 IU)

#### 4. Role of Minerals

Many studies have documented the functionality of trace elements in enhancing and maintaining immune responses thereby decreasing rate of infection. Gombart *et al.* showed that minerals enact the role of barriers against pathogens, act as antioxidant enhancing the innate and adaptive immunity as well elevates the antibody production [71]. Some of the minerals play the role of enzymatic co-factors which are essential in immunity (Figure 3) The nutritional status of a person can indicate the possibility of some bacterial and viral infections [72]. Table 9 shows the recommended doses of Zinc, Copper, Iron, Selenium, Magnesium and Manganese for all.

##### Zinc

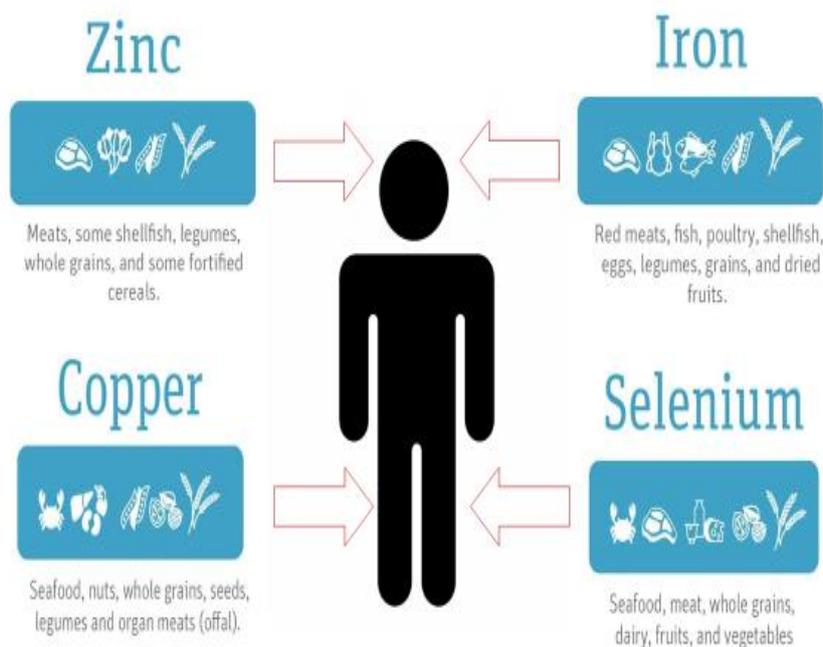
Zinc is essential to the cell activity of natural killer cells and cytokine release. It is involved in antibody and interferon production [71]. It modulates the responses of immune cells like macrophages, B cells and neutrophils T cells [73]. It is an important constituent of enzymes like polymerases and proteases and also cofactor of enzymes like superoxide dismutase, which is an antioxidant enzyme required for producing metallothionein. This cysteine rich protein maintains cellular immunity by protecting from free radicals [72]. Other researchers have also documented the role of metallothionein as a sensor of the intracellular matrix [74], it acts as an anti-oxidant through many interlinked processes [75]. Studies on animals have shown that there is a strong correlation between immunity and levels of zinc, deficiency leads to immunity loss [76]. The use of zinc has been beneficial in reducing the infection in the respiratory tract [77]. Doses of zinc at 75mg/day can help in reducing the symptoms associated with common cold in 2 days [78]. Zinc has been used in treating measles [79], hepatitis virus, herpes simplex virus, human papillomaviruses [80], HIV [81]. Zinc can play an important role in activation of immune response and treating viral infections.

##### Copper

The use of copper as an anti-bacterial and anti-viral agent has been known since long, it is used as a disinfectant too. Owing to its unpaired electron, it undergoes redox reaction, thereby destroying the genetic material of viruses by free radical generation. The free radicals are responsible for oxidative damages as observed by Vincet *et al.* in Herpes simplex virus [82]. The effectiveness of copper against other viruses like influenza and noroviruses have also been studied by other workers [82]. The cellular defense functions of antioxidant

enzyme superoxide dismutase are dependent on copper [81]. The production of interleukin -2 is also dependent on copper thereby plays a role in the T cell development, inflammatory and adaptive immune responses [71].

The antiviral activity of copper was investigated by some researchers and they documented that 6mM of cupric ion was efficacious against HIV virus [82]. Copper ions hindered the process of reverse transcription of the RNA template of the HIV virus.



**Figure 3.** Micronutrients inhibit the severity of COVID-19 infection and increased immunity

### Selenium

Selenium is key micronutrient required in many physiological processes such as enhancement of immune responses, protection from oxidative stress, cellular differentiation, free radical scavenging and maintenance of antibody levels. The viral infections are associated with generation of reactive oxygen species leading to oxidative stress which is damaging to the cells [71]. Selenium is an important constituent of selenocysteine which contains selenoprotein enzymes essential for antioxidant activity [84-86], regulation of oxidation-reduction reaction, production of natural killer cells and interferon [71]. Selenium is required for regulating the gene expression for formation of selenoprotein [84]. It was documented by some researchers that 200µg/day supplementation of selenium showed virucidal action during infections [71], which proves selenoprotein S plays a role in immune function. Other workers also reported the supplementing selenium was beneficial against hepatitis, influenza A viruses and HIV [86]. The authors reported that selenium is involved in reduction of oxidative stress, increment of CD8+ T cells, production of Interleukin-2 and proliferation of T cells.

### Iron

Iron is an essential micronutrient which is vital for synthesis of protein and DNA, cell proliferation, lymphocytes maturation and gene regulation [74,75,87]. Homeostasis of iron is very important as through Fenton reaction hydroxyl radicals are generated which damages lipids, proteins and deoxy ribose nucleic acid [88]. The iron-bound protein, Lactoferrin is the first line of defense against pathogens [89]. The host and the viruses are

competing with each other for acquiring iron as the replication of virus requires iron too [90]. Many other researchers have correlated the elevated levels of iron to promotion of viral replication in Hepatitis B [91], and HIV infection [92]. Thus, to inactivate the virus, iron chelates can be used thereby removing free iron and regulating iron levels in cells leading to control of gene expression required for metabolism of iron [90].

**Table 9.** Recommended doses of Zinc (Zn), Iron (Fe), Copper (Cu), Selenium (Se), Magnesium (Mg) and Manganese (Mn)

Sl. No.	Elements	Recommended Daily Dose (mg)	Tolerable Upper Intake Limit (mg)
1.	Zinc (Zn)	11 mg	40 mg
2.	Iron (Fe)	8 mg	45mg
3.	Copper (Cu)	900µg	10000 µg
4.	Selenium (Se)	55 µg	400 µg
5.	Magnesium (Mg)	310 mg	400 mg
6.	Manganese (Mn)	1.8 mg	11 mg

Patients suffering from COVID-19 infection have lower levels of sodium, potassium, calcium, phosphorus and the decrease in level increases with severity [93-95]. Stress is commonly associated with pandemics and magnesium supplementation can help in recovering from post-traumatic stress disorder. It is vital in immunoglobulin synthesis, binding of the lymphocyte, and other immune functions [96]. Magnesium is effective against viral infections as shown by some researchers [97]. Manganese is an important trace element; its deficiency leads to impaired antibody production hence plays a vital role in immune responses [98]. Manganese and cobalt can play supportive role in COVID-19 management and treatment. Iodine based products can be used as disinfectant against SARS-CoV-2 for gargling, throat spray, medical instrument disinfection, handwash and other external usage [99]. Sulphur might also show some protective action against SARS-CoV-2 [100].

This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.

#### 4. Bioavailability

The nutrients which are bioavailable for the cell metabolism of the host cell after digestion of the food is quite significant. The bioavailability is defined as quantity of nutrients released from the matrix which is at the disposal for absorption by the gastrointestinal tract. The bioavailability of the nutrients may vary [101] and is dependent on number of factors which can be internal and external. The former includes the gender, age, nutritional and biological status. The later includes the form of the nutrient, association with other nutrients, food matrix structure and amount of non-nutrient component present. Bioavailability can be measured by *in-vitro*, *ex-vivo* and *in-vivo* methods [102,103]. The bioavailability of proteins, lipids and carbohydrates is higher (around 90%) than micronutrients (ranging from 1-90%). The bioavailability of fat-soluble vitamins can be enhanced if taken with lipid supplementation. The bioavailability can be increased or decreased if the substance administered is having a synergistic or anti-synergistic effect. Absorption of iron is increased in presence of vitamin A and C but decreases when phytates and polyphenols are administered. The combined effect of vitamin C along with quercetin is helpful in controlling respiratory viral infections [104]. The age factor also influences the rate of absorption of minerals like zinc, calcium and iron, rate of absorption is greater compared to the elderly [105]. Intaking zinc at 150 mg per day and selenium 200 mg per day

would be effective in combating viral infections [97]. Care must be taken to consume food in correct combination so as to gain synergistic effect and for better nutrient absorptivity.

### **Way forward**

In current critical situation with the non-availability of curative viral drugs, nutrients play a vital role in controlling and maintaining normal bodily functions and health. They are critical in boosting immunity and resisting infection. Some of these nutrients are involved in protecting the body directly or indirectly from infections. The nutrients namely vitamins, minerals, sulphated polysaccharides and lactoferrin are directly countering the viruses or engaged in activating the immune cells by binding to the cell surface receptors. Some of the nutrients stop the viruses from getting absorbed or adsorbed to the surface of the cells. The immunity can be enhanced by the immunomodulatory action of nutrients and by regulating the macrophage functions. Minerals also modulate the activities of macrophages, T cells, B cells and neutrophils. The body needs to be kept hydrated that helps in the transmission of nutrients to all parts of the body and maintenance of body functions. Proper and balanced diet rich in nutrients both macro and micro can work out as a preventive solution to combat the virus. More clinical based investigations are required to highlight the mechanism of action of these nutrients in preventing the spread of infections. More studies are required in context to the concomitant use of nutrient supplements with antiviral drugs for efficient recovery.

### **Conflict of interest**

The authors have no conflict of interest to declare.

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### **Author Contributions**

SA & SD made a significant contribution to conduct the review, whether that is in the conception, literature review, drafting, preparation of data, acquisition of data, and interpretation. SS gave valuable insights and checking was done by TD. After critically reviewing the article, the authors gave final approval of the version to be published; have agreed on the journal to which the essay has been submitted; and agree to be accountable for all aspects of the work.

### **Disclosure**

The authors declare that they do not have any financial involvement. This also includes honoraria, expert testimony, employment, ownership of stocks or options, patents or grants received or pending, or royalties.

### **Peer-review:**

External peer-review was done through double-blind method.

### **Data and materials availability:**

All data associated with this study are present in the paper.

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