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Anti-Viral Immune Enhancer Properties of Some Micro-Nutrients and Functional Herbs With the Potential to Augment the Treatment of COVID-19 Patients.

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ABSTRACT

The world is currently experiencing a severe acute respiratory system challenge in 2021, which is a global pandemic caused by COVID-19 and is killing thousands of people worldwide. With having no particular vaccine and/or medical treatment and increased mortality over time consequently threatening community health and economics, urgent and accessible alternative strategies to mitigate this disease are required. Based on earlier studies on other coronavirus family members like MERS and SARs CoV, this review summarizes the potential use of particular micronutrients and herbs to lower risks, decrease the mortality rate, and/or treat current COVID-19. The authors conducted an online search using the terms MERS, SARS, and respiratory tract infection viruses in order to achieve that goal. The results of the systematic study showed that several nutrients including vitamin; D, A, E, C, B complex, zinc, selenium, Iron, and herbs such as garlic, black seed and licorice can be used as urgent supporting agents that can improve immune system and help mitigate against COVID-19. In conclusion, to control the COVID-19 outbreak, it has been suggested that all feasible measures, including preventative and prophylactic measures as well as community nutrition status, should be taken into account.

Introduction

In 2020, the world is suffering from a severe acute respiratory system, a pandemic that is caused by a novel coronavirus [1] which firstly emerged from Wuhan City of China in 2019. The virus was initially termed 2019-nCoV and then WHO renamed this to COVID-19 [2]. The virus belongs to B type coronaviruses which is a large group of viruses present universally and caused previous epidemics (SARS-CoV-2) in China in 2002 [3] and Middle East respiratory syndrome (MERS)-CoV in the Middle east in 2012 [4]. The COVID-19 genome (27-32kb) is an enveloped single positive stranded, RNA. The genome length is 29,881 bp which is responsible for encoding 9860. Furthermore, the structural protein is encoded by N, M, E and S genes. On the other hand, ORG region encodes 16 un-structural proteins [5].

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The disease has recently emerged and spread very rapidly among more than 145 countries as reported by [6] and so far, there are more than 1,415,000 confirmed cases with more than 81 thousand deaths. The symptoms

start from mild to severe flu and/or respiratory failure death with dissimilar death rates. It is associated with higher fatality in respect of male sex, advancing age, obesity, diabetes, hypertension, climatic factors, and in the UK and North America, with darker-skinned ethnicities [7,8]. Now, as there is internationally agreed functional vaccine, Synergistic effect of diet to boost immune system alongside with vaccines can be more powerful to combat the virus.

Dietary intervention and nutritional status is a suitable and applicable alternative to fight against diseases that have been shed light on by numerous researchers [9,10]. Furthermore, because of a high

percentage of similarity between high percentage of similarity between coronaviruses particularly MERS, SARS, and SARS-COV-2 [8], immune-enhancers and other nutrients-based treatment of coronaviruses can be considered to the current coronaviruses as described earlier [9]. The authors have stated that different vitamins and minerals can be a synergistic treatment along with vaccines in order to enhance immunity against this virus.

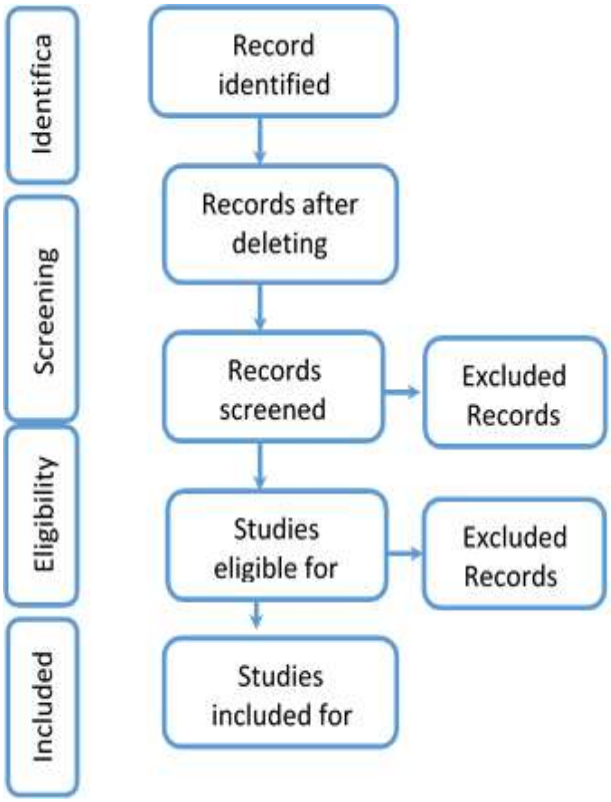
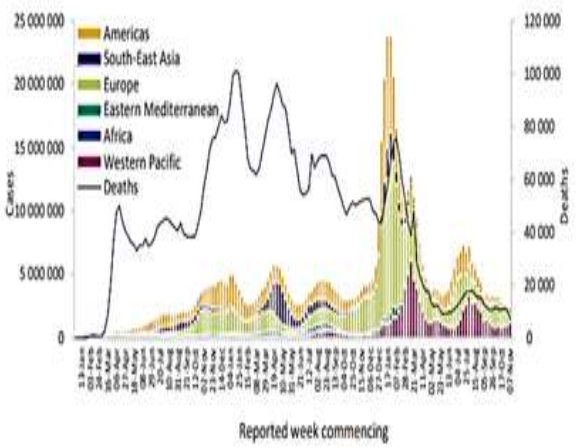


Figure 1. Number of confirmed COVID-19 cases, by date of the report and WHO region, as of 5 December 2021* accessed on 14th December 2021; data available from



https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---accessed on 6 December 2022

Therefore, diet and herbs based on extensive research in relation to SARS, MERS, and respiratory tract infection of these major viral pathogens were searched for in the scientific data basis. The obtained articles and their findings are concisely presented by their functional properties and special viral preventative characteristics with defined modes of action. Furthermore, the potential nutritional benefits of the aforementioned viruses and possibly COVID-19 and their possible mechanism have also been presented in this review.

Methodology and data extraction

This study was started at the beginning of April 2020 and reviewed the articles published in Web of Science and PubMed and searched online for the articles meeting our criteria which are peer-published research literature about nutrients and their relation to Coronavirus; SARS and MERS.

Furthermore, the study also searched for the proposed mechanism of action and possible therapeutic interfere with the immune system and above-mentioned viruses and potentially VOCI-19. The articles were imported into Mendeley's (Mendeley:1.19.4.0: Elsevier) bibliographic database. The Articles were screened and checked by researchers. Duplicate articles were removed and final articles to be eligible for inclusion in the review were selected.

2. Flow diagram explaining different steps of the systemic review

Nutrient-based potential immune enhancers for COVID-19

Nutrition is known to play a major role in clinical practice with its fundamental role in supporting a robust and effective immune system in humans. The data on nutritional support for COVID-19 patients remains fragmentary and vague. This often can be due to the prior nutritional history and current status of patients with symptoms whether mild or severe and the potential of malnutrition to enhance the risks of poor outcomes in the advanced stages of infection as reported by [11] .

Adequate protein and essential amino acid intake are well recognized along with a balanced energy supply in the diet comprising fat and carbohydrate in an optimum ratio. These macronutrients must be supported by a complement of both trace elements, minerals, and vitamins for effective metabolism and release of energy and the synthesis of key proteins such as the pro-

inflammatory and anti-inflammatory interleukins and cytokines and numerous other cell-mediated communication pathways dependent on specific proteins as components with both the innate and acquired immune cascade associated with combating infection at the cellular and humoral level. These can be operational at the intestinal mucosal interface and the systemic level. It was reviewed recently by [12], that pre-existing micronutrient deficiencies, even if only a single micronutrient, can impede immune function and increase susceptibility to infectious disease challenges. Evidenced study shows that population groups are more susceptible to micronutrient deficiencies, while certain disease pathologies and treatment practices may enhance risk. It was further stated by these authors that these groups tend to suffer increased morbidity and mortality from infectious diseases. It was suggested that optimization of general nutritional status, including micronutrients, can be effective in reducing the incidence of such diseases including COVID-19. The nutritional implications for the optimum interaction to mitigate against the onset symptoms and recovery potential for Covid-19 have been reviewed by [13].

However, they have proposed an unexplored and novel concept: by using traditional remedies or herbal plants to combat the pandemic to the treatment of COVID-19 patients and an immediate need for effective therapeutics against SARS-CoV-2 [14]. On the other scientific the body shielding and immune-modulating foods, to discern the efficacy of these foods against viral infections, especially SARS-CoV-2 [15,16]. Various studies investigated those plant-based foods that contain the powerful antioxidant glutathione and bioflavonoid quercetin. which plays a vital role to enhance the immunity of people and prevent various infections to control COVID-19 [17].

We focus here on the micronutrient class as potential support for optimal regulation and performance in combatting COVID-19 as immune-enhancing agents. We aimed to highlight specific groups of micronutrients and also herbal remedies that could be of value in mitigating or reducing the more serious manifestations of the symptoms of this pandemic. Also, the study had examined the impact of licorice with vitamin C to see the effect on the severity of the diseases. The study found that licorice can be used as an alternative treatment to reduce symptoms of COVID-19.

Table (1) the impact of some vitamins and minerals on immune system [18]

1	**Selenium**	• **Decrease oxidative stress** • **Improve adaptive immunity (T and B cells)** • **Decrease viral infection** • **Decrease infection I respiratory system in newborn babies.**
2	**Zinc**	• **Improve resistance against infection** • **Improve lymphocytes (T cells) and modifying production of cytokines** • **Decrease inflammation and oxidative stress**
3	**Vitamin A**	• **Improve immunity against infection** • **Developing phagocyte roles** • **Increasing number of lymphocytes**
4	**Vitamin c**	• **Reduce oxidative damage** • **Reduce infection severity especially pneumonia**
5	**Vitamin D**	• **Improve resistance against infection especially upper respiratory tract,** • **Decreased morbidity and mortality** • **Increasing number of lymphocytes** • **Decreased risks of autoimmune system**
6	**Vitamin E**	• **Improve immune systemic (adaptive) against infection**
7	**Vitamin B9**	• **Improve number and function of** • **Lymphocytes** • **Decrease susceptibility to infection**
8	**Vitamin B12`**	• **Improve resistance against infection** • **Improve T cell number and natural killer cells (NK)**
9	**Vitamin B6**	**Improving immune system and response such as lymphocytes production of cytokine and formation of antibodies**

Fat-soluble vitamin

Vitamin D

Vitamin D (VIT-D) is a fat-soluble vitamin and is associated with immune system function. In other words, deficiency of this vitamin could lead to vulnerability to diseases particularly flu and colds [19]. One of the ways of VIT-D synthesis occurs is by exposure to sunlight and generating 7-dehydocholesterol and subsequently due to a thermal reaction becomes VIT-D. On the other hand, VIT-D3 or oral VIT-D is transformed to 25-Hydroxy vitamin D in the liver to various hormones and metabolites and

finally calcitriol in the kidneys and also distributed systemically to other key tissues and organs. People who have insufficient exposure to sunlight (280-315nm) might suffer from VIT-D deficiency and are more at risk of becoming sick, especially people who work at night and are housebound may suffer from VIT-D deficiency including the elderly people. This is commonly observed at the end of winter. Coincidently, COVID-19 was firstly started in winter and mostly severely affected middle-aged to elderly people who might have VIT-D deficiency [20]. Underlying conditions may mediate increased risk – for example, diabetes is commoner in South Asians, and hypertension is commoner in black, African and Caribbean populations. "Vitamin D deficiency may also be important – skin pigmentation (melanin) inhibits the ability of Ultraviolet B in the sun's rays to stimulate vitamin D synthesis in the skin – consequently vitamin D deficiency is commoner in people of BAME origin.

It is widely recognized that vitamin D is important in supporting antiviral immune responses and in quenching potentially harmful inflammatory responses. "Therefore low vitamin D levels in people with darker skin could contribute to their worse outcomes." [21] have previously undertaken a national research study determining the risk factors for COVID-19, with a focus on understanding why BAME people are at a higher risk based on a systematic review and meta-analysis of individual participant data by these authors [21].

It was stated that there are complex socio-economic factors that would contribute to the number of ethnic minorities in some countries with the virus. Additionally, supplementation to prevent acute respiratory tract infections is advocated in their assessment. The prevalent of COVID-19 in some countries like China and Korea might partially be attributed to the low level of 25-Hydroxy vitamin D, especially in the winter season. It has been discovered that 25-Hydroxy VIT-D in postmenopausal women between July 2013 and February 2014 were ~14 ng/ml [22]. Similarly, in Korea between October 2011 and May 2014, 25-Hydroxy vitamin D concentrations of elderly people above 60 were ~15 ng/ml and ~18 ng/ml for women and men respectively [23]. The potential of VIT-D to reduce risks of viral diseases have been stated earlier such as Ebola, Measles, Mumps, and HIV [24]. In addition, it is crucial to maintain 25-Hydroxy VIT-D serum above 30ng/ml. The adequate VIT-D should not just reduce the risks of common flu and associated pneumonia, but also reduce the risks of coronavirus. A very recent study also found that supplementing VIT-D can be protective against acute respiratory infections particularly in people suffering from VIT-D deficiency [21].

Several studies proposed the anti-viral activity of VIT-D and explained mechanisms by which VIT-D reduces viral infections [25,28]. A comprehensive study by Jolliffe et al., 2019 was undertaken to examine whether VIT-D could prevent manifestations of COPD (Chronic Pulmonary Obstructive Disease) in susceptible patients. Their systematic review and meta-analysis of individual participant data from randomized controlled trials gave invaluable insights into how the vitamin could be used in clinical practice to mitigate these events. This could have important implications for the role of VIT-D in the mitigation of less severe COVID-19 infection. The meta-analysis by these authors showed no overall effect of VIT-D supplementation on the rate of moderate or severe COPD developments in patients. However, subgroup evaluations showed clinically and statistically significant shielding influence of VIT-D supplementation among patients with baseline circulating 25(OH) D concentrations of less than 25nmol/L. Given the high prevalence of profound VIT-D deficiency in people with COPD 26 and the large suppression in exacerbation rates observed with vitamin D supplementation in this cohort there is growing interest in using this as a biomarker for predisposition of the disease risk.

The results of the study supported a strategy of routinely testing vitamin D status in patients with COPD who experience manifestations of the disease and presenting dietary supplementation to those with blood circulating 25 (OH) D concentrations of less than 25nmol/L. A better model for how VIT-D can work may arise from animal studies such as those by Nonnecke et al (2014) who discovered that low levels of VIT-D caused coronavirus infections in young calves and possibly in pigs due to partial inability of young animals to satisfy vitamin D requirements from sunshine exposure.

Proposed mechanism of the effect of Vitamin D on the immune system

There are several proposed mechanisms regarding the effect of VIT-D on the immune system especially on viruses [29]. VIT-D improves cellular immunity through enhancing antiviral peptides such as defensins

[30] and cathelicidin [31] Cathelicidins possess anti-microbial activity against some microbes including enveloped viruses like coronavirus and can cause cell membranes to perturb and diminish the effects of endotoxins [32]. Furthermore, cathelicidin, LL-37 can impose direct impact on the virion and limit cytokine proliferation of flu virus in mice lungs and asthma patients [33] Similar results were found in COVID-19 patients in china [34]. It has also been believed that VIT-D can diminish the generation of pro-anti-inflammatory Th1 [35] and induce anti-inflammatory cytokines by microphages and the upregulation of mitogen-activated protein kinase phosphatase-1 and then controlling $_{P}$38 activation [36]. VIT-D can also affect the acquired immune system particularly if the second viral epidemic will happen as experienced in 1918–1919 with the influenza pandemic. People who experienced H1N1 influenza had relative immune and the epidemic majority caused the fresh youngsters [37]. Anti-viral activity of VIT-D has also been linked to gene expression that is associated with anti-oxidants generation in the body particularly glutamate–cysteine ligase modifier subunit and glutathione reductase. These anti-oxidants can spare vitamin D which has antimicrobial properties [38].

Vitamin E

VIT-E is a fat-soluble vitamin and plays several roles in the body and is involved in including anti-oxidant and free radical scavenging ability [39]. Human clinical trials and animal-based studies have demonstrated the benefits of consuming VIT-E. Supplementation of VIT-E for four months' duration significantly improved cell-mediated immunity in healthy elderly people. The authors have concluded that taking 200mg/day of VIT-E increases antibody titer response to viral infection (hepatitis B) by six-folds as well as significant anti-body in response to tetanus vaccine [40]. It has been reported that viral infection can be very dangerous when anti-oxidants like VIT-E are not present [41,42]. The results of a study showed that administering 1 g of VIT- C and 200 mg of VIT-E in elderly women significantly improved the immune system including the proliferative response of lymphocytes to the mitogen phyto hemagglutinin and phagocytic functions of polymorpho nuclear neutrophils [43]. Furthermore, to protect lungs from injury or inflammatory attacks by viruses like influenza, nuclear factor- -like-2 mediated anti-oxidant systems [44,45]. In addition, studies have shown that vitamins Like E in pre-ruminant calves can result in the bovine coronavirus [46] (Table 2).

Proposed mechanism of the effect of Vitamin E on the immune system

It has been reported that during a viral infection such as influenza, the free radical compounds are provoked resulting from unsaturated lipid oxidation of the cell membrane causing localized peroxidation. Furthermore, with an increase of free radicals all over the cells are infected, the pathogenicity of the viruses becomes severe. Consequently, all the naturals' anti-oxidants in the body are decreased including VIT-E [47]. These results suggest that anti-oxidants like VIT-E noticeably decrease risks of viral infection infectious and can be used in the case of COVID-19 (Figure 3).

Vitamin A

Vitamin A (VIT-A) is a fat-soluble vitamin and has three active forms that function and play numerous roles in the body including retinoic acid, retinal, and retinol. VIT-A deficiency can be related to the risks of many diseases [20]. VIT-A deficiency has also been linked to viral and bacterial infections such as measles and diarrhea [48]. Similarly, VIT-A supplementation was seen to decrease morbidity and mortality in some viral and bacterial diseases such as measles, diarrhea, measles-associated pneumonia, malaria [49], and human immunodeficiency virus infection (HIV) [50]. Furthermore, VIT-A also attenuated the negative effect of some life threatening diseases like HIV and malaria in children. Results for earlier studies have stated that VIT-A can be protective against acute respiratory infection in pre-school aged children [51]. Similar results were found later [52]. VIT-A has also been studied on coronavirus. It has been revealed that VIT-A deficiency reduced the effectiveness of coronavirus vaccines and lead to more susceptibility to viral infections [53] Moreover, it was noticed that chickens fed with marginally deficient in the VIT-A diet were profoundly affected when exposed to the coronavirus [54]. This might suggest that the more deficient VIT-A diet, the more susceptible to viral particularly coronavirus infection could be in humans.

Proposed mechanism of the effect of Vitamin A on the immune system

Vitamin A can interfere with the immune system either directly or indirectly through several mechanisms [55]. It has been reported that VIT-A can directly influence the host via main functions in

immune cells metabolism [56] and indirectly epithelial membrane function and cell differentiation [57]. It has also been suggested that adequate intake and status of VIT-A may improve defensive response to detrimental microbes, induce mitogen-stimulated T-cell proliferation production [58] and the response of anti-body for specific antigen[59,60] increase the potential to generate immunoglobulin A and G [61] Furthermore, VIT-A can increase the ability of CD4 cell to stimulate B-cell to respond to specific antigen [55] and enhance Th-2 type cytokine gene expression [62,63], and increase the potency of neutrophils to phagocyte detrimental microbial [64]. Therefore, VIT-A could be the supplementary treatment for covid-19 infections.

Water soluble vitamins

Vitamin B complex:

Vitamin B complexes are water-soluble vitamins that play several roles including acting as coenzymes and according to their types in the human body and their deficiency can cause associated health complications [65]. They are important therefore in several cases of modulating diseases. For instance, Riboflavin and UV light (B2) were strongly linked with reduction of titer of coronavirus in human blood plasma [66]. Vitamin B3 (Nicotinamide) showed significant effects on inhibiting neutrophil infiltration of the lungs during lung injury although caused hypoxemia [67]. Vitamin B5 supplementation noticeably modulated Innate Immunity and Adaptive Immunity and decreased colony-forming units Mycobacterium tuberculosis strain (H37Rv) in the lungs of rats [68]. Vitamin B6 deficiency can affect both cell-mediated and humoral immune cell functions [69], retarding the immune response (Delayed hypersensitivity) and impairing antibody response [70] particularly to pathogenic [71] and Differentiation and maturation of lymphocytes were modulated by VIT-B deficiency [72]. Vitamin B6 has been linked to the weakening immune system particularly in elderly people infected with the immunodeficiency virus [73]. Earlier research by Courtemanche et al (2004) found that folic acid deficiency is associated with weakening immune system in humans. Supplementing B6 vitamin in animal feed significantly improved immune response through affecting immunoglobulins G, A, and E, interferon-γ, interferon-γ and mRNA expression [74]. Vitamin B12 (cobalamin) supplementation significantly enhanced viral response to patients chronically infected with hepatitis C virus [75]. In a study about the impact of B12 on immune in low protein diet, it was found that supplementation of B12 significantly white blood cell and lymphocytes in rats [76]. B12 plays an important role in cell replication and DNA synthesis, more importantly, it acts as immunomodulatory through involvement in the synthesis of T-lymphocytes; a member of the immunity system, and the correct abnormal ratio between CD4/CD8. Vitamin B12 deficiency has also been linked with quicker infection with HIV virus [77]. Therefore, to reduce the risks of viral infections it is important to take vitamin B [78].

Proposed mechanism of the effect of Vitamin B complex on the immune system

Vitamin B deficiency of particularly B6 is connected with the suppression of TH1 and induces TH2 thereby decreasing lymphocyte proliferation and growth, ameliorating anti-body response, and attenuating pro-inflammatory cytokines IL1β IL-2, IL-2 receptor [79]. Vitamin B12 can protect and keep immune system resulting from malnutrition. Folic acid deficiency weakens the immune system via altering the ability of CD8 T-lymphocytes cells to proliferate in action with mitogen activation [80]. These effects can be seen with inadequate level VIT-B. It can be also seen that in adequate level of vitamin b complex can weaken the immune system and make the body to be more susceptible to different microbial infections including COVID-19.

Vitamin C:

Vitamin C (VIT-C) or ascorbic acid is a water-soluble compound and is well documented scientifically. Despite its role in collagen synthesis, it is better known for its anti-oxidant and anti-inflammatory properties and immune enhancer [81]. It has been investigated that VIT-C improved endothelial cellular function [82], [83], reduced atrial fibrillation incidents [84,85], improved blood pressure [86], improved ejection fraction of left ventricular action [87,88], decreased incidents of colds [89] shortened cold recovery duration [90] and decreased bronchoconstriction [91]. Several previous researchers have supported the idea that VIT-C has anti-viral activity and can enhance the immune system and possess the effect on severe acute respiratory tract infection. There is also evidence that VIT-C consumption can positively influence pneumonia [92]. VIT-C can also behave like anti-sensitivity to relief influenza-like symptoms including running nose, swollen paranasal sinuses and sneezing [61]. Fisher et

al (2012) studied the influence of VIT-C on abdominal sepsis-induced acute lung injury of mice; it was found that 200mg/kg of parenteral VIT-C protected the mice from the detrimental effect of sepsis [93]. Giving the same amount of VIT-C to mice reduced pro-coagulant and pro-inflammatory profile which enhance lung vascular injury [94]. Previous researches on animal have shown that VIT-C improved resistance of cultures of tracheal organs of chick embryo infected by avian coronavirus [95]. Therefore, in the absence of specific treatment for COVID-19, VIT-C could be taken into consideration [81].

Table (2) Antiviral properties of some nutrients and their action on specific viruses

Nutrients	Influence on specific viruses
Vitamin D	Calves coronavirus
Vitamin E	bovine coronavirus, Coxsackievirus,
Vitamin A	Chicken coronavirus HIV and acute respiratory infection, measles
Vitamin B	Human coronavirus, MERS-COV; ventilator lung injury
Vitamin C	Avian coronavirus; lower respiratory tract infections, Influenza
Zinc	SARS-Coronavirus , influenza virus and poliovirus, measles virus
Selenium	Avian coronavirus, influenza virus
Iron	Viral mutation, acute respiratory infection
PUFA	Influenza virus, HIV, Hepatitis C virus

***SARS-COV= Severe acute respiratory syndrome coronavirus, HIV=human immunodeficiency virus, PUFA=Poly unsaturated fatty acids**

Proposed mechanism of the effect of Vitamin C on the immune system

Several mechanisms have been proposed for the influence of VIT-C on immune system and antimicrobial effects. Inflammation and injury due to oxidation and damage to alveolar-capillary membrane coincidentally happened with acute respiratory distress syndrome which is known by low level of oxygen. This was also seen in COVID patients. In a recent study about clinical features of COVID-19 patients, a clear increase of oxidative stress and markers of inflammation (high-sensitivity C-reactive protein) was observed [34]. Furthermore, transcription of nuclear factor erythroid2 related factor-2 is an important gene expressing factors that plays am essential role on detoxification and anti-oxidant gene expressing and prevent the cells from oxidative stress [96].

Similarly, VIT-C plays an important role as anti-oxidant against oxidative stress which is a cellular response alongside with enzymes during inflammations [97]. It has also been suggested that VIT-C can protect subjects from detrimental influence of sepsis though amelioration of pro-inflammatory responses, improvement of epithelial membrane functions, diminish abnormities from sepsis-related coagulation and enhance alveolar fluid clearance [93]

Trace elements:

Zinc:

Zinc is dietary micronutrient which is required by the body for many functions associated with development and growth. Zinc also plays an important role in cell functions and enhancing and priming the immune system. It is also involved in more than a hundred enzymes related to carbohydrate metabolism and energy generation, protein breakdown and CO2 transportation, Iron synthesis nucleic acid synthesis [98]. In contrast, Zinc deficiency can increase vulnerability to infectious disease as a result of dysfunction of cell mediated and macromolecules mediated immunity [99]. In an in vitro study, it was found that intracellular Zn2+ concentration with zinc-ionophores like pyrithione (PT) managed efficiently inhibiting RNA replication of viruses including influenza and poliovirus. Moreover, the investigation also found that even low concentration of zinc and pyrithione (2 µM Zn2+ and 2 µM PT) impaired SARS-Coronavirus replication. Transporting zinc into cells resulted in inhibiting picornavirus impairing RNA replicating and polyprotein processing [100]. It was also seen that zinc could inhibit replication rhinoviruses which can cause upper and sometimes lower respiratory [101].

In a study concerning zinc gluconate and its influence of cold symptoms, it was found that giving 13.3 mg significantly reduced the duration of common cold [102]. Singh & Das (2013) have stated that giving a dose ≥ 75 mg/day of Zinc significantly reduced cold duration when administered within 24 hours of onset of symptoms. High dose (2,000 –3,000 mg ZnO/kg diet) of zinc oxide ameliorated the symptoms of gastroenteritis virus infections which they believe it also might work for coronaviruses like SARS-CoV [103]. Thus Zinc might not just influence the symptoms of viruses, it might potentially COVID-19, but it could also influence the virus per se [20]. Therefore, Zinc deficiency is frequently caused by modern food habits; previous research has shown that zinc deficiency predisposes patients to viral infections such as herpes simplex, the common cold, hepatitis C, the severe acute respiratory syndrome coronavirus (SARS-CoV-1), and human immunodeficiency virus [104]

Proposed mechanism of the effect of Zinc on the immune system

Several mechanisms that have been suggested on how zinc can modulate immune response and inhibit the influence of viruses that cause diseases like pneumonia, respiratory infection [105]. It has been tested and found that zinc can inhibit the RNA replication of viruses [106]. Moreover, Zinc can inhibit TNA polymerase in several viruses including coronavirus [107], [108]. Zinc chelation is another factor that could modulate cellular pathway and perturb virus replication. Furthermore, Zinc chelating can also activate nuclear factor kappa and impart anti-viral properties through enhancing interferon-mediated antiviral signaling that render epithelial cells resistance viral infection [109]. Zinc chelation influenced 2A proteinase of rhinovirus [110] and RdRp elongation in case of SARD corona [109]. Zinc also has shown to change different stages of viral infection of various viruses including poliovirus and picornaviruses through inhibition of protease activity [111]. Therefore, the role of Zinc seems to be as different as the strategies of the RNA replicated if different viruses are at play as pathogens to the host in question.

Selenium

Selenium is a very important dietary element that plays an important role in the well-being of the host. Previous investigations have shown that selenium deficiency can cause several health problems including infectious diseases [112,114]. In a recent study the impact of the combined influence of selenium with ginseng stem-leaf saponins on live avian coronavirus vaccines in chickens was assessed, the results showed synergistic effect enhanced immune response against the coronavirus vaccine [115].

Viruses taken in Selenium deficiency recovered mice rendered the virus to mutate and evolution genomic and still cause significant effect on healthy and adequate-selenium mice [116]. Similarly, an animal based challenge experiment, virus mild strain of influenza causes a severe pneumonitis and virulent was observed selenium deficient-mice in comparison to selenium-adequate mice [117]. Therefore, adequate selenium can reduce viral infection and help the host to recover soon. Thus, selenium can be a suitable option for patients with COVID-19 to reduce the symptoms and risks of the virus.

Recently an international team of scientists [118] were the first to demonstrate a significant, positive link between regional selenium status and the outcome of SARS-CoV-2 infection for COVID-19 patients in China. These reports are similar to widely disseminated findings for selenium, because it is well established that vitamin D3 increases the expression of several selenium-containing proteins and other antioxidant and anti-inflammatory genes involved in the infection process. Zhang et al. (2020) was demonstrated that by antisense and/or proteolysis, SARS-CoV-2 may be targeting genes that are upregulated by Se and/or vitamin D3 (e.g. thioredoxin reductase 1, glutathione peroxidase 1, and key enzymes involved in glutathione synthesis), resulting in virus-mediated knockdown at both the mRNA and protein levels [118].

Proposed mechanism of the effect of Selenium on the immune system

Several mechanisms have been proposed for the influence of selenium on microbes and immune systems. Selenium intervenes with oxidative stress and can alter viral replication and decrease viral pathogenicity [119]. Selenium can vastly improve the immune response and scavenge and protect cell damage from free radicals [120]. This has been attributed to genome mutation of the influenza virus that increases virulent action of influenza which caused infection and coupled with lack of glutathione peroxidase (a selenium dependent enzyme) activity as a result of selenium deficiency, both increased oxidative stress in mice selenium deficiency (Figure 3). Previous research by Nelson et al (2001) stated that oxidative stress causes damage to the RNA of the virus and triggers a change to the genome with increased virulent activity. Another possible mechanism could be the dominance of different censuses sequence of the virus genome aided increasing oxidative stress of the host. Anti-viral activity of selenium may result from the fact that nutritional deficiency can increase oxidative stress which then induces the RNA replication of and significant influence on the host. Moreover, viral infection requires more defensive nutrients like selenium (Selenoproteins and Selenocysteine) and increases the deficiency, therefore in an already deficient-selenium host the influence and infections could be amplified under these conditions [119]. Noticeable increase in the lytic activity of natural cell killer activation of mice spleen was seen when 2.0 ppm

of selenium for 8 weeks was added to diet [121]. Zinc deficiency can interfere with cell-mediated immune functions through altering between TH1 and TH2 cells and reduced the function of TH1 cells [122].

Iron

Iron is an essential element in human life and contributes in many body and cell functions [123] including DNA synthesis, repair, replication and transcription [124]). Serum Iron status is controlled by special iron regulatory proteins (IRP1/IRP2) [125]. Iron deficiency can make individuals more susceptible to infections. Therefore, they are interchangeably used to assess any infection and/or iron deficiency [126]. Very early research has shown that parenteral iron prevented children from infection upper tract infection [127].

Piccinelli & Samuelsson (2007) have stated that Iron deficiency is associated with recurrent of acute respiratory infection in children suffering from anemia. To study the influence of low level of serum iron on lower respiratory infection, the researcher found that infection was more prevalent by 5.75 folds comparing to the control group (Ramakrishnan & Harish, 2006). Similarly, anemic children were also found to be two folds more vulnerable to lower respiratory tract infection than non-anemic children [128]. Abdel-Maksoud et al (2016) have pointed out that anemia was strongly related to respiratory tract infection and pneumonia in children (Table 1).

Proposed mechanism of the effect of Iron on the immune system

Adequate status is essential for proliferation of immune cell function and maturation especially lymphocytes to produce specific response to infections, and thus preventing from infections [129]. Another possible mechanism could be to increase circulating red blood cell numbers which can prevent the patients from hypoxemia and worsening the infection [130]. Furthermore, viruses attack and infect Iron-supported cells via binding attaching to transferrin receptor1 during cell invasion. Moreover, other viruses interfere with Iron homeostasis through altering expression of responsible proteins. Iron supplementation during infection and inflammation is limited and body turns to iron-withholding state which is responsible for declining plasma iron [123]. Thus to reduce the infection, general and respiratory tract infection and like COVID-19, health professionals and policy makers take iron and its deficiency at the community level into account (Figure 3).

Dietary lipids

Polyunsaturated fatty acids:

Polyunsaturated fatty acids (PUFAs) have been linked with several health benefits including elevating the response of both the innate and acquired immune system in humans. Early studies confirmed that PUFAs at concentration 5-25 microgram/ml minute of contact deactivated enveloped viruses including influenza [131]. A number of PUFAs such as arachidonic acid, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) proved anti-hepatitis C virus [132]. Furthermore, consuming a high amount of unsaturated fatty acids was connected with reducing the risk of pneumonia [133]. To study the influence of PUFA derived-lipid mediators protecting D1 (PD1) significantly ameliorated RNA replication.

In addition, PD1 also affected the survival and pathogenicity of the virus even under the condition where antiviral drugs failed to protect them from death. Morita et al (2013) have reported that PD1 can inhibit replication of the influenza virus and ameliorate the severity of the virus [134].

Proposed mechanism of the effect of PUFA on the immune system

The influence of PUFAs and the highly unsaturated fatty acids HUFA's on microbes particularly viruses have been confirmed in different investigations as mentioned before. A number of mechanisms have been proposed. PUFAs with anti-viral activities are present a number of defensive molecules such as lymphocytes and macrophages which are released at appropriate stimulation. Furthermore, molecule; NADPH-superoxide generated by macrophages, neutrophils, and lymphocytes with its anti-microbial properties is stimulated by PUFAs [135] (Figure 3).

It should also be noted that among lipids, the HUFA omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can inactivate enclosed viruses by altering the optimal host lipid conditions for viral replication. In addition, EPA and DHA inhibit cyclooxygenase enzymes (COX), and therefore, suppressing prostaglandin (pro-inflammatory) production as stated by [136,135,134,133,132] Indeed, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), can induce an inflammatory response to

COVID patients and ameliorate some need for intensive care unit (ICU) admission. EPA and DHA replace arachidonic acid (ARA) in the phospholipid membranes. EPA and DHA can metabolize by oxidation pathways to synthesis less inflammatory eicosanoids and in turn pro-resolving lipid mediators (SPMs) as reported recently by [137]. It was mentioned that DHA can greatly assist in quenching the cytokine storm seen in advanced stages leading to the respiratory failure and mortality [138].

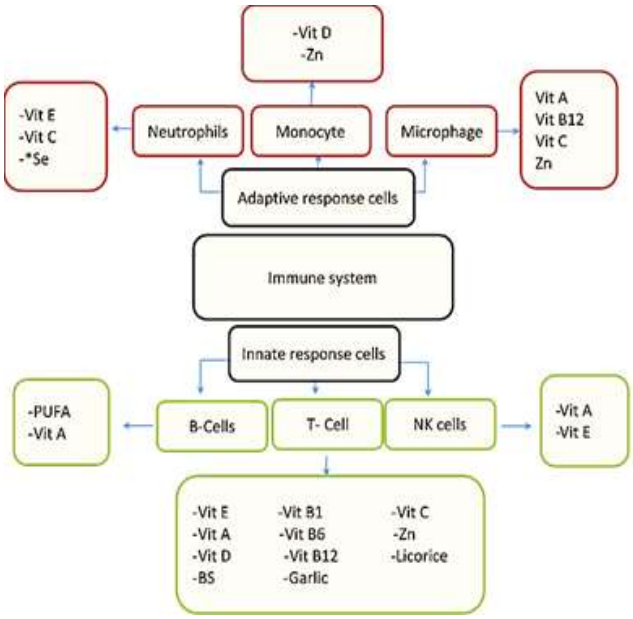


Figure (3) the potential intervention of nutrients and herbs on immune system cells *Se: Selenium, Zn:Zinc, PUFA: Polyunsaturated fatty acids, BS; Black seed

Excessive coagulation, leukopenia, lymphopenia, hypoxemia, and oxidative stress are common in critically challenged Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) patients in addition to the other symptoms associated with this pathology. Most investigations have focused primarily on the anti-inflammatory characteristics of EPA and DHA, suggesting that the lower inflammatory lipid mediators produced from these compounds together with EPA and DHA derived SPMs could assist in the management of the cytokine storm, ameliorating inflammation and lung tissue injury [139].

Nutrient-based potential immune enhancers for COVID-19

Garlic:

Garlic is a plant well documented for treating and mitigating established diseases particularly noted for its anti-microbial properties [140]. A number of early studies have proven the virucidal influence of garlic extracts (Table 2). It has been reported that garlic can inhibit various viruses including, herpes simplex virus type 1, herpes simplex virus type 2, parainfluenza virus type 3, vaccinia virus, vesicular stomatitis virus, and human rhinovirus type 2 [141]. It has also been reported that constituent compounds such as allicin and other thiosulfates of garlic had veridical activities. In a study about the influence of garlic extracts, it has been reported that the extract displays an anti-viral effect on coronavirus in chicken embryos [142]. Also, another compound like quercetin has shown an inhibitory effect on SARS-COV [143]. Thuy et al (2020) very recently investigated the influence of garlic essential oil on SARS-CoV-2 resistance. The authors have concluded that garlic essential oil showed a strong anti-coronavirus which can protect the human body from the aforementioned virus invasion. Moreover, very early studies have shown the anti-veridical activity of garlic.

Garlic extracts were tested against several viruses including rhinovirus, it was found that garlic extracts showed antiviral activity and the antiviral order was as followings ajoene > allicin > allyl methyl thiosulfinate > methyl allyl thiosulfinate[141]. A very recent review about the role of Garlic on Covid-19 has concluded that garlic can be an effective herb to prevent susceptibility to Covid-19 infection by upregulating the immune system [144].

Proposed mechanism of the effect of Garlic the immune system

Evidence exists that garlic extract could have an effect on the virus in the replication phase [142]. Another mechanism could be through sulfur atoms. The greater the number of sulfur atoms the more biological activities will be present [145]. Another antiviral factor is the presence of allicin and other thiosulfinates which inhibit viral replication (Figure 3). Also it has been reported that inhibiting angiotensin-converting enzyme 2 is essential to prevent infection from coronavirus and that was done through mainly allyl disulfide and allyl trisulfide in garlic [146]. Furthermore, quercetin also showed inhibitory effect on SARS-COV through an inhibiting protease enzymes which are required SARS multiplication [143]. Therefore, Garlic can be an easy and cheap option to prevent viral and probably COVID-19 infections.

Black seed

Black seed (BS) Nigella sativa belongs to the plant family of Ranunculaceae. BS is another herbal

plant that possesses anti-microbial activity including anti-viral activity [147]. It has been reported that BS and its components can improve the immune system and may suppress the severity of avian influenza viruses [148] and HIV [149] (Table 2). The anti-viral activity of BS has been studied particularly on the influence of BS on coronavirus [150].

A reviewed study from eight studies concluded that BS compounds like thymoquinone, α-hederin, nigelledine, thymohydroquinone, and hederagenin had moderate to high affinity towards SARS Covid- 2 proteins and enzymes which inhibit the virus's replication. The Bronchodilatory effect of BS has also been studied in several trials. [151]. In randomized blinded research, patients with asthma received boiled BS extraction of 50 and 100 mg/kg. The extract of BS proved bronchodilator traits and improved breathing [152]. A similar case study showed that giving two capsules to 500mg of BS to 73 asthma patients' resulted in a significant improvement in peak expiratory flow and forced expiratory volume [153].

Proposed mechanism of Black seeds on the immune system

The effect of BS on viruses has been well-documented and a number of mechanisms have been proposed. The anti-viral activity of BS has been linked to enhancing IFN-gamma synthesis and increase CD4+ helper T cells as well as improving their suppressing role and microphage number [148]. This is despite improvising viral load [154] and decrease viral replication [150] (Figure 3).

Table 2. antiviral properties of some herbs and their action on specific viruses

	Herbs	Influence on specific viruses
1	Garlic	*SARS-COV Chicken coronavirus, rhinovirus
2	Black seed	Coronavirus, avian influenza, HIV, HCV
3	Licorice	SARS-CoV, HIV

*SARS-COV= Severe acute respiratory syndrome coronavirus, HIV=human immunodeficiency virus

Licorice

Licorice is classed as an herb and has been used as a food supplement and medicine in traditional cultures in some countries. Licorice and its components have been studied and shown to possess proven medicinal and particularly virucidal properties against several viruses including herpes virus, HIV, hepatitis virus, SARS coronavirus, and influenza virus. Fiore et al (2008) have stated that licorice is traditionally used to treat symptoms of respiratory viral infections including SARS. Aqueous extraction of licorice showed an inhibitory effect against the human respiratory syncytial virus [155]. Also, licorice derivatives have also shown very effective anti-viral activity against SARS CoV [156]. Glycyrrhizin compounds found in licorice were tested against two isolated SARS-CoV in comparison with some antiviral drugs. The results showed that Glycyrrhizin was most effective against SARS replication than the conventional drugs [157].

A recent study showed that when diammonium glycyrrhizinate was applied in combination with Vit-C to self-quarantined patients, they went through severe symptoms of COVID-19, but recovered when the treatment was applied. This could suggest licorice derivatives to have a therapeutic effect on COVIV-19[158].

Proposed mechanism of the effect of Licorice on the immune system

Aqueous extraction of licorice prevented the human respiratory syncytial virus by curbing its attachment and internalization as well as IFN secretion through stimulating mucus cell activity [155]. Licorice can also significantly reduce its transportation to the membrane and reduce its fluidity and viral infusion as well as viral latency [159]. Licorice components like glycyrrhizins can have potent effects on SARS-CoV through the pathway of cell signaling including casein Kinase ll, protein kinase C, and transcription factors like nuclear factor -B as well as activator protein 1. It also stimulates the synthesis and releases Nitrous oxide in microphages which inhibits virus replication [160]. Glycyrrhizin from licorice can bind to serum proteins like albumin [161] as well as recombine with virus reverse transcripts in the control phosphorylation of proteins [162]. Furthermore, it has been stated that licorice extracts can be considered as a COVID-19 treatment approach since it affects several viruses through, downregulating pro-inflammatory cytokines, thereby inhibiting hyper-production of airway exudes and thrombin [163]. From the aforementioned statements, it can be understood that dietary nutrients individually or even together can enhance both innate and adaptive immune and might also reduce risks of COVID-19 infection. Therefore, using these nutrients in combination can lead to an effective and synergic influence on the immune system and allow a more

productive defense to be established prior to COVID-19 exposure and initial pathogenic insult. Such measures could be introduced during clinical treatment to enhance other chemotherapeutic agents and in the future introduced alongside novel vaccines to enhance their efficacy in a similar fashion to adjuvants. However, more research is needed to prove this concept in practice to help alleviate this global pandemic.

Conclusions

In summary, in order to boost the innate and acquired immune systems and lower the risks of the novel COVID-19, it is crucial to provide the community with general and home-based nutrients, as there is currently no specific vaccine or medical treatment for the corona virus global pandemic. Therefore, in this review, the potential use of some selected micronutrients and herbs are presented for the novel COVID-19 based on previous research about some related corona and respiratory infection tract viruses. Based on this review, we can conclude that most infections have the potential to become severe when a population as a whole lacks or has insufficient amounts of essential nutrients. Thus, adding more vitamin D, A, E, C, zinc, iron, selenium, and polyunsaturated fatty acids to the diet or taking supplements of these nutrients, along with some common herbs like licorice, black seed, and garlic, may be very beneficial in boosting immune system function and potentially lowering the risk of COVID-19 susceptibility. In order to safeguard the public and lower the death rate from coronavirus infection, health professionals and legislators should evaluate the patient's nutritional status before focusing on boosting the immune system.

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خصائص معززة المناعة المضادة للفيروسات لبعض المغذيات الدقيقة والأعشاب الوظيفية مع إمكانية زيادة علاج مرضى كوفيد–19

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الخلاصة:

يعاني العالم حاليًا في عام 2021 من تحدي حاد وشديد للجهاز التنفسي، يتمثل بجائحة عالمية ناتجة عن فيروس كورونا (كوڤيد–١٩) التي أدت إلى آلاف الوفيات في جميع أنحاء العالم). مع عدم وجود لقاح معين و/أو علاج طبي وزيادة معدل الوفيات بمرور الوقت مما يهدد صحة المجتمع واقتصاده، هناك حاجة إلى استراتيجيات بديلة عاجلة ويمكن الوصول إليها للتخفيف من هذا المرض. تلخص هذه المراجعة مكانية استخدام مغذيات دقيقة وأعشاب محددة لتقليل المخاطر، وانخفاض معدلات الوفيات و/أو علاج كوفيد–19 الحالي بهذه العناصر الغذائية والأعشاب المعززة للمناعة بناءً على أبحاث سابقة أجريت على أفراد آخرين من عائلة الفيروسات التاجية مثل **MERS** و**SARS CoV**. ولهذا الغرض، أجرى المؤلفون بحثًا عبر الإنترنت باستخدام الكلمات الرئيسية **MERS** و**SARS** وفيروسات عدوى الجهاز التنفسي. وأظهرت نتائج الدراسة المنهجية وجود العديد من العناصر الغذائية بما في ذلك فيتامينات **D** و**A** و**E** و**C** و**B** وكذلك استخدام المعادن مثل الزنك والسيلينيوم والحديد والأعشاب مثل الثوم والبذور السوداء وعرق السوس كعوامل داعمة عاجلة يمكنها ان تساهم في تحسين جهاز المناعة والمساعدة في التخفيف من كوفيد–19. في الختام، للسيطرة على تفشي مرض كوفيد–19، تم اقتراح أن تؤخذ في الاعتبار جميع التدابير الممكنة، بما في ذلك التدابير الوقائية والوقائية وكذلك الحالة التغذوية للمجتمع.

الكلمات المفتاحية: *كوفيد–19، العناصر الغذائية، الأعشاب، الفيتامينات، المعادن، عدوى الجهاز التنفسي، الجهاز التنفسي، الفيروسات*