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MICRONUTRIENTS POTENTIALS OF MEDICINAL PLANTS-GILOY AND PAPAYA TO OVERCOME COVID-19

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ABSTRACT
COVID-19 is an acute and infectious disease characterized by pneumonia and ARDS. The disease is caused by SARS-CoV-2, which belongs to the Corona viridae family along with MERS-CoV and SARS-CoV- 1. The viral genome is a positive RNA that encodes approximately 26 proteins that work together to ensure the survival, reproduction and spread of the virus in the host. The virus is transmitted by contact with aerosol droplets from infected people. The pathogenesis of COVID-19 is very complex and includes suppression of host antiviral and innate immune responses, induction of oxidative stress, followed by hyperinflammation known as"cytokine storm" leading to acute lung injury, tissue fibrosis and pneumonia. A number of vaccines and medicines are currently being evaluated for effectiveness, safety and dosage against COVID-19 and will take a long time to validate. Therefore, research on the recovery of natural compounds may offer opportunities against COVID-19. Several nutrients have been shown to have immune- enhancing, antiviral, antioxidant and anti-inflammatory effects. These include Zn, vitamin D, vitamin C, curcumin, cinnamaldehyde, probiotics, selenium, lactoferrin, quercetin, etc are found spectroscopically with the help of Nanotechnology. A group of these phytonutrients in the right combination as a supplement can help strengthen the immune system and prevent viruses. spread, prevents the disease from progressing to a severe stage, and further prevents hyperinflammation, providing both prophylactic and therapeutic support against COVID-19.

Keywords: *SARS-CoV-2, COVID-19, pathogenesis, food supplements, immune-boosting, antioxidant, anti-inflammation.*

INTRODUCTION
CORONA VIRUS (SARS-COV) -2 INFECTION - SEVERE ACUTE RESPIRATORY SYNDROME So far, the infection has spread to almost all countries in the world and WHO has declared it a pandemic. At the time of writing this review, more than 23 million confirmed cases and more than 800,000 deaths have been observed. In India, there have been more than 3 million positive cases and more than 57,000 deaths. Mortality rates of 2-16%, rapid spread of the disease, and high mortality in susceptible populations (mainly over 60 yearsand alsoin patients with underlying diseases). suchas diabetes, cardiovascular disease, etc.) brought a global shutdown and life came to a standstill, causing yet another global recession since 2008.

Corona virus disease (COVID-19) was first reported in late 2019 in the Chinese city of Wuhan. The incubation period is expected to be 2 to 14 days. The mode of transmission involves surfacecontact with aerosol droplets frominfected individuals, followed by contact withthe nose, eyes, and mouth. Evidence also suggests vertical transmission to newborns, including through feces (1-3). Coronaviruses are enveloped and their genome is positive single- stranded RNA (+SSRNA). These viruses belong to the large family Corona viridae and to the subfamily Corona virinae, which infect birds and mammals. The genome size of these viruses varies between 26 and 32 kb (4). The virusbinds to angiotensin-converting enzyme 2 (ACE2)receptors in cells through its spike (S) glycoprotein. The S protein has two domains, S1 and S2. S1 binds to the peptidase domain of ACE2, called the receptor-binding domain (RBD), while S2 catalyzes membrane fusion, thereby releasing genetic material into cells (5). Inside the cell, RNA is the template for structural proteins suchas copyase (R1a/ab), envelope (E), spike (S),membrane (M), nucleoprotein (N) and several non-structural proteins (NSP 1). – 16), uncharacterized protein 14, protein 9b (6). Among them, nonstructural proteins are expected to participate in host-protein interactions and modulate host cell signaling pathways. The onset of clinical disease and its progression to a severe stage can vary between individuals and depend on their immune system and the presence of co- morbidities. In general, typical clinicalsymptoms are dry cough (67%), fever (88%), fatigue (38%), muscle pain (14.9%), shortness of breath (18.7%), other symptoms are headache, sore throat, running. nose and gastrointestinal symptoms. Pneumonia is a serious manifestationof infection (2).

PATHOGENESIS OF COVID-19
The details of the pathogenesis of SARS-CoV-2 infection are not clearly understood. Available evidence indicates that thepathogenesis of infection can be classified into two stages. Stage 1: Asymptomatic stage with orwithout detectable virus. Stage 2: symptomatic stage with high viral load (4). The virus enters the respiratory

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epithelium after binding to its S- protein ACE2 receptors and then through the cell's transmembrane protease serine

2 (TMPRSS2). The virus suppresses or slows down the host's innate interferon (IFN) immune response. The mechanisms by which it modulates the host IFN response are not fully understood. Available evidence from other members of the same family suggests that the virus inhibits type1 IFN production and signaling downstream of the interferon α/β receptor (IFNAR) (7). The virus disrupts downstream signaling by ubiquitination and degradation of RNA sensor adapter molecules such as mitochondrial antiviral signaling (MAVS) protein and tumor necrosis factor-associated factors (TRAF) 3/6 and by preventing interferon regulatory factor (IRF) 3 nuclear translocation. . (8). When type 1 IFN is secreted, the virus inhibits IFN signaling by inhibiting signal transducer and activator oftranscription (STAT) 1 phosphorylation (9). Viral proteins that modulate host type 1 IFN responses include structural (such as M, N) and NSPs.. After the weakening of the IFN system, virus replication takes place in the cells. Viral replication in turn triggers the activation of monocytes, macrophages and granulocytes, leading to a hyperinflammatory state described as a "cytokine storm" that massively secretes proinflammatory cytokines, including interleukin (IL)-1, IL-6, IL-6. -8, IL -12, tumor necrosis factor(TNF)-α, etc. This leads to tissuehyperinflammation and subsequent tissue fibrosis and lung inflammation (4, 7, 10). Studies also show the involvement of oxidative stress in the pathogenesis of COVID-19. Available evidence indicates that SARS-CoV-2 infection causes oxidative stress by directly increasing the production of reactive oxygen species (ROS) (11) and indirectly by suppressing host antioxidant defenses mediated by nuclear factor (erythroid derived 2)-like 2. (NRF). - 2) (10). In addition, granulocytosis also promotes the production of superoxide ions, a typeof ROS, and further production of proinflammatory cytokines in response to SARS-CoV-2 infection (12). A study by Lin et al (13) showed that viral protease 3CLpro significantly increases ROS production in HL-CZ cells. In addition, the study found that elevated oxidative stress leads to apoptosis and inflammation. Another study on human HCoV- 229E infection shows that lack of expressionof the NRF-2 target, glucose-6-phosphate dehydrogenase (G6PDH), leads toincreased ROS and virus production (14). Moreover, NRF-2 levels were found to be suppressed in lung biopsies of COVID- 19 patients, on the other hand, NRF-2 activators were found to suppress SARS-CoV-2 replication and the inflammatory response (10). However, it is not known how SARS-CoV-2infection inhibits NRF-2 signaling. Inaddition, studies also suggest that SARS-CoV-2 infection triggers the activation of NF-κB-like receptor (TLR) signaling pathways to induce oxidative stress and hyperinflammatory response, ultimately leading to acute lung injury (11).

STRATEGIES TO BEAT SARS-COV-2 WITH FOOD SUPPLEMENTS

In terms of prevention, stage 1 is crucial because individuals in this stage are carriers and can spread the infection without knowing it. Screening individuals in stage 1, strengthening a specific adaptive immune response, and using antiviral drugs are critical to prevent viral entry, replication, and disease progression to stage 2. Therefore, global strategies may include exogenous antiviral drugs and/or immune-enhancing nutritional supplements. In addition tomaintaining the general health of patients affected by stage 2 infection, treatment can focus on tailoringstrategies, including the use of nutritional supplements, which can suppress ongoing oxidative stress, acute inflammation andcytokine production. storm to prevent destructionand damage to affected tissues. In conclusion, in addition to symptomatic treatment, strategies to combat SARS-CoV-2 infection include enhancing the immune response in phase 1, whilesuppressing it in phase 2 can be effective.

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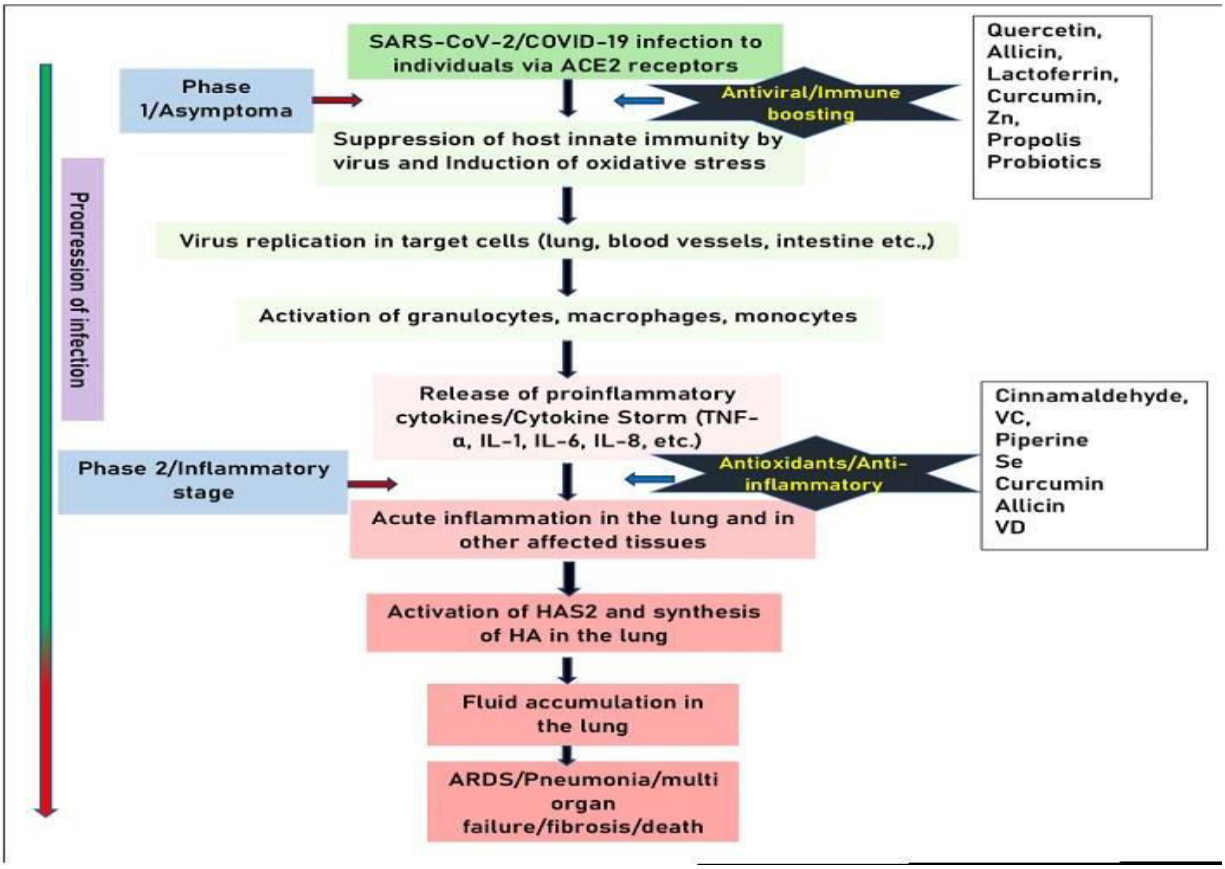
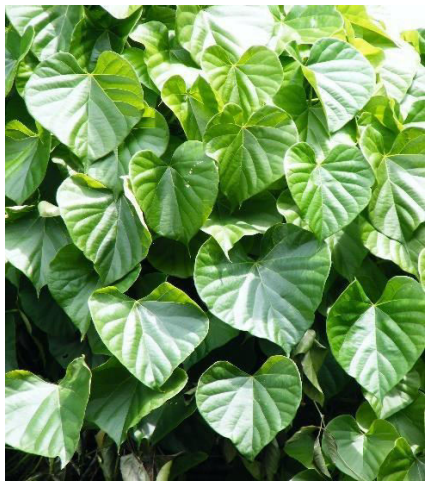


IMMUNE BOOSTING, ANTIOXIDANTS AND ANTI-INFLAMMATORY SUPPLEMENTS AGAINST COVID-19

There is currently one vaccine; Sputnik V,approved by the Ministry of Health of the Russian Federation. It was quickly adopted asa corona vaccine, but experts have expressed concerns about the effectiveness andsafety of the vaccine because it has yet to be evaluated in phase 3 clinical trials. Currently,most countries around the world are interested in developing corona vaccines, some of them have been in human trials, while most are in various stages of research and development. In addition, there are no specific medications for use against COVID-19, and no nationally or internationally relevant data on the effect of dietary supplements on the risk or severity of COVID-19. The development of along with the treatment of COVID- 19. Therefore, In this Present Study we have new antiviral drugs for COVID-19 is a major challenge and requires a lot of time andeffort to design and validate. Several lines of evidence show that many dietary supplements of various spices, herbs, fruits, roots and vegetables can reduce therisk or severity of several viral infections by increasing the immune response, especiallyin people with inadequate food sources, and also fighting them. - inflammatory, free radical scavenging and virucidal effect. These nutrients can be reused to reduce the pathological effects caused by SARS-CoV-2 infection. Therefore, the use of natural compounds can provide alternative preventive and therapeutic support taken the tender leaves of Giloy and Papaya.Spectrocial and Statistical Analysis are used to confirm the presence of nutrients in them

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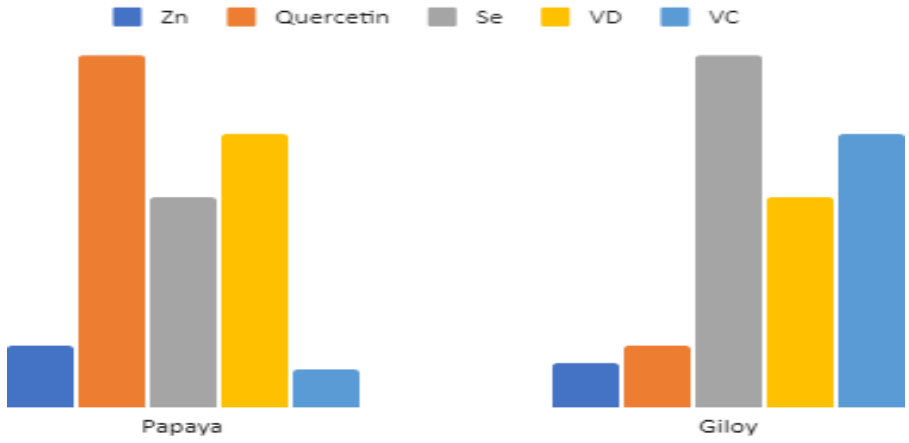
Papaya Giloy

Element	Wavelengthnm	Papaya	Giloy
Zn	517	0.71254	0.511581
Quercetin	504	4	0.71254
Se	424	2.4	4
VD	420	3.1	2.4
VC	408	0.445	3.1



AMOUNT OF MINERALS IN GILOY AND PAPAYA LEAVES

The following section describes the beneficial effects of some nutrients.

QUERCETIN

Quercetin is a well-known antioxidant with anti-inflammatory and antiviral bioactivity. It suppresses TNF-α production in LPS-induced macrophages (101), IL-8 production in lung A549 cells (102), and TNF-α andIL-1α mRNA levels in glial cells (103). It also inhibits the production of cyclooxygenase (COX) and lipoxygenase (LOX) enzymes in rat liver epithelial cells (104). Research has also shown that quercetin has antiviral effects against both RNA and DNA viruses. It inhibits virus entry and virus-cell fusion (105) and reduces proinflammatory cytokine expression and rhinovirus-induced lung inflammation in mice (106). Additionally, a metabolite of quercetin (4',5-diacetyloxy-3,3',7-trimethoxyflavone) has been shown to inhibit picornavirus replication by inhibiting the RNA replication complex (107). Studies have also found that due to the presence of a hydroxyl group, quercetin-3β-galactoside binds to the viral protease 3CLpro and inhibits its proteolytic activity (108). In the context of SARS virus infection, the SUMMIT supercomputer using drug docking screen and gene enrichment analysis (GSEA) found that quercetin, VD and estradiol interfere 85, 70 and 61% of SARS-CoV-2. viral proteins in human cells. Based on these findings, the study also predicts that the ternary combination (Quercetin/VD/Estradiol) compared to the 2-component (VD/Quercetin) can affect 73% of human genes encoding SARS-CoV-2 targets that arestrongly associated with the mitigation of COVID-19 to substances (109). Furthermore, the increased ability of estradiol to affect human genes encoding SARS-CoV-2 targets compared to testosterone suggestsa plausible explanation for the apparently higher male mortality in this corona pandemic (109).

Consistent with these findings, a randomized intervention trial using estradiol or VD as a palliative agent is listed in the clinical trial (https://clinicaltrials.gov/ct2/show/NCT04359329).

In addition, as observed in predictive models. that quercetin binds the S protein of SARS-CoV-2 at its host receptor region or at the S protein-human ACE2 interface, preventing viral entry into cells, indicating its therapeutic potential (110). This prediction is consistent with reports that both quercetin and the structurally similar luteolin inhibit SARS-CoV virus infection (111). In addition, other studies have found that quercetin in combination with VC has synergistic antiviral and immunomodulatory effects against COVID-19 (47).Overall, several studies show thatquercetin has potential active against SARS-CoV-2 and can be used as a prophylactic and therapeutic agent in the fight against COVID-19

SELENIUM (SE)

Selenium is abundant in common foods such as corn, garlic, onions, cabbage and broccoli. It is an important trace element that plays an important role in various physiological processes and theimmune system. Selenium achieves its biological effect by binding the body's selenium proteins. Optimal selenium status (100 µg/day) promotes T-cell proliferation, NK-cell activity and innate cell functions. In addition, it supports a stronger

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vaccine react and strong immunity against pathogens. It also suppresses severe inflammation in tissues such as the lungs and intestines (77). Studies have shown that selenium supplementation modulates the inflammatory response in patients with respiratory distress syndrome by restoring lung antioxidant levels and suppressing IL-1β and IL-6 levels (78). Selenium supplementation inhibits pathogen-induced NF-κB activation and downstream proinflammatory cytokinerelease (79). The antiviral properties of selenium have been found to be mediated by its antioxidant activity. Selenium-deficient HIV+ patients generally have reduced activity of the antioxidant glutathione peroxidase (77). On the other hand, selenium supplementation has been shown to improve the numbers of CD+ T cells (80) and activity of glutathione peroxidase and other antioxidant selenoenzymes and catalase (81). In general, selenium enhances immunity through its non-enzymatic roleas a cofactor for enzymes involved in critical post-translational protein modifications. Selenium supplementation may be useful in the fight against COVID-19 because it plays animportant role in suppressing inflammation and boosting antioxidant and innate immunity

VITAMIN D (VD)

VD is a fat-soluble vitamin that plays an important role in immunomodulatory, antioxidant, and antiviral reactions (29, 30). Human airway epithelia constitutively express the vitamin D receptor, which allows VD to protect against respiratory infections. VD inhibits NF-κB p65 activation by regulating the NF- κB inhibitory protein I-kappa-B-alpha (IκB-α) (31). VD also decreases the expression level of pro- inflammatory type 1 cytokines such as IL-12, IL-16, IL-8, TNF-α, IFN-γ, while increasing type 2 cytokinessuch as IL-4, IL-5, IL - 10 and regulatory T cells (32, 33). VD increases the level of antioxidants NRF-2 and facilitates the balanced functioning of mitochondria, prevents oxidation of proteins associated with oxidative stress, lipid Peroxidation and DNA damage (30). Epidemiological data suggest an increased susceptibility to acute respiratory viral infections in VD- lack (30). 34).), while its supplementation improves innate immune responses against respiratory infections, including influenza A and B, parainfluenza 1 and 2, respiratory syncytial virus (RSV), and chronic hepatitis C (35, 36). Although VD has not been reported to directly affectviral replication or viral load, studies indicate that VD may promote antiviral activity by inhibiting virus- induced inflammation. Perhaps this function of VD can help prevent the cytokine storm in SARS-CoV-2 infection. In a randomized controlled trial (RCT), the addition of VD at a monthly high dose (100,000 IU/month) compared to a standard dose (12,000 IU/month) helps to reduce the incidence of acute respiratory infections, especially in the elderly. term maintenance. residents (37). In addition, evidence alsosuggests that VD can complement the effectiveness of drug therapy, as observed with ribavirin therapy in medical patients with chronic hepatitis C virus (HCV) genotype 1 and HCV genotype 2e3 infections (33, 34,38, 39) . The beneficial effect of the dietary supplement was observed in all age groups and in subjects withchronic diseases (40). The elderly are most often deficient in these important micronutrients. Thus, they mayreceive the most significant benefit from additional VD therapy (41).

ZINC (ZN)

Zinc is an important metal involved in many biological processes because it acts as a cofactor, a signaling molecule and a structural element. It regulates inflammatory activity and has antiviraland antioxidant functions (19). Studies in a rat model show that Zn deficiency increases oxidative stress, proinflammatory TNF-α and vascular cell adhesion molecule (VCAM)-1 expression, and causes remodeling of lung tissue, which was partially reversed by Zn supplementation (20). Zn deficiencyshows increased TNF-α, IFN-γ, and FasR signaling and induction of apoptosis in lung epithelial cells (21) and also increases Janus kinase (JAK)-STAT signaling in lungs under septic conditions (22).). Zinc can also modulate viral entry, fusion, replication, translation of viral proteins, and virus formation of respiratory viruses (19, 23). Speth et al. (24) showed that Zn exposure (100 μM) decreases the activity of recombinant human ACE-2 in rat lungs. Zn2+ cations, especially in combination with the Zn ionophore pyrithione, have been shown to inhibit the activity of SARS coronavirus RNA polymerase (RNA-dependent RNA polymerase, RdRp) by preventing its replication (25). Studies have shown that oral Zn supplementation reduces the incidence of acute respiratory infections by 35%. Zn also shortens the duration of flu-like symptoms by two days and improves the speed of recovery The recommended dose ranges from 20 to 92 mgper week in various studies (27).

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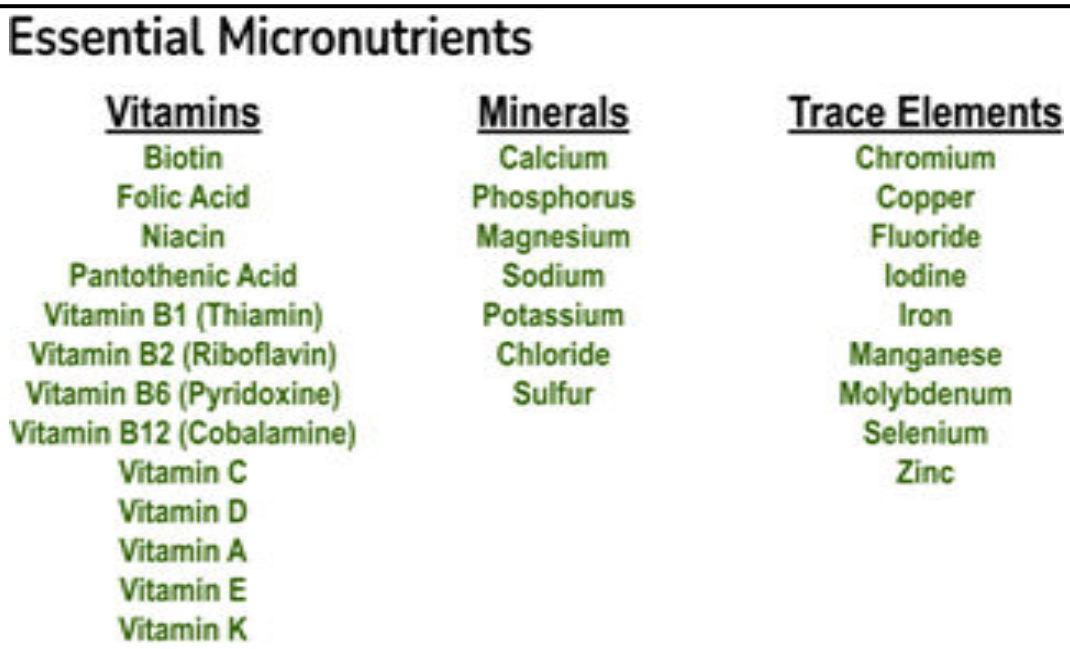

VITAMIN C (VC)

Vitamin C may protect against infection because it plays a key role in immune system health (42). This vitamin supports the function of various immune cells and improves their defense against infections. VC supplementation has been shown to reduce the durationand severity of upper respiratory tract infections (most of which are caused by viral infections), including the common cold (43). The recommended dose of VC was 1-3 g/day. The recommended daily allowance(RDA) for VC is 60 mg. Various spices, herbs, fruits and vegetables have been found to be excellent sources of VC

CONCLUSIONS

Currently, one corona vaccine is Sputnik V, developed by the Gamaleya Research Institute in Moscow, which has been approved by the Ministry of Health of the Russian Federation. It was quickly adopted as a corona vaccine, but experts have expressed concerns about the effectiveness and safety of the vaccine because it has not yet been evaluated in phase 3 clinical trials. Currently, there are more than 100 different vaccines in research and development stages in the world. Some are in human clinical trials and have been rigorously tested for safety, efficacy and dose standardization. Similarly, several drug candidates have been identified, most of which are in various stages of research and development, while some have been renewed and approved for emergency use in this pandemic. Prominent approved for emergency use include hydroxychloroquine, favipiravir, remdesivir,tocilizumab, etc. In addition, no significant studies support the use of certain nutritional supplements as adjunctive therapy in the treatment of patients with COVID-19. A large body of existing literature provides scientific evidence for the immune-enhancing, anti-inflammatory, antioxidant, and antiviral properties of several phytonutrients. Preliminary studies indicate that some of them have been found to have anti-SARS-CoV-2 activity and are rapidly progressing to clinical trials (Table 2). Repurposing the right combination of these nutrients to achieve functional synergy in the form of ready-made food supplements can provide both prophylactic and adjuvant treatment against COVID-19.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financialrelationships that could be construed as a potential conflict of interest.

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