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Role of functional food components in COVID-19 pandemic: A review

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Abstract

COVID-19 is highly contagious disease which is caused by a novel coronavirus (SARS-CoV-2) and its outbreak has affected millions of people with thousands of deaths worldwide. The nutrients in food have an important role in modulation of immune system, developing functional abilities and prevention of diseases along with maintaining our health, growth and development. The various components of functional foods are potentially beneficial components, found naturally in foods which help in prevention and reduction of risk factors for several diseases. These functional food components have immunomodulatory and antiviral properties which are of prime importance towards healthy immune system. The dietary supplementation of foods with functional food components like vitamins (A, B, C, and D), minerals (selenium, zinc, and iron) and phenolic compounds can act as treatment or preventive therapy for COVID-19 patients. The functional foods include foods fortified with above mentioned functional components along with the foods rich in these functional components like fruits, vegetables, nuts, seeds, etc. These various functional food components like vitamins or minerals can be used as adjuvant in COVID-19 infected patients. These adjuvants help in stimulation the immune system which increases the response towards a vaccine, without having any specific antigenic effect.

1. Introduction

Coronavirus disease 2019 (COVID-19) caused by a novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), originated in the city of Wuhan, Hubei Province, Central China and has spread quickly to many countries till date (Li *et al.*, 2020a). The name coronavirus was derived from the Latin word “corona” which means “crown” depicting the crown-like structure of the viral particle. COVID-19 has posed a high risk to global public health and the symptoms include fever, tiredness, dry cough whereas, in severe cases, it can be even fatal (Lei *et al.*, 2020).

Nutrition plays an important role in improving well-being and can mitigate the risk and morbidity associated with coronavirus disease 2019 (COVID-19) which is caused by the severe acute respiratory syndrome coronavirus 2 (Coelho-Ravagnani *et al.*, 2020). Nutritional status is a crucial factor for optimal prognosis in SARS-CoV-2 infected individuals and can determine the clinical severity of COVID-19 (Laviano *et al.*, 2020). Zhang and Liu (2020) have suggested dietary supplementation as a treatment option for COVID-19 patients and as preventive therapy against lung infection. The dietary supplementation includes selected vitamins like vitamin A, B, C, and D; minerals like selenium, zinc, and iron; and omega-3 fatty acids.

The various functional foods have immune boosting properties and the healthy immune system plays an important role in maintaining human health whereas nutrition plays an important role in the

modulation of immune function (Thakur *et al.*, 2019). Functional foods enhance the immune system capacity leading towards the prevention and control of pathogenic viral infections. The various components in functional foods and nutraceuticals contain various immune-boosting components like polyphenols, terpenoids, flavonoids, alkaloids, sterols, pigments, unsaturated fatty-acids, micronutrient, vitamins and minerals (Alkhatib, 2020). During COVID-19 pandemic, it has been reported that the mortality rate was higher among the patients who were having one or more chronic diseases. The chronic diseases weaken the immune system and increase the susceptibility of the individual towards COVID-19 like in elderly people. So, various functional foods and their bioactive compounds can be utilised to boost our immune system which further help in combating viral diseases including COVID-19 (Butler *et al.*, 2020; Martirosyan, 2020). In present review, the role of various functional food components in immune system and their role in COVID-19 prevention and treatment have been discussed further.

2. Behaviour of coronavirus

Coronaviruses (CoVs) belongs to the family Coronaviridae, subfamily Orthocoronavirinae and order Nidovirales. The four genera within the subfamily, Orthocoronavirinae are Alpha coronavirus (α -CoV), Beta coronavirus (β -CoV), Gamma coronavirus (γ -CoV) and Delta coronavirus (δ -CoV). The important four structural proteins are essential for SARS-CoV-2 assembly and infection which are, namely; spike surface glycoprotein, the membrane protein, the envelope protein and the nucleocapsid protein (Yang and Leibowitz, 2015; Banerjee *et al.*, 2019; Li *et al.*, 2020a). The virus infecting humans (SARS-CoV-2) is the seventh member in the family of CoVs. A wide range of upper respiratory tract infections like common cold is caused by four human CoVs (HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1), whereas atypical pneumonia is caused by SARS-CoV

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and MERS-CoV (Li *et al.*, 2020a). Morphologically, corona viruses have non-segmented positive-sense, single-stranded ribonucleic acid (ssRNA) enveloped by structural proteins and surface is associated with the club-shaped protein (spikes) which is observed under the 2-D transmission electron microscopy (Fehr and Perlman, 2015; Singh *et al.*, 2020).

During COVID-19 infection process, the virus particles spread through the respiratory tract which further infect the surrounding uninfected cells (Seyed *et al.*, 2020). After entering into alveolar epithelial cells, there is rapid replication of virus which triggers a strong immune response resulting in development of cytokine storm syndromes and pulmonary tissue damage. Cytokine storm syndromes are also referred to as hypercytokinaemia, which are group of disorders and characterised by the uncontrolled production of pro-inflammatory cytokines leading towards acute respiratory distress syndrome (ARDS) and multiple organ failure such as lungs, heart, intestine and blood vessels (Wang and Ma, 2008; Channappanavar and Perlman, 2017; Villar *et al.*, 2019; Li *et al.*, 2020a). After infection, there is an incubation period of 2-14 days until the onset of symptoms and the common symptoms are fever, dry cough and tiredness. The less commonly occurring symptoms are headache, loss of taste and smell, sore throat, diarrhea, aches and pain, *etc.* Among serious symptoms, there is difficulty in breathing with chest pain or pressure followed by loss of speech and movement. Out of total, about 80 % of cases are with mild symptoms or may be asymptomatic while rest of 15% and 5% are severe who need oxygen and ventilation, respectively (Lauer *et al.*, 2020; Seyed *et al.*, 2020; Singal, 2020; Saleem *et al.*, 2021).

3. Functional foods

The term 'functional food' was firstly used in Japan and further it was reported that food can be used for other functions rather than nutrient supply, gastronomic pleasure and energy (López-Varela *et al.*, 2002). The Functional Food Center (FFC) defines "functional food" as natural or processed foods that contains known or unknown biologically-active compounds; the foods, in defined, effective, and non-toxic amounts, provide a clinically proven and documented health benefit for the prevention, management, or treatment of chronic disease (Martirosyan and Singh, 2015). In Japan, functional foods have been legislated in the FOSHU (Foods of Specified Health Use) legislation and the food products which meeting specific requirements are given FOSHU stamp. In Europe, experts decided in the FUFOS (Functional Food Science in Europe) project to adopt the term 'functional food' with a consensus definition. The criteria for defining functional foods under FOSHU (Foods of Specified Health Use) and FUFOS (Functional Food Science in Europe) in Japan and Europe has been explained in Figure 1 (López-Varela *et al.*, 2002).

The potential immunomodulatory and antiviral properties can be gained from various functional food plants, such as ginger, garlic, turmeric, black pepper, liquorice, pomegranate and elderberry (Yang *et al.*, 2020). The various bioactive compounds like polyphenols and carotenoids have antiviral efficacy. For example, polyphenols has been reported to influence the regulation of immune cells, the synthesis of pro-inflammatory cytokines and the suppression of pro-inflammatory gene expression (Yahfoufi *et al.*, 2018). The functional foods and components contain biologically-active compounds which are having immune-boosting properties. These natural compounds are not involved in the direct inhibition response

against corona virus, but strengthen the immunity which acts as preventive defence against COVID-19. The prebiotics, probiotics, and ayurvedic products reduce the stress level of the body, strengthen the immune response in our body and keep the gut healthy by maintaining microflora and bacterial colonies (López-Varela *et al.*, 2002; Singh *et al.*, 2020).

4. Functional food components and COVID-19

The various viral infections in human are characterized by a compromised immune function and deficient micronutrient stores, particularly vitamins and trace elements (Calder *et al.*, 2020). The efficient functioning of the immune system can be maintained by consuming various nutraceuticals within a variety of functional foods and supplementation of such functional foods (Figure 2) with adequate dietary intake boosts up the immune system and provides an important antiviral prevention of COVID-19 (Alkhatib, 2020; Gombart *et al.*, 2020; Grant *et al.*, 2020). The majority of functional food which boosts up antiviral immune defence includes variety of plant, animal, and fungi species such as teas, roots, mushrooms, fermented plants/leaves, olive-based products, oily fish, seeds, fruits, vegetables, popular beverages and protein-rich foods like chicken extract and soybean peptides. Fruits and vegetables plays an important role in human nutrition and health because of the abundance of bioactive or functional compounds like polyphenolics, vitamins-C, folic acid, dietary fibres and minerals (Sharma *et al.*, 2019; Sharma *et al.*, 2020). The bioactives from fruits and their by-products can be used for the formulation of new products with positive pharmacological effects which can maintain or improve health (Hamid *et al.*, 2020). These foods have immunoprotective properties due to the antioxidation and anti-inflammation compounds like naturally occurring vitamins and minerals (*e.g.*, vitamins like A, C, D, B₆, B₁₂, E and minerals like zinc, copper, iron, and selenium), and other phenolic compounds (López-Varela, 2002; Alkhatib and Tuomilehto, 2019). The potential antiviral benefits or role in COVID-19 of different compounds present in functional foods have been further discussed in detail and some important aspects have been mentioned in Tables 1-3.

4.1 Vitamins

Among all vitamins, vitamin A, B, C, D, and E have been reported to be most effective on immune system, and play an important role in prevention of several viral infections including COVID-19. On the basis of enhancement of immune system, group B vitamins (42.18%) are most studied followed by vitamin A, D, and E (26.66%, 22.22% and 13.33%). With respect to prevention/treatment of COVID-19 infection, most of the studies had been focused on vitamin D (66.66%) followed by vitamin C (50%), E (33.33%) and A (16.66%), respectively (Dehghani-Samani *et al.*, 2020). These different vitamins act as immune promoting functional component in various functional foods and sufficient vitamin intake can be recommended to prevent viral infections like COVID-19 infection.

4.1.1 Vitamin A

Vitamin A is having anti-inflammation properties and it plays a crucial role in enhancing immune function which further plays regulatory roles in cellular and humoral immune responses or processes. It plays various important functions in human body like maintaining vision, promoting growth and development, and protecting epithelium and mucus integrity in the body (Huang *et al.*, 2018; Thakur *et al.*,

2019). Villamor and Fawzi (2005) have reported that vitamin A supplementation to preschool children can decrease the risks of mortality and morbidity from some diseases like diarrhea, measles, human immunodeficiency virus (HIV) infection, and malaria. 9-cis-retinoic acid which is a metabolite of vitamin A is required for CD8⁺ T normal functioning of B lymphocytes including antibody generation and also for lymphocyte survival and proliferation (Ross 1996 and Calder, 2020).

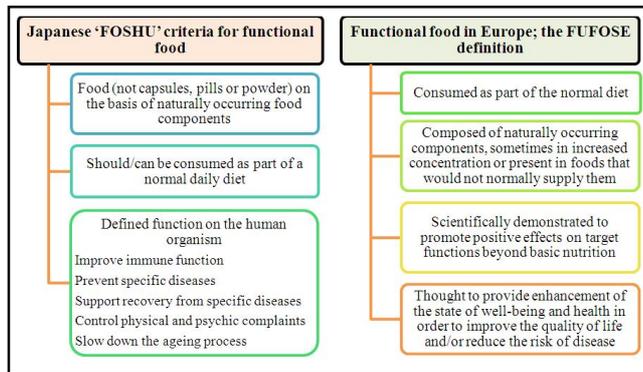


Figure 1: Criteria for defining functional foods under FOSHU (Foods of Specified Health Use) and FUFOS (Functional Food Science in Europe) in Japan and Europe (Lo'pez-Varela *et al.*, 2002).

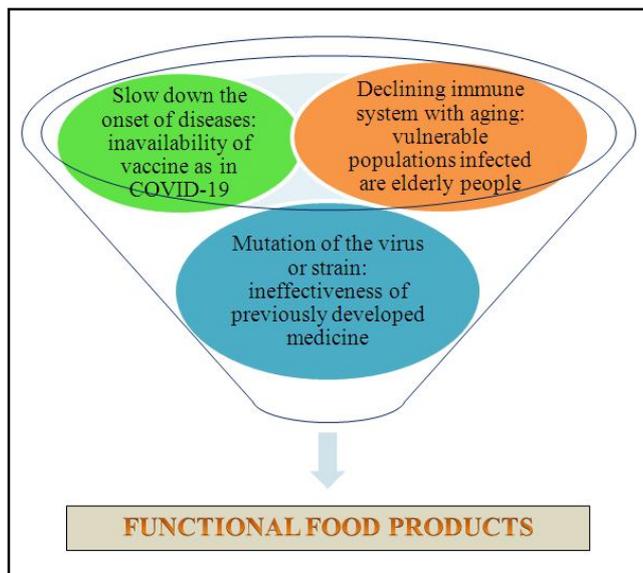


Figure 2: Development of specific functional foods products for viral diseases (Martirosyan, 2020).

4.1.2 Vitamin B

Vitamin B has important role in assisting in proper activation of innate and adaptive immune responses and decreasing the pro-inflammatory cytokine levels, improves respiratory function, maintains endothelial integrity and prevents hypercoagulability which in turn can reduce the length of stay in hospital during viral infection. On the basis of above benefits, vitamin B status should be assessed in COVID-19 patients and could be used as a non-pharmaceutical adjunct to current treatments (Michele *et al.*, 2020; Zhang and Liu, 2020; Shakoor *et al.*, 2021). Vitamin B₁ has been

reported to have antioxidative effect, suppression of oxidative stress and role in NF- κ B regulation in the immune system (Mikkelsen *et al.*, 2017). On the basis of role of Vitamin B₁, Dehghani-Samani *et al.* (2020) suggested the need of further studies on its effect in COVID-19 infected patients. In SARS-CoV-2 virus infection, antibodies and T-cells are helpful to eliminate the virus and thiamine deficiency can potentially result in inadequate antibody responses with more severe symptoms. So, by maintaining adequate levels of thiamine, it will help in assisting in the proper immune responses during SARS-CoV-2 infection (Shakoor *et al.*, 2021). The researchers further reported that riboflavin together with UV light causes irreversible damage to nucleic acids rendering microbial pathogens and could alleviate some of the risk of transfusion transmission of COVID-19 as well as reducing other pathogens in blood products for critically ill COVID-19 patients.

Vitamin B₆ is an essential factor for maintenance of lymphoid tissues and their immunological functions like different kind of cell-mediated reactions and antibodies related reactions (Chandra and Sudhakaran, 1990). Pyridoxal 52-phosphate which is active form of vitamin B₆ can dampen the cytokine storm and inflammation caused due to excessive T cell response and secretion of pro-inflammatory cytokines during COVID-19 infection (Shakoor *et al.*, 2021). Vitamin B₉ (folate) plays a key role in the nucleic acid synthesis and normal cellular function with potential pathologic impact and during its deficiency supplementation with folate should be encouraged in COVID-19 hospitalized patients (Meisel *et al.*, 2021). Sheybani *et al.* (2020) reported that folic acid could be used to inhibit the furin enzyme which further affect the structure of the protein and interfere with its proteolytic capability. The researchers further suggested the use of folic acid as a safe drug and in the early stages of the COVID-19 disease it could be useful in the prevention or management of associated respiratory diseases. Vitamin B₁₂ and its active forms hydroxo-, adenosyl- and methylcobalamin has various important functions in human which includes red blood cell synthesis, nervous system health, myelin synthesis, cellular growth and the rapid synthesis of DNA (Mikkelsen *et al.*, 2017; Shakoor *et al.*, 2021). Santos (2020) has reported vitamin B₁₂ therapy can reduce the oxidative stress along with improving circulation and further COVID-19-related organ damage and symptoms can be reduced with the help of methylcobalamin supplements.

4.1.3 Vitamin C

Vitamin C is a potential therapeutic option in management of COVID-19 due to its various pharmacological characteristics; antiviral, antioxidant, anti-inflammatory and immunomodulatory effects; leucocyte migration to sites of infection; phagocytosis and bacterial killing; natural killer cell activity and T lymphocyte function (especially of CD8⁺ cytotoxic T lymphocytes) and antibody production (Abobaker *et al.*, 2020; Calder, 2020). In China and United States, the use of high dose of intravenous vitamin C has shown promising results in management of COVID-19 during the treatment of infected patients with no reported adverse reactions with the short-term use of its high doses. The possible beneficial effects of vitamin C in management of COVID-19 are indirect antiviral effects by improving host's innate immunological responses, immunomodulatory effects by improving T cell functions with increased production of immunoglobulins, anti-inflammatory effect by decreasing the risk of cytokine storm, antioxidant effects by decreasing oxidative stress induced lung

inflammation with restoring endothelial function and decreases the duration of mechanical ventilation or vasopressor requirements in critically ill patients (Abobaker *et al.*, 2020). Carr and Rowe (2020)

reported that vitamin C administration will improve outcomes in COVID-19 on the basis of clinical trials of patients with pneumonia and sepsis, and preliminary observational and interventional studies.

Table 1: Antiviral functional food sources of immune promoting vitamins: functions and effects on respiratory system

| Vitamin | Antiviral functional food sources | Key mechanism of action | Recommendations and deficiency | RDA* (for Indians 2020) | References |
|-------------------------|---|--|--|---|--|
| Vitamin A | Orange, carrots, sweet potatoes, broccoli, pumpkin, squash, kale, spinach, milk, cheese, oily fish, liver, eggs, fortified cereals, apricots, papaya, peaches, mango, tomato juice, cantaloupe melon. | <ul style="list-style-type: none"> • Maintains lymphocyte pool and T lymphocyte synthesis, results in resistance to infection. • Epithelial cell differentiation and immune competence are maintained • Improves functions of neutrophils, macrophages and natural killer cells. • Key role in the division of T lymphocytes • Prevention and treatment of respiratory tract infection | <p>Recommended as part of a balanced diet.</p> <p>Deficiency leads to night blindness.</p> | 1000 µg/day for men and 850 µg/day for women | <p>Mahalanabis <i>et al.</i>, 2004</p> <p>Tanumihardjo <i>et al.</i>, 2016</p> |
| Vitamin B ₆ | Garlic, cloves, walnut, sunflower seeds, safflower, pistachio nut, poultry chicken, liver, sugarcane, oyster mushroom, fish, eggs, whole grain cereals, green leafy vegetables, fortified cereals, fruits, tofu, soya beans | <ul style="list-style-type: none"> • Aids in the control of the inflammatory response. • Operation of NK cells. • Participates in the synthesis of amino acids, cytokines, and antibodies. • Proliferation, differentiation and maturation of lymphocytes. | <p>Should be part of a balanced diet.</p> <p>Periphera neuritis, eczema, angular stomatitis, hyperirritability, convulsive seizures, and pathological electroencephalograms.</p> | 1.9-3.1 mg/day for men and 1.9-2.4 mg/day for women | <p>Meydani <i>et al.</i>, 1991</p> <p>Saeed <i>et al.</i>, 2016</p> |
| Vitamin B ₁₂ | Meat, fish, shellfish, eggs, milk, cheese, yeast extract, fortified breakfast cereals. | <ul style="list-style-type: none"> • Acts as immunomodulator • Acts on the NK cells functions • Assists in T lymphocytes production, • Contribution in antibodies production and its metabolism | <p>Recommended as a part of a balanced diet. Deficiency leads pernicious anemia.</p> | 2.5 µg/day for men and women | <p>Saeed <i>et al.</i>, 2016</p> <p>Maggini <i>et al.</i>, 2018</p> |
| Vitamin B ₉ | Green leafy vegetables like spinach, cabbage, kale, broccoli, brussels sprouts, peas, fortified cereals, chick peas | <ul style="list-style-type: none"> • Adds to the conservation of innate immunity • Contribute to the antigen-specific antibody response • Expansion of T cells | <p>Dietary intake is highly recommended. Deficiencies associated with elevated blood homocysteine levels.</p> | 300 µg/day for men and 220 µg/day for women | <p>Budi <i>et al.</i>, 2015</p> <p>Saeed <i>et al.</i>, 2016</p> |
| Vitamin C | Aonla, barbados cherry, oranges, lemon, red and green peppers, strawberries, blackcurrants, kiwi, broccoli, brussels sprouts, and potatoes | <ul style="list-style-type: none"> • Immunosenescence and positive regulation of the ageing phase, • Modulation of the low-grade inflammatory pathway in a positive way • Improves phagocyte chemotaxis and motility. • Improvement of antibody amounts, specificity and replication. • Modulates the synthesis of inflammatory cytokines. • Function in respiratory infection prevention and management | <p>Dietary intake is preferred. Supplementation is required during low dietary intake. Deficiency leads to scurvy.</p> | 80 mg/day for men and 65 mg/day for women | <p>Monacelli <i>et al.</i>, 2017;</p> <p>Carr and Maggini, 2017</p> <p>Mousavi <i>et al.</i>, 2019</p> |

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|-----------|---|---|---|------------------------------|------------------------------------|
| | | <ul style="list-style-type: none"> • Reduces the number of pathogens. • Reduces the pathogenic potential of viruses, bacteria and other pathogens (fungi and parasites) | | | |
| Vitamin D | Oily fish, liver, eggs, fortified foods, spreads and some breakfast cereals | <ul style="list-style-type: none"> • Viral replication is reduced. • In bronchial epithelial cells it stimulates the innate immune response. • Stimulates the division of monocytes into macrophages. • Antibacterial protein synthesis is stimulated. • Stimulates the mechanisms involved in pathogen elimination. • Supplementation appears to guard against respiratory tract infections (mostly in people with hypovitaminosis). | Supplementation is required during low dietary intake Deficiency leads to abnormal calcium homeostasis resulting rickets in children or osteomalacia in adults | 600 IU/day for men and women | Medrano <i>et al.</i> , 2018 |
| Vitamin E | Nuts and seeds, vegetable oils, wheat germ | <ul style="list-style-type: none"> • Membrane anti - oxidant protection • Enhances lymphocyte proliferation • Increases NK cell activity • Have anti-inflammatory properties (against colds and pneumonia) | Dietary intake is recommended. Supplementation is required during low dietary intake. | 8-10mg tocopherol/d | Hemila, 2016 Lee and Haan, 2018 |

*RDA range is only for sedentary, moderate and heavy workers as per recommendations of NIN (National institute of nutrition) Hyderabad India.

4.1.4 Vitamin D

The active form of vitamin D is 1, 25-dihydroxy Vit D₃ (1,25(OH)₂D₃) has roles in bone formation by regulating the calcium and phosphorus metabolisms. It also leads to immunomodulation of different immune cells *via* affecting the monocytes, macrophages, dendritic cells, T-cells and B-cells, with important effects on innate and adaptive immune responses (Baek *et al.*, 2010; Dehghani-Samani *et al.*, 2020). Ali (2020) reported that vitamin D supplementation is safe and effective against acute respiratory tract infections and the people having higher risk of vitamin D deficiency during COVID-19 should take vitamin D supplements to maintain the circulating 25(OH)D in the optimal levels (75-125 nmol/l). The vitamin D serum concentrations should be inbetween 40 and 60 ng/ml (100-150 nmol/l) during all the year and can reduce the risk of respiratory tract infections including COVID-19 infection (Cutolo *et al.*, 2020). The various mechanisms involved with the adequate vitamin D availability and reduction in the risk of viral and COVID-19 infections has been mentioned in Figure 3.

4.1.5 Vitamin E

Vitamin E is a potent antioxidant and important nutrient for maintaining the immune system, especially in the elderly people (Moriguchi and Muraga, 2000). It plays a role in the differentiation of immature T cells in the thymus with ability to modulate host immune functions and decrease in cellular immunity with ageing or degenerative diseases can be improved by the intake of a high vitamin E rich diet (López-Varela *et al.*, 2002). Vitamin E acts as an essential

factor in enhancing the production of natural killer cells and interleukins with significant contribution in the proliferation of lymphocytes and elicits a robust immune reaction against pathogens (Gombart *et al.*, 2020; Junaid *et al.*, 2020). The above all findings support the potential therapeutic use of vitamin E against COVID-19.

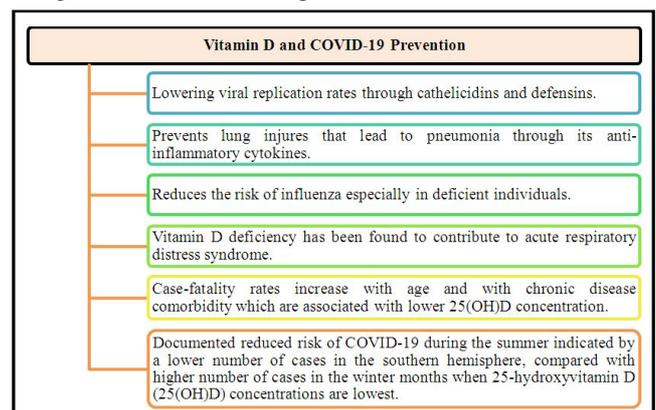


Figure 3: Mechanisms involved with the adequate vitamin D availability and reduction in the risk of viral and COVID-19 infections (Martineau *et al.*, 2019 and Alkhatib, 2020).

4.2 Minerals

A number of trace elements iron, zinc, selenium and copper have been shown to be important for adequate functioning of the immune

system and play a crucial role in biological processes, such as oxygen transport, cell growth and differentiation, and protection against oxidative stress. While their deficiencies can affect the antibody responses, cell-mediated immunity, and natural killer (NK) cell activity (Thakur *et al.*, 2019).

4.2.1 Zinc

Zinc is associated with immunological properties and is very essential for highly proliferating cells, normal development and functioning of cell-mediating innate immunity and acts as an essential cofactor for thymulin which modulates cytokine release and induces proliferation (Maggini *et al.*, 2007; Prasad, 2009; Alpert, 2017). Due to its immune response and antiviral action, zinc may be considered as adjunct therapeutic agent for COVID-19 patients and zinc supplementation can be used to mitigate the severity of disease in this population (Bhatt *et al.*, 2020). Finzi (2020) reported that high dose of zinc lozenges (zinc citrate/gluconate 23 mg, and zinc acetate 15 mg) given to COVID-19 patients resulted in improvement of oxygenation with zinc gluconate along with alleviation of symptoms.

4.2.2 Selenium

Selenium is an essential micronutrient which helps in up-regulation of expression of the α and β subunits of the IL-2 receptor along with boosting up the immune system by increasing the cytotoxicity of killer cells, numbers of lymphocytes and promotes antibody production by B lymphocytes (McKenzie *et al.*, 2002; Thakur *et al.*, 2019). Selenium is required for the effective and efficient functioning of the immune system. It enhances the function of cytotoxic effector cells and have an important role in maintaining T cell maturation and functions, as well as for T cell-dependent antibody production (Bae and Kim, 2020). Kieliszeka and Lipinski (2020) reported that selenium can potentially be used in the recent battle against coronavirus epidemic. Selenium deficiency has been found associated with mortality in COVID-19 and a sufficient selenium level is important for recovery from the disease (Moghaddam *et al.*, 2020; Zhang *et al.*, 2020)

4.2.3 Iron

Iron is a part of the haem protein present in haemoglobin and in human body it is responsible for supplying oxygen to tissues. As a part of cytochromes it plays an important role in the transportation of the mitochondrial electron and it effects in broad spectrum leading to impairment of the respiratory burst, killing of bacteria, proliferation of T-cells and development of cytokines (Kumar and Choudhry, 2010; Dhok, 2020). Iron chelation therapy could be considered to improve survival and overall long-term outcome in appropriate setting of critically ill patients with COVID-19 due to the beneficial effects of iron chelation therapy on the inflammatory status as well as on the fibrogenesis occurring in the lungs (Perricone *et al.*, 2020). Ferrous/ferric oxide which is an inert material is used for preparing nano-particles in nanotechnology and these nano-materials are used widely in the global fight against COVID-19 pandemic by preparing personal protection equipment's (PPE's) diagnostic tests and manufacture effective vaccines or antiviral drugs (Bhatt *et al.*, 2020; Liu *et al.*, 2020)

4.2.4 Copper

Copper is an essential micronutrient which is involved in the functions of critical immune cells like T helper cells, B cells, neutrophils, natural

killer (NK) cells and macrophages which are involved in the killing of infectious microbes including SARS-CoV-2, cell-mediated immunity and the production of pathogen specific antibodies (Raha *et al.*, 2020). Studies conducted by Andreou *et al.* (2020) supports the combination of copper, N-acetylcysteine (NAC), colchicine and nitric oxide (NO) with antiviral agents, remdesivir or EIDD-2801, as a treatment for patients infected with SARS-CoV-2. Copper destroys the replication and propagation abilities of SARS-CoV, influenza and other respiratory viruses which help to reduce the transmission of several infectious diseases by limiting nosocomial infectious transmission. Copper oxide or nano-compounds may be used for preparing nano-particles in nanotechnology which are further used to manufacture filters, face masks, clothing, *etc.* (Cortes and Zuñiga, 2020). Copper signalling, its vulnerability, method of assessment and interpretation, administration route and dosage opens up new perspectives regarding therapeutic copper administration against critically ill COVID-19 patients (Fooladi *et al.*, 2020).

4.3 Phenolic compounds

Phenolic compounds are a class of the most widely distributed secondary metabolites in plants and are commonly found in various products of natural origin like fruits, vegetables, food grains, seeds, flowers, tea, wine, honey and forages. Phenolic compounds have been recognized as dietary factors responsible for potential effects on human health and they have been widely used to increase functionality of some foods (Quirós-Sauceda *et al.*, 2014). The various phenolic compounds have unique antioxidant activity which contributes towards its medicinal value and human health benefits (Kashyap *et al.*, 2017 and Thakur *et al.*, 2020). Traditionally, the polyphenols rich plant derived folk medicines are used to cure disorders of the blood stream including blood pressure, antiviral effects, stomach disorders, antiseptic action, dressing of burns or inflammation and inhibition of direct acting mutagens. These are the major class of compounds that show great activity against various viruses such as retrovirus, hepatitis virus, herpesvirus, HIV virus, influenza virus, herpes simplex virus, dengue virus, polio virus, *etc.* (Kamboj *et al.*, 2012; Wan-Fei *et al.*, 2017).

Due to the tremendous pharmacokinetic properties, flavonoid and phenolic compounds are most promising active compounds among the chemically diverse natural therapeutic agents used for against SARS-CoV-2 (Sayed *et al.*, 2020; Islam *et al.*, 2020). Rathinavel *et al.* (2020) reported that phenolic compounds such as quercetin, rosmarinic acid and hesperetin show good binding affinity with SARS-CoV-2 viral protein targets with an excellent physicochemical or pharmacokinetic property and these phenolic drugs may best suit to treat COVID-19. These researchers further suggested use of these phenolic compounds for COVID-19 treatment practices as they can act as nutritional supplements and promote the immune system of the body to combat COVID-19 infection. The polyphenolic drugs can act as antiviral in nature as they can inhibit coronavirus enzymes, which are required for virus replication and infection. For the inhibition of viral proteases, the various natural substances like betulinic acid, indigo, luteolin, quinomethyl triterpenoids, quercetin and gallates can act as a potential key to designing antiviral therapies. These polyphenols might provide a starting point for the research on the use of plant extracts for the development of new anti-Covid-19 formulations and these formulations containing phytochemicals have high safety for patients with no side effects (Chojnacka *et al.*, 2020). Khalil and Tazeddinova (2020) reported that polyphenols can be considered as a potential and valuable source for designing new drugs that could be used for the treatment of COVID-19 infection.

Table 2: Antiviral functional food sources of immune promoting minerals: functions and effects on respiratory system

| Mineral | Antiviral functional food sources | Key mechanism of action | Recommendations and deficiency | RDA* (for Indians 2020) | References |
|----------|--|---|--|---|--|
| Zinc | Shellfish, meat, cheese, grains, seeds, cereals, seeded or wholegrain breads | <ul style="list-style-type: none"> • Zinc deficiency: reduction in innate immunity. • Role in immune cell maturation and differentiation. • Increases the number and function of natural killer cells • Inflammatory cytokine regulation • Involvement in anti-inflammatory pathways | <p>Supplementation is required during low dietary intake especially in older adults.</p> <p>Deficiency leads to depressed immunity, growth failure, diarrhoea, anorexia, altered skeletal function and reproductive failure.</p> | 17 mg/day for men and 13.2 mg/day for women | Bonaventura <i>et al.</i> , 2015 Maares and Haase, 2016 |
| Selenium | Fish, shellfish, eggs, meat, nuts like brazil nuts | <ul style="list-style-type: none"> • Necessary for the activity of selenoproteins, which is vital for the host's antioxidant protection | <p>Supplementation is recommended when intake is low. Its deficiency has been linked to 2 endemic diseases in children and adolescents.</p> | 40 µg/day for men and women | Zhang and Liu, 2020 |
| Iron | Meat, liver, beans, nuts, dried fruit, fortified cereals, wholegrains, dark green leafy vegetables (spinach, kale) | <ul style="list-style-type: none"> • Iron is needed for the development and action of inflammatory cytokines including IFN-, TNF-, IL-2, and IL-10. • Generation of reactive oxygen species (ROS) that destroys the pathogen that infects immune system. • Helps to control the proportion of T helper and cytotoxic T cells. | <p>Dietary intake is recommended. Supplementation is required during low dietary intake. Major deficiency-anemia</p> | 19 mg/day for men and 29 mg/day for women | Budi <i>et al.</i> , 2015; Center, 2016 Wu <i>et al.</i> , 2018 |
| Copper | Nuts, shellfish, liver, some vegetables | <ul style="list-style-type: none"> • Linked with superoxide dismutase (SOD) enzyme, which is involved in the protection against reactive oxygen species (ROS). • Classified as a free radical scavenger and maintains intracellular antioxidant balance. • In animal studies, it is involved in T cell differentiation and proliferation, antibody formation, and cellular immunity. | <p>Dietary intake is highly recommended. Anemia, vascular complications, osteoporosis, and neurological symptoms are also signs of copper deficiency.</p> | 2 mg/day for men and women | Maggini <i>et al.</i> , 2007; Saeed <i>et al.</i> , 2016; Alpert, 2017 Maggini <i>et al.</i> , 2018 |

Table 3 : Antiviral functional food sources of immune promoting phenolic compounds and their mode of action

| Bioactive components | Bioactive components sources | Key mechanism of action | References |
|--|---|---|---|
| Polyphenols | Apple, pomegranate, aonla, apricots, papaya, peaches, mango, pumpkin, spinach, broccoli, orange, tomato, berries, jamun | Prevent and counteract inflammation by mitigating inflammatory response in adipocytes, macrophages, and additional immune cells | Godfrey <i>et al.</i> , 2012; Hamid <i>et al.</i> , 2017; Lin <i>et al.</i> , 2017; Kaihatsu <i>et al.</i> , 2018 |
| Curcumin | Turmeric | Immunomodulator, modulate dendritic cells and anti-inflammatory | Thakur <i>et al</i> 2018; Giancetti and Fierabracci, 2020; |
| Catechins(-)-epigallocatechin-3-gallate (EGCG) | Green tea, apples, blueberries, gooseberries, grape seeds, kiwi, strawberries, red wine | Enveloped DNA, (+)-RNA and (-)-RNA viruses may be inhibited by natural catechins, but by inhibiting reverse transcriptase <i>in vitro</i> and <i>in vivo</i> , EGCG showed a high capacity to prevent the initial stages of infections, including binding, postadsorption entrance, and genomic multiplication, by interfering with viral protein complexes as well as cellular processes | Levy <i>et al.</i> , 2020; Li <i>et al.</i> , 2020b; Rahimi <i>et al.</i> , 2020; Wahedi <i>et al.</i> , 2020 |
| Quercetin | Apples, berries, brassica vegetables, grapes, onions, tea and tomatoes | Pro-metabolic, anti-inflammatory, and antiviral effects | |
| Resveratrol | Grapes, berries, mulberry,peanuts, and mainly red grapes/wine | Viral RNA replication inhibition, cell death reduction, inhibition of apoptosis | |
| Anthocyanins | Pomegranate, berries, jamun | Anti-inflammatory, antioxidant, antiplatelet, anticarcinogenic, cardioprotective and immunomodulatory | |

5. Conclusion

COVID-19 a worldwide pandemic declared by WHO due to a novel virus which has grapple the world with inevitable threat to maintain good immune system as well as health, thus leads mankind to rethink about the natural remedies to improve immunity of human being through maintaining proper nutrition. Thus, maintaining good nutrition through natural bioactive compounds from natural sources has capability to provide good immunity with lower risk of viruses attack. Here is the need of functional food arises that will fulfil the requirement of dietary food functional components which helps in protecting the body from various diseases. Hence, foods having different functional components like vitamins (A, B, C, and D), minerals (selenium, zinc, and iron) and polyphenolic compounds (quercetin, resveratrol, catechins, anthocyanins) can act as natural therapeutic agents against SARS-CoV-2 or preventive therapy for COVID-19 patients besides improving immunity of the body to combat COVID-19 infection. Thus, with the increasing spread of the virus worldwide, it can be an alternate to combat COVID-19 infection with the consumption of various types of functional foods.

Conflict of interest

The authors declare that there are no conflicts of interest relevant to this article.

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