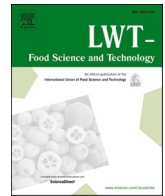




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Food nutrients as inherent sources of immunomodulation during COVID-19 pandemic

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) - a novel coronavirus has rapid spread, and caused community infection around the globe. During the absence of a vaccine, people focused more on an immunity-boosting diet and needed clear knowledge about immunity-boosting foods. However, after the vaccination drive, the importance of food as a natural source of immunomodulation cannot be neglected. So, the purpose of this review was to describe the role of vital nutrient in boosting immune system of body apart from other factors like adequate sleep, exercise, and low stress levels. Macrophages, neutrophils, natural killer cells, dendritic cells, B-cells, and T-cells are the important components having important role in maintaining immunity of the human body. The first four-act as the initial mediators of innate host defense, and the latter two produce antibodies for pathogen destruction. The review investigated vital nutrients like vitamin-C, A, E and D, iron, zinc, folic acid, probiotics, and prebiotics affecting these immune components in some extent. Fruits, vegetables, spices, herbs, seeds, nuts, cereals, millets, and superfoods like chlorella and spirulina are good sources of these nutrients. However, fortified foods, functional foods, encapsulated foods with bioactive compounds and plant-based foods have shown immense potential in boosting immunity against viral infections like COVID-19. Some clinical trials and retrospective cohort studies have shown reduction in the severity of COVID-19 patients with relation to plant-based diet, vitamin D and C doses, probiotic, and zinc salts application.

1. Introduction

The Novel Coronavirus disease-2019 (COVID-19) is a contagious disease characterized by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Kim et al., 2021). This disease has wreaked havoc worldwide, claiming more than 5.5 million lives and infecting close to 323 million people by 16 January 2022 (WHO, 2022). The virus that is reported to have originated from Wuhan, China has spread to over 200 countries in a span of just 6 months (Keni et al., 2020). People with certain prior ailments like diabetes, cancer, hypertension, cardiovascular illness, neurological disorder, and respiratory issues are at a higher danger of having COVID-19 complexities. However, the persons with more youthful age, vigorous resistance, nil fundamental sicknesses and no habit of smoking or vaping, are likely to battle the surge of the infection, since in that case, the COVID-19 can only bring about a minor

viral infection (Liu et al., 2020).

The vaccine is now available for fighting against COVID-19 but still the importance of natural forms of inhibition and remedy cannot be neglected. In this aspect, the food and dietary habit play key perspectives in deciding general wellbeing and resistance (Lindgren et al., 2018). The body requires the nutrients supplied from natural source in the form of food to fight against illness. Consumer sought to be progressively mindful of these issues of choosing food nourishments that can enhance the capacity of the immune framework. The immune system consists of a versatile network of specialized cells, tissues, organs, proteins, and other chemicals, which has evolved to safeguard the host and body from a range of microbes and pathogens as well as cancer cells (Carr & Maggini, 2017). Various factors like diet, environment, genes, lifestyle, sleeping pattern, regular exercise, etc. affect the reaction of these components when any external agents like virus, bacteria, fungi,

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etc. attack the human body. This immune system can be badly affected through intake of diet with deficient amount of nutrients i.e., malnourished diet. However, the malnourishment can be reduced by the supply of fortified or supplemented foods. The idea of taking nourishments through regular diet, or via supplementation give insusceptible benefits (Handu et al., 2021; London, 2010). The factors governing the innate and adaptive immunity are first discussed in this review. The importance of vital nutrients in improving the immune system with their working mechanisms are reviewed. Some common foods rich in vital nutrients are discussed in brief followed by describing about the trending foods with potential to boost the immunity and fight against the COVID-19 disease.

2. Factors responsible for boosting and maintaining immunity in human being

The immune types are broadly classified into innate and adaptive immunity. The former acts as first line of defence and applies physical and biochemical barriers with a non-specific, leukocyte-mediated cellular response to guard against pathogens. Monocytes, neutrophils, natural killer cells and dendritic cells are the components which mediate the cellular response for guarding against pathogens. However, if the pathogens get passed against these innate components then a more complex, adaptive and antigen-specific response called adaptive immunity system is triggered which produces highly targeted antibodies and kills the pathogen (Castelo-Branco & Soveral, 2014). The response in adaptive immunity is mediated by T and B lymphocytes. The immune role and working mechanism of each immune component are summarised in Table 1 and discussed in detail in the subsequent sections.

Table 1
Vital immune regulating components and their mechanisms.

Component	Immune role	Immune system	Main mechanism in protecting immunity	References
Macrophages	First line of immune defense against pathogens	Innate immunity	Killing of prey through acidification after phagocytosis supported by solute carriers membrane protein	O'Neill and Pearce (2016); Sedlyarov et al. (2018)
Neutrophils	Initial mediators of the rapid innate host defense	Innate immunity	Respond to microbial infections through phagocytosis, reactive oxygen species generation and neutrophil extracellular traps	Castelo-Branco and Soveral (2014); Malech et al. (2014)
Natural killer cells	Host defense against tumors and pathogens	Innate immunity	Protect by signaling immune system through cell cytotoxicity and cytokine secretion	Castelo-Branco and Soveral (2014); Condotta and Richer (2017)
Dendritic cells	First alert of pathogen's presence	Innate immunity	Promote the release of cytokines by natural killer cells	Agrawal and Gupta (2011)
B-cells	Antibody production and responding to antigens	Adaptive and Innate	Carry out immune response through release of cytokines	Vaughan et al. (2011); Hoffman et al. (2016)
T-cells	Killing of infected or malignant cells	Adaptive and Innate	First recognition through major histocompatibility complexes then clonal expansion for killing pathogen-infected host cells	Tortura and Derrickson (2017); Condotta and Richer (2017)

2.1. Macrophages and phagocytes

Macrophages are represented as the first line of immune defense against pathogens. Due to their flexible and versatile surface, macrophages engulf every foreign object that crosses their way which are assumed to be harmful for the health of the organism. The pathogens are enclosed in intracellular membrane vesicles called 'phagosome' by a process known as 'phagocytosis' and then the macrophages kill their prey with acid (Artyomov et al., 2016; O'Neill & Pearce, 2016; Sedlyarov et al., 2018). The acidification process comes into play for killing the microbes (Table 1).

2.2. Natural killer cells and dendritic cells

Dendritic cells (DCs) and natural killer (NK) cells have important contributions in immune regulation. The initial recognition of pathogens, their phagocytosis and processing of antigens are caused by DCs. The first warning of the presence of pathogens are directed by these cells and establish a connection between innate and adaptive immune responses (Agrawal & Gupta, 2011). On the other hand, NK cells perform host defense against tumors and pathogens. These occur due to secretion of variety of cytokines (particularly interferon (IFN)- γ) which signal the immune system to do its job (Condotta & Richer, 2017). These secretions are carried out by two mechanisms viz. cell cytotoxicity and cytokine secretion and done by two main subpopulations, CD56dimCD16+ NK cells and CD56brightCD16- NK cells (Castelo-Branco & Soveral, 2014).

2.3. Neutrophils

Neutrophils are the primary mediators of the rapid innate host defense against most bacterial and fungal pathogens. They are short-lived phagocytic cells which are continuously circulated in blood vessels and reached to the infection site through cytokines and chemokines, mainly interleukin -1 (IL-1) and interleukin -8 (IL-8). There are three main mechanisms viz. phagocytosis (requiring opsonization), generation of reactive oxygen species and degranulation (releasing enzymes and antimicrobial peptides) and neutrophil extracellular traps (NETosis) by which these phagocytic cells get responded to microbial and parasitic infections (Castelo-Branco & Soveral, 2014).

2.4. B-cells

B cells are a kind of white blood cells (WBC) of the lymphocyte subtype and called as B lymphocytes. These cells have the function of producing antibodies having unique receptors on their cell surfaces for responding them specifically to different antigens and can modulate immune responses independently of antibody production (Vaughan et al., 2011).

The B cells play an immunomodulatory role in regulating the immune response through release of cytokines (Hoffman et al., 2016).

2.5. T-cells

T cells are very important in both adaptive and innate immune responses. They mature in the thymus, express T cell receptors (TCRs) and are categorized in two main subsets by the cell surface expression of either cluster of differentiation (CD) 4 or CD8 (Castelo-Branco & Soveral, 2014). These CD4 and CD8 contribute to T cell recognition and activation by binding to either major histocompatibility complex (MHC) class I or II (Maggini et al., 2018). Antigen-presenting cells containing MHC II molecules present peptides to be later recognized by CD4⁺ helper T cells and result in secretion of cytokines. In case of nucleated cells, CD8⁺ cytotoxic T cells recognize peptides that are presented by MHC I molecules. This recognition result in secretion of cytokines like TNF- α or IFN- γ (Tortura & Derrickson, 2017).

3. Vital nutrients providing immunomodulation to human

The ingestion of these foods normalizes immune function and reduces pathogenic infection. The most vital nutrients which help in boosting the immune system of the body are vitamin C, vitamin E, vitamin A, vitamin D, folic acid, iron, zinc, prebiotics, and probiotics (Arshad et al., 2020; London, 2010; O'Sullivan et al., 2005). The vital role of nutrients in boosting immunity along with their target mechanism are described in Table 2. The effect of vital nutrients on the immune components of the body are shown in Fig. 1.

3.1. Vitamin C

Vitamin C plays a crucial role in immune system, predominantly in immune cell function. Studies found recovering from acute respiratory infection in patients after the supplementation of vitamin C. The immune-modulating influence is likely due to its behavior as a cofactor for several gene regulatory and biosynthetic enzymes. This vitamin augments phagocytosis, enhances microbial killing, raises oxidant generation, and accelerates neutrophil passage to the site of infection (Carr & Maggini, 2017). Some results of clinical trials done on vitamin C supplementation on COVID-19 patients has been shown in Table 3.

3.2. Vitamin A

Retinal, retinol, and retinoic acid (RA) are the most biologically active forms of vitamin A and are important for maturation of epithelial cells, morphological formation of the epithelium, stratification, epithelial keratinization, and differentiation. Epithelium lines cover both outer and inner surfaces of organisms and functions as the "front line" defense against pathogen attack. The vitamin A increases the antigen immunity function of tissues by promoting mucin secretion at both the intestine and respiratory tracts. The deficiency of this vitamin leads to shrinkage of epithelial cells and occurrence of squamous keratinization in digestive tract, skin, respiratory tract, cornea and genitourinary system. Simultaneously, the keratinized epithelial tissues' resistance to foreign pathogens declines, and mechanical barrier function reduces, thus lowering down the innate immune functioning and later endorsing respiratory tract infections, diarrhoea, and other diseases (Huang et al., 2018).

3.3. Vitamin E

Vitamin E consists of tocopherols (α -, β -, γ -, and δ -tocopherols) and tocotrienols (α -, β -, γ -, and δ -tocotrienols) found in food and exhibits antioxidant activities. Only α -tocopherol meets the human requirements as other forms are non-convertible. A dietary intrusion of the vitamin E supplements enhances cell-mediated and humoral immune responses in

diverse species of animals causing increase in lymphocyte proliferation, immunoglobulin levels, antibody responses, NK cell activity, and production of IL-2. The immune stimulatory effect of vitamin E has shown increase in resistance against several pathogens like *D. pneumoniae* type 1 (Lee & Han, 2018).

3.4. Vitamin D

In relation with immune system, vitamin D showed a role in modulating both innate system and adaptive system (Childs et al., 2019). In innate system, toll like receptors (TLR) help macrophages to identify lipopolysaccharide (LPS) which is a substitute for bacterial immunity system. Further, peptides having potent bactericidal activity such as β -defensin 4 and cathelicidin are produced after cascade of events due to engagement of TLRs. Finally, the bacterial cell membrane of ingested bacteria gets interrupted and potent anti-micro bacterial activity is formed due to colocalization of those formed peptides with ingested bacteria within phagosomes (Kaminogawa & Nanno, 2004).

3.5. Iron

Iron has shown to influence the activation of Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF- κ B), a transcription factor needed for the expression of genes involved in innate immunity and inflammation. These NF- κ B cells also control the activation, differentiation and effector function of inflammatory T cells which provide healing disposition (Liu et al., 2017; Moreau & Rosenblum, 2019). Antibody and cell-mediated responses are carried by antigen-specific B and T lymphocytes, respectively, whose activation, proliferation and differentiation are important for proper adaptive immunity system. Development of lymphocyte depends on the ability to gain iron via Transferrin receptor 1 (TfR1). Thus, iron deficiency influences the functioning of innate and adaptive arms of the immune system (Karacabay & Ozdemir, 2012).

3.6. Folic acid

Deficiency in serine level can prevent proper antibody formation and can interfere with effector T cells functioning. Glycine to serine conversion is dependent upon folic acid whose deficiency prevents conversion and reduces serine level, thus affecting the immune system (Jayawardena et al., 2020). Various cellular pathways like DNA production and repair also get negatively affected due to folate deficiency in diet. This further reduces the metabolic reactions resulted from disruption of homeostasis and leads to immune dysfunctions like improper antigen presentation, distressed cytokine production, unmodulated autoimmune responses, disruption in immune cell function,

Table 2

Role of nutrient in maintaining immunity system.

Nutrient	Target/Mechanism	Effect on immunity	References
Vitamin C	Augments phagocytosis, oxidant generation and neutrophil passage to infection site; increases neutrophil apoptosis; declines neutrophil necrosis and histamine levels	Enhances microbial killing; reduce acute respiratory infection	Carr and Maggini (2017)
Vitamin A	Enhance serum level of Immunoglobulin G, M & A; production of specific antibodies	Improves innate immune functioning	Huang et al. (2018)
Vitamin E	Increases lymphocyte proliferation, immunoglobulin levels, antibody responses, NK cell activity, and production of IL-2, macrophage activity	Protection against <i>D. pneumoniae</i> type 1	Lee and Han (2018)
Vitamin D	Improves responding activity of T cells, B cells, DCs and monocytes	Help fighting respiratory infections & tuberculosis	Clancy (2003); Childs et al. (2019)
Iron	Lymphocyte development depends upon iron which regulated the antibody and cell-mediated responses	Improves innate and adaptive immune system	Karacabay and Ozdemir (2012)
Folic acid	Improves glycine to serine conversion, DNA production and repairment, homeostasis and immune cell function	Improves cell mediated and humoral immunity	Childs et al. (2019); Jayawardena et al. (2020)
Zinc	Prevents free radical-induced injury, Enhance macrophages, phagocytosis, cytokine levels, T and B cell growth	Well-functioning of immune cells	Prasad (2008); Wessels et al. (2017)
Prebiotics and probiotics	Stimulate cell-mediated immune effector roles, phagocytosis; inactivates procarcinogens	Improves local immune response and gut health	(Guillot, 2000; O'Sullivan et al., 2005)

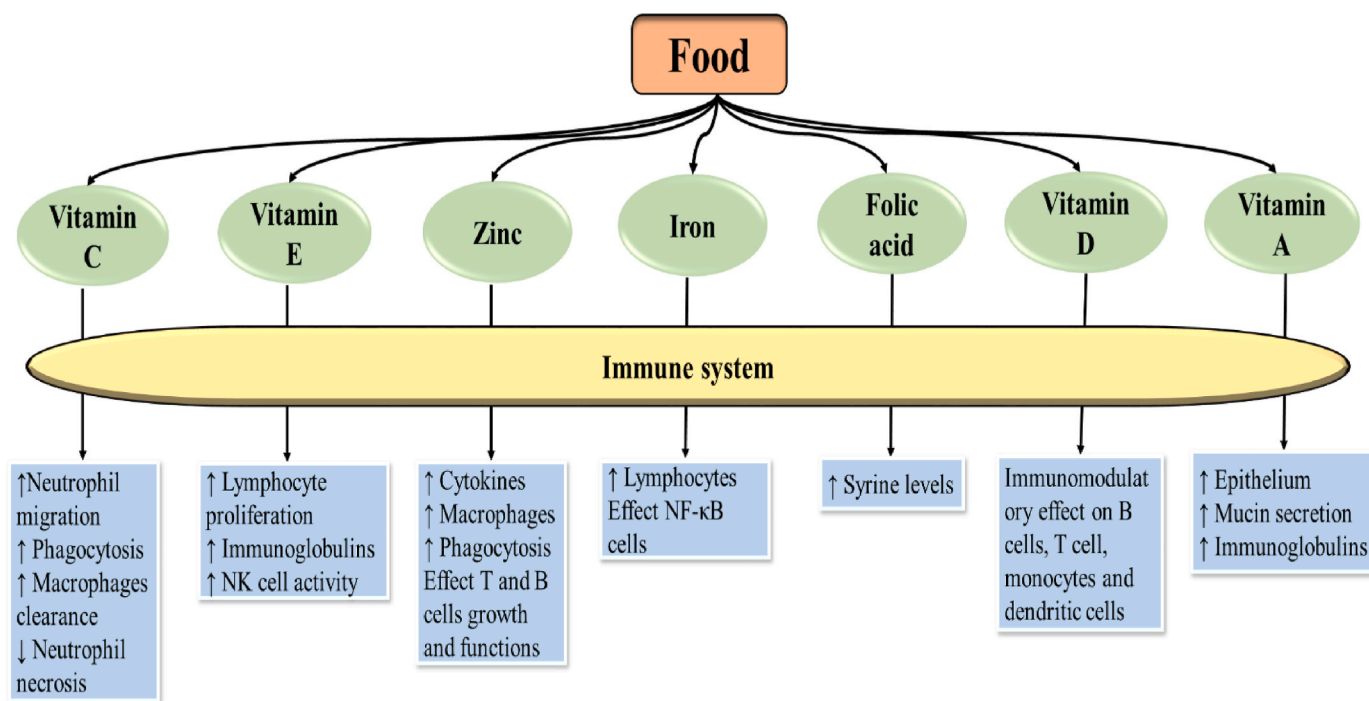


Fig. 1. Vital micronutrients and their immune boosting mechanism.

Table 3

Clinical trials and retrospective cohort study of COVID-19 patients intervened with potential nutrient or diet.

Type of food or nutrient intervened	Participants/In-vitro models	Type of study	Number of participants	Observation	References
Plant based diet	Front-line healthcare workers	Clinical trials	2884 (138- moderate-to-severe COVID-19 severity, 430-very mild to mild COVID-19 severity and 2316-controls)	73% and 59% reduction in moderate-to-severe COVID-19 severity following plant-based diet	Kim et al. (2021)
High-dose intravenous Vitamin C	Normal patients	Clinical trials	50 (moderate to severe symptoms of COVID-19)	10–20g per day doses over a period of 8–10 h has improved oxygenation index and all patients get cured and discharged from hospital	Cheng (2020)
Vitamin D	Hospitalized patients	Retrospective cohort study	780 laboratory-confirmed infection of SARS-CoV-2.	Elder men with pre-existing conditions and low levels of vitamin D below normality were associated with increasing risk of suffering from COVID-19	Raharusuna et al. (2020)
Probiotic	Patients requiring hospitalization	Clinical trials	40 COVID-19 patients with age ≥18 years requiring hospitalization	The primary outcome was cases with discharge to ICU.	Bioithas (2020)
Zinc salts (zinc citrate, zinc gluconate, or zinc acetate)	laboratory-confirmed COVID-19 patients	Uncontrolled case based clinical trials	4 COVID-19 patients (a 63-year-old, 57-year-old female, 41-year-old female, 26-year-old female)	Symptomatic and objective measures of disease began to improve within 24 h after initiation of zinc lozenges	Finzi (2020)

and ineffective viral clearance (Childs et al., 2019).

3.7. Zinc

Zinc is important for development and functioning of cells mediating innate immunity, neutrophils, and NK cells of the immune system. Zinc deficiencies suppress the cytokines, causes severe weakening of both the adaptive and the innate immune system (Prasad, 2008). However, its excess can also impair the immune system. Therefore, a balanced zinc homeostasis is essential for either protecting against invading pathogens or defending the human body against an overreactive immune system causing severe allergies and autoimmune diseases. Thus, zinc can act as a door keeper to adequate functioning of immune cells and immune system and its anti-oxidative properties can prevent free radical-induced injury during inflammation (Wessels et al., 2017). Some results of clinical trials done on zinc salts intervention on COVID-19 patients has been shown in Table 3.

3.8. Probiotics and prebiotics

Probiotics are useful microbes that can arouse cell-mediated immune effector roles, secretion of interferon gamma by blood cells, improved phagocytosis, and an upsurge in complement receptors' action on phagocytes resulting in gut milieu alternation, activation of a local immune response, and down-regulation of the mucosal secretory response to pathogens (O'Sullivan et al., 2005). These are acted by three possible modes: producing immuno-stimulants, creating antimicrobial compounds, and competitively eliminating other bacteria (Galdeano et al., 2019). These are generally encapsulated within a matrix of prebiotics and other carrier agents so that they can be protected from outside stress. It must be ensured that adequate quantities of viable organisms reach the intestinal tract by resisting the stomach acidic environment and bile digestion. They have the ability to be attached to epithelial cells, produce antimicrobial factor, colonise the intestinal tract, impede enteric pathogens, inactivate procarcinogens and modulate metabolic

activities (Guillot, 2000).

4. Nutrient rich food source with potential immunity boosting benefits

The consumption of nutrients through natural source can provide long-lasting immune boosting effect. These natural sources are fruits, vegetables, cereals, millets, spices, herbs, nuts, oilseeds and some superfoods like chlorella and spirulina. The role of these nutrient rich sources is discussed in brief in subsequent section. The relationship between various foods, nutrients and immune components are described in a generalized manner in Fig. 2.

4.1. Fruits and vegetables

The nutrients from fruits and vegetables considered as whole foods behave as modulators of immune system. Certain vegetables like tomato, ringer pepper, mushroom and green vegetables like broccoli, spinach, kale, beans are always acceptable choices as immunity promoters to manufacture flexibility in the body against diseases. Consumption of cabbage, cauliflower and brussel sprout shows high prompt result against any microbial infection as it contains active component called isothiocyanates and helps in regulating gut metabolism. Seaweed also triggers the immune system, improves brainpower and fights against anemia, dermatitis, and obesity. Mushroom has the potential to act as immunomodulators that activate immune system where lentinan is an immune-boosting component that is highly present in Shiitake mushroom. Pure lentinan has already been used earlier against hepatitis B patients and has shown good results (London, 2010).

4.2. Spices and herbs

Spices and herbs have been used in diets in the form of tea or by incorporating into food products. Garlic, ginger, and turmeric possesses antiviral, antifungal, and antibacterial properties which can help in lowering the blood pressure and prevent virus infection. Both onion and garlic contain sulfuric compounds which boost immune system by increasing the action of helper T and NK cells (London, 2010).

Holy basil or ‘tulsi’ (*Ocimum sanctum*), is inhabitant to Southeast Asia, and has been used for centuries to enhance the body’s stress and immune responses through compounds like essential oils, flavonoids and polyphenols. Moreover, a comprehensive review on 24 human studies discovered positive therapeutic effects of basil on immunity, cognition, and metabolism (Jamshidi & Cohen, 2017).

Echinacea (purple Kansas cornflower) is the North American herb consumed for preventing regular cold and diseases in the upper respiratory tract and has received one of the best practical functional food segments. It encourages the body to develop more WBC, such as T lymphocytes and regulates the secretion of IFNs to act against infections. *Andrographis* is another herb used as Ayurvedic medicine which was used for fighting against Indian flu epidemic during 1919. It has better capability than placebo for decreasing the symptoms of respiratory infections (London, 2010).

4.3. Seeds and nuts

Seeds are good substitute for meat, fish, and eggs since they are rich sources of fibre, protein, iron, zinc and vitamins (De, 2020). Supplements rich in omega-3 unsaturated fats, like, flax seeds, beans, and a few nuts should always be remembered for their immense benefits. Walnuts are accepted as a source of healthful compounds including vitamin E and omega-3, both of which are influential immune boosters. Brazil nuts are good sources of vitamin B, vitamin E, and selenium. Raw almonds are abundant in fatty acids and essential amino acids, which are prerequisite for optimum immunity (London, 2010).

4.4. Cereals and millets

Cereals like black rice and brown rice contains abundant antioxidants, vitamins, and nutrients. The former is rich in amino acids, iron, zinc, copper, carotene, and fiber which helps in detoxifying the body from harmful build-ups. On the other hand, the brown rice is rich in several nutrients such as calcium, iron, magnesium, manganese, phosphorous, potassium, selenium, vitamin B, vitamin E, and vitamin K. All these nutrients are vital and have proven to help in maintaining the good immune response (De, 2020).

Millets are nutritionally superior to major cereals (wheat and rice) for carbohydrate and energy, and are good sources of protein, high dietary fibre, vitamins, minerals, antioxidants, and micronutrients. The richness of vitamins and minerals in millets perform vital role in body to boost the immune response towards pathogens. However, no direct result proven the statement of boosting immunity by millets are available but many scientists advice that the consumption of correct proportion of minerals, vitamins, and antioxidants through grains would optimize the functioning of the immune system (Muthamilarasan & Prasad, 2020).

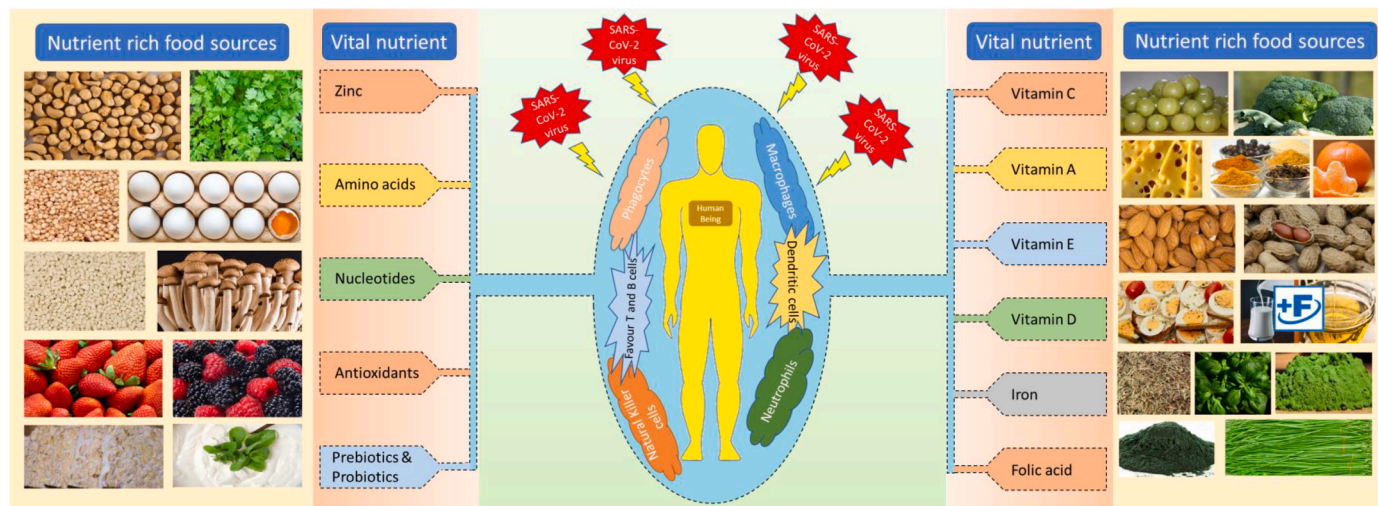


Fig. 2. Defense against CoVID-19 through various immune components fueled by vital nutrients obtaining from nutrient rich food sources.

4.5. Superfoods

Microalgae like chlorella and spirulina are regarded as superfoods due to having immense nutritional attributes than conventional foods. These foods are highly rich in proteins, iron, folate, and vitamin B₁₂ which is generally not present in plant-based foods. Spirulina contains all essential amino acids and is a rich source of vitamins, minerals, pigments, chlorophyll, essential fatty acids, polysaccharides, and phenolic compounds, and similar with the case of chlorella, however, this does not contain complete protein (Sugiharto, 2020). In a 90-days study of supplementing vitamins (vitamin A, B₁, B₂, B₆, B₁₂, C, D and E), minerals (selenium and zinc, etc.), and plant extracts such as laminaria, chlorella, equinacea, and spirulina among studied group, showed significantly lower incidence ($p = 0.013$) of acute respiratory infections compared to the placebo group. This showed the counteracting ability of mixture of micronutrients and plant extracts from the damages caused by free radicals produced for pathogen removal and consequently boosting the immune system (Iriondo-DeHond et al., 2020).

5. Potential foods with immunity boosting role against COVID-19

The foods having immense potential in boosting immunity are fortified foods, encapsulated food (targeted delivery of nutrition) and functional foods (specific property-based food). An emerging trend of plant-based food has appeared which might have some positive impact to prevent further emergence of such pandemic as that of Covid-19. All these kinds of foods and their importance related to Covid-19 have been discussed in detail in subsequent subsections.

5.1. Fortified food and its importance in Covid-19

Food fortification is method of addition of nutrients in food either present already or absent to prevent or correct the demonstrated deficiency in population or specific population groups. Several micronutrients like iron, folic acid, vitamin B₁₂, zinc, vitamin A, vitamin D, etc. are being fortified in foods like oil, milk, rice, and salt. The functions of major nutrients on the immunity have been discussed previously. However, in the Covid-19 prospective, vitamin D has been found to play a major role in preventing the severity of COVID-19 and the risk of death. The clinical investigation showed a linkage of acute respiratory tract infections, particularly epidemic influenza with low levels of serum vitamin D. A correlation between vitamin D levels and the severity and mortality of COVID-19 patients was also observed in studies (Handu et al., 2021). In addition, a negative association between serum 25(OH) D levels (a marker for Vitamin D insufficiency) and COVID-19 severity was reported in some studies. This promotes to add vitamin D in the diet through dietary intake via food fortification as a potential protective measure against the infection and mortality (Vaughan et al., 2021). The encapsulation of vitamin D is the most suitable method of fortification because it protects from degradation before reaching to target site in body. The microencapsulation technique provide stability, homogeneity and higher bioavailability of vitamin D, whereas nanoencapsulation maintains stability during thermal processing and storage (Handu et al., 2021).

5.2. Functional food and its importance in Covid-19

Functional foods are foods which provide health benefits or reduce risk of evolution of existing or possible diseases beyond its nutritional value. These foods can help patients in improving the post COVID-19 complications alongside therapy. Afroz et al. (2021) listed potential functional food such as Indian pennywort, ginger, turmeric, black cumin, tomato, fenugreek, fish oil, garlic, momordica (bitter gourd), peppermint and pumpkin having potential to improve health against disease like cardiovascular, respiratory and nephrological problems

which are the complications of post COVID-19 infections. The extract of Indian pennywort can be helpful for diabetic patients having post COVID-19 complications. The ginger-rich diet has aided patients having allergic asthma symptoms and acute respiratory distress syndrome (common problems of patients with COVID-19). Similar responses are shown by turmeric due to its targeted action on proinflammatory NF- κ B pathway and can improve post COVID-19 respiratory symptoms and complications. Curcumin in turmeric was earlier effective against influenza A virus, herpes simplex virus and inhibited SARS-CoV replications.

The flaxseeds as a functional food have also shown potential to improve immunity against viral infections by managing the cytokine storm (very common during COVID-19 infection) and decrease IL-6 and IL-1 β level in plasma. Moreover, the omega-3 fatty acids present in flaxseeds with antioxidants can effectively reduce inflammation and the cytokine storm and improved oxygenation (Ghosh & Dutta, 2021).

5.3. Encapsulated food and its importance in Covid-19

The bioactive components like antioxidants, minerals, vitamins, polyphenols, omega (ω)-3 fatty acids, probiotics, etc. has already been discussed about its potential to boost immunity against COVID-19. However, the active compounds are highly sensitive to low pH of the belly and resulted in poor bioavailability in our gastrointestinal (GI) tract. Thus, the encapsulation of active compounds can be a great technique to impart targeted release and may become useful against viral disease like COVID-19. Some examples like milk and lassi having soya lecithin encapsulated vitamin-D₃ can be used as a proper human supplement against COVID-19 (Tripathy et al., 2021). Some results of clinical trials done on probiotic intervention on COVID-19 patients has been shown in Table 3. The work under encapsulation of bioactive compounds related to COVID-19 are at a nascent stage which require substantial research to showcase the positive effects on the immune system.

5.4. Plant based food and its importance in Covid-19

The COVID-19 pandemic has reminded about the severe consequences of zoonotic viral epidemics which can be associated with live-stock farming. The plant-based product, insect sources of proteins, and 'cultivated meat' are the new gap filling deliverables in the future global food supply (Rzymiski et al., 2021). A study on more than half a million participants from the US and UK was done where 31815 COVID-19 cases were documented. Those who consumed a healthy plant based diet (PBD) had a 10% reduction in risk of COVID-19 and a 40% reduction in severity of COVID-19 (Kassam & Freeman, 2021). Further, a study on the 2884 front-line healthcare workers from six countries (France, Germany, Italy, Spain, UK, USA), was done where 568 suffered from COVID-19 and remaining were controls. Those who reported consuming PBD and PBD or pescatarian diets having high vegetables, legumes and nuts quantity and low poultry, red and processed meats quantity showed 73% and 59% lower odds of moderate-to-severe COVID-19, respectively compared to those who did not follow these diets (Kim et al., 2021). It does not mean to have any combination of PBD can reduce chances of being severely affected from COVID-19. Same author has revealed greater odds of moderate-to-severe COVID-19 in participants following the low carbohydrate, high protein diets. So, proper formulation is needed to have a healthy PBD to combat against such viral infection during COVID-19 pandemic.

6. Conclusion

The review has begun with a discussion on various immune modulators regulating either innate or adaptive immunity and both. These components are macrophages, phagocytes, NK cells, DCs, neutrophils, B-cells, and T-cells. All have their specific role in maintain and boosting

the immune system of the body. Further, these components in some extent get affected from present nutrition level of the body besides other external factors like adequate sleep, exercise, low stress levels, etc. The major nutrients whose influence on the immune system reviewed was vitamin-C, A, E and D, iron, zinc, folic acid, probiotics, and prebiotics. These nutrients if consumed from natural source can provide a long-lasting immune system. Cabbage, cauliflower, mushroom, garlic, ginger, turmeric, holy basil, seeds, Brazil nuts, black and brown rice, millets, chlorella, and spirulina have been observed to contain high nutritional properties. These can be formulated to make immune boosting diet for fighting against COVID-19. The foods fortified with vitamin D, functional foods, encapsulated foods with bioactive compounds and plant-based foods have shown immense potential to be consumed for fighting against COVID-19. Some clinical trials and retrospective cohort study shown improvement in oxygenation index and reduction in severity of COVID-19 patients with relation to plant-based diet, vitamin D and C doses, probiotic, and zinc salts application.

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Declaration of competing interest

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To all the community people undergoing this pandemic.

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