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Review paper

The relevance of nutrition as a step forward to combat COVID-19

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Abstract

A new type of single-stranded RNA virus that belongs to the coronavirus's family named SARS-CoV-2 has recently appeared, with fast-growing human to human transmissions. This virus has posed an important global health threat. Many nutrients can support the immune system and help in preventing or in ameliorating the response to viral infections. In the case of COVID-19, the unique pathophysiology of the coronavirus needs to be understood, in order to determine whether any potential nutrition intervention is indicated. A literature survey that comprised of ongoing research was conducted to evaluate the benefits of the bioactives present in food, such as: plant-derived extracts, vitamins, minerals, probiotics, and prebiotics, against the mechanisms of the COVID-19 infection. Although no food is yet confirmed to help in the prevention or in the treatment of the coronavirus transmission alone, exploring the possible implications of nutrition-infection interrelationships is of utmost importance. Well-designed and controlled clinical studies are emerging to explain whether the higher consumption of fruits, vegetables, protein-rich foods, unsaturated fatty acids, and other natural functional foods may aid in combating the COVID-19 infection. Meanwhile, a healthy and balanced diet is traditionally practised in viral infections that support the healthy gut microbiota profile. The human immune system function should be a vital prophylactic measure, along with adequate physical activities and sleeping habits. The consumption of immune-supportive nutrients is also encouraged in the elderly, comorbid, and in the immune-compromised as well as in malnourished individuals, in order to minimise the complications and the negative outcomes that are associated with the COVID-19 disease.

Keywords: COVID-19 nutrition, macronutrients, micronutrients, bioactive compounds, malnutrition

Introduction

A novel coronavirus (SARS-CoV-2) has been identified as originating in Wuhan, China. This virus has rapidly and widely spread in other countries, causing an outbreak of COVID-19 (Ralph et al., 2020), with thousands of infections and deaths reported daily. The World Health Organization (WHO) has declared COVID-19 as a global pandemic. It is an easily transmissible challenging disease for people and healthcare systems worldwide. This coronavirus primarily targets the human respiratory system, and it hassled to multi-organ failures and fatalities (Huang et al., 2020). SARS-CoV-2 can attack the mucosal epithelium and can cause gastrointestinal symptoms, which further damage the nutritional status, especially in the elderly. Those patients with the worst outcomes and the higher mortality rates are reported to include immune-compromised subjects, mainly the elderly, or polymorbid individuals, as well as the malnourished (Barazzoni et al., 2020). Regarding this matter, extensive public health measures beyond direct clinical activities are emerging, in order to optimise the diet regimen and to rationalise the utilisation of nutrients.

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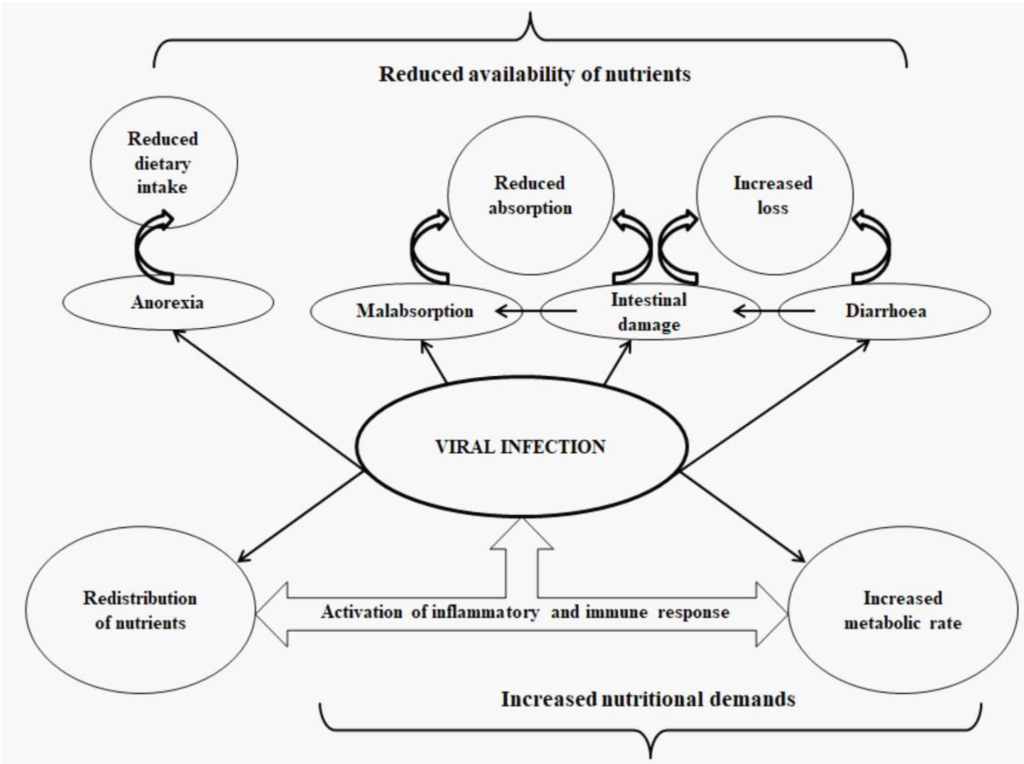

Fig. 1. Nutritional management-associated factors that have to be considered in patients with viral infections, including COVID-19.

Inadequate nutrition can lead to long-lasting negative effects that deteriorate both physical and mental health (Hislop et al., 2006). Nutrition, as a key determinant of health, has a profound effect on the immune system function and the susceptibility of the disease. This must be considered in a framework for action, in order to maintain optimal nutrition to combat viral infections, including COVID-19.

Nutrition considerations for COVID-19

Nutrition is a key pre-requisite, in order to maintain good health. In the absence of large-scale and long-term data for the impact of specific nutrients on the outcomes for those individuals that are infected with COVID-19, the role of nutrition is only supportive. However, this is considered vital because the body needs extra energy and nutrients during infection, especially when accompanied by fever, due to the higher metabolic rate and the activation of the inflammatory and immune response. Additionally, the vast majority of viral infections are associated with the reduced availability of nutrients, further compromising the nutritional status of the patients (Fig. 1). Relevant data for the nutritional management of COVID-19 patients is yet to come, as many food compounds and nutrients are undergoing clinical trials, on how they affect the immune responses or inhibit the viral load in general. Some individuals are trying to protect themselves, by purchasing and consuming healthy food products. However, the spread of misinformation related to nutrition and dietary intake, mainly through social media, may provoke confusion regarding the proper choice (Naja and Hamadeh, 2020). Herein, a very important issue is the safety and the sustainability of food sources that need to be maintained. Although there is no indication that the coronavirus can be transmitted through the contact with food, recommendations concerning food safety include a high level of hygiene, keeping the food clean, and at safe temperatures, with thorough cooking, as well as with the use of safe water and raw materials.

Macronutrients

Since the WHO has declared COVID-19 as a pandemic, the undertaken measures to reduce the spread of the virus have negatively affected the daily routines of people. This has led to boredom, subsequently contributing to obesity, as a consequence of the higher consumption and/or low expenditure of calories. The stress that is associated with the continuous news regarding the virus, may force people to use food as a comfort, which can also lead to overconsumption. The most often used example of comfort foods is sugary products, which are known to stimulate the production of serotonin. Serotonin positively manages the stress and it improves the mood (Muscogiuri et al., 2020). Other palatable products that are rich in fat, salt, and calories contributing to weight gain are also proven to stimulate the production of serotonin. Obesity, due to the higher intake of carbohydrate-rich foods, could increase the risk of developing diabetes, heart conditions, and lung diseases, which are highly correlated to further complications of the COVID-19 disease (Wu et al., 2020a). On the contrary, insufficient calories in the diet are associated with a significant decline of the T-dependent-antigen-specific lymphocyte proliferation and the antibodies response (Saeed et al., 2016). Adequate hydration, which is mainly provided by drinking at least eight glasses of plain water a day for the majority of the adult population, instead of consuming sweetened beverages, also helps the immune function and reduces the overconsumption of calories.

Nutrition that comprises of adequate proteins is critical for the normal immune function. The direct relationship between protein-energy malnutrition and immunodeficiency are reported to reflect the susceptibility to infection by influenza and the Zika viruses (Osman, 2016). Protein-energy malnutrition, followed by changes in the cell-mediated immunity, the bactericidal function of the neutrophils, the complement system, the secretory immunoglobins A, and the antibodies response, may lead to a poor quality of life. In addition, protein depletion deteriorates the function of the physical barriers, with the dissipation of collagen, and the connective tissues in the skin (Saeed et al., 2016). Protein-rich foods are of utmost importance in the nutrition of patients who are infected by viruses, including SARS-CoV-2, in order to maintain an optimal protein status and to avoid the risks of losing body weight, further skeletal muscle mass, disability, and the additional morbidity due to the infection.

Individual amino acids are also important for the nourishment of the immune system. Dietary taurine, creatine, carnosine, anserine, and 4-hydroxyproline, which is highly abundant in beef, are beneficial nutrients that are able to promote defence against infections by bacteria, fungi, parasites, and viruses (including coronavirus), through enhancing the metabolism and the functions of the monocytes, the macrophages, and the other cells of the immune system (Wu, 2020). The consumption of foods that contain serotonin and melatonin, or precursors for their synthesis, such as amino acid tryptophan, have been suggested to enhance the mood and to better regulate the satiety and the energy intake. Serotonin, as well as serotonin-containing foods like oats, bananas, cherries, and almonds, has been reported to reduce the intake of carbohydrates and fats (Muscogiuri et al., 2020).

Some milk proteins and peptides have been shown to provide antioxidant and antiviral properties. Compounds, such as lactoferrin, lactadherin, and glycomacropeptide, have interfered with the growth of some viruses, by binding to the viral receptor sites *in vitro*. Therefore, they may help to alleviate symptom severity or the complications that are linked to viral infections (Pan et al., 2006). It has been hypothesised that the beneficial effects of lactoferrin are the result of direct antiviral activities that are exerted in the gastrointestinal tract and in the systemic immune-modulation (Wakabayashi et al., 2014). Other possible mechanisms for the action of lactoferrin involve a direct attachment to the viral particles, or by blocking their cellular receptors, thus inhibiting the entry of the virus into the host cells (Redwan et al., 2014).

Human immune cells contain polyunsaturated fatty acids (PUFAs). Their membranes are typically rich in arachidonic acid producing eicosanoids that are important in inflammation and regulation of B and T lymphocyte function, but also contain eicosapentanoic and docosahexanoic acids which increases the level of anti-inflammatory resolvins (Calder, 2008). Depending on what type of fat is mostly abundant in the diet (saturated fatty acids, unsaturated fatty acids, trans-fatty acids), contents of fatty acids in immune cell membranes can be altered. Hence, the diet may influence fatty acids composition of immune cells consequently leading to alterations in their function against pathogens through a variety of complex mechanisms such as phagocytosis, T cell signaling and antigen presentation capability. Supportive evidence that polyunsaturated fatty acids may serve as anti-inflammatory mediators on anti-viral $CD8^+$ T cell responses and dietary supplementation, may aid in alleviating the immunopathology that is associated with diverse viral infections. This was observed upon lymphocytic choriomeningitis virus infections in FAT-1 transgenic mice (Won Kang et al., 2019). PUFAs have been reported to exert antimicrobial properties through a direct action on the microbial cell membranes, the stimulation of the free radicals generation, increasing the formation of the cytotoxic lipid peroxides, as well as their bioactive metabolites, such as prostaglandins, lipoxins, resolvins, protectins, and maresins that enhance the phagocytic action of the leukocytes and macrophages (Das, 2018). Another potential mechanism of antimicrobial action is the cytokine-induced release of PUFAs from the cell membrane lipid pool. Antiviral activities resulting in the inhibition of viral replication have been suggested for prostaglandin E1 and prostaglandin A, which are derived from dihomo-γ-linolenic, arachidonic, and eicosapentaenoic acid. Das (2018) highlighted the possibility that the macrophages, T cells, and other immunocytes deliver PUFAs to the target tissue, in order to eliminate infections, thus helping in the healing of wounds, by suppressing inflammation. Moreover, PUFAs have been reported to enhance the growth of useful bacteria selectively, while at the same time, preventing the proliferation of harmful microbiota

(Costantini et al., 2017). These situations have implied that the dietary supplementation of unsaturated fatty acids could not cause any deleterious shifts in the composition of the intestinal microflora. Docosahexaenoic acid has been shown to have potential anti-inflammatory properties. In addition, the neuroprotective effects against the Zika virus infection in human SH-SY5Y cells, predominantly enhances the proliferative capacity of the infected cells, preventing mitochondrial dysfunction, and reducing the intracellular reactive oxygen species (Braz-De-Melo et al., 2019). Furthermore, low levels of fatty acids, such as docosahexaenoic acid in maternal milk, correlate directly with the low levels of immunity in malnourished children (Saeed et al., 2016). The increased consumption of α-linolenic and *cis*-linoleic acid, as well as eicosapentaenoic and docosahexaenoic acid found in fish, might reduce the risk of pneumonia (Das, 2018). Recently, it was also suggested that the oral or intravenous administration of bioactive fats, like arachidonic acid, might improve the resistance to SARS-CoV-2, as well as, the recovery from the COVID-19 disease (Das, 2020). When considering the above findings, it could be valuable that the nutrition of COVID-19 infected people is rich in unsaturated fatty acids. This has been shown to improve the immune system profile, instead of saturated and trans-fats, which contribute to obesity, as well as to a further risk for developing cardiovascular and metabolic disorders.

Micronutrients and other bioactives

1. Minerals

According to one recent review, multiple micronutrient supplementations may modulate the immune function and reduce the risk of infection. Vitamin D, vitamin C, and zinc are considered as micronutrients, which support the immune function in the best way (Gombart et al., 2020).

The SARS-CoV-2 virus enters into human cells via the angiotensin-converting enzyme 2 (ACE2) receptor proteins on the cell surfaces (Li et al., 2020a). The virus inactivates the ACE2 enzyme, which is found in multiple tissues, including in the mucosal lining of the upper respiratory system, the lung, the digestive system, the liver, the kidney, and the brain. This enzyme is dependent on potassium and sodium, in order to regulate the blood pressure, indicating that interventions using these micronutrients may have inhibitory effects on viral replication, as a consequence of their binding to the cell receptors. In one study that was conducted in China, which was not peer-reviewed, the continuous renal loss of potassium in COVID-19 patients that resulted from ACE2 degradation has been reported (Chen et al., 2020a). During their hospital stay, the patients were given potassium supplements that contained 3 grams of potassium, to which the patients responded well, especially as they began to recover. In addition, it was suggested that the potassium loss may give a good prognosis and it may be a reliable and sensitive biomarker, directly reflecting on the recovery process. Although potassium may help in the treatment of moderate to severe cases of COVID-19, it should not be included in a preventive nutritional strategy, in order to avoid potential interactions with certain drugs. Potassium supplementation appears to be only convenient in the critically ill when the virus degrades the ACE2 receptors, in order to replenish the deficit of this micronutrient. Foods that are considered as a source of potassium include spinach, broccoli, potatoes, sweet potatoes, mushrooms, peas, cucumbers, zucchini, eggplant, pumpkins, tomatoes, bananas, oranges, cantaloupe, honeydew, apricots, and grapefruit.

Zinc is known to play an important role in the immune system (Saeed et al., 2016). It can function as an anti-inflammatory agent, due to a reduction in the C-reactive protein levels and the inflammatory cytokines in the elderly, as well as an anti-oxidative agent, due to decreased lipid peroxidation (Bao et al., 2010). Zinc-deficient subjects, especially within the older population, may experience increased susceptibility to infections. This may be a result of reduced non-specific immunity, including the neutrophils and the natural killer cell function, as well as with complement activities, or by reduced numbers of the B and T lymphocytes, and even by suppressed antibody production (Katona and Katona-Apte, 2008). Zinc supplementation has been found to be associated with a significant decrease in the incidence of infections, the tumour necrosis factor-α (TNF-α) levels, and the oxidative stress markers, as plasma zinc concentrations have been found significantly higher (Prasad et al., 2007). A recent study has demonstrated an *in vitro* inhibition of the coronavirus RNA-dependent RNA polymerase activity by zinc ions (Velthuis et al., 2010). The most common food products that are rich in zinc are oysters, crab, and lobster, and to a lesser extent, chicken, red meat (especially beef), cheese, kidney beans, nuts, pumpkin, sesame seeds, lentils, cashews, and almonds.

Selenium is an essential co-factor of the antioxidant enzyme, glutathione peroxidase, which has a protective effect against oxidative stress. A deficiency in selenium can lead to immune dysfunction and increased virulence of pathogens (Beck, 2007). Important sources of selenium are Brazil nuts, tuna, shellfish, eggs, sunflower seeds, and shitake mushrooms.

2. Vitamins

Along with minerals, the consumption of foods that are rich in vitamins and other nutrients has also been reported to help in protection against viruses (Gibson et al., 2012; Naik et al., 2010). Vitamin A comprises of a group of fat-soluble compounds, including retinol, retinoic acid, and β-carotene, and these are known to support the health of the mucosal epithelium. Vitamin A deficiency is related to an increased receptiveness to various pathogens in the eye, and in the respiratory and gastrointestinal tract

(Saeed et al., 2016). Correspondingly, vitamin A may be a supportive nutrient, in order to protect the barrier function, as a consequence of COVID-19 damage to the mucosal tissues. Experiments in rats have suggested that *all-trans* retinoic acid has reduced the protein expression of ACE2 (Zhou et al., 2013), which is a cellular receptor required for the entry of SARS-CoV-2 (Li et al., 2020a). In addition, a preliminary study found that a derivative of vitamin A, isotretinoin, mediated the down-regulation of ACE2 (Sinha et al., 2020). Food sources of vitamin A include cod liver oil, beef liver, carrots, spinach, broccoli, black-eyed peas, and sweet potatoes.

Although there is no evidence for vitamin C to protect against coronavirus, it supports the immune function and the repair of tissue. Supplementation of vitamin C appears to be capable of preventing and treating respiratory and systemic infections (Carr and Maggini, 2017). Conversely, a vitamin C deficiency may cause a higher susceptibility to infections (Saeed et al., 2016), which in turn, reduces the vitamin C levels, due to the increased inflammatory responses and metabolic requirements. Foods rich in vitamin C include guava, kiwi, strawberries, oranges, red peppers, papaya, broccoli, tomato, kale, grapefruit, mangoes, spinach, pineapple, and lemons.

It has been hypothesised that a vitamin D supplementation might be a useful measure for reducing the risk of influenza, COVID-19 infections, and deaths (Grant et al., 2020). The proposed mechanisms comprise of an induction of cathelicidins and defensins that can lower the viral replication rates, with a reduction in the pro-inflammatory cytokines that are associated with an inflammation of the lining of the lungs, leading to pneumonia, as well as with increased levels of the anti-inflammatory cytokines. The potential benefit of a vitamin D supplementation has been associated with the occurrence of COVID-19 in the winter season when the concentrations of vitamin D are the lowest. This relationship of a vitamin D deficiency and the respiratory distress syndrome produces fatal outcomes that are often reported in older adults and those with co-morbidities. These are associated with lower vitamin D levels and with fewer cases of COVID-19 in countries of the Southern Hemisphere in the end of the summer. Grant et al. (2020) suggested relatively high plasma concentrations of vitamin D_3 to be reached, above 40-60 ng/mL, emphasising the need of controlled large-scale trials to confirm these assumptions. In addition, chronic diseases, such as cancer, hypertension, cardiovascular diseases, and diabetes, which significantly increase the risk of death from respiratory tract infections, have been reported to be more often in individuals with a vitamin D deficiency (Muscogiuri et al., 2017). Vitamin D is not found in sufficient amounts in most foods, except in fish, liver, egg yolk, and milk products with added vitamin D; thus, the exposure to sunlight is important and additional supplementation may be appropriate at low levels.

Vitamin E increased both the cell-dividing and interleukin-producing capacities of naive T cells, leading to a significantly improved resistance to the influenza virus in mice, and with a reduced risk of acquiring upper respiratory infections in nursing home residents (Meydani et al., 2005). Its deficiency has been shown to increase viral pathogenicity and to alter the immune responses, resulting in specific viral mutations (Beck, 2007). Hence, vitamin E might be considered as a driving force to reduce the virulence of COVID-19. The main dietary sources of vitamin E are vegetable oils, sunflowers, soybean, wheat germ, corn, olives, seeds, nuts, avocados, spinach, broccoli, olive oil, trout, and shrimps.

3. Plant bioactives

For the subgroups of patients with severe COVID-19, a cytokine storm syndrome has been reported. A cytokine profile of severe COVID-19 disease was associated with increases in interleukin IL-2, IL-7, the granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and TNF-α (Huang et al., 2020). The suppression of cytokine release by curcumin correlated well with the clinical improvement in experimental disease models, where a cytokine storm played a significant role in mortality (Sordillo and Helson, 2015). In this study, curcumin found in turmeric was shown to block the cytokine release, but most importantly, it blocked the key pro-inflammatory cytokines, IL-1, IL-6, and TNF-α. The study suggested this as a potential therapy for patients with Ebola, together with other severe viral infections. Polyphenol curcumin showed antiviral activities against a wide spectrum of viruses, including the influenza virus, hepatitis C, HIV, Zika virus, herpes simplex virus 2, and the human papillomavirus (Haslberger et al., 2020).

The bioactives of bergamot fruit extract, bergapten and citropten, were found to be strong inhibitors of the IL-8 expression and have been proposed for their anti-inflammatory properties to reduce lung inflammation in patients with cystic fibrosis, but this needs to be further studied (Borgatti et al., 2011). Flavonoids, such as resveratrol, quercetin, apigenin, and luteolin, reduce the cytokine expression, and their secretion may have a therapeutic potential in the treatment of inflammation-related diseases, such as the cytokine modulators (Leyva-López et al., 2016). The flavonoids from litchi seeds, quercetin, and kaempferol have been reported to inhibit the activity of the enzyme SARS-CoV 3 chymotrypsin-like protease, which is vital for the replication of SARS-CoV-2, indicating a possible benefit against SARS-CoV-2 (Yang et al., 2020). Quercetin is known to possess strong and long-lasting anti-inflammatory capacities since in several *in vitro* studies, with different cell lines inhibited the production of TNF-α and IL-8 (Haslberger et al., 2020). In mice that were injected with the influenza virus, quercetin restored the concentrations of the antioxidative enzymes, including catalase, the reduced glutathione, and superoxide dismutase, and it was suggested as protecting the lung tissue (Kumar et al., 2005). Quercetin is found in leafy green vegetables, broccoli, apples, grapes, peppers, luteolin-7-glucoside, and apigenin-7-glucoside in olives and star fruit, while kaempferol is found in dill, spinach, and cabbage. However, prospective clinical trials on how quercetin and other plant-derived bioactive compounds affect the viral load in humans are limited.

Based on computer virtual screening, without conducting *in vivo* and *in vitro* anti-viral experiments, many flavonoids from different sources (α-glucosyl hesperidin, hesperidin, rutin) and xanthones, such as 3,5-dimethoxy-1-[(6-*O*-β-D-xylopyranosyl-β-D-glucopyranosyl)oxy]-9*H*-xanthen-9-one, have been reported to be meaningful in the treatment of the COVID-19 infection (Wu et al., 2020b). Sources of hesperidin include oranges, tangerines, grapefruit, and lemons, but it can also be found as a food supplement. Haslberger et al. (2020) overviewed the potential of several bioactives (quercetin, curcumin, epigallocatechin gallate, phloretin, berberine, sulforaphane, thymoquinone, and the sage polyphenols), in order to influence the mechanisms of different viral infections, such as influenza, HIV, Zika, avian influenza virus, SARS-CoV, and so forth. In general, the past few decades studying of antiviral action mechanisms of plant-based natural compounds have revealed their significant influence on the viral life cycle, such as viral entry, replication, assembly, and release, as well as virus-host-specific interactions. In case of coronavirus, the initial exploring has indicated that the antiviral effects of natural bioactives could be possibly achieved through inhibition of the virus interaction at the target cell membrane (receptor-binding domain of S-protein) or inhibition of virus replication (Xian et al., 2020).

Infections are inevitably tied to nutrition. However, not all biologically active ingredients that are present in food have been elaborated regarding their interactions with the infection pathways. In time, the properties of the discussed micronutrients (minerals, vitamins, antioxidants, and the other plant bioactives), establish hope of being of service in the resistance of viral infections, including COVID-19. However, well-defined clinical trials are needed, in order to address the specific micronutrients and their dosages, to optimise preventive effects against infection.

Malnutrition and COVID-19

The nutritional status of individuals has been considered for a long time, as an indicator of resilience against destabilisation as well as in determining the resistance to infections in general. In view of this concept, the host diet might have some direct effect on the pathogen itself. Malnutrition is a systemic alteration, due to an imbalance between the nutrient intake and the energy requirements. This interferes with the various physical barriers or the immune responses, causing a significant decrease in the defence mechanisms (Maldonado Galdeano et al., 2019). Malnutrition can make a person more susceptible to infection, and infection can also contribute to malnutrition, which causes a vicious cycle. An inadequate dietary intake leads to further weight loss, it lowers immunity, and promotes mucosal damage and an invasion by the pathogens (Katona and Katona-Apte, 2008). A relatively high prevalence of malnutrition in elderly patients with COVID-19 in Wuhan, China, was reported in a recent study. Both indicators low calf circumference and hypoalbuminemia, which ascertained malnutrition, have been witnessed in most of the patients examined (Li et al., 2020b). Three reasons, which are likely to be the most responsible for malnutrition in elderly patients with COVID-19 have been discussed. First reason leading to malnutrition is the expenditure of albumin and even the muscle proteins. Inflammatory response of the infections in general as well as in coronavirus infection, spends these proteins for the increased synthesis of the acute-phase proteins, including the C-reactive protein, ferritin, TNF-α, and the interleukin family factors, processes which may lower the serum levels of albumins and total proteins. Those patients who have suffered the loss of muscle should be given nutrient-rich, or fortified foods, or specific dietary supplements, in order to regain the weight and the muscle mass that have been lost. The presence of co-morbidities is the second reason that has led to higher rates of malnutrition in elderly patients with COVID-19. For example, in patients with diabetes mellitus co-morbidity disorders in the metabolism of carbohydrates, fats, and proteins were apparently manifested. Gastrointestinal symptoms, like abdominal pain, diarrhoea, vomiting, and poor appetite are commonly associated with SARS-CoV-2, due to the highly expressed ACE2 in the gastrointestinal tract (GIT), and this has been reported to be the third cause that exacerbates malnutrition in elderly patients. There was a high prevalence of malnutrition in elderly patients with COVID-19 in China, but there have also been negative outcomes reported in older, co-morbid, and hypoalbuminemic patients in other countries. Lymphopenia, as a marker of malnutrition, has been shown to be associated with negative outcomes in patients with COVID-19, progressing from a cough to dyspnea, respiratory failure as well as the admission to intensive care units for mechanical ventilation (Arentz et al., 2020; Zhou et al., 2020). The nutritional status can influence the genetic make-up of the pathogens and thereby, alter their virulence, alerting nutritional researchers to explore the possible implications of the nutrition-COVID-19 infection interrelationships. It would be useful to conduct a systematic survey of the various nutritional deficiencies of energy, protein, and specific micronutrients, in order to determine which could influence the evolution of the virus (Naja and Hamadeh, 2020). The survey could start with micronutrients, such as iron, zinc, and vitamins A, E, B_6, and B_{12}, that have been shown to be essential for the maintenance of the immune function as well as micronutrients with antioxidant properties, such as vitamin E, vitamin C, the carotenoids, selenium, and zinc (Gleeson et al., 2004; Muscogiuri et al., 2020).

An early evaluation of the nutritional risks that may be very high in the critically ill COVID-19 patients, with gastrointestinal functions and aspiration risks, together with timely enteral nutritional support, are important features for a patient's prognosis. Those patients who are older adults, with co- or polymorbidity, should be mandatory checked for malnutrition, through the screening and nutritional assessment. In addition, obesity may mask malnutrition. Therefore, obese patients should be screened according to their ability to preserve healthy body weight and a skeletal muscle mass (Barazzoni et al., 2020).

Although there are no strict recommendations on how to adapt available nutrition guidelines during the disease, nutritional support in clinical practice should be strengthened, especially for the elderly patients with diabetes mellitus, low calf circumferences, or low albumin (Li et al., 2020b). While waiting for more specific directions on the nutritional management of patients with COVID-19 in the intensive care units, the available guidelines that are established by the European Society for Clinical Nutrition and Metabolism (ESPEN), are likely to cover the patient's needs at the present (Barazzoni et al., 2020). According to this issue, nutritional intervention and therapy needs should be considered as an integral part of the clinical approach for critically ill patients with COVID-19. For the most of the patients in intensive care units, the proteins and calories that are required to meet the nutritional demands, hydration, and medications, will be supplied through feeding tubes. For patients with a normal intestinal function, a relatively high-energy whole-protein formula will be used. Predigested peptide preparations that are easily absorbed and utilised are preferred in patients with intestinal damage. In the case of hyperglycemic patients, a glycemic controlling formula may be given. However, introducing a patient to enteral nutrition is usually delayed in life-threatening hypoxaemia (Singer et al., 2019). The effects of specific enteral formula in pneumonia-related COVID-19 cases, as well as the benefits of drug therapy, such as corticosteroids, or anti-interleukins, are still questioned. As stated in the ESPEN guidelines for the nutritional management of individuals with the SARS-CoV-2 infection, if non-intubated patients in intensive care units could not meet the energy requirements with an oral diet, or oral nutritional supplements by the enteral route, then peripheral parenteral nutrition should be prescribed (Barazzoni et al., 2020).

Interaction between gut microbiota and COVID-19

Gut microbiota constantly interacts with the host immune system, by regulating various physiological functions, including dietary digestion and partially immune protection, hence, influencing the homeostasis. A fundamental role of microbiota on the induction, training, and the function of the host immune system helps forward the synbiotic relationship of the host, with highly diverse microbiota being maintained (Belkaid and Hand, 2014). A diverse microbiome is one that contains many different species, each of them having a special function in immunity and health. However, that diversity declines with age. The cross-interaction between gut microbiota and the lungs is referred to as the gut-lung axis. This has been shown to influence the health of the respiratory tract, manifesting associated dysbiosis, or changes in the composition of the gut microbiota in respiratory tract infections (Chan et al., 2020; Groves et al., 2020; Keely et al., 2012). A recent review summarised the data about the role of gut microbiota in lung diseases, taking into account that respiratory virus infections cause gut microbiota perturbations (Dhar and Mohanty, 2020). This issue pointed to the fact that the reduced diversity of gut microbiota is connected to more fatal outcomes of COVID-19 in elderly subjects, thus raising the possibility of improving the microbiota profile, by personalised nutrition, or by supplementation to be used in prevention and curing. Since a healthy gut microbiome is enrolled in preventing immune over-reactions that can damage the lungs, it has a crucial role in mounting a response to the plethora of pathogenic bacteria and viruses, potentially, COVID-19. Additionally, COVID-19 patients may suffer gastrointestinal (GI) symptoms, such as abdominal pain and diarrhoea (Huang et al., 2020), due to either a direct viral infection of the intestinal mucosa or an anti-infective therapy. In this sense, an important finding was the presence of SARS-CoV-2 in the faeces of some patients. This was probably due to the expression of the ACE2 receptors on the enterocytes of the small intestine, besides the alveolar epithelial cells (Chen et al., 2020b; Wu et al., 2020c). The micro-ecological balance in these patients is disturbed and they are likely to have significant reductions in the numbers of commensal microbiota. An intestinal microbial imbalance often leads to bacterial translocation and to a secondary infection. Nutritional supports when using beneficial microbes, such as probiotics, may restore the intestinal balance (Baud et al., 2020). In addition, gut bacteria produce many other beneficial compounds, such as vitamin B12. Furthermore, they also activate vitamin A from food, which helps in regulating the immune function.

Although all the interactions between the gut microbiome and the immune system are not fully understood, there is data confirming the link between the

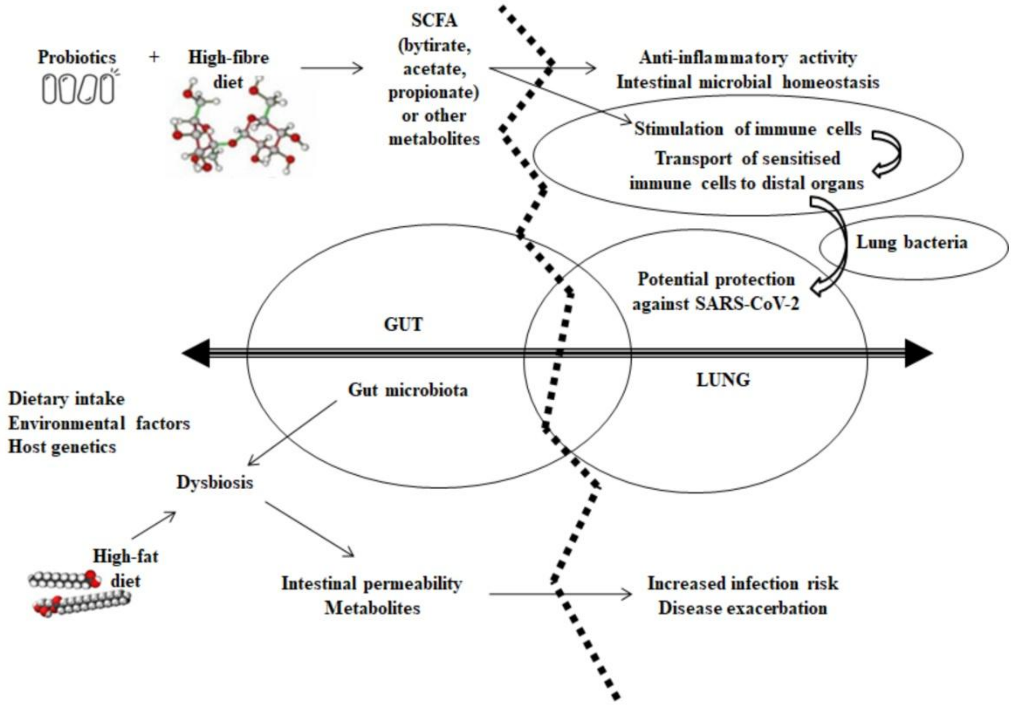

Fig. 2. Gut microbiota-lung interrelationships (gut-lung axis) encourage a new model of nutritional approach to improve the response against the SARS-CoV-2 infection considering nutrients that are proven in shaping the intestinal microbiota.

microbiome and inflammation and/or infection. Certain dietary components have been shown to be significant determinants of gut microbial composition, being able to modify the characteristics of the immune responses (Wypych et al., 2017). Microbiome diversity, as a way to strengthen the immune system, may be increased by using a wide range of high-fibre foods or prebiotic ingredients. Prebiotics, like inulin, polydextrose, oligosaccharides, resistant starch, and so forth, undergo fermentation by the intestinal microbiota, thus providing energy for the host microbiota, and strengthening the gastrointestinal associated lymphoid tissue. In addition, fermented milk products, like yoghurt and kefir, are rich sources of natural probiotics, which also support the diversity of the human microbiome and hence general health. Since the types of consumed food significantly affected the range and the types of microbes in the gut, it is essential to choose appropriate foods to support the immune system, rather than to use food supplements, as these supplements can boost the immune system. Herein, an overactive immune response is sometimes likely to have a similar risk as an under-effective one.

Potential role of probiotics and prebiotics against COVID-19

Many researchers are investigating the use of probiotics and prebiotics in the prevention and treatment of diseases. They are looking into the possibility of using probiotics and prebiotics in the prevention or in the treatment of COVID-19. When considering various mechanisms, especially the anti-inflammatory and immunomodulatory effects of probiotics, prebiotics, and fermented foods, these compounds may directly, or indirectly, contribute to the progress against COVID-19. The mechanisms of action of the probiotics and prebiotics are possible and relevant to respiratory tract infections, via the recovery of dysbiosis in the intestinal microbiota (Fig. 2). Additionally, the knowledge that the immune system has evolved in response to the continual exposure of different microbes, it is possible that further contact with the dietary microbes, such as probiotics, will have a positive impact on the immune function. By the use of these dietary compounds, which are capable of modulating the functions of the systemic and mucosal immune cells, intestinal epithelial barrier can be enhanced. Probiotics are able to compete with the pathogens for nutrients, producing antimicrobial compounds, while at the same time, modifying the GI microbiota. Many health benefits to the host are attributed to probiotic administration including several immune response-related diseases, such as allergy, eczema, and viral infections. In case of available vaccines against specific pathogens, probiotics have been reported to provide more effective immune response in the hosts (Yan and Polk, 2011).

There is research data supporting the evidence that certain probiotic strains can reduce the incidence and the severity of viral respiratory tract infections. In mice, protective effects of an intranasal inoculation of *Lactobacillus reuteri* F275 against the lethal pneumovirus infection were observed (Garcia-Crespo et al., 2013). The preventive effects of an intranasal treatment with *Lactobacillus rhamnosus* GG in a neonatal mouse model with an influenza infection have indicated the importance of the toll-like receptor 4 (TLR4) signalling pathway (Kumova et al., 2019). For the probiotic strain, *Enterococcus faecium*, anti-viral effects against the transmissible gastroenteritis coronavirus (TGEV) have been demonstrated (Chai et al., 2013). Some lactobacilli, such as *Lactobacillus helveticus* and *Lactobacillus casei*, during bovine milk fermentation, release bioactive peptides with a high affinity to inhibit the angiotensin-converting enzyme (Li et al., 2019), which the SARS-CoV-2 virus uses as a cell receptor to invade human cells (Li et al., 2020a). Certain studies in humans have shown that specific probiotics can reduce the incidence and the duration of common upper respiratory tract infections, especially in children (Luoto et al., 2014; Wang et al., 2016), as well as in adults (King et al., 2014), and nursing home residents (Wang et al., 2018). The lack of detailed and confirmed knowledge about the optimal strain to be used, the dosing regimens, the time, and the duration of intervention, imposes the need for more trials. Furthermore, the relevance of these findings for COVID-19, as a lower respiratory tract infection and inflammatory disease, is unknown. The outcomes of probiotic treatments are more often involved with upper respiratory tract infections. Nevertheless, meta-analyses of randomised clinical trials have shown that prophylaxis with probiotics may generally reduce respiratory tract infections while decreasing the incidence of sepsis and ventilator-associated pneumonia (Weng et al., 2017).

Probiotics, such as *Lactobacillus rhamnosus* GG, can improve the intestines, the lung barrier, and the homeostasis while increasing the regulatory T cells, improving the anti-viral defence, and decreasing the pro-inflammatory cytokines in respiratory and systemic infections (Johnstone et al., 2015). *Lactobacillus plantarum* DR7 was found to reduce the plasma levels of the pro-inflammatory cytokines, such as interferon gamma (IFN-γ) and TNF-α, in middle-aged individuals, while increasing of the anti-inflammatory cytokines, IL-4 and IL-10, in young adults (Chong et al., 2019). Since a severe lower respiratory tract illness is associated with the COVID-19 infection, patients may challenge an excessive inflammatory response similar to the cytokine release syndrome, which has been related to increase complications and mortality (Mehta et al., 2020). Thus, the immunomodulatory effects of the probiotics may directly reduce the COVID-19 infection risk and the severity of the disease, making their clinical benefits relevant to the individuals who have developed or are at risk of developing COVID-19. Of particular relevance is the possible use of probiotics to prevent major COVID-19 complications, such as the acute respiratory distress syndrome, whilst balancing the levels of the pro-inflammatory and immunoregulatory cytokines, and at the same time, minimising the immune response-derived damage to the lungs (Baud et al., 2020). The benefits may be mediated by the beneficial effects of probiotics on the immune system, or through the modulation of the inflammatory responses, similar to those causing severe illnesses in COVID-19 patients. Antiviral activity, which has not been shown against SARS-Co-V2, has been documented against common respiratory viruses, including influenza, rhinovirus, and the respiratory syncytial virus. Baud et al. (2020) reported examples of probiotic products, which effects were documented in human studies, and may have relevance in reducing the burden of the coronavirus pandemic.

Improving the gut barrier integrity, as well as affecting the gut-lung axis, may also be part of the probiotic’s mechanism of action. In this context, it is very important that certain lactobacilli are more prevalent in the upper respiratory tract of healthy people when compared to those with chronic rhinosinusitis (De Boeck et al., 2020). This research was comprised of other viruses that showed that certain lactobacilli could even block the attachment of viral particles to human cells, thus making possible the local supplementation with lactobacilli, in order to contribute towards an enhanced defence against the inhaled virus. The authors underlined the need for conducting an exploratory study, with clinicians and virologists, on whether specific strains of lactobacilli in the nasopharynx and in the oropharynx could potentially reduce the viral activities via a multifactorial mode of action, including barrier-enhancing and anti-inflammatory effects, thus reducing the risk of secondary bacterial infections in COVID-19. However, the possible relevance of the immunomodulatory effects of locally or orally administrated probiotics that involve rapid and transient neutrophil recruitment, together with the pro-inflammatory mediators with the exclusion of the Th1 cytokines, or other immunomodulatory effects, to the SARS-CoV-2 infections in humans, is a crucial question yet to be answered.

When compared to probiotics, fewer data is available about the usage of prebiotics in preventing or treating respiratory issues. However, prebiotic oligosaccharides in infant formulae have been shown to reduce upper respiratory infections (Arslanoglu et al., 2008; Shahramian et al., 2018). Certain prebiotics, such as non-digestible carbohydrates in whole grains, were reported to reduce pro-inflammatory cytokine IL-6 and insulin resistance **(**Keim and Martin, 2014)**.** Prebiotics, such as wheat bran fructooligosaccharides and galactooligosaccharides, have been found to increase butyrate production, thereby, reducing the inflammation in patients with asthma and cystic fibrosis (Anand and

Mande, 2018). The beneficial effects of prebiotics seem to be predominantly mediated by the enhanced production of gut microbiota that is secreted as metabolites, such as the short-chain fatty acids (SCFAs), butyrate, acetate and propionate (Rooks and Garrett, 2016).

Although, no probiotics or prebiotics have been shown yet to prevent or treat COVID-19, or to inhibit the growth of SARS-CoV-2, the probiotic strains that have been documented for anti-viral effects and/or possess the ability to regulate immune responses in the respiratory system should be considered for clinical trials, as an integral part of the miscellanea to reduce the burden and the severity of the novel disease.

Conclusion

Poor nutrition, due to an insufficient intake of essential nutrients, excessive calories, or insufficient diet quality, can compromise the normal immune function and increase the general susceptibility to infections. The interdisciplinary approach of drawing upon the combined expertise from nutritionists and virologists should make important contributions to our understanding of the mechanisms of viral pathogenesis, in order to provide practical information on how to maximise the host resistance to the COVID-19 infection. One way to optimise health and hence help against COVID-19 is to practice an appropriate diet involving protein-rich foods, such as milk products, legumes, and fish, together with whole grains rich in fibres, fresh fruits, and vegetables. A healthy and balanced diet should be accompanied by adequate physical activities, thus promoting an optimal weight and good sleeping habits. The utilisation of plant-derived bioactives, herbs, and other functional compounds, such as probiotics and prebiotics, with their potential benefits, in supporting the human immune system against COVID-19, without substantial evidence, it is tentatively suggested. Meanwhile, healthcare providers and consumers are preferred to be cautious with such natural products until their benefits in treating viral infections extrapolated to COVID-19 are validated in clinical studies.

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Резиме

Значење на исхраната во справување со КОВИД-19

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Неодамна идентификуваната лоза SARS-CoV-2 што припаѓа на фамилијата коронавируси е едноставен вирус чиј геном е изграден само од рибонуклеинска киселина. Овој вирус се карактеризира со брза трансмисија меѓу луѓето и претставува важен глобален ризик за здравјето. Во превенција или подобрување на состојбата на пациентите при вирусни иинфекции, се користат голем број хранливи материи како поддршка на имуниот систем. Меѓутоа, уникатната патофизиологија на вирусот SARS-CoV-2, која е уште предмет на истражување, го наметнува прашањето дали кај овие пациенти треба да се направи нутритивна интервенција. Овој литературен преглед опфаќа податоци од тековни истражувања насочени кон евалуирање на придобивките од биоактивните состојки на храната кај пациенти инфицирани со SARS-CoV-2, како што се: растителни екстракти, витамини, минерали, пробиотици и пребиотици. Истражувањето на потенцијалното влијание на меѓусебната поврзаност на исхраната и COVID-19 инфекцијата има многу големо значење, и покрај тоа што не е потврдено дека определена храна може да помогне во превенција или во третман на ова заболување. За да се утврди дали зголемениот внес на овошје, зеленчук, храна богата со протеини, незаситени масни киселини, но и на други видови природна функционална храна може да помогнат за успешно справување со COVID-19 инфекцијата, неопходни се добро дефинирани и контролирани клинички испитувања. Во меѓувреме, треба да се советува традиционално применувата исхрана при вирусни инфекции, што подразбира здрав и избалансиран начин на исхрана и поддршка на нормалната цревна микрофлора. Суштински важна превентивна мерка претставува нормалната функција на имуниот систем, што треба да се потпомогне со соодветна физичка активност и квалитетен сон. Со цел негативните последици поврзани со COVID-19 инфекцијата да се сведат на минимално ниво, особено кај повозрасните лица, кај лицата со ко-морбидитети, како и кај имуно-компромитираните пациенти и оние со недоволна исхранетост, се препорачува внес на хранливи материи што ја поддржуваат и/или стимулираат функцијата на имунолошкиот систем.