Chapter 5

Nutritional Support: Another Treatment for Fighting COVID-19

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INTRODUCTION

The world is now experiencing the third major epidemic of coronavirus infections. The declaration of a global pandemic has generated excessive release of information, a phenomenon named "Infodemia" [1]. In addition to quarantines, other public health measures that can reduce the risk of infection and help COVID-19 treatment are needed [2]. There is a lot of misinformation regarding the relationship between COVID-19 and food. According to the European Food Safety Authority (EFSA), there is currently no evidence that food is a likely source or route of transmission of the virus. Marta Hugas, EFSA's chief scientist, has stated "Experiences from previous outbreaks of related coronaviruses, such as severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), show that transmission through food consumption did not occur. At the moment, there is no evidence to suggest that coronavirus is any different in this respect" [3].

Since there is no scientific evidence of the virus spread through food, the EFSA is not involved in COVID-19 outbreaks [3]. With regard to food safety, the World Health Organization (WHO) is the main official regulatory body, and it has published "Food and Nutrition Tips during Self-Quarantine". The WHO recommends keeping hands, kitchens, and utensils clean, separating raw and cooked food to avoid cross-contamination, cooking food thoroughly, keeping food at safe temperatures (< 5 ºC or > 60 ºC), and using safe water and raw material [4].

Currently, food supplements that are supposed to prevent, treat, or cure COVID-19 are being commercialized, taking advantage of the COVID-19 pandemic and consumer concerns about them. Food supplement vendors attempt to increase their profits through unauthorized and prohibited nutritional and health claims by promoting and selling these food supplements [5]. The European Union reminds consumers that food supplements are foods intended to complement the normal diet. These products cannot attribute properties to prevent, treat, or cure a human disease, nor refer to these properties at all [5]. Consequently, there are no food supplements able to prevent, treat, or cure coronavirus infection, and therefore, there cannot be any product on the market with such claims [6].

According to the "Handbook of COVID-19 Prevention and Treatment" written by medical experts from the Zhejiang University School of Medicine (FAHZU) in China, two of the proposed treatment strategies for fighting COVID-19 are microecological and nutritional support [7]. In China, the COVID-19 epidemic has led to a rebound in demand for plant extracts with immune supporting effects [2,8]. Maintaining a healthy diet to support your immune system is important in order to improve your health and strengthen the body's ability to fight other invasive viruses [9]. Nutritional supplements based on food ingredients may have potential to reinforce the immune system or interfere in the virus-cell interaction, or both. Therefore, the present chapter aims to provide knowledge on the mechanisms of infection of SARS-CoV-2 and the main biochemical disorders associated with COVID-19 and propose the nutritional guidelines and food compounds that may have the potential to reduce the risk of reaching a critical status due to the disease. The potential of the antiviral, antioxidant, and anti-inflammatory supplements, anticoagulants, and gastrointestinal function enhancers alone or in combination with drugs to treat COVID-19 patients will be discussed.

Microecologics Intervention

Based on the experience of Chinese healthcare colleagues, viral infection of the intestinal mucosa or anti-viral and anti-infective drugs causes gastrointestinal symptoms such as abdominal pain and diarrhea in some COVID-19 patients. Their intestinal microecological balance is altered as is evident in the significant reduction of intestinal probiotics, such as *Lactobacillus* and *Bifidobacterium* [7].

Gastrointestinal microbiota play an important role in the maintenance of the health and well-being of the host and exerts beneficial effects on systemic metabolism and the immune system [10]. An imbalance within the gastrointestinal microbiota with relative predominance of aggressive bacteria and insufficient concentration of protective species has been associated with several inflammatory processes, bacterial translocation, and secondary infection, so it is important to maintain the balance of intestinal microecology [7,10]. A balanced intestinal microecology can reduce bacterial translocation and secondary infection [7].

According to the WHO, probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [11]. The most commonly used probiotics are *Lactobacillus* and *Bifidobacterium*, followed by *Streptococcus*, *Enterococcus*, *Propionibacterium*, *Bacillus*, and *Escherichia* [12]. A balanced microbiota can increase dominant gut bacteria, inhibit intestinal harmful bacteria, reduce toxin production, and reduce infection caused by gut microflora dysbiosis [7]. Dysbiosis is defined as an alteration of gut microbiota composition and a cause or a consequence of disorder [13].

Upper respiratory tract infections (URTIs) are illnesses caused by an infection of mucosal surfaces in the nose, sinuses, and the pharynx or larynx, or both, and one of the most common viruses that cause URTIs are coronaviruses [14]. Several studies have reported the effectiveness of probiotics on the prevention and reduction of the risk of various symptoms of URTIs [12,14–16]. A systematic review written by King *et al.* provides evidence from a number of good-quality randomized control trials (RCT) that the average duration of respiratory illness episodes, the number of days of illness per person, and the number of days absent from day work or school were significantly reduced with probiotic treatment (*Lactobacillus* and *Bifidobacterium*) compared with placebo [16]. In another study, probiotics were found to be better than placebo since they reduced the number of participants experiencing episodes of acute URTIs by about 47% and the duration of an episode of acute URTI by about 1.89 days [15]. Interestingly, in a very recent study, a recombinant *Lactobacillus plantarum* strain expressing the SARS-CoV-2 spike protein has been developed, and authors conclude that it may provide a promising "food-grade oral vaccine" candidate against SARS-CoV-2 infection [17].

Gerritsen and Ormel [14] describe the possible mechanisms proposed to explain these beneficial effects at a local and systemic level. At a local level, there is a competitive exclusion of the pathogens by the probiotic bacteria. When administering a probiotic food supplement the bacterial strains can temporarily colonize the upper respiratory tract, thereby inhibiting and excluding pathogens in this area [14]. On the other hand, at a systemic level, probiotics are able to bring out a strong immune response against pathogens in the respiratory tract via the innate immune system (enhancing phagocytic activity), via acquired immunity (inducing specific immunoglobulins) and by enhancing local immunity (increasing the production of T helper, Th1, cells and cytokines) [14]. These combined strengths may be responsible for the beneficial effect of probiotics in URTIs.

Therefore, as recommended by the medical experts in China, hospitals should perform intestinal flora analysis to discover any disturbance early. Then, antibiotics could be adjusted and probiotics prescribed, reducing the chances of intestinal bacterial translocation and gut-derived infection [7]. Fecal transplantation, the transfer of stool from a healthy donor into the gastrointestinal tract of a patient, should also be considered as a novel treatment option to restore intestinal microbiota [18].

A balanced intestinal microecology can improve the gastrointestinal symptoms of patients. It can reduce water in feces, improve fecal consistency and defecation frequency, and reduce diarrhea by inhibiting intestinal mucosal atrophy [7]. Besides probiotics, nutrition support with prebiotics and dietary fiber is important to maintain intestinal microecological balance. Dietary fibers are carbohydrate polymers that, neither digested nor absorbed, are subjected to bacterial fermentation in the gastrointestinal tract and thus impact the gastrointestinal microbiota [19]. Some dietary fibers-defined as "selectively fermented ingredients that result in specific changes, in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit(s) upon host health"-can also be classified as prebiotic [20]. There is evidence suggesting that oral β-glucan supplementation, a type of dietary fiber, may improve symptom severity and duration of respiratory infections and allergies [21]. β-glucans can be found in the walls of bacteria, fungi, yeasts, algae, oats, and barley. In addition, clinical data seems to indicate that β-glucans support overall immune health in children, athletes, and allergic patients [21,22].

There is a vital cross talk between the mucosal tissues of the human body, as exemplified by intestinal complications during respiratory disease, and *vice versa*. Dietary fiber or prebiotic consumption is another strategy to improve the gut-lung axis function [23,24]. An *in vivo* study reported that dietary fiber and some of their fermentation products, short chain fatty acids (SCFAs), protect against the development of allergic airway inflammation by modulating immune function in mice [25]. Changes in the intestinal microbiota after dietary fiber intake and a low incidence of asthma has been also reported in humans [26]. In addition, drinking unpasteurized milk during the first year of life has shown to protect against respiratory tract infections in children [27].

Intake of prebiotics, probiotics, and synbiotics has been demonstrated to modify the composition of the gastrointestinal microbiota and restore the microecological balance [10]. The concept of synbiotics has been proposed recently to characterize colonic food with prebiotic and probiotic properties as a health-enhancing functional food. It is of great importance to maintain an intestinal microecological balance in order to support the immune system and reduce the risk of respiratory infection.

Nutritional Support

Nutritional status influences the individual risk for the progression of SARS-CoV-2 infection. In fact, according to the European Society for Clinical Nutrition and Metabolism (ESPEN), obesity is one of the most prominent risk factors increasing the COVID-19 mortality [28]. During the lockdown period, there might be an increase in undernourishment and obesity due to limited cooking skills, a more sedentary lifestyle, a change in food purchasing, eating behaviors (higher consumption of ultra-processed foods high in saturated fats, sugars, and refined carbohydrates), and perceptions of food safety [28].

Healthy nutrition is very important before, during, and after an infection. It is crucial for health, particularly in times when the immune system might need to fight back. Infections take a toll on the body, especially when they cause fever; the body needs extra energy and nutrients. Therefore, maintaining a healthy diet is very important during the COVID-19 pandemic. While no foods or dietary supplements can prevent COVID-19 infection, maintaining a healthy diet is an important part of supporting a strong immune system [29]. The Food and Agriculture Organization of the United Nations (FAO) recommends, as a part of a healthy diet, to [29]:

- Eat a variety of foods to ensure adequate intake of nutrients.
- Eat plenty of fruits and vegetables.
- Consume whole grains, nuts, and healthy fats rich in unsaturated fatty acids.
- Reduce the intake of saturated fats, sugar, and salt.
- Drink water regularly.
- Limit consumption of alcohol.

According to the experience of Chinese healthcare professionals, severe and critically ill COVID-19 patients who are in a state of severe stress are at high nutritional risks [7]. Early evaluations of nutrition risk, gastrointestinal functions, and aspiration risks and timely enteral nutritional support are important to the patient's prognosis. Identification of risk and presence of malnutrition should be an early step in general assessments for all patients [30]. In the context of the COVID-19 pandemic, it is important to avoid nutritional risks in severely affected patients or in patients with other non-communicable metabolic disorders.

Avoiding Nutritional Risk in Critically Ill Patients

As long as oral feeding is possible, it is always preferred in hospitalized patients [31]. Immunonutrition, the potential to modulate the activity of the immune system by interventions with specific nutrients, is intended to improve the clinical course of critically ill and surgical patients, who will often require an exogenous supply of nutrients through the parenteral or enteral routes [32]. A specific nutrition plan for COVID-19 patients should provide nutritional support, nourish intestines, improve intestinal mucosal barrier and intestinal immunity, and maintain intestinal microecology [7].

When spontaneous oral intake is inadequate, enteral feeding is preferred over parenteral feeding. Undergoing complete nutritional support to maintain muscle tone, microbiota, and intestinal immunity and lower risk of infectious complications should be guaranteed with enteral nutrition in critically ill patients with respiratory failure [33,34]. Enteral feed falls into the category of "foods for special medical purposes", which "is intended for the dietary management of patients with a limited, impaired or disturbed capacity, for example, to take ordinary food because of a specific disease, disorder or medical condition" [35]. For patients with intestinal damage, predigested dipeptides and tripeptides, which are more efficacious and better tolerated than whole-protein formulas, are recommended [36]. It may be of interest to add some of these peptides with antiviral properties, such as gluten hydrolysates with angiotensin-converting enzyme inhibitory properties [37]. In addition, very recent studies recommend that patients with acute respiratory distress syndrome (ARDS) or acute lung injury, should be given enteral diets with eicosapentaenoic acid, gamma-linolenic acid, and antioxidant agents that may have a potential clinical benefit in oxygenation and days of ventilation [38]. The modulation of the inflammatory response by specific lipid emulsions could offer additional benefits over corticosteroids and anti-interleukin-6 drugs and must be further studied [31].

Indications given by medical experts in China recommend to heat nutrients in enteral feeding to reduce intolerance [7]. Special attention has to be paid to thermal processing of enteral feed since it can be an exogenous source of advanced glycation end products (AGEs) with harmful effects on human health. Sustained exposure to AGEs can affect the body's native defenses, setting the stage for abnormally high oxidative stress and inflammation, which are precursors of disease [39]. N^{ε}-carboxymethyl-lysine (CML) has been found in a range of 6,300 to 178,500 ng/mL in enteral diets [40]. These authors found a linear correlation between protein/amino acids and CML in enteral formulations [40]. Future research is needed to evaluate the health impact of these compounds in such nutritional products and to mitigate its appearance. yu

Ensuring an adequate enteral nutrition in critically ill COVID-19 patients has proven to be challenging due to intestinal dysmotility, bowel ischemia, malabsorption [41], and in some instances, parenteral nutrition might be needed (see below). The ESPEN has recently published further information on the nutritional management of individuals with SARS-CoV-2 infection in a concise guidance by proposing 10 practical recommendations. It is focused on those in the intensive care unit or in the presence of older age and polymorbidity, which are associated with malnutrition and its negative impact on patient survival [30].

Dietary Support of Patients with Chronic Diseases and COVID-19

1. Gastrointestinal disorders

Although fever, cough, and respiratory symptoms are considered the main symptoms of infection by SARS-CoV-2, a number of prominent gastrointestinal (GI) symptoms have been reported, including anorexia, diarrhea, nausea, vomiting, abdominal pain, GI bleeding, and even bowel necrosis (Table 1). Interestingly, cases of digestive problems with no associated respiratory symptoms, particularly in children, have also been described [42–45], and it has been suggested that GI symptoms, especially diarrhea, may be underestimated in COVID-19 patients [46]. Furthermore, COVID-19 patients with digestive symptoms were more prone to a worse prognosis than those without them [42,43,47]. In view of the accumulating evidences, a prospective multicenter study on the assessment of GI symptoms of SARS-CoV-2 infection (GI-COVID-19), led by the European Society of Neurogastroenterology & Motility (ESNM) (https://www.esnm.eu/gi-covid19/), is currently being performed with the aim to obtain more robust data on the prevalence, clinical features, and long-term consequences of SARS-CoV-2 infection and COVID-19 on the GI tract.

Table 1. Gastrointestinal symptoms associated with SARS-CoV-2 infection and COVID-19.

GI symptom	Minimum and maximum reported incidence range* (% and number of patients per study)	Observations
General	3% (1/41)-79% (159/201)	• Patients with digestive symptoms had higher mean liver enzyme levels, lower monocyte count, longer prothrombin time, and received more antimicrobial treatment than those without digestive symptoms
Anorexia	12.2 (17/139)-50.2% (101/201)	• The most frequent in adults • More frequent in severely ill patients than not (66.7% vs 30.4%) • May be due to the inflammatory state, hypoxia, liver function injury, depression or adverse reactions to therapeutic drugs • Assessment is difficult (subjective nature)
Diarrhea	2% (2/99)-49.5% (146/295)	• Most frequent regardless of the age • Mean duration: 4.1 ± 2.5 days • Observed before and after diagnosis • Similar incidence in severe and non-severe cases
Vomiting	2% (5/204)-66.7% (4/6)	• Children: 6.5% (2/31)-66.7% (4/6) • Adults: 3.6% (5/138)-15.9% (32/201) • Similar incidence in severe and non-severe cases
Nausea	1% (1/99)-29.4% (59/201)	• Similar incidence in severe and non-severe cases
Abdominal pain	1% (2/204)-6.0% (12/201)	• More frequent in severely ill patients than not (8.3% vs 0%)
GI bleeding	4% (2/52)-13.7% (10/73)	• Unclear cause: hypoxemia and necrosis affecting the mucosa; previous use of corticosteroids and NSAIDs, physiological stress; direct damage of the mucosa by the virus
Other GI findings		
GI dysmotility (ileus), bowel ischemia and malabsorption$	• Critically ill COVID-19 patients • In contrast with critically ill patients with other conditions (septic shock, burning-injures), an enteric neuropathy due to infection of the enteric nervous system seems to contribute to GI dysmotility	
Bowel necrosis#	• 47-year-old male patient, with history of type 2 diabetes mellitus • In spite of respiratory status improvement, after 14 days in the intensive care unit, leukocytosis hypotension and abdominal distension developed. • Small bowel ischemia with perforation and patent mesenteric vessels found on CT scan and exploration in the operating room • Necrosis characteristics: yellow discoloration (rather than black or purple ischemic changes), distributed either circumferentially or antimesenterically (patchy and without anatomic transition zones); the yellow necrotic areas were extremely thin and friable • Fatal outcome; the family declined an autopsy • Discussion: although the direct tissue injury from virus cannot be discarded, necrosis might be due to microvascular thrombosis and associated inflammation related with hypercoagulability	
Kawasaki-like hyperinflammatory syndrome&	• Children with no previous or only mild COVID-19 symptoms but high titers of IgG/IgM against SARS-CoV-2 (late phase of viral infection, even after seroconversion) • Resembles Kawasaki disease (KD) complicated by macrophage activation syndrome • Increased incidence and severity than KD associated with other viral infections, may affect also children at older ages (> 5 yo) • GI symptoms: prodromal diarrhea, abdominal pain, hepatomegaly	

* Includes data from: [42,43,48–50]; $ [41,51]; #Case report [52]; &[53].

The nutritional management of GI manifestations of COVID-19 needs to take into account the quality and severity of symptoms as well as the mechanisms involved, including both direct infection of enterocytes and indirect effects of immune response to infection [54–57]. Infection may ultimately lead to gut barrier function breakdown (from mild leaky gut to frank inflammation), with possible bacterial invasion and immune system activation [58,59], dysfunction of the enteric nervous system [51], and remote consequences in other organs including the respiratory system (gut-lung axis, [23,60,61]) and the central nervous system (CNS) (vomiting center, brain-gut axis, [57]). Possible dietary adaptations in patients already diagnosed with GI diseases also need to be considered.

As mentioned, GI symptoms induced by SARS-CoV-2 may remind those associated with common gastroenteritis. Therefore, in addition to rehydration therapy to maintain electrolyte balance, treatment is usually symptomatic and may include loperamide and even adsorptive agents (clays) to relieve diarrhea, probiotics to mitigate intestinal microflora dysbiosis, and antispasmodics if accompanied by abdominal pain [43]. These measures might be enough to help complete recovery of GI symptoms associated with SARS-CoV-2 infection. However, most patients present at admission with severe inflammation and anorexia leading to a drastic reduction of food intake will need targeted nutritional support [62], including parenteral nutrition when enteral nutrition is not tolerated [63]. Indeed, nutritional care of critically ill COVID-19 patients is particularly tricky for different reasons, including the occurrence of intestinal dysmotility, bowel ischemia, and malabsorption [41]. Thus, guidelines for treatment of this population in the ICU should include recommendations for testing of absorption, reduced tolerance of elevated gastric residual due to the risk of aspiration, and early initiation of parenteral nutrition to achieve nutritional goals [41]. Once the risks affecting enteral nutrition are over, enteral nutrition should be restored as soon as possible, and oral eating should be encouraged [63] with increased vigilance when monitoring for refeeding syndrome and its associated complications [41]. Thus, the initial treatment of enteral nutrition should be based on low energy, small doses, and multiple feedings and gradually transition to full energy to reduce GI reactions or intolerance [64] coupled with swallowing rehabilitation to recover from dysphagia [34].

Patients with already diagnosed GI disorders may be particularly vulnerable during this pandemic because of the infection itself or the associated conditions, or both. Among these, stress may be particularly impactful in patients suffering from functional GI disorders, such as irritable bowel syndrome (IBS), or may increase the occurrence of flares in patients suffering from organic GI diseases, such as inflammatory bowel diseases (IBD). During stress, infection, and inflammation, proinflammatory mediators may cross the compromised blood-brain barrier (BBB), and together with increased oxidative stress, may damage the nervous tissue. Furthermore, like influenza, coronaviruses are neurotropic virus and can be found in the CNS [65]. Likewise, stress and the immune response to these infections enhances the hypothalamic-pituitary axis (HPA) activity and may cause tryptophan depletion in the brain, causing mood alterations and sleeping disorders because of uncoupled melatonin synthesis [66,67]. Tryptophan exerts huge health benefits [68]. Importantly, the angiotensin-converting enzyme 2 (ACE2) receptors (key for SARS-Cov2 infection), are expressed on the enterocytes and are essential for dietary tryptophan absorption, through stabilization of B^0AT-1 (SLC6A19), an amino acid transporter [69]. Tryptophan absorption via the B^0AT1/ACE2 transport pathway activates intestinal mammalian target of rapamycin (mTOR) and p70 S6 kinase (p70S6K), resulting in secretion of α-defensins, cysteine-rich cationic peptides with antibiotic activity against a wide range of bacteria, and other microbes [70] that contribute to maintaining the intestinal microbiota composition [71]. Thus, the aberrant absorption of tryptophan in the small intestine, like in ACE2 knockout mice, may lead to manifestations of colitis, such as diarrhea [71,72]. Pellagra, caused by the deficiency of niacin (vitamin B3), whose synthesis requires tryptophan, is characterized by intestinal inflammation and protein malnutrition [71]. In addition, the reduced expression of intestinal ACE2 potentially leads to reduced levels of tryptophan in plasma and indirectly, of serotonin in the brain [73,74], which is essential for the regulation of physiological emotion and for coping with stress [75,76]. Intestinal ACE2 are down-regulated in chronically stressed mice [77]. Although expression and activity of ACE2 in colonic inflamed tissue is more controversial [78–81], increased tryptophan metabolism was associated with activity of IBD [82]. Furthermore, it has been postulated that intestinal inflammation may occur because of SARS-CoV-2 mediated reduction of mucosal ACE2 following entry, resulting in elevated angiotensin II (the effector peptide of the classical renin-angiotensin system pathway), reduced Ang 1-7 levels (the effector peptide of the alternative RAS pathway), increased tumor necrosis factor α (TNFα), and tryptophan deficiency [80]. Thus, for many reasons, the intake of foods rich in tryptophan [68], may be beneficial in both GI and non-GI patients during the pandemic.

Irritable bowel syndrome is considered a chronic disorder of the brain-gut axis and is exacerbated under stressful conditions [83]. Another kind of IBS is post-infectious IBS (PI-IBS). So far, coronavirus infections have not been reported to be associated with the development of PI-IBS [84,85], and no report has been published to date in the context of the current pandemic, but SARS-CoV-2 is a new entity, with higher tropism for and higher impact on the GI tract than those of other coronaviruses [54,57]. Furthermore, it has been acknowledged that, in comparison with PI-IBS reported after bacterial infection, few studies have evaluated the incidence of viral PI-IBS [86].

At present, no specific treatment options do exist for PI-IBS and the same guidelines as for general IBS treatment are followed, including dietary and pharmacological management (Figure 1A; [87]). IBS diet is very individual, meaning that what works for one IBS patient might not work for another. According to the suggestions made by the Canadian Society of Intestinal Research, IBS symptoms may be alleviated by eating a healthy, balanced diet, rich in soluble dietary fiber, low in fat, and should include a large amount of fruits and vegetables as well as three meals and 2-3 snacks a day [88]. They also recommend to:

- Eat all cooked vegetables, except perhaps cabbage, cauliflower, and broccoli, which might cause too much gas.
- Try fruits without the skins. Some people might have problems with melons, apples, and citrus fruits.
- Some IBS patients benefit from increasing the dietary fiber content of their diet. A soluble fiber supplement before a potential trigger meal may protect against developing symptoms. The increase of dietary fiber should be slow and combined with a water intake of 1.5-2 L/day.
- Bran fiber may aggravate some symptoms of IBS.
- Bread, pasta, rice, bagels, and crackers, including rye, whole wheat, white, gluten free, etc., are usually tolerated unless in presence of celiac disease or a gluten intolerance.
- Some IBS patients find seeds challenging.
- Dairy products only cause problems for lactose intolerants. If so, lactose-free products or lactase pills are recommended.
- Eat all meat, chicken, and fish.
- Some people have problems with heavily spiced, sauced, or fried foods.
- The following snack foods are preferred: pretzels, baked potato chips, rice cakes, frozen yogurt, low fat yogurt, and fruit.
- Look for low-fat products.
- Prepare foods by grilling, boiling, baking, or steaming with little to no oil.

If these suggestions cause a negative reaction, for PI-IBS as well as for mixed- or diarrhea-IBS, the low FODMAPs diet (a diet low in “Fermentable Oligo-, Di-, Mono and Polyols”) may reduce symptoms. This type of diet should be performed under medical supervision and for a limited period (Figure 1A).

Advantages and disadvantages of the low FODMAP have been recently revised [89]. In contrast, constipation-IBS might benefit more from the use of water soluble fibers and probiotics [87]. Of note, the previously mentioned European GI-COVID-19 study will prospectively determine the incidence, characteristics, and risk factors of PI-IBS development (https://www.esnm.eu/gicovid19/). Whether dietary guidelines for treating IBS of any kind will require some adjustment in the context of SARS-CoV-2 infection is still unknown.

The United European Gastroenterology (UEG) has opened registries to identify the impact of SARS-CoV-2 infection and COVID-19 in patients diagnosed with IBD (https://ueg.eu/p/153; https://covidibd.org). The relatively scarce data reported so far indicate that IBD patients do not have an increased risk of developing COVID-19 and associated mortality compared with the general population [44,50,90], but older age, smoking, and active disease were identified as potential additional risk factors of vulnerability, through alterations in ACE2 and TMPRSS2 expression [90,91]. The lack of increased risk in IBD versus the general population occurs despite the higher use of immunosuppressive drugs in IBD patients (Figure 1B), maybe because of correct adherence of this population to protection measures [44] or because these medications might attenuate viral-induced respiratory inflammation, leading to an asymptomatic or mild COVID-19 course in IBD patients, who subsequently might not seek testing [90]. In any case, diarrhea was reported to be frequent in IBD patients, sometimes as the only symptom at onset of COVID-19 infection, but it may be easily misdiagnosed [44]. Thus, IBD patients presenting with diarrhea during the outbreak should be tested for SARS-CoV-2 infection so that an IBD flare is adequately discriminated from diarrhea due to this virus and inappropriate use of corticosteroids. Other therapies that may favor COVID-19 progression and even fatality are avoided [44,92–94]. Dietary recommendations for IBD patients have been recently elaborated on by the International Organization for the Study of Inflammatory Bowel Diseases [95]. Although there are several dietary patterns commonly recommended for patients with IBD (e.g., Mediterranean diet, Specific Carbohydrate Diet, Crohn's Disease Exclusion Diet), RCT testing these dietary patterns are still lacking, and the authors limited their recommendations to particular components of the diet, with some differences for Crohn's disease and ulcerative colitis (Figure 1B).

Finally, since a worse nutritional status represents a negative prognostic factor for SARS-CoV-2 [34,47], conventional advice of a healthy diet (or that adapted for GI patients) applies during the pandemic, although at least three factors related with lockdown should be considered in order to optimize its benefits. The first one is the likely physical inactivity and weight gain whose health consequences may be at least partially prevented or alleviated with the practice of indoor or outdoor exercise, together with increased intake of dietary fiber, and the use of hypocaloric diets (low in fat and carbohydrates), high-protein foods, and immunomodulatory foods, such as pro- and prebiotics and some vitamins (i.e., vitamin A, C and D) and minerals (i.e., Se, Zn) [28,98]. All these recommendations are suggested for maintaining GI health. Of note, apart from its beneficial effects on gut microbiota, the intake of fiber (together with adequate hydration) keeps the GI tract motor function active (which may be particularly affected by low physical activity [99]), potentially preventing constipation and associated complications [100]. The second factor is insufficient sunlight exposure, which leads to low vitamin D levels. To avoid hypovitaminosis D, vitamin D dietary supplements and foods with high vitamin D contents (fatty fish, cod liver oil, egg yolks…) may be helpful [98]. Apart from its effects on bone health, supplementation with vitamin D has a protective effect against bacterial and viral acute respiratory tract infection and contributes to the expression of proteins of the mucosal adhesion complexes in the digestive tract [101–103]. It also regulates cellular innate immunity by lowering production of pro-inflammatory Th1 cytokines, reducing the "cytokine storm". Indirect evidence supports the idea of its potential usefulness as a co-factor in combating SARS-CoV-2 infection (maybe in the gut too), although there is a lack of results from RCT [104].

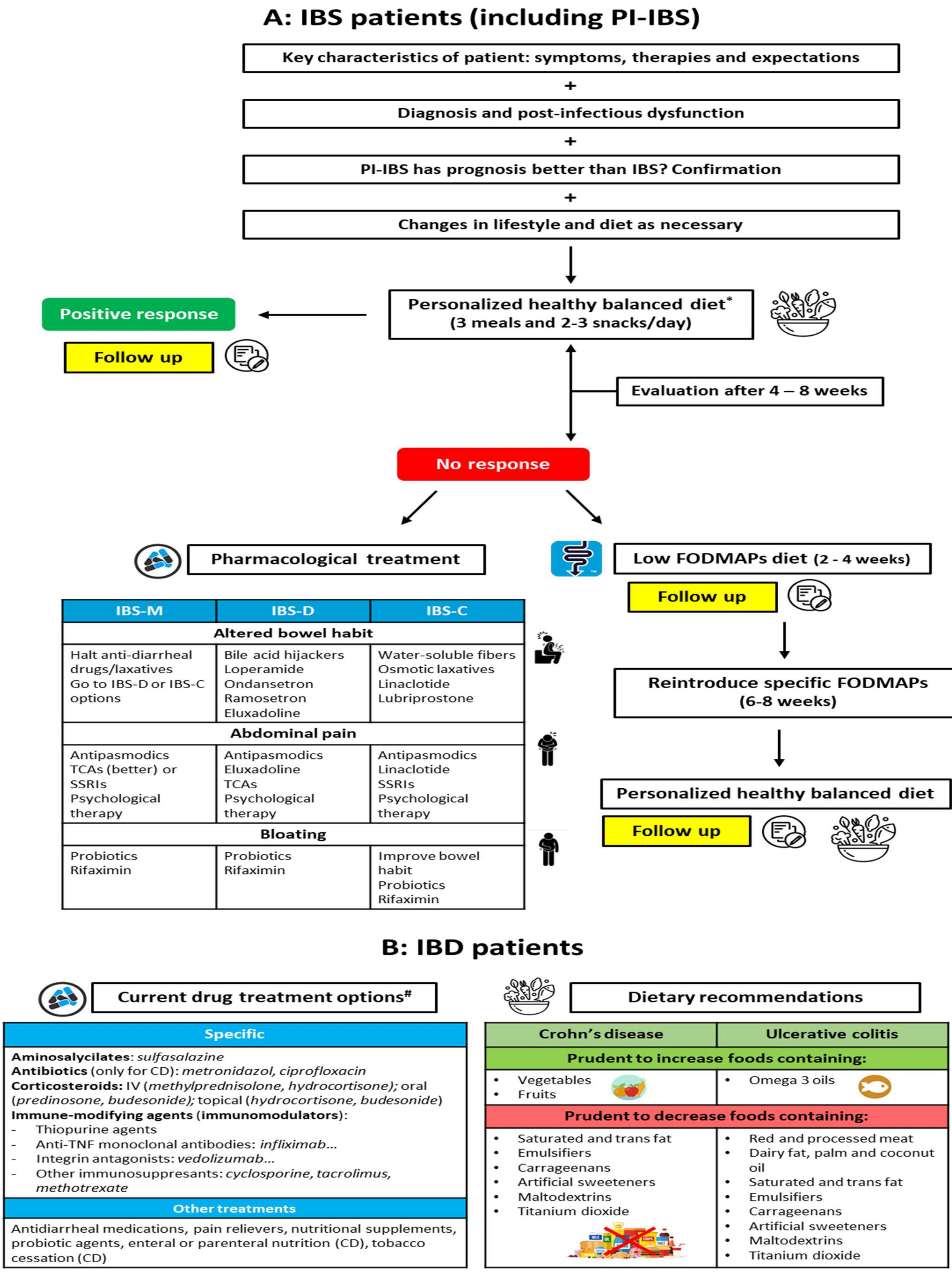

Figure 1. Pharmacological and dietary treatment of IBS and IBD patients. Panel A: Algorithm treatment for IBS patients (adapted from [87,88]). Panel B: Current drug treatment options (adapted from [96,97]) and dietary recommendations for

IBD patients (adapted from [95]). *See text for description of IBS-personalized healthy balanced diet. #Treatment is complex depending on the specific disease and whether the patient is in an active phase (flare) or in remission; since pharmacological treatment is out of the scope of this chapter, here only a list of the different kinds of drugs is provided (see [97] for further information). Crohn's disease, CD; Fermentable oligo-, di-, mono and polyols, FODMAPs; Inflammatory bowel disease, IBD; Intravenous, IV; Irritable bowel syndrome, IBS; constipation-IBS, IBS-C; diarrhea-IBS, IBS-D; mixed-IBS, IBS-M; Post-infectious IBS, PI-IBS.

Finally, the last factor has to do with social isolation, which may amplify the burden of neurocognitive, mental, cardiovascular, and autoimmune problems, especially in the elderly, and may favor the development of depression. anxiety, and sleeping disorders-particularly in vulnerable populations, such as young people with sedentary behaviors [98]. Furthermore, it is quite likely that a second wave of psychological morbidity in the form of depression and mood disorder occurs after the acute infective phase of SARS-CoV-2 [105]. Diet and some food supplements may be extremely helpful because of their anti-inflammatory, antioxidant, and even mood-stabilizer effects [66,67]. In these regards, the recommendations of the recently established discipline of Nutritional Psychiatry may be very helpful to prevent and/or counteract the development of viral psychogenic sequelae with high impact on the brain-gut axis [106].

1. **Non-communicable metabolic chronic disorders**

There is limited information regarding risk factors for severe COVID-19, but we are learning about this new pandemic every day. According to the Centers for Disease Control and Prevention, the following conditions and risk factors might put patients at higher risk for severe COVID-19: asthma, chronic kidney disease, chronic lung disease, diabetes, liver disease, hemoglobin disorders, immunocompromised, being 65 year and older, being in a nursing home, serious heart conditions, and severe obesity [107].

A very recent study described the clinical characteristics and outcomes of patients with COVID-19 hospitalized in 12 hospitals in New York City during one month [108]. Of the total hospitalized patients (n = 5700), 41.7 % were obese and 33.8 % diabetic [108]. Severe obesity (body mass index > 40 kg/m^2) increases the risk of ARDS, which is a major complication of COVID-19 [107]. People living with severe obesity can have multiple serious chronic diseases and underlying health conditions that can increase the risk of severe illness from COVID-19. On the other hand, diabetic patients normally have impaired immune response [109] and poor glycemic control, which impairs several aspects of the immune response to viral infection and also to the potential secondary infection in the lungs [110].

Both obesity and diabetes are considered the real pandemics of the 21st century [111,112]. It is of great importance to reduce the incidence of these metabolic disorders in order to decrease the severity of COVID-19. There are many links between excessive body weight and type 2 diabetes, and one common and fundamental cause of both epidemics is an unhealthy diet [113]. There is evidence from epidemiological studies that supports a protective effect of the Mediterranean diet on weight gain and the development of type 2 diabetes [113]. This diet is based on high consumption of vegetables, fruits, legumes, nuts, fish, cereals, and olive oil, which leads to high ingestion of dietary fiber, antioxidants, magnesium, and unsaturated fatty acids [113]. Figure 2 shows the double food and environmental pyramid based on the Mediterranean diet.

The double food and environmental pyramid links the nutritional value of food with its environmental impact, considering their carbon, water and ecological footprints [114]. It is of great interest that foods with a lower environmental impact are those recommended for a healthy nutrition. A healthy nutrition based on the Mediterranean diet is recommended to reduce the risk of obesity and diabetes and the risk of COVID-19, while contributing to the sustainability of the planet.

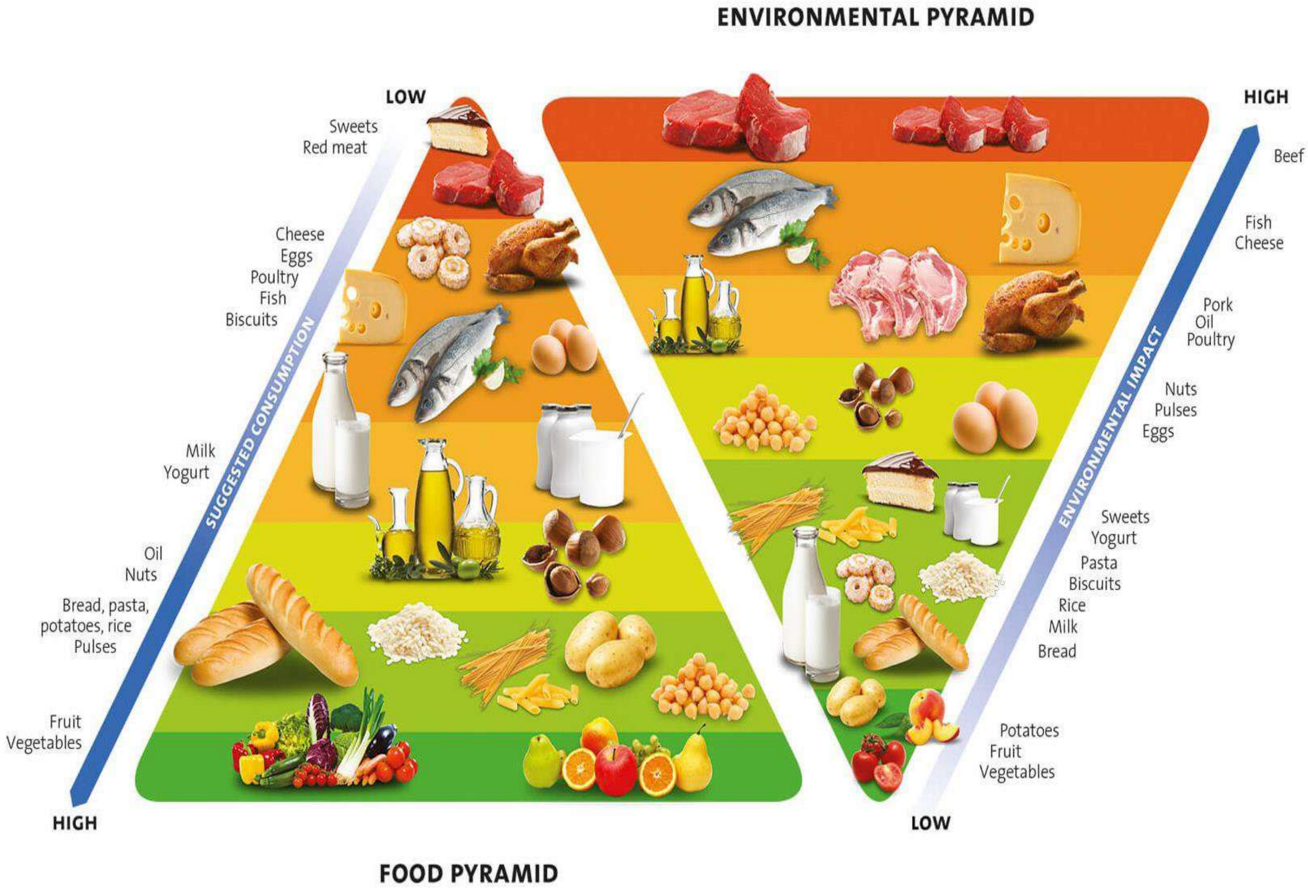

Figure 2. The double food and environmental pyramid model developed by the Barilla Center for Food & Nutrition (BCFN) Foundation [114].

Treatment Support

Nutritional status appears to be a relevant factor that influences the outcome of patients with COVID-19, but not much information has emerged so far on the impact of early nutritional support in COVID-19 patients [31]. Immunonutrition could have an important preventive role by helping the body to fight against potentially lethal viruses, such as coronaviruses. Nutrition has the potential to be used to activate the host's immune response required for viral clearance and infection recovery [115]. The European Food Information Council (EUFIC) recommends a healthy diet, being physically active, reducing stress, and getting enough sleep to help support normal immune functioning [116]. Undernutrition leading to impairment of immune function can be due to insufficient intake of energy and macronutrients and/or due to deficiencies in specific micronutrients [117]. In particular, protein-energy malnutrition has an effect on different aspects of the immune function, such as cell-mediated immunity and humoral responses, and on susceptibility to infection [117]. The recommended daily amount of protein ranges from 0.80 to 0.83 g per kilogram of body weight for both men and women with modest levels of physical activity [118]. It is of great importance to have a sufficient dietary intake of proteins to ensure the correct functioning of the immune system.

Long-chain polyunsaturated fatty acids (PUFAs), omega-3, and omega-6 fatty acids, are important mediators of inflammation and adaptive immune responses [119]. Metabolites of arachidonic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) have both pro- and anti-inflammatory actions, regulate phagocytic action of macrophage and other immune cells, and have the ability to reduce microbial load [120]. In addition, PUFAs have the potential to inactivate enveloped viruses, such as SARS-CoV-2. Therefore, these fatty acids should also be considered when looking for options to fight COVID-19.

Some micronutrients also play an important role in our immune system [121]. Worldwide health institutions recommend eating a healthy balanced diet that allows us to get these micronutrients through our food during the COVID-19 pandemic. Gombart *et al.* have very recently reviewed the effect of micronutrients in the immune system [121]. In this review, they conclude that "although contradictory data exist, available evidence indicates that supplementation with multiple micronutrients with immune-supporting roles may modulate immune function and reduce the risk of infection" [121].

According to the European Commission Regulation (EU) 432/2012, the micronutrients that "contribute to the normal function of the immune system" are: copper, folate, iron, selenium, zinc and vitamins A, B12, B6, C and D [122] (Table 2). Supplementing diet with these micronutrients has a direct effect on the immune system at different levels [121]. Briefly, vitamins A, D, C, E, and zinc are required to ensure the structural and functional integrity of physical and biochemical barriers of the body, which are the first line of defense against pathogens. Vitamins A, D, C, E, B6, and B12, folate, iron, zinc, copper, selenium, and magnesium are responsible for the correct cell-mediated processes of innate and adaptive immunity, such as cell proliferation, differentiation, function, and movement [121]. In addition, the activation of the complement system and release of pro-inflammatory cytokines requires vitamins A, D, and C, zinc, iron, and selenium. Micronutrients are also involved in self-protection of immune cells by antioxidant mechanisms, (vitamins C and E, zinc, iron, magnesium, copper, and selenium), inhibitory actions (vitamins D, B6, and E), and elimination of supernumerary cells by apoptosis to limit tissue damage (vitamin C) [121].

Table 2 shows the recommended daily allowances (RDAs) of micronutrients and those foods enriched in micronutrients that contribute to the correct function of the immune system. In addition, information regarding absorption and bioavailability of micronutrients is included. Bioavailability is included in developing reference intakes since new information constantly emerges and new complexities enter into the development of reference values and standards [123].

Besides the effect of these micronutrients on the immune system, there is evidence of their effect also on respiratory health [115]. In fact, low levels of micronutrients such as vitamins A, E, B6 and B12, zinc and selenium have been associated with adverse clinical outcomes during viral infections [124]. Results from a RCT proved that dietary supplementation with vitamins and minerals reduces the incidence of acute respiratory infections in susceptible adults [125]. After a 90-day period of supplementation with vitamins (vitamin A, B1, B2, B6, B12, C, D and E), minerals (selenium and zinc, etc.), and plant extracts such as *Laminaria*, *Chlorella* and *Equinacea*, and the cyanobacteria *Spirulina* among others, the supplemented group had a significantly lower incidence ($p = 0.013$) of acute respiratory infections compared to the placebo group [125]. This mixture of micronutrients and plant extracts was intended to support the immune system and to counteract the damage caused by free radicals produced for pathogen removal.

Some of the defenses against infection of the human body depend on an adequate supply of vitamin A; consequently, it is known as an "anti-infective" vitamin [119]. Previous studies reported that supplementation with vitamin A reduced morbidity and mortality in different infectious diseases, such as measles, diarrheal disease, measles-related pneumonia, human immunodeficiency virus (HIV) infection, and malaria [124]. Therefore, vitamin A could be a potential agent for the treatment of coronavirus and the prevention of lung infection. Since vitamin A is fat soluble, excessive amounts are stored and accumulate in the liver. Excessive amounts of vitamin A can have significant toxicity (hypervitaminosis A), but large amounts of β-carotene and other provitamin A carotenoids have not been associated with major adverse effects [126].

Vitamin C, a water-soluble vitamin, supports immune functions and protects against infections caused by coronavirus by preventing, shortening, and alleviating diverse infections [119]. Controlled studies have shown that vitamin C prevents, shortens and alleviates the common cold [127]. In addition, five controlled trials found significant effects of vitamin C against pneumonia, and there is some evidence that it may also have effects on other infections [127]. Infections normally activate phagocytes that release reactive oxygen species, increasing oxidative stress. Vitamin C is a well-known antioxidant that can counteract these effects [115].

Table 2. Micronutrients responsible for the normal function of the immune system, the Recommended Dietary Allowances (RDAs) for adults and their dietary food source.

Micronutrient	RDAs (For adults) *	Food source (Serving size) *	Amount of micronutrient per serving*	Absorption and bioavailability
Copper	900 µg	Beef liver (3 oz) Oysters (3 oz) Chocolate (1 oz) Potatoes (1 potato) Mushrooms (1/2 cup)	12,400 µg 4850 µg 938 µg 675 µg 650 µg	From 75 % to 12 % of dietary copper when the diet contains only 0.4 mg/day or 7.5 mg/day, respectively [128].
Folate	400 µg	Beef liver (3 oz) Spinach (1/2 cup) Black-eyed peas (1/2 cup) White rice (1/2 cup) Asparagus (4 spears)	215 µg 131 µg 105 µg 90 µg 89 µg	At least 85 % of folic acid is estimated to be bioavailable when taken with food, while only about 50% of folate naturally present in food is bioavailable [129].
Iron	8 mg (male) 18 mg (female)	Oysters (3 oz) White beans (1 cup) Chocolate (3 oz) Beef liver (3 oz) Lentils (1/2 cup)	8 mg 8 mg 7 mg 5 mg 3 mg	From 14 % to 18 % from mixed diets (including substantial amounts of meat, seafood, and vitamin C to enhance the bioavailability of non-heme iron) and from 5 % to 12 % from vegetarian diets [130].
Selenium	55 µg	Brazil nuts (6 - 8 nuts) Tuna (3 oz) Halibut (3 oz) Sardines (3 oz) Ham (3 oz)	544 µg 92 µg 47 µg 45 µg 42 µg	From 8 % to 94 % depending on the type of food [131].
Zinc	11 mg (male) 8 mg (female)	Oysters (3 oz) Beef chuck (3 oz) Crab (3 oz) Beef patty (3 oz) Lobster (3 oz)	74 mg 7 mg 7 mg 5 mg 3 mg	The bioavailability of zinc from grains and plant foods is lower than that from animal foods, due to phytates [132]. Absorption decreases with increasing amounts of zinc in a meal. Absorption of 92 – 64 % in high zinc diet and 81 – 39 % in low zinc diet [133].
Vitamin A **	900 µg (male) 700 µg (female)	Beef liver (3 oz) Sweet potato (1 whole) Spinach (1/2 cup) Carrots (1/2 cup) Ricotta cheese (1 cup)	6,582 µg 1,403 µg 573 µg 459 µg 263 µg	Bioavailability of carotenoids is frequently assessed by absorption efficacy. Absorption of vitamin A is of 70 – 90 % and of the provitamin A carotenoids is 20 – 50 % [134].
Vitamin B12	2.4 µg	Clams (3 oz) Beef liver (3 oz) Trout (3 oz) Salmon (3 oz) Tuna (3 oz)	84 µg 71 µg 5 µg 5 µg 3 µg	The overall bioavailability of vitamin B12 is believed to be approximately 50 %, with the different cobalamin forms having similar bioavailabilities [135].
Vitamin B6	1.7 mg (male) 1.5 mg (female)	Chickpeas (1 cup) Beef liver (3 oz) Tuna (3 oz) Salmon (3 oz) Chicken breast (3 oz)	1.1 mg 0.9 mg 0.9 mg 0.6 mg 0.5 mg	About 75 % of vitamin B6 from a mixed diet is bioavailable [136].
Vitamin C	90 mg (male) 75 mg (female)	Red pepper (1/2 cup) Orange (1 unit) Kiwi (1 unit) Green pepper (1/2 cup) Broccoli (1/2 cup)	95 µg 70 µg 64 µg 60 µg 51 µg	Bioavailability of vitamin C is high at lower doses (≈100 % at 200 mg), but drops to less than 50% at higher doses (1250 mg) [137].
Vitamin D	15 µg	Cod liver oil (1 tablespoon) Trout (3 oz) Salmon (3 oz) Mushrooms (1/2 cup) Milk (1 cup)	34 µg 16 µg 14 µg 9 µg 3 µg	Absorption efficiency from 55 to 99 %. Hydorxylated vitamin D ($25(OH)D_3$) has higher bioavailability due to a greater retention than that of non-hydroxylated vitamin D (vitamin D_2 and vitamin D_3) [138].

It has been reported that vitamin D has the potential to reduce the risk of viral infections [104,121,139]. The mechanisms by which vitamin D reduces the risk of infection have been grouped into three categories: physical barrier, cellular natural immunity, and adaptive immunity [140]. Viruses disturb junction integrity leading to an increased risk of infection, and vitamin D helps to maintain tight and gap junctions preventing this from happening [104]. In addition, it induces cathelicidins and defensins that are able to lower viral replication and reduces pro-inflammatory cytokines that produce lung inflammation, leading to pneumonia, as well as increases concentrations of anti-inflammatory cytokines [104]. Vitamin D is considered to be a safe strategy to protect against acute respiratory tract infections [104,115,141]. In fact, levels of vitamin D are low in European countries that have had high coronavirus infection and mortality rates [142]. An adequate vitamin D status according to that recommended by national and international public health agencies will have benefits for COVID-19 [142]. However, further research from RCT is required to fully investigate this association.

A recent study shows an association between the reported cure rates for COVID-19 and selenium status [143]. These results are in agreement with the evidence of the antiviral, antioxidant, and anti-inflammatory properties of selenium, which influences viral pathogenicity [143,144]. Therefore, selenium supplementation may be another strategy to help prevent COVID-19 [115]. On the other hand, zinc is also essential for the correct functioning of the immune system [115]. It has been reported that the combination of zinc and pyrithione at low concentrations inhibits the replication of SARS coronavirus [119]. Further studies are needed to prove the efficacy of zinc supplementation.

Antiviral Supplements

The binding of a virus to a target receptor present in the host cell represents the first step in most viral infections. Former reports on SARS-CoV showed that tropism of this virus mainly includes airway epithelial cells, alveolar epithelial cells, vascular endothelial cells, and macrophages in the lung. All of these cell populations express the ACE2 receptor used by SARS-CoV [145,146]. Similar to SARS-CoV, SARS-CoV-2 employs ACE2 as a receptor to bind host cells; thus, it is most likely that these cell types are also targeted by this virus.

Along with ACE2, the SARS-CoV-2 cell entry depends on the protease TMPRSS2 for proper stimulation and processing of the viral protein spike (S). SARS spike protein S is located on the surface of the virus particles and provides the distinctive ‘crown’ look of the viral particles. The S protein includes two subunits, S1 and S2. The amino-terminal domain of S1 subunit has been described to contain the receptor-binding domain (RBD), which in SARS-CoV, extends from amino acid residue 318 to 510 [147,148] and binds to ACE2. The S2 subunit involves a fusion peptide (FP) sequence and two HR1 and HR2 [149]. The amino acid sequences of the RBDs of SARS-CoV and SARS-CoV-2 display 72% similarity and show extremely comparable tertiary structures.

After RBD binding to ACE2, the SARS-CoV-2 virion is engulfed into the endosome, and the S1 subunit is cleaved, whereas S2 subunit folds and HR1 and HR2 regions are brought together. This process induces the membrane fusion and discharges the viral package into the cytoplasm [150]. Interestingly, it has been shown that the SARS-CoV-2 RBD binds to ACE2 with greater affinity than that of SARS-CoV [151], and similarly to MERS-CoV and human coronavirus OC, the SARS-CoV-2 S protein is potentially cleaved at a furin-like cleavage site, which is not found in SARS-CoV [152]. These two features would contribute to the amplified infectivity of SARS- CoV-2 relative to SARS-CoV.

Once the virus genome gets inside the host cell through the endosome, (+) ssRNA viruses, the group to which the SARS-CoV-2 belongs, need to develop a scaffold to accomplish the replication process [153,154]. The scaffold is mainly composed of lipid-based membranes, which are derived from the endoplasmic reticulum (ER) by the action of some viral enzymes. They are mostly located in the perinuclear area of the host cells; subsequently, proteins involved in the virus replication are embedded into these membranes [155]. There is no certainty on the actual function of these compartments, which are known as double membrane vesicles (DMVs), but it has been suggested that their function might be to increase local concentration of virus particles and prevention of innate immune system recognition of the virions or virus RNA during the replication and assembly of virus components [153,156,157]. Indeed, replicase activity has also been found to be resistant to the enzymatic activity of nucleases and proteases in cell extracts, which has been interpreted as derived from scaffold membrane protection [154]. Particular structure of replication complexes were reported for SARS-CoV-1 [158], with an interconnected DMV network but not of it to the cytoplasm (Figure 3). Virus nonstructural proteins nsp3, nsp4, and nsp6 seem to be involved in DMV development in SARS-CoV-1 virus strains [159]. Whether SARS-CoV-2 develops these lipid-based membranes is still unknown, although it may be expected that its replication process parallels that of SARS-CoV-1, MERS, and other beta-coronaviruses.

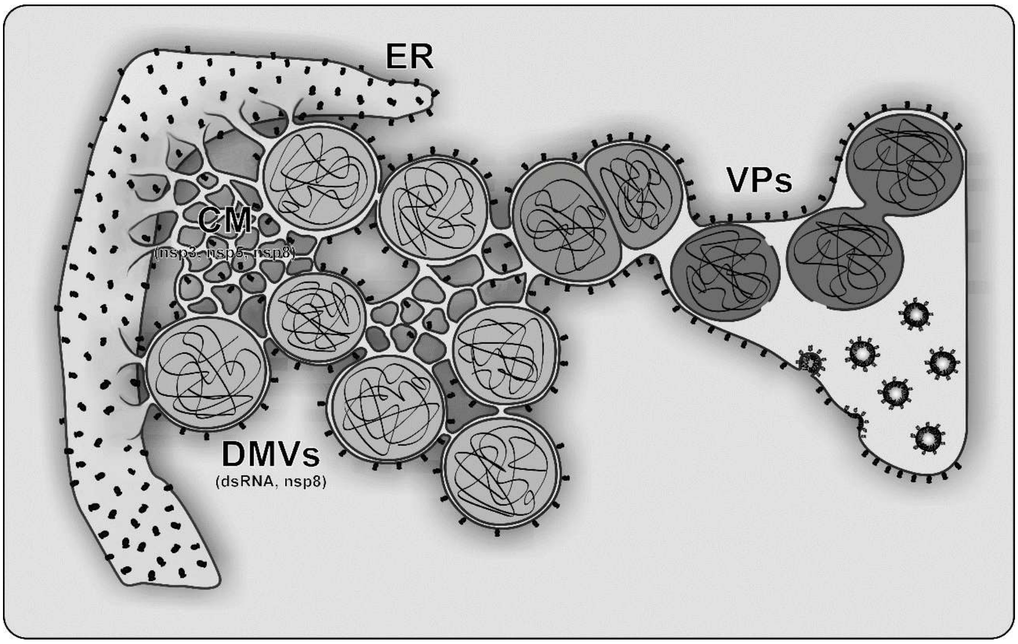

Figure 3. Model for DMVs and SARS-CoV-induced modified ER membranes triggering the reticulovesicular network. The model is drawn after electron tomography. CM, convoluted membranes; DMV, double-membrane vesicle; VP, vesicle packet; and ER, endoplasmic reticulum. From Knoops, K. *et al.*; SARS-coronavirus replication is supported by a reticulovesicular network of modified endoplasmic reticulum. *PLoS Biol.* 2008, 6, 1957–1974, doi:10.1371/journal.pbio.0060226.g009 [158].

Based on the mechanism of viral entry, which requires both ACE2 and the protease TMPRSS2, one obvious idea for the development of antivirals against SARS-CoV-2 would involve blocking either the host target ACE2 receptor or TMPRSS2, or both. In this regard, monoclonal antibodies targeting the S protein might impede virus entry, and it has been shown that a recombinant RBD portion of S protein from SARS-CoV conferred the highest immunogenicity versus other recombinant S protein fragments tested [160]. It would be expected that SARS-CoV-2 performs like SARS-CoV. Thus, hopefully these contributions will successfully develop neutralizing monoclonal antibodies against S protein soon. Figure 4 shows the virus mechanism of infection and summarizes multiple antiviral strategies that have shown promising results in previous research [161]. Novel antivirals that are being developed target virus-cell interaction, virus proteases, and virus replication [161].

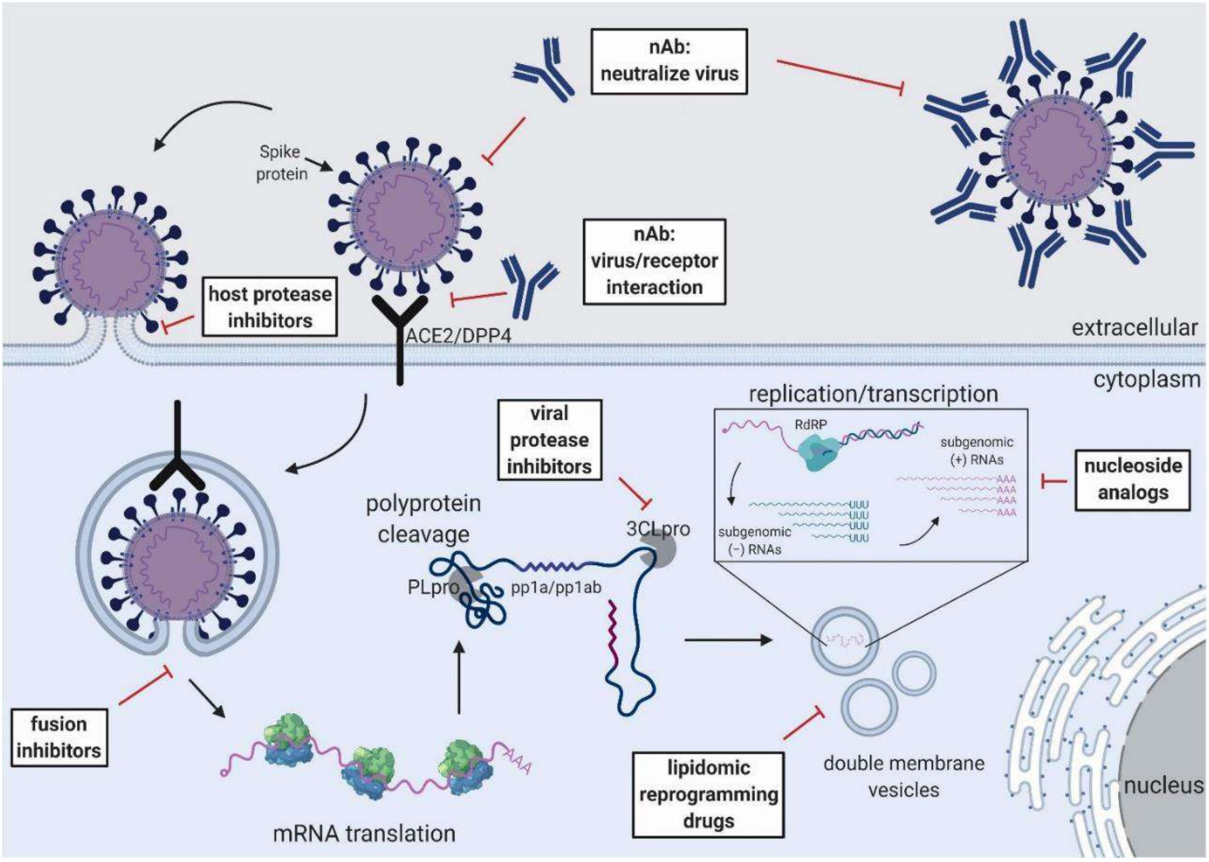

Figure 4. Representation of SARS-CoV-2 virus cell entry, replication and antiviral targets. Image from Tse LV, *et al.;* The current and future state of vaccines, antivirals and gene therapies against emerging coronaviruses. *Front. Microbiol*. 2020, 11:658. doi: 10.3389/fmicb.2020.00658 [161].

On the other hand, compounds clinically accepted for other indications that target these molecules have been reported. In this regard, it has been anticipated that several Janus kinase (JAK) inhibitors (e.g., baricitinib and ruxolitinib), could inhibit ACE2-mediated endocytosis [162]. Delivery of high concentrations of a soluble form of ACE2 (i.e., APN01) would putatively inhibit the virus entry into host cells. This strategy is currently in clinical trials [163].

The second molecule involved in viral entry, the TMPRSS2 protease, has been targeted by specific inhibitors such as camostat mesylate [164] and nafamostat mesylate [165,166], which have both been approved to treat other pathological conditions. No clinical trials specifically testing these drugs against SARS-CoV-2 in patients have been developed so far, although camostat mesylate prevented the lung cell entry of the virus *in vitro*, validating the use of this drug in the future.

Even though inhibition of the virus spike protein binding to the ACE2 receptor as well as neutralization by antibodies and further destruction by the innate immune cells of the virus are primary targets to consider when avoiding infection, action on the lipid dependence of virus replication has also been suggested [167–169]. In addition to the membrane scaffold rising and lipids necessary for virion coating, host cell lipid metabolism is also sequestered by the virus replication machinery for energy supply through β-oxidation in the mitochondria [167,168,170]-a fact that might explain the preference of SARS-CoV-2 for alveolar type II cells, which have abundant mitochondria. The fatty acid β-oxidation metabolic pathway is primarily dependent on palmitoyl-CoA. An exogenous supply of palmitic acid (C16:0) given to cells infected with HCoV-229E, another known human coronavirus strain, has been shown to promote virus replication in cell culture, but supply of linoleic acid (C18:2) or arachidonic acid (C20:4) suppressed virus replication [167]. Accordingly, action on lipid metabolism might help fight against COVID-19. A retinoid phenyl-derivative and RAR-α agonist (AM580 or NR1B1) an orphan drug known as tamibarotene [171], has been shown to interfere with the sterol regulatory element binding protein (SREBP) of the host cell [168]. This type of proteins is related to bHLH-zip transcription factors that have defined regulatory roles in lipid homeostasis of the host cell. Betulin, a triterpene with lupane structure isolated from bark of birch trees, was reported to inhibit SREBP maturation, thus reducing cholesterol and fatty acid syntheses [172]. It could be a candidate to be used against SARS-CoV-2.

Because of the emergency of the COVID-19 pandemic, a number of accelerated clinical trials have been launched worldwide with the aim of repurposing or repositioning approved drugs originally raised for the treatment of different diseases or medical conditions (https://covid-nma.com/living_data/index.php). They are assayed at the level of virus replication inhibition and are therefore evaluated on their ability to drop the virus load or to counteract the pathological effects in the patients at a mild to severe or critical stage. All these assays include compounds, such as N-heterocycles and benzyl derivatives, with lipid-related structure. Umifenovir (Arbidol, Figure 5), an indole derivative, is currently used in China and Russia as antiviral treatment against influenza infection, and it acts by inhibiting fusion between the viral envelope and the host cell membrane, thus preventing virus genome entry into the target cell. Remdesivir was developed to treat Ebola and Marburg virus infection; results on this compound are contradictory in diverse clinical trials, but it has been recently approved by the US administration to treat COVID-19 patients [173]. The combination of lopinavir and ritonavir (brand name Kaletra, Figure 5) is included in the WHO's List of Essential Medicines (hdl: 10665/325771) and currently used in patients with HIV infection; these compounds display protease inhibition properties, thus impeding virus replication. A clinical trial is going on in China to test the effect of a small antioxidant molecule, α-Lipoic acid (ALA), in COVID-19 patients with critical pathophysiological outcomes [174]; the authors claim that results are promising though statistical differences between the treated group and the placebo group were poorly significant; however, important concerns may be raised against the experimental setup and data analysis of this assay. Favipiravir (Figure 5), a fluorinated derivative of pyrazimecarboxamide currently used in Japan (brand name Avigan) to treat influenza and also assayed against other RNA viruses, is undergoing clinical trial in regard to SARS-CoV-2 (ClinicalTrials.gov Identifier: NCT04310228) in combination with an agonist of the interleukin IL-6 receptor, tocilizumab, to counteract the cytokine storm that has been reported in a number of COVID-19 infected patients as one of the most insulting outcomes; indeed, it has been reported that Germany has made stockpile of this product to treat COVID-19 in university hospitals [175]. A Canadian government funded clinical trial (COLCORONA) raised to check colchicine's ability to reduce inflammation (a factor leading to the ARDS, organ failure, and death that is observed in a number of COVID-19 patients) is recruiting volunteers in different countries [176]. The anti-parasite ivermectin has also been found to have applicability in virus load reduction [177], and clinical trials are under way. Intravenous administration of vitamin C is studied in two clinical trials (ClinicalTrials.gov Identifiers: NCT04323514 and NCT04363216) in order to take advantage of its antioxidant and anti-inflammatory properties together with promotion of lymphocyte development and function. Two immunomodulating drugs, fingolimod (trade name Gilenya) and methylprednisolone are tested in two clinical trials in China (ClinicalTrials.gov Identifiers: NCT04280588 and NCT04273321, respectively) for their potential to counteract the excessive inflammatory disease triggered by COVID-19 [150]. Two other clinical trials, NCT04291053 and ChiCTR2000030388, aim to explore the anti-inflammatory properties of plant extracts currently used in the Traditional Chinese Pharmacopeia, namely *Trametes robiniophila Murr* (Huaier) and *Salvia miltiorrhiza* (Chinese red sage). Further clinical trials are expected to be raised as new lipid-related molecules are discovered to prompt antiviral properties in *in vitro* assays in the near future.

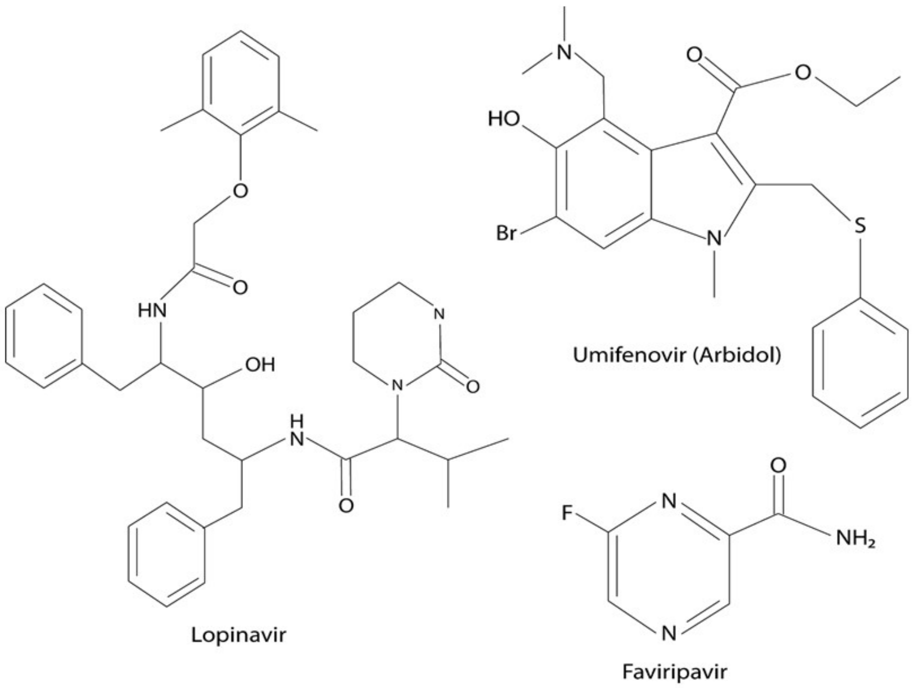

Figure 5. Structures of some compounds used in clinical trials for COVID-19.

Finally, from a nutritional point of view, it is recommended to keep healthy food habits, together with continuous moderate physical exercise, to keep the body at the best physiological stage possible in order to minimize the impact of viral infection and avoid co-morbidities. Daily uptake of proper doses of vitamins C and E, ω-3 and ω-6 PUFAs, zinc (Zn), and other essential nutrients from fruits, vegetables, nuts, and seeds-in addition to the necessary amount of proteins-may fortify immune system function and help individuals cope with ill-related stress, exhaustion of body energetic capacity, and side-effects of the clinical treatments [120,178].

Speeding-up drug discovery to treat COVID-19 is urgently required [179]. Since there is no specific antiviral drugs or vaccines against SARS-CoV-2, the main treatment strategy for COVID-19 is supportive care, which is supplemented by the combination of antibiotics, antivirals, corticosteroids, and convalescent plasma [2]. Natural compounds have played a crucial role in drug development against different diseases. Some natural products with anti-coronavirus activity are the major constituents of some common dietary supplements, are able to inhibit viral replication, and can interact with key viral proteins that are associated with virulence [180].

A very recent review published by Islam *et al*. has gathered information about some natural products that are able to block the virulence of coronaviruses through their inhibitory action against viral proteins such as chymotrypsin-like protease, papain-like protease, S protein and ACE2, in addition to the inhibitory effect against viral replication or virulence [181]. These authors concluded that the extracts with strongest effects against SARS-CoV *in vitro* were a crude extract from *Lycoris radiata* [182] and an extract obtained by the combination of *Rheum officinale* Baill. and *Polygonum multiflorum* Thunb, herbs widely used in Chinese Medicine/Pharmacopeia. The combined extract was found to inhibit the interaction of SARS-CoV (S) protein and ACE2 [183]. Pure compounds such as lycorine, homoharringtonine, silvestrol, ouabain, tylophorine, and 7-methoxycryptopleurine also showed strong inhibitory effects against different strains of coronavirus [180].

Table 3 shows natural compounds that have been identified by combined virtual screening and supervised machine learning, against three targets of SARS-CoV-2 (S protein, nucleocapsid protein, and 2'-o-ribose methyltransferase) [179]. Among these natural products, some of them bind with high affinity to more than one target protein (Table 3). More studies need to be carried out for further drug development focused on these compounds that bind to multiple targets. Natural products are known to bind to multiple targets, leading to an increased therapeutic efficacy and a decreased probability of developing resistance to one of the targets [179]. Amyrin, loniflavone, phillyrin, sericoside, tirucallin A, euphol, ilexsaponin B2 and B, forsythiaside, and tingenin B are natural compounds normally found in plants used in Traditional Chinese Medicine (TCM). In China, TCM is being used to treat 85 % of COVID-19 patients [2]. There is clinical evidence that TCM was an effective treatment in patients infected with SARS-CoV [2,184]. For instance, triterpene glycosides isolated from *Bupleurum* spp, *Heteromorpha* spp. and *Scrophularia scorodonia* interfere in viral attachment and penetration; phenolic compounds from *Isatis indigotica* and *Torreya nucifera* are able to inhibit SARS-CoV enzymes [184]. Because of the homology of SARS-CoV and SARS-CoV-2, TCM is expected to be a potential agent against SARS-CoV-2. In addition, the Chinese licorice plant *Glycyrrhiza uralensis* may have a potential antiviral effect against SARS-CoV-2. A licorice extract enriched in liquiritin has shown to prevent virus replication in cellular models [185]. Further studies are needed to confirm this effect in humans. To date, there are more than 50 clinical trials being carried out to assess the efficacy and safety of TCM as a potential treatment against COVID-19 [2].

Some of the candidate natural compounds identified *in silico* are present in food (Table 3). Hydrolyzable tannins (strictinin and punicalagin) are able to bind to the three studied targets of SARS-CoV-2 [179]. Pomegranate is the main source of this type of tannins. Antiviral properties such as viral growth inhibition, viral infectivity reduction, binding to host cell receptors, and virus structural damage have been reported for pomegranate in *in vitro* and cell-based assays [186]. Proanthocyanidins, which are able to bind to spike protein and nucleocapsid protein, are abundant in grape seeds, grapes, apples, nuts, sorghum, cinnamon, beans, and berries [187]. Elderberries are rich in bioactive anthocyanins [188]. Black elderberry *Sambucus nigra* has been traditionally used to treat cold and flu symptoms. *In vitro* studies have shown that a liquid elderberry extract has different inhibitory potentials towards influenza virus [188]. A recent meta-analysis of RCT has shown that supplementation with elderberry substantially reduced upper respiratory symptoms [189]. It would be of great interest to further study the influence of elderberry in COVID-19.

On the other hand, antiviral properties against other viruses have been reported *in vitro* and *in vivo* for the flavonoid rutin found in passionflower, buckwheat, tea, and apple [190,191]. Results from the *in silico* studies showed that 3,5-dicaffeoylquinic acid, 3,4,-dicaffeoylquinic acid, and 4,5-dicaffeoylquinic acid are able to bind to 2'-o-ribose- methyltransferase (Table 3) [179]. Chlorogenic acids from *Schefflera heptaphylla,* a popular TCM plant, and coffee beans have previously shown anti-viral properties against respiratory viruses in cell-based studies [192,193]. In addition, other compounds present in coffee, caffeine and caffeic acid, have been described as antiviral compounds since they directly inhibited influenza virus infection in cellular models [194]. Natural products can be an important complementary medicine in the fight against COVID-19 because of their natural origin, safety, and low cost compared to synthetic drugs [181].

Table 3. Candidate natural compounds against viral proteins of SARS-CoV-2 obtained *in silico* [179] and their natural sources.

Natural compound	**Binding site**	**Natural source**
Amyrin	Spike protein and nucleocapsid protein	*Protium kleinii, Protium heptaphyllum, Symplocos cochinchinensis, Alstonia boonei, Memecylon umbellatum* [195].
Loniflavone	Spike protein and 2'-o-ribose-methyltransferase	*Lonicera japonica* [196], *Caesalpinia pyramidalis* [197].
Procyanidin	Spike protein and 2'-o-ribose-methyltransferase	Apple, grape seeds and sorghum [187].
Phillyrin	Spike protein	*Forsythia suspensa* [198].
Proanthocyanidin	Spike protein and nucleocapsid protein	Grape seed, grapes, apple, nuts, sorghum, cinnamon, beans and berries [187,199].
Sericoside	Spike protein and nucleocapsid protein	*Terminalia sericea* [200].
Punicalagin	Spike protein, nucleocapsid protein and 2'-o-ribose- methyltransferase	Pomegranate [186].
Strictinin	Spike protein, nucleocapsid protein and 2'-o-ribose- methyltransferase	Cloves, guava, pomegranate and tea [201,202].
Rutin	Spike protein and 2'-o-ribose-methyltransferase	Passion flower, buckwheat, tea, and apple [190].
Tirucallin A	Spike protein, nucleocapsid protein and 2'-o-ribose- methyltransferase	*Euphorbia tirucalli* [203].
Euphol	Nucleocapsid protein	*Euphorbia tirucalli* [204].
Ilexsaponin B2 and B3	Nucleocapsid protein	*Ilex pubescens* [205].
Forsythiaside	Nucleocapsid protein	*Forsythia suspensa* [206].
Tingenin B	2'-o-ribose- methyltransferase	*Elaeodendron schlechterianum* [207] and *Maytenus* sp. [208].
Dicaffeoylquinic acids	2'-o-ribose- methyltransferase	Coffee, carrots and quinces [209].

Anti-inflammatory Supplements

A recent study from China showed that COVID-19 is associated with a cytokine elevation profile known as "cytokine storm syndrome", a hyperinflammatory state characterized by fulminant multi-organ failure and elevation of cytokine levels [210]. Medical experts state that more evidence is needed before making recommendations on the treatment options for cytokine storm [210]. Nevertheless, there are food bioactive compounds that may have the potential to be used as anti-inflammatory supplements for preventing or delaying the multi-organ failure that leads to precipitated death in COVID-19 patients.

Epidemiological, clinical, and nutritional studies support that dietary phenols improve human health by lowering risk and preventing degenerative diseases [211]. Dietary polyphenols reduce inflammation by acting as antioxidants and suppressing the pro-inflammatory signaling transductions [212]. A healthy nutrition can be combined with supplementation with natural multifunctional bioactive compounds with antioxidant, anti-inflammatory, and antiviral properties to prevent or treat COVID-19. In this context, increasing garlic consumption is recommended for its antioxidant and antiviral properties attributed to allicin, one of the main bioactive compounds present in garlic [213].

On the other hand, adding some spices to food, such as turmeric or ginger, should also be considered

[213]. Curcuma isolated from turmeric is known to have anti-inflammatory and immunomodulatory properties [214]. Based on COVID-19 death data, Rocha and Assis observed that COVID-19 deaths from high curcumin consuming countries (Indonesia, Malaysia, India, Pakistan, Bangladesh, Sri Lanka and Burma) are apparently very low compared to those from developed countries [215]. Since there is some consistency between epidemiological and laboratory findings given that curcumin apparently down-regulates ACE2 gene receptor expression [216], a major pathway in SARS-CoV-2 cell entry, it may be of help to fight against COVID-19 disease. Despite the theoretical concerns and uncertainty regarding the effect of renin–angiotensin–aldosterone system (RAAS) inhibitors on ACE2 and the way in which these drugs might affect the propensity for or severity of COVID-19, medical experts state that RAAS inhibitors should be continued in patients in otherwise stable condition who are at risk for or have COVID-19 [217].

Another multifunctional natural plant with potential to be used in the context of the COVID-19 pandemic is *Aloe vera*. This plant is composed by a large amount of bioactive ingredients, such as vitamins, minerals, amino acids, polysaccharides, and anthraquinones, and has antibacterial, anti-inflammatory, antioxidant, wound healing-promoting, and immunity-enhancing functions [218]. Furthermore, polysaccharides extracted from *A. vera* have shown significant anti-influenza virus properties *in vivo* and *in vitro* [219]. Interestingly, *Cannabis sativa*, also a plant with several multifunctional therapeutic cannabinoids [220,221], is being studied for the treatment and prevention of coronavirus infections. In an on-going study, cannabinoids are intended both to suppress the exacerbated immune response caused by COVID-19 and to interfere in the virus-cell interaction [222].

Anticoagulants

Besides inflammation, infection with SARS-CoV-2 and the resulting COVID-19 has been associated with a prothrombotic state, characterized by increases in fibrin, fibrin degradation products, fibrinogen, and D-dimers that have been associated with worse clinical outcomes [223]. To date, data are not sufficient to prove the safety and efficacy of using therapeutic doses of anticoagulants in patients with COVID-19 [223]. Therefore, further prospective trials are needed to define the risks and potential benefits of therapeutic anticoagulation in patients with COVID-19.

A very recent study concludes that important considerations for the preventive and therapeutic use of anticoagulant agents should be considered to mitigate the thrombotic events in these high-risk COVID-19 patients [224]. There are traditional herbs that have shown *in vivo* blood-thinning properties, such as *Korean Red Ginseng, Ganoderma japonicum, Cinnamomum cassia Presl, Glycyrrhiza uralensis Fisch* and *Laminaria japonica Aresch* [225], that may be considered in the context of the COVID-19 pandemic.

CONCLUSION

There is currently no evidence that food is a likely source or route of transmission of the virus. Unfortunately, the importance of the adapted nutrition and exercise in the recovery process is frequently underestimated. On the other hand, no data supporting that diet and dietary supplements can prevent, treat, or cure COVID-19 is already available. However, the nutritional conditions of the patients determine their immunological state and their capacity to face the disease and their recovery. Discharge from the hospital after SARS-CoV-2 infection is only the start of recovery. A healthy diet and some supplements can be helpful. In addition, some natural components present in edible plants and foods that have a positive effect in key biochemical events involved in COVID-19 illness, such as antioxidant, anti-inflammatory and anticoagulant supplements, and virus cell entry blocking agents, can also play a fundamental role in the patient's recovery.

Consequently, COVID-19 support initiatives including education programs about the role of a precise or personalized nutrition in patient care and nutrition are needed. Global research that defines nutrition guidelines for patients should be conducted with the collaboration of healthcare professionals, virologists, pharmacologists, functional foods experts who have a background in immunonutrition, microbioma, and chronic diseases, and the food industry.

To date, there is not an effective strategy to reduce the risk and treat a second wave of infection, which is expected. People must continue with social distancing, appropriate hygiene measures, and an adequate nutrition to avoid another lockdown. For a healthy, green recovery from COVID-19, we must come together to support all countries in following the global dietary guidelines proposed by WHO and FAO. Data so far collected seems to indicate that food rich in proteins, dietary fiber, probiotics, minerals, and vitamins should be included in the daily diet, providing a nutritional support for fighting COVID-19. Useful and updated information to achieve the goal is provided in the present chapter.

SUMMARY

- There is currently no evidence that food is a likely route of transmission for the virus. The WHO recommends keeping hands, kitchen and utensils clean, separating raw and cooked food to avoid cross-contamination, cooking food thoroughly, keeping food at safe temperatures (< 5 ºC or > 60 ºC), and using safe water and raw material.
- Two of the proposed treatment strategies for fighting COVID-19 are microecological and nutritional support.
- Gastrointestinal microbiota play an important role in the maintenance of the health and well-being of the host and exert beneficial effects on systemic metabolism and the immune system. A bal-anced intestinal microecology can reduce bacterial translocation and secondary infection. Intake of dietary fiber, prebiotics, probiotics, and synbiotics has been demonstrated to modify the com-position of the gastrointestinal microbiota and restore the microecological balance. This is of great importance in order to support the immune system and reduce the risk of respiratory infection.
- Nutritional status has influence on the individual risk for the progression of SARS-CoV-2 infec-tion.
    - Oral feeding is always preferred in hospitalized patients. When it is not possible, enteral feeding is preferred over parenteral feeding. Complete nutritional support to maintain muscle tone, microbiota, and intestinal immunity and to lower risk of infectious compli-cations must be guaranteed with enteral nutrition in critically ill patients with respiratory failure.
    - Patients with GI disorders may be particularly vulnerable during this pandemic because of the infection itself and/or the associated conditions, particularly stress. Obesity and diabetes are also risk factors for COVID-19. A healthy nutrition based on the Mediterra-nean diet is highly recommended to reduce the risk of obesity and diabetes and, therefore, the risk of COVID-19.
- Immunonutrition has the potential to be used to activate the host's immune response required for viral clearance and infection recovery. A healthy nutrition is very important before, during and after an infection.
    - Since protein malnutrition has been associated with a higher susceptibility to infection, it is of great importance to have a sufficient dietary intake of proteins to ensure the correct functioning of the immune system.
    - PUFAs have the potential to inactivate enveloped viruses, such as SARS-CoV-2. There-fore, these fatty acids should also be considered as a means to fight COVID-19 with.
    - Micronutrients that "contribute to the normal function of the immune system" include

copper, folate, iron, selenium, zinc and vitamins A, B12, B6, C and D. Supplementing diet with these micronutrients has a direct effect on the immune system at different levels.
  - Vitamin C is a well-known antioxidant that can counteract the reactive oxygen species caused by infection.
  - Vitamin D has the potential to reduce the risk of viral infections by acting on the physical barrier, cellular natural immunity, and adaptive immunity.
  - Selenium and zinc supplementation may be another strategy for preventing COVID-19 because of their effect on viral pathogenicity and the immune system.
- The SARS-CoV-2 cell entry depends on ACE2 and the protease TMPRSS2. Further studies on natural antivirals that interact with key viral proteins and inhibit viral replication are needed to speed up drug discovery to treat COVID-19.
- COVID-19 is associated with a cytokine elevation profile. Food bioactive compounds, mainly dietary polyphenols, may have the potential to be used as anti-inflammatory supplements for pre-venting or delaying the multi-organ failure and elevation of cytokine levels that leads to precipi-tated death in COVID-19 patients.
- Infection with SARS-CoV-2 has also been associated with a prothrombotic state. Use of natural anticoagulant agents should be considered when trying to mitigate the thrombotic events in these high-risk COVID-19 patients.

REVIEW QUESTIONS

1. Are foods considered a source of transmission of SARS-CoV-2?
   a. Yes, coronavirus has a high survivability on food products or packaging.
   b. No, currently there is no evidence to support transmission of SARS-CoV-2 associated with food.
   c. No, coronaviruses are generally thought to be spread from person to person through res-piratory droplets.
   d. Answers b and c are correct.

2. Which of the following “Food and Nutrition Tips during Self-Quarantine” is NOT recom-mended by the World Health Organization (WHO)?
   a. Keep kitchen and utensils clean.
   b. Do not cook raw food.
   c. Keep food at safe temperatures (< 5 ºC or > 60 ºC).
   d. Wash your hands frequently.

3. Are there food supplements to prevent, treat or cure COVID-19?
   a. Yes, dietary fiber, proteins and PUFAs prevent coronavirus infection.
   b. Yes, vitamin C and D have been proved to cure COVID-19.
   c. No, no data supporting that diet and dietary supplements can prevent, treat or cure COVID-19 is already available.
   d. Yes, a healthy nutrition based on the Mediterranean diet is one of the treatments of COVID-19.

4. What are the recommendations for a balanced intestinal microbiota?
   a. Supplementation with prebiotics, probiotics and synbiotics.

   b. Increase the intake of dietary fiber.
   c. Use fecal transplantation when there is a need to restore intestinal microecology.
   d. All of the above.

5. Which one of the following symptoms is not related to COVID-19?
   a. Blurry vision
   b. Cough
   c. Diarrhea
   d. Abdominal pain

6. Which of the following conditions is NOT a risk factor for COVID-19?
   a. Obesity
   b. Diabetes
   c. Liver disease
   d. Allergies

7. Which food is a source of vitamin D?
   a. Trout
   b. Red pepper
   c. Broccoli
   d. Chicken breast

8. The best natural antiviral candidate should interfere with:
   a. ACE2
   b. Spike protein S
   c. As many viral infection mechanisms as possible
   d. TMPRSS2

9. Further clinical studies are needed to find bioactive compounds present in foods and edible plants with:
   a. Anti-inflammatory properties
   b. Antioxidant capacity
   c. Antiviral properties
   d. All of the above

10. To keep the body at the best physiological stage possible in order to reduce the virus infection impact to the lowest level and avoid co-morbidities, you should NOT:
    a. Be physically active
    b. Drink alcohol
    c. Keep healthy food habits
    d. Drink water regularly

Answers: 1. (**D**); 2. (**B**); 3. (**C**); 4. (**D**); 5. (**A**); 6. (**D**); 7. (**A**); 8. (**C**); 9. (**D**); 10. (**B**)

List of Abbreviations:

Advanced glycation end products, AGEs; Acute respiratory distress syndrome, ARDS; α-Lipoic acid, ALA; Angiotensin-converting enzyme 2, ACE2; Barilla Center for Food &

Nutrition, BCFN; Blood-brain barrier, BBB; Central nervous system, CNS; Constipation-IBS, IBS-C; Coronavirus disease of 2019, COVID-19; Crohn's disease, CD; Docosahexaenoic acid, DHA; Diarrhea-IBS, IBS-D; Double membrane vesicles, DMVs; Eicosapentaenoic acid, EPA; Endoplasmic reticulum, ER; European Food Safety Authority, EFSA; European Society for Clinical Nutrition and Metabolism, ESPEN; European Society of Neurogastroenterology & Motility, ESNM; European Food Information Council, EUFIC; Food and Agriculture Organization of the United Nations, FAO; Fusion peptide, FP; Fermentable oligo-, di-, mono and polyols, FODMAPs; Gastrointestinal, GI; Human immunodeficiency virus, HIV; Glycosylated hemoglobin, HbA1c; Hypothalamic-pituitary axis, HPA; Intensive care unit, ICU; Inflammatory bowel diseases, IBD; Intravenous, IV; Irritable bowel syndrome, IBS; Janus kinase, JAK; Kawasaki disease, KD; Middle East respiratory syndrome coronavirus, MERS-CoV; Mixed-IBS, IBS-M; N^{ε}-carboxymethyl-lysine, CML; National Institute of Health, NIH; Nonsteroidal anti-inflammatory drugs, NSAIDs; Polyunsaturated fatty acids, PUFAs; Post-infectious IBS, PI-IBS; Randomized control trials, RCT; Receptor-binding domain, RBD; Recommended daily allowances, RDAs; Renin–angiotensin–aldosterone system, RAAS; Retinol activity equivalents, RAE; Severe acute respiratory syndrome coronavirus, SARS-CoV; Short chain fatty acids, SCFAs; spike protein, S; Sterol regulatory element binding protein, SREBP; T helper, Th1; Traditional Chinese Medicine, TCM; Tumor necrosis factor α, TNFα; United European Gastroenterology, UEG; Upper respiratory tract infections, URTIs; World Health Organization, WHO; Zhejiang University School of Medicine, FAHZU.

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