Review

Dietary supplements for the management of COVID-19 symptoms

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Keywords

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Summary

SARS-CoV-2, the etiological agent of COVID-19, caused a pandemic in 2020, which is only recently slowing down. The symptoms of COVID-19 range from cough to fever and pneumonia and may persist beyond the active state of the infection, in a condition called post-COVID syndrome. The aim of this paper is to review the relationship between COVID-19 and nutrition and to discuss to most up-to-date dietary supplements proposed for COVID-19 treatment and prevention. Nutrition and nutritional dysregulations, such as obesity and malnutrition, are prominent risk factors for severe COVID-19. These factors exert anti-inflammatory and proinflammatory effects on the immune system, thus exacerbating or reducing the immunological response against the virus. As for the nutritional habits, the Western diet induces a chronic inflammatory state, whereas the Mediterranean diet exerts anti-inflammatory effects and has been proposed for ameliorating COVID-19 evolution and symptoms. Several vaccines have been researched and commercialized for COVID-19 prevention, whereas several drugs, although clinically tested, have not shown promising effects. To compensate for the lack of treatment, several supplements have been recommended for preventing or ameliorating COVID-19 symptoms. Thus, it is critical to review the dietary supplements proposed for COVID-19 treatment. Supplements containing α-cyclodextrin and hydroxytyrosol exhibited promising effects in several clinical trials and reduced the severity of the outcomes and the duration of the infection. Moreover, a supplement containing hydroxytyrosol, acetyl L-carnitine, and vitamins B, C, and D improved the symptoms of patients with post-COVID syndrome.

COVID-19 pandemic

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the causative agent of coronavirus disease-2019 (COVID-19), which has been depicted as a public health emergency of global concern by the World Health Organization (WHO). The contagion probably started in Wuhan city, Hubei Province, China, in December 2019 and has infected over 428 million people and has caused the death of over 6 million (WHO website, accessed on March 29th, 2022). The high spread of SARS-CoV-2 is mainly because of its method of transmission: it spreads between people during close contact via small droplets produced during talking, sneezing, and coughing [1].

Coronaviruses

Coronaviruses are positive-sense single-stranded RNA viruses with crown-shaped peplomers and are members of the family *Coronaviridae*. Apart from the RNA, coronaviruses consist of spike protein (S-protein), envelope protein (E-protein), membrane glycoprotein (M-protein), and nucleocapsid protein (N-protein) [2]. The RNA of coronaviruses is 26-32 kilo bases (kb) in length and is the largest viral genome known. Specifically, the viral RNA of SARS-CoV-2 is 29 kb in length and encodes approximately 9860 amino acids [2, 3]. SARS-CoV-2 exhibits 50% similarity with the Middle East respiratory syndrome coronavirus (MERS-CoV) and 80% phylogenetic identity with severe acute respiratory syndrome coronavirus (SARS-CoV), the causative agents of global outbreaks in 2011 and 2002, respectively. Coronaviruses are divided into four main genera: α-coronavirus, β-coronavirus, γ-coronavirus, and δ-coronavirus. SARS-CoV-2, MERS-CoV, and SARS-CoV are all β-coronaviruses [2, 3].

The N protein forms the nucleocapsid and binds the RNA genome. This protein is involved in viral genome replication and in the host's cellular response to the virus [4]. The S protein is a type 1 membrane glycoprotein that is divided into two subunits, namely, S1 and S2. S1 is involved in receptor binding, whereas S2 mediates the fusion of viral and cellular membranes [2]. The M protein acts on the cellular membranes and facilitates the formation of new viral particles [5]. Finally, E protein is yet to be fully understood. This protein is highly expressed in host cells, but only a portion is incorporated into the new viral particles. E protein has three main roles: participation in viral assembly, action during the release of virions, and implication in viral pathogenesis [6, 7]. Binding of the S protein to its receptor initiates the attachment of the viral particle to the host cell. The specificity is permitted by the receptor binding domain of the S1 subunit, which varies depending on the coronavirus. SARS-CoV-2 binds to angiotensin converting enzyme 2 (ACE2). Following receptor binding, the cathepsin TMPRRS2 cleaves the S protein, and the viral membrane fuses with the cellular membrane [2].

Symptoms

SARS-CoV-2 infection is asymptomatic in 40% of the cases [8] but causes severe and very severe symptoms in 14 and 5% of the infected patients, respectively [9]. The most common symptoms are, in order, cough, weakness, taste disorder, myalgia, and fever [10], resulting in dyspnea and pneumonia. Additionally, severe complications, such as acute respiratory distress syndrome, acute heart injury, and secondary infections, are seen in the infected individuals, thus worsening the outcome of the infection. Symptoms are more severe in the elderly, while the infection and mortality rates are low in children [9]. Higher viral loads are found in symptomatic patients, thus contributing to a higher chance of secondary transmission of the disease [11]. The symptoms may appear gradually and can disappear spontaneously, with the incubation period lasting 3-15 days [9]. Severe symptoms are related to alterations in circulating leukocytes and to the activation of the cytokine cascade. SARS-CoV-2 antigens are presented by antigen-presenting cells, such as macrophages and dendritic cells, to the T cells, thereby leading to their activation, differentiation, and cytokine release [12]. The dysregulated secretion of IL-6, IL-1β, IL-10, and TNF-α alters the lung tissue and causes respiratory distress [13]. IL-6 appears to be relevant for the immunopathology of SARS-CoV-2. Indeed, IL-6 exacerbates the chronic inflammation at the base of COVID-19 [14, 15]. The cytokine storm can trigger systemic inflammation and result in multiple organ failure. Moreover, helper T cells can activate T-dependent B cells, thus stimulating the production of virus-specific antibodies, whereas cytotoxic T cells can kill viral-infected cells [16].

COVID-19 treatment and prevention

Several compounds have been tested against coronaviruses during the SARS-CoV pandemic and the MERS-CoV outbreaks. Although it was expected that one or more compounds could serve as an effective antiviral therapy, this approach has so far had little impact on the clinical outcomes of patients with COVID-19 globally [17]. Antiviral treatments are critical for people awaiting vaccines as well as for immunocompromised people who do not respond well to vaccination. Antiviral compounds can be divided into four main groups based on their mode of action: compounds that inhibit SARS-CoV enzymes, compounds that inhibit viral entry, interferons, and drugs that inhibit host processes involved in viral replication [17].

Compounds that inhibit SARS-CoV enzymes can be nucleoside analogs that act on the polymerase enzyme (remdesivir [18] and molnupiravir [19]) or can be directed against the proteases Mpro and PLpro (ebselen [20] and GC-376 [21]). Entry inhibitors act on the viral spike glycoprotein, and they can be monoclonal antibodies, single-domain antibodies, polyclonal antibodies, fusion inhibitors, or soluble ACE2. Interferons stimulate antiviral responses in human cells, slowing cellular metabolism, interfering with membrane formation, and inducing cytokine release. Finally, host-targeting compounds act on cellular proteins, signaling pathways, or cellular organelles exploited by viruses for their replication. These compounds can regulate host proteases, nucleotide and protein synthesis, and endosomal trafficking, whereas the mechanism of action of some compounds is unknown [17].

Over 20 vaccines against SARS-CoV-2 were approved all over the world by November 2021. Although their modes of action varied, they proved to exhibit a high efficiency in preventing COVID-19 [22-24]. Some vaccines contain nucleoside-modified messenger RNA, such as BNT16b2 developed by Pfizer/Biontech and mRNA-1273 developed by Moderna. Moreover, the vaccines can be vectors that contain SARS-CoV-2 antigens, such as AZD1222 developed by AstraZeneca and Sputnik V. Another group of vaccines comprises protein subunits, such as NVX-CoV2373. Finally, CoronaVac developed by Sinovac Life Sciences uses the conventional method of inactivated viruses [23, 24]. The outbreak of SARS-CoV-2 variants suggested the use of vaccine mixing, with a hope of increasing the effectiveness. This method has so far been successful, without severe side effects [23].

COVID-19 and nutrition

Nutrition is one of the main factors that influence health. Good nutrition can improve well-being and mitigate or even prevent most chronic diseases (e.g., diabetes, hypertension, and obesity). COVID-19 is no different, and the nutritional status is a crucial determinant for the prognosis of patients with the infection [25]. Upon observing mortality rates in population clusters, it becomes clear that people with comorbidities related to nutrition, such as type 2 diabetes and obesity, are at an increased risk for severe symptoms and mortality [26]. These risk factors are exacerbated by the consumption of the typical Western diet, which contains high amounts of saturated fatty acids, refined carbohydrates, and sugars [27, 28]. The Western diet chronically activates the innate and adaptive immune responses, thus stimulating a chronic inflammatory state. This dietary pattern activates macrophages, neutrophils, and dendritic cells via toll-like receptor 4. Moreover, the diet inhibits T and B lymphocyte function and maturation, possibly via oxidative stress [27]. Finally, Western diet lowers the host defense against viruses [26]. Bad nutrition is correlated with low social status. Minorities face barriers in embracing healthy food choices mainly because of a high rate of poverty and a decreased quality of healthcare [29]. As for the dietary recommendations, several countries have released their own guidelines through their health organizations, which are in agreement on most recommendations [25]. They encourage the consumption of whole grain, fruits, and vegetables. These foods provide vitamins, minerals, and water, which are important for a healthy status. Vitamins A, C, D, E, B_6, and B_{12} and zinc have a role in the maintenance of physical barriers as well as in the differentiation and functioning of innate immune cells [30]. Moreover, vitamins and micronutrients act as scavengers of reactive species of oxygen, thus decreasing oxidative stress [30]. An adequate hydration is also suggested [25]. Water is essential for several cellular and physiological processes, among which body temperature regulation and heart functioning are pertinent [31]. The Mediterranean diet has been proposed to be beneficial in preventing and ameliorating COVID-19 symptoms. The diet is characterized by a high intake of fruits, vegetables, legumes, olive oil, and nuts, which are anti-inflammatory foods that are rich in vitamins and minerals [16, 32]. These foods contain bioactive compounds, such as polyphenols, which exhibit anti-inflammatory, antithrombotic, and antioxidant properties. Hence, the Mediterranean diet has beneficial effects on immune health and offers protection against several infections as well as noncommunicable diseases [16].

COVID-19 and obesity

Obesity is among the most prominent risk factors for severe COVID-19, together with type 2 diabetes, cardiovascular diseases, chronic respiratory diseases, hypertension, and cancer [33]. The increased risk is attributed to several factors: impaired respiratory mechanics, low respiratory muscle strength and lung volumes, weakened immune system, and chronic basal inflammation [25, 33]. Chronic inflammation is a common feature in obesity and results from metabolic tissue stress and adipose tissue dysfunction. Hypertrophic adipocytes evolve in their proinflammatory state, stimulating the release of chemotactic mediators and the recruitment of leukocytes. The leukocytes, in turn, release proinflammatory cytokines, stimulating local and systemic chronic inflammation states [34]. Adipose tissue is involved in regulating the immunity owing to the release of leptin and adiponectin. Leptin influences hematopoiesis in the bone marrow and also regulates the expression of proinflammatory cytokines by innate immune response cells. Adiponectin stimulates inflammatory resolution because of its anti-inflammatory and insulin-sensitizing properties. Obesity has been shown to be correlated with decreased functioning and activation of T cells. Furthermore, excess fat increases the probability of developing cytokine storm, a severe complication of SARS-CoV-2 infection [35]. People with obesity show disrupted lung mechanics and physiology, reduced lung volumes, and decreased compliance and respiratory muscle efficiency [34]. Finally, ACE2, the SARS-CoV-2 receptor, is highly expressed in mature adipocytes; thus, its expression is high in people with obesity. Higher expression of ACE2 could contribute to the increased risk of severe complications in patients with COVID-19 who are obese [34]. Obesity prevalence varies between different countries (40% in USA, 20% in Italy, and 6.2% in China) and between different social status, being usually higher in poor people [28, 34]. Moreover, the pandemic influenced the physical activity and nutritional habits of people to a great extent. People reduced the level of their physical activity and preferred staying home; also, they consumed more of processed foods that are high in sodium, sugar, and fats. These new habits contributed to weight gain, increasing the risk of obesity and, thus, the risk of COVID-19 complications [34, 36].

COVID-19 and malnutrition

Another common risk factor for COVID-19 is malnutrition [1, 37]. Therefore, prevention, diagnosis, and treatment of malnutrition have been proposed to be included in the routine management of patients with COVID-19 [38]. Several physiological effects explain the role of malnutrition in worsening the outcomes of SARS-CoV-2 infection. Reduced adipose tissue causes a reduction in the release of adipocytokines and leptins, thus leading to immunosuppression. Malnutrition causes the T cells to produce less of IL-2 and IFN-γ and further impairs complement activation and induces thymic atrophy [39]. Malnutrition is common in elderly patients with COVID-19 because of several disease outcomes: inflammatory state, which catabolizes the muscle proteins, worsening frailty; gastrointestinal disorders, which reduce nutrient absorption; and anxiety, which lowers the appetite [1]. Moreover, diabetes, a typical risk factor for COVID-19, can influence the metabolism of macronutrients, thereby leading to malnutrition [40]. Considering the correlation of malnutrition with COVID-19 and the fact that prolonged hospitalization can cause a decrease in body weight and muscle mass, patients with COVID-19 should increase their protein and micronutrient levels by consuming oral nutrient supplements [1, 16].

COVID-19 and natural molecule supplementation

Supplements could be used to prevent COVID-19. Indeed, some vitamins and minerals improve immunity, and supplements are recommended for individuals who cannot meet dietary requirements owing to specific challenges [25]. As new therapeutics are still being explored and tested for COVID-19, natural molecules could fill the gap. Many natural molecules can influence the viral endocytic pathway and could be used to treat SARS-CoV-2 infection [3]. For instance, methyl-β-cyclodextrin is a macromolecule that can inhibit SARS-CoV-2 attachment to host cells. The molecule can lower the cholesterol content in the cell membranes and decrease viral infectivity, reducing the binding of the viral spike glycoproteins to the ACE protein. Furthermore, the molecule redistributes cholesterol among the raft and nonraft cell membrane regions and influences the expression of ACE2 [3]. Phytosterols, natural plant sterols with a cholesterol-like structure, mimic the action of methyl-β-cyclodestrin. These sterols lower the cholesterol level in the cell membrane and further reduce the infectivity of several viruses, such as hepatitis B virus and HIV [3]. Regular phytosterol intake can decrease LDL cholesterol by up to 10% [41]. Flavonoids are other natural molecules with antiviral properties. These molecules can block viral attachment and entry, inhibit viral replication, and disrupt the translation and processing of viral proteins. Examples include kaempferol, which inhibits coronaviruses by blocking the assembly and release of virions, and luteolin, which interferes with SARS-CoV entry by binding to the S2 protein. Flavonoids also regulate the main protease of SARS-CoV-2, but more research is needed to confirm this hypothesis [3]. Flavonoids have been proven to lower SARS-CoV-2 infectivity by targeting two-pore channels [42]. Myoinositol is the precursor for inositol-3-phosphate, a second messenger of G-protein coupled receptors. Myoinositol exerts beneficial effects in pneumology, promoting surfactant maturation. Furthermore, the molecule reduces the IL-6 cascade by acting on phophatidyl-inositol-3-kinase, thus inhibiting many other inflammatory processes. Catechins from green tea have also been recently tested and have been proven to inhibit viral replication, probably by acting on proteases [43]. Another natural molecule, hydroxytyrosol, has been tested against SARS-CoV-2. The molecule is extracted from olive oil and leaves and can modify the composition of the plasma membrane, thereby affecting viral entry. Hydroxytyrosol is antiviral, acting on the viral envelope, and anti-inflammatory, decreasing the production of IL-6 and TNF-α, which have been correlated with severe cases of COVID-19 [44-46]. Furthermore, acetyl L-carnitine can downregulate the production of proinflammatory cytokines and is an amino-acid-derived compound that transports long-chain fatty acids into the mitochondria, thus permitting oxidation and energy production. Acetyl L-carnitine is used for treating several diseases, including diabetes and neurological disorders, and it has been associated with the overall improvement of health and reduction of fatigue [47].

Vitamin D, which comes from the diet and is also synthetized by the human body, is a key molecule that offers protection against viral infections because the activation of its receptor regulates the innate and acquired immune systems. Vitamin D3 is produced in the skin by exploiting ultraviolet B radiation. Subsequently, vitamin D3 or oral vitamin D is converted to the active form calcitriol as a result of metabolic reactions in the liver and kidneys [48]. Respiratory epithelial cells express the vitamin D receptor, and vitamin D decreases the expression of IL-8. Furthermore, vitamin D increases the expression of antimicrobial substances by macrophages and other leukocytes. However, up to 50% of the population has vitamin D deficiency, which is linked to an increased susceptibility to acute viral infections [9]. Moreover, hypo-vitamin D is an independent risk factor in the overall population for total mortality [48]. Vitamin D status has been associated with the severity of COVID-19. A study has shown that countries south of latitude 35° north have a lower mortality rate, which can be attributed to increased vitamin D production [49]. Vitamin B has also been recently tested for COVID treatment owing to its beneficial effects on mitochondrial function, inflammation, digestion, and toxin elimination [47]. Finally, other molecules, such as vitamin C, zinc, and selenium, have also been proposed for COVID-19 supplementation mainly because of their antioxidant properties (Tab. I) [25].

A COVID-19 supplement was tested in 2020 and yielded promising results. Its main therapeutic molecules were α-cyclodextrin and hydroxytyrosol, and it was supplemented in the form of a spray. The supplement's *in vitro* antioxidant properties were proved, and it was found to be safe at all the tested doses [50, 51]. It was tested on a group of 149 healthy volunteers without any side effects, and none of them were infected by the virus although many were at a high risk for the infection because of their job. The supplement was also tested on positive subjects, who became negative in half the time of a control group of positive nontreated patients with a comparable viral load. Another new supplement composed of hydroxytyrosol, acetyl L-carnitine, and vitamins B, C, and D was proposed in 2021 for the treatment of post-COVID syndrome [47]. Although it was a pilot observational study, the use of the supplement increased the self-reported levels of energy and decreased self-reported tiredness and tension, with few side effects, in twenty subjects [47]. Despite the limitations of these studies, the final results suggest the use of these supplements to prevent SARS-CoV-2 infection, to reduce the viral load, to shorten the duration of the treatment, or to ameliorate the symptoms of post-COVID syndrome [47, 52].

Conclusion

Nutrition and nutritional dysregulations, such as obesity and malnutrition, seem to be involved in SARS-CoV-2

Tab. I. Natural molecule supplementation in COVID-19.

Molecules	Action mechanism	Outcomes
Methyl-β-cyclodextrin	Inhibit SARS-CoV-2 attachment to host cells	Reduction of the cholesterol content in the cell membranes and decrease viral infectivity
Phytosterols	Cholesterol-like structure, mimic the action of methyl-β-cyclodestrin	Reduction of the cholesterol level in the cell membrane and further reduce the infectivity of several viruses
Flavonoids	Block viral attachment and entry, inhibit viral replication, and disrupt the translation and processing of viral proteins	Reduction SARS-CoV-2 infectivity by targeting two-pore channels
Myoinositol	Reduces the IL-6 cascade by acting on phophatidyl-inositol-3-kinase	Inhibition og many other inflammatory processes
Hydroxytyrosol	Decreasing the production of IL-6 and TNF-α	Antiviral and anti-inflammatory: acting on the viral envelope
Acetyl L-carnitine	Downregulate the production of proinflammatory cytokines	Increase oxidation and energy production
Vitamin D	Activation of receptors that regulates the innate and acquired immune systems	Increases the expression of antimicrobial substances by macrophages and other leukocytes
Vitamin B	Mitochondrial function	Inflammation, digestion, and toxin elimination
Catechins	Acting on proteases	Inhibit viral replication

pathogenesis. Indeed, nutrition influences the immune system, modulating its responses. Several supplements have been proposed for preventing or ameliorating COVID-19 symptoms. Dietary supplements containing hydroxytyrosol reduced the severity of the infection and improved the symptoms of patients with post-COVID syndrome in many clinical trials. New research and clinical studies will help identifying other effective natural molecules against SARS-CoV-2 infection.

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Conflicts of interest statement

Authors declare no conflict of interest.

Author's contributions

MB: study conception, editing and critical revision of the manuscript; GB, MCM, FF, MF, SN, LL, GMT, GF, FB, PG, STC: literature search, editing and critical revision of the manuscript. All authors have read and approved the final manuscript.

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