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Review

Are Nutraceuticals Effective in COVID-19 and Post-COVID Prevention and Treatment?

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Abstract: The beginning of the end or the end of the beginning? After two years mastered by COVID-19 pandemic, we are now witnessing a turnaround. The reduction of severe cases and deaths from COVID-19 has led to an increasing importance of a new disease called post-COVID syndrome. Post-COVID is the term used to denote persistence of symptoms in those who have recovered from SARS-CoV-2 infection. Immune, antiviral, antimicrobial therapies, as well as ozone therapy, have been used to treat COVID-19 disease. Vaccines have then become available and administered worldwide to prevent the insurgence of the disease. However, the pandemic is not over yet at all, given the emergence of new omicron variants. New therapeutic strategies are urgently needed. In this view, great interest was found in nutraceutical products, including vitamins (C, D and E), minerals (zinc), melatonin, probiotics, flavonoids (quercetin) and curcumin. This review summarizes the role of nutraceuticals for the prevention and/or treatment of COVID-19 disease and post-COVID syndrome.

Keywords: post-COVID; Long-COVID; COVID-19; nutraceuticals; nano-nutraceuticals

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1. Introduction

COVID-19, namely Coronavirus Disease, is today's most infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The virus is an enveloped, single-stranded, positive-sense ribonucleic acid (RNA) viruses and belongs to the family Coronaviridae (subfamily Coronavirinae) [1]. It was first detected on 12 December 2019 in Wuhan City, Hubei Province, China [2]. Since then, it quickly spread to other countries round the world, becoming a threat to global health [3]. The pandemic breakout has attained worrisome proportions, stunning national healthcare systems into inaction and necessitating worldwide deployment. Its alarmingly quick transmission and a considerable percentage of morbidity and mortality made the World Health Organization recognize it as a pandemic on March 11, 2020 [4]. Globally, on 5 Aug 2022, there have been 579.092.623 confirmed cases of COVID-19, including 6.407.556 deaths, reported to WHO.

As of 2 Aug 2022, a total of 12.308.330.588 vaccine doses have been administered [5]. COVID-19 is now recognized as a multi-organ disease with a broad spectrum of manifestations. The first variants of COVID-19 [6] led to fever, dry cough, fatigue, and myalgia, and for some, bacterial superinfection in most case of COVID-19 patients. In severe cases, symptoms progress to COVID-19-associated acute respiratory distress syndrome (CARDS) and respiratory failure requiring intensive care unit (ICU)-level care. After the COVID-19 era, that is not finished at all yet [7], with new variants emerging (including BA.4 and BA.5 omicron) [8,9], we have now entered the post-COVID era. Fortunately, today in most cases, COVID-19 has become very similar to a flu-like illness. Mainly, the hassle of quarantine remains, as well as the fear of infecting weak people, with previous pathologies (o diseases) or people who are not vaccinated. What worries the most is what will happen next, indeed a lot of the individuals, recovered from COVID-19, have developed persistent or new symptoms lasting weeks or months, a condition that is called "Post-COVID syndrome" [10]. The number of people suffering from symptoms after SARS-CoV-2 infection is dramatically increasing. They report a myriad of symptoms affecting different systems: neurocognitive post-COVID (brain fog, dizziness, loss of attention, confusion), autonomic post-COVID (chest pain, tachycardia, palpitations) [11], gastrointestinal post-COVID (diarrhea, abdominal pain, vomiting), respiratory post-COVID (general fatigue, dyspnea, cough, throat pain), musculoskeletal post-COVID (myalgias, arthralgias), psychological-related post-COVID (post-traumatic stress disorder, anxiety, depression, insomnia), and other manifestations (ageusia, anosmia, parosmia, skin rashes) [12]. Post-COVID syndrome is increasingly recognized as new clinical entity in the context of SARS-CoV-2 infection and has been defined a second pandemic [13]. This disease is not easy to study, since symptoms usually seen in post-COVID can also be present in the general population that has been exposed to other infectious agents or to a catastrophic situation, like the current pandemic, and be mostly related to lockdown, unemployment, anxiety, fear, social alarm, or others. Furthermore, in most cases it is very difficult to trace the variant responsible of the onset of the disease, also because the post-COVID syndrome becomes evident after some time, even long after the disease has ended. Thus, it is difficult to decide if "possible" and "probable" cases must be considered as post-COVID symptoms. Moreover, post-COVID syndrome may differ on the basis of the variant of COVID-19 that has determined the disease. Fortunately, the prevalence of post omicron COVID-19 condition is lower than that of the other strains [14]. Given the number and heterogenicity of symptoms attributable to post COVID and the emergence of new variants, including the most recent BA.4 and BA.5 [15], several studies are still addressed to the prevention and treatment these diseases. Regarding post-COVID syndrome, the first variants usually led to pneumonia-pulmonary fibrosis in post-COVID patients [16]. Now, post-COVID patients complain asthenia, general fatigue, dyspnea, and weakness. Currently, several vaccines and drugs are being evaluated for the prevention and treatment of COVID-19 [17,18]. New therapeutic strategies have also been suggested, including repurposing [19,20] and several effective treatment research trials are currently underway. Other developing non-traditional drug development methods include physical exercise [21], yoga and meditation [22], faster and less expensive methodologies to discover new effective anti-SARS-CoV-2 medicines. Nutraceuticals have a proven ability of immune-boosting, antiviral, antioxidant, anti-inflammatory effects [23]. These include Zn, vitamin D, vitamin C, curcumin, cinnamaldehyde, probiotics, selenium, lactoferrin, quercetin, and others [24]. Therefore, their use provides possible alternative prophylactic and therapeutic support along with standard therapies for COVID-19 in adults and children [25–27]. Moreover, dietary habits and lifestyle changes may influence the course of the disease [28,29]. The aim of this review is to examine the role of nutraceuticals, prebiotics and probiotics and diet supplementation in the prevention and treatment of SARS-CoV-2 viral infection and post-COVID syndrome.

2. Post-COVID syndrome

Currently, there is no universally accepted definition of post-COVID syndrome. It was defined for the first time by Greenhalgh et al. [30] as COVID-19 associated illness extending for more than three weeks after the onset of symptoms, and chronic COVID-19 as persistent symptoms extending beyond 12 weeks after the onset of symptoms [31]. Depending upon the duration of symptoms, post COVID or long COVID was divided into two stages-post acute COVID where symptoms extend to more than 3 weeks, but less than 12 weeks, and chronic COVID where symptoms extend beyond 12 weeks (Figure 1) [30].

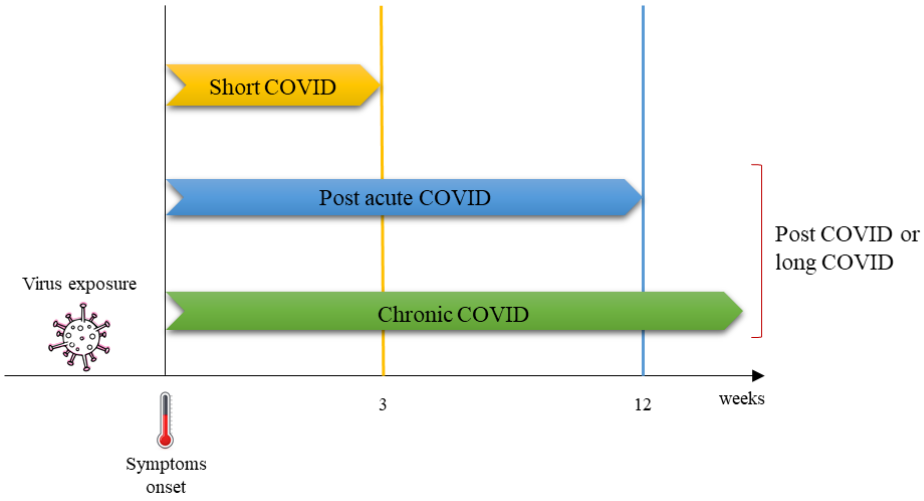

Figure 1. First classification of post-COVID [30].

Then, several studies reported new terms, such as Long-COVID, Long Haulers and Chronic- COVID: thus, a new classification was needed [32]. An integrative classification of post-COVID symptoms was proposed, which lasted to more than 24 weeks, and is: Post-Acute COVID (symptoms from week 5 to week 12), Long post-COVID (symptoms from week 12 to week 24) and Persistent Post-COVID (symptoms lasting more than 24 weeks) (Figure 2).

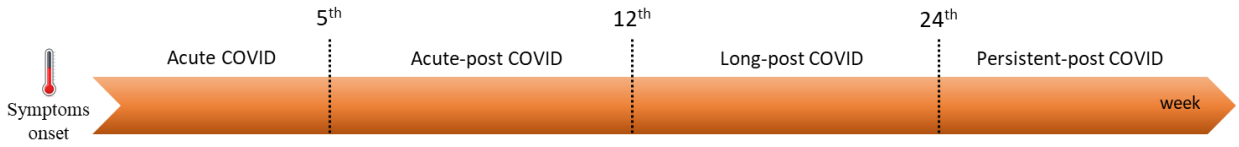

Figure 2. Classification of post-COVID as reported by Fernandez-de-Las-Penas et al. [12]

The definition of "Long-COVID" is not always the same. The terms "Post-COVID syndrome", "Long COVID" or "Long Haulers" are sometimes used interchangeably to mean the same thing [33,34]. However, this is not exactly true. In most cases, Long-COVID is used to mean post-acute COVID [35], or post-acute sequelae of COVID-19, a condition characterized by the persistence of COVID-19 symptoms beyond 3 months [36]. However, some authors use the term "Long COVID" to indicate symptoms extending beyond 12 weeks from initial symptoms, which is chronic COVID-19 [37]. In our opinion, it is better to refer to the classification of post-COVID to avoid mistakes.

3. Nutraceuticals and dietary supplements against COVID-19 disease and post-COVID syndrome

The term nutraceutical is a combined terminology for nutrition and pharmaceuticals that popularly reflects the food or its part that has medicinal benefits on health. Nutraceuticals comprise active phytochemicals isolated from plants, dietary supplements, and

functional foods with medicinal properties [38,39]. Nutraceuticals have numerous advantages over synthetic drugs, as they are generally easily accessible and have negligible side effects if administered at the already used and tested dosages. Nutraceuticals include "immune boosting" foods and nutrients, which are those that can regulate the immune system, as zinc, vitamins, curcumin, resveratrol and selenium [40]. Considering COVID-19, where there is a lack of effective preventive and curative drugs available and where the mutants of the SARS-CoV-2 spread enormously affecting a great number of populations, one of the crucial weapons is a robust immune system. The most common therapies for COVID-19 are represented by antiviral agents, antimicrobials, anti-inflammatories, immunomodulators, angiotensin II receptor blockers, bradykinin B2 receptor antagonists and corticosteroids [41]. Along with conventional treatment strategies, the additional use of nutraceuticals has been considered possibly beneficial in the treatment and/or prevention of COVID-19 and post-COVID-19 [42–47]. Higher age, obesity, weakened immune system, and underlying diseases such as diabetes mellitus are the known risk factors associated with COVID-19 disease severity [48]. For these reasons, the role of nutraceuticals, probiotics, and supplements in reducing the risk of SARS-CoV-2 infection or mitigating the symptoms of COVID-19 has been widely investigated [49]. The use of nutraceuticals for COVID-19 has been often studied in relation to their interaction with angiotensin-2 converting enzyme (ACE2), the functional receptor of SARS-CoV-2 [50]. The binding between SARS-CoV-2 spike glycoprotein with ACE2 receptor leads to ACE2 downregulation and the resulting enhance in the level of angiotensin-2 (Ang II) and augmentation of Ang II/Ang II receptor type 1 (AT1R) axis activation that are associated with proinflammatory responses [51]. Consequently, natural compounds that can reduce the ACE2 activity may be useful in the treatment of the patients with COVID-19. SARS-CoV-2 utilizes its spike glycoprotein which has a homotrimeric structure to enter the host cells. This spike glycoprotein receptor-binding domain (RBD) interacts with the ACE 2 on the host cells. The recent Omicron variant has caused great concern with 32 mutations in the spike glycoprotein including unprecedented 15 mutations in the RBD [52]. Numerous molecular modeling docking studies on natural compounds have been carried out to assess their anti-ACE2 activity through their ability to prevent RBD–ACE2 interaction [53–55]. Laboratory and clinical data support the possible benefits that some bacterial and molecular products may exert on the immune response to respiratory viruses and their regulatory role in systemic inflammation or endothelial damage, which represent two crucial aspects of COVID-19 [56]. In this regard, the use of probiotics, prebiotics, and postbiotics has been also studied in the fight against SARS-CoV-2 infection [57]. There is clinical evidence that modulation of the intestinal microbiota through the use of these supplements might positively control COVID-19 progression. Some of the main findings were represented by the decrease in the duration of the disease and the severity of symptoms as fatigue, olfactory dysfunction and breathlessness, nausea and vomiting and other gastrointestinal symptoms of COVID-19 disease [58]. Vitamin C, vitamin D and vitamin E, flavonoids, prebiotics, probiotics, zinc and melatonin are the principal dietary supplements that are currently being evaluated for their use in COVID-19 [59]. Moreover, recent studies showed that the administration of high doses of the vitamins C, D, and E, in addition to omega-3 fatty acids and zinc may potentially have a clinical benefit for hospitalized patients [60]. Due to their immunomodulatory and antioxidant effects, these supplements may reduce the viral load, the disease severity, and hence the hospital stay. Moreover, the lack of these nutritional substances is associated with higher susceptibility to infections and dysfunction of the immune system. However, there are no explicit randomized controlled trials (RCTs) on the role of vitamin supplementation in the context of COVID-19 infection, neither in the prevention nor in the treatment. Therefore, clinical trials are needed to confirm the role these dietary supplements may have for COVID-19 prevention and treatment [61,62]. The use of nutraceuticals in post-COVID syndrome is currently under study. Several reports are described in adults [63,64], older [65] and children [66,67], for different

symptoms, also including olfactory loss [68], telogen effluvium [69], depression and anxiety [70].

3.1. Vitamins

Vitamins are micronutrients that perform an essential role in the proper structuring and functioning of proteins as well as in several physiological processes and signaling pathways in the body. The term "micronutrients" refers to the fact that these nutrients are required in small, usually microgram, amounts daily. However, in critical illness, the requirements for these micronutrients can increase significantly [71]. Their usefulness in COVID-19 patients has been demonstrated and recent studies are addressed to the investigation of their mechanism of action [72].

3.1.1. Vitamin C

Vitamin C, also known as ascorbic acid (Figure 3), is a powerful molecule with pleiotropic functions. It has been demonstrated to play an important part in immune function; it serves as antioxidant, antiviral, anticancer and exerts antithrombotic effects among many other physiological benefits [73].

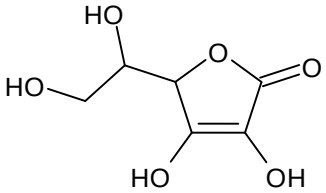

Figure 3. Structure of vitamin C

At pharmacological doses, vitamin C may be beneficial to patients affected by CARDS and other respiratory illnesses. In addition, high-dose intravenous vitamin C (HDIVC) may be beneficial in patients with different viral diseases [74]. Vitamin C exerts its antiviral properties by supporting lymphocyte activity, increasing interferon-α production, modulating cytokines, reducing inflammation, improving endothelial dysfunction, and restoring mitochondrial function. High dose of vitamin C has the potential to have a virucidal effect since it inhibits viral growth when multiplied *in vitro* [75]. Current evidence describes the possible use of vitamin C in the prevention or treatment of patients with SARS-CoV-2 infection [76,77]. Its use has been suggested used as a primary preventative measure for susceptible populations such as the elderly, those suffering from comorbidities, and healthcare workers with higher exposure risks [78]. Vitamin C can suppress the cytokine storm, reduce oxidative stress, decrease inflammation, prevent thrombotic complications, and diminish alveolar and vascular damage [79]. However, the negative effect of vitamin C is that it can result in urinary stones or nephropathies [80]. The recently reported randomized trial in sepsis demonstrated poorer outcome in those patients receiving vitamin C [81]. Other studies are ongoing, or have recently finished, to evaluate the use of vitamin C in the treatment of COVID-19 (Table 1). A double-blind RCT by Majidi et al. (2021) [48] evaluated the effect of vitamin C supplementation on the biochemical and pathological parameters and survival duration in critically ill patients with COVID-19. The daily supplementation of 500 mg vitamin C for 2 weeks significantly increased the survival duration of the COVID-19 patients during the post-supplementation period. This study also demonstrated that the vitamin C supplementation had no adverse effect on the kidney function, arterial blood gas parameters and other serum electrolytes including sodium, calcium, and phosphorus. In one of the first RCTs, Liu et al (2020) [82] had hypothesized that HDIVC could be added to the treatment of CARDS and multiorgan dysfunction related to COVID-19. The authors predict that HDIVC could suppress cytokine storms caused by COVID-19, help to improve pulmonary function and reduce mortality for patients with COVID-19. Furthermore, HDIVC showed advantages in terms of

stability, availability, safety and cost compared with other treatments. Zhao et al. (2021) [83], in a retrospective case series study, evaluated the beneficial effects of HDIVC in patients with COVID-19 pneumonia in severe condition. Twelve patients were enrolled: six severe and six critical. All patients received high-dose intravenous vitamin C (average 163 mg/kg in severe patients), but on average, about a 10% higher dose was given to critically ill patients. Patients had significant improvements in C-reactive protein (CRP), lymphocyte count, and CD4. After HDIVC therapy, greater improvements were observed in severe patients than in critical ones. HDIVC (11 g per day average or more for a 70-kg person) was shown to be beneficial in terms of inflammatory response and immune and organ function for the treatment of COVID-19 patients. In a retrospective before-after case-matched clinical study, Zhao et al (2021) [84] studied the outcome and clinical courses of patients with moderate COVID-19 treated with an HDIVC protocol (100 mg/kg/day) for seven days from admission with a control group treated without the HDIVC. The HDIVC and control groups each comprised 55 patients. For the primary outcomes, there was a significant difference in the number of patients that evolved from moderate to severe type between the two groups. There was a substantial decrease in the number of patients in the HDIVC that evolved from moderate to severe disease ($p = 0.03$). Additionally, compared to the control group, there was a shorter duration of systemic inflammatory response syndrome (SIRS, $p = 0.0004$) and lower SIRS occurrence ($p = 0.0086$) during the first week. A recent placebo-controlled pilot study by Zhang et al. (2021) of high dose intravenous ascorbate in 56 critically ill COVID-19 patients showed significantly reduced mortality [85]. The trial was carried out in 3 hospitals located in Hubei, China, and used a daily dose of 24 g of ascorbate. HIDIVC did not affect ventilation-free days, but possibly provided a potential signal of benefit in oxygenation for critically ill patients with COVID-19, with an improvement in PaO_2/FiO_2 ratio.

Table 1. Studies regarding the use of vitamin C in the treatment of COVID-19

Dose of Vitamin C	N° of participants	Duration of Intervention	Outcome of Interest	Ref.
500 mg	120 hospitalized critically ill patients with COVID-19	14 days	a higher mean survival duration compared with that of the control group (8 vs. 4 days, $p < 0.01$)	[48]
24 g of IVC	308 adults diagnosed with COVID-19 and transferred into ICUs	7 days	ventilator-free days in the 28 days since admission to the ICU. Changes in SOFA scores, in plasma biomarkers of inflammation and in pulmonary infection.	[82]
162.7 mg/kg for severe and 178.6 mg/kg for critical patients.	12 COVID- 19 patients (six severe and six critical)	3 months	improvement of CRP, body temperature, lymphocyte counts, $CD4^+$ T cell counts, P/F and SOFA score	[84]

100 mg/kg/day and a rate of 1 g/h for 7 days recovery	55 moderate COVID-19 patients	1 month	a shorter duration of SIRS (P = 0.0004); lower CRP levels (P = 0.005) and higher number of $CD4^+$ T cells from Day 0 (on admission) to Day 7 (P = 0.04)	[84]
24 g of IVC	56 critical COVID-19 patients	7 days	improvement in P/F ratio (P = 0.01); decline in IL-6 (P = 0.04)	[84]

3.1.2. Vitamin D

Over the last decade, the key role of vitamin D in inflammation and immunoregulation has been increasingly recognized [86]. The prognostic and therapeutic role of vitamin D in COVID-19 has been widely studied [87–89]. Recently, clinical trials and *meta*-analysis studies regarding the role of vitamin D in preventing COVID-19 infection, progression and severity, have been reported [90,91]. Vitamin D deficiency seems to aggravate COVID-19 [92]. The severity of hypovitaminosis D appears to relate to the prognosis of COVID-19 since COVID-19 cases with hypovitaminosis D were more prone to experience severe COVID-19 (relative risk 1.59 with P = 0.02 if vitamin D insufficiency < 30 ng/mL) [93]. Moreover, hypovitaminosis D was found to be associated with greater COVID-19 mortality risk (IRR = 1.56 with P < 0.001 if vitamin D deficiency; P = 0.404 after adjustment [94]. Vitamin D is not only a fat-soluble vitamin but also a steroid hormone, playing a vital role in modulating the immune system together with maintaining serum calcium homeostasis [95]. Vitamin D can be derived from supplements in the form of vitamin D2 (ergocalciferol) or D3 (cholecalciferol) (Figure 4). Sun exposure remains the main source of vitamin D, whereby skin exposure to ultraviolet B (UVB) radiation results in the conversion to its hydroxylated metabolites, through the activity of specific hydroxylases. Among these, calcifediol (25-hydroxyvitamin D3) and calcitriol (1,25-dihydroxyvitamin D3) are the immunologically active forms.

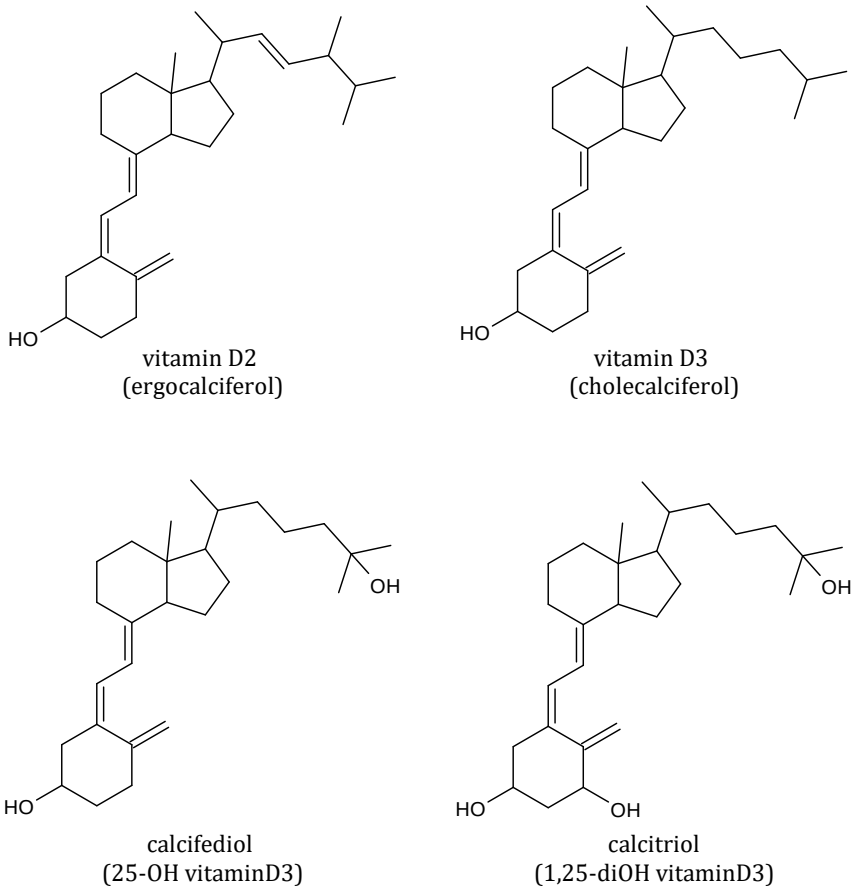

Figure 4. Structures of vitamin D2, D3 and its main metabolites

By binding to the vitamin D response elements (VDRE) located in the promoter region of various genes, it may prevent COVID-19 adverse outcomes by regulating the renin-angiotensin system (RAS), the innate and adaptive cellular immunity, the physical barriers, and the host frailty and comorbidities. First, vitamin D reduces pulmonary permeability in animal models of CARDS by modulating the activity of RAS and the expression of the ACE2 [96]. SARS-CoV-2 infection downregulates ACE2 activity and accumulates toxic Ang II and metabolites, which subsequently develop into CARDS or fulminant myocarditis. Vitamin D mitigates lipoprotein (LPS)-induced acute lung injury by inducing the ACE2/Ang 1–7 axis and by suppressing both renin and the ACE/Ang II/AT1R axis [97]. Further, vitamin D modulates multiple mechanisms of the immune system to contain the virus including reduction of the entry and replication of SARS-CoV-2, decreases concentration of pro-inflammatory cytokines and increases levels of anti-inflammatory cytokines, enhances the production of natural antimicrobial peptide and activates defensive cells such as macrophages that could destroy SARS-CoV-2 [98,99]. Accordingly, there is a growing number of data showing an association between serum calcifediol and the different clinical outcomes of SARS-CoV-2 infection, particularly concerning COVID-19 related severity and mortality, as further underlined by some pilot meta-analysis studies. Since the publication of these studies, several new data have been released, that have cast some light even on the calcifediol thresholds defining vitamin D status possibly associated with the SARS-CoV-2 infection susceptibility and COVID-19 related outcomes [100]. A preliminary study that evaluated the antiviral potential of various molecules against SARS-CoV-2 documented the inhibitory effect of calcitriol on the nasal epithelium infected with the virus [101]. In addition, a study investigating the targets of *SARS-CoV-2* using genomics guided tracing has also confirmed the role of vitamin D in COVID-19. Glinsky (2020) explored vitamin D as a putative repressor of ACE2 expression and found

that vitamin D appeared to inhibit ACE2 expression in human bronchial smooth muscle cells by means of the VDR and other transcription factors. Of the 332 genes coding for the prey proteins of *SARS-CoV-2*, vitamin D affects the expression of 84 (25%). These prey proteins carry out a host of cellular functions which are disrupted by infection. This suggests that, in addition to inhibiting the expression of ACE2, vitamin D is able to disrupt the function of 19 out of 27 (70%) *SARS-CoV-2* proteins [102]. Annweiler et al. (2020) [92] hypothesized that high-dose vitamin D supplementation could improve the prognosis of COVID-19 in high-risk older patients. The first reports indicated that cases with COVID-19 had, on average, significantly lower calcifediol levels compared with negative patients (respectively, 11.1 ng/mL versus 24.6 ng/mL, $P = 0.004$) [103]. Similarly, significant inverse correlations were found in 20 European countries between the mean serum calcifediol concentrations and the number of COVID-19 cases, as well as with mortality [104]. A RCT study showed that a 5000 IU daily vitamin D3 supplementation for 2 weeks reduces the time to recovery for cough and gustatory sensory loss among patients with sub-optimal vitamin D status and mild to moderate COVID-19 symptoms. This was also seen from their decreases in BMI and IL-6 levels over time [105]. A randomized prospective open-label study in India of 87 patients with COVID-19 and hypovitaminosis D also reported that supplementing vitamin D in addition to standard care improved inflammatory markers significantly. In the patients that received 60,000 IU of daily supplemental vitamin D for eight days, levels of C-reactive protein, lactase dehydrogenase, IL-6, ferritin, as well as neutrophil to lymphocyte ratios showed significant improvement compared to patients receiving no supplements [106]. Further studies have revealed that using Vitamin D 200,000–300,000 IU bolus and then reducing to a maintenance dose, lessens the severity and risk of contracting COVID-19 [107]. The issues and morbidities associated with COVID-19, such as pneumonia/CARDS, inflammation, inflammatory cytokines, and thrombosis, can be ameliorated by vitamin D [108]. Furthermore, severe COVID-19 patients are often predisposed to bone fragility and osteoporosis, that can be related to vitamin D deficiency and altered platelet-related parameters. Thus, the association between vitamin D and PLT influencing the risk and outcome of COVID-19 disease has been studied [109]. Finally, hypovitaminosis D was found to be associated with greater COVID-19 mortality risk (IRR = 1.56 with $P < 0.001$ if vitamin D deficiency; $P = 0.404$ after adjustment) [110]. Most of the abovementioned reasons and evidence reinforce the use of supplementation with vitamin D as potential prophylaxis against COVID-19, especially considering the tolerability and excellent safety profile offered by even high doses of vitamin D. Recently, it has been speculated that vitamin D may play a complementary role in the development of vaccine efficacy [111]. Actually, vitamin D deficiency (calcifediol below 50 nmol/L) is still widespread despite its important role [112].

3.1.3. Vitamin E

Supplementation with nutrients that are a source of vitamin E has been used to control nutritional deficiencies, obesity and promote adequate nutritional status in COVID-19 patients by possibly improving immune response and antioxidant status during the infectious phase [113]. The term vitamin E refers to a class of liposoluble compounds, comprising tocopherols and tocotrienols, all presenting a hydroxylated chromanol ring attached to a hydrophobic phythyl side chain. Despite the existence of multiple tocopherol and tocotrienol vitamers, the attribute of 'vitamin' is only given to α-tocopherol [114]. α-TOH is a lipid-soluble antioxidant required for the preservation of cell membranes, as it acts as a defense against oxidative stress [115]. It traps reactive species generated by oxidative stress, such that its antioxidant and therapeutic properties may be applied to prevent the oxidative explosion associated with SARS-CoV-2 [116]. Even though vitamin E has very little evidence of antiviral actions, it is able to reduce inflammatory cytokine production, promote T cell proliferation and differentiation and influence inflammatory responses in different tissues, including the lungs, via direct scavenging oxidative stress and

modulation of oxidative eicosanoid pathways and prostaglandin synthesis [117]. Vitamin E has been revealed to enhance the immune response both in animal and human models through the following mechanisms: decreased production of nitrogen oxide resulting in prostaglandin E2 downregulation and inhibition of cyclooxygenase-2, initiation of T-lymphocyte signals, and modulation of the Th1/Th2 balance. Furthermore, it acts as an immunomodulator through protein kinase C [118]. Investigations of antioxidant vitamins effectiveness, especially vitamin E, are still ongoing as a potential treatment for COVID-19 patients. Nevertheless, several studies showed immunoregulatory functions and preventive functions from the oxidative disruption caused by vitamin E. This has contributed to its recognition as a potential supplement for COVID-19 treatment [117]. Vitamin E supplementation at a high dose of 500 mg/kg can also act as a therapeutic drug to inhibit ferroptosis, one of the central mechanisms of programmed cell death in COVID-19 patients, and reduce ferroptosis damage to multiple organs, including lung, kidney, liver, intestine, heart and nervous system [119,120]. The use of Vitamin E has been also studied in vulnerable populations such as the elderly and pregnant women, conditions in which the effect of COVID-19 infection is particularly dangerous for the health [121]. In pregnancy important alterations occur in the hematological, immune, cardiovascular and respiratory systems. As COVID-19 mainly affects these systems, doctors have concerns regarding COVID-19's influence on pregnant women. In effect, COVID-19 may cause obstetric complications like miscarriage, preterm labor, pre-eclampsia, and fetal distress [122]. Increased ROS has been reported due to the production of free superoxide radicals and mitochondrial activity of placental origin during pregnancy. Poorly controlled OS results in the development of trophoblast dysregulation, which can lead to obstetric complications such as hypertensive disorders and fetal growth retardation [123]. As an antioxidant molecule, vitamin E can decrease oxidative stress (OS) during pregnancy [124]. A recent study evaluated maternal serum afamin and vitamin E levels in pregnant women with COVID-19 and its association with composite adverse perinatal outcomes. Afamin is a specific binding pleiotropic glycoprotein for vitamin E and it is an indicator of OS. This prospective, case-control study consisted of 60 pregnant women with COVID-19 infection and 36 age-matched pregnant women without any defined risk factors. The study in the group of women with COVID -19 showed high levels of afamin and low levels of vitamin E in all trimesters of pregnancy. This suggests the increased oxidant status and consumption of antioxidants in the etiopathogenesis of COVID-19 [125].

3.2. Zinc

The transition metal zinc (Zn), after iron, is the second most abundant trace metal in the human body, and it is essential for multiple cellular functions, including the preservation of immune health, playing a critical role in antiviral immunity. Zn also acts as an anti-inflammatory agent and functions as an antioxidant, membrane stabilizer. Zn deficiency can lead to immunodeficiency and severe lymphopenia, which is caused by a corresponding decrease in developing B cells in the bone marrow; furthermore, Zn potentiates a type-I Interferon effect. Marked neutrophilia is detected in severe COVID-19 patients. Interestingly, coronavirus RNA polymerase activity appears to be inhibited by zinc, which could confer this metal a role in preventing coronavirus entry into cells and reducing coronavirus virulency [126]. Due to the immunomodulatory and anti-viral properties of zinc, it has the potential to be a supportive treatment in COVID-19 patients [60]. It has been suggested that zinc supplementation may increase the efficacy of other treatments currently under investigation such as hydroxychloroquine [127]. Furthermore, a retrospective study including 141 individuals affected by COVID-19 in the general practice setting showed that zinc in combination with low-dose hydroxychloroquine was associated with significantly fewer hospitalizations [128]. A case series of four COVID-19 patients treated with high-dose zinc also showed both clinical symptomatic improvements [129]. Studies have shown that zinc supplementation is able to decrease COVID-19 related

symptoms such as lower respiratory tract infection. These effects have been suggested to be due to inhibition of viral uncoating, binding and replication, and may be relevant to COVID-19. To date, there is no definitive knowledge regarding the amount of zinc that may be required to have a therapeutic effect on COVID-19 patients. Factors such as the presence of pre-existent zinc deficiency, the variance in zinc bioavailability caused by different formulation, dose and delivery methods, especially the issues affecting oral zinc absorption, may all influence the clinical outcomes [130]. A RCT provided the first evidence showing the safety and feasibility of intravenous zinc treatment and the ability of administering high-dose intravenous zinc to reverse the acute phase zinc deficiency associated with COVID-19 [131]. These findings support further investigation of this treatment in larger RCTs.

3.3. Melatonin

Melatonin (*N*-acetyl-5-methoxytryptamine, Figure 5) is a multifunctional hormone, which is secreted mostly by the pineal gland, and maximally at nighttime; its secretion is extremely high in infants and adolescents, much lower in the elderly.

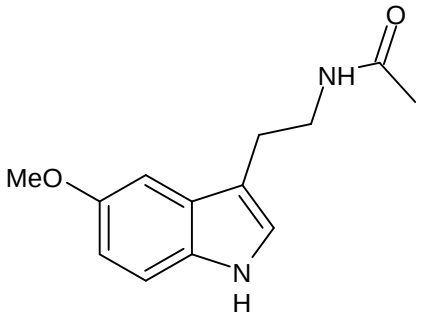

Figure 5. Structure of melatonin

Basically, this molecule helps to regulate many other hormones and maintains the body's circadian rhythm. Melatonin is significantly involved in the complex network of psycho-neuroendocrine immunology (PNEI), stress management and aging mechanisms; furthermore, this compound interacts with cortisol and with a series of immunity and inflammasome pathways, which have been shown to derange in COVID-19 [113]. In principle, melatonin should be useful in protecting against the SARS-CoV2 infection and to reduce the symptoms of COVID-19 patients. Most importantly, use of melatonin is one of the only treatments which may significantly reduce the mortality of severe COVID patients. Since the primary target of melatonin is the host immune system, its protective effects against a SARS-CoV-2 infection will not be weaker against any of the gene-mutated new variants. This advantage exceeds what any specific vaccine or antiviral drug can achieve. Furthermore, its broad protective effects prepare the host against the future upcoming pandemics with different pathologies [132]. Melatonin is not virucidal, but it has indirect anti-viral actions due to its anti-inflammation, anti-oxidation and immune enhancing features. Anti-inflammatory effects are thought to be through sirtuin-1 (SIRT-1) mediated downregulation of macrophage polarization and suppression of nuclear factor kappa-B (NF-κB). The anti-oxidative effect of melatonin cooperates with its anti-inflammatory actions by up-regulating anti-oxidative enzymes (e.g. superoxide dismutase), down-regulating pro-oxidative enzymes (e.g. nitric oxide synthase), and it may also interact directly with free radicals, functioning as free radical scavenger. Furthermore, melatonin exerts regulatory actions on the immune system and directly enhances the immune response by improving proliferation and maturation of natural killing cells, T and B lymphocytes, granulocytes and monocytes in both bone marrow and other tissues [133]. Its direct inhibitory effects on the entry of the SARS-CoV-2 virus into the human host have recently been explored [134]. Melatonin can bind to both SARS-CoV-2 RBD and ACE 2

demonstrating the fact that it can strongly prevent viral entry into the host cells through dual binding effects. It is also known that melatonin is a significant calmodulin inhibitor. Calmodulin is required for the stability and activation of ACE2. So, it appears that melatonin has a 2 prolonged effect on ACE2, one by binding it and the other by inhibiting calmodulin [122]. It also has been hypothesized that melatonin significantly inhibits inflammasome stimulation which could indirectly reduce the intensity of the cytokine storm and lung destruction [135]. Moreover, it can cause a restoration of circadian rhythm and mitochondrial metabolism [136]. By restoring antioxidant status and restoring sleep patterns in critically ill COVID 19 patients, melatonin could serve as an adjuvant in COVID 19 management [137]. Recently, Hasan et al. (2021) [138] completed a single-center, prospective, RCT which was specifically designed to test the protective effects of melatonin in severe COVID-19 patients. All patients received standard therapy with oxygen intubation, remdesivir (as an antiviral), levofloxacin (for protection against secondary bacterial infection), dexamethasone (as an anti-inflammatory) and enoxaparin (as an anticoagulant). Half of them additionally received 10 mg melatonin. The results were highly promising with 13 deaths out of 76 patients in the conventional therapy group (mortality rate of 17.1%) compared to only 1 death out of 82 patients in melatonin group (mortality rate of 1.2%). Thus, the mortality of the severe COVID-19 patient was reduced by 93% as a result of melatonin treatment compared to the conventional treatment alone patients. Based on the evidence mentioned above, melatonin should be strongly recommended for the treatment of COVID-19 patients.

3.4. Flavonoids

Flavonoids are a large class of phytochemicals commonly found in several foods and vegetables in the human diet with numerous valuable pharmacological properties, including antioxidant, antitumor and anti-inflammatory effects [139]. Different flavonoids have been also investigated *in vitro* and *in vivo* regarding their antiviral properties [140]. Flavonoids have shown antiviral activity via inhibition of viral protease, RNA polymerase, and mRNA, virus replication, and infectivity [141]. More importantly, flavonoids demonstrated anti-viral and immunomodulatory activities against coronaviruses [142]. Therefore, flavonoids are currently a widely discussed source of agents potentially applicable in the management of COVID-19 [143]. Several inflammatory pathways associated with SARS-CoV-2 can potentially be targeted by flavonoids, such as the modulation of with NOD-like receptor protein 3 (NLRP3) inflammasome, toll-like receptors (TLRs) or bromodomain containing protein 4 (BRD4), and the activation of the nuclear factor erythroid-derived 2-related factor 2 (Nrf2) or the effects on ACE2 [144]. Furthermore, they also modulate the immune system to improve the organism defense, modulating macrophage profile and natural killer cells, and increasing anti-inflammatory mechanisms [145]. An instructive molecular modeling study revealed that epicatechin from *Hypericum perforatum* provided a better static and dynamic inhibition for ACE2 with highly favorable pharmacokinetic properties than the other known ACE2 inhibiting compounds, ensuring solid binding with critical amino acid residues of ACE2 [146]. Another study showed that the citrus flavonoid naringin is able to inhibit ACE2 enzyme showing estimated docking energy very low (− 6.85 kcal/mol) [147]. Several flavonoids, including apigenin, fisetin, luteolin, kaempferol, jusanin and quercetin have been effectively used for the prevention and/or treatment of COVID-19 [148,149] and post-COVID [150–152].

3.4.1. Quercetin

Quercetin (also known as 3,3′,4′5,7-pentahydroxyflavone, Figure 6) is a widely distributed plant flavonoid, found in several vegetables, leaves, seeds, and grains, where it is conjugated with residual sugars to form quercetin glycosides [153].

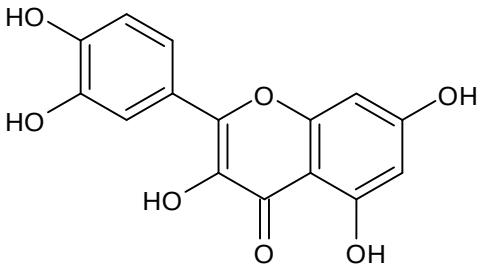

Figure 6. Structure of quercetin

It shows antioxidant, anti-inflammatory, anti-cancer and immunoprotective effects and it can prevent many chronic diseases, added to the ability to inhibit lipid peroxidation, platelet aggregation, capillary permeability, and stimulate mitochondrial biogenesis. Furthermore, quercetin has been studied for its promising antiviral effects due to its ability to inhibiting polymerases, reverse transcriptase, proteases, suppressing DNA gyrase, and binding viral capsid proteins [154]. The prophylactic phytochemical quercetin supplementation, in the form of foods or nutraceuticals, may help in the management of COVID-19 through multiple mechanisms [155]. Molecular docking studies have highlighted that quercetin is able to inhibit the major druggable targets of SARS-CoV-2 including 3-chymotrypsin-like protease (3CLpro) and papain-like protease (PLpro), which are two enzymes essential for viral replication and therefore important drug targets [156], RNA-dependent RNA polymerase and spike (S) protein [157]. Nguyen et al. (2012) [158] demonstrated that quercetin inhibits the activity of recombinant SARS-CoV 3CLpro by up to 80%. More recently, Abian et al. (2020) reported that quercetin inhibits SARS-CoV-2 3CLpro activity by destabilizing its structure [159]. Recent molecular modeling studies assess that quercetin inhibits 3CLpro and PLpro with a docking binding energy corresponding to −6.25 and −4.62 kcal/mol, respectively [160]. Furthermore, quercetin has additional activities specifically aimed at counteracting COVID-19. Specifically, it alters the expression of 98 of 332 (30%) of genes encoding protein targets of SARS-CoV-2 in human cells, thus it potentially interferes with the activities of 23 of 27 (85%) SARS-CoV-2 proteins [161]. Moreover, quercetin inhibits protein disulfide isomerase (PDI), an enzyme implicated in platelet-mediated thrombin formation at the site of vascular injury and may mitigate coagulation abnormalities associated with patients with COVID-19 [162]. Finally, it may interact with NLRP3 [163]. These receptors are activated by SARS-CoV-2 leading to a cytokine storm and destructive inflammation and causes ALI/CARDS in patients with COVID-19 [164]. Activation or inhibition of the NLRP3 inflammasome is influenced by regulators such as thioredoxin interacting protein (TXNIP), SIRT1 and NRF2. The anti-inflammatory activity of quercetin is related to the suppression of the NLRP3 inflammasome by acting on these regulators. Additionally, quercetin suppresses inflammation through interference in various signaling pathways, especially NF-κB [165]. With regard to human studies, the interim results from one of RCT revealed that quercetin supplementation enhanced viral clearance and partially reduced the symptoms severity [166]. In another RCT, were evaluated the therapeutic efficacy of quercetin in combination with antiviral drugs in hospitalized COVID-19 patients. The results showed that quercetin was able to reduce the hospitalization period. Also, the serum levels of quantitative C-reactive protein (q-CRP), lactate dehydrogenase (LDH), and alkaline phosphatase (ALP) were decreased more effectively after taking quercetin [167]. Moreover, a pilot, controlled and open-label RCT demonstrated that the administration of Quercetin Phytosome® (QP), a novel bioavailable form of quercetin, statistically shortened the timing of molecular test conversion from positive to negative, reducing at the same time symptom severity and negative predictors of COVID-19 [168]. Di Pierro et al. (2021) [169] established that the administration of a daily dose of QP for 30 days in 152 COVID-19 outpatients resulted in a reduction in the frequency and length of hospitalization, the need for noninvasive oxy-

gen therapy, progression to intensive care units, and in the number of deaths. In combination with standard care, when used in the early stages of viral infection, quercetin could improve the early symptoms and help in preventing the severity of progression of COVID-19. In addition, the results also confirmed the very high safety profile of quercetin and suggested possible anti-fatigue and pro-appetite properties. Recently, Rondanelli et al. (2022) [170] evaluated also the potential effect of 3 months' supplementation with QP (250 mg twice a day) as prevention against symptomatic COVID-19. This pilot study, which was carried out on 120 subjects (males, 63; females, 57; age 49 ± 12), demonstrated that QP administration determined a 14% higher protection factor of contracting the COVID-19 infection. The results obtained are encouraging, but further studies including a larger number of participants and with a longer follow-up are required to permit to consider quercetin for regular prophylaxis of COVID-19.

3.5. Curcumin

Curcumin (diferuloylmethane, Figure 7) is the primary curcuminoid derived from the rhizome of Turmeric (*Curcuma longa*). It has shown diverse biological functions, such as anti-inflammatory, antioxidant, anticancer and antimicrobial properties. Besides the antifungal and antibacterial properties, it may also act as an anti-viral compound, by inhibiting the replication in a wide-range of viruses [171]. Therefore, it was proposed as a potential treatment against COVID-19 [172].

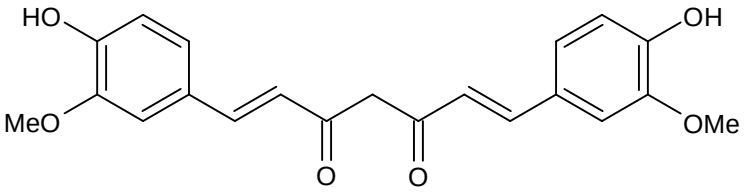

Figure 7. Structure of curcumin

Curcumin is, in fact, an interesting compound to study for management or treatment of COVID-19, thanks to its relative safety and to its broad-spectrum of antiviral activity against enveloped viruses, including SARS-CoV-2, by multiple mechanisms such as direct interaction with viral membrane proteins, disruption of the viral envelope, inhibition of viral proteases and induce host antiviral responses. Moreover, it may suppress SARS-CoV-2 infection by directly modifying spike protein and or ACE2 and inducing host antiviral responses by targeting NRF2 and HMGB1 and exert immunomodulatory activity by blocking NF-κB, inflammasome, HMGB1, and IL-6 driven inflammatory responses. Finally, it dampens ROS production by inhibiting NADPH oxidase and alleviates oxidative tissue injury by increasing antioxidant defenses by modulating NRF2 [173]. Manoharan et al. (2020) [174] indicated curcumin as a wonder drug in COVID-19 management as it is a potential inhibitory agent by blocking the host viral interaction (viral spike protein—ACE2 receptor) at an entry site in humans and it may also act as an attenuator via modulating the proinflammatory effects of Ang II-AT1 receptor-signaling pathways by reducing respiratory distress in the treatment of COVID19. Moreover, they elucidated that emulsion form of topical application of curcumin may effectively prevent the SARS-CoV2 infection in humans, as the viral entry site of ACE2 receptor is predominantly distributed at the nasal cells, mucosal surface of respiratory tract and eyes. Finally, Liu et al. (2020) [175] suggested curcumin as a therapeutic agent against pneumonia and acute lung injury or fatal CARDS in humans resulting from coronaviral infection. Several computational studies underline the ability of curcumin to interact with several target proteins of SARS-CoV-2. Shanmugarajan et al. (2020) [176] showed that curcumin inhibits the binding of spike glycoprotein to ACE2 receptor, thereby attenuating the viral infection. Patel et al. (2021) [177] showed that curcumin and its derivatives act as inhibitors of the spike protein

displaying binding energies, ΔG, ranging from -10.98 to -5.12 kcal/mol (6CRV) and -10.01 to -5.33 kcal/mol (6M0J). The most interesting compound was bis-demethoxycurcumin, which showed the best binding affinity to the spike protein of SARS-CoV2. Jena et al. (2021) [178] described the potential of catechin and curcumin to interact with the S protein of SARS-CoV-2 and ACE2 of human cell membrane and also to the RBD/ACE2-complex.

In vitro studies are specified below. Marín-Palma et al. (2021) described the combined antiviral/anti-inflammatory effects of curcumin during SARS-CoV-2 infection [179]. They demonstrated that curcumin (10 μg/mL) exhibited antiviral effect of 99% and 99.8%, against DG614 strain and Delta variant, respectively, suggesting that this nutrient affects the SARS-CoV-2 replicative cycle and exhibits virucidal effect: these effects seemed to be independent of the virus strain/variant. Moreover, the pro-inflammatory cytokines (IL-1β, IL-6, and IL-8) released by peripheral blood mononuclear cells (PBMCs) triggered by SARS-CoV-2 were decreased after treatment with curcumin. The study by Bormann et al. [180] demonstrated that curcumin potently neutralizes SARS-CoV-2 in Vero E6 and human Calu-3 cells at low subtoxic concentrations. Furthermore, curcumin treatment significantly reduced SARS-CoV-2 RNA levels in cell culture supernatants. The effectiveness of curcumin on outcomes of hospitalized COVID-19 patients has also been recently reviewed [181]: the adjunct treatment with different formulations of curcumin led to reductions in typical symptoms, duration of hospitalization, and deaths in COVID-19 patients and, at the same time, to the amelioration of cytokine storm manifestation by reducing pro-inflammatory factors and stimulating anti-inflammatory pathway. Interestingly, the bioavailability of curcumin can be increased by 2000% when using piperine as an adjuvant. A double-blind, controlled RCT indicated that administration of a combination of curcumin and piperine reduced the days of remission of symptoms, the oxygen requirement. Dose-escalating studies have indicated the safety of curcumin over 3 months [182].

3.6. Prebiotics and probiotics

Gastrointestinal disorders are usual in COVID-19 patients and may impact the host's intestinal microbiota, meaning there are changes in the diversity and population of beneficial bacteria and that these are associated with disease severity [183,184]. Dysbiosis has been vastly associated with COVID-19 severity [185]. The reduction of gut microbiota richness persists even six months after recovery following SARS-CoV-2 infection [186]. The modulation of the intestinal microbiota by probiotics, prebiotics, synbiotics, postbiotics, paraprobiotics, and psychobiotics represent a potential adjuvant approach for enhancing the health of COVID-19 patients [187,188]. Specific probiotic intake can reduce gastrointestinal symptoms of COVID-19 and the effects of using antibiotics which worsen these symptoms and reconstitute the gut microbiome, along with consequent modulation of the immune system, a decrease in vulnerability to infections and increased number of resistance genes [189]. A therapeutic approach with probiotics can modulate other key points in the severity of COVID-19 cases: improved production of Treg cells to control inflammation [190], reduced D-dimer level involved in COVID-19 coagulopathy [191]; and intensification in immune efficacy of COVID-19 vaccine [192,193]. However, more studies should be carried out to evaluate the effects of probiotics and establish the right doses, intervention time and action mechanisms against COVID-19. Two important groups of prebiotics are represented by fructo-oligosaccharides and galacto-oligosaccharides which exist in low quantities in foods and show beneficial effects on human health [194]. Among prebiotics [195], tea polyphenols (TPs) have been shown to regulate the gut microbiota to prevent or alleviate COVID-19 through the gut-lung axis [196]. Gut and lungs have been demonstrated to be part of a shared mucosal immune system and have inflammatory process and immune responses linked by the gut-lung axis [197,198]. Therefore, the fine-tuning of host-microbiota balance in the lung and gut can be useful in fighting against COVID-19. Given the ability of probiotics to act as immunomodulator,

anti-inflammatory, antioxidant, and antiviral, the use of probiotics may be a way to support the reconstitution of the gut microbiota [199]. Probiotics are living micro-organisms which provide benefits to the host's health when administered in adequate doses [200]. Some their general mechanisms are represented by inhibition of bacterial adherence and invasion capacity in the intestinal epithelium, enhancement of the gut barrier function and boosting of the immune system [201]. Probiotics have been reported to confine the virus entryby healing the ACE2 containing epithelial barrier. Probiotics also release ACE-inhibitory peptides that could reduce Ang II expression and induce the synthesis of short chain fatty acids that regulate blood pressure and inflammation. They reduce NO production and stress oxidative and this can lead to the downregulation of inflammatory (NLRP3 and NF-κB) pathways. Bacteriocin and other anti-, as well as proinflammatory cytokines, produced by the effects of probiotics, might balance pro- and anti-inflammatory cytokine levels and increase the T-cell count in the SARS-CoV-2-infected patients. Finally, probiotics might also reduction in hyaluronan synthesis, which eventually could improve CARDS [202]. Some clinical trials regarding the study of probiotics for management of COVID-19 are already undergoing and the results may provide future direction for the prevention of this pandemic [203]. The beneficial effects of the consumption of probiotics may contribute to the prevention and treatment of some symptoms of COVID-19, provided they are associated with a healthy diet. Some representative RCTs of probiotic intervention in COVID-19 are summarized in Table 2.

Table 2. Some representative RCTs of probiotic intervention in COVID-19.

Study type	Study subjects	Age group	Number enrolled	Intervention/ treatment	Primary Outcome measures	Ref
Single-blind RCT	patients with COVID-19	≥18 y	152	Oxygen-ozone therapy with dietary supplements SivoMixx *	Number of patients, in treatment, needing orotracheal intubation	[204]
RCT	COVID-19 patients requiring hospitalization	18–60 y	300	Combination of *Lactobacillus plantarum CECT7481*, *L. plantarum CECT 7484*, *L. plantarum CECT 7485*, and *Pediococcus acidilactici CECT 7483* vs Placebo	Severity progression of COVID-19, Stay at ICU, Mortality ratio.	[205]
Double-blind RCT	People with household contact of	≥1 y	182	Probiotic (*Lactobaciltus rhamnosus*	Changes in Shannon bacteria diversity	[206]

	COVID-19 patient			*GG*) vs Placebo		
Double-blind RCT	Healthcare workers without COVID-19	≥20 y	314	Probiotic (Lactobacillus) vs Control (Maltodextrin)	Incidence of SARS-CoV-2 infection in healthcare workers	[207]
Open label RCT	COVID-19 patients requiring hospitalization	≥18 y	40	Dietary Supplement: Probiotic vs No intervention	Cases with discharge to ICU	[208]
Double-blind RCT	COVID-19 patients with diarrhea	≥18 y	108	Synbiotic (Omnibiotic AAD: 2 Bifidobacterium strains, Enterococcus, 7 Lactobacillus strains) vs Placebo	Duration of diarrhea	[209]

*SivoMixx: *Streptococcus thermophilus* DSM322245; *Bifidobacterium lactis* DSM32246; *Bifidobacterium lactis* DSM32247; *Lactobacillus acidophilus* DSM32241; *Lactobacillus helveticus* DSM32242; *Lactobacillus paracasei* DSM32243; *Lactobacillus plantarum* DSM32244 and *Lactobacillus brevis* DSM27961.

3.7. Nano-nutraceuticals

Nanotechnology is widely used in different field of research with countless biomedical science applications, from cancer nanomedicine [210] to antimicrobial activity [207,208] and finally, advancements in the area of nanomedicine in healthcare have been carried out in fighting the COVID-19 pandemic [211–215]. Nanomedicine applications and lipid-based nanoparticles can also help in the development of effective vaccines and/or therapeutics against COVID-19 [216]. Potential immuno-nanomedicine strategies to fight COVID-19 have been also proposed [217]. Recently, nano-nutraceuticals have been suggested to manage pre- and post-COVID infections [218–220], including fisetin flavonoid nanoparticles [221], resveratrol and zinc nanoparticles [222], and curcumin nanoparticles [223]. Actually, for example the clinical use of curcumin is hindered by its low oral bioavailability. The use of several formulations, including packaging with nanoparticles, liposomes, and micelles represents a suitable strategy to improve curcumin bioavailability [224]. Sharma et al. reported that curcumin-encapsulated polysaccharide nanoparticle (CUR–PS-NPs) potently inhibit the release of cytokines, chemokines, and growth factors associated with damage of SARS-CoV-2 spike protein by deactivation of MAPK/NF-κB signaling in epithelial cells [225]. The nano-formulation of curcumin termed "Nanocurcumin" increases dissolution rate, saturation solubility, bioavailability, and drug stability. Tahmasebi et al. (2021) [226] in a randomized, double-blind-placebo controlled trial study showed that the nanocurcumin treatment led to changes in anti-inflammatory factors, including increased the number of suppressor Treg cells, as well as elevated levels of transcription factor FOXP3, IL10, IL35, and TGF-β, and increased secretion of anti-inflammatory cytokines in the Nanocurcumin-treated group compared to the placebo group. The same research group [227] also demonstrated that Nanocurcumin was

able to reduce the frequency of Th17 cells and their related inflammatory factors in the curcumin intervention group in both mild and severe COVID-19 patients.

4. Conclusions

It is now established that nutrition and nutritional supplements are an important role in the prevention and treatment of COVID-19 disease and post-COVID syndrome. Post-COVID syndrome is referred to a variety of symptoms with a duration beyond the acute phase of COVID-19. It is mainly characterized by pulmonary, musculoskeletal, digestive and neurological problems. It represents an emerging global crisis. However, the mechanisms by which SARS-CoV-2 may cause post-COVID syndrome and the best therapeutic options are not clearly defined. Besides the common therapies used for COVID-19, flavonoids, curcumin, melatonin, prebiotics, probiotics and vitamin C, D and E have shown encouraging data suggesting their use to prevent and counteract the symptoms of COVID-19 pandemic infection and they are currently under study in the prevention and treatment of post-COVID syndrome, as well. Nano-nutraceuticals may represent new strategies for the development of new therapies to curb COVID-19 and post-COVID syndrome. In any case, new studies are urgently needed to further investigate the molecular mechanisms played by nutraceuticals in the prevention and treatment of post-COVID syndrome. This will allow a more rational and efficient use of these safe products.

Abbreviations

ACE2 = Angiotensin-2 converting enzyme

ALP = Alkaline phosphatase

Ang II = Angiotensin II

AT1R = Ang II receptor type 1

BRD4 = Bromodomain containing protein 4

CARDS = COVID-19-associated acute respiratory distress syndrome

COVID-19 = Coronavirus Disease

CRP = C-reactive protein

HDIVC = High-Dose Intravenous Vitamin C

ICU = Intensive care unit

IVC = Intravenous vitamin C

LDH = Lactate dehydrogenase

LPS = Lipoprotein

NF-κB = Nuclear factor kappa-B

NLR = Nod-like receptor

NLRP3 = NLR family pyrin domain containing 3

NRF2 = Nuclear factor erythroid-derived 2-related factor 2

OS = Oxidative stress

PBMCs = Peripheral blood mononuclear cells

P/F = PaO_2/FiO_2

PNEI = Psycho-neuroendocrine immunology

q-CRP = Quantitative C-reactive protein

QP = Quercetin Phytosome®

RAS = Renin-angiotensin system

RBD = Receptor-binding domain

RCT = Randomized controlled trial

SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2

SIRS = Systemic inflammatory response syndrome

SIRT-1= Sirtuin-1

SOFA = Sequential Organs Failure Assessment

TLRs = Toll-like receptors

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