Nutraceuticals and Dietary Supplements for Older Adults with Long COVID-19

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KEYWORDS

• Geriatrics • Gerontology • Frailty • Sarcopenia • Fatigue • Nutrition • Bioactive foods • Therapy

KEY POINTS

- Long-term persistence of COVID-19–related symptoms after SARS-CoV-2 infection impacts quality of life.
- Several mechanisms may be involved in the persistence of COVID-19 symptoms, including chronic inflammation, immunometabolic processes, endothelial dysfunction, and gut dysbiosis.
- Bioactive foods, supplements, and nutraceuticals may be used for the management of long-term COVID-19 clinical sequelae.

INTRODUCTION

SARS-CoV-2 infection affects multiple organs owing to the ubiquitous distribution of its target receptor ACE-2.[1] Increasing interest has been paid to the postacute phase of COVID-19. The time to recover from an acute COVID-19 episode ranges from 2 to 6 weeks depending on disease severity.[2] However, a substantial share of people reports clinical sequelae weeks or months after symptom onset. This condition, known as postacute COVID-19 syndrome, postacute sequelae of COVID-19, or long COVID syndrome, encompasses long-lasting signs and symptoms, such as cough, dyspnea,

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fatigue, difficulties with memory and concentration ("brain fog"), sleep disorders, gastrointestinal complaints, and musculoskeletal problems.[3,4]

A recent systematic review showed that more than half of COVID-19 survivors (mostly middle-aged men hospitalized during the acute phase) had at least one long-lasting symptom at 6 months.[5] Results from a digital questionnaire in a cohort of middle-aged nonhospitalized patients with COVID-19 from Denmark showed that persistent symptoms lasting for more than 4 weeks were experienced by 36% of participants who had been symptomatic during the acute phase.[6] Recently, our group showed that persisting symptoms were common in older adults who had been hospitalized for COVID-19, with approximately 50% of the sample presenting with 3 or more symptoms after 3 months of hospital discharge.[7] Symptom persistence was more frequent in those who experienced fatigue during acute COVID-19.

The mechanisms of chronic COVID-19 manifestations have not been yet unveiled. Several hypotheses are currently being tested.[4,8] These include viral persistence associated with chronic inflammation, autoimmune processes, alterations in immunometabolic pathways, dysbiosis, endothelial damage, and unresolved organ damage.[3,4,8] It is noteworthy that some of the immunologic and systemic features of long COVID resemble signs of accelerated or premature aging, and may aggravate pre-existing age-associated degenerative conditions, such as sarcopenia and cognitive decline.[9–11]

Specific treatments for long COVID are currently lacking. Patient management mostly relies on symptomatic treatments and recommendations to conduct an active and healthy lifestyle. A plethora of dietary supplements and natural bioactive substances have been tested for their potential to contrast long COVID.[12,13] In this review, the possible actions of nutraceuticals and dietary supplements on mechanisms associated with long COVID are described. A brief overview of ongoing studies investigating the effects of specific nutraceuticals in patients with long COVID attending the outpatient service at the Fondazione Policlinico A. Gemelli IRCCS (Rome, Italy)[14] is presented.

DISCUSSION

Amino Acids

Amino acids play a crucial role in cell metabolism and modulate several biological processes (eg, inflammation, glucose homeostasis, redox balance) that may be involved in post-COVID clinical sequelae.[4,8,15] Amino acids support the increased metabolic demands of activated immune cells by contributing critical intermediates to biosynthetic and energy-producing pathways, such as glycolysis, tricarboxylic acid (TCA) cycle, and oxidative phosphorylation pathways.[15]

Glutamine replenishes TCA cycle intermediates that have been consumed in biosynthetic processes in T cells, macrophages, and plasma cells through anaplerosis.[16–18] In immune cells, glutamine is also used for glutathione and in hexosamine biosynthetic pathways and supplies amino groups for other amino acids via transamination.[19]

The branched-chain amino acids (BCAAs) leucine, isoleucine, and valine are essential amino acids with well-established effects on protein synthesis and glucose homeostasis. BCAAs mainly act through the stimulation of cellular anabolic signaling pathways (eg, phosphoinositide 3-kinase-protein kinase B, mammalian target of rapamycin [mTOR]).[20] BCAAs may exert direct and indirect effects on immune function.[15] In vitro models have shown that BCAAs are essential for proliferating lymphocytes to synthesize proteins and nucleotides in response to stimulation.[21] BCAAs can be incorporated into and oxidized by immune cells. The amount of BCAAs incorporated into proteins is higher in lymphocytes, followed by eosinophils and neutrophils.[21] In immune cells, BCAAs are also sources of the coenzyme A (CoA) derivatives acetyl-CoA and succinyl-CoA, which enter the TCA cycle and support mitochondrial bioenergetics.[15] BCAAs may also improve gut mucosal surface defense by stimulating soluble immunoglobulin A secretion.[22]

Arginine is a semiessential amino acid involved in multiple biological processes. Its main activities on the immune system derive from its conversion to nitric oxide (NO) by NO synthase (NOS) and its metabolism through arginase, that competes with NOS for arginine availability in most immune cells.[23] NO is known to have direct and indirect antiviral activity through the generation of immunomodulatory oxidized phospholipids.[24–26] NO also exerts potent anti-inflammatory effects via inhibition of leukocyte recruitment.[27,28] Several studies in animal models have shown that the mechanisms of NO action on leukocyte function involve the activation of guanylyl cyclase, followed by the generation of cyclic GMP that suppresses the expression of P-selectin, a crucial mediator in leukocyte adhesion.[29] Reduced arginine bioavailability may impair T-cell response and function.[30] In patients with COVID-19, a decrease in plasma arginine levels with concomitant increase in arginase activity was associated with impaired T-cell proliferative capacity, which can be restored in vitro by arginine supplementation.[31] Arginine, through its action on NO synthesis, may also modulate endothelial and respiratory functions and exert antithrombotic and cytoprotective activities.[32] Preliminary data suggest that oral arginine supplementation added to standard therapy reduced the need of respiratory support and the duration of in-hospital stay in patients with severe COVID-19.[33] Because of its modulating activities on inflammation and endothelial function, arginine has also been indicated as a plausible agent to contrast COVID-19 sequelae.

Collectively, available evidence suggests that amino acids are crucial to modulate immune response and several other mechanisms involved in both acute and chronic COVID-19. In older adults, the physiologic changes associated with the aging process (eg, increased splanchnic extraction, anabolic resistance, chronic inflammation) may further increase the need of adequate amino acid supplies.[34] Protein/amino acid malnutrition in older adults is associated with immune dysfunction and sarcopenia, the latter being aggravated by reduced mobility and inflammatory processes induced by COVID-19.[35]

Given these premises, it is reasonable to focus on the achievement of an adequate amino acid intake in COVID-19 survivors, also through oral supplementation. In particular, amino acid intake should be monitored in older people who are at greater risk of malnutrition as a specific consequence of SARS-CoV-2 infection.

Hydroxy-Beta-Methylbutyrate

Beta-hydroxy-beta-methyl butyrate (HMB) is the active metabolite of leucine.[36] HMB, through the stimulation of mTOR-dependent pathways, modulates several physiologic processes, including protein metabolism, insulin activity, skeletal muscle hypertrophy, cell apoptosis, and muscle stem cell proliferation and differentiation.[37]

Oral supplementation of HMB (3 g/d) mitigates the decline in muscle mass and preserves muscle function in older adults and frail people, especially during hospital stay and recovery.[38] Interestingly, HMB may modulate the immune and inflammatory response, especially under stressful conditions.[39] HMB supplementation was found to have short-term anti-inflammatory and anticatabolic effects and to improve pulmonary function in patients with chronic obstructive pulmonary disease in an intensive care unit setting.[40]

Possible effects of HMB on brain have also been explored, starting from the evidence that HMB crosses the blood-brain barrier in rats.[41] HMB was found to promote neurite outgrowth in vitro,[42] and long-term HMB supplementation in rats attenuated age-related dendritic shrinkage of pyramidal neurons in the medial prefrontal cortex,[43] thus suggesting possible beneficial effects on cognition.[44,45]

Based on its well-established effects on muscle mass preservation and its potential biological activities on physiologic systems perturbed by COVID-19, HMB may represent a useful support for older patients suffering from long-term COVID-19 sequelae.

Tricarboxylic Acid Cycle Intermediates

Malic acid, citric acid, and succinic acid are TCA cycle intermediates with a well-established role in mitochondrial energy metabolism. Once considered byproducts of cellular metabolism to be used for the biosynthesis of macromolecules (eg, lipids, nucleotides, proteins), TCA cycle intermediates are now recognized as important mitochondrial signaling molecules regulating multiple cellular functions.[46] Indeed, TCA cycle metabolites may also modulate chromatin remodeling, DNA methylation, posttranslational protein modifications, platelet activity, and immunity.[15,47,48]

Supplementation with TCA cycle intermediates may help preserve mitochondrial biogenesis and function and fulfill the increased metabolic demands of older people recovering from COVID-19. In this context, TCA cycle metabolites may support the beneficial effects of amino acid supplementation in the prevention of mitochondrial dysfunction, oxidative damage, and muscle loss.[49] Novel formulas combining mixtures of amino acids plus TCA intermediates, such as citric, succinic, and malic acid, and B group vitamins, were tested for their effects on mitochondrial bioenergetics and antioxidant response both in vitro and in animal models of aging.[50,51] In murine neural stem cells and human-induced pluripotent stem cells, mitochondrial function, oxidant scavenging mechanisms, and neuronal stem cells differentiation were boosted via activation of the mechanistic target of rapamycin complex 1 and nuclear factor erythroid 2 like 2 (Nrf2)-mediated gene expression.[50] In a mouse model of accelerated muscular and cognitive aging, the combination of amino acids plus TCA cycle metabolites and cofactors preserved mitochondrial efficiency, muscle mass, and physical and cognitive abilities by acting on proliferator-activated receptor γ coactivator 1α and NRF2 in skeletal muscle and hippocampus.[51]

Further investigation is warranted to evaluate the potential effects of TCA cycle metabolites (alone or combined with other nutrients) to contrast long-term consequences of COVID-19.

Micronutrients

Nutritional surveys indicate that vitamin and mineral deficiencies are highly prevalent in older adults. Micronutrient deficiencies are associated with increased risk of noncommunicable diseases, such as fatigue, cardiometabolic disease, musculoskeletal disorders, and cognitive impairment.[52] Micronutrients, including selenium, iron, zinc, and magnesium, are also critical for the proper functioning of the immune system.[53]

Selenium

Selenium is an essential trace element and is mainly present in the form of selenoproteins. Selenium is involved in several physiologic processes, including neurologic, endocrinologic, cardiovascular, and immune functions.[54]

Several studies have investigated the role of selenium in modulating the immune response, and for this reason, a putative role for selenium has been evoked in the context of COVID-19.[55] Evidence in human, animal, and cellular models suggests that selenium plays an important role in response to viral infections, including respiratory viruses,[56] while its deficiency seems to increase host susceptibility to infections.[55,57] In viral infections, selenoproteins inhibit type I interferon responses and viral transcriptional activators.[54,55] Selenium supplementation stimulates innate immune system and increases $CD4^{+}$ T cells and natural killer cell response.[58] Selenium also modulates the secretion of proinflammatory interleukins by inhibiting nuclear factor κB (NF-κB).[55] Selenium deficiency has been correlated to greater secretion of interleukin-6 (IL-6) in older adults,[59] whereas higher levels of selenium are associated with reduced C-reactive protein (CRP) circulating levels.[60] Low plasma concentration of selenium was also correlated with increased tissue damage and organ failure, prothrombotic activity, and overall mortality in patients in intensive care, which could explain a correlation with severity of symptoms in patients with COVID-19 and possible COVID-19 sequelae in long haulers.[3,61–63] Several studies have reported that circulating selenium concentrations were lower in patients with COVID-19 as compared with healthy controls and associated with COVID-19 severity and mortality.[64,65]

Low selenium levels may increase individual susceptibility to SARS-CoV-2 infection, influence the severity of the disease,[66,67] and be related to postacute sequelae and long-lasting symptoms.[68]

Iron

Iron is essential for all living organisms, being a crucial component of hundreds of proteins involved in fundamental biological processes, including oxygen transport, energy production, and nucleic acid synthesis.[69] During viral infections, the rapid viral proliferation determines a competition for iron between the invading pathogen and the host.[70] Moreover, iron homeostasis influences both the innate and the adaptive host immune response. In fact, hypoferremia is linked to altered B- and T-lymphocyte proliferation and function[71] and is associated with higher levels of proinflammatory cytokines and reactive oxygen species.[72] Low-iron levels have been associated with the severity of respiratory insufficiency, acute multiorgan failure, and mortality in patients with COVID-19.[73–75] Iron status parameters, such as ferritin, transferrin, and hepcidin, which respectively serve to store, transport, and absorb iron in the human body, may be considered risk factors and clinical biomarkers for COVID-19 prognosis.[76] In particular, meta-analyses have correlated high-ferritin levels with COVID-19 severity and mortality.[77–79] Ferritin stimulates the expression of proinflammatory cytokines, such as IL-1β, IL-6, IL-12, and tumor necrosis factor-α (TNF-α),[71] and a gradual reduction of its circulating levels has been demonstrated in patients with COVID-19 after infusion of monoclonal antibodies targeting IL-6 receptor.[200] Preliminary data from a prospective observational cohort study in patients with mild to critical COVID-19 show that alterations in iron homeostasis may persist for at least 2 months after acute infection and are associated with nonresolving lung disorders and impaired physical performance.[80] Iron deficiency was associated with elevated levels of inflammation markers, such as IL-6 and CRP.[80] Finally, low-iron levels could theoretically impair the efficacy of COVID-19 vaccination,[71] underlining the importance of monitoring iron levels, especially in older adults with long COVID.

Based on the available evidence, iron supplementation, especially in older adults with low iron and hemoglobin levels, could be particularly useful for reducing the level of inflammation, mitigating persistent symptoms (such as fatigue and dyspnea), and improving immune response to vaccination.

Zinc

Zinc is the second most abundant trace metal in the human body after iron and is essential for the maintenance of immune health, cell homeostasis, and reproduction.[81,82] Zinc deficiency is quite common in the general population and is also associated with immune dysfunction, affecting both the innate and the adaptive immune systems.[83,84] Inadequate zinc intake has been associated with increased risk of upper- and lower-respiratory tract infections, especially in older adults,[85,86] whereas supplementation with zinc gluconate seems to reduce duration and severity of common cold symptoms.[87]

Zinc may inhibit coronavirus RNA polymerase activity in vitro and viral replication in cultured cells.[88] Zinc has also an immunomodulatory, antioxidant, and anti-inflammatory role that could influence the trajectory of SARS-CoV-2 infection, and its supplementation could ameliorate lung function, enhance mucociliary clearance, and reduce ventilator-induced lung injury in critical patients with COVID-19.[85] Lower serum zinc levels were found in patients with severe COVID-19 with acute respiratory distress syndrome and associated with a higher rate of complications and in-hospital length of stay.[64,85] Zinc deficiency could also be connected to the onset and persistence of symptoms such as anosmia and dysgeusia, which can last for a variable amount of time after resolution of acute infection.[89]

Zinc supplementation was tested for its potential role in contrasting the consequences of SARS-CoV-2 infection. However, available data on the efficacy of zinc supplementation for the management of patients with COVID-19 are scarce and contradictory.[64,90,91] A prospective randomized clinical trial, COVID A to Z study, evaluated the efficacy of a treatment with zinc gluconate, ascorbic acid, or their combination in shortening the duration of COVID-19 symptoms.[92] The study failed to demonstrate a significant improvement in symptoms, and the study was stopped for futility.

Further studies are needed to evaluate the effects of zinc or mixtures of micronutrients, including zinc in both acute COVID-19 and in long COVID-19 syndrome.

Magnesium

Magnesium is essential for several physiologic functions and biochemical reactions and may exert important anti-inflammatory and antioxidant functions.[93,94]

Although severe magnesium deficiency with clinical symptoms is quite rare, hypomagnesemia is frequent in patients in the intensive care unit, regardless of the cause of admission, and is associated with increased mortality, higher need for ventilator support and incidence of sepsis, and longer hospital stays.[95] Although there are no significant data on magnesium homeostasis in patients with COVID-19, it has been suggested that magnesium deficiency could modulate the progress and severity of SARS-CoV-2 infection.[96] Magnesium supplementation protects organs and tissues from damage through multiple mechanisms and could potentially influence the natural history of COVID-19.[96]

It is well known that magnesium exerts anticholinergic, antihistaminic, and anti-inflammatory activities, reduces the risk of airway hyperreactivity and wheezing, and promotes bronchodilation by inhibiting bronchial smooth muscle contraction via blockage of calcium channels.[94,97] A systematic review demonstrated that a single infusion of 1.2 or 2 g of magnesium sulfate in adults with exacerbations of asthma was associated with a reduction in hospitalization rate and improved lung function in patients who did not respond to standard treatment (ie, oxygen, nebulized short-acting β2-agonist, and intravenous corticosteroids).[98] In addition, magnesium reduces the secretion of transforming growth factor β1, thereby preventing lung fibrosis,[99] a rare but fearsome consequence of COVID-19.

Magnesium plays a role in modulating the innate and adaptive immune system.[93,94] Subclinical magnesium deficiency is correlated with low-grade chronic inflammation, which can be crucial for the prognosis of COVID-19 and the persistence of COVID-19 symptoms.[93] It has been demonstrated that magnesium sulfate supplementation downregulates inflammatory response and oxidative stress by inhibiting chemokine and cytokines, such as IL-1, IL-6, IL-8, TNF-α, and CRP, which are often significantly elevated in severe COVID-19 cases.[93,94] Magnesium may also modulate the adaptive immune system, influencing the proliferation and the activation of $CD4^+$ and $CD8^+$ T lymphocytes.[96] Furthermore, magnesium exerts an important role in maintaining endothelial function and vascular integrity.[100] In response to an acute inflammation stimulus, such as SARS-CoV-2 infection, the endothelium increases the secretion of prothrombotic factors. Accumulating evidence suggests that the endothelium might be directly affected in patients with COVID-19.[101] Magnesium supplementation, especially in older adults, could help prevent the risk of thromboembolism in COVID-19 and long-term consequences in COVID-19 survivors.[102] In critically ill patients with COVID-19, magnesium sulfate supplementation can represent a supportive treatment with promising beneficial effects.[94] A retrospective observational study demonstrated that in hospitalized patients with COVID-19 aged 50 years and older, a combination of oral vitamin D3, magnesium, and vitamin B12 supplementation for up to 14 days significantly reduced the need of oxygen therapy compared with controls.[103]

Despite the lack of clinical trials and well-powered studies in patients with COVID-19, magnesium supplementation seems to find a potential application in controlling respiratory symptoms, but also in modulating inflammation, cardiovascular and neurologic disorders, and electrolyte abnormalities. The monitoring of magnesium status should be encouraged, as it may influence immune homeostasis and help decrease morbidity and mortality in patients with COVID-19.[93]

Bromelain

Bromelain is a proteolytic enzyme derived from the fruit and stem of pineapple. Bromelain is commonly used as an anti-inflammatory agent, although its potential biological activity spans from respiratory, digestive, immune, and circulatory systems to anticancer and antimicrobial therapy.[104]

Bromelain regulates inflammatory processes through the modulation of NF-κB and cyclooxygenase 2 pathways that regulate the synthesis of inflammatory cytokines and prostaglandin E2 and thromboxane A2, respectively.[105] Moreover, bromelain has fibrinolytic and antithrombotic properties[106,107] and may also exert analgesic effects by regulating the synthesis of pain mediators, such as bradykinin.[108] The decrease in bradykinin levels induced by bromelain may also indirectly act on inflammatory response through the regulation of vascular permeability and reduction in edema. Bromelain showed immunomodulatory effects both in vitro and in vivo.[109] Bromelain may simultaneously enhance and inhibit T-cell responses by acting on accessory cells and directly on T cells. Moreover, bromelain enhanced T-cell–dependent, antigen-specific, B-cell antibody responses in vivo.[109]

In vitro studies suggest that bromelain may also inhibit SARS-CoV-2 infection by targeting ACE-2, transmembrane serine protease 2, and SARS-CoV-2 S-protein.[110]

Considering its multiple potential activities on mechanisms involved in acute and chronic COVID-19 phases, bromelain could represent a candidate therapeutic agent for the management of COVID-19. In this context, bromelain may also increase the absorption of curcumin and other bioactive compounds with possible anti–COVID-19 activities after oral administration.[111] Currently, data about the properties of bromelain on persistent symptoms related to long COVID-19 are lacking, but it can be hypothesized that its biological activities might help in the process of recovery from chronic fatigue, joint pain, and myalgia.[104]

Troxerutin

Troxerutin is a flavonoid derived from rutin that can be found in tea, coffee, cereals, fruits, and vegetables. Troxerutin exerts multiple biological functions, including antioxidant, anti-inflammatory, nephroprotective, antithrombotic, antidiabetic, and neuroprotective effects.[112] Following ingestion, flavonoids are partially digested by microbiome, which facilitates the absorption by small or large bowel.

Troxerutin exerts its antioxidant functions through direct free radical scavenging activity[113] and by enhancing the activity of glutathione and antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase.[114] Through its antioxidant activities, troxerutin might preserve epithelial cells, fibroblasts, and lymphocytes from oxidative stress-induced apoptosis.[113]

Troxerutin was found to protect against gentamycin-induced acute kidney injury in rats through the downregulation of inflammatory cytokines (IL-10, TNF-α, and IL-6), the reduction of apoptotic cell death, and the induction of renal tissue regenerative capacity, by acting on p38 mitogen-activated protein kinase signaling.[115]

Troxerutin protects the hippocampus against amyloid-beta induced oxidative stress and apoptosis by reducing the acetylcholinesterase activity and oxidative stress.[114] In a rat model of traumatic brain injury, troxerutin exerted multiple protective effects through the regulation of endothelial NOS activity.[116] Moreover, troxerutin demonstrated anxiolytic- and antidepressant-like activities in rodents.[117]

In rat models of type 1 and type 2 diabetes, troxerutin preserved male fertility and protected against diabetic cardiomyopathy through the reduction of reactive oxygen species and its activity of NF-κB, serine/threonine kinase 1, and insulin receptor substrate 1.[118,119]

Data on the activity of troxerutin in COVID-19 are currently lacking. However, its antioxidant and anti-inflammatory properties might be helpful for both the acute and the chronic consequences of SARS-CoV-2 infection.

Lactoferrin

Lactoferrin is an iron-binding glycoprotein, which acts as a host defense molecule against microbes. Lactoferrin is mainly secreted from exocrine glands and is present in granules in neutrophils following infections.[120] Lactoferrin prevents microbial and viral adhesion to human cells through its iron-chelating ability, which reduces availability of iron used for microbial growth, aggregation, and biofilm formation.[121] The activity of lactoferrin is mostly bacteriostatic, but a lethal effect has been demonstrated. One of its derivates, lactoferricin, tends to inactivate the lipid A from lipopolysaccharide of gram-negative bacteria. Lactoferrin may also have a bactericidal effect on gram-positive bacteria. Lactoferrin exerts its antiviral activity through different mechanisms at the mucosal level, including binding to heparan sulfate glycosaminoglycans, viral particles, and viral receptors, thus limiting viral entry.[122]

In vitro, bovine lactoferrin blocks human cell apoptosis induced by influenza A virus.[123] In vitro and in vivo studies showed that lactoferrin may also inhibit cytomegalovirus[124] and herpes simplex virus infection.[125] The antiviral activity of lactoferrin has been demonstrated against a multitude of viruses, including respiratory syncytial virus, poliovirus, hepatitis B virus, hepatitis C virus, alphaviruses, hantavirus, human papillomavirus, adenovirus, and enterovirus.[126] Given its immunomodulatory and antiviral properties, the use of lactoferrin was also proposed to contrast SARS-CoV-2 infection.[127] In vitro and in silico assays showed that lactoferrin may have an antiviral activity against SARS-CoV-2 through direct attachment to both SARS-CoV-2 spike S glycoprotein and cell surface components.[128] Lactoferrin may also modulate the inflammatory cascade through the reduction of IL-6, TNF-α, and ferritin levels.[129] A preliminary study testing the antiviral effect of oral and intranasal liposomal bovine lactoferrin in asymptomatic and patients with mild to moderate COVID-19 showed that lactoferrin treatment induced fast symptom resolution compared with standard care.[130] Treatment with lactoferrin also elicited a significant decrease in serum ferritin, IL-6, and D-dimer.

Based on available evidence, lactoferrin may represent a promising molecule to be used in both patients with acute COVID-19 or patients with postacute COVID-19 syndrome. Further investigations are needed to corroborate the positive preliminary findings obtained in patients with COVID-19, and to determine whether lactoferrin supplementation alone or with other bioactive compounds may result in additive beneficial effects against acute and postacute COVID-19.

Probiotics

The gastrointestinal system may be affected during acute and postacute COVID-19.[131] Gastrointestinal symptoms, such as diarrhea, nausea, vomiting, and loss of appetite, are commonly experienced by people with COVID-19. SARS-CoV-2 RNA may be detected in stools even after viral clearance in the respiratory tract.[132] Moreover, alterations in gut microbiota were associated with COVID-19 severity, possibly as a consequence of a "leaky gut" phenomenon and the release of microbial products and toxins into systemic circulation.[133,134] Long-term antibiotic therapies, hospitalization, stress, comorbidities, and the direct action of SARS-CoV-2 on ACE2 receptor at the gastrointestinal level are associated with gut dysbiosis. Perturbations in gut microbiota may persist months after acute COVID-19 and may be associated with long-term complications.[135]

Probiotics are “live microbes that, when administered in adequate amounts, confer health benefits on their hosts.”[136] Probiotics (mainly Bifidobacteria and Lactobacilli) may exert relevant immunomodulatory functions on the gut-lung axis.[137] Probiotics increase host mucosal defense through the stimulation of immunoglobulin A secretion, induce polarization of the immune response toward Th1, modulate cytokine production, and produce metabolites, such as short chain fatty acids, that contribute to set the tone of the immune system.[138] Probiotics may have also anti-inflammatory,[139] antioxidant,[140] and antiviral properties.[141] Interestingly, an in silico molecular docking approach suggested that metabolites from *Lactobacillus plantarum* may have potential antiviral activity against SARS-CoV-2 by targeting helicase nsp13.[142] Probiotics may also have synergistic antiviral activities when combined with compounds with antimicrobial properties. For instance, Lacticaseibacillus paracasei DG strain enhances the lactoferrin anti–SARS-CoV-2 response in Caco-2 cells.[143]

Numerous studies are currently testing the use of different mixtures of probiotics as adjunctive treatment for the management of both acute and postacute COVID-19.[141,144,145] Preliminary evidence suggests that probiotics administration may reduce secondary infections in people with severe COVID-19.[146] The consumption of a specific bacterial formulation containing strains of *Streptococcus thermophilus*, *Lactobacillus acidophilus*, *Lactobacillus helveticus*, *Lactobacillus paracasei*, *L plantarum*, *Lactobacillus brevis*, and *Bifidobacterium lactis* was associated with remission of gastrointestinal symptoms and reduced risk of respiratory failure in hospitalized patients with COVID-19.[145] In COVID-19 outpatients, the administration of a mixture of

Lactiplantibacillus plantarum and *Pediococcus acidilactici* strains improved viral clearance and reduced both respiratory and gastrointestinal symptoms compared with placebo.[147]

Further studies are needed to assess the effects of specific probiotic formulations and/or the combination of probiotics with other bioactive compounds on long-term COVID-19 sequelae.

The use of probiotics may be particularly recommended in older patients with COVID-19, in whom age-related factors, including frailty, multimorbidity, and malnutrition, may aggravate gut dysbiosis.

Vitamin D

Vitamin D plays a crucial role in the regulation of calcium and bone metabolism.[148] Accumulating evidence from preclinical and observational studies suggests that vitamin D could be involved in many extraskeletal pathways, including immune and muscle function, reproduction, and energy metabolism.[148] Vitamin D may modulate different aspects of the innate and adaptive immune response.[149] Both vitamin D receptor and enzymes involved in vitamin D metabolism are expressed by several immune cell types, including lymphocytes, monocytes, macrophages, and dendritic cells.[149]

Vitamin D may support innate immunity by stimulating the synthesis of several antimicrobial peptides, including cathelicidins and defensivins.[150] Vitamin D may also regulate the activity of antigen-presenting cells, T- and B-cell differentiation, and the balance between proinflammatory and anti-inflammatory cytokines.[151] Low vitamin D levels were associated with increased risk of numerous immune-related conditions, including type 1 diabetes,[152] multiple sclerosis,[153] and rheumatoid arthritis.[154] Furthermore, people with vitamin D deficiency tend to be more prone to develop acute respiratory infections.[155]

Vitamin D deficiency has been associated with increased risk of SARS-CoV-2 infection and worse clinical outcomes, including more severe lung impairment, need for respiratory support and intensive care, and mortality.[156,157] Hence, vitamin D supplementation has been tested as a candidate adjunctive treatment for COVID-19. In asymptomatic or mildly symptomatic individuals with SARS-CoV-2 and vitamin D deficiency, a 7-day administration of high-dose vitamin D (60,000 IU of cholecalciferol per day) accelerated viral clearance compared with placebo.[158] Vitamin D supplementation taken before or during COVID-19 was associated with better 3-month survival in older adults hospitalized for COVID-19 compared with nonsupplemented peers.[159] However, a recent living systematic review found insufficient evidence to determine the benefits of vitamin D supplementation as a treatment of COVID-19, owing to the heterogeneity of studies, including different supplementation strategies, formulations, vitamin D status of participants, and reported outcomes.[160]

As for postacute COVID-19, data on the association between vitamin D levels and the persistence of symptoms are scarce. In a small group of COVID-19 survivors from Dublin, persistent fatigue and reduced exercise tolerance were not associated with vitamin D levels.[161]

Because of the multiple effects of vitamin D on biological pathways associated with long COVID and its relevance for the overall health status, vitamin D supplementation should be considered to avoid the detrimental consequences of vitamin deficiency. This holds true in particular for vulnerable people, such as older COVID-19 survivors, in whom vitamin D may also contrast geriatric conditions, such as frailty and sarcopenia, that are associated with negative health outcomes and may further reduce the quality of life.[162]

Pollen-Based Herbal Extracts

Pollen, the male gametophyte of the flower, has long been used for therapeutic purposes by various ancient civilizations.[163] Pollen contains a mixture of amino acids, carbohydrates, minerals, and bioactive substances that vary depending on the plant source and geographic origin, climatic conditions, soil type, and the activity of bees.[164]

Purified cytoplasm of pollen (PCP) is a nonhormonal herbal remedy used to manage vasomotor symptoms and sleep and mood disorders in menopausal women.[165] Even if the mechanisms of action of PCP are not fully understood, this compound seems to act as a selective serotonin reuptake inhibitor (SSRI)-like agent to increase serotonin availability in hypothalamic serotonergic neurons. This explains, at least partly, its efficacy in controlling thermoregulation, and sleep and mood disorders in menopausal woman, without the adverse effects of currently prescribed SSRIs.[166] Another putative mechanism action of PCP could be based on the precursors of serotonin. Indeed, tryptophan and methyl serotonins have been identified in low concentrations in PCP extracts, even if their contribution to intraneuronal serotonin synthesis could be negligible.[166] Studies conducted in women with symptomatic menopause demonstrated that PCP supplementation improved sleep quality and quality of life and reduced hot flushes, fatigue, and muscle and joint pain.[165,167] The most common symptoms complained of by COVID-19 long haulers are fatigue, muscle weakness, and sleep difficulties, with a higher risk of developing anxiety or depression. Given the accumulating evidence on the effects of PCP in contrasting these symptoms in menopausal women, it could be speculated that PCP may be used as a remedy to mitigate persisting symptoms in long COVID patients.

Beetroot Juice

Beetroot juice, which is obtained from the red beetroot (*Beta vulgaris*), has spurred much attention owing to its potential beneficial effects on cardiovascular health, metabolic homeostasis, inflammation, and pulmonary function.[168–170] The multiple health benefits of beetroot juice have traditionally been attributed to its high nitrate (NO_3^-) content. Following ingestion, beetroot juice (as well as other nitrate-rich foods, such as leafy green vegetables) increases NO availability through the nitrate-nitrite-NO pathway.[171] Dietary nitrate administration in the form of beetroot juice has been extensively studied in sport nutrition, owing to its purported beneficial effects on physical performance.[172] In this context, beetroot juice may improve both endurance and power exercise performance through increasing NO bioavailability, which in turn modulates mitochondrial respiration, reduces oxygen cost of exercise, and improves muscular and cerebral perfusion.[173,174] Recent evidence has shown that the stimulation of the nitrate-nitrite-NO pathway by beetroot juice consumption may improve endothelial function, as measured by flow-mediated dilation, in persons with or at risk of endothelial dysfunction, including older adults,[175] people with peripheral artery disease,[176] pregnant women,[177] and persons with hypercholesterolemia[178] and hypertension.[179] Moreover, beetroot juice ingestion was associated with a reduction in blood pressure in normotensive[180] and hypertensive people,[181] and in older adults.[182] Interestingly, higher baseline blood pressure, being overweight or obese, and male sex were associated with better response to beetroot juice supplementation.[183] Beetroot juice consumption may also increase NO bioavailability in upper and lower airways, which boosts innate immune defense and protects against respiratory tract infections.[184] In people with chronic obstructive pulmonary disease, nitrate-rich beetroot juice improves exercise tolerance as measured by the Borg Rating of Perceived Exertion scale.[185]

Accumulating evidence in preclinical models of inflammatory diseases suggests that inorganic nitrate and nitrite may modulate the inflammatory response by acting on neutrophil and monocyte/macrophage recruitment and activation.[171] Only a few studies have investigated the effects of beetroot juice ingestion on the inflammatory response in humans. In healthy older volunteers and individuals with hypercholesterolemia, both acute and medium-term supplementation with beetroot juice was associated with a reduction in proinflammatory monocyte-platelets aggregates.[178,186] Moreover, a decrease in neutrophil activation was observed within 3 hours of beetroot juice supplementation.[186]

Besides nitrate, beetroot juice also contains a plethora of bioactive ingredients with antioxidant and anti-inflammatory properties, including polyphenols, carotenoids, betalains, and organic acids.[169,187] In particular, betalains, a class of natural pigments that includes the red-violet betacyanins and the yellow-orange betaxanthins,[188] have gained much attention owing to their ability of stimulating the activity of antioxidant enzymes and inhibiting the inflammatory cascade.[169,187] Betanin, the most abundant betalain found in beetroots, may directly scavenge reactive oxygen species[189] and increase the expression of catalase, superoxide dismutase, and glutathione peroxidase through the activation of Nrf2/antioxidant response element pathway.[190] Moreover, betanin and its derivatives may exert anti-inflammatory effects through the inhibition of COX2[191] and lipoxygenase 1.[192] Betanin may also inhibit NF-κB, a master regulator of the inflammatory response.[193] Very few studies have investigated the anti-inflammatory effect of betanins in humans.[194] Ten-day supplementation with betalain-rich beetroot extracts reduced the concentration of TNF-α and IL-6 in people with osteoarthritis.[195] Consumption of both raw beetroot juice and cooked beets reduced intracellular adhesion molecule-1, vascular endothelial adhesion molecule-1, CRP, IL-6, E-selectin, and TNF-α in adults with hypertension.[181] Although both supplementation forms were effective, people consuming beetroot juice showed greater improvement in systemic inflammatory parameters, as well as in blood pressure and endothelial function.[181] Collectively, these findings suggest that beetroot juice may have multiple beneficial effects on crucial physiologic functions that could be exploited against COVID-19 and its systemic consequences.[196]

Further studies are needed to investigate the effects of supplementation with beetroot juice and/or its derivatives in patients with COVID-19 across disease stages and during recovery.

Ongoing Studies

Based on the putative beneficial effects against several processes involved in long COVID, a panel of bioactive foods, nutraceuticals, and supplements is being tested in the outpatient service at the Fondazione Policlinico A. Gemelli IRCSS (Rome, Italy) (**Fig. 1**)

A combination of amino acids and malic, succinic, and citric acid (Amino-Ther Pro; Professional Dietetics, Milan, Italy) has been tested in patients with long COVID with malnutrition and fatigue. Preliminary data on the first 20 patients show improvement in nutritional status and better performance on the handgrip strength and five-repetition chair-stand test after 2 months of treatment (The Gemelli Against COVID-19 Post-Acute Care Study Group, 2022).

In a second pilot study, patients with persistent fatigue received a combination of amino acids and micronutrients (including magnesium, selenium, iron) (ApportAl; PharmaNutra, Pisa, Italy). After 6 weeks of treatment, muscle mass and strength improved with a significant reduction of inflammatory markers (CRP and IL-6) (The Gemelli Against COVID-19 Post-Acute Care Study Group, 2022).

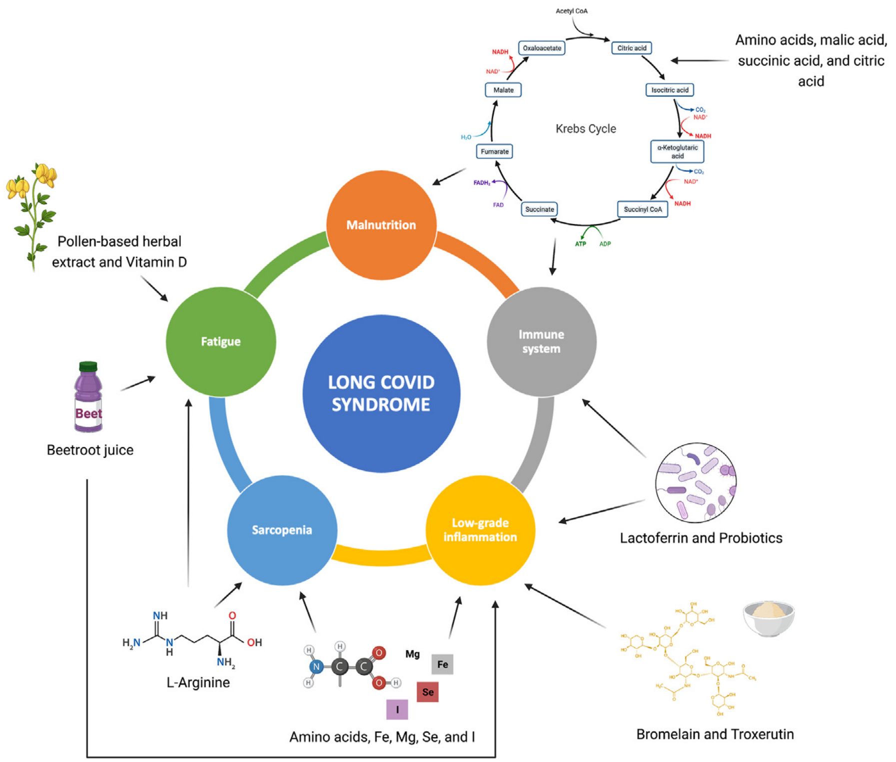

Fig. 1. Long COVID pathophysiological processes potentially targeted by the nutraceuticals and dietary supplements described in the study.

L-Arginine plus vitamin C (Bioarginina C; Farmaceutici Damor, Naples, Italy) has been tested in COVID-19 survivors with persistent fatigue. Preliminary results on the first 46 patients treated with Bioarginina C indicate reduction in fatigue, better physical performance, and better quality of life (The Gemelli Against COVID-19 Post-Acute Care Study Group, 2022).

A combination of bromelain and troxerutin (BromeREX; Pharma G, Anzio, Italy) has been tested in patients with long COVID with increased inflammation. In the first 20 participants treated with bromelain and troxerutin, attenuation of post–COVID-19 symptoms and significant reduction of serum CRP levels were observed (The Gemelli Against COVID-19 Post-Acute Care Study Group, 2022).

A combination of lactoferrin and *L paracasei* (Pirv-F20; Farmagens Health Care, Rome, Italy) has been administered to persons with long COVID. Preliminary data suggest a significant reduction in inflammatory status and improvement in fatigue, dyspnea, and joint and muscle pain (The Gemelli Against COVID-19 Post-Acute Care Study Group, 2022).

A pollen-based herbal extract (Femal; Shionogi, Milan, Italy) has been prescribed to women with persistent fatigue, sleep disorders, and cognitive distress (brain fog) following an acute COVID-19 episode. A substantial improvement in persistent symptoms and quality has been observed (The Gemelli Against COVID-19 Post-Acute Care Study Group, 2022).

A beetroot juice (Aureli Mario S.S. Agricola, Ortucchio, Italy) with a well-characterized phytochemical profile[197] has been tested in COVID-19 survivors with fatigue. Changes in physical performance (6-minute walking test, handgrip strength), endothelial function, inflammatory status, urinary and fecal metabolomics, and metagenomics are being evaluated. Preliminary data suggest that beetroot juice supplementation induces favorable immune and metabolic changes (The Gemelli Against COVID-19 Post-Acute Care Study Group, 2022).

Results from the authors' ongoing studies may indicate novel strategies for the management of long COVID as part of multimodal interventions. An example of such interventions combining personalized nutrition counseling and physical activity was successfully in the Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies" (SPRINTT) project.[198] A multimodel intervention inspired by SPRINTT is currently being implemented at the authors' outpatient clinic.[199]

SUMMARY

Long COVID affects a large share of persons of all age groups but may be especially burdensome for vulnerable older adults. Long COVID has a complex pathophysiology encompassing inflammatory and autoimmune processes, perturbations in metabolic pathways, and alterations in endothelial function and redox homeostasis.

The management of long COVID requires a multidimensional approach that should include a comprehensive nutritional assessment. Several food bioactive compounds, nutraceuticals, and supplements may target specific pathways involved in long COVID and may, therefore, be used as an adjunctive therapy to manage the condition.

CLINICS CARE POINTS

- Long COVID affects a large share of persons of all age groups but may be especially burdensome for vulnerable older adults.
- Long COVID has a complex pathophysiology, and its management requires a multidimensional approach that should include a nutritional assessment.
- Food bioactive compounds and nutraceuticals may target specific pathways involved in long COVID.

DISCLOSURE

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FURTHER READING

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