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Review Article

Impact of nutrition on long COVID

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ABSTRACT

Long COVID is characterized by a group of persistent symptoms following the acute SARS-COV2 infection, which presented a multifaceted challenge to the healthcare systems all over the globe. The long COVID symptoms span various organ systems including the respiratory, cardiovascular, gastrointestinal, and neurological manifestations. Mitochondrial dysfunction and immune dysregulation play crucial roles in the long COVID pathophysiology. Recently nutritional intervention gained much attention in managing post-viral syndromes. Effective interventions like supplementation of omega-3 fatty acid, macro and micro nutrients, and vitamins help to reduce systemic inflammation and counteract muscle wasting. Other approaches like nutritional recovery, dietetic interventions, continuous nutritional care post-hospital discharge, nutritional rehabilitation programs, whole-diet approaches like Mediterranean diet, plant-based diet, and caloric optimization, improve overall functional recovery. Physical activity and exercise regimes have been shown to improve fatigue, dyspnea, and cognitive function. Tailored exercise regimes may promote safe rehabilitation. Certain ineffective interventions, such as non-personalized approaches, high dose of antioxidants, use of herbal products that are not clinically validated need to be addressed. Dietary interventions such as personalized nutritional counseling have been demonstrated to improve physical performance in long COVID patients. Further research is needed to refine protocols and identify optimal combinations of dietary and movement-based therapies to support the recovery of long-COVID patients. This narrative review focuses on the ongoing researches that reveals the intricate relationship between nutrition and long COVID recovery and also establishes effective protocols for nutritional care.

1. Introduction

SARS-CoV-2 virus with its 29.9 kb single-stranded RNA inserts into the human DNA and reprograms the larger size human DNA and changes the human cellular machinery to redirect the host macromolecules for its own survival and life cycle.[1] The virus particle reprograms the human DNA resulting in metabolic dysregulation of the host.[2] The SAR-CoV-2 virus favors the host metabolic pathways for its own survival and action by specifically interacting with the host cell targets. The interaction of the virus with the host impairs the host cell bioenergetics, immune response, and redox homeostasis.[3] Thus, the SARS-CoV-2 virus induces human metabolic reprogramming/dysregulation (HMRD) in the infected human host and produces severe consequences.[4] The virus-induced HMRD was not reduced even after the host declared virus free through negative RT-PCR tests. Long COVID or post-acute sequelae of SARS-CoV2 infection (PASC) affects numerous individuals who have recovered from COVID-19 infection.[5,6] As a PASC, the survivors of COVID-19 showed certain clinical manifestations.[7,8] The PASC includes severe clinical symptoms that may cause metabolic dysfunctions in the cardiovascular, gasterointestinal (GI), central and peripheral nervous system (CNS/PNS), pulmonary, skeletomuscular, reproductive, and endocrine systems.[9,10] The pathophysiology of long COVID involves persistent viral reservoirs, immune system dysregulation, tissue damage, and multi-organ failure.[8] Onset of metabolic diseases like Type 2 diabetes mellitus (T2DM), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), dysautonomia, and postural orthostatic tachycardia syndrome (POTS) were found in PASC.[9,11,12] The complexity of multisystem symptoms requires a broad scale perspective including multiple organ systems[13] (Fig. 1). Long COVID diagnosis and management are highly challenging as its complications involve persistent viral reservoirs, dysregulation of immune system, and long-term tissue damage.[14]

2. Pathophysiology of long COVID and nutritional relevance

The SARS-CoV-2 invasion and infection induce human-pathogen interactions and result in host metabolic reprogramming (HMR), iron

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Abbreviation list

25-OHD	25-hydroxyvitamin D
ACE2	Angiotensin-converting enzyme 2
AD	Alzheimer's disease
ADAMTS-13	A disintegrin and metalloproteinase with thrombospondin motifs-13
Ang-2	Angiotensin-2
ARDS	Acute respiratory distress syndrome
BBB	Blood brain barrier
BM	Bone marrow
BMD	Bone mineral density
BMI	Body mass index
BMSCs	Bone marrow stem cells
CCL	C-C motif chemokine ligand
$CD4^+$, $CD8^+$	Cluster of differentiation 4+, 8+
CFQ	Cognitive failures questionnaire
CFS	Chronic fatigue syndrome
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CVDs	Cardio vascular diseases
CXCL	C-X-C motif chemokine ligand
DCs	Dendritic cells
EBV	Epstein-Barr virus
EFAs	Essential fatty acids
eGFR	Effective glomerular filter rate
EPCs	Endothelial progenitor cells
EPO	Erythropoietin
FAS	Fatigue assessment scale
FeRD	Iron (Fe)-redox dysregulation
GDNF	Glial derived neurotrophic factor
GFAP	Glial fibrillary acidic protein
GI	Gastero intestinal
HADS	Hospital anxiety and depression scale
HEP	Hepcidin
HMRD	Human metabolic reprogramming/dysregulation
HO-1	Heme oxygenase-1
hsCRP	High sensitive C-reactive protein
HSCs	Hematopoietic stem cells
IBW	Ideal body weight
ICU	Intensive care unit
IGFBP-4	insulin growth factor binding protein 4
IL	interleukin
ITP	Immuno thrombocytopenia
IU	International unit
LBP	lipopolysaccharide binding protein
LF	Laoferrin
M-CSF	Macrophage colony stimulating factor
ME	Myalgic encephalomyelitis
MMP	Matric metallo proteinase
MSCs	Mesenchymal stem cells
mtDNA	mitochondrial DNA
MUFAs	Mono unsaturated fatty acids
NF-κB	Nuclear factor kappa B
NFL	Neurofilament light chain
NGF- β	Neurotrophic growth factor- β
NLRP3	Nod like receptor protein family 3
NMDARs	*N*-methyl-d-aspartate receptors
NO	Nitric oxide
OPG	Osteoprotegerin
Ox-LDL	Oxidised low-density lipoprotein
PASC	Post-acute sequelae of SARS-CoV2 infection
PBD	Plant-based diet
PD	Parkinson's disease
PF4	Platelet factor 4
PNS	Peripheral nervous system
POTS	Postural orthostatic tachycardia yndrome
PUFAs	Poly unsaturated fatty acids
RBD-SD-1	Recombinant receptor binding spike protein of SARS-CoV-2
RCT	Randomized controlled trial
ROS	Reactive oxygen species
SCFA	Short chain fatty acids
SOC	standard of care
Syk	Spleen tyrosine kinase
T2DM	Type 2 diabetes mellitus
TCA	Tri chloroacetic acid
TGF-β	Transforming growth factor-beta
TNF- α	Tumour necrosis factor-alpha
VEGF	Vascular endothelial growth factor
VWF	von Willebrand factor
VZV	Vvaricella-zoster vvirus
WPB	Weibel-palade bodies

(Fe)-redox dysregulation (FeRD), altered mitochondrial function, which further leads to disturbance in cellular energy homeostasis, which cumulatively results in compromised host defense.[15] The post-COVID syndrome can last for weeks, months, or years and affect various organs of the body, such as the heart, lungs, brain, muscles, joints, and blood vessels. The pathophysiology is complex, and a plethora of multiple overlapping mechanism leads to a weak immunologic response.[16] SARS-CoV2 virus hijacked the host cell machinery and manifests mitochondrial dysfunction by disturbing mitochondrial membrane potential, mitochondrial permeability, pore opening, increased reactive oxygen species (ROS), and disturbs the redox homeostasis.[17,18] In particular the ORF9b of SARS-CoV2 RNA evades host mitochondria and releases host mitochondrial DNA (mt-DNA) into the cytoplasm, which triggers the mt-DNA induced inflammasome and suppresses innate and adaptive immunity.[19] Thus, the altered mitochondrial functions induce hyper-inflammation with cytokine storm and massive outburst of ROS.[20] Most significant mechanism of the virus induced hypoxia is termed as 'Warburg' effect, which involves the initiation of complex host pathogen interaction by SARS-CoV2 virus, alteration of mitochondrial function by disrupting the glycolysis and Tri chloroacetic acid (TCA) cycle, which affect many metabolic pathways of amino acids, fatty acids, nucleotide and antioxidant synthesis, which in turn compromise host endocrinal, cardiovascular, gastrointestinal, pulmonary, reproductive and neurocognitive functions which are all requires high energy demand and mitochondrial oxygen consumption.[21,22]

The viral residuals induce chronic phase of long COVID. This viremia and insufficient antibody contribute to the systemic inflammation, damage the CNS by endothelitis and disrupting blood brain barrier (BBB), thereby causing neuronal loss.[23,24] SARS-CoV2 infection selectively targets the mitochondria of neurons, leading to brain fog and eventually impairing cognitive function.[25] The persistent immunologic response and viral induced cytokine storm rush the production of pro-inflammatory cytokines interleukin-7 (IL-7) and interferon- γ (IFN-γ).[26] The continuous activation of IL-6, IL-1β and tumour necrosis factor-α (TNFα) produce multiple organ specific effects such as cardiac dysrhythmias, neuroinflammation, neurodegeneration, renal injury, peripheral insulin resistance, bone resorption and hair loss in post--COVID.[27] Activation of NLRP3 inflammasome in addition to IL-18 and IL-1β affects cerebral function, and the NLRP3 inflammasome leads to the accumulation of amyloid- β peptides, resulting in neurodegenerative

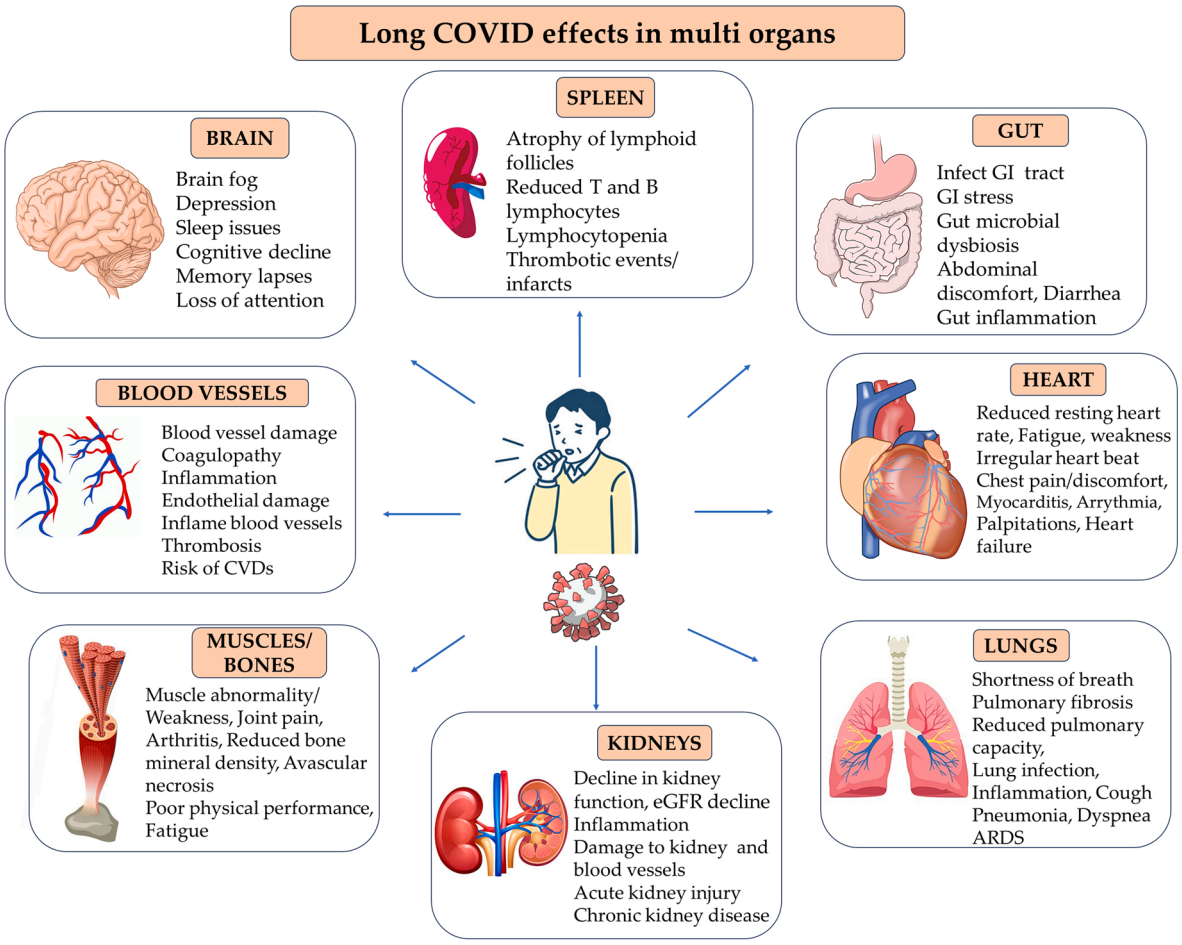

Fig. 1. Post-Acute Sequelae of SARS-CoV2 infection (PASC) and its multi organ impact. GI-gastero intestinal; ARDS-acute respiratory distress syndrome; eGFR-effective glomerular filter rate; CVDs-cardio vascular diseases.

conditions.[28] The hyper-inflammatory condition causes loss of appetite, altered intestinal absorption, disturbed gut permeability, and malnutrition.[29,30] The malnutrition induces inflammatory signalling and results in increased risk of microbial infections, dysbiosis.[31] In individuals with long COVID, changes were found in hematological parameters such as anemia, lymphopenia, alterations in red blood cells, and elevated inflammatory markers like ferritin, D-dimer and IL-6.[32] Other evidences suggest that some long COVID patients reported lower haemoglobin levels, enhanced D-dimer levels, and thrombocytopenia.[33,34] The D-dimer assessment carried out in patients after a median of 94 days following COVID-19, it was found that D-dimer was elevated under long COVID conditions. The persistent elevation of D-dimer is recognized as a marker for coagulation activation that predisposes long COVID patients to thromboembolic complications. Thus, a significant proportion of long COVID patients show a hypercoagulable state with increased risk of thrombotic events.[33] Long COVID individuals show pronounced immune dysregulation, exhibited immune alterations, including T cell alterations, reduced $CD4^+$, $CD8^+$ memory cells, lack of naive T cells and B cells, elevated expression of type I and type III interferons, increased IL4, IL6 secreting $CD4^+$ T cells at a median of 14 months after infection.[35]

Long COVID patients develop more predictive symptoms such as fatigue, headache, shortness of breath, hoarse voice, and myalgia. These illnesses were found more prevalent among women, elderly people, and people with obesity.[36] Long COVID effects involve the cardiovascular system. Longitudinal studies report dial damage, heart failure in general population and in elderly people with co-morbidities.[37] High risk of muscle weakness and poor physical strength are observed in post-acute COVID-19 patients.[38] Other reports demonstrate cutaneous manifestations and alopecia in patients.[39,40] Neurologic complications, such as anosmia, cognitive and motor impairment,[41] hyposmia, pain and insomnia, hypometabolism in brain regions orbital gyrus, olfactory gyrus, temporal lobe, amygdala, hippocampus, thalamus, pons/medulla rain stem, and cerebellum.[42]

3. Bone marrow and stem cell exhaustion in long COVID

SARS-Cov-2 infection has been recognized for its direct and indirect effects on bone health, driven by the cellular and inflammatory mechanisms. The post-acute sequelae of SARS-CoV-2 infection changes the bone health by affecting bone marrow (BM) cells, altering bone structure, and number of osteoclast cells. The inflammatory cytokine storm triggered by the virus stimulate osteoclast activity and produce bone loss. Hypocalcemia, reduced bone mineral density (BMD), and prevalence of vertebral fractures were become more prevalent after COVID infection.[43] Epidemiological data indicated that in several cases, skeletal health was also significantly affected by SARS-CoV-2 infection. The presence of ACE2 receptors on bone cells leads to direct infection of virus in BM cells. In addition to ACE2 receptors, virus remodels the bone, and affects the osteoclast through ACE2/Ang-(1–7)/MasR axis.[44] The recombinant receptor binding spike protein of SARS-CoV-2 (RBD-SD-1) was used to study the SARS-CoV-2 virus trophism in 33 kinds of human tissues, among all the tissues, the RBD-SD-1 probe was strongly binded with BM cells. This indicates that SARS-CoV-2 virus interactions with BM niche, especially hematopoietic stem cells (HSCs).[45] The BM stem cell exhaustion arises from the acute infection, and immune responses elicited by vaccination is a significant contributor to COVID

pathophysiology. SARS-CoV-2 infection affects the BM microenvironment, causing damage to HSCs and endothelial progenitor cells (EPCs).[46] COVID virus infect the EPCs directly and disrupts the homeostasis haemoglobin, thus the red blood cells become a direct target of covid virus.[47] COVID infection alters and significantly affects blood cells and BM of patients, resulting in conditions such as cytopenia, pancytopenia, hemophagocytosis, and BM necrosis. The immunomodulatory therapies help in minimizing the hyperinflammation condition of long COVID. Mesenchymal stem cells (MSCs) are effectively used in immunomodulatory therapies due to its anti-inflammatory and tissue-regenerative properties.[48]

The effect of SARS-Cov-2 virus on blood cells indicates that the viral infection involves the BM as its the place of production and maturation of blood cells. Hence investigating the effects of virus on BM is necessary.[49] In long COVID context, the bone marrow stem cell exhaustion arises due to depletion and functional disturbance in stem cells of bone marrow. The inflamamtory milieu arised from viral infection attenuates the differentiation capacities of bone marrow stem cells (BMSCs), thus causing the exhaustion of HSCs and MSCs. Bone abnormalities in COVID patients are common due to its direct infection of bone marrow cells. The bone abnormalities can be due to the viral particle onto ACE2 receptors on $CD14^{+}$ monocytes, a precursor to osteoclasts.[44] SARS-CoV-2 virus cause aseptic necrosis of the bone by binding to ACE2 receptors of endothelial cells, lungs, other tissues, and penetrates the endothelial cells of the vessels and produce vascular damage by inflamamtory syndrome and coagulation.[49] The acute inflammatory conditions induce collagen changes and affect bone health.[50] Another contributing factor is the hypoxic condition induced by viral infection. The low oxygen level in tissues produce bone resorption by increasing osteoclasts. Additionally, the bone mineralization gets affected through acidosis. Hypoxia upregulates erythropoietin (EPO), glycoprotein, which supresses the formation of bones. Other conditions, such as anemia and chronic obstructive pulmonary disease (COPD) also produce hypoxic conditions and further impact the bone health which, reduce BMD and increase the risk of bone fractures.[43] Direct invasion of SARS-CoV-2 in HSCs induces the mechanism of hypoxia or hyperinflammation in hematopoietic system and leads to stress in erythropoiesis, lymphopenia, neutrophilia and thrombocytopenia.[51] On the other side, not only the COVID infection, but the vaccination also developed BM suppression, pancytopenia, and thrombocytopenia. A 74-years old male reportedly developed BM suppression seven days after receiving Pfizer SARS-Cov-2 vaccine.[52]

COVID vaccines showed side effects such as mild to severe anaphylaxis and immuno thrombocytopenia (ITP)[53] that targets the immune system, and destroys the platelets produced by megakaryocytes in BM. And the function of platelets in inflammatory signalling and preventing microbial invasion are slowed down during COVID infection. The autoantibodies arised by COVID infection also trapped the platelets and destroyed it. In some cases, COVID-19 increased immature platelets and increased coagulation.[49] To control the immune dysfunction, non-pharmacological therapies can effectively halt the immune dysregulation. Immunomodulation by using stem cells can be an effective option. MSCs are now promising and efficient candidates in pre-clinical studies. MSC transplantation in severely ill COVID patients significantly improved the pulmonary functions.[54] Most importantly, MSCs are ACE-2 negative genetically, and unlikely to encourage the viral attachment in transplanted cells. When critically ill COVID-19 patients treated with MSCs derived from human umbilical cord, it improved functional outcomes. Hence, the MSCs can help modulating the immune response in a positive way.[54] BMSC exhaustion is a vital mechanism in long COVID that affects the BM derived stem cells, particularly HSCs. These stem cell populations undergo persistent activation during COVID infection, resulting in impaired haematopoiesis, and chronic inflammation. Long COVID condition altered the hematologic functions, which is a reflection of underlying BM exhaustion. In other scenarios, vaccine-induced BM exhaustion also occurs. To investigate the disability and reversibility of BMSC function in long COVID conditions, further pre-clinical and clinical research is required to analyse the possibilities of regenerative therapies using stem cell restoration.

4. Biomarkers of long COVID

As the exact mechanism and symptoms of long COVID still remain unknown. Identifying the biomarkers is currently of greater scientific focus. Researchers work on biomarkers for long COVID to evaluate most frequent symptoms like immunological and inflammatory conditions, endothelial and vascular dysfunction, and also the metabolic and clotting abnormalities.[55] Blood-based biomarkers are significantly important indicators, or act as therapeutic targets for diagnosing and treating long COVID. A systemic review carried out by Lai and team, focused on the blood-based biomarkers associated with long COVID symptoms and progression, identified about 113 biomarkers categorised under 6 biological sections including cytokines/chemokine, biochemical, vascular, neurological, acute phase proteins, and other markers.[56] Acute phase proteins, including albumin, CRP, ferritin, fibrinogen; biochemical markers, including 1-methylnicotinamide, β-glucan, glutamine/glutamate ratio, indole 3- acetic acid, L-Cysteine, Lactate dehydrogenase, L-glutamine, L-methionine, Pipecolic acid, Quinolinic acid, S-Sulfocysteine, Taurine, Tryptase, Cytokine; and chemokine markers, such as, C-C motif chemokine ligand (CCL) 2–7, CCL 19, CCL 20, CCL 23, C-X-C motif chemokine ligand (CXCL) 1, CXCL9-11, G-CSF, GM-CSF, IFN-α, β, γ, IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-7, IL-10, IL-10Rβ, IL-12β, IL-13, IL-17, IL-18, IL-33, IP-10, Macrophage colony stimulating factor (M-CSF), tumour growth factor- α (TGF-α), TGF-β, TNF-α, TNF-β; neurological markers like glial derived neurotrophic factor (GDNF), glial fibrillary acidic protein (GFAP), neurotrophic growth factor- β (NGF- β), Neurofilament light chain (NFL), Neurotrophin-3; vascular markers, including Ang-2, D-dimer, Factor VIII, Matric Metallo Proteinase-1,9 (MMP 1,9) vascular endothelial growth factor (VEGF), von Willebrand factor (VWF) antigen, VWF propeptide; and other markers like Artemin, Caspase 8, Cystatin-5, Cystatin C, insulin growth factor binding protein 4 (IGFBP-40), lipopolysaccharide binding protein (LBP), miRNA21, OPG, Sirtuin 2 and zonulin.[56] In order to monitor and treat long COVID symptoms, studying the clinically relevant circulating biomarkers has become essential to understand patients' clinical condition. Increased levels of NFL and GFAP in serum are signs of neuronal damage or progressing neurodegenerative diseases like Alzheimer's disease (AD),[57] or Parkinson's disease (PD).[58] The immune response elicited in long COVID patients results in higher levels of pro-inflammatory cytokines/chemokines, including IL-4, IL-6, IL-7, TNF-α, C-C motif chemokine ligand 2 (CCL-2), CRP, and ferritin. Elevated levels of NFL, vascular endothelial growth factor (VEGF), and reduced haemoglobin levels are marked evidence for worsening long COVID symptoms.[55] During the convalescent phase of COVID-19, the common inflammatory and immunological markers such as IL-6, TNF-α, antiphospholipid antibodies, and lupus anticoagulant were found in patients.[59] Long COVID may be related to microvascular inflammation causing clumping and clotting of red blood cells and platelets, thrombotic complications. Bellone et al. evaluated the levels of VWF, and Factor VIII in PASC/long COVID patients. Their results show that VWF and factor VIII levels were found elevated for at least 2 years in patients with long COVID symptoms.[60] These alterations promote pulmonary micro thrombosis and continuous endothelial activation. Another study reviewed the VWF/A Disintegrin and Metalloproteinase with Thrombospondin Motifs-13 (ADAMTS-13) axis imbalance and endotheliopathy in long COVID and its relevance to dysregulated angiogenesis, immuno thrombosis, sustained endothelial and coagulation activation. Analysis of 50 patients during their convalescent phase showed elevated VWF-ADAMTS-13 ratio, platelet factor 4 (PF4), Weibel-Palade bodies (WPB), Angiotensin-2 (Ang-2), and Osteoprotegerin (OPG) proteins.[61] WPB found in endothelial cells store and release important VWF, Ang-2, PF 4, and P-selectin molecules responsible for inflammatory responses.[61] Neurological long COVID sequelae accelerated by IL-6, TNF-α, and CRP, which induce immune cells and activate neuroinflammation. The proteins responsible for

maintaining neuronal stability of axons and astrocytes NFL, and GFAP are biomarkers of neuronal damage.[62,63] COVID patients with headaches and persistent neuropathic pain showed elevated serum levels of NFL and GFAP.[64,65] Long COVID patients with pulmonary fibrosis showed elevated IL-6, TNF-α, and TGF-β.[66] A cross-sectional Mount Sinai-Yale long COVID (MY-LC) study involving 275 participants showed decreased systemic serum cortisol, and serum galectin 1 concentration acts as a significant predictor of long COVID. In addition, significant immunological differences were found. The populations of non-conventional monocytes, double-negative B cells, conventional dendritic cells, and memory $CD4^+$ T cells were decreased. Long COVID individuals had higher levels of antibodies to SARS-CoV-2, Epstein-Barr virus (EBV), and varicella-zoster virus (VZV) antigens, and marked changes in circulating cytokines and hormones also noted.[35] Oxidised low-density lipoprotein (ox-LDL), increased fungal cell wall polysaccharide (1,3)-β-d-glucan, intestinal permeability marker zonulin were found in long COVID individuals, and these markers clearly show the alteration in gut integrity, tight junction permeability, and fungal translocation. Increased ox-LDL, a major contributor to atherosclerosis stimulates the inflammation leading to prolonged expression of TNF-α and IL-6 genes. The inflammation induced by ox-LDL activates TLR-4 dependent inflammasome.[67,68] The translocation of β-d-glucan in the plasma of long COVID individuals directly proportional to inflammation and elevated levels of host metabolites, which in turn activate the *N*-methyl-d-aspartate receptors (NMDARs) and tryptophan catabolism pathway that has been associated with neurotoxic effects through higher levels of quinolinic acid and S-Sulfocysteine.[69] The translocated β-d-glucan also induces inflammasome through by activating spleen tyrosine kinase/Nuclear factor kappa B (Syk/NF-κB) pathway. As a consequence of this, PASC contributes to the elevated and sustained levels of immune activation and inflammation.[69] The long COVID management and patient care require knowledge about long COVID biomarkers and symptom management approaches. The biomarkers may serve as diagnostic and prognostic markers (Table 1).

Table 1
Long COVID biomarkers.

Category	Bio markers	References
Pro-inflammatory markers	IL-2, IL-6, IL-7, IL-12β, IL-17, IL-18, IL-33 TNF-α, TNF-β, IFN-α, β, γ CCL2-7, CCL 19, CCL 20, CCL 23, CXCL 1, CXCL9-11 IL-1α, 1β, IP-10	56,66
Anti-inflammatory markers	IL-4, IL-10, IL-10Rβ, IL-13, TGF-β	66
Blood based markers	CRP, Ang-2, D-dimer, Factor VIII, VWF antigen, VWF propeptide	56,61
Protein markers	G-CSF, GM-CSF, M-CSF, GDNF, GFAP, NGF- β, NFL, Neurotrophin-3, MMP-1, MMP-9, VEGF, Artemin, Caspase 8, Cystatin-5, Cystatin C, IGFBP-4, LBP, miRNA21, OPG, SIRT 2 and zonulin, Tryptase	56,61,63
Biochemical markers	1-methylnicotinamide, β-glucan, glutamine/ glutamate ratio, indole 3- acetic acid, L-Cysteine, Lactate dehydrogenase, L-glutamine, L-methionine, Pipecolic acid, Quinolinic acid, S-Sulfocysteine, Taurine	56,69
Signalling pathways	Syk/NF-κB pathway, NF-κB signalling, NMDARs and tryptophan catabolism pathway, NLRP3 inflammasome pathway	67,68

IL-interleukin; TNF-α, β-tumour necrosis factor-alpha, beta; IFN-α, β, γ-interferon-alpha, beta, gamma; CCL- C-C motif chemokine ligand; CXCL- C-X-C motif chemokine ligand; IP-10- interferon gamma induced protein; TGF-β – tumour growth factor beta; CRP- c-reactive protein; Ang-2- Angiotensin-2; VWF- Von Willebrand factor; G-CSF- granulocyte colony stimulating factor; , GM-CSF- granulocyte-macrophage colony stimulating factor, M-CSF- macrophage colony stimulating factor, GDNF-glial derived neurotrophic factor; GFAP-glial fibrillary acidic protein; NGF- β-neuronal growth factor beta; NFL-neurofilament light chain; MMP-1, 9- matrix metalloproteinase 1,9; VEGF-vascular endothelial growth factor; IGFBP-4- insulin growth factor binding protein 4; LBP-lipopolysaccharide binding protein; OPG- Osteoprotegerin; NF-κB -Nuclear factor kappa B; Syk/NF-κB -Spleen tyrosine kinase/Nuclear factor kappa B; NLRP3-nod like receptor protein family 3.

5. Underlying mechanisms of nutrients

A complex interplay exists between nutrients and immune functions in long COVID. Various inflammatory mediators, pro-, anti-inflammatory cytokines are being regulated by specific nutritional components. Nutrients and dietary patterns influence the regulation of cytokines and chemokines. Large amount of pro-inflamamtory cytokines is released both in acute and chronic COVID conditions. Minerals, co-enzymes, and vitamins have a significant impact on the inflammatory response triggered by COVID virus. Supplementation with vitamins A, B1, B2, B3, B5, B6, B7, B9, B12, C, D, E, and K controls the TNF-α, IL-1β, and IL-6 release.[70] In COVID-infected individuals, health is compromised due damage in the gastrointestinal tract, liver, and vasculature that results in impaired nutrient absorption, which affects metabolic processes. These disruptions are due to the immune dysregulation, chronic inflamamtion, gut microbial imbalances. Long-COVID condition involves virus-induced metabolic reprogramming resulting in mitochondrial dysregulation, oxidative stress, reduced host defensive mechanisms, altered signalling pathways. These reasons are collectively suppressing the host appetite and reduce the intake, delay the recovery and worsen the nutritional deficiency.[71] Proteins are essential for repairing and maintaining cellular structures, including mitochondria. The lack of amino acids like L-carnitine in long COVID causes dysregulation in fatty acid transport to mitochondria, β-oxidation and ATP production. L-carnitine is an immune regulator that helps controlling pro-inflamamtory IL-6, IL-1, and TNF-α.[72] A diet with optimal carbohydrate to fat ratio is essential to improve mitochondrial performance through glucose metabolism.[73] Long chain omega-3 PUFAs favourably support immune function, inflammation, and oxidative stress at different stages of COVID infection. In case of long COVID, omega-3 PUFAs and their metabolites enhance the process of clearing chronic inflammation, restoring homeostatis of tissues.[74]

A randomized controlled trial studied mitochondria-derived vesicles and inflammatory profile of adults with long COVID after supplementation with red beetroot juice for 14 days. The study showed remarkably reduced serum levels of IL-1β, IL-8, TNF-α, without affecting mitochondrial circulating markers. Polyphenols from red beetroot are naturally potential antioxidants capable of regulating inflamamtory profiles in patients with long COVID.[75] Nutritional components like phytochemicals enhance mitochondrial biogenesis and control oxidative damage. Dietary components are significantly restoring the mitochondrial function. For example, curcumin is reported to have positive effect on both COVID-19 and long COVID.[76] Intake of iron is useful in reducing inflammation, fatigue and dyspnea, and also improve immune response to vaccination.[77] Zinc helps inhibiting coronavirus RNA polymerase activity invitro and viral replication in cultures cells.[78] Magnesium exhibits anti-inflammatory properties, and helps in regulating innate and adaptive immune responses. Magnesium sulfate supplementation reduced inflammatory response, and oxidative stress by controlling chemokines and cytokines such as IL-1, IL-6, IL-8, TNF-α, and CRP.[79,80] Supplementation of amino acids and micronutrients like magnesium, iron, and selenium significantly reduced CRP and IL-6.[81] Vitamins, in particular vitamin D have been highlighted for modulating mitochondrial dynamics and enhanced oxidative stress responses. By improving redox status, the interventions with vitamins and polyphenols mitigate systemic inflamamtion and thereby addresscore components of long COVID. Probiotic supplementation helps restore gut microbiota. Re-establishing gut microbiome positively influences the systemic inflamamtion, mitochondrial health and reduces immune dysregulation.[82] Vitamins reduce inflammatory and oxidative stress markers like IL-6, TNF-α, sTNF-RI, sCD163, oxLDL via regulating gut permeability and systemic inflammation.[83] Overall diets rich in both macro- and

micronutrients can significantly support mitochondrial health, reduce oxidative stress, and improve immune responses in long COVID patients.

6. Functional role of nutrient components in managing long COVID

The long COVID syndrome is characterized by malnutrition, loss of fat free mass and low-grade inflammation, fatigue, sleep disturbances, dyspnea, joint pains, anxiety, chest pain, brain fog, cognitive dysfunction, thromboembolism, loss of hair, and chronic kidney disease.[84] The nutritional assessment and status including the evaluation of dietary intake, anthropometric measures and body composition has become essential to manage the long COVID symptoms. The supplementation of nutrition using proper guidelines tailored by nutritionists has become a prominent strategy to ensure patients' recovery.[85] Malnutrition has a high impact on the recovery of patients from long COVID syndrome. Nutritional intervention plays a crucial role in managing long COVID by alleviating symptoms, and improving physical and mental well-being.[85] Nutritional status has emerged as a pivotal factor in modulating immune response and mitigate the pathological process on long COVID. Improving the nutritional status through targeted supplementation and dietary modifications could aid in restoring immune balance and promote recovery.[26] Vitamin D deficiency may exacerbate chronic inflammation and impair glycemic control,[86] and also controls the pro-inflammatory cytokines, induces macrophages and produces anti-inflammatory cytokines to reduce the risk of acute respiratory distress syndrome (ARDS).[87] Vitamin D deficiency may contribute to the exacerbation of long COVID. Its immunomodulatory properties are believed to influence the persistence of PASC.[88] Nutritional interventions that include antioxidants and anti-inflammatory nutrients can help counteract oxidative stress and modulate the pro-inflammatory cytokine release which are central to the long COVID pathogenesis.[26] Though the prohormone is mainly obtained through sun exposure to a great extent, a minor contribution can be taken over through diet. 25-hydroxyvitamin D (25OHD), an inactive precursor of vitamin D is reported to be higher in meat and fish eaters in comparison to vegetarians and vegans.[89]

The most important aspect of nutritional management is early screening and assessment for malnutrition. The health consequences in PASC require host-system targeted nutritional interventions such as immune-modulators, antioxidants, micro-, macro-nutrient metabolic optimizers, natural plant-based anti-inflammatories to manage PASC.[4] The interventions include prophylactic nutritional support, individualized calorie and protein targets, specific micronutrient supplementation such as vitamin D, vitamin C, zinc, omega-3-fatty acids to support immune functions and reduce inflammation.[90] Sarcopenia, a kind of progressive and skeletal muscle disorder, is known to occur as a long COVID complication leading to loss of muscle mass, muscle strength, physical functioning especially in older patients. A minimum daily protein requirement of 0.83 g of good quality protein/kg body weight per day is required for a healthy subject and supplementation with β-hydroxy-β-methyl butyrate or creatinine in the form of balanced diet support the muscle mass restoration and enhance fast physical recovery.[91] A systemic scoping review involving review of literature studies with participants aged 18 years of older with long COVID, who underwent a nutritional intervention highlighted that nutritional intervention is important in rehabilitation programs and to address malnutrition and muscle wasting.[92]

6.1. Macronutrients and micronutrients

The amount of protein intake directly impacts the immune system. The post COVID-19 patients' protein requirements are suggested to be higher to reduce sarcopenia and muscle mass reduction.[93] Long COVID patients are recommended to include high-quality plant and animal proteins about 15–30 g protein per meal based on ideal body weight (IBW), ensuring the intake of all essential amino acids.[94] Restriction of carbohydrates and sugar may exacerbate viral outcomes, because the pathogen-clearing $CD4^+$ and $CD8^+$ T cells require energy from glucose and anaerobic glycolysis.[95] On the contrary higher carbohydrate increase the respiratory quotient. High-glycemic index inducing carbohydrates such as white flour, refined sugar result in overload of the mitochondria and produce more free radicals. Even a small rise in glycemic index could cause immediate inflammatory response, increased cytokines, C-reactive protein (CRP), increased levels of TNF-α and IL-6.[96] Hence, maintaining a balanced carbohydrate diet is crucial both during and post-COVID. Choosing a wise amount of carbohydrate like high quality carbohydrates low glycemic load foods such as vegetables, fruits, nuts, seeds, whole grains, these do not induce post-prandial inflammatory responses. Based on the patient's glycemic control and ventilator dependency usually 30%–50% non-protein calories have been required, and the glucose must not exceed 5 $mg \cdot kg^{-1} \cdot min^{-1}$.[97] Dietary fibres are complex carbohydrates and significantly important to reduce hs-CRP, IL-6, TNF-α. Taking whole grains supports gut microbiome, lowers gut inflammation and increased SCFA production.[96] Regarding fat intake, the adequate intake of essential fatty acids (EFAs), correct proportion of poly unsaturated fatty acids (PUFAs) and mono unsaturated fatty acids (MUFAs) within 30%–45% of calories from fats could be useful in patients with pneumonia and ARDS occurred due to COVID-19.[98] Fats are essential for absorption of fat-soluble vitamins (A, D, E, and K), immune function and inflammation reduction.[90]

Micronutrients vitamin A, C, D, E, B6, B12, folate, iron, zinc, selenium, copper, and magnesium support the host-viral resistance, innate immune activation.[99] Micronutrients include 12 types of vitamins, macro-minerals and trace elements and certain ultra trace elements like nickel and boron. Vitamin A is important for epithelial cell morphology, formation of healthy mucus layers in respiratory tract and intestine, for mucus secretion and to improve antigen specific and non-specific immune functions.[100] Low vitamin A individuals showed increased risk of developing lung dysfunction and respiratory disease.[101] Vitamins A, C, D, E, Zn, Fe, Cu, and Se regulate IFN production, which is crucial for anti-viral innate immune response and antiviral cytokines, to induce inflammatory response and also for mitochondrial antiviral signalling.[99] Vitamin D regulates immune cells neutrophils, natural killer cells, macrophages, monocytes, production of pro- and anti-inflammatory cytokines, differentiation and function of T cells, and production of viral specific antibodies[99] (Fig. 2). Preliminary trial using vitamin K2/D3 in treating long COVID found to efficiently reduce long COVID symptoms. Intake of vitamin K2/D3 improved systemic inflammatory markers and gut dysfunction.[68] Vitamin D helps in the regulation of dendritic cells (DCs), monocytes/macrophages, T cells, and B cells. It also promotes the synthesis of antimicrobial peptides and enhances the production of anti-inflammatory cytokines like IL-10 and suppresses TNF-α. On the other hand, vitamin K reduced IL-6. Vitamin K3 and D3 have demonstrated anti-inflammatory effects. Treatment with vit K2/D3 supplementation found reduce long COVID index and symptoms.[68]

Although the exact pathophysiology Vitamin K2/D3 helps improving long COVID symptoms by attenuating systemic inflammation. A Randomized clinical trial (RCT) study carried out in adults experiencing ≥ 2 moderate long COVID symptoms shows that daily intake of 240 μg vitamin K2 and 2 000 IU vitamin D3 for 24 weeks reduced long COVID index by 7.1% and reduced the ox-LDL, inflammatory markers, serum TNF R1 and serum CD163 and fungal translocation marker 1,3- β-d-glucan. This study concludes that daily intake of vitamins K2 and D3 improved the RECOVER long COVID index, gut and inflammatory markers.[68] Vitamin C helps in production of IFNs, enhancing serum complement proteins and induce proliferation of T cells, maintain redox homeostatis.[102] Vitamin A helps regulate natural killer cells and macrophages, downregulates IL-2, TNF- α and aids in antibody production by B cells.[103] Various active forms of vitamin A including retinol, retinal, and retinoic acid promote various important biological functions. Retinoic acid helps in promoting immediate response to invasion of

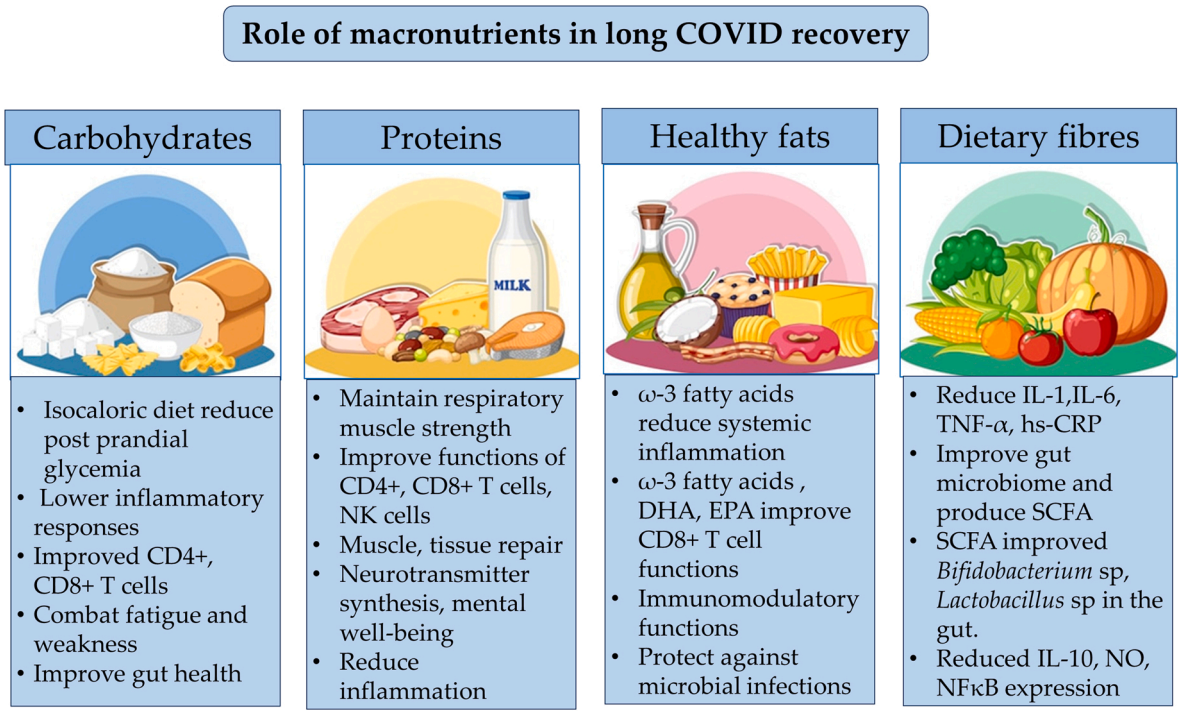

Fig. 2. The essential macronutrients-carbohydrates, proteins, fats and dietary fibres and their role in supporting immune function and overall well-being in individuals with Long COVID sequelae. $CD4^{+}$,CD8+- cluster of differentiation 4+, 8+; hs-CRP-high sensitive C reactive protein; IL-interleukin; TNF-α-tumour necrosis factor-alpha; SCFA-short chain fatty acids; NO-nitric oxide; NF-κB -Nuclear factor kappa B.

pathogen, activates natural killer cells.[104] Individuals with low vitamin A showed histopathological changes in pulmonary epithelial lignin and lung parenchyma. This result in increased risk of lung dysfunction and respiratory disease.[105] Vitamin E protects the integrity of respiratory epithelial barriers, against oxidative damage, induces production of interferon γ and IL-2.[106] Trace elements like Zn, Se, and Mg modulate enzymes, transcription factors which are needed for various biological functions including immune functions. The anti-viral properties, immune activation, complement protein activities, antioxidation, antibody production.[99] The role of micronutrients in managing long COVID sequelae is illustrated in Fig. 3.

6.2. Lactoferrin

The hyperferritinemia induced by FeRD continues for weeks or months in Long COVID patients. Managing such prolonged hyperferritinemia condition can be identified by ferritin, transferrin and lactoferrin (LF). FeRD is a sensitive, specific and useful in predicting the PASC condition.[107] The free iron released into the circulation produces inflammation and increases the blood viscosity. Thus, the hyperinflammation condition disrupt coagulant pathways and increase the risk of thrombosis in PASC patients.[108] During PASC, these redox regulators LF, heme oxygenase-1 (HO-1), erythropoietin (EPO) and hepcidin (HEP) acts as barriers and protect the host from free radical damage and hyper immune responses.[81] Nutritional modification plays a significant role in managing chronic inflammatory conditions, including those seen in long COVID specific nutrients, bioactive compounds, minerals, vitamins and trace elements enhance immune function by reducing inflammation and maintaining the post-infectious inflammatory response. Immunomodulators such as N-acetylcysteine, polyphenolic compounds, probiotics and prebiotics are also tested for managing long COVID condition to address immune dysregulation, chronic inflammation, and post-viral fatigue. LF is a multifunctional glycoprotein known for its various activities such as improving anti-viral, anti-bacterial effects, and immuno booster activities.[109] The iron binding role of LF is crucial for inflammatory processes, and to balance iron in blood and tissues. The function of LF in iron homeostasis disrupts the viral infection and inflammation, the iron chelating activity of LF reduces the disease severity.[110] The anti-viral activity, immune boosting property, the influence of LF on iron homeostasis can be further evaluated for its potential mechanism as therapeutic agent for long COVID patients. The iron binding LF present in milk produces innate host defence. Oral LF supplementation prevent the oxidative damage, influence the inflammatory responses and plays a therapeutic role in clinical management of PASC.[107] The effect of LF on fatigue, mental symptoms, muscle strength and cognitive functions in long COVID patients was investigated by Redel and colleagues through randomized, double-blind, placebo-controlled trial for 12 weeks. Long COVID patients received 1200 mg LF daily for 6 weeks, and 6 weeks of follow up were assessed with Fatigue Assessment Scale (FAS), Hospital Anxiety and Depression Scale (HADS), Cognitive Failures Questionnaire (CFQ), and muscle strength tests. The study results showed that the score of HADS fear and depression, CFQ, and FAS were decreased but not significant with placebo. Improvement in fatigue was seen in both placebo and LF group at week 6, but not continued to show improvement in the following weeks.[111]

6.3. Probiotics and prebiotics

Probiotics are able to restore gut microbiota, reduce gut microbial dysbiosis, and act as an important factor as a preventive and therapeutic strategies in combating long COVID. Though the clinical involvement of probiotics in long COVID is currently not fully described, one study indicated that probiotics could help in improving the long COVID psychological symptoms.[112] Dietary supplements with probiotics and prebiotics balance the gut microbiome and regulate the bidirectional gut-lung interaction.[113] Probiotics and prebiotics enhance the activity of macrophages, regulate the production of short chain fatty acids, and balance T cells.[114] Some probiotics are reported to interact with Angiotensin-Converting Enzyme 2 (ACE2) receptor or release peptides

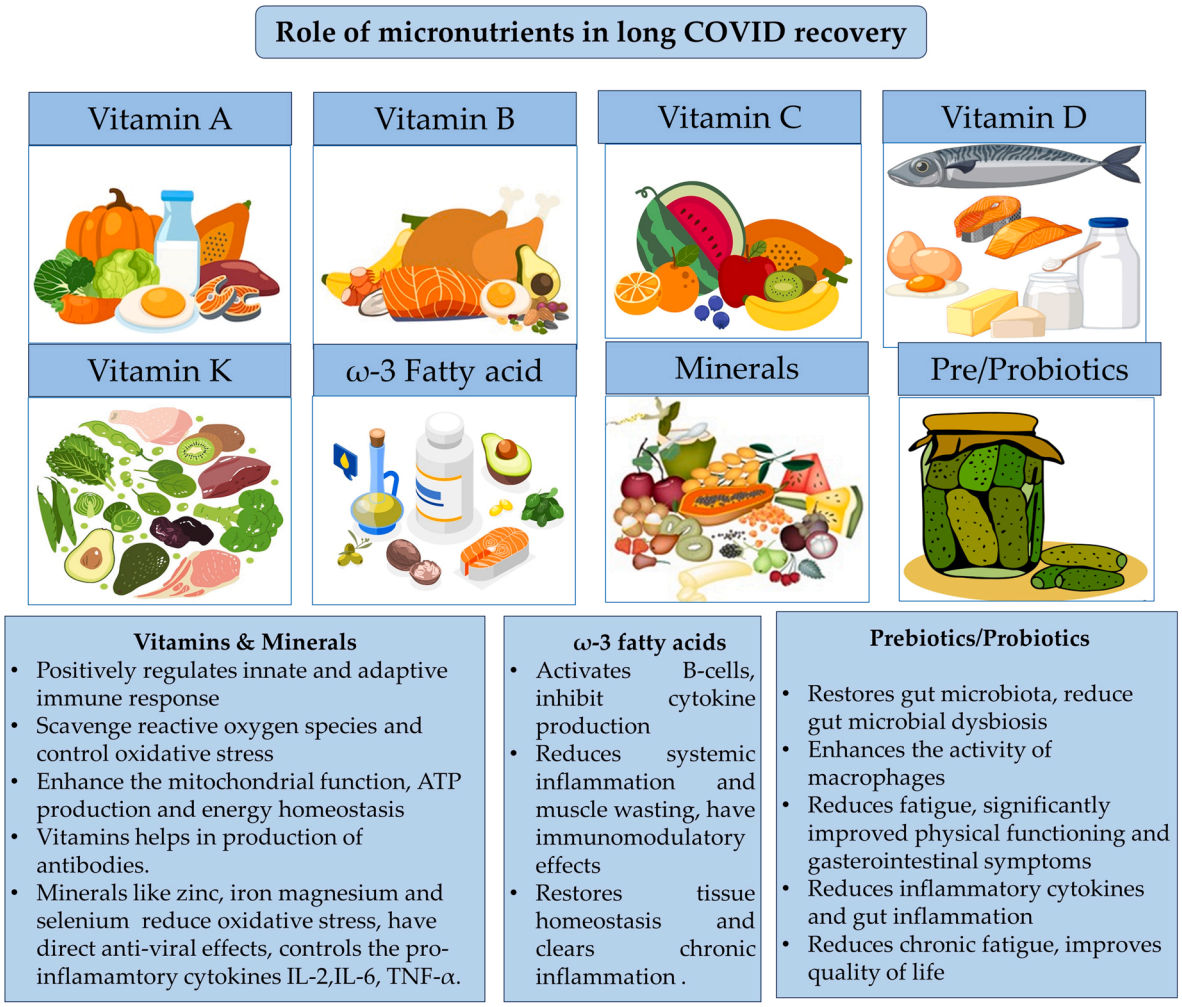

Fig. 3. The functions of micronutrients, prebiotics and probiotics in alleviating long COVID symptoms. ATP- Adenosine triphosphate; IL-2, IL-6 – Interleukin-2, 6; TNF-α-tumour necrosis factor-alpha; ω-3 fatty acids-omega-3 fatty acids.

with high affinity for ACE2 receptors.[115] Immunologically probiotics positively enhance natural killer cells, interferons, T and B lymphocytes, and antigen-presenting cells in the lungs.[116] Certain probiotics, *Bifidobacterium bifidum, Bifidobacterium breve, Bifidobacterium longum, Lactobacillus rhamnosus, Lactobacillus casei, Lactobacillus gasseri, Pediococcus pentosaceus,* and *Leuconostoc mesenteroides* are found to reduce the burden of COVID-19.[116] Probiotics alleviate the long COVID respiratory issues. Another study demonstrated the link between members of Proteobacteria and long COVID symptoms. The stool samples of recovered health care workers at 3 months after discharge compared to healthy controls showed that altered gut microbiota of health care coworkers recovered from COVID-19 at 3 months after discharge. The 16sRNA sequencing revealed that health care workers had reduced bacterial diversity and significantly higher relative abundance of opportunistic pathogens. This clearly shows that gut microbiota plays an important role in the recovery from long COVID sequelae.[117] Probiotics are being studied for improving the psychological symptoms observed in long COVID patients. The neuroinflammation in long COVID involves high cytokine levels, T-cell and natural killer cell proliferation, monocyte activation, neuronal damage, $CD8^+$ T lymphocyte infiltration, and microglial activation.[118–120] Probiotics modulate the pro-inflammatory cytokines, reduce microglial activation. In addition the byproducts short chain fatty acids (SCFA) protect the blood brain barrier integrity, control neuroinflammation, and overall contribute to the neurological health improvement. The metabolites like GABA and serotonin produced by probiotics and gut microbiota help in coordinating the brain functions and mitigate the anxiety.[121] Prebiotic components such as polyunsaturated fatty acids, resistant starch, arabino-oligosaccharides, oligosaccharides, fructans, galactomannan, lactosucrose, psyllium, lactobionic acid, and polyphenols improve gut microbiota by bolstering the growth and survival of probiotics.[122,123] Prebiotics are found to control gasterointestinal symptoms in patients suffered by COVID infection.[124] Prebiotics regulate immune response positively by reducing the pro-inflammatory IL-6 and improving anti-inflammatory IL-10.[125]

A mixture of prebiotics and probiotics SIM01 consists of beneficial strains *Bifidobacterium adolescentis, B. bifidum, B. longum* and prebiotic compounds like galacto-oligosaccharides, xylo-oligosaccharides, and resistant dextrin given to patients with COVID-19. After 6 weeks of treatment, SIM01 improved the gut microbiota most abundantly the butyrate producing bacteria in the gut. SIM01 suppressed the pathogenic bacteria *Klebsiella* which is associated with long COVID.[126] Another clinical study evaluated the effect of probiotic mixture VSL#3®, a combination of *B. breve*, *B. longum*, and *B. infantis* and *Lactobacillus acidophilus, L. plantarum, L. casei, L. bulgaricus,* and *Streptococcus thermophilus* on the fatigue and other symptoms in long COVID syndrome. This randomized, double blind, placebo controlled clinical study with probiotic mixture VSL#3® reduced fatigue, and significantly improved physical functioning and gasterointestinal symptoms.[127] Probiotic or bacteriotherapy are beneficial in enhancing gut microbial homeostasis, supporting host immune response to pathogens. However, there is a lack of evidences about how probiotic components help in alleviating long COVID symptoms. Still certain clinical trial evidences

are compelling that probiotic supplements during COVID infection have potential impact on the disease symptoms and disease course. The effects of probiotics in treating COVID symptoms are significant particularly in respiratory and gasterointestinal symptoms, and also showed lower risks.[128] Extensively probiotics can also be recommended for long COVID patients to prevent the follow up symptom progression. Table 2 summarizes the detailed studies using various nutrients and supplements in alleviating long COVID symptoms.[68,81,83,92,111,129–145]

6.4. Medicinal plants, phytochemicals, and plant-based diet

Phytochemicals are of great interests in reducing viral infection risks. The bioactive component of turmeric, curcumin show strong anti-inflammatory and anti-viral activities.[146] A clinical study states that oral curcumin administration reduces the recovery time, needs for oxygen, mechanical ventilation, length of hospitalization, and many inflammatory markers.[147] Flavonoid quercetin is also found with its preventive properties, anti-inflammatory, anti-oxidant, and immuno-modulation activities.[148] In addition to the food practices and physical exercises, sleep is essential for proper immune function, emotional balance, muscle restoration, metabolism, and cognitive functions.[147] Intake of polyphenols-rich diet for 8 weeks could significantly alter gut microbiome, enhance gut repair, thereby control immune response, cytokine release.[149] Flavonoid-rich diet increased butyrate producing bacteria such as *Roseburia, Eubacterium, Bifidobacterium,* and *Bacteroides.*[150] Vitamins A, B, C, E, and K, omega-3-fatty acids, and mono-unsaturated fatty acids exhibit anti-inflammatory, immunomodulatory effects.[151] Mediterranean diet with trace elements like iron, copper, zinc, sodium, potassium, molybdenum, magnesium, and calcium, exhibits anti-viral, anti-oxidant activity, inhibits NF-κB signalling, and promotes IFN-α synthesis and T cell regulation.[152] Anti-inflammatory diet in particular the Mediterranean diet shows promising effects. A study conducted among 305 individuals who are in Mediterranean diet found lower uric acid levels, reduced body mass index, and increased high density lipoprotein cholesterol level. These findings suggested that dietary patterns mitigated the systemic inflammation, improved metabolic health by alleviating long COVID symptoms. Thus, the dietary patterns positively influence immune responses, gut microbiome composition, metabolite production, inflammatory status. The fibre rich foods reduce oxidative stress and alleviate long COVID symptoms. Flavonoid containing foods control the inflammatory reactions and exhibit anti-vital activities as well.[153]

Plant-based diet (PBD) high in vitamins, folate, fibre, and phytochemicals like carotenoids, flavonoids, and polyphenols[96,154] enhanced immune functions, neurotransmitter release, improved sleep, reduction of pain and inflammation, and was good at mental health, which suggested that plant-based diet can have positive effect COVID consequences.[155] Plant-based diet includes minimally processed fruits, vegetables, grains, legumes, nuts, seeds, and herbs, excluding animal products like red meat, poultry, fish, eggs, and dairy products.[156] The positive effect of PBD promoted gut health and balanced microbiota and high level of beneficial microorganism.[157] Medicinal plants possess a vital role in fighting against fatigue caused by different factors. The minimal toxicity and easy accessibility of medicinal plants make it as a prospective one in managing post long COVID.[158] A RCT study using herbal combination of *Eleutherococcus*, *Rhodiola rosea* extract, and Schisandra extracts revealed that the herbal combination decreased the duration of post COVID-19 fatigue.[159] Another RCT study with essential oil blend derived from *Thymus vulgaris* L. *Citrus* × *aurantium* L. (Orange peel), *Syzygium aromaticum* (L.) Merr. & L.M.Perry (Clove bud), and *Boswellia sacra* Flück. (Frankincense) showed reduced fatigue scores on Multidimensional Fatigue Symptom Inventory (MFSI) among participants who breathed the essential oil blend for 14 days.[160] HRG80 Red Ginseng is a herbal formulation from Panax Ginseng that possesses greater concentration of bioavailable ginsenosides significantly, and is found to improve post-COVID fatigue.[161] The network pharmacology study by Zhang et al. revealed that the active components of Bu-Zhong-Yi-Qi (a traditional Chinese herbal formula) decoction has positive effects on inflammatory signalling pathways, thereby targeting crucial protein including IL-1β, IL-6, CHRM1, OPRM1, MAPK3, and VEGFA.[162] One important principal component plant called Radix Astragali has shown great potential in alleviating post COVID fatigue by enhancing anti-inflammatory mechanism and reducing the IL-6, IL-1β, and TNF-α.[158] The Traditional Chinese medicines such as herbs and herbal blends like Bu-Zhong-Yi-Qi, Dang-Gui-Shao-Yao-San, and Qing-jin-Yi-qi granules already addressed in controlling post COVID fatigue. However most of the studies focused on fatigue lack clinical studies to confirm their effectiveness in other molecular pathways of long COVID pathophysiology.

7. Lifestyle and rehabilitation for long COVID recovery

The risk of COVID infection, disease severity, and disease related mortality created a global burden and an urge to make prominent steps, in order to change the risky situation. Changes in lifestyle and diet or nutritional interventions, including regular exercises, adequate sleep, plant-based diets, and maintaining optimal diet promote positive health outcomes during and after COVID infection.[147] Obese individuals are more likely to get infected with COVID and become vulnerable target for infection due to the increased expression of ACE2 receptors in adipose tissues compared to lungs, in which the adipose tissue can become a viral reservoir.[163] Another study analysed participants with obesity showed significantly higher PASC score that acts as an indicator of long COVID. And post-vaccination, obese individuals pose higher risk of prolonged COVID-19 symptoms.[164] Long COVID management involves differential diagnosis and comprehensive evaluation of organ damage, post-ICU effects, metabolic and endocrine disorders. As for rehabilitation, exercise-based therapy are important management elements to develop functional improvement in long COVID.[165] 8 weeks of aerobic exercises, resistance training/respiratory muscle training program in long COVID patients significantly reduced dyspnea, fatigue, depression and improved functional capacity.[166]

Physical activity and exercise are the critical components in long COVID management. Tailored exercise regimens can modulate long COVID symptoms by enhancing cardiovascular health, improving mood, and reducing inflammation. The reduced physical activity during COVID infection due to social distancing and quarantine, reduces the ability of organ systems to fight back the viral infection, causing risks to immune, respiratoty, cardiac, musculoskeletal, and brain. In a work by Woods and team, they highlighted how COVID viral infection damaged physiological systems of human, physical inactivity associated viral outbreaks to the body, and promising strategies to recover from the potential damage.[167] Physical inactivity is associated with many serious effects like reduced insulin sensitivity, mitochondrial function, and lipoprotein metabolism.[168] Long-term bed rest and prolonged physical inactivity disrupt the mitochondrial homeostasis, reduce protein synthesis, and increase protein degradation. Disturbance in the mitochondrial homeostasis causes systemic inflammation, reactive oxygen species generation, production of pro-inflammatory cytokines and functional decline.[169] The higher physical fitness improves immune responses to vaccination, reduces chromic low-grade inflammation and improves various immune markers in several diseases.[170] Regular physical activity modulates inflammatory pathways, reduces fatigue and cognitive dysfunction, and attenuates PASC. Physical fitness affects the SARS-CoV-2 infections and its severity. But during the COVID-19 pandemic, physical activity and exercise had both positive and negative impact on individual health. It was found that infection was increased and caused cardiac damage due to inflammatory reaction in the muscle cells and coronary.[171,172] Regular physical activity also had positive effects on cardiorespiratory fitness and longevity. Regular physical activities have anti-depressive and neuroprotective effects. Exercises have positive effects on the brain and induce endorphin release

Table 2
Various studies on nutritional interventions in long COVID.

S. No	Nutrients/supplements	Study type	Study group	Key findings	References
Intervention with fermented products/probiotics/prebiotics/synbiotics					
1	Synbiotic preparation (SIM01) mixture of Prebiotics- galacto-oligosaccharides, xylo-oligosaccharides, resistant dextrin; Probiotics- *B. adolescentis, B. bifidum; B. longum.* Placebo – low doses of vitamin C (1 mg sachets) Twice daily for 6 months	Randomized, double blind, placebo-controlled trial	SIM01 $n = 232$ Placebo $n = 231$	Reduced fatigue, memory loss, concentration, gasterointestinal discomforts and improved physical functioning	129
2.	Bacteriotherapy formulation SLAB51 (Sivomixx800®, Ormendes, Switzerland) contained *S.thermophilus* DSM 32245®, *B. lactis* DSM 32246®, *B. lactis* DSM 32247®, *L. acidophilus* DSM 32241®, *L. helveticus* DSM 32242®, *L. paracasei* DSM 32243®, *L. plantarum* DSM 32244®, and L. *brevis* DSM 27961®· The supplementation received thrice daily throughout their stay.	Retrospective Observational study	$n = 58$ patients hospitalized for COVID-19 and discharged to home care. $n = 24$ patients received standard treatment + oral bacteriotherapy; $n = 34$ patients received conventional standard treatment.	Patients underwent oral bacteriotherapy showed significant reduction in chronic fatigue and higher levels of lactate, arginine and asparagine in serum.	130
3	Blend of 5 species of probiotic lactobacillus: *L. plantarum* (Lp90); *L. rhamnosus* (LRa05); *L. bulgaricus* (LB42); *L. lactis* (La61); *L. paracasei* (LC86) and prebiotic inulin derived from chicory.	Clinical trial study	$n = 126$; had one or more symptoms related to their COVID infection at the time of trial entry	Probiotic treatment improved the gut health. Subject well-being and GI symptoms by reducing fatigue, cough and gut inflammation.	131
4	14 g of Fermented fruit syrup from Noni (*Morinda citrifolia* Linn) as BioRex Noni in the morning after breakfast and 14 g of fermented fruit syrup from papaya (*Carica papaya* Linn.) as BioRex papaya after dinner for 20 days. Placebo group received 5% honey diluted by tap water following the same protocol.	Randomized, placebo-controlled clinical laboratory study	$n = 188$ adults, 38–69 years of age who suffered moderate or severe COVID-19 infection ($n = 157$ delta variant virus; $n = 31$ omicron variant virus).	Il-6 and Il-8 and nitri oxide metabolites reduced significantly. The polymorphonuclear leukocyte capacity to phagocyte anti-oxidant activity and ATP content were remarkably increased. Oral-pharyngeal microbiota remains unchanged.	132
5	Oral food supplement containing 4% echinacoside from *Echinacea angustifolia,* Rosehip, vitamin C, Lyophilized royal jelly and zinc. 2 capsules/day for 2 months	Randomized, double blind, placebo-controlled trial	$n = 33$ long COVID patients with mean age of (47.6 ± 16.05) years	Inflammatory parameters like neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ration and C-reactive protein were significantly reduced in oral food supplement period compared to placebo period. Fatigue reduced and quality of life improved	133
Intervention with different types of vitamins					
6	240 μg K2 (pure MK-7 form) and 2 000 IU vitamin D3 or standard of care for 6 weeks.	Single site RCT	$n = 151$ participants; 46 years median age. $n = 98$ received VitK2/D3; $n = 53$ received standard of care. Adults experienced ≥ 2 moderate long COVID symptoms for atleast 3 months after COVID-19 infection were selected for the study.	The treatment group showed improved 25(OH) D levels. Participants received Vit K2/D3 showed a 7.1% reduction in long COVID symptoms compared to control group. Vit K2/D3 improved the RECOVER long COVID index, number of symptoms, gut and inflammatory markers.	68
7	Intervention group received 1 300 mg magnesium chloride+4 000 IU vitamin D; control group received 4 000 IU vitamin D for 4 months.	Open-label, randomized, controlled clinical trial	$n = 60$ long COVID patients diagnosed with hypomagnesemia, vitamin D deficiency and mild to moderate depression. $n = 30$ intervention; $n = 30$ control group.	Mild to moderate depression was studied using Beck Depression Inventory (BDI). BDI scores were significantly reduced in intervention group and control group. Combined oral supplementation of magnesium and vitamin D is effective in patients with hypomagnesemia and vitamin D deficiency.	83
8	Two broad categories of interventions included in the study, one is focused on nutrients such as multiple B group vitamins, vitamin C, vitamin D, acetyl-l-cartinine and mineral supplements, other one is multidisciplinary rehabilitation programs.	Systemic scoping review	5 pilot studies. $n = 2$ pilot studies focused on nutrients; $n = 3$ pilot studies focused on multidisciplinary rehabilitation programs	The nutritional rehabilitation is important for recovery from inflammation, malnutrition and sarcopenia	92
9	Vitamin D	Phase 3 open label RCT	$n = 6\,200$ people aged ≥ 16 years $n = 3\,100$ people assigned to receive no offer of postal Vit D test ot Vit D supplements; $n = 1\,550$ assigned to offer postal Vit D test with supply of 800 IU Vit D/day; $n = 1\,550$	Vitamin D supplementation was found not associated with reduction in risk of COVID-19.	134

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Table 2 (*continued*)

S. No	Nutrients/supplements	Study type	Study group	Key findings	References
			assigned to offer postal Vit D test with supply of 3 200 IU Vit D/day		
10	Studies with essential vitamins including Vit C, Vit D, Vit E, Vit k, Vit B1 (thiamine), Vit B2 (riboflavin), Vit B3 (niacin), Vit B5 (pantothenic acid), Vit B6 (pyridoxine), Vit B7 (biotin), Vit B9 (folic acid), Vit B12 (cyanocobalamin)	Systemic review according to Cochrane Handbook for Systematic Reviews and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement	RCTs articles published in English or Italian with direct effects including vitamin administration. Placebo/SOC in relation to prevention and management of COVID-19 and Long COVID in people of any age.	The effects of vitamin D in preventing COVID-19 and long COVID were contrasting, No conclusion can be drawn on the effect of multivitamins, Vit A and Vit B in COVID management. Vit D showed improvement in long term complications of COVID-19	135
11	60 000 IU of Vitamin D weekly for 8 weeks. Placebo group received starch powder capsule once weekly for 8 weeks.	Randomized, double-blind, placebo-controlled trial	$n = 80$ patients, 18–60 years with post-COVID fatigue or neuropsychiatric symptoms; $n = 40$ post COVID patients; $n = 40$ placebo.	Vitamin D group patients showed significant improvements in CFQ, DASS-anxiety and ACE. No significant changes were found PQSI, DASS depression, TMT, IL-6 or CRP levels. Vit D supplementation v = benefitted the post COVID patients by reducing fatigue, anxiety and improving cognitive symptoms with very low side effects.	136
12	Single oral dose of 200 000 IU Vitamin D3 diluted in 10 ml peanut oil solution. Placebo group received only 10 ml peanut oil solution.	Multicentre, double-blind, placebo-controlled, randomized clinical trial	$n = 144$ patients with mean age 54.3 years; $n = 71$ vitamin D3 group; $n = 71$ placebo group	No significant differences were observed between Vit D3 and placebo group for fever, fatigue, myalgia, joint pain, runny nose, nasal congestion, hypertension, diabetes, cardiovascular disease, Quality of life upto 1 year of follow up.	137
13	Oral tablets of 600 mg Vitamin B1 daily for 8 weeks along with supportive therapy (vitamin C, famotidine, zinc). Control group received only the supportive therapy.	An open-label, randomized, controlled trial	$n = 66$ with mean age 49.35 years, recovered COVID-19 patients experiencing post-COVID syndrome.	After 5 weeks of vitamin B3 supplementation, treatment group showed significantly shortened symptoms like myalgia, anosmia, ageusia, fatigue and sleep disturbances compared to control group. The recovery rate in vitamin B3 group was twice than that of the control group.	138
14	Patients received 14 days oral vitamin A 25 000 IU per day and aerosolised diffuser olfactory training for combination treatment; olfactory training alone for standard care; observation for control for 4 weeks.	Pilot trial study	$n = 24$ long COVID patients with persistent olfactory dysfunction, randomly assigned for combination treatment $n = 10$; standard care $n = 9$; control $n = 5$.	Scores of olfactory function assessed by butanol threshold tests, smell identification scores and olfactory cortical network analysed by resting state fMRI showed significantly higher scores in combination treatment group compared to other groups.	139
Intervention with nutraceuticals/amino acids/other proteins					
15	Amino-Ther Pro (10 amino acids + vitamins B1 and B6 + organic acids), 2 servings/day for 8 weeks	A pilot observational case-control study	$n = 66$ COVID survivors with mean age (61.0 ± 11.8) years; $n = 33$ intervention; $n = 33$ control group.	Skeletal muscle index, physical performance was measured by using Handgrip dynamometry, 1-min chair-stand, 6-min walk test, and quality of life was assessed by EuroQol visual analogue scale. Nutritional supplementation imparted a positive effect on nutritional status, functional recovery and quality of life.	81
16	1 200 mg Lactoferrin daily for 6 weeks.	Randomized, double-blind, placebo-controlled trial	Long COVID patients aged 18–70 years, within 12 months after SARS-CoV-2 infection.	Lactoferrin and placebo group showed significant reduction in fatigue in week 0 and week 6 as measure by Fatigue Assessment Scale. No efficacy of lactoferrin were found in outcomes of anxiety, depression and cognitive failure.	111
17	Nutraceutical formulation of active ingredients containing β-caryophyllene (one serving - 40 mg), Pregnenolone (40 mg), Dehydroepiandrosterone (30 mg), Bromelain (416 mg), St. John's Wort extract (150 mg), Boswellia Serrata gum/resin extract (100 mg), Quercetin (40 mg), Zinc picolinate (12 mg) and Vitamin D (1 000 IU)	One arm open label clinical trial	$n = 51$ COVID long hauler patients. Ingredients one serving twice a day with food for 4 weeks.	The severity score for symptoms like fatigue, physical weakness, palpitations, brain fog, shortness of breath, gastero intestinal disorders, loss of smell, taste senses, anxiety, joint pain, rashes, cough and insomnia improved after 2 weeks and even more improved after 4 weeks.	140
18	1.66 g L-Arginine +500 mg Vitamin C combination (Bioarginina® C, Farmaceutici Damor, Naples, Italy) or placebo supplementation for 28 days	RCT	Trial participants aged 20–60 years with previous confirmed SARS-CoV2 infection, and negative COVID-19 test atleast 4 weeks prior to enrollment and long covid diagnosis	Participants showed improved L-arginine concentrations and L-arginine/ADMA increased compared to placebo participants. A marker of	141

(*continued on next page*)

Table 2 (*continued*)

S. No	Nutrients/supplements	Study type	Study group	Key findings	References
			as per national and international criteria	NO biosynthetic capacity increased compared to placebo.	
19	22 g collagen peptides supplementation or an isocaloric carbohydrate diet twice daily for 6 weeks.	Two arm randomized double blind-controlled intervention	$n = 59$ adults post ICU patients, ≥ 18 years.	Patients showed improved as well as higher scores of physical functioning	142
20	PIRV-F20® a combination of lactoferrin, lysozyme, lactobacillus, resveratrol, vitamins and oligo elements for 6 weeks.	A single-center retrospective study	$n = 44$ long COVID patients with mean age (49.1 ± 18.1) years with atleast one persistent long COVID syndrome.	Intervention group showed significant improvement in 6-min walking test and exercise capacity compared to control. In muscular strength, echocardiographic parameters and perception of symptoms no differences were found between control and intervention groups	143
21	Apportal® one sachet daily for 28 days. It contains 19 nutrients including Vitamin B group, minerals in Sucrosomial® forms like iron, zinc, magnesium and selenium, amino acids arginine and carnitine, plant extracts Panax ginseng and *Eleutherococcus senticosus*.	Observational study	$n = 201$ participants, (48.11 ± 13.16) years age, who had contracted COVID-19 and overcame the acute phase of infection at least 3 days withour fever and other symptoms except ageusia and anosmia	Quality of life and health status were accessed through EuroQoL-5D questionnaire and mental fatigue was measured by modified chalder questionnaire. Significant improvement in all indexes was observed after 14 and 28 days of intervention. Apportal® reduced chronic fatigue, improved quality of life and health status.	144
22	Apportal® one sachet daily for 28 days. It contains 19 nutrients including Vitamin B group, minerals in Sucrosomial® forms like iron, zinc, magnesium and selenium, amino acids arginine and carnitine, plant extracts Panax ginseng and *Eleutherococcus senticosus*.	Observational exploratory study	$n = 30$ participants with (56.14 ± 13.9) years of age, still suffering long COVID sequelae and admitted to post COVID outpatient service.	Muscle strength and physical performance were evaluated by hand held hydraulic dynamometer and 1-min sit-to-stand test respectively. Body composition and blood biochemistry were also accessed. Hand grip strength and physical performance improved, ferritin levels reduced	145

IU- international unit; ICU- intensive care unit; RCTs-randomized clinical trials; SOC- standard of care. CFQ- Chalder Fatigue scale; DASS- Depression, Anxiety and Stress Scale; PSQI-Pittsburgh Sleep Quality Index; ACE-Addenbrooke's Cognitive Examination; ATP-adenosine tri phosphate.

particularly after running. Regular exercise also attenuated symptoms of quarantine-induced depression.[167,173] Many studies focused on the effect of physical activities in COVID infection and post infection are listed in Table 3.[174–183]

8. Limitations and future directions

Treating long COVID poses numerous challenges like lack of consensus on its definition and diagnosis, limited understanding of pathophysiology including immune dysregulation, heterogeneity of symptoms, misattributions, and stigma as well. Addressing multiple symptoms in a single individual and treating it separately is challenging. The weak evidence based on long COVID treatments is due to the limitation in designing the clinical trials for long COVID. Many symptoms differentiated among each patient, appearance and warning of symptoms, lack of streamlined methodological formats, sample sizes, follow up periods.[184] Common attributes involving synergistic effects of diet, physical activities and rehabilitation can be supportive in reducing the long COVID symptoms. The sequelae of damaged tissues, viral particles persistence in organs, immune dysregulation, elevated auto immunity, chronic inflamamtion, tissue hypoxia, coagulopathy and endothelial damage are complicated, but synergistic effects of various dietary components can be helpful. The nutritional strategies face multifaceted challenges. One common nutritional approach is not feasible and applicable to all patients; hence an individualized dietary intervention is necessary.[185] The malnutritional condition further delays the recovery time and increases the hospitalization period. According to the nutritional supplement protocol of non-critical COVID patients by Caccialanza and team, their observation states that patients during hospitalization affected by severe inflammatory status and anorexia, which leads to reduced intake of food. In their protocol, initially the patients supplemented with oral food supplements, if patients could not be able to tolerate the intake of oral food supplements, they are switched to intravenous supplementation of nutrition including whey proteins, vitamins and minerals to meet the recommended dietary allowance (RDA) required for their health.[186]

9. Conclusion

Nutritional interventions offer an integrative approach that may address underlying malnutrition, micronutrient deficiencies, chronic inflammation and metabolic dysregulation observed in patients with long COVID conditions. Executing a prompt and accurate nutritional care is still a great challenge owing to the differences in each patient's need and circumstances. Although few trials combine dietary supplements with nutraceuticals and functional foods in long COVID patients, the details of dosage, route of administration, duration of intervention, ratio of combining the supplements still remains a big challenge. Maintaining healthy hygienic life style, body weight control and healthy food habits were recognized as important factors in controlling the severity of long COVID symptoms. The intervention with functional foods, nutraceutical and dietary supplements are essential to enhance the immune function, to control the oxidative stress, and inflammation. Various studies involving clinical trials explaining the importance of nutritional therapy in lowering the adverse long-term effects of COVID infection. Still identifying the individual patient specific need for nutritional supplements, the limited required quantity and duration of nutrient interventions. Possible mechanism of action of the supplements and nutrients to expect the positive and negative effects of the interventions.

CRediT authorship contribution statement

Subramanian Thangaleela: Writing – review & editing,

Table 3
Role of exercises and physical activities in alleviating long COVID symptoms.

S. No	Type of study	Intervention	Study subjects	Key findings	References
1	Systemic review and meta-analysis	Exercises such as aerobic exercise, multimodal exercise, breathing exercise, and Taichi	9 studies involving 672 individuals	Exercises significantly improved long COVID fatigue, no significant effect was found in long COVID anxiety, depression and cognitive impairment. Multimodal exercises had benefits on long COVID fatigue, dyspnea and depression. Passive control group with intervention frequency $\leq$ 4 times/week showed positive effects on long COVID symptoms.	174
2	Cross-sectional Retrospective study	Regular exercises	309 teacher-training college students	Students who have daily physical activity practices had fewer symptoms. Sustained physical activity reduced burden of symptoms	175
3	Systemic review and meta-analysis	Physical exercise- based rehabilitation	23 studies involving 1579 individuals who had COVID-19.	Physical exercise-based rehabilitation reduced COVID-19 symptoms including dyspnea, fatigue, depression and improved quality of life	176
4	Comparative study	Exercise rehabilitation 4 weeks, 3 sessions/week	38 long COVID patients received exercise rehabilitation, 38 coronary artery disease patients, 38 fibromyalgia patients.	Cardiorespiratory and muscular parameters were improved after exercise rehabilitation in all three groups.	177
5	RCT	Exercise focused intervention for 3 months	62 patients with post COVID syndrome	Fatigue was significantly decreased.	178
6	RCT	Online therapeutic exercise for 8 weeks	70 previously hospitalized COVID-19 survivors.	Patients in intervention group experienced improvements in hand grip strength, balance and frailty.	179
7	Systematic review of RCTs	Exercise interventions	8 studies included Sample sizes ranged from 39 to 119 with mean 56.	Exercise interventions showed short-term improvements in symptoms dyspnoea, fatigue, physical function and quality f life among people with long COVID	180
8	A systematic review and non-linear dose–response meta-analysis	Regular physical activity	16 studies were included.	Regular physical activity lowered COVID-19 outcomes, reduced the risk of sever COVID-19.	181
9	Retrospective study	8 weeks of resistance training	Post COVID elders tested positive for COVID 3–12 months before	Moderate intensity resistance training for 8 weeks did not sufficiently improved body mass and body composition.	182
10	Two-arm RCT	Personalized resistance exercise intervention and usual care for 12 weeks	Individuals from a community and post-hospitalized with long COVID	Resistance exercise improved exercise capacity, health, quality of life, grip strength and reduced anxiety and depression.	183

RCT-randomized control trial.

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Declaration of competing interest

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