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ABSTRACT

‘Severe acute respiratory syndrome coronavirus 2’ (SARS-CoV-2) is a highly transmissible viral pathogen responsible for the ongoing ‘coronavirus disease 2019’ (COVID-19) pandemic. The current re-purposed antiviral interventions against SARS-CoV-2 are classified into two major groups: Group-1 represents the family of drugs, mainly the vaccines that directly target the virus, and Group-2 includes a specific class of inhibitors that interfere with the host-cell machinery, which is critical for viral infection and replication. Global efforts to control COVID-19 pandemic with vaccines and repurposed therapeutics represent only a phased victory. The emergence of several SARS-CoV-2 variants of concern (VOCs) has compromised several vaccinations and pharma-therapeutic protocols, which highlights the dire necessity for specific antiviral interventions that target highly conserved domains, which are less likely to mutate in the SARS-CoV-2 genome. Several bioactive phytochemicals that block viral enzymes such as nsp5/main proteinase (M\textsuperscript{pro}) and RNA-dependent nsp7/nsp8/nsp12 RNA-dependent RNA-polymerase (RdRp) complex, are extensively investigated in this direction. The SARS-CoV-2 infection triggers a complex human host-pathogen interaction(s) resulting in ‘host metabolic reprogramming’ (HMR), iron (Fe)-redox dysregulation (FeRD), and altered mitochondrial function that cumulatively disrupt several metabolic pathways involved in cellular energy and antioxidant enzyme function; thereby, compromise the innate host defense. The circulatory/RAAS axis contributes to FeRD and any alteration or imbalance in the Fe-redox homeostasis (Fe-R-H) may lead to ‘new onset’ metabolic disorders (i.e., diabetes). Such inherent body damage and its long-term health consequences in post-acute sequelae of COVID-19 (PASC) require effective nutritional intervention strategies, particularly at the interface of organ system functions and immune system dynamics. The long-term sequelae of PASC indicate an accelerated rate of immune exhaustion in COVID-19 patients, due to prolonged antigen stimulation (also due to vaccine exposure). Abnormal immune metabolism may also cause systemic perturbations (i.e., FeRD), ROS/RNS production, oxidative and nitrosative stress, which could trigger multi-organ disorders ranging from mild symptoms to an incapacitating state and reduced quality of life that could last for weeks or longer following recovery from COVID-19. The five most long-term clinical manifestations of PASC include fatigue, headache, attention disorder, hair loss, and dyspnea. This narrative review elucidates the intricate impairments and sequelae associated with eight major physiological systems in COVID-19 survivors (i.e., pulmonary, neuro-cognitive, cardiovascular, renal, gastrointestinal/hepato-biliary, endocrinal, skeleton-muscular, and reproductive) – triggered by the FeRD, amplified by the HMR, altered mitochondrial function and ACE2/RAAS axis. We have attempted to explain the ongoing epidemic of the residual, non-viral host metabolic disorders and complications in COVID-19 survivors and the supportive role of specific host system-targeted nutritional interventions such as natural plant-based anti-inflammatories, immune-modulators, antioxidants, and macro-/micronutrient metabolic optimizers to manage PASC, the newly emerged post-COVID metabolic syndrome.

Key Words: COVID-19, Post-Acute Sequelae of COVID-19 (PASC), Host Metabolic Reprogramming (HMR), Iron (Fe)-Redox Dysregulation (FeRD), Food Bioactives, Nutritional Interventions
1. INTRODUCTION

‘Severe acute respiratory syndrome coronavirus 2’ (SARS-CoV-2) is a highly transmissible viral pathogen responsible for the ongoing ‘coronavirus disease 2019’ (COVID-19) pandemic. The COVID-19 pandemic continues to affect millions of people worldwide. The current global statistics include 540 million cases, about 6.3 million deaths [W.H.O. 2022]. The SARS-CoV-2 is a single-stranded positive-sense RNA virus with high mutation rate (up to a million-fold higher than their hosts) and such extreme genetic rearrangement correlates with enhanced adaptability and virulence, a trait that works for the viral advantage [Duffy 2018]. Its replication machinery is highly error-prone without correction systems; therefore, these viruses are prone to several genetic alterations during an infectious life cycle [Perales and Domingo 2016]. Accordingly, SARS-CoV-2 could rapidly evolve, pose high risk of transmission, and frequently develop drug resistance as well as evade vaccine-induced immunity [Duffy 2018, Pruijssers and Denison 2019]. Such genomic advantage makes the SARS-CoV-2 pathogen a major challenge to develop effective antiviral strategies and control COVID-19.

Considering that vaccination is an effective strategy to control COVID-19 pandemic, a massive public health campaign in history, has administered more than 11.9 billion doses across 185 countries with a rate of about 19.3 million vaccinations per day [W.H.O. 2022]. However, the ability of SARS-CoV-2 to evade vaccine-induced immunity—is a global concern; since a large population has been vaccinated and the pressure of herd immunity could force genomic adaptation to evolve novel viral variants as ‘escape’ mutants. Such genetic drift in tandem with the evasion of immune recognition, has contributed to the emergence of several SARS-CoV-2 variants of concern (VOCs) [Koyama et al. 2020, Naidu et al. 2022]. Accordingly, the recent spread of Omicron variant (B.1.1.529) compromised several vaccination and public health safety protocols [Minka and Minka 2022]. These VOCs show increased transmissibility and/or immune evasion, traits that are linked to mutations in the viral spike (S) protein [Harvey et al., 2021b; Tao et al., 2021]. Such high number of mutations in the S-protein domain raises concern that this CoV pathogen could evade antibodies elicited by natural infection or vaccination and the therapeutic monoclonal antibodies may also become less effective [Hoffmann et al. 2022]. There is a desperate need for an effective COVID-19 vaccine to control rapid transmission of the viral pathogen, and to contain the emergence of potential SARS-CoV-2 variants. Unfortunately, there is no effective ‘multivalent vaccine’ yet that could provide immune protection against multiple SARS-CoV-2 variants.

The genomic size of an organism is inversely related to the error rate during replication, also in case of SARS-CoV-2 (RNA length ~30 kb), which translates to one nucleotide substitution for every 2-3 genomes synthesized [Swanstrom and Schinazi 2022]. In general, most mutations are deleterious; however, a subset of mutations may potentially give rise to a viral phenotype [Holmes 2011], such as the VOC Omicron (B.1.1.529). A typical SARS-CoV-2 infected individual is estimated to produce about 1-100 billion virions during peak phase of CoVID-19 [Sender et al. 2021]. Taken together, its high viral replication rate in tandem with inherent genetic mutability, its compact genomic size with lack of metabolic machinery makes SARS-CoV-2 an extremely challenging druggable antiviral target. Current global health crisis highlights the dire necessity for specific antiviral intervention strategies that target highly conserved domains, which are less likely to mutate in the SARS-CoV-2 genome [Krumm et al. 2021].

2. VIRAL PATHOGEN-DIRECTED COVID-19 INTERVENTIONS

The current re-purposed antiviral interventions against SARS-CoV-2 could be classified in two major groups: Group-1 are family of drugs, mainly the vaccines that directly target the virus, and
**Group-2** includes type of inhibitors that interfere with the host-cell machinery critical for viral infection and replication.

### 2.1. Group-1: COVID-19 Vaccines

Four COVID-19 vaccines, two mRNA-based: BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), and two adenoviral vector-based: Ad26.COV2.S (Janssen/Johnson & Johnson) and ChAdOx1 nCoV-19 (Oxford/AstraZeneca) have been approved or granted Emergency Use Authorization (EUA) for COVID-19 control in many nations worldwide. The ChAdOx1 nCoV-19 vaccine has not yet received a EUA or approval from the US-FDA [US-FDA/EUA 2022].

**COVID-19 vaccines and the ‘original antigenic sin’**: Based on meta-transcriptome sequencing of the bronchoalveolar lavage fluid from COVID-19 patients, the viral pathogen seems to evolve in vivo after infection, a characteristic that may determine its virulence, infectivity, and transmissibility [Roncati and Palmieri 2020]. Therefore, this unprecedented race to develop COVID-19 vaccine should exercise caution that the viral antigen candidates are safe and not detrimental to host immune responses. Immune enhancement, also known as ‘immune backfiring’, could manifest in multiple ways such as antibody-dependent enhancement (ADE), a process in which a virus could leverage antibodies to aid infection; or cell-based enhancement, a category that includes allergic inflammation caused by Th2 immunopathology [Peeples 2020]. The anecdotal reports of COVID-19 reinfections may suggest the relevance of ADE, where the viral antibodies (from immunization or an initial natural infection) might have enhanced the viral entry into host cells [Lan et al. 2020].

**Covid-19 vaccine and autoimmune sequelae**: During autoinflammatory and autoimmune syndromes, viruses could activate an aberrant innate and acquired immune response, with increased synthesis of cytokines, mainly TNF-α, IL-6 and IL-1β, IL-17, IL-18, in genetically predisposed individuals [Cas o et al. 2020]. Such immune hyperactivation and excess cytokine release is evident in COVID-19 patients with multiorgan failure and fatality outcomes [Rodriguez and Brodin 2020]. Molecular mimicry between SARS-CoV-2 antigens and the human proteome could play an important role is this response [Vojdani and Kharrazzian 2020]. Thus, after an infection or vaccination, the host immune responses elicited by SARS-CoV-2 antigenic epitopes may cross-react with human proteins that share peptide sequences and trigger severe autoimmune sequelae. From a clinical context, SARS-CoV-2 shares 6 minimal immune determinants with the Kawasaki antigen inositol-trisphosphate 3-kinase C that could predispose likely cross-reactions and consequent autoimmune Kawasaki disease in COVID-19 patients [Ehrenfeld et al. 2020]. Moreover, the SARS-CoV-2 spike protein has been shown to share 13 out of 24 pentapeptides homologous to the human lung surfactant proteins [Kanduc and Shoenfeld 2020]. Therefore, identification of human tissue cross-reactive epitopes in COVID-19 vaccine is critical to avoid any possible autoimmune sequelae. Only peptide sequences uniquely belonging to SARS-CoV-2 could represent the basis for safe and specific vaccinations protocols.

**COVID-19 vaccine-induced endocrine disorders** include vaccine-associated thrombosis and thrombocytopenia (TTS) with adrenal hemorrhage, derangements in glycemic control including new onset type 2 diabetes mellitus, and subacute thyroiditis [Mirza et al. 2022]. TTS is a serious but rare adverse event associated with exposure to adenovirus vector vaccines Ad26.COV2.S and ChAdOx1 nCoV-19 has raised immunization safety concerns [Long et al. 2021, See et al. 2021]. Symptoms of this novel vaccine-induced clinical syndrome include severe headache, blurred vision, seizure, severe and persistent abdominal pain, painful swelling of the lower leg, and chest pain or dyspnea. The TTS mimics autoimmune heparin-induced thrombocytopenia
(HIT) mediated by platelet-activating antibodies against platelet factor 4 [Lai et al. 2021]. It is also known as vaccine-induced prothrombotic immune thrombocytopenia (VIPIT) in some European nations and Canada [Aleem and Nadeem 2022].

A systematic review of 160 cases from 16 countries, revealed that the TTS onset occurs at a median of 9 (4) days after vaccination with a high mortality rate of 36.2% [Waqar et al. 2021]. Venous thrombosis (61%) in TTS is prevalent and about 66.3% affected could develop cerebral venous sinus thrombosis (CVST), predominantly among the female patients (aged <55 years). By April 12, 2021, ~7 million doses of Ad26.COV2.S vaccine were given in the US, with 6 cases of CVST with thrombocytopenia were reported, which called for a temporary national pause in vaccination with Ad26.COV2.S on April 13, 2021. The initial 12 US cases of CVST with thrombocytopenia after vaccination resulted in severe outcomes [See et al. 2021]. The newly emerged TTS is a major concern for the global implementation of mass COVID-19 vaccination campaigns and requires stringent caution with the ongoing COVID-19 vaccine development protocols.

2.2. Group-2: COVID-19 Antiviral Drugs

Specific novel anti-SARS-CoV-2 medications are anticipated to play a major role in protecting people who are unvaccinated or immunocompromised, as well as at periods when vaccinations fail to protect against circulating SARS-CoV-2 variant (Chavda et al., 2021f). The antiviral strategies for COVID-19 control fall under four categories: i) inhibitors of viral entry, bioactives that block human cell surface receptors such as ACE2 (TMPRSS2), neuropilin-1, and heparan sulfate that SARS-CoV-2 uses for cellular invasion; ii) inhibitors of viral proteases (i.e., Mpro, RdRp), enzymes that hydrolyze long viral polypeptides to generate functional proteins; iii) inhibitors of viral replication, transcription, and translation, i.e., nucleoside analogs that mimic RNA bases that a virus could potentially incorporate into copies of it’s genome; and iv) inhibitors of viral assembly and release, i.e., bioactives that target host cellular processes that were hijacked for transport and assembly of viral particles.

Repurposed Drug Therapeutics:

In the United States, the Coronavirus Treatment Acceleration Program (CTAP) initiated by the FDA, is an emergency plan to scrutinize and introduce new effective therapeutics to COVID-19 patients, supported by extensive safety and efficacy evaluation [US-FDA/CTAP 2022]. As of March 19, 2022, the CTAP review included (vaccines excluded) over 690 drug development programs (in planning stages), over 470 trials (under review), about 15 COVID-19 treatments (authorized for emergency use) and only 1 antiviral drug (remdesivir) approved. Currently, the diversity of COVID-19 interventional strategies under CTAP investigation include: 50+ antiviral treatments, 60+ cells/gene therapies, 120+ immunomodulators, 60+ neutralizing antibodies, 110+ other interventions and 40+ combination therapeutics (from other drug categories) [US-FDA 2022]. As of March 2022, over 7710 ongoing clinical trials were registered on ClinicalTrials.gov, which include 1,252 vaccine-related, 1,120 drug intervention and 155 dietary supplement studies [NIH/US-NLM 2022].

Current Status: Despite robust efficacy in vitro data against the SARS-CoV-2 pathogen and previous clinical data from other human coronaviruses such as SARS and MERS, the repurposed drugs have failed to demonstrate beneficial effects against COVID-19 in human clinical studies [Indari et al. 2021, Martinez et al. 2021, Basu et al. 2022].
3. HUMAN HOST-DIRECTED COVID-19 MANAGEMENT STRATEGIES

3.1. Host Metabolic Reprogramming (HMR) in COVID-19

Viruses hijack the host cellular metabolic machinery to extract adequate energy and carbon skeletons required for their entry and further molecular constructions of viral progeny inside a host cell. The SARS-CoV-2 infection could activate a complex human host-pathogen interactions leading to ‘host metabolic reprogramming’ (HMR). The HMR could alter mitochondrial function with significant disruption of glycolysis/TCA cycle affecting several metabolic pathways of amino acid, fatty acid, nucleotide, and antioxidant synthesis [Moolamalla et al. 2021, Shen et al. 2021]. The impact of HMR on COVID-19 pathobiology is reflected during hyper inflammatory response (‘cytokine storm’) while compromising the innate host defense. This could sequentially trigger an array of clinical manifestations, either an asymptomatic condition or progressive onset of mild, moderate to severe phases of COVID-19 with life-threatening acute respiratory distress syndrome (ARDS), vascular dysfunction, multiple organ failure, and death. Therefore, nutritional restoration of HMR could provide a potential strategy to combat COVID-19 and its post sequelae.

3.2. Tri-Phasic Symptomatic Progression of COVID-19

The symptomatic progression of COVID-19 requires that a genetically competent (virulent) SARS-CoV-2: i) infects and invades a susceptible host via specific cell surface receptors, ii) induces HMR to ensure ready access to an active host cellular machinery for an uninterrupted viral propagation, iii) inactivates the innate host defense to evade viral elimination, and iv) exits the infected host cell and repeats the viral propagation cycle for exponential growth and transmission [Sicari et al. 2020]. In accordance with its virulence spectrum and host susceptibility pattern, the symptomatic outcomes of COVID-19 manifest in a tri-phasic manner as ‘iron (Fe)-redox’ disruptive hematological syndromes [Naidu et al. 2022].

**Phase-I / Hypoxia/Hypoxemia (an acute depletion of oxygen (O₂) transport in the blood):** During the initial encounter, the SARS-CoV-2 anchors to the human angiotensin-converting enzyme 2 (ACE2) receptors on alveolar epithelia, alters the renin-angiotensin-aldosterone system (RAAS), subsequently lowers both blood pressure and lung function of the infected host [Ni et al. 2020]. Reduced O₂ transport that ensues from low hemoglobin (Hb) levels in the hypoxic blood circulation (‘hypoxemia’), alters the mitochondrial function by ‘switching off’ the oxidative phosphorylation (OXPHOS)/tricarboxylic acid (TCA) cycle in favor of anaerobic glycolysis [Ferraro et al. 2021]. Therefore, beyond the classical pulmonary immune-hyperinflammation and ARDS, COVID-19 manifests also as a hypoxia-induced hematological syndrome with ‘iron-related’ HMR [Debuc and Smadja 2021].

**Phase-II / Hyperferritinemia (an excess presence of iron storage protein, ferritin, in the blood):** In its subsequent infectious phase, SARS-CoV-2 induces hyper release of proinflammatory cytokines to stimulate synthesis of both ferritin and hepcidin, the ultimate mediators of iron dysregulation [Edeas et al. 2020]. This pathological condition shows high iron content in reticuloendothelial cells with elevated serum ferritin levels. Excess iron load further generates reactive oxygen species (ROS) through Haber-Weiss reaction, which leads to oxidative stress, mitochondrial dysfunction and ferroptosis [Singh et al. 2020]. Taken together, hyperferritinemia, cellular imbalance in iron metabolism plays a critical role in the pathogenesis of COVID-19 [Muhoberac 2020].
Phase-III / Thromboembolism (formation of blood clots with severe obstruction of veins, arteries, and circulation): During this severe stage of COVID-19, hematological parameters such as anemia of inflammation (AI), low counts of peripheral blood lymphocytes/eosinophils with increased polymorphonuclear-to-lymphocyte ratios are prominent risk factors [Sun et al. 2020; Bergamaschi et al. 2020]. Altered iron metabolism, iron-restricted erythropoiesis due to hyper-inflammation are predisposing factors for AI [Wessling-Resnick 2018; Weiss et al 2019]. The hemolysis-derived heme could initiate oxidative and inflammatory stress that may lead to microvascular thrombosis, organ ischemia and multi-organ failure in severe COVID-19 cases [Wagener et al. 2020; Varga et al. 2020].

3.3. Host Iron (Fe)-Redox Dysregulation in COVID-19

The significant role of iron metabolism in HMR and altered mitochondrial bioenergetics is evident in the pathobiology of COVID-19 [Terpos et al. 2020; Naidu, Wallace, Davies et al. 2021]. Throughout the tri-phasic clinical progression of COVID-19, the SARS-CoV-2 pathogen categorically targets the host hematopoietic system and alters the host ‘iron (Fe)-redox homoeostasis (Fe-R-H)’ [Naidu et al. 2022]. The Fe-R-H dysregulation could also trigger several clinical manifestations in COVID-19 patients including: i) decrease the functional hemoglobin (Hb), ii) increase the cellular iron overload, iii) release free toxic heme into the circulation, iv) manifest hypoxemia and systemic hypoxia, v) reduce nitric oxide (NO•) synthesis, vi) activate coagulation pathway(s), vii) trigger ferroptosis with oxidative stress and lipoperoxidation, and viii) induce mitochondrial degeneration [Cavezzi et al. 2020]. Therefore, regulation and maintenance of systemic Fe-R-H is critical for the clinical management of COVID-19.

Interestingly, the Fe-R-H dysregulation and its associated physiological disorders or disease states continue for extended periods (for weeks or even months) in COVID-19 patients discharged as RT-PCR (SARS-CoV-2) negative survivors [Taribagil et al. 2021]. These observations further emphasize the need to identify intricate pathophysiological mechanisms underlying the Fe-R-H dysregulation in COVID-19. Based on the consequential clinical manifestation of SARS-CoV-2 infection (i.e., COVID-19) and the ‘post-acute sequalae of COVID-19’ (PASC), this disease should be considered as an Iron (Fe)-Redox Dysregulation (FeRD) Syndrome.

A robust correlation between COVID-19 and the host Fe-R-H dysregulation is also observed among specific population groups with hemoglobin (Hb) anomalies [Rapozzi et al. 2021, Naidu et al. 2022]. Global data indicate higher COVID-19 case fatality rates (CFR) among men than women, a ratio >1·0, ranging up to 3·5 in some cases [Global Health 2022], a gender trait attributed to the low Hb levels in females compared to males [Conti and Younes 2020; Jin et al. 2020]. Also, most newborns from COVID-19 positive mothers were uninfected with the virus [Naidu, Clemens, Pressman, Zaigham, Kadkhoda et al. 2022], which could be related to the absence (and delayed synthesis) of Hb β-chain in neonatal erythropoiesis [Sankaran and Orkin 2013]. Interestingly, the low incidence of COVID-19 cases reported from certain Mediterranean territories is noteworthy, since this geographical region is known for high prevalence of β-thalassemia (blood condition linked to abnormalities in the β-chains of Hb) [Drouin 2020; Motta et al. 2020].

4. NUTRITIONAL STRATEGIES TO REVERSE HOST Fe-R-H DYSREGULATION (FeRD) IN COVID-19

Intro
4.1. Fe-R-H regulators for nutritional management of COVID-19

The Fe-R-H regulators, such as lactoferrin (LF), hemeoxygenase-1 (HO-1), erythropoietin (EPO), and hepcidin modulators are innate bioactive molecules involved in iron metabolism, detoxification of free iron-induced ROS, modulation of antioxidant responses and serve as the first barriers against SARS-CoV-2 infection [Naidu et al. 2022]. These Fe-R-H regulators could play a vital role in alleviating cellular oxidative stress and inflammation, particularly during the 'cytokine storm' in COVID-19 pathobiology.

Lactoferrin, the iron-binding protein found in milk and several exocrine secretions, could also interact with anionic compounds (HSPG, ACE2 etc.), translocate into the nucleus, modulate immune as well as inflammatory responses, and regulate the physiological Fe-R-H [Naidu et al. 2022]. Accordingly, LF is considered a potential natural intervention in the clinical management of COVID-19 [Chang et al. 2020; Campione et al. 2020; Naidu, Clemens, Pressman, Zaigham, Davies et al. 2022]. Based on iron sequestration and Fe-R-H restoration effects in vivo, LF could potentially benefit COVID-19 patients to relieve oxidative stress and hyper-inflammation [Naidu, Wallace, Davies et al. 2021]. Several LF-based intervention technologies are undergoing extensive clinical trials for COVID-19 control.

Hemoxygenase-1 (HO-1) regulates the Fe-R-H and provides cytoprotective function via endogenous mechanisms to sustain body's antioxidant response against oxidative stress [Consoli et al. 2021]. The protective role of HO-1 against SARS-CoV-2 is probably an emergency inducible defense mechanism to ameliorate oxidative stress from heme-released oxidants in severe cases of COVID-19. Several natural phychochemicals are known to upregulate HO-1; thus, may provide protection from thrombotic events and vascular inflammation during COVID-19 [Naidu et al. 2022]. Nimboide, a limonoid tetranortriterpenoid from neem plant (Azadirachta indica) [Mahapatra et al. 2012], resveratrol (3,4',5-trihydroxy stilbene) and curcuminoids (with α, β-unsaturated carbonyl groups) are potential inducers of HO-1 expression through Nrf2/antioxidant-responsive element (ARE) pathway [Chen et al. 2005; Jeong et al. 2009]. Quercetin, the phytophenols, could induce HO-1 expression via mitogen-activated protein kinase (MAPK)/Nrf2 pathway [Yao et al. 2007].

Erythropoietin (EPO) could protect pulmonary vascular beds and counteract hypoxic pulmonary vasoconstriction [Nairz et al. 2012]. Neurological manifestations are prominent among COVID-19 patients, Also, EPO could relieve acute and chronic-progressive downstream sequelae of central and peripheral nervous systems, which are now becoming common neurological manifestations among COVID-19 patients [Naidu, Wallace, Davies et al. 2021; Collantes et al. 2021]. A combination therapy of EPO with anti-coagulants or anti-thrombotic agents (i.e., heparin) could circumvent complications in hospitalized COVID-19 patients [Nairz et al. 2012].

Hepcidin is a promising intervention target for management of COVID-19 with iron overload syndromes. [Blanchette et al. 2016; Banchini et al. 2020]. Several dietary phytoestrogens could up-regulate hepcidin expression, control systemic iron levels, prevent iron-induced toxicity and provide protection against several oxidative stress-induced pathological disorders [Bayele et al. 2015]. Genistein, the isoflavone-related estrogen could induce hepcidin transcription by both bone morphogenetic protein 6 (BMP6) and signal transducer and activator of transcription 3 (STAT3) signaling [Zhen et al. 2013]. Quercetin, a strong post-prandial hepcidin inducer, has been shown to reduce iron overload [Kaltwasser et al. 1998]. Epigallocatechin-3-gallate (EGCG) may reduce iron toxicity by chelation or blocking the iron release/efflux from cells [Perron et al. 2009]. As potential inducers of hepcidin expression, phytoestrogens are promising adjunctive
supplements to reduce iron overload and prevent any sequelae of iron-induced toxicities such as hyperferritinemia, coagulopathies and/or thromboembolism, the prominent clinical manifestations among COVID-19 patients [Sonnweber et al. 2020; Edeas et al. 2020; Habib et al. 2021].

4.2. Ferroptosis inhibitors for nutritional management of COVID-19

Ferroptosis is an iron-catalyzed, non-apoptotic form of regulated necrosis that causes oxidative damage of cellular lipid membranes leading to severe mitochondrial dysfunction. The ferroptosis-mediated Fe-R-H dysregulation could cause suppression of erythropoiesis and anemia, which is a prominent feature in severe cases of COVID-19. During ferroptosis, the accumulation of oxidized phospholipids in myocardial and renal tissues could be responsible for ischemic-reperfusion injury, a detrimental factor for cardiac damage and MODS in COVID-19 [Jacobs et al. 2020]. Ferroptosis is linked to several neurological disturbances including cognitive impairment, ageusia and anosmia in COVID-19 [Vaira et al. 2020]. Ferroptosis could also be involved in the development of acute lung injury/acute respiratory distress syndrome (ALI/ARDS), a major contributor for high morbidity and mortality in COVID-19 [Liu et al. 2022]. Therefore, ferroptosis inhibitors could provide a potential intervention strategy to alleviate thromboembolism and improve prognosis in COVID-19 patients [Yang and Lai 2020, Naidu et al. 2022].

The pharmaceutical drugs ferrostatin-1 (Fer-1) and liproxstatin-1 (Lip-1) are potent lipophilic free-radical scavengers that could prevent lipid peroxidation and protect from ferroptosis. Melatonin inhibits platelet activation and ferroptosis through activation of Nrf2 and HO-1 signaling pathways [Ma et al. 2020]. This chrono-biotic hormone is considered a potential intervention to treat hemolytic, thrombotic, and thrombocytopenic conditions, the widespread clinical manifestations among COVID-19 patients [Naveenkumar et al. 2021, Naidu et al. 2022].

Several phytochemicals are potential ferroptosis inhibitors. The phytoflavone quercetin could upregulate cellular GSH and inhibit ferroptosis of renal proximal tubular epithelia by reducing malondialdehyde (MDA) and oxidative damage of lipid membranes [Wang, Quan, Cao et al. 2020]. Similarly, curcumin could inhibit renal tubular epithelial ferroptosis from myoglobin-mediated inflammation and oxidative stress through activation of cytoprotective enzyme HO-1 [Guerrero et al. 2019]. Glycyrrhizin from licorice (Glycyrrhiza glabra) could provide anti-ferroptotic liver protection through up-regulation of Nrf2, and HO-1 and down-regulation of lactate dehydrogenase (LDH), MDA, and free iron [Wang et al. 2019]. Phyto-tannins chebulagic and chebulinic acids are natural iron-chelators that inhibit ferroptosis through free radical scavenging and other regular antioxidant pathways [Yang et al. 2021]. Dietary phytophenols such as piceatannol and astringin strongly inhibit ferroptosis via preferential transfer of hydrogen atoms as conventional antioxidants. [Chen, Li, Ouyang et al. 2021].

4.3. Anticoagulants for COVID-19 management

The severe phase of COVID-19 is a highly prothrombotic disease state resulting from hyperinflammation, endothelial dysfunction, platelet and complement activation, derangement of RAAS system, and hypoxemia. The ARDS and multi-organ failure in COVID-19 have been attributed to markers of coagulopathy such as ‘prothrombin time’ (PT) prolongation, elevated fibrin degradation products, reduced platelet count, and significantly elevated D-dimers [Giannis et al. 2020; Tang, Li, Wang et al. 2020]. Therefore, thromboprophylaxis with anticoagulant therapy has been widely practiced as a COVID-19 clinical management protocol is several healthcare facilities worldwide [Naidu et al. 2022].
Heparin in nebulized unfractionated form, provides a powerful anti-coagulant and mucolytic support to ameliorate respiratory symptoms, lower pulmonary dead space, and reduce ventilatory support in COVID-19 patients. Heparin is a promising prophylactic against VTE and could also relieve hypoxia-mediated symptoms in COVID-19 patients [Negri et al. 2020]. Heparin-induced thrombocytopenia (HIT), a rare complication of heparin therapy, is estimated to occur in few patients. The repurposing of heparin and its derivatives as first-line therapy against SARS-CoV-2 is a promising strategy; however, this clinical approach needs further evaluation [Naidu et al. 2022].

4.4. Iron (Fe)-chelators for nutritional management of COVID-19

Iron is an essential element for all living cells; however, free unbound iron from Fe-R-H dysregulation contributes to mitochondria dysfunction, and dysbiosis of microbiota in lungs/gut [Edeas et al. 2020]. Iron overload, free radical-induced tissue damage, thrombosis and erythrocyte dysfunction are implicated in hyperferritiniemia, immune dysfunction and coagulopathy, a hallmark of severe COVID-19 [Muhoberac et al. 2020]. Furthermore, free iron could target vascular tissues (i.e., hepatic, cardiac and endocrine cells), and cause severe damage to the corresponding organ function [Laforge et al. 2020]. Dysregulated Fe-R-H is a major cause of diffused endothelial inflammation with systemic involvement that could trigger an array of pathobiological during SARS-CoV-2 infection. Iron chelators inhibit IL-6 synthesis by down-regulation of NF-kB, and could suppress endothelial inflammation, a major risk factor for multiorgan failure in COVID-19 [Dalamaga et al. 2020]. Furthermore, naturally occurring iron chelators, such as LF and transferrin (TF) could exert antiviral, anti-inflammatory and immunomodulatory effects and could be of high therapeutic value in the ongoing COVID-19 pandemic [Naidu et al. 2021, 2022]. Therefore, iron chelators could play a potential role to ameliorate the systemic manifestations of COVID-19.

The FDA-approved oral chelators deferoxamine (DFO), deferiprone, and deferasirox can offer therapeutic solutions to treat iron overload and clinical conditions associated with free radical pathology [Kontoghiorghes and Kontoghiorghe 2020]. The natural siderophore DFO selectively removes iron from ferritin and hemosiderin to reduce the iron overload [Bellotti and Remelli 2021. The potent antioxidant and free radical scavenging activities of DFO could be beneficial for highly vulnerable COVID-19 patients.

Phyto-chelators: Several plant-based compounds such as caffeic acid, curcumin, α-lipoic acid (ALA), and phytic acid are natural chelators that are known to protect cells from iron overload and restore mitochondrial membrane integrity, redox potential, and function. Caffeic acid, a plant-based iron-chelator, redox modulator, and a powerful natural antioxidant could prevent lipid peroxidation in biological membranes [Hynes and O’Coinceanainn 2004]. Caffeic acid chelates could also interfere with viral attachment to heparan sulfate proteoglycans (HSPG) on cell surface [Langland et al. 2018]. Curcumin from the Indian herb turmeric (Curcuma longa) is an iron-chelator that could inhibit iron-catalyzed pathways of oxidative stress and protect cellular DNA, lipids, and protein from free radical damage [Rainey et al. 2019]. α-lipoic acid (ALA) could increase intracellular levels of glutathione (GSH), prevent the Nrf2 pathway activation during iron overload and restore mitochondrial membrane integrity, redox potential, and function [Camiolo et al. 2019]. Phytic acid, abundant in edible legumes, cereals, and seeds, is an iron chelator with antioxidant activity could potentially inhibit iron-catalyzed hydroxyl (OH•) radical formation [Graf et al. 1987].

5. POST-ACUTE SEQUELAE OF COVID-19 (PASC)
Post-acute sequelae of COVID-19 (PASC), also referred to as the 'long COVID', has emerged as a novel clinical condition in COVID-19 survivors with lingering symptoms (or develop new ones) and failing to return to their baseline health. Accordingly, PASC is considered a post-COVID-19 sequelae with persistent symptoms and/or delayed or long-term complications beyond 4 weeks from the onset of acute or the initial phase of SARS-CoV-2 infection [Carfi et al. 2020, Nalbandian et al. 2021]. Based on the duration of persistent clinical manifestations, PASC has been further categorized: i) ‘post-acute COVID’ with symptoms and abnormalities that persist 4-12 weeks; and ii) ‘chronic COVID’ with symptoms and abnormalities that persist >12 weeks and not attributable to alternative diagnoses [van Kampen et al. 2021, Shah et al. 2021]. A recent cohort (based on 250,351 COVID-19 survivors from 2,100 studies), reported the high global prevalence of PASC: 54.0% at 1 month (short-term), 55.0% at 2 to 5 months (intermediate-term), and 54.0% at 6 or more months (long-term) [Groff et al. 2021]. The burden of individual PASC sequelae vary by demographic groups (age, race, and sex) but consistently higher among patients with existing metabolic syndromes and in survivors from severe acute infection [Xie et al. 2021].

The PASC is a multi-organ disorder ranging from mild symptoms to an incapacitating state and reduced quality of life that could last for weeks or longer following recovery from COVID-19 [Moghimi et al. 2021; Parker et al. 2021]. The five most long-term clinical manifestations of PASC include fatigue (58%), headache (44%), attention disorder (27%), hair loss (25%), and dyspnea (24%), and generally have an impact on everyday functioning. [Lopez-Leon et al. 2021]. Other common symptoms include shortness of breath, cough, joint pain, chest pain or tightness, loss of smell/taste, sore throat, diarrhea, depression, anxiety. Few less frequently observed symptoms include insomnia, palpitations, anorexia, tingling fingertips, and skin rashes [Ramakrishnan et al. 2021].

5.1. Host Metabolic Dysfunction Sequelae in PASC

The PASC pathology is a cumulative outcome of several viral-mediated alterations to host metabolism at cellular level such as: i) SARS-CoV-2 infection-induced tissue damage, ii) hyperinflammation-mediated multiorgan impairment, iii) immune exhaustion/dysregulation, iv) hormonal disturbances from maladaptation of ACE2-related pathways, v) coagulopathies due to endothelial damage/microvascular injury, iv) post-viral autoimmunity, vi) microbial dysbiosis, vii) critical care-associated sequelae or a combination of all above [Nalbandian et al. 2021, Moghimi et al. 2021, Ramakrishnan et al. 2021].

Dormant viral reservoirs: The prolonged symptoms of PASC may be attributed to the earlier endothelial and tissue damage caused by SARS-CoV-2 during its acute clinical phases of infection. The multi-organ tropism of SARS-CoV-2 could also play a role in the lingering long-term sequelae of PASC, where the virus or viral epitopes may remain dormant and trigger chronic inflammatory responses. The dormant viral epitopes may also activate of the adaptive immune cascade, which may lead to a persistent hyperinflammatory syndrome. The viral persistence and its probable genetic mutations could provoke anti-viral ‘antibody waves’ leading to immune exhaustion which may further explain SARS-CoV-2 re-infections [Ramakrishnan et al. 2021].

Host immune exhaustion: The long-term sequelae of PASC suggests an accelerated rate of immune exhaustion in COVID-19 patients, a dysfunction of antigen-specific immune cells due to prolonged antigen stimulation (also vaccination) [Diao et al. 2020, Zheng et al. 2020]. Abnormal
immune-metabolism in may cause systemic perturbations such as Fe-R-H dysregulation, ROS/RNS production, oxidative and nitrosative stress [Naidu et al. 2022].

**Viral-induced autoimmunity** is a possible contributing factor in the development of PASC. The SARS-CoV-2 virus may develop autoreactive T cells and antibodies to survive the post-acute infection or even develop post-viral clearance [Sette and Crotty 2021].

**Host mitochondrial dysfunction** may predispose COVID-19 survivors to long-term health consequences and patients with metabolic syndromes such as diabetes and obesity are at higher risk of PASC manifestation [Scherer et al. 2022]. Altered mitochondrial function and cellular energy deprivation leads to HMR with a metabolic switch from high energetic OXPHOS to low energetic glycolysis in COVID-19 patients [Singh et al. 2020, Naidu et al. 2022]. Such patients demonstrate impaired cellular bioenergetics with altered metabolic pathways, including amino acids, lipids, sugars, and oxygen, using the limited energy reserves [Naviaux et al. 2016]. A similar mechanism could be responsible for the chronic fatigue observed in PASC patients. In COVID-19 patients, the glycemic abnormalities could persist for at least 2 months after recovery patients suggesting the impact of metabolic alterations in the pathobiology of PASC [Montefusco et al. 2021].

**Altered host gut microbiome** in COVID-19 patients, in tandem with inflammatory and hematological markers, is an indicator of disease severity and dysfunctional immune response [Yeoh et al. 2021]. The dysbiosis of gut microbiota persists for up to 30 days in COVID-19 survivors, which could play a critical role in the later onset of lingering PASC symptoms.

**The renin-angiotensin system (RAAS)/ACE2 axis** plays a pivotal role in metabolic homeostasis and in the regulation of multiple organ functions in the body. ACE2, the enzyme critical for RAS activity, is also a host cell receptor for viral entry and the SARS-CoV-2 infections leads to a decline in ACE2 expression, subsequent increase in Ang II levels and potential overactivation of RAS [Ni et al. 2020]. Elevated plasma Ang II levels have been associated with acute lung injury (ALI) and ARDS in severe cases of COVID-19 [Wu et al. 2020]. The imbalance between ACE2/angiotensin axis and RAS have also been implicated in multi-organ dysfunction syndrome (MODS) in COVID-19 [Rysz et al. 2021]. The persistence of these clinical manifestations in post recovery suggests a significant involvement of ACE2 in PASC patients.

### 6. NUTRITIONAL STRATEGIES FOR PASC MANAGEMENT

Nutrition could play a key role in the management of PASC. Several food bioactives could deliver multifunctional benefits to different host cellular targets, help reduce symptomatic burden and revitalize affected skeleton-muscular systems, through independent as well as synergistic mechanisms. Hyper-inflammatory state during COVID-19 could negatively affect the muscle protein synthesis and this progressive disorder leads to severe catabolic wasting of skeletal muscle mass and function loss, a condition known as sarcopenia [Crispo et al. 2021]. Acute sarcopenia is prevalent among elderly COVID-19 patients, with direct implications in PASC onset and recovery [Piotrowicz et al. 2021]. Nutritional support to restore muscle mass is critical in the management of PASC. The minimum protein requirement is about 0.83 g/kg body weight per day for elderly subjects. In addition, supplementation with leucine, β-hydroxy-β-methyl-butyrarate or creatine could be effective [Gielen et al. 2021]. Such supplemental support (or in the form of a balanced diet) may help support muscle mass restoration in PASC patients with post-COVID-19 syndrome.
PASC is characterized by malnutrition, loss of fat-free body mass, and low-grade inflammation. The recovery of these patients might be complicated by persistent symptoms such as functional impairment (i.e., fatigue and sarcopenia), dysphagia (particularly the intubated patients), loss of appetite, and taste/smell alterations (ageusia/anosmia) [Cereda et al. 2021]. Therefore, the nutritional strategies for PASC management should address to rectify nutritional deficiencies for adequate recovery of physical and functional wellbeing, as well as mental health of patients. The primary goal is to prevent complications and support recovery to enable COVID-19 and PASC patients to achieve the best possible nutritional, physical, functional and mental health status.

6.1. Pulmonary impairments in PASC

Respiratory system is the most affected organ in COVID-19 and its clinical impact may extend into the post-COVID-19 phase even after a patient recovery. In the respiratory sequelae, the SARS-CoV-2 invasion of alveolar cells leads to acute perivascular inflammatory response with severe tissue damage to pulmonary parenchyma (from vasculitis and endotheliitis), and to pulmonary vascular endothelium (due to huge infiltration of inflammatory cells) [Scholkmann et al. 2020]. The ensuing breach of endothelial–epithelial barrier allows the infiltration of monocytes/neutrophils and extravasation of a protein-rich exudate into the alveolar space, consistent with other forms of ARDS [Huppert et al. 2019]. The ARDS and atypical pneumonia could exert lasting damage to the lung alveoli through irreversible scarring or fibrosis in COVID-19 patients. This could lead to long-term breathing problems as well as the development of pulmonary fibrosis [Carsana et al. 2020]. Pulmonary vascular micro-thrombosis and macrothrombosis have been observed in 20–30% of patients with COVID-19 [Ackermann et al. 2020]. The increased pulmonary microthrombi and macrothrombi formation in COVID-19 patients [Klok et al. 2020] may also contribute to the long-term respiratory PASC sequelae.

**Pulmonary-PASC Symptoms:** Several COVID-19 survivors show long-term pulmonary post-discharge sequelae that include dyspnea (with or without chronic oxygen dependence), fatigue, impaired lung diffusion capacities, cough, and pulmonary fibrosis [Huang et al. 2021]. Dyspnea is a common persistent symptom across varying degrees of initial COVID-19 severity and these survivors show reduced functional capacity and increased exertional desaturation of lungs [Cortés-Telles et al. 2021]. Long-term risks of chronic pulmonary embolism and consequent pulmonary hypertension cannot be ruled out [Nalbandian et al. 2021].

6.2. Neuro-cognitive Impairments in PASC

Several neuro-COVID-19 impairments during PASC involve the the central nervous system – CNS (i.e., central demyelination, seizures, encephalopathy/encephalitis, neurocognitive dysfunction, strokes); the peripheral nervous system – PNS (i.e., Guillain-Barré syndrome/other neuropathies, neuralgias, myopathy, myositis), and the autonomous nervous system – ANS (i.e., dysautonomia, temperature and exercise intolerance), which increases long-term post-infectious disability [Thakur et al. 2021, Buoite Stella et al. 2022, Naidu et al. 2022]. The long-term neurological indications of COVID-19 could be attributed to direct viral infection, severe systemic and neuro-inflammation, microvascular thrombosis and neurodegeneration [Heneka et al. 2020]. The SARS-CoV-2 infection could damage brain parenchyma and vessels, possibly affect the blood–brain and blood–cerebrospinal fluid barriers, which regulate neurons, supportive cells and brain vasculature [Reichard et al. 2020]. Systemic/neuro-inflammation could lead to cognitive decline and the likelihood of neurodegeneration in COVID-19 survivors [Ramakrishnan et al. 2021]. Furthermore, SARS-
CoV-2 could affect the ANS and cause multiple neurological complications such as dysautonomia, orthostatic hypotension, and postural tachycardia syndrome (POTS) in PASC patients [Buoite Stella et al. 2022].

**Neuro-PASC symptoms:** Neurological complications in COVID-19 survivors frequent and represent a risk that compromises their functional capacity and the quality of life [Nordvig et al. 2021]. More than half of COVID-19 survivors experience fatigue, apathy, executive deficits, impaired cognitive control, and reduction in global cognition; attributed to GABAergic impairment resulting from viral-induced neuro-inflammation [Ortelli et al. 2021]. Neuromuscular manifestations such as dizziness, headache, myopathy, and olfactory and gustatory disturbances are frequently reported in PASC pathology [Shimohata 2021]. Migraine-like as well as late-onset headaches are prevalent PASC symptoms even after 6 weeks among 38% of post-discharged patients [Nalbandian et al. 2021]. The underlying pathophysiology could be linked to the activation of peripheral trigeminal nerve endings by the SARS-CoV-2 directly or via vasculopathy and/or increased circulating pro-inflammatory cytokines and hypoxia [Bolay et al. 2020]. Anosmia or partial loss of taste and smell resulting from olfactory dysfunction is a long-term PASC symptom reported persisted in more than 66% of European and US patients [Chiesa-Estomba. 2020, Garrigues et al. 2020].

Cough is another common PASC manifestations that lasts for weeks or months after SARS-CoV-2 infection. Such incessant post-COVID cough hypersensitivity state could be due to virus-mediated neurotropism, and neuroimmunomodulation of the vagal sensory nerves [Song et al. 2021]. Neuro-PASC patients demonstrate a specific immunological signature composed of humoral and cellular responses that are biased towards different SARS-CoV-2 structural proteins compared to healthy COVID convalescents, including a significant elevation in nucleocapsid (N)-specific antibody and T cell response [Visvabharathy et al. 2021].

**Cognitive-PASC symptoms:** Cognitive dysfunction, emotional distress, and functional decline are found to be prominent clinical symptoms in COVID-19 survivors at 4 months after acute infection [Vannorsdall et al. 2021]. Psychological indications such as anxiety and depression; as well as mental health impairments such as delirium, brain fog, memory loss, hallucination, confusion, depression, and anxiety are long-term PASC manifestations [Rubin 2020, Sudre et al. 2021]. Post-COVID brain fog could result from dysautonomia, deconditioning or ‘post-traumatic stress disorder’ (PTSD) [Kaseda and Levine 2020]. Long-term cognitive impairment has been reported in 20–40% of ICU discharged patients [Nalbandian et al. 2021]. Also, COVID-19 seem to pose an increased risk of long-term cognitive decline in elderly population [Liu et al. 2021].

### 6.3. Cardiovascular Impairments in PASC

The cardiovascular manifestations of COVID-19 19 may initially arise from subclinical pathology (i.e., myocarditis, pericarditis, palpitations, and right ventricular dysfunction) and ultimately evolve into myocarditis, stress cardiomyopathy, myocardial infarction, postural tachycardia syndrome (POTS), and arrhythmia [Chilazi et al. 2021]. In most cases, myocardial injury is a direct outcome of COVID-19 severity, where ensuing myocardial fibrosis or scarring could manifest re-entrant arrhythmias [Liu et al. 2020]. Incidentally, the stress cardiomyopathy during the COVID-19 pandemic has been remarkably high (7.8%) compared to the pre-pandemic period (<2%), despite the unchanged CFR and re-hospitalization rates [Jabri et al. 2020]. Based on the MRI data, the rate of myocardial inflammation seems to have increased as high as 60% after a 2-month diagnosis of COVID-19 [Puntmann et al. 2020].
Consequences of the viral spike (S) protein/ACE2 axis: The COVID-19 pathology perpetuates via the ACE2 receptor-mediated viral invasion of cardiac tissue (pericytes, cardiomyocytes, cardio-fibroblasts, epicardial adipose tissue, endothelia, and vascular cells), hyperinflammation, endothelial dysfunction with severe damage to myocardial/pericardial structural integrity and altered conduction system [Siripanthong et al. 2020]. Such histopathological changes lead to cardiac sequelae (thromboembolism and blood pressure abnormalities) in PASC patients [Deshmukh et al. 2021, which are mediated by the dysregulation of RAAS and Kinin-Kallikrein System (KKS)] [Cooper et al. 2021]. Furthermore, COVID-19 survivors also demonstrate persistent cardio-metabolic demand with reduced cardiac reserve, and RAAS dysregulation.

ACE2, the type-I transmembrane metallo-carboxy-peptidase, is a critical regulator of the RAAS, and plays a vital role in the Fe-R-H status of cardiovascular and immune systems [Naidu et al. 2022]. The SARS-CoV-2 pathogen gains cellular entry is via the docking of the viral spike (S) protein to the membrane bound ACE2 [ ]; and this infection process down-regulates ACE2 and/or sheds ACE2 from the cell surface [Cook and Ausiello 2022]. Such reduced ACE2 expression on cell surface could dysregulate Fe-R-H and initiate a plethora of cardiovascular impairments observed in COVID-19 and PASC [Chung et al. 2020].

Cardio-PASC Symptoms: The cardiovascular system is affected not only during the acute phase of COVID-19, but also during the post-recovery phase. Cardiomyopathy could develop in post-COVID-19 patients due to persistent hyperinflammation, hypoxia, microvascular injury/thrombosis, coronary thrombotic/plaque rupture events, and direct viral cardiotoxicity from abnormal troponin levels [Sandoval et al. 2020]. Fulminant myocarditis has been reported in several COVID-19 survivors even after weeks of undetectable viral pathogen (RT-PCR negative); however, some of these cases resulted in high fatality outcomes due to cardiac arrest [Inciardi et al. 2020]).

6.4. Renal impairments in PASC

Renal involvement in COVID-19 is frequent, which ranges from mild proteinuria to acute kidney injury (AKI). During the first COVID-19 wave, AKI was reported in nearly 1 in 3 COVID-19 patients and about 9% required kidney replacement therapy (KRT) [Lumlertgul et al. 2021]. Viral-induced hyperinflammatory response and ischemic/hypoxic stress seems to be responsible for tubular, endothelial, and glomerular damage, a hallmark of septic AKI in COVID-19 [Diao et al. 2021, Long et al. 2022]. Interestingly, several COVID-19 patients without any signs of AKI during the acute phase, show a gradual decline in renal function in 6–12-month follow-up period [Copur et al. 2022]. The severity of COVID-19, older age, patients with comorbidities (diabetes, hypertension, and cardiovascular disease) are more prone to develop AKI [Yende and Parikh 2021].

Renal-PASC symptoms: Renal sequelae leading to a progressive decline in kidney function has been widely reported in COVID-19 survivors. A decreased eGFR (estimated glomerular filtration rate) has been reported as a major indication in 35% of patients at 6-months in the post-acute COVID-19 [Huang et al. 2021]. Collapsing glomerulopathy with involution of the glomerular tuft in addition to acute tubular injury (which is newly termed as the ‘COVID-19-associated nephropathy – COVAN’), may particularly impact patients of African ancestry, in some regions of the world [Velez et al. 2020]. SARS-CoV-2-induced thrombotic microangiopathy with diffused cortical necrosis and microthrombi may also cause acute renal injury [Jhaveri et al. 2020].
**Host metabolic targets for renal re-optimization:** SARS-COV-2 infection could trigger the activation of multiple inflammatory pathways including angiotensin II, cytokine storm, C-reactive protein (CRP), TGF-β signaling, complement activation, and lung-kidney crosstalk could cause AKI. Hyper-inflammation plays a key role in the pathogenesis of AKI in patients; therefore, targeting these pathways with bioactive nutrients may represent a novel and specific dietary intervention for AKI resolution in PASC [Chen et al. 2021].

**Nutritional management of renal-PASC:**

### 6.5. Gastrointestinal and Hepato-biliary Impairments in PASC

COVID-19 patients with gastrointestinal (GI) and hepato-biliary sequelae tend to experience severe clinical manifestations (i.e., ARDS and MODS) of SARS-CoV-2 infection [Dong et al. 2021]. Gut impairment in COVID-19 patients has also been linked to the up-regulation of ACE2 and the ACE2 receptors in the GI tract [Hammoud et al. 2021]. Prolonged fecal shedding of SARS-CoV-2 virus (RT-PCR positive) for >4 weeks after the onset of COVID-19 symptoms, as well as viral persistence for a mean of 11 d after negative RT-PCR of respiratory samples has been reported [Wu et al. 2020]. COVID-19 could alter the gut microbiome, including the enrichment of opportunistic infectious agents and depletion of beneficial commensals [Donati et al. 2020]. Intestinal microflora are known to influence the ‘gut-lung axis’ and could alter the course of respiratory infections [Bradley et al. 2019]; accordingly, a butyrate-producing probiotic strain *Faecalibacterium prausnitzii*, associated with gut health was negatively correlated with the disease severity [Miquel et al. 2013, Zuo et al. 2020]. Long-term consequences of COVID-19 on the GI tract, especially on post-infectious irritable bowel syndrome and dyspepsia is currently under clinical investigation (NCT04691895).

**GI/Hepato-PASC symptoms:** Gastrointestinal (GI) sequelae such as diarrhea, nausea, acid reflux, loss of appetite, abdominal pain, and anorexia were observed in PASC patients at 90 days post discharge [Weng et al. 2021]. In a systematic review (total studies: 43 / total patients: 18,246) diarrhea was reportedly common among 11.5% of the COVID-19 patients, followed by nausea and vomiting (6.3%) and abdominal pain (2.3%) [Silva et al. 2020]. Also, abnormal liver function with increased ALT and AST levels was reported in 19% of PASC patients [Mao et al. 2020].

*Host metabolic targets for GI re-optimization:*

*Host metabolic targets for hepato-biliary re-optimization:*

**Nutritional management of GI and hepato-biliary-PASC:**

### 6.6. Endocrine impairments in PASC

SARS-CoV-2 affects most endocrine glands including the pancreas, thyroid, and adrenal glands [Lundholm et al. 2020]. The viral pathogen could affect endocrine system through various routes (i.e., direct viral injury, immunological and inflammatory damage) in emerging new-onset metabolic syndromes such as the development of type 1 diabetes mellitus, worsening of glycemic control (in pre-existing type 2 diabetes mellitus), primary Leydig cell damage, critical illness-related corticosteroid insufficiency, central hypocortisolism, pituitary apoplexy, immunemediated hypophysitis, diabetes insipidus, sick euthyroid syndrome, subacute thyroiditis, and bone demineralization with enhanced fracture risk [Pal and Banerjee 2020, Makrydakis et al. 2020].
2022]. These metabolic syndromes not only predispose the risk of severe COVID-19 but also increase the host susceptibility to SARS-CoV-2 infection and aggravate pre-existing endocrine disorders [Puig-Domingo et al. 2021]. Recent studies have indicated that patients with history of diabetes have increased susceptibility to SARS-CoV-2 infection [Singh et al. 2020, Abdi et al. 2020]. Also, COVID-19 patients with underlying metabolic and vascular disorders have reportedly 50% case fatality rate (CFR) [Steenblock et al. 2021].

**Endocrin-PASC / new-onset metabolic syndromes:** Disrupted hypothalamic–pituitary–thyroid (HPT) axis with abnormal thyroid function is a prominent endocrine manifestation in COVID-19 [Scappaticcio et al. 2021]. The parathyroid dysfunction with hypocalcemia is reported in two-thirds of COVID-19 patients [Elkattawy et al. 2020]. Both non-severe (1-2%) and severe (17%) COVID-19 patients show pancreatic injury [Liu et al. 2020]. Incidence of hyperglycemia in these patients is high (50%) [Ceriello et al. 2020], which is significantly associated with increased risk of mortality [Saand et al. 2021]. Endocrinopathies in COVID-19 survivors include, hypopituitarism, central diabetes insipidus, SIADH, thyroid abnormalities, hyperglycemia, adrenal insufficiency, orchitis and alteration in sperm morphology [Mirza et al. 2022]. Diabetic ketoacidosis (DKA) in COVID-19 survivors with no prior history of diabetes mellitus has been reported [Suwanwongse and Shabarek 2021]. Also, subacute thyroiditis with clinical thyrotoxicosis could ensue within weeks after the resolution of COVID-19 [Brancatella et al. 2020]. SARS-CoV-2 infections could cause latent thyroid autoimmunity with new-onset Hashimoto’s thyroiditis186 or Graves’ disease [Mateu-Salat et al. 2020].

**Host metabolic targets for endocrine re-optimization:** ACE2 receptors are expressed in various endocrine tissues; thus, making the system a vulnerable target for SARS-CoV-2 infection [Lazartigues et al. 2020, Mirza et al. 2022]. In endocrine system, ACE2 are localized in the paraventricular nucleus of hypothalamus [Chigr et al. 2020], in the acidophilic cells of parathyroid glands [He et al. 2006], in the pancreatic ductal, acinar and islet cells [Liu et al. 2020], and co-expressed with TMPRSS2 in thyroid [Rotondi et al. 2021] and adrenocortical cells [Mao et al. 2021]. Since ACE2 is an important component of the RAAS axis and a crucial entry point of SARS-CoV-2, the dynamics of ACE2 expression in endocrine tissue are also of contemporary relevance [Rath et al. 2021].

**Nutritional management of endocrin-PASC:** Considering the pathobiological impact of endocrine disorders on COVID-19 pandemic, metabolic re-optimization with nutritional management should be considered an immediate priority. New-onset diabetes in PASC is not merely an extension of SARS-CoV-2 virulence but a combination of several host responsive intrinsic factors with chronic effects on host metabolism [Accilli 2021]. Hyperglycemia-mediated aberrant glycosylation of ACE2 receptors could facilitates receptor-mediated viral invasion and increase the possibility of SARS-CoV-2 reinfection; therefore, glucose control with a strict dietary regimen an effective metabolic strategy for managing critically ill COVID-19 patients [Brufsky 2020, Gianchandani et al. 2020].

**6.7. Skeleto-muscular impairments in PASC**

Skeleto-muscular impairments are common in both acute COVID-19 and PASC [Soares et al. 2022], which include sarcopenia, cachexia, myalgia, myositis, rhabdomyolysis, atrophy, peripheral neuropathy, and Guillain-Barré Syndrome. The risk of developing sarcopenia during COVID-19 illness or after recovery is relatively high [Seixas et al. 2022]. In critically ill patients, the diaphragm damage has distinct myopathic features, which may contribute to long-term dyspnea and fatigue in COVID-19 survivors [Shi et al. 2021]. Also, SARS-CoV-2 could affect the skeleto-muscular system indirectly via regulation of nerve impulses and blood supply. The viral
interaction with ACE2 could dysregulate the RAAS activity and induce severe consequences such as loss of muscle mass, strength, physical dysfunction and delay the COVID-19 recovery process [Gonzalez et al. 2020]. Elevated levels of IL6, the pro-inflammatory cytokine, could also trigger myalgia and joint pain [Roschel et al. 2020].

**Skeleto-muscular-PASC Symptoms:** Myalgia (muscle pain)/fatigue is the third most common symptom (after fever, cough and sore throat) related to COVID-19 disease severity [Paliwal et al. 2020]. Elderly COVID-19 patients with preexisting metabolic syndromes (i.e. diabetes, obesity, CVD) are highly prone to severe muscle injuries in later stages of COVID-19 [Pitscheider et al. 2021]. Weight loss is common usually affecting non-fat mass (especially in obese patients), which may inflict dystrophic damages to skeletal muscle in COVID-19 survivors [Haraj et al. 2021]. One in five hospital admitted COVID-19 patients show serious weight loss and 73% experience high risk of sarcopenia [Wierdsma et al. 2021]. Rhabdomyolysis, an acute muscle injury with intense muscle soreness, fatigue, weakness, and lower limb pain/twitching, often observed in elderly patients, is a characteristic feature of severe COVID-19 [Jin and Tong 2020]. COVID-19-related sarcopenia and rhabdomyolysis could lead to long-term disabilities.

**Host metabolic targets for skeleton-muscular re-optimization:** Skeletal muscle is the largest body tissue involved in glucose metabolism [Riuuzzi et al. 2018]; therefore, a primary target for SARS-CoV-2 infection [Ali and Kunugi 2021A]. The viral-induced hyper-inflammatory response may also exacerbate mitochondrial dysfunction with subsequent myofibrillar breakdown and muscle degradation [Piotrowicz et al. 2021]. Elevated synthesis of creatine kinase (CK), lactate dehydrogenase (LDH), and myoglobin (a heme-containing globular protein) in hypercatabolic conditions trigger oxidative stress and leads to severe myocyte damage in COVID-19 [Welch et al. 2020].

**Nutritional management of skeleto-muscular-PASC:** Several COVID-19 survivors may have sequelae of muscle wasting and require progressive dietary plan for gradual recovery to pre-onset mobility function. Malnutrition has been attributed for muscular and immune dysfunction in COVID-19 [Ali and Kunugi 2021B]. Age-related sarcopenia, similar to muscle loss in COVID-19, could be effectively reversed by high protein supplementation [Liao et al. 2019]. Accordingly, effective nutritional strategies (i.e., protein-rich diet, and specific bioactive food supplements) could minimize the risk of sarcopenia in vulnerable COVID-19 patients [Chapple et al. 2020, Cawood et al. 2020]. Specific marine protein hydrolysates are shown to interact with SARS-CoV-2 enzymes (Mpro and monoamine oxidase A) and may reduce the viral load and associated disease severity [Yao et al. 2020]. Oral administration of L-glutamine could shorten the hospital stay and lower the CFR in COVID-19 patients [Cengiz et al. 2020]. Also, exposure to sunlight could stimulate vitamin D synthesis and promote muscle protein synthesis as well as strengthen the immune system [Xu et al. 2020]. Specific nutritional regimen (i.e., protein diet and amino acid supplements) with adequate physical exercise may help restore skeletal muscle metabolism and avert the after-effects of physical disability in COVID-19 survivors.

6.8. Reproductive impairments in PASC

The hypothalamic–pituitary–adrenal (HPA), -thyroid (HPT), and -gonad (HPG) axes are readily impaired during SARS-CoV-2 infection, which may lead to sexual dysfunction in males [Pal 2020]. In general, the testis is shielded from external factors by the blood–testicular barrier; however, SARS-CoV-2 could easily breach this physiological hurdle and cause inflammation [Massarotti et al. 2021]. Host receptor (ACE2) and serine protease (TMPRSS), both critical for the viral cellular entry, are widely co-expressed in the testes; which makes the male reproductive system a potential target for SARS-CoV-2 infection [Zupin et al. 2020]. ACE2 is
also abundant in gametocytes, Sertoli cells and spermatogonia stem cells, that makes testis a high-risk organ in COVID-19 [Vishvkarma and Rajender 2020]. Thus, male gonads may be potentially vulnerable to SARS-CoV-2 infection; therefore, caution should be exercised by expectant women and couples planning natural pregnancy or assisted reproduction.

**Male reproductive complications:** Male patients with COVID-19 demonstrate elevated levels of prolactin and LH in contrast to low testosterone and follicle stimulating hormone (FSH), which indicates primary testicular damage during active illness [Selek et al. 2021]. However, several COVID-19 patients exhibit damaged seminiferous tubules, reduced Leydig cell number, swollen Sertoli cells and mild lymphocytic inflammation in the testes [Yang et al. 2020]. Severe damage to seminiferous tubules with interstitial edema, congestion, RBC exudation in testes, and epididymis, indicate a potential testis injury in COVID-19. Furthermore, semen specimens from most patients (39%) indicate oligo-zoospermia (increased seminal levels of IL-6, TNF-α, and MCP-1) with impaired spermatogenesis [Li et al. 2020]. These patients also show scrotal discomfort, which is suggestive of viral orchitis. Also, a number of patients (31%) showed significant alterations in semen parameters including sperm DNA fragmentation and reduced sex-related hormone ratios, i.e., testosterone to luteinizing hormone (T:LH) and FSH:LH [Ma et al. 2021]. Furthermore, SARS-CoV-2 has also been detected in the semen of males with acute infection as well as in recovering patients [Polack et al. 2020]. These results collectively suggest that COVID-19 may lead to potential male fertility issues. Therefore, COVID-19 survivors especially individuals in reproductive age, andrological consultation and evaluation of gonadal function including semen analysis has been highly recommended [Corona et al. 2020].

**Female reproductive complications:** The SARS-CoV-2 could also invade the female reproductive system through the ACE2/TMPRSS2-mediated host viral entry mechanism. The ACE2 receptor is widely expressed in the ovary, uterus, vagina, and placenta, which in tandem with Ang II and Ang-(1-7) regulates the follicle development/ovulation, modulate luteal angiogenesis/degeneration, influence the regular changes in endometrial tissue and embryo development in the female reproductive tract [Jing et al. 2020]; therefore, COVID-19 could possibly affect ovulation and pregnancy. There is an abundance of ACE-2 receptors in the ovaries and oocytes; however, the existing data on possible ovarian dysfunction in COVID-19 survivors or any long-term sequelae on female fertility needs further investigation [Segars et al. 2020, Stanley et al. 2020].

**Host metabolic targets for reproductive re-optimization:** Both male and female COVID patients could develop sexual and reproductive health issues on the long run, partly due to the ACE2/TMPRSS2 axis that enables SARS−COV-2 entry into either reproductive systems (i.e., male gonads or female ovaries) [Omolaoye et al. 2021]. Interestingly, ACE 2 is highly expressed in the testes of infertile men than normal [57], which suggests that COVID-19 may cause male reproductive disorders via ACE2 activated pathway and men with reproductive issues may be more susceptible to SARS-CoV-2 infection. The degree of ACE2 expression is age-related; accordingly, the middled-aged have demonstrated higher incidence of SARS-CoV-2 infection compared to young men [Shen et al. 2020]. Several postulated mechanisms include Fe-R-H dysregulation, inflammation-induced oxidative stress, HPA dysfunction and direct gonadal damage [Dutta and Sengupta 2021, Seymen 2021, Mannur et al. 2021].

**Nutritional management of reproductive-PASC:**

7. **NUTRITIONAL STRATEGIES FOR COVID-19 MANAGEMENT: A GLOBAL HEALTH PERSPECTIVE**
Malnutrition (as undernutrition) is highly prevalent in COVID-19, which is about 37% among general inpatients, 52.7% among elderly inpatients and 66.7% among patients admitted in ICU [Latif et al. 2021]. Duration of hospital stay for malnourished patients infected with SARS-CoV-2 is significantly higher (almost double) than the non-malnourished cases [Yu et al. 2021]. Nutritional inadequacy during hospitalization exacerbates the likelihood of long-term PASC syndrome. Malnutrition could delay healing and increase the duration of hospitalization. Monitoring the nutritional status is critical in the management of hospitalized COVID-19 patients and in the rehabilitation of PASC individuals. Therefore, an early dietary support with oral nutritional supplements (ONS), enteral and parenteral nutrition, may ameliorate such detrimental effects and play a vital role in clinical management as well as aiding the recovery of hospitalized patients [Volkert et al. 2019]. The European Society for Parenteral and Enteral Nutrition (ESPEN) recommends that COVID-19 patients should be given ONSs that provide at least 400 kcal/day and ≥30 g protein/day [Barazzoni et al. 2020].

It is important to consider the specific nutritional needs of COVID-19/PASC patients. The SARS-CoV-2 infection could severely compromise the dietary intakes of PASC patients in several ways [Holdoway 2020]. The pulmonary-related COVID-19 issues such as coughing and breathlessness, dry mouth due to oral breathing, use of inhalers and oxygen therapy, may cumulatively affect the eating and drinking regimen of COVID-19 patients [British Lung Foundation (BLF), 2020]. Also, the sensory loss of smell (anosmia) or taste (ageusia), the distinctive symptoms of COVID-19, could affect patient’s appetite and desire to eat [Xydakis et al. 2020]. A raise in body temperature may increase the nutritional demand; however, the ensuing hyper-inflammatory response could suppress the appetite and lead to muscle catabolism [Gandy 2019]. The decline in muscle mass (sarcopenia) is a whole-body process that also affects respiratory, masticatory and swallowing functions, which may also have a negative impact on nutrient intake and increase the risk for malnutrition. In a cohort, more than 90% of COVID-19 patients showed some degree of dysphagia, with the need of a modified diet’s consistency or nasogastric feeding [Brugliera et al. 2020]. Furthermore, the aging process profoundly alters several physiological functions in the body, that eventually decreases the body’s ability to cope with stressors. Many such changes are subtle but could negatively impact nutrient intake and lead to malnutrition.

### 7.1. Phytochemical Blockers of Viral-Host Interaction

Antiviral drugs with proven efficacy are not yet available to prevent transmission or facilitate treatment of COVID-19. Natural compounds, especially plant-derived bioactives, have emerged adjuvant interventional options to overcome the limitations of existing antiviral drugs against COVID-19 [Patil et al. 2021]. In the ongoing COVID-19 pandemic, several clinical practices have integrated complementary or traditional medicine, as adjuvant therapeutic protocol with the Western medicine [Wan et al. 2020, Mani et al. 2020]. Computational drug repurposing is a promising alternative that enables prioritization of existing compounds through rapid high through-put screening analyses [Harrison 2020]. Several ongoing in silico studies have demonstrated the antiviral potential of natural compounds and these phytochemicals also have multifunctional effects such as anti-inflammatory, antiviral, antioxidant, cardioprotective, and exhibit potent therapeutic benefits in the treatment of COVID-19 associated clinical manifestations. The ‘repurposing’ of approved antiviral drugs with adjuvant combination(s) of well characterized phytochemicals could be one of the rapid and safe strategies to combat the COVID-19 pandemic [Naidu, Tripathi et al. 2021; Naidu, Mustafa, et al. 2021b].

### 7.2. Phytochemical Inhibitors of Viral Replication
Natural compounds and bioactives from medicinal herbs widely used for centuries in global healthcare, could pave a new direction in the development of novel anti-COVID-19 prophylactics and therapeutics [Mahrosh and Mustafa 2021]. Interestingly, many potential drugs in current practice are based on the structure of natural compounds with desired biological activities. Almost half the drugs approved between 1981 and 2014 by the US-FDA, were derived from or mimicked a natural compound [Newman and Cragg 2016]. Based on high diversity, complex molecular structure(s), broad-spectrum activity including inhibition of viral transcription and translation, as well as considering their overall safety and non-cytotoxicity, phytochemicals may serve as promising anti-COVID-19 interventions [Lalani and Poh 2020, Chojnacka et al. 2020]. For example, several plant-derived flavonoids are potential inhibitors of SARS-CoV-2 with comparable or higher potency as that of antiviral drug, remdesivir [Tahir et al. 2020]. Such natural antiviral agents that target highly conserved SARS-CoV-2 replication enzymes (i.e., Mpro or RdRp) provide two advantages: (i) the potential for broad-spectrum antiviral activity, and (ii) reduced risk of mutation-mediated drug resistance [Naidu, Tripathi, et al. 2021].

**Natural Inhibitors of SARS-CoV-2 Main Protease (Mpro):** Mpro also known as the chymotrypsin-like protease (3CLpro), is one of the well characterized antiviral targets among CoV pathogens [Grum-Tokars et al. 2008]. Along with the papain-like protease (PLpro), Mpro is critical to process polyproteins that are translated from the viral RNA [Hilgenfeld 2014]. Therefore, Mpro is considered as one of the key antiviral targets to combat COVID-19 [Joshi et al. 2020]. Antiviral agents targeting the Mpro enzyme could significantly reduce the risk of mutation-mediated drug resistance and display broad-spectrum antiviral activity [Goyal and Goyal 2020]. The phytochemical Mpro inhibitors could effectively target the large surface area of viral enzyme dimers [Hartini et al. 2021].

Medicinal herbs *Isatis tinctoria*, *Torreya nucifera*, *Psoralea corylifolia*, and *Rheum palmatum* could elicit potent anti-Mpro activity [Mandal et al. 2021]. *Baicalein*, a natural compound commonly used in traditional Chinese medicine, is a potent inhibitor of SARS-CoV-2 Mpro. In a randomized, double-blind, single-dose clinical trial (n=72), baicalein (100-2800 mg) was well tolerated in the treatment of acute, or chronic hepatitis [Li et al. 2014]. The Mpro inhibitor NLC-001, a phytochemical supplement that is currently undergoing a human clinical trial in Israel, as a potential oral intervention against COVID-19 [Goldet et al. 2020]. Natural phytochemicals, *pentagalloylglucose* (PGG), and *epigallocatechin-3-gallate* (EGCG) demonstrate potent inhibition of SARS-CoV-2 Mpro [Chiu et al. 2021]. Based on the pH milieu, Mpro could form dimers, tetramers, or even highly active octamers [Zhang et al. 2020]. *Quercetin* demonstrates a unique redox-based mechanism and inhibits the SARS-CoV-2 Mpro by altering the thermostability of the enzyme [Abian et al. 2020]. *Quercetin* is a promising scaffold to engineer new functional groups for the development of novel SARS-CoV-2 Mpro inhibitors.

**Natural Inhibitors of SARS-CoV-2 RNA-dependent RNA polymerase (RdRp):** RdRp also known as the ‘nsp12’, plays a central role in the replication and transcription cycles of SARS-CoV-2 [Gao et al. 2020]. The RdRp enzyme polymerizes a high quantity of nucleotides to support an uninterrupted viral replication in the infected host [Naidu, Clemens, et al. 2022]. Due to its high evolutionary stability, RdRp has no counterpart in human cells; therefore, represents a unique antiviral target [Gordon et al. 2020, Vicenti et al. 2021]. Several FDA-approved RdRp nucleotide analog inhibitors (NAIs) against RNA viral pathogens have been repurposed and evaluated for clinical management of COVID-19 [Chien et al. 2020]. Furthermore, high throughput screenings and in-silico studies have also elucidated the anti-RdRp activity of several FDA-approved non-nucleotide analog inhibitor (NNAI) drugs [Tian et al. 2021]. Unfortunately, the first open label, randomized, controlled trials with popular repurposed NAI drugs such as remdesivir, favipiravir, lopinavir-ritonavir, ribavirin, sofosbuvir, etc., showed poor efficacy against SARS-
Considering the high morbidity/mortality rates of COVID-19 pandemic and lack of effective antiviral drugs, the repurposing of traditional antiviral phytonutrients and natural bioactives could be a promising strategy [Mahrosh and Mustafa 2021]. A few phytochemical RdRp inhibitors as potential intervention(s) for COVID-19 control are described below.

**Suramin**, a phytochemical from eastern white pine tree needles (*Pinus strobus*) is a potent NNAI against SARS-CoV-2 RdRp enzyme. A dosage of 100 µM suramin totally blocks the formation of RdRp–RNA complex compared to a 5 mM dosage of remdesivir; thus, the RdRp inhibition potency of suramin is at least 20-fold higher than remdesivir [Yin et al. 2020]. Suramin also inhibits SARS-CoV-2 infection in cell cultures by blocking cellular entry of the virus [Salgado-Benvindo et al. 2020]. **Silibinin**, a flavonolignan from the herb ‘milk thistle’ (*Silybum marianum*), directly inhibits the SARS-CoV-2 RdRp enzyme, and reduces the signal transducer and activator of transcription (STAT3)-induced lung and systemic inflammation in the infected host [Bosch-Barrera et al. 2020]. The dual action of silibinin to inhibit viral replication machinery as well as host cytokine storm provides a strong rationale for clinical evaluation of this phytochemical for COVID-19 management.

**Black tea polyphenols** – theaflavin 3,3’-digallate (TF3), theaflavin 3-gallate (TF2a) and procyanidin B2 could effectively inhibit RdRp activity by blocking active site(s) in the enzymatic scaffold [Lung et al. 2020]. **Baicalein**, a bioactive flavone found in the root of *Scutellaria baicalensis*, an ‘East Asian skullcap’ plant, could block viral replication in cell culture systems by inhibiting the RdRp activity [Song et al. 2021, Zandi et al. 2021]. **Corilagin**, is a gallotannin from plants *Caesalpinia coriaria*, *Alchornea glandulosa* and *Punica granatum* (pomegranate) bind directly to RdRp and inhibit the viral polymerase activity [Li et al. 2021]. **Lycorine** is a potent NNAI against SAR-CoV-2 RdRp enzyme with efficacy higher than the antiviral drug remdesivir [Jin et al. 2021]. Propolis from (honeybee products) contains phenolics such as ellagic acid, hesperetin, and kaempferol that show high-affinity interactions with the SARS-CoV-2 RdRp and considered as effective COVID-19 inhibitors [Shaldam et al. 2021].

Apart from the NNAI spectrum these natural plant-based RdRp inhibitors also provide multifunctional dietary health benefits [Naidu, Mustafa, et al. 2021]. Accordingly, these phytonutrients could provide synergistic or additive benefits with pharmaceutical drugs in immune modulation, anti-inflammation, and relieve oxidative stress in COVID-19 patients [Patil et al. 2021]. Some predicted drugs and potential phytoceutical compounds that inhibit SARS-CoV-2 RdRp and considered as effective COVID-19 inhibitors [Aronsksyy et al. 2021].

### 7.3. Dietary/Natural Anti-inflammatories

Hyperinflammatory responses and inflammasome activation induced upon SARS-CoV-2 infection are associated with severe symptoms of COVID-19 [Pan et al. 2021]. Once the ‘cytokine storm’ ensues, anti-viral intervention alone is not sufficient to ameliorate the pathobiology of COVID-19. Additional anti-inflammatory treatments such as JAK inhibitors, IL-6 inhibitors, TNF-α inhibitors, colchicine, etc., are widely used in the clinical management of the disease [Stebbing et al. 2020]. The immunomodulatory activity of several plant-based dietary nutrients could play a beneficial role in the down-regulation of cytokine storm during COVID-19 [Liskova et al. 2021]. The Nrf2/Keap1 signaling pathway mainly regulates anti-inflammatory gene expression, which could effectively contain SARS-CoV-2 infection [Cuadrado et al. 2020]. Therefore, identification of new Nrf2-dependent anti-inflammatory phytochemicals has become a key investigative point in drug discovery [Ahmed et al. 2017].
**Hesperidin** is a glycosidic flavonoid from citrus species known to augment cellular antioxidant defenses via the ERK/Nrf2 signaling pathway [Parhiz et al. 2015]. Hesperidin elicits anti-inflammatory effects via inhibition of the PI3K/AKT signaling pathway and suppress the secretion of proinflammatory cytokines such as INF-γ and IL-2, thus may reduce the potential risks of cytokine storm in COVID-19 [Qi et al. 2019, Haggag et al. 2020]. Phytochemicals Rutin and Punicalagin are effective SARS-CoV-2 Mpro inhibitors [Majumder and Mandal 2020, Falade et al. 2020] as well as potent Nrf2 activators [Tian et al. 2016, Yan et al. 2016].

Quercetin could inhibit inflammasome NLR family pyrin domain containing 3 (NLRP3) in macrophages [Saeedi-Boroujeni and Mahmoudian-Sani 2021]. Inflammasomes are cytosolic multi-protein complexes formed in response to cytosolic pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), which generate activated cytokines IL-1β and IL-18 [Zhao and Zhao 2020]. In a prospective randomized clinical study quercetin supplementation (1-g daily/30 days) at an early stage of COVID-19 seem to reduce the frequency and duration of hospitalizations, the need for non-invasive oxygen therapy, progression to intensive care units, and the CFR [Di Pierro et al. 2021].

Several polyphenols (quercetin, resveratrol, catechins), N-acetylcysteine (NAC), and palmitoylethanolamide (PEA) could block inflammatory pathways (i.e., NLRP3 inflammasome-mediated IL-1β synthesis and pro-inflammatory cytokine release); as well as inhibit viral replication (by blocking the viral proteases, Mpro and RdRp) [Naidu, Tripathi, et al. 2021a; Naidu, Mustafa, et al. 2021b]. Several natural compounds demonstrate antiviral activity by modulation of immune cell cascade (macrophages, dendritic cells, etc.), generation of cytotoxic (antiviral) factors such as nitric oxide (NO•), cytokotic T lymphocytes from CD8+ T lymphocytes, T helper cells from CD4+ T lymphocytes, activation of phagocytes, and proliferation of B lymphocytes. [Jayawardenena et al. 2020]. Myo-inositol, a naturally occurring polyol, widely found in foods, and actively synthesized in the body, seems to reduce IL-6 levels, and mitigate the inflammatory cascade (‘cytokine storm’), a prominent clinical manifestation of COVID-19 [Bizzarri et al. 2020].

Fe-redox dysregulation (FeRD) with ensuing free radical (ROS/RNS) oxidative damage, is a common denominator in all symptomatic clinical phases of COVID-19 [Naidu et al. 2022]. Glutathione (GSH) is the ‘master’ antioxidant in all tissues; the high GSH levels (reduced form) emphasizes its regulatory role in several processes including free radical scavenging (oxidative stress), and resolving hyper-inflammation, the risk factors for multi-organ failure in COVID-19 [Polonikov 2020]. GSH supplementation with GSH may provide an effective strategy to resolve inflammation and oxidative stress in COVID-19 and PASC patients [Guloyan et al. 2020]. GSH intervention is a promising approach; however, it requires high doses for therapeutic efficacy, due to its poor bioavailability. Dietary supplementation with GSH precursors cysteine and glycine could be an alternate approach for effective PASC management [Silvagno et al. 2020].

Several plant-derived compounds are natural antioxidants capable of neutralizing or scavenging harmful free radicals, modulating several oxidative stress-mediated signaling pathways and protect cellular systems. Phytochemicals from Cat’s claw (Cadambine & Epiafzelechin-4β-8-epicatechin) and Ayurvedic medicinal herb ‘Tulsi’ (Isorientin 4’-O-glucoside) are active regulators of COX-mediated inflammatory pathways [Yuan et al. 2020]. Quercetin is a naturally occurring plant flavanol from the flavonoid group of polyphenols, is a powerful scavenger of free radicals (i.e., ROS and RNS), hence classified as a redox nutraceutical known to reduce oxidative stress and inflammation [Xu et al. 2019].
8. CONCLUSION AND FUTURE PERSPECTIVE
The World Health Organization (WHO) has emphasized the benefit of adequate nutrition to enhance the immune system, especially at the time of COVID-19 infection. The European Society for Clinical Nutrition and Metabolism (ESPEN) gave concise guidelines for an effective nutritional management of COVID-19 aimed at the prevention and treatment of malnutrition in these patients [Barazzoni et al. 2020]. The Food and Agriculture Organization (FAO) of the UN, Center for Disease Control and Prevention (CDC), Dietary Association of Australia (DAA) and United National Children’s Fund (UNICEF) have proposed various health/dietary guidelines and advice pertaining to COVID-19 pandemic. Guidelines and advice mostly include the consumption of fruits, vegetables, fish oil, probiotics, whole grains, cereals, and nuts. These foods could substantially improve the immune system and thereby elicit overall protection from SARS-CoV-2 infection and lower the risk of COVID-19 related health issues as well as improve the recovery of patients [WHO 2020, de Faria Coelho-Ravagnani et al. 2021]. Intake of functional foods/nutraceuticals and dietary supplements rich in various micronutrients with antioxidant, anti-inflammatory, and immunomodulatory properties could lower the risk of SARS-CoV-2 infection and help rapid recovery from COVID-19 [Wong et al. 2021, Chiu et al. 2021].
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