Research Update: Addressing the long-COVID crisis with natural medicines

CONTENTS

What is long-COVID?

The advent of the COVID-19 pandemic at the end of 2019 has undoubtedly changed the world forever. As of July 2022, there have been nearly 600 million confirmed cases, including over 6 million deaths.[1] While this data highlights the large number of people who have contracted COVID-19, the consequences may persist much longer in some people. The term long-COVID has been defined as signs and symptoms that continue to develop after the acute infection phase and include both ongoing symptomatic COVID-19 (signs and symptoms from four weeks up to 12 weeks) and post-COVID-19 syndrome (>12 weeks).[2] It has been estimated that one-third of patients will have persisting symptoms for over six months after contracting the initial infection,[3] which significantly impacts individuals, employers and healthcare systems. Consequently, there is a dire need to provide effective treatment options and support patients suffering from long-term symptoms.

Why are some people affected?

While people with certain risk factors, such as high blood pressure, smoking, diabetes and obesity, are more likely to have severe COVID-19 symptoms, it is relatively unknown why some people have a prolonged recovery.[4] Persistent viraemia due to weak or absent antibody response,[5] reactivation of other viruses,[6] inflammatory and immune reactions,[7-9] mental health conditions,[10,11] alterations to the gut microbiome,[12] and microvascular dysfunction[13] may contribute to developing long-COVID. A retrospective study found that older age, female sex, requiring hospital assessment, and patients with a preexisting asthma diagnosis were also more susceptible to developing long-COVID.[14] However, other studies have found no relationship between initial disease severity.[15] As dozens of long-COVID phenotypes have been identified, detecting and predicting those at risk remains challenging.

Manifestations of long-COVID

The persistence of symptoms observed in the acute stage of the virus are often the most common manifestations of long-COVID.[16] More than 200 symptoms have been identified, encompassing various physical, neurological and neuropsychiatric symptom domains. The most common manifestations that have been reported include fatigue, shortness of breath, cough, chest pain, ageusia (loss of taste), anosmia (loss of smell), gastrointestinal (GI) symptoms, memory loss, brain fog, insomnia, anxiety and depression.[17-19]

Supporting the body systems

The virus responsible for causing COVID-19, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), enters cells via the angiotensin-converting enzyme-2 (ACE2) receptor.[20] After entry, the virus undergoes replication and maturation, activating and infiltrating immune cells by various cytokines and provoking an inflammatory response. It is clear that COVID-19 is more than a viral respiratory disease, but rather is a disease that damages multiple organs besides the lungs. ACE2 receptors are present in numerous cells throughout the body, including the heart, liver, gastrointestinal tract (GIT), oral and nasal mucosa, arterial and venous endothelial cells and the nervous system,[22] highlighting the destructive systemic effects of SARS-CoV-2.

While no guidelines for post-COVID have been provided by governing bodies, a holistic and multidisciplinary approach that supports the body systems affected is essential to reduce the catastrophic outcomes of long-COVID.

Figure 1: Potential contributing mechanisms of long-COVID

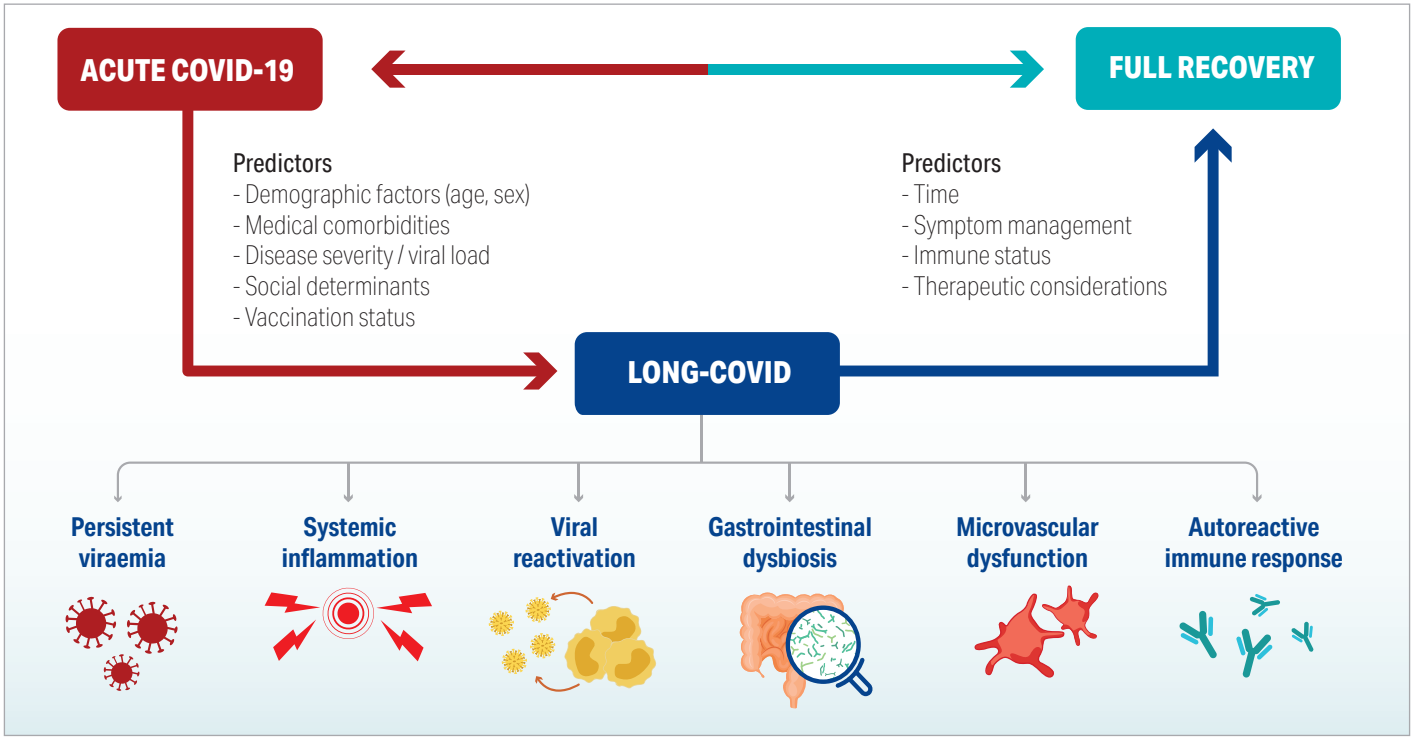
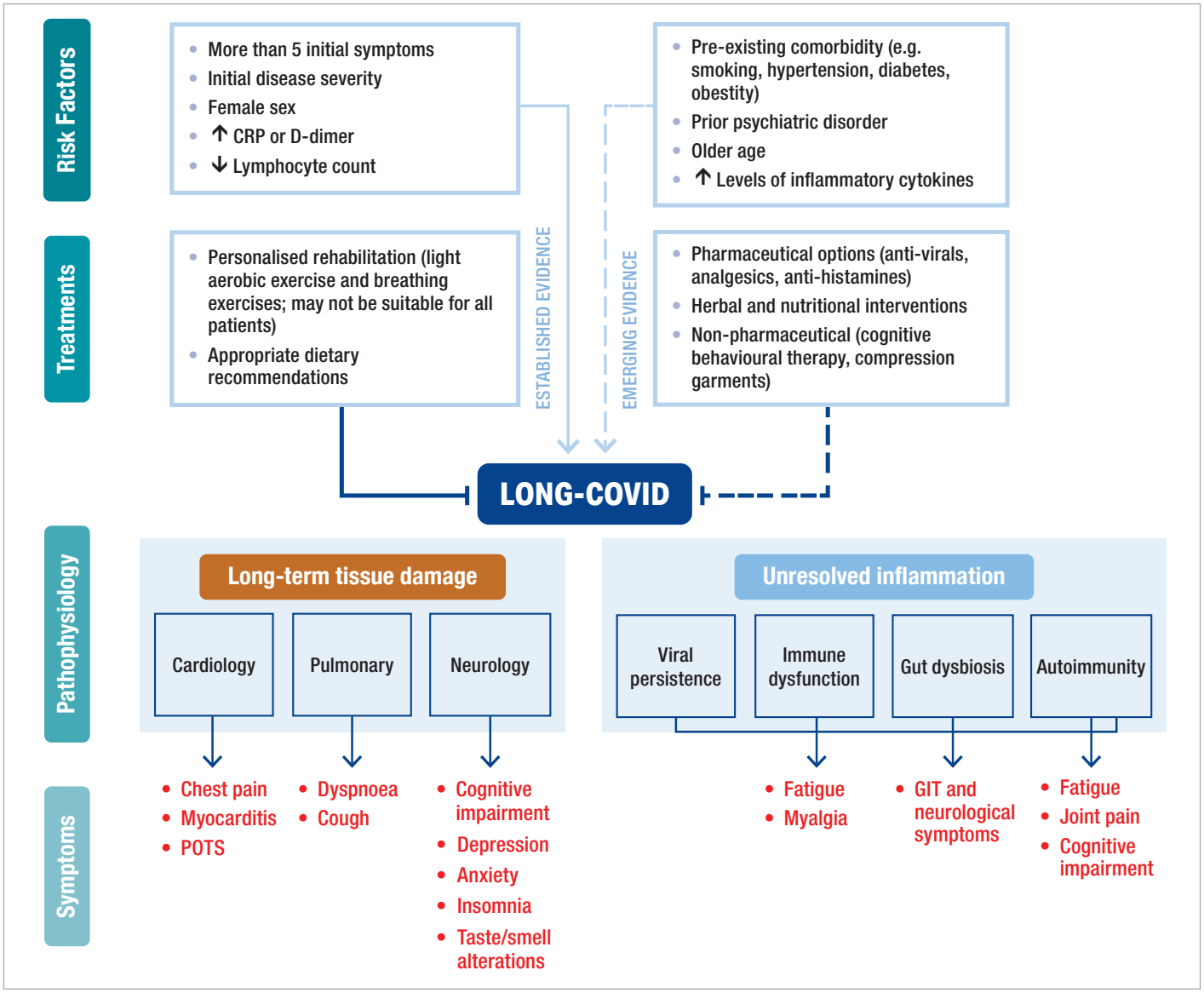


Figure 2: An overview of the symptoms, pathophysiology, and potential risk factors involved in long-COVID[21]



Inflammation and the immune system

In patients with long-COVID, research has uncovered that inflammation and immune system dysregulation occur for at least eight months after the initial infection.[23] A recent study has found high levels of pro-inflammatory cytokines persist in patients after disease resolution, which was accompanied by an absence of T and B cell subsets. These findings suggest that SARS-CoV-2 infection exerts prolonged residual effects in the innate and adaptive immune systems, which may be driving the symptomology of long-COVID.

Persistent symptomology may also be driven by SARS-CoV-2 dysregulation of the hosts immune response during acute infection, allowing previously harboured pathogens to reactivate and drive new chronic symptoms.[24] Specifically, Epstein-Barr virus (EBV) has been detected soon after or concomitantly with COVID-19 infection, including after initially asymptomatic infections.[6]

Naturopathically, therapies which target the immune dysfunction induced by the reactivation of pathogens may offer a feasible therapeutic approach for this subset of patients. Moreover, several nutrients, including vitamins A, C, D and zinc, play an important role in innate and adaptive immune systems and they may be essential to promote optimal immune function and help control the impact of infections.[25]

Immune dysregulation

Rice bran arabinoxylan compound

Rice bran arabinoxylan compound (RBAC) is a denatured hemicellulose that has been shown to exhibit potent immunomodulatory effects, including the modulation of cytokine production.[26-29] RBAC additionally counteracts the decline of NK cell activity,[30] highlighting its potential role in immunodeficient states. RBAC has also been shown to improve outcomes in a number of viral illnesses, including HIV,[31] influenza[32] and chronic hepatitis C infection,[33] and may, therefore, provide beneficial effects in patients with viral reactivation following long-COVID.

Mushrooms

Classed as biological response modifiers, mushrooms are valuable agents capable of modifying the hosts' defence response and consequently are utilised in treating and preventing diseases that stem from immunodeficient states.[34] The β-glucans found in reishi, shiitake and coriolus are responsible for enhancing immune-

modulatory pathways by stimulating the activity of both innate and adaptive immune systems and affecting the production of NK cells, macrophages and T cells.[35] Furthermore, these mushrooms may restore healthy immune system function by increasing secretory IgA,[36] increasing the number of $CD3^+$, $CD4^+$, and $CD8^+$ T cells;[37-39] and decreasing pro-inflammatory cytokines thereby enhancing immune recovery.

Vitamin C

During infections, vitamin C levels decrease as the metabolic demand requires high amounts of this vitamin due to increased inflammation.[40] Vitamin C in COVID-19 pathology inhibits inflammation and activates the immune response by regulating the production of cytokines, mitigating oxidative stress and acting upon the differentiation and proliferation of T and B lymphocytes.[41] Evidence also suggests that high dose intravenous vitamin C reduces EBV-associated antigen levels, including IgM and IgG,[42] which may be crucial in improving recovery from long-COVID.

Vitamin D

Evidence has accumulated on the regulatory role of vitamin D on the immune system due to its numerous functions in both innate and adaptive immunity. Vitamin D reduces the expression of inflammatory cytokines, increases antimicrobial activity by enhancing cathelicidin antimicrobial peptide and defensin β-2 and upregulates the phagocytic activity of immune cells to aid in the clearance of pathogens.[43,44] Vitamin D may be vital for long-COVID patients with EBV reactivation as supplementation has significantly reduced humoral immune responses to the latent antigen.[45]

Vitamin A

Vitamin A is a key regulator of innate and adaptive immune cells and has been shown to augment the interferon-based immune response to RNA viruses, decreasing their replication.[46-50] Low vitamin A may occur during infection, potentially due to the acute phase response and the slower speed of mobilisation from stores.[51] Moreover, vitamin A deficiency may promote an excessive inflammatory response by increasing the production of IL-2 and TNF-α,[52] while supplementation reverses these effects.[53]

Zinc

Zinc deficiency is known to impair or completely suppress phagocyte and lymphocyte activity, resulting in diminished cytokine and antibody responses.[54] Zinc may benefit patients with latent infections by reducing inflammation, improving mucociliary clearance, modulating anti-viral immunity and preventing ventilator-induced lung injury.[55] Furthermore, correcting a zinc deficiency through supplementation has been shown to strengthen the immune system response and mitigate mortality from infectious diseases.[56]

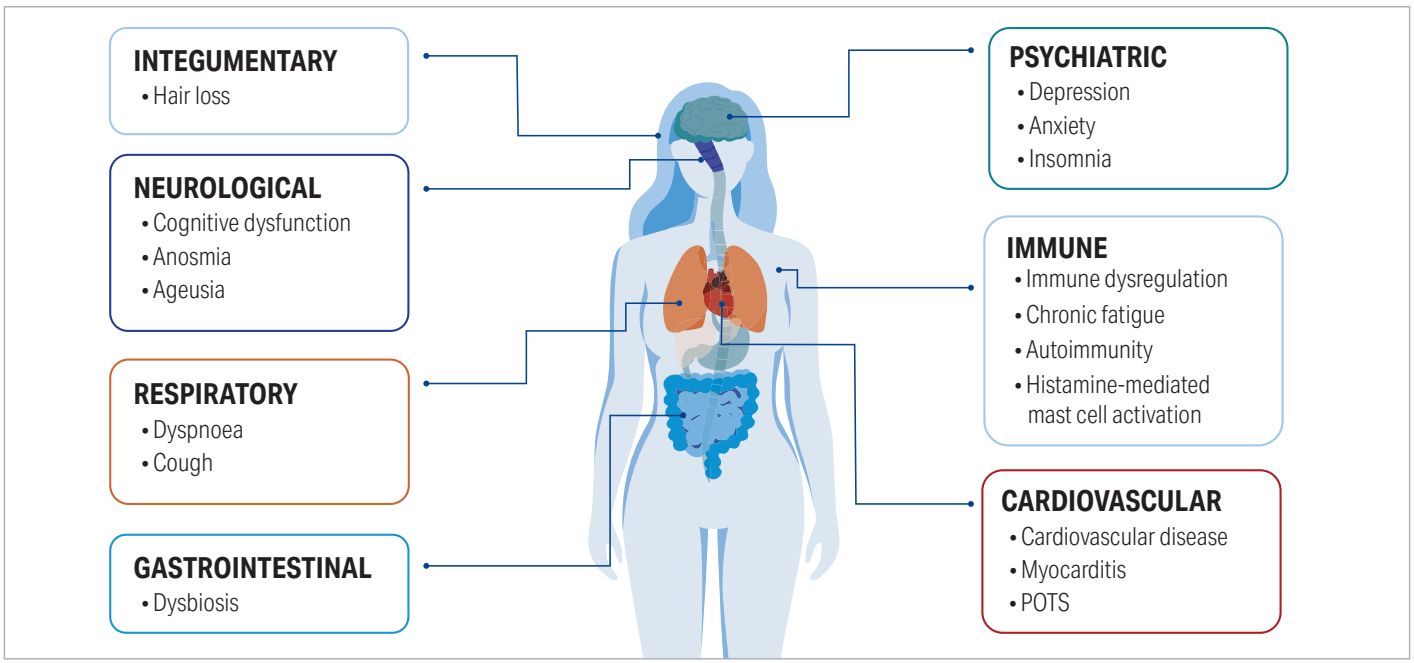
Chronic fatigue

As post-viral fatigue has been associated with several infectious diseases, such as EBV, Ross River virus, and herpes viruses, there is no surprise that chronic fatigue is becoming a major symptom of long-COVID.[57] In fact, fatigue is the most persistent and debilitating manifestation of long-COVID, with studies revealing up to 80% of subjects will experience this symptom post-infection.[58,57] Though the data is still emerging, reports suggest that increased levels of pro-inflammatory cytokines, immune dysregulation, and mitochondrial dysfunction may be common causes of post-viral fatigue. Moreover, the persistence of fatigue three months post-infection appears to be associated with moderate to severe depression and reduced cognitive performance, suggesting changes in neurotransmitters, oxidative stress, and inflammation may be contributing factors.[59] Thus, management approaches that address these multifactorial pathophysiologies should be evaluated in patients with post-COVID fatigue.

Adaptogens

Western herbalists commonly use adaptogens to enhance work performance, reduce fatigue, and treat debility symptoms following intense physical and psychological stress. Given their known beneficial effects on mental and physical fatigue, a recent randomised,

Figure 3: Common clinical manifestations observed in long-COVID[16]



placebo-controlled trial assessed the efficacy of three adaptogens in 100 subjects with long-COVID.[60] Patients were randomly assigned to receive a fixed combination of rhodiola, Siberian ginseng and schisandra or a placebo for 30 days.[60] After the trial period, physical performance (measured by daily walk time), fatigue and pain scores improved in the treatment group, and IL-6 levels decreased. Though this pilot trial has its limitations, including small trial size and short duration, it enhances the existing knowledge that adaptogens increase physical performance and could be considered in patients with post-COVID fatigue.

Coenzyme Q10 (CoQ10)

The literature has previously reported an association between chronic fatigue syndrome (CFS), increased oxidative stress and reduced CoQ10 levels.[61] Acknowledged for its antioxidant activity, CoQ10 is an essential component of the mitochondrial respiratory chain and is involved in synthesising adenosine triphosphate (ATP).[62] Supplementation at 150mg per day for 12 weeks has been shown to significantly increase plasma levels of CoQ10 in CFS patients, which correlated with decreased oxidative stress and fatigue scores.[63] A systematic review of 16 studies additionally concluded that CoQ10 supplementation reduces fatigue in patients with statin-induced fatigue and fibromyalgia.[64] While further research is required, restoring antioxidant levels with CoQ10 may alleviate chronic fatigue and help support recovery after infection.

Vitamin C

Conditions recurrently linked to fatigue, such as autoimmunity and chronic viral infections, are highly associated with oxidative stress, inflammation, blood flow disorders, and neurotransmitter metabolism.[65] Thus, vitamin C's antioxidant, anti-inflammatory, endothelial-restoring, and immunomodulatory effects might be a suitable treatment option. In a systematic review, high dose intravenous (IV) vitamin C showed a significant reduction in fatigue, mainly in patients with cancer, herpes zoster, allergies, and post-operative conditions.[57] Although vitamin C plasma levels have not been evaluated in patients with long-COVID, a deficit is most probable as deficiencies in infections are frequently observed.[66] Therefore, high-dose vitamin C could be a beneficial treatment option in treating fatigue in patients with long-COVID.

Vitamin D

Before the current pandemic, low vitamin D concentrations were associated with fatigue and muscle weakness in the general population.[67] A correlation has been observed between fatigue scores, reduced exercise tolerance and vitamin D deficiency in 149 patients post-COVID infection.[68] In a preliminary study, a multivitamin food supplement containing vitamin D alongside B group vitamins, vitamin C, acetyl-L-carnitine and hydroxytyrosol improved perceived fatigue in patients with long-COVID.[69] While these results are promising, higher-quality trials are essential. Screening for vitamin D deficiency in patients with long-COVID may be an important modifiable risk factor.

B vitamins

Acknowledging that B vitamins play an imperative role in mitochondrial energy production, it can be assumed that a subsequent deficiency is likely to induce an energy deficit, exacerbating fatigue and post-exertional malaise. While B vitamins should be used in synergy, folate and B12 have shown promise in patients with CFS, particularly regarding reactivated EBV infection.[70,71]

Magnesium

Chronic fatigue may be associated with lipid peroxidation, low ATP levels, oxidative stress and, consequently, mitochondrial dysfunction.[72] In preclinical studies, magnesium supplementation has been shown to improve mitochondrial function, increase ATP production and reduce oxidative stress in mice.[73] Furthermore, magnesium supplementation was found to have an overall beneficial effect as well as symptom reduction in patients with CFS and fibromyalgia.[74] Given low magnesium levels have been associated with COVID-19 severity,[75] supplementation could be a therapeutic option for post-COVID fatigue by improving mitochondrial function and reducing oxidative stress.

Probiotics and enzymes

In a randomised controlled trial, a probiotic blend with a multi-enzyme formulation significantly improved energy levels, muscle strength, concentration and memory in patients with post-COVID fatigue.[76] After 14 days of treatment, fatigue resolved in 91% of individuals who took the enzyme and probiotic supplement and only 15% who took the placebo. Since long-COVID fatigue is assumed to be accompanied by oxidative stress, inflammation and immune dysfunction, the anti-inflammatory, antioxidant and immunomodulatory properties of systemic enzymes and probiotics make them an ideal therapeutic option in disease management.[76]

Autoimmunity

Long-COVID symptoms are reported to have an unpredictable flare and share immunological and clinical features with other autoimmune diseases (AID)s, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).[77] New research suggests high quantities of autoantibodies are produced by the body months after contracting SARS-CoV-2 infection, highlighting the hypothesis that COVID-19 increases AID development.[78] While further investigations are essential regarding treatment options, herbs and nutrients that address the potential contributing factors, such as chronic inflammation, oxidation and immune dysregulation, should be considered.

Curcumin

Researchers have studied curcumin in various inflammatory autoimmune conditions,[79,80] and it has been shown to exert therapeutic benefits by attenuating oxidative stress and regulating inflammatory cytokines and pro-inflammatory signalling pathways in immune cells. Both animal and human studies have demonstrated that curcumin regulates cytokines that contribute to the manifestation of various AIDs, including RA and SLE.[80-82]

Mushrooms

As recurrent infections and associated chronic inflammation are thought to play a role in autoimmune disease development, managing the immune imbalance should be achieved. Employed as anti-inflammatory and immunomodulatory compounds, mushroom metabolites, particularly β-D-glucans, have demonstrated the ability to downregulate the gene expression of different inflammatory mediators.[34] Certain medicinal mushrooms, such as reishi, shiitake and coriolus, can improve immune surveillance and signalling to assist in chronic immune conditions, such as autoimmunity.[34,36,83]

Green tea

Beyond its anti-inflammatory activity, recent evidence suggests epigallocatechin gallate (EGCG) has desirable effects during the initiation and development of autoimmunity.[84] Animal models have demonstrated that EGCG suppresses the proliferation of autoreactive T cells, decreases Th1 and Th17 populations, increases T-regulatory populations and reduces pro-inflammatory cytokines. These results imply green tea may have therapeutic potential in managing T-cell-mediated autoimmune diseases, such as RA and SLE.[84]

Quercetin

Quercetin has a variety of biological activities and possesses antioxidant, anti-inflammatory, and immunomodulatory actions, making it an attractive option for AID management. In human clinical trials, quercetin supplementation significantly reduced pain, early morning stiffness, inflammatory markers (TNF-α) and active disease in women with RA compared to placebo.[85]

Vitamin D

Vitamin D has exhibited immunosuppressive effects via inhibiting T cell stimulatory functions of dendritic cells, which have emerged as a central player in the progression of autoimmunity.[86] Studies confirm low vitamin D levels impair self-tolerance by compromising the regulation of dendritic cells, T-lymphocytes and Th1 cells.[87] Given vitamin D deficiency has been associated with the manifestation of multiple AIDs along with COVID-19 severity, supplementation should be considered.[88]

Selenium

Selenium is an essential element that plays a pivotal role in the antioxidant defence system and is crucially involved in regulating immune responses and dampening chronic inflammatory conditions. By suppressing NF-kB, selenium downregulates the leukotriene pathway and attenuates autoimmunity-associated inflammatory processes.[89] The majority of studies indicate a profound selenium deficiency in patients with AIDs, likely linked to disease activity, chronic inflammation and elevated autoreactive immune system activity.[90] Besides potentially contributing to AID development, a selenium deficiency has also been identified as a mortality risk factor in COVID-19.[91] As COVID-19 may also contribute to low selenium status, it could be hypothesised that severe deficiency contributes to long-COVID symptoms.[90] Therefore, monitoring selenium status may be essential in ensuring recovery of long-term health issues, including autoimmune reactions to peripheral and central antigens.

Histamine-mediated mast cell activation

The hyper-inflammatory responses observed in long-COVID have been hypothesised to be partially mediated by mast cell (MC) activation.[92] Theories to explain this ideology include stress-induced cytokine storm, SARS-CoV-2 activation of mast cells (MCs) and microglia, loss of MC regulation and development of autoantibodies that react with MC receptors.[92] As MCs activate and synthesise many chemokines and cytokines, the liberation of resulting chemical mediators produces a multitude of symptoms, many of which long-COVID patients suffer.[93]

Nigella seed oil

Studies on nigella seed oil have demonstrated numerous biological effects and benefits in mast cell-related conditions. The therapeutic effect of nigella seed oil on patients with allergic diseases may be attributed to its ability to inhibit histamine receptors and decrease mast cell release and degranulation.[94,95] Nigella seed oil has been shown to have inhibitory effects on both the cyclooxygenase and the 5-lipoxygenase pathways of arachidonic acid metabolism and on membrane lipid peroxidation, thereby reducing systemic inflammation.[96,97] Moreover, nigella significantly decreased airway hyperresponsiveness through a reduced number of leukocytes, macrophages, eosinophils, and levels of several asthma-related interleukins.[98] A recent review highlighted nigella's potential in improving COVID-19 outcomes by virtue of its antiviral and immunomodulatory activities and its ability to reduce pro-inflammatory cytokines and enhance anti-inflammatory cytokines.[99]

Quercetin

In vitro studies have demonstrated that quercetin inhibits histamine release by acting as an MC stabiliser and inhibiting MC and basophil degranulation.[100,101] Quercetin assists with gastrointestinal cytoprotection and inhibits the release of histamine and serotonin from intestinal mast cells.[102] Downstream in the allergic response, quercetin inhibits platelet aggregation, and impedes enzymes involved in releasing inflammatory mediators, including phospholipase A and lipoxygenase.[103] Moreover, quercetin inhibits the production of NLRP3 inflammasomes (a critical component of the innate immune system) and suppresses cytokines by interfering with various signalling pathways, which may play an essential role in controlling the systemic inflammation associated with COVID-19.[104]

Vitamin C

Vitamin C is an important nutrient for disorders involving MC activation due to its role in the breakdown of histamine. The underlying mechanisms suggest both a nonenzymatic degradation of histamine and an inhibition of the histamine-forming enzyme histidine decarboxylase.[105] In human clinical trials, vitamin C has been shown to reduce histamine concentrations in patients with and without allergies,[105] seasickness,[106] and airway infection.[107] Vitamin C may, therefore, represent a therapeutic option in patients presenting with symptoms and diseases associated with pathologically increased histamine concentrations.

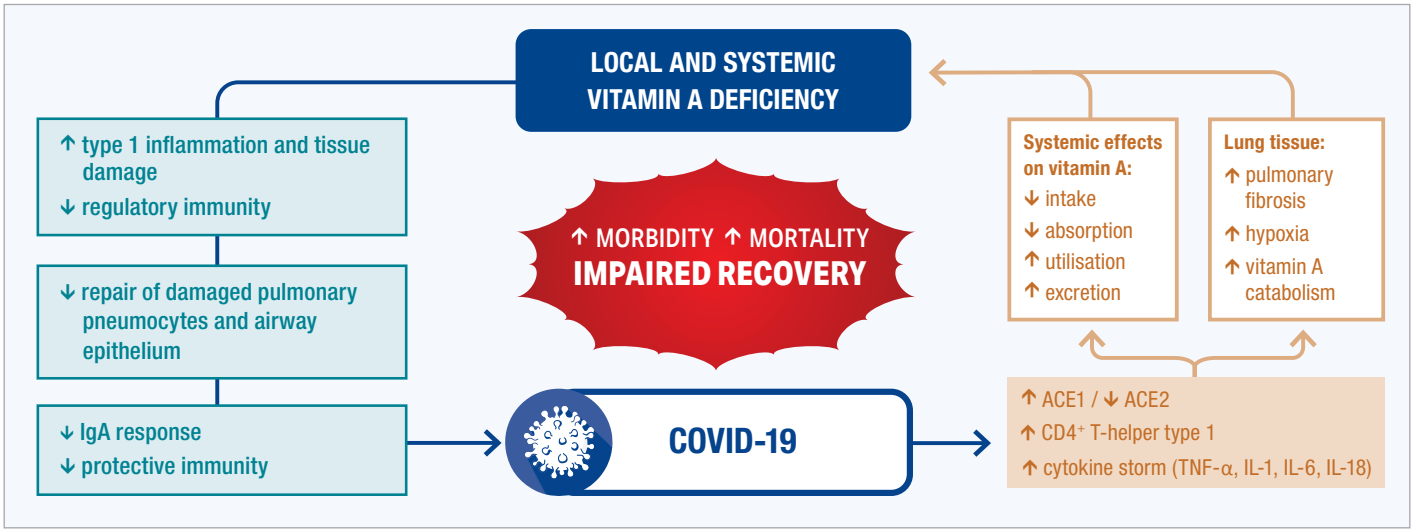
Palmitoylethanolamide (PEA)

PEA has been shown to be effective in several mast cell-mediated disease models in humans, *in vivo* and *in vitro* and is thereby considered an endogenous modulator of MC activation.[108] PEA is known to regulate the activity of microglial cells and inhibit MC activation in both the central nervous system and periphery, thus reducing sustained inflammation.[109] PEA has also been shown to reduce atopic conditions in domestic animals,[110,111] potentially by inhibiting histamine, prostaglandins and TNF-α induced by IgE.[112] The efficacy of PEA in controlling MC behaviour is likely accountable for its anti-inflammatory, anti-angiogenic, anti-oedema and analgesic effects. Further human trials are justified; however, it is reasonable to propose PEA to manage conditions involving MC degranulation.

Vitamin D

MCs have been shown to activate automatically in a vitamin D deficient environment. On the contrary, exposure to vitamin D increased the expression of the vitamin D receptor in MCs, thereby inhibiting their activation.[113] Evidence also suggests that vitamin D attenuates the

Figure 4: Potential interactions between vitamin A deficiency and COVID-19 recovery[130]



pro-inflammatory MC response suggesting a potential role in treating allergic and inflammatory conditions.[114]

Respiratory system

Dyspnoea and cough

Dyspnoea and cough are the most commonly reported respiratory symptoms associated with long-COVID. While these features may reduce over time, complete resolution is not inevitable, and lung physiology and imaging abnormalities have been observed six months post-infection.[115] Biochemical mechanisms of SARS-CoV-2 suggest that hyper inflammation, activation of immune cells and the release of cytokines and chemokines contribute to alveolar endothelium damage, leading to apoptosis and degeneration.[116] The viral infection also increases the permeability of alveolar cells, facilitating the migration of inflammatory cells and allowing fluid influx into the airspaces, leading to breathing difficulties.[116]

N-acetyl-cysteine (NAC)

Known as the precursor to glutathione, NAC is a mucolytic agent, which dissolves sputum, inhibits the production of oxides and improves antioxidant levels.[117] Glutathione and glutathione-associated enzymes are critical to lung health, representing the first line of defence against external agents in the lower respiratory tract. Consequently, a deficiency of glutathione is associated with several chronic lung diseases, such as asthma, chronic obstructive pulmonary disease (COPD) and acute respiratory distress syndrome.[118] Endogenous glutathione deficiency also appears to be a crucial factor enhancing SARS-CoV-2-induced oxidative damage to the lung, with the degree of deficiency correlating with disease severity.[119] Increasing glutathione levels with NAC may therefore reduce or limit the extent of epithelial and endothelial lung damage and improve the clinical course.[120] As NAC has demonstrated positive effects in other chronic respiratory diseases such as COPD,[117] bronchitis,[121] and cystic fibrosis,[122] it should be considered in patients with productive coughs, sputum and dyspnoea.

Curcumin

Curcumin may protect patients with long-COVID by targeting the pro-inflammatory NF-κB pathway, which has been associated with lung injury.[123] Curcumin may also subdue the activity of bradykinin by inhibiting cyclooxygenase enzymes, thereby suppressing cough.[124] In a clinical trial, curcumin (500mg twice daily) and standard therapy improved forced expiratory volume and airway obstruction compared to standard treatment alone in bronchial asthmatic patients.[125] Although clinical trials have not reported the effects of curcumin on respiratory impairments in long-COVID sufferers, a decrease in cough and dyspnoea in patients with acute infection has been identified,[126,127] which is a promising indicator that encourages further investigations.

Vitamin A

Vitamin A maintains the health of epithelial cells of the respiratory tract, which function as the front line of defence against pathogenic invasion.[128] Animal data suggest vitamin A metabolites play a crucial role in the alveoli's maintenance and regeneration, thus influencing the lung's elastic recoil.[129] SARS-CoV-2 infection may deplete vitamin A stores, impair the lungs' ability to repair damaged epithelial surfaces and could potentially lead to chronic scarring and reduced pulmonary capacity.[130] Given its role in reducing inflammation, repairing respiratory epithelium and preventing fibrosis, vitamin A status may be particularly important during recovery from lung complications associated with COVID-19 (see Figure 4).

Gastrointestinal system

Dysbiosis

While COVID-19 is primarily a respiratory illness, data suggests a link between dysbiosis and long-term complications from the virus. Compelling evidence has shown substantial involvement of the GI system in COVID-19 infection, including enhanced ACE2 expression along the GIT.[131] Results of previous studies have found that individuals who experience severe COVID-19 have reduced microbiota diversity, higher amounts of opportunistic pathogens and reduced gut commensals that have significant immunomodulatory and anti-inflammatory effects (see Figure 5).[132-134] A recent prospective cohort study found that 76% of patients with COVID-19 had at least one symptom at six months post-infection, which correlated with altered gut microbiota composition.[12] Modifying the gut microbiome may, therefore, aid recovery of long-COVID symptoms.

Probiotics and prebiotics

In an experimental trial, a *Lactobacillus* probiotic blend (10 billion colony forming units) and inulin derived from chicory (200mg) for one month significantly improved self-reported GI symptoms, along with cough, fatigue and subjective well-being scores in patients with long-COVID.[135] Interestingly, participants who were more likely to have dysbiosis at the beginning of the trial, such as being inactive, requiring hospitalisation and older males with GIT symptoms, had a statistically significantly better response to the probiotics.

Neurological system

The direct viral effects on the central nervous system (CNS) resulting in tissue damage to the brain, unresolved systemic inflammation, immune dysfunction and mitochondrial impairment are the potential mechanisms underlying the neuropsychiatric complications of long-COVID (see Figure 7).[136] The most commonly disclosed neuropsychiatric sequelae were found to be depression, anxiety, sleep difficulties and cognitive impairments.[137]

Depression and anxiety

The immune response to SARS-CoV-2 infection and the associated severe systemic inflammation appears to be the primary mechanism contributing to developing post-COVID depression and anxiety.[137] COVID-19 patients show heightened levels of cytokines,[139] which are known factors involved with psychiatric disorders. Neuroinflammation, blood-brain-barrier disruption, peripheral immune cell invasion into the CNS, neurotransmission impairment and hypothalamus-pituitary-adrenal (HPA) axis dysfunction may represent the pathways underpinning psychiatric disorders in long-COVID.

Curcumin

Curcumin holds promise in managing depression and anxiety associated with long-COVID due to its potential to attenuate neuroinflammation and oxidative stress. Various randomised, controlled trials have assessed the efficacy of curcumin for the treatment of depression as either a monotherapy or as an adjunct to conventional antidepressants.[140-142] Oral supplementation with curcumin alongside escitalopram reduced plasma levels of inflammatory cytokines (IL-1β and TNF-α) and increased BDNF compared with placebo treatment in depressed patients.[143] Administration of curcumin (1g per day of Curcumin C3 Complex®) as an adjunct to antidepressants was more effective for reducing depression and anxiety symptoms in patients with major depressive disorder than antidepressant medication alone.[144] A recent trial found that SSRIs were effective in patients with post-COVID depression, potentially via targeting neuroinflammation.[145] As such, it can be assumed from the existing evidence that curcumin would have similar efficacy in managing this debilitating condition.

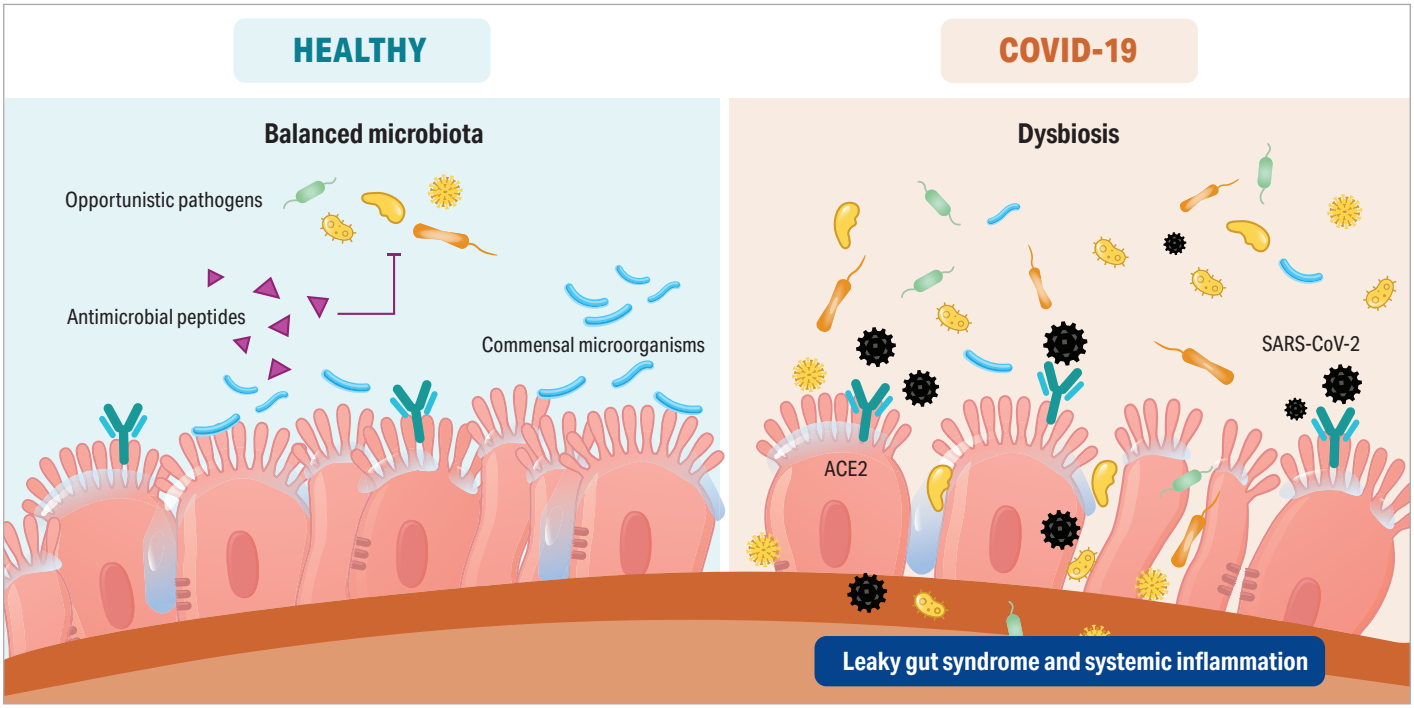
Saffron

Saffron may be a suitable therapy for managing the long-term effects of SARS-CoV-2 infection, particularly anxiety and depression.[146] Numerous studies have found saffron to be equally effective as antidepressants and superior to placebo at improving depressive symptoms. Results of clinical trials have conclusively demonstrated significant improvements in symptoms of anxiety and comorbid depression after saffron supplementation.[147-150] Since saffron inhibits the reuptake of monoamine neurotransmitters, reduces pro-inflammatory cytokines, and defends cells against oxidative stress,[151-155] it may be highly valuable to address the excessive inflammation associated with post-COVID mood disorders.

Psychobiotics

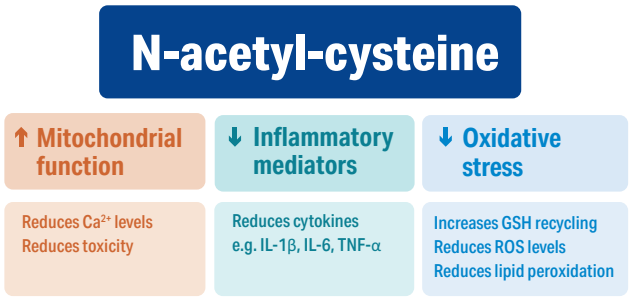
A review on gut microbiota composition in neuropsychiatric disorders and COVID-19 has revealed a shared gut microbial signature defined by a low diversity of bacterial communities with a specific decrease in short-chain fatty acids and serotonin-producing bacteria.[156] Moreover, a plethora of evidence indicates that pathophysiological pathways involved in mood disorders are associated with increased intestinal permeability and inflammatory activation,[157] similar features observed in SARS-COV-2 infection.[156] Cerebiome®, a combination

Figure 5: Dysbiosis in long-COVID



of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175, has been shown to reduce serum levels of pro-inflammatory cytokines and demonstrated a significant increase in anti-inflammatory cytokines.[158] It has also been shown to reduce the activity of enzymes responsible for converting tryptophan to kynurenine, leading to higher serotonin levels and thus exerting their antidepressant effects.[159] COVID-19-associated neuropsychiatric disorders have been connected to brain inflammation, changes in the gut-brain axis, and gut microbiota alteration; therefore, probiotics could be a potential adjunct therapy for preventing and alleviating the psychological manifestations of COVID-19.[160]

Figure 6: The potential mechanisms of action of NAC for treating psychiatric disorders in long-COVID[168]



N-acetyl-cysteine (NAC)

NAC is a potent antioxidant and a precursor to glutathione, the most abundant intracellular antioxidant in the brain and periphery.[161] In addition, NAC has direct effects on glutamate neurotransmission, possesses intrinsic anti-inflammatory effects and may reverse mitochondrial dysfunction,[162,163] making it an ideal agent for post-COVID mood disorders. While clinical trials involving NAC for the neuropsychiatric sequelae of long-COVID are absent, various studies have found doses between 1,200mg – 2,400mg per day to be efficacious in managing depression, anxiety and post-traumatic stress disorder.[164-167]

Palmitoylethanolamide

Findings of a recent study have highlighted the ability of PEA to modulate monoaminergic neurotransmission, synaptic plasticity and neurogenesis, all of which are central mechanisms that are markedly altered in major depressive disorder and related dysfunctions.[169] A clinical trial confirmed the beneficial effects of PEA given as an add-on treatment to citalopram, showing a more rapid antidepressant activity with no additional side effects.[170] While further studies are required, it has been hypothesised that PEA may be administered in post-COVID syndrome to mitigate the SARS-CoV-2-induced inflammation,[171] which is commonly observed in patients with mood disorders.

Omega-3 fatty acids

The demonstrated efficacy of omega-3 fatty acids in managing mood disorders is primarily due to their ability to reduce pro-inflammatory cytokines, restore the (HPA)-axis, and modulate neurotransmission through lipid rafts (membrane structures which modulate membrane fluidity and trafficking).[172] Omega-3 fatty acids may also restore tissue homeostasis and offer a promising strategy for long-COVID. Several epidemiological studies have shown that consumption of omega-3 fatty acids is associated with a lower risk of depression, and supplementation may exert antidepressant effects.[173,174] Despite the promising results of omega-3 fatty acids in mood disorders, further high-quality trials are essential to test, validate, and translate these proposed effects into the context of long-COVID.

Insomnia

Studies of sleep in long-COVID patients have shown a drastic reduction in sleep quantity and quality, which affects up to 53% of individuals.[175,176] The mechanism of action is not clear; however, the debilitating physical symptoms, the impact of anxiety and depression, and residual systemic inflammation of COVID-19 are thought to interfere with sleep. While herbs and nutrients may be required in specific individuals, the importance of proper sleep hygiene principles should not be overlooked when treating patients with sleep disturbances.

Passionflower, hops and valerian

By modulating the melatonin and GABA/benzodiazepine receptors, passionflower, hops, and valerian have long been utilised for the treatment of nervous tension and sleep disorders. This specific trio of herbs has both traditional and scientific support for sleep disturbances, with several monographs and herbal texts referring to the combination of these herbs for sleep and nervous unrest.[177] A clinical trial involving 91 patients with insomnia found the combination to have the same efficacy as zolpidem (Ambien) in improving sleep latency, total sleep time, number of nightly awakenings and insomnia severity index scores.[178] The absence of research on the efficacy of these herbs in COVID-19 patients is evident; however, they can be considered a choice of therapy based on the results of existing studies regarding the efficacy and safety of these herbs in insomnia.

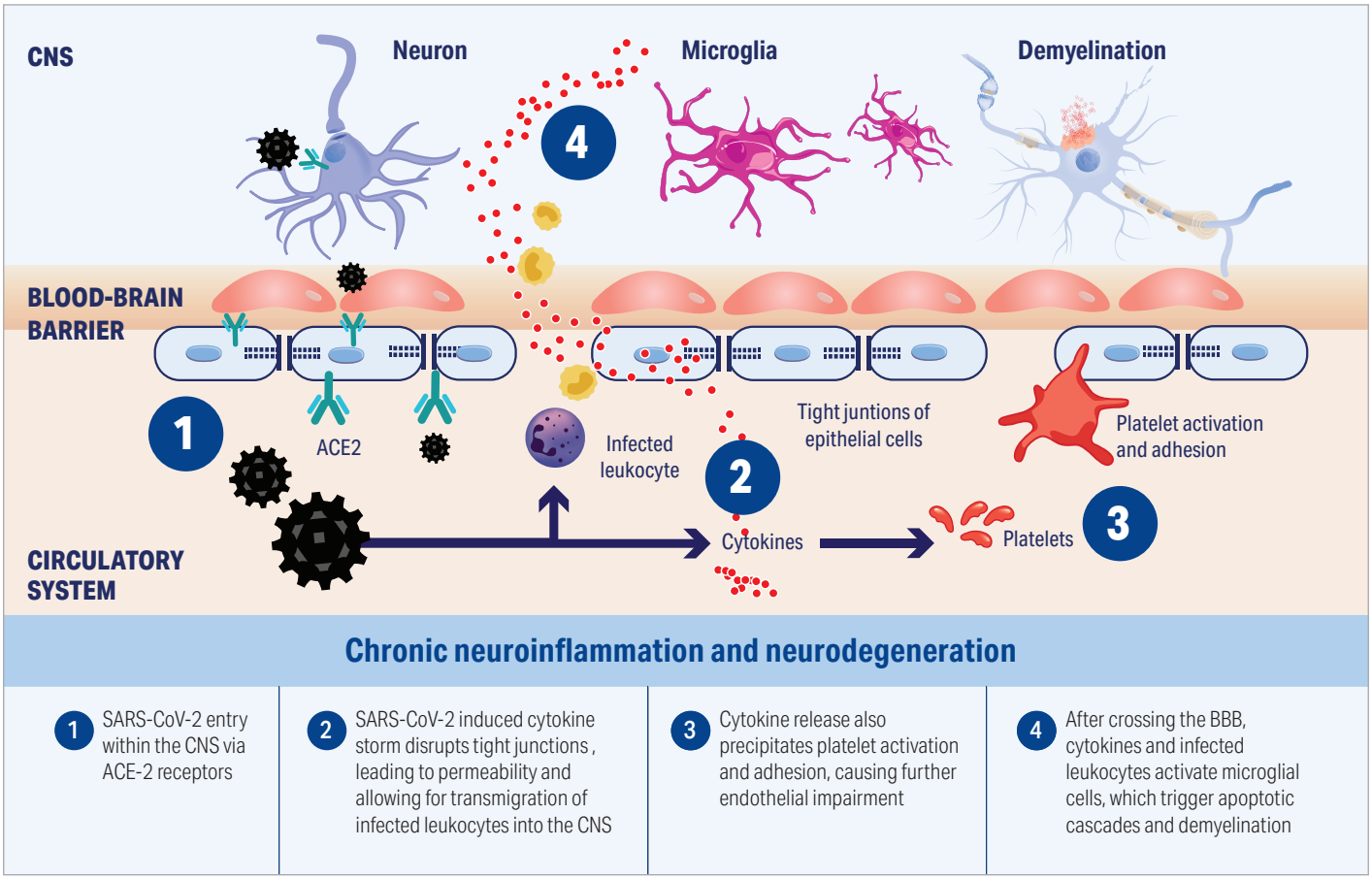
Magnesium

Magnesium is a valuable inclusion in a sleep-support regime based on its effects on regulating the neuroendocrine system and the benefits it fosters on conditions such as anxiety and depression, both of which may be involved in the aetiology of long-COVID insomnia. A recent systematic review suggested an association between higher magnesium intake and sleep quality, and supplementation positively affects sleep scores, efficiency, and time.[179] A reduction in sleep quality may contribute to fatigue, anxiety, depression and changes in the autonomic nervous system function, as well as elevation of inflammatory markers and immune system dysfunction.[180] As such, it is crucial to improve sleep in patients with long-COVID to improve disease recovery.

Cognitive dysfunction

Cognitive dysfunction is a commonly reported symptom of long-COVID, occurring in around 70% of patients.[182,183] Cognitive symptoms often experienced by patients include difficulty concentrating, brain fog, forgetfulness, and semantic disfluency (saying or typing the wrong words).[184] There are multiple mechanisms whereby SARS-CoV-2 infection engenders cognitive impairment, including direct viral encephalitis, neuroinflammation and disturbed redox homeostasis.[185,186] It has also been recognised that systemic sequelae including endothelial dysfunction, mitochondrial autoimmunity, latent viral reactivation and autonomic nervous system dysfunction may play a role in the development of cognitive decline.[21]

Figure 7: The potential pathophysiological mechanisms implicated in the manifestation of long-COVID in the CNS[138]



Ginkgo and bacopa

Ginkgo and bacopa are evidence-based complementary medicines suitable for various age groups that target several different mechanisms related to cognitive dysfunction. Both herbs possess antioxidant, anti-inflammatory, cholinergic and neuroprotective effects, with various clinical trials reporting improvements in memory, learning, attention and recall after supplementation.[187-191] As long-COVID patients experiencing cognitive deficits may also suffer from psychological disorders, such as anxiety, ginkgo and bacopa may provide dual benefits given their anxiolytic properties.

Polyphenols

The pathogenesis of 'brain fog' is not yet fully understood; however, inflammation may be an instigating factor. Infectious agents, such as SARS-CoV-2, stimulate mast cells that release microglial activating mediators, which lead to increased levels of inflammatory cytokines and chemokines and contribute to the pathogenesis of a broad range of neurodegenerative diseases.[192] Therefore, inhibiting mast cells and regulating anti-inflammatory pathways may help manage cognitive decline associated with long-COVID. Several clinical studies have concluded that polyphenols, such as quercetin, curcumin, resveratrol and green tea, have potential use as therapeutic agents in preventing or alleviating cognitive impairment.[193]

Glutathione

In the case of COVID-19, it has been shown that severe disease is triggered by conditions leading to decreased glutathione levels.[194] Moreover, patients hospitalised with COVID-19 were found to have reduced levels of glutathione and elevated levels of oxidative damage.[195] Several studies have reported a deficiency of glutathione and the activity of glutathione-related enzymes in numerous brain disorders such as Alzheimer's disease, Parkinson's disease and Huntington's disease. Significant biological changes related to oxidative pathology have been found in brain tissue of individuals affected by these conditions.[196,197]

B vitamins

Elevated homocysteine may also contribute to 'brain fog' and cognitive deficits described by long-COVID patients. It has been suggested that SARS-CoV-2 induces an increased demand for methyl groups, whilst simultaneously impairing their supply due to viral-induced oxidative stress.[198,199] Elevated homocysteine is commonly observed in patients with cognitive impairment, dementia and Alzheimer's disease, and lowering homocysteine with B group vitamins has been shown to slow cognitive decline and brain atrophy in this cohort.[200]

Anosmia and ageusia

Olfactory dysfunction is a common presenting symptom of COVID-19. The SARS-CoV-2 virus infects olfactory neurons and the olfactory bulb via the ACE2 receptor, where it can activate microglia and release pro-inflammatory mediators, leading to anosmia and ageusia. While the sense of smell and taste often returns within weeks for the majority of patients, approximately 10-20% report persistent moderate or severe smell and taste impairment.[201,202]

Vitamin A

Vitamin A plays a decisive role in the regeneration of olfactory receptor neurons,[203] and promotes olfactory neurogenesis due to its ability to regenerate the olfactory epithelium.[204] An early clinical

study reported marked improvement in olfactory function in patients following intramuscular injections of vitamin A (50-100,000IU per week).[205] In a more recent study, 10,000IU of vitamin A administered intranasally daily for eight weeks improved odour function in patients with post-infectious and post-traumatic olfactory dysfunction.[206] These results have spiked interest in vitamin A, with researchers currently investigating the potential role of aerosolised vitamin A in treating anosmia associated with COVID-19.

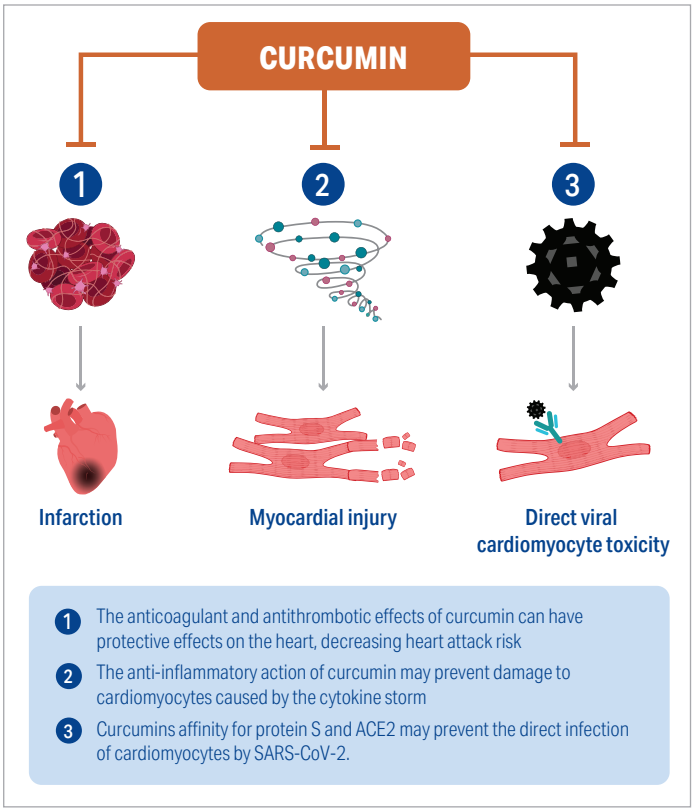
Vitamin D

Mounting evidence suggests vitamin D receptors are present in the nervous system, and a deficiency may lead to the neurological decline of cranial nerves, resulting in reduced olfactory function.[207] Epidemiological studies have found a relationship between vitamin D deficiency and smell and taste impairments in aging adults,[207] and smell dysfunction in children with rhinitis.[208] In two case studies, treatment with vitamin D (10,000IU-50,000IU) also improved olfactory function in patients with vitamin D deficiency.[209] While more extensive studies are required, assessing vitamin D status in patients with olfactory dysfunction may be prudent for effective resolution.

Zinc

It has been reported that a zinc deficiency may induce anosmia due to the decreased activity of zinc-dependent carbonic anhydrate that is involved in the perception of taste and smell.[210] Patients with a drop in zinc levels in response to COVID-19 infection may also experience lower type 1 interferons that are required for controlling SARS-CoV-2 replication.[211,212] Thus, it has been proposed that patients with baseline zinc deficiency may have prolonged anosmia, blunted interferon responses, and consequently, more severe disease outcomes.[213] One study concluded that zinc therapy at 50mg of elemental zinc twice daily may have a role in shortening the duration of smell recovery in patients with COVID-19.[214] While there is limited data, zinc supplementation should be considered, particularly in patients most at risk of a zinc deficiency, such as the elderly and those with chronic health conditions.

Figure 8: Potential use of curcumin for cell damage caused by SARS-CoV-2 in the heart



Palmitoylethanolamide

During COVID-19 infection, the virus consumes the membrane phospholipids of infected cells to build its phospholipid envelope. Consequently, the tissue suffers from an acute deficiency of precursor molecules (phosphatidylethanolamine) for synthesising endogenous palmitoylethanolamide (PEA), which is essential for controlling neuroinflammation.[215] A pilot study of 12 patients with anosmia/hyposmia persisting ≥ 90 days after SARS-CoV-2 infection found that ultramicronised PEA (700mg daily) combined with luteolin and olfactory training improved olfactory function two-fold compared with control patients who received the rehabilitation training alone.[202]

Omega 3-fatty acids

Omega-3 fatty acids may potentially aid recovery from post-viral olfactory loss owing to their anti-inflammatory and neuro-regenerative properties. Studies have demonstrated that omega-3 fatty acids may restore the olfactory nerve and could be used alongside olfactory training in patients with post-infectious olfactory dysfunction.[216] While there is no evidence that omega-3 supplementation is effective in patients with COVID-19, it may be valuable as an adjunctive agent.

Cardiovascular system

Cardiovascular disease

A recent review provided evidence that COVID-19 patients exhibit an increased incidence of CVDs well beyond the acute phase of the disease, including cerebrovascular disorders, dysrhythmias, inflammatory heart disease, ischemic heart disease, heart failure and thromboembolic disease.[217] Putative mechanisms including viral invasion of cardiomyocytes, dysregulation of the renin-angiotensin-aldosterone system, autonomic dysfunction, and elevated levels of pro-inflammatory cytokines have been proposed.[218] It is vital to control known risk factors of CVDs to improve the prognosis of long-COVID and to decrease the disease incidence.

Curcumin

The broad range of biological activities of curcumin, including its antioxidant, cardio-protective, anti-inflammatory, immunomodulatory, hypoglycaemic and hypolipidaemic effects, make it an ideal option in managing CVD complications associated with long-COVID.[219] A recent systematic review demonstrated that curcumin significantly lowered pro-inflammatory cytokines (IL-6, IL-1β), increased anti-inflammatory cytokines (IL-10) and decreased typical symptoms, hospitalisation and all-cause mortality in patients with COVID-19.[220] While no studies assess its effects on long-COVID, these results suggest curcumin may improve disease outcomes by restoring the pro-inflammatory/anti-inflammatory balance observed in patients with CVD complications.[221]

Bacillopeptidase F

Endothelial dysfunction involves an imbalance in substances released from the endothelium that control the dilation and constriction of blood vessels, favouring those that promote vasoconstriction. Endothelial inflammation and increased oxidative stress leads to the development of various long-COVID cardiovascular complications,

such as hypertension, atherosclerosis and further vascular damage.[222] Bacillopeptidase F, an isolated enzyme secreted from *Bacillus subtilis* var. natto, is proving to be a promising therapeutic for lifestyle diseases associated with endothelial dysfunction, clotting abnormalities, and poor peripheral circulation. Both animal and human clinical studies have demonstrated that Bacillopeptidase F possesses fibrinolytic, anti-hypertensive, anti-atherosclerotic, and anticoagulant activities,[223,224] highlighting its potential relevance in the management of CVD complications associated with COVID-19.

Bromelain

Several *in vitro* and *in vivo* studies indicate that bromelain may reduce or minimise symptoms associated with several CVDs, including thrombophlebitis, angina, transient ischemic attack, atherosclerosis, and coronary artery disease.[225,226] Bromelain has been described as a potential treatment for CVDs as it inhibits blood platelet aggregation, thus minimising the risk of arterial thrombosis and embolism,[227] which has been associated with SARS-CoV-2 infection.[228]

Magnesium

Magnesium is a cofactor for over 300 enzymatic reactions, such as those responsible for regulating blood pressure, glycaemic control and lipid peroxidation, and plays a vital role in cardiovascular health. Since magnesium is instrumental for the functioning of the mitochondria and maintains the body's antioxidative and inflammatory pathways, a deficiency has been implicated in multiple CVDs such as hypertension, cardiomyopathy, cardiac arrhythmia, tachycardia, congestive heart failure, atherosclerosis, and dyslipidaemia.[229] Low magnesium levels have also been found in COVID-19 patients;[230] therefore, supplementation may be warranted in those at risk of CVD.

Vitamin E

Vitamin E is best known for its positive effects on the cardiovascular system as it has been shown to inhibit platelet aggregation and adhesion, improve endothelial function and decrease lipid peroxidation.[231] Its ability to reduce oxidative stress is of particular importance regarding CVDs, as oxidation of LDL is a key process in atherogenesis.[232] Although clinical studies are required, vitamin E may be beneficial in the prevention of CVDs associated with long-COVID.

Omega-3 fatty acids

Epidemiological evidence suggests that increased intake of omega-3 fatty acids reduces morbidity and mortality associated with CVD.[233] Data suggests a higher intake of omega-3 fatty acids has a beneficial effect on lipid profiles by replacing saturated fatty acids and lowering triglyceride levels, thereby stabilising atherosclerotic plaques and reducing the incidence of thrombus formation.[234] Furthermore, omega-3 fatty acids can enrich cell membranes and alter the lipid raft structure and function, leading to improved autonomic tone, elevated arrhythmic thresholds and reduced blood pressure.[235] Several experimental, clinical and epidemiological studies hypothesise that the cardioprotective effects of omega-3 fatty acids are attributed to their immunomodulatory properties and ability to reduce oxidative stress and inflammatory chemokines, cytokines, and pro-inflammatory metabolites.[236,237] Considering their favourable safety profile, it is reasonable to consider omega-3 fatty acids as potential adjuvant therapies for the clinical management of long-COVID patients.

Myocarditis

Myocarditis is an inflammatory disease of heart tissues and is an important cause of heart failure, sudden death and dilated cardiomyopathy.[238] Ongoing myocardial inflammation has been reported after COVID-19 infection, even in mildly symptomatic or asymptomatic patients.[24] Potential features of myocarditis include the dominance of T helper 1 (Th1) or Th2 subsets in the heart and the overproduction of pro-inflammatory cytokines causing heart cell injury.[238] While myocarditis often requires pharmaceutical interventions, nutrients and herbs that exert anti-inflammatory, antioxidant, and cardioprotective effects could be considered to prevent disease progression.

Curcumin

The impact of curcumin has been studied using a number of rodent models with various types of myocarditis, including viral,[239] parasite-induced,[240] and autoimmune.[241] Curcumin has been shown to inhibit signalling pathways and the expression of inflammatory cytokines in the myocardium, including TNF-α, IL-1, and IL-1β, thus reducing the inflammatory response.

Coenzyme Q10

Viral infections deplete CoQ10 and total antioxidant levels,[242] and by correcting this deficit, supplemental CoQ10 may support recovery after infections. According to preliminary studies, CoQ10, in conjunction with standard treatments, improved the recovery of cardiac function, alleviated oxidative stress and inflammation and improved quality of life in patients with viral myocarditis.[243,244]

Quercetin

Numerous biological actions of quercetin have been described *in vitro* and *in vivo*, including antioxidant, anti-inflammatory, anti-thrombotic and vasodilatory activity.[245] Quercetin has decreased malondialdehyde content, increased superoxide dismutase and catalase activity, and regulated anti-inflammatory and anti-apoptosis processes to protect against myocardium damage.[246,247] Various *in vitro* and *in vivo* studies have demonstrated that treating myocarditis with quercetin is associated with elevated numbers of T-regulatory cells and anti-inflammatory cytokines and reduced secretion of pro-inflammatory cytokines and myocardial apoptosis.[248-250] Although a lack of robust clinical trials is unmistakable, quercetin is a promising candidate for supporting patients with myocarditis following SARS-CoV-2 infection.

Zinc

Zinc regulates angiotensin-converting enzyme and matrix metalloproteinases, which are involved in the myocardial wall structure.[251] Zinc deficiency has been shown to increase autophagy and hypertrophy of the myocardium, causing degeneration and fibrosis of cardiomyocytes and upregulating pro-inflammatory cytokines. Intracellular zinc additionally plays a critical role in the redox signalling pathway, whereby specific triggers such as ischemia and infarction lead to the release of zinc and cause myocardial damage. Replenishing with zinc has improved cardiac function and prevented further damage in such states.[252]

Vitamin C

The overwhelming inflammatory stress of COVID-19 contributes to the development of myocardial damage often observed in patients

with acute infection. In a retrospective cohort study involving patients with COVID-19, high dose IV vitamin C ameliorated myocardial injury by alleviating hyper-inflammation (high sensitivity C-reactive protein, TNF-α, IL-6, IL-8).[253] A meta-analysis involving children with viral myocarditis also demonstrated IV vitamin C and conventional therapy reduced myocardial injury biomarkers and was more efficacious compared to standard treatment alone.[254] Though studies on long-COVID are evidently required, vitamin C may increase myocardial contractility, improve left ventricular function, and promote myocardial function recovery.

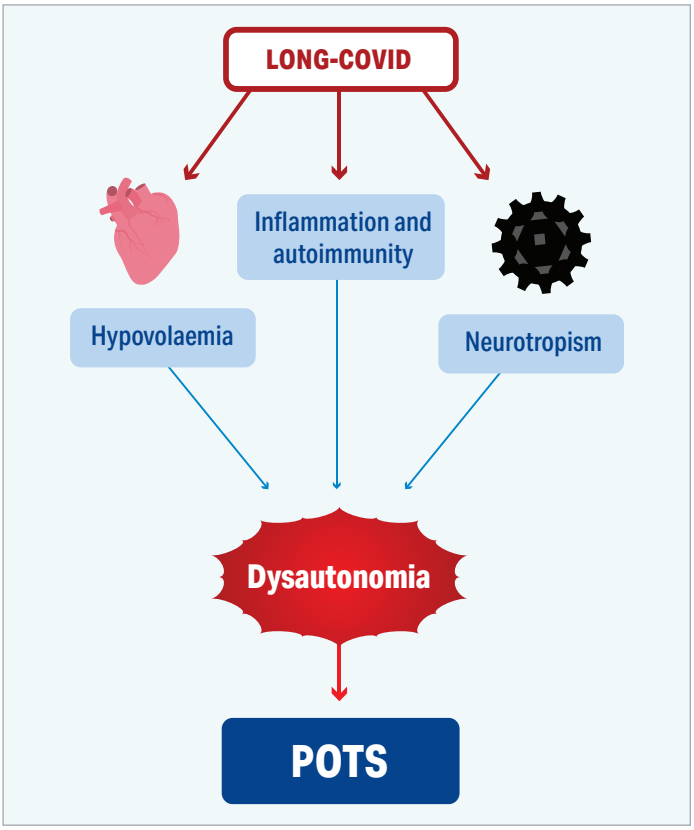
Vitamin D

As the vitamin D receptor (VDR) mediates regulatory effects of vitamin D on cardiomyocyte function, inflammation, and gene transcription, a deficiency may play a pivotal role in the pathogenesis of inflammation in myocarditis.[255] In a mouse model of autoimmune myocarditis, vitamin D improved cardiac function, reduced cardiac inflammation and regulated autophagy dysfunction.[256] Vitamin D can also induce antimicrobial molecules in immune cells to inhibit inflammation by reducing pro-inflammatory cytokines.[257] Therefore, upregulating vitamin D has therapeutic potential in managing myocarditis post-COVID-19 owing to its anti-inflammatory, antioxidant, anti-apoptotic, immunity and autophagy modulation properties.

Postural orthostatic tachycardia syndrome

Long-COVID symptoms are hypothesised to be attributed to dysautonomia, defined as a malfunction of the autonomic nervous system (ANS).[258] The most prevalent cardiovascular dysautonomia in patients with long-COVID is postural orthostatic tachycardia syndrome (POTS), with a prevalence of up to 41%.[259,260] POTS is defined as a persistent increase in heart rate of at least 30 beats per minute within 10 minutes of standing, along with symptoms of palpitations, chest pain and/or orthostatic intolerance.[261] The interaction of the ANS and cardiac rhythm abnormalities are well known; however, there remains limited data on long-COVID, dysautonomia and the aetiology of POTS. Although not mutually exclusive or exhaustive, possible underlying mechanisms include hypovolaemia, neurotropism, inflammation, and autoimmunity (see Figure 9).[261,262]

Figure 9: Possible underlying mechanisms of POTS[258]



Primary nutrition recommendations most often include diet modification and micronutrient supplementation to improve or maintain nutrition status when symptoms have resulted in suboptimal oral intake. Supported self-management is also recommended, such as avoiding known symptom triggers, increasing fluid and salt in the diet, utilising body compressions, modifying exercise and psychotherapy.[263]

Magnesium

The importance of magnesium in preventing arrhythmias and tachycardia has long been established and as such, may be a valuable nutrient for those with POTS. Magnesium deficiency can reduce the amount of intracellular potassium and affect the sodium-potassium pump's activity, which may disturb the resting membrane potential of the cardiac cells, resulting in cardiac arrhythmias.[264] In a recent systematic review, IV magnesium was found to be effective in controlling dysautonomia, particularly cardiac arrhythmia and heart block.[265]

Nutrient deficiencies

Vitamin deficiencies have been described in patients with POTS, particularly adolescents. In various studies, vitamin B12, vitamin B1, vitamin D and iron deficiencies have been associated with POTS, and supplementation may reduce orthostatic symptoms.[266-268] Nutritional deficiencies should, therefore, be monitored and corrected when present.

Integumentary system

Hair loss

The dermatological symptoms of COVID-19, which were initially considered to be of little significance, have proven to be varied and complicated. Telogen effluvium, defined as diffuse hair loss, affects approximately 25% of COVID-19 patients,[269] potentially due to the release of inflammatory cytokines as a consequence of the viral infection.[270] Moreover, specific comorbidities have been associated with an increased risk of developing post-COVID telogen effluvium, including hypertension, diabetes mellitus and dyslipidaemia. While often self-limiting, hair loss has a significant emotional impact. Practitioners should provide appropriate psychological support to their patients whilst considering the role of complementary strategies to enhance hair regrowth.

Vitamin D

Vitamin D receptors are expressed in hair follicle cells and can modulate keratinocyte proliferation and hair growth cycling.[271] As a correlation between telogen effluvium and low serum vitamin D levels has been reported,[272,273] evaluating serum vitamin D levels in patients with long-COVID hair loss may be essential to prevent further hair fall.

Iron

Iron deficiency is well known to be linked to hair loss, and

supplementation may benefit those affected.[274] COVID-19 infection has been associated with alterations in iron homeostasis, with up to 30% of patients suffering from iron deficiency two months after initial infection.[275] Practitioners should assess iron biomarkers to see if iron deficiency contributes to long-COVID hair loss.

Zinc

Zinc is required for more than 300 enzymes, necessary for nucleic acid and protein synthesis and cell division, all of which are essential for hair growth.[276] While the results of zinc supplementation in hair loss are inconsistent,[277] patients with long-COVID hair loss should be screened for zinc deficiency.

Lifestyle & dietary recommendations

Physical activity

Physical activity is known to be critical for the proper function of virtually all physiological systems; however, it is crucial to determine the optimal intensity. Moderate levels of intense exercise have been associated with reduced levels of TNF-α, while high-intensity exercise may increase inflammatory cytokines and induce higher levels of perceived stress.[278] As such, in patients suffering from multisystem inflammation, caution should be used when considering the form and duration of exercise. In a recent study including 50 long-COVID patients, an exercise rehabilitation program that included three sessions per week of combined aerobic and resistance exercise markedly improved cardiorespiratory and musculoskeletal fitness over eight weeks.[279] In patients with long-COVID, individualised exercise programs that mitigate the negative health consequences of physical inactivity without worsening symptoms should be considered a clinical priority.

Tai chi

Tai chi has been shown to affect multiple physical and psychological processes positively and is proposed to regulate respiration, heart rate and blood pressure.[280,281] Tai chi may improve lung function by counteracting fibrotic scar tissue formation, with studies supporting its use in chronic obstructive pulmonary disease.[282,283] Tai chi is also promoted to improve blood and energy flow and balance the autonomous nervous system,[284] and, therefore, may counteract fatigue and reduce anxiety and depression.[280,282] The practice has been shown to benefit the cardiovascular system and may improve exercise capacity, balance and muscular control, all of which may occur after COVID-19 infection.[280,282] While clinical trials are needed, implementing Tai chi in long-COVID-affected individuals should be recommended, particularly in patients with decreased muscular strength, fatigue, anxiety and breathing difficulties.

Dietary recommendations

It is well known that a diet high in saturated fats and refined sugar increases inflammation and reduces the activity of neutrophils and phagocytes.[285] Moreover, poor dietary habits modify the microbiome and disturb GI permeability, resulting in further inflammation and altering immune activity. Conversely, certain dietary habits may promote a healthy immune response, decrease inflammation and preserve the integrity of the GIT. Several studies have confirmed the beneficial effects of the Mediterranean diet on diseases associated with chronic inflammation, including CVDs, neurodegenerative diseases and type 2 diabetes.[286,287] As such, the Mediterranean diet may represent a strategic therapeutic approach to addressing long-term complications related to COVID-19.[286]

Long-COVID has also been characterised by malnutrition and loss of muscle mass, theoretically due to muscle catabolism, prolonged bed rest, GIT symptoms, and olfactory dysfunction.[288] Therefore, it is not surprising that sarcopenia and malnutrition are commonly observed in older patients with long-COVID. Consequently, establishing protein requirements and ensuring that protein supply is divided among all meals is paramount.[289]

While clinical trials are essential, an overall healthy diet rich in fruits and vegetables, omega-3 fatty acids, quality protein, fibre and a low intake of trans-fats and refined carbohydrates enhances physical and psychological well-being. Nonetheless, practitioners must recommend dietary interventions that considers the patients preferences, culture, capacity and health status as well as any underlying deficiencies or intolerances that may inhibit adequate recovery.

Summary

Managing long-COVID is challenging and complex due to the heterogeneity of presentations, multi-organ involvement, and the lack of robust evidence currently available. Natural health practitioners must remember that while evidence for natural compounds in long-COVID is limited, there is a plethora of evidence regarding various nutrients and herbal medicines that address the known disease drivers and underlying pathophysiology. Practitioners are in an ideal position to support patients by providing a comprehensive and systematic assessment based on the needs of each individual to aid in their recovery from long-COVID.

Therapeutic supplemental considerations

SYMPTOM	INGREDIENT	DOSAGE SUGGESTION (DAILY)
IMMUNE SYSTEM		
Immune dysregulation	Rice bran arabinoxylan compound	1g – 3g
	Mushrooms (reishi, shiitake, coriolus)	Formulations vary (consider 2 – 6 capsules)
	Vitamin C	500mg – 2g
	Vitamin D	1,000 – 5,000 IU (depending on baseline levels)

SYMPTOM	INGREDIENT	DOSAGE SUGGESTION (DAILY)
Immune dysregulation	Vitamin A	10,000 – 50,000 IU
	Zinc	50mg
Fatigue	Adaptogens (withania, Siberian ginseng, rhodiola)	Formulation vary (consider 2 – 3 capsules)
	Coenzyme Q10	150mg – 600mg
	Vitamin C	1 – 4g
	Vitamin D	1,000 - 5,000 IU (depending on baseline levels)
	B vitamins (B12, folic acid)	Formulations vary
	Magnesium	300 – 600mg
	Proteolytic enzymes	Formulation vary (consider 3-6 capsules)
	High potency probiotic formula	At least 10 billion CFU
Autoimmunity	Green tea	500mg – 6g
	Curcumin C3 Complex®	1g – 6g
	Mushrooms (reishi, shiitake, coriolus)	Formulations vary (consider 2 – 6 capsules)
	Quercetin	500mg
	Vitamin D	1,000 – 5,000 IU (depending on baseline levels)
	Selenium	200 – 600 mcg
Histamine-mediated mast cell activation	Nigella seed oil	900 – 3600mg
	Quercetin	1000 – 2000mg
	Vitamin C	1 – 4g
	Palmitoylethanolamide	600mg – 1.8g
	Vitamin D	1,000 – 5,000 IU (depending on baseline levels)
RESPIRATORY SYSTEM		
Dyspnoea and cough	N-acetyl-cysteine	600mg – 2.7g
	Curcumin C3 Complex®	1 – 6g
	Vitamin A	10,000IU – 50,000IU
GASTROINTESTINAL SYSTEM		
Dysbiosis	High potency probiotic formula	At least 10 billion CFU
	Prebiotic fibre blend	Formulations vary (consider 1 – 2 tsp)
NEUROLOGICAL SYSTEM		
Depression and anxiety	Curcumin C3 Complex®	500mg – 1.5g
	Saffron	30mg – 100mg
	Psychobiotics (Cerebiome®)	3 billion – 10 billion CFU
	N-acetyl-cysteine	1.2g – 2.4g
	Palmitoylethanolamide	600mg – 1800mg
	Omega-3 fatty acids	1g – 2g

SYMPTOM	INGREDIENT	DOSAGE SUGGESTION (DAILY)
Insomnia	Valerian, hops, passionflower	Formulations vary (consider 2–4 capsules)
	Magnesium	300 – 400mg before bed
Cognitive decline	Bacopa and ginkgo	300mg – 450mg (BacoMind™) 120mg – 240mg (Ginkgo)
	Glutathione	> 400mg
	Polyphenols (quercetin, curcumin, resveratrol, green tea)	Formulations vary
	B vitamins	Formulations vary
Olfactory dysfunction	Vitamin A	10,000 – 50,000IU
	Vitamin D	1,000 – 5,000 IU (depending on baseline levels)
	Zinc	50mg – 100mg
	Palmitoylethanolamide	600 – 1800mg
	Omega-3 fatty acids	2g – 4g
CARDIOVASCULAR SYSTEM		
Cardiovascular risk	Curcumin C3 Complex®	1 – 6g
	Bacillopeptidase F	125mg – 250mg
	Bromelain	400 – 800mg
	Magnesium	300 – 600mg
	Vitamin E	100IU – 800IU
	Omega-3 fatty acids	1g – 3g
Myocarditis	Curcumin C3 Complex®	1 – 6g
	Coenzyme Q10	150 – 600mg
	Quercetin	500 – 2000mg
	Zinc	50mg
	Vitamin C	1 – 4g
	Vitamin D	1,000 – 5,000 IU (depending on baseline levels)
CARDIOVASCULAR SYSTEM		
POTS	Magnesium	300 – 600mg
	Nutrient deficiencies (iron, B12, B1, vitamin D)	Variable – assess individual deficiencies
INTEGUMENTARY SYSTEM		
Hair loss	Vitamin D	1,000 – 5,000 IU (depending on baseline levels)
	Iron	24 – 100mg (assess individual deficiency)
	Zinc	50mg

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