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COMMENT

Insights into potential therapeutic approaches for long COVID

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Long COVID (also called "post-COVID condition" or "post-COVID-19 syndrome") was first defined in adults by WHO in October, 2021 [1,2]. Usually, it occurs 3 months after the onset of COVID-19. It is a series of complex symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis in individuals with a history of probable or confirmed SARS-CoV-2 infection [3,4]. At least 65 million individuals globally are estimated to have long COVID, mostly are hospitalized cases (50%–70%), and others are non-hospitalized and vaccinated cases [5]. As the estimated cumulative global incidence of long COVID is continuously growing each year, it represents a substantial and ongoing challenge to global health.

Long COVID encompasses dozens of symptoms across multiple organ systems. In circulatory system, it can cause endothelial dysfunction, myocardial inflammation, and cardiac impairment, and increase risk of postural orthostatic tachycardia syndrome (POTS), deep vein thrombosis, pulmonary embolism, and stroke [6–8]. In neurological and cognitive systems, it may lead to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), neuroinflammation, reduced cerebral blood flow, and small fiber neuropathy [9–11]. Shortness of breath and cough are the most common respiratory symptoms in respiratory system. Many people with long COVID will be found abnormal gas exchange of lungs [12,13]. In reproductive system, irregular menstruation and increased severity of premenstrual symptoms are more likely to occur in women [14]. Long COVID can also attack immune system to cause autoimmunity, gastrointestinal tract to cause gut dysbiosis, pancreas to cause diabetes, as well as kidney, spleen, and liver to cause organ injury [15–17].

Despite long COVID affecting a substantial portion of the patient population, there are currently no approved prevention and treatments for long COVID. Many pathogenetic mechanisms of long COVID have been proposed, e.g., perturbations of the immune system, coagulation system, etc. Understanding the cause of long COVID is quite important for the identification of potential therapeutic targets. Currently, the related biological drivers are listed below [18]. (1) Acute SARS-CoV-2 infection is associated with the subsequent risk of long COVID. Viral replication and systemic spread are required to initiate the pathways of long COVID. (2) Persistence of SARS-CoV-2 virus after acute infection is also a central problem for long COVID. Reports indicated that some people could harbor replicating virus for months or even a year. (3) Long COVID is associated with chronic inflammatory state, and linked to specific markers of inflammation and immune dysfunction (interleukin-1 β, interleukin-6, tumor necrosis factor, etc.). Myeloid/macrophage cell, mast cell, and T cell activations may participate in this process. (4) Thrombotic events and microclots may also contribute to long COVID. It is reported that the spike protein binds fibrinogen, resulting in conformational changes in this protein. (5) Alterations in the microbiome and fecal microbiota transplantation are associated with long COVID. (6) Long COVID has been tied to metabolic derangements, including dysfunction of mitochondria. There is evidence that SARS-CoV-2 virus alters mitochondrial structure and function, and effects on its gene expression. Then, according to the mechanism above, a series of non-pharmaceutical procedures and pharmacological treatment approaches have been showed effective and we will make a summary as below (Fig. 1 and Table 1).

Non-pharmaceutical interventions

Non-pharmaceutical interventions are recommended to those people in the first 6 months after acute infection and with more minimal symptoms [19]. An online, home based, supervised, group physical and mental health rehabilitation program was proved effective at improving

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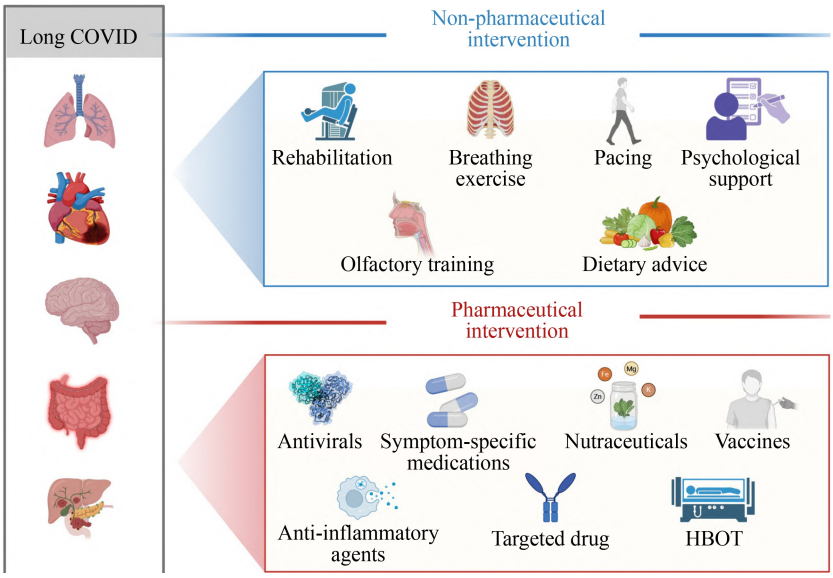

Fig. 1 The non-pharmaceutical and pharmaceutical interventions for long COVID.

health related quality of life in adults with post-COVID condition [20]. It was also demonstrated that breathing and chest mobility exercises have the potential to enhance cardiorespiratory fitness level and improve the function of weakened respiratory muscles in long COVID patients [21,22]. Moreover, pacing strategies, psychological support, cognitive and speech rehabilitation, attention to lifeworld context, olfactory training for anosmia, and dietary advice would be helpful as well [23–25]. Notably, there is new evidence that unmoderated exercise in post-COVID condition can exacerbate inflammatory and other pathological process, leading to a worsening of symptoms and delayed recovery. As a result, cautious exercise adoption is likely to be safer and more effective to increase the quality of life in long COVID patients [26,27].

Pharmaceutical interventions

SARS-CoV-2 antivirals

A randomized, double-blind, placebo-controlled phase 3 trial showed that ensitrelvir (approved in Japan for COVID-19 treatment) usage in the acute COVID-19 phase may reduce the risk of various symptoms associated with long COVID [28]. In nonhospitalized individuals (mild-to-moderate COVID-19) who have at least one risk factor for the development of severe COVID-19, the use of ritonavir-boosted nirmatrelvir and molnupiravir in the acute phase could also reduce the risk of long COVID, while in low-risk groups, the efficacy of these drugs for long COVID has not been evaluated [29–32]. However, the results from PRINCIPLE trial revealed that favipiravir had only a marginal positive impact on post-COVID condition [33]. The effectiveness of many other antiviral drugs has not yet been evaluated and further exploration is still needed. Moreover, it is evidenced that the spike protein of SARS-CoV-2 virus may be related to neurotoxic effects in long-COVID. Monoclonal antibodies that target the spike protein might be effective in this case [34].

Symptom-specific medications

In a case series study, low-dose naltrexone (LDN) could alleviate chronic fatigue syndrome or myalgic encephalomyelitis in long COVID patients [35]. LDN could also reduce the immune-mediated thrombotic complications in long COVID [36]. Anticoagulant regimens are a promising way to address abnormal clotting [37]. Apheresis has also shown promise to alleviate long COVID symptoms, which has been theorized to help remove microclots and has been shown to reduce autoantibodies [38]. However, it is quite expensive and long-term benefits are uncertain. Famotidine, a H2 antihistamine, is used to alleviate a wide range of symptoms, especially neuropsychiatric symptoms [39]. Moreover, β-blockers are usually used for POTS, intravenous immunoglobulin for immune dysfunction, sodium-glucose cotransporter 2 inhibitor and glucagon-like peptide 1 receptor agonists for improving cardiovascular and renal function, and systemic corticosteroids for fatigue, breathlessness, and cough symptoms [40–42].

Anti-inflammatory agents

A RCT study demonstrates that a combined plant extract

Table 1 Alternative therapeutical approaches to long COVID

Treatment	Effects	References
Non-pharmaceutical interventions		
Group physical and mental health rehabilitation	Improved health related quality of life in adults	[20]
Breathing and chest mobility exercises	Enhanced cardiorespiratory fitness, improved respiratory muscle function	[21,22]
Pacing strategies	Reduced triggering post-exertional symptom exacerbation	[24]
Olfactory training	Improved olfactory disorders	[25]
Pharmaceutical interventions		
Ensitrelvir (acute phase)	Reduced risk of multiple Long COVID symptoms	[28]
Nirmatrelvir/ritonavir (Paxlovid), Molnupiravir	Lowered long COVID risk in high-risk patients	[29–32]
Favipiravir	Minimal effect on long COVID	[33]
Anti-spike monoclonal antibodies	May reduce neurotoxic effects	[34]
Low-dose naltrexone (LDN)	Reduced fatigue and immune-mediated thrombosis	[35,36]
Anticoagulants	Improved abnormal clotting	[37]
Apheresis	Reduced microclots and autoantibodies, but uncertain long-term benefits	[38]
Famotidine (H2 blocker)	Alleviated a wide range of symptoms, especially neuropsychiatric symptoms	[39]
SGLT2 inhibitors/GLP-1 agonists	Enhanced cardiovascular and renal function	[42]
Systemic corticosteroids	Reduced fatigue, breathlessness, and cough	[41]
Combined plant extract	Reduced moderate-severe long COVID symptoms, particularly fatigue	[43, 44]
Sulfur thermal water inhalation	Improved exercise capacity, reduced inflammation	[45]
Enzymatically liberated salmon oil	Reduced inflammation, improved lung function	[46]
Quercetin (Nrf2 modulator)	Anti-inflammatory effects	[47]
Metformin (early use)	41.3% lower long COVID risk	[48]
PEA-LUT (palmitoylethanolamide + luteolin)	Reduced neuroinflammation, improved chronic olfactory loss	[50,51]
Anti-fibrin monoclonal antibody (5B8 derivative)	May protect against neuroinflammation, under phase 1 trial	[52]
Symbiotic	Alleviated fatigue, memory loss, difficulty in concentration, gastrointestinal upset, and general unwellness	[53,54]
Creatine-glucose, vitamins (B, C, D, E), minerals (Mg, Zn, Se), CoQ10	Reduced fatigue, anxiety, and cognitive issues	[55–59]
AXA1125	Improved fatigue-based symptoms	[60]
Vaccination	15%–41% lower long COVID risk	[5,61]
BC007 (DNA aptamer drug)	Resolved fatigue, taste loss, and microcirculation issues	[62]
Hyperbaric oxygen therapy (HBOT)	Improved cognition, psychiatric, fatigue, sleep, and pain	[63]
Acupuncture	Reduced brain fog, joint pain, blood stagnation	[64]

(CPE) formulation, containing *Citrus aurantifolia*, *Tiliacora triandra*, *Cannabis sativa*, *Alpinia galanga*, and *Piper nigrum*, shows benefits in alleviating moderate to severe long COVID symptoms, particularly fatigue [43]. These plants are known for their antioxidant and anti-inflammatory properties. Essential oils (EOs) from specific medicinal plants have also demonstrated efficacy in alleviating long COVID symptoms [44]. In another pilot study with small sample size, sulfur thermal water inhalation therapy significantly improves exercise capacity and inflammatory biomarkers of patients with long-COVID [45]. Besides, enzymatically liberated salmon oil treatment also provides a broad inflammation-resolving effect in long-COVID, as well as improves lung barrier function and enhances immune memory [46]. Quercetin is a major component of the flavonoid subclass, which is a nuclear factor erythroid-derived 2-like 2 (Nrf2)-interacting nutrient that contributes to the reduction of inflammation, suggesting the therapeutic latency of quercetin and its derived-products against long COVID [47]. Furthermore, metformin (initiated within 7 days of SARS-CoV-2 infection) has been shown to reduce the risk of long COVID by 41.3% in a randomized controlled trial [48]. It is deduced that metformin ameliorates inflammatory reaction by regulating mTOR signaling pathway. Some monoclonal antibodies that target IL-1β, TNF-α, interferons, and IL-6 have emerged and been discussed for long COVID treatment. However,

interventions that precisely target a single pathway might be insufficient to reverse broad inflammatory response in long COVID or might simply result in counter-regulatory responses that are equally harmful. More upstream therapies aimed at modulating various arms may be more efficacious. Baricitinib, a Janus kinase (JAK) inhibitor that targets the STAT3 pathway, is planned for a multi-center study. A trial of rapamycin, an immunomodulator that works via multiple pathways, is also underway [49].

Since neuroinflammation is closely associated with neurological and cognitive dysfunctions in long COVID, a series of anti-inflammatory agents are utilized for treatment. Co-ultramicronization of palmitoylethanolamide (PEA) with luteolin (PEALUT) proved to be a high-potential therapeutic instrument for the treatment of neuroinflammation and chronic olfactory loss in long COVID, which may be correlated with PPAR-α and GPR55 receptors at the protein level [50,51]. A recent study found that fibrinogen, the central structural component of blood clots, is also correlated with neuroinflammation. Fibrin binds to the SARS-CoV-2 spike protein and forms pro-inflammatory blood clots that promote neuroinflammation and neuronal loss after infection, as well as innate immune activation in the brain. A monoclonal antibody targeting the inflammatory fibrin domain could provide protection from neuronal injury and represent a therapeutic intervention for patients with long COVID. A humanized affinity-matured derivative of 5B8 has entered phase 1 clinical trials in healthy individuals to assess safety and tolerability [52].

Nutraceuticals

Some non-pharmacological supplements have shown promise in treating long COVID. Gut microbiome modulation is quite important for the management of long COVID. A randomized, controlled trial proves that a symbiotic preparation (SIM01) could alleviate multiple symptoms of long COVID at 6 months after COVID infection [53]. Another study also indicates that taking the symbiotic mixture for 3 months could improve tissue metabolism and mitigate clinical features of ME/CFS [54]. Moreover, the supplementation of creatine-glucose, vitamins (high-dose B group, C, D, E) and minerals (magnesium, zinc, selenium), and coenzyme Q_{10} may also benefit patients with post-COVID syndrome by reducing fatigue, alleviating anxiety, and improving cognitive symptoms, with minimal side effects [55–59]. Supplements like N-acetylcysteine have also shown promise in small, uncontrolled studies in long COVID treatment through the mechanisms of mitochondrial pathology. An early-phase of AXA1125, a combination of five amino acids and N-acetylcysteine, showed some benefit as well [60].

Other interventions

Previous studies indicate that vaccines provide partial protection for long COVID, with a reduced risk between 15% and 41% [5]. In people who had already developed long COVID, the impact of vaccination differs among people. Postvaccination symptoms (fatigue, joint pain, taste and olfactory abnormalities) were relieved, worsened, and unchanged in 16.7%, 21.4%, and 61.9% patients, respectively [61]. Besides, in a case report, BC007, a DNA aptamer drug with a high affinity to G-protein-coupled receptor (GPCR-Aabs), successfully healed a patient with chronic fatigue syndrome, loss of taste and impaired capillary microcirculation in the macula and peripapillary region after SARS-CoV-2 infection [62]. Another study documented significant improvements in cognitive, psychiatric, fatigue, sleep and pain symptoms among long COVID patients who underwent hyperbaric oxygen therapy (HBOT) [63]. Case studies also indicate that acupuncture could help to improve brain fog, reduce joint pain, and alleviate blood stagnation in long COVID [64].

Taken together, evidence for long COVID treatments is beginning to emerge, but it is still limited. Notably, randomized controlled trial with high grade of evidence is urgently needed. Since patients with long COVID may suffer more than one symptom, treatment strategies often come from multidisciplinary decision and a multi-drug therapy would be recommended to these patients to relieve symptoms. The key barrier to developing long-COVID treatments has been uncertainty surrounding the condition's root cause [65]. As the emerging and deep exploration of the biological and pathophysiological mechanism underlying long-COVID, specific biomarkers and targeted drugs would precisely guide the diagnostic and therapeutic strategies for long-COVID in the near future.

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Compliance with ethics guideline

Conflicts of interest Jingya Zhao, Yingqi Lyu, and Jieming Qu declare that they have no conflict of interest.

This manuscript is a comment article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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