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Therapeutic options for the treatment of post-acute sequelae of COVID-19: a scoping review

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Abstract

Objectives This scoping review aimed to summarize the available studies to address the question of which therapeutic agents can be utilized for patients with post-acute sequelae of COVID-19 (PASC).

Methods We conducted a systematic search in medical databases, including PubMed and Embase, for studies aligned with our objectives published between January 1, 2020, and July 22, 2024. For each study, we summarized the main symptoms targeted, study design, therapeutic regimens, evaluation tools, and clinical outcomes.

Results A total of 413 studies were identified, and 39 studies were included in this review based on relevance to the research objectives. We primarily focused on high-level evidence studies, such as meta-analyses and randomized controlled trials, but observational studies were included when evidence was scarce. Therapeutic agents evaluated included hyperbaric oxygen, ivermectin, metformin, naltrexone, micronutrient supplements, antifibrotic agents, antiviral agents, and selective serotonin reuptake inhibitors (SSRIs). Among these, hyperbaric oxygen, antifibrotic agents, antiviral agents, and SSRIs demonstrated promising results. However, the heterogeneity of PASC symptoms posed challenges in synthesizing findings for specific symptom-based outcomes.

Conclusion Given the heterogeneity of symptoms, this review highlights the need for standardized and targeted research to better address the diverse therapeutic needs of patients with PASC.

Clinical Trial Not applicable.

Keywords PASC, Long COVID, Post-acute COVID-19 syndrome, Therapeutic agents

Introduction

Although the World Health Organization (WHO) has declared the end of the Coronavirus disease 2019 (COVID-19) pandemic, it remains an important concern that patients continue to experience symptoms after SARS-CoV-2 infection. The mechanisms of these symptoms, referred to various term such as "Long COVID", "Long post-COVID symptoms", "Post-acute sequelae of COVID-19 (PASC)" and "Post-COVID-19 syndrome", have not yet been clearly defined. WHO defined PASC as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation [1]. Other organizations, such as the

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Centers for Disease Control and Prevention (CDC) and the National Institutes of Health, have defined it as symptoms lasting for more than 4 weeks [2, 3]. PASC includes a wide range of symptoms, such as fatigue, cough, shortness of breath, cognitive dysfunction, and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

The CDC reported that, as of March 2024, approximately 6.7% of adults in the U.S. were experiencing PASC [4]. In South Korea, among confirmed COVID-19 patients, 39.9% visited healthcare facilities due to newly developed condition within 3 months post-infection [5]. Despite the high prevalence of PASC, management of the PASC remains difficult and complex. Recently, there have been some guidelines that recommend various medications and rehabilitation for certain symptoms [6–8]. Nevertheless, it is still challenging due to lack of robust clinical data and the ambiguity in the diagnosis of PASC.

Therefore, we aimed to provide a narrative scoping review of specific medications for PASC that includes the latest insights. This review summarizes the latest evidence on potential medications and offers treatment options for clinicians to use in their actual practice.

Methods

To achieve clarity and transparency and to avoid poor reporting, we used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [9]. Given the rapidly evolving nature of PASC research, we aimed to capture a wide range of emerging evidence, including exploratory studies that might have been excluded under a pre-planned protocol. Our approach adhered to PRISMA-ScR guidelines to ensure methodological transparency and comprehensiveness (Supplementary Table 1). Additionally, we applied the Joanna Briggs Institute (JBI) Critical Appraisal Checklist to qualitatively assess the methodological rigor of included studies, evaluating aspects such as sample size, blinding, and control measures where applicable. The quality assessment of the literature was conducted independently by two researchers. Any agreements and disagreements between the evaluators were then reconciled and analyzed through a researcher meeting in which both researchers participated.

Table 1 Keywords of medications

Drugs	Keywords
Hyperbaric oxygen	Hyperbaric Hyperbarics Cell respiration Oxygenation (oxygen, oxygenate, oxygene)
Ivermectin	Ivermectin Ivermectine Ivermectins
Metformin	Metformin Metformine Metformins
Naltrexone	Naltrexone Naltrexone
Omega-3 fatty acids	Fatty acids Omega-3 Omega-3 fatty acids
Micronutrient supplement	Vitamin s Vitamine Vitamins
Antifibrotic Agent	Nintedanib Pirfenidone
Antiviral agent	Nirmatrelvir-ritonavir
SSRI	Selective serotonin reuptake inhibitors

Searching strategy and inclusion/exclusion criteria

We searched scientific and medical databases (PubMed, Embase, and Cochrane library) for relevant studies published between January 1, 2020, and July 22, 2024. The database search was conducted on the July 22, 2024. We restricted the search language to English only. The following keywords were used in the databases: long Covid-19 (long COVID, post-acute COVID-19 Syndrome and after COVID) and treatment medications, which are listed in Table 1. We conducted analyses including both meta-analyses and randomized clinical trials, and included observational studies when data were insufficient.

The inclusion criteria were as follows: (1) the articles reported the clinical results including the main symptoms targeted, study design, regimen, evaluation tools, clinical outcomes, total number of participants, specific number of PASC and related death/hospitalization; (2) MeSH (Medical Subject Headings) terms and keywords for methods; (3) English literature. The exclusion criteria were as follows: (1) case reports; (2) no relevant data; (3) gray literature (conference proceedings, dissertations, and theses) (4) unavailable full text. Due to the time-sensitive nature of this research, it was not feasible to access the full texts of all identified papers, and thus, only the most relevant and accessible studies were included in the review. Studies were excluded if, (1) they focused on the treatment effect in the acute phase of COVID-19 rather than long COVID, (2) the full text was not available, or (3) they were laboratory studies rather than clinical studies. Many chemical experiments were initially included because the active ingredients of the treatments were searched together; however, all of these were excluded.

Data extraction and outcomes

Data extraction was conducted by the reviewers (EJK and YBS) in consultation with a senior author (JYS). Descriptive data extracted in this scoping review included the author, main symptoms targeted, study design, regimen, evaluation tools, clinical outcomes.

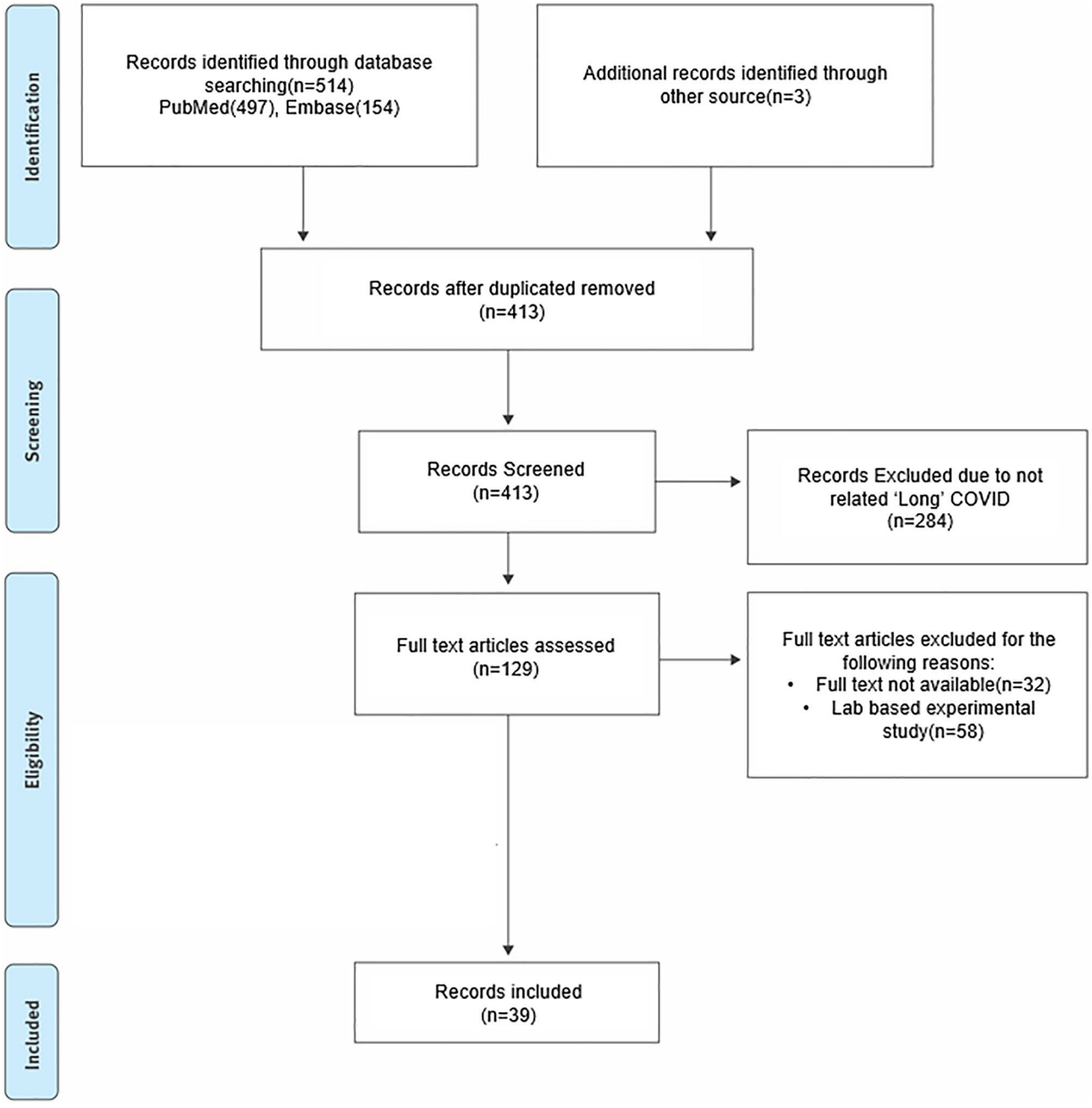

Fig. 1 Flowchart of selection process for the scoping review

The goal of study was to synthesize the research results on various treatments mentioned in the PASC and to gain insight into medicine that can be used in actual clinical settings. A scoping review differs from a systematic review in that it does not require an assessment of the risk of bias of the included literature and uses a qualitative analysis that analytically reinterprets the literature rather than synthesizing the results of individual studies into an integrated estimate.

Results

We identified 517 records, 104 of which were excluded as duplicates. Title and abstract screening were conducted for the remaining 413 articles, 284 of which were excluded because of being unrelated to PASC. For 32 articles, we failed to access the full text due to access limit. Additionally, 58 articles were excluded because they were not clinical trials. Finally, 39 articles were included in the review (Fig. 1). The target symptoms, study design, drug regimen, and outcomes for the therapies included in this

scoping review are summarized in Supplementary Tables 2 and 3.

Hyperbaric oxygen therapy

The mechanism by which hyperbaric oxygen therapy (HBOT) may exert beneficial effects on PASC remains unclear. Generally, HBOT is known to reduce acute phase inflammatory proteins, cytokines, and interleukins, thereby mitigating inflammatory responses. Additionally, it has been reported to enhance growth factors and pro-angiogenic cytokines, thereby promoting the recovery of damaged tissue [10]. Based on these mechanisms, experimental and clinical studies suggest that HBOT may benefit the cognitive system, especially in cases of brain injury or neurodegenerative disease [11]. Recent findings have also reported increases in mitochondrial respiration and mitochondrial mass with HBOT, prompting experimental research into mitochondrial imbalance or dysfunction as a therapeutic target for HBOT [12]. These mechanisms hold promise for alleviating PASC symptoms, particularly those related to brain function and chronic fatigue.

The primary symptoms expected to improve with HBOT in PASC cases are related to cognitive dysfunction, although studies have also explored its effects on fatigue and cardiac function. One study found improvements in cognitive function, attention, executive function, energy level, sleep quality, psychiatric symptoms and pain [13]. Another study reported improvements in quality of life, sleep quality, and reductions in psychiatric and pain symptoms within one month of treatment, with sustained effects observed after one year [14]. Regarding brain function, structural and functional magnetic resonance imaging has shown that HBOT can improve disruptions in white matter tracts and enhance connectivity organization within neural pathways [15]. Cardiac function was also positively affected, with improvements in global work efficiency and normalization of global longitudinal strain, suggesting that HBOT may support the recovery of left ventricular systolic function [16]. However, as all these studies were conducted with fewer than 40 participants, larger-scale studies are necessary to establish more robust evidence for these effects.

In terms of safety, 12 out of 20 patients in one study experienced adverse events (AEs), with a total of 31 AEs reported. Of these, 20 events appeared to be related to HBOT, commonly including cough, chest pain, and chest discomfort; however, no severe AEs were reported, and most were transient [17]. HBOT carries a risk of two main complications: barotrauma to the middle ears or sinuses and pulmonary overpressurization due to pressure effects [18]. Additionally, oxygen toxicity can result in pulmonary and neurological damage, as described by the VENTID acronym (vision changes, ears ringing, nausea, muscle twitching, irritability, and dizziness), as well as ophthalmological complications. Given the current limited evidence, HBOT should be considered with a careful risk-benefit assessment.

Ivermectin

Ivermectin, used as an antiparasitic agent, has been shown to inhibit viral replication of the SARS-CoV-2 virus in vitro [19]. Although the mechanism of ivermectin is unclear, it is hypothesized that it inhibits viral replication by suppressing the importin α/β1-mediated transport of viral proteins across the nuclear membrane [20]. Based on this mechanism, in the early days of COVID-19 pandemic, ivermectin was considered a promising therapeutic option for COVID-19 treatment. However, in a large randomized controlled study, ivermectin did not reduce hospitalizations or emergency room visits due to SARS-CoV-2 infection [21]. Subsequent studies have not shown ivermectin to be effective against SARS-CoV-2 infection. The efficacy of ivermectin against SARS-CoV-2 infection has not been proven in subsequent studies.

There were few studies evaluating the long-term effects of ivermectin. In the COVID-OUT study, unlike metformin, ivermectin had no effect on the incidence of PASC [22]. In another study, there was no meaningful improvement in recovery, hospital admissions, or long-term results in patients with PASC following ivermectin treatment [23].

Ivermectin has generally been safe to use, with no major side effects reported. However, there is limited research on the relationship between ivermectin and PASC. No studies have demonstrated a clear benefit, making the use of ivermectin controversial. Therefore, administering ivermectin for PASC patients is not reasonable.

Metformin

Metformin, a biguanide antihyperglycemic drug, is widely used as an oral medication for patients with diabetes. Beyond its blood glucose-lowering effects, it has been found to possess anti-inflammatory properties, raising expectations for its potential usefulness in conditions where excessive inflammatory responses are problematic. In the context of acute respiratory distress syndrome (ARDS) caused by COVID-19, metformin has been reported to inhibit NLRP3 inflammasome activation and IL-1β production in macrophages [24]. Animal studies have further demonstrated its ability to reduce cytokine storms, prevent microvascular damage, and inhibit secondary fibrosis [25]. Based on these findings, clinical studies have reported a reduction in severe infections when metformin is used during the acute phase of COVID-19, leading to various repurposing studies aimed at acute phase treatment [26]. However, clinical studies focusing on the effects of metformin solely in PASC remain scarce.

A study conducted in 2023 investigated the preventive effects of metformin on PASC by organizing patient groups as follows: metformin with ivermectin, metformin with fluvoxamine, metformin with placebo, ivermectin with placebo, fluvoxamine with placebo, or placebo with placebo [22]. Once acute infection was confirmed, metformin was administered at 500 mg on day 1, 500 mg twice daily on days 2–5, and then 500 mg in the morning and 1000 mg in the evening until day 14. Among the 1126 patients observed for nine months, 93 (9.3%) reported PASC, with a hazard ratio for metformin of 0.59 (95% CI 0.39–0.89; $p = 0.012$). No clinically concerning AEs were observed.

Further clinical research is needed to confirm whether metformin effectively prevents PASC. Since this study involved the initiation of metformin treatment during the acute phase of COVID-19, its efficacy specifically for PASC patients remains uncertain. However, as studies have reported no concerning AEs when metformin was administered to adult patients without diabetes, it is plausible that clinical trials focusing exclusively on PASC patients could be conducted, and forthcoming research results are anticipated with interest.

Naltrexone

Naltrexone, a cyclopropyl derivative is a potent opioid antagonist. Low dose naltrexone (1.5–4.5 mg daily) is known to have immunomodulatory and anti-inflammatory properties, and has been used off-label to reduce symptom severity in conditions such as fibromyalgia, Crohn's disease, multiple sclerosis, and complex regional pain syndrome [27]. In this context, low-dose naltrexone has been tried to manage PASC. Low-dose naltrexone is hypothesized to alleviate PASC symptoms through neuroinflammation modulation by antagonizing toll-like receptors 4 on microglia and macrophages, leading to reduced production of pro-inflammatory cytokines (e.g., IL-6, TNF-alpha) and oxidative stress [28, 29]. This beneficial impact on neuroinflammation might be linked to the reduction of fatigue, pain, and cognitive impairment in patients with PASC. In addition, low-dose naltrexone may temporarily block opioid receptors, triggering a compensatory increase in endogenous opioid production, which would improve pain sense and mood [30].

According to the observational studies, 52–67% of patients receiving low dose naltrexone reported improvements in PASC symptoms including fatigue, pain, and cognitive function (brain fog, memory and concentration) [29, 31, 32]. In a retrospective cohort study by Tamariz et al., low dose naltrexone showed a hazard ratio of 5.04 for improvement compared with physical therapy alone among 108 patients with PASC ($p = 0.02$) [29]. Low dose naltrexone was well-tolerated with minimal side effects. Only mild fatigue and diarrhea were reported. Across the observational studies, low dose naltrexone consistently showed beneficial therapeutic effects for the PASC patients with substantial improvements in quality of life [29, 31–34].

These studies underscore the potential of low dose naltrexone for managing PASC symptoms, although further randomized controlled trials are essential to validate these findings and establish standardized dosing protocols.

Palmitoylethanolamide

Palmitoylethanolamide (PEA) is a cannabimimetic compound known for its anti-inflammatory effects and neuroprotective properties. The anti-inflammatory mechanism of PEA primarily involves downregulating mast cells and acting as an agonist for peroxisome proliferator-activated receptor alpha (PPARα), which reduces the production of inflammatory mediators and inhibits the activation of inflammatory cells [35]. Moreover, PEA has been reported to have neuroprotective effects by acting on the mast cell–microglia axis. Considering these mechanisms, PEA becomes a potential therapeutic to improve neruo-inflammation after SARS-coV-2 infection. Recent studies have shown that PEA restores gamma-aminobutyric acid type B (GABAB) receptor activity and cortical plasticity in PASC patients by confirming long-interval intracortical inhibition (LICI) and long-term potentiation (LTP)-like cortical plasticity [36].

Research has provided significant evidence to support the role of PEA in improving olfactory function. Several randomized controlled trials have provided evidence for the efficacy of Palmitoylethanolamide-Luteolin (PEA-LUT) in improving olfactory threshold, discrimination, and identification ability in PASC patients with olfactory dysfunction [37, 38]. Patients who received ultramicronized PEA-LUT (umPEA-LUT) in combination with olfactory training (OT) showed a greater improvement in parosmia symptoms compared to patients who received OT alone [39]. The umPEA-LUT-treated patients showed the greatest improvement in TDI scores (21.8 ± 9.4 to 29.7 ± 7.5, $p < 0.01$) followed by patients on umPEA-LUT with OT (19.6 ± 6.29 to 27.5 ± 2.7, $p < 0.01$). Patients in the combination (umPEA-LUT with OT) and umPEA-LUT groups had significantly improved TDI scores compared to alpha-lipoic acid and control groups ($p < 0.001$). Thus, PEA may be a therapeutic option that can be used in patients with olfactory dysfunction. In addition, umPEA-LUT was shown to significantly improve cognitive dysfunction, supporting the assertion that it may be effective in improving other neuroinflammatory symptoms associated with PASC. Treatment with co-ultraPEA-LUT showed a significant improvement in Prospective–Retrospective Memory Questionnaire (PRMQ) score (T0: 51.94 ± 10.55, T1: 39.67 ± 13.02, $p < 0.01$) and Montreal

Cognitive Assessment (MoCA) raw score (T0: 25.76 ± 2.3, T1: 27.2 ± 2, $p = 0.026$) [40].

Although its effect on improving olfactory dysfunction, no significant improvement in olfactory function was observed in patients on PEA-LUT alone without OT [41]. OT remains the cornerstone of treatment for patients with olfactory dysfunction after SARS-CoV-2 infection and PEA could be a potential supplementary treatment with its safety confirmed in these trials. In addition to improving olfactory function, PEA has shown efficacy in alleviating other general PASC symptoms in observational studies [42, 43]. A large-scale randomized controlled trial is warranted to investigate this aspect further.

Micronutrient supplement

Historically, the effects of vitamins in infectious diseases have been a topic of extensive discussion. While the theoretical basis for their positive outcomes remains partially understood, several positive findings have been reported. Vitamin A enhances antibody responses by increasing lymphocyte numbers [44]. Vitamin B, although its effects vary by subtype, is generally involved in the cytotoxic immune response of natural killer cells and CD8 + T cells [45]. Vitamin C is known for its antioxidant and anti-inflammatory effects, while vitamin D plays a crucial role in the maturation of immune cells through its receptors on B cells, T cells, and antigen-presenting cells, alongside its immunomodulatory effects [46, 47]. Vitamin E, fundamentally recognized for its antioxidant properties, also exhibits anti-inflammatory effects and immunomodulatory functions [48]. Based on these existing foundations, numerous studies have investigated the therapeutic potential of these vitamins in COVID-19 and their role in preventing PASC. Additionally, organic compounds such as alpha-lipoic acid and L-arginine have been included in such studies. However, research on their efficacy when administered in PASC conditions remains limited. Randomized controlled trials focusing on single compounds are rare, with studies often conducted using compound mixtures or observational designs, making it challenging to isolate the pure therapeutic effects of these agents in PASC.

A randomized controlled trial conducted on PASC patients experiencing persistent fatigue evaluated the effects of a mixture of L-arginine and vitamin C (1.66 g L-arginine plus 500 mg liposomal vitamin C) administered for one month. The study demonstrated a significant improvement in the 6-minute walk distance after one month (40.5 m; placebo: 75 m, $p = 0.001$) and handgrip strength (7.5 kg compared to placebo: 6.6 kg, $p = 0.03$). Furthermore, endothelial function, assessed through brachial artery dilation following a transient period of forearm ischemia, showed notable improvement (4.3% vs. 9.4%, $p = 0.03$) [49]. Conversely, in a study involving PASC patients with persistent anosmia for over three months, alpha-lipoic acid (300 mg, twice daily for three months) was used as an adjuvant to olfactory training. The study found no significant differences between the treatment and control groups in the Connecticut Chemosensory Clinical Research Center (CCCRC) score ($p = 0.63$), olfactory threshold ($p = 0.50$), identification score ($p = 0.96$), or Visual Analog Scale score ($p = 0.97$) [50].

A meta-analysis investigating the preventive effects of vitamin supplementation during the acute phase of COVID-19 on the development of PASC concluded that no definitive conclusions could be drawn [51]. The lack of sufficient studies, heterogeneity in research design, and the generally low quality of the available data underscore the need for further investigation. Similarly, studies on the effectiveness of micronutrient supplementation in the PASC phase remain insufficient. Given the relatively low risk of AEs associated with micronutrient supplementation, there is a pressing need for well-designed, objective studies to provide better guidance for clinical practice.

Antifibrotic agents

Acute respiratory distress syndrome was reported to develop in 42% of patients with COVID-19 pneumonia, and 61–81% of those requiring intensive care [52]. Pulmonary fibrosis has been identified as a significant long-term complication of severe COVID-19, particularly in patients with ARDS. Several studies have reported beneficial effects of antifibrotic agents, particularly pirfenidone and nintedanib, in the treatment of pulmonary fibrosis associated with severe COVID-19 and PASC [53–56]. Nintedanib inhibits pathways involving fibroblast growth factor, vascular endothelial growth factor, and platelet-derived growth factor, thereby reducing fibrosis and inflammation, while pirfenidone targets profibrotic cytokines such as TGF-β and TNF-α, decreasing fibroblast activation and collagen synthesis [55].

In a randomized study comparing the efficacy and safety of two antifibrotic agents, in treating lung fibrosis in patients with PASC ($n = 30$), both nintedanib and pirfenidone significantly improved pulmonary function (forced vital capacity and diffusing capacity), 6-minute walk test (6MWT) distances and oxygen saturation levels over 12 weeks [53]. In particular, nintedanib showed greater improvement in 6MWT distance ($p = 0.02$) and oxygen saturation levels ($p = 0.005$), but accompanied by more frequent adverse events including diarrhea (80%) and nausea/vomiting (66.6%). In a retrospective cohort study of 5,000 patients receiving pirfenidone or nintedanib, pulmonary function parameters were preserved at baseline levels after 12 months [54]. Nintedanib showed higher rates of gastrointestinal adverse events. Another retrospective cohort study analyzed the impact

of antifibrotic agents on 1-year mortality among COVID-19 patients with acute respiratory failure [55]. Patients in the antifibrotic group had a significantly higher survival probability compared to the control group (84.42% vs. 69.87%, hazard ratio 0.434 [95% CI 0.264–0.712]). Nintedanib demonstrated a statistically significant reduction in 1-year mortality compared to the control group ($p = 0.013$), while pirfenidone improved survival rates without achieving statistical significance ($p = 0.601$). A single-center, prospective observational study evaluated the efficacy of nintedanib and pirfenidone in managing lung fibrosis when combined with steroids (steroids alone vs. steroid plus pirfenidone vs. steroid plus nintedanib) [56]. Nintedanib demonstrated a significantly greater improvement in the chest computed tomography severity score compared to pirfenidone and steroids alone.

Early administration of antifibrotic agents might be associated with better outcomes in lung function and fibrosis resolution in patients with PASC [53–56]. The studies highlight the importance of antifibrotic therapy as part of a multidisciplinary approach to the management of COVID-19-induced pulmonary fibrosis and emphasize the need for further large-scale randomized controlled trials to refine treatment strategies. Although some studies have reported that these treatments are associated with GI problems, they can still be used with caution.

Anti-viral agents

The mechanism by which early antiviral treatment prevents PASC remains unclear. It is hypothesized that the SARS-CoV-2 virus infection leads to PASC by sustaining inflammation in the body over an extended period [57, 58]. In this perspective, early antiviral treatment inhibits viral proliferation and reduces the viral load in the body, which is expected to improve the symptoms related to COVID-19.

Recent studies have validated the effectiveness of early antiviral administration in preventing PASC. Two meta-analyses of observational studies showed that early administration of antiviral drugs significantly prevented PASC compared with non-antiviral treatment [59, 60]. Additionally, early administration of antiviral drugs reduced the risk of PASC-related hospitalization and death [60].

Observational studies have shown a reduction in PASC with remdesivir [61, 62], but randomized clinical trials have not shown a significant difference, indicating no clear long-term benefit of remdesivir [63]. Oral antivirals demonstrated more favorable outcomes in observational studies, which confirmed the effects of both nirmatrelvir/ritonavir (NMV-r) and molnupiravir in reducing PASC incidence, hospitalization, and death [64–66]. Individual studies have shown significant beneficial effects of oral antiviral agents on long-term cardiovascular risk [67] and neuropsychiatric sequelae [68]. On the other hand, in the target trial emulation study comparing matched cohorts receiving NMV-r versus no treatment, no significant differences were observed in the incidence of most post-COVID-19 conditions (29 out of 31), except for venous thromboembolism and pulmonary embolism [69].

It is reasonable to assume that early antiviral treatment would be effective in preventing PASC. However, there are limitations, as most of the studies included in the meta-analysis are observational and rely on health insurance data. Additionally, studies on the effectiveness of antiviral agents after a PASC diagnosis are insufficient, and research on their safety profile remains limited. A recently published double-blind randomized clinical trial, the STOP-PASC study, which evaluated the efficacy of a 15-day course of NMV-r in patients with PASC, also failed to demonstrate any significant benefit [70]. Thus, the efficacy of antiviral therapy in patients with PASC is questionable and requires further study.

Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are hypothesized to reduce the risk of PASC through several key mechanisms, including immunomodulation, antiplatelet effect, enhancement of vagal activity, and neurotransmitter regulation [71, 72].

In a retrospective study using data from the National COVID Cohort Collaborative (N3C) including 17,908 patients, SSRIs with sigma-1 receptor (S1R) agonist activity (e.g., fluvoxamine, fluoxetine, escitalopram) had a 29% reduction in relative risk (RR) of PASC compared to unexposed patients (RR = 0.704; 95% CI, 0.58–0.85; $p < 0.001$), while Non-S1R Agonist SSRIs (e.g., sertraline, paroxetine) showed a 21% reduction in RR of PASC compared to unexposed patients (RR = 0.79; 95% CI, 0.67–0.93; $p = 0.005$) [73]. In another retrospective study of the N3C database comprising 302,626 patients, SSRI use during acute COVID-19 was associated with a lower risk of PASC (adjusted risk ratio 0.92 [95% CI: 0.86–0.99]) compared to non-SSRI users [72]. However, a systematic review and meta-analysis of 14 clinical studies found that fluvoxamine did not consistently prevent the development of PASC [74]. Nonetheless, some studies have reported reductions in neuropsychiatric symptoms, including fatigue and depression, in patients treated with fluvoxamine. These discrepancies may arise from variations in dosing regimens, timing of administration, and patient characteristics.

Given their anti-inflammatory and neuropsychiatric properties, SSRIs present a promising therapeutic option for PASC. However, to determine their true clinical efficacy, future large-scale, well-controlled randomized trials and mechanistic studies are crucial.

Conclusion

We conducted a scoping review of nine potential therapeutic options for PASC that are currently under consideration. This is summarized in Supplementary Tables 2 and 3.

In addressing the ongoing challenges posed by PASC, this review provides a comprehensive review of emerging treatment options. Despite significant progress in identifying potential therapeutic strategies, the current landscape highlights critical gaps in robust clinical evidence. There are several limitations to this study. First, this review does not include studies published after the completion of the literature search, suggesting that ongoing updates will be necessary. Additionally, due to time constraints and the need for conciseness, we have focused on eight key medications that have been extensively studied and practical. The treatments mentioned above show promising results in mitigating PASC symptoms, yet they often lack large-scale randomized controlled trials to conclusively validate efficacy and safety. Thus, a deeper understanding of the pathophysiological mechanisms underlying PASC is essential, and future research should prioritize rigorous, multidisciplinary investigations to address these limitations and refine treatment protocols.

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Data availability
All data supporting the findings of this study are available within the paper and its Supplementary Information.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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