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Medicinal plants for the management of post-COVID-19 fatigue: A literature review on the role and mechanisms

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ABSTRACT

Background: COVID-19 infection has a lasting impact on human health, which is known as post-COVID-19 conditions. Fatigue is one of the most commonly reported post-COVID-19 conditions. Management of fatigue in the post-COVID-19 era is necessary and emerging. The use of medicinal plants may provide a strategy for the management of post-COVID-19 fatigue.

Methods: A literature search has been conducted by using PubMed, Embase and Cochrane library databases is performed for studies published up to March 2024. Keywords, such as "post-COVID-19 conditions, persistent COVID-19 symptoms, chronic COVID-19, long-term sequelae, fatigue, post-COVID-19 fatigue, herbal plants, medicinal herbs, traditional Chinese medicine, pharmacological mechanisms, pharmacological actions" are thoroughly searched in Englsih and Chinese. This study reviews the pathophysiology of post-COVID-19 fatigue and potential herbal plants for managing post-COVID-19 fatigue.

Results and conclusion: Representative medicinal plants that have been extensively investigated by previous studies are presented in the study. Three common mechanisms among the most extensively studied for post-COVID-19 fatigue, with each mechanism having medicinal plants as an example. The latest clinical studies concerning the management of post-COVID-19 fatigue using medicinal plants have also been summarized. The study shows the potential for improving post-COVID-19 fatigue by consuming medicinal plants.

1. Introduction

Since the emergence of SARS-CoV-2-infected pneumonia (COVID-19) in 2019, the global number of reported cases has continued to increase.[1] According to the report of the World Health Organization, as of September 4, 2023, in excess of 770 million confirmed cases of novel coronavirus and more than 6 million deaths have been reported worldwide. The clinical presentation of COVID-19 primarily impacts the respiratory system, but it is evident that COVID-19 is a systemic disease with various manifestations. The severity of the COVID-19 infection ranges from mild to severe symptoms.[2]

There has been a shift in SARS-CoV-2 variants of concern from Delta to Omicron during 2021, resulting in lower viral loads, reduced disease severity, and fewer hospitalizations.[3] This change has led to expectations of a gradual return to normalcy. However, COVID-19 has had lasting impacts on people's daily lives and overall health, characterized as "Post-COVID-19 manifestations", "long COVID" or "post-acute sequelae of SARS-CoV-2 infection", including a variety of symptoms that beyond the acute phase of the disease.[4] In accordance with the NICE guideline regarding Post-COVID-19 conditions,[5] post-COVID-19 conditions arise either during or subsequent to an SARS-CoV-2 infection and last for more than 4 weeks. The involvement of a wide variety of organs is observed in post-COVID-19 manifestations. Among the symptoms frequently disclosed by individuals, fatigue, arthralgia, dyspnea, headache, depression/anxiety, and insomnia are the most prevalent, with fatigue being reported by 64 % of individuals.[6] Despite efforts to explore the causes of fatigue, current knowledge remains restricted because fatigue is a complex issue with no single clear cause. In the realm of fatigue, diverse forms are recognized. For instance, central fatigue involves decreased voluntary muscle activation,[7] while peripheral fatigue pertains to a loss of maximal force due to factors affecting the neuromuscular junction.[8] Muscle fatigue manifests during intense physical exertion.[9] Chronic fatigue encompasses subtypes such as chronic fatigue syndrome (CFS), idiopathic chronic fatigue (ICF).[8] Some of these diverse forms of fatigue are believed to share some clinical phenotypic similarities with post-COVID fatigue; however, it is crucial to

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avoid conflating other types of fatigue with post-COVID-19 fatigue.[10,11]

Post-COVID-19 fatigue is diagnosed when fatigue persist for over four weeks after the acute infection.[12] Post-COVID-19 fatigue cannot be fully attributed to a simple disease or a singular pathogenetic mechanism. The pathophysiological mechanisms of post-COVID-19 fatigue are multifactorial.[13] The potential mechanisms include mitochondrial dysfunction, inflammation, abnormalities in the nervous system, oxidative stress damage, etc.[14–17] However, the term "Post-COVID-19 fatigue" is relatively recent, there is insufficient research regarding it.[15] Evidence concerning the pathophysiological mechanisms of post-COVID-19 fatigue is somewhat scattered. Our study aims to conduct a literature search to integrate promising mechanisms, providing insights into the pathophysiology of post-COVID-19 fatigue. Additionally, there are currently no guidelines available to offer insights into managing patients with post-COVID-19 fatigue.[18] Medicinal plants present a potential treatment approach. Therefore, another objective of our study is to explore the utilization of medicinal plants for managing post-COVID-19 fatigue, as well as understanding their roles and underlying mechanisms.

2. Methods

We conducted a narrative review of the literature in accordance with standardized guidelines for composing narrative reviews.[19] In this review, a literature search using PubMed, Embase and Cochrane library databases was performed for studies published until March 2024 by two authors. Keywords, such as "post-COVID-19 conditions, persistent COVID-19 symptoms, chronic COVID-19, long-term sequelae, fatigue, post-COVID-19 fatigue, herbal plants, medicinal herbs, traditional Chinese medicine, pharmacological mechanisms, pharmacological actions" are thoroughly searched in Englsih and Chinese. No specific criteria for study design were applied. The initial screening of articles was based on their titles and abstracts. Articles that still lacked clarity based on the title or abstract underwent further review during the full-text assessment. There are various causes and classifications of fatigue, but in our search, we specifically focus on the pathophysiology of post-COVID-19 fatigue. Articles that discuss the pathophysiology of fatigue due to other causes are not considered. When exploring the possible pharmacological mechanisms of medicinal plants against post-COVID-19 fatigue, we include and summarize articles related to medicinal plants with significant potential to improve post-COVID-19 fatigue. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. The different stages of the review process were illustrated using the PRISMA flow diagram (Fig. 1).

3. 3 Current insights into the pathophysiology of post-COVID-19 fatigue

Diseased-related fatigue associated with medical conditions can manifest as a symptom in a range of diseases, such as neurodegenerative disorders, cancer, rheumatological conditions, and heart diseases. Fatigue can present as a symptom without a clear underlying cause, as evidenced in chronic fatigue syndrome.[13] Post-COVID-19 fatigue differs from these forms of fatigue and has emerged in recent years, thus in comparison, research on the pathophysiology of post-COVID-19 fatigue is more limited. Azzolino et al. has categorized the pathological mechanisms of post-COVID-19 fatigue into mitochondrial dysfunction, inflammation, abnormalities in the autonomic nervous system, disturbances in sleep patterns, poor nutritional status, etc.[20] Combining findings from previous studies, the most commonly identified pathological mechanisms of post-COVID-19 fatigue include mitochondrial dysfunction, inflammation, oxidative damage, autonomic nervous system abnormalities, and central nervous system abnormalities [15,21,22] (Fig. 2).

3.1. Mitochondrial dysfunction

Viral infections in general are recognized to influence the mitochondrial function of the host cell. Mitochondria are essential organelles responsible for producing body's energy. Through mitochondrial respiration, adenosine triphosphate (ATP), a critical energy-carrier that fuels chemical reactions in the body is produced.[23] Mitochondria are also the primary generators of reactive oxygen species (ROS) within cells. Moreover, they play crucial roles in maintaining cell balance and influencing both innate and adaptive immunity.[24] When mitochondria experience dysfunction, their fundamental bioenergetic, antioxidant, and regulatory functions are disturbed, leading to reduced ATP production, disrupted cell death processes, and an increase in ROS production.[25] Numerous researchers have concentrated on exploring ways to correct mitochondrial dysfunction caused by SARS-CoV-2.[26,27] Recent study has versified that SARS-CoV-2 possesses the ability to influence metabolic pathways of host mitochondria, enabling them beneficial to the virus.[21] One study observed that COVID-19 patients experienced a metabolic shift towards glycolysis and exhibited elevated mitokines levels in peripheral blood mononuclear cells (PBMCs). These changes were attributed to malfunction of mitochondria and the resulting energy

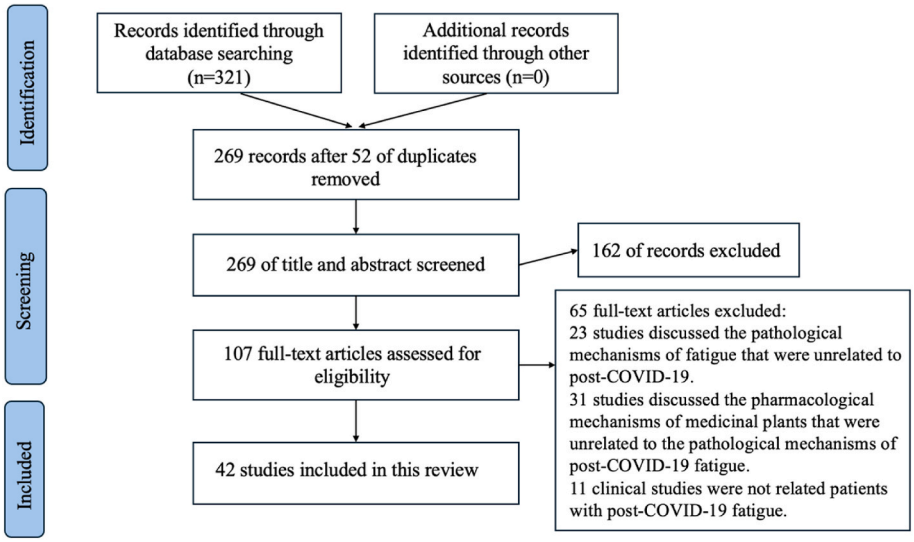

Fig. 1. Study selection flowchart based on PRISMA.

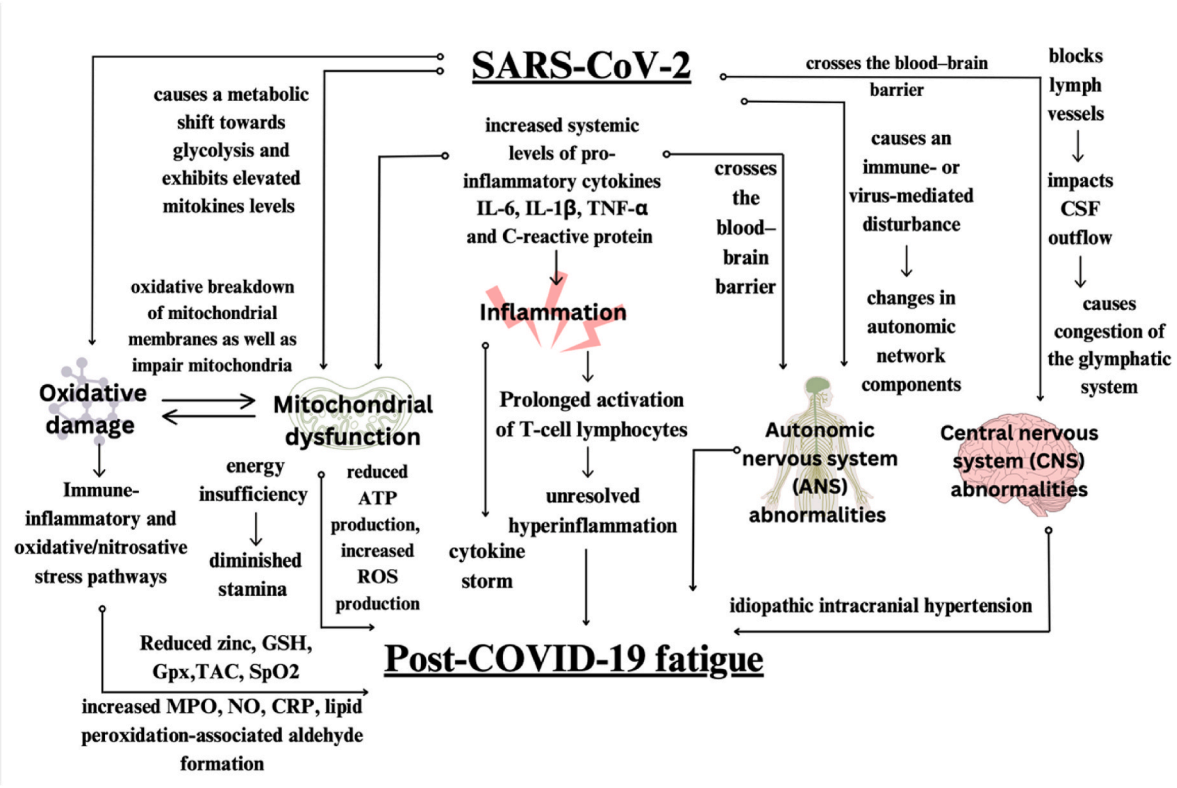

Fig. 2. Overview of pathophysiological mechanisms underlying post-COVID-19 fatigue
CSF: Cerebrospinal fluid; IL-6: Interleukin-6; IL-1β: Interleukin-1β; TNF-α: Tumor Necrosis Factor-α; ATP: Adenosine Triphosphate; ROS: Reactive Oxygen Species; GSH: Glutathione; Gpx: Glutathione Peroxidase; TAC: Total Antioxidant Capacity; SpO2: Peripheral Oxygen Saturation; MPO: Myeloperoxidase; NO: Nitric Oxide; CRP:C-Reactive Protein.

deficiency in individuals affected by COVID-19[28]. Another recent study has revealed that SARS-CoV-2 infection causes the downregulation of a specific member of the mitochondrial complex I. This finding implies that the virus may compromise host cells by targeting mitochondria.[28]

Mitochondrial dysfunction has been demonstrated to be related to post-COVID-19 fatigue.[29] In a study conducted by Hejbøl et al. within the muscle biopsies of sixteen patients experiencing post-COVID-19 fatigue, abnormal mitochondrial structures were observed. These mitochondrial changes in the muscle tissue contribute to fatigue by reducing the energy supply in the affected individuals.[30] Research findings indicated that COVID-19's influence can serve as a secondary factor, aggravating muscle weakness and reducing exercise tolerance, thus leading to fatigue in post-COVID-19 patients.[31] Moreover, maintaining a sedentary lifestyle has been demonstrated to be linked with alterations in mitochondrial morphology of skeletal muscle, including mitochondrial fission, changes in transcription and translation of mitochondrial proteins, alterations in the composition of membrane lipid, and increased emission of reactive oxygen species.[32] Therefore, individuals recovering from COVID-19 who have engaged in physical inactivity may also be susceptible to the development of post-COVID-19 fatigue.

3.2. Inflammation

COVID-19 is marked by an inappropriately excessive production of pro-inflammatory cytokines and dysregulated immune response, which can lead to cytokine storm, causing certain symptoms of SARS-COV-2 infection.[33] Post-COVID-19 fatigue is result from the virus's specific targeting of neurons, enabling evasion of the host's immune system. SARS-CoV-2 has the capability to enter a latent state with limited replication within neurons, subsequently activating inflammasomes—key receptors in the innate immune system.[17] This activation potentially leads to a cytokine storm, which refers to an uncontrolled release of a large number of cytokines, leading to further widespread inflammation.[34] Highlighted among the cytokines released by immune cells are IFN-α, IFN-γ, TNF-α, TGF-β, IL-1β, IL-2, IL-4, IL-6, IL-12, IL-18, and IL-33, with their altered concentrations linked to different clinical symptoms observed in post COVID-19, potentially leading to cytokine storm.[35–37] It has been documented that the presence of post-COVID-19 fatigue is marked by increased systemic levels of pro-inflammatory cytokines IL-6.[38] A vivo study conducted by Garcia-Oscos et al. have demonstrated that a hyper-inflammatory state induced by elevated IL-6 levels may lead to reduced Gamma–aminobutyric acid (GABA) receptor density, which underlie neuromotor and cognitive fatigue.[39] In a recent investigation conducted by Ortelli et al. a cohort of 12 individuals who had recuperated from COVID-19 and reported experiencing fatigue were examined.[38] All 12 individuals exhibited a hyper-inflammatory acute phase, as evidenced by significantly increased C-reactive protein (CRP) and IL-6 levels.[38] Such inflammatory mediators have the capability to cross the blood–brain barrier and can serve as stress signals, ultimately resulting in dysfunction of autonomic nervous system, which include fatigue. Moreover, persistent inflammatory reactions may cause mitochondrial dysfunction, thereby compounding muscle wasting and inducing fatigue.[20] Persistent low-grade inflammation and impaired function of mitochondria have been identified to cause fatigue. Given that mitochondria represent the primary site for energy production, energy insufficiency attributed to mitochondrial dysfunction and inflammatory processes can lead to diminished stamina and heightened fatigue.[40] Furthermore, lymphocytes, especially T cells as well as natural killer cells, are involved in the resolution of inflammation after infection.[41] Prolonged activation of T-cell lymphocytes may lead to the extension of unresolved hyperinflammation, consequently contributing to the development of inflammation-related persistent symptoms, such as fatigue.[42]

3.3. Oxidative damage

Oxidative damage within organs results in tissue damage and hinders the replenishment of energy, ultimately leading to fatigue. ROS are recognized as a contributor to the body's reaction to oxidative stress and consequent fatigue, as they may initiate the oxidative breakdown of mitochondrial membranes as well as impair mitochondria.[43,44] Malondialdehyde (MDA), derived from the peroxidation of lipids, serves as a significant marker of oxidative stress within the human body. Certain evidence suggested a correlation between elevated ROS and MDA levels with the onset of post-COVID-19 symptoms.[14] Immune-inflammatory and oxidative/nitrosative stress (IO&NS) pathways play a significant role in fatigue.[45] It involves the activation of the body's immune system and inflammatory response, coupled with heightened oxidative and nitrosative stress.[46] Research has indicated that fatigue following COVID-19 is a disorder associated with IO&NS mechanisms, suggesting their contribution to the neuroimmune and neuro-oxidative origins of post-COVID-19 fatigue.[14,47] These mechanisms are closely associated with indicators such as zinc, glutathione (GSH), glutathione peroxidase (Gpx) and total antioxidant capacity (TAC).[14,48] A study conducted by Al-Hakeim et al. found that post-COVID-19 fatigue patients displayed notable abnormalities, characterized by reduced levels of crucial antioxidants including zinc, Gpx, GSH, TAC, Peripheral Oxygen Saturation (SpO2), heightened body temperature, and increased CRP.[14] Al-Hakeim et al. suggested that post-COVID-19 fatigue is influenced by oxidative stress and antioxidant imbalances, particularly decreased Gpx and zinc levels, decreased SpO2, elevated myeloperoxidase (MPO) and nitric oxide (NO) production, and lipid peroxidation-associated aldehyde formation.[14]

3.4. Autonomic nervous system (ANS) abnormalities

The ANS is a component of the peripheral nervous system (PNS) tasked with regulating involuntary functions in the body. It controls and regulates various physiological processes such as heart rate, blood pressure, digestion, respiratory rate, pupillary reflex, and body temperature. The ANS has a pivotal role in preserving internal homeostasis and responding to changes in the external environment to ensure the body functions optimally.[49] A recent study by Baker et al. employing non-invasive behavioural and neurological tests on 39 post-COVID-19 fatigue individuals and 53 controls, revealed significant alterations in peripheral blood oxygen saturation, heart rate, body temperature, heart rate variability, and galvanic skin response in the post-COVID-19 fatigue group in contrast to the control group.[50] These findings suggest a connection between post-COVID-19 fatigue and dysregulation in the ANS. A study has proposed that the pathophysiology of fatigue following COVID-19 caused by ANS abnormalities may be associated with an immune- or virus-mediated disturbance to the ANS.[51] Routes such as hematogenous pathways and transneuronal pathways, can serve asentry points for viruses to access the nervous, affecting neurons and then potentially causing changes in autonomic network components, leading to ANS abnormalities.[52] The paraventricular nucleus (PVN), is a nucleus in the hypothalamus. It is responsible to control ANS functions that regulate the body's stress response.[53,54] The interaction between SARS-CoV-2 and ACE-2 receptors within the PVN circuitry can cause ANS abnormalities, which then causes daytime fluctuations in fatigue states.[55] Besides, There's a hypothesis that COVID-19 infection impacts the ANS by triggering a cytokine storm. This cytokine storm occurs because of the activation of the sympathetic nervous system, which subsequently triggers the release of pro-inflammatory cytokines.[51] The occurrence of post-COVID-19 fatigue is therefore linked to both inflammation and ANS abnormalities. Moreover, ANS abnormalities may be caused by autoimmune-mediated disruption to the ANS. This refers to a neuropathy resulted from an immune response targeting peripheral nerves may play a significant role in the pathogenesis of post-COVID-19 fatigue.[56] In this case, there could be a link between post-COVID-19 fatigue and autonomic disorders like postural orthostatic tachycardia syndrome (POTS), vasovagal syncope (VVS), and orthostatic hypotension (OH).[51]

3.5. Central nervous system (CNS) abnormalities

Cognitive symptoms following COVID-19, such as fatigue, might be attributed to the existence of the SARS-CoV-2 spike protein within the CNS.[57] The spike protein comprises the S1 subunit, which contains a receptor-binding domain (RBD) that binds to ACE2, and the S2 subunit, which contains a transmembrane anchor facilitating the fusion of viral and host cell membranes.[58] The free spike protein possesses the potential for various direct pathological effects on diverse cell types. These encompass the triggering of an immune response and the release of cytokines, causing inflammation that harms the nervous system.[57,59] Several studies indicate similarities in symptoms, biological abnormalities, and pathogenesis between ME/CFS and post-COVID-19 fatigue.[29,60] A study has shown that in ME/CFS patients, the immune activation in the CNS is marked by increased Chemokine (C–C motif) ligand 1 (CCL1) levels and an inverse relationship involving colony-stimulating factor 1(CSF1), colony-stimulating factor 2(CSF2), interleukin 1 receptor antagonist(IL-1RA) and interleukin 17F (IL-17F).[61] From this, it can be inferred that similar mechanisms may exist in individuals with post-COVID-19 fatigue. Furthermore, another study observed that intracortical GABAergic circuits in the primary motor cortex was significantly disrupted in individuals with post-COVID-19 fatigue.[38] Activated microglial and astrocytic cells in neuroinflammation may lead to the release of neural cytokines, potentially causing GABAergic dysfunction and contributing to diminished cortical excitability.[38,62]

Post-COVID-19 fatigue is not only associated with the presence of the SARS-CoV-2 spike protein within the CNS, but relevant research also indicate its connection to an abundance of cerebrospinal fluid (CSF) in the glymphatic system.[63] CNS is linked to the glymphatic system, a network of perivascular channels spanning the entire brain that facilitate CSF recirculation.[64] SARS-CoV-2 often leads to potential damage to olfactory sensory neurons and support cells.[65] The cribriform plate, crucial for CSF drainage, is in close proximity to olfactory nerve fibers. The virus may block lymph vessels, impacting CSF outflow, and additionally contribute to the congestion of the glymphatic system, leading to subsequent toxic build-up within the CNS.[63] Post-COVID-19 fatigue is caused by idiopathic intracranial hypertension, caused by an abundance of CSF within the glymphatic system.[63]

4. Promising medicinal plants for addressing post-COVID-19 fatigue

In China, medicinal plants has a prominent role in the management of fatigue caused by various underlying factors. Although prior research has indicated the efficacy of medicinal plants in managing fatigue, there remains an insufficiency of supporting evidence regarding its effectiveness in alleviating fatigue among individuals recovering from COVID-19. Owing to the minimal toxicity and widespread accessibility of medicinal plants, the exploration of single herbs and plant-based formulas have a prospective avenue in managing post-COVID-19 fatigue. In this section, representative medicinal plants in the form of both single herbs and formulas that have been frequently utilized and demonstrated effective outcomes in clinical studies are summarized. These clinically proven effective herbal medicines are further reviewed for their potential pharmacological mechanisms. Some herbal medicines that have been demonstrated *in vitro* or in vivo to be potentially associated with post-COVID-19 fatigue are also discussed. Table 1 provides a summary of medicinal plants that have been clinically proven effective in addressing post-COVID-19 fatigue.

Table 1
Overview of medicinal plants clinically effective in managing post-COVID-19 fatigue.

Medicinal plants in clinical studies	Study type	Pharmacological actions related to post-COVID-19 fatigue	Reference
Bu-Zhong-Yi-Qi decoction	A retrospective study and a case study	1, Anti-inflammation: targets various proteins, including IL-1β, IL6, CHRM1, OPRM1, MAPK3, VEGFA, COX-2, iNOS, TNF-α, etc., with a particular emphasis on inhibiting IL-6, IL-1β, and TNF-α in managing post-COVID-19 fatigue. 2, Antioxidant activity: boosts SOD activity and reduces MDA and ROS levels.	[62] [66–69] [70]
Dang-Gui-Shao-Yao San	A retrospective study	1, Anti-inflammation: decreases levels of inflammatory mediators, including IL-2, IL-1β, TGF-β, RAGE, TLR2, etc., with a particular emphasis on inhibiting IL-2, IL-1β, and TGF-β in managing post-COVID-19 fatigue. 2, Antioxidant activity: exhibits a free radical scavenging activity, inhibits lipid peroxide formation, and enhances SOD activity.	[62] [71–73] [74]
Ling-Gui-Zhu-Gan decoction	A retrospective study	Antioxidant activity: possesses antioxidant properties, reduces the generation of MDA and ROS, enhances SOD activity, and modulates the balance between oxidants and antioxidants.	[62,75]
Qingjin Yiqi granules	An RCT	Antioxidant activity: boosts SOD activity and reduces MDA and ROS levels, increases Akt and Nrf2 mRNA expression within skeletal muscle	[63] [76,74]
extracts of Eleutherococcus, Rhodiola rosea, and Schisandra	An RCT	Restoration of impaired mitochondrial function: Rhodiola rosea promotes cell apoptosis, arrests the cell cycle in the S phase, and regulates the p53 signaling pathway by reducing Bcl-2 expression, which suggests its potential for alleviating post-COVID-19 fatigue.	[64] [77,78]
HRG80 red ginseng	A prospective study	Restoration of impaired mitochondrial function: decreases lactic acid and lactate dehydrogenase levels, improves skeletal muscle mitochondrial density and morphology, enhances Na^+-K^+-ATPase and cytochrome *c* oxidase activities, activates the AMPK/PGC-1α pathway. These effects lead to restored ATP levels, complex I functionality, mitochondrial membrane potential, and biogenesis, thereby contributing to its anti-fatigue properties.	[79,80]
Medicinal plant-based essential oil blend comprising Thyme, Orange peel, Clove bud, and Frankincense.	An RCT	The exact mechanism of action related to post-COVID-19 fatigue has not been investigated yet.	/

4.1. Recent clinical studies on the use of medicinal plants in the management of post-COVID-19 fatigue

In this section, six recent studies including one retrospective study, three randomized clinical trial, one prospective study, one case study were summarized to explore the efficacy of medicinal plants in addressing post-COVID-19 fatigue. Tokumasu et al. conducted a retrospective study involving 102 samples to reveal the efficacy of kampo medicine in managing post-COVID-19 fatigue.[79] The study revealed that 71.6 % of patients were prescribed Hochuekkito (Chinese name: Bu-Zhong-Yi-Qi decoction) for managing general fatigue, which exhibited the highest frequency of use. The second and third most frequently employed herbal formulas were Tokishakuyakusan (Chinese name: Dang-Gui-Shao-Yao San) and Ryokeijutsukanto (Chinese name: Ling-Gui-Zhu-Gan decoction), respectively. This retrospective study demonstrates the use of medicinal plants in the form of herb-based formulas for post-COVID-19 fatigue management clinically.

Apart from the retrospective study, three RCTs have also demonstrated the use of medicinal plants in two different forms for the managing post-COVID-19 fatigue. A RCT conducted by Pang et al. found that Qingjin Yiqi granules (QJYQ) could improve post-COVID-19 fatigue by improving the borg scores comparing to the control group.[66] In the study, 194 out of 388 patients were involved in the QJYQ treatment group for a duration of 14 days. At the start, both groups had similar Borg scale scores. After 14 days, the QJYQ group's score was 7.89 ± 0.09, and the control group's was 8.37 ± 0.10. There was a significant difference in Borg scores between the two groups ($p = 0.026$), favoring the QJYQ group.[66] Significant improvement in fatigue has been shown. Another RCT conducted by Karosanisze et al. investigated the effect of an herbal combination containing Eleutherococcus, Rhodiola rosea extract, and Schisandra extracts on various post-COVID-19 symptoms. The study involved a total of 100 participants, with 50 individuals assigned to the intervention group and 50 individuals to the control group. The results showed that this herbal combination decreased the duration of post-COVID-19 fatigue, and there was a statistically significant difference between the two groups.[67] Besides, a RCT conducted by Hawkins et al. evaluated the viability of using an essential oil blend via inhalation as treatment for female COVID-19 survivors who are experiencing post-fatigue for over 5 months.[68] The essential oil blend was derived from the following botanical sources: Thymus vulgaris L. (Thyme), Citrus × aurantium L. (Orange peel), Syzygium aromaticum (L.) Merr. & L.M.Perry (Clove bud), and Boswellia sacra Flück. (Frankincense). The results showed that participants who breathed in the essential oil blend for 14 days notably reduced fatigue scores on the Multidimensional Fatigue Symptom Inventory (MFSI).[68]

In an open-label prospective study conducted by Teitelbaum et al. a total of 188 participants diagnosed with chronic fatigue syndrome/fibromyalgia Syndrome (CFS/FMS), diagnosed by severe fatigue including post-COVID-19 fatigue, underwent a one-month treatment trial involving the consumption of HRG80 red ginseng root powder.[69] HRG80 is an herbal formulation derived from Panax ginseng, featuring a greater concentration of bioavailable ginsenosides compared to conventional ginseng. Of the 188 participants, 60.1 % reported feeling recovered, with 13.3 % describing their condition as much better. This investigation indicated that HRG80 Red Ginseng could significantly improve post-COVID-19 fatigue.[69] Apart from this prospective study, a case study reported by Oka explored the recovery of a 55-year-old female who experienced chronic fatigue syndrome after turning negative from severe COVID-19[72]. The patient's severe fatigue lasted over six months. In addition to dietary changes, adaptive coping strategies, gradual exercise, and pharmacotherapy using amitriptyline, the patient also incorporated hochuekkito (Chinese name: Bu-zhong-yi-qi decoction) for 21 weeks. Following this approach, the patient improved her fatigue levels significantly by improving subjective level of fatigue and Brief Fatigue Inventory (BFI) score. The patient's fatigue, as measured on the numerical rating scale, reduced from 5 to 0, and their BFI score dropped from 7.0 to 0.5[72]. To conclude, it can be observed from the limited clinical studies that the potential for the use of medicinal plants in the field of post-COVID-19 is promising. However, more rigorous clinical trials are required to validate the effectiveness of medicinal plants and to gain deeper insights into their safety profiles.

4.2. Possible mechanisms underlying the action of medicinal plants

The potential mechanisms through which medicinal plants alleviate post-COVID-19 fatigue include anti-inflammation, antioxidant activity, restoration of impaired mitochondrial function, and correction of autonomic nervous system abnormalities, which primarily target four of the previously summarized pathological mechanisms. While there is a significant amount of research on the use of medicinal plants to alleviate fatigue, insufficient evidence exists regarding the mechanisms of medicinal plant treatments for fatigue specifically caused by COVID-19. Therefore, we aim to evaluate the mechanisms through which medicinal plants alleviate various forms of fatigue in order to gain valuable insights into how they might specifically treat post-COVID-19 fatigue.

4.2.1. Anti-inflammation

Physical fatigue is primarily attributed to inflammatory factors. Medicinal plants can relieve fatigue by anti-inflammatory effects. A network pharmacology study conducted by Zhang et al. revealed that the main active components of Bu-Zhong-Yi-Qi decoction impact signaling pathways associated with inflammation by targeting various proteins, including IL-1β, IL6, CHRM1, OPRM1, MAPK3, and VEGFA.[81] Post-COVID-19 fatigue is suggested to result from an inflammatory response involving biomarkers such as IL6 and IL-1β. In addition to Zhang 's study, other studies also indicate that Bu-Zhong-Yi-Qi decoction can inhibit the inflammatory response, thereby improving fatigue.[82,71] A medicinal plant named Radix Astragali is renowned in oriental medicine for enhancing immune responses. It serves as the king drug in Bu-Zhong-Yi-Qi decoction. A study highlighted its anti-inflammatory properties in zymosan air-pouch mice by lowering IL-1β, COX-2, iNOS, TNF-α, and IL-6 expression and NO generation.[72] In another investigation conducted by Xie et al. a comprehensive exploration of Astragali Radix against fatigue was undertaken using network pharmacology.[73] This analysis identified 16 active AR compounds and pinpointed 7 core targets. Core compounds in Astragali Radix, such as quercetin, kaempferol, formononetin, and isorhamnetin, combat fatigue partly through their anti-inflammatory effects. Formononetin scavenges DPPH radicals and promotes IL-4 release to ease fatigue. Isorhamnetin reduces TNF-α and IL-12 production and boosts heme oxygenase 1, exerting anti-inflammatory effects.[73] Quercetin has the capability to decrease IL-6 and STAT3 plasma concentrations, thereby inhibiting the inflammatory response linked to fatigue.[83] From these, it can be seen that Radix Astragali and Bu-Zhong-Yi-Qi decoction have great potential to alleviate post-COVID-19 fatigue by targeting anti-inflammatory mechanisms, such as the reduction of biomarkers like IL-6, IL-1β, and TNF-α. These actions can profoundly impact inflammation and immune responses, potentially offering beneficial effects on post-COVID-19 fatigue.

Dang-Gui-Shao-Yao San has been reported to modulate the inflammatory process by decreasing levels of inflammatory mediators, including IL-2, IL-1β, TGF-β, RAGE, and TLR2.[84] Among these, cytokines IL-2, IL-1β, and TGF-β have been demonstrated to be linked to post--COVID-19[80], whereas TLR2 is linked to chronic fatigue resulting from other medical illnesses and conditions.[85] Macamides are the predominant and distinctive constituents of Lepidium meyenii (Maca).[86] Among bioactive constituents of macamides, N-benzyl-(9Z, 12Z)-octadecadienamide emerges as one of the most biologically potent.[70] Zhu et al. demonstrated that N-benzyl-(9Z, 12Z)-octadecadienamide possesses anti-inflammatory characteristics.[87] In their research, N-benzyl-(9Z, 12Z)-octadecadienamide was shown to have anti-fatigue property by using a rat model subjected to endurance swimming-induced stress was assessed. The results demonstrated that the treatment with N-benzyl-(9Z, 12Z)-octadecadienamide in mice caused significant reductions in inflammatory factors including IL-1β and IL-6, which are crucial factors implicated in post-COVID-19 fatigue. Histological analysis further demonstrated that N-benzyl-(9Z, 12Z)-octadecadienamide improved fatigue by suppressing the Interleukin (IL)-1β production.[87] Thus, its potential in addressing post-COVID fatigue becomes evident.

4.2.2. Antioxidant activity

Oxidative damage leads to tissue damage and disrupts the restoration of energy, ultimately resulting in fatigue. ROS are acknowledged significant contributors to oxidative damage. Enzymes central to the oxidative stress response, such as glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase, play a role in breaking down ROS. This process helps mitigate the harm caused by oxidative stress reactions in the body.[76] Besides, cells employ another significant mechanism to protect themselves from oxidative stress by initiating the Nrf2-ARE signaling pathway. This pathway regulates the activation of genes responsible for eliminating ROS from the system.[74] Ginseng Radix Rhizoma, another essential ingredient in the Bu-Zhong-Yi-Qi decoction, contains ginsenoside Rb1 as a key compound. A study revealed that Ginsenoside Rb1 could increase physical activity and feeding frequency in postoperative fatigue syndrome (POFS) rats, while boosting SOD activity and reducing MDA and ROS levels.[75] Research has shown a correlation between elevated levels of ROS and MDA with post-COVID-19 symptoms such as fatigue.[14] This suggests that Ginsenoside Rb1 may be associated with alleviating post-COVID-19 fatigue. Ginsenoside Rb1 also increased Akt and Nrf2 mRNA expression within skeletal muscle, suggesting that Ginsenoside Rb1's impact on POFS might involve activating the PI3K/Akt pathway, leading to Nrf2 nuclear translocation.[75,88] Ginsenoside Rb1, along with ginsenoside Rb2 and glycyrrhizic acid, forms the main components of QJYQ.[89] The presence of Ginsenoside Rb1 suggests that QJYQ also contributes significantly to antioxidant activity, potentially offering anti-post-COVID-19 fatigue effects. Dang-Gui-Shao-Yao San has been documented to exhibit a free radical scavenging activity, inhibit lipid peroxide formation, and enhance SOD activity.[90] Similarly, Ling-Gui-Zhu-Gan decoction has been reported to possess antioxidant properties, reducing the generation of MDA and ROS, while enhancing SOD activity.[91] Wang et al.observed that Ling-Gui-Zhu-Gan decoction 's protective effect against cell injury may be attributed, at least in part, to its modulation of the balance between oxidants and antioxidants.[91] These findings suggest that Dang-Gui-Shao-Yao San and Ling-Gui-Zhu-Gan decoction hold potential for improving post-COVID-19 symptoms.

Another medicinal plant named Huangjing Sanqi Extract consisting

of Polygonati Rhizoma, and Notoginseng Radix et Polygonati Rhizoma is a well-known herb against fatigue. Yang et al. created fatigue mouse models, and oxidative status related to fatigue was examined. Huangjing Sanqi Extract was shown to significantly decrease MDA levels while elevate SOD and Gpx levels.[92] Wang et al. conducted a Network Pharmacology to evaluate the Potential Anti-fatigue Mechanism of Polygonati Rhizoma.[93] The results showed that the interaction between E2F1 and the PI3K-AKT pathway is of significant importance in mediating the anti-fatigue effects of Polygonati Rhizoma.[93] The interaction between E2F1 and the PI3K-AKT pathway has been found to modulate protection against oxidative stress through the upregulation of gene expressions which are associated with Nrf2 and the antioxidant response mechanisms.[80] These findings collectively imply that Huangjing Sanqi Extract has the potential to alleviate post-COVID-19 fatigue. Another study led by Lee et al. investigated the potential anti-fatigue properties of extracts from Radix Astragali and Radix Salviae Miltiorrhizae in an animal model.[77] Their findings revealed a significant reduction in the levels of ROS, NO, and MDA in the groups treated with extracts. Furthermore, administration of these extracts led to a substantial improvement in antioxidant levels, including TAC, GSH, Glutathione S-Transferase (GST), SOD, and catalase, compared to the control group.[77] Radix Astragali, with its primary constituents Astragalus polysaccharides and flavonoids, demonstrates the capability to eliminate superoxide, hydrogen peroxide, superoxide anion, and DPPH free radicals, contributing to the improvement of fatigue.[82] This improvement is likely attributed to the enhanced activity of antioxidant entities, specifically GPx and SOD.[82] Given the substantiated association of ROS, NO, MDA, GPx and TAC with COVID-19 fatigue, it suggests the potential of the extracts from Radix Astragali and Radix Salviae Miltiorrhizae to alleviate post-COVID-19 fatigue.

4.2.3. Restoration of impaired mitochondrial function

Mitochondria, serving as a crucial energy generator in the body, influence various cellular processes via a sequence of electron transfer activities. Fatigue can be attributed, in part, to mitochondrial dysfunction, and medicinal plants have the potential to restore mitochondrial function, consequently alleviating fatigue. In a network pharmacology study, 36 potential compounds and 244 targets were identified for Shengqi Fuzheng injection.[77] Ten key targets related to CRF were shared. Enrichment analysis suggested that Shengqi Fuzheng injection could enhance muscle cell mitochondrial function through AMPK activation and PI3K/Akt inhibition. This also affected the expression of Manganese Superoxide Dismutase (MnSOD), B-cell lymphoma 2 (Bcl-2), and Bcl-2-associated X protein (Bax), impacting mitochondrial metabolism and apoptosis regulation,[77] suggests potential for improving post-COVID-19 fatigue. Panax Ginseng is an essential component of Shenqi Fuzheng Injection. In an in vivo study conducted by Li et al. it was demonstrated that Panax Ginseng provided protective effects on mitochondria through the inhibition of mitochondrial swelling and enhancement of energy metabolism.[78] Moreover, Panax Ginseng served as a preventive antioxidant by boosting the activities of creatine kinase. Consequently, Panax Ginseng displayed pharmaceutical attributes linked to anti-hypoxic antioxidation and energy generation.[94] In another study, Zhang et al. conducted a chronic fatigue syndrome mouse model.[95] These fatigue mice were administered red ginseng extracts orally. The treatment resulted in decreased levels of lactic acid, lactate dehydrogenase, and urea, along with improved skeletal muscle mitochondrial density and morphology. Furthermore, red ginseng extracts boosted Na + -K + -ATPase and cytochrome *c* oxidase activities while activating the AMPK/PGC-1α cascade pathway.[95] These combined effects restored ATP levels, complex I functionality, mitochondrial membrane potential, and mitochondrial biogenesis, contributing to the anti-fatigue properties of red ginseng.[95] Additionally, a medicinal plant named Rhodiola rosea is frequently investigated for its ability to improve mitochondrial function.[96] A study conducted by Zhang et al. showed that Rhodiola rosea could promote cell apoptosis, arrest the cell cycle in the S phase, and regulate the p53 signaling pathway by reducing Bcl-2 expression, which suggested its potential for alleviating post-COVID-19 fatigue.[97] Shengqi Fuzheng injection, Panax Ginseng, red ginseng, and Rhodiola rosea show potential in restoring impaired mitochondrial function, with mechanisms resembling those involved in combating post-COVID-19 fatigue.

Another medicinal plant named Maca (Lepidium meyenii Maca) has gained popularity as a plant-based food with diverse pharmacological properties. In a study led by Zhu et al. the effects of Maca aqueous extract on muscle fatigue induced by exercise were examined both in vivo and *in vitro*.[98] The results suggested that Maca effectively reduces the buildup of metabolites, including blood urea nitrogen, blood lactic acid, and ROS levels. Also, Maca mitigates metabolic stress by elevating NAD+/NADH levels. Through these, Maca may enhance energy metabolism within skeletal muscle, potentially promoting the generation and function of mitochondria.[98] Consequently, this may contribute to improving post-COVID-19 fatigue.

4.3. Limitation

The latest clinical studies on TCM have shed light on the efficacy of certain herbs or herbal formulas, such as Bu-Zhong-Yi-Qi, Dang-Gui-Shao-Yao San, and Qingjin Yiqi granules, in alleviating post-COVID-19 fatigue. However, overall, there are few clinical studies directly related to post-COVID-19 fatigue with medicinal plants. research on the mechanisms of these TCM herbs or herbal formulas in addressing post-COVID-19 fatigue remains insufficient. Additionally, while some TCM herbs or formulas show potential mechanisms for addressing post-COVID-19 fatigue, there is a lack of direct clinical studies to confirm their effectiveness.

The latest clinical studies on Traditional Chinese Medicine (TCM) have shed light on the efficacy of certain herbs or herbal formulas, such as Bu-Zhong-Yi-Qi, Dang-Gui-Shao-Yao San, and Qingjin Yiqi granules, in alleviating post-COVID-19 fatigue. However, there is a scarcity of clinical studies directly investigating the use of medicinal plants for post-COVID-19 fatigue. Most studies focus on general fatigue or fatigue caused by other reasons. Additionally, research on the mechanisms of these TCM herbs or herbal formulas, which have been clinically proven effective, in addressing post-COVID-19 fatigue remains insufficient. Furthermore, while some TCM herbs or formulas show potential mechanisms for addressing post-COVID-19 fatigue, there is a lack of direct clinical studies to confirm their effectiveness.

5. Conclusions and future perspectives

In conclusion, the emergence of post-COVID-19 fatigue as a long-lasting symptom of the disease has posed challenges to individuals. While the understanding of the pathophysiology of post-COVID-19 fatigue is still evolving, it is increasingly evident that multiple factors, such as inflammation, mitochondrial dysfunction, oxidative damage, autonomic nervous system abnormalities, and central nervous system abnormalities play a primary role. Clinical studies suggest that certain medicinal plants have the potential to effectively alleviate post-COVID-19 fatigue. These plants have been found to possess mechanisms of action related to fatigue, such as anti-inflammatory properties, antioxidant activity, and the restoration of impaired mitochondrial function, which may be relevant to post-COVID-19 fatigue. In the future, more research should be conducted on the clinical efficacy of medicinal plants, and efforts should also focus on identifying the chemical compounds within these plants that have therapeutic effects on post-COVID-19 fatigue.

Author contributions

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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