Review Articles

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Plant adaptive agents: promising therapeutic molecules in the treatment of post-viral fatigue

Yiqi Yan[1,2,3], Rui Han[1,2,3], Yaolei Ma[1,2,3], Han Zhang,[1,2,3], Patrick Kwabena Oduro[4,*], Xiaoying Wang[5,*], Wei Lei[1,2,3,*]

Abstract

In recent years, the spread of the coronavirus disease 2019 (COVID-19) in China has been effectively controlled by implementing national prevention and control measures. However, a large number of recovered patients are plagued by fatigue, whether acute or chronic, and other fatigue-related syndromes that severely affect their quality of life. Post-viral fatigue syndrome (PVFS) is a widespread chronic neurological disease with no definite etiological factor(s), definitive diagnostic test, or approved pharmacological treatment, therapy, or cure. In this study, we performed a bibliometric analysis and the results suggested that neuroinflammation played a role in the development of PVFS. Therefore, we briefly analyzed the mechanisms underlying the development of neuroinflammation in patients with COVID-19. To identify effective drugs to alleviate PVSF, we summarized four traditional herbal phytoadaptations and discussed their molecular mechanisms in improving neurological fatigue. Our study showed that ginseng, Acanthopanax, Rhodiola, and Schisandra played beneficial roles in alleviating PVSF.

Keywords: Adaption, COVID-19, Fatigue, Long COVID, Pody-viral fatigue syndrome, Traditional Chinese medicine

Graphical abstract: http://links.lww.com/AHM/A45.

Introduction

Although the global coronavirus disease 2019 (COVID-19) pandemic has been controlled, it will continue to persist and influence the lives of people around the world. Pharmacological treatments effectively relieve lethal respiratory symptoms and promote physical recovery. However, post-recovery fatigue often becomes perplexing and results in mental sluggishness, depression, and even suicide[1–2].

To date, several studies reported that almost 55% of hospitalized COVID-19 patients showed at least three debilitating symptoms within 2 months of recovery including fatigue, muscle weakness, and diffuse muscle pain[3–4]. Previous studies have shown that a variety of viral infectious diseases contribute to increased fatigue in patients, including influenza, glandular fever (infectious mononucleosis), human herpesvirus-6 infection, certain enteroviruses, rubella, and severe acute respiratory [5]. The constant presence of fatigue and debilitating symptoms after recovery from viral infection not only severely reduces the quality of life, but also facilitates the occurrence of severe diseases, such as cancers and cerebrovascular diseases. Therefore, persistent fatigue after viral infection is regarded medically as post-viral fatigue syndrome (PVFS) and has attracted our attention.

Although PVFS is prevalent, little is known about the mechanisms underlying its occurrence. Some researchers consider that PVFS may have similar causes and pathogenesis as chronic fatigue syndrome (CFS) and myalgic encephalomyelitis[6]. However, this was not the case here. PVFS is inevitably generated by specific events-conditions that occur after viral infections, including an excessive immune response, neurological dysfunction, neuro-endocrine system alterations, imbalance in the gut microbiota, and an autoimmune response[7]. Due to its complicated and indefinite pathogenesis, effective and economical therapeutic strategies against PVFS in recovered COVID-19 patients are deficient and require urgent development[8].

Traditional Chinese medicine (TCM) has played an important role in fighting epidemics, with outstanding contributions to antiviral and symptom improvement[9]. TCM herbs are also expected to play an effective role in relieving post-viral fatigue. Some traditional herbs are often used to relieve fatigue, such as ginseng herbs and extracts, rhodiola, and rhodiola extracts, which

[1] Laboratory of Pharmacology of Traditional Chinese Medicine Formulae Co-Constructed by the Province-Ministry, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China; [2] State Key Laboratory of Component Traditional Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China; [3] Institute of Traditional Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China; [4] Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, New York, NY, USA.

*Corresponding author. Wei Lei, Laboratory of Pharmacology of Traditional Chinese Medicine Formulae Co-Constructed by the Province-Ministry, School of Integrative Medicine, State Key Laboratory of Component Traditional Chinese Medicine, Institute of Traditional Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China, E-mail: l_wei8910@163.com; Xiaoying Wang, School of Chinese Materia Medica Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China, E-mail: wxy@tjutcm.edu.cn; Patrick Kwabena Oduro, Jacobs School of Medicine and Biomedical Sciences, University at Buffalo, State University of New York, NY 14203, USA, E-mail: pkoduro@buffalo.edu.

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can effectively relieve fatigue caused by external stress and maintain homeostasis of the body[10]. These herbs and herbal extracts, which can relieve fatigue and maintain homeostasis, are called phytoadaptogens. In this study, we determined the potential mechanisms of PVSF using the Web of Science Search Platform (https://www.webofscience.com/wos/). The PubMed database (https://pubmed.ncbi.nlm.nih.gov/) and VOSviewer1.6.18 software summarize several major phytoadaptations in TCM and discuss the active mechanisms of these phytoadaptations to provide a reference direction for the development of effective fatigue-relieving drugs.

Adaptogen

The concept of adaptogens was first proposed by Soviet researchers in the study by Schisandra, who believed that substances that can be called adaptogens must have the following characteristics: 1. Adaptogens must be non-specific and have a broad-spectrum function to counteract damage caused by stressors; 2. Adaptogens must have a homeostatic effect, preventing disorders caused by external stressors; 3. Adaptogen ingredients must be harmless to the body[11]. Adaptogens are a class of medicinal plants that can enhance non-specific resistance of the body and maintain homeostasis of the human body under stressful conditions, thus achieving resistance to external stress[12]. Adaptogens act in a “multi-target-multi-pathway” manner and exert effects mainly involving the neuro-immuno-endocrine system and hypothalamic-pituitary-adrenal axis (HPA axis)[13].

In 1969, American scientist Brekhman expanded the definition of adaptogens to the following statements: 1) Adaptogens should appropriately reduce external stress-induced damage; 2) After a single dose or multiple doses, adaptogens must exhibit a stimulatory response and effectively improve the depressed state of the body; 3) The stimulatory effect of adaptogens must be distinct from that of traditional central nervous drugs and anabolic substances; 4) Adaptogens cannot be toxic or harmful substances and do not damage the normal functions of the body[14].

The above definitions of adaptogens are based on empirical knowledge of medicinal plants that have been used for centuries in traditional medicinal systems, and the assumption that some plants may meet these criteria. However, studies and past experience with a large number of botanical preparations have shown that only a few plants satisfy these requirements. The inductive approach to classify adaptogens was newly defined, and the adaptogens were divided into three main categories: First, primary adaptogens are in line with the traditional definition and are supported by specific scientific criteria that are able to act as non-specific modulators to enhance the body’s resistance to various external stresses, act directly on the HPA axis, protect and restore the body’s homeostasis, and are capable of carrying out synthetic and metabolic functions. Second, secondary adaptogens meet most of the standard definitions of adaptogens, but lack sufficient scientific validation. Although secondary adaptogens can act on the endocrine and immune systems, they do not act directly on the HPA axis to maintain homeostasis. Third, adaptogenic concomitants that do not meet the traditional definition of adaptogens can stimulate the HPA axis activity and activate anabolic effects to achieve the same effect as adaptogens[15]. As the concept of adaptogen has evolved over the past half century, according to the U.S. Food and Drug Administration (FDA) on the definition of adaptogens, it has been continuously supplemented and refined. The concept of adaptogen as a new concept has been widely recognized and used as a functional term in the last decade. At present, the following plants have been identified as having adaptogenic effects: Radix Ginseng, Acanthopanax senticosus, Rhodiola Rosea, and Schisandra chinensis[16–20].

Radix Ginseng, Acanthopanax senticosus, Rhodiola Rosea, Schisandra chinensis are herbs easily available in China with large production and abundant origin, and they have been studied intensively in the previous period. China is rich in herbal resources, and there are some other drugs that can be used as plant adaptation elements; however, in this study, we mainly explored the effect of these four drugs on fatigue after viral infection. Therefore, these drugs were selected for this review.

Neural fatigue mechanism after virus infection

Fatigue is a complex physiological manifestation often associated with alterations in several human biological activities. The lack of clarity of specific mechanisms is the main reason that prevents researchers from completely overcoming the fatigue syndrome. Based on an extensive search, we found 251 relevant studies on post-viral fatigue as a keyword using the Web of Science platform and analyzed the literature related to post-viral fatigue to summarize the potential causes of fatigue after viral infection. A viral neurological predisposition was found for all symptoms of COVID-19 infection reported in the literature, including cough[21], dyspnea[22], and fatigue[23]. A well-recognized symptom of long-term COVID is “Brain fog,” which is characterized by fatigue and the lack of ability to concentrate, and may severely affect memory and cognition[24]. In a study that included 214 hospitalized patients with COVID-19, 78 patients had neurological lesions[25]. Similar findings have been reported in other studies on viral infections. Combined with an analysis of the literature, it is suggested that viral infection of the nervous system may be the main cause of fatigue after viral infection (Figure 1).

Previous studies have reported that neocoronary pneumonia causes intense neuroinflammatory invasion, similar to that caused by the SARS virus, leading to intense fatigue symptoms after infection[26]. In prognostic studies of HIV infection, researchers have also found that the severe neurological damage that accompanies HIV infection is strongly associated with extreme fatigue and a lack of ability to live a normal life in patients with the later stages of HIV infection[27]. The same neuroinflammatory infections have been found in other viral infectious diseases; for example, altered cognitive levels and depression in patients with chronic hepatitis C were significantly associated with neurological infestation in patients[28], while infections in humans, including human herpes zoster virus, influenza virus, and herpes simplex virus, all have significant effects on the nervous system[29–31].

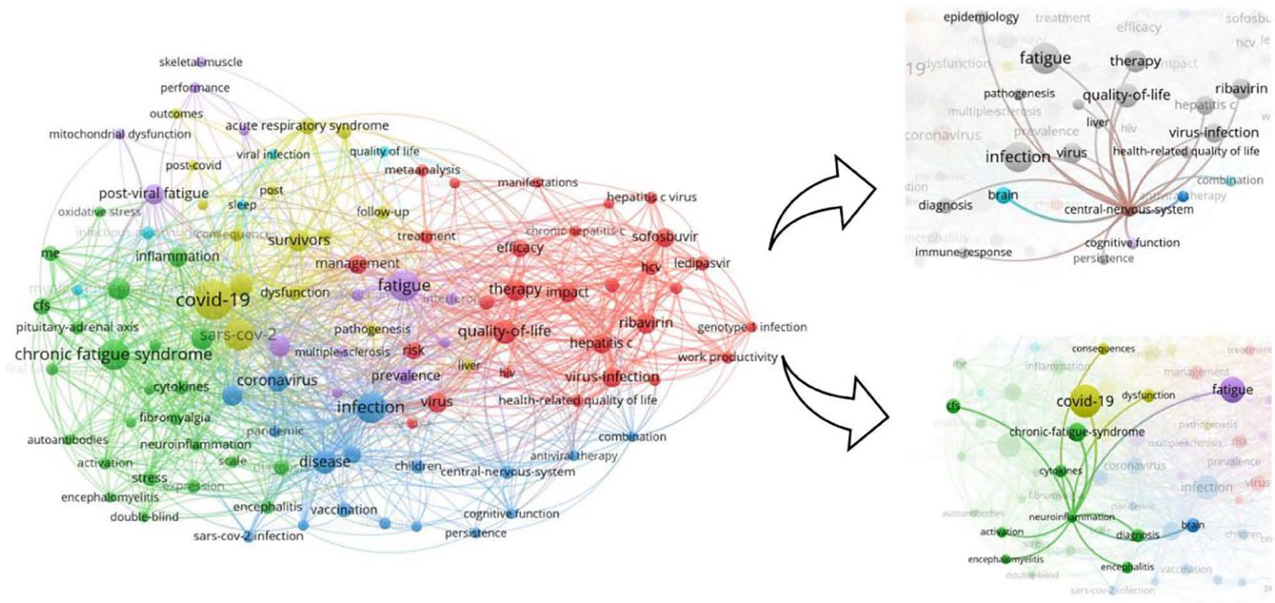

Figure 1. Using bibliometrics to reflect post-viral fatigue.

COVID-19 patients are in a hyper-inflammatory state with high levels of interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), β interleukin 1 (IL-1β), and other inflammatory cytokines in the acute phase of COVID-19. These inflammatory cytokines invade the central and peripheral nervous systems and result in headaches, myelitis, neurocognitive disorders, and fatigue[32]. Previous research indicated that IL-6 and IL-1β could disrupt GTPases located in endothelial cells, thus destroying the blood–brain barrier (BBB) and intruding into the central nervous system (CNS)[33]. Therefore, increased levels of inflammatory cytokines (CXCL5, CCL11, IL-6, and IL-1β) have been observed in the cerebrospinal fluid (CSF) after mild SARS-CoV-2 infection in mice[34]. In COVID-19 patients, although no SARS-CoV-2 RNA was detected in the CSF, inflammatory cytokines were elevated in the CSF[35]. After crossing the BBB and invading the CNS, inflammatory cytokines are destroyed. IL-6 can decrease the density of cortical GABAergic receptors and damage the balance between synaptic inhibition and excitation[36]. IL-1β attacks neurons, astrocytes, and neural stem cells, leading to glutamate excitotoxicity and abating adult neurogenesis, resulting in disordered learning, memory, and sensory abilities[37].

Besides peripheral inflammatory cytokines intruding into the CNS in COVID-19 patients, SARS-CoV-2 may also generate some direct injuries to the CNS and result in neural fatigue. Although cells in the CNS express no TMPRSS2 and few ACE2 receptors, SARS-CoV-2 can also activate endothelial cells, disrupt the BBB, and initiate inflammatory progression by releasing S or N proteins, which is unique to SARS-CoV-2 and cannot be observed after exposure to HKU.1, MERS-CoV, or SARS-CoV-1[38–40]. Indeed, the accumulation of S1 protein in the brain parenchyma has been confirmed, and S1 accumulation causes a sustained microglial inflammatory response[41]. Above all, SARS-CoV-2 infection-induced neural fatigue is mainly attributed to injury caused by neural inflammation. Therefore, effective agents for ameliorating neural inflammation in COVID-19 patients and recovered patients will be helpful for treating PVFS (Figure 2).

Molecular mechanisms of neural fatigue relief by adaptogens

Inhibition of inflammatory factor release

Microglia have important functions in the CNS, especially in neuroinflammatory and degenerative diseases[42]. Several ginsenosides have been shown to inhibit pro-inflammatory cytokines (TNF-α and IL-1β) while inducing M2 polarization in macrophages and microglia, and these M2 polarized cells can inhibit inflammation progression and promote inflammation regression[43]. Rhodioloside extracted from Rhodiola rosea has an inhibitory effect on microglial hypoxic inflammation[44]. However, it is unclear whether this inhibition is due to energy metabolic processes in microglia. Schisandra chinensis extract reduces the levels of pro-inflammatory cytokines (including IL-1β, TNF-α, and NO) and inhibits Aβ1-42-induced phosphorylation of NF-κB and IκBα, as well as p38, JNK, and ERK proteins in microglia[45]. Activation of the p38 CREB pathway and Nrf2 translocation are closely associated with acanthopanax sentic (ASE)-induced HO-1 expression. These results suggest that acanthopanax induces HO-1 expression through the p38 CREB pathway and plays an important role in generating anti-neuroinflammatory and neuroprotective responses[46]. Because of the above findings, That adaptogens improve the inflammatory environment of nerve cells is a clear effect, paving the way for improving fatigue status.

Relief of oxidative stress balance in the nervous system

Viral infections and nutritional deficiencies may further exacerbate the immuno-oxidative physiology of post-infection fatigue[47]. Neuroantioxidant-targeted therapy may have clinical efficacy against post-infection fatigue. The presence of ginsenoside Rb2 effectively promotes the reduction of Ca^{2+} and ROS levels in BV2 cells, reduces oxidative stress levels, and protects neural cells[48]. Rhodioloside, a phenylpropanoid glycoside isolated from Rhodiola rosea, has potent antioxidant properties,

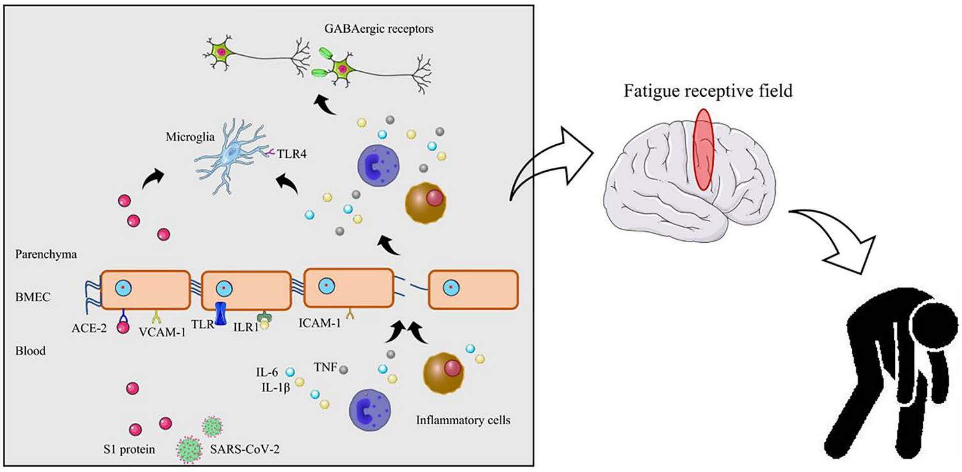

Figure 2. Viral infection with neurological tendencies. IL: Interleukin; ACE2: Angiotensin-converting enzyme 2; BMEC:Brain microvascular endothelial cells; GABAergic: GABAergic receptor; ICAM: ntercellular cell adhesion molecule; TLR: Toll-like receptor; TNF: Tumor necrosis factor; VCAM: Vascular cell adhesion molecule; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

and culturing PC12 cells with rhodioloside significantly reduces apoptosis and attenuates the collapse of mitochondrial membrane potential (MMP)[49]. In addition, Rhodiola can induce an increase in nitric oxide (NO), promote nitric oxide synthase (nNOS) and inducible nitric oxide synthase (iNOS) overexpression by inhibiting MPP.[50]. VO extracted from the stem of Schisandra chinensis improved the activity of super oxide dismutase (SOD), malonaldehyde (MDA), and glutathione peroxidase (GSH-Px) [51]. The neurotrophic factor GFAP and microglia CD11b showed significant improvements in histopathological changes[52]. Regulation of oxidative stress levels in the nervous system may depend on the mitochondrial pathway of genesis, and improvement of the imbalanced stress status may promote energy recovery, thus providing ideas for fatigue after viral infection.

Improving HPA axis dysfunction

Adaptogens are the material basis of the body's response to external stimuli and can be coupled to the immune and stress response systems in the body[53]. A variety of stress situations with different patterns of stress can stimulate adjustments to produce responses to different stresses. Although it is debated whether HPA axis dysfunction is secondary or primary, modulation of HPA axis function is still considered the main way to adapt protoplasts to improve the fatigued state of the body[54]. Ginseng has been shown to be effective in normalizing the overactivated HPA axis and reducing the elevation of several inflammatory and neurological factors caused by the over-activation of the HPA axis[55]. A variety of plant adaptogens have been found to improve HPA axis hyperactivation.

Pharmacological effects and clinical applications of Adaptogen

Radix Ginseng

Radix Ginseng has been used extensively in clinical treatment and in daily life, and some health supplements for improving sub-health often contain ginseng ingredients[56]. The main components of ginseng are saponins and polysaccharides, and their candidate mechanisms include effects on the cardiovascular and HPA systems[57], deceleration of platelet aggregation[58], neuroprotective effects[59], modulation of neurotransmission[60], and promotion of NO synthesis effects[61]. Among these components, ginsenoside is one of the main active constituents of ginseng and have multiple effects such as endocrine regulation, immune enhancement, and regulation of the CNS[62]. Detailed information about the improvement of fatigue symptoms by ginseng is provided in Table 1.

Acanthopanax senticosus

Acanthopanax senticosus is a commonly used adaptogenic herb that has been used to treat a variety of stress-induced physiological changes, allergic conditions[69], inflammatory conditions, and cancer[70]. As an alternative to ginseng, it is also known as a potent herb. It is also widely used in Asia to control blood pressure and treat mental and emotional disorders[71]. The main components of Acanthopanax are phenylpropanoids, lignans, and coumarins, which exert anti-fatigue, stamina-enhancing, and lipid metabolism-improving effects[72] (Table 2).

Rhodiola Rosea

Rhodiola rosea extract has been used as a dietary supplement to non-specifically enhance natural resistance to physical and behavioral stress, attenuating fatigue and depression[76]. Rhodiola rosea, whose roots are commonly used, contains phenylpropanoids (rosmarinic acid, rosin, and rosmarinic acid), phenolic compounds (rhodiol and p-tyrosol), flavonoids, and organic acids (gallic acid)[77]. Reports have demonstrated that it helps cope with various psychological and physical stresses by improving the body's ability to avoid injury and promoting adaptation to environmental stresses, including oxidative stress, anxiety, and physical exercise[78] (Table 3).

Schisandra chinensis

Schisandra chinensis is used in the treatment of diabetes, chronic cough, thirst, night sweats, hypertension, and obesity[84]. Schisandra chinensis extract effectively

Table 1

Studies on the anti-fatigue effects of Radix Ginseng

Component	Effect	Clinical
Ginsenoside	Cholesterol degradation ↑ Cholesterol excretion ↑ Cholesterol turnover ↑[63]	Significant reduction in fatigue in subjects after 8 wk of dosing twice daily
Ginseng water extract	Supplement energy ↑, Endurance ↑, Immunity ↑[64]	1–2 g ginseng extract per day can effectively reduce the fatigue degree and sensory fatigue of 92 chronic fatigue subjects[65]
Ginsenoside	Inflammation ↓[66]	Compared with the placebo, the fatigue score of the intervention group was significantly improved after the 8-wk administration of 2000 mg[67]
Ginsenoside	Cytochrome P450 3A4 enzyme system ↓ inflammation ↓	800 mg for 30 d significantly improves fatigue[68]

Table 2

Studies on the anti-fatigue effects of Acanthopanax senticosus

Component	Effect	Clinical
Acanthopanax senticosus	Christensen's score ↓ Transferrin content ↓ Prealbumin content ↓ Nitrogen excretion ↓	Compared with the control group, the indicators of the experimental group decreased significantly, indicating that the application of eleuthero injection can alleviate postoperative fatigue syndrome[73].
Acanthopanax senticosus extract	Search frequency of each group after sleep deprivation ↑ Search time ↓ Cognitive rate ↓	Computer intermediate frequency acupuncture point stimulation combined with eleuthero capsule treatment can alleviate the physical and mental symptoms of patients, and the anti-fatigue effect is remarkable[74].
Acanthopanax senticosus	FS-14 ↓ Self-Rating Depression Scale ↓ Self-Rating Anxiety Scale ↓	After sleep deprivation, the body's antioxidant capacity decreases over time, thus increasing fatigue, and Acanthopanax extract can significantly improve fatigue[75].

Table 3

Studies on the anti-fatigue effects of Rhodiola Rosea.

Component	Effect	Clinical
Rhodiola extract SHR-5	HPA axis ↑, cortisol ↑ HSP70 and HSP72 ↑ neuropeptide Y ↑, reactive oxygen species ↓, c-Jun N-terminal kinase1 ↓	SHR-5 can improve mental performance and attention in cognitive function in fatigue[79–80]
Rhodiola Rosea	Lactic acid ↓, malonic dialdehyde ↓, superoxide dismutase ↑, nerve growth factor ↑	Rhodiola Rosea has noticeable effect of allaying tiredness[81–82]
Rhodiola Rosea	C-reactive protein ↓, O_2 uptake ↑, CO_2 output ↑, time to exhaustion ↑, fatigue index ↓ mental fatigue and general-well being ↑	Rhodiola Rosea can reduce CRP levels and improved fatigue indices[19,80,83]

HPA: hypothalamic-pituitary-adrenal; SHR: Shevtsov V; CRP: C-reactive protein.

inhibited aortic damage and has also been implicated in improving endurance, exercise accuracy, and physical performance, as well as controlling arterial blood pressure and improving metabolic markers[85–87]. In particular, Schisandra chinensis nourishes Yin and tranquilizes the mind and has been used in clinical practice to treat neurasthenia by Schisandra chinensis preparations, infusions, or syrups[88]. Clinical research has shown that the preparation of Schisandra chinensis can significantly improve neurasthenia patients with tiredness, insomnia, dreaminess, mental trance, forgetfulness, spontaneous sweating, and night sweating[89]. These results suggest that the preparation of Schisandra chinensis may have a therapeutic effect on CFS (Figure 3). The main components of Schisandra chinensis are lignans, polysaccharides, and triterpenes (Table 4).

Conclusion and future directions

For many years, the anti-fatigue effects of drugs have been an important research topic. Western medicines with anti-fatigue effects, such as sertraline, paroxetine, and venlafaxine, are commonly used in interventions for depression. For example, sertraline and paroxetine inhibit 5-HT reabsorption, which increases the concentration of 5-HT in the brain and increases the level of cortical excitation, thus providing an anti-fatigue effect. Venlafaxine inhibits the uptake of 5-HT and it inhibits the uptake of NE. The goal is to increase the level of arousal and combat fatigue. Owing to the single pathway of action, the anti-fatigue effect is accompanied by other adverse effects, such as alterations in the gastrointestinal system, blood system, and heart function.

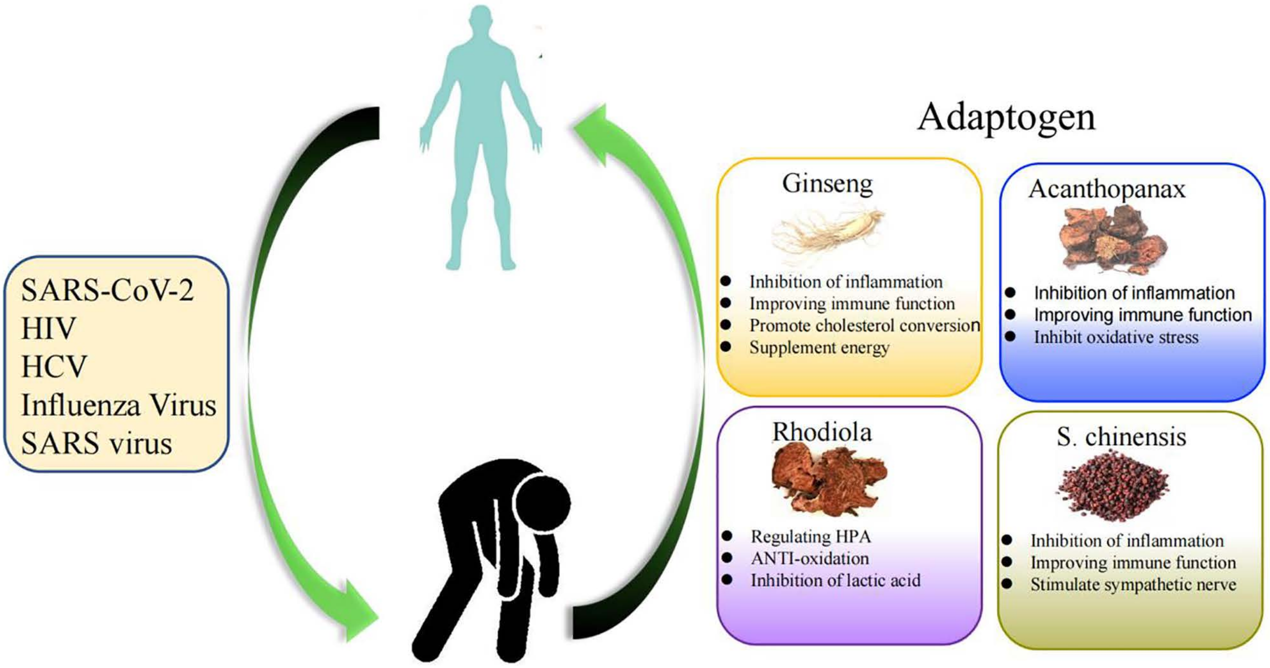

Figure 3. The role of adaptogens in improving fatigue post-viral fatigue. HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; SARS - CoV-2: Severe acute respiratory syndrome coronavirus 2.

Table 4

Study on anti-fatigue of Schisandra chinensis

Component	Effect	Clinical
Schisandra chinensis	Sympathetic nervous system↑ Adrenal function↑	Reduce non-specific fatigue parameters of human body[85]
Schisandra chinensis extract	Cardiovascular and respiratory system↑	Alleviating the fatigue state of 50 patients with chronic fatigue[90]
Schisandra chinensis	Redox process↑ metabolize↑	Increased lung ventilation relieves fatigue in 92 patients[91]

Many years of research have also confirmed that herbs and herbal preparations have significant anti-fatigue effects, and there are many mechanisms of action underlying these. These natural medicines may have an anti-fatigue action by improving glycogen storage, reducing metabolite accumulation, enhancing antioxidant enzyme activity, and regulating immune response. However, there is gap in the research on regulating fatigue caused by specific viral infections in humans. However, it remains clear from the available studies that the mechanism of infestation of fatigue after viral infections may be multifaceted, with the intrusion of the nervous system being the initiating factor of the fatigued state; thus, the disruption of the oxidative stress balance by the invasion of inflammation, and the alteration of homeostasis *in vivo* by the over-activation of the immune and endocrine systems.

Adaptogenic plants are known to be effective in improving stress fatigue states in humans and play a role in maintaining homeostasis in the nervous system. These adaptogenic plants exert immunomodulatory functions, reduce the release of pro-inflammatory and inflammatory cytokines, improve mitochondria-mediated energy production, and modulate the endocrine system. A variety of adaptogens may serve as promising agents for the treatment of fatigue following viral infections.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Yiqi Yan, Patrick Kwabena Oduro, Han Zhang, Xiaoying Wang, and Wei Lei contributed to the idea of this article. Rui Han and Yaolei Ma performed the literature search. Yiqi Yan and Patrick Kwabena Oduro drafted the manuscript.

Ethical approval of studies and informed consent

Not applicable.

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