Acupuncture and Herbal Medicine

Traditional Chinese medicine for chronic fatigue syndrome: theoretical foundations, mechanisms, and clinical management approaches

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Abstract

Chronic fatigue syndrome (CFS), a complex, debilitating disorder that significantly challenges global health systems, is characterized by unrelenting fatigue, cognitive disturbances, and a series of other symptoms that do not improve with rest. While the etiology of CFS remains unclear, emerging research underscores the involvement of neuroendocrine-immune network disruption, metabolic irregularities, and gut microbiota dysbiosis. Current treatments for CFS range from pharmacological interventions, such as antidepressant and immunosuppressant therapies, to non-pharmacological therapies like cognitive behavioral therapy and graded exercise, but these approaches often fall short in fully alleviating symptoms due to various side effects and limited efficacy. Traditional Chinese medicine (TCM), with its unique therapeutic approach involving herbal medicines, acupuncture, and massage, presents a promising alternative by addressing underlying imbalances, enhancing quality of life, and potentially mitigating fatigue symptoms. This review delves into the efficacy of TCM in managing CFS and the possible underlying mechanisms, highlights recent advancements, and advocates for rigorous clinical trials to help solidify its role in integrative healthcare. By bridging contemporary research with traditional modalities, this paper aims to expand the therapeutic strategies against CFS, offering new hope for comprehensive, effective management.

Keywords: Acupuncture, Complementary therapies, Fatigue, Herbal medicine, TCM

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Introduction

Chronic fatigue syndrome (CFS) is a multifaceted disorder that profoundly impacts patient's quality of life. It is marked by intense fatigue, cognitive impairments, sleep disturbances, autonomic dysfunction, and widespread pain (Figure 1), with symptoms worsening with both physical and mental exertion[1]. Officially recognized by the Centers for Disease Control and Prevention (CDC) in 1988, CFS was documented in medical literature as early as 1934, reflecting a long history of clinical observation and research[2–4].

Etiological studies on CFS highlight an intricate interplay involving potential viral infection[5–7], autoimmune dysfunction[8–11], and neuroendocrine anomalies resulting from reduced hypothalamic-pituitary-adrenal (HPA) axis activity[12–14] as well as immune impairment driven by abnormal cytokine production[15–16]. Despite significant research advancements, the exact cause of CFS remains elusive, complicating the development of effective treatments.

The current therapeutic options for CFS are diverse yet limited, ranging from immunological and pharmacological strategies to behavioral therapies and complementary and alternative medicine. Notably, the U.S. Food and Drug Administration (FDA) has not yet approved any medication designed specifically for CFS treatment, which underscores the necessity of exploring novel therapeutic approaches[17].

Bowen Yang and Tianlin Wang contributed equally to this study.

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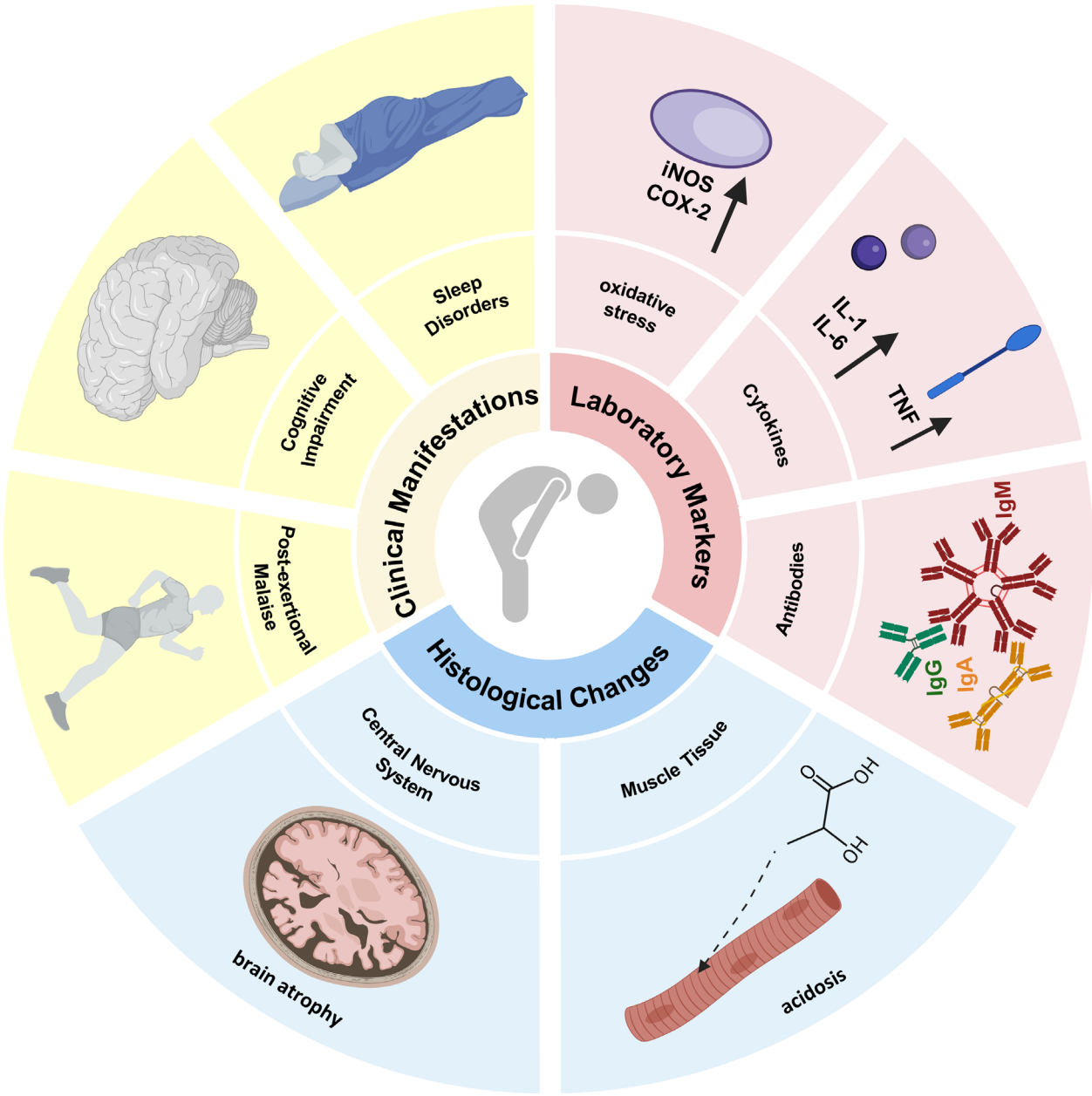

Figure 1. Comprehensive schematic overview of CFS. This diagram categorizes various aspects of CFS—specifically, clinical manifestations, histological changes, and laboratory markers. Clinical manifestations are further divided into cognitive impairment, sleep disorders, post-exertional malaise, and brain atrophy as visualized by the central nervous system section. Histological changes refer to the changes in central nervous system and muscle tissues that indicate specific pathological features such as brain atrophy and muscle acidosis. Laboratory markers include inflammatory cytokines (IL-1, IL-6, TNF-α), oxidative stress indicators, and general immune response components (eg, IgM, IgG, and IgA antibodies). This image was created using BioRender.com. CFS: Chronic fatigue syndrome; COX, Cyclooxygenase; IL: Interleukin; iNOS: Inducible nitric oxide synthase; TNF: Tumor necrosis factor.

Therefore, this review aimed to clearly articulate the research objective—assessing the evidence regarding the clinical efficacy of traditional Chinese medicine (TCM) in the management of CFS as well as the potential underlying mechanisms—to guide the entire manuscript.

Epidemiology

Research indicates that the global prevalence of CFS is approximately 0.89%, with adults and minors affected at a rate of 0.65% and 0.55%, respectively[4], highlighting CFS as a significant public health issue across age groups. However, prevalence rates differ by country, likely reflecting variations in genetic predisposition, sociocultural influences, and healthcare efficiency. For instance, the prevalence is about 0.2% in the UK[18] and ranges from 0.5% to 1% in the USA[19], 0.094% to 0.14% in Australia[20], 0.58% to 0.77% in Korea[21], and can be as high as 0.76% in Japan[22] (Table 1).

In adult populations, the proportion of female patients significantly exceeds that of males (women are 1.5–2 times more likely to develop CFS), and middle-aged women are particularly susceptible to CFS[23]. This gender disparity suggests that underlying biological and possibly environmental factors influence susceptibility. Furthermore, the incidence of CFS shows noticeable variations depending on occupation[24], suggesting that

Table 1
Prevalence of CFS by geographical region

Region	Prevalence	References
UK	0.2%	[18]
USA	0.5–1%	[19]
Australia	0.094%–0.14%	[20]
South Korea	0.5%–0.77%	[21–22]
Japan	0.76%	[22]

CFS: Chronic fatigue syndrome.

job-related stress and lifestyle factors could also have contributory roles.

However, the accuracy of these prevalence estimates could also be influenced by factors such as over-reliance on physician reports and unverified telephone surveys[25]. To improve the accuracy and reliability of epidemiological data on CFS, it is crucial to implement more robust and systematic methods such as community-based sampling and comprehensive surveys. These approaches will help gather more representative data to enhance our understanding of the true burden of CHS on societies and inform targeted healthcare strategies.

Associated conditions

Multiple sclerosis

CFS and multiple sclerosis (MS) are both complex diseases that share some overlapping symptoms, such as fatigue and cognitive impairment. However, they differ significantly in the underlying pathological mechanisms, disease course, and diagnostic criteria. MS, a chronic autoimmune disease affecting the central nervous system, is characterized by a primary demyelination process that leads to focal lesions in white and gray matter, eventually leading to widespread damage and neurodegeneration throughout the brain[26]. Unlike the cognitive changes observed in CFS, the cognitive alterations in MS are closely associated with demyelination, resulting in plaque formation and subsequent disruption of axonal transmission[27]. The diagnosis of MS requires demonstrating that the criteria for dissemination in time (DIT) and dissemination in space (DIS) have been met[28]. Additionally, the diagnostic process often includes further assessments based on magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis[29].

Cancer

Cancer patients often experience cancer-related fatigue (CRF), an extreme form of tiredness triggered by the disease or its treatments. While CRF shares symptoms with CFS, the two are fundamentally different[30]. CRF is characterized as a multidimensional subjective experience that encompasses the physical, emotional, and cognitive aspects of fatigue. Moreover, this fatigue is disproportionate to the patient's recent activity level and significantly disrupts daily life. The pathogenesis of CRF may be linked to multiple factors, including energy deficiency, inflammation, neuroendocrine system disorders, circadian rhythm changes, serotonin system dysfunction, and genetic factors[31]. Moreover, studies indicate that cancer and its treatments can activate the immune system, leading to the release of pro-inflammatory cytokines, which in turn can impact the central nervous system and result in symptoms such as fatigue[32].

Long COVID

Long COVID, also known as post-acute sequelae of SARS-CoV-2 infection (PASC), refers to a range of physical and neuropsychiatric symptoms persisting for more than 12 weeks after the acute phase of COVID-19[33]. These symptoms include fatigue, difficulty breathing, chest pain, among others, which are often similar to those of CFS[33]. Research indicates that patients with long COVID exhibit a unique pattern of immune dysregulation characterized by prolonged activation of certain innate immune cells (such as monocytes and plasmacytoid dendritic cells), activation of $CD8^+$ memory T cell subpopulations, and continuous expression of specific anti-viral cytokines like IFN-λ[34–41]. Despite potential variances in etiology and pathology between long COVID and CFS, these immune dysregulation patterns exhibit notable similarities to the pathological mechanisms observed in CFS.

Fibromyalgia

CFS and fibromyalgia are both characterized by chronic fatigue and muscle pain as their main manifestations. However, despite the overlap in symptoms such as widespread muscle pain, persistent fatigue, sleep disturbances, cognitive impairments, and emotional symptoms, there are significant differences in diagnostic criteria, etiology, and treatment approaches between the two conditions. In terms of diagnosis, fibromyalgia is primarily identified based on the presence of widespread tender points on the body[42], whereas the diagnosis of CFS focuses on excluding other medical conditions that could cause similar fatigue symptoms. Regarding treatment strategies, fibromyalgia may involve the use of antidepressants, anticonvulsants, and analgesics to alleviate pain and emotional symptoms[43]. In contrast, the treatment for CFS emphasizes enhancing patient energy levels and uses a multimodal symptom management approach to achieve therapeutic effects.

Clinical manifestations

Post-exertional malaise

A key clinical manifestation of CFS is persistent fatigue, also known as post-exertional malaise (PEM), that persists despite rest. This fatigue is often prolonged and significantly worsens following physical or mental activity[44]. Common symptoms of CFS patients include muscle and joint pain, persistent headaches, and a general feeling of discomfort following exertion. A cross-sectional survey reported that 90% of CFS patients experience PEM affecting both physical and cognitive functions[45]. Experimental evidence indicates that the recovery period following cardiopulmonary exercise tests is significantly prolonged in CFS patients compared to individuals in the general population[46].

Cognitive impairment

CFS patients frequently experience cognitive impairments marked by diminished memory, lack of concentration, challenges in verbal expression, and reasoning difficulties, collectively referred to as "brain fog"[47]. These cognitive dysfunctions, particularly those affecting memory and executive functions, have a considerable impact on the daily functioning and work efficiency of patients. However, instrumental functions such as calculation, language, and visuospatial abilities tend to be relatively preserved[48–49].

Sleep disorders

Sleep disorders are highly prevalent among individuals with CFS, who frequently report poor sleep quality characterized by frequent nocturnal awakenings or early morning waking[50]. These sleep disturbances may also be compounded by nighttime respiratory issues and breathing disorders. During wakefulness, CFS patients often exhibit hypocapnia and hyperventilation, which can disrupt breathing during sleep, primarily leading to central sleep apnea[51–54]. Notably, although compromised sleep quality undoubtedly worsens fatigue and symptoms in CFS patients, even with adequate sleep, mental and skeletal muscle fatigue persist, as the primary cause of fatigue is not related solely to sleep. Both mental and muscle fatigue are linked to inadequate blood flow, particularly in skeletal muscles, and additional energy disruptions stemming from mitochondrial dysfunction[55].

Laboratory markers

Blood and immune marker assessment results of CFS patients reveal notable differences when compared to those of healthy individuals. Specifically, biochemical abnormalities such as elevated levels of D-lactic acid and increased concentrations of 5-hydroxytryptamine (5-HT) are observed[56–57]. Changes in immunoglobulin (ie, IgA, IgG, IgM) levels, decreased zinc concentration, and reduced activity of natural killer (NK) cells also suggest impaired immune system functionality in CFS patients[58–62]. Furthermore, reductions in the concentrations of glutamine and ornithine in the blood may indicate abnormalities in amino acid metabolism and dysregulation of the urea cycle[63]. Hormonally, CFS patients have significantly lower levels of cortisol, indicating a reduction in HPA axis function, which may contribute to the fatigue experienced by these patients[64–65]. Additional research has revealed increased levels of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), and nuclear factor κB (NF-κB) products in the blood of CFS patients, particularly post-exertion, with plasma nitrate levels as high as three times those in healthy individuals[66–69]. These findings suggest significant oxidative stress and inflammatory responses in CFS patients. Elevated levels of inflammatory markers such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor (TNF) in some CFS patients may be closely associated with the persistence and exacerbation of CFS symptoms[70]. A 2016 study on CFS revealed abnormalities in 20 metabolic pathways, with the levels of most metabolites being reduced, indicating a hypometabolic state and a metabolic response resembling an evolutionarily conserved stress response, with diagnostic accuracies of 94% to 96% using specific metabolites[71]. The laboratory markers of CFS are summarized in Table 2.

Histological changes

Central nervous system

Imaging techniques such as MRI have revealed significant abnormalities in the brain structure and function of individuals with CFS, notably reduced hippocampal volume and indications of brain inflammation[72]. More advanced imaging modalities like diffusion tensor imaging (DTI), functional MRI (fMRI), and magnetization transfer imaging (MTI) have identified brain volume loss (BVL) and cerebral atrophy as prominent biomarkers of disease progression and neuronal damage in CFS[73]. The average brain volume loss in CFS patients exceeds that in healthy controls, which is primarily attributable to demyelination and axonal damage in both gray and white matter[74]. Changes in gray matter volume and thickness play a crucial role in cognitive functions and serve as early indicators of pathological alterations in CFS. In one study, voxel-based morphometry (VBM) analysis demonstrated a significant correlation between fatigue and localized brain atrophy, particularly highlighting cognitive fatigue associated with atrophy in the occipital and parietal lobes and the gray/white matter of the precuneus[75]. Additionally, studies on cerebral blood flow (CBF) indicate diminished blood flow and altered functional connectivity in CFS patients, notably affecting the right parahippocampal and occipital regions and being closely linked to the level of fatigue[76].

Muscle tissue

Muscle magnetic resonance spectroscopy analysis has shown that certain CFS patients generate excessive amounts of acid in their peripheral muscles, which is also insufficiently cleared post-exercise, resulting in acidosis[77]. In one study, investigations of skeletal muscle cells in CFS patients indicated elevated myogenin expression under basal conditions, impaired activation of AMP-activated protein kinase (AMPK), and diminished stimulation of glucose uptake[78]. Heightened expression of myogenin may detrimentally affect exercise capacity[79]. Furthermore, AMPK plays a pivotal role in skeletal muscle response to exercise—it becomes active during energy deficits (eg, during muscle contraction), subsequently halting ATP-consuming processes and initiating ATP production processes. In normal skeletal muscle, this pathway enhances glucose uptake by muscle cells[80]. However, in CFS patients, skeletal muscle cells exhibit a significantly reduced capacity for glucose utilization, suggesting potential bioenergetic dysfunction upstream in the tricarboxylic acid (TCA) and urea cycles[81]. This lack of substrates subsequently negatively impacts ATP production[82].

Etiology

CFS is a complex disease, and its precise causes remain poorly understood. Contemporary medical research has identified several potential etiological factors, including

Table 2

Biomarkers and their clinical implications in CFS

Biomarkers	Comparison with healthy individuals	Possible clinical implications	References
D-Lactic acid levels	Elevated	May indicate abnormal cellular energy metabolism	[57]
Tryptophan concentration	Increased	May be associated with amino acid metabolism disorders	[56]
Immunoglobulin (IgA, IgG, IgM) levels	Concentration variations	May suggest compromised immune system function	[59–60, 62]
Zinc concentration	Decreased		[61]
NK cell activity	Reduced		[58]
Glutamine and ornithine concentrations	Decreased	May indicate amino acid metabolism disorders and urea cycle dysregulation	[63]
Cortisol levels	Significantly decreased	May indicate HPA axis dysfunction, associated with fatigue	[64]
Inducible iNOS, COX-2, and NF-κB product levels	Increased	Enhanced oxidative stress response	[66–68]
Plasma nitrate concentration	Can be up to 3 times higher after exercise compared to normal individuals		[69]
Inflammatory marker (IL-1, IL-6, TNF) levels	Elevated Levels	May be closely related to the persistence and exacerbation of CFS symptoms	[70]
Metabolic pathways including sphingolipid, phospholipid, purine, cholesterol, microbiome, pyrroline-5-carboxylate, riboflavin, branch chain amino acid, peroxisomal, and mitochondrial metabolism	Dysregulated	The cellular metabolic response in CFS patients is homogeneous	[71]

CFS: Chronic fatigue syndrome; COX-2: Cyclooxygenase 2; HPA: Hypothalamic-pituitary-adrenal; iNOS: Inducible nitric oxide synthase; IL: Interleukin; NF-κB: Nuclear factor κB; NK: Natural killer; TNF: Tumor necrosis factor.

neuroendocrine-immune dysfunction, metabolic and mitochondrial abnormalities, inflammation, and gut microbiome dysbiosis[83].

Central nervous system dysfunctions

Central nervous system abnormalities play a pivotal role in the pathogenesis of CFS, which is characterized by reduced volumes of specific brain areas such as the hippocampus as well as altered neural conduction pathways. Brain volume loss or cerebral atrophy is considered a significant risk factor for fatigue development, with its impact on fatigue severity becoming more evident over time, although the exact correlation necessitates further investigation[84]. Additionally, some studies suggest that memory impairment in CFS patients may be associated with reduced gray matter volume in specific brain regions[85]. For instance, reductions in gray matter volume in the right parahippocampal gyrus and the posterior part of the left parahippocampal gyrus, along with bilateral reductions in the volume of the frontal cortex, have been significantly correlated with increased fatigue levels[86]. However, it is worth noting that other studies found no significant differences in gray matter volume between CFS patients and healthy individuals[87].

Most studies indicate a significant negative correlation between fractional anisotropy (FA) values of CFS patients and their fatigue scores[88], and the associated structural impairments substantially affect information processing speed and cognitive functions. Additionally, activation of glial cells in the central nervous system of CFS patients can lead to the release of neuroimmune inflammatory cytokines such as IL-1β. These inflammatory cytokines can induce the expression of serotonin transport proteins in astrocytes, resulting in reduced extracellular serotonin levels and ultimately decreasing the activation of serotonin 1A receptors, thereby triggering symptoms of fatigue[89].

Endocrine system abnormalities

Dysfunction of the endocrine system, particularly HPA axis abnormalities and low cortisol levels, is closely associated with the onset of CFS. Glucocorticoid receptors play a key role in CFS, mediating inflammatory responses and regulating the function of the HPA axis. Studies have found that CFS patients have lower cortisol levels[64], enhanced glucocorticoid receptor function[90], and increased IL-6 and TNF-α production[70]. Glucocorticoids can directly or indirectly suppress the expression of pro-inflammatory cytokines, thereby modulating immune responses[91]. Additionally, the activation of immune-inflammatory responses and oxidative and nitrosative stress reactions in CFS patients can lead to weakening of HPA axis activity[92]. Interactions between the HPA axis and other systems may also play a significant role in the progression of CFS.

Immune system dysregulation

Immune dysfunction is considered one of the key pathogenic factors in CFS. Reduced HPA axis activity leads

to abnormal cytokine production, which in turn causes immune damage in the form of an increase in $CD16^+/CD3^-$ NK cells[93]. CFS patients may also experience immune system dysfunction marked by diminished cytotoxicity mediated by T and NK cells, along with alterations in cytokine profiles and immunoglobulin levels[94]. NK cells not only participate in anti-tumor, anti-viral infection, and immune regulation processes but also play a role in hypersensitivity reactions and the onset of certain autoimmune diseases[95–96]. However, research on the role of NK cells in CFS remains inconclusive, warranting further investigation. Additionally, calcium signaling, which is closely linked to mitochondria and the endoplasmic reticulum, significantly influences immune cell function[97]; thus, abnormalities in calcium signaling could lead to immune system dysfunctions and related impairments[98]. Impaired activity of transient receptor potential melastatin 3 (TRPM3) calcium channels has been observed in NK cells in CFS[58,99]. Moreover, immune-inflammatory responses and autoimmune reactions can lead to decreased mitochondrial membrane potential activity, increased mitochondrial membrane permeability, disruption of ATP production, reduction in creatine phosphate synthesis, and consequent adverse effects on oxidative phosphorylation[100]. These processes ultimately affect energy metabolism, leading to symptoms such as fatigue.

The microbiome and its role in CFS

In recent years, the correlation between the gut microbiome and CFS has gained significant attention. The gut microbiome and its metabolic products play crucial roles in regulating the immune, neurological, and endocrine systems and the brain-gut axis. Clinical studies have highlighted notable differences in gut microbiota composition between CFS patients and healthy individuals, characterized mainly by increased *Enterococci* and *Streptococci* levels, decreased *Bacteroides* levels, and a significant reduction in *Actinobacteria* abundance[101]. Alterations in the gut microbiome and its metabolic products can lead to excessive production of pro-inflammatory factors by intestinal mucosal cells, thus triggering inflammatory responses. For instance, the gut microbiome modulates T cell differentiation through tryptophan metabolism, thereby influencing immune system function[102]. Therefore, dysbiosis of the gut microbiome may indirectly contribute to CFS pathogenesis by disrupting immune regulation and metabolic pathways. Modulating the quantity, diversity, and mucosal barrier function of the gut microbiome holds promise as an effective strategy for alleviating fatigue symptoms in CFS patients.

Viral triggers of CFS

Infectious factors, particularly bacteria and viruses, are considered significant contributors that can trigger or exacerbate CFS. Given that some individuals develop CFS after a viral infection or exhibit symptoms of viral illnesses during CFS, it has been speculated that certain viruses may act as triggers for the disease, a phenomenon known as "post-viral fatigue syndrome"[103]. Some studies have also suggested a potential link between CFS and viral infections. For instance, research indicates that some CFS patients had been infected with viruses such as the Epstein–Barr Virus (EBV) or human herpesvirus 6 (HHV-6) prior to illness onset[104]. These viral infections can cause long-term immune system dysregulation, which in turn can lead to the development of CFS. Furthermore, studies indicate that individuals recovering from COVID-19 may present with symptoms resembling those of CFS, which can persist for more than 6 months[105].

Metabolic dysfunction in CFS

Abnormalities in energy metabolism are also considered significant factors associated with CFS. Metabolomic analysis of plasma samples from CFS patients using nuclear magnetic resonance (NMR) revealed notable differences in the concentrations of TCA cycle and urea cycle intermediates[81]. Research has also indicated a connection between CFS and pyruvate dehydrogenase (PDH) dysfunction leading to increased consumption of amino acids that supply alternative pathways for the TCA cycle[106]. Abnormalities in metabolic pathways—including sphingolipid, phospholipid, purine, cholesterol, microbiome, pyrroline-5-carboxylate, riboflavin, branched-chain amino acid, peroxisomal, and mitochondrial metabolism pathways—have been identified in CFS patients, indicating a heterogenous and robust cellular metabolic response[71].

In summary, CFS is a complex disease involving multifactorial and multisystem interactions. Investigating its pathogenesis is crucial for gaining new insights and developing approaches for its diagnosis and treatment.

CFS in TCM theory

The primary symptoms of CFS align closely with the TCM term "Deficiency Fatigue." As early as during the Eastern Han Dynasty, Zhang Zhongjing discussed this condition in "*Essential Prescriptions of the Golden Coffer*." Additionally, symptoms such as palpitations, insomnia, anxiety, and depression fall under categories like "constraint" and "organ agitation." Throughout history, TCM practitioners have attributed the causes of this condition to be multifaceted: 1) it may stem from congenital insufficiency leading to deficiencies in organs, *qi*, blood, *yin* and *yang*; 2) improper diet later in life can damage the spleen and stomach, resulting in weakened *qi* and blood production and loss of organ and meridian nourishment; 3) excessive physical labor and emotional stress can also affect organ function; 4) improper convalescence care may damage *qi*, blood, *yin* and *yang*.

TCM studies suggest that CFS is closely linked to liver, spleen, and kidney function, with the core pathological mechanism being organ function decline resulting in insufficient *qi* and blood supply to the body[107]. According to TCM theory, the kidneys are the congenital constitutional foundation, responsible for bone and marrow production. Abundant kidney essence correlates with robust vitality, physical strength, and skeletal integrity, whereas excessive physical exertion and desires can deplete kidney essence, potentially causing muscle and bone weakness and body heaviness. The spleen is the

acquired constitutional foundation, facilitating nutrient transformation, transportation, and limb and muscle nourishment. When spleen's *qi* is abundant, it efficiently transforms and transports food and drink essence throughout the body, promoting muscle and limb vigor. However, worry, overthinking, and irregular eating can impair the spleen's *qi*, thus hindering its transformative functioning and causing nutrient distribution imbalance, leading to muscle fatigue and limb weakness. The liver governs discharge and is the primary blood storage and regulation organ. TCM practitioners explain "Extreme Exhaustion" as fatigue, which is foundational for enduring physical and mental strain.

In summary, according to TCM theory, each organ governs distinct physical and mental aspects. Imbalances in organ function caused by external pathogens and internal injuries may induce corresponding physical and mental symptoms, thereby contributing to CFS.

Correlation between TCM syndromes and modern biological mechanisms of CFS

Although TCM and modern biomedical frameworks stem from different paradigms, several conceptual overlaps highlight potential intersections. Below, we outline the primary TCM syndromes in CFS alongside corresponding modern biological sub-mechanisms and identify the current gaps in mechanistic validation (Table 3).

Despite the potential significance of these overlaps, several gaps impede their integration. Only a few studies have systematically profiled CFS patients by TCM pattern and correlated them with metabolomic, proteomic, or genomic signatures; clinical trials of TCM formulas often report symptomatic benefits without including pre- and post-treatment molecular assessments; variability in pattern diagnosis among practitioners undermines reproducibility and underscores the need for a standardized framework; and computational approaches such as network pharmacology remain under-utilized for linking the effects of herbal compounds to modern CFS pathways. Addressing these limitations will require consensus-driven TCM pattern criteria, large-scale omics-based biomarker discovery in well-characterized cohorts, and mechanistic trials that integrate traditional efficacy endpoints with contemporary laboratory assessments.

Diagnostic criteria for CFS

Diagnostic standards in contemporary medicine

Due to the lack of clarity regarding the etiology and pathological mechanisms of CFS, most current diagnostic criteria are based on expert consensus. Several internationally recognized CFS diagnostic standards include the 1994 CFS case definition[3], the 2010 revised Canadian ME/CFS clinical case definition[108], the 2011 International Consensus Criteria for ME[109], and the latest diagnostic criteria issued by the UK National Institute for Health and Care Excellence (NICE)[110]. A significant difference in other standards compared to the CDC-1994 criteria is that both adults and children can be diagnosed with CFS if the primary symptoms persist for more than 3 months[110]. Notably, the diversity of diagnostic criteria significantly increases the heterogeneity in diagnoses, and numerous confounding factors affect both the accuracy of clinical research and the reliability of diagnoses by physicians. A systematic review of 55

Table 3

Correlations between TCM syndromes and modern biological mechanisms in CFS

TCM syndrome	Core clinical features	CFS mechanism	Proposed overlap
Qi deficiency	Fatigue, weakness, shortness of breath, spontaneous sweating	Mitochondrial dysfunction; reduced ATP production	Inadequate cellular energy mirrors the "insufficient *qi*" concept: poor oxidative phosphorylation may underlie the sensation of depleted life-force
Blood deficiency	Pale complexion, dizziness, insomnia, palpitations	Microcirculatory impairments; endothelial dysfunction	Reduced capillary perfusion and dysregulated nitric oxide pathways could correspond to "blood" failing to nourish tissues
Yin deficiency	Night sweats, insomnia, dry mouth, restlessness	HPA axis hyporesponsiveness with flattened cortisol rhythms	A deficit in "cooling, nurturing *yin*" may reflect inadequate glucocorticoid tone, leading to disturbed sleep and stress intolerance
Yang deficiency	Cold intolerance, limb heaviness, low basal metabolic rate	Hypometabolic profiles; reduced core body temperature and basal metabolism	Diminished "warming, activating *yang*" parallels findings of lower resting metabolic rate and dysregulated thyroid/adrenal output
Liver *qi* stagnation	Emotional lability, irritability, headaches	Autonomic dysregulation; heart-rate variability	Impaired autonomic tone (vagus/sympathetic imbalance) may map onto disrupted "flow" of liver *qi*, manifesting as palpitations and mood swings
Spleen *qi* deficiency	Poor appetite, bloating, loose stools, muscle fatigue	Gut dysbiosis; nutrient malabsorption; systemic low-grade inflammation	Impaired digestion and barrier function ("spleen" dysfunction) may promote a leaky gut, fueling chronic inflammation and fatigue
Kidney essence depletion	Signs of premature aging, lower back and knee weakness, tinnitus	Neuroendocrine aging markers; altered sex steroid/adrenal metabolite levels	Declining "kidney essence" could correlate with age-related decline in mitochondrial DNA copy number and neurosteroid levels

CFS: Chronic fatigue syndrome; HPA: hypothalamic-pituitary-adrenal; TCM: Traditional Chinese medicine.

studies comparing and evaluating existing CFS diagnostic criteria indicated that most studies have significant limitations and lack assessments of the repeatability and feasibility of case definitions[111]. Nevertheless, the 1994 CFS diagnostic criteria remain widely accepted in the medical community (Table 4).

TCM diagnostic approaches

In TCM, CFS is categorized into several types (Table 5)—specifically, "Liver Depression and Spleen Deficiency (LDSD)" and "Heart and Spleen Deficiency (HSD)," "Spleen and Kidney *yang* Deficiency (SKYD)," and "Liver and Kidney Insufficiency (LKI)"[112].

- The primary symptoms of LDSD include emotional dysregulation, irritability, distension and pain in the chest and ribs, bloating, poor appetite, loose stools, abdominal pain leading to diarrhea, and decreased pain after bowel movements, with a wiry and slow pulse. These symptoms collectively reflect the pathological state of liver *qi* stagnation combined with spleen *qi* weakness.
- The main manifestations of HSD are palpitations, mental fatigue, a pallid complexion, fullness in the epigastric region, poor appetite, loose stools, a pale tongue, and weak pulse, reflecting an intrinsic link between insufficient heart blood and spleen *qi* weakness.
- Symptoms of SKYD include aversion to cold, lumbar soreness, abdominal bloating, poor appetite, loose stools, cold knees, and tinnitus, with a pale, swollen tongue and a deep, delayed pulse, all pointing to a deficiency in spleen and kidney *yang*.
- LKI is characterized by back pain, soreness and weakness, dry mouth and throat, weakening of the lower limbs, dizziness, a red tongue with scanty coating, and a deep, thin pulse, reflecting a deficiency in liver and kidney essence and blood.

The diagnosis of these patterns is not limited to patient symptoms but also includes unique TCM diagnostic methods, such as tongue and pulse analysis (Figure 2). Through comprehensive analysis, physicians can formulate personalized treatment plans, which include herbal medicine, acupuncture, and dietary therapy, aimed at harmonizing the imbalance of *yin* and *yang* within the body and restoring a state of health balance. This method of pattern differentiation and treatment profoundly demonstrates the unique understanding of TCM in the individualized treatment of diseases and is an indispensable part of clinical TCM practice.

Treatment

Contemporary treatment for CFS

Modern medical treatments for CFS mainly include pharmacotherapy and non-pharmacological treatments. However, due to a poor understanding of the causes and pathological mechanisms of CFS, these treatments have limitations and low predictability of effectiveness.

Pharmacotherapy

Regarding pharmacotherapy, since there are no specific drugs available, the clinical treatment of CFS primarily

Table 4

CFS diagnostic criteria

Criterions	Descriptions
Primary symptom	Severe fatigue, lasting for more than 6 months, that is not relieved by adequate rest
Secondary symptoms (at least four of the following)	1. Sore throat
	2. Difficulty with concentration or a decline in short-term memory
	3. Tender lymph nodes
	4. Muscle pain
	5. Joint pain without accompanying redness or swelling
	6. New onset headaches
	7. Unrefreshing sleep
	8. Post-exertional malaise lasting more than 24 h after physical or mental exertion
Exclusion criteria	Fatigue that can be explained by a primary medical condition

CFS: Chronic fatigue syndrome.

Table 5

TCM-based syndrome differentiations of CFS

TCM syndrome	Manifestations	Key points of differentiation
Liver depression and spleen deficiency	Emotional imbalance or irritability and anger	Distending pain in the hypochondria, abdominal bloating, poor appetite, loose stools, abdominal pain with a desire to defecate, pain relief after diarrhea, wiry and slow pulse
Heart and spleen deficiency	Palpitations and fatigue	Sallow complexion, epigastric fullness, poor appetite, abdominal bloating, loose stools, pale tongue, weak pulse
Spleen-kidney *yang* Deficiency	Cold intolerance, sore waist	Abdominal bloating, poor appetite, loose stools, cold knees, tinnitus, pale and swollen tongue, deep and slow pulse
Liver and kidney insufficiency	Lower back pain, weakness, and lack of strength	Dry mouth and throat, weakness in the lower limbs, tinnitus, dizziness, red tongue with little coating, deep and thin pulse

CFS: Chronic fatigue syndrome; TCM: Traditional Chinese medicine.

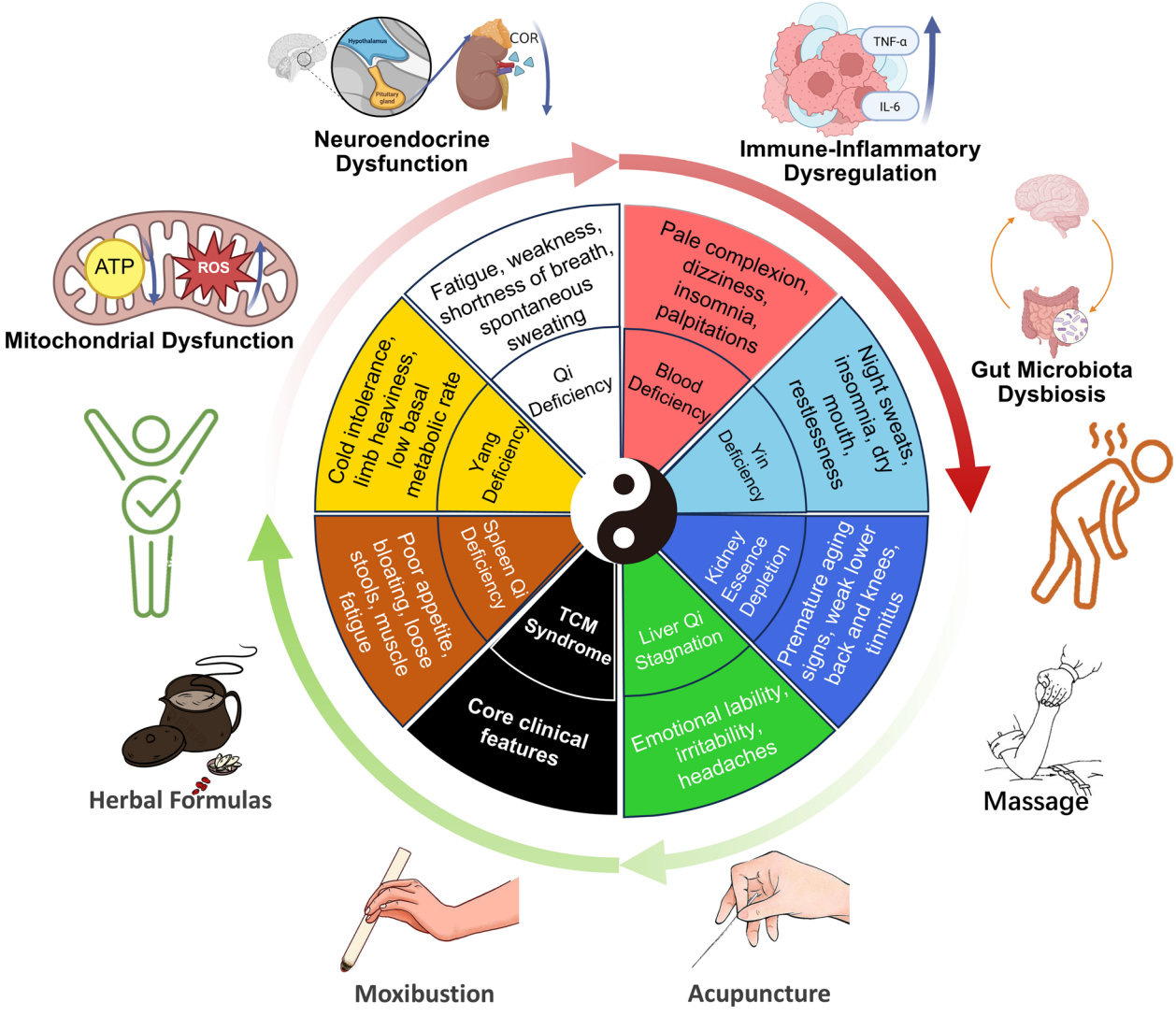

Figure 2. Integrative TCM and modern biomedical perspectives on CFS. This figure presents an integrated model of CFS pathogenesis from the perspective of TCM, correlated with modern biomedical insights. The central wheel depicts core clinical features and TCM syndrome differentiations—including *qi* deficiency, *yang* deficiency, Blood deficiency, *yin* deficiency, Spleen *qi* deficiency, Kidney essence depletion, and Liver *qi* stagnation—each associated with distinct symptom profiles. Surrounding the core wheel, the corresponding modern biological mechanisms are annotated: mitochondrial dysfunction, neuroendocrine dysregulation, immune-inflammatory activation, and gut microbiota dysbiosis. These represent mechanistic underpinnings of fatigue, metabolic abnormalities, immune imbalance, and neurological symptoms observed in CFS. The outermost ring illustrates common TCM interventions—herbal formulas, moxibustion, acupuncture, and massage—targeted at restoring systemic balance through individualized treatment. This integrative framework underscores the potential of TCM in complementing the modern understanding and management of CFS. CFS: Chronic fatigue syndrome; IL: Interleukin; TNF: Tumor necrosis factor.

involves symptom-alleviating medications, including anti-anxiety and anti-depressant medications, steroids, anti-viral drugs, and immunosuppressants[113]. While these drugs can alleviate symptoms such as anxiety, depression, and sleep disorders, they can also induce a range of adverse reactions[114]. For example, anti-depressants may cause nausea, headaches, and insomnia, while steroids can lead to ulcers, acne, osteoporosis, and immune suppression[115–116], and these side effects can affect patient compliance and treatment outcomes.

Cognitive behavioral therapy

Cognitive behavioral therapy (CBT) is a psychological treatment technique that focuses on changing the irrational cognitive patterns of patients to shape rational cognition and behavioral patterns[117]. Its application in treating CFS has proven effective, particularly in reducing negative emotions and behaviors[118]. CBT can significantly lower the fatigue scores of CFS patients and improve symptoms of anxiety and depression[119]. The UK NICE recommends CBT as an effective method for CFS treatment[120]. However, CBT requires patients to have specific personality traits and psychological qualities as well as good receptivity and execution abilities[121]. Inappropriate application may lead to counterproductive results, which demand high standards and professional training for doctors conducting CBT[122]. Thus, although CBT has demonstrated therapeutic effects, it does not cure CFS and imposes high demands regarding the personal traits and mental state of patients, making it unsuitable or less beneficial for all patients.

Graded exercise therapy

Graded exercise therapy (GET) is another non-pharmacological treatment method and involves gradual

aerobic exercise[123]. It positively impacts the treatment of CFS, improving physical, physiological, and psychological dysfunctions. Randomized controlled trials (RCTs) have demonstrated that exercise therapy effectively alleviates fatigue symptoms in CFS patients and enhances sleep quality and life quality[124]. Studies also suggest that aerobic exercise may aid in the repair of neurons in the hippocampal area, possibly acting through specific signaling pathways[125]. However, GET requires patients to be in good physical condition and involves a lengthy treatment period with limited applicability. Excessive exercise may exacerbate CFS symptoms, as even moderate exercise can induce fatigue in patients[126]. Thus, treatment plans must be carefully tailored to each patient's circumstances—individual differences must be considered, and adjustments should be made based on patient feedback and progress to mitigate potential adverse effects. It must also be noted that not all CFS patients are suitable for or benefit from exercise therapy, and GET does not offer a cure.

The primary goal of CFS treatment is to alleviate symptoms and tailor treatment strategies to the individual circumstances of the patient. A comprehensive treatment plan that integrates medications, CBT, and GET may be most effective for some CFS patients. In contrast to the potential instability and side effects of medications and the limitations of CBT and GET, TCM methods such as herbal medicine, acupuncture, and massage offer advantages in terms of simplicity and effectiveness.

Current treatment bottlenecks for CFS

Despite decades of research, fewer than 5% of myalgic encephalomyelitis/CFS patients ever return to their pre-illness activity levels[127]. Pharmacological options (selective serotonin reuptake inhibitors [SSRIs], corticosteroids, anti-virals, and immunosuppressants) deliver only modest, short-lived relief and can cause problematic side effects (nausea, insomnia, weight gain) that often prompt discontinuation. In the landmark fluoxetine trial, no benefit over placebo was observed, and typical SSRI-associated adverse events were common[115]. A systematic review of 26 RCTs across 20 drug classes concluded that no medication can be universally recommended, as response rates seldom exceeded 40% to 50% and relapse within 3 to 6 months was routine[113].

Behavioral therapies fare little better. In the PACE trial (n = 641 patients), CBT and GET resulted in only moderate, transient improvements in fatigue and physical function compared to specialist medical care, and up to 25% of GET group patients experienced worsened post-exertional malaise. Long-term adherence was poor, and both interventions have since been downgraded in NICE guidelines[123].

Thus, transient benefits, high relapse rates, and significant side-effect profiles underscore an urgent need for safer, more durable approaches. TCM, which combines herbal, acupuncture, moxibustion, and massage therapies, offers well-tolerated, multimodal strategies that may help restore systemic balance and achieve longer-lasting symptom control.

TCM treatment for CFS

TCM treatment for CFS follows the principles of syndrome differentiation and treatment, integrating a patient's clinical presentation and constitutional characteristics and the causes and mechanisms of CFS to formulate personalized treatment plans. Below, we first summarize key clinical trials on TCM therapies for CFS (Table 6) and then provide detailed descriptions of each modality.

Herbal formulas

CFS manifests through diverse symptoms that TCM addresses using specific herbal remedies designed to correct underlying imbalances within the body. Symptoms such as low mood, chest oppression, flank pain, poor appetite, abdominal bloating, and irregular bowel movements suggest a dysfunction between the liver and spleen—crucial organs for regulating emotions and energy flow (*qi*) and the transformation and transportation of nutrients. Herbal formulas such as modified Xiaoyao powder and Chaihu Shugan powder are particularly effective for these symptoms. Modified Xiaoyao powder, or "Free and Easy Wanderer Plus," includes ingredients like *Bupleurum* (Chai Hu) for relieving liver *qi* stagnation, *Angelica* root (Dang Gui) to enrich blood, peony root (Bai Shao) for blood nourishment, and white *Atractylodes* (Bai Zhu) to strengthen the spleen. Chai Hu Shu Gan powder, which also contains *Bupleurum*, emphasizes moving *qi* and alleviating pain with additions like Szechuan Lovage root (Chuan Xiong) and citrus peel (Chen Pi) to enhance blood circulation and regulate *qi*.

For those experiencing palpitations, insomnia, memory decline, a pale complexion, and fatigue, Guipi decoction and Ganmai Dazao decoction are recommended. Guipi decoction boosts *qi* and blood with ingredients like *Astragalus* (Huang Qi) and ginseng (Ren Shen), while longan fruit (Long Yan Rou) calms the spirit. Ganmai Dazao decoction, aimed at calming the spirit and nourishing the heart, contains soothing agents like licorice (Gan Cao) and jujube (Da Zao).

Patients with cold limbs, soreness in the loins and knees, and listlessness may benefit from Wenshen Lipi formula, which addresses *yang* deficiency in the spleen and kidneys using warming elements like cinnamon (Rou Gui) and prepared aconite (Fu Zi). This formula enhances the body's *yang* energy, improving metabolism and strengthening kidney function.

Finally, for symptoms such as dizziness, tinnitus, dry eyes, and emotional instability indicative of liver and kidney insufficiencies, Yishen Qianggan Kangpi formula and Liuwei Dihuang pills are effective. These formulas focus on nourishing the liver and kidneys, with Liuwei Dihuang pills incorporating *Rehmannia* (Shu Di Huang) to nourish kidney *yin* and essence and *Cornus* fruit (Shan Zhu Yu) to strengthen both organs.

Each of these formulas reflects the holistic approach of TCM toward treating complex syndromes like CFS, where multiple organ systems are addressed simultaneously to restore balance and health. This integrative method ensures that treatment is tailored to the specific pattern of imbalance, offering a targeted and effective strategy for managing symptoms.

Table 6

Clinical trials on TCM interventions for CFS

Study	Intervention	N	Key Outcomes	TCM Pattern	Evidence Level (Oxford)
Dai et al. 2024[128]	Sijunzi decotion (oral granules) vs. placebo	127	• 63/64 responders (~99%) • ↑Lactobacillus abundance	Spleen deficiency	2b
Wang et al. 2024[129]	Huangqi injection + Buzhong Yiqi acupuncture vs. vitamin B supplementation	200	• 88.5% vs. 54.3% • ↑ SOD; ↓ MDA & ox-LDL (P<0.05)	*qi* deficiency	2b
Yu et al. 2023[130]	Acupuncture (BL62, KI6, LI4, LR3, ST36, SP6) vs. sham	84	• ↑ Total sleep time & efficiency; ↓ awakenings & wake after sleep onset (P<0.05) • ↑Morningness-Eveningness Questionnaire post-treatment & at 1- and 3-month follow-up (P<0.01) • ↓Insomnia Severity Index, Fatigue Severity Scale, & Epworth Sleepiness Scale post-treatment & follow-up (P<0.05) • ↓ Plasma corticosterone (P<0.01)	*yin–yang* imbalance	2b
Sun et al. 2022[131]	Back-shu acupuncture + massage vs. Back-shu acupuncture only	84	• ↑ $CD3^+$, $CD4^+$, $CD4^+/CD8^+$; ↓ $CD8^+$ • ↓ TC, TG, LDL-C; ↑ HDL-C	Liver stagnation & spleen deficiency	2b
Han et al. 2022[132]	Yishen Qianggan Kangpi formula vs. Western medicine	110	• 96.4% vs. 65.5% • ↑ GSH-Px & SOD; ↓ LPO (P<0.05) • ↓ IL-6, IFN-γ, & LAC (P<0.05) • ↑ $CD4^+/CD8^+$ ratio & $CD4^+$; ↓ $CD8^+$	Liver & kidney deficiency	2b
Feng et al. 2020[133]	Thunder-fire moxibustion vs. clear moxibustion	90	• Thunder-fire: ↓ $CD3^+$ & $CD8^+$ • Clear: no change	CFS, non-specific	2b
Wang 2020[134]	Sanren + Sijunzi decotion vs. vitamin B + oryzanol supplementation	72	• Improvements in infection, stress, and immune, nervous system, & digestive parameters (details not specified)	Spleen deficiency & dampness	2b
Liu et al. 2019[135]	Chaihu Guizhi decotion vs. placebo	72	• ↑ Serum IgG, IgA, & IgM	Liver stagnation & spleen deficiency	2b
Shi 2019[136]	Erxian decoction vs. vitamin B1 supplementation + gluten + barley	80	• Clinical index in the treatment group was significantly higher than that in the control group (P < 0.01)	CFS, non-specific	2b
Tan 2019[137]	Assist-*yang* fire moxibustion vs. simple fire therapy	60	• Improved immune responses	*yang* deficiency	2b

CFS: Chronic fatigue syndrome; GSH-Px: Glutathione peroxidase; IL: Interleukin; LPO: Lipid peroxide; MDA: Malondialdehyde; SOD: Superoxide dismutase; TCM: Traditional Chinese medicine.

Moxibustion

Moxibustion, a TCM therapy, involves burning moxa wool over specific meridians and acupoints to stimulate warmth, harmonize *qi* and blood, and promote *yang* energy, making it effective for treating deficiency fatigue disorders like CFS[138]. It encompasses direct techniques such as moxa stick and grain moxibustion, as well as indirect methods like interposed material moxibustion and medicinal cake moxibustion (MCM)[139]. Numerous studies have demonstrated that moxibustion can have significant benefits when used to treat CFS. For example, in one study (n = 72 CFS patients), moxibustion at the Gao Huang acupoint (BL43) resulted in a higher overall effectiveness rate (88.9%) than regular acupuncture control treatment (72.2%)[140]. In another study (n = 30 CFS patients), gentle moxibustion on key acupoints like Guanyuan and Qihai was found to have therapeutic benefits[141]. Moxibustion not only supplements deficiencies and warms the body but also regulates organ functions. A meta-analysis of 15 studies further confirmed the effectiveness of CFS in treating CFS[142]. Notably, MCM has demonstrated superior therapeutic effects, as it benefits from both the thermal effects of moxibustion and transdermal drug absorption. For instance, using Xiaoyao powder. MCM effectively improved various symptoms associated with LDSD syndrome in CFS[143]. Moreover, interposed ginger moxibustion, a safe and effective intervention, has shown significant effects in alleviating fatigue and physical symptoms in CFS patients[144].

While moxibustion may occasionally lead to burns and other adverse reactions, standardized operations can effectively mitigate these incidents[145]. Overall, moxibustion offers a simple, economical, and effective treatment option for CFS, suitable for both therapeutic and preventive purposes, especially for the modern sub-healthy population.

Acupuncture

Acupuncture, a widely utilized modern clinical treatment, has demonstrated significant effectiveness against CFS. The stimulation of specific acupoints can replenish *qi* and blood, balance *yin* and *yang*, and it is associated with minimal side effects[146]. For instance, a study on 60 female CFS patients revealed that acupuncture on acupoints such as Kidney Shu, Spleen Shu, Qihai, Guanyuan, and Zusanli significantly improved symptoms[147]. Additionally, combining acupuncture with moxibustion has shown enhanced efficacy compared to acupuncture alone[148]. The "Jin Three Needles" technique, representative of the Southern acupuncture school, has proven effective for CFS treatment, significantly improving fatigue and psychological state in 80 patients with an effectiveness rate of about 87.5%[149]. Commonly used acupoints for CFS treatment include BL13, BL15, BL18, BL20, BL23, ST36, SP6, CV4, and CV6, which also provide valuable clinical insights[150].

Massage

Massage therapy has been shown to effectively alleviate fatigue in CFS patients, improving their quality of life and physical capacity. Key areas of manipulation include the Du channel on the back and the bilateral bladder meridians. By stimulating these meridians and related areas, massage promotes the circulation of *qi* and blood, harmonizes *yin* and *yang*, and helps replenish and expel pathogenic factors. Personalized treatment plans are tailored to address specific symptoms of CFS. Additionally, as a treatment involving physical contact, massage helps reduce tension, restlessness, and anxiety in patients, facilitating communication and addressing emotional issues associated with CFS. Studies have highlighted the efficacy of abdominal massage, which involves techniques such as rubbing, kneading, pushing, moving, and vibrating the abdomen. This approach has been found to be more effective for treating patients with Heart and Spleen Deficiency syndrome compared to oral administration of Gui Pi pills, resulting in reduced fatigue and improved concentration[151]. Furthermore, research comparing conventional massage with pivot massage techniques along the *shao yang* and *shao yin* meridians demonstrated a higher overall effectiveness rate (91.42%) in the pivot massage group compared to the conventional massage group (77.14%) after 3 months. The pivot massage group also showed greater improvements in clinical symptoms, Fatigue Scale-14 (FS-14) scores, and quality of life scores[152]. Combining back acupoint and head massage to address sleep disorders has also been shown to more effectively alleviate fatigue in CFS patients[153]. These studies indicate that massage therapy can play a significant role in improving sleep quality in individuals with CFS[154].

Comparative effectiveness of TCM and contemporary management approaches for CFS

A literature review to identify studies comparing the effectiveness of TCM treatments with contemporary management strategies for CFS showed that TCM treatments may offer significant benefits in alleviating CFS symptoms compared to conventional approaches such as vitamin B supplementation.

For instance, participants (200 CFS patients) in a 2024 multi-center RCT[129] were divided into two groups—100 patients received Huangqi (*Astragalus*) injection combined with Buzhong Yiqi acupuncture, while the other 100 received vitamin B supplements. After 2 weeks of treatment, various parameters were assessed, including TCM syndrome scores, fatigue symptoms, and serum superoxide dismutase (SOD), malondialdehyde (MDA), and oxidized low-density lipoprotein (ox-LDL) levels. The TCM treatment group achieved an effective rate of 88.54%, significantly higher than the 54.34% rate in the vitamin B group. Furthermore, the TCM group had significantly greater reductions in Fatigue Severity Assessment Scale (FSAS) scores for physical fatigue, mental fatigue, and sleep/rest response ($P < 0.05$) and higher SOD levels, while MDA and ox-LDL levels were significantly reduced ($P < 0.05$). No serious adverse events or reactions were reported in either group.

Similarly, an RCT by Han et al.[132] compared the efficacy of conventional Western medicine with a TCM approach using the Yishen Qianggan Kangpi formula. Of the 110 CFS patients included, 55 patients received conventional treatment, while the other 55 received the TCM formulation. After 8 weeks of treatment, the TCM group showed significant improvements in antioxidant enzyme levels (GSH-Px and SOD) and decreased lipid peroxide (LPO) levels compared to the control group ($P < 0.05$). Moreover, serum inflammatory marker (IL-6, IFN-γ, and lactic acid) levels were significantly lower in the TCM group, while immune function markers ($CD4^+$/$CD8^+$ ratio and $CD4^+$ cells) improved ($P < 0.05$). Scores on the FS-14 and TCM symptoms (including fatigue, weak waist and knees, dry eyes, loose stools, and muscle aches) were also significantly improved in the TCM group. The total effective rate in the TCM group was 96.36%, compared to 65.45% in the control group ($P < 0.05$). These findings suggest that TCM treatments may be more effective in reducing inflammation compared to Western medicine therapies, enhancing antioxidant capacity, and improving immune function in CFS patients with liver and kidney deficiencies.

In a 2019 study, researchers recruited 160 patients with CFS characterized by liver depression and spleen deficiency who had been treated at their hospital from July 2015 to December 2016[155]. Participants were randomly divided into two groups—treatment group patients ($n = 78$) received modified Xiaoyao powder, while control group patients ($n = 82$) received compound vitamin B and oryzanol; both treatment courses lasted 3 weeks. The treatment group showed a significantly higher total effective rate compared to the control group (89.74% *vs*. 68.29%, $\chi^2 = 10.992$, $P < 0.05$). Additionally, fatigue scale scores, TCM symptom scores, and overall CFS symptom scores were significantly lower in the treatment group compared to the control group after treatment ($P < 0.05$). These results suggested that modified Xiaoyao powder is more effective in treating CFS characterized by liver depression and spleen deficiency.

In the same year, another group published the results of an RCT involving 80 CFS patients who were randomly divided into an observation group and a control group, with 40 patients each[136]. Observation group patients were treated with Erxian decoction once daily (120 mL

morning and evening), while control group patients received vitamin B1 (20 mg), gluten (20 mg), and barley (four tablets). The efficacy index in the observation group was significantly higher compared to that in the control group ($P < 0.01$). These findings indicated that Erxian decoction is effective in treating CFS and holds promise for broader application in clinical practice.

To further strengthen the review, we assessed the quality of the studies cited, and noted that most were described as RCTs, which generally provide a higher level of evidence compared to observational studies. However, several significant limitations must be acknowledged. All the studies cited were published in Chinese databases rather than SCI-indexed journals, raising concerns about accessibility, peer review standards, and overall study quality. For instance, the trial by Wang et al. involved 200 participants and had a multi-center design, adding some robustness, but the short treatment duration of 2 weeks limits conclusions regarding long-term efficacy and safety. Moreover, potential biases such as blinding and allocation concealment were not explicitly addressed, raising questions regarding the reliability of the results. Similarly, although the study by Han et al.[132] provides insights into antioxidant and immune-modulating effects, it had a small sample size of 110 participants and lacked transparency regarding blinding, leading to concerns of selection bias; the study's reliance on a subjective symptom scale like the FS-14 may have also introduced measurement bias. Additionally, the 2019 studies on modified Xiaoyao powder and Erxian decoctions faced limitations such as small sample sizes, short follow-up periods, and a lack of consideration for confounding factors like lifestyle or concurrent treatments, which are crucial for evaluating the true effects of these interventions.

Overall, while several RCTs suggest that TCM may be promising in treating CFS compared to contemporary management approaches, the evidence remains limited due to issues such as small sample sizes, short treatment durations, lack of rigorous blinding, and reliance on subjective outcome measures. Therefore, there is a need for larger-scale, well-controlled trials published in internationally recognized journals. Future studies should focus on establishing standardized protocols, clearly defining outcome measures, and employing rigorous blinding to minimize bias and provide more definitive evidence regarding the efficacy of TCM for treating CFS.

Molecular mechanisms of TCM treatment

In this section, we explore the potential molecular mechanisms through which TCM treatments may exert beneficial effects in the context of CFS management. We also evaluate the strengths and limitations of these approaches to provide a detailed analysis. For a summarized view of all preclinical mechanistic findings, please refer to Table 7.

Herbs

Ginseng (Ren Shen)

Ginseng and its active components are believed to have therapeutic effects in CFS through diverse mechanisms, including enhancing the activity of antioxidant enzymes, reducing free radical levels and oxidative damage, modulating immune responses, and improving skeletal muscle function. Moreover, ginseng is known to contain numerous active components such as ginsenosides and ginseng polysaccharides, which have been proven to effectively combat fatigue[35].

The antioxidant response of ginseng is particularly notable. Its extract enhances the activities of SOD and catalase, effectively reducing the generation of free radicals, thus protecting the body from oxidative damage and delaying the onset of fatigue[177]. Additionally, ginseng extracts significantly lower serum levels of lactate, urea nitrogen, creatine kinase, MDA, and lactate dehydrogenase. They have also been shown to reduce MDA levels in the liver and gamma-aminobutyric acid and serotonin levels in brain tissues of Kunming mice, while simultaneously increasing swimming time, serum glutathione peroxidase, glucose, and SOD levels, as well as glycogen levels and SOD activity[178].

Ginseng has also been shown to prevent corticosterone-induced behavioral and neurophysiological abnormalities, enhance cell proliferation in the hippocampal dentate gyrus, upregulate Bax, phosphorylated protein kinase B (commonly known as Akt), phosphoinositide 3-kinase (PI3K), brain-derived neurotrophic factor (BDNF), tropomyosin receptor kinase B (TrkB), and phosphorylated cAMP response element-binding protein (CREB) levels, and downregulate cleaved caspase-3 and B-cell lymphoma 2 (Bcl-2) levels, thereby improving symptoms in CFS patients[163,179–180]. Furthermore, ginseng activates the PI3K/Akt/mammalian target of rapamycin (mTOR) signaling pathway, promotes the oxidation of fats for energy supply, and lowers serum levels of lactate dehydrogenase, blood urea nitrogen, and free fatty acids, conserving glycogen and protein during exercise[181–182].

A systematic review and meta-analysis of the efficacy and safety of ginseng and its herbal formulations in treating fatigue showed that ginseng herbal formulations can improve fatigue severity, particularly in cancer patients, although the effects were modest[183]. Another systematic review summarized the potential anti-fatigue mechanisms of ginseng extracts and their bioactive compounds, particularly focusing on their anti-viral, immune remodeling, endocrine system modulating, and metabolic actions, and suggested that ginseng is a potentially promising treatment for long-term COVID, especially targeting fatigue[184].

Ginsenosides, particularly Rb1 and Rg1, are key active components in ginseng extracts and have significant effects against fatigue. Studies indicate that Rb1 reduces inflammation and inhibits the activity of indoleamine 2,3-dioxygenase, prevents calcium homeostasis imbalance and mitochondrial membrane potential reduction in skeletal muscle cells, reduces MDA content, and enhances SOD activity in skeletal muscle cells, thus countering exercise-induced muscle cell damage and combating exercise fatigue[185].

Rg1 enhances mitochondrial function, reduces mitochondrial swelling and membrane permeability, promotes mitochondrial biogenesis, and activates the AMP-activated protein kinase (AMPK)/peroxisome proliferator-activated receptor gamma coactivator-1alpha (PGC-1α) signaling pathway, thereby exerting an

Table 7

Experimental and molecular mechanistic studies on TCM interventions for CFS

Study	Treatment	Phenotype	Molecular Mechanisms	Subjects
Yang et al. 2024[156]	Electroacupuncture	Weight loss; increased open-field activity; altered maze performance	Modulation of hippocampal protein phosphorylation to support synaptic function, cytoskeletal organization, and signaling	36 SD rats
Wei et al. 2023[157]	Astragalus polysaccharide	Weight loss; increased immobility; maze deficits	Restored gut microbial balance, enhanced short-chain fatty acid production, and activation of antioxidant pathways via Nrf2 while inhibiting NF-κB.	C57BL/6 mice
Wang et al. 2023[158]	Electroacupuncture	Improved maze learning and memory	Upregulated ERK, CREB, and BDNF signaling to strengthen hippocampal neuron structure and improve memory.	40 Wistar rats
Zhong et al. 2023[143]	Medicinal-cake moxibustion	Increased immunoglobulin levels; improved general condition	Enhanced humoral immunity by increasing serum IgA, IgG, and C3 levels and reducing the levels of T-cell inhibitory factors (Tim-3 and LAG-3)	50 SD rats
Lei et al. 2023[159]	Ginsenoside Rg1	Increased endurance and body weight	Regulated EGFR, AKT1, and VEGFA expression and modulated taurine and mannose-6-phosphate metabolism to combat fatigue	32 SD rats
Li et al. 2022[160]	Guipi decotion	Reduced immobility; lower corticosterone	Activation of the PI3K/Akt and BDNF/CREB pathways and balancing of apoptotic proteins (Bax/Bcl-2, caspase-3) to protect neurons	72 SD rats
Miao et al. 2022[161]	Danggui Buxue decotion	Improved fatigue behavior and cognition	Modulating amino-acid and glycerolipid metabolism—especially glycine, serine, and threonine metabolism pathways—to alleviate fatigue	40 SD rats
Huang et al. 2022[162]	Angelica + Astragalus extract	Enhanced exercise performance	Inhibited NF-κB activation and pro-inflammatory cytokines (IL-1β, IL-6) while boosting catalase activity	48 ICR mice
Li et al. 2022[160]	Atractylodes polysaccharides	Prolonged swim endurance	Increases antioxidant defense by increasing SOD activity and lowering malondialdehyde levels	80 ICR mice
Araki et al. 2021[163]	Guipi decotion	Reduced depression-like behavior; improved memory	Prevented corticosterone-induced neuronal damage by preserving neurotrophic factors and supporting hippocampal neurogenesis	15 ddY mice
Feng et al. 2021[164]	Electroacupuncture	Improved maze performance	Suppressed NF-κB p65 expression in the hippocampus to reduce neuroinflammation and support cognitive function	48 SD rats
Li et al. 2021[165]	Xiaoyao powder	Reduced depressive-like behaviors	Regulated arachidonic-acid metabolism and MAPK signaling to alleviate depression-like symptoms	64 SD rats
Mu et al. 2020[166]	Paeoniflorin	Reduced depression-like behavior	Balanced monoamines and neurotrophic factors, reduced HPA-axis overactivation, and reduced oxidative damage	101 SD rats
Li et al. 2019[167]	Moxibustion	Reduced depression-like behaviors	Enhanced tryptophan transport and serotonin synthesis while diverting metabolism away from the kynurenine pathway	77 Wistar rats
Li et al. 2019[168]	Abdominal massage	Improved motor activity and sleep	Increased hippocampal BDNF and CREB mRNA levels, promoted neuronal recovery and improved fatigue-related symptoms	30 SD rats
Li et al. 2019[169]	Abdominal massage	Improved motor activity and mood	Balanced intracellular calcium levels and downregulated MAPK/ERK signaling to protect neurons and reduce fatigue	30 SD rats
Yang et al. 2018[170]	Electroacupuncture	Improved motor activity and sleep	Lowered pro-inflammatory cytokine (IL-1β and IL-6) levels to support neuronal integrity and reduce fatigue	36 Wistar rats
Wang et al. 2018[171]	Mechanical massage	Improved motor activity and sleep	Reduced IL-1β and IL-6 levels and restored hippocampal and hypothalamic neural architecture	36 SD rats
Chen et al. 2018[172]	Saikosaponin A	Reduced depression/anxiety behaviors	Restored HPA-axis balance and enhanced BDNF-TrkB neurotrophic signaling to ease depression and anxiety	72 Wistar rats
Zhao et al. 2017[173]	Xiaoyao pills	Improved motor activity and sleep	Regulated HPA-axis hormones (ACTH, cortisol, CRH) and reduced peripheral inflammation to improve fatigue	40 SD rats
Yu et al. 2017[174]	Modified Xiaoyao powder	Reduced depression/anxiety behaviors	Suppressed inflammatory cytokines (IL-1β, IL-6, TNF-α) and raised hippocampal serotonin levels to alleviate mood symptoms	60 SD rats
Cao et al. 2016[175]	Danzhi Xiaoyao powder	Reduced anxiety; preserved neuron survival	Inhibited α-synuclein overexpression, lowered corticosterone levels, and increased PP2A levels to protect neurons under stress	50 SD rats
Merzoug et al. 2014[176]	Quercetin	Reduced anxiety/depression behaviors	Scavenged free radicals and modulated corticosterone levels to reduce oxidative stress and improve mood	68 Wistar rats

ACTH: Adrenocorticotropic hormone; AKT1: Phosphorylated protein kinase B; BDNF: Brain-derived neurotrophic factor; CREB: cAMP response element-binding protein; CRH: Corticotropin-releasing hormone; EGFR: Epidermal growth factor receptor; HPA: Hypothalamic-pituitary-adrenal; IL: Interleukin; NF-κB: Nuclear factor κB; PI3K: Phosphoinositide 3-kinase; PP2A: Protein phosphatase 2A; SOD: Superoxide dismutase; TNF-α: Tumor necrosis factor α.

anti-fatigue effect[186]. Rg1 also influences various pathways related to fatigue behavior, including regulating the epidermal growth factor receptor (EGFR) signaling pathway, reducing the $CD4^+/CD8^+$ T cell ratio, and increasing liver and muscle glycogen levels, all of which contribute to its anti-fatigue effects[159,179,187].

In a recently published paper, researchers investigated the potential therapeutic mechanisms of Qingjin Yiqi granule (QJYQ), a herbal formulation clinically used for post-COVID-19 treatment, in treating CFS[188]. They found that the bioactive compounds in QJYQ, specifically the ginsenosides Rb2 and RG4, exhibited high binding affinity to endothelial cell-selective adhesion molecule (ESAM), suggesting a possible therapeutic pathway. The study followed 4,212 adults aged ≥65 years over a 7-year period, identifying 435 CFS cases. Using causal modeling and multivariate logistic regression, frequent cough and insomnia were identified as novel causal factors for CFS. Further proteome-wide Mendelian randomization analysis revealed a causal link between elevated ESAM levels and both frequent cough and insomnia in CFS. The study concluded that QJYQ may help treat CFS by targeting ESAM, though further validation in animal models is needed.

Ginseng polysaccharides are also vital active components with anti-fatigue effects and the ability to regulate immune responses. These polysaccharides alleviate exercise-induced fatigue by reducing insulin secretion and enhancing gluconeogenesis[189] and also increase the activities of SOD and glutathione peroxidase (GSH-Px), lower MDA levels, and reduce the production of free radicals, thereby protecting the body from oxidative damage[190].

The therapeutic actions of ginseng, ginsenosides, and ginseng polysaccharides in treating CFS encompass antioxidative stress, energy metabolism regulation, immune modulation, neuroprotection, and anti-apoptotic effects. These research findings suggest that ginseng and its components are promising candidates for the treatment of CFS. However, given the limitations of the research methods used and the lack of sample diversity in previous studies, more methodologically rigorous studies are needed to validate the anti-fatigue effects of ginseng and its components and to provide standardized guidelines for clinical application.

Astragalus (Huang Qi)

Astragalus and its polysaccharide components are recognized for their therapeutic effects on CFS through various mechanisms, including immune response modulation, gut microbiota regulation, and antioxidant and anti-inflammatory actions. Clinical research has consistently shown the beneficial impacts of *Astragalus* and its extracts in managing CFS. For example, *Astragalus* effectively modulates immune responses by inhibiting the proliferation of Th17 cell populations, which play a crucial role in the production and release of pro-inflammatory cytokines[191]. This modulation is essential for managing inflammatory responses and underscores its potential for broader therapeutic use.

Further investigations have revealed that *Astragalus* exhibits significant antioxidant and anti-inflammatory effects in neuronal cells. This is particularly evident through its interaction with butyrate, which plays a critical role in neuroprotection and in maintaining the health and functionality of the nervous system[157]. Additionally, studies mimicking high-altitude conditions have demonstrated that *Astragalus* extracts can enhance the activity of antioxidant enzymes and reduce the production of reactive oxygen species, effectively mitigating oxidative stress and fatigue induced by physical exertion[192].

The compound's scope of influence extends to traditional medicine practices; *Astragalus* injection solution combined with tonic-center-reinforcing acupuncture has shown significant effects in enhancing the body's antioxidant stress capacity, increasing SOD levels, and reducing serum MDA and ox-LDL levels[129]. Furthermore, studies on complex extracts primarily containing *Astragalus* have demonstrated their ability to reduce the levels of lactate dehydrogenase, creatine kinase, and the inflammatory cytokines IL-1β and IL-6 and effectively prevent inflammation mediated by NF-κB activation[162]. Metabolic pathway analysis to explore the underlying metabolic influence suggested that these extracts may alleviate CFS by regulating sphingolipid metabolism, glycerophospholipid metabolism, valine, leucine, and isoleucine biosynthesis, as well as the D-serine and D-ornithine metabolism[193]. Studies have also found that the metabolism of glycine, serine, and threonine is closely associated with the therapeutic improvement of CFS by *Astragalus* complex extracts[161], thus broadening the understanding of its mechanisms of action.

With regard to rehabilitation, *Astragalus* has demonstrated its efficacy in reducing Fatigue Severity Scale, Fugl-Meyer Assessment, and visual fatigue scale scores and treating post-stroke fatigue. It can also enhance quality of life indicators such as the Stroke-Specific Quality of Life Scale score, Barthel Index, and Modified Barthel Index, all while causing minimal adverse reactions[194]. This highlights its potential role in alleviating fatigue during the recovery phase of acute diseases. The combined use of *Astragalus* with other herbal extracts, such as *Angelica* and deer antler, has been proven to improve chronic fatigue and influence muscle fatigue by maintaining high lactate levels[195], highlighting how this strategy can further enhance the efficacy of *Astragalus*. In the emerging field of post-COVID-19 fatigue research, *Astragalus* has attracted further interest and has been explored for its potential to alleviate fatigue. A real-world observational study showed that a compound extract containing *Astragalus* significantly improved fatigue levels and quality of life of patients with post-COVID-19 fatigue[196], further confirming the potential value of *Astragalus* in relieving various types of fatigue.

Astragalus polysaccharides play a significant role in regulating the gut microbial community structure. They increase the abundance of beneficial bacteria and promote the production of short-chain fatty acids and growth of anti-inflammatory bacteria, which are all crucial for maintaining gut health and reducing inflammatory responses. Additionally, *Astragalus* polysaccharides can reverse the abnormal expression of Nrf2 and NF-κB and their downstream factors in the brain-gut axis, alleviating the reduction of short-chain fatty acid levels in

the cecal contents of CFS patients, thus revealing the potential role of *Astragalus* polysaccharides in regulating the brain-gut axis and improving CFS symptoms[157].

In terms of metabolic and inflammatory regulation, *Astragalus* polysaccharides demonstrate anti-fatigue activity by reducing serum lactate and ammonia levels and increasing glycogen deposition in the liver and muscles[197]. This action has potential benefits for enhancing athletic performance and endurance. When combined with other herbal extracts, *Astragalus* polysaccharides can reduce intracellular reactive oxygen species levels induced by hydrogen peroxide, thus enhancing cell protective effects[162]. This synergistic action may improve the therapeutic effects of *Astragalus* polysaccharides. Additionally, *Astragalus* polysaccharides were shown to reduce TNF-α secretion in Caco-2 cells, thereby modulating inflammatory responses[191]. This anti-inflammatory action is significant for controlling chronic inflammation and the development of related diseases. The antioxidant properties of *Astragalus* polysaccharides are crucial for protecting cells from oxidative damage and delaying the development of fatigue.

In clinical applications, *Astragalus* polysaccharide injections could significantly improve fatigue response rates in breast cancer patients by over 75%[191]. This result emphasizes the potential application of *Astragalus* polysaccharides in the treatment of CRF.

Collectively, these research findings indicate that *Astragalus* and *Astragalus* polysaccharides produce therapeutic effects on CFS through multiple mechanisms, including regulation of the gut microbiota and metabolites, alleviation of oxidative stress and inflammation, improvement of exercise capacity and endurance, immune function modulation, neuroprotection, and impact on post-stroke fatigue. These discoveries provide scientific justification for the use of *Astragalus* and *Astragalus* polysaccharides in the treatment of CFS and pave the way for future research and clinical practice.

Atractylodes (Bai Zhu)

Atractylodes might exert therapeutic effects in CFS through multiple mechanisms, including enhancing the activity of antioxidant enzymes, reducing oxidative damage, regulating the expression of neurotrophic and anti-inflammatory factors, and modulating immune functions. Neurophysiologically, as a primary ingredient in Gui Pi decoction and other TCM formulations, *Atractylodes* has been shown to prevent behavioral and neurophysiological abnormalities in mice subjected to long-term corticosterone treatment, including depressive-like behaviors and spatial memory impairments, while also enhancing the survival rate of hippocampal cells and the number of newly generated immature neurons[163]. These effects are likely related to the regulation of neurotrophic factors and antioxidant enzyme expression by *Atractylodes*.

Atractylodes and its formulations can enhance the levels of immunoglobulins (IgA, IgG, IgM), potentially improving the immune function of CFS patients[171]. *Atractylodes* formulations can also reduce inflammatory responses by inhibiting the overexpression of IL-1β, IL-6, and TNF-α mRNA in hippocampal tissue and increasing the content of 5-HT in the hippocampus, thereby regulating neurotransmitter levels and improving depressive symptoms in rats[198]. Additionally, these formulations affect the endocrine system by increasing levels of adrenocorticotropic hormone (ACTH), corticosterone, and hypothalamic corticotropin-releasing hormone (CRH)[173]. They can also suppress the upregulation of α-synuclein and corticosterone in the hippocampus caused by chronic stress, as well as the downregulation of protein phosphatase 2A (PP2A) at the mRNA and protein levels, thus combating depressive symptoms[175].

In terms of antioxidative effects, *Atractylodes* polysaccharides increase the activity of SOD in mouse serum and reduce MDA content, suggesting that they exert their anti-fatigue effects by enhancing antioxidant capacity and reducing oxidative damage[160]. In the treatment of CRF, the mechanisms of action of *Atractylodes* primarily involve compounds such as quercetin, kaempferol, and luteolin, which function through targets such as AKT1, TNF, and IL-6. Thus, it regulates cytokines, cancer signaling pathways, and metabolic pathways, suggesting its anti-cancer fatigue effects[160].

Bupleurum (Chai Hu)

Bupleurum, also known as Chai Hu, offers multiple therapeutic benefits for CFS. It boosts the activity of antioxidant enzymes, reduces oxidative damage, and modulates both neurotrophic and anti-inflammatory factors as well as immune functions. For instance, Bupleurum and white peony root (Bai Shao) in the formulation Xiaoyao powder work synergistically to reduce arachidonic acid levels and inhibit the activities of enzymes like prostaglandin-endoperoxide synthase 1 (PTGS1) and prostaglandin-endoperoxide synthase 2 (PTGS2). This not only regulates arachidonic acid metabolism but also has anti-depressant-like effects[165].

Additionally, *Bupleurum* polysaccharide (BCP-2) demonstrates several robust effects. It significantly extends the endurance of mice in forced swimming tests, boosts glycogen reserves, enhances the antioxidant system, and lowers concentrations of blood urea nitrogen, lactate, lactate dehydrogenase, and creatine kinase. These beneficial outcomes are facilitated through the modulation of the AMPK and Nrf2 signaling pathways within skeletal muscle, thus mitigating physical exhaustion[199].

Moreover, saikosaponin A, a principal compound in *Bupleurum*, plays a pivotal role in neural health. It effectively reinstates the normal functioning of the HPA axis in rats subjected to chronic unpredictable mild stress and enhances hippocampal BDNF-TrkB signaling. This is particularly significant in easing symptoms associated with perimenopausal depression[172].

Rhodiola rosea (Hong Jing Tian)

Rhodiola rosea, a traditional medicinal herb, is recognized for its diverse potential benefits and reputed for its anti-fatigue, anti-depressant, anti-anxiety, and neuroprotective properties[200]. Notably, randomized, double-blind, placebo-controlled clinical trials have shown that the *Rhodiola* extract SHR-5 can significantly enhance quality of life and alleviate fatigue. This effect is thought to stem from its regulatory influence on the HPA axis, particularly through reducing cortisol levels to ease stress responses[201].

Other clinical studies have validated that standardized *Rhodiola* extracts can effectively modulate cortisol responses and boost mental performance, notably enhancing concentration in healthy individuals and lessening fatigue in those suffering from fatigue syndrome[202]. Despite these promising results, some systematic reviews have raised concerns about inconsistencies in research findings and methodological shortcomings that compromise the reliability of these assessments[200]. However, a study on nano-formulated *Rhodiola* combined with aerobic exercise revealed a more pronounced anti-fatigue effect compared to standard doses, suggesting that an improvement in bioavailability could enhance its efficacy[203].

While the preliminary results from both clinical and animal studies are encouraging, further investigation is crucial to substantiate their outcomes. More rigorous clinical trials are particularly needed to confirm the effectiveness of *Rhodiola* in treating CFS and its potential role in managing cognitive impairments and fatigue associated with post-COVID syndrome[204]. Furthermore, a deeper exploration into its molecular mechanisms of action, including its antioxidant and anti-inflammatory activities and its beneficial impacts on cardiovascular and reproductive health, is necessary[205–206].

In conclusion, while TCM formulations have demonstrated significant potential in addressing fatigue and associated symptoms, there is a pressing need for high-quality research to fully elucidate their clinical applications and delve into their molecular mechanisms of action. Specifically, it is crucial to investigate the precise effects and safety of these herbs in targeted treatments to ensure their effective and secure integration into modern therapeutic practices.

Moxibustion

Moxibustion has been shown to finely regulate neurotransmitter receptor levels, particularly the expression of 5-HT1A receptor mRNA, and effectively relieve physical fatigue and emotional symptoms such as depression and irritability caused by CFS[167]. Notably, this mechanism could be a novel strategy for the neurological treatment of CFS. Multiple studies have also demonstrated the significant effects of moxibustion on the immune system in CFS treatment. For example, thunder-fire moxibustion can regulate peripheral blood T lymphocyte subgroups, indicating its potential to modulate immune functions[133]. Additionally, moxibustion at acupoints such as stomach 36 (ST36) and bladder 13 (BL13) can reduce serum levels of inflammatory factors such as IL-1B, IL-6, and TNF-α, validating its positive effects on immune regulation[193]. Moxibustion at the Conception Vessel 4 (CV4) and Sea of Qi (CV6) acupoints enhances the levels of the immunoglobulins IgA, IgM, IgG and the complement components C3 and C4, thus balancing humoral and cellular immune functions; these findings offer new insights for the immunological treatment of CFS[207–208]. The "warming and tonifying" properties of moxibustion regulate *qi* and blood, help repair organs, and harmonize the nervous, endocrine, and immune systems, effectively enhancing immune function.

Moxibustion has also been shown to significantly regulate the endocrine system by modulating HPA axis function and affecting melatonin and salivary cortisol levels, thereby improving circadian rhythm disturbances in CFS patients[130,209]. Techniques like Panlong moxibustion can regulate serum CRH, ACTH, and cortisol levels, optimizing HPA axis function[171]. By lowering ACTH and cortisol levels and reducing HPA axis overactivation, moxibustion effectively alleviates CFS symptoms, offering a promising therapeutic approach for endocrine dysregulation in CFS[173].

Acupuncture and massage

Electroacupuncture on the head was found to significantly repair neurons in the hippocampus and hypothalamus of CFS model rats, improving morphology and number of intact nerve cells[170]. Another study found that electroacupuncture effectively enhanced learning and memory abilities in a rat model of CFS[158]. In another study, abdominal massage increased BDNF and CREB mRNA expression in the hippocampal area, promoting neuronal recovery[168]. This massage technique also regulated $Ca2^{+}$ concentrations and ERK and MAPK protein expression in the hippocampus, reducing neuronal apoptosis[169].

From an immunological perspective, mechanical massage treatment of CFS model rats with symptoms of kidney deficiency reduced serum IL-1B and IL-6 levels, demonstrating the positive role of massage in immune regulation[171]. Research also suggests that acupuncture can potentially help treat CFS by adjusting the T-bet/GATA-3 ratio in the plasma of rat models[210]. Furthermore, combined acupuncture and massage treatment for patients with CFS characterized by liver stagnation and spleen deficiency resulted in improvements in lymphocyte subgroups ($CD3^{+}$, $CD4^{+}$, $CD8^{+}$, $CD4^{+}$/$CD8^{+}$) compared to those in the control group, further validating the effectiveness of these methods in regulating immune functions[131].

Regarding endocrine treatment, electroacupuncture has been shown to significantly reduce NF-κB and COX-2 expression in the hippocampus and hypothalamus and to alleviate inflammatory responses and prevent neuronal damage in CFS model rats[164]. These findings offer new insights and methods for the endocrine treatment of CFS.

Commonalities and discrepancies across preclinical mechanistic studies

Preclinical studies on TCM in CFS models have uncovered consistent mechanistic motifs—namely, enhanced antioxidant defenses (↑SOD, CAT, GSH-Px), suppression of inflammatory mediators (↓MDA, NF-κB, IL-1β, TNF-α), activation of neuroprotective pathways (CREB/BDNF, PI3K/Akt/mTOR) and immune rebalancing (restored $CD4^{+}$/$CD8^{+}$ ratios, elevated IgA/IgG/C3, reduced Tim-3/LAG-3). However, the overall quality of these studies is limited by small sample sizes, variable induction protocols (forced-swim, chronic stress, immune challenges, etc), inconsistencies between treatment regimens (in terms of doses,

durations, routes), and lack of appropriate sham or vehicle controls and blinding or randomization details in some cases. Future study should prioritize standardized CFS models, harmonized treatment protocols, rigorous control arms, and comprehensive outcome panels—including behavioral, neuroendocrine, oxidative, immune, and metabolomic measures—to validate and translate mechanistic insights into clinically actionable strategies.

Conclusion and perspectives

Research on TCM for CFS is currently focused on several key areas. First, understanding the etiology and pathological mechanisms of CFS along with TCM syndrome differentiation will provide theoretical support for clinical treatment. Second, evaluating the efficacy of various therapies through clinical trials or systematic reviews would help identify safe and effective treatment options for easier clinical adoption. Third, determining experimental indicators will aid in exploring the mechanisms underlying TCM treatments for CFS from a modern medical perspective, facilitating the establishment of objective evaluation criteria.

TCM modalities—herbal decoctions, acupuncture, moxibustion, and massage—have demonstrated clinically meaningful reductions in fatigue and emotional symptoms, enhancing quality of life with favorable safety profiles. However, progress is hampered by heterogeneous diagnostic criteria, variable treatment protocols, and the scarcity of large-scale RCTs with long-term follow-up. Objective biomarkers, standardized evaluation criteria, and direct comparisons with western therapies are also lacking, complicating assessments of relative efficacy.

Another key challenge is the lack of universally accepted standard medications for CFS, which undermines the design of robust comparative studies. Without well-defined positive controls, benchmarking TCM against conventional treatments remains difficult, leaving a significant evidence gap.

To further advance the field, future investigations should adopt uniform diagnostic and treatment protocols; implement randomized, placebo-controlled trials with extended follow-up periods; and integrate molecular, physiological, and patient-reported outcomes. Prioritizing biomarker discovery and mechanism-driven endpoints will strengthen the evidence base and facilitate personalized, evidence-based use of TCM for CFS management.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Bowen Yang, Tianlin Wang, Ke Xiong, Xueqi Ding, Mengrui Zhang, Ming Huang, and Xiaohao Wu conducted the literature review and wrote the draft manuscript. Ming Huang and Xiaohao Wu corrected the draft. All authors agree to be accountable for all aspects of work to ensure integrity and accuracy.

Ethical approval of studies and informed consent

Not applicable.

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Data availability

All relevant data are within the manuscript.

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