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Traditional Chinese Medicine for Cancer-Related Fatigue: Evidence, Mechanisms, and Clinical Translation

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Abstract: Cancer-related fatigue (CRF) is one of the most prevalent and distressing symptoms experienced by patients with cancer and cancer survivors. It is characterized by persistent physical, emotional, and cognitive exhaustion that is disproportionate to recent activity and is not sufficiently relieved by rest. Because CRF is influenced by inflammation, immune dysregulation, neuroendocrine disturbance, mitochondrial dysfunction, sleep disruption, psychological distress, and treatment-related toxicity, many patients continue to experience clinically significant fatigue despite standard supportive interventions. Conventional management strategies, including exercise, psychosocial interventions, sleep optimization, and selected pharmacological approaches, are recommended in supportive oncology, but their effectiveness may be limited by heterogeneous responses, poor adherence, and the complex symptom burden of cancer patients. Traditional Chinese Medicine (TCM) offers a complementary framework for CRF through syndrome differentiation, restoration of healthy qi, regulation of qi and blood, and patient-tailored multimodal interventions. This review summarizes the TCM conceptualization of CRF, current evidence for herbal medicine, acupuncture, moxibustion, mind-body exercise, acupressure, dietary regulation, and supportive TCM interventions, potential biological mechanisms involving inflammatory regulation, neuroendocrine-metabolic disturbance, gut microbiota homeostasis, and psychoneuroimmunological processes. Clinical translation, safety considerations, outcome assessment, and future research priorities are also discussed. Current evidence supports the potential role of TCM as an adjunctive component of supportive cancer care. However, substantial heterogeneity in study design, syndrome classification, and outcome assessment continues to limit interpretation. Future research should prioritize standardized methodologies, biomarker-integrated evaluation, and pragmatic clinical studies capable of informing real-world implementation.

Keywords: Cancer-Related Fatigue; Traditional Chinese Medicine; Herbal Medicine; Acupuncture; Moxibustion; Supportive Oncology; Clinical Translation

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1. Introduction

1.1 Definition and Clinical Burden of Cancer-Related Fatigue

Cancer-related fatigue (CRF) remains one of the most prevalent and difficult-to-manage symptoms in supportive oncology. CRF is commonly defined as a distressing, persistent, and subjective sense of physical, emotional, or cognitive tiredness relat-

ed to cancer or cancer treatment, which is disproportionate to recent activity and interferes with usual functioning [1]. Unlike ordinary fatigue, it is not adequately relieved by rest and may persist during active treatment, after treatment completion, or throughout survivorship [1]. Patients may experience reduced physical endurance, impaired concentration, emotional distress, sleep disturbance, and decreased participation in daily activities [2]. These manifestations make CRF one of the most clinically important symptoms in oncology supportive care [3].

The prevalence of CRF varies according to cancer type, disease stage, treatment modality, assessment tool, and timing of evaluation [4]. It is frequently reported during chemotherapy, radiotherapy, targeted therapy, endocrine therapy, and survivorship [2]. In addition to physical exhaustion, CRF may worsen treatment adherence, social participation, work capacity, and quality of life (QoL) [5]. Studies in Chinese cancer populations have also shown that fatigue is associated with sleep disturbance, physical inactivity, and other modifiable clinical factors [6]. These findings suggest that CRF should not be regarded as a minor treatment-related complaint, but as a multidimensional clinical syndrome requiring systematic assessment and management.

CRF also has implications beyond symptom burden. Severe or persistent fatigue may reduce patients' ability to tolerate treatment, maintain rehabilitation activities, and engage in self-management [7]. In breast cancer survivors, fatigue may coexist with psychological distress and reduced exercise adherence, further complicating long-term recovery [8]. For children and adolescents with cancer, fatigue may interfere with physical activity, school participation, and psychosocial adaptation [9]. Therefore, improving fatigue management has become an important component of patient-centered oncology care.

1.2 Limitations of Current Management

Current management of CRF generally includes screening for reversible causes, exercise interventions, psychosocial support, sleep management, nutritional optimization, and selected pharmacological approaches [10]. These recommendations are broadly consistent across major international guidelines, including those issued by ESMO and NCCN [11]. However, clinical implementation remains challenging. Patients with advanced cancer, severe fatigue, anemia, pain, poor performance status, or treatment-related toxicity may have difficulty adhering to exercise programs [8]. Psychological and educational interventions may also be limited by access, cost, patient acceptance, and availability of trained providers [12].

Pharmacological treatment for CRF remains limited. Wakefulness-promoting agents haven't consistently demonstrated clinically meaningful benefits across cancer populations [13]. Corticosteroids may provide short-term symptom relief in selected advanced cancer or palliative care settings, but prolonged use is restricted by potential adverse effects, including myopathy, immunosuppression, hyperglycemia, and mood changes [10].

Another limitation is that conventional approaches may not fully address the multifactorial nature of CRF. Chemotherapy-related inflammatory changes and cytokine dysregulation have been associated with fatigue severity [14]. Neuroendocrine disturbance, including altered cortisol rhythm, may also contribute to persistent fatigue in cancer survivors [15]. Mitochondrial dysfunction and impaired energy metabolism have been proposed as important contributors to persistent fatigue and reduced cellular energy availability [16]. Because these mechanisms may interact with sleep disturbance, psychological stress, nutritional status, and treatment toxicity, a single intervention targeting only one pathway may be insufficient for many patients.

1.3 Rationale for Traditional Chinese Medicine in Cancer-Related Fatigue

Traditional Chinese Medicine (TCM) has long been used in supportive care for patients with chronic weakness, reduced vitality, poor appetite, sleep disturbance, and treatment-related discomfort [17]. In the context of CRF, TCM emphasizes personalized assessment through pattern-based management and treatment principles such as strengthening healthy qi, tonifying the spleen and kidney, nourishing qi and blood, regulating the liver, resolving phlegm, activating blood, and harmonizing yin and yang [18]. These principles are not intended to replace biomedical diagnosis, but they may provide a structured approach for tailoring supportive interventions to different fatigue presentations.

TCM interventions are inherently multimodal and may include CHM, acupuncture, moxibustion, mind-body exercise, and acupressure. These approaches target different aspects of symptom burden and are often combined according to pattern classification rather than used in isolation [19-23].

The potential relevance of TCM also lies in its overlap with modern concepts of systems biology and integrative medicine.

CRF is unlikely to be explained by a single pathway [1, 14, 16]. Similarly, TCM interventions may influence multiple biological and psychosocial domains, including inflammatory signaling, immune function, neuroendocrine regulation, mitochondrial metabolism, oxidative stress, sleep quality, emotional state, and gut microbiota (GM) [24, 25]. Clinical efficacy, mechanism, safety, and feasibility should be assessed using rigorous research designs and standardized reporting.

1.4 Aim and Scope of This Review

This review discusses TCM conceptualization, biological mechanisms, clinical evidence, mechanistic research, safety considerations, and future directions for CRF management.

2. Methods

2.1 Review Design

This article was designed as a narrative review. A narrative approach was considered appropriate because the topic involves heterogeneous sources of evidence, including TCM theory, clinical studies, systematic reviews, mechanistic research, supportive oncology guidelines, and clinical translation, safety, and future research priorities. Unlike a systematic review, this article did not aim to answer a narrowly defined intervention question or quantitatively pool effect sizes. Instead, it aimed to provide an interpretative synthesis of evidence, mechanisms, and clinical translation issues related to TCM for CRF [26].

2.2 Literature Search

Relevant literature published up to March 2026 was identified from PubMed, Web of Science, Embase, the Cochrane Library, CNKI, and Wanfang Data. No language restrictions were applied during literature retrieval. The search terms included “cancer-related fatigue” , “cancer fatigue”, “Traditional Chinese Medicine”, “Chinese herbal medicine”, “herbal medicine”, “acupuncture”, “electroacupuncture”, “moxibustion”, “acupressure”, “Tai Chi”, “Qigong”, “Baduanjin”, “syndrome differentiation”, “supportive oncology”, “inflammation”, “immune regulation”, “neuroendocrine function”, “mitochondrial dysfunction”, “oxidative stress”, “gut microbiota”. Search was supplemented by manual screening of reference lists from relevant reviews and guidelines.

2.3 Source Selection

Clinical trials, systematic reviews, meta-analyses, mechanistic studies, clinical guidelines, expert consensus documents, and representative TCM theoretical sources were considered. Priority was given to studies directly related to CRF, cancer supportive care, or TCM interventions in oncology populations. Studies involving non-cancer fatigue models, non-fatigue symptoms, or non-oncology populations were used only when they provided mechanistic context and were not interpreted as direct clinical evidence for CRF.

2.4 Narrative Synthesis

The included literature was synthesized thematically according to TCM conceptualization, biomedical mechanisms, clinical evidence, mechanistic evidence, clinical translation, safety, and clinical translation, safety considerations, and future research priorities. Because the purpose was interpretative synthesis rather than quantitative evidence pooling, no meta-analysis was performed. Formal risk-of-bias assessment was not conducted, which is acknowledged as a limitation of this review. To improve transparency and methodological clarity, the review was prepared with reference to the Scale for the Assessment of Narrative Review Articles [26].

3. Traditional Chinese Medicine Conceptualization of Cancer-Related Fatigue

3.1 Historical and Theoretical Understanding of Fatigue-Related Symptoms

Fatigue-related symptoms in TCM are commonly interpreted through syndrome patterns involving qi deficiency, spleen dysfunction, blood deficiency, and prolonged depletion caused by chronic illness [27]. Classical theories generally attribute persistent fatigue to insufficiency of qi and blood, impaired spleen transformation, kidney essence depletion, disharmony of yin and yang, or prolonged disease damaging healthy qi [18]. In a modern oncology context, these classical concepts should be used as theoretical background rather than direct evidence of efficacy for CRF.

Cancer and anticancer treatment may consume healthy qi, impair spleen function, and weaken qi-blood production over time, resulting in persistent fatigue and reduced recovery capacity [18]. This interpretation is consistent with the TCM view that

prolonged illness often leads to deficiency, while stagnation, phlegm, stasis, and toxin may develop as secondary pathological factors [18]. Contemporary studies of Chinese herbal medicine (CHM) for CRF also commonly emphasize qi deficiency, spleen deficiency, and deficiency-excess complexity as important theoretical foundations [28].

Historical formulas such as Si Jun Zi Tang, Bu-Zhong-Yi-Qi-Tang, Shen Ling Bai Zhu San, Gui Pi Tang, and Ba Zhen Tang are often discussed in relation to fatigue, weakness, poor appetite, and qi-blood insufficiency [17, 19]. However, their application in CRF should be evaluated according to modern clinical evidence, cancer type, treatment stage, pattern classification, and patient safety rather than historical use alone.

3.2 Core Pathogenesis of Cancer-Related Fatigue in Traditional Chinese Medicine

From a TCM perspective, CRF may be summarized as a condition dominated by root deficiency with secondary excess [18, 28]. The root commonly involves deficiency of healthy qi, spleen qi, kidney essence or kidney yang, and insufficient production of qi and blood [18]. Secondary excess may include phlegm-dampness, blood stasis, toxin accumulation, and liver constraint [18]. This framework is clinically useful because many patients with CRF present with deficiency manifestations, such as weakness, reduced appetite, spontaneous sweating, and poor endurance, together with excess-related manifestations, such as heaviness, distension, pain, emotional constraint, or tongue changes.

The spleen is central to this framework because it governs transformation and transportation in TCM theory [27]. When spleen function is impaired, food essence cannot be efficiently transformed into qi and blood, which may manifest as fatigue, poor appetite, loose stools, heaviness, and reduced muscle strength [27]. Clinically, this theoretical pattern overlaps with the frequent coexistence of fatigue, nutritional problems, gastrointestinal symptoms, and reduced physical activity in cancer patients [6, 29].

Kidney deficiency is also relevant, especially in patients with long disease duration, advanced cancer, older age, repeated chemotherapy or radiotherapy, or persistent fatigue after treatment [18]. Kidney essence or kidney yang deficiency may manifest as deep fatigue, cold intolerance, low back soreness, weakness of the knees, reduced endurance, and slow recovery [18]. However, direct high-quality clinical evidence linking kidney-deficiency patterns specifically to CRF remains limited and should be further verified.

Liver constraint and emotional disturbance may contribute to fatigue through impaired qi movement, sleep disruption, mood symptoms, and reduced motivation [18]. This is clinically relevant because fatigue frequently coexists with anxiety, depression, and sleep disturbance in cancer survivors [8, 15]. Blood stasis, phlegm-dampness, and toxin accumulation may further complicate the condition, particularly in patients with pain, heaviness, edema, gastrointestinal dysfunction, or chronic inflammation [18]. These concepts may be cautiously linked with biomedical mechanisms such as inflammatory activation, impaired circulation, altered metabolism, and treatment-related tissue injury [14, 24].

3.3 Common Syndrome Patterns Associated with Cancer-Related Fatigue

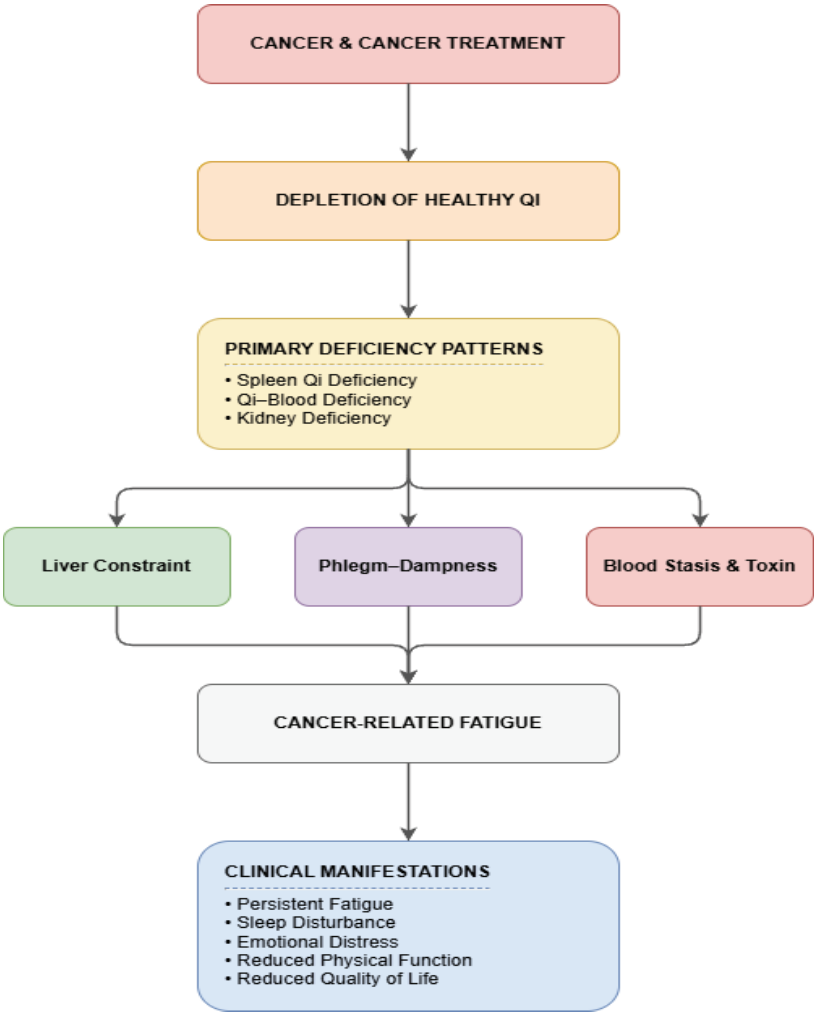
Pattern classification remains central to the TCM understanding of CRF. Although individual presentations vary considerably, clinical reports consistently indicate that most patients exhibit manifestations related to deficiency syndromes, often accompanied by secondary excess patterns. Commonly reported patterns include spleen qi deficiency, qi and blood deficiency, liver constraint with spleen deficiency, spleen–kidney yang deficiency, and mixed patterns involving phlegm-dampness, blood stasis, or toxin accumulation [28]. Rather than representing fixed diagnostic categories, these patterns frequently overlap and evolve throughout the course of cancer treatment and recovery.

Among the deficiency patterns, spleen qi deficiency and qi–blood deficiency are most frequently described in patients with CRF. Clinically, these patients often present with persistent tiredness, reduced appetite, poor physical endurance, shortness of breath, dizziness, palpitations, and impaired recovery after activity [27]. Such manifestations are commonly observed during chemotherapy, prolonged hospitalization, nutritional compromise, or recovery from intensive treatment. Consequently, therapeutic approaches aimed at strengthening spleen function and replenishing qi and blood form the basis of many CHM prescriptions used in CRF management. Prescription analyses have consistently identified qi-tonifying herbs such as Astragalus membranaceus, Codonopsis pilosula, Atractylodes macrocephala, and Poria cocos as core components of clinical practice [17, 29]. Not all patients with CRF present solely with deficiency manifestations. Emotional distress, sleep disturbance, appetite fluctuation, and gastrointestinal symptoms are common in cancer survivors and may correspond to patterns described

as liver constraint with spleen deficiency [30]. In patients with prolonged disease duration, repeated treatment exposure, advanced age, or marked functional decline, manifestations of spleen–kidney yang deficiency may become more prominent, including cold intolerance, reduced vitality, low back soreness, and delayed recovery [18]. Mixed excess patterns involving phlegm-dampness, blood stasis, or toxin accumulation are more often considered when fatigue coexists with pain, heaviness, edema, digestive dysfunction, or chronic treatment-related complications.

An important feature of TCM pattern classification is its dynamic nature. A patient initially presenting with predominant qi deficiency may subsequently develop manifestations associated with blood stasis, phlegm-dampness, emotional disturbance, or treatment-related complications. Therefore, pattern identification should be viewed as an ongoing clinical process rather than a one-time diagnostic label. This flexibility may be particularly relevant in CRF, where symptom burden frequently changes according to treatment stage, disease status, and recovery trajectory. The dynamic relationships among healthy qi depletion, pattern evolution, and fatigue manifestation are summarized in Figure 1.

Figure 1. Traditional chinese medicine conceptualization of cancer-related fatigue



Cancer and anticancer treatments may contribute to the depletion of healthy qi, resulting in the development of deficiency patterns involving spleen, kidney, and qi-blood systems. As disease progresses, secondary pathological factors such as liver constraint, phlegm-dampness, blood stasis, and toxin accumulation may further aggravate symptom burden and contribute to clinical heterogeneity. The interaction between deficiency and excess patterns is considered a key feature of CRF in TCM and may manifest as persistent fatigue, sleep disturbance, emotional distress, reduced physical function, and impaired quality of life.

4. Biomedical Mechanisms and Their Links to Traditional Chinese Medicine Pathogenesis

CRF is not explained by a single biological abnormality. Current evidence suggests that fatigue may arise from the

combined effects of inflammatory activation, neuroendocrine disturbance, circadian disruption, impaired energy metabolism, psychological stress, sleep problems, and reduced physical activity [1]. This complexity is important for TCM because CRF often presents as a mixed condition rather than a single fixed syndrome. In clinical practice, patients may show signs of deficiency, stagnation, dampness, stasis, or emotional constraint at the same time. Therefore, the relationship between biomedical mechanisms and TCM pathogenesis should be understood as a conceptual bridge, not as a one-to-one correspondence.

4.1 Inflammation and Immune Dysregulation

Inflammation is one of the most frequently discussed biological mechanisms of CRF. A systematic review of patients receiving chemotherapy showed that changes in inflammatory cytokines were associated with fatigue in cancer populations [14]. Pro-inflammatory mediators such as interleukin-6, tumor necrosis factor-α, and C-reactive protein have been repeatedly examined in relation to fatigue severity [1]. These inflammatory signals may affect the central nervous system, sleep regulation, appetite, motivation, and cognitive function [1].

From a TCM perspective, persistent inflammatory activity may be interpreted within patterns involving toxin, blood stasis, and impaired healthy qi, but these terms should be used as clinical interpretive concepts rather than biological equivalents of cytokine activation [18].

4.2 Neuroendocrine Dysfunction and Sleep–Circadian Disruption

Fatigue in cancer survivors is closely related to stress regulation and sleep. The hypothalamic–pituitary–adrenal axis is involved in the physiological response to stress, and altered cortisol rhythm has been reported in fatigued cancer survivors [15]. This finding suggests that CRF may persist even after the completion of active treatment because the body's stress-regulation system remains disturbed.

Sleep disturbance is another major contributor. Insomnia, fragmented sleep, and reduced sleep efficiency can aggravate fatigue, while fatigue itself may reduce daytime activity and further disrupt sleep rhythm [1]. This reciprocal relationship is clinically important because patients often present with a cluster of symptoms rather than fatigue alone.

In TCM terms, fatigue accompanied by insomnia, irritability, poor concentration, emotional distress, and reduced motivation is often interpreted through patterns such as liver constraint, heart-spleen deficiency, or disharmony between yin and yang. This does not mean that these TCM patterns are identical to HPA-axis dysfunction. Rather, both frameworks emphasize that fatigue is closely connected with sleep, emotion, and stress adaptation.

4.3 Mitochondrial Dysfunction, Oxidative Stress, and Energy Homeostasis

Energy metabolism is another important mechanism in CRF. Mitochondria are responsible for ATP production and cellular energy supply, and mitochondrial dysfunction has been proposed as a contributor to persistent fatigue [16]. When mitochondrial efficiency is reduced, patients may experience low endurance, exercise intolerance, and prolonged recovery after activity.

Cancer treatment may further influence mitochondrial function through oxidative stress, inflammatory activation, and metabolic injury [1]. Increased oxidative stress may impair skeletal muscle performance and contribute to reduced physical capacity [16]. These mechanisms are particularly relevant for patients who report weakness, reduced walking tolerance, and difficulty resuming daily activities after treatment.

Some TCM-related experimental studies have begun to explore this pathway. For example, Jian Pi Sheng Sui Gao was reported to improve mitochondrial dysfunction and oxidative stress in experimental models of CRF through AMPK-SIRT1- and HIF-1-related mechanisms [25]. This type of evidence is useful for mechanism generation, but it should not be overinterpreted as definitive clinical proof.

4.4 Gut Microbiota, Metabolic Regulation, and Emerging Mechanisms

In recent years, GM has emerged as a potential contributor to CRF. Growing evidence suggests that cancer, anticancer treatments, dietary changes, and reduced physical activity may alter gut microbial composition and function, thereby affecting immune responses, metabolic homeostasis, and neuroendocrine signaling [31]. The GM communicates with the host through multiple pathways, including immune modulation, microbial metabolites, neurotransmitter regulation, and intestinal barrier function. Disruption of these pathways may contribute to systemic inflammation, altered energy metabolism, mood

disturbance, and fatigue [31]. Although the exact relationship between microbiota dysbiosis and CRF remains incompletely understood, the gut–brain axis has become an increasingly important area of investigation.

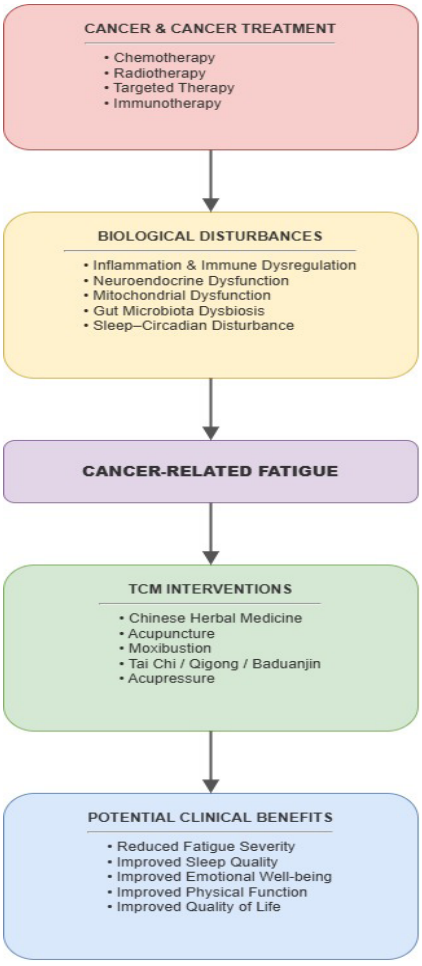
Several TCM interventions may influence GM composition and metabolic regulation. Experimental studies have suggested that herbal formulas can alter microbial diversity, regulate short-chain fatty acid production, and modulate inflammatory signaling pathways. However, most available evidence originates from animal studies or non-cancer populations, and direct clinical evidence in CRF remains limited.

From a TCM perspective, the relationship between the spleen and gastrointestinal function has long been emphasized [18]. Although the TCM concept of spleen function cannot be equated with the GM, emerging microbiome research provides an interesting biological perspective through which certain TCM theories may be explored and tested in future studies.

4.5 Integrating Biomedical Mechanisms with Traditional Chinese Medicine Pathogenesis

The multifactorial nature of CRF presents a challenge for both biomedical and TCM frameworks. Studies examining inflammatory cytokines, neuroendocrine function, mitochondrial metabolism, sleep disruption, and gut microbiota have collectively shown that fatigue arises from interacting biological and behavioral processes rather than from a single pathological pathway [1, 14-16]. Similarly, TCM describes CRF as a condition involving both deficiency and excess, with multiple pathological factors influencing symptom presentation [18]. This complexity mirrors clinical observations in TCM, where patients with similar cancer diagnoses often present with markedly different symptom profiles. Some individuals predominantly exhibit signs of qi deficiency and reduced vitality, whereas others present with emotional distress, sleep disturbance, digestive dysfunction, or manifestations interpreted as phlegm-dampness and blood stasis. Rather than viewing biomedical mechanisms and TCM theories as competing explanations, they may be considered complementary frameworks describing different dimensions of the same clinical phenomenon. The relationships between major biological disturbances implicated in CRF and the potential targets of TCM interventions are summarized in Figure 2.

Figure 2. Conceptual framework of cancer-related fatigue and potential targets of Traditional Chinese Medicine interventions



Cancer and anticancer treatments may contribute to multiple biological disturbances associated with cancer-related fatigue. TCM interventions, including Chinese herbal medicine, acupuncture, moxibustion, mind–body exercise, and acupressure, may influence several interconnected pathways and contribute to improvements in fatigue and related outcomes.

5. Clinical Evidence for Traditional Chinese Medicine in Cancer-Related Fatigue

5.1 Current State of Clinical Evidence

The clinical evidence base for TCM in CRF includes systematic reviews, randomized trials, and mechanistic studies evaluating CHM, acupuncture, moxibustion, mind-body exercise, and acupressure [19, 21, 22, 27]. However, the overall quality of evidence remains heterogeneous. Differences in cancer type, disease stage, treatment status, fatigue severity, pattern classification criteria, intervention protocols, and outcome measures complicate comparisons across studies [17]. Consequently, although many reports suggest beneficial effects, the certainty of evidence remains lower than that for established supportive care interventions such as exercise and psychosocial therapy [17].

An important observation across literature is that improvements in fatigue are frequently accompanied by changes in sleep quality, emotional well-being, appetite, and physical functioning [21-23]. This pattern suggests that TCM interventions may influence multiple symptom domains simultaneously, which is consistent with the multidimensional nature of CRF.

5.2 Evidence Supporting Chinese Herbal Medicine

The clinical literature on CHM for CRF is dominated by prescriptions targeting qi deficiency, impaired spleen function, and insufficient qi–blood generation. Across different cancer populations, qi-tonifying herbs such as Astragalus membranaceus, Codonopsis pilosula, Atractylodes macrocephala, and Poria cocos appear repeatedly in prescription analyses, suggesting a relatively consistent therapeutic strategy despite variation in individual formulas [29]. Bu-Zhong-Yi-Qi Decoction is among the most frequently discussed formulas in the CRF literature. Beyond its traditional use for fatigue and reduced vitality, experimental studies suggest potential effects on inflammatory regulation, oxidative stress, immune function, and energy metabolism [18]. Similar observations have been reported for Astragalus-containing prescriptions, although the majority of mechanistic evidence remains preclinical [28]. Interpretation of the available evidence requires caution. Most studies have been conducted in East Asian populations, frequently involve small sample sizes, and often use heterogeneous diagnostic and treatment protocols. Consequently, it remains unclear which patient subgroups derive the greatest benefit and whether findings can be generalized to broader oncology populations.

5.3 Evidence Supporting Acupuncture-Based Therapies

Acupuncture is the most frequently investigated non-pharmacological TCM intervention for CRF and has been incorporated into several supportive oncology programs [21]. Clinical studies have reported improvements in fatigue severity, sleep quality, emotional well-being, and overall QoL following acupuncture treatment [21]. Unlike herbal medicine studies, acupuncture trials often target symptom management directly and therefore provide a useful perspective on non-pharmacological fatigue interventions.

The potential value of acupuncture may extend beyond fatigue reduction alone. Fatigue in cancer survivors rarely occurs in isolation and is commonly accompanied by insomnia, pain, anxiety, depression, or reduced physical functioning. Improvements across several symptom domains have been reported following acupuncture interventions, suggesting that acupuncture may be particularly relevant for symptom clusters rather than isolated fatigue symptoms [20]. Nevertheless, interpretation of acupuncture evidence remains challenging. Considerable variability exists in acupoint selection, stimulation methods, treatment frequency, control conditions, and practitioner expertise [19]. Furthermore, sham-controlled designs remain controversial because many sham procedures may produce physiological effects. These methodological issues should be considered when interpreting study outcomes.

5.4 Emerging Evidence for Multimodal and Integrative Interventions

Increasing attention has been directed toward interventions that combine multiple therapeutic components rather than relying on a single modality. This trend reflects the recognition that CRF is a multidimensional symptom influenced by physical, psychological, behavioral, and biological factors [1]. Mind-body exercise programs such as Tai Chi, Qigong, and Baduanjin have demonstrated potential benefits for fatigue, sleep quality, emotional health, and physical functioning [23]. Unlike

conventional exercise programs, these approaches combine movement, breathing regulation, attentional focus, and relaxation, which may improve adherence among patients with limited exercise tolerance.

Other supportive interventions, including acupressure, dietary regulation, and TCM nursing approaches, have also shown preliminary benefits. Self-administered acupressure has been associated with improvements in fatigue and sleep quality among breast cancer survivors [22]. However, the evidence supporting these approaches remains considerably less robust than that for herbal medicine and acupuncture.

A notable development in recent years has been the growing interest in integrated supportive care models that combine conventional oncology treatment with tailored TCM interventions. Most multimodal studies remain small and heterogeneous, making it difficult to determine the relative contribution of individual intervention components.

5.5 Interpretation of the Current Evidence

Overall, the strongest clinical evidence currently relates to CHM and acupuncture [17, 19], whereas evidence for moxibustion, acupressure, dietary regulation, and TCM nursing remains preliminary [17-19, 21]. Existing studies are limited by small samples, heterogeneous protocols, variable pattern classification, and inconsistent fatigue outcomes. The available evidence therefore supports TCM as an adjunctive component of supportive cancer care, not as a replacement for established oncology treatment. The principal TCM interventions, representative evidence, and commonly reported outcomes are summarized in Table 1.

Table 1. Traditional Chinese Medicine interventions for cancer-related fatigue

Intervention	Main Clinical Focus	Representative Evidence	Major Outcomes
Chinese herbal medicine	Qi deficiency, impaired spleen function, qi–blood deficiency	Systematic reviews, RCTs, observational studies	Fatigue, QoL, physical function
Acupuncture	Fatigue with sleep disturbance, pain, emotional symptoms	RCTs, meta-analyses	Fatigue, sleep quality, emotional well-being
Moxibustion	Fatigue associated with deficiency patterns	Small RCTs	Fatigue, vitality
Tai Chi Qigong Baduanjin	Reduced activity tolerance and functional decline	RCTs	Fatigue, physical function, sleep
Acupressure	Self-management of persistent fatigue	RCTs	Fatigue, sleep quality
Multimodal TCM approaches	Complex symptom burden	Emerging clinical studies	Fatigue, symptom clusters, QoL

Abbreviations: TCM, Traditional Chinese Medicine; CRF, cancer-related fatigue; QoL, quality of life; RCTs, randomized controlled trials.

6. Mechanistic Basis of TCM Interventions in CRF

Understanding the biological basis of CRF is only the first step toward improving clinical management. An equally important question is whether TCM interventions can meaningfully influence the pathways implicated in fatigue development. Over the past decade, mechanistic research has increasingly accompanied clinical investigations, providing preliminary evidence that some TCM interventions may modulate biological processes associated with CRF. However, the strength of evidence varies considerably across different mechanisms, and most findings should be regarded as hypothesis-generating rather than definitive.

6.1 Evidence for Inflammatory and Immune Regulation

Mechanistic studies have reported changes in inflammatory biomarkers following TCM interventions. Experimental investigations involving Astragalus-containing prescriptions have reported reductions in pro-inflammatory cytokines and modulation of immune responses [28]. Similar findings have been described for Bu-Zhong-Yi-Qi Decoction, which has been linked to alterations in inflammatory signaling pathways and immune regulation in both laboratory and animal studies [18].

Despite these observations, evidence directly connecting biomarker changes with fatigue improvement remains limited. Most studies evaluate molecular outcomes separately from patient-reported fatigue measures, making causal interpretation difficult. Furthermore, inflammatory responses vary substantially according to tumor type, treatment exposure, and disease stage. Consequently, it remains unclear whether anti-inflammatory effects represent a primary mechanism of symptom improvement or simply reflect broader physiological changes associated with recovery.

6.2 Evidence for Metabolic and Mitochondrial Modulation

Several preclinical studies have focused on pathways related to cellular energy production and metabolic homeostasis. Among the most notable examples is Jian Pi Sheng Sui Gao, which has been reported to influence oxidative stress, apoptosis, and mitochondrial function through AMPK-SIRT1-HIF-1-associated signaling pathways [25].

These findings are of particular interest because reduced physical endurance and delayed recovery are common features of CRF. However, current evidence remains largely experimental. Direct confirmation that improvements in mitochondrial function translate into clinically meaningful reductions in fatigue is still lacking. Future studies incorporating both biological markers and validated fatigue assessments are needed to clarify the clinical significance of these observations.

6.3 Evidence for Multisystem Regulation

One notable characteristic of TCM intervention studies is that improvements are often observed across multiple symptom domains rather than fatigue alone. Clinical trials of acupuncture have reported concurrent improvements in fatigue, sleep quality, and psychological well-being [21]. Similar patterns have been observed in studies evaluating Tai Chi and Qigong, where benefits extend beyond fatigue to include physical function and emotional health [23].

These findings suggest that TCM interventions may exert effects across interconnected physiological and behavioral systems. Rather than acting through a single pathway, they may influence symptom networks involving sleep, mood, activity levels, stress adaptation, and perceived vitality. This perspective is consistent with the multidimensional nature of CRF and may help explain why isolated biomarkers often fail to fully capture treatment response.

6.4 Challenges in Mechanistic Interpretation

Although mechanistic studies have expanded rapidly, several limitations continue to restrict interpretation. First, much of the available evidence originates from cell-based experiments or animal models, which may not accurately reflect the complexity of CRF in clinical settings. Second, intervention protocols vary considerably among studies, limiting reproducibility and comparison. Third, biological outcomes and clinical outcomes are frequently reported separately, making it difficult to determine whether observed molecular changes are directly relevant to symptom improvement.

Another challenge is the tendency to overinterpret mechanistic findings. Demonstrating that an intervention influences a biological pathway does not necessarily establish that the pathway mediates fatigue improvement. Similarly, direct equivalence between TCM concepts and individual biological mechanisms is not supported by current evidence. Future mechanistic studies should integrate biomarkers, pattern classification, and validated fatigue outcomes within the same study design.

7. Clinical Translation, Safety Considerations, and Outcome Assessment

Although growing evidence supports the potential role of TCM in the management of CRF, translating research findings into routine oncology practice remains challenging. Current international guidelines emphasize exercise, psychosocial intervention, sleep optimization, and management of contributing factors as the foundation of CRF care, while evidence for complementary approaches continues to evolve [11]. One reason is the marked heterogeneity of CRF itself. Fatigue experienced during chemotherapy or radiotherapy often differs from fatigue observed in long-term cancer survivors, both in symptom presentation and underlying contributing factors (19). Sleep disturbance, emotional distress, pain, anorexia, reduced physical activity, and treatment-related adverse effects frequently coexist and may influence both symptom severity and treatment response [1].

This complexity has important implications for clinical decision-making. Current studies often evaluate mixed patient populations despite substantial differences in cancer type, treatment stage, nutritional status, comorbidities, and psychosocial burden. Such heterogeneity may partly explain the inconsistent findings reported across intervention studies. In TCM

practice, pattern-based management is intended to address these individual differences [18]. However, considerable variation exists in pattern classification criteria among published studies, limiting comparability and reducing the reproducibility of research findings [19]. Greater consensus regarding syndrome definitions and reporting standards would improve both clinical interpretation and future evidence synthesis.

Another issue concerns outcome assessment. Most clinical studies rely primarily on patient-reported outcome measures, reflecting the inherently subjective nature of fatigue. Instruments such as the Brief Fatigue Inventory and the Functional Assessment of Chronic Illness Therapy–Fatigue scale are widely used and have demonstrated acceptable validity in oncology populations [19]. Nevertheless, different instruments capture different dimensions of fatigue, including severity, interference with daily activities, emotional impact, and quality of life. As a result, comparisons between studies remain difficult, even when similar interventions are evaluated.

For this reason, there is increasing interest in multidimensional assessment strategies. Patient-reported outcomes remain essential but may be complemented by objective measures of physical function, activity monitoring, sleep assessment, and selected biological indicators. CRF has been associated with alterations in inflammatory signaling, neuroendocrine regulation, and energy metabolism [1]. Consequently, combining symptom scales with relevant biomarkers may provide a more comprehensive evaluation of treatment response. Such approaches may be particularly valuable when investigating TCM interventions, which often aim to improve overall functional status rather than a single symptom domain.

Safety is another consideration that deserves greater attention in future studies. Although acupuncture and CHM are generally regarded as safe when administered appropriately, adverse events should be reported systematically rather than assumed to be negligible. Acupuncture-related events are typically mild and self-limiting, with transient pain, bruising, and minor bleeding being the most frequently reported complications [21]. Herbal interventions require additional consideration because herb–drug interactions remain a potential concern in patients receiving chemotherapy, targeted therapy, or immunotherapy. The quality and consistency of herbal products may also vary according to cultivation, processing, and manufacturing practices. These issues highlight the need for rigorous quality control and transparent safety reporting in future clinical trials.

An important question is how TCM can be integrated appropriately into evidence-based supportive cancer care. Current supportive oncology programs increasingly emphasize multidisciplinary management involving exercise therapy, nutritional support, psychological intervention, symptom monitoring, and survivorship care. Within this framework, TCM may be most appropriately positioned as a complementary component rather than a replacement for established supportive care strategies. Future research should therefore focus not only on efficacy, but also on implementation, patient selection, treatment timing, and cost-effectiveness in real-world clinical settings.

8. Limitations and Future Research Priorities

Despite encouraging findings, several limitations continue to affect the interpretation and clinical application of current evidence. First, substantial heterogeneity exists across published studies. Differences in cancer type, treatment stage, intervention protocol, pattern classification criteria, and outcome assessment methods make direct comparison difficult and contribute to variability in reported results [17, 19].

A second limitation concerns study quality. Although randomized controlled trials have become increasingly common, many investigations remain single-center studies with relatively small sample sizes and short follow-up periods [17]. Long-term effects are therefore insufficiently understood, particularly for cancer survivors experiencing persistent fatigue after treatment completion.

Mechanistic research presents additional challenges. Experimental studies have identified potential effects of TCM interventions on inflammatory pathways, mitochondrial function, immune regulation, and gut microbiota homeostasis [18, 25]. However, most findings originate from animal models or laboratory investigations. The extent to which these biological changes contribute to clinically meaningful fatigue improvement remains uncertain. Future studies should integrate biomarker assessment with validated clinical outcomes to strengthen translational relevance.

Another unresolved issue involves the standardization of pattern classification. While patient-tailored treatment is a defining feature of TCM practice, inconsistent syndrome classification limits reproducibility and complicates evidence

synthesis. Developing consensus-based diagnostic frameworks may improve both clinical research quality and international communication.

Future studies should prioritize multicenter RCTs, pragmatic effectiveness studies, standardized pattern classification, validated fatigue outcomes, transparent safety reporting, and biomarker-informed designs. These priorities are essential for determining patient subgroups, optimal treatment timing, and integration within multidisciplinary supportive care.

9. Conclusions

CRF remains a prevalent and clinically significant symptom across the cancer continuum, with substantial effects on function, quality of life, and survivorship.

TCM offers a distinctive clinical perspective through pattern-based management and multimodal interventions that combine herbal medicine, acupuncture, mind-body exercise, and supportive care strategies. Existing evidence suggests potential benefits for fatigue and related symptom clusters, particularly sleep disturbance, emotional distress, and reduced functional capacity. At the same time, the current evidence base remains limited by methodological heterogeneity, inconsistent diagnostic frameworks, and insufficient long-term follow-up.

Future progress will depend less on demonstrating whether TCM can influence fatigue and more on clarifying which patients are most likely to benefit, how interventions should be integrated into multidisciplinary supportive care, and which outcome measures best capture meaningful clinical change. Greater integration of biomarker research, patient-reported outcomes, and real-world effectiveness studies may help bridge the gap between traditional theory and modern oncology practice. Whether these potential benefits can be translated into routine oncology practice will depend on stronger clinical evidence, standardized methodologies, and better integration with contemporary supportive care frameworks.

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Conflict of Interests

The authors declare that there is no conflict of interest regarding the publication of this paper.

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