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Review

Anti-fatigue effect of traditional Chinese medicines: A review

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A B S T R A C T

A third of the world's population suffers from unexplained fatigue, hugely impacting work learning, efficiency, and health. The fatigue development may be a concomitant state of a disease or the side effect of a drug, or muscle fatigue induced by intense exercise. However, there are no authoritative guides or clinical medication recommendations for various fatigue classifications. Traditional Chinese medicines (TCM) are used as dietary supplements or healthcare products with specific anti-fatigue effects. Thus, TCM may be a potential treatment for fatigue. In this review, we outline the pathogenesis of fatigue, awareness of fatigue in Chinese and western medicine, pharmacodynamics mechanism, and substances. Additionally, we offer a comprehensive summary of fatigue and forecast the potential effect of novel herbal-based medicines against fatigue.

Contents

1. Introduction

Unhealthy diet, lack of rest, physical activity deficiency, unreasonable exercise, high-intensity work, mental tension, sore throat, tender lymph nodes, multi-joint and muscle pain, headaches, and long-term bad mood are increasingly prevalent in a fast-paced living environment (van't Leven et al., 2010, Finsterer and Mahjoub 2014, Zielinski et al., 2019). Therefore, a large of individuals are in sub-healthy conditions (a special state between health and disease) and experience "unexplained fatigue." A third of the world's population suffers chronic fatigue for six months or even longer (Cook and Boore 1997, Klimas et al., 2012). There are several rea-

Abbreviations: ATPase, adenosine triphosphatase; BUN, blood urea nitrogen; CFS, chronic fatigue syndrome; CRP, C-reactive protein; FST, forced swimming test; GSH-Px, glutathione peroxidase; HG, hepatic glycogen; HPA, hypothalamic-pituitaryadrenal axis; IL-6, interleukin-6; LA, blood lactic acid; LDH, lactate dehydrogenase; LST, weight-loaded swimming test; MDA, malondialdehyde; PGC-1α, receptor-gamma coactivator-1α; POFS, postoperative fatigue syndrome; TCM, traditional Chinese medicines; SOD, superoxide dismutase.

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sons for fatigue, such as 'Qi' and 'Xue' deficiency (Peijiang and al 2001, xingzhe et al., 2022), postoperative fatigue, 'Pi Xu,' depression, poor sleep, energy imbalance, physical disability, aging, and long-term exercise (Luo et al., 2019). Meanwhile, diabetes, hyperthyroidism, anemia, high body fat, and liver disease, among other health conditions, may also cause fatigue (Swain 2006, Fox et al., 2020, Nocerino et al., 2020, Monahan et al., 2021). Fatigue can be a direct manifestation of disease or the side effect of some medications. Besides, fatigue can cause some illnesses. Fatigue is a complex and comprehensive physiological phenomenon without a clear mechanism and standard treatment.

Traditional Chinese medicine (TCM) has revealed its unique advantages in treating fatigue owing to the characteristics of multiple components, targets, and pathways. Studies have shown that TCM can alleviate fatigue through many pathways, such as antioxidation, decreasing the accumulation of metabolites, anti-inflammation, promotion of exercise endurance, and regulation of the hypothalamic–pituitaryadrenal axis (HPA) function, energy metabolism, gut microbiota, and immune system. Therefore, developing regulators/nutrients from TCMs against fatigue is of utmost importance.

Therefore, this review aims to provide a comprehensive guide for drug development against fatigue by overviewing the classification and cause of fatigue, the mechanism, the composition of natural medicine, and relevant animal model trials.

2. Fatigue in western medicine

Fatigue is a disabling symptom in which physical and cognitive functions are limited by interactions between performance and perceived fatigability (Enoka and Duchateau 2016). Fatigue is a common phenomenon in the general population. Fatigue generation is complex, with multiple causes and mechanisms (Twomey et al., 2017) (Fig. 1). There are three main classes of fatigue: general, chronic, and disease-related fatigue.

2.1. General fatigue

General fatigue, which mainly results from muscle fatigue, is created by intense long-time physical activity and is an effort by central and peripheral interactions (Boyas and Guével 2011, Twomey et al., 2017, Sadler and Cressman 2019), which are a classic dichotomy and have long been acknowledged. Peripheral fatigue is a consequence of an overactivity-induced decline in muscle function. There are three theories explaining peripheral fatigue: 1) the exhaustion theory, which entails the exhaustion of muscle and liver glycogen(Zhou and Jiang, 2019); 2) the radical theory, which is the imbalance between oxidation and the antioxidant system (Ding et al., 2011, Qin et al., 2014); and 3) the clogging theory, which is the accumulation of metabolites(Wang et al., 2008). Central fatigue is a sensation mediated by the central nervous system (CNS). It is a consequence of the failure of the CNS to transmit motor impulses or perform voluntary activities.

2.2. Chronic fatigue

Chronic fatigue syndrome (CFS) is unexplained fatigue that lasts six months or longer. This kind of fatigue cannot be alleviated by rest and is accompanied by at least four of eight case-defining symptoms, including sore throat, tender lymphadenopathy, impaired memory or concentration, myalgia, arthralgia, unrefreshing sleep, postexertional malaise, and headaches (Campos et al., 2011, Bower 2014, Fox et al., 2020). The pathophysiology of CFS is severely understood, and the biomarker is difficult to quantify. Some studies have reported that viral infection, endocrine, neuroendocrine, psychology, inflammation, and immunologic factors mediate the psychosocial response to CFS (Bower 2014, Thong et al., 2020). Neuroimmunological interactions and chronic immune activation have been implicated as major factors in the pathogenesis of CFS (Bower and Lamkin 2013). Other factors may include inflammation, oxidative stress, and mitochondrial dysfunction.

2.3. Disease-related fatigue

Fatigue is a common symptom of several chronic and mental diseases, such as acquired immune deficiency syndrome, cancer, heart failure, chronic kidney disease, multiple sclerosis, CFS, rheumatoid arthritis, and chronic obstructive pulmonary disease (Klimas et al., 2012, Bruno and Sethares 2015, Nocerino et al., 2020, Johansson et al., 2021). Additionally, postoperative fatigue syndrome is a universal condition after surgery (Chen et al., 2015, Lu et al., 2016). The pathophysiological mechanism of disease-related fatigue is unclear, although existing studies are mainly related to inflammation (Herlofson et al., 2018). The change of plasma C-reactive protein and interleukin-6 (IL-6) was prospectively associated with new-onset fatigue, which suggests that

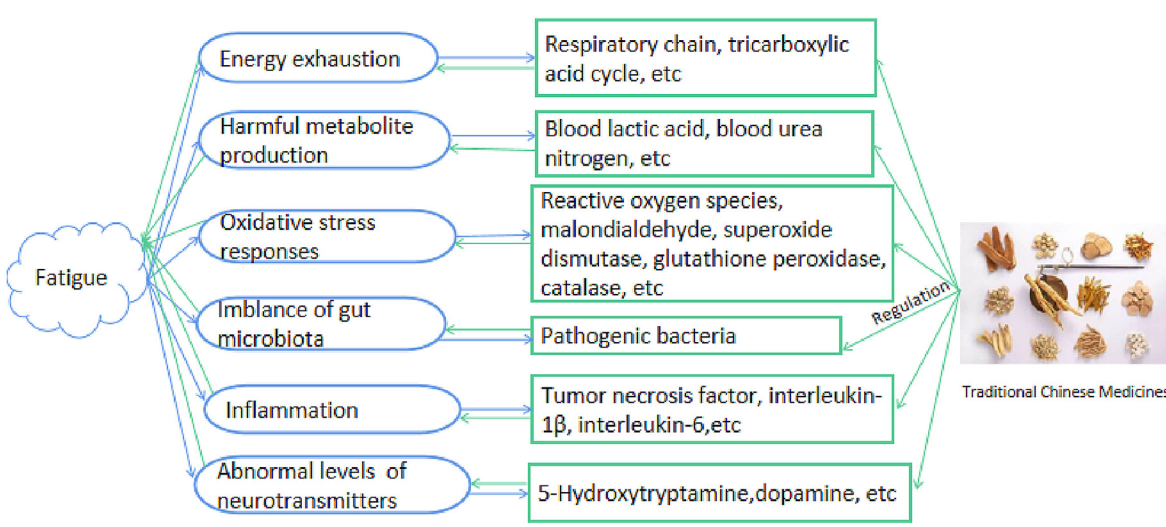

Fig. 1. Pathogenesis of fatigue and its management through TCM.

inflammation has a role in fatigue development (Lee and Giuliani 2019).

3. Fatigue in TCM

Fatigue has a long history in TCM. The word 'fatigue' was first recorded in 'Synopsis of the Golden Chamber' (xingzhe et al., 2022). Fatigue belongs to the 'deficiency' and 'consumptive disease' categories. The meaning of central fatigue is the closest to that of mental fatigue. Long-term and large-scale exercises easily led to an imbalance between 'Yin'and 'Yang' in the body, manifested as a deficiency of 'Qi' and 'Xue' (Jingtao 2014). The etiology and pathogenesis of fatigue are closely related to the dysfunction of 'Zangfu organs', mainly involving the dysfunction of 'Pi', 'Gan', and 'Shen', especially 'Pi' (Jingtao 2014). The TCM theory considers that the 'Pi' regulates water and nutrient metabolism. When the function of 'Pi' is normal, nutrients are easily absorbed and utilized by the body, thus providing sufficient energy and nutrition to the body. When the 'Pi' is abnormal (e.g., 'Pi Xu') (Jun et al., 2021), nutrient absorption and utilization are impaired, resulting in inadequate energy nutrition and supply, leading to fatigue. The 'Gan' has the function of storing 'Xue' and dredging 'Qi.' The undredged 'Qi' of 'Gan' will lead to depression and the dredging of 'Qi' of 'Gan' may alleviate fatigue (Chen and You 2022). The abnormal life rhythm caused by various stress aspects can easily cause 'Gan' dysfunction and further induce muscle weakness and body fatigue. The 'Shen' has the function of storing the essence of life, whereas the dysfunction of 'Shen' (e.g., 'Shen xu') will lead to decreased immunity, night sweats, and poor memory, which are connected with fatigue (Zhang et al., 2022).

4. Fatigue management by TCM

Many TCMs have been found to relieve fatigue. The animal models that evaluate the anti-fatigue efficacy of TCM mainly include forced weight-loaded swimming/running experiments,

Table 1
Anti-fatigue effects of herbal prescriptions.

Prescriptions	Composition	Mechanisms	Experimental models
Yangqi Shengye Tang (Hao 2010)	Polygonati Rhizoma, Ophiopogonis Radix, and Crataegi Fructus	Reducing interleukin-6 (IL-6) content; increasing the levels of immunoglobulin G and A	Weight-loaded swimming test (LST)
Bazhen Soup (Zhao et al., 2020)	Angelicae Sinensis Radix, Ginseng Radix et Rhizoma, Poria, Paeoniae Radix Alba, Atractylodis Macrocephalae Rhizoma, Chuanxiong Rhizoma, Rehmanniae Radix Praeparata, and Glycyrrhizae Radix et Rhizoma Praeparata Cum Melle	Degrading malondialdehyde (MDA) content of skeletal muscle; improving superoxide dismutase (SOD) activity; scavenging free radical	LST
Liqi Tiaobu Tang (Wang et al., 2010)	Bupleuri Radix, Aurantii Fructus, Astragali Radix, Ziziphi Spinosae Semen, Schisandrae Chinensis Fructus, Salviae Miltiorrhizae Radix et Rhizoma, Ginseng Radix et Rhizoma, Chuanxiong Rhizoma, and Angelicae Sinensis Radix	Increasing the content of T cell and T/C cell ratio; recovering the function of the hypothalamic–pituitaryadrenal axis	LST
Lizhong Pill (Li et al., 2013)	Zingiberis Rhizoma, Ginseng Radix et Rhizoma, Atractylodis Macrocephalae Rhizoma, and Glycyrrizae Radix et Rhizoma Praeparata Cum Melle	Exciting the adrenal cortex system	LST
Duoxuekang Capsule (Chen et al., 2021a)	Phyllanthi Fructus, Rhodiolae Crenulatae Radix et Rhizoma, Hippophae Fructus, and Zingiberis Rhizoma Recens	Decreasing lactate dehydrogenase (LDH) activity; increasing the hepatic glycogen (HG) level	LST
Huangjing Sanqi Extract (Yang et al., 2020a, 2020b)	Polygonati Rhizoma, and Notoginseng Radix et Rhizoma	Promoting energy metabolism, and antioxidation	LST
Yangxin Tablet (ling et al., 2021)	Astragali Radix, Ginseng Radix et Rhizoma, and Codonopsis Radix	Elevating cellular immune function	Officers and soldiers on a long voyage
Buqi Shengxue Formula (He 2021)	Panacis Quinquefolia Radix and Astragali Radix	Increasing hemoglobin level	Young athletes
Sijunzi Decoction (Hao 2014)	Ginseng Radix et Rhizoma, Poria, Atractylodis Macrocephalae Rhizoma, and Glycyrrhizae Radix et Rhizoma.	Enhancing the organ index of immune organs	Forced swimming test (FST)
Danggui Buxue Decoction (Miao et al., 2018)	Angelicae Sinensis Radix, and Astragali Radix	Promoting hematopoietic function; regulating the immune system	FST
Xiyangshen Pill (Zhao and Wang 2005)	Panacis Quinquefolia Radix, and Ginseng Radix et Rhizoma Rubra	Enhancing HG content; decreasing blood urea nitrogen (BUN), and blood lactic acid (LA) levels	FST
Hongjingtian Formula (Yi-bo et al., 2021)	Rhodiolae Crenulatae Radix et Rhizoma, Angelicae Dahuricae Radix, Schisandrae Chinensis Fructus, Cistanches Herba, and Lycii Fructus	Decreasing BUN and LA contents; increasing HG level	FST
Maca Xiyangshen Capsule (Sun and Zhang 2021)	Lepidium Meyenii, and Panacis Quinquefolii Radix	Decreasing LA and BUN contents; increasing HG content	FST
Yinyanghuo Pill (Wang et al., 2020)	Panacis Quinquefolii Radix, and Epimedii Folium	Decreasing LA and BUN content; increasing HG level	LST
Renshen Huangqi Tablet (Ren and Li 2021)	Astragali Radix, and Ginseng Radix et Rhizoma	Increasing HG level; reducing BUN level	LST

forelimb grip strength experiments, open field experiments, and tail suspension tests (Chen et al., 2016a, 2016b, Baguley et al., 2017, Baguley et al., 2019). Indicators currently used to evaluate the effect of anti-fatigue mainly include antioxidant indexes (such as reactive oxygen species, malondialdehyde, superoxide dismutase, glutathione peroxidase, and catalase (Chen and Zhang 2011, Chen et al., 2019, Chen et al., 2021)), accumulation of harmful metabolites (such as blood lactic acid and blood urea nitrogen (Chen et al., 2011)), energy metabolites (respiratory chain and tricarboxylic acid cycle (Gao et al., 2018)), and inflammation (such as tumor necrosis factor, IL-1β, and IL-6 (Herlofson et al., 2018)). The pharmacological effects and mechanisms of TCM on fatigue management (Tables 1–3) mainly include inhibition of inflammatory response, regulation of the immune system and HPA axis, remedy of the synthesis and release of neurotransmitters, enhancement of mitochondrial biogenesis, regulation of endogenous antioxidant system, amelioration of metabolite production, and improvement of glycogen storage (Fig. 1). Additionally, the anti-fatigue ability of several TCMs, such as Buqi Shengxue Formula composed of Panacis Quinquefolia Radix and Astragali Radix, and Yangxin tablet composed of Astragali Radix, Ginseng Radix et Rhizoma, and Codonopsis Radix, has been confirmed in clinical tests by evaluating the improvement of fatigue symptoms and several classic physiological and biochemical indexes (He 2021, ling et al., 2021), indicating the credible therapy of TCMs.

Currently, anti-fatigue bioactive components of TCM mainly include polysaccharides, polyphenols, flavonoids, terpenes, peptides, and proteins. Polysaccharides, a macromolecule, are composed of numerous monosaccharides and are widely distributed in animals, plants, and fungi. Polysaccharides can increase glycogen storage and reduce metabolite accumulation, which may be mainly related to the regulation of the immune systems (Cao 2013, Cai et al., 2014, Tian Jiajun, Qin Yang ,Wang Nanping, 2021). Polyphenols and flavonoids contain polyhydroxy and have high antioxidant activity (Hu et al., 2010, Li and Zhang 2013), which may be the main mechanism for their anti-fatigue ability. Terpenes isolated from TCMs are typical components of anti-fatigue substances (Tang et al., 2008, Zu et al., 2016). The reduction of metabolite accumulation may be the main mechanism of terpenes. Peptides and proteins exhibit their anti-fatigue effect mainly via the inhibition of oxidative stress (Qi et al., 2014, Bao et al., 2016, Feng et al., 2021).

At present, although most anti-fatigue TCMs are in the procedure of preclinical research, a few drugs are in clinical research, such as modafinil and zaleplon (ChiCTR20000031407), moringa tablet (ChiCTR2100047631), Shen-Mai injection (ChiCTR1800015478), and Korean ginseng (ChiCTR-IPR-17012151), which consists of chemosynthetic drugs and natural TCMs. Generally, chemosynthetic drugs own the single and known constituents and pharmacological mechanism, while TCMs possess

Table 2
Anti-fatigue effects of single herbs.

Single herbs	Mechanisms	Experimental models
Chaenomeles speciosa (Sweet) Nakai (Lang 2012)	Elevating maximal oxygen consumption, increasing the blood glucose level, and decreasing the LA level	Volunteers working in thermal environment
Pyracantha fortuneana (Maxim.) Li (Hou et al., 2002)	Enhancing LDH and glutathione peroxidase (GSH-Px) activity in the brain; decreasing the MDA content in the brain	LST
Gastrodia elata Bl. (Huang 2019)	Decreasing BUN content and increasing HG content	Sleep deprivation model
Lycium barbarum L. (Hu et al., 2022)	Increasing HG content	LST and climb-mouse experiment
Cistanche deserticola Y.C.Ma (Wang 2019)	Reducing LA content and enhancing adenosine triphosphatase (ATPase) activity	Rotate stick experiment
Thamnolia vermicularis (Sw.) Ach. (Maying and Zhang, 2010)	Accelerating recovery rate of blood glucose and LA clearance; increasing HG and decreasing BUN level	LST
Hypericum perforatum L. (Ye et al., 2014)	Increasing activity of SOD and GSH-Px; decreasing the content of MDA	LST
Lepidium meyenii Walp. (Zhu et al., 2021)	Increasing HG level; decreasing BUN level	FST
Dimocarpus longan Lour. (Guo et al., 2019)	Increasing HG content; decreasing LA and BUN levels	LST
Acanthopanax senticosus (Rupr. et Maxim.) Harms (Nam et al., 2011)	Increasing tissue glycogen content; reducing LA and BUN level	FST
Ophiopogon japonicus (Linn.f) Ker-Gawl. (YinFei et al., 2020)	Alleviating the oxidative effect of free radicals; reducing the decomposition of amino acids; increasing hemoglobin content	LST, climbing test, and rotarod test
Sasa borealis (Hack.) Makino et Shibata (Song et al., 2019)	Enhancing endogenous antioxidation	Exhaustive swimming without any load
Aegle marmelos (L.) Corrêa (Lalremruta and Prasanna 2012)	Reducing the duration of immobility and anxiety; increasing locomotor activity	Forced swimming every day for 15 min to induce a state of chronic fatigue
Areca catechu L. (HeShuang et al., 2009)	Increasing HG content; decreasing BUN and LA contents	LST
Salvia miltiorrhiza Bge. (Wang et al., 2021)	Improving energy metabolism; regulating the oxidant-antioxidant balance	LST
Vitis vinifera L. (Xianchu et al., 2018)	Anti-inflammation; antioxidation	FST
Antrodia cinnamomea (Liu et al., 2017)	Antioxidation	FST
Astragalus membranaceus (Fisch.) Bge. (Yeh et al., 2014)	Raising contractibility of skeletal muscle; increasing the activity of SOD and expression of α-action mRNA in skeletal muscle; inhibiting lipid peroxidation in blood and skeletal muscle.	FST and gastrocnemius and soleus muscle contractibility experiment
Trigonella foenum-graecum L. (Yan et al., 2022)	Decreasing LA, and BUN levels, increasing muscle glucose content	LST
Cordyceps sisensis (Berk.) Sacc. (Kumar et al., 2011)	Increasing HG content; reducing the accumulation of harmful metabolites	Swimming training (without load)

Table 3
Anti-fatigue effects of TCM constituents.

Monomers and ingredient groups	Mechanisms	Experimental models
Polysaccharides from *Lepidium meyenii* Walp (Li et al., 2017, Tang et al., 2019)	Increasing HG content; decreasing BUN level; up-regulating mitochondrial biogenesis; antioxidation	FST; mouse leg grip-strength test; rotarod test; LST; treatment with H_2O_2 in C2C12 skeletal muscle cells
Oligosaccharides from *Amorphophallus konjac* C. K.Koch (Zeng et al., 2018)	Antioxidation; increasing blood glucose content	LST
Polysaccharides from *Avena sativa* Linn. (Chao et al., 2009)	Increasing non-esterified fat acid content, and glycogen storage	Running performance test
Polysaccharides from *Lycium barbarum* L. (Wu and Guo 2015)	Changing glycerophospholipid and tyrosine metabolism; inhibiting lipid peroxidation; elevating catalase and GSH-Px activity; decreasing MDA level	FST
Polysaccharides from *Polygonatum sibricum* Red. (Cui et al., 2018)	Decreasing LA and BUN contents; increasing HG content	FST
Polysaccharides from *Polygonatum alte-lobatum* Hayata (Horng et al., 2014)	Decreasing BUN and MDA contents; increasing SOD activity; scavenging free radical	Exhaustive treadmill exercise
Polysaccharides from *Gynostemma pentaphyllum* (Thunb.) Makino (Qi and Huang 2014)	Scavenging ROS and increasing glycogen levels in skeletal muscle	FST
Polysaccharides from *Hericium erinaceus* (Bull.) Pers. (Zhang 2015)	Increasing HG content; decreasing BUN and LA content	LST
Polysaccharides from *Dendrobium officinale* Kimura et Migo (Chen et al., 2021b)	Increasing glycogen storage; antioxidation	LST
Polysaccharide from *Ziziphus jujube* Mill. var. spinosa (Bunge) Hu ex H. F. Chow (Chi et al., 2015)	Improving immune function; antioxidation	Mimic the multiple-factor pathogenesis of CFS using electric shock, restraint stress, and cold-water-swim
Polysaccharides from Radix Rehmanniae Preparata (Tan et al., 2012)	Increasing HG content; decreasing BUN and LA contents	LST
Protein-bound polysaccharides from *Epimedium brevicorum* Maxim. (Chi et al., 2017)	Improving tyrosine, arginine, and proline metabolism	Mimic the multiple-factor pathogenesis of CFS using restraint-stress, forced exercise, and crowed and noisy environment
Polysaccharides from *Abelmoschus esculentus* (L.) Moench (Gao et al., 2018)	Decreasing BUN and LA contents; increasing HG, muscle glycogen, and adenosine triphosphate levels; enhancing LDH and ATPase activity	LST
Polysaccharides from *Ganoderma lucidum* (Curtis) P. Karst. (Hu et al., 2012)	Increasing antioxidant enzymes activity; decreasing MDA content in skeletal muscle	FST
Polysaccharides from *Zea mays* L. (Yang et al., 2020a, 2020b)	Decreasing BUN and LA content; increasing LDH activity and HG content	LST
Polysaccharides from *Polygonatum cyrtonema* Hua. (Shen et al., 2021)	Decreasing LA, BUN, and MDA levels; increasing HG, muscle glucose, and adenosine triphosphate content in muscle	LST
Adventitious root protein from *Panax ginseng* C.A.Mey. (Wang et al., 2022)	Activating the adenosine 5′-monophosphate-activated protein kinase/ glucose transporter type 4 signaling pathway to promote glucose uptake	LST
Polysaccharides from *Codonopsis pilosula* (Franch.) Nannf. (Cai et al., 2014)	Preventing lipid peroxidation; antioxidation	LST
Flavonoids from *Saussurea involucrate* (Kar. et Kir.) Sch.Bip. (Su et al., 2014)	Increasing SOD and GSH-Px activity; decreasing LA content	FST
Flavonoids from *Sophopra japonica* L. (Tao 2013)	Antioxidation	FST
Flavonoids from Wasps drone pupae (Xi et al., 2018)	Eliminating metabolic accumulation	LST
Flavonoids from *Pueraria lobata* (Willd.) Ohwi (Wang et al., 2012)	Antioxidation	FST
Flavonoids from *Astragalus englerianus* Ulbr. (Xiao et al., 2014)	Scavenging free radical	Free radical scavenging capability assay
Flavonoids from *Taraxacum mongolicum* Hand. -Mazz. (Liu et al., 2020)	Delaying LA production	FST
Polyphenols from *Camellia sinensis* (L.) O. Ktze. (Yi 2016)	Anti-inflammation; antioxidation	Athletes
Polyphenols from *Euryale ferox* Salisb. ex DC (Wu et al., 2013)	Antioxidation	FST
Polysaccharides from *Angelica sinensis* (Oliv.) Diels (Choi et al., 2022)	Increasing muscle glucose content	FST
Peptide from *Hippocampus kelloggi* Jordan et Snyder (Guo et al., 2017)	Increasing production of serum glucose, free fatty acid, HG, and adenosine triphosphate; reducing L-lactate, and citrate content	Rotarod test
Saponins from *Panax notoginseng* (Burk.) F.H.Chen (Yong-Xin and Jian-Jun 2013)	Increasing HG content; decreasing LA content	LST
Small-molecule oligopeptides from *Panax quinquefolium* L. (Li et al., 2018)	Antioxidation; improving mitochondrial function	FST
Peptide from Pseudosciaena crocea (Zhao et al., 2016)	Inhibiting oxidative reaction	LST
Peptide from Sheep Placenta (Wang et al., 2018)	Decreasing MDA and LA levels; enhancing GSH-Px and SOD activity; increasing HG content	LST

(continued on next page)

Table 3 (*continued*)

Monomers and ingredient groups	Mechanisms	Experimental models
Polysaccharides from *Polygonum multiflorum* Thunb. (Kai et al., 2016)	Improving HG content, and SOD activity; decreasing BUN, LA, and MDA levels	LST
Cyanidin-3-glucoside (Matsukawa et al., 2017)	Activating lactate metabolism through skeletal muscle receptor-gamma coactivator-1α (PGC-1α) upregulation	LST
Quercetin (Zhang and Iop 2017, Chen et al., 2021)	Enhancing muscle function; antioxidation	LST and non-loading swimming tests
Anwulignan (Zhang et al., 2019)	Regulating nuclear factor erythroid-2 related factor 2, and PGC-1α signaling pathway	LST, rotarod test, grip strength test, and tail suspension test
Securinine (Wang 2012)	Reducing BUN level; increasing glycogen level	LST
Betaine (Hoffman et al., 2009)	Decreasing BUN and LA contents; increasing HG content	LST
Ginsenoside Rb1 (Tan et al., 2013, Chen et al., 2015, Liu et al., 2021)	Improving energy metabolism; suppressing skeletal muscle oxidative stress	Postoperative fatigue syndrome (POFS) induced by major small intestinal resection model
Ginsenoside Compound K (Lan and Liang 2022)	Antioxidation	FST
Ginsenoside Rg3 (Yang et al., 2018)	Up-regulating concentration of LDH and SOD; decreasing MDA level	POFS model
N-benzyloleamide (Yang et al., 2016)	Increasing HG content; decreasing LA and BUN content	LST
Luteolin-6-C-neohesperidoside (Duan et al., 2017)	Decreasing LA and BUN levels; enhancing antioxidant enzymes activity	FST
Neoagarotetraose (Zhang et al., 2017)	Modulating gut microbial composition, and function in intense exercise	A forced exercise wheel-track treadmill
γ-aminobutyric acid (Chen, et al., 2016a)	Increasing HG content; decrease LA and BUN content	LST
Dihydromyricetin (Zou et al., 2014)	Reducing LA and BUN content; decreasing LDH, CK, and GSH-Px activity; increasing glycogen content	LST
Hypericin (Sun et al., 2022)	Normalizing changes in LA, BUN, creatine kinase, MDA, and HG level, and LDH activity in the liver; improving GSH-Px and SOD activity, and total antioxidant capacity; decreasing the release of tumor necrosis factor-α, interleukin-6, and interleukin-1β	Mice swimming for 120 min for six weeks (for six consecutive days per week)
Salidroside (Ma et al., 2015)	Enhancing antioxidant enzyme activities in mitochondria	LST

the extreme complex active ingredients mechanism and mechanism, which creates a mode of action of the multi-compound, multi-target, and multi-pathway.

5. Conclusion

Fatigue has become a serious threat to human health. Many TCMs exhibit anti-fatigue activity via the action of their constituent compounds on several pathways and targets. However, a few TCMs have been used as nutritional supplements or clinical drugs against fatigue, which may be ascribe to the complex chemical ingredients and action mechanisms, difficult quality control and unstable quality. It is necessary to explore the anti-fatigue effect of TCM and its related mechanisms. In addition, anti-fatigue medicinal substances of TCM are seldom and poorly understood, which instigates the need for more relevant studies in the field. With deep research, it is of utmost significance that more TCMs with an anti-fatigue effect can be found and used in clinical settings.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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