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Exploration of the Application of Food as Medicine Liver Function Regulator in the Treatment of Fatigue Based on the Theory of "Liver is the Basis of Resistance to Fatigue"

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Abstract: ***Fatigue disorder is characterized by a core pathogenesis of Deficiency of the Five Zang Organs and Deficiency and Debility of Qi, Blood, Yin, and Yang, manifesting as chronic weakness and fatigue. Based on the Traditional Chinese Medicine theory that "Liver is the Basis of Resistance to Fatigue," this article systematically explores the pathological relationship between the liver and Fatigue disorder, as well as the therapeutic value of Food as Medicine Liver Function Regulator. As the "Liver is the Basis of Resistance to Fatigue," failure of its Blood storage and disorder of its free coursing and discharging may lead to concurrent impairment in the transformation of essence, qi, and form, thereby forming a vicious cycle progressing from Loss of softness of the liver body to reckless stirring of ministerial fire and ultimately to scorching yin results in fatigue taxation. By integrating theoretical exposition with empirical analysis, the study elucidates the pivotal role of the liver in the pathogenesis of Fatigue and identifies Food as Medicine substances, including rose flower, wolfberry, mulberry, and fingered citron, for interventions aimed at Regulating the liver.***

Keywords: Fatigue, Chronic Fatigue Syndrome, Food as Medicine, Liver is the Basis of Resistance to Fatigue, Traditional Chinese Medicine**.**

1. Introduction

Fatigue is the abbreviated designation for "deficiency depletion with taxation damage," also known as Deficient Consumption; it is chiefly caused by factors such as dietary irregularities, excessive fatigue and overexertion, constitutional insufficiency, severe and protracted illness, and missed or improper treatment, which result in severe depletion and impairment of essence and qi, damage to both bodily form and function, and a disorder with chronic debility as its core manifestation [1]. Fatigue disorder encompasses a broad range, and fatigue and Chronic Fatigue Syndrome in the sense of modern Western medicine both fall within the category of Fatigue [2]. Traditional Chinese Medicine has a long-standing understanding of Fatigue and has developed distinctive knowledge and insight regarding its intervention and regulation; the theory of "Liver is the Basis of Resistance to Fatigue" is one such example. The theory of "Liver is the Basis of Resistance to Fatigue" derives from the TCM classic Huangdi Neijing, specifically from the chapter "Plain Questions: Treatise on the Visceral Manifestations and the Six Qi Divisions." This theory not only defines the physiological characteristics of the liver in resistance to fatigue, but also, through the triadic functional framework of "Blood storage-governing the sinews-free coursing and discharging," reveals the central role of the liver as the regulatory pivot of qi and blood in the human body. This theory integrates physiology, pathology, and treatment, providing a classical foundation for the treatment of Fatigue from the perspective of the liver, and it remains an important guiding principle in TCM clinical practice to this day. The concept of Food as Medicine originated in the Huangdi Neijing concept of preventive treatment, expressed in the statement that "grains, meats, fruits, and vegetables provide nourishment exhaustively"; it was subsequently enriched through works such as the Shennong Bencao Jing and the Bencao Gangmu, gradually forming a dietary therapeutics system based on the four qi and five flavors and the theories of nature, flavor, and channel tropism, with inherent advantages for the treatment of Fatigue, a widespread condition, and for the regulation of fatigue-prone constitutions. In recent years, a variety of studies and experiments have further investigated Food as Medicine substances, and their mechanisms of action and active constituents have gradually become clearer to the public. Therefore, based on the Traditional Chinese Medicine theory that 'Liver is the Basis of Resistance to Fatigue,' this study systematically investigates the distinctive value of Food as Medicine substances in the treatment of Fatigue disorder, thereby providing a new perspective for clinical practice.

2. The Close Relationship Between the Liver and Fatigue

Fatigue, as a disorder primarily manifested by weakness and tiredness, is described by Zhang Zhongjing in the Essential Prescriptions of the Golden Casket, in the section on 'Pulse, Patterns, and Treatment of Blood Impediment and Fatigue disorder,' as having as its principal pathomechanism the depletion of yin, yang, qi, and blood and the decline of zang-fu functional activity. The liver, as one of the five zang organs, coordinates the whole-body qi dynamic of the heart, lung, spleen, and kidney through its robust function of free coursing and discharging, driving the ceaseless generation and circulation of qi throughout the upper and lower, left and right aspects of the human body [3]. Wherever qi permeates, it can moisten and nourish. The Ming-dynasty Five Treatises on Shenrou states: 'When Liver qi declines, free coursing and discharging become inadequate; this is termed timidity and

weakness, and its manifestation is lassitude and an inability to endure exertion' [4]. This indicates that timidity and weakness of liver function lead to concomitant impairment in the transformation of essence, qi, and form; later, the Qing-dynasty Golden Mirror of the Medical Lineage [5] elaborated upon the theory of the Inner Canon and stated: 'When the liver is deficient, qi becomes timid; when qi is timid, blood does not nourish the sinews, essence does not transform into qi; therefore, the body becomes emaciated and the spirit fatigued.' This is precisely what is meant by the phrase 'concomitant impairment in the transformation of essence, qi, and form,' further clarifying that Fatigue symptoms arise when insufficiency of free coursing and discharging due to Liver qi deficiency causes the subtle essences to fail to transform, with consequent malnourishment of the physical form and spirit. As stated in the Plain Questions, chapter 'Discussion of Pain': 'All diseases arise from qi.' Disorder of Liver qi affects not only the liver itself; in the course of transmission and transformation, it also impacts the other zang-fu organs and thereby generates disease. The Duyi Suibi states: "A physician who is adept at Regulating the liver is thereby adept at treating a hundred diseases," which likewise demonstrates the importance of treating the liver. Therefore, treating from the liver provides a therapeutic approach for Fatigue disorder, namely, "repeated application of Regulating the liver, with nourishing essence to transform form." At the same time, the liver is yin in body and yang in function; this distinctive physiological characteristic makes it an organ that encompasses and harmonizes both yin and yang. The liver governs free coursing and discharge, and its function pertains to yang; it also governs Blood storage, and its body pertains to yin. Imbalance between the liver's body and function leads to impairment of the transformation of essence, qi, and form in all respects. First, deficiency of liver yin in its bodily aspect constitutes the material-basis damage of Fatigue. When liver blood is depleted, the physical form loses nourishment. The liver stores blood; blood pertains to yin and constitutes the foundation of the yin aspect of the body. In prolonged Fatigue, chronic disease consumes and damages yin-blood; when Deficiency of liver blood arises, the bodily form loses moistening and nourishment, which may manifest as malnourishment of the eyes, insufficient moistening of the sinews and vessels, and dysregulation of the Chong and Ren vessels. When liver yin is deficient and impaired, deficient fire causes internal disturbance. Liver yin is the functional foundation of liver yang; when yin is depleted, yang becomes hyperactive, giving rise to deficient heat. This may manifest as deficient fire scorching the collaterals and incipient stirring of internal wind, as stated in the Linzheng Zhinan Yian [6] that "Loss of softness of the liver body, reckless stirring of ministerial fire, scorching yin results in fatigue taxation," thereby revealing the core pathomechanism of Fatigue disorder. Secondly, hyperactivity and exuberance of liver yang in its functional aspect constitute a manifestation of functional dysregulation in Fatigue. When free coursing and discharging become disordered and the qi dynamic becomes constrained and stagnant, the liver, whose function is to govern free coursing and discharging, is in Fatigue prone to depression of Liver qi or hyperactive counterflow. This manifests as emotional depression and counterflow qi invading the spleen, which is the pathological expression of the dictum that "the liver is a firm viscus, by nature it prefers free flow and extension and abhors depression and constraint." At the same time, reckless stirring of ministerial fire consumes qi and damages yin. Because ministerial fire is lodged within the liver, in Fatigue, if yin fails to restrain yang, ministerial fire becomes excessively exuberant. Clinically, this is expressed as intense fire consuming qi and vacuous yang floating upward and outward. As stated in the Plain Questions, in 'Discourse on Generating Qi and Connecting with Heaven,' "As for yang qi, when there is vexing overexertion, it becomes exuberant," meaning that under conditions of sustained overexertion, the body's yang qi loses its capacity to remain hidden internally, instead floating outward and giving rise to a state of vacuous hyperexcitability. Finally, insufficiency of the liver body and hyperactivity of liver function are mutually causal, forming a chronic disorder in which "deficiency transforms into hyperactivity, thereby causing still greater deficiency"; Ye Tianshi, in Clinical Guide to Medical Cases [6], emphasized: "At the onset, disease is in qi; when prolonged, it will inevitably enter blood," which precisely reflects the pattern of transmission whereby prolonged hyperactivity of liver function damages the liver body. The essence of Fatigue lies in the proposition that "the transformation of essence, qi, and form is altogether impaired"; as the liver is central to regulating the qi dynamic and Blood storage, disequilibrium between its body and function runs through the entire course of Fatigue.

3. The Connotation of "Liver is the Basis of Resistance to Fatigue"

The statement "Liver is the Basis of Resistance to Fatigue" first appears in the Plain Questions, in the chapter 'Treatise on the Visceral Manifestations Corresponding to the Six Sections': "Liver is the basis of exhaustion from overstrain, the residence of the hun (ethereal soul); its efflorescence is in the nails, its fullness is in the sinews, thereby generating blood and qi... this is lesser yang within yang, corresponding to the qi of spring." . "Ba" is interchangeable with "pi" (pí, fatigue). Wang Bing of the Tang dynasty, the earliest annotator of the Plain Questions, stated: "Ba is pronounced pi." The liver governs the sinews, and all human movement is accomplished through the force of the sinews; this is interpreted as "fatigue," thereby explaining why the liver is the basis of exhaustion from overstrain. First, the liver governs the sinews and is in charge of movement. As stated in the Leijing: "Ba means fatigue. The liver governs the sinews, and the sinews govern movement; therefore, the liver is the basis of exhaustion from overstrain." This indicates the liver's dominant role over the sinews and channels, thereby influencing the degree of fatigue perceived by the body and whether motor capacity declines. The Huangdi Neijing Suwen Zhuzheng Fawei records: "Ba is pronounced pi and is synonymous with fatigue. The liver governs the sinews; labor fatigue, weariness, and exhaustion from overstrain all pertain to the strength of the sinews; therefore, the liver is the basis of exhaustion from overstrain." This suggests that "exhaustion from overstrain" denotes resistance to fatigue, and further indicates that the fundamental basis of the body's capacity to resist fatigue lies in the liver. Secondly, The liver stores blood. As stated in the Plain Questions, "Generation of the Five Zang": "All sinews are connected to the joints." This indicates that the sinews constitute the bodily network mediating movement. Since the liver governs the sinews, liver blood nourishes the sinews and

channels so as to maintain motor function, thereby giving rise to the liver's function of Blood storage. The liver is the "sea of blood," regulating the distribution of blood volume: during movement, blood is conveyed throughout the body to provide energy, whereas at rest, blood returns to the liver for storage. This mechanism ensures a balanced energy supply as the body alternates between activity and rest. If liver blood is deficient and the sea of blood becomes depleted, tiredness and physical weakness readily ensue. As stated in the Plain Questions, "Treatise on Flaccidity": "The liver governs the body's sinews and membranes… when Liver qi becomes heated, bile is discharged and the mouth turns bitter; when the membranes become dry, the sinews become tense and contract." It has been pointed out that insufficiency of liver blood or liver heat can lead to malnourishment of the sinews and connective tissues, giving rise to weakness and spasm of the limbs, that is, fatigue and motor dysfunction, directly supporting the association between "exhaustion from overstrain" and "fatigue." Finally, the liver governs free coursing and discharge, and qi and blood share the same source. The liver's regulation of the qi dynamic can both promote the movement of blood and maintain coordination among the zang-fu organs; it also assists the spleen and stomach in transporting and transforming water and grain to generate qi and blood, thereby nourishing the liver in return. At the same time, the liver regulates the emotions and, through free coursing and discharging, maintains the smooth flow of mental activity. Excessive emotional stimulation, such as constraint and anger, or sustained mental exertion, such as excessive deliberation, can consume Liver qi and liver blood, further resulting in mental fatigue and vacuity of spirit-consciousness. "Liver is the Basis of Resistance to Fatigue" is founded on a systematic exposition of the liver governing the sinews, The liver stores blood, and its function of free coursing and discharging; it proposes that the essential meaning of "the liver is the basis of exhaustion from overstrain" lies in a highly condensed expression of the liver's two core physiological functions—Blood storage to nourish the physical body, and free coursing and discharging to regulate psychospiritual activity. This theory incisively reveals the liver's dual pivotal role in maintaining human health: it not only provides sustained support for physical movement (the basis of the physical form), but also serves as the regulatory center for preserving the stability of mental and emotional activity (the basis of the spirit). Accordingly, "the liver is the basis of exhaustion from overstrain" not only highlights the liver's distinctive status as fundamental to vital activity, but also closely accords with the holistic health view in the Huangdi Neijing that "the physical form and the spirit are both maintained together." This theoretical innovation provides a solid theoretical foundation for the clinical application of liver-based treatment strategies to intervene in Fatigue.

4. "Liver is the Basis of Resistance to Fatigue" and Its Relationship with Fatigue

Traditional Chinese Medicine has a long history of understanding Fatigue. In Essential Prescriptions of the Golden Casket, the etiopathogenesis, clinical manifestations, pulse characteristics, therapeutic methods, and formulas for Fatigue disorder were systematically integrated, thereby pioneering a theoretical system for pattern differentiation and treatment of Fatigue disorder and providing a classical theoretical foundation for modern clinical diagnosis and treatment. In contemporary medicine, the category of "Fatigue disorder" has become even broader and more diverse, encompassing many chronic diseases marked by functional decline as well as consumptive disorders. The disease term "Fatigue" first appeared in Zhang Zhongjing's Essential Prescriptions of the Golden Casket, in the chapter "Pulse Patterns, Manifestations, and Treatment of Blood Impediment and Fatigue disorder": "The five kinds of taxational impairment cause extreme deficiency, emaciation, abdominal fullness, and inability to take food and drink; injury due to food, injury due to anxiety, injury due to drinking, injury due to sexual activity, injury due to hunger, injury due to overwork, and injury to the qi of the channels, nutritive qi, and defensive qi." The disease term "Fatigue" was first proposed, and seven categories of injury were summarized: diet, emotions, sexual activity, hunger, overexertion and fatigue, and dysregulation of the meridians, ying, and wei. Constitutional weakness, failure to receive adequate nourishment in utero, parental debility and chronic illness, senescence with bodily decline, or insufficient feeding may all hinder the enrichment of the essence-qi derived from water and grain, resulting in deficiency and debility of the five zang-organs. Under such conditions, even slight emotional dysregulation or invasion by exogenous pathogenic factors may impair liver function, causing the liver to lose its function of free coursing and discharging, Liver qi to invade the stomach, and the spleen and stomach to become disharmonized. Once the spleen and stomach are damaged, transportation and transformation lose their proper function, the subtle essence of water and grain cannot be transformed and generated, and qi, blood, and essential subtle substances become deficient in their source of generation. Consequently, they are unable to nourish the entire body, giving rise to soreness and weakness of the sinews and bones; essence-qi cannot adequately enrich the kidneys, vitality declines, and the zang-fu organs and meridians are deprived of nourishment. Over time, "accumulated deficiency develops into impairment, and accumulated impairment develops into Fatigue," ultimately resulting in the pattern of Fatigue.

Fatigue disorder is characterized by multiple chronic fatigue syndromes of deficiency-related weakness, with a prolonged disease course and long-standing deficiency that is difficult to restore; this accords with the Liver's physiological characteristics and pathological changes under the theory of "Liver is the Basis of Resistance to Fatigue," whereby the Liver is both the bearer of bodily Fatigue and the carrier of mental and emotional fatigue. As stated in the Plain Questions, "when Liver qi declines, the sinews are unable to move," indicating the Liver's decisive role in the generation of bodily fatigue; if the decline worsens further, severe disease develops, with manifestations of sinew exhaustion, including contracture of the limbs and pain in all ten fingers, and muscle exhaustion, including muscular emaciation and numbness of the skin. In the Plain Questions, "Discussion of the Arcane Canon of the Numinous Orchid Chamber," it is stated: "Liver is the official of the general, from whom strategy and deliberation emerge." This indicates that the liver is the "general," governing strategy, deliberation, and decision-making. If the Liver loses its function of free coursing and discharging, strategy and deliberation become indecisive and worry and overthinking become excessive,

leading to mental exhaustion and giving rise to emotional fatigue. The Spiritual Pivot, "Ben Shen," states: "The liver stores blood; blood houses the hun… when Liver qi is deficient, there is fear; when it is replete, there is anger." The liver stores the hun, and the hun is one aspect of mental activity. When there is Deficiency of liver blood, the hun loses its nourishment, resulting in fright, restlessness, frequent dreaming, and easy waking; When Liver qi becomes hyperactive and rises counterflow, it gives rise to anger and depletes the spirit; both further aggravate mental fatigue. Taken together, these observations substantiate the rationale for treating Fatigue from the perspective of the liver.

5. The Role of Food as Medicine Liver Function Regulator in the Treatment of Fatigue

5.1 New Understandings of Traditional Medicinal Efficacy and Essentials of Clinical Application

Complete Record of Sagely Beneficence · Liver Fatigue [7] states: 'In liver Fatigue, the face and eyes are dry and dark, the mouth is bitter, the spirit is not settled, there is fearfulness with inability to sleep alone, and in severe cases the sinews become tense and the nails wither.' This passage explains that liver damage causes the hun to become unsettled, producing both mental and physical fatigue, including anxiety, insomnia, and sinew spasm, thereby indicating that regulating the liver is the key therapeutic method in the treatment of Fatigue. The concept of Food as Medicine has endured through the ages and can be traced as early as the Western Han dynasty to the "Xiuwu Xun" chapter of the Huainanzi authored by Liu An [8]. Through the legend of "Shennong tasting the hundred herbs," it first articulated the condition in remote antiquity in which the boundary between medicinals and foods was indistinct, thereby revealing the process by which human beings came, through practice, to recognize the dual properties of substances as both food and medicine. This account became the theoretical source of the Food as Medicine concept. In the Qianjin Yaofang authored by Sun Simiao of the Tang dynasty, a special chapter on "food therapy" was established, advocating that "only when dietary therapy fails to heal should medicinals be prescribed." It recommends substances such as wolfberry and jujube for nourishing Liver Blood and relieving the "five taxations and seven impairments." It also records that lard wine may "treat vacuity-cold due to liver taxation and guange with taxation-related obstruction: seven sheng of pork fat, two sheng of fresh ginger juice, decoct over a low flame until three sheng remain, then add five ge of wine and decoct together, dividing the preparation into three doses." During the Ming and Qing periods, the concept of Food as Medicine underwent further development. Li Shizhen's Compendium of Materia Medica, a comprehensive synthesis of materia medica theory, records 1,892 medicinals, of which more than 300 are common food materials, and provides detailed accounts of their medicinal properties and dietary contraindications. It documents chrysanthemum, cassia seed, wolfberry, honeysuckle, osmanthus, and niulaogen, among other Food as Medicine materials, as having marked liver-nourishing and liver-protective effects. In addition, Wang Mengying's Dietary Materia Medica of Suixiju from the Qing dynasty [9]. Wang Mengying used dietotherapy for Regulating the liver; for example, watermelon juice was used to clear liver fire, and rose flower tea to disperse liver qi depression, for the treatment of fatigue following warm disease, reflecting the clinical reasoning of "using food in place of medicinals." Its essence lies in achieving "treating disease before its onset" through "dietary nourishment," thereby conferring unique value in chronic disease prevention and health management

In the course of modern social development, states of Fatigue and chronic fatigue have become increasingly commonplace in everyday life; Professor He Hua emphasized beginning with the liver, with particular stress on regulating Liver qi [10], National Medical Master Zhang Lei stated in clinical practice that the liver is one of the key zang-organs in the treatment of chronic fatigue; on the basis of the "integrated view of the five zang-organs," treatment is administered through coordination of the spleen and kidney, once again confirming the rationality of "Liver is the Basis of Resistance to Fatigue" [11]. In addition, Chai Kequn, a supervisor for the inheritance of academic experience from nationally renowned veteran Traditional Chinese Medicine experts and a distinguished Traditional Chinese Medicine physician of Zhejiang Province, has also indicated that, in cases of Chronic Fatigue Syndrome caused by stagnation of Liver qi, the treatment should be supplemented with substances such as finger citron, rose, and lily bulb to soothe the Liver and relieve depression [12]. Similarly, in the experiential prescriptions used by National Medical Master Zhang Zhiyuan, medicinals such as ginseng, Astragalus, Chinese yam, longan aril, and cinnamon are also frequently selected for purposeful application [13]. As Chinese medicinals with dual medicinal and dietary use, these medicinal substances not only serve as indispensable components of clinical prescriptions, but also exhibit the pervasive food attributes that enable their integration into the daily lives of the general population.

Although Food as Medicine substances possess the nature of food, the characteristics of the four qi and five flavors that they embody as Chinese medicinals require that their application follow pattern differentiation and treatment, with selection based on the patient's constitution as well as the relative exuberance or decline of yin and yang in the body and the changing tendencies of cold and heat.

5.2 Modern Pharmacological Research on Food as Medicine Liver Function Regulator

Rose flower, wolfberry, mulberry fruit, and finger citron are four Food as Medicine Liver Function Regulator medicinal substances commonly used in the treatment of Fatigue; they may be used clinically and also processed for dietary consumption in daily life. On this basis, their principal mechanisms of action are discussed separately.

Rose flower is also recorded in classical texts such as the Bencao Gangmu Shiyi as having the alternative name Paihuai flower. Jiangsu and Zhejiang are recognized as daodi (authentic) producing areas, with high yield and superior quality, and constitute the core production regions for rose flower. Its nature and flavor are sweet, slightly bitter, and warm, and it has the effects of soothing the liver and regulating qi, promoting the movement of qi and relieving constraint, and invigorating the blood and alleviating pain, as

stated in the Bencao Zhengyi [14]. It is stated that: “rose flower possesses the richest fragrance, clear without turbidity, harmonious without harshness; it softens the liver and arouses the stomach, promotes qi movement and invigorates the blood, and diffuses and unblocks constraint and stagnation, entirely without the disadvantages of pungent-warm, rigid, and drying properties.” This classical passage emphasizes that rose flower, by virtue of its fragrant, light, and agile nature, can soothe the liver and regulate qi, harmonize qi and blood, and, because its medicinal nature is mild and does not injure yin, is suitable for the long-term regulation of chronic fatigue due to liver depression and qi stagnation, as manifested by low mood and lassitude, distention and oppression in the chest and hypochondria, and accompanying symptoms of indigestion. Bencao Congxin [15]. It is also recorded as being able to “soothe the depressed qi of the liver and gallbladder, fortify the spleen, and reduce fire.” Finger citron, also known as foshougan, has a pungent, bitter, and sour flavor and a warm nature; it is efficacious in soothing the liver and rectifying qi, harmonizing the stomach and relieving pain, and drying dampness and transforming phlegm. In the Qing-dynasty Bencao Biandu, Zhang Bingcheng recorded of finger citron that it “rectifies qi and relieves diaphragmatic oppression; it is appropriate only for those with qi stagnation of the liver and spleen,” thus explicitly indicating its characteristic of regulating the qi dynamic of the liver and spleen. Both possess the actions of soothing the liver and relieving constraint, rectifying qi and unblocking stagnation; in clinical practice, they may be used together as a complementary medicinal pair. They exert favorable therapeutic effects on persistent fatigue in chronic fatigue of the liver-depression and qi-stagnation pattern, characterized by failure of rest to provide relief and accompanied by limb lassitude, depressed mood or irritability, chest oppression, and distending pain in the hypochondriac region. Modern pharmacological research has found that rose flower is rich in a variety of bioactive constituents. Lu Leizhen [16] and others reviewed research progress indicating that rose flower contains polyphenols, flavonoid compounds, polysaccharides, proteins, terpenes, vitamins, and other constituents; through synergistic interactions, these components exhibit multiple biological activities, such as antibacterial effects, hypoglycemic, antihypertensive, and lipid-lowering effects, sleep-promoting effects, and immunoregulatory effects. Zhao Dong [17] and others demonstrated, through the mouse rotarod test, that rose anthocyanins in rose flower exert a certain alleviating effect on exercise-induced fatigue in mice, and that the flavonoid constituents of rose flower have antidepressant effects, significantly improving depressive symptoms in rats in experimental studies; the underlying mechanisms involve metabolic regulation in hippocampal tissue (including amino acid, purine, and lipid metabolic pathways) and regulation of the structure and function of the gut microbiota [18]. At the same time, rose flower has also shown certain advantages in improving sleep; Luo Kunduo [19]. His research indicated that citronellol in rose flower is the key active constituent responsible for its sedative-hypnotic effects. Animal experiments confirmed that rose tea can significantly shorten sleep onset latency in experimental mice and exerts evident sedative and mind-calming effects. rose flower also has related applications in modern health care; for example, the health food rose flower capsules, prepared using rose flower as the raw material, also have fatigue-relieving effects [20]. Through various experiments and analyses of the diverse bioactive constituents of rose, it has been confirmed that rose flower exerts protective effects on the liver and positively alleviates physical fatigue; it can also improve sleep quality and mitigate anxiety and depressive symptoms. Liu, W. X [21] have shown that bergapten (BP) significantly alleviates acetaminophen (APAP)-induced hepatocellular injury by enhancing the glutathione metabolic pathway and inhibiting oxidative stress. Studies have shown that bergamot essential oil reduces hyperalgesic responses in multimodal pain models (nociceptive/inflammatory/neuropathic) by regulating peripheral nociceptor sensitization, inhibiting the release of inflammatory mediators, and modulating central glutamatergic signaling, thereby alleviating limb and muscle soreness associated with Chronic Fatigue Syndrome [22]. Saiyudthong [23] have found that fingered citron essential oil improves depressive behavior in CRS rats through non-HPA-axis-dependent mechanisms involving monoamine neurotransmitters, BDNF, and neural circuit regulation. Chinese medicinal preparations derived from fingered citron, such as Compound Foshou Granules and Compound Foshou Oral Liquid, are used as adjunctive therapies for depression and can effectively alleviate anxiety and depressive states [24].

wolfberry, also known as gouqizi, is sweet in flavor and neutral in property, and enters the Liver and Kidney meridians. Its genuine producing regions are concentrated in Gansu, Ningxia, and Qinghai, with Zhongning in Ningxia as the core area. It has the functions of nourishing the Liver and Kidney, replenishing essence, and improving eyesight. *Records of Integrating Chinese and Western Medicine* [25] Jingyue’s Complete Works refers to it as “the finest medicament for nourishing the liver and kidney” [26]. It records that wolfberry “nourishes yin without causing yin debility, and supports yang while enabling yang to flourish,” emphasizing wolfberry’s characteristics of nourishing liver blood, mildly supplementing liver yin, and harmonizing the yin-yang balance of the liver. A large body of domestic and international research has shown that the gouqizi polysaccharides contained in wolfberry exert marked reparative and protective effects on the liver, thereby ameliorating the state of Fatigue. Lycium barbarum Polysaccharides (LBP) can significantly increase hepatic glycogen reserves. Luo Qun [27] found that LBP regulates hepatic mitochondrial function, promotes glycogenolysis for energy supply, and reduces the generation of urea nitrogen, a product of protein metabolism. Meanwhile, in animal experiments, Peng [28] and colleagues found that rats fed LBP exhibited prolonged exhaustive swimming time, with improved serum glucose, ATP, and glycogen levels, indicating that optimization of hepatic energy metabolism constitutes an important basis for anti-fatigue effects. wolfberry exerts anti-Fatigue effects by protecting the liver’s metabolic, antioxidant, and detoxification functions, optimizing energy reserves (glycogen) and the efficiency of energy utilization, and reducing the production of fatigue-related metabolic waste products (lactic acid and urea nitrogen). Moreover, in clinical practice, its combination with other Chinese medicinals may further amplify these advantages; for example, experimental studies showed that gouqizi combined with ginseng was superior to the ginseng group and the gouqizi group in enhancing exercise endurance

in mice, reducing the accumulation of metabolic products, and increasing glycogen storage levels [29].

Mulberry fruit is also known as wushen and heishen, and is chiefly produced in Jiangsu, Zhejiang, and other regions. Its flavor is sweet and sour, and its nature is cold. In the Bencao Yanyi, it is praised as "the essence of the mulberry," and records throughout successive dynasties consistently describe its functions of nourishing yin and supplementing blood, generating fluids and moistening dryness, and darkening the hair and improving visual acuity. In Wang Shixiong's Qing-dynasty Sui Xi Ju Yin Shi Pu [9] it is described as being able to "nourish the liver and kidney and replenish blood and fluids," indicating the superior efficacy of mulberry fruit in nourishing the liver. It is especially well suited to Fatigue of the liver-kidney yin deficiency pattern, and can significantly ameliorate the accompanying manifestations, including fatigue and lack of strength, soreness and weakness of the lower back and knees, vexing heat with insomnia, night sweating, as well as bodily symptoms such as contraction or numbness of the sinews and vessels and aching joints. Extracts from mulberry fruit increase the activity of hepatic antioxidant enzymes, such as superoxide dismutase (SOD) and glutathione (GSH), reduce malondialdehyde (MDA) levels, attenuate free radical-induced damage to hepatocytes, maintain the normal structure and function of hepatocytes, and thereby ensure the liver's central role in energy metabolism and detoxification. In addition, the aqueous extract of mulberry fruit significantly prolonged the weight-loaded swimming time of ICR mice through three pathways—enhancement of antioxidant defense, regulation of energy metabolism, and clearance of fatigue-related metabolic products—and exhibited a dose-dependent effect, with the high-dose group showing the greatest efficacy, thereby providing an experimental basis for the development of mulberry fruit as an anti-fatigue functional food [30]. At the same time, mulberry polysaccharides and anthocyanins can significantly prolong the time to exhaustion in swimming in mice, thereby further confirming their anti-fatigue effects [31]. In the course of modern food processing, mulberry fruit can be processed into a variety of dosage forms, among which a low-sugar electuary prepared by substituting isomaltooligosaccharide for sucrose has emerged as an innovative product, offering good palatability and the capacity to improve liver function [32].

In summary, Fatigue disorder, on the basis of its pathological characteristics of chronic fatigue that is protracted and difficult to resolve and that implicates the Liver, is closely related to the theory of "Liver is the Basis of Resistance to Fatigue"; accordingly, treatment should proceed from the liver while also being guided by syndrome differentiation. Among Food as Medicine substances, medicinals with the function of Regulating the liver, by virtue of their distinctive dual attributes as both therapeutic agents and foods, are not limited to simple treatment alone, but are better able to embody the characteristic of "integrating medicine into food"; they offer high safety during routine consumption and strong patient adherence, making them a preferred option for subhealth regulation and the prevention and treatment of chronic diseases. In so doing, they both carry forward the Traditional Chinese Medicine wisdom of "treating disease before it arises" and accord with the full-cycle demands of modern health management — "prevention – regulation - rehabilitation." In recent years, numerous studies have shown that medicinal substances with Liver Function Regulator effects within Food as Medicine possess particular advantages and potential in the treatment of Fatigue disorder. Nevertheless, current research remains incomplete: the multi-component, multi-target effects in the treatment of chronic fatigue are difficult to quantify, specific biomarkers are lacking, and the dosage, dosage forms, and compatibility principles for clinical application in Traditional Chinese Medicine still require further investigation. Based on the Traditional Chinese Medicine theory of "Liver is the Basis of Resistance to Fatigue," this article aims to explore in depth the pathological mechanisms of Fatigue disorder and to systematically investigate the therapeutic effects of Food as Medicine Liver Function Regulator substances. Through the integration of theoretical exposition and empirical research, this study not only provides a scientific basis for optimizing clinical treatment protocols for Fatigue disorder, but also lays a theoretical foundation for the development of novel medicines with distinctive characteristics of Traditional Chinese Medicine, with the aim of improving therapeutic efficacy and quality of life in patients with Fatigue.

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