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Exploring the Anti-Epileptic Mechanism of Chaihu Longgu Muli Decoction from the Perspective of "The Heart and Gallbladder Have a Separate Connection"

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Abstract: ***Epilepsy is a chronic central nervous system disorder characterized by abnormal synchronous neuronal discharges, posing a serious threat to global public health. The classic Chinese medicine formula Chaihu Longgu Muli Decoction has demonstrated significant anti-epileptic efficacy in clinical practice. Guided by the TCM theory that "The Heart and Gallbladder Have a Separate Connection," and incorporating the principles of meridian interconnectivity and Qi transformation, this study analyzes the core pathogenesis of epilepsy as "dysfunction of the Gallbladder Pivot leading to Qi stagnation, phlegm, and fire, which ascend to disturb the Heart Spirit." Modern medical research supports this theory, confirming that bile acid metabolism disorders and neuroinflammatory responses are common in epilepsy patients. Through a systematic analysis of the composition and compatibility of Chaihu Longgu Muli Decoction, this article reveals its triple mechanism of action: "unblocking and facilitating the Gallbladder Pivot," "clearing and transforming phlegm-fire," and "restoring the ascending and descending movement of Qi." This multi-target, multi-level approach enables systematic intervention in the complex pathological network of epilepsy. This study not only offers innovative insights into TCM treatment of epilepsy from the unique perspective of "The Heart and Gallbladder Have a Separate Connection," but also highlights the systemic advantages of TCM formulas in holistic regulation and multi-target intervention. Furthermore, it provides important theoretical foundations and new research directions for clinical application, integrative medicine approaches, and TCM treatment of complex neurological disorders.***

Keywords: The Heart and Gallbladder Have a Separate Connection; Epilepsy; Chaihu Longgu Muli Decoction; Phlegm-fire disturbing the heart; Bile acid metabolism; Neuroinflammation.

1. INTRODUCTION

Epilepsy is a chronic, recurrent, paroxysmal central nervous system dysfunction disorder caused by sudden, abnormal, excessive, and synchronous discharges of brain neurons. Epidemiological data indicate that there are approximately 65 million epilepsy patients worldwide [1], with over 10 million cases in China and about 400,000 new cases reported annually. It has become the second most common neurological disorder threatening the health of Chinese residents, after cerebrovascular disease [2]. The unpredictability, suddenness, and potential social stigma associated with epileptic seizures significantly impair patients' daily lives, learning, employment, and social interactions [3]. Moreover, epilepsy often leads to psychiatric comorbidities such as anxiety and depression, substantially increasing the socioeconomic burden and reducing the quality of life for patients and their families [4]. More seriously, status epilepticus or unexplained sudden death in epilepsy represents a significant risk for patients [5], particularly those with drug-resistant epilepsy.

From a modern biomedical perspective, the pathogenesis of epilepsy is highly complex, involving a "network" of multiple pathophysiological processes. Key elements include: genetic factors (e.g., mutations in channel genes such as SCN1A and KCNT1) [6], ion channel dysfunction (leading to an imbalance between neuronal excitability and inhibition, such as excessive glutamatergic activity or insufficient γ-aminobutyric acid (GABA) inhibition) [7], neurotransmitter system dysregulation (e.g., glutamate, GABA, monoamine transmitters) [8], abnormal synaptic plasticity and altered neural network structure [9], glial cell activation (involving neuroinflammation, reactive oxygen species burst, and oxidative stress damage mediated by astrocytes and microglia) [10], blood-brain barrier dysfunction [11], abnormal peripheral immune system activation [12], and energy metabolism disorders (e.g., mitochondrial dysfunction) [13]. These factors interact intricately, collectively constituting the pathological network of epilepsy.

Current primary treatments for epilepsy include anti-epileptic drugs (AEDs), which can control seizures in about two-thirds of patients. However, approximately 30% of patients develop drug-resistant epilepsy [14]. For these individuals, surgical interventions (such as focal resection, hemispherectomy, laser interstitial thermal therapy, vagus nerve stimulation, responsive neurostimulation, deep brain stimulation, etc. [12]) and dietary approaches like the ketogenic diet [15] serve as alternative or adjunctive options. Although numerous AEDs are available, they often present limitations such as incomplete efficacy, drug resistance, and significant central and peripheral side effects (e.g., cognitive impairment, hepatorenal toxicity, hematological suppression, allergic reactions) [16]. These challenges have motivated the medical community to explore safer and more effective treatment strategies.

Traditional Chinese Medicine (TCM) has a history of over 2,000 years in preventing and treating epilepsy, accumulating rich clinical experience and a unique theoretical framework. In classical TCM texts, epilepsy falls under categories such as “Xian Syndrome” and “Goat Wind Epilepsy.” Although understandings of its etiology and pathogenesis have varied across historical periods, a core consensus remains. From the Suwen·Treatise on Extraordinary Diseases, which attributes the condition to “fetal disease arising from maternal fright,” to the Essential Prescriptions of the Golden Cabinet emphasizing “phlegm-rheum causing mischief,” the Treatise on the Origins and Symptoms of Diseases elucidating “Heart Qi deficiency with Gallbladder Qi excess, and turbid phlegm ascending to harass,” Danxi's Mastery of Medicine directly stating “phlegm clouding the Heart orifices,” and the Compendium of Medicine concluding “epilepsy involves phlegm-pathogens rebelling upwards,” all classical sources identify the interplay of pathological factors such as wind, fire (heat), phlegm, stasis, fright, and deficiency as the core mechanism underlying epilepsy [17]. Among these, “phlegm evil” is regarded as the central pathological product, and “divine mechanism failure” (disturbed mind/brain spirit) is its ultimate outcome [18]. It is noteworthy that the pivotal hub governing the core pathological links—rebellious Qi movement, dysfunction of the Zang-Fu organs (especially impaired free coursing and discharging of the Liver and Gallbladder), and internal generation of phlegm and stasis—often lies in the dysfunction of the Shaoyang pivot mechanism. Zhang Zhongjing’s Treatise on Cold Damage and Miscellaneous Diseases describes Shaoyang disease with symptoms such as “alternating chills and fever,” “fullness and discomfort in the chest and hypochondrium,” and “vexation with a tendency to vomit.” These manifestations show a high correlation with the paroxysmal and recurrent nature of epileptic seizures, as well as premonitory symptoms like inexplicable fear, palpitations, chest tightness, and nausea. Thus, how does dysfunction of the Shaoyang meridian disrupt the mind (brain) and trigger epileptic seizures? The theory of “The Heart and Gallbladder Have a Separate Connection” reveals the unique relationship between the heart and gallbladder, providing a key to understanding this crucial pathogenesis.

2. THE CONNOTATION AND PHYSIOLOGICAL AND PATHOLOGICAL BASIS OF THE THEORY THAT “THE HEART AND GALLBLADDER HAVE A SEPARATE CONNECTION”

The theory of the “Separate Heart-Gallbladder Connection” or “Heart Connecting with the Gallbladder” traces its earliest conceptual origins to the Yellow Emperor's Inner Canon. It was explicitly proposed and systematically expounded by the Ming dynasty physician Li Chan in the Gateway to Medicine·Treatise on the Penetrating Connections of the Five Zang Organs: “The Five Zang organs have penetrating connections, each having its specific counterpart... The Heart connects with the Gallbladder; the Spleen connects with the Small Intestine; the Lung connects with the Bladder; the Kidney connects with the Sanjiao; the Liver connects with the Large Intestine...” [19]. This theory does not imply direct anatomical adjacency or channel connection between the heart and gallbladder, but rather highlights a unique functional and pathological relationship (“different channels”) based on the meridian system, coordination of Qi transformation, and the mutual generation and restraint among the Zang-Fu organs according to Yin-Yang and Five Element theory.

2.1 Meridian Interconnection: The Physical Basis of the Heart-Gallbladder Connection

The meridian system forms the core bridge between the heart and gallbladder. The Lingshu·Meridian details the circulation of the Gallbladder Meridian of Foot-Shaoyang: “The Gallbladder Foot-Shaoyang Channel originates at the outer canthus of the eye, ascends to the temple region... A branch descends from the supraclavicular fossa to the axilla, runs along the chest, passes through the hypochondrium... Another branch... descends into the chest, pierces the diaphragm, connects with the Liver and belongs to the Gallbladder...” Crucially, it explicitly states: “The Foot-Shaoyang Channel, running through the interior of the chest and pertaining to the Gallbladder, disperses upwards to the Liver and penetrates the Heart.” [20]. This meridian starts from the head, passes downward through the chest and diaphragm to connect with the liver and gallbladder. Its Qi and blood traverse the cardiac region

during circulation, forming a direct pathway for Gallbladder Qi to reach the Heart. The Ling Shu·Classic of Sinew Channels further notes that a branch of the Foot-Shaoyang sinew channel "attaches to the chest and breasts," an area encompassing the precordial region and nipples, where the Heart's Pectoral Qi gathers. Additionally, the Pivotal Treatise on Medicine states: "The Spleen, Stomach, Liver, and Gallbladder... each have a connecting cord attached beside the Pericardium Network, communicating with the Heart." The Pericardium acts as the "outer protector" of the Heart, receiving pathogens on its behalf. This emphasizes that Qi from the liver, gallbladder, spleen, stomach, and other organs can reach the heart through the meridian system. Thus, the close meridian connections provide a material basis for the exchange of Qi and blood and functional interaction between the heart and gallbladder.

2.2 Qi Transformation: Functional Coordination Between the Heart and Gallbladder

The "Opening-Closing-Pivot" theory, originating from the Suwen·Treatise on the Separation and Combination of Yin and Yang, serves as a crucial foundation for the penetrating connections among the Zang-Fu organs. This theory summarizes the functional dynamics of the Three Yangs and Three Yins: "Taiyang is the Opening, Yangming is the Closing, Shaoyang is the Pivot. For the Three Yins: Taiyin is the Opening, Jueyin is the Closing, Shaoyin is the Pivot."

Shaoyang as the Pivot: Positioned between the exterior and interior, it acts as the hub regulating the exit, entry, opening, and closing of Yang Qi throughout the body. Gallbladder Pertains to Shaoyang: The Gallbladder Foot-Shaoyang Channel governs the functional role of the Shaoyang pivot mechanism. Zhang Jingyue's Commentary: As annotated by Zhang Jingyue, "Shaoyang being the Pivot means that Yang Qi is positioned between the exterior and interior, capable of exiting or entering, like a pivot mechanism."[21] The Gallbladder, as the "Fu of Central Essence" and the "Official of Impartial Judgment," normally performs the following functions: Regulating Qi Mechanism: Free coursing of Gallbladder Qi ensures smooth movement of Qi throughout the body, coordinating the functions of the Five Zang and Six Fu organs, and balancing Qi, Blood, Yin, and Yang. The Suwen·Treatise on the Six Segments and Zang Manifestations emphasizes: "The function of all eleven Zang-Fu organs depends on the Gallbladder." The Za Bing Yuan Liu Xi Zhu·Gallbladder Disease Origins similarly states: "All eleven Zang-Fu organs rely on Gallbladder Qi for harmony." As the "Official of Impartial Judgment," the Gallbladder's decisive function plays a key role in maintaining harmonious and orderly Qi movement.

Governing Ministerial Fire (Gallbladder Fire): Ministerial Fire pertains to Shaoyang and resides within the Gallbladder. The relationship between Sovereign Fire (Heart Fire) and Ministerial Fire is close. The Heart, located in the Upper Jiao, pertains to Fire; the Gallbladder attaches to the Liver, pertaining to Wood. Wood generates Fire—this Five Phase relationship means Ministerial Fire ascends to warm the Sovereign Heart, keeping Heart Yang warm and free-flowing, and the spirit-mind clear and bright. The Suwen·Divine Orchid Secret Classic clearly states "Gallbladder Qi communicates with the Heart." Conversely, Heart Qi and Blood can descend to nourish the Gallbladder, maintaining its clear and functional nature.

Promoting Bile Secretion and Assisting Middle Jiao Transportation: The Gallbladder stores and excretes bile, "storing the refined juice." Bile originates from the surplus Qi of the Liver. Its normal secretion and excretion are vital for the Spleen and Stomach's transformation of water and grains, and the ascending of the clear and descending of the turbid. This process is crucial for producing Qi, Blood, and Body Fluids from postnatal sources, which in turn nourish the Heart Spirit.

Physiological Harmony: Smooth Gallbladder Qi movement promotes the orderly distribution of Ministerial Fire. Normal Ministerial Fire ensures proper warming by Heart Fire (Sovereign and Ministerial Fires in their proper positions), leading to sufficient Heart Qi, vigorous blood circulation, and a tranquil spirit-mind. Conversely, sufficient Heart Qi (Sovereign Fire illuminating) can warmly nourish the Gallbladder (Wood warmed by Fire), maintaining the free and harmonious flow of Gallbladder Qi. Thus, a harmonious state is achieved: "Heart and Gallbladder interconnected, Sovereign and Ministerial Fires positioned properly, the Pivot mechanism functioning smoothly, enabling the use of the Spirit-Mind mechanism."

2.3 Heart and Gallbladder Diseases: Pathological Interrelationship

When pathogenic factors (e.g., emotional depression, exogenous damp-heat, improper diet, congenital deficiency) cause dysfunction of the Shaoyang Pivot, the Gallbladder, as the seat of Shaoyang, is primarily affected, resulting in Gallbladder Depression. Gallbladder Qi becomes blocked and difficult to flow, leading to: Gallbladder

Depression Transforming into Fire (Heat): Prolonged depression generates internal heat. Ministerial Fire leaves its position and moves recklessly, forming "exuberant Gallbladder Fire." Refining Fluids into Phlegm: Intense Gallbladder Fire scorches body fluids. Combined with impaired pivot function and Sanjiao water passage obstruction, water-dampness accumulates into rheum, which is then scorched into phlegm-heat.

Qi Depression Generating Wind: The Liver and Gallbladder are interior-exteriorly related. Gallbladder depression often affects the Liver, causing impaired free coursing. Liver Qi becomes urgent, and extreme depression transforms into wind; alternatively, accumulated phlegm-heat can also generate wind.

Disturbing the Heart Spirit via the Heart-Gallbladder Connection: Pathological conditions of the Gallbladder can ascend via the "Separate Heart-Gallbladder Connection" to disturb the Heart Spirit. Gallbladder Fire flares upwards to harass the Heart, either directly along the Gallbladder channel (which penetrates the Heart) or via the connection between Ministerial and Sovereign Fires. Phlegm-heat clouds the clear orifices: Gallbladder heat refining fluids into phlegm, combined with phlegm-heat, rebels upwards, obstructing clear Yang and congesting the Heart orifices (Brain orifices).

This pathological process of "Gallbladder disease affecting the Heart" manifests clinically as common epileptic symptoms: "restlessness with fright and fear, irritability and anger, palpitations and severe anxiety, poor sleep with excessive dreams, and even paroxysmal loss of consciousness and limb convulsions"—signs of "unsettled Heart Spirit and loss of mental governance." The Jing Yue Quan Shu succinctly summarizes: "When Gallbladder Qi flows freely, Heart Qi is harmonious; when Gallbladder Qi is depressed, Heart Qi stagnates." Furthermore, the Zhu Bing Yuan Hou Lun directly points out the pathological characteristic in epilepsy of "Heart Qi deficiency with Gallbladder Qi excess," revealing that during epilepsy, hyperactive and rebellious Gallbladder Qi—primarily referring to chaotic Qi, Fire, and Phlegm—disturbs Heart Qi, i.e., the regulatory function of the Heart Spirit. This disturbance constitutes the key pathological link leading to Heart Qi deficiency and loss of mental function [22].

3. ANALYZING THE CORE PATHOGENESIS OF EPILEPSY BASED ON THE THEORY THAT "THE HEART AND GALLBLADDER HAVE A SEPARATE CONNECTION": GALLBLADDER DYSFUNCTION LEADS TO QI STAGNATION, PHLEGM AND FIRE, AND DISTURBS THE MIND

Based on the theory of "The Heart and Gallbladder Have a Separate Connection," combined with discussions from ancient and modern physicians and clinical practice, the core pathogenesis of epilepsy can be summarized as: "dysfunction of the Shaoyang (Gallbladder) pivot, leading to Qi stagnation and phlegm (dampness) obstruction, which transforms into heat (fire); internal generation of phlegm-heat (fire); wind stirring phlegm, disturbing the heart (brain), resulting in spirit malfunction."

3.1 Gallbladder Pivot Dysfunction as the Initiating Factor and Core Mechanism

The term "Shu" denotes a pivot, hub, or critical point. "Dan Shu" specifically refers to the pivot mechanism of the Shaoyang channel governed by the Gallbladder. As elucidated in the Seeking Truth in Medicine: "The pivots of the human body are the Liver and Gallbladder... When the pivot functions normally, it resists external pathogens, regulates the internal Zang organs, ensures the smooth flow of Qi and Blood, and thus prevents disease." Various factors—including emotional disturbances (particularly fright or fear), improper diet, congenital deficiency, fetal weakness, or external pathogenic invasion (e.g., damp-heat)—can lead to stagnation of the Qi mechanism. When Gallbladder Qi fails to course freely, its regulatory and decisive functions are compromised, resulting in emotional and mental dysregulation. Patients often exhibit emotional instability and heightened susceptibility to fright, described as "timid and easily startled," which is both a cause and a common symptom of epilepsy. The Treatise on the Three Causes, Unified as One, of Diseases, Syndromes, and Formulas states that epilepsy "arises from fright, causing disharmony of the Zang Qi, which becomes depressed and generates phlegm-rheum." The Shaoyang Sanjiao, known as the "Official of Dredging Ditches" and the "source of waterways," plays a key role in fluid metabolism. Dysfunction of the Gallbladder Pivot directly impairs Sanjiao's Qi transformation, leading to obstruction of water passages. As noted in the Popular Guide to Cold Damage: "When the Qi mechanism of the Sanjiao is not free-flowing [23]," water-fluid metabolism is disrupted, resulting in the accumulation of dampness, rheum, and phlegm.

3.2 Phlegm and Fire as the Key Pathological Mediators

Turbid phlegm is a core pathological product in epilepsy, with its formation and progression occurring in three stages: Formation of Phlegm: Gallbladder depression transforming into fire scorches body fluids, condensing them into phlegm. The Supplement to Pattern Identification and Treatment states: "Fire is the root of phlegm; phlegm is the manifestation of fire." Concurrently, impaired Sanjiao water passage function causes stagnation of fluids. The Suwen·Divine Orchid Secret Classic records: "The Sanjiao is the Official of Dredging Ditches, from which the waterways emerge." The interaction of these processes results in sticky, congealed phlegm that readily obstructs the Qi mechanism. The Danxi Xinfa directly states: "Xian syndrome (epilepsy) is primarily attributed to phlegm, arising due to fire stirring."

Nature of Phlegm: Phlegm ascends and descends following the movement of Qi. As described in the Guide to Clinical Practice with Case Studies: "Phlegm ascends with fire, upwardly blocking the clear orifices." Turbid phlegm rebels upward along the Gallbladder channel, congesting the clear orifices and clouding the Spirit-Mind mechanism. The Systematic Differentiation and Treatment of Diseases further notes: "The head is the confluence of all Yang; phlegm obstruction prevents Yang Qi from ascending." Phlegm obstructing the brain collaterals leads to dysfunction of the Original Spirit (Yuan Shen).

The concept of "phlegm-fire" in traditional Chinese medicine corresponds to the modern medical triad of "neuroinflammation-oxidative stress-metabolic disorder": Abnormal activation and proliferation of astrocytes release proinflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α), whose elevated levels exacerbate neuronal damage [24]. Mitochondrial dysfunction in epileptic foci [25] is characterized by significantly reduced superoxide dismutase (SOD) activity and increased levels of malondialdehyde (MDA), a marker of lipid peroxidation, leading to a neuronal energy crisis.

Reduced bile acid synthesis impairs intestinal barrier function [26], allowing endotoxins such as lipopolysaccharide (LPS) to enter the bloodstream. LPS then activates key inflammatory signaling pathways, including Toll-like receptor 4 (TLR4)/nuclear factor κB (NF-κB) [27], exacerbating systemic inflammation and affecting the central nervous system.

3.3 Mutual Reinforcement of Wind and Fire Leading to Loss of Mental Governance

Prolonged accumulation of phlegm-fire inevitably generates internal wind and agitation. The interplay of the three pathogenic factors—"Wind, Fire, and Phlegm"—triggers epileptic seizures. On one hand, Gallbladder Fire stirs Liver Wind. The Suwen states: "All wind manifestations such as tremors and dizziness belong to the Liver." Gallbladder depression affects the Liver, causing Liver Yang to transform into wind. On the other hand, phlegm-heat generates wind. The Standards of Pattern Identification and Treatment notes: "Extreme heat generates wind; abundant phlegm stirs wind." When phlegm-fire becomes intense and congested, it scorches body fluids, producing internal wind.

From a modern pathological perspective, this process corresponds to abnormal synaptic plasticity and impaired GABAergic inhibition: Excessive phosphorylation of N-methyl-D-aspartate receptors (NMDARs) leads to increased calcium ion influx, inducing hypersynchronous neuronal discharges, disrupting intracellular signaling, and promoting neuronal death [28]. Concurrently, reduced expression of glutamic acid decarboxylase 67 (GAD67) and decreased GABA levels significantly impair central inhibitory function, collectively contributing to epileptic seizures [29]-[30].

4. ANTI-EPILEPTIC MECHANISM OF CHAIHU LONGGU MULI DECOCTION

Chaihu Longgu Muli Decoction is composed of Bupleurum (Chai Hu), Dragon Bone (Long Gu), Scutellaria (Huang Qin), Ginger (Sheng Jiang), Ginseng (Ren Shen), Cinnamon Twig (Gui Zhi), Poria (Fu Ling), Pinellia (Ban Xia), Rhubarb (Da Huang), Oyster Shell (Mu Li), and Jujube (Da Zao). In this formula, Bupleurum—which is indicated for "heart and abdominal disorders"—and Scutellaria—which "treats various heats"—serve as the Monarch herbs to unblock and facilitate the Shaoyang pivot mechanism and clear fire resulting from Gallbladder depression. The main active ingredient of Bupleurum, saikosaponin D, inhibits intestinal reabsorption [31], reduces bile acid concentration, suppresses calcium overload, and promotes bile secretion. The primary active component of Scutellaria, baicalin, effectively regulates bile acid metabolism and maintains intestinal microecological balance [32]. Together, these two herbs synergistically achieve the effect of "dredging the Gallbladder and clearing fire."

Dragon Bone, which “astringes floating and ascending Qi,” and Oyster Shell, which “reduces heat and subdues Yang,” are used together as Minister herbs to constrain Liver Wood and subdue ascending Yang Qi. The Annotations on the Shen Nong's Classic of the Materia Medica states: “Phlegm is water; it ascends following fire. Dragon Bone can guide rebelliously ascending fire and flooding water back to their source. When used together with Oyster Shell, it becomes a divine combination for treating phlegm.” Modern research confirms that dragon bone is rich in calcium carbonate, calcium phosphate, and other components that exert inhibitory effects on the central nervous system, including sedative-hypnotic and antispasmodic actions; oyster shell also exhibits calming and tranquilizing properties [33]. The Seeking Truth in Materia Medica notes: “Dragon Bone’s actions are similar to those of Oyster Shell” and “it possesses remarkable effects in astringing desertion, settling fright, and calming the ethereal soul” [34]. The combination of Dragon Bone and Oyster Shell enhances their ability to heavily settle and quiet the spirit while pacifying and suppressing the flaring of Ministerial Fire.

Ginseng—which “supplements the five Zang organs, quiets the spirit-mind, stabilizes the ethereal and corporeal souls, and arrests palpitations due to fright”—Pinellia—which “treats phlegm-rheum”—and Poria—which “transforms phlegm-drool”—act together as Assistant herbs to tonify Qi, calm the spirit, resolve phlegm, and eliminate dampness, thereby interrupting the generation of phlegm-fire. Ginsenoside Rb1 helps maintain neural homeostasis and reduces brain tissue damage by inhibiting neuronal apoptosis and enhancing neuronal regeneration and plasticity [35]. Pinellia ternata exhibits sedative and anti-inflammatory effects; its active compound carvacrol inhibits neuroinflammation by reducing levels of nitric oxide (NO), prostaglandin E2 (PGE2), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and COX-2 activity, thereby counteracting oxidative stress and exerting neuroprotective effects in the hippocampal dentate gyrus [36]. Pachymic acid, a functional component of Poria cocos, also demonstrates neuroprotective activity [37]. Together, these three ingredients synergistically promote the repair of hippocampal neuroplasticity.

Rhubarb—which “expels the stale and promotes the new”—and Cinnamon Twig—which “frees the blood vessels, rectifies insufficiency of coursing, and guides all medicines”—are employed as Envoy herbs to collaboratively restore the ascending and descending functions of the Qi mechanism. Rhubarb modulates the intestinal microbiota and strengthens the intestinal barrier [38]. Its active ingredient, emodin, regulates bile acid synthesis via the FXR/CYP7A1/SHP pathway [39], thereby addressing “gallbladder pivot dysfunction” from a metabolic perspective. Cinnamaldehyde and total volatile oil from cinnamon twig alleviate overexcitement of the central nervous system [40], further enhancing the “restoration and descending” effect.

Thus, when the Gallbladder Pivot is unblocked, Heart Fire naturally subsides; when phlegm-fire is cleared, the Spirit-Mind regains governance; and when Qi transformation is regulated, the “Heart-Gallbladder Axis System” functions normally. Ultimately, the trinity function of “unblocking the Gallbladder Pivot – clearing phlegm-fire–restoring ascending/descending” is achieved, systematically correcting the pathological mechanism of epilepsy.

Modern research has shown that Chaihu Longgu Muli Decoction reduces inflammatory response, oxidative stress, and astrocyte activation by downregulating the COX-2/PGE2 pathway, thereby mitigating damage to hippocampal neurons in epileptic rats and exerting anti-epileptic effects [41]. This prescription also enhances activation of the AMPK-Nrf2 axis and regulates mitochondrial oxidative phosphorylation, increasing antioxidant expression in epileptic rats and alleviating oxidative stress [42]. The decoction significantly prolongs the latency of global tonic-clonic seizures in pentylenetetrazol-induced epileptic rats, upregulates glutamate transporter levels and glutamine synthetase activity, and shortens seizure duration in a dose-dependent manner in mouse models, demonstrating neuroprotective and anti-epileptic efficacy. Additionally, it inhibits the TLR4 pathway by reducing miR-146a-3p and miR-146a-5p levels, decreases inflammatory factors in the hippocampal dentate gyrus of temporal lobe epileptic rats, and ameliorates seizure onset [43]. Furthermore, compared with epileptic model rats, those treated with the decoction show significantly reduced expression of NLRP3, Caspase-1, IL-1β, and TNF in the hippocampal dentate gyrus, indicating therapeutic efficacy against temporal lobe epilepsy.

Network pharmacology studies reveal that Chaihu Longgu Muli Decoction also acts on targets such as CHRNA2, GABRA1, and IL-1β. Animal experiments demonstrate that it upregulates GABA expression and downregulates dopamine (DA) levels in lithium-pilocarpine-induced epileptic rats, protecting neurons in the CA1 region of the hippocampus [44]. Wang Xin et al. found that the decoction reduces serum levels of glial fibrillary acidic protein, neuropeptide Y, and S100β in epileptic patients, thereby improving their quality of life [45].

5. CONCLUSION

The "multi-target, multi-level, and multi-system" integrated intervention model of Chaihu Longgu Muli Decoction offers a new paradigm for addressing the challenges in epilepsy treatment and underscores the unique value of TCM compound prescriptions in managing complex systemic diseases.

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