

Exploring the Mechanism of Qibi Tiaoshen Granules in Treating Autism Spectrum Disorder Based on the “Spleen-Kidney-Brain” Axis and Mitochondrial Energy Metabolism

Du Juan, Du Qiao*

Xi'an TCM Hospital of Encephalopathy, Xi'an 710032, Shaanxi, China

*Correspondence Author

Abstract: Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder, whose pathogenesis involves the interplay of multiple factors. Qibi Tiaoshen Granules (QTSG) are a proprietary hospital preparation developed by Xi'an Hospital of Traditional Chinese Medicine Encephalopathy, based on the “three-stage, four-dimensional” rehabilitation and treatment system centered on “opening the orifices and regulating the spirit.” This formulation has shown favorable clinical efficacy in the treatment of ASD. This paper systematically reviews the traditional Chinese medicine (TCM) pathogenesis of ASD and the formula rationale of QTSG, and explores its potential molecular mechanisms from two core perspectives: the “spleen-kidney-brain” axis and mitochondrial energy metabolism. In the formula, Lujiaojiao (deer antler glue) and Renshen (ginseng) tonify the kidney and replenish essence to nourish the brain marrow; Guizhi (cinnamon twig) and Fuling (Poria) warm and activate the spleen yang to transform and generate subtle essences; and Shichangpu (sweet flag rhizome) and Yuanzhi (polygala root) resolve phlegm and open the orifices to regulate the spirit. Collectively, these ingredients exert synergistic actions of warming and tonifying the spleen and kidney, resolving phlegm and opening the orifices, and regulating the spirit to relieve blockages. At the mechanistic level, QTSG may exert its therapeutic effects by regulating the gut microbiota-gut-brain axis to improve the neuroimmune microenvironment, enhancing mitochondrial energy metabolism to ensure neuronal energy supply, and modulating neurotransmitter balance to restore synaptic plasticity. This review provides a theoretical basis for the broader clinical application of QTSG in ASD and identifies future directions for experimental research.

Keywords: Autism spectrum disorder, Qibi Tiaoshen Granules, Spleen-kidney-brain axis, Mitochondrial energy metabolism.

1. Introduction

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders characterized by core features including social interaction deficits, language and communication impairments, restricted interests, and repetitive stereotyped behaviors. Over the past decade, the prevalence of ASD has increased rapidly. According to the U.S. Centers for Disease Control and Prevention (CDC), the annual prevalence of ASD is 2.76% [1]. Given its high heterogeneity and comorbidity rates, ASD severely affects the quality of life of affected children and their families, and has become a major challenge in the global public health field.

The etiological mechanisms of ASD have not yet been fully elucidated. Current evidence suggests that ASD arises from complex interactions between genetic and environmental factors, involving multiple pathological mechanisms, including synaptic structural and functional abnormalities, neurotransmitter system imbalances, neuroinflammation and immune dysregulation, mitochondrial dysfunction and oxidative stress, as well as gut microbiota dysbiosis [2–3]. Due to the marked heterogeneity of ASD, there is currently no specific pharmacotherapy targeting the core symptoms. The mainstream interventions remain primarily behavioral rehabilitation training, while pharmacological treatments are mainly directed at comorbid symptoms [4].

2. TCM Pathogenesis of ASD and Formula Rationale of Qibi Tiaoshen Granules

2.1 Core Pathogenesis of ASD

Although there is no disease name exactly corresponding to “autism” in ancient Chinese medical literature, its clinical manifestations—such as “childish dullness,” “delayed speech,” “lack of intelligence,” “inability to walk at several years of age,” and “delayed teething”—allow it to be classified under categories including “five delays,” “dementia,” “depression syndrome,” and “fetal weakness” [5]. Synthesizing the discourses of ancient physicians through the ages with modern clinical observations, the disease location of ASD is primarily in the brain, and is closely related to dysfunction of the heart, spleen, and kidney. Its core pathogenesis can be summarized as “spleen-kidney deficiency as the root and phlegm turbidity obstructing the orifices as the manifestation,” with deficiency, phlegm, and blood stasis forming a mutually causal cycle that makes the condition protracted and difficult to cure.

The kidney stores essence, generates marrow, and connects with the brain. The Yellow Emperor's Inner Classic – Plain Questions (Suwen) states: “The kidney generates bone marrow.” The Spiritual Pivot – On the Seas (Lingshu) states: “The brain is the sea of marrow.” The kidney stores the innate essence, which transforms into marrow; marrow aggregates to form the brain. Therefore, the prosperity or decline of kidney essence directly determines the enrichment or depletion of brain marrow. Adequate kidney essence ensures abundant brain marrow and nourishment of the spirit, manifesting as intelligence, fluent speech, and appropriate behavior; deficiency of kidney essence leads to insufficiency of brain marrow and malnourishment of the spirit, manifesting as

cognitive impairment, speech retardation, blunted responsiveness, and social incapacity [6]. The learning difficulties, poor comprehension, and language developmental delays commonly seen in ASD children precisely align with the pathogenesis of “insufficiency of the sea of marrow.” Modern research has also confirmed that children with ASD exhibit neuronal developmental abnormalities, synaptic pruning deficits, and aberrant neural network connectivity [7], which are intrinsically consistent with the traditional Chinese medicine (TCM) theory of “brain marrow malnourishment and failure of spirit-function.”

The spleen governs transportation and transformation and serves as the foundation of acquired constitution. It transports and transforms water-grain essences, generates qi and blood, and delivers them upward to the brain, providing the material foundation for the nourishment of brain marrow and the activities of spirit-function. The Spiritual Pivot – On the Absolute Fasting of Ordinary People (Lingshu) states: “When the stomach is full, the intestines are empty; when the intestines are full, the stomach is empty. Through this alternating fullness and emptiness, qi is able to move upward and downward, the five viscera are stabilized, the blood and vessels are harmonized, and the spirit dwells therein.” Children with ASD frequently present with clinical manifestations of spleen-stomach dysfunction, including poor appetite, picky eating, abdominal distension, loose stools, or constipation. Epidemiological studies have shown that the prevalence of gastrointestinal symptoms in children with ASD is significantly higher than in typically developing children, with 9%–91% of ASD children experiencing abdominal pain, constipation, diarrhea, nausea, or abdominal distension [8]. When the spleen fails to transport and transform properly, essences are not generated, qi and blood lack resources, pure yang fails to ascend, and the brain orifices are deprived of nourishment; concurrently, retained water-dampness accumulates and transforms into phlegm. Spleen deficiency and phlegm turbidity serve as mutual causes, forming a vicious cycle.

Phlegm turbidity obstructing the orifices is the critical link in the pathogenesis. Phlegm turbidity is both a pathological product of spleen deficiency and a pathogenic factor that further damages the spirit-function. The Spiritual Pivot – On the Pathogenic Conditions of the Zang-Fu Organs (Lingshu) states: “The twelve meridians and the three hundred and sixty-five collateral vessels all convey their blood and qi upward to the face and into the orifices.” When phlegm turbidity accumulates, it blocks the meridians and obscures the clear orifices above, leading to clouded consciousness, apathetic expression, and blunted responses to external stimuli; protracted phlegm turbidity may transform into fire due to stagnation, and phlegm-fire disturbing the heart results in irritability, restless sleep, and aberrant behavior. The restricted interests, stereotyped behaviors, social avoidance, and gaze avoidance commonly observed in ASD children can be regarded as external signs of “blockage of spirit-function.” Furthermore, phlegm turbidity obstructs the collaterals, leading to qi stagnation and blood stasis; the intermingling of phlegm and stasis further aggravates cerebral collateral obstruction, rendering the condition protracted and difficult to resolve.

In summary, the pathogenesis of ASD results from the combined effects of congenital insufficiency and acquired malnourishment. Kidney essence deficiency leads to insufficiency of brain marrow, constituting the root of the disease; spleen deficiency with impaired transportation and transformation leads to failure to generate essences and internal generation of phlegm turbidity, constituting the basis of the disease; phlegm turbidity obstructing the orifices and failure of spirit-function constitute the manifestation of the disease. The sequence of “deficiency generating phlegm, phlegm blocking the spirit-orifices, and spirit-function failure” constitutes the complete pathogenetic chain underlying the development and progression of ASD.

2.2 Formula Analysis of Qibi Tiaoshen Granules

Qibi Tiaoshen Granules consist of six herbal ingredients: Lujiaojiao (deer antler glue), Guizhi (cinnamon twig), Shichangpu (sweet flag rhizome), Yuanzhi (polygala root), Renshen (ginseng), and Fuling (Poria). The formula is precisely designed and closely addresses the core pathogenesis of ASD, namely “spleen-kidney deficiency and phlegm turbidity obstructing the orifices.”

Warming and tonifying the spleen and kidney to treat the root. Lujiaojiao, a substance of flesh and blood, is salty and warm in nature, enters the kidney meridian, and is skilled at tonifying kidney yang, supplementing essence and blood, and strengthening sinews and bones—making it a key herb for replenishing essence and enriching marrow. Renshen greatly supplements primordial qi, tonifies the spleen and lung, calms the spirit, and enhances intelligence, and is hailed as the “supreme herb that supplements the five viscera, stabilizes the spirit, and anchors the ethereal soul.” When these two herbs are used in combination, Lujiaojiao replenishes kidney essence to nourish brain marrow, while Renshen supplements spleen qi to generate essences, together achieving dual supplementation of the spleen and kidney and coordinated regulation of both congenital and acquired foundations. Guizhi, pungent and warm in nature, enters the heart, lung, and bladder meridians; it warms and unblocks the meridians and assists yang in transforming qi, supporting the warming and tonifying effects of Lujiaojiao and Renshen while its “unblocking” property prevents stagnation caused by tonic herbs. Fuling, sweet and bland in nature and neutral in property, invigorates the spleen and drains dampness, both assisting Renshen in fortifying the spleen for transportation and transformation and eliminating the source of phlegm generation.

Resolving phlegm and opening the orifices to treat the manifestation. Shichangpu, pungent, warm, and aromatic, is skilled at transforming phlegm-dampness, opening blocked orifices, and calming the spirit. The Divine Farmer’s Materia Medica (Shennong Bencao Jing) states that it “opens the heart orifices, supplements the five viscera, unblocks the nine orifices, sharpens the eyes and ears, and produces speech.” Yuanzhi, bitter, pungent, and warm, enters the heart and kidney meridians; it calms the spirit, enhances intelligence, connects the heart and kidney, and expels phlegm to open the orifices. The Shennong Bencao Jing states that it “treats coughing and counterflow, supplements insufficiency, dispels

pathogenic qi, benefits the nine orifices, sharpens intelligence, clears the ears and eyes, improves memory, and strengthens willpower.” The combination of Shichangpu and Yuanzhi is a classic TCM herbal pair for “opening the orifices and awakening the spirit,” capable of both resolving phlegm turbidity to unblock the brain orifices and calming the spirit to stabilize the ethereal soul.

The complete formula achieves supplementation with unblocking, warming with clearing, and addresses both the root and manifestation simultaneously. Lujiaojiao and Renshen supplement the deficiency of the spleen and kidney to nourish brain marrow; Shichangpu and Yuanzhi resolve phlegm and open the orifices to regulate spirit-function; Guizhi warms and unblocks, while Fuling drains and promotes transformation, to assist transportation and transformation. The six herbs together perfectly embody the principle of “opening the orifices and regulating the spirit”—“opening the orifices” refers to unblocking the clear orifices obstructed by phlegm turbidity, while “regulating the spirit” refers to tonifying and restoring the spirit-function damaged by spleen-kidney deficiency. This formula rationale is highly consistent with current concepts advocated in TCM pediatrics, such as “simultaneous regulation of form, qi, and spirit” and “heart-brain communication.”

3. Potential Mechanisms of Qibi Tiaoshen Granules in Treating ASD

3.1 Regulation of Neuro-Energy Metabolism via the “Spleen–Kidney–Brain” Axis

In recent years, the “spleen–kidney–brain” axis theory has provided a novel theoretical framework for elucidating the mechanisms of TCM in treating ASD. Traditional Chinese medicine holds that the spleen, kidney, and brain are mutually interdependent and synergistic in physiology, and reciprocally influence each other in pathology. The kidney stores essence and generates marrow, which aggregates to form the brain; however, the enrichment of kidney essence depends on the spleen’s function of transporting and transforming water-grain essences. Conversely, the essences generated by the spleen’s transportation and transformation must rely on the kidney’s consolidating and storing function to ascend and nourish the brain [9].

From a modern biological perspective, the biological basis of kidney essence can be analogized to neurotrophic factors, neural stem cells, and structural components of neurons; the spleen’s function of transportation and transformation can be analogized to the digestion, absorption, and metabolic utilization of nutrients (glucose, amino acids, fatty acids, etc.). Dysfunction of the spleen and kidney leads, on one hand, to insufficient supply of neurotrophic substances, and on the other hand, to impairment of key steps in cerebral energy metabolism.

Mitochondrial energy metabolism serves as an important bridge connecting the spleen-kidney and brain function. Mitochondria are known as the “powerhouses” of cells, generating ATP through oxidative phosphorylation to provide energy for neuronal activity. Accumulating evidence indicates mitochondrial dysfunction in children with ASD, including

reduced activity of mitochondrial respiratory chain complexes, decreased ATP production, and enhanced oxidative stress. Neurons are highly energy-demanding cells and are extremely sensitive to energy supply. Impairment of mitochondrial energy metabolism can lead to compromised synaptic plasticity, reduced neurotransmitter synthesis, and abnormal neural network synchronization, thereby affecting higher-order brain functions such as social cognition.

In Qibi Tiaoshen Granules, Lujiaojiao is rich in collagen, amino acids, and trace elements, which may serve as the material basis for “supplementing the kidney and enriching essence,” potentially promoting neuronal repair and synaptic remodeling by providing neurotrophic precursors. Ginsenosides Rg1 and Rb1 from Renshen have been demonstrated to improve mitochondrial function, attenuate oxidative stress, and promote neural stem cell proliferation and differentiation. Cinnamaldehyde from Guizhi possesses antioxidant and anti-inflammatory activities that may alleviate mitochondrial damage. Therefore, this formula may exert neuroprotective effects through the “spleen–kidney–brain” axis by improving energy metabolism.

3.2 Regulation of the Neuroimmune Microenvironment via the Gut–Brain Axis

The “microbiota–gut–brain” axis is currently one of the hotspots in ASD mechanism research. The gut microbiota communicates bidirectionally with the central nervous system through neural, immune, and endocrine pathways, influencing brain development and behavioral phenotypes. Children with ASD commonly exhibit gut microbiota dysbiosis, characterized by a reduction in beneficial bacteria (e.g., *Bifidobacterium* and *Lactobacillus*), enrichment of opportunistic pathogens (e.g., *Clostridium*), and decreased microbial diversity and stability [10–11].

The TCM theory that “the spleen serves as the defense” emphasizes the core role of the spleen in the body’s defense system, involving transportation and transformation, protection and consolidation, and coordination of qi and blood. From a modern medical perspective, the functions of the spleen are closely related to the intestinal immune barrier and gut microbiota homeostasis. Children with ASD commonly present with spleen deficiency patterns, and “failure of the spleen as the defense” may lead to impaired intestinal barrier function, endotoxin translocation, and release of pro-inflammatory cytokines, which in turn affect the central nervous system through the gut–brain axis, driving the neuroinflammatory process in ASD.

Renshen and Fuling in Qibi Tiaoshen Granules constitute a classic herbal pair for invigorating the spleen and supplementing qi. Modern pharmacological studies have shown that ginseng polysaccharides and ginsenosides can regulate gut microbiota structure [12], promote probiotic proliferation, and enhance intestinal immune barrier function; Fuling polysaccharides exhibit immunomodulatory and gut microbiota-regulating effects, reducing intestinal mucosal permeability and alleviating systemic inflammatory responses [13]. α -Asarone and other components in the volatile oil of Shichangpu possess anti-inflammatory and neuroprotective effects [14]. Therefore, this formula may regulate the gut

microbiota–gut–brain axis through “invigorating the spleen and consolidating the defense,” thereby suppressing neuroinflammation and improving ASD-related behaviors.

3.3 Regulation of Neurotransmitters and Synaptic Plasticity via “Heart–Brain Communication”

Zhang Xichun, in his *Records of Combining Chinese and Western Medicine* (Yixue Zhongzhong Canxi Lu), proposed the theory of “heart–brain communication,” positing that the heart and brain are interconnected in their functions of governing the spirit. The heart spirit and the brain spirit flourish and decline together; the core pathogenesis of ASD lies in “failure of heart–kidney interaction and derangement of both heart spirit and brain spirit.” From a modern neurobiological perspective, the functions of the “heart” are closely related to the autonomic nervous system, limbic system, and neuroendocrine network. Dysregulation of the heart spirit may be viewed as neurotransmitter imbalance and aberrant neural network function.

Yuanzhi is a classic TCM herb for “calming the spirit and enhancing intelligence.” Modern studies have found that tenuigenin can inhibit acetylcholinesterase activity, regulate dopamine and serotonin systems, and promote synaptophysin expression, thereby improving learning and memory ability. α -Asarone from Shichangpu can cross the blood–brain barrier and regulate the glutamate/GABA system balance, exerting anticonvulsant and sedative effects—and glutamate/GABA imbalance is considered a core mechanism of the excitation/inhibition imbalance hypothesis in ASD. Ginsenosides can regulate monoamine neurotransmitter levels, including dopamine and norepinephrine, improving attention and social behavior. Guizhi may regulate synaptic transmission through activation of the TRPA1 channel. Lujiaoiao contains various neuroactive peptides that may participate in synaptic repair and remodeling.

Therefore, Qibi Tiaoshen Granules may improve social interaction ability and cognitive function in children with ASD through multi-target regulation of neurotransmitter systems, restoration of excitation/inhibition balance, and promotion of synaptic plasticity.

4. Conclusion and Perspectives

Qibi Tiaoshen Granules, with Lujiaoiao and Renshen supplementing the kidney and enriching essence to nourish brain marrow, Guizhi and Fuling warming and activating spleen yang to generate essences, and Shichangpu and Yuanzhi resolving phlegm and opening the orifices to regulate spirit-function, closely address the core pathogenesis of ASD, namely “spleen–kidney deficiency and phlegm turbidity obstructing the orifices.” From a modern mechanistic perspective, this formula may exert synergistic effects through the following three pathways: (1) improving mitochondrial energy metabolism via the “spleen–kidney–brain” axis to ensure neuronal energy supply; (2) regulating gut microbiota and the immune microenvironment via the “gut–brain” axis to alleviate neuroinflammation; and (3) modulating neurotransmitter balance and synaptic plasticity via “heart–brain communication” to improve social cognitive function.

The above mechanistic analysis is primarily based on TCM theoretical deduction and pharmacological evidence from individual herbal ingredients, and awaits systematic experimental validation. Future studies may employ network pharmacology and molecular docking techniques to predict core targets, establish ASD animal models, and observe the effects of Qibi Tiaoshen Granules on social behavior and cognitive function, thereby providing a more robust scientific basis for the clinical application of this formulation.

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