Journal of Clinical and Nursing Research, 2024, Volume 8, Issue 5
http://ojs.bbwpublisher.com/index.php/JCNR
Online ISSN: 2208-3693
Print ISSN: 2208-3685

Discussion on Traditional Chinese Medicine Treatment of Liver-Depression-Spleen-Deficiency Type Insomnia Based on the State-Target Theory and the Regulation of Microbiome-Gut-Brain Axis

Kai Wu[1], Yongjie Gong[1], Shan Yang[1], Yalan Yu[2]*

[1]First Clinical College, Shaanxi University of Traditional Chinese Medicine, Xianyang 712000, Shaanxi Province, China
[2]Xi'an TCM Hospital of Encephalopathy, Xi'an 710000, Shaanxi Province, China

***Corresponding author:** Yalan Yu, 1149909593@qq.com

Abstract: Insomnia has become an urgent clinical problem in modern society. Current research has found that the gut flora-gut-brain axis plays an important role in regulating insomnia. The state-target theory is a product of the combination of traditional Chinese medicine and modern molecular biology technology. This paper clarifies the correlation between the state-target theory, the intestinal flora-gut-brain axis, and liver-depression-spleen-deficiency insomnia. The use of traditional Chinese medicine to regulate the structure and abundance of intestinal flora was also explored, aiming to integrate traditional Chinese medicine with Western medicine for the prevention and treatment of liver-depression-spleen-deficiency insomnia.

Keywords: State-target theory; Microbiome-gut-brain axis; Liver-depression and spleen deficiency; Insomnia; Traditional Chinese medicine

Online publication: June 14, 2024

1. Introduction

Insomnia is a disease characterized by chronic and frequent difficulty in falling asleep, difficulty in maintaining sleep, and lack of sleep satisfaction, and it is clinically classified as a sleep disorder. Studies have found that 45.4% of patients experience varying degrees of insomnia, making it an urgent problem [1]. Intestinal flora is referred to as the "second largest genome" of humans [2]. The intervention of neurological diseases based on the Microbiome-Gut-Brain Axis (MGBA) has become a hot research topic in recent years [3]. It has been found that the gut-brain axis can serve as a bridge for gut flora to regulate insomnia through three pathways: neuroendocrine, immune, and vagal [4]. Patients with insomnia often suffer from metabolic disorders, a chronic inflammatory state, intestinal flora imbalances, intestinal microecological disorders, and intestinal barrier disruption, which ultimately lead to inflammatory responses and neurotransmitter secretion disorders [5]. Liver

depression and spleen deficiency have gradually become one of the main symptoms of modern insomnia patients [6]. Therefore, there is an urgent need to explore the relationship between MGBA and insomnia associated with liver depression and spleen deficiency.

Academician Xiaolin Tong proposed the state-target theory, which is based on the principles of precision diagnosis and treatment in Chinese medicine. This theory combines traditional Chinese medicine with modern medical and pharmacological research findings [7]. By taking the symptom as the target, the evidence as the basis, and the disease as the reference, it not only diagnoses and treats symptoms and evidence but also addresses the root cause of the disease [8]. When yin and yang are balanced, the body is in homeostasis, and physiological functions are organized. However, an imbalance in yin and yang leads to different forms of "disease states." This paper used the state-target theory as a guide, based on the biological mechanisms of MGBA, to clarify the correlation between state-target theory, MGBA, and insomnia of the liver-depression-spleen-deficiency type. New ideas for using Chinese medicine to regulate the intestinal flora for the treatment of liver-depression-spleen-deficiency-type insomnia were also explored.

2. The application of state-target theory in liver-depression-spleen-deficiency type insomnia

Insomnia falls under the category of "insomnia" in traditional Chinese medicine (TCM), and liver-depression-spleen-deficiency is a classification for a specific type of insomnia with distinct TCM symptoms. The state-target theory emphasizes a macroscopic view of the disease. The "state" represents a collection of TCM "symptoms," "evidence," and "syndromes," providing an overall generalization of a certain stage of the disease [9]. It encompasses the notions of state, dynamics, and posture. This theory is rooted in TCM's dynamic approach to disease diagnosis and treatment. The state, dynamics, and posture of insomnia vary at different stages of development. The concept of Liver Depression and Spleen Deficiency Type Insomnia clarifies the posture of insomnia as a "stagnant state" and "positive deficiency state."

2.1. "Stagnant" state

Sleep is an essential physiological function, and the smoothness and organization of qi are fundamental for normal physiological functions and mental activities [10]. "The liver is the main regulator" is a high-level summary of the role of liver qi in regulating the body's qi, promoting the circulation of essence, blood, and fluids throughout the body, and managing the qi of the spleen and stomach [11]. This regulation is crucial for maintaining normal sleep. The Discriminative Record of Unconsciousness states: "When qi is depressed for a long time, liver qi is not at ease; when liver qi is not at ease, liver blood is depleted, and the blood cannot moisten the heart, leading to insomnia." Liver loss of detachment, stagnation of qi and blood, not reaching the skin or internal organs, results in qi deficiency, internal disturbance of the mind, and restless sleep [12]. *Suwen Tiaonilun* [13] notes: "Gastric uneasiness leads to insomnia," suggesting that insomnia should be treated from the perspective of the spleen and stomach. The spleen is responsible for transportation, the stomach for acceptance, and both are hubs for qi lifting in the body. If the spleen is stagnant, the stomach is out of harmony, fluid distribution is disordered, and phlegm and dampness accumulate, leading to poor circulation of qi and blood, resulting in insomnia [14]. Contemporary Professor Shen Hong also stated: "Liver loss of detachment and disharmony of the spleen and stomach result in restlessness" [15]. According to the "Five Elements Theory," there is a significant relationship between the liver and the spleen, often leading to concurrent diseases and mutual problems. Liver qi stagnation can impair spleen transportation, and spleen stagnation can disrupt liver excretion. Therefore, the "stagnant state" is a high-level generalization of liver and spleen dysfunction and qi imbalance.

2.2. "Positive deficiency" state

The liver stores blood, which is essential for the soul. The soul's yang nature and its movement in and out are closely related to the balance of yang and yin. When the yang of the soul resides in the yin of the liver, sleep occurs [16]. Liver blood insufficiency, which fails to nourish the soul, leads to insomnia and dreams. *Blood Evidence* [17] states: "Blood does not nourish the liver, and fire disturbs the soul, causing dreams and sleeplessness." The spleen governs the qi and blood, and spleen deficiency results in insufficient blood, causing disturbances and insomnia. The *Jingyue Encyclopedia of Unconsciousness* [18] notes: "Without evil, there is no insomnia; insufficient blood fails to nourish the heart, leading to insomnia." Liver and spleen dysfunction prevents normal physiology, and prolonged disease results in insufficient qi and blood, failing to nourish the heart and causing insomnia.

3. State-target theory and the microbiome-gut-brain axis

Intestinal flora is a crucial component of human intestinal microecology. The intestinal flora has a complex composition, with lactobacilli, enterococci, clostridia, enterobacteria, and bifidobacteria being the predominant bacteria in healthy individuals. Four phyla – Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria – account for 98% of the total intestinal flora [19]. The Microbiome-Gut-Brain Axis (MGBA) is a system where intestinal microorganisms, the autonomic nervous system (ANS), the central nervous system (CNS), and the enteric nervous system (ENS) form a bidirectional communication network between the brain and gastrointestinal tract [20]. When the organism is in a disease state, the total number of intestinal flora, the percentage of flora, metabolites, and intestinal microecology can change [21], affecting the CNS through the gut-brain axis. Thus, the intestinal flora as a disease target is closely related to the state-target theory.

3.1. "Stagnant" state and the microbiome-gut-brain axis

The liver and spleen assist in the elevation of qi and maintain the microecological balance of the intestinal tract and the "internal homeostasis" of material metabolism [22]. This aligns with modern research findings that intestinal flora is involved in the body's material metabolism and promotes neurotransmitter synthesis to regulate biological mechanisms. Zhang *et al*. [23] found that norepinephrine levels in the hypothalamus of rats with liver qi stagnation decreased, while the levels of epinephrine, dopamine, and serotonin (5-HT) significantly increased through animal experiments. It has been found that intestinal flora with disturbed structure and abundance induces abnormal secretion of 5-HT through the brain-gut axis, leading to sleep disorders [24]. Spleen congestion and intestinal flora dysbiosis can manifest as gastrointestinal symptoms such as abdominal pain, abdominal distension, and fecal disorders, and intestinal microecological imbalance reflect the spleen congestion state to a certain extent [25].

3.2. "Positive deficiency" state and the microbiome-gut-brain axis

According to *Suwen Cifalun*: "Zheng qi exists within the body, and evil cannot interfere," and Zheng qi is the foundation of the body's defense against external evils. The normal functioning of the liver and spleen is essential for maintaining positive qi in the human body. Liver and spleen dysfunction leads to a lack of qi and blood biochemistry, impairing the body's defense functions. This is consistent with the role of normal intestinal flora in promoting the body's immune function and preventing the proliferation of harmful bacteria. The body's largest immune system is the mucosal immune system, and spleen deficiency can cause erosion and rupture of the gastrointestinal mucosa, leading to a decline in immunity [26]. By constructing a mouse model of spleen qi deficiency, Huang [27] confirmed that the intestinal flora of mice with spleen qi deficiency was imbalanced,

with decreased species uniformity and abundance, increased pathogenic bacteria, and a higher number of flora species. Li [28] used an aqueous extract of *Angelica sinensis* to modulate the intestinal microbial structure of mice with blood deficiency syndrome and found that the abundance of beneficial bacteria represented by *Lactobacillus* and *Muribaculaceae* significantly increased at the genus level. It was found that intestinal flora can contribute to the development and maturation of the immune system, reduce the number of intestinal pathogenic bacteria, and regulate the immune response of the intestinal mucosa, thus maintaining the internal and external immune homeostasis of the intestinal tract [29,30].

4. The role of the microbiome-gut-brain axis in liver-depression-spleen-deficiency type insomnia

Modern studies have found that the composition and abundance of intestinal flora affect the biological clock and sleep-wake cycle [31]. Insomnia patients often exhibit intestinal microecological imbalances, including reduced flora abundance, decreased beneficial flora, and increased harmful flora. These imbalances lead to neurotransmitter secretion disorders, chronic inflammatory states, and autonomic dysregulation, which are key factors causing insomnia. Additionally, the dominant genera of intestinal flora differ in insomnia patients with different TCM syndromes, which may relate to the clinical manifestations of these syndromes [32]. It is currently believed that insomnia is related to various factors, including neuroendocrine, immune, and vagus nerve pathways. The gut-brain connection primarily operates through these pathways, and this bidirectional regulation affects the sleep and mental state of the host [4]. The MGBA's impact on insomnia can be summarized into three major pathways: neuroendocrine, immune-inflammatory, and vagus nerve.

4.1. Neuroendocrine pathway

Neuroendocrine cells in the gut form the body's largest endocrine organ [33]. Modern research has shown that the pathogenesis of insomnia is closely related to various neurotransmitters such as 5-HT and gamma-aminobutyric acid (GABA) [34]. Intestinal flora can influence the hypothalamic-pituitary-adrenal axis and the central nervous system by regulating the secretion of neurotransmitters like 5-HT, which in turn affects sleep. For example, gut flora synthesizes neurotransmitters such as GABA (produced by *Bifidobacterium bifidum* and *Lactobacillus*) and 5-HT (produced by *Enterococcus*, *Streptococcus*, and *Escherichia coli*), which affects brain function and transmits messages to nerve cells in the gut via the MGBA [35].

4.2. Immunoinflammatory pathways

Intestinal flora can directly influence the body's immune system [31] and promote sleep by enhancing the activity of pro-inflammatory factors [36]. The intestine serves not only as a digestive organ but also as a critical immune organ, with the intestinal mucosa playing a key role as a "defense barrier" against foreign pathogens. Intestinal flora interacts with immune cells through immunoregulatory pathways, regulating the secretion of cytokines and prostaglandin E2, thus affecting brain function [37]. Gut flora promotes the maturation of CNS immune cells and activation of peripheral immune cells, releasing various pro-inflammatory cytokines (such as IL-1α and TNF) that impact the central nervous system [38].

4.3. Vagal pathway

Modern anatomy has revealed that sensory neurons from the intestinal muscles form synaptic contacts with motor neurons in the gut, which are involved in intestinal motility and hormone secretion [39]. Additionally, the synaptic connections formed by the enteric nervous system with the vagus nerve create an information pathway

between the gut and the brain. Neurotoxins produced by gut flora, such as dextro-lactic acid and ammonia, may enter the CNS via the vagus nerve, affecting brain function, stress response, and sleep structure [40,41]. Cutting the vagus nerve was able to eliminate the effects produced by *Lactobacillus rhamnosus* on the CNS, indicating that the vagus nerve plays a crucial role in the communication between gut microbes and the CNS [42].

5. Exploring Chinese medicine for the prevention of liver-depression-spleen-deficiency type insomnia based on the state-target theory and the microbiome-gut-brain axis

"Homeostasis is the key to maintaining the life activities of the human body, and once imbalance occurs, disorders of qi and internal organs ensue" [43]. The "target" includes the disease target for the disease, the symptom target for the symptom, and the target for imaging examination and physical and chemical indices [44]. The clinical aim is to adjust the disease state of "stagnation and deficiency," and regulate the richness and structural composition of intestinal flora to improve the state and achieve precise medical treatment.

5.1. Liver and spleen method

The author believes that liver qi stagnation and spleen stagnation are manifested primarily in the body's "stagnation" state, while the deficiency of positive qi is not apparent. Premature use of replenishment methods is not conducive to correcting the disease state. Therefore, the primary treatment principle of "dredging the liver and regulating the spleen" was established. Yu *et al*. [45] used the Nourishing the Heart and Regulating the Liver Formula to significantly reduce the relative abundance of *Ruminococcus* and *Clostridium* in patients with liver-depression type insomnia, while significantly increasing the relative abundance of *Mycobacterium* and *Enterococcus faecium*, indicating the formula's regulatory effect on intestinal bacterial flora. Chaihu plus dragon bone and oyster soup has the effect of calming the liver and mind. Chen [46] found that it could increase the diversity of intestinal flora in sleep-deprived rats, particularly increasing the flora that improved insomnia and adjusted mood. Wang *et al*. [47] constructed a mouse model of spleen-stagnation type and used spleen-tonifying and stagnation-resolving oral solution, enhancing the diversity of intestinal flora, increasing the proportion of beneficial bacteria, and improving the structure of intestinal flora.

5.2. Regulating Zhengqi and replenishing deficiency

Deficiency of positive qi is the final state of the body's functional decline after prolonged disease. Long-term liver qi stagnation and spleen stagnation lead to dysfunction of the liver and spleen, resulting in the deficiency of qi and blood in the internal organs. Consequently, the mind is not nourished, leading to insomnia. At this stage, replenishing positive qi is crucial. Zhao *et al*. [48] used Buzhong Yiqi Decoction to treat patients with spleen deficiency insomnia, finding it had a positive effect on the patient's disordered intestinal flora. It increased the maintenance of intestinal homeostasis, reduced intestinal pathogenic bacteria, and had regulatory effects on intestinal immunity and metabolism, thereby improving sleep. Ren *et al*. [49] used sour jujube nut soup on sleep-deprived mice and found it adjusted the intestinal flora structure, increasing beneficial bacteria and reducing harmful bacteria.

6. Summary

Based on the state-targeting theory, this paper divides traditional insomnia of liver-depression-spleen-deficiency type into depression state and positive-deficiency state. It analyzes the correlation between these states, the microbiome-gut-brain axis, and liver-depression-spleen-deficiency type insomnia through research on the

biological mechanism of the microbiome-gut-brain axis. By drawing on the results of research on Chinese medicine pharmacology, it selects prescription drugs that regulate the abundance and structural composition of intestinal flora to regulate the state and achieve the target. This approach can improve clinical efficacy and opens a new direction for TCM to prevent and treat insomnia of liver-depression and spleen-deficiency type. The state-targeting theory fully leverages the advantages of traditional Chinese medicine in diagnosis and treatment and incorporates modern molecular biology technology, allowing for the true combination of Chinese and Western medicine in the clinic. Future research will further explore the mechanisms and targets of the methods of regulating the liver and spleen, as well as replenishing deficiency in the treatment of liver-depression-spleen-deficiency type insomnia, aiming to address different TCM evidence of insomnia from the perspective of intestinal flora.

Disclosure statement

The authors declare no conflict of interest.

References

[1] Chinese Medical Association Neurology Branch, Chinese Medical Association Neurology Branch Sleep Disorders Group, 2018, Guidelines for the Diagnosis and Treatment of Insomnia in Chinese Adults (2017 Edition). Chinese Journal of Neurology, 51(5): 324–335.

[2] Qin J, Li R, Raes J, et al., 2010, A Human Gut Microbial Gene Catalogue Established by Metagenomic Sequencing. Nature, 464(7285): 59–65. https://doi.org/10.1038/nature08821

[3] Huang Q, Zeng L, Wang GC, et al., 2022, Progress in the Treatment of Insomnia by Regulating Intestinal Flora in Chinese Medicine Based on the Theory of Microbiome-Gut-Brain Axis. Tianjin Traditional Chinese Medicine, 2022(4): 39.

[4] Li Y, Hao Y, Fan F, et al., 2018, The Role of Microbiome in Insomnia, Circadian Disturbance and Depression. Front Psychiatry, 9: 669. https://doi.org/10.3389/fpsyt.2018.00669

[5] Gomes AC, Hoffmann C, Mota JF, 2018, The Human Gut Microbiota: Metabolism and Perspective in Obesity. Gut Microbes, 9(4): 308–325. https://doi.org/10.1080/19490976.2018.1465157

[6] Yun X, Wu F, Xu Y, et al., 2023, Discussion on Insomnia Based on "Microbiome-Gut-Brain Axis". Modern Chinese Medicine Clinics, 30(3): 31–36 + 42.

[7] Zhao L, 2020, State-Targeted Diagnosis – The Historical Choice of Chinese Medicine from Macro to Precision. Liaoning Journal of Chinese Medicine, 2020(1): 4.

[8] Tong X, 2010, On the Application of the Combined Diagnosis and Treatment Model of Symptoms, Evidence and Diseases in Clinical Practice. Journal of Traditional Chinese Medicine, 2010(4): 4.

[9] Duan J, Wang X, Guo R, et al., 2023, Discussion on the Application of "State-Target Theory" to Diarrhea of Spleen and Stomach Diseases in Traditional Chinese Medicine. Journal of Changchun University of Traditional Chinese Medicine, 39(4): 362–366.

[10] Yuan Y, Chen S, Zhang H, 2022, Academic Experience of Prof. Zhang Huili in Treating Insomnia from Liver Theory. Chinese Medicine Clinical Research, 2022(22): 14.

[11] Ren X, Liu S, Wang X, et al., 2020, Collection of Professor Yang Zhihong's Experience in Treating Insomnia. Shaanxi Traditional Chinese Medicine, 461(5): 120–122.

[12] Shen Y, Zhang Q, 2010, Theoretical Analysis of the Liver and Insomnia. Journal of Liaoning University of Traditional Chinese Medicine, 12(5): 2.

[13] Li X, Ma Y, Wu Q, 2021, Experience of Treating Insomnia from the Theory of Spleen and Stomach in the Middle Jiao. Global Chinese Medicine, 14(8): 3.

[14] Li L, Yang S, 2022, Yang Shuyu's Experience in Treating Insomnia from the Perspective of Liver and Spleen. Journal of Traditional Chinese Medicine, 63(23): 5.

[15] Lai Y, Bai L, 2015, New Progress in the Study of External Treatment of Insomnia in Chinese Medicine. Inner Mongolia Traditional Chinese Medicine, 34(4): 2.

[16] Li J, Yang L, Guo R, 2023, Guo Rongjuan's Experience in Treating Anxiety Insomnia from Liver Theory. Chinese Medicine Journal, 29(6): 186–189.

[17] Tang Z, 2020, Blood Evidence. People's Health Press, Beijing.

[18] Zhang J, 2016, Jingyue Quanquan. China Medicine Science and Technology Press, Beijing.

[19] Tremaroli V, Bäckhed F, 2012, Functional Interactions Between the Gut Microbiota and Host Metabolism. Nature, 489(7415): 242–249. https://doi.org/10.1038/nature11552

[20] Goyal D, Ali SA, Singh RK, 2021, Emerging Role of Gut Microbiota in Modulation of Neuroinflammation and Neurodegeneration with Emphasis on Alzheimer's Disease. Prog Neuropsychopharmacol Biol Psychiatry, 106: 110112. https://doi.org/10.1016/j.pnpbp.2020.110112

[21] Cai Y, Deng Y, Li D, et al., 2023, A New Strategy for the Prevention and Treatment of Type 2 Diabetes Mellitus in Traditional Chinese Medicine Based on the "State-Target Theory-Regulation of Microbiome". Journal of Traditional Chinese Medicine, 51(2): 1–5.

[22] Zhu J, Len Y, Zhou X, et al., 2019, Analyzing the Pathogenesis of Diabetes Mellitus from the Theory of Qi Elevation Based on Intestinal Flora. Chinese Journal of Experimental Formulary, 2019(21): 7.

[23] Zhang H, Qiao M, Sun L, 2008, Analysis of Hypothalamic Monoamine Neurotransmitters in Rats with Liver Qi Depressive Syndrome Model. Journal of Traditional Chinese Medicine, 49(2): 3.

[24] Si Y, Wei W, 2022, A Comprehensive Study on the Relieving Effect of *Lilium brownii* on the Intestinal Flora and Metabolic Disorder in p-Chlorphenylalanine-Induced Insomnia Rats. Pharmaceutical Biology, 60(1): 131–143.

[25] Li S, Chen G, Du H, et al., 2021, Discussion on the Relationship Between the Theory of "Soil Congestion and Wood Depression" and the Development of Chronic Hepatitis B Based on Intestinal Flora Dysbiosis. Chinese Journal of Traditional Chinese Medicine, 36(6): 4.

[26] Yao Y, Song Y, Zhao T, 2000, Morphologic Study of Gastrointestinal Mucosa in a Rat Model of Spleen Deficiency. Chinese Journal of Integrative Medicine and Digestion, 8(1): 8–10.

[27] Huang L, 2021, Evaluation of the Efficacy of HAPS in Mice with Spleen Qi Deficiency and Its Effect on Intestinal Immune Function, thesis, Guangdong Pharmaceutical University.

[28] Li H, 2019, Progress in the Study of Quality Biomarkers of Traditional Chinese Medicine. Chinese Herbal Medicine, 50(19): 6.

[29] Round JL, Mazmanian SK, 2009, The Gut Microbiota Shapes Intestinal Immune Responses During Health and Disease. Nat Rev Immunol, 9(5): 313–323. https://doi.org/10.1038/nri2515

[30] Reikvam DH, Erofeev A, Sandvik A, et al., 2011, Depletion of Murine Intestinal Microbiota: Effects on Gut Mucosa and Epithelial Gene Expression. PLoS One, 6(3): e17996. https://doi.org/10.1371/journal.pone.0017996

[31] Peng W, Shen Z, Wang Y, et al., 2019, Research Progress of Intestinal Flora on Sleep Regulation. Chongqing Medicine, 48(19): 5.

[32] Luo J, Wu Y, Huang F, et al., 2018, Study on the Difference of Intestinal Flora in Patients with Primary Insomnia of Different Chinese Medicine Certificates. China Journal of Traditional Chinese Medicine Information, 25(4): 28–34.

[33] Raybould HE, 2010, Gut Chemosensing: Interactions Between Gut Endocrine Cells and Visceral Afferents. Auton Neurosci, 153(1–2): 41–46. https://doi.org/10.1016/j.autneu.2009.07.007

[34] Zhang J, Xin X, Quan F, 2020, Progress of Chinese and Western Medicine Research on Insomnia. Xinjiang Traditional Chinese Medicine, 38(2): 2.

[35] Luo C, Zhang J, Pan J, 2013, One-Year Course and Effects of Insomnia in Rural Chinese Adolescents. Sleep, 36(3): 377–384.

[36] Krueger JM, Opp MR, 2016, Sleep and Microbes. Int Rev Neurobiol, 131: 207–225. https://doi.org/10.1016/bs.irn.2016.07.003

[37] Feng Q, Chen WD, Wang YD, 2018, Gut Microbiota: An Integral Moderator in Health and Disease. Front Microbiol, 9: 151. https://doi.org/10.3389/fmicb.2018.00151

[38] Pan LM, Shi YY, Bu F, et al., 2022, Research Progress of Jiaotai Pill in the Treatment of Primary Insomnia. Journal of Liaoning University of Traditional Chinese Medicine, 24(11): 177–181.

[39] Powley TL, Wang XY, Fox EA, et al., 2008, Ultrastructural Evidence for Communication Between Intramuscular Vagal Mechanoreceptors and Interstitial Cells of Cajal in the Rat Fundus. Neurogastroenterol Motil, 20(1): 69–79. https://doi.org/10.1111/j.1365-2982.2007.00990.x

[40] Sharon G, Sampson TR, Geschwind DH, et al., 2016, The Central Nervous System and the Gut Microbiome. Cell, 167(4): 915–932. https://doi.org/10.1016/j.cell.2016.10.027

[41] Bonaz B, Picq C, Sinniger V, et al., 2013, Vagus Nerve Stimulation: From Epilepsy to the Cholinergic Anti-Inflammatory Pathway. Neurogastroenterol Motil, 25(3): 208–221. https://doi.org/10.1111/nmo.12076

[42] Bravo JA, Forsythe P, Chew MV, et al., 2011, Ingestion of *Lactobacillus* Strain Regulates Emotional Behavior and Central GABA Receptor Expression in a Mouse via the Vagus Nerve. Proc Natl Acad Sci U S A, 108(38): 16050–16055. https://doi.org/10.1073/pnas.1102999108

[43] He Y, Jin H, Liu Z, et al., 2022, Construction of a New Thinking of Traditional Chinese Medicine Based on the Theory of "State-Target Causation". China Journal of Basic Chinese Medicine, 28(12): 1961–1963 + 1992.

[44] Tong X, 2021, State-Targeted Medicine: The Future Development of Traditional Chinese Medicine. Chinese Journal of Integrative Medicine, 41(1): 16–18.

[45] Yu Y, Min C, Zhan F, et al., 2021, Clinical Observation on the Treatment of Insomnia of Liver-Depression Type with the Compound Liver-Regulating and Heart-Supporting Formula of "Treating From the Liver Theory" and Its Effect on the Regulation of Intestinal Flora Structure. Chinese Herbal Medicine, 44(9): 2210–2213.

[46] Hong J, 2021, Effects of the Addition and Subtraction of Chaihu Plus Long Bone Oyster Decoction on the Intestinal Flora of REM Sleep-Deprived Rats, thesis, Beijing University of Chinese Medicine.

[47] Wang X, Shi L, Zhang Y, et al., 2023, Effects of Tonifying Spleen and Eliminating Accumulation Oral Solution on Gastrointestinal Function and Intestinal Flora Structure in Mice with Spleen Deficiency and Food Accumulation. Modern Drugs and Clinics, 38(8): 1865–1871.

[48] Zhao C, Xiao R, Yang L, et al., 2020, Discussion on the Therapeutic Effect of Buzhong Yiqi Decoction in Treating Insomnia of Spleen Deficiency Type from the Perspective of Intestinal Flora. Journal of Guangzhou University of Traditional Chinese Medicine, 37(11): 2057–2063.

[49] Ren X, Li T, 2020, Effects of Sour Jujube Nut Soup on Liver Function and Specific Intestinal Bacteria in Mice with Chronic Sleep Deprivation. Drug Evaluation Research, 43(2): 226–231.