

Research Progress on the Treatment of IBS-D with Huanji Zhixie Decoction Based on the Gut-Brain Axis Mechanism

Wei Zhang¹, Pengnian Zhang¹, Tao Yu^{2,*}

¹Shaanxi University of Chinese medicine, Xianyang 712046, Shaanxi, China

²Shaanxi Provincial Hospital of Chinese medicine, Xi'an 710003, Shaanxi, China

*Correspondence Author

Abstract: Irritable Bowel Syndrome with Diarrhea (IBS-D) is a functional gastrointestinal disorder with unclear etiology, and the curative effect of Western medicine on symptom relief is limited. Traditional Chinese Medicine (TCM) syndrome differentiation focuses on the core pathogenesis of "liver depression and spleen deficiency" and emphasizes regulating the liver and invigorating the spleen in treatment. Based on clinical experience from 4,800 cases, Professor Yu Tao modified Tongxie Yaofang (Puerariae Lobatae and Atractylodis Macrocephalae Decoction for Diarrhea with Pain) and developed the self-formulated "Huanji Zhixie Decoction" (Relieving Spasms and Stopping Diarrhea Decoction), which has achieved remarkable clinical results in strengthening the spleen, soothing the liver, eliminating dampness and relieving diarrhea. Modern research suggests that this decoction regulates 5-hydroxytryptamine (5-HT), hypothalamic-pituitary-adrenal (HPA) axis and inflammatory pathways through the microbiota-gut-brain axis, improving gut-brain interaction through multiple targets, and providing a safe and effective new strategy of integrated traditional Chinese and Western medicine for IBS-D treatment.

Keywords: Internal Medicine of Traditional Chinese Medicine, Irritable Bowel Syndrome, Gut-Brain Axis, Huanji Zhixie Decoction, Traditional Chinese Medicine.

1. Introduction

Irritable Bowel Syndrome (IBS) is a chronic functional gastrointestinal disorder characterized by recurrent abdominal pain associated with changes in bowel habits and stool consistency [1]. According to the Rome IV criteria, IBS is classified into four subtypes based on the predominant bowel habit: diarrhea - predominant (IBS-D), constipation - predominant (IBS-C), mixed (IBS-M), and unclassified (IBS-U), with IBS-D being the most common subtype in China [2,3]. The exact etiology and pathogenesis of IBS-D remain unclear; current mainstream views suggest that it is closely related to multiple factors including abnormal gastrointestinal motility, gut-brain axis dysfunction, visceral hypersensitivity, history of intestinal infection, central sensory disorders, and psychosocial factors [4]. Due to the unclear mechanism, Western medicine focuses on symptom relief and quality of life improvement. In recent years, although drugs such as 5-HT receptor antagonists, antispasmodics, and probiotics have been introduced, combined with dietary regulation and psychological intervention, IBS-D symptoms can be alleviated to some extent. However, adverse drug reactions reduce patient compliance, and combined medication is often required, increasing the economic burden, resulting in suboptimal overall efficacy. TCM intervention in IBS with traditional methods such as Chinese herbal medicine and acupuncture can significantly relieve symptoms, with the core lying in syndrome differentiation based on individual patients and formulating treatment principles accordingly, opening up a new approach different from Western medicine for disease management. Existing viewpoints confirm that IBS-D is caused by the disorder of "gut-brain axis" communication interwoven with multiple factors, and the superimposed psychosocial disorders make treatment more complex, so multidisciplinary collaborative intervention is particularly

urgent [5]. Integrated traditional Chinese and Western medicine treatment for IBS: Western medicine focuses on gut-brain axis and peptide disorders, using 5-HT₃ antagonists, probiotics, etc. for rapid symptom control; TCM classifies gut-brain disorders as "Xiexie" (diarrhea) [6], with long-term physical regulation through syndrome differentiation decoctions, acupuncture, cupping therapy, etc., with fewer side effects and stable curative effects. The combination of the two has the advantages of multiple targets and combination of rapid and slow effects, while the challenges lie in evidence level, standard unification and mechanism connection.

Liver qi stagnation runs through the entire course of IBS. The liver governs planning and emotional activities; excessive anger leads to failure of the liver to disperse and unfavorable flow of qi movement, resulting in "pain due to obstruction"; excessive liver wood invades earth (spleen), spleen deficiency leads to dysfunction in transportation, failure to generate qi and blood, resulting in "pain due to malnutrition", thus causing abdominal pain and stuffiness. Liver depression attacking the spleen leads to internal retention of water-dampness, which flows down to the large intestine causing diarrhea; if spleen deficiency fails to lift clear qi and descend turbid qi, resulting in weak conduction, constipation may also occur. Therefore, "liver depression and spleen deficiency" is the most common syndrome type of IBS, mostly presenting as diarrhea-predominant type clinically, and the treatment should focus on suppressing wood (liver) and supporting earth (spleen), regulating both liver and spleen, with representative prescriptions such as Tongxie Yaofang, Chaihu Guizhi Decoction, and Danggui Shaoyao Powder. Tongxie Yaofang can decrease IL-12, increase IL-10, and inhibit HPA axis hyperactivity, thereby relieving diarrhea, pain and regulating mood; Chaihu Guizhi Decoction can regulate intestinal flora and gastrointestinal hormone levels; kaempferol, stigmasterol, etc. in Danggui Shaoyao Powder

exert anti-inflammatory and analgesic effects through TNF, calcium signaling pathway and targets such as PTGS2, JUN, IL-6 [7]. Cai Guangxian [8] et al. believed that the liver governing dispersion corresponds to HPA axis function, and the spleen governing transportation is related to gastrointestinal motility; the biological essence of liver-spleen disharmony is gut-brain axis imbalance, which provides an objective basis for treating IBS from the perspective of “regulating liver and invigorating spleen”.

Thousands of years of TCM clinical practice have confirmed that Tongxie Yaofang has significant curative effect on IBS with liver depression and spleen deficiency syndrome. Modern research points out that intestinal flora imbalance is closely related to the occurrence and development of IBS, and gut-brain axis disorder is also a key pathogenesis; changes in bacterial spectrum can affect the expression of gut-brain peptides such as 5-HT in the central nervous system and intestines, while brain stress can also reshape intestinal structure and function [9,10]. Based on this, taking the theory of “formula-syndrome correspondence” and “disease-syndrome combination” animal experiments as the outline, clarifying the mechanism of Tongxie Yaofang intervening in IBS with liver depression and spleen deficiency syndrome through the microbiota-gut-brain axis can not only provide empirical evidence for targeted new drug research and development, but also open up ideas for safe and effective gastrointestinal-specific drugs. Professor Yu Tao [11] has accumulated nearly 4,800 cases of IBS-D patients in years of outpatient clinics, and based on this, modified Tongxie Yaofang to develop the self-formulated “Huanji Zhixie Decoction”. He believes that liver depression and spleen deficiency, damp obstruction and qi stagnation are the core of this disease: spleen deficiency with excessive dampness is the “root”, liver depression and qi stagnation is the “branch”, and pain is caused by obstruction, so the treatment should follow the principle of “treating diarrhea with purgative methods”. The formula uses Yigong San (Four Gentlemen Decoction with Chenpi) to strengthen the spleen and replenish qi, Sini San (Frigid Extremities Decoction) and Tongxie Yaofang to soothe the liver, regulate the spleen, eliminate dampness and relieve diarrhea, combining the three formulas and modifying according to symptoms, achieving remarkable curative effects in clinical application. This article discusses the research progress of Huanji Zhixie Decoction in the treatment of IBS-D based on the gut-brain axis mechanism, aiming to provide reference comprehensive strategies and the latest evidence for medical staff and patients.

2. Research Progress on the Pathogenesis of IBS-D Based on the Gut-Brain Axis

2.1 The Gut-Brain Axis and Its Role in IBS-D

The gut-brain axis constructs a neuroendocrine-immune regulatory network composed of five systems: central nervous system, enteric nervous system, autonomic nervous system, endocrine system and immune system: the central nervous system issues instructions through sympathetic and parasympathetic nerves; the enteric nervous system integrates luminal signals for immediate regulation; the autonomic nervous system synchronizes emotions and intestinal conditions; the endocrine system releases hormones for

long-distance fine-tuning; the immune system converts microbial signals into chemical language, with five domains collaborating to maintain dynamic gut-brain balance [12]. As the only organ in the body simultaneously innervated by multiple systems mentioned above, the gastrointestinal tract is highly sensitive to psychological stress and emotional changes [13]. Studies have found that IBS-D patients generally have gut-brain axis dysfunction, manifested as abnormal central pain processing, imbalanced autonomic nervous tension and amplified intestinal sensory signals [14,15]. Abnormal gut-brain axis can lead to increased gastrointestinal motility, abnormal secretion and decreased pain threshold, which are important pathological bases for recurrent abdominal pain and diarrhea in IBS-D patients [16].

2.2 Abnormal Gut-Brain Peptides and Neurotransmitters

Gut-brain peptides are small molecular peptides distributed in both the central nervous system and the gastrointestinal tract, with dual identities of hormones and neurotransmitters: they can be released by the enteric nervous system (ENS) as neurotransmitters to rapidly regulate gastrointestinal secretion and motility locally, and can also directly act on specific receptors on intestinal sensory nerve endings or smooth muscle cells to finely regulate intestinal sensory sensitivity and peristaltic rhythm; when abnormalities occur in synthesis, release or receptor expression, they can interfere with gut-brain axis information transmission and functional coordination, inducing a series of symptoms such as abdominal pain, motility disorders or emotional disturbances [17]. More than 60 types have been discovered so far, with 5-hydroxytryptamine (5-HT) being the key neurotransmitter. Gut-brain peptides are important mediators of gut-brain axis information transmission, among which 5-hydroxytryptamine (5-HT) plays a crucial role in the pathogenesis of IBS-D. Studies have shown that the level of 5-HT and the expression of its receptors in the intestinal mucosa of IBS-D patients are abnormal, which are closely related to the degree of diarrhea and visceral hypersensitivity [18]. In addition, corticotropin-releasing factor (CRF) can enhance intestinal permeability and promote increased gastrointestinal motility by activating the hypothalamic-pituitary-adrenal (HPA) axis, making IBS-D symptoms significantly worse after mental stress and emotional fluctuations [19]. This mechanism is highly consistent with TCM’s understanding of pathogenesis that “emotional internal injury leads to failure of liver to disperse and counterattack the spleen” [20].

2.3 Interaction Between Intestinal Flora and Gut-Brain Axis

In recent years, the “microbiota-gut-brain axis” has become a research hotspot in IBS-D. Intestinal flora not only participates in nutrient metabolism and immune regulation, but also participates in gut-brain axis information transmission through metabolites, neurotransmitter synthesis and vagal nerve signals [21]. Multiple studies have shown that IBS-D patients have changes such as decreased diversity of intestinal flora, reduced beneficial bacteria and increased harmful bacteria [22-24]. Intestinal flora imbalance can damage the intestinal mucosal barrier, activate low-grade inflammatory responses, and exacerbate visceral hypersensitivity by affecting 5-HT synthesis and nerve signal

amplification [25]. In addition, abnormal intestinal flora is closely related to emotional disorders such as anxiety and depression: reduced symbiotic bacteria and increased pathogenic bacteria can damage the intestinal barrier, allowing pathogenic molecules such as lipopolysaccharide to infiltrate into the blood and activate systemic low-grade inflammation; pro-inflammatory factors are uploaded through the vagus nerve, triggering microglial activation in the hippocampus and amygdala, reducing the levels of 5-HT, GABA and BDNF, and inducing anxiety and depression-like behaviors; negative emotions in turn increase cortisol through the HPA axis, which in turn inhibits the growth of beneficial bacteria, forming a “microbiota-immune-brain” vicious cycle, further aggravating gut-brain axis disorder [26].

3. Research Progress on TCM Treatment of IBS-D Based on the Gut-Brain Axis

TCM emphasizes the holistic view and syndrome differentiation treatment, believing that emotional activities, visceral functions and intestinal conduction are closely related. The heart governs mental activities, the liver governs dispersion, and the spleen governs transportation, which jointly participate in emotional regulation and coordination of digestive functions [27,28]. Modern research holds that TCM treatment concepts of “simultaneous treatment of brain and intestines” and “simultaneous regulation of liver and spleen” are highly consistent with the multi-system coordinated regulation mechanism of the gut-brain axis [29].

Tongxie Yaofang is a representative formula for treating IBS-D with liver depression and spleen deficiency syndrome. Studies have shown that Tongxie Yaofang can down-regulate intestinal mucosal 5-HT levels, reduce excessive release from enterochromaffin cells, decrease serum and local free 5-HT concentrations, thereby weakening stimulation to intestinal sensory nerve endings, increasing visceral pain threshold, relieving excessive peristalsis, and synchronously reducing abdominal pain frequency and urgency degree [30]; at the same time, it can regulate intestinal flora structure, increase the proportion of beneficial bacteria, enhance the tight junction of intestinal mucosal barrier, reduce bacterial product translocation, inhibit low-grade inflammatory response, and decrease pro-inflammatory factor expression [31,32]. In addition, this formula also has certain advantages in improving patients' emotional disorders such as anxiety and depression, and can synchronously down-regulate stress-related indicators to achieve dual relief of intestinal and brain symptoms [33].

4. Discussion on the Gut-Brain Axis Mechanism of Huanji Zhixie Decoction in Treating IBS-D

Huanji Zhixie Decoction was developed by Chief Physician Yu Tao on the basis of Tongxie Yaofang, combined with Yigong San to strengthen the spleen and replenish qi and Sini San to soothe the liver and relieve depression. The formula uses Bupleuri Radix to soothe liver qi and Codonopsis Radix to tonify spleen qi as monarch drugs, first regulating liver depression and then tonifying spleen deficiency. Paeoniae Radix Alba combined with Aurantii Fructus soothes the liver

and relieves stagnation; Atractylodis Macrocephalae Rhizoma, Poria Cocos, Pogostemonis Herba, Citri Reticulatae Pericarpium and Saposhnikoviae Radix dry dampness, ascend clear qi, dispel wind and regulate qi; Crataegi Fructus, Massa Medicata Fermentata and Hordei Fructus Germinatus promote digestion and aid transportation, all serving as minister drugs to assist monarch drugs in restoring spleen ascending and liver descending functions. Aucklandiae Radix and Arecae Semen promote qi circulation and relieve stagnation, embodying the principle of “treating diarrhea with purgative methods”; Sepiae Endoconcha astringes to stop diarrhea, preventing excessive qi circulation; Glycyrrhizae Radix Preparata harmonizes all medicinal ingredients, acting as envoy drug. The entire formula is modified from Tongxie Yaofang, Sini San and Yigong San: Tongxie Yaofang dispels wind, soothes the liver and regulates liver-spleen harmony; Yigong San strengthens the spleen and regulates qi simultaneously, tonifying without causing stagnation; Sini San regulates qi movement and soothes the liver and spleen. Aurantii Fructus, Aucklandiae Radix and Arecae Semen purge the intestines without damaging healthy qi; Sepiae Endoconcha astringes the intestines without retaining pathogens; combined, they soothe the liver, strengthen the spleen, eliminate dampness and relieve stagnation, hence achieving definite curative effect in clinical treatment of IBS-D. Flexible modifications are made according to symptoms: for example, Magnoliae Officinalis Cortex and Arecae Pericarpium are added for severe abdominal distension; Granati Pericarpium and Euryales Semen are added for excessive diarrhea; Ziziphi Spinosa Semen and Polygoni Multiflori Caulis are added for poor sleep, adhering to the original formula's core while considering individual differences, fully reflecting the precision of TCM syndrome differentiation and flexible application of formulas, thus achieving rapid curative effect and low recurrence rate after thousands of clinical verifications. Based on comprehensive existing research, it is speculated that Huanji Zhixie Decoction may exert its therapeutic effect on IBS-D through the following pathways: Regulating the levels of gut-brain peptides such as 5-HT and improving gastrointestinal sensory and motor functions; Improving intestinal flora structure and restoring microbiota-gut-brain axis homeostasis; Reducing visceral hypersensitivity and relieving abdominal pain; Soothing the liver to relieve depression, calming the mind and relieving emotional stress on intestinal function [18-20].

5. Conclusion and Prospects

Gut-brain axis disorder is one of the core mechanisms in the occurrence and development of IBS-D, providing an important entry point for TCM treatment. Existing studies have shown that TCM formulas represented by Tongxie Yaofang have clear advantages in regulating the gut-brain axis. As an empirical formula verified by long-term clinical practice based on classic formulas, Huanji Zhixie Decoction has good clinical efficacy and solid theoretical basis.

At present, research on Huanji Zhixie Decoction in treating IBS-D is still dominated by experience summary, lacking systematic experimental research from the perspective of multi-pathway and multi-target gut-brain axis. In the future, combined with network pharmacology, animal experiments and clinical research, in-depth exploration of its mechanism

of action can further improve the evidence-based level of Huanji Zhixie Decoction in treating IBS-D.

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