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Exploration of the Mechanism of the Method of Warming and Tonifying the Spleen and Kidney in Treating Diarrhea-predominant Irritable Bowel Syndrome Based on the "Brain-Gut Axis" Theory

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Abstract: ***In the treatment of IBS-D, TCM commonly employs prescriptions that warm and tonify the spleen and kidney to address IBS-D cases characterized by spleen-kidney yang deficiency. These include the Changkang Formula, Tongxie Sishen Decoction, Wenshen Jianpi Guchang Formula, Jiuxie Formula, Wenshen Jianpi Formula, and Wenshen Jianpi Decoction. The compositions of these formulas are mainly based on modifications of the Sishen Pill. The TCM approach of warming and tonifying the spleen and kidney can suppress the expression levels of 5-HT and SP in the serum and colon tissues of rat models with spleen-kidney yang deficiency. Additionally, it can elevate the levels of GAS, CORT, and ACTH in the serum. This approach can regulate the p38 MAPK/JNK signaling pathway and downregulate the expression of the c-Fos gene in the colon tissues, dorsal root ganglia, and hippocampal tissues of IBS-D rat models. By doing so, it can modulate the brain-gut axis function and alleviate the symptoms of IBS-D in rat models with spleen-kidney yang deficiency. In the context of treating patients, the TCM method of warming and tonifying the spleen and kidney can also reduce the levels of BDNF, NPY, GAS, 5-HT, CGRP, VIP, SST, D-lactic acid, DAO, and SP in the serum of IBS-D patients with spleen-kidney yang deficiency. It can downregulate the expression of TrkB, BDNF, and CGRP in patients and increase the levels of motilin and NO in the serum. Through these mechanisms, it can regulate the brain-gut axis function, alleviate visceral hypersensitivity in IBS-D patients, improve the inflammatory response, and enhance the colonic barrier function, thereby alleviating clinical symptoms such as diarrhea and abdominal pain in IBS-D patients. Evidently, the monomers and compound formulas of TCM for warming and tonifying the spleen and kidney can alter the content of brain-gut peptides. The regulation of the "gut-brain axis" in the treatment of IBS-D has demonstrated effectiveness.***

Keywords: IBS-D, Warming and invigorating the spleen and kidney, Brain-gut axis, Brain-gut peptides, Sishen Pills.

1. Introduction

Irritable bowel syndrome (IBS) is a prevalent functional bowel disorder. Its symptoms manifest as recurrent abdominal discomfort or pain, accompanied by alterations in bowel habits or changes in the form of stools [1]. Currently, routine clinical examinations lack morphological and biochemical abnormalities that can account for the symptoms of IBS. The Rome IV criteria propose that IBS can be classified into four major subtypes according to the primary changes in bowel habits: diarrhea-predominant IBS(IBS-D), constipation - predominant IBS (IBS-C), mixed IBS (IBS-M), and unsubtyped IBS (IBS-U) [2]. In China, with the gradual improvement of living standards, dietary patterns, lifestyle habits, and living environments have also changed accordingly. As a result, the consultation rate for IBS has been increasing year by year. A global study has indicated that among IBS patients, IBS-D has the highest prevalence, accounting for approximately 23.4% [3]. It is particularly common among females and individuals under 50 years of age in China [4]. IBS-D is often associated with mental disorders such as anxiety and depression [5]. As one of the common functional disorders of the digestive tract [1], IBS imposes a substantial economic burden [6]. Therefore, actively improving the treatment efficiency of this disease is of great significance.

There is no explicit record of IBS-D in existing ancient Chinese medical literature. Based on the clinical manifestations of IBS-D, this disease can be categorized into the traditional Chinese medicine concepts of "diarrhea" and "abdominal pain". The pathological location involves the liver, spleen, kidney, large intestine, and small intestine. Traditional Chinese medicine theory holds that yang deficiency of the spleen and kidney is a crucial pathological mechanism of IBS-D. When the spleen qi is deficient and declining, the body's water metabolism becomes abnormal, thereby leading to symptoms such as diarrhea. As stated in "Suwen · The Great Treatise on the Correspondence between Yin and Yang", "Excessive dampness leads to loose stools." Prolonged spleen deficiency with excessive dampness will gradually affect the spleen yang. As a result, the accumulation of dampness and water becomes more severe. Over time, abnormal transportation of qi, blood, and body fluids can also affect the kidney yang. Moreover, the yang qi of the kidney is the foundation of the yang qi of all internal organs, and the spleen yang is rooted in the kidney yang. When the kidney yang is deficient and unable to warm and assist the spleen yang, it can also lead to yang deficiency of the spleen and kidney, resulting in abnormal distribution of body fluids. Thus, symptoms such as diarrhea with undigested food, cold pain in the abdomen, and early morning diarrhea can be observed. Clinically, the method of warming and tonifying the spleen and kidney has demonstrated good therapeutic effects in treating IBS-D [7].

In addition, traditional Chinese medicine postulates that the brain is the residence of the primordial spirit and commands

the spirits of the five zang-organs and six fu-organs. Meanwhile, the kidney stores essence, and essence gives rise to brain marrow. When the kidney essence is sufficient, the brain marrow is full, and the spirit is robust. As described in "Lingshu · The Channels", "When a person is first born, essence is formed first, and upon the formation of essence, brain marrow is generated." The spleen is responsible for ascending the clear substances. It absorbs nutrients such as the refined essence of food and water and transports them upward to the heart, lungs, head, and eyes. As recorded in "Lingshu · On the State of a Normal Person without Food Intake", "When the five zang-organs are stable, the blood vessels are harmonious and smooth, and the spirit can reside. Thus, the spirit is the refined qi of food and water." This indicates that the qi and blood transformed and generated by the spleen and stomach serve as the material basis for mental activities. Simultaneously, mental activities can also influence the normal functioning of the gastrointestinal tract. As stated in "Suwen · The Treatise on Pain", "When one indulges in excessive thinking, the mind becomes fixated, the spirit becomes concentrated, and the healthy qi stagnates and fails to flow, thus leading to qi stagnation." Excessive rumination can damage the spleen, resulting in impaired spleen transportation and symptoms such as loose stools. Therefore, brain disorders can affect the spleen and kidney, and spleen and kidney disorders can also impact the brain. The two are interconnected, showing similarities to the "brain-gut axis" concept in Western medicine.

To date, a substantial amount of research has verified that the traditional Chinese medicine approach of tonifying the kidney and invigorating the spleen can alleviate the symptoms of IBS-D through the "brain-gut axis" and exert therapeutic effects. However, there is still a lack of systematic elaboration. Therefore, this article systematically reviews the mechanism of action of the traditional Chinese medicine method of warming and tonifying the spleen and kidney in intervening in patients with IBS-D of the spleen and kidney yang deficiency type and rat models based on the "brain-gut axis" by reviewing relevant domestic and international literature in recent years. It is hoped that this review will provide better treatment strategies and research directions for the future.

2. Overview of IBS-D and the Brain-Gut Axis

The brain-gut axis refers to a bidirectional communication pathway formed among the central nervous system (CNS), the autonomic nervous system (ANS), the enteric nervous system (ENS), and the hypothalamic - pituitary - adrenal (HPA) axis. This pathway involves multiple aspects, including neural, endocrine, and immune systems, for information transmission [8]. Once the brain receives and integrates relevant information, it can transmit signals to the gastrointestinal tract via the CNS, ANS, ENS, and HPA axis, thereby inducing corresponding physiological and pathological alterations. Conversely, gastrointestinal dysfunction can impact the CNS, leading to emotional changes such as anxiety. This reciprocal interaction between the brain and the gastrointestinal tract through the brain - gut axis is termed as brain-gut interaction [9]. Research has indicated that patients with irritable bowel syndrome exhibit a higher degree of activation in regions associated with emotional arousal (such as the anterior cingulate cortex) and those related to endogenous pain processing and modulation (such as the basal ganglia) [10].

The underlying pathogenesis of IBS - D remains incompletely understood. Currently, there is a consensus that the dysregulation of the "brain - gut axis" caused by various factors, which gives rise to distinct pathophysiological mechanisms, might be the key factor contributing to the manifestation of IBS symptoms. These mechanisms include visceral hypersensitivity, intestinal motility disorders, increased intestinal permeability, immune activation, and alterations in the intestinal microbiota [10,11]. In a study by Rogers GB et al. [12] involving 26 patients with IBS and 11 healthy controls, functional magnetic resonance imaging (fMRI) was employed to detect changes in brain functional regions during stimulation. The results revealed that rectal distension stimulation enhanced the excitability of regions such as the anterior cingulate cortex, insular cortex, prefrontal cortex, and thalamus. Notably, both the activation area and the intensity of MRI signal changes in these regions were significantly greater in IBS patients compared to the healthy control group. At present, the treatment of IBS - D in Western medicine mainly encompasses symptomatic therapies such as antispasmodic and antidiarrheal medications, anti - infective agents, intestinal microbiota regulators, and antidepressants [13]. Although these treatments can provide short - term symptom relief, they are associated with drawbacks such as a high recurrence rate and the potential for dependence [14]. The abnormal regulation of the brain-gut axis, being a crucial pathogenic mechanism of IBS - D, can influence intestinal motility and visceral sensation through the secretion levels of brain-gut peptides, thereby leading to symptoms characteristic of IBS-D, such as abdominal discomfort and changes in bowel habits. Brain - gut peptides are small-molecular-weight substances distributed in both the brain and the gastrointestinal tract. They play a significant role in regulating visceral sensation, gastrointestinal motility, and psychological states. As the molecular link between the brain and the gastrointestinal tract, brain - gut peptides are involved in every aspect of the brain - gut axis and exert a crucial regulatory effect on gastrointestinal motility, sensation, and secretion. Among them, inhibitory brain-gut peptide hormones such as somatostatin (SST), cholecystokinin (CCK), vasoactive intestinal peptide (VIP), nitric oxide (NO), and calcitonin gene-related peptide (CGRP) tend to inhibit gastrointestinal motility. In contrast, excitatory brain-gut peptide hormones, including gastrin (GAS), ghrelin, substance P(SP), 5-hydroxytryptamine (5-HT), and motilin (MTL), can promote gastrointestinal motility and accelerate gastrointestinal emptying. The occurrence of IBS-D is induced when there is an abnormal secretion of brain -gut peptides, resulting in a dysregulation of the ratio between excitatory and inhibitory brain-gut peptides [15,16]. Research has demonstrated that 5-HT is a major determinant in the development of both the enteric nervous system and the central nervous system. Moreover, it serves as a regulator of IBS - related symptoms and emotional states [17, 18].

3. Progress on Treating IBS-D from the Perspective of Warming and Tonifying the Spleen and Kidney Based on the Brain-Gut Axis

Although the concept of the "brain-gut axis" has not been explicitly defined in TCM, discussions regarding the intricate relationship between the brain and the intestines can be traced back to the "Huangdi Neijing" over two thousand years ago. In the "Suwen·Treatise on Febrile Diseases" of the "Huangdi Neijing", it is stated that "When the Yangming Meridian is invaded by pathogens, as it is related to the muscles, its channels run along the nose and connect to the eyes, thus leading to body fever... and insomnia." This indicates that pathogenic invasion of the Yangming Stomach Meridian can disrupt the normal physiological function of the brain, resulting in insomnia. Meanwhile, the "Treatise on Cold - Induced Disorders" records, "In cases of Yangming disease, the patient experiences profuse sweating. As body fluids are depleted, the stomach becomes dry, the stool hardens, and once hardened, delirium occurs." This implies that disorders within the gastrointestinal system can potentially cause abnormal mental states. Evidently, there exists a close connection between the spleen, stomach, and the brain. The concept of the brain - gut axis thus holds significant importance in understanding and treating diseases of the digestive system.

The Sishen Pills, a classic formula in TCM, are composed of Psoralea corylifolia, Myristica fragrans, Evodia rutaecarpa, Schisandra chinensis, Zingiber officinale, and Ziziphus jujuba. These pills possess the pharmacological effects of warming the kidney and invigorating the spleen, as well as astringing the intestines to arrest diarrhea. They are widely recognized as the standard prescription for treating diarrhea caused by deficiency of spleen - kidney yang. In clinical practice, modifications of the Sishen Pills are frequently employed to address IBS-D cases characterized by spleen-kidney yang deficiency [19]. The "Jingyue Quanshu·Diarrhea" states, "The kidney serves as the gateway of the stomach, with its orifices located in the two lower orifices. Hence, the opening and closing of urination and defecation are governed by the kidney. When the yang qi within the kidney is insufficient, the fire of the Mingmen (vital gate) weakens, and excessive yin cold prevails. Consequently, in the early hours after midnight, when the yang qi has not yet recovered and the yin qi reaches its peak, continuous diarrhea ensues." Wang Ang's "Yifang Jijie" (Collection and Explanation of Medical Formulas) remarks, "Persistent diarrhea is predominantly attributed to the decline of the Mingmen fire and cannot be solely ascribed to the malfunction of the spleen and stomach." This suggests that the root cause of diarrhea lies in the deficiency of kidney yang, which leads to the inability of the spleen yang to receive proper warmth and nourishment. As a result, the spleen fails to perform its normal transportation and transformation functions, leading to the accumulation of internal dampness and turbidity, ultimately manifesting as diarrhea. In the Sishen Pills, Psoralea corylifolia is utilized in a relatively large dosage as the principal herb to warm and tonify the fire of the Mingmen. Myristica fragrans serves as the deputy herb, warming the spleen and stomach while astringing the intestines to halt diarrhea. Evodia rutaecarpa is added as an adjuvant to disperse yin cold. Schisandra chinensis functions as an envoy to astringe, warm, and consolidate; Zingiber officinale warms the stomach and dispels cold; and Ziziphus jujuba tonifies the spleen and stomach. The combined action of these herbs synergistically achieves the effects of warming the kidney, invigorating the spleen, astringing the intestines, and arresting diarrhea. Since the deficiency of spleen - kidney yang is a crucial pathological mechanism underlying IBS D, treating IBS-D with modified Sishen Pills aligns with the disease's pathogenesis and often yields favorable therapeutic outcomes. Research conducted by Li Siqi et al [20] demonstrated that after treating rats with the Sishen Pills, the levels of GAS, corticosterone (CORT), and adrenocorticotropic hormone (ACTH) in the serum of the treated rats were significantly elevated compared to those of the model group. Moreover, the Sishen Pills can modulate the p38 mitogen - activated protein kinase/c - Jun N - terminal kinase (p38 MAPK/JNK) signaling pathway, reducing the activity of transient receptor potential vanilloid 1 (TRPV1) neurons. This, in turn, alleviates the visceral hypersensitivity of IBS-D rats, thereby playing a role in relieving abdominal pain associated with IBS-D.

Changkang Formula is an empirical prescription gradually developed by Professor Wang Deming, a renowned senior traditional Chinese medicine expert. It is based on the medication experience of "Tongxie Yaofang" and "Sishen Pill" and has been summarized over many years of clinical practice. Composed of Saposhnikovia divaricata, fried Paeonia lactiflora, Cuscuta chinensis, Coptis chinensis, Rehmannia glutinosa, Cicada slough, and Fagopyrum dibotrys, it is commonly used in clinical settings for the treatment of irritable bowel syndrome with diarrhea (IBS-D). ZHANG et al [21] established an IBS-D rat model by subjecting rats to maternal separation (MS), restraint stress, and gavage with a senna leaf decoction. They discovered that treatment with Changkang Formula significantly inhibited the expression levels of 5-HT and SP in the serum and colon tissues of IBS-D rats. This not only improved the inflammatory response but also enhanced the colonic barrier function, thereby exerting a therapeutic effect on IBS-D.

Tongxie Sishen Decoction is a combined formula of Tongxie Yaofang and Sishen Pill. LIANG Jin et al [22] conducted research and found that in the treatment of IBS-D patients with Tongxie Sishen Decoction, the levels of motilin and NO significantly increased after treatment compared to before treatment, while the levels of CGRP, VIP, and SST significantly decreased. After treatment, the levels of CGRP, VIP, and SST in the observation group were significantly lower than those in the control group, while the levels of motilin and NO were significantly higher.

Wenshen Jianpi Guchang Formula is derived from Sishen Decoction. It consists of Psoralea corylifolia, Myristica fragrans, Evodia rutaecarpa, Dioscorea opposita Thunb, Rehmannia glutinosa Libosch, Radix Aconiti Lateralis Preparata, Ginseng Radix et Rhizoma, fried Atractylodes macrocephala Koidz, Cuscuta chinensis Lam, Citrus medica L, Amomum villosum Lour, Citrus reticulata Blanco, and Glycyrrhiza uralensis Fisch. This formula strengthens the effect of warming the kidney and stopping diarrhea. Research by FAN Xiaolin et al [23] indicated that Wenshen Jianpi Guchang Formula combined with Du Meridian moxibustion could reduce the levels of brain-derived neurotrophic factor (BDNF), neuropeptide Y (NPY), GAS, and 5-HT in the serum of IBS-D patients with spleen-kidney yang deficiency. This effectively regulated gastrointestinal hormones and neural factors.

Jiuxie Formula is composed of Psoralea corylifolia, Myristica fragrans, Saposhnikovia divaricata, Citrus reticulata Blanco, Atractylodes macrocephala Koidz, Paeonia lactiflora Pall, Codonopsis pilosula (Franch.) Nannf, Dioscorea opposita Thunb, Poria cocos (Schw.) Wolf, Rhus chinensis Mill., Terminalia chebula Retz., Astragalus membranaceus (Fisch.) Bunge, Lablab purpureus (L.) Sweet, Prunus mume (Sieb.) Sieb. et Zucc, Amomum tsaoko Crevost et Lemarie, Curcuma longa L., Halloysitum Rubrum, and Glycyrrhiza uralensis Fisch. Research by ZHENG Weiwei et al [24] demonstrated that either using Jiuxie Formula alone or in combination with Fire Dragon moxibustion could reduce the levels of D-lactic acid, diamine oxidase (DAO), SP, and VIP in the serum of patients. This regulated the function of the brain-gut axis and alleviated the symptoms of IBS-D.

Wenshen Jianpi Formula is composed of Psoralea corylifolia, Myristica fragrans, Evodia rutaecarpa, Schisandra chinensis (Turcz.) Baill, Pseudostellaria heterophylla (Miq.) Pax ex Pax et Hoffm, Atractylodes macrocephala Koidz, Curcuma aromatica Salisb, Zingiber officinale Roscoe, and Ziziphus jujuba Mill. The early immediate gene c-Fos is a marker of nociceptive neuron activation. After induction by second messengers, it can rapidly respond to incoming information from stimuli such as neurotransmitters and nerve impulses [25]. Research by JIANG Tianyuan et al [26] showed that Wenshen Jianpi Formula could downregulate the expression of the c-Fos gene in the colon tissue, dorsal root ganglia, and hippocampal tissue of IBS-D model rats. This indicates that it is an important target for the formula to regulate visceral hypersensitivity.

Wenshen Jianpi Decoction is composed of Psoralea corylifolia, Myristica fragrans, Schisandra chinensis (Turcz.) Baill., Codonopsis pilosula (Franch.) Nannf., Atractylodes macrocephala Koidz., Poria cocos (Schw.) Wolf, Evodia rutaecarpa, Citrus reticulata Blanco, Amomum villosum Lour., Aucklandia lappa Decne., Zingiber officinale Roscoe, Euryale ferox Salisb., and Ziziphus jujuba Mill. Research by FU Yanqun et al. [27] showed that Wenshen Jianpi Decoction combined with Compound Glutamine Capsules could downregulate the expression of tropomyosin receptor kinase B (TrkB), BDNF, and CGRP in patients. This suggests that this treatment method can significantly regulate the BDNF/TrkB signaling pathway in the treatment of IBS-D.

Cinnamomum cassia Presl is a crucial herb for treating deficiency of the life gate fire. It is pungent, sweet, and extremely hot in nature, and it pertains to the kidney, spleen, heart, and liver meridians. It has the functions of replenishing fire to assist yang, dispelling cold to relieve pain, warming the meridians, and guiding fire back to its origin. It is a commonly used herb in traditional Chinese medicine for warming and strengthening the spleen and kidney. As stated in “Tangye Bencao”: “It supplements the deficiency of the life gate and promotes yang to reduce yin.” Research has shown that by establishing IBS-D rat models through maternal separation (MS) and induction with 2,4,6-trinitrobenzenesulfonic acid (TNBS), it was found that cinnamon extract could reduce the defecation frequency and visceral hyperalgesia of MS rats in a dose-dependent manner. It also effectively improved visceral hyperalgesia in TNBS rats. This may be achieved by regulating 5-HT synthesis, thereby alleviating the intestinal symptoms of IBS-D rats [28].

4. Conclusion

In the treatment of IBS-D, TCM commonly employs prescriptions that warm and tonify the spleen and kidney to address IBS-D cases characterized by spleen-kidney yang deficiency. These include the Changkang Formula, Tongxie Sishen Decoction, Wenshen Jianpi Guchang Formula, Jiuxie Formula, Wenshen Jianpi Formula, and Wenshen Jianpi Decoction. The compositions of these formulas are mainly based on modifications of the Sishen Pill. The TCM approach of warming and tonifying the spleen and kidney can suppress the expression levels of 5-HT and SP in the serum and colon tissues of rat models with spleen-kidney yang deficiency. Additionally, it can elevate the levels of GAS, CORT, and ACTH in the serum. This approach can regulate the p38 MAPK/JNK signaling pathway and downregulate the expression of the c-Fos gene in the colon tissues, dorsal root ganglia, and hippocampal tissues of IBS-D rat models. By doing so, it can modulate the brain-gut axis function and alleviate the symptoms of IBS-D in rat models with spleen-kidney yang deficiency. In the context of treating patients, the TCM method of warming and tonifying the spleen and kidney can also reduce the levels of BDNF, NPY, GAS, 5-HT, CGRP, VIP, SST, D-lactic acid, DAO, and SP in the serum of IBS-D patients with spleen-kidney yang deficiency. It can downregulate the expression of TrkB, BDNF, and CGRP in patients and increase the levels of motilin and NO in the serum. Through these mechanisms, it can regulate the brain-gut axis function, alleviate visceral hypersensitivity in IBS-D patients, improve the inflammatory response, and enhance the colonic barrier function, thereby alleviating clinical symptoms such as diarrhea and abdominal pain in IBS-D patients. Evidently, the monomers and compound formulas of TCM for warming and tonifying the spleen and kidney can alter the content of brain-gut peptides. The regulation of the “gut-brain axis” in the treatment of IBS-D has demonstrated effectiveness. Based on the current state of research, there are several areas in the treatment of IBS-D that warrant improvement: 1) IBS-D is frequently associated with mental and psychological disorders, which require due attention from clinicians. 2) Common therapeutic agents for IBS-D include antidiarrheal drugs, antispasmodics, non-absorbable intestinal antibiotics, probiotics, and neurotransmitter-modulating medications [29]. However, to date, no ideal treatment method has achieved optimal results. Moreover, some 5-HT receptor modulators are associated with numerous adverse effects, and the sole use of Western medicine in treatment still poses many challenges. 3) The TCM approach of warming and tonifying the spleen and kidney has demonstrated remarkable clinical efficacy in treating IBS-D of the spleen-kidney yang deficiency type. By regulating the “gut-brain axis”, it can intervene in the onset and progression of IBS-D. Further exploration of the therapeutic targets and pathways of this treatment approach is a research priority, as it can provide evidence-based support for further disease management.

In summary, the TCM method of warming and tonifying the spleen and kidney can treat IBS-D by regulating the “gut-brain axis”, modifying the expression levels of brain-gut peptides, thereby reducing the inflammatory response and

improving the intestinal barrier function. This method plays a pivotal role in reducing the incidence and recurrence rate of IBS-D in patients with spleen-kidney yang deficiency. Consequently, future research will actively explore the mechanism of TCM in treating IBS-D on the basis of integrating traditional Chinese and Western medicine. This aims to enhance the treatment efficacy of IBS-D and provide theoretical and practical references for future investigations.

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