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Research Progress of Traditional Chinese Medicine in the Treatment of IBS-D and Bile Acid-intestinal Flora Imbalance

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Abstract: ***Irritable bowel syndrome with diarrhea (IBS-D) is a common functional bowel disease, and its pathogenesis is closely related to the imbalance of intestinal flora-biliary acid metabolism axis. Studies have shown that IBS-D patients generally have abnormal bile acid metabolism and intestinal flora imbalance, which aggravate intestinal barrier damage, visceral hypersensitivity and diarrhea symptoms through interaction. Based on the core pathogenesis theory of 'liver depression and spleen deficiency', traditional Chinese medicine shows unique advantages in the treatment of IBS-D by synergistically regulating the function of bile acid-intestinal flora axis through multiple targets. Mechanism studies have shown that soothing liver and invigorating spleen prescriptions (such as Tongxie Yaofang and Xiaochaihu Decoction) can repair bile acid enterohepatic circulation and reduce serum abnormal bile acid levels. Spleen-invigorating and dampness-removing prescriptions (such as Gegen Qinlian Decoction) reshape the flora structure and increase the abundance of beneficial bacteria such as Bifidobacterium by regulating inflammatory factors such as IL-10 and TNF-α. In addition, acupuncture, moxibustion and other external therapies improve bile acid secretion by regulating the brain-gut axis and 5-HT signal. The existing evidence shows that traditional Chinese medicine can synergistically restore the homeostasis of flora and the balance of bile acid metabolism through the 'multi-component-multi-target' comprehensive regulation mode, which provides new ideas for the treatment of IBS-D. In the future, it is necessary to deepen the mechanism research, clarify the active components of traditional Chinese medicine and the host-microorganism interaction network, and promote the development of precision treatment.***

Keywords: Traditional Chinese medicine, Intestinal flora, Bile acid metabolism, Intervention.

1. Introduction

Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disease characterized by abdominal pain, abdominal distension accompanied by changes in bowel habits (frequency, traits). The global prevalence rate is about 5%~20%. According to the main defecation traits, IBS can be divided into diarrhea type (IBS-D), constipation type (IBS-C), mixed type (IBS-M) and undetermined type (IBS-U). Among them, IBS-D is mainly characterized by recurrent diarrhea, abdominal pain before and after defecation, which seriously affects the quality of life of patients. The pathogenesis of IBS-D has not been fully elucidated. Traditional views focus on visceral hypersensitivity, gastrointestinal motility disorders, abnormal brain-gut axis interaction, low intestinal inflammation and psychological factors. In recent years, the metabolic imbalance of bile acids (BAs) and the imbalance of Gut Microbiota and their interaction in the pathogenesis of IBS-D have been paid more and more attention. The 'bile acid-microbiota axis' composed of the two has become a research hotspot. Traditional Chinese medicine has a long history in the treatment of IBS-D and has a definite curative effect. In traditional Chinese medicine, it belongs to the category of 'diarrhea' and 'abdominal pain'. The main pathogenesis includes liver depression and spleen deficiency, spleen deficiency and dampness, spleen and stomach weakness, spleen and kidney yang deficiency, etc. The treatment is based on the basic principles of soothing the liver and invigorating the spleen, replenishing qi and removing dampness, warming and tonifying the spleen and kidney. Through the comprehensive regulation of compound decoction, Chinese patent medicine, acupuncture and other means, it can not only effectively alleviate the clinical symptoms, but also has unique advantages in regulating the overall function of the body and restoring the homeostasis of the internal environment. Modern pharmacological studies have shown that the efficacy of traditional Chinese medicine is closely related to its regulation of bile acid metabolism and improvement of intestinal flora disorders. Therefore, it is of great significance to further explore the mechanism of traditional Chinese medicine intervention in the prevention and treatment of IBS-D by 'bile acid-bacteria axis', which is of great significance to promote the modernization of traditional Chinese medicine and realize precise treatment.

1.1 Research Background and Significance

Irritable bowel syndrome (IBS) is a functional bowel disease characterized by recurrent abdominal pain accompanied by changes in bowel habits. The diagnosis of IBS needs to exclude organic gastrointestinal lesions [1]. In recent years, the overall prevalence of IBS in the general population in China is 1.4%~11.5%. Women are slightly higher than men, and young and middle-aged (18~59 years old) are more common [2]. According to Rome IV diagnostic criteria, IBS is divided into four subtypes: diarrhea type (IBS-D), constipation type (IBS-C), mixed type (IBS-M) and undetermined type (IBS-U) [3]. IBS-D is the main subtype of IBS, accounting for 46% -62% of the total IBS [4]. Recent studies have shown that the imbalance of Gut Microbiota (GM) -Bile Acid (BA) axis may be a key link in the pathogenesis of IBS-D [5]. At present, the research on the mechanism of IBS in western medicine focuses on multiple dimensions such as intestinal microecological imbalance, abnormal regulation of brain-gut axis, visceral hypersensitivity, gastrointestinal motility disorder and psychosocial factors [6]. It is worth

noting that IBS is one of the most costly gastrointestinal diseases, and its clinical features include the lack of specific therapeutic drugs and the recurrence of symptoms. Because of the good curative effect of traditional Chinese medicine on IBS-D, the research of traditional Chinese medicine on IBS has become a hot spot. This article intends to explore the abnormal expression of bile acid-intestinal flora in the pathogenesis of irritable bowel syndrome and the intervention of traditional Chinese medicine.

2. Bile Acid Metabolism and Intestinal Flora Imbalance in IBS-D

2.1 The Role of Intestinal Flora-biliary Acid Interaction in Irritable Bowel Syndrome

The imbalance of gut microbiota-biliary acid axis has been proved to be closely related to the core symptoms of IBS-D, such as diarrhea and visceral hypersensitivity. The following is to analyze its pathological mechanism from three dimensions: abnormal bile acid metabolism, dysbacteriosis and imbalance of their interaction.

2.1.1 Abnormal bile acid metabolism and irritable bowel syndrome

Bile acid (BA) is a major substance in the liver, which is produced by cholesterol in the liver through a series of enzymatic reactions [8] Primary bile acid (PBA), which is synthesized in hepatocytes, is secreted into the gallbladder through the bile salt export pump and released into the duodenum through the regulation of the Oddi sphincter. It is metabolized into secondary bile acid (SBA) through the action of intestinal flora. About 95% of BA is reabsorbed into intestinal epithelial cells in the terminal small intestine (mainly the terminal ileum), and then passes through the organic solute transport protein α/β on the cell basement membrane to leave the intestinal epithelial cells, enters the portal vein system, and is transported to the liver through blood circulation. After being treated by hepatocytes, it is discharged into the intestine through the gallbladder with the newly synthesized PBA, and begins a new hepatoenteral circulation. The remaining BA is excreted through feces [8] Under physiological conditions, bile acids not only participate in lipid absorption and energy metabolism, but also maintain the integrity of intestinal mucosal barrier, regulate immune response and flora homeostasis [9-13]. However, bile acid metabolic imbalance can induce a variety of pathological changes, such as inflammatory bowel disease (IBD), hepatocellular carcinoma (HCC), colorectal cancer (CRC), metabolic syndrome [14]. More and more studies have found that abnormal bile acid metabolism is closely related to the occurrence and development of IBS-D. Studies have found that 68% of IBS-D patients have abnormal increase in fecal bile acid excretion or poor absorption [15]. Studies have found that the group of fecal BA pools in IBS-D patients is characterized by an increase in primary BA and a decrease in secondary BA, and may be related to diarrhea and visceral hypersensitivity, providing evidence for BA regulation in the treatment of IBS-D [16]. A study observed the correlation between intestinal flora and excessive bile acid excretion in IBS-D by comparing IBS-D patients and healthy volunteers through clinical and basic experiments. The intestinal microflora rich in Clostridium led to excessive bile acid excretion in IBS-D patients [17].

2.1.2 Intestinal flora imbalance and irritable bowel syndrome

Intestinal flora is a large and diverse microbial colony that settles in the human intestinal tract. The flora and the host co-evolve in a symbiotic relationship, which can play a role in maintaining the mucosal barrier, providing nutrients, regulating immune function, and resisting pathogens [18]. Intestinal flora imbalance is considered to be related to the pathophysiology of IBS. IBS-D patients generally have intestinal flora imbalance, mainly due to the decrease of flora diversity, the decrease of dominant flora, and the number of pathogenic bacteria [19] Compared with healthy individuals, the intestinal flora of IBS patients has changed, and the level of potential harmful bacteria of Enterobacteriaceae and Bacteroides has increased [20]. The intestinal flora of IBS-D patients showed significant imbalance: the abundance of Escherichia, Prevotella and Clostridium was abnormally increased, while the beneficial bacteria such as Bifidobacterium and Lactobacillus were significantly reduced. It is worth noting that the number of mucosal bifidobacteria was significantly negatively correlated with the degree of abdominal pain and the frequency of episodes [21].

2.1.3 Imbalance of intestinal flora-biliary acid metabolism interaction and irritable bowel syndrome

Intestinal flora is closely related to bile acid metabolism. The interaction between intestinal flora and bile acid is not only reflected in the influence of flora on bile acid metabolism, but also bile acid plays an important role in the structure and function of intestinal flora [22-23]. On the one hand, intestinal flora has an effect on the synthesis and metabolism of bile acids. Studies have confirmed that there are many bacteria in the intestinal tract can produce bile acid hydrolase, such as Lactobacillus, Clostridium, Enterococcus, Bifidobacterium and so on [24]. After feeding the mouse antioxidant Tempol, LI et al. [25] showed a series of changes in the intestinal flora, such as the transformation of Firmicutes to Bacteroides in the cecal tissue, and the significant decrease in the levels of Lactobacillus and Clostridium. The significant inhibition of farnesoid X receptor (FXR) ((FXR) is the main nuclear receptor of bile acids, and its abnormal signaling pathway can lead to bile acid synthesis and enterohepatic circulation disorder) signal transduction, reducing the production of bile acid hydrolases, resulting in a significant increase in bile acids in the intestine. On the other hand, bile acids can promote the growth of bile acid-metabolizing bacteria and inhibit the growth of bile acid-sensitive bacteria, thereby maintaining bacterial homeostasis, inhibiting bacterial overgrowth in the small intestine, protecting intestinal barrier function and inhibiting bacterial translocation [26]. Studies have shown that [27], low concentration of deoxycholic acid can reduce the transepithelial resistance of colon tissue, increase the permeability of intestinal epithelium, thereby increasing the absorption of bacteria in colon tissue; the decrease of bile absorption in the small intestine leads to the increase of free bile acid after entering the colon, the increase of bile acid concentration, the inhibition of intestinal beneficial bacteria, and the imbalance of intestinal flora.

3. TCM Diagnosis and Treatment of IBS-D

3.1 Understanding of IBS-D in TCM Theory

There is no name of 'irritable bowel syndrome' in Chinese medicine. According to the clinical manifestations of IBS-D, most scholars attribute it to the category of 'abdominal pain' or 'diarrhea' in traditional Chinese medicine. Although IBS-D is located in the intestine, it is also closely related to the liver and spleen. Modern doctors have more understanding of its pathogenesis, but most of them believe that it is mainly related to liver and spleen dysfunction. Spleen deficiency and dampness are the basis, and liver qi stagnation runs through the whole process of the disease. The treatment is mainly based on invigorating spleen, soothing liver and drying dampness [28-29]. It is proposed that "spleen deficiency and liver excess" is the core pathogenesis of IBS, which is intrinsically related to the imbalance of intestinal flora-biliary acid axis. In addition, 'Danxi heart method · diarrhea' pointed out that ' the disease of diarrhea is mostly caused by wet soil, and the evil of wind and wood is also helpful. Visceral association: 'liver-gallbladder' corresponds to bile acid metabolism, and 'spleen-gut' corresponds to bacterial homeostasis. Intestinal flora imbalance is an important basis for spleen deficiency. Traditional Chinese medicine believes that the spleen is the 'acquired foundation, the source of qi and blood biochemistry, and the spleen is considered as the spleen'. It has the function of receiving food, turning water into subtle, and transferring subtle substances to the whole body. The spleen and stomach are healthy, and the food intake can be digested and absorbed, and the qi, blood and body fluid are nourished to maintain normal development and physiological activities [30]. If the spleen and stomach are weak and the health is lost, there will be clinical manifestations such as anorexia, loose stools, and abdominal distension. Studies suggest that intestinal flora imbalance will aggravate such symptoms [31]. This is similar to the understanding of the spleen as the acquired foundation of traditional Chinese medicine. Based on the theory of 'Huangdi Neijing' and 'Ganru Pi' [32], some scholars believe that the basic chemical composition of spleen-invigorating Chinese medicine is mainly carbohydrates, and polysaccharide components can be used as prebiotics to promote the growth of probiotics in the intestine, thereby restoring the homeostasis of intestinal flora. The strength of spleen and stomach function is related to the abundance of intestinal flora and the number of species. The dysfunction of spleen leads to the imbalance of intestinal flora. It is speculated that the intestinal flora is the microscopic material basis of the function of the spleen. Spleen deficiency is an important cause of intestinal flora disorder.

Abnormal secretion of bile acid is the microscopic manifestation of liver depression. Based on the theoretical knowledge of traditional Chinese medicine, the bile is attached to the liver, and the bile is the residual gas of the liver. When the bile is lowered, the gas of the lung and stomach is lowered, which can ensure the transportation and absorption of water and grain. If the liver function is normal, the bile is excreted smoothly. If the liver fails to discharge, it can affect the secretion and excretion of bile, leading to spleen and stomach dysfunction and disease [33] Therefore, it is believed that 'liver depression' is associated with abnormal bile acid metabolism. Modern medicine has confirmed that bile acid is the most important component of bile, which is metabolized and generated in the liver, participates in digestion, especially plays an important role in the digestion and absorption of lipids, which is consistent with the understanding of traditional Chinese medicine.

The spleen is the yin in the yin, the yang in the non-yin does not rise, the soil has the nature of the thick, the non-straight wood does not reach. The liver qi rises and the middle earth is dredged to help the spleen rise, clear and transport. In the pathological state, liver depression also leads to the imbalance of the central axis of the spleen and stomach, and the ability to transport and transform the water and grain is weakened, while the spleen deficiency and inability to nourish the liver qi can also lead to liver depression, which is highly fitted with the interaction mode that the intestinal flora promotes the metabolism and absorption of bile acids, and the bile acids contribute to the digestion and absorption function and the stability of the intestinal microenvironment [34]. Therefore, IBS-D liver depression and spleen deficiency is closely related to intestinal flora-biliary acid metabolism disorder.

3.2 The Mechanism of Traditional Chinese Medicine in the Treatment of IBS-D

3.2.1 Regulating bile acid metabolism

Traditional Chinese medicine can regulate bile acid metabolism through a variety of ways to improve IBS-D symptoms. For example, Yuan Yali [35] found that the disorder of bile acid metabolism-TGR5 signaling pathway plays an important role in the pathogenesis of IBS-D, which may be involved in the occurrence of IBS-D by affecting intestinal microecology, intestinal mucosal barrier function, visceral hypersensitivity, gastrointestinal motility and brain-gut axis interaction. At the same time, the bile acid metabolism-TGR5 axis is closely related to the pathogenesis of 'liver depression and spleen deficiency' in traditional Chinese medicine. Mou et al [36] have shown that bile acids can change the structure of intestinal microbial community and the level of metabolites, and different kinds of bacteria have an effect on all aspects of bile acid metabolism, thus affecting the composition of bile acids. The two affect each other, promote each other, and regulate each other, which is in line with the internal relationship between 'liver and gallbladder' and 'spleen and stomach' in traditional Chinese medicine.

3.2.2 Regulating intestinal flora

Traditional Chinese medicine has a significant effect in regulating intestinal flora. Liu Jiaxing [37] and other studies have shown that Sishen Pills can treat IBS-D by increasing the number of intestinal flora, reducing the number of harmful flora, and regulating the balance of intestinal microecology. Zhang Xingxing [38] and other studies have shown that compared with the normal group, the number of intestinal bifidobacteria and lactobacilli in IBS-D patients decreased, the number of enterobacteria increased, and intestinal CR decreased, suggesting that IBS-D patients with liver depression and spleen deficiency syndrome do have intestinal microecological imbalance, which may be one of its pathogenic mechanisms.

3.2.3 Multi-target comprehensive treatment

The treatment of IBS-D by traditional Chinese medicine is not only limited to the regulation of bile acid metabolism and intestinal flora, but also can play a comprehensive therapeutic role through a variety of ways. For example, Chen Huan [39] and other studies have shown that the method of warming kidney and invigorating spleen is effective in the treatment of IBS-D, which can not only significantly improve the clinical symptoms, but also reduce the recurrence rate and improve the quality of life of patients. The method of warming kidney and invigorating spleen is an important part of clinical application by reducing visceral sensitivity, regulating brain-gut interaction, regulating immunity, alleviating inflammatory response and improving the efficacy of IBS-D. Wang Lu [40] found that tetracosanoic acid in psoralen, sitosterol in nutmeg and quercetin in evodia rutaecarpa may be the material basis for its anti-IBS-D effect. The two classical prescriptions represented by spleen deficiency and dampness and spleen and kidney yang deficiency have commonalities in therapeutic targets and pathways, both of which have the characteristics of 'multi-component, multi-target and multi-pathway', and are mostly related to the regulation of inflammatory response.

3.3 Chinese Medicine Treatment of IBS-D

In many traditional Chinese medicines to regulate the intestinal flora of irritable bowel syndrome-biliary acid, the most widely used is the prescription with the effect of soothing liver and invigorating spleen, especially the addition and subtraction of Tongxie Yaofang (Atractylodes macrocephala, Paeonia lactiflora, tangerine peel, windproof). It has the effect of tonifying spleen and softening liver, removing dampness and relieving diarrhea, and is often used to treat the pain and diarrhea of liver-spleen disharmony. Yao Sijie [41] studies suggest that, compared with the western medicine group Pinaverium Bromide, Tongxie Yaofang can effectively increase the number of intestinal Lactobacillus acidophilus, Bifidobacterium and Streptococcus faecalis in IBS-D patients with liver stagnation and spleen deficiency, and improve the clinical symptoms such as abdominal pain and diarrhea. Wang Xin [42] and other researchers found that paeoniflorin, as the main active ingredient of Paeoniae Radix Alba and Paeoniae Radix Rubra, is a water-soluble monoterpene glycoside. It may reshape the intestinal flora structure of colitis mice, regulate the flora-mediated bile acid metabolism disorder, and then repair the intestinal barrier damage, reduce intestinal inflammation, and finally play a protective role in colitis mice. Zhang X [43-44] found that Tongxie Yaofang could reduce the levels of total bile acid (TBA) and DCA in serum and feces of IBS-D model animals (restraint stress + senna leaf), up-regulate the expression of ASBT in ileum, promote the reabsorption of bile acid and reduce the load of bile acid in colon. The expression of FXR, SHP in liver and FGF15/19 in ileum (FGF15 in rodents) was up-regulated, and bile acid synthesis was inhibited by negative feedback (such as reducing CYP7A1 expression). Wang L [45-46] significantly increased the diversity of intestinal flora, increased the abundance of beneficial bacteria such as Bifidobacterium and Lactobacillus, and reduced the proportion of opportunistic pathogens such as Enterobacteriaceae (such as Escherichia coli) and Desulfovibrio. Increase the content of SCFAs (especially butyric acid), repair the intestinal barrier (increase the expression of tight junction protein Occludin, ZO-1), and reduce low-grade intestinal inflammation (reduce TNF-α, IL-6, IL-1β).

Spleen-based prescriptions regulate bile acid-intestinal flora imbalance in diarrhea-predominant irritable bowel syndrome. Li Jie [47] found that the modified Xiaochaihu decoction with the effect of soothing liver and promoting gallbladder can promote bile excretion and reduce the concentration of serum glycochenodeoxycholic acid and taurochenodeoxycholic acid, indicating that the modified Xiaochaihu decoction has a certain regulatory effect on the serum bile acid of patients. Wang Yantian [48] and other studies have found that Chaishen Jieyu Decoction has the effect of soothing the liver and regulating qi, strengthening the spleen and stopping diarrhea. It can effectively regulate the bile acid metabolism of IBS-D model mice, repair the synthesis and transformation of bile acid in the liver and intestine circulation, increase the content of conjugated bile acid and play a role in protecting the intestine. Zhao Yinfeng et al. [49] believed that in the treatment of IBS-D patients with spleen deficiency and dampness obstruction, compared with the western medicine group Pinaverium Bromide Tablets combined with Montmorillonite Powder, the traditional Chinese medicine Jianpi Qushi Decoction (composition: Jiaoshanzha, Yiyiren, Chaoguya, Chaobaizhu, Amomum villosum, Atractylodes Rhizoma, etc.) can significantly increase the number of Bifidobacterium and Lactobacillus and reduce the number of Staphylococcus.

The prescription of eliminating dampness mainly regulates the bile acid-intestinal flora imbalance of diarrhea - predominant irritable bowel syndrome. For example, Huang Yulong [50] found that Gegen Qinlian Decoction can effectively control the symptoms of diarrhea and abdominal pain in the treatment of IBS-D spleen-stomach damp-heat syndrome through clinical efficacy observation, and has a certain therapeutic effect. Its mechanism of action is related to the regulation of serum IL-10, TNF-α expression, regulation of the number of Bifidobacterium and Lactobacillus acidophilus. Chi Meihua et al. [51] treated 35 patients with IBS-D of spleen-stomach damp-heat type with Ge Lian Huo Su Decoction, and the total effective rate was 94.3%.

In addition to oral administration of traditional Chinese medicine, external treatment of traditional Chinese medicine is also very effective in the treatment of IBS-D patients, such as acupuncture, moxibustion, massage, auricular points, etc., and has the advantages

Li Jing [52] used dialectical thinking in his randomized controlled trial. In the acupuncture group, Baihui, Yintang, Tianshu, Zusanli, Shangjuxu, Sanyinjiao and Taichong were treated with acupuncture at 'Tiaoshen Jianpi', while the western medicine group was treated with pinaverium bromide tablets. After observation, it was found that acupuncture at 'Tiaoshen Jianpi' could relieve the abdominal pain of IBS-D patients in the early stage, and the curative effect was better than that of the western medicine group. In the later stage of treatment, it could significantly improve the degree and frequency of abdominal pain, improve the satisfaction of defecation, reduce the interference of disease on life, and optimize the quality of sleep. The overall curative effect was

better than that of pinaverium bromide tablets. Through clinical observation, Zheng Jie [53] found that compared with the control group of pinaverium bromide tablets, patients with IBS-D of liver depression and spleen deficiency syndrome treated with acupuncture therapy combined with moxibustion have a better therapeutic effect. The therapeutic mechanism may be to improve the intestinal barrier function of patients. 5-HT may affect the secretion of bile acid through the brain-gut axis Huo Yongli [54] and other studies have found that the effect of hot ointment rubbing combined with Tongxie prescription in the treatment of IBS-D of liver depression and spleen deficiency syndrome is better than that of conventional pinaverium bromide treatment, which can significantly reduce the adverse symptoms of gastrointestinal tract and improve the quality of life of patients. The clinical effect is significant. of simple operation and low price in clinical application.

4. Conclusion

The 'bile acid-bacteria axis' composed of bile acid metabolism disorder, intestinal flora imbalance and their interaction plays a central role in the pathogenesis of IBS-D, which is an important pathological basis leading to diarrhea, abdominal pain and visceral hypersensitivity. Chinese medicine treatment of IBS-D has the characteristics of overall regulation and multi-target intervention. A large number of basic and clinical studies have confirmed that traditional Chinese medicine therapies such as classical prescriptions (such as Tongxie Yaofang and Shenling Baizhu Powder), single herbs and active ingredients (such as berberine and total glucosides of paeony), acupuncture and moxibustion can effectively interfere with the vicious cycle of 'bile acid-microbiota axis' by regulating FXR/FGF19 signaling pathway, promoting bile acid reabsorption (up-regulating ASBT), inhibiting excessive synthesis of bile acid (inhibiting CYP7A1), remodeling intestinal flora structure (increasing probiotics and inhibiting harmful bacteria), enhancing intestinal barrier function, reducing low-grade inflammation and regulating brain-gut axis. Therefore, the clinical symptoms and quality of life of IBS-D patients were significantly improved.

Although the current research has achieved fruitful results, it still needs to continue to deepen in terms of mechanism depth, clinical research quality, individualized precise intervention, and traditional Chinese medicine-bacteria interaction. In the future, we should make full use of modern scientific and technological means to clarify the precise network of TCM regulation 'axis', promote precise treatment based on 'combination of disease and syndrome' and 'micro - classification', develop innovative drugs, and explore optimized integrated treatment plans. This is not only an important direction for the modernization of traditional Chinese medicine, but also will provide a more effective and safer strategy for the prevention and treatment of IBS-D, a complex disease, and ultimately benefit the majority of patients.

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