

Review

Treatment of Irritable Bowel Syndrome by Chinese Medicine: A Review*

CHEN Guan-ru^{1,2}, XIE Xiao-fang^{1,2}, and PENG Cheng^{1,2}

ABSTRACT Irritable bowel syndrome (IBS) is a common refractory disease. Chinese medicine (CM) has remarkable efficacy and advantages on the treatment of IBS. This review summarized the articles focusing on the treatment of IBS with CM to sum up the latest treatment methods for IBS and the underlying mechanisms. Literature analysis showed that prescriptions, acupuncture, and moxibustion are the primary methods of CM treatment for IBS. The potential mechanisms center on the regulation of the enteric nervous system, the alleviation of visceral hypersensitivity, the stability of intestinal flora, and the regulation of the immune system.

KEYWORDS irritable bowel syndrome, Chinese medicine, literature review

Irritable bowel syndrome (IBS) is the most common functional gastrointestinal disorder, characterized by continuous or intermittent abdominal pain, abdominal distension, and changes in bowel habit. In IBS, there is no obvious intestinal structural abnormalities, but the whole intestine has an excessive or abnormal response to stimulation.^(1,2) Based on clinical manifestations, IBS is usually classified into 4 types: diarrhea-predominant IBS (IBS-D), constipation-predominant IBS (IBS-C), mixed IBS (IBS-M), and unspecified IBS (IBS-U).⁽³⁾ The prevalence of IBS varies worldwide. In Asia, IBS affects 2.9% to 15.6% of the population, whereas in the United States and Britain, the disease occurs in 14% to 24% of women and 5% to 19% of men.⁽⁴⁾ Although there is no direct evidence that the incidence of IBS is related to age and gender, IBS occurs more commonly in women, especially in women younger than 50 years old.⁽⁵⁾

The pathogenesis of IBS is complex, which may be related to a disruption in the central nervous system pain processing, visceral hypersensitivity, abnormal colonic motility, and emotional stress.^(6,7) The therapeutic principle for IBS is focused on regulating intestinal motor function and reducing intestinal sensitivity. In addition, emerging research has increasingly focused on the role of intestinal flora in the development of IBS and clinical treatment.⁽⁸⁾ The direct and indirect costs related to IBS are estimated to be up to ¥123 billion in China, and US\$10 billion in the USA.⁽⁹⁾ Despite the availability of numerous drugs to control IBS symptoms, many patients do not respond well to these

drugs.⁽¹⁰⁾ Some frequently-used medications, such as antispasmodic and anticholinergic medications, do not improve all symptoms of IBS and may exacerbate some symptoms like bloating and constipation.⁽¹¹⁾ Treatment for IBS using Chinese medicine (CM) has attracted increasing attention due to the advantages of convenience, simplicity, cost-effectiveness, and few side effects. To summarize the experience and provide support for the treatment of IBS with CM, the authors highlight the different therapy methods and their possible mechanisms.

Etiology and Pathogenesis of IBS in CM

IBS may be characterized as "diarrhea", "abdominal pain" and "constipation" in CM. According to CM theory, illness is a result of a yin-yang disharmony in the organ system. The etiology of IBS is mainly attributed to the weakness of PI (Spleen) and Wei (Stomach) or damage to the Gan (Liver), Pi, and Wei caused by diet, emotion, and other factors,

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1. School of Basic Medicine, Chengdu University of Traditional Chinese Medicine, Chengdu (611137), China; 2. State Key Laboratory of Southwestern Chinese Medicine Resources, Chengdu (611137), China

Correspondence to: Prof. PENG Cheng, E-mail: cctcmpengcheng@126.com

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resulting in intestinal dysfunction. Gan qi stagnation and Pi-Wei weakness are important factors in the occurrence of this disease.^(12,13)

Syndrome Differentiation of IBS

Syndrome differentiation is a key feature of CM system. The primary purpose of treatment based on syndrome differentiation is to clarify the main etiology and pathogenesis for selecting the best individual treatment plan according to the situation of each patient. According to the specific clinical manifestations of patients determined from inspection, smelling, requesting, and pulse-taking, CM classifies IBS into different syndromes, among which the major syndromes include Gan depression and Pi deficiency, Pi-Wei weakness, Pi-Shen (Kidney) yang deficiency, cold and heat complexity.⁽¹⁴⁾

Treatments of IBS in CM

CM Prescriptions

CM prescriptions, also known as recipes or formulas, are the key forms of CM for treating diseases. Many prescriptions have been created and applied to the clinical treatment of IBS. Modern research has shown that some of these prescriptions can significantly improve bowel symptom scores and the global symptom profile.⁽¹⁵⁾ Shengling Baizhu Powder (SLBZP, 参苓白术散), Tongxie Yaofang (TXYF, 痛泻要方), Fuzi Lizhong Decoction (FZLZD, 附子理中汤), Banxia Xiexin Decoction (BXXXD, 半夏泻心汤) are prescriptions commonly used to treat IBS. These prescriptions are also recommended by the Spleen and Stomach Disease Branch of the Chinese Academy of CM for the diagnosis and treatment of IBS based on expert consensus.⁽¹⁶⁾ In addition to these prescriptions, Wumei Pill (乌梅丸), Sishen Pill (四神丸), Simo Decoction (四磨汤), Dajianzhong Decoction (大建中汤) and other classic prescriptions are also used by doctors to treat IBS according to clinical manifestations.

Acupuncture and Moxibustion

The use of acupuncture for the treatment of functional diseases has a long history. Acupuncture can alleviate defecation frequency, and improve intestinal symptoms in patients with diarrhea.^(17,18) Compared to other treatment options, acupuncture may improve IBS with the fewest side effects.⁽¹⁹⁾ Pishu (BL 20, usually used to treat abdominal distension and diarrhea), Zhongwan (RN 12, usually used to treat stomachache, abdominal distension, and vomiting),

and Zusanli (ST 36, widely used in the treatment of various gastrointestinal diseases) are the acupoints usually used in clinical. According to different manifestations of patients, clinicians may add other acupuncture points in the treatment to achieve the best individual therapeutic effect.

Moxibustion is a traditional CM therapy used to improve general health and treat chronic conditions by stimulating specific points with heat generated by burning herbal preparations containing dried mugwort leaves. It is often used as an auxiliary or alternative treatment to acupuncture. Moxibustion can effectively relieve the symptoms of IBS-D such as diarrhea, abdominal pain, and abdominal discomfort. This treatment has the effect of warming meridian and inspiring qi of Zang-Fu organs.^(20,21)

Adjuvant Therapies

Diet may play an essential role in the development and treatment of IBS. Dietary fiber supplements are the most widely recommended agents for the IBS treatment. For IBS-D patients, these agents can relieve the symptoms of diarrhea by decreasing stool transit, enhancing the water-holding properties of the stool, and providing bulk for the stool. Eliminating specific food, such as coffee, dairy, beans, and fatty foods is also considered effective for IBS-D patients. Increased dietary fiber is frequently recommended for IBS-C patients. Consuming enough fiber (about 20–30 g/d) can lead to a significant improvement in constipation. Fiber plays a role in the treatment of constipation; however, its value for IBS treatment or, specifically, in the relief of abdominal pain or diarrhea associated with IBS is controversial.⁽²²⁾

Psychological factors are also essential to the occurrence and development of IBS. In addition to gastrointestinal symptoms, IBS patients generally experience anxiety and depression. Mindfulness-based stress reduction can reduce IBS symptoms and the feasibility and efficacy of this approach for the reduction of IBS symptom severity and stress symptoms have been demonstrated. Although psychological treatment has no side effects, long-term curative effect is difficult to achieve with this approach.⁽²³⁾

Mechanism of CM in Treating IBS

Regulating Enteric Nervous System

CM prescriptions may affect neurotransmitters

and hormones in the enteric nervous system. Neurotransmitters in the gut can stimulate intestinal secretion and colonic motility.⁽²⁴⁾ Studies on the effects of serotonin and other neurotransmitters as well as gastrointestinal hormones have been conducted to explore the effects of CM treatment on intestinal motor function.

SLBZP can decrease the expression of 5-hydroxytryptamine (5-HT) and vasoactive intestinal peptide (VIP), increase the level of neuropeptide tyrosine (NPY) in IBS-D patients, suggesting that SLBZP may alleviate IBS by regulating the gastrointestinal hormone and 5-HT levels.⁽²⁵⁾ Yang, et al⁽²⁶⁾ found that SLBZP combined with glutamine can restore intestinal mucosal barrier function as well as the level of 5-HT. TXYF was reported to reduce the fecal moisture content, 5-HT and substance P (SP) levels, as well as the expression of corticotropin releasing hormone in IBS-D model rats.⁽²⁷⁾ FZLZD can reduce the pro-inflammatory response, inhibit the release of serum 5-HT in rats, and inhibit the suppress of intestinal smooth muscle.⁽²⁸⁾ Xiaoyao Powder (XYP, 逍遥散) can reduce the level of 5-HT in colic mucosa and increase the level of 5-HT transporter, suggesting that the possible mechanism of IBS treatment with XYP is to reduce neuronal excitability by regulating the 5-HT signaling pathway.⁽²⁹⁾ Xiangsha Liujuanzi Decoction (XSLJZD, 香砂六君子汤) can affect the brain-gut axis and neuropeptide production, it can also increase the levels cholecystokinin (CCK) and VIP in the serum. XSLJZD was also reported to decrease the mRNA expression of these neuropeptides in the hypothalamus of IBS rats.⁽³⁰⁾ Simo Decoction can relieve abdominal pain and diarrhea in IBS patients, the potential mechanisms may be related to regulating the expression of serum 5-HT, norepinephrine (NE) and MPO, and improving the state of anxiety and depression.⁽³¹⁾ The mechanism of Sijunzi Decoction (四君子汤) in the treatment of IBS is also related to the regulation of enteric nervous system. The mRNA expressions of 5-H₃ and 5-H₄ receptors in intestinal mucosa of IBS patients treated by Sijunzi Decoction are significantly lower than those in the control group, and the expression of related inflammatory factors in serum is also inhibited.⁽³²⁾ Ganmai Dazao Decoction (甘麦大枣汤) can improve the anxiety behavior, inhibit intestinal peristalsis, and reduce the levels of 5-HT, SP and calcitonin gene related peptide (CGRP) in intestinal tissues of IBS rats.⁽³³⁾ Acupuncture can

also alleviate abdominal pain and discomfort of IBS patients by decreasing the expression of 5-HT and NPY.⁽³⁴⁾

Research on the Chinese herbs used to treat IBS is also increasing. Ginseng total saponins, the main active ingredients of Ginseng, can inhibit the activity of 5-HT₃A receptor channels expressed in *Xenopus laevis* oocytes.⁽³⁵⁾ *Fructus aurantii* can enhance gastrointestinal motility by regulating 5-HT and VIP in the gastrointestinal tract of rats.⁽³⁶⁾ Studies also showed that 4 polyacetylenes from *Radix Bupleuri* can exhibit antidepressant activity and the mechanism may be associated with increase of 5-HT and NE.⁽³⁷⁾

Regulating Contraction of Intestinal Smooth Muscle

By regulating the contraction of smooth muscle and inhibiting intestinal activity, CM can improve the symptoms of diarrhea and cramps.⁽³⁸⁾ TXYF exhibits an inhibitory effect on bowel movement and intestinal peristalsis. It can inhibit the contraction of isolated rat colonic smooth muscle by preventing the influx of extracellular Ca²⁺.⁽³⁹⁾ He, et al⁽⁴⁰⁾ claimed that TXYF can alleviate IBS through an islet-intestinal axis regulation mechanism. The study demonstrated that TXYF can increase the serum content of glucagon-like peptide-1 and decrease the expression of somatostatin in IBS-D model rats.

The essential oil and water extract of *Tangerine peel* has been demonstrated to inhibit the spontaneous motion of gastrointestinal smooth muscles. These ingredients can also inhibit intestinal contractions or spasms induced by acetylcholine.⁽⁴¹⁾ Electroacupuncture (EA) in ST 36 can down-regulate the expression of colon vimentin protein, improve gastrointestinal motility in IBS-D rats, and stimulate the contraction of smooth muscle.⁽⁴²⁾

Reducing Visceral Sensitivity

Visceral hypersensitivity is a major mechanism underlying abdominal pain in IBS patients.⁽⁴³⁾ TXYF can lower visceral sensitivity by regulating mast cells (MCs) activation in IBS-D patients.⁽⁴⁴⁾ This formula can balance the expression of the brain-derived neurotrophic factor and tropomyosin receptor kinase B, thereby alleviating visceral hypersensitivity in IBS-D rats.⁽⁴⁵⁾ Hu, et al⁽⁴⁶⁾ found that TXYF can prolong the incubation period of diarrhea and defecation caused by castor oil, reduce the amount of defecation caused by stress, relieve

colonic pain caused by mustard oil, and prolong the time of colonic stool excretion. Sini Powder (SNP, 四逆散) can improve the symptom scores, rectal threshold feeling, and maximal tolerance volume of the rectum in IBS-C patients. The mechanism may be related to inhibition of dopaminergic synapses and activation of amphetamine addiction signaling pathways.^(47,48) XYP can improve mental status by elevating the levels of brain NE and dopamine, relieve gastrointestinal smooth muscle spasms, reduce visceral sensitivity, and regulate the brain-gut axis to achieve IBS treatment.⁽⁴⁹⁾ Sishen Pill (四神丸) can inhibit the release of calcium in intestinal smooth muscle cells, improve the visceral sensitivity caused by intestinal spasm, and prevent the occurrence of diarrhea.⁽⁵⁰⁾ Dajianzhong Decoction can reduce the visceral pain of IBS rats by down-regulating the expression of SP in colon and reducing the activity of MCs.⁽⁵¹⁾

SKI3246, the ethanol extract of *Atractylodes*, dose-dependently relieves acid-induced visceral hypersensitivity, indicating that *Atractylodes japonica* might be an effective therapeutic herb for IBS.⁽⁵²⁾ The essential oil and water extract of patchouli can effectively reduce visceral hypersensitivity of rats with IBS, increase the threshold of rectal dilation pain, and effectively regulate the colon movement of rats.⁽⁵³⁾

Acupuncture can also relieve visceral hypersensitivity. EA in Tianshu (ST 25) can inhibit visceral pain in IBS rats, possibly associated with the effects on acting MCs and down-regulation of the expression of tryptase and SP proteins in colonic tissues.⁽⁵⁴⁾ EA in Shangjuxu (ST 37) and ST 25 can improve visceral hypersensitivity of IBS rats by diminishing the P2X purinoceptor 4 receptor immunoreactivity in the colon.⁽⁵⁵⁾

Regulating Intestinal Flora

Microbial factors play a key role in IBS pathophysiology and gut microbes can damage the host immune system as well as gut barrier function. Changes in the gut microbes have also been found in IBS patients.⁽⁵⁶⁾ Chinese herbal medicine can be metabolized into active metabolites through the action of gut microbes.⁽⁵⁷⁾ TXYF can affect the diversity of gut microbes and alter the relative abundance of *Akkermansia* and *Clostridium* in gut flora populations.⁽⁵⁸⁾ *Lactobacillus* is a commonly found bacterial community in the gastrointestinal tract. It can enhance

the intestinal barrier by preventing cell growth and has a regulatory effect on intestinal immune function. Research has shown that compared to a blank control group, significant changes in the *Lactobacillus* population were observed in the group after treatment with SLBZP, suggesting that SLBZP has an effect on the regulation of *Lactobacillus*.⁽⁵⁹⁾ In many Chinese herbs, such as *Atractylodes*, polysaccharides can be partially hydrolyzed into monosaccharides, which act as prebiotics to promote the growth of probiotics in the intestine, restore the homeostasis of intestinal flora, and then improve intestinal function.⁽⁶⁰⁾

After treatment with EA, the intestinal diversity of IBS patients increased, the imbalance of bacterial flora improved, and the ratio of *Firmicutes* to *Bacteroidetes* decreased. The improvement of symptoms in patients was correlated with the change in the relative richness of bacterial flora.⁽⁶¹⁾ Zhu, et al⁽⁶²⁾ found that IBS model rats had a higher abundance of *Prevotella*, *Bacteroides*, and *Clostridium XI* and a lower abundance of *Lactobacillus* and *Clostridium XIVa* compared with normal rats. These changes in microbiota profiles can be reversed by moxibustion treatment. The regulation of gut microbes may be a crucial mechanism for the treatment of IBS by moxibustion. Moxibustion can also increase the relative DNA abundance of *Lactobacillus*, *Faecalibacterium prausnitzii*, and *Bifidobacterium* and decrease *Escherichia coli* in the gut of IBS rats.⁽⁶³⁾

Regulating Immune System

The activation of the immune system is deeply involved in IBS.⁽⁶⁴⁾ SLBZP can significantly reduce the total symptom scores, decrease the peripheral blood cluster of differentiation 8 (CD8⁺) levels, and increase the CD3⁺ and CD4⁺ levels in IBS-D patients. These findings suggest that changes in the T-lymphocyte subsets and the ratio of these factors may be the mechanism for the therapeutic effect of SLBSP on IBS-D patients.⁽⁶⁵⁾ Tan, et al⁽⁶⁶⁾ suggested that FZLZD can regulate the expression of CD4⁺, and CD8⁺ and the number of MCs in the intestinal mucosa of IBS-D model rats, reduce the release of intestinal inflammatory substances, improve intestinal immune function, maintain immune homeostasis, and achieve a therapeutic effect. SNP can improve the level of T lymphocyte subsets and increase the levels of CD3⁺ T cells and CD4⁺ T cells in IBS-D patients to alleviate IBS.^(67,68)

EA can decrease the expression of toll-like receptor 4 (TLR4) mRNA, the protein expression of TLR4 and MC tryptase, and the number of MCs with degranulation in the colonic tissue.⁽⁶⁹⁾ Moxibustion can significantly increase the T8⁺ cells in peripheral blood and correct abnormal T4⁺/T8⁺ cell ratios, indicating that moxibustion can correct abnormal immune dysfunction in IBS.⁽⁷⁰⁾

Regulating Inflammatory Factors

The pathogenesis of IBS is often accompanied by mild inflammation. Therefore, the treatment of IBS can be improved to a certain extent by regulating inflammatory factors. Guo, et al⁽⁷¹⁾ found that TXFYF can significantly reduce the expression of p38 mitogen activated protein kinase (MAPK) mRNA in colon tissues, reduce p38 MAPK, cAMP response element-binding proteins, and serum IL-1, IL-6 and TNF- α levels, and increase the level of serum SOD. This suggests that the therapeutic mechanism of TXFYF in IBS-D might be related to the improvement of the body's anti-oxidative stress, inhibition of p38 MAPK signaling pathway, and regulation of its downstream inflammatory factors. Luo, et al⁽⁷²⁾ found that FZLZD can modify the clinical symptoms of IBS-D patients, reduce the levels of TNF- α , IL-6, and IL-8 in the serum, and inhibit the inflammatory response. BXXXD affects IBS mainly through inhibiting the inflammatory reaction, maintaining intestinal function, and improving psychological regulation. It can also influence the levels of gut hormones and regulate the hypothalamic pituitary adrenal axis, thereby alleviating gastrointestinal symptoms.^(73,74) SNP can reduce the protein expression of c-Fos in different brain regions in IBS rats and interfere with the regulation of brain and intestinal axis disorders.⁽⁷⁵⁾ Wumei Pill can decrease the levels of serum IL-2, IFN- γ and NPY, and increase the expression of serum IL-10 in IBS-D patients.⁽⁷⁶⁾ In addition, essential oil of *Rhizoma Atractylodis Macrocephalae* can reduce inflammation and protect against intestinal barrier damage via the myosin light chain kinase (MLCK) pathway.⁽⁷⁷⁾

Conclusions

CM prescriptions, acupuncture and moxibustion are the main methods of CM treatment of IBS. The treatment mechanism of CM for IBS centers on the regulation of the enteric nervous system, the alleviation of visceral hypersensitivity, the maintenance of intestinal microbiological stability, the

regulation of the immune system, and the inhibition of inflammatory response.

Treatment of IBS with CM is still regarded as an alternative therapy to Western medicine. However, with in-depth research on CM and the discovery of its therapeutic advantages, CM treatment of IBS has gained broader recognition and support. Current studies on the mechanism of CM in the treatment of IBS have focused on prescriptions and acupuncture, while researches on single herbs and their ingredients in the treatment of IBS are relatively few. Due to the complex ingredients used in CM and the characteristics of multiple targets in the treatment of IBS, the mechanism still needs to be further explored. To sum up, the correct application of CM for the treatment of IBS requires not only an understanding of CM theory and CM diagnosis, but also the exploration of CM treatment based on modern research.

Conflict of Interest

The authors declare no competing financial interests or personal relationships that could influence the work reported in this paper.

Author Contributions

Chen GR was responsible for conducting the work and wrote the main manuscript text. Xie XF was responsible for the analysis of articles. Peng C was coordinating professor of the project and wrote the main manuscript text.

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