

## HARMONY IN SIGNALING: TRADITIONAL CHINESE MEDICINE'S ROLE IN MODULATING PATHWAYS IN IRRITABLE BOWEL SYNDROME

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### **Abstract:**

*Irritable bowel syndrome (IBS), characterized by recurrent abdominal pain and gastrointestinal symptoms, remains a challenging functional bowel disorder with unclear specific pathogenesis. Visceral hypersensitivity, abnormal brain-gut axis interaction, and low-grade intestinal inflammation are believed to contribute to IBS. Clinical interventions include dietary adjustments, exercise, symptomatic drugs, and psychological therapies, but standardized approaches are lacking, leading to variable treatment outcomes and frequent relapses. Traditional Chinese Medicine (TCM) offers a multifaceted approach to IBS treatment, improving patient symptoms and quality of life through diverse pathways and multi-target strategies. Yet, there is a scarcity of comprehensive literature summarizing the signaling pathways influenced by TCM from an IBS pathogenesis perspective. To address this gap, this review provides an overview of the signaling pathways related to IBS that are modulated by TCM.*

**Keywords:** Irritable bowel syndrome (IBS), Traditional Chinese Medicine (TCM), Signaling pathways, gastrointestinal symptoms, Pathogenesis

### **Introduction**

Irritable bowel syndrome (IBS) is a functional bowel disease with recurrent abdominal pain, abnormal defecation or change in bowel habit as the main symptom, or with gastrointestinal symptoms such as abdominal bloating and gastrointestinal gas<sup>[1]</sup>. Currently, it is believed that the main pathogenesis of IBS is visceral hypersensitivity, abnormal brain-gut axis interaction, and low-grade inflammation of the intestinal tract, but its specific pathogenesis has not yet been clarified. Clinically, IBS is mainly intervened by diet, exercise, symptomatic therapeutic drugs and psychological interventions, but there is no uniform standard, and the overall treatment effect is fair but easy to relapse. Therefore, research and clarification of the pathways of IBS can help guide clinical diagnosis and treatment. The pathways of TCM in treating IBS are numerous, and it can improve the symptoms and quality of life of patients through multi-pathway and multi-targeted treatment of IBS. However, there are fewer articles summarizing the signaling pathways related to IBS regulated by TCM with the pathogenesis of IBS as the starting point, therefore, this review summarizes the signaling pathways of IBS regulated by TCM.

### **1. Chinese medicine intervention in IBS-related signaling pathways**

#### **1.1 Toll-like receptor 4/nuclear factor $\kappa$ B signaling pathway**

Toll-like receptor 4 (TLR4)/nuclear factor  $\kappa$ B (NF- $\kappa$ B) signaling pathway regulates the transcription of inflammation-related genes and is at the centre of immune regulation<sup>[2]</sup>. Toll-like receptor not only binds specifically to the  $\kappa$ B sequence of Ig protein genes to regulate T and B cell maturation and activation, but also regulates the transcription of inflammatory factors and cytokines, and participates in various inflammatory processes patients' intestinal mucosal biopsies showed low inflammatory responses, while TLR4/NF- $\kappa$ B signaling pathways were found in IBS patients. and activation, but also regulates the transcription of inflammatory factors and cytokines, and participates in various inflammatory processes. Intestinal mucosal biopsies of IBS patients show low inflammatory responses, and the TLR4/NF- $\kappa$ B signaling pathway can disrupt the balance between pro-inflammatory and anti-

inflammatory factors, thus affecting the prognosis of IBS<sup>[3]</sup>. The TLR4/NF- $\kappa$ B signaling pathway is involved not only in intestinal inflammatory responses but also in IBS visceral hypersensitivity.

Chu Haoran<sup>[4]</sup> and others demonstrated that moxibustion of "Tianshu" and "Shangjuxu" can effectively reduce the inflammatory response of rat colon mucosa. Zhao et al.<sup>[5]</sup> showed that Qinghua antidiarrheal formula could inhibit the TLR4/NF- $\kappa$ B signaling pathway, thus maintaining the balance between pro-inflammatory and anti-inflammatory factors. Wu Jing<sup>[6]</sup> et al. showed that Dajianzhong Tang could inhibit key molecules such as substance P (SP), TLR4, and NF- $\kappa$ B (p65), and then achieve the purpose of analgesic effect on visceral pain rats in IBS model.

### **1.2 5-hydroxytryptamine signaling pathway**

5-Hydroxytryptamine (5-HT) is a brain-gut peptide synthesised and released by enteroendocrine cells in the gastrointestinal mucosa, which can affect gastrointestinal motility and visceral sensitivity by regulating gastrointestinal motility and secretion<sup>[7]</sup>. It has been shown that the pain threshold for rectal dilatation is significantly lower in IBS patients compared to controls<sup>[8]</sup>. The development of psycho-gastroenterology has led researchers to recognise brain-gut axis dysfunction as one of the major pathogenic mechanisms of IBS<sup>[9]</sup>, with the involvement of 5-HT as a neuromodulatory peptide that controls brain-gut axis neurotransmission.

Zhang Wei<sup>[10]</sup> et al. found that the addition and subtraction of the elicitor drug Fang Feng from the Essentials of Painful Diarrhoea Formula could improve visceral pain sensitivity in rats. This experiment also proved that Fangfeng also has the effect of enhancing the regulation of 5-HT signaling pathway by the Essentials of Pain and Diarrhoea formula. An intestinal soup can regulate the visceral hypersensitivity of IBS-D patients by decreasing 5-HT in the serum of patients and achieve the relief of abdominal pain and diarrhoea in patients<sup>[11]</sup>. Liang Ruifeng et al.<sup>[12]</sup> found that Painful Diarrhoea Essentials can improve the symptoms of IBS rats by regulating the content of brain-gut peptides, such as 5-HT and SP, in different target points of the brain-gut axis. Warm stomach and intestinal regulating granules can down-regulate the expression of brain and intestinal peptides (5-HT, SP) in the hypothalamus and intestinal mucosa, and regulate the balance of brain-intestinal interactions, thus improving the gastrointestinal peristaltic disorders and sensory abnormalities<sup>[13]</sup>.

### **1.3 Transient receptor potential vanilloid 1 signaling pathway**

The transient receptor potential channel vanilloid 1 (TRPV1) acts as a homotetramer whose activation is associated with chronic inflammatory pain and peripheral neuropathy<sup>[14]</sup>. Sensitisation and up-regulation of TRPV1 sensitises afferent nerves, leading to visceral hypersensitivity<sup>[15]</sup>. When TRPV1 is sensitised, extracellular Ca<sup>2+</sup> and Na<sup>+</sup> are inwardly flowing, releasing gastrointestinal peptides such as calcitonin gene-related peptide (CGRP) and SP, leading to gastrointestinal hypersensitivity reactions<sup>[16]</sup>.

Buckwheat extract was found to inhibit the peak TRPV1 current in dorsal root neurons of the lumbosacral spinal cord in IBS rats to improve nociceptive hypersensitivity in model rats<sup>[17]</sup>. Han Yafei et al.<sup>[18]</sup> experimentally demonstrated that Painful Diarrhoea and Intestinal Formula could reduce visceral hypersensitivity in IBS rats by decreasing colonic nerve growth factor and TRPV1 protein expression. Fang Jiansong et al.<sup>[19]</sup> found that liver-sparing and spleen-strengthening formula could down-regulate the sensitization of TRPV1, thereby reducing visceral hypersensitivity, regulating gastrointestinal motility and alleviating IBS symptoms in IBS rats.

### **1.4 Mitogen-activated protein kinase signaling pathway**

The mitogen-activated protein kinase (MAPK) signaling pathway has three subfamilies: c-Jun amino-terminal kinase 1/2, extracellular signal-regulated kinase (ERK) and p38, which are involved in the mechanisms of IBS such as low-grade inflammation in the intestine and visceral hypersensitivity mechanisms of IBS development such as intestinal low-grade inflammation as well as visceral hypersensitivity p38 MAPK cascade, when activated, plays an important role in cellular responses such as inflammation, cell proliferation and differentiation, and apoptosis, which induces intestinal low-grade inflammation. ERKs are important signal transducing protein kinases and activation of ERK1/2 is particularly critical for the regulation of visceral hypersensitivity<sup>[20]</sup>. p38 MAPK signaling pathway also has an important role in gastrointestinal dyskinesia and pain perception in the body. One study has identified the MAPK/ERK signaling pathway as one of the signaling pathways involved in brain-gut interaction in IBS<sup>[21]</sup>.

Guo Junxiong et al.<sup>[22]</sup> demonstrated that the pain and diarrhoea formula could inhibit the activation of the p38 MAPK signaling pathway and reduce the inflammatory response. It was found that the combination of acupuncture Hejiao and Qiaolu Essentials could inhibit the abnormal activation of MAPK/ERK signaling pathway, significantly improve the anxiety and depression status of patients with IBS-D, and alleviate the clinical symptoms of the patients<sup>[23]</sup>. Sijunzi Tang combined with Siwei San can regulate the changes in the MAPK/ERK signaling pathway mediated by abnormal levels of brain gut peptides such as 5-HT and SP, thus improving peripheral sensitisation and central sensitisation<sup>[24]</sup>.

### **1.5 Stem cell factor/tyrosine kinase receptor signaling pathway**

The stem cell factor (SCF)/tyrosine kinase receptor (c-kit) signaling pathway, consisting of SCF and its cognate receptor c-Kit, is a major regulator of the survival and function of a wide range of neural crest-derived cells, mainly those involved in visceral sensing, smooth muscle contraction and inflammation. Alterations in the SCF/c-Kit signaling pathway lead to disturbances in the neuroendocrine-immune network, providing an explanation for the visceral hypersensitivity, abnormal intestinal contractile strength and low-grade inflammation in IBS.

Cangzhu oil may alleviate symptoms in IBS-D model rats by inhibiting SCF/c-kit signaling, thereby reducing the expression of inflammatory factors<sup>[25]</sup>. Li Hui et al.<sup>[26]</sup> found that quenching wind and transforming dampness formula could inhibit the overexpression of SCF/c-Kit signaling pathway and reduce visceral hypersensitivity in IBS rats. Rui et al.<sup>[27]</sup> showed that Painful Diarrhoea Essential Formula could improve the symptoms of diarrhoea in rats.

### **1.6 Other related signaling pathways**

#### **1.6.1 Janus kinase/signal transducer and activator of transcription signaling pathway**

The Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway is involved in many cellular processes, including cell division, cell death and regulation of immune function. JAK2/STAT3 is an important pathway that mediates apoptosis and inflammatory signal transduction in cells. JAK2/STAT3 is an important pathway mediating apoptosis and inflammatory signaling. Some studies have confirmed that the development of visceral hypersensitivity is closely related to the activation of the JAK /STAT signaling pathway<sup>[28]</sup>. Lai Lei<sup>[29]</sup> found that Painful Diarrhoea Essentials could inhibit the JAK/STAT signaling pathway involved in the intestinal inflammatory response to alleviate the visceral hypersensitivity of IBS through her study.

#### **1.6.2 Brain-derived neurotrophic factor/tyrosine kinase receptor B signaling pathway**

Brain-derived neurotrophic factor (BDNF) affects enteric nervous system development and has a nociceptive and sensitising effect. Tyrosine kinase receptor B (TrkB), a functional receptor for BDNF, plays an important role in cell signaling. Pan Xiaoou<sup>[30]</sup> et al. experimentally confirmed that dendrobine could improve the symptoms of pain and diarrhoea in IBS model mice by reducing the release of 5-HT and SP, inhibiting the expression of BDNF, and decreasing the sensitivity of viscera.

#### **1.6.3 Phosphatidylinositol 3-kinase/protein kinase B signaling pathway**

Phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) has an important role in the pathogenesis of tumours, inflammation and immune diseases. It has been found that the PI3K/AKT signaling pathway induces cellular autophagy and is involved in intestinal mucosal barrier changes<sup>[31]</sup>. Xia Li Xian et al.<sup>[32]</sup> found that Painful Diarrhoea Essentials may reduce the occurrence of cellular autophagy and restore the intestinal mucosal barrier by inhibiting the PI3K/AKT signaling pathway, thus reducing visceral hypersensitivity.

## **2. Interconnections between pathways**

The development of IBS is quite complex, and its specific pathogenesis has not been fully clarified. The above signaling pathways do not play a single role in each other, but rather interact with each other to produce a cascade response that is amplified step by step, thus affecting the biological process. Therefore, TCM can intervene in multiple signaling pathways and regulate the expression of different proteins to prevent and treat IBS.

When TLR4 is activated by stimulation, TLR4 regulates the transcription of cytokine SCF, and the SCF/ c-kit signaling pathway activates its downstream signaling pathways, such as: the JAK/ STAT signaling pathway, the MAPK signaling pathway and the PI3K pathway, which interact with each other and are involved in the formation of visceral

hypersensitivity and intestinal inflammation in IBS. In addition, SCF increases the activation of intestinal MC induced by the receptor c-Kit, which causes MC to secrete 5-HT and so on, thus leading to intestinal motility disorders and visceral hypersensitivity<sup>[33]</sup>. BDNF and TRPV1 are also closely related to 5-HT. TRPV1 regulates intestinal motility by mediating the release of 5-HT<sup>[34]</sup>. The decrease of the expression of BDNF affects the synthesis of 5-HT<sup>[35]</sup>, and the decrease of BDNF expression affects 5-HT synthesis<sup>[35]</sup>, and BDNF also affects 5-HT synthesis<sup>[35]</sup>. At the same time, BDNF also agonises the MAPK and PI3K/AKT signaling pathways, which are involved in the development of IBS.

### **3. Discussion**

In summary, Chinese medicine takes the holistic concept and evidence-based treatment as the starting point, and sums up the effective methods of treating IBS based on traditional compound prescriptions and modern prescription. The pathogenesis of IBS is the result of multifactors, and some scholars have proposed that IBS is caused by the irregular regulation of neuroimmunoendocrine network, and the traditional Chinese medicine compound prescriptions and acupuncture methods (e.g., the essential formula for pain and diarrhoea) can improve the symptoms of IBS by interfering with multiple signaling pathways, which coincides with the view that multiple mechanisms of IBS co-causes the disease.

The treatment of IBS with TCM has a broad application prospect, but there are still certain shortcomings: (1) the specific pathogenesis of IBS has not been fully elucidated at this stage, and the research on the intervention of TCM in the signaling pathway of IBS is relatively weak, and the role of various pathways in the pathogenesis of IBS and the interrelationships among various pathways still need to be further investigated; (2) in the replication of the model of IBS, there are fewer TCM evidence types, and the modelling methods used for different TCM evidence types are the same or similar, which may lead to confusion of the evidence; (3) in the study on the mechanism of TCM treatment of IBS, there is a great deal of potential for application. (2) During the replication process of IBS model, fewer Chinese medicine types are involved, and the modelling methods used for different Chinese medicine types are the same or similar, which may easily cause confusion of symptoms; (3) In the research on the mechanism of Chinese medicine in treating IBS, most of them focus on the study of a single protein of the signaling pathway, neglecting the study of other functional proteins affecting the signaling pathway; (4) Currently, Chinese medicine treatments are mostly for one person on one side, which has a strong targeting, and large-scale clinical applications need to be promoted by large samples. If a large-scale clinical application is to be promoted, a large sample of control studies is needed. In conclusion, there is still much room for the development of TCM in the treatment of IBS through the regulation of signaling pathways, and it is necessary to combine TCM with modern science and technology to continuously explore and provide strong objective evidence for the treatment of IBS with TCM.

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