

# Progress of research on the mechanism of action of Chinese medicine for functional constipation based on intestinal flora

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**Abstract:** Functional constipation is a common clinical non-organic disease, and long-term constipation, if not effectively treated, can bring many negative effects to patients. In recent years, intestinal flora has been a hot topic in the treatment of constipation. Dysbiosis of the intestinal flora can promote the onset and development of chronic functional constipation through a series of pathways. Therefore, based on the several mechanisms of constipation caused by intestinal flora, this paper discusses some research results and progresses in the treatment of constipation by Chinese medicine, and systematically summarizes that Chinese medicine may play a role in the treatment of functional constipation by regulating the ratio and quantity of flora, participating in the metabolic transformation of flora, protecting the intestinal mucosal barrier and influencing the expression of neurotransmitters related to the brain-intestinal bacterial axis. The aim is to establish a systematic theoretical basis for the diagnosis and treatment of constipation by Chinese medicine through influencing intestinal flora, and to provide a new treatment idea for constipation by Chinese medicine.

**Keywords:** intestinal flora; cerebral enterobacterial axis; intestinal mucosa; metabolism; traditional Chinese medicine

## 1. Introduction

Nowadays, the prevalence of constipation is on the rise, and its development is related to a variety of factors, such as social factors, dietary structure, medication or psychological factors. Constipation not only causes discomfort in defecation, but also contributes to some common anorectal diseases such as anal fissure and hemorrhoids, and for patients with underlying diseases such as hypertension and heart disease, it can also aggravate these diseases, posing a great threat to the physical and mental health of patients<sup>[1]</sup>. Currently, Western medicine mainly uses laxatives to treat constipation, but laxatives cannot be applied for a long time, and they not only produce dependence on constipated patients, but also may cause adverse effects such as blackening of the large intestine<sup>[2]</sup>. It has been reported that constipation persists in 20-40% of patients after appropriate application of modern medications for laxatives<sup>[3]</sup>. With the continuous research of many scholars on the diagnosis and treatment of functional constipation, it has been found that compared with Western medicine, the treatment of constipation with Chinese herbal medicine has shown the unique advantages of low cost, safety and cost-effectiveness<sup>[4]</sup>. Long-term application is possible. It has been shown that dysbiosis of the intestinal flora is an important part of the pathogenesis of functional constipation<sup>[5]</sup>. Therefore, the author explores several possible mechanisms of action of TCM in the treatment of constipation from the perspective of the development mechanism of intestinal flora affecting functional constipation, in order to provide a new perspective and reference basis for TCM treatment of constipation.

## 2. Intestinal flora

The total number of microorganisms in the human gut is about  $10^{14}$ , with more than 1000 species, which is about 10 times the total number of cells in the human body<sup>[6]</sup>. These microorganisms reside in the human intestinal tract and have different influences and effects on the functional state of the human gut. These microbial communities can be divided into beneficial and pathogenic bacteria according to their role in the human body. Beneficial bacteria are the dominant species in the human intestine, mostly specialized anaerobic bacteria, which can maintain the balance of intestinal ecology and promote nutrient absorption in the intestine by regulating the human immune system. The main beneficial bacteria in the human body are Lactobacillus, Bifidobacterium, Bacillus, etc. Pathogenic

bacteria are mostly parthenogenic aerobic bacteria with a small proportion in the intestinal flora, which can have pathogenic effects on the body under certain conditions. When the normal ecological balance is disrupted, the number of dominant bacteria in the body decreases, and the immune function of the body decreases, pathogenic bacteria will invade the body and break the normal ecological balance of the intestine, inducing corresponding diseases of the intestine, such as constipation, ulcerative colitis, etc. Therefore, maintaining the ecological balance of intestinal colonies plays an important role in the prevention and treatment of diseases, especially in the prevention and treatment of intestinal-related diseases.

### **3. Intestinal flora and constipation**

#### ***3.1 Imbalanced flora structure contributes to constipation***

Patients with constipation have an imbalance of intestinal flora, which is mainly reflected in the decrease of the dominant species and the increase of pathogenic species in the intestine<sup>[7]</sup>. The dominant bacteria play a role in promoting defecation mainly through their production of related metabolites that alter the intestinal environment. For example, lactobacilli acidify the intestine by producing metabolites, including short-chain fatty acids, which lower the pH value in the intestine<sup>[8]</sup>, this promotes intestinal motility and reduces the time of fecal transit through the colon to relieve constipation. Bifidobacterium bifidum metabolites contain multiple types of organic acids<sup>[9]</sup>, mainly acetic acid, lactic acid and formic acid. These acidic metabolites can facilitate the excretion of feces by stimulating the human intestinal wall and promoting intestinal peristalsis. At the same time, the increase in organic acid content can also increase the osmotic pressure in the intestine, allowing water to enter the high osmotic pressure area of the intestine from the low osmotic pressure area, increasing the water content of the stool and thus producing a laxative effect<sup>[10]</sup>. The pathogenic bacteria will accelerate the absorption of these beneficial metabolites, inhibit intestinal motility and promote constipation. For example, the production of methanogenic bacteria increases the absorption of short-chain fatty acids in humans<sup>[11]</sup>. This prevents it from performing its function of promoting bowel movement and produces constipation. Therefore, when the structural ratio between the dominant and pathogenic bacteria in the intestine is imbalanced, the metabolites produced by the relevant dominant bacteria will be reduced, and the intestinal environment will not become an effective channel conducive to defecation, and intestinal peristalsis will slow down, thus leading to constipation.

#### ***3.2 Flora imbalance affects brain enterobacterial axis neurotransmitter levels***

The "brain-gut axis" refers to the bi-directional pathway between the enteric nerve and the central nervous system, which involve neurological and immune regulation<sup>[12]</sup>. The change of intestinal flora can affect the change of gastrointestinal function and brain nervous system through neural, immune and endocrine pathways, based on the interactive regulatory relationship with the brain-intestinal axis of intestinal flora, there is a new concept, namely "brain-intestinal axis". Brain and intestinal peptides are regarded as important targets of the brain and intestinal axis, and have a very important role in the regulation of gastrointestinal function<sup>[13]</sup>. Brain intestinal peptides mainly include 5-hydroxytryptamine (5-HT), substance P (SP), nitric oxide (NO), vasoactive intestinal peptide (VIP)<sup>[14]</sup>, etc. These substances mainly have a regulatory effect on the functional state of the gastrointestinal tract and can promote peristalsis by contracting the smooth muscles of the gastrointestinal tract. In recent years, the correlation between constipation and neurotransmitters based on flora imbalance has been more studied in 5-HT. 5-HT signaling pathway has been reported as a key factor in the pathogenesis of chronic constipation<sup>[15]</sup>. The neurotransmitter 5-HT is an important cholinergic transmitter secreted and synthesized by chromophores of the intestinal mucosa<sup>[16]</sup>. It can promote intestinal motility by increasing intestinal osmotic pressure and increasing intestinal water content. SERT is a transmembrane transporter protein<sup>[17]</sup>. It has a strong affinity for 5-HT. It can take up and inactivate the excessive accumulation as well as physiologically effective 5-HT substances in mucosal or neuronal synapses and is involved in mediating gastrointestinal motility. In recent years, it has been shown that imbalance of intestinal flora can affect the synthesis of the brain intestinal peptide 5-HT or SERT levels, thus causing intestinal malfunction and inducing constipation. Yano, J. M. et al<sup>[18]</sup>. found that *Clostridium perfringens* could affect 5-HT synthesis and intestinal motility through the production of soluble metabolites. By establishing an intestinal flora depletion model and transplanting mice with intestinal flora from different populations, Liu<sup>[19]</sup> found that SERT expression in the colonic tissues of mice increased due to intestinal flora dysbiosis and reduced 5-HT expression in intestinal tissues, thus

suggesting that the pathogenesis of constipation may be related to intestinal flora dysbiosis upregulating SERT levels. The above study shows that brain intestinal peptide substances and intestinal motility are closely related, among which 5-HT is a key factor in the pathogenesis of constipation patients, and SERT level can affect 5-HT expression and play its physiological role, so constipated patients can produce flora metabolites due to intestinal flora imbalance to affect 5-HT synthesis or SERT level, which in turn affects the peristaltic function of the gastrointestinal tract, slowing down the speed of defecation and eventually leading to constipation.

### ***3.3 Dysbiosis destroys the intestinal barrier***

Imbalance of intestinal flora can lead to dysregulation of the intestinal microecological environment, causing certain disturbances in the reception and transmission functions of intestinal epithelial cells and possible dysregulation of the immune response, resulting in a lack of essential micronutrients (such as short-chain fatty acids) and redox potential in the intestinal mucosa, leading to increased permeability of the intestinal mucosa and damage to the intestinal mucosal barrier. In addition, it leads to a dramatic increase in intestinal pathogenic bacteria and the release of a large number of toxins that affect the normal structure and function of the intestinal barrier, leading to enterogenic endotoxemia and promoting the occurrence of various metabolic syndromes. Long-term constipation will aggravate the dysbiosis of intestinal flora and make the protective effect of intestinal mucosa weaken or disappear, thus forming a vicious cycle of constipation - flora imbalance - barrier destruction - constipation. Therefore, the restoration of intestinal flora in homeostasis is important for the treatment of constipation and the prevention of intestinal mucosal damage and other diseases caused by constipation.

## **4. Chinese medicine and intestinal flora**

In recent years, more and more TCM studies have begun to focus on intestinal flora. Providing new perspectives and strategies for understanding and applying TCM in the treatment of constipation. Chinese herbal medicines have an effect on normal flora in the body, which can have a positive effect on the healing of diseased tissues, and they can also regulate and enhance human immune<sup>[20]</sup>. The dynamic and balanced relationship of intestinal flora is also connected with many ideas of Chinese medicine. In his elaboration of the relationship between TCM and intestinal microecology, Liu Feng<sup>[21]</sup> believes that the holistic concept of "Heaven and man correspond to each other" is actually consistent with microecology, so TCM treatment of intestinal diseases should also start from the overall structure to understand and adjust the flora. Liu Weihong<sup>[22]</sup> pointed out that the proliferation of intestinal colonies can be regarded as Yang, autolysis as Yin, Yin and Yang, reflecting the microscopic Yin-Yang balance of intestinal colonies. The spleen is the basis of the latter, and it is an important source of nutrition to maintain the ecological balance of the intestinal tract. The lung and the large intestine are adjacent to each other, and the heat evidence of the lung is usually accompanied by the manifestation of constipation, so modern doctors mostly treat from the internal organs, and regulate the intestinal flora by strengthening the spleen and treating the lung to treat intestinal related diseases. Lu Lin's study<sup>[23]</sup> found that bifidobacteria were reduced in the stool of patients with spleen deficiency diarrhea, and the use of spleen strengthening herbs can directly promote the increase of bifidobacteria. In clinical practice, most of the tonic herbal medicines or compound prescriptions are used to maintain the balance of intestinal flora, mainly by adjusting the number and structure of flora, i.e., replenishing beneficial bacteria and reducing harmful bacteria, to achieve the purpose of "supporting the positive and eliminating the evil" in Chinese medicine. Studies have reported that the polysaccharide of *Radix Codonopsis* can accelerate the proliferation of bifidobacteria and inhibit the physiological activities of pathogenic microorganisms such as *Escherichia coli* and *Staphylococcus aureus*<sup>[24]</sup>. Thus, the clinical application of Chinese medicine for the treatment of constipation can completely start from the adjustment of intestinal flora, through a series of ways to regulate the intestinal microecological balance to achieve the role of treatment of disease. Several mechanisms of the role of traditional Chinese medicine on intestinal flora are summarized below, in order to provide new ideas for the use of traditional Chinese medicine in the treatment of constipation.

### ***4.1 Regulation of the ratio and number of intestinal flora***

Different types of bacteria form a specific number and ratio in the intestine, which together maintain the stability of the intestinal microecological environment. In patients with constipation, due

to poor living habits and changes in dietary structure, the intestinal flora will be imbalanced, mainly in the form of changes in the proportion and quantity of the floral structure, which in turn will aggravate constipation. Most studies have shown that the change of intestinal flora in patients with constipation is mainly based on the relative decrease of bifidobacteria, lactobacilli and other dominant flora and the relative increase of *Clostridium perfringens* and other potentially pathogenic bacteria<sup>[25]</sup>. A variety of single herbs, herbal compound and herbal preparations have been found to significantly improve the ratio and number of intestinal flora in patients, increasing the number of dominant bacteria and reducing the number of pathogenic bacteria in the intestine, and restoring the normal micro-ecological balance of the intestine. Xu et al<sup>[26]</sup>. Found that *Astragalus* significantly increased the abundance of dominant species such as *Clostridium* and *Bifidobacterium* and improved the dysbiosis of the intestinal microbiota ratio, thus optimizing the intestinal microecological environment. Shi Xuekui et al<sup>[27]</sup>. Used antibiotics to cause intestinal flora dysbiosis in mice given aqueous decoction of *Huang Lian* and found that the number of *Lactobacillus* and *Bifidobacterium* appeared to increase and could be restored to normal levels. Some studies have shown that both *Da Cheng Qi* punch and *Da Huang* have some inhibitory effect on clinical pathogenic bacteria, and *Da Cheng Qi Tang* can increase the number of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* and reduce the number of Gram-negative bacilli in the intestinal tract<sup>[28]</sup>. Its monarch rhubarb can also optimize the intestinal micro-ecological environment, and has a regulatory effect on improving intestinal flora dysbiosis. Liu Yuting's experiments<sup>[29]</sup> showed that ginseng and lingzan could promote the proliferation of dominant intestinal bacteria in mice and inhibit the growth of *Escherichia coli*, which had a significant positive regulatory effect on intestinal flora dysbiosis. It can be seen that Chinese herbal medicines, herbal extracts and formulas can prevent and treat diseases by regulating the ratio of flora, increasing the number of beneficial bacteria and decreasing the number of harmful bacteria.

#### ***4.2 Involvement in metabolic transformation of bacterial flora***

In recent years, the metabolic relationship between Chinese medicine and flora has attracted attention. The human body lacks enzymes to hydrolyze polysaccharides, and there is a certain polarity after entering the intestine, so Chinese medicine is not easily absorbed by the human body in the intestine, and the intestinal flora encodes a variety of enzymes that can promote the catalytic reaction of Chinese medicine, which is more conducive to be absorbed by the human body<sup>[30]</sup>. Five major classes of herbal components have been found to affect intestinal flora and interact with intestinal flora to promote their absorption and utilization in the human gut, including flavonoids, glycosides, alkaloids, phenylpropanoids and organic acids<sup>[31]</sup>. Most of the glycosylated flavonoids reach the colon and are broken down into phenolic acids or other metabolites, which can be absorbed by the body in the presence of colonic microflora. Therefore, the flavonoids present in the colon have a regulatory effect on the intestinal flora. Glucosides are water-soluble sugar, which is not easily digested and absorbed by the intestine and is not highly bioavailable. They can be decomposed by the flora into glycosides with high bioavailability after a long stay in the intestine and exert certain pharmacological effects on the intestine. Alkaloids are nitrogenous organic compounds from the biological world, which can be promoted by intestinal flora to undergo hydrolysis or dehydration reactions. Phenylpropanoids can produce lactone hydrolysis or demethylation in the presence of intestinal flora. Small amounts of organic acids are absorbed as prototypes in the stomach and small intestine and then hydrolyzed by the action of esterases in the intestinal mucosa and intestinal flora. The production of organic acids is associated with *Clostridium perfringens*, *Lactobacillus*. *Lactobacillus* can promote intestinal peristalsis and inhibit the reproduction of harmful bacteria, which has a better regulation of the intestinal microecological environment. Therefore, these herbal ingredients can play a role in regulating the intestinal function through metabolic transformation with intestinal flora. In addition, some scholars have also studied some Chinese herbal compounds and found that their flora regulating effects on constipation patients are also accomplished by participating in the metabolic transformation of flora. He Lu's experiments<sup>[32]</sup> showed that *Si Mo Tang* could effectively improve the metabolism of energy and nutrients by intestinal flora and increase the replication and transcription of genetic information, thus alleviating the symptoms of spleen deficiency and constipation in mice. Liu Deliang<sup>[33]</sup> used the KEGG database to identify the relationship between metabolic function and host metabolites, and concluded that the level of carbohydrate metabolism was elevated after constipation, and the body produced more energy through carbohydrate intake, and the level of glucose metabolism decreased to near normal after the liquid-boosting soup intervention. It is suggested that the liquid-boosting soup may play a therapeutic role by regulating carbohydrate metabolism. The above study indicates that Chinese herbal medicine affects the composition and metabolism of intestinal flora, and intestinal flora can also participate in the metabolic transformation of Chinese herbal medicine, and the two interact to

influence each other, thus achieving the effect of treating diseases.

#### **4.3 Protection of the intestinal mucosal barrier**

The intestinal mucosal barrier consists of chemical, microbial, physical and immune barriers, which effectively prevent harmful substances and pathogenic microorganisms from invading the intestine and are the first gate for the intestine to maintain a healthy state. Dysbiosis of intestinal flora is an important cause of intestinal mucosa damage. Studies have shown that dysbiosis is often accompanied by a series of pathological changes such as decreased expression of tight junction proteins, increased permeability of intestinal mucosa and destruction of intestinal mucosal tissue<sup>[34]</sup>. Chinese medicine can regulate the intestinal mucosal barrier by regulating the intestinal flora and thus play a role in protecting the intestinal mucosal barrier. At the present stage, a variety of single herbs, herbal compounds and herbal preparations have been found to have significant protective effects on the intestinal mucosal barrier<sup>[35]</sup>. Qiu Bangdong et al<sup>[36]</sup>. Found that turtle shell decoction pill could improve intestinal flora disorders in model rats by decreasing intestinal permeability and increasing intestinal tight junction protein expression. In addition to inhibiting the proliferation and multiplication of pathogenic bacteria, probiotics can also colonize the mucosal surface of the digestive tract to form a biological barrier, thus preventing the invasion of pathogenic bacteria<sup>[37]</sup>. The clinical use of fresh raw ground increases the number of intestinal probiotics and also protects the structural integrity of the intestinal mucosa<sup>[38]</sup>. Zeng Hongliang et al<sup>[39]</sup>. Found that the compound formula Cangjiao Fang could not only protect the intestinal mucosal barrier and improve intestinal microcirculation, but also promote the gastrointestinal motility function. The above research shows that traditional Chinese medicine and Chinese medicine compound can improve intestinal microcirculation, reduce intestinal permeability and increase intestinal tight junction protein expression by adjusting intestinal flora structure and increasing the number of probiotic bacteria, thus playing the role of protecting intestinal mucosal barrier.

#### **4.4 Affects neurotransmitters associated with the brain-brain-enterobacterial axis**

The involvement of gut microorganisms in the treatment of gastrointestinal diseases has also been extensively studied, and a series of interactions between the gut flora and the brain-gut axis, or the "brain-gut axis", has occurred. They have a regulatory effect on gastrointestinal function. Modern research has shown that some herbal medicines can exert therapeutic effects on gastrointestinal diseases by affecting these neurotransmitters in the brain-intestinal bacterium axis. In a study related to herbal treatment of IBS patients, Gong Linzheng<sup>[40]</sup> found that tonifying Zhong Yi Qi Tang could improve the treatment outcome of IBS patients by upregulating neurotransmitter levels such as 5-hydroxytryptamine (5-HT) in the body<sup>[41]</sup> and restoring the normal movement of intestinal nerves under the regulation of neurohumoral factors. An Rong<sup>[42]</sup> found that the painful diarrhea formula can reduce the synthesis and absorption of 5-HT by increasing the intestinal flora of TRPA in rats with irritable bowel syndrome, and its action on the central nervous system can improve the depression of patients, and its action on the gastrointestinal tissues can reduce intestinal sensitivity and abdominal pain symptoms. Modern pharmacological studies have shown that Jichuan Decoction and its dismantled formula Ming can significantly increase the content of small intestinal tissue and substance P (SP) and gastric motility (MTL) and decrease the level of growth inhibitor (SS) in aged mice<sup>[43]</sup>. This promotes intestinal motility, and its mechanism of action is associated with increased levels of serum SP substances. By increasing the expression of nitric oxide synthase (NOS), Yi Qi Kai Secret formula can promote the release of NO, exert the protective effect of NO on Cajal cells, and promote colon propulsion by upregulating VIP, which can effectively relieve the constipation symptoms of patients<sup>[44]</sup>. The above studies have shown that herbal medicine can play a role in improving constipation by upregulating 5-HT levels in the brain-intestinal bacterium axis, promoting NO release, and increasing the levels of VIP substances and SP substances.

### **5. Summary**

Intestinal diseases are very closely related to the host, and in recent years, many scholars have started to study the mechanisms of various diseases caused by intestinal flora disorders in order to find better treatments for the diseases. Chinese medicine has the advantages of low adverse effects, low dependence, and safety and economy, but its specific mechanism regarding the treatment of constipation is still unclear. This paper explores several possible mechanisms for the treatment of

constipation with Chinese herbal medicine based on intestinal flora, providing a new perspective and theoretical basis for the study of constipation with Chinese herbal medicine, but there are few relevant studies in this field, the available literature is insufficient, and the sample size of experimental data is small. However, there are few studies in this field, insufficient literature available, and small sample size of trial data, and further in-depth studies are needed to establish a more systematic and evidence-based basis for the treatment of constipation in Chinese medicine, which will bring better diagnostic and therapeutic efficacy and promote the dissemination and application of Chinese medicine in the world.

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