

# Research Progress on the Mechanisms of Functional Constipation

Dan Xu<sup>1,a</sup>, Hua Jiang<sup>1,\*</sup>, Mengfei Kuang<sup>1,b</sup>, Ya Liu<sup>1,c</sup>

<sup>1</sup>Shaanxi University of Chinese Medicine, Xi'an, China

<sup>a</sup>xudan16397@163.com, <sup>b</sup>1027547369@qq.com, <sup>c</sup>460092726@qq.com

\*Corresponding author: jhsd2004@163.com

**Abstract:** Functional constipation (FC) is a prevalent digestive disorder that significantly affects the physical and mental health of individuals. While short-term efficacy of pharmacological treatments for FC is satisfactory, long-term outcomes are often suboptimal, with notable adverse reactions, high relapse rates upon discontinuation, and potential development of drug dependence. The underlying mechanisms of FC remain unclear, and modern medicine has proposed various theories regarding its pathogenesis. Current understanding suggests that FC is primarily associated with colonic motility disorders, weakened pelvic floor muscle function, abnormal mucosal immune regulation, dysbiosis of the gut microbiota, and dysregulation of the brain-gut axis. Unraveling the mechanisms contributing to FC has significant implications for developing more effective therapeutic medications, alleviating the economic and psychological burdens on patients, and enhancing their overall quality of life.

**Keywords:** Functional constipation, mechanisms, treatment, research progress

## 1. Introduction

Functional constipation (FC) refers to chronic constipation without organic causes, structural abnormalities, or metabolic disorders, excluding irritable bowel syndrome [1]. Clinical manifestations of FC include hard stools, difficulty in defecation, feeling of incomplete evacuation, and reduced frequency of bowel movements. According to the Rome III diagnostic criteria for FC, the symptoms should persist for at least 6 months [2]. Pathophysiologically, FC can be classified into subtypes, including slow transit constipation, defecatory disorders, mixed constipation, and normal transit constipation [3]. Epidemiological surveys and retrospective studies have shown that the prevalence of constipation is 18.1% in the elderly and 18.8% in children, significantly higher than the general population's prevalence of 8.2%. The rural population has a constipation rate of 7.2%, significantly higher than the 6.7% in urban areas [4]. Prolonged constipation can lead to an array of anorectal disorders such as anal fissures, hemorrhoids, and rectal prolapse. It can also cause depression, anxiety, cardiovascular disease, and even life-threatening complications, severely affecting people's quality of life and overall health [5].

## 2. Understanding and Treatment of Functional Constipation in Traditional Chinese Medicine

Functional constipation falls under the category of "constipation" in Traditional Chinese Medicine (TCM) and is documented as "difficult passage of stools" and "obstruction of bowel movements" in the earliest TCM text, the Huangdi Neijing (Yellow Emperor's Inner Canon) [6]. Other ancient texts describe it as "spleen constraint," "retention and constriction," and "blockage and obstruction". The etiological factors contributing to this condition include diet, emotions, age, and external pathogens [7][8]. The pathogenesis of constipation is primarily attributed to heat accumulation, qi stagnation, cold coagulation, blood stasis, and constitutional deficiency, which lead to impaired intestinal transmission. The main causes of constipation are inherent constitutional deficiencies, improper dietary habits, emotional imbalance, chronic illnesses resulting in physical weakness and reduced mobility, as well as incorrect medication use. These factors contribute to inadequate lubrication of the large intestine, impaired transmission function, and difficulty in bowel evacuation. Although the disorder primarily affects the large intestine, it has connections with the functions of all the major organs and viscera [9].

According to Traditional Chinese Medicine (TCM), constipation is primarily attributed to excessive yang in the body, accumulation of heat in the digestive system, disharmony in emotions leading to

stagnation of qi, deficiency of qi and blood, and weakness in the lower body with the emergence of yin-cold. Therefore, constipation can be classified into four types: heat-induced, qi stagnation, deficiency-related, and cold-type<sup>[10]</sup>. The pathogenesis of constipation is influenced by factors such as improper diet, emotional imbalance, aging and physical weakness, and intrusion of external pathogens. The underlying mechanisms involve heat accumulation, qi stagnation, cold coagulation, and deficiency of qi and blood leading to abnormal transmission in the large intestine. The key factor lies in the impairment of the large intestine's transmission function. In cases of constitutional yang deficiency, the inadequate warmth from yang qi fails to stimulate proper intestinal peristalsis, leading to abnormal transmission in the large intestine. Additionally, if there is obstruction from blood stasis due to an accumulation of a foreign body like a metallic or stone object, it can also lead to difficulty in bowel movements<sup>[11]</sup>. The classic text "Shang Han Za Bing Lun" (Treatise on Cold Damage and Miscellaneous Diseases) documents various treatment methods for constipation, including warming the lower abdomen, invigorating purgation, and moistening the intestines. It also provides relevant formulas such as Cheng Qi Tang, Ma Zi Ren Wan, and Da Chai Hu Tang. Subsequently, later generations of physicians have continuously supplemented these internal treatment methods with external therapies. These external methods include acupuncture, application of herbal patches on specific acupoints, acupoint embedding, acupoint injections, herbal enemas, massage therapy, ear acupressure, localized medication, as well as lifestyle and dietary guidance<sup>[12]</sup>.

### **2.1. Internal Therapies**

In the treatment of functional constipation, classical formulations with documented efficacy can be found in ancient medical texts. Constipation can be classified into seven types based on symptomatic presentation: (1) Heat Accumulation Type: Treated with Mahazi Ren Wan with modifications for clearing heat and moistening the intestines. (2) Yang Deficiency Type: Characterized by difficult defecation, this type is treated by warming yang and eliminating turbidity, with primary emphasis on the Jichuan Decoction. (3) Yin Deficiency Type: Managed primarily with Zengye Tang to nourish yin and moisten dryness. (4) Qi Deficiency Type: Symptoms include weak bowel movements and subtle abdominal pain. The treatment approach is to invigorate qi and fortify the spleen, with primary use of the Huangmao Decoction. (5) Qi Stagnation Type: Addressed with the Liuluo Tang formula for promoting qi flow and eliminating stagnation. (6) Blood Deficiency Type: Characterized by difficult defecation and a pallid complexion, this type is treated with the Runchang Pill to nourish blood and invigorate the intestines. (7) Cold Accumulation Type: Requiring the promotion of warmth and downward movement, the Wenpi Tang formula is employed. Common symptoms include hard, painful defecation in the lower abdomen, which temporarily improves with warmth.

### **2.2. External Therapies**

External therapeutic approaches for the treatment of constipation encompass acupuncture, massage, acupoint application, herbal enemas, as well as various other interventions such as auricular point stimulation and topical medications. Traditional Chinese medicine (TCM) practices such as acupuncture and massage offer a gentler means of rectifying visceral imbalances, promoting gastrointestinal motility, and effectively addressing constipation. (1) Acupuncture and Massage: Acupuncture and massage in TCM are employed to gently regulate visceral disharmony, stimulate peristalsis in the gastrointestinal tract, and prove effective in treating constipation. These modalities aim to correct imbalances in the body's energy flow, enhancing overall well-being and alleviating constipation. (2) Acupoint Application: Acupoint application, in the form of herbal patches, can also be employed as an effective treatment for constipation. Specific acupoints, such as the "Shenque" point, may be selected based on the guidance of a healthcare provider. This method is straightforward, easy to administer, and generally devoid of side effects, making it particularly suitable for individuals with constipation resulting from Yin deficiency or habitual constipation, which is often observed in the elderly population. (3) Herbal Enemas: Herbal enemas have a rich historical background in clinical application, dating back to the ancient Chinese medical text, the "Shang Han Lun." These enemas involve the direct introduction of herbal substances into the colon. By bypassing the digestive system, these remedies deliver therapeutic constituents directly to the affected areas, thus minimizing potential systemic side effects. Herbal enemas not only act by absorption through the colonic mucosa but also exhibit a colonic dialysis effect. Consequently, herbal enemas have demonstrated favorable outcomes in the treatment of constipation.

### 3. Understanding and treatment of functional constipation in modern medicine

In modern society, people not only have a fast pace of life but also face significant job pressures. Improper lifestyles, such as staying up late, smoking, and alcohol consumption, along with diverse dietary choices that include cold and greasy foods, can easily affect the function of the spleen and stomach, leading to constipation. The etiology of functional constipation (FC) is rather complex, and it can be categorized into primary and secondary factors. Primary factors can be attributed to functional impairments of various muscles, including the pelvic floor muscles, abdominal muscles, anal sphincter muscles, and the physiological sphincter. Rectocele is relatively common among female patients as a manifestation of primary factors. Additionally, neurological disorders and dysbiosis of the gut microbiota may also contribute as primary factors to constipation. Secondary constipation, on the other hand, is typically caused by a multitude of factors such as psychological and psychosocial elements, dietary habits, lifestyle choices, genetic predispositions, and cultural factors. There is a close association between constipation and psychological disorders. Moreover, disruptions in the gut microbiota can lead to aberrations in neurobehavioral functions. Currently, the precise pathological mechanisms underlying FC remain unclear, but multiple factors may be linked to its occurrence. These factors include dysregulation of gut microbiota function, disruption of the intestinal mucosal barrier, abnormalities in neurotransmitter function (e.g., abnormal 5-HT expression), and anomalies in the expression of water channel proteins.

#### 3.1. Gut Microbiota and Functional Constipation

The gut microbiota is an essential component of the human microbiota, with approximately 100 trillion bacteria residing in a healthy individual's gastrointestinal tract<sup>[13]</sup>. Within the microbiota, a dynamic balance exists among beneficial bacteria, pathogenic bacteria, neutral bacteria, and opportunistic pathogens, which is closely associated with intestinal health and disease. The gut microbiota performs various functions, including nutrient digestion and absorption, substance metabolism, and barrier protection. It participates in the digestion and absorption of food, competes with pathogens to inhibit their growth and reproduction, thus protecting the intestinal mucosal barrier and maintaining host health. Research indicates that patients with functional constipation (FC) experience an altered dynamic balance of the gut microbiota due to prolonged fecal retention in the intestines, leading to a significant decrease in the abundance of beneficial bacteria, primarily *Bifidobacterium* and *Lactobacillus*, which are important probiotics<sup>[14]</sup>. Imbalances in the structure and abundance of the gut microbiota, characterized by a reduction in beneficial bacteria, an increase in harmful bacteria, and disruptions in metabolite production, can contribute to the development and exacerbation of various systemic diseases, including functional constipation. Disruption of the gut microbiota structure can cause abnormal intestinal motility. The relationship between gut microbiota and intestinal transit may be bidirectional. Prolonged colonic transit in FC can promote the proliferation and colonization of slow-growing species, leading to profound structural and functional changes in the entire microbiota. On the other hand, environmental factors can induce changes in the gut microbiota, which, in turn, may contribute to the pathogenesis of FC through microbial metabolic activities<sup>[15]</sup>. Studies have shown differences in the species abundance and composition of the gut microbiota between constipated patients and healthy volunteers, particularly at the genus level<sup>[16]</sup>. Huang L et al.<sup>[17]</sup>, using 16S rRNA sequencing targeting the V4 region, found significant differences in the composition of the gut microbiota at the phylum and genus levels between constipated patients and healthy controls. Therefore, there is a close association between the gut microbiota and functional constipation.

#### 3.2. Intestinal Immune Barrier and Functional Constipation

The intestinal mucosal barrier is composed of biological, chemical, mechanical, and immune barriers<sup>[18]</sup>. Among these four barriers, only the immune barrier plays a specific immunological role, while the other three barriers collectively contribute to non-specific immunity. The intestinal mucosal immune barrier works in coordination with immune responses and can locally eliminate invading pathogens, preventing excessive activation of systemic immune reactions. When the intestinal immune barrier is impaired or dysfunctional, it loses the ability to clear pathogens and disrupts the stability of the intestinal environment, potentially leading to gut dysbiosis and constipation. Therefore, the immune barrier acts as a "soldier," playing a crucial role in defending the gastrointestinal mucosa. It serves as an important line of defense against the adhesion and growth of pathogenic bacteria in the intestinal mucosa.

### **3.3. Short-Chain Fatty Acids and Functional Constipation**

Short-chain fatty acids (SCFAs), also known as volatile fatty acids (VFAs), are organic fatty acids with a carbon chain length of less than six carbon atoms. They include acetic acid, propionic acid, isobutyric acid, butyric acid, isovaleric acid, and valeric acid [19]. After rapid absorption in the colon, SCFAs not only store energy but also lower osmotic pressure. They play a crucial role in maintaining the normal function of the large intestine and the morphology and function of colonic epithelial cells. Research has shown that SCFAs participate in the energy supply of intestinal epithelial cells, regulate intestinal pH and electrolytes, maintain intestinal mucosal barrier permeability, influence intestinal sensitivity and motility, and exhibit anti-inflammatory and anti-tumor effects. They play important roles in intestinal diseases and psychoneurological disorders [20]. Moreover, SCFAs are directly or indirectly involved in the interaction between the brain, gut, and microbiota, playing a significant role in gastrointestinal motility disorders such as functional constipation [21].

SCFAs play a pivotal role in safeguarding the intestinal immune barrier, thereby reducing systemic inflammatory responses and preserving immune homeostasis in the body. The effects of SCFAs on the intestinal immune barrier can be delineated as follows: (1) Regulation of Inflammatory and Anti-inflammatory Mediators: SCFAs participate in the modulation of pro-inflammatory and anti-inflammatory mediators. They have the capacity to activate Toll-like receptors (TLRs) on the surface of intestinal epithelial cells, leading to the production of inflammatory cytokines and chemokines. This activation induces a non-specific immune response in the body, thereby shielding intestinal health and mucosal integrity. This action is instrumental in maintaining intestinal homeostasis [22]. (2) Involvement in T Cell Proliferation and Differentiation: SCFAs participate in signal transduction processes that regulate the proliferation and differentiation of naïve T cells, thereby modulating the immunological function of the intestinal mucosa. (3) Regulation of B Lymphocytes Differentiating into Plasma Cells and sIgA Production: SCFAs also exert a regulatory influence on B lymphocytes, guiding their differentiation into plasma cells responsible for secretory immunoglobulin A (sIgA) production.

### **3.4. 5-HT and Functional Constipation**

Serotonin (5-hydroxytryptamine, 5-HT), a heterocyclic amine known as serotonin, is primarily and widely distributed within the central nervous system, enteric nervous system, and the secretory cells of the gastrointestinal mucosa, accounting for 80% of its total presence. As a vital regulatory neurotransmitter in the intestinal mucosa, it participates in the processes of intestinal motility and sensory regulation by accelerating smooth muscle contractions and enhancing intestinal peristalsis, playing a significant role in intestinal peristalsis [23]. 5-HT is capable of regulating gastrointestinal motility, visceral sensitivity, and intestinal secretion, and it plays a role in the pathological process of constipation. Plasma 5-HT levels are diminished in patients with functional constipation. The intestinal tract can activate the second-order neurons through 5-HT receptors, promoting chronic post-synaptic sites and initiating intestinal wall peristalsis, while its decreased levels correspondingly reduce intestinal peristalsis. 5-HT in intestinal tissues is mainly secreted and released by enterochromaffin cells, strengthening intestinal transit and intestinal fluid secretion, and affecting the constriction and dilation of blood vessels in intestinal tissues. In the gastrointestinal tract, its receptors can be expressed in various layers of tissue [24]. It can be inferred from the above that a reduction in the secretion and release of 5-HT can inhibit intestinal peristalsis, thereby promoting the occurrence and development of constipation.

### **3.5. Aquaporins and Functional Constipation**

Aquaporins (AQPs) are a family of proteins with the function of transmembrane water transport, participating in the regulation of fluid and electrolyte transport and metabolism in the digestive tract. Currently, nine subtypes of AQPs have been identified in the mammalian digestive tract, with AQP3 closely associated with water absorption in the colon [25]. AQP3 is predominantly located at the basal and apical membranes of absorptive epithelial cells in the proximal colon, where its primary function involves transferring water and solutes from the luminal side to the intercellular spaces, thus reducing water content in the colon [26-27]. Research has suggested that the expression of AQP3 increases in the colon tissues of rats induced with morphine, while pretreatment with fluoxetine can inhibit the upregulation of AQP3 expression and improve constipation symptoms in rats [28]. Additionally, a study by Risako et al. [29] found that the active compound sennoside A in rhubarb exerts therapeutic effects on

constipation by modulating gut microbiota and reducing AQP3 expression in colon tissues. The above-mentioned research findings indicate a close association between abnormal AQP3 expression in colon tissues and functional constipation. Lowering AQP3 expression may be considered as an effective approach to improving symptoms of functional constipation.

### **3.6. Treatment of Functional Constipation**

The preferred approach for treating functional constipation (FC) is non-pharmacological interventions, including toilet posture and behavior education, dietary recommendations, and regular physical activity<sup>[30]</sup>. Modern medical treatment for FC mainly includes: (1) General Treatment: Establishing a positive mindset and developing a healthy diet and lifestyle are the fundamental prerequisites for curing the disease; (2) Pharmacological Treatment: Pharmacological options include laxatives, prokinetic agents, and probiotics. For mild constipation, fiber-based laxatives or bulk-forming agents like bran or methylcellulose can be used. For moderate to severe constipation, increasing fluid intake and using osmotic laxatives. In severe cases, a combination of polyethylene glycol 4000 (macrogol) and lactulose is used to prevent excessive use of a single medication beyond safe limits; (3) Surgical Treatment: Surgical treatment may be considered for constipation patients who have undergone at least 6 months of strict and regular medication treatment without improvement and who have evident anatomical or structural abnormalities; (4) Traditional Chinese Medicine Treatment: This includes herbal medicine, acupuncture, massage, and enema; (5) Other Treatments: These include biofeedback therapy and sacral nerve stimulation. Biofeedback therapy involves training patients to coordinate their anal and pelvic muscles and has an efficacy rate of around 70%. It is an effective treatment for outlet obstructive constipation and can be safely repeated<sup>[31]</sup>. Sacral nerve stimulation involves stimulating the sacral nerves with an implantable device to enhance their control over effector organs and restore normal organ function. Compared to traditional surgical methods, sacral nerve stimulation offers advantages of safety, minimally invasive procedures, and reversibility, with an efficacy rate of approximately 80%<sup>[32]</sup>.

## **4. Conclusion and Prospects**

Functional constipation (FC) is a common clinical condition, and chronic constipation poses significant harm to the human body<sup>[33]</sup>. With the improvement of people's material life and the increasing variety of diets, the number of individuals affected by constipation is also on the rise. However, the treatment of constipation remains a longstanding challenge<sup>[34]</sup>. FC has complex and diverse causes, necessitating a detailed inquiry into relevant medical history during clinical diagnosis and treatment. Combined with necessary auxiliary examinations and multidisciplinary consultations, it is important to identify key factors contributing to the onset of FC, apply differentiated treatment plans tailored to individual needs, and accurately diagnose the condition using holistic and evidence-based approaches<sup>[35]</sup>. Currently, both traditional Chinese medicine (TCM) and Western medicine lack effective treatment methods for FC. Western medicine primarily relies on laxative medications or surgical procedures, while TCM employs syndrome differentiation and treatment. However, neither approach can provide a complete cure for constipation. In modern medicine, numerous theories exist regarding the pathogenesis of FC. Presently, it is believed that FC is mainly associated with disorders in colonic motility, weakened pelvic floor muscle function, abnormal mucosal immune regulation, dysbiosis of the gut microbiota, and abnormal brain-gut axis regulation<sup>[36]</sup>. Understanding the pathogenic mechanisms of FC provides avenues and targets for precise prevention and regulation, which holds positive significance for the development of more effective treatment drugs, reducing the economic and psychological burden on patients, and enhancing their quality of life<sup>[37]</sup>.

In summary, functional constipation has complex etiology and pathogenesis, directly or indirectly impacting overall health. Currently, both traditional Chinese medicine (TCM) and Western medicine have their own characteristics in the treatment of this condition. However, in clinical practice, individualized treatment plans should be formulated based on the patient's specific symptoms. Although Western medicine shows better short-term effects in treating functional constipation, the long-term outcomes are not ideal, and the recurrence rate is relatively high. On the other hand, TCM, with its emphasis on syndrome differentiation and a holistic approach, has higher acceptance among patients. Therefore, a combination of TCM and Western medicine, taking the essence and discarding the dross, should be considered in clinical practice to achieve complementarity, adapt to the changing times, and promote long-term development<sup>[38]</sup>.

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