Review

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Considering traditional Chinese medicine as adjunct therapy in the management of chronic constipation by regulating intestinal flora

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SUMMARY Chronic constipation is one of the most common gastrointestinal disorders worldwide. Due to changes in diet, lifestyle, and the aging population, the incidence of chronic constipation has increased year by year. It has had an impact on daily life and poses a considerable economic burden. Nowadays, many patients with chronic constipation try to seek help from complementary and alternative therapies, and traditional Chinese medicine (TCM) is often their choice. The intestinal flora play an important role in the pathogenesis of constipation by affecting the body's metabolism, secretion, and immunity. Regulating the intestinal flora and optimizing its composition might become an important prevention and treatment for chronic constipation. TCM has unique advantages in regulating the imbalance of intestinal flora, and its curative effect is precise. Therefore, we reviewed the relationship between intestinal flora and chronic constipation as well as advances in research on TCM as adjunct therapy in the management of chronic constipation by regulating intestinal flora. Some single Chinese herbs and their active ingredients (*e.g.*, *Rheum palmatum*, *Radix Astragalus*, and *Cistanche deserticola*), some traditional herbal formulations (*e.g.*, Jichuan decoction, Zengye decoction, and Zhizhu decoction) and some Chinese patent medicines (*e.g.*, Maren pills and Shouhui Tongbian capsules) that are commonly used to treat chronic constipation by regulating intestinal flora are highlighted and summarized. Moreover, some external forms of TCM, and especially acupuncture, have also been found to improve intestinal movement and alleviate constipation symptoms by regulating intestinal flora. We hope this review can contribute to an understanding of TCM as an adjunct therapy for chronic constipation and that it can provide useful information for the development of more effective constipation therapies.

Keywords chronic constipation, traditional Chinese medicine, adjunct therapy, intestinal flora

1. Introduction

Chronic constipation is one of the most common gastrointestinal disorders worldwide. According to the Rome IV standard, chronic constipation is divided into four sub-types: functional constipation, irritable bowel syndrome with constipation, opioid-induced constipation, and functional defecation disorder, which includes insufficient propulsion of stools and coordination disorders during defecation (*1*). In recent years, due to changes in diet, lifestyle, and the aging population, the incidence of chronic constipation has increased year by year with a global prevalence of around 10-15% of the population (*2*). Although chronic constipation is not a life-threatening condition, it detrimentally impacts quality of life. It leads to mental and psychological disorders and even increases the mortality rate of cardiovascular and cerebrovascular diseases (*3,4*). In addition, chronic constipation poses a substantial health care burden. Direct costs attributed to constipation-related health care in the US are estimated to be more than US$230 million per year (*5*). Therefore, investigate the pathogenesis of and effective therapies for chronic constipation is crucial.

Currently, the main therapies for chronic constipation involve lifestyle changes such as a high fiber diet and exercise, prescription laxatives, and surgery if indicated (*6*). Unfortunately, more than 50% of patients fail to respond to these standard treatments mainly due to dissatisfaction with efficacy, safety, adverse reactions, and cost (*7*). That is to say, the treatment of chronic constipation remains challenging. Therefore, a safe and cost-effective treatment for chronic constipation is

urgently needed. Nowadays, many patients with chronic constipation try to seek help from complementary and alternative therapies, and traditional Chinese medicine (TCM) is often their choice (*8*).

Increasing evidence suggests that the intestinal flora are involved in the development and progression of constipation (*9*). The intestinal flora maintain intestinal homeostasis through various complex mechanisms. Regulating the intestinal flora and optimizing its composition may become an important prevention and treatment for chronic constipation. TCM can prevent and treat chronic diseases through multiple targets, channels, and mechanisms, and it has a certain regulatory effect on the intestinal flora. Therefore, this paper has analyzed the relationship between intestinal flora and chronic constipation as well as the advances in research on TCM in regulating the intestinal flora of chronically constipated patients. It also summarizes the efficacy and mechanism of TCM in preventing and treating chronic constipation by regulating intestinal flora in order to provide new ideas for the prevention and treatment of chronic constipation using TCM.

2. The relationship between chronic constipation and intestinal flora

Constipation is a common intestinal problem, and its development is closely related to a disorder of intestinal micro-flora. There are a large number of diverse microbial groups in the human intestine that are mutually inhibited and interdependent, maintaining the steady state of the intestinal environment. This steady state is mainly a dynamic balance that affects the life and health of the host by regulating the composition of flora, metabolites, neurotransmitters, and participating in immune response. When the homeostasis of the intestinal environment is disrupted, the human body is more susceptible to neurological diseases, cardiovascular diseases, and metabolic diseases, and particularly functional gastrointestinal diseases. The link between chronic constipation and an intestinal microbial imbalance has been corroborated by numerous studies (*10*).

2.1. Constipation and an imbalance of the intestinal flora

Constipation will not only lead to a disorder of intestinal microbes but also affect the metabolism of flora, further aggravating constipation symptoms (*11*). The feces of patients with constipation accumulate in the intestine for a prolonged period, leading to an increase in pathogenic bacteria and a decrease in beneficial bacteria. This, in turn, increases harmful metabolites, damages the intestinal barrier, disrupts the stable balance of the intestinal environment, and creates a vicious cycle. Clinical studies have indicated that constipated patients have a significantly altered abundance and diversity of intestinal flora compared to healthy individuals. In addition, certain metabolites, and particularly chenodeoxycholic acid and biliverdin, have been found to be significantly enriched (*12*). This indicates that the intestinal microbial community of chronically constipated patients is clearly abnormal.

Animal experiments further revealed the key role of intestinal flora in the pathogenesis of constipation (*13*). The researchers analyzed the colon movement pattern and fecal pellet transport in perfusion experiments and found that compared to healthy control mice, the ratio of intestinal motility and contraction, outflow/contraction volume, contraction speed, and the speed of fecal pellet propulsion in pseudo-sterile mice decreased. To further verify the key role of gut microbiota in the development of constipation, Ge *et al*. extracted gut microbiota from constipated patients and transplanted it into germ-free mice and then measuring their intestinal motility. Results indicated that these mice had significantly worse bowel movements, with fewer and smaller fecal pellets, lower fecal water content, delayed gastrointestinal transit time, and weaker spontaneous contractions of the colon smooth muscle (*14*).

Taken together, these studies fully demonstrate the impact of intestinal micro-flora on intestinal motility and its crucial role in constipation. Therefore, maintaining a stable state of intestinal micro-flora is highly significant in preventing and treating chronic constipation.

2.2. Correcting the imbalanced intestinal flora can alleviate chronic constipation

Disordered intestinal micro-flora is closely related to chronic constipation, so restoring the balance of intestinal micro-flora has become an effective method for treating chronic constipation. In this context, fecal microbiota transplantation (FMT), as a treatment to restore the balance of intestinal flora, shows great potential in relieving chronic constipation symptoms (*15*). First of all, FMT treatment has a significant effect on relieving chronic constipation. According to a clinical study, the cure rate of 34 patients who did not respond to conventional laxative drugs was as high as 73.5% after three rounds of FMT. FMT is more effective than traditional laxatives. During the treatment, the composition of intestinal flora improved, the levels of NO and 5-hydroxytryptamine (5-HT) in the serum increased, and intestinal peristalsis was enhanced (*16*). Secondly, FMT treatment can significantly increase the α diversity of intestinal flora. In a retrospective clinical trial, researchers compared the changes in fecal microbial composition in patients with functional constipation before and after FMT treatment. Results indicated that the abundance of *Clostridiales*, *Fusicatenibacter*, and *Paraprevotella* increased, while the abundance of some flora, including *Lactobacillus*, decreased. These changes in flora abundance may be related to the relief of patients' clinical symptoms (*17*).

In addition, probiotics, as a beneficial ingredient, also have a positive effect on alleviating chronic constipation symptoms. Systematic reviews and meta-analyses have indicated that probiotics can increase the frequency of bowel movements and improve overall chronic constipation symptom scores (*18*). For instance, the findings of a double-blind, randomized, placebo-controlled trial revealed that an intervention in the form of *Lactobacillus* HN019 + *Lactobacillus rhamnosus* HN001 in patients with functional constipation for 4 weeks effectively increased the frequency of bowel movements and relieved symptoms of hard stool by optimizing the intestinal micro-flora (*19*). In addition, an intervention in the form of a bacterial mixture in loperamide-induced constipated rats improved the intestinal transport capacity and fecal water content in constipated rats, and at the same time it up-regulated the biosynthesis of 5-HT (*20*). *Bifidobacterium lactis* TY-S01 acts to prevent constipation. It can accelerate intestinal peristalsis in constipated mice, maintain the water content of feces, and prevent the intestinal barrier from being destroyed. At the same time, TY-S01 can also maintain normal levels of 5-HT, motilin (MTL) and substance P (SP) in constipated mice, preventing an intestinal microbial imbalance in constipated mice and increasing the level of short-chain fatty acids (SCFAs) in feces of constipated mice (*21*).

To sum up, these studies further suggest that an imbalance in intestinal flora is closely related to chronic constipation. Therefore, regulating the production of intestinal micro-flora and intestinal metabolites can effectively treat chronic constipation.

2.3. Potential mechanisms by which the intestinal flora modulate constipation

The "intestinal-brain axis" is a neuroendocrine network that dynamically communicates between intestinal flora and brain (*22*). It mainly consists of the central nervous system (CNS), enteric nervous system (ENS), autonomic nervous system (ANS), intestinal flora, and its metabolites (*23*). The intestinal flora play a vital role in the gut-brain axis, which maintains homeostasis among the gastrointestinal tract, CNS, and microbial systems (*24*). The intestinal flora regulate intestinal function through its fermentation metabolites, including SCFAs, secondary bile salts (BAs), and methane, which play a key role. These substances can activate the corresponding receptors in enteroendocrine cells (ECs), enterochromaffin cells (ECCs), and neuron cells to synthesize biological compounds, thereby regulating intestinal movement (*25*). In addition, the intestinal flora can also synthesize and release a variety of neurotransmitters, such as tryptophan, 5-HT, SP, vasoactive intestinal polypeptide (VIP), acetylcholine (Ach), and gastrin (GAS). These neurotransmitters can regulate the contraction and relaxation of intestinal smooth muscle, thereby affecting intestinal peristalsis and defecation (*26*). In general, the intestinal flora play a key regulatory role in the gastrointestinal tract (Figure 1).

2.4. Intestinal flora, metabolites, and chronic constipation

SCFAs are beneficial metabolites produced by the decomposition of indigestible carbohydrates by intestinal flora. They play an important role in maintaining intestinal health and have functions such as stimulating intestinal peristalsis and retaining water in the intestine. The types of SCFAs include acetic acid, propionic acid, and butyric acid, which play various physiological roles in the human body. In a recent study, fecal samples from 30 patients with severe chronic constipation were examined and their levels of SCFAs were found to be significantly lower than those of the control group (*27*). This may be due to the feces remaining in the distal colon for too long, leading to an increase in harmful bacteria such as Desulfovibrio, Enterobacter faecalis, Lactococcus, and Rosea, which can affect the fermentation of intestinal microorganisms and decrease the concentration of SCFAs in feces. To alleviate symptoms in chronically constipated patients, researchers suggested supplementing their diet with fiber. After fiber supplementation, there was an increase in the level of SCFAs rich in butyrate in the intestine, acceleration of gastrointestinal transit, and an increase in the thickness of the mucosal layer. This may be because dietary fiber intake stimulates the secretion of colon hormones and enhances the expression of tight junction proteins, thereby maintaining the integrity of the intestinal barrier (*28,29*). Animal experiments indicated that the ratio of intestinal propulsive contractions to non-propulsive contractions, the speed of intestinal contractions, and the speed of fecal pellet propulsion increased after SCFAs were injected into GF mice. This indicates that SCFAs can effectively restore intestinal contractility (*13*). In addition, the symptoms of constipation were relieved and the level of SCFAs in the intestine increased after a Bifidobacterium intervention was implemented in mice with loperamide-induced constipation. The specific mechanism involves decreasing the pH level in the colon by increasing the level of butyric acid and propionic acid in the intestine. A lower pH level helps enhance the peristalsis of intestinal smooth muscle, thus alleviating constipation symptoms. At the same time, a low intestinal pH can also increase the number of Lactobacillus and Bifidobacterium and decrease the number of Clostridium, further maintaining the balance of the intestinal microecology (*30*). In a word, SCFAs are of great significance in relieving constipation symptoms.

Bile acids (BAs) are not only involved in the digestion and absorption of fat but also serve as important signaling molecules in the intestine. They regulate intestinal movement and colonic fluid secretion by stimulating intestinal chromaffin cells to release 5-HT.

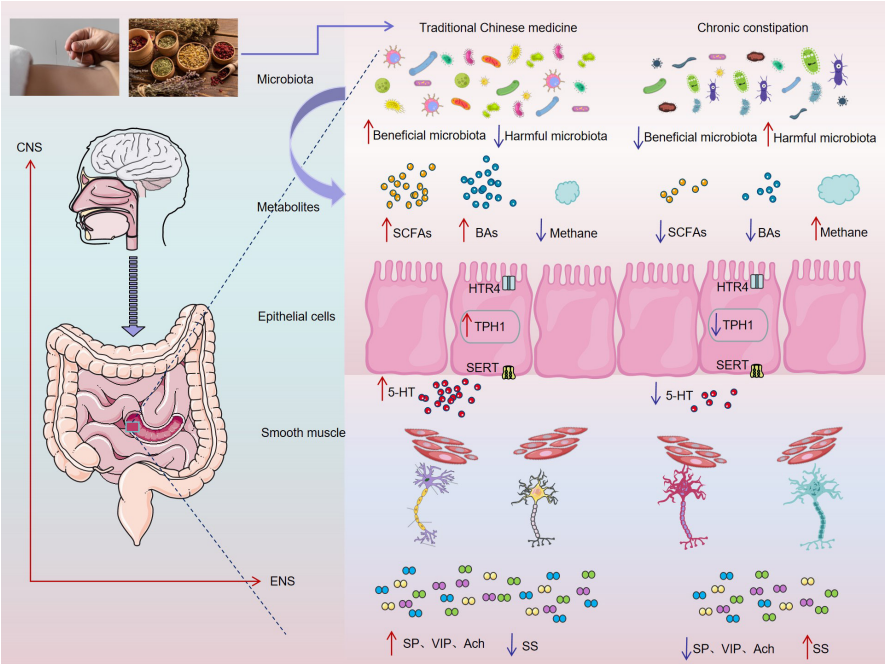

Figure 1. The potential mechanisms by which the intestinal flora modulate constipation when treated with traditional Chinese medicine. *Abbreviations*: CNS: central nervous system; ENS: enteric nervous system; SCFAs: short-chain fatty acids; BAs: secondary bile salts; 5-HT: 5-hydroxytryptamine; HTR4: 5-HT4 receptor; TPH1: Tryptophan hydroxylase 1; SERT: serotonin transporter; SP: substance P; VIP: vasoactive intestinal polypeptide, Ach: acetylcholine; SS: somatostatin.

This mechanism is helpful in maintaining the normal physiological function of the intestine and ensuring the full absorption of nutrients and smooth discharge of waste (*31,32*). In addition, BAs also play a key role in maintaining a balanced intestinal flora. They can promote the growth of beneficial bacteria and inhibit the reproduction of harmful bacteria. When the level of BA is insufficient, an imbalance in intestinal flora may result in slow intestinal peristalsis, leading to issues such as constipation (*33*). After an intervention in the form of Bacillus subtilis in a mouse model of constipation, the constipation symptoms of mice were markedly alleviated. Metabonomic results indicated that the BA content of mice increased significantly, and the 5-HT released by ECs cells through the BA receptor TGR5/TRPA1 pathway also increased significantly (*34*). Elobixibat is a new laxative for constipation that increases BA flow to the colon by inhibiting the ileal BA transporter. This action promotes the secretion of more water in the intestinal tract and stimulates intestinal peristalsis, effectively treating chronic constipation (*35*). Moreover, studies have found that apple juice (AJ) has the potential to relieve constipation. AJ can reduce BA reabsorption in the intestine, promote intestinal peristalsis, and alleviate constipation symptoms by down-regulating the expression of the BA transporter (*36*).

Methane is a gas produced by the fermentation of carbohydrates by intestinal flora in an anaerobic environment. Under normal circumstances, the generation and excretion of methane has no negative impact on human health. When the intestinal flora is unbalanced and too much methane is produced, however, it can affect the intestinal environment and cause a series of digestive system problems (*37*). The number of beneficial Bifidobacterium and Lactobacillus bacteria in stool samples of patients with functional constipation significantly reduced compared to that in healthy individuals. In addition, their methane respiratory emissions are also higher. These beneficial bacteria are crucial to maintaining intestinal health, and their decrease suggests an imbalance in the intestinal flora, which may result in intestinal dysfunction (*38*). Methane is a gas that cannot be used by the human body, so the methane breath test is widely used to detect methane production. In an experiment, researchers found that the number of methane-producing bacteria and methane production in patients with chronic constipation is higher than in healthy individuals (*39*). This further confirms the relationship between an imbalance in intestinal flora, methane, and constipation. In addition, when the researchers studied subjects with constipation-dominant IBS, they found that their respiratory methane level was also high. This may be related to the relative abundance of methanogenic bacteria (mainly *Methanobrevibacter*) in their feces and the absolute abundance of *Methanobrevibacter smithii* in their feces. These findings provide further evidence for the role of methane in intestinal diseases (*40*).

2.5. Intestinal flora, neurotransmitters and chronic constipation

Studies have confirmed that intestinal flora can stimulate

the release of 5-HT from intestinal chromaffin cells (EC) through metabolites of SCFAs and BAs, thus promoting intestinal peristalsis (*32*). 5-HT needs to bind with the 5-HT4 receptor (HTR4) to stimulate secretion and peristalsis reflex and promote intestinal peristalsis (*41*). Selective HTR4 agonists, such as procarbide, can be used to treat constipation (*42*). Tryptophan hydroxylase 1 (TPH1) is the key enzyme for 5-HT synthesis. Increasing its activity significantly improves the synthesis of 5-HT in the intestine and further promotes intestinal peristalsis. Colon transport was found to improve significantly after oral administration of butyrate to GM mice, but this change was not observed in TPH1 KO mice, which may be related to the role of 5-HT in the intestine. This demonstrates that increasing the production of 5-HT-producing bacteria in the intestine can help alleviate constipation (*13*). MTL is a gastrointestinal hormone that can not only secrete gastric acid but also increase intestinal peristalsis. A study found that the serum MTL level in children with constipation was significantly lower than that in the healthy control group, suggesting that the decrease in MTL levels may be related to the pathogenesis of constipation (*43*). The neurotransmitters SP and VIP were found to be decreased in the colon of patients with constipation compared to their levels in healthy individuals (*44*). SP has the ability to inhibit the release of inflammatory factors, reduce inflammatory reactions, strengthen the tight connections between intestinal mucosal epithelial cells, improve the integrity of the intestinal barrier, and ultimately reduce intestinal injury (*45*). VIP can promote intestinal peristalsis and fluid secretion when it acts on the intestinal mucosa and submucosal neurons (*46*). In addition, VIP, as an effective anti-inflammatory mediator, can maintain the homeostasis of intestinal flora by protecting the intestinal epithelial barrier (*47*). Somatostatin (SS), an inhibitory neurotransmitter, can relax gastrointestinal smooth muscle, reduce gastrointestinal peristalsis, and increase gastrointestinal transit time (*48*). The excitatory neurotransmitter ACh is involved in regulating intestinal peristalsis and secretion (*49*). A new type of lactic acid bacteria was found to significantly increase the defecation volume and fecal moisture content in constipated mice. At the same time, it increased the serum levels of MTL, SP, Ach, and VIP in mice while decreasing the level of SS (*50*).

To summarize, the intestinal flora, metabolites, and neurotransmitters are closely related to constipation. By regulating SCFAs, BAs, methane, 5-HT, and other substances, they help to maintain the balance of intestinal flora and alleviate constipation symptoms. Therefore, attention must be paid to the intestinal flora and its metabolites in the process of preventing and treating chronic constipation.

3. TCM for chronic constipation based on intestinal flora

According to the theory of TCM, constipation is located in the large intestine. Its pathogenesis mainly lies in the disorder of the *zang-fu* organs, dysfunction of the spleen and stomach, an imbalance of the liver and kidney, and a deficiency of *Qi* in the lungs and a deficiency of *Qi* and blood. These factors can affect the conducting function of the large intestine and lead to constipation. Therefore, regulating the function of the *zang-fu* organs is key to treating constipation. TCM treatment involves formulating an individualized treatment plan based on the type of syndrome. This approach can effectively regulate the functions of the *zang-fu* organs and alleviate symptoms, providing unique advantages. Chinese medicine treatments mainly include internal and external treatments. Internal treatments include Chinese medicine decoctions, Chinese patent medicine preparations, and single Chinese medicine remedies. External treatments include acupuncture, use of acupoints, acupoint catgut embedding, and massage. TCM causes minimal adverse reactions and has a marked curative effect, making it an important supplementary and alternative therapy for constipation. Numerous scientific studies have confirmed that TCM can treat constipation by improving the composition of intestinal flora, regulating the level of microbial metabolites, protecting the function of the intestinal mucosal barrier, and balancing the intestinal microecosystem.

3.1. Single Chinese herbs and their active ingredients

Several single Chinese herbs and their active compounds have been found to have a potentially beneficial effect at treating chronic constipation by regulating intestinal flora. Therefore, a brief overview of the pharmacology of the most commonly used ingredients and their effects on constipation is presented below (Table 1).

Rheum palmatum (Da-Huang in Chinese) is a drug commonly used to treat constipation. It can significantly reduce the time food takes to pass through the digestive system, increase the amount of water in feces, and improve the hormonal balance of the digestive tract. It also helps protect the mucous layer of the colon by regulating the intestinal flora and its byproducts (*51*). In addition, rhubarb contains sennoside A, a natural anthraquinone compound. Studies have found that a conventional dose of sennoside A for less than a week can effectively alleviate constipation symptoms in mouse models. This is mainly achieved by increasing the abundance of beneficial intestinal bacteria such as Lactobacillus and Romboutsia while reducing the abundance of harmful bacteria like *Akkermansia* and UCG_005. It also regulates the expression of the colonic aquaporins AQP1 and AQP3. However, a point worth noting is that sennoside A should not be used for extended periods of time as its laxative action can weaken and potentially damage the colon (*52*).

Radix Astragalus (Huang-Qi in Chinese) is a well-

Table 1. Most commonly used herbs to treat chronic constipation by regulating intestinal flora and their active ingredients

Herbs or active ingredients	Source	Subjects	Type of model	Changes in intestinal flora	Mechanisms	*Ref.*
Rheum palmatum	Rheum palmatum	Rats	Loperamide	Ligilactobacillus↑; Prevotellaceae↑; Limosilalactobacillus↑; UCG-001↑	Regulating the intestinal flora and its metabolites.	*51*
Sennoside A	Rheum palmatum	Mice	Loperamide	Lactobacillus↑; Romboutsia↑; *Akkermansia*↓; UCG_005↓	Regulating the abundance of intestinal flora and aquaporin.	*52*
Astragaloside IV	Radix Astragalus	Rats	Loperamide	Firmicutes↑; Lactobacillales↑; Lactobacillus↑; Lactobacillus reuteri↑	Regulating the composition of the intestinal flora and producing butyric acid.	*55*
Astragalus polysaccharide	Radix Astragalus	Rats	D-galactose and mixture	Blautia↑; Lactobacillus↓	Altering gut microbiota and improving the gut environment to alleviate constipation.	*56*
Platycodon grandiflorum polysaccharides	Platycodon grandiflorum	Rats	Loperamide	Bacteroidetes↑; Firmicutes↓; Roseburia↑; Butyricimonas↑; Ruminiclostridium↑; *Clostridia*_UCG-014↓; Lactobacillus↓; Enterococcus↓	Adjusting the composition of flora and the number of bacteria producing butyrate increases, leading to increased levels of neurotransmitters and promoting intestinal peristalsis.	*58*
Chrysanthemum morifolium polysaccharide	Chrysanthemum morifolium	Rats	Loperamide	Lactobacillus↑; Romboutsia↑; Lachnospiraceae_NK4A136_group↓; Roseburia↓	Increasing species abundance and flora diversity, improving the composition of flora, regulating neurotransmitter levels, promoting intestinal peristalsis, and relieving constipation.	*60*
Cistanche deserticola polysaccharides	Cistanche deserticola	Rats	D-galactose and mixture	Ruminococcus↑	Regulating the composition of the microbiota and the metabolites of the microbiota.	*64*
Cinnamic acid	Radix Scrophulariae	Mice	Loperamide	Rikenella↑; Monoglobus↑; *Lachnospiraceae*_NK4A136_group↑; Akkermansia↑; Desulfovibrionaceae↑; Lachnoclostridium↑; Monoglobus↑; Acinetobacter↑; Anaerofustis↑;	Improving the composition and abundance of intestinal microflora and regulating the production of SCFAs.	*66*
Volatile oil	Citrus aurantium; Rhizoma Atractylodis	Rats	Diphenoxylate	Proteobacteria↑; Allobaculum↑; Ruminococcaceae↑; Romboutsia↓	Improving the composition and metabolites of the microbiota, regulating neurotransmitters, and promoting intestinal motility.	*68*

Note: Abbreviations: SCFAs: short-chain fatty acids.

known herbal medicine with purported tonic properties that has been widely used to treat a variety of diseases in China and Southeast Asia for thousands of years (*53*). The long-term administration of *Radix Astragalus* has been found to significantly modulate the intestinal flora of hens by increasing the abundance of *Romboutsia* and *Lactobacillus* (*54*). Astragaloside IV, one of the active ingredients of *Radix Astragalus*, has been found to effectively promote intestinal transit in mice with loperamide-induced slow transit constipation by inhibiting the loss of ICCs, mediating the regulation of the gut microbiota composition, and enhancing butyric acid generation (*55*). Astragalus polysaccharide is also one of active ingredients of *Radix Astragalus*. It has been reported to be effective against constipation by altering gut microbiota and improving the gut environment (56). Microbiome analysis revealed that Astragalus polysaccharide increased the relative abundance of *Blautia* while decreasing the relative abundance of *Lactobacillus* in elderly rats with constipation. In addition, Astragalus polysaccharide reduced the levels of acetate, butyrate, and propionate in fecal samples, correspondingly regulating glycolysis/gluconeogenesis metabolism and pyruvate metabolism.

Platycodon grandiflorum (Jie-Geng in Chinese), a traditional Chinese medicinal herb acting on the lung meridian, has been widely used to treat pulmonary and respiratory disorders (*57*). According to the theory of TCM, the lungs and large intestine are connected. Therefore, after regulating the function of the lungs, the conductive function of the large intestine can be restored, which is helpful in relieving constipation. Notably, *Platycodon grandiflorum* polysaccharides are the main active ingredients isolated from *Platycodon grandiflorum*. An animal study indicated that it promoted intestinal peristalsis by increasing the levels of expression of 5-HT-related proteins and mediated the composition of the intestinal flora, thereby alleviating constipation (*58*). 16S rRNA gene sequencing indicated that *Platycodon grandiflorum* polysaccharides significantly enriched the relative abundance of butyrate-producing bacteria, including *Roseburia*, *Butyricimonas*, and *Ruminiclostridium*, while suppressed several pernicious bacteria, such as *Clostridia* UCG-014, *Enterococcus*, and *Lactobacillus*.

Chrysanthemum morifolium (Ju-Hua in Chinese) is a well-known edible medicinal plant that is widely consumed as herbal tea in Asia and some other regions (*59*). It has been reported to have various physiological effects, such as anti-inflammatory and free radical scavenging activity. The bioactive components of *Chrysanthemum morifolium* are mainly flavonoids, polysaccharides, volatile oils, terpenoids and organic acids. Recently, Wang *et al*. suggested that *Chrysanthemum morifolium* polysaccharide has potential regulatory effects on functional constipation (*60*). By increasing the abundance of beneficial bacteria and decreasing the abundance of pathogenic bacteria, it may improve the composition of intestinal microorganisms and thus promote intestinal motility.

Cistanche deserticola (Rou-Cong-Rong in Chinese), known as "desert Ginseng," is a traditional and precious Chinese herbal medicine (*61*). According to the theory of TCM, *Cistanche deserticola* can supplement the kidney, boost the essence of blood, and moisten the intestines to free stool. It is commonly used to treat conditions such as impotence, seminal emission, infertility, general weakness with lassitude of the loins and knees, and chronic constipation (*62*). The bioactive components of *Cistanche deserticola* mainly include phenyl ethanol glycosides, polysaccharides, flavonoids, and so on. Polysaccharides are a principal component that has significant effects on constipation (*63*). Liu *et al*. found that *Cistanche deserticola* polysaccharides significantly regulated the abnormalities of behavioral indices, microbial richness and diversity, and metabolite profiles that were induced by constipation in aged rats (*64*). From an intestinal microbiological point of view, *Cistanche deserticola* polysaccharides significantly increased the prevalence of beneficial bacteria while reducing the potentially pathogenic bacterial population.

Scrophulariae Radix (Xuan-Shen in Chinese) is one of the most popular traditional Chinese herbs that serves to cool the blood, nourish yin, purge fire, and remove toxins according to the Pharmacopoeia of the People's Republic of China (2020 Edition). It is usually used to treat rheumatism, pharyngalgia, arthritis, constipation and conjunctival congestion (*65*). Cinnamic acid is an organic acid isolated from *Scrophulariae Radix* that can effectively regulate the biological activity of intestinal flora. Jiang *et al*. found that cinnamic acid effectively treated slow transit constipation by ameliorating the composition and abundance of the intestinal microbiome to regulate the production of SCFAs (*66*). It significantly improved the diversity and abundance of the beneficial microbiome. Moreover, the production of SCFAs, including acetic acid, butyric acid, propionic acid and valeric acid, was significantly promoted by cinnamic acid.

Citrus aurantium (Zhi-Shi in Chinese) and *Rhizoma Atractylodis Macrocephalae* (Bai-Zhu in Chinese) are a classical drug pair that have been widely used to treat gastrointestinal motility disorders for thousands of years, and they display a definite advantage in the treatment of chronic constipation (*67*). According to the Pharmacopoeia of the People's Republic of China (2020 Edition), *Citrus aurantium*, commonly known as bitter orange, can treat stool obstruction and it has the ability to break up *Qi* and eliminate stagnation and dissolve and disperse phlegm, while *Rhizoma Atractylodis Macrocephalae* replenishes *Qi* and it tonifies the spleen, removes water from the intestinal track, and promotes water circulation. Volatile oil is an active ingredient of *Citrus aurantium* and *Rhizoma*

Atractylodis Macrocephalae that has been reported to alleviate constipation in rats by altering the host metabolome and intestinal microbiota composition (*68*). It promotes intestinal peristalsis, increases fecal water content, regulates the levels of gastrointestinal hormones (GAS and SP), reduces the inflammatory response (IL-6 and TNF-α), and regulates brain-intestinal peptides (5-HT and VIP). In addition, volatile oil improves the composition of the intestinal microbiota by reducing harmful bacteria and promoting beneficial bacteria.

3.2. Traditional herbal formulations

Traditional herbal formulations (or Kampo in Japanese) are compound formulations that mostly have been used for thousands of years (*69*). Several traditional herbal formulations have been found to have a potentially beneficial effect at treating chronic constipation by regulating intestinal flora. Therefore, a brief overview of the pharmacology of the most commonly used traditional herbal formulations and their effects on constipation is presented below (Table 2).

A Jichuan decoction is a classical and famous traditional herbal formula that has been extensively used for chronic constipation and other gastroenteric disorders for hundreds of years. It consists of six herbs including *Angelica sinensis* (Dang-Gui in Chinese), *Achyranthes bidentata* (Niu-Xi in Chinese), *Alisma orientalis* (Ze-Xie in Chinese), *Cistanche deserticola* (Rou-Cong-Rong in Chinese), *Cimicifuga foetida* (Sheng-Ma in Chinese), and *Citrus aurantium* (Zhi-Shi in Chinese). Lin *et al*. found that the Jichuan decoction exhibited excellent activity against loperamide-induced chronic constipation in rats (70). It alleviated chronic constipation by inhibiting the cAMP/PKA/AQPs signaling pathway and maintaining inflammatory/intestinal flora homeostasis. In addition, the Jichuan decoction also maintained intestinal health by reducing the apoptosis rate of enteric glial cells (*71*).

A Zengye decoction, a well-known traditional herbal formulation, consists of three herbs including *Radix Scrophulariae* (Xuan-Shen in Chinese), *Radix Rehmanniae* (Sheng-Di in Chinese) and *Radix Ophiopogonis* (Mai-Dong in Chinese). It has been widely used in many Asian countries for thousands of years to treat constipation and diseases related to a *yin* deficiency. Liu *et al*. found that the Zengye decoction regulated the intestinal microbiota of constipated rats to normal levels and it changed the endogenous metabolites of the host through the intestinal microbiota, resulting in therapeutic action (*72*). It reduced the level of harmful bacteria, such as *Desulfovibrio*, *Ruminococcus*, *Prevotella* and *Dorea*, and increased the abundance of *Oxalobacter*, *Clostridium*, and *Roseburia*.

A Simo decoction is a famous traditional herbal formula that has been used to treat gastrointestinal diseases for hundreds of years. It consists of four herbs,

Table 2. Most commonly used traditional herbal formulations to treat chronic constipation by regulating intestinal flora

Herbal formulations	Composition	Subjects	Type of model	Changes in intestinal flora	Mechanisms	*Ref.*
Jichuan decoction	Six herbs: Angelica sinensis, Achyranthes bidentata, Alisma orientalis, Cistanche deserticola , Cimicifuga foetida , and Citrus aurantium	Rats	Loperamide	Bacteroidetes↑; Lactobacillus↑; Erysipelas↑; Lachnospira↓; Verrucobacterium↓; Helicobacter↓	Promoting intestinal movement by inhibiting the cAMP/PKA/AQPs signaling pathway, reducing inflammation, and maintaining intestinal flora homeostasis.	*70*
Zengye decoction	Three herbs: Radix Scrophulariae, Radix Rehmanniae and Radix Ophiopogonis	Rats	Restricted water, loperamide, and D-galactose	Oxalobacter↑; Clostridium↑; Roseburia↑; Desulfovibrio↓; Ruminococcus↓; Prevotella↓; Dorea↓	Regulating intestinal microbiota to normal levels and changing the endogenous metabolites of the host.	*72*
Simo decoction	Four herbs: Fructus aurantii, Aucklandiae Radix, Semen arecae, and Linderae Radix	Mice	Sennae Folium and controlling the diet and water intake	Bacteroides↑; Alistipes↑; Faecalibacterium↑; Subdoligranulum↑; Lactiplantibacillus↑; Phascolarctobacterium↑	Increasing the abundance of beneficial bacteria via the brain-bacteria-gut axis, promoting a healthy intestinal environment, and reducing oxidative stress.	*73*
Xiao Chengqi formula	Three herbs: Rheum palmatum, Citrus aurantium, and Magnolia officinalis	Rats	Loperamide	Roseburia spp.↑	Promoting the colonization of beneficial bacteria and increasing the butyl aminobenzene level after metabolism.	*74*
Zhizhu decoction	Two herbs: Citrus aurantium and Rhizoma Atractylodis Macrocephalae	Mice	Diphenoxylate	Bifidobacteriaceae↓; Pseudomonadaceae↓; Rikenella↓; Shigella↑; Bifidobacterium↓; Pseudomonas↓; Clostridium↑	Regulating the intestinal microflora, activating the AHR signaling pathway, and promoting neuronal excitability.	*76*

Note: Abbreviations: AHR: aryl hydrocarbon receptor.

Fructus aurantii (Zhi-Ke in Chinese), *Aucklandiae Radix* (Mu-Xiang in Chinese), *Semen arecae* (Bin-Lang in Chinese), and *Linderae Radix* (Wu-Yao in Chinese). Mounting evidence proves that the Simo decoction can treat constipation by regulating intestinal microbiota and related oxidative stress indicators. It can increase the abundance of beneficial bacteria through the brain-bacteria-gut axis in association with intestinal mucosal microbiota, promote a healthy intestinal environment, and reduce oxidative stress (*73*).

Xiao-Cheng-Qi-Tang, an ancient traditional herbal formula, has been used as a heat-clearing, intestine movement, and cathartic herb for thousands of years. It consists of three herbs, *Rheum palmatum* (Da-Huang in Chinese), *Citrus aurantium* (Zhi-Shi in Chinese), and *Magnolia officinalis* (Hou-Pu in Chinese). Zhou *et al*. found that Xiao-Cheng-Qi-Tang improved the defecation of patients with slow transit constipation by protecting ICC activity, promoting the colonization of *Roseburia* spp. to promote peristalsis, and increasing the butyl aminobenzene level after metabolism (*74*). In addition, Liu *et al*. suggested that the anti-inflammatory activity of Xiao-Cheng-Qi-Tang was at least partially mediated by intestinal bacterial metabolism (*75*).

A Zhizhu decoction, consisting of *Citrus aurantium* (Zhi-Shi in Chinese) and *Rhizoma Atractylodis Macrocephalae* (Bai-Zhu in Chinese), is widely used in the treatment of functional gastrointestinal diseases caused by a spleen deficiency and *Qi* stagnation syndrome. The Zhizhu decoction has been reported to have beneficial laxative action on constipation in mouse models, which may be attributed to its ability to alter the composition of intestinal flora and activate the aryl hydrocarbon receptor (AHR) signaling pathway (*76*). In addition, the Zhizhu decoction increases the expression of Ach, SP, and 5-HT in the colon while decreasing the expression of VIP.

3.3. Chinese patent medicines

Chinese patent medicines are a form of Chinese herbal medicine that are isolated from single herbs or traditional herbal formulations and that are prepared using modern advanced pharmaceutical technology. There are various dosage forms including injections, tablets, pills, capsules, and liquids. Compared to traditional decoctions, Chinese patent medicines are safer, more effective, and easier to use (*69*). Thus, Chinese patent medicines are becoming increasingly popular in China and are attracting attention worldwide. A brief overview of the pharmacology of the most commonly used Chinese patent medicines that have been approved by the State Food and Drug Administration (FDA) of China and their effects on constipation is briefly presented below (Table 3).

Maren pills are a well-known Chinese patent medicine consisting of six medicinal herbs including *Rheum palmatum* (Da-Huang in Chinese), *Magnolia*

Table 3. Most commonly used Chinese patent medicines to treat chronic constipation by regulating intestinal flora

Chinese patent medicines	Composition	Subjects	Type of model	Changes in intestinal flora	Mechanisms	*Ref.*
Maziren pills	Six herbs: Rheum palmatum, Magnolia officinalis, Fructus aurantii, Amygdalus communis, Cannabis sativa, and Paeonia lactiflora	Mice	Senna leaf and food restriction	Bacteroides↑; Firmicutes↓	Alleviating symptoms and colon inflammation in constipated mice, reducing the level of VIP in the colon, increasing the level of SP, regulating the composition of flora.	*77*
		Rats	Loperamide	Lactobacillus↑; Prevotella↓	Activating 5-HT pathway, regulating SCFAs metabolism and regulating the composition of intestinal flora.	*78*
Shouhui Tongbian capsules	Eight herbs: Fallopia multiflora, Cassiae Semen, Lycii Fructus, Panax ginseng, Aloe vera, Colla corii asini, Citrus aurantium and Rhizoma Atractylodis Macrocephalae	Mice	Loperamide	Lactobacillus↑; Firmicutes/Bacteroides↑	Remodeling the composition of gut microbes and regulating production of intestinal metabolites.	*79*
		Mice	Loperamide	Verrucomicrobiota↑; Firmicutes/Bacteroides↑	Correcting gut microbiota dysbiosis and activating bacterial metabolite-mediated intraintestinal 5-HT synthesis.	*80*

Note: Abbreviations: VIP: vasoactive intestinal polypeptide; SP: substance P; 5-HT: 5-hydroxytryptamine; SCFAs: short-chain fatty acids.

officinalis (Hou-Pu in Chinese), *Fructus aurantii* (Zhi-Ke in Chinese), *Amygdalus communis* (Xing-Ren in Chinese), *Cannabis sativa* (Huo-Ma-Ren in Chinese), and *Paeonia lactiflora* (Bai-Shao in Chinese). Widely used in clinical practice, Maren pills have been proven to increase the frequency of defecation and alleviate clinical symptoms of patients with constipation. Yu *et al*. found that Maren pills effectively alleviated symptoms and colon inflammation in mice with slow transit constipation, they reduced the level of VIP in the colon, they increased the level of SP, they regulated the composition of flora, and they relieved constipation (*77*). In addition, Maren pills increased the levels of acetic acid, propionic acid, and butyric acid, activated the 5-HT pathway, and promoted intestinal movement by regulating the composition of intestinal flora (*78*).

Shouhui Tongbian capsules are a Chinese patent medicine widely used to treat constipation. The prescription of Shouhui Tongbian Capsule consists of 8 Chinese herbs, *Fallopia multiflora* (He-Shou-Wu in Chinese), *Cassiae Semen* (Jue-Ming-Zi in Chinese), *Lycii Fructus* (Gou-Qi-Zi in Chinese), *Panax ginseng* (Ren-Shen in Chinese), *Aloe vera* (Lu-Hui in Chinese), *Colla corii asini* (E-Jiao in Chinese), *Citrus aurantium* (Zhi-Shi in Chinese), and *Rhizoma Atractylodis Macrocephalae* (Bai-Zhu in Chinese). Lin *et al*. found that Shouhui Tongbian capsules ameliorated the development of loperamide-induced constipation in rats by remodeling the composition of gut microbial and regulating production of intestinal metabolites (*79*). Notably, they increased the relative abundance of *Lactobacillus* and the ratio of *Firmicutes* to *Bacteroides* (F/B). In addition, Shouhui Tongbian capsules alleviated constipation by regulating the intestinal flora imbalance, altering microbial metabolites, stimulating the release of intestinal 5-HT, and protecting intestinal neuron differentiation (*80*).

3.4. External treatment with TCM

External forms of TCM, a unique traditional treatment with a long history in China, refer to treatments including acupuncture, moxibustion, massage, and use of acupoints. These external treatments were reported to be effective and also able to avoid adverse consequences such as abdominal pain, an electrolyte disturbance, melanosis coli, and severe drug dependence after long-term use of laxatives (*81*). Therefore, a brief outline of the most commonly used TCM external treatments and their effects on constipation is presented below (Table 4).

Acupuncture has been markedly effective in treating functional constipation. A study revealed the mechanism of action of acupuncture at three acupoints (Tianshu (ST25), Shangjuxu (ST37), and Fujie (SP14)) in alleviating the clinical symptoms of patients. It helped to reconfigure the intestinal flora and increase the level of butyric acid, an SCFA that is crucial for maintaining

Table 4. Most commonly used TCM external treatments for chronic constipation by regulating intestinal flora

External treatment	Acupuncture point	Subjects	Changes in intestinal flora	Mechanisms	Ref.
Acupuncture	Tianshu (ST25); Shangjuxu (ST37); Fujie (SP14)	Functionally constipated patients(n = 80)	Bifidobacterium↑; g_Lactobacillus↑; Pseudomonas↓; g_Pseudomonas↓; f_Peptostreptococcaceae↓; g_Eubacterium_corprostanoligenes_group↓	Adjusting the composition of intestinal flora and increasing the level of butyric acid	*82*
Electro-acupuncture	Tianshu (ST25); Shangjuxu (ST37)	Functionally constipated mice	Staphylococcaceae↑; Muribaculaceae↓; Enterobacteriaceae↓	Re-balancing the gut microbiota and promoting the generation of butyric acid	*83*
Electro-acupuncture	Bilateral Zusanli	Spinal cord injury rats	Proteobacteria↓; Clostridia↓; Gammaproteobacteria↓; Erysipelotrichia↓	Modulating microbiota and metabolites and regulating the 5-HT system.	*84*
Acupoint massage	-	Chronic function patients (n = 104)	Pseudobutyrivibrio↑; Ruminiclostridium↑; Fusicatenibacter↓	Improving the microbial composition	*85*

intestinal health. The specific microorganisms affected by acupuncture can be predicted using 16S rRNA technology, providing a new method with which to evaluate the effectiveness of acupuncture (*82*).

Electroacupuncture (EA) can increase the frequency and intensity of acupoint stimulation based on common acupuncture techniques, allowing for more effective treatment on the meridians. In experimental studies, EA has been found to significantly improve intestinal movement in constipated mice and alleviate constipation symptoms. However, EA did not reverse slow colonic transit in pseudosterile (PGF) mice, indicating that intestinal microflora play a crucial role in the treatment of constipation with EA. To further explore this mechanism, researchers used 16S rRNA sequencing technology to quantify intestinal microorganisms and found that EA treatment restored the ratio of Firmicutes to Bacteroides and increased the production of butyric acid in constipated mice by increasing the abundance of Staphylococcus, which helps alleviate constipation (*83*). In addition, EA has also been found to regulate the 5-HT system by regulating microorganisms and metabolites, thereby alleviating constipation symptoms caused by spinal cord injury. 5-HT is a neurotransmitter that plays a significant role in regulating intestinal movement (*84*).

Acupoint sticking therapy for constipation involves laxative action as well as the use of acupoints. A clinical study confirmed that acupoint therapy changed the composition of intestinal microflora related to cytokines in constipated patients and relieved constipation symptoms (*85*).

4. Conclusion

Overall, Chinese medicine has a marked curative effect on chronic constipation. It alleviates constipation symptoms and also regulates intestinal flora and metabolites, reduces inflammatory reactions, and protects the intestinal mucosal barrier. This provides various options for treating constipated patients. When using TCM to treat constipation, however, we must follow the principle of syndrome differentiation and treatment. This study summarizes several TCM medicines and external treatments for chronic constipation by regulating intestinal flora. The hope is that this study will provide valuable information for further research on the mechanism of TCM in treating chronic constipation by regulating intestinal flora.

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