

Review

Shouhui Tongbian Capsule in treatment of constipation: Treatment and mechanism development

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ABSTRACT

Constipation is common in the diseases of the digestive system in clinics. With the change in diet structure and the increase in life pressure, the prevalence rate increases year by year. In traditional Chinese medicine (TCM), the location of the disease of constipation is in the large intestine, which is related to the dysfunction of lung, spleen, liver, kidney and other viscera. Its pathogenesis is conductive dysfunction of large intestine. Based on the theory, Shouhui Tongbian Capsule (SHTB) is composed of eight traditional Chinese medicines, including *Polygoni multiflori Radix* (Heshouwu in Chinese), *Aloe* (Luhui in Chinese), *Cassiae Semen* (Juemingzi in Chinese), *Ginseng Radix et Rhizoma* (Ren Shen in Chinese), *Lycii Fructus* (Gouqizi in Chinese), *Asini Corii Colla* (Ejiao in Chinese), *Aurantii Fructus Immaturus* (Zhishi in Chinese), and *Atractylodis Macrocephalae Rhizoma* (Baizhu in Chinese), which could help to release excessive turbid, and nourishing *yin* and supplementing *qi* in the treatment. This study has been carried out to review the latest advances of SHTB in the treatment of constipation. The results showed that significant effect of SHTB was found in the treatment of constipation, such as functional constipation, and constipation associated with tumor chemotherapy, colitis, type 2 diabetes and chronic cardiac failure. Besides, obvious adverse reactions were not observed. SHTB could effectively treat five types of constipation, provide direction for the future exploration of SHTB in the treatment of other types of constipation.

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1. Introduction

With a worldwide prevalence of around 15%, constipation is a common digestive system disease in the clinic and seriously affects the quality of life of patients, which is mainly manifested by a decrease in the frequency of bowel movements, dry and hard stools, and difficulty in defecation (Bharucha & Lacy, 2020; Camilleri et al., 2017; Zhang, Shen, Zhang, & Ye, 2017). Long-term constipation could cause gastrointestinal dysfunction, secondary psychological disorders, cardiovascular and cerebrovascular diseases, and even colorectal cancer in severe cases (Belsey, Greenfield, Candy, & Geraint, 2010; Nehra, Bruce, Rath-Harvey, Pemberton, & Camilleri, 2000; Staller et al., 2022). Modern medical treatments for constipation are symptomatic treatments, which include gastrointestinal excitomotor, laxatives, osmotic agents, lubricating agents and probiotics (Stern & Davis, 2016; Vriesman, Koppen, Camilleri, Di Lorenzo, & Benninga, 2020) (Fig. 1). This treatment strategy is effective in improving constipation symptoms in the short term, but the long-term application may have adverse reactions and even aggravate the condition. Besides, western medicine might have problems such as easy recurrence after stopping the drug, drug dependence, and aggravation of constipation. Nevertheless, TCM stresses treatment simultaneously on root and symptom and dialectical treatment, which would regulate the body's balance of *qi*, blood, *yin* and *yang* holistically (Cheng, Bian, Zhu, Wu, & Sung, 2011; Wang et al., 2022; Whiting & Ford, 2011). With the development and increased acceptance of TCM, TCM has been widely used in the clinical treatment of constipation, which has remarkable efficacy with fewer adverse reactions.

Constipation was first recorded in the *Yellow Emperor's Classic of Internal Medicine* (Huangdi Neijing in Chinese) as “difficult defecation, unfavorable later” (Luo, Zhu, & Liao, 2017). TCM believes that while the cause of constipation is in the large intestine, it is closely related to the lungs, spleen, stomach, liver, kidneys and other organs (Meng, Zhu, Jiao, Guo, & Gao, 2018). External evil invading the stomach, improper diet, burn the planks, affect-mind dissatisfaction, debility in old age, vacuity following illness, and drug effect were common causes of constipation (Liu, Chen, Zhang, Fu, & Lei, 2021; Wang et al., 2022; Zhang, Shen, Zhang, & Ye, 2017). Synthesizing the theory of the etiology and pathogenesis of constipation in ancient and modern doctors, Yu Meng et al. classified constipation as *sthenia* constipation and *deficient* constipation. In TCM, Ben deficiency refers to *yin* deficiency of liver and kidney, *qi* and blood deficiency of spleen and stomach, and Biao excess refers to the evil of wind, fire, phlegm and blood stasis. And, chronic constipation is considered to be Ben deficiency and Biao excess and usually fell under the category of *deficient* constipation, which was caused

by the deficiency of *qi*-blood and *yin*-*yang* in the Zang-fu viscera (Feng, 2020; Mao, Mei, Gan, Xu, & Liu, 2021; Yang, Wang, & Xiong, 2019).

Based on TCM syndrome differentiation and treatment of constipation, Shouhui Tongbian Capsule (SHTB) are composed of *Polygoni Multiflori Radix* (*Polygonum multiflorum* Thunb.), *Aloe* (*Aloe barbadensis* Mill.), *Cassiae Semen* (*Cassia obtusifolia* L.), *Lycii Fructus* (*Lycium barbarum* L.), *Ginseng Radix et Rhizoma* (*Panax ginseng* C. A. Mey.), *Atractylodis Macrocephalae Rhizoma* (*Atractylodes macrocephala* Koidz.), *Aurantii Fructus Immaturus* (*Citrus aurantium* L.) and *Asini Corii Colla* (*Equus asinm* L.), which could nourish *yin* and boost *qi*, simultaneous reinforcement and reduction, address both symptoms and root causes (Gong et al., 2022; Guan, Zhuang, Fan, Deng, & Zhang, 2021; Wang et al., 2021; Xu, Liu, Li, Yu, & Li, 2021; Zhang, Han, Zhang, Tian, & Yu, 2021). We use the accepted format for writing of plant names and the full plant names has been checked via The Plant List (<https://www.theplantlist.org>) on October 30, 2022. *Ginseng Radix et Rhizoma* and *Aloe* are believed as the principal drugs in this prescription, which are used for reinforcing vigor, cleaning away liver-heat, and enhancing *qi* while nourishing fluid. Xichun Zhang (AD 1860 to 1933), a famous doctor of the Chinese and western Huitong School in the late Qing Dynasty, the constipation with deficiency syndrome should be treated not only through defecating, but also using tonifying *qi* with *Ginseng Radix et Rhizoma*. *Aloe* is bitter-cold, which was recorded to be mainly used as a laxative in “EBERSPAPYRUS” found in the ancient Egyptian pyramids. *Polygoni Multiflori Radix* and donkey-hide gelatin are believed as the adjuvant drugs, which are used for tonifying, moistening dryness, nourishing blood, and moistening the intestines. In the book of *Encountering with Origin of Herbal Classic* (Benjing Fengyuan in Chinese), it was recorded that *Polygoni Multiflori Radix* was used to treat the boring of *jin* and *Xue* and constipation caused by wind invasion. Both *jin* and *Xue* are derived from the essence of diet, water and grain, which both belong to the *yin* fluid of human body. In *Ren-Zhai's Straight Directions of Prescriptions* (Renzhai Zhizhi Fang in Chinese), a clinical comprehensive medical book that focused on the treatment of miscellaneous diseases in internal medicine, it was introduced that donkey-hide gelatin could treat old or deficient people with constipation. *Lycii Fructus*, *Cassiae Semen*, *Atractylodis Macrocephalae Rhizoma* and *Aurantii Fructus Immaturus* are assistant drugs, which are used for cold purgation, moving stagnation, tonifying *qi*, enriching *yin*, and moistening the intestines for relaxing bowel. In the *Miscellaneous Records of Famous Physicians* (Mingyi Bielu in Chinese), which was a collection of the ancient Chinese medicine doctors over the ages, it was recorded that *Lycii Fructus* could help to strong *yin*, and benefit the large and small intestine, especially it was

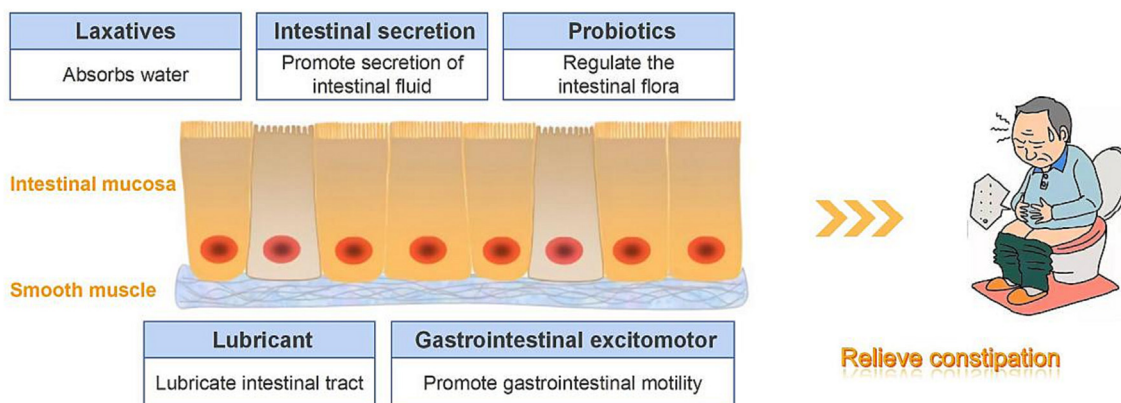


Fig. 1. Mechanism of western medicine in treatment of constipation.

mostly used for constipation with *yin* deficiency. *Cassiae Semen* was first recorded in the *Compendium of Materia Medica* (*Bencao Gangmu* in Chinese), which elaborated Li Shizhen's contribution to Chinese ethno-botany in the following aspects: explanations of plants' names, plant taxonomy, plant morphology and growth environment. It is bitter and salty in taste, slightly cold in nature, and attributed to the large intestine meridian, which not only has the function of moistening the intestine, but also has the effect of clearing liver and improving vision, which means that the prescription of clearing the liver and reducing fire, and detoxifying, which could treat febrile ophthalmopathy. In *Penerating the Mysteries of Materia Medica* (*Bencao Tongxuan* in Chinese) by Zhongzi Li (AD 1588–1655), in which the clinical application of each drug was highlighted, it was recorded that *Atractylodis Macrocephalae Rhizoma* was a medicine for invigorating the spleen and stomach. In the *Synopsis of the Golden Chamber* (*Jingui Yaolue* in Chinese), the earliest extant monograph on the diagnosis and treatment of miscellaneous diseases in our country by Zhongjing Zhang (about AD 150–154 to about AD 215–219), which was the doctor in the last years of the Eastern Han Dynasty, established the principle of “syndrome differentiation and treatment”, and was honored as “medical sage” by later generations, used *Aurantii Fructus Immaturus* and *Atractylodis Macrocephalae Rhizoma* to promoting *qi* to eliminate stagnation which means that *qi* is eased using active drugs to reduce pectoral and abdominal distention. Besides, *Aurantii Fructus Immaturus* is messenger drug, which is used for dissipating stagnant *qi* and removing food retention. The advantage of SHTB lies in reinforcement and elimination in combination. It can comprehensively improve gastrointestinal function by comprehensive conditioning which includes tonifying *qi*, moistening the intestines and relaxing the bowels (Bai et al., 2022; Lu et al., 2020; Sun et al., 2021).

This paper summarizes the clinical (Table 1) and basic research progress of SHTB in the treatment of chronic constipation in recent years, especially in the treatment of functional constipation, malignant tumor chemotherapy-related constipation, colitis constipation, type 2 diabetes constipation, chronic heart failure constipation. The relevant mechanisms mainly involve promoting intestinal motility, promoting intestinal fluid secretion, regulating gastrointestinal hormones, enhancing interstitial cells of cajal (ICC) energy metabolism and proliferation, regulating immunity, improving blood glucose, regulating *qi* activity and so on (Fig. 2). The purpose of our work above is to provide references and help for the clinical treatment of chronic constipation with SHTB.

2. SHTB for treatment of functional constipation

2.1. Clinical research

Conventional constipation drugs including osmotic laxatives, prokinetic agents, probiotics separately combined with SHTB for the treatment of functional constipation are significantly more effective than the conventional drug alone.

Firstly, osmotic laxatives in combination with SHTB is effective in the treatment of functional constipation. In a clinical study, the efficacy of SHTB in treating 2396 patients with dysfunctional constipation was observed. It was found that effectiveness and quality of life of patients were significantly improved after prolonging the duration of SHTB. Furthermore, SHTB could regulate intestinal flora, and the regulating effect was more obvious in patients with shorter disease duration (Zhang, Han, Zhang, Tian, & Yu, 2021). Zhou et al. selected 98 elderly patients with functional constipation, which were divided into a control group (taking lactulose oral solution) and an study group (adding SHTB on the basis of the control group) and continuous treated for 4 weeks, judged the efficacy

of the two groups, and counted the recurrence after stopping the drug (Zhou & Zhou, 2019). The results showed that the total effective rate of the study group was significantly higher than that of the control group, the improvement of the degree of bowel difficulty and frequency of spontaneous bowel movement were significantly better than that of the control group, and the recurrence rate 4 weeks after stopping the drug was significantly lower than that of the control group. In summary, SHTB can effectively improve the treatment effect of functional constipation and reduce the recurrence rate (Zhou & Zhou, 2019). Moreover, Liu et al. took 78 elderly patients with functional constipation as the research object, of which the study group was treated with lactulose oral solution combined with SHTB and the control group was treated with lactulose oral solution (Liu & Jiang, 2020). Then the clinical efficacy, clinical symptom score and anorectal kinetic indicators of the two groups were observed. The results indicated that the total effective rate of treatment in the study group was significantly higher than that in the control group. The scores of difficulty of defecation, frequency of spontaneous defecation, the rectal pressure and external sphincter pressure were all significantly reduced after treatment in both groups, and degree of reduction in the study group was more significant than that of the control group (Liu & Jiang, 2020). Thus, SHTB could significantly improve anorectal motility, alleviate defecation difficulties, and promote spontaneous defecation.

Secondly, prokineticagents combined with SHTB has significant effect on functional constipation. Zhou et al. took 127 patients with functional constipation as the study object, and the control group was given mosapride, and the study group was given SHTB and mosapride (Zhou, Yuan, Liu, Wang, & Li, 2021). After 4 weeks of treatment, the efficacy and symptom scores of the two groups were recorded and the adverse reactions were observed. The results showed that the total effective treatment rate of the study group was significantly higher than that of the control group. After treatment, the scores of bowel dysfunction and fecal traits in both groups decreased compared with before treatment, and the decline was more significant in the study group than in the control group. In addition, the scores of difficulty in defecation and stool characteristics in both groups were higher than before treatment, and the degree of increase in the study group was significantly higher than that in the control group (Zhou, Yuan, Liu, Wang, & Li, 2021). From the above study, the addition of SHTB on the basis of mosapride can significantly improve the clinical signs and symptoms of functional constipation, thereby improving the quality of life.

Thirdly, probiotics combined with SHTB are more effective than probiotics alone for the treatment of functional constipation. Tan et al. took 183 elderly patients with functional constipation with *qi* and *yin* deficiency as the study object (Tan, Wang, Zhou, & Si, 2021). All patients received conventional treatment, in control group 1 Bifidobacterium Triple Viable Capsule was added on the basis of conventional treatment, in control group 2 SHTB was added on the basis of conventional treatment, and in the study group SHTB was used combined with Bifidobacterium Triple Viable Capsule. In the study, the effect of treatment for 4 weeks in three groups was observed, and the evaluation indicators included total treatment efficiency, the incidence of adverse reactions, recurrence rate, TCM syndrome score, Bristol score, bowel difficulty score, serum gastrin motilin, P substance and other gastrointestinal hormone levels, canal resting pressure, canal systolic blood pressure, and maximum tolerable capacity. The results showed that the total treatment efficiency, Bristol score, resting pressure, and systolic blood pressure in the study group were significantly increased compared with control groups 1 and 2. Moreover, the recurrence rate, TCM symptom score, and bowel difficulty score were significantly reduced. In short, SHTB combined with Bifidobacterium Triple Viable Capsule in the treatment of functional constipation in

Table 1
Clinical research progress of SHTB in treatment of chronic constipation.

No.	Types of constipation	Control groups		Treatment groups		Application duration	Total effective rate (%) (control/treatment)	References
		n	Intervention	n	Intervention			
1	Functional constipation	none	none	2396	SHTB (0.70 g each time, three times a day)	Two weeks	99/none	Zhang et al., 2021
2	Functional constipation	49	Lactulose oral solution (15 mL each time, twice a day)	49	SHTB (0.70 g each time, three times a day)	Four weeks	75.5/91.8	Zhou et al., 2019
3	Functional constipation	39	Lactulose oral solution (15 mL each time, twice a day)	39	Lactulose oral solution (15 mL each time, twice a day) and SHTB (0.70 g each time, three times a day)	Two weeks	79.49/94.87	Liu et al., 2020
4	Functional constipation	63	Mosapride (5 mg each time, three times a day)	64	Mosapride (5 mg each time, three times a day) and SHTB (0.70 g each time, three times a day)	Four weeks	77.78/90.63	Zhou et al., 2021
5	Functional constipation	122 (control group 1 and 2)	Control group 1 (Bifidobacterium Triple Viable Bacterian Capsules, 0.42 g each time, three times a day); control group 2 (SHTB, 0.70 g each time, three times a day)	61	Bifidobacterium Triple Viable Bacterian Capsules (0.42 g each time, three times a day) and SHTB (0.70 g each time, three times a day)	Four weeks	80.33/83.61/95.08	Tan et al., 2021
6	Functional constipation	75	Lactulose oral solution (30 mL each time, once a day)	75	Lactulose oral solution (30 mL each time, once a day) and SHTB (0.70 g each time, three times a day)	Two weeks	69.33/85.33	Yuan et al., 2021
7	Tumor chemotherapy-related constipation	31	Diet adjustment	32	Diet adjustment and SHTB (0.35–0.70 g each time, 2–3 times a day)	From the beginning of the first day of chemotherapy to the third day after the end of chemotherapy	77/91	Gao et al., 2019
8	Tumor chemotherapy-related constipation	40	Lactulose oral solution (15 mL each time, twice a day)	40	Lactulose oral solution (15 mL each time, twice a day) and SHTB (0.70 g each time, three times a day)	Two weeks	75/90	Zhang et al., 2020
9	Tumor chemotherapy-related constipation	48	Castor oil (10 mL each time, three times a day)	48	Castor oil (10 mL each time, three times a day) and SHTB (0.70 g each time, three times a day)	Two weeks	66.7/87.5	Li et al., 2021
10	Tumor chemotherapy-related constipation	30	Tongbianling Capsule (1.25 g each time, once a day)	30	SHTB (0.35 g each time, three times a day)	Two weeks	90/93	Li et al., 2020
11	Opiates and tumor-related constipation	42	Lactulose oral solution (15 mL each time, twice a day)	42	Lactulose oral solution (15 mL each time, twice a day) and SHTB (0.70 g each time, three times a day)	Two weeks	80.95/90.48	Feng, 2020
12	Colitis-associated constipation	44	Mosapride (5 mg each time, three times a day)	44	Mosapride (5 mg each time, three times a day) and SHTB (0.35 g each time, three times a day)	Two weeks	77.27/90.91	Zhang et al., 2017
13	Type 2 diabetic constipation	48	Mosapride (5 mg each time, three times a day)	48	Mosapride (5 mg each time, three times a day) and SHTB (0.35 g each time, three times a day)	Four weeks	62.5/93.75	Cui, 2020
14	Chronic heart failure -related constipation	30	Biantong Capsule (1.05 g each time, twice a day)	30	SHTB (0.35 g each time, three times a day)	Two weeks	66.67/93.33	Shen et al., 2021

the elderly with *qi-yin* deficiency is remarkable, and the symptoms of constipation in patients are significantly reduced, and the anorectal kinetics are significantly improved. Besides, there are few adverse reactions and low recurrence rates in the study group (Tan, Wang, Zhou, & Si, 2021).

The above clinical studies have found that SHTB could relieve functional constipation by promoting intestinal motility, promoting intestinal secretion, regulating gastrointestinal hormones and other mechanisms of action. In terms of promoting intestinal motility, studies have shown that SHTB significantly increased the canal systolic blood pressure and resting pressure in patients with functional constipation, reduced the maximum tolerance

capacity, and significantly improved the symptoms of constipation (Tan, Wang, Zhou, & Si, 2021). Zhou et al. found that SHTB significantly improved the degree of defecation difficulty, defecation time, frequency of defecation, abdominal pain and bloating in patients with functional constipation (Zhou & Zhou, 2019). In terms of promoting intestinal secretion, Tan et al. evaluated the traits and water content of stool before and after the application of SHTB through the Bristol stool classification, and the results showed that SHTB could significantly increase the water content of stool, improve stool traits, and have a significant effect on functional constipation (Tan, Wang, Zhou, & Si, 2021). In terms of regulating gastrointestinal hormones, it was found that the

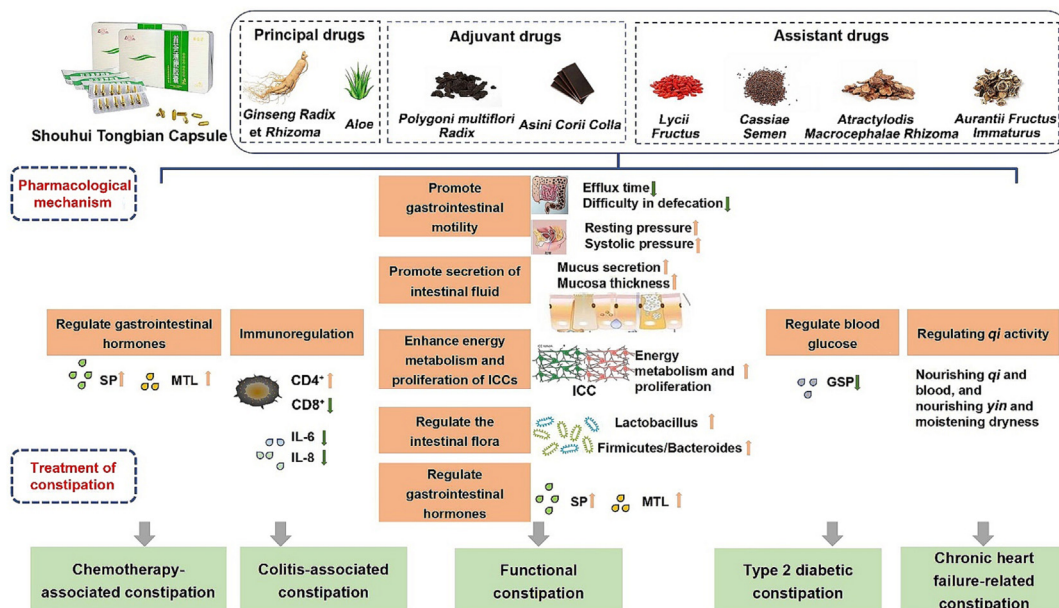


Fig. 2. Mechanisms of Shouhui Tongbian Capsule in treatment of different types of constipation.

concentrations of serum motilin (MTL) and P substance (SP) in the SHTB treatment group were significantly higher than before treatment, and the increase of the study group was higher than that in the control group (Zhou, Yuan, Liu, Wang, & Li, 2021; Yuan, Zhang, Wang, Shi, & Li, 2021). Because gastrointestinal hormones such as MTL and SP could increase smooth muscle contraction, peristalsis and emptying motility of the gastrointestinal tract. Thus, SHTB could regulate gastrointestinal hormones, promote gastrointestinal movement and improve the symptoms of constipation in patients (Yuan, Zhang, Wang, Shi, & Li, 2021; Zhou, Yuan, Liu, Wang, & Li, 2021).

2.2. Basic research

Multiple animal experiments have confirmed that SHTB could effectively improve functional constipation. Lin et al. established a rat model of constipation induced with loperamide hydrochloride (LH), and then the rats were treated with different doses (35, 70 mg/kg bw) of three times a day (Lin et al., 2022). Gastric emptying rate, fecal moisture content and body weight of all rats were assessed weekly. The results showed SHTB could alleviate gastric emptying rate, fecal moisture content and the decrease of body weight in LH induced constipation (Lin et al., 2022). Li et al. used SHTB to treat a slow-transit functional constipation rat model constructed from intragastric administration of compound diphenoxylate (Li et al., 2018). The rats were divided into six groups: normal group, model group, cistanche oral liquid group, SHTB low dose group, SHTB middle dose group, and SHTB high dose group. After seven consecutive days administration of drugs above, the effects of SHTB on the time of first black stool excretion, the rate of carbon ink propulsion of the small intestine, and the number of defecation particles in 12 h were observed. It was found that the low-, middle- and high-dose groups of SHTB all significantly shortened the first bowel time of rats and increased the carbon ink propulsion rate of the small intestine and the number of defecation particles for 12 h. The number of colonic mucosal mucous cells in the middle- and high-dose rat groups both increased significantly compared with the model group. It was concluded that SHTB could improve functional constipation by promoting bowel movement and increasing colonic mucus secretion (Li et al.,

2018). Zheng et al. used SHTB to treat a mouse model of slow-transport functional constipation induced by intragastric administration of loperamide hydrochloride. The mice were divided into five groups: blank group, model group, SHTB high-, middle- and low-dose groups. The drugs were continuous administrated for 14 d, and the first defecation time, 6 h defecation particle number, stool wet and dry weight, and fecal moisture content were recorded. The results showed that SHTB significantly shorten the excretion time of the first melena, increased the number of stool particles, stool wet weight and dry weight, which thereby improved the symptoms of slow-transmission functional constipation induced by LH (Zheng, Guo, Zhang, Pan, & Zeng, 2021). In another basic study in mouse, Bai et al. evaluated the effect of SHTB using LH-induced constipation mouse model (Bai et al., 2022). And the results showed SHTB could significantly accelerate enteric motility and ameliorate LH-induced experimental constipation (Bai et al., 2022).

SHTB could improve constipation not only by promoting intestinal motility and intestinal fluid secretion, but also by regulating intestinal flora and enhancing the energy metabolism and promoting the proliferation of ICCs (Bai et al., 2022; Lin et al., 2022; Zhang, Han, Zhang, Tian, & Yu, 2021). In the regulation of intestinal flora, SHTB could increase the relative abundances of *Lactobacillus* and the ratio of Firmicutes to *Bacteroides* (F/B). Moreover, the contents of propionic acid and acetic acid were obviously increased in the rats treated with SHTB (Lin et al., 2022). Another study found that SHTB significantly accelerated enteric motility and ameliorated LH-induced experimental constipation, which might be caused by modulating gut microbiota dysbiosis, altering microbiota metabolites, and enhancing intestinal 5-hydroxytryptamine (5-HT) production from enterochromaffin cells and enteric neuron growth of the enteric nervous system in the small intestine and colon (Bai et al., 2022). On the other hand, SHTB could treat functional constipation via enhancing the energy metabolism and promoting the proliferation of ICCs that are pacemaker cells of gastrointestinal motility. In the experiments of loperamide hydrochloride-induced slow-transit functional constipation mouse, the content of adenosine triphosphate (ATP) synthase and isocitric acid dehydrogenase, ICC-specific marker c-Kit and stem cell factor (SCF)-positive cells in intestinal tissues increased significantly after SHTB applied. The

study showed that SHTB might increase the activity of ATP synthase and mitochondrial isocitric acid dehydrogenase in intestinal cells, upregulate the c-Kit/SCF signaling pathway, promote ICC proliferation, enhance intestinal nerve information transmission, promote intestinal motility, and thus improve constipation symptoms (Zheng, Guo, Zhang, Pan, & Zeng, 2021). In another study, the gastrointestinal stromal cell GIST-882 was used as the research object, it was found that SHTB could promote the proliferation of GIST-882 cells, maintain mitochondrial structural integrity, increase mitochondrial membrane potential, upregulate the activity of isocitric acid dehydrogenase, increase ATP content in cells, and promote the expression of SCF/c-Kit and CDK2/cyclin A signaling pathway-related proteins. The above showed that SHTB could accelerate the synthesis of ATP by upregulating the activity of mitochondrial isocitric acid dehydrogenase, activate the SCF/c-Kit and CDK2/cyclin A signaling pathways, enhance the energy metabolism of gastrointestinal stromal cells and promote their proliferation (Zhang, Zheng, Li, Sun, & Zeng, 2021).

In addition, SHTB treating constipation in mice may be associated with reducing intestinal inflammation and permeability, regulating the expression of intestinal barrier-related proteins, and protecting the intestinal barrier. The application of SHTB could effectively reduce the first melena stool time of mice with slow-transport constipation, increase its ink propulsion rate, significantly reduce the level of tumor necrosis factor- α (TNF- α) and D α -lactate in serum, improve the infiltration of lymphocytes, plasma cells and other inflammatory cells in colon tissue, significantly increase the colon tissue Occludin, Claudin 5, zonula occludens-1 (ZO-1) and TIMP-1 protein expression levels, significantly reduce protein expression levels of matrix metalloprotein (MMP)-9 and MMP-2, alleviate their damage to the intestinal barrier, upregulate Claudin 5 protein expression levels, and protect the intestinal barrier of constipation mice (Li et al., 2022).

3. SHTB for treatment of organic constipation

3.1. Malignant tumor chemotherapy-induced constipation

Constipation is one of the most common adverse reactions after chemotherapy for malignant tumors, and its incidence is about 15% to 70% (Li & Cheng, 2020). Chemotherapy constipation is mainly caused by chemotherapy drugs such as cisplatin, vinblastine, vincristine, as well as adjuvant drugs such as 5-HT₃ receptor inhibitors and opioid analgesics (Li, Zhao, Hu, & Ma, 2021; Nie, Wang, & Zhu, 2021). In addition to inhibiting and killing tumor cells, chemotherapy drugs also have a certain toxic effect on normal cells, so the digestive system and immune function of the body suffer from varying degrees of damage, making the digestive system dysfunctional, of which constipation and vomiting are particularly common. Adjuvant drugs such as 5-HT₃ receptor inhibitors and opioid analgesics have obvious inhibitory effects on gastrointestinal peristalsis, which can easily cause constipation (Ding, Liu, Yan, Hu, & Yao, 2020; Gu, Tang, & Huo, 2020). According to the dialectical concept of TCM, malignant tumor chemotherapy-related constipation is a sign of syndrome of deficiency *Ben* and excessive *Biao*, and most of them belong to the deficiency type. Treatment of constipation of deficiency type should be based on the tonify of healthy *qi*, which focuses on tonifying *qi*, replenishing blood, warming *yang* and enriching *yin*. The sweet and warm medicines that could moisten the intestines are applied according to conditions of the patient, which could help to achieve the goal of treating both the symptoms and the root (Chen & Lin, 2020). SHTB is a proprietary Chinese patent medicine prepared based on this theory, which plays a role in tonifying *qi* and blood, cultivating liver and kidneys, moistening dryness and relaxing the bowels, and ultimately improving intestinal function.

A number of studies have shown that SHTB have significant effects on constipation after chemotherapy, which could effectively promote patients to defecate and improve constipation. In a clinical trials involving 63 patients with post-chemotherapy constipation, SHTB was found to be significantly more effective than dietary therapy in the control group (Gao, Liang, Shi, & Liu, 2019). Another study of SHTB in the treatment of constipation after chemotherapy for malignant biliary and pancreatic tumors showed that the bowel scores (interval between bowel movements and time per bowel movement) were significantly lower than the lactulose control group and that the total effective rate in the SHTB group was significantly higher than the control. The results indicated that SHTB could significantly improve constipation after chemotherapy for hepatobiliary and pancreatic malignancies and effectively relieve bowel pain and reduce defecation time (Zhang, Liu, Zhang, Lv, & Liu, 2020). Another study showed that SHTB had a significant effect on constipation in patients with gastric and colorectal cancer after chemotherapy, which could significantly improve defecation difficulty, defecation frequency score and defecation time (Li, Zhao, Hu, & Ma, 2021). SHTB could also significantly improve the symptoms of constipation and defecation interval time, stool character, defecation difficulty after chemotherapy (Li & Cheng, 2020).

Opioids are commonly used and effective analgesics for the treatment of acute and chronic pain, and long-term repeated use of opioids can lead to gastrointestinal dysfunction, of which opioid-associated constipation is the most common (Wang & Sun, 2016). At present, western medicines for the treatment of opioid-related constipation mainly include laxatives, prokinetic drugs, secretory agents, microecological preparations and opioid receptor antagonists, but the efficacy of the above drugs still cannot meet the needs of patients. Feng (2020) took 84 elderly patients with malignant tumor and constipation who had taken opioid analgesics as the research object. The results showed that after 14 d of taking SHTB, the efficacy of TCM syndrome was significantly higher than that of the control group, and the recurrence rate of constipation was significantly lower than that of the control group.

Therefore, SHTB has a significant effect on the treatment of chemotherapy-related constipation of malignant tumors, and the mechanism is mainly related to the increase of the serum content of SP and vasoactive intestinal peptide (VIP) in patients (Shi & Lv, 2021).

3.2. Colitis-associated constipation

Patients with colitis-associated constipation have extensive inflammatory changes in the colonic mucosa with the main clinical features of constipation and abdominal pain (Lin, Xu, & Xu, 2019). Western medicine is usually used in clinical treatment, which is less effective and recurrent (Zhang, Shen, Zhang, & Ye, 2017). In TCM theory, the core pathogenesis of colitis-associated constipation is spleen deficiency and dampness toxin, which could be generally divided into spleen deficiency liver stagnation, spleen and kidney *yang* deficiency, *qi* and *yin* deficiency and other syndromes (Xu & Chen, 2021). SHTB is just suitable for this pathogenesis and plays a “tonic, moisten, relieving pain” comprehensive conditioning role in *qi* deficiency or *yin* deficiency constipation, that is, nourishing *yin* and benefiting *qi*, and reinforcing and eliminating in combination. A clinical study of constipated colitis showed that the total efficacy of the SHTB treatment group was significantly higher than the control group and that the frequency of bowel movements was significantly increased with the difficulty of bowel movements significantly improved. Moreover, serum testing showed that interleukin (IL)-6 and IL-8 levels were significantly lower than before treatment and that the percentage of CD4⁺ cells was obviously increased, especially in the SHTB-treated group. In

summary, SHTB could reduce the level of inflammatory factors in patients with colitis-associated constipation, promote the recovery of immune function, and thus play a role in the treatment of colitis-associated constipation (Yu, 2020).

3.3. Type 2 diabetic constipation

In recent years, the number of people with type 2 diabetes in developing countries has surged, and the prevalence of type 2 diabetes in China has reached $(11.2 \pm 0.7)\%$ (Li et al., 2020). Constipation is a common complication of diabetes, and about 25% of patients with diabetes suffering from constipation. In clinical practice, type 2 diabetic constipation is characterized by difficulty defecation, reduction in the number of bowel movements, and hard stool. The current treatment of diabetic constipation is based on blood glucose control and auxiliary symptomatic treatment such as prokinetic drugs and laxatives (Yu, 2013). In TCM, diabetes is considered as consumptive thirst, which belongs to the syndrome of deficiency *Ben* and excessive *Biao*, which is caused by deficiency of both vital energy and *yin* with dryness-heat, dampness turbidity, and blood stasis (Liu, Chen, Zhu, Zhang, & Yang, 2018; Zhu, Lou, & Wang, 2018). SHTB has the effects of tonifying *yin*, replenishing *qi*, draining turbidity and laxative.

In a clinical study involving 96 patients with constipation due to gastric palsy in type 2 diabetes, the clinical efficacy, constipation symptom points, quality of life self-assessment scale scores and adverse drug reactions of patients with constipation were better than those in the SHTB treatment group. In addition, the levels of glycosylated serum protein in the SHTB treatment group were significantly lower than in the pre-treatment and significantly lower than in the control group. In summary, SHTB can improve vagus nerve damage by reducing the level of glycosylated serum protein, thereby promoting gastrointestinal peristalsis and improving constipation caused by type 2 diabetes (Cui, 2020). Another clinical study found that warm acupuncture and moxibustion combined with SHTB could significantly ameliorate gastrointestinal hormone levels, enhance the gastric emptying rate, and improve symptoms and therapeutic effects in patients with diabetic gastroparesis (Huang, Wang, Chu, & Dai, 2022).

3.4. Chronic heart failure-associated constipation

Heart failure patients need long-term bed support, so their activity is more limited and prone to a variety of complications. Constipation is one of the common complications of heart failure patients, with an incidence of up to 37.31% (Wu & Li, 2022). At present, the clinical treatment of chronic heart failure constipation mostly adopts western medicine, such as oral laxatives, Kaiserlu enema, etc., but the efficacy is not satisfactory to patients. In the theory of TCM, patients with heart failure were short of heart *qi* deficiency, lacking intestine nourishment, losing the order of gastrointestinal peristalsis, which causes *qi* and blood deficiency, intestinal juice lack and stool obstruction (Wang, Zhang, & Zhou, 2018). SHTB is beneficial to the effect of tonifying *qi* and *yin*, upbearing the pure and downbearing the turbid, which can make the *qi* movement smooth and return the intestines to normal. The study showed that SHTB could effectively treat constipation in heart failure while improving the quality of sleep of patients. The TCM syndrome score and the Pittsburgh sleep quality index score were both decreased after SHTB treatment, and the total effective rate was significantly higher than that of the control group (Shen & Peng, 2021).

Heart failure patients were weakening heart *qi*, shorting of tonifying for the gastrointestinal tract, losing the order of gastrointestinal peristalsis, while losing a large number of body fluids after long-term application of diuretics, which caused dry stools and

poor bowel movements. SHTB are beneficial to the effect of tonifying *qi* and *yin*, upbearing the pure and downbearing the turbid, which can not only nourish the heart and blood, and fortify the spleen and replenish *qi*, but also enrich *yin* and moisten dryness, and moisten the intestines and laxative, so that the *qi* movement is smooth, and the gastrointestinal function returns to normal. Biantong capsules are composed of white art (stir-fried), cistanche, angelica, mulberry, citrus fruit, and aloe vera, which have the effects of enriching the kidney, fortifying the spleen, moistening the intestines, and relaxing the bowels. This medicine has the characteristics of moisturizing and tonic and is mainly used for chronic debilitating constipation. Besides, SHTB and Biantong Capsules are similar in composition and usage. However, researchers found that SHTB had better clinical effects on the treatment of constipation than Biantong Capsules, which might be related to the fact that SHTB plays better roles in tonifying *qi* and blood and moisturizing the intestines in patients with heart failure.

4. Discussion

Although SHTB could significantly improve a variety of constipation, it has different pharmacological mechanisms for different types of constipation. The pharmacological mechanisms of SHTB for the treatment of functional constipation mainly include promoting gastrointestinal motility via enhancing the secretion of gastrointestinal hormones of SP and MTL, promoting secretion of intestinal fluid, enhancing energy metabolism via increasing the activities of ATP synthase and mitochondrial isocitrate dehydrogenase of the intestinal cells and up-regulating c-Kit/SCF signaling pathway to promote the proliferation of ICCs, regulating the intestinal flora. In addition, SHTB is effective in the treatment of organic constipation. For the chemotherapy-associated constipation, SHTB could improve it primarily through the regulation of gastrointestinal hormones including SP and MTL. In the treatment of colitis-associated constipation, SHTB might exert therapeutic effect by reducing the levels of IL-6 and IL-8, improving the percentages of CD4⁺ and CD8⁺, reducing the levels of inflammatory factors and promoting the recovery of immune function to treat colitis-associated constipation. For type 2 diabetic constipation, SHTB could reduce the level of glycated serum protein and improve the damage of vagus nerve, thereby promoting gastrointestinal peristalsis to relieve constipation. In the treatment of chronic heart failure-related constipation, SHTB could improve constipation by nourishing *qi* and blood, and nourishing *yin* and moistening dryness.

In summary, SHTB could treat functional constipation and chemotherapy-induced constipation both by regulating the levels of gastrointestinal hormones. The mechanism of increasing the activities of ATP synthase and mitochondrial isocitrate dehydrogenase and promoting the proliferation of ICCs is only involved in functional constipation. The modulation of inflammatory factors including IL-6 and IL-8 and the percentages of CD4⁺ and CD8⁺ is only involved in colitis-associated constipation. Moreover, the decrease of the level of glycated serum protein is only involved in type 2 diabetic constipation. Modern pharmacological mechanisms of SHTB in the treatment of chronic heart failure-related constipation is still not yet carried out.

5. Conclusion and future perspectives

Constipation is a common gastrointestinal dysfunction disorder in clinical practice, and the number of people with constipation is increasing year by year due to the influence of living conditions and mental and psychological factors. TCM holds that while the cause of constipation is in the large intestine, it is closely related

to the lungs, spleen, stomach, liver, kidneys and other organs. The pathogenesis theory of colon defecation difficulty and intestinal peristalsis losing order is widely recognized. SHTB could comprehensively improve gastrointestinal function through comprehensive conditioning which includes tonifying *qi*, moistening the intestines, and relaxing the bowels. It could tonify *yin*, boost *qi*, simultaneous reinforcement and reduction, address both symptoms and root causes, which could treat constipation symptomatically. In fact, many clinical and basic studies have shown that SHTB are effective in treating constipation. The current roles of SHTB in the treatment of a variety of constipation mainly involve the treatment of functional constipation, chemotherapy-related constipation of malignant tumors, colitis constipation, type 2 diabetic constipation, chronic heart failure constipation and so on. At the same time, more aspects and deeper clinical effects, treatment mechanisms and pharmacological toxicology need to be further studied.

CRedit authorship contribution statement

Liping Gong: Data curation, Formal analysis, Visualization, Writing – original draft. **Hang Du:** Writing – review & editing. **Xin Guo:** Writing – review & editing. **Jianchao Li:** Data curation. **Xiaomin Zhu:** Formal analysis. **Xianhui Shen:** Data curation. **Zhiyan Huang:** Data curation. **Kaiyi Wu:** Supervision. **Guimin Zhang:** Conceptualization, Project administration. **Rong Sun:** Supervision, Conceptualization, Project administration, Validation.

Declaration of Competing Interest

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

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