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Review

Treatment of constipation with *Aloe* and its compatibility prescriptions

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ABSTRACT

Constipation is a common and prevalent digestive system disease in clinical practice, which seriously affects human physical and mental health. Currently, chemical drugs have good short-term therapeutic effects. However, because of their adverse reactions, easy recurrence after drug discontinuation, and dependence with long-term use, the long-term efficacy is unsatisfactory. The pathogenesis of constipation is mainly attributed to dysfunction of zang-fu organs and imbalance of qi-blood and yin-yang, with the syndrome being asthenia in origin and asthenia in superficiality. *Aloe* is a traditional Chinese medicine with cold properties and a bitter taste, and one of the most commonly used herbs for constipation. Based on *Aloe* and its monomer components, combined with the existing compatibility studies of *Aloe* and several Chinese patent drugs represented by *Aloe*, this paper comprehensively and systematically introduced the research progress of *Aloe* and its compatibility prescriptions in the treatment of constipation from basic experiments to clinical observations, providing theoretical basis and medication guidance for the clinical rational application of *Aloe* and its prescriptions in the treatment of constipation. At the same time, it also provides the direction for future research on the mechanism of *Aloe* in the treatment of constipation.

Contents

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1. Introduction

Constipation is a common digestive system disease in clinical practice, mainly manifested by dry stool, difficulty defecating, reduced frequency of defecation or feeling of inadequate defecation, which is mostly caused by abnormal colorectal and anal function (Li & Yu, 2011). Functional constipation can be generally classified into constipation disorder, mixed constipation, normal transit constipation, and slow transit constipation (STC) (Shahid, Ramzan, Maurer, Parkman, & Fisher, 2012). STC is the main type of chronic constipation, often causing difficulty in defecation complicated by abdominal pain, abdominal distension, loss of appetite, emotional disorders, etc., characterized by a significant increase in intestinal transit time (Wong, Hebbard, Gibson, & Burgell, 2020; Wang & Wu, 2019). STC has become an epidemic with an increasing incidence, especially affecting the quality of life of elderly patients (Zhao et al., 2011). Despite the high incidence of STC worldwide, its etiology remains poorly understood. A large number of studies have shown that there are many factors in the pathogenesis of STC, such as changes in intestinal nervous system and metabolism, abnormal mucosal secretion, imbalance of flora and abnormal gastrointestinal hormones, etc. (Bharucha & Lacy, 2020; Bharucha & Wald, 2019). From the perspective of traditional Chinese medicine (TCM) theory, constipation is generally divided into excessive and deficient patterns. The excessive pattern is characterized by presence of heat or qi stagnation, while the deficient patterns are characterized by depletion of qi, yin or yang. Constipation is primarily caused by improper dietary habits, consumption of spicy foods, or emotional distress leading to qi stagnation. This results in a disruption of large intestine function and can also occur after experiencing fever-induced dehydration, which hinders intestinal moisture retention. Additionally, advanced age may contribute to deficiencies in both qi and blood circulation, further impeding proper large intestine functioning (Wei, Zeng, Luo, Liang, & Huang, 2019). Therefore, it is necessary to adopt an interdisciplinary approach to explore its pathological features and develop therapies based on multi-components and multi-targets.

The treatment of constipation is particularly important. TCM and Western medicine have their own advantages. Currently, drug therapy is the main means of functional constipation, and commonly used drugs in clinical practice include gastrointestinal motility drugs, laxatives, secretory drugs and microbial ecological agent. The efficacy of these treatments may be limited to the short term, as prolonged usage can result in gastrointestinal dysfunction, electrolyte imbalances, drug dependency, and other associated complications (Fukudo, Hongo, Kaneko, Takano, & Ueno, 2015; Huang, Zhu, Qu, & Qin, 2018; Wang & Wu, 2019). Western medicine treatment has good short-term efficacy, but no long-term efficacy in that there are often adverse reactions, easy to relapse after drug discontinuation, long-term dependence and other problems; the effect of single chemical drug is generally not good, so most of them are combined (Lin et al., 2015). TCM, emphasizing holistic concept and syndrome differentiation, not only has significant curative effect, but also basically has no drug dependence (Wei, Zeng, Luo, Liang, & Huang, 2019). Through syndrome differentiation and treatment, TCM adjusts the entrails, regulates the balance of *yin* and *yang*, *qi*-blood-body fluid, and achieves the role of promoting intestinal movement and defecation (Li & Cao, 2021).

Many pharmacological and clinical studies have identified various therapeutic effects of *Aloe* extract, including antibacterial, antiviral and anticancer activities, as well as immunomodulatory and liver protective properties (Chen et al., 2014). According to *Chinese Pharmacopoeia* (2020 edition), *Aloe* has a cold and bitter taste belonging to liver and large intestine meridians (Chinese Pharmacopeia Commission, 2020). It has the effect of purging, clearing liver and killing insects, which can be used to treat heat constipation, liver fire headache, eye red convulsion, insect accumulation abdominal pain, scabies, and hemorrhoids fistula. Also, it has been recorded as one of the ten most commonly used herbs for constipation (Huang, Yu, & Yu, 2024; Zhong et al., 2016). Outside of China, in ancient Egypt, India, and Southeast Asia, there are records of *Aloe* being used to treat constipation. In fact, *Aloe* was already used as a medicine in North Africa between the 20th and 30th centuries BC. *Aloe* was introduced to Western medicine as a laxative in 50 BC (Foster, Hunter, & Samman, 2011). Clinically, there are few cases of using *Aloe* alone to treat constipation, and *Aloe* is often combined with other drugs or participates in the treatment of constipation as the main component of a prescription (Yue et al., 2020; Wang et al., 2022). This article mainly summarizes the effect mechanism and clinical efficacy of *Aloe* and its representative prescription in the treatment of constipation, and provides guidance for clinical safe use of *Aloe* and further research.

2. *Aloe* in treatment of constipation

Aloe has been used as a medicinal plant for thousands of years. *Aloe* mainly uses its leaf parts and the gel juice extracted to treat constipation. Lin et al. and Zhang observed the laxative effect of *Aloe* on constipated mice and its effect on intestinal peristalsis and intestinal wall reabsorption of water in mice (Lin et al., 2005; Zhang, 2008). It was found that compared with the model group, using low (25%), medium (50%) and high (100%) doses of *Aloe* juice suspension to gavage mice could shorten the initial defecation time of constipation mice to varying degrees, increase the number of black stools in 6 h, the weight of dry and wet feces and the water content of feces, showing a significant dose–effect relationship. The medium and high dose groups of *Aloe* can improve the small intestine ink propulsion rate of mice; at the same time, *Aloe* can also increase the content of MTL, SP and VIP in plasma and intestinal tissue of model mice. Lu et al. found that *Aloe* juice (1:1) can reduce the frequency of colonic slow wave in mice with constipation induced by compound diphenoxylate, significantly reduce the coefficient of variation of colonic slow wave frequency, and increase the amplitude of colonic slow wave in mice, suggesting that *Aloe* could effectively improve the colonic motor function of constipated mice (Lu et al., 2013). Zheng et al. observed that without affecting the body weight of mice, eating *Aloe* capsule (0.225, 0.45 g/kg, i.g) lasting 10 d can promote the small intestine movement of constipation mice caused by compound diphenoxylate, significantly shorten the initial defecation time of mice, and increase the amount and weight of defecation within 6 h (Zheng et al., 2013).

Cao et al. used double-blind method to observe the effect of *Aloe* products on defecation in patients with functional habitual constipation (Cao, Zhang, Lin, Lin, & Huang, 2005). After 7 d of treatment, the defecation frequency, defecation patterns and fecal traits of the patients in the *Aloe* group were significantly improved compared with the placebo group. No adverse reactions were observed during the clinical observation, and no abnormalities were spotted in the safety indicators. Li et al. observed the effect of *Aloe* stem pluged in anus on relieving constipation in the elderly (Li, Li, Zhang, & Zheng, 2004). The total effective rate and defecation pleasure of *Aloe* stem plugged in anus group were higher than those of soapsuds enema group and Glycerine Enema injection group. Li used *Aloe* solution enema to treat 50 cases of stroke constipation, and achieved satisfactory results (Li, 2003). After one *Aloe* solution enema, 44 cases defecated after 30 min–4 h, and the symptoms were relieved. The symptoms were relieved in six cases after 2 times of medication. In general, the patients can defecate 2–3 times after each medication, and the symptoms of abdominal pain and distention disappear.

In terms of food therapy, *Aloe* can be cooked with other ingredients to make various delicacies. For example, *Aloe* can be combined with jellyfish skin, cucumber and other ingredients to make a refreshing and delicious salad. This dish is not only delicious, but also has the functions of increasing appetite, promoting digestion and so on, which is helpful for improving constipation symptoms (Bai, 2003).

In conclusion, the research on *Aloe* drugs and diets provides an effective natural therapy to treat constipation. However, when using *Aloe*, we need to pay attention to eating it in an appropriate amount to avoid adverse reactions. At the same time, for specific groups of people, for example those with deficiency and cold of the spleen and stomach and pregnant women, eating *Aloe* should be avoided.

3. Components of *Aloe* in treatment of constipation

According to previous reports, *Aloe* has many fascinating and valuable components and compounds, mainly including anthraquinone and naphthone, polysaccharides, proteins and enzymes, organic acids, etc. (Dagne, Bisrat, Viljoen, & Van Wyk, 2000). Among these chemical components, anthraquinone is the main active component found in aloe latex, which includes aloin A, aloin B (isoaloin), aloin emodin, rhein, aloin and aloin saponin I, II, III, IV, etc. (Van Wyk, Van Rheede van Oudtshoorn, & Smith, 1995). In addition to water, aloe polysaccharide (AP) is the main component of aloe gel, and the most common AP is glucose-mannose polysaccharide (Liu et al., 2019). Among them, ingredients such as aloe emodin, rhein, quercetin and aloe gel have been reported to have the effect of improving constipation.

3.1. Rhein

Rhein is an important anthraquinone substance in Chinese herbs such as *Aloe* and rhubarb, which has anti-tumor, antibacterial, anti-inflammatory, immunosuppressive and purgative effects (Cheng, Jiang, Xu, & He, 2021). Sun et al. used compound diphenoxylate to establish a mouse constipation model, measured the colon transport function of mice, compared the changes of EMG in the colon of mice, and detected the expression of AQP3 in the colon mucosa of mice (Sun et al., 2018). The results showed that the first defecation time of mice was reduced after rhubaric (50 mg/kg, i.g) treatment, and the frequency of red stools and small intestine promotion rate in 6 h were significantly increased. The slow wave frequency and amplitude of colonic myoelectric activity increased in rhein group, and the mean optical density and positive expression area of AQP3 in colonic mucosa decreased. In conclusion, rhein can improve the motor function and colonic myoelectricity of constipated mice, and reduce the expression of AQP3 in colonic mucosa, thus effectively relieving constipation symptoms.

3.2. Aloe-emodin

Aloe-emodin (AE) and emodin are isomers, and AE also has antitumor activity, antibacterial activity, immunosuppression and purging effect (Dong et al., 2020). Wang et al. established a model of chronic transit constipation by intragastric administration of compound difenoxate tablet suspension, and tested the laxative effect of aloe-emodin on constipated mice (Wang, Zhu, Sun, Wang, & Du, 2020). The results showed that AE (25 mg/kg, i.g) significantly promoted the increase of SP and VIP content in the myenteric plexus of the model mice. At the same time, the coefficient of variation of slow wave amplitude and slow wave frequency in constipated mice tended to be more normal than before, suggesting that AE had a certain effect on increasing the number of colonic propulsive contraction waves in constipated mice, which might be related to the effect of AE on the structural and functional recovery of intestinal plexus. Lv found that aloe-emodin, rhein and chrysophanol all had a softening effect on stool in rats with fluid-consuming constipation, and the combination of aloe-emodin (50 mg/kg, i.g) and rhein (100 mg/kg, i.g) had the strongest softening effect on stool (Lv, 2023). They can significantly increase the fecal water content, 6 h defecation quantity, 6 h defecation weight, colon defecation time and small intestine carbon dust propulsion rate of constipated rats. Aloe-emodin, rhein and chrysophanol can up-regulate the expression of VIP, CAP1, PKA, CFTR, AQP3, AQP4 and AQP8 mRNA and their proteins, decrease the expression of ENa C, NHE3 mRNA and their proteins, and decrease the concentration of Na^+-K^+-ATPase in colon tissue of model rats, improving gastrointestinal motility and promoting fecal excretion.

3.3. Quercetin

Quercetin, the main component of flavonoids, comes from a wide range of sources and has various biological activities such as anti-oxidation, anti-inflammation, anti-infection and anti-tumor (Hosseini, Razavi, Banach, & Hosseinzadeh, 2021). At the same time, quercetin can be used as a raw material to protect intestinal mucosa, promote the recovery of intestinal function and relieve chronic transit constipation. Zhang (2014) used compound diphenoxylate tablets suspension to establish a chronic transit constipation model in mice, and the results showed that quercetin (100, 200, 400 mg/kg, i.g) could significantly shorten the time of first defecation and increase the total defecation weight and number of grains within 6 h. Besides, quercetin can significantly reduce the content of malondialdehyde (MDA) in the serum of mice, improve colon pathology, and increase the number of colon villi, digestive cells and glands in model mice. Quercetin also significantly increased the number of lactobacillus and decreased the number of enterococcus in the intestinal tract of mice. Moreover, quercetin can significantly decrease the expression of TNF-α and IL-6 mRNA in colon, and high dose of it can significantly increase the expression of EGF mRNA. Kim et al. established a constipation model of SD rats induced by loperamide, and found that the gastrointestinal motility, stool frequency and histological structure of rats were significantly restored after quercetin (10, 20, 40 mg/kg, i.g) treatment (Kim et al., 2018). The mucosal thickness, muscle thickness, flat lumen surface thickness, number of goblet cells, and number of Lieberkuhn crypts were significantly increased in the quercetin treatment group. In addition, intestinal mucin secretion, mAChR expression and downstream signaling

pathways were also significantly restored after QCT treatment. Liu and Zhi found that quercetin (25, 50 mg/kg, i.g) can significantly increase the intestinal transit rate, motilin, gastrin, substance P levels and short-chain fatty acid (SCFA) concentration in constipation rats, reduce somatostatin levels, and improve gastrointestinal motility in rats. Quercetin can also alleviate loperamide-induced constipation by increasing the levels of interstitial cell Cajal markers (c-Kit and SCF) as well as AQP3 (Liu & Zhi, 2021). Yu et al. determined that quercetin can be used as a regulator of CaCC chloride channel activity (Yu, Jiang, Jin, Ma, & Yang, 2016). Quercetin (50, 100, 200 μmol/L) activates Cl-transport in a dose-dependent manner and activates CaCC-mediated Cl current in HT-29 cells. *In vivo* studies further showed that quercetin could promote the secretion of liquid in the ileum of mice. Therefore, the regulation of quercetin on CaCC chloride channels may represent a potential therapeutic strategy for the treatment of CaCC-related diseases such as constipation, secretory diarrhea and hypertension.

3.4. Aloe and other extracts

Jiang et al. observed the effect of aloe gel juice (10 mL/kg, i.g) on colonic electrophysiological changes of constipated mice (Jiang et al., 2012). It was found that compared with the constipation group, the frequency of colonic slow wave in the *Aloe* group was decelerated, the coefficient of variation of colonic slow wave frequency was decreased, the amplitude of slow wave was increased and the coefficient of variation of colonic slow wave amplitude was decreased. There was a significant difference between the two groups. Sun et al. found that aloenin (0.036 mg/kg, i.g), fructooligosaccharide (163 mg/kg, i.g) and aloenin (0.036 mg/kg, i.g)-fructooligosaccharide (163 mg/kg, i.g) compound could shorten the first defecation time of KM constipation mice, increase the number of fecal particles, fecal weight and charcoal propulsion rate (Sun, Zhang, Li, & Abdur, 2021); At the same time, aloenin-fructooligosaccharides compound of each dose group has a synergistic effect on the relief of constipation, and the effect of the high dose group is the best. It is concluded that aloenin, fructooligosaccharide and aloenin-fructooligosaccharide compound all have the effect of moistening the intestines and relaxing the bowels.

Chu et al. evaluated the efficacy of prebiotic UG1601 (containing inulin, lactitol and aloe gel) in inhibiting constipation-related adverse events in subjects with mild constipation (Chu et al., 2019). The study found that after the use of prebiotics, the concentrations of serum cluster of differentiation (CD) 14 and lipopolysaccharide (LPS) in patients with constipation were significantly reduced, and changes in the composition of intestinal microbiota, including the decrease of firmicutes and the increase of butyric acid-producing bacteria, may help improve symptom scores and alleviate endotoxemia. A summary of mechanism of *Aloe* and its compounds in treating constipation was presented in Fig. 1.

4. Chinese herbal compounds of *Aloe*

4.1. Compatibility of Aloe in treating constipation

In basic research and clinical practice, *Aloe* is often used in conjunction with other Chinese herbs to treat constipation, such as Hemp fimble seeds and *Sennae Folium* (Fanxieye in Chinese) (Zhang, 2017; Quan et al., 2023; Li et al., 2020). The addition of *Aloe* is commonly found in medicinal diet and health food products aimed at promoting bowel function.The medicinal diet containstremella-aloe porridge, aloe-honey, aloe-pork rib soup, aloe yogurt and aloe tea, and the health products include Aloe Capsules, Aloe Softgel, Aloe Oral Liquid and so on (Cheng, Chen, Pi, & Chen, 2021). These products are intended to effectively clear heat, detoxify the body, and provide moisture for the bowels.

4.1.1. Aloe plus Hemp fimble seeds

Aloe is a purgative drug, commonly used in heat constipation; Hemp fimble seed, sweet and smooth, is moist and fatty in quality.

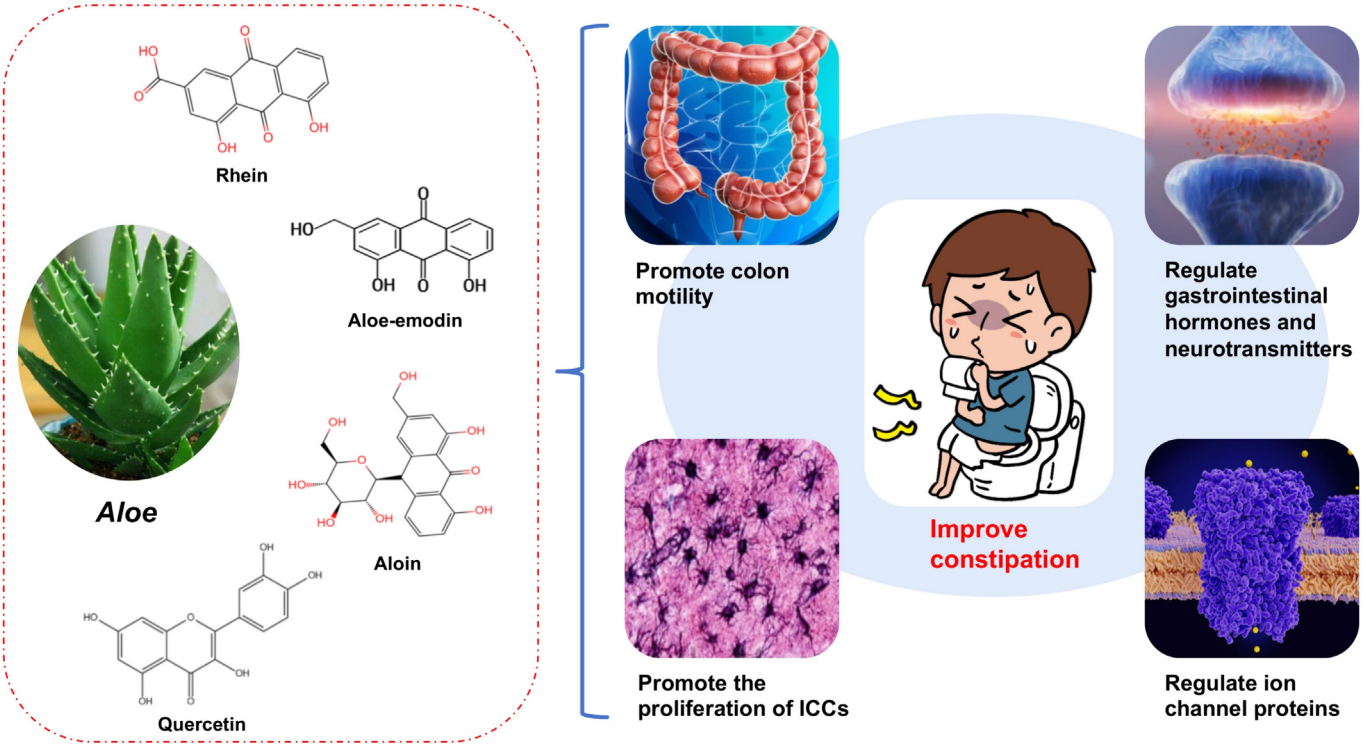

Fig. 1. Mechanism of *Aloe* and its compounds in treating constipation.

It is a laxative drug that can relax bowel and relieve constipation. It is commonly used in intestinal dryness and constipation, and has the effect of nourishing and tonifying deficiency. The hemp seed can restrict the bitter and cold nature of *Aloe*. The combination of the two is used to moisten the intestines and relax the bowels, inducing mild diarrhea (Zhang, 2017; Quan et al., 2023). Wang et al. studied the effects of aloe powder (0.15 g/kg, i.g), hemp seed oil (0.33 g/kg, i.g) and their compatibility (aloe powder 0.15 g/kg + hemp seed oil 0.33 g/kg, i.g) on gastrointestinal motility and water metabolism in mice with constipation caused by compound diphenoxylate (Wang et al., 2022). Compared with model group, small intestine propulsion rate, serum 5-HT level and substance P level were significantly increased, and VIP level was significantly decreased in each administrated group. Moreover, the epithelial cells and goblet cells of colonic mucosa were increased, and the thickness of colonic mucosa was also significantly increased. Zhu et al. studied the laxative effect of the compatibility of *Aloe* and *Cannabis Fructus* (Huomaren in Chinese) on constipation mice induced by compound diphenoxylate (Zhu et al., 2021). It was found that the medium dose (0.45 g/kg, i.g) group could significantly up-regulate AQP9 mRNA expression and protein level, and down-regulate AQP3 mRNA expression and protein level. In summary, the compatibility of *Aloe* and *Cannabis Fructus* can significantly improve the constipation caused by compound diphenoxylate in mice and shorten the residence time of feces in the intestine. The compatibility of the two may enhance gastrointestinal motility by regulating the contents of intestinal neurotransmitters 5-HT, VIP and SP, reduce AQP3, increase AQP9 expression, reduce intestinal reabsorption of water and increase intestinal secretion, jointly achieving the laxative effect.

4.1.2. Aloe combined with American ginseng and Sennae Folium

American ginseng can replenish qi and nourish yin, clear heat and generate fluid, which can be used to replenish qi without dryness, and its effect of nourishing spleen and clearing heat can neutralize the toxic and side effects of *Sennae Folium* (Fanxieye in Chinese) and *Aloe* such as damaging spleen and stomach (Jing, 2002). Yue et al. explored the effect and mechanism of different compatibility doses of freeze-dried power of Curacao aloe leaves (133, 267 mg/kg, i.g), extract of *Sennae Folium* (33.33, 66.66 mg/kg, i.g) and extract of American ginseng (42.67, 85.34 mg/kg, i.g) on moistening and relieving bowels in constipated mice given loperidine suspension (Yue et al., 2020). Compared with the model group, the ink propulsion rate of each dose group was significantly increased, and the defecation test results of each dose group were positive. The expression of GDNF mRNA and protein in each group was increased, whereas the expression of iNOS mRNA and protein was decreased. Li et al. explored the laxative effect and mechanism of freeze-dried power of Curacao aloe leaves (133.30, 266.60 mg/kg, i.g), single herb of *Sennae Folium* extract (33.30, 66.60 mg/kg, i.g) and their combination with American ginseng extract (42.70, 85.30 mg/kg, i.g) on constipation mice (Li et al., 2020). Compared with the model group, the first black stool time of each dose group was shortened, and the number of black stool grains in 6 h was increased. The ink propulsion length and ink propulsion rate of the *Aloe* group and the *Aloe* plus American ginseng group were significantly increased. The content of AchE in the serum of mice in *Aloe* plus American ginseng group was significantly increased, and the mRNA expression of GDNF in small intestine of mice was significantly up-regulated. Li et al. (2020) found that in terms of the phylum level, the relative abundance of Bacteroidetes in the intestinal flora of mice in the *Aloe* (133.30, 266.60 mg/kg, i.g) plus *Sennae Folium* (33.33, 66.66 mg/kg, i.g) group showed a decreasing tendency, while the relative abundance of Firmicutes showed an increasing trend. In terms of the order level, the relative abundance of Lactobacillus in the *Aloe*-American ginseng-*Sennae Folium* group was higher than that in the model group, while the relative abundance of Enterobacteriaceae was lower than that in the model group. In summary, the combination of *Aloe*, American ginseng and *Sennae Folium* has a good laxative effect, which can increase the expression of GDNF in mice, promote the release of AchE, inhibit the production of NO, effectively improve the species richness and diversity of intestinal flora, restrain the growth of harmful intestinal flora and promote the growth of intestinal probiotics, improve the imbalance of intestinal flora structure in constipation mice, so as to play a good laxative effect. A summary of mechanism of the combination of *Aloe* in treating constipation was presented in Fig. 2.

4.2. Chinese patent medicines represented by Aloe in treating constipation

4.2.1. Shouhui Tongbian Capsules

Shouhui Tongbian Capsules is composed of *Polygonum multiflorum* Thunb. (Heshouwu in Chinese), *Aloe*, Cassiae Semen (Jueming zi in Chinese), *Asini Corii Colla* (Ejiao in Chinese), *Lycii Fructus* (Gouqizi in Chinese), *Ginseng Radix* et *Rhizoma* (Renshen in Chinese), *Atractylodis Rhizoma* (Cangzhu in Chinese) and *Aurantii Fructus Immaturus* (Zhishi in Chinese). It is used to treat functional constipation by nourishing yin, replenishing qi, tonifying and purging at the same time (Guan, Zhuang, Fan, Deng, & Zhang, 2021). Shouhui Tongbian Capsules has a good effect on functional constipation. From the current research, its effect mechanism mainly involves four aspects: accelerating intestinal motility, promoting intestinal fluid secretion, improving ICC energy metabolism and promoting its proliferation, and regulating gastrointestinal hormone levels (Gong et al., 2022).

Li et al. found that the medium (0.27 g/kg, i.g) and high (0.71 g/kg, i.g) doses of Shouhui Tongbian Capsules could significantly shorten the first defecation time of rats with slow transit functional constipation induced by compound diphenoxylate, and significantly increase the number of 12 h defecation particles and the small intestine carbon ink propulsion rate, indicating that Shouhui Tongbian Capsules can improve the symptoms of functional constipation by promoting intestinal motility (Li et al., 2018). Zheng et al. established a mouse model with slow transit functional constipation induced by loperamide hydrochloride, and found that the number of c-Kit and SCF positive cells in the colon of Shouhui Tongbian Capsules (100, 200, 400 mg/kg, i.g) treatment group was significantly higher than that in the model group, indicating that Shouhui Tongbian Capsules may promote ICC proliferation through c-Kit / SCF signaling pathway (Zheng, Guo, Zhang, Pan, & Zeng, 2021). In addition, the contents of Adenosine Triphosphate (ATP) Synthase and Isocitrate dehydrogenase in the intestinal tissue of mice in the middle and high dose groups of Shouhui Tongbian Capsules were significantly higher than those in the model group. This study showed that Shouhui Tongbian Capsules may increase the activity of ATP synthase and mitochondrial isocitrate dehydrogenase in intestinal cells, up-regulate SCF/c-Kit signaling pathway, promote ICC proliferation, enhance intestinal nerve information transmission, and thus improve intestinal motility. Bai et al. established a mouse model of experimental constipation induced by loperamide hydrochloride, and found that Shouhui Tongbian Capsules (100, 200, 400 mg/kg, i.g) significantly improved LH-induced experimental constipation, and accelerated intestinal motility by promoting the biosynthesis of 5-HT in enterochromaffin cells in the small intestine and colon and the growth of intestinal neurons in the enteric nervous system (ENS) (Bai et al., 2022). In addition, SHTB significantly regulates the ecological imbalance of the intestinal microbiota and may change the metabolites of the microbiota to enhance intestinal 5-HT production. Finally, fecal microbiota transplantation studies have con-

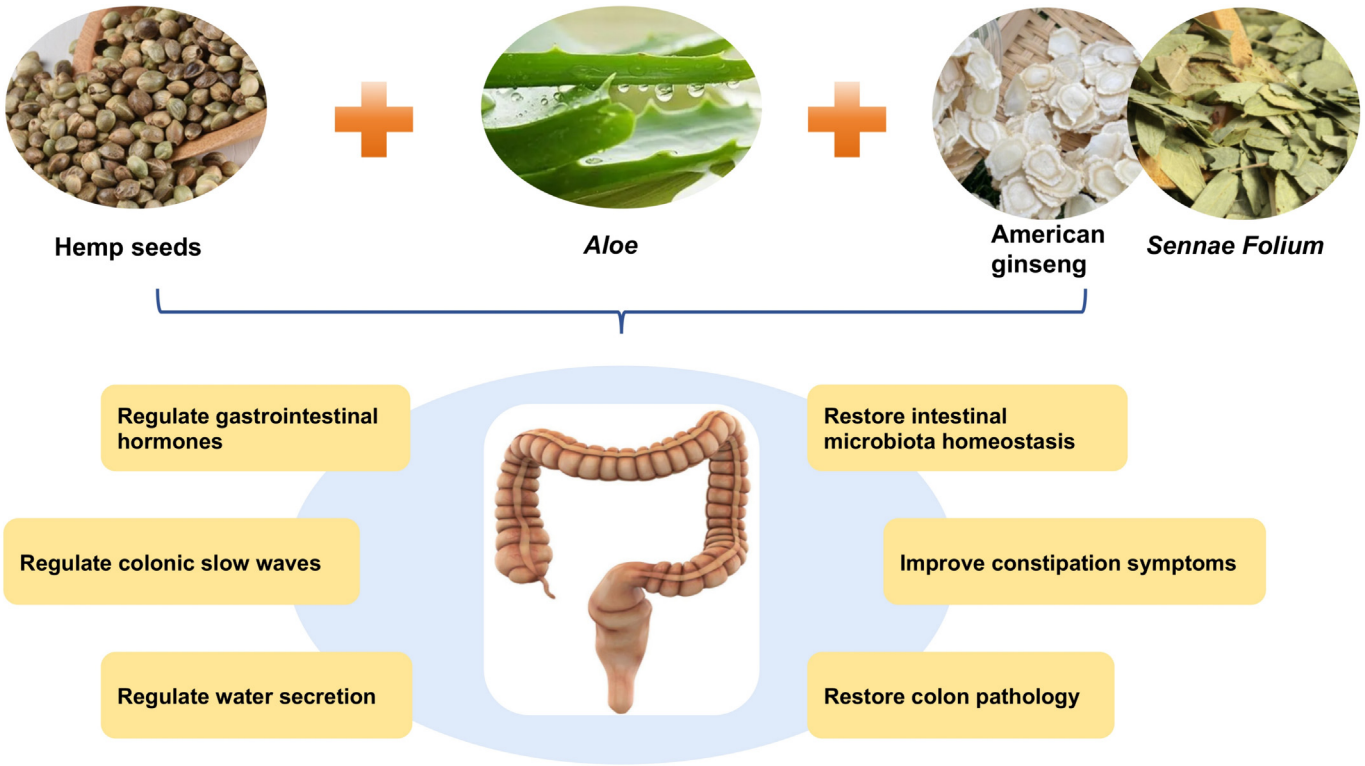

Fig. 2. Mechanism of the combination of *Aloe* in treating constipation.

firmed that the effect of SHTB on 5-HT production and constipation depends on regulating intestinal microbiota dysbiosis.

Zhou et al. explored the effect of Shouhui Tongbian Capsules combined with mosapride on serum gastrointestinal hormone levels and quality of life in patients with functional constipation (Zhou, Yuan, Liu, Wang, & Li, 2021). It was found that the serum SP and MTL of the patients after four weeks of treatment with Shouhui Tongbian Capsules combined with mosapride were higher than those before treatment, and the serum NO was lower than that before treatment. On the basis of mosapride, combined with Shouhui Tongbian Capsules in the treatment of functional constipation patients can better relieve clinical symptoms, alleviate adverse signs, promote the improvement of quality of life, and have a definite curative effect. Yuan et al. found that after two weeks of treatment with Shouhui Tongbian Capsules combined with lactulose oral liquid, patients' symptom scores such as fecal traits, defecation difficulties, incomplete defecation, defecation interval and other symptoms decreased (Yuan, Zhang, Wang, Shi, & Li, 2021). Moreover, serum MTL and SP increased, and the treatment effect was better than that of lactulose oral liquid alone. This indicates that Shouhui Tongbian Capsules combined with lactulose oral liquid can effectively improve the clinical symptoms of elderly patients with constipation, regulate anxiety and depression, and improve serum gastrointestinal hormone levels. Tan et al. observed the effect of Shouhui Tongbian Capsules combined with Bifidobacterium Triple Viable Capsules in the treatment of functional constipation (FC) in the elderly with deficiency of both qi and yin (Tan, Wang, Zhou, & Si, 2021). It was found that Shouhui Tongbian Capsules combined with Bifidobacterium Triple Viable Capsules was effective in the treatment of FC in the elderly with deficiency of both qi and yin. It can significantly improve the symptoms of constipation, effectively up-regulate the levels of gastrointestinal hormones such as MTL, GAS and SP, significantly improve the anorectal dynamics index, reduce the recurrence rate, and have high drug safety.

4.2.2. Aloe Pearl Capsules

Aloe Pearl Capsules is composed of *Aloe*, *Common aucklandia*, *Pearl*, etc. Aloe is bitter and cold in taste, and has the effects of purging heat, dredging meridians, killing insects and detoxifying. Common aucklandia has the function of promoting qi and relieving pain, and invigorating spleen to promote digestion; pearls have the effect of calming the liver and suppressing yang, tranquilizing the mind and calming the panic, and clearing the liver and improving acuity of vision. The combined use of various drugs has the effect of clearing heat and promoting qi, and guiding stagnation and laxatives (Xu, Wang, & Sun, 2006).

The results of two pharmacological experiments also showed that Aloe Pearl Capsules (2.5, 5.0, 10 g/kg, i.g) significantly enhanced the defecation function of fluid-consuming constipation rats, shortened the first defecation time, softened feces, significantly promoted the secretion of intestinal water in rats, and increased the expansion of intestinal segments. It can significantly increase the amplitude and frequency of intestinal muscle contraction in rabbits *in vivo*, prevent excessive absorption of water in the intestinal cavity, and restore the normal motor function of the intestine (Pang, Chen, & Liu, 2009; Wang, Shun, Tang, Xu, & Xu, 2007).

Two clinical controlled studies analyzed the efficacy and comprehensive nursing intervention measures of Aloe Pearl Capsules in the treatment of patients with myocardial infarction and constipation (Liu, 2016; Shen, 2015). It was found that the treatment of patients with myocardial infarction and constipation with Aloe Pearl Capsules combined with comprehensive nursing intervention measures can effectively improve the patients' clinical efficacy, and quickly improve the symptoms of defecation and constipation. Zheng and Nong (2017b) evaluated the efficacy of deanxit combined with Aloe Pearl Capsules in the treatment of functional constipation in elderly patients with anxiety and depression. It was found that the scores of constipation symptoms, self-rating anxiety scale (SAS) and self-rating depression scale (SDS) in the treatment

group of deanxit combined with Aloe Pearl Capsules were significantly improved compared with those before treatment, and the curative effect was better than that of the control group. They (Zheng & Nong, 2017a) also evaluated the efficacy of Aloe Pearl Capsules combined with Bacillus Coagulans Tablets in the treatment of senile functional constipation. After combined treatment, the scores of defecation difficulty, fecal traits, defecation time and the overall score were significantly reduced, and there were no obvious abnormalities in blood routine, urine routine, liver and kidney function and electrolyte. The results showed that Aloe Pearl Capsules combined with Bacillus Coagulans Tablets in the treatment of senile functional constipation can obtain better clinical curative effect, effectively improve the symptoms of constipation, reduce the pain of patients and have no obvious toxic and side effects.

4.2.3. Compound Aloe Capsules

Compound Aloe Capsules is a kind of national protected varieties of TCM, which is mainly made of four TCMs, namely Indigo Naturalis, *Aloe*, Amber and Cinnabar (Huang, Chen, Lin, & Lin, 2006). Among them, Indigo Naturalis has the effects of cooling blood and removing freckles, clearing heat and detoxifying, purging fire and relieving convulsions. *Aloe* has the effects of detoxification, purging fire, killing insects and removing blood stasis. Amber has the effects of blood stasis dispersing and hemostasis, tranquilizing nerves, and promoting diuresis for stranguria. Cinnabar has the effects of sedation, hypnosis, detoxification and antisepsis. The combination of these drugs plays a role in clearing heat and moistening intestines, regulating liver and kidney, calming the heart and tranquilizing the mind. It is commonly used in clinical treatment of dry feces, habitual constipation, and abdominal pain and distention caused by long-term constipation (Ge et al., 2002; Pei, 2013).

Jie et al. observed the laxative effect of Compound Aloe Capsules by using the animal models of water loss induced constipation, compound diphenoxylate induced constipation and atropine induced gastrointestinal motility disorder in mice (Jie, Hong, & Fan, 2007). It was found that Compound Aloe Capsules (0.35, 0.70 g/kg, i.g) could promote the defecation of animals in each constipation model. Compared with the model group, the rate of black stool and the number of black stool grains increased within 8 h. At the same time, each group of Compound Aloe Capsules can improve the intestinal propulsion rate of mice with gastrointestinal motility disorder caused by atropine, and has a significant effect on promoting defecation. Ge et al. studied the main pharmacological effects of Compound Aloe Capsules related to the treatment of constipation (Ge et al., 2002). The results showed that Compound Aloe Capsules (0.2, 0.4, 0.8 g/kg, i.g) could shorten the first defecation time of mice with fluid-consuming constipation, increase the weight of black stool granules and black stool weight, and increase the percentage of small intestine carbon powder propulsion, which was significantly different from that of the blank control group.

Mei explored the effect of Compound Aloe Capsules on constipation caused by Oxycodone Hydrochloride Sustained-release Tablets in patients with digestive tract tumors (Mei, 2018). The results showed that the total effective rate of the treatment group was significantly higher than that of the control group. After treatment, the defecation time, frequency and trait scores of patients were significantly reduced, and those in the observation group were significantly lower than the control group. Guan observed the clinical efficacy of Cisapride Tablets combined with Compound Aloe Capsules in the treatment of functional constipation in the elderly (Guan, 2017). It was found that Cisapride Tablets group, Aloe tablets group and the combination group were all effective in the treatment of functional constipation in the elderly, and the therapeutic effect of the combination of the two was better than that of the Cisapride Tablets group and Aloe Capsules group. Yang investigated the efficacy of Cisapride combined with Compound Aloe Capsules in the treatment of senile chronic constipation (Yang, 2005). Results showed the effective rate of the combined treatment group was 94.6 %, which was significantly different from that of the control group. The adverse reactions were mild and the patients' compliance was good.

4.2.4. Other Chinese patent medicines

Lu et al. used compound diphenoxylate suspension to establish a mouse constipation model to explore the laxative effect of Aloe Soft Capsules (Lu, Hu, Fu, & Kong, 2015). It was found that Aloe Soft Capsules (0.2, 0.4, 1.2 g/kg, i.g) could significantly shorten the time of the first black stool in mice, increase the number of defecation grains in constipation mice within 6 h, and improve the ink propulsion rate of small intestine in constipation mice. Xie et al. studied the laxative function of Aloe Paidu Capsules on constipation mice (Xie, Wang, Sun, Feng, & Wang, 2009). It was found that the ink propulsion rate of each dose (0.24, 0.48, 1.44 g/kg, i.g) treatment group was higher than that of control group, and the difference was statistically significant. The first black stool time of each dose group was significantly shorter than that of the model group. The number of feces in the middle and high dose groups was significantly higher than those in the control group, indicating that the Aloe Paidu Capsules has a laxative function. Wu et al. used compound diphenoxylate to establish a mouse constipation model to observe the laxative effect of Aloe Ganoderma Capsules (Wu, Zhao, Xue, Qiao, & Xu, 2008). The results showed that under the condition of not affecting the mice's weight, Aloe Ganoderma Capsules (0.34, 0.68, 1.36 g/kg, i.g) could increase the ink propulsion rate, shorten the first defecation time, and increase the total amount of defecation.

Jiao et al. observed the clinical efficacy of Angelica Aloe Capsules in the treatment of functional constipation in the elderly (Jiao et al., 2018). Results showed that the total effective rate of Angelica Aloe Capsules in the treatment of senile functional constipation was significantly better than that of placebo control group. It has obvious improvement effect on the main clinical symptoms such as dry stool, poor defecation, unfulfilled bowel intention, abdominal distension and abdominal pain, confirming Angelica Aloe Capsules's effectiveness in the treatment of functional constipation.

Zhao observed the clinical efficacy and adverse reactions of Atractylodes Aloe Capsules in patients with constipation (Zhao, 2014). It was found that compared with the control group, the frequency of defecation increased significantly, and the scores of defecation status and fecal traits decreased significantly, with highly significant differences. The hemoglobin, red blood cells, white blood cells, serum total protein, albumin, aspartate aminotransferase, alanine aminotransferase, total cholesterol, triglycerides, high-density lipoprotein, blood glucose, creatinine and urea nitrogen were all in the normal range before and after the test. There was no abnormality in the routine examination of urine and stool, and there was also no significant change in dietary structure. It shows that Atractylodes Aloe Capsules has good laxative function and no obvious adverse reactions. A summary of clinical study on treatment of constipation with traditional Chinese patent medicines containing *Aloe* was presented in Table 1.

5. Discussion

With the change of people's diet structure and the acceleration of the pace of life, the prevalence of constipation has increased year by year, and it has become an increasingly common and frequent

Table 1
Clinical study on treatment of constipation with traditional Chinese patent medicines containing *Aloe*.

Drugs	Control group		Treatment group		Time (week)	Total effective rate (%,control/ treatment)	Indicators/efficacy	References
	n	Intervention	*N*	Intervention				
Shouhui Tongbian Capsules	63	Mosapride, 5 mg/time, 3 times/d	64	Control + Shouhui Tongbian Capsules, 2 capsules/time, 3 times/d	4	77.78/90.63	The stool characteristics, difficulty in defecation, interval between defecation, and discomfort scores of the two groups were lower than before treatment, and the treatment group was lower than the control group.	Zhou, Yuan, Liu, Wang, & Li, 2021
	75	Lactulose oral solution 30 mL, once a day	75	Control + Shouhui Tongbian Capsules, 2 capsules/time, 3 times/d	2	69.33/85.33	The scores of stool characteristics, difficulty in defecation, incomplete defecation, and interval between defecation in both groups decreased, and the treatment group was lower than the control group; After treatment, the SAS and SDS scores of both groups decreased, and the treatment group had a lower score.	Yuan, Zhang, Wang, Shi, & Li, 2021
	61	Bifidobacterium Triple Viable Capsules, 2 capsules/time, 3 times/ d	61	Control + Shouhui Tongbian Capsules, 2 capsules/time, 3 times/d	4	83.33/95.08	Traditional Chinese medicine syndrome score and difficulty in defecation score in the treatment group were lower than those in the control group, while Bristol score, MTL, GAS, and SP levels were higher than those in the control group; The resting pressure and systolic pressure of the anal canal in the treatment group were higher than those in the control group.	Tan, Wang, Zhou, & Si, 2021
Aloe Pearl Capsules	35	Routine treatment and routine care	35	Control + Aloe Pearl Capsules, 2 capsules/time, 2 times/ d	2	48.6/91.4	The treatment group can quickly improve the symptoms of difficulty in defecation and constipation, which can effectively improve the constipation symptoms of myocardial infarction.	Shen, 2015
Aloe Pearl Capsules	30	Aloe Pearl Capsules, 2 capsules/time, 2 times/ d	30	Control+Dailixin, 1 tablet/time, 2 times/d	4	3.09/5.63*	The treatment group showed significant improvement in various constipation symptoms, SAS and SDS scores after treatment, and the efficacy was better than that of the control group.	Zheng & Nong, 2017b
	20	Coagulation of Bacillus subtilis live bacterial tablets, 3 pieces/time, 3 times/d	20	Control+ Aloe Pearl Capsules, 2 capsules/time, 2 times/ d	4	2.5/6.6*	After treatment, the two groups of patients had difficulty in defecation, stool characteristics, defecation time score, and total score decreased, and the treatment group had a lower score.	Zheng & Nong, 2017a
Compound Aloe Capsules	30	Lactulose oral solution, 15 mL/time, 3 times/d	30	Control+ Compound Aloe Capsules, 2 capsules/time, 2 times/ d	2	76.67/93.33	The defecation time, frequency, and trait scores of the two groups after treatment were significantly reduced, and the treatment group was significantly lower than the control group.	Li et al, 2018
	30	Cisapride tablet, 2 tablets/time, 2 times/d	30	Control+ Compound Aloe Capsules, 2 capsules/time, 2 times/ d	4	63.33/90.00	Through the evaluation of the clinical score scale for constipation patients, it was found that both groups had therapeutic effects on elderly functional constipation, and the treatment group had better therapeutic effects than the control group.	Guan, 2017
	64	Cisapride 10mg, 3 times/d	94	Control+ Compound Aloe Capsules, 1–2 capsules/time, 2 times/ d	4	64.6/94.6	After taking the medication, two groups of patients have formed soft or pasty stools 1–2 times a day or once every 2 d without difficulty in defecation, and the treatment effect of the treatment group is better than that of the control group.	Yang, 2005
Angelica Aloe Capsules	60	Placebo 2 capsules/time, 2 times/ d	60	Angelica Aloe Capsules, 2 capsules/time, 2 times/ d	1	33.93/89.30	The total effective rate of treating elderly functional constipation in the treatment group is significantly better than that in the control group. The treatment group has a significant improvement effect on major clinical symptoms such as dry stools, obstructed bowel movements, incomplete bowel movements, and abdominal distension and pain.	Jiao et al, 2018
Atractylodes Aloe Capsules	51	Placebo 1 bag/time, 2 times/d	52	Atractylodes Aloe Capsules, 1 bag/time, 2 times/d	1	\	Compared with the control group, the treatment group showed a significant increase in defecation frequency, and a significant decrease in the scores of two indicators: defecation status and fecal characteristics.	Zhao, 2014

Note: MTL: motilin, GAS: gastrin, SP: substance P, SAS:anxiety self rating scale, SDS:depression self rating scale.
* The decreasing value representing symptom scores.

clinical disease. Dysfunction of defecation in patients with constipation causes abdominal pain, abdominal distension, anxiety, depression, etc., which seriously affects the quality of life. Severe cases can often cause acute intestinal obstruction, intestinal perforation, cardiovascular and cerebrovascular diseases. Western medicine treatment has a good short-term effect, but no long-term good effect, and there are often problems such as great adverse reactions, easy recurrence after drug withdrawal, and drug dependence. TCM believes that constipation belongs to the syndrome of deficiency of qi and blood in the body. The accumulation of dryness

and heat, as well as the deficiency of body fluid, leads to the loss of dampness in the intestines. Hence, the main cause of the disease is deficiency of entrails, qi-blood, and yin-yang, with the syndrome being asthenia in origin and asthenia in superficiality. Therefore, the treatment should be based on tonifying qi and blood, nourishing yin fluid and purging stool (Zhou & Zhou, 2019; Zhou & Liu, 2019; Shen, Zhang, & Ye, 2017).

Aloe vera (L.) Burm. f. is a herbaceous plant of Liliaceae (Yang, Zhu, Tang, & Wen, 2022). *Traditional Chinese Pharmacology* records that topical application of aloe honey juice can prevent and cure chemotherapeutic phlebitis, reduce vascular intimal injury, and it has the effects of purging heat and stagnation, eliminating malnutrition, killing insects, clearing heat and cooling liver, and is a common product for draining liver fire and eliminating malnutrition (Li & Wang, 2011). *Aloe* is bitter and cold in nature and belongs to the channel tropism of liver, stomach and large intestine. Since it has the effects of purging heat, removing stagnation, killing insects and cooling the liver, it can be used for heat concentration constipation. TCM has used *Aloe* to treat constipation for hundreds of years. Modern medical research has proved that multiple components of *Aloe*, especially anthraquinones, can promote defecation and enhance intestinal peristalsis (Cheng, Chen, Pi, & Chen, 2021). Starting from *Aloe* and its monomer components, combined with the existing compatibility relationship of *Aloe* and several Chinese patent medicines represented by *Aloe*, this paper comprehensively and systematically introduces the research progress of *Aloe* and its compatibility prescriptions in the treatment of constipation.

Aloe can effectively strengthen the intestinal peristalsis of mice and reduce the water absorption function of intestinal wall, increase the frequency and weight of defecation in mice, and play a role in the treatment of constipation. *Aloe* can increase the contents of MTL, SP and VIP in plasma and intestinal tissue of constipated animals, which is closely related to gastrointestinal motility and playing an important role in regulating gastrointestinal motility (Cheng, Chen, Pi, & Chen, 2021; Ge, Wang, Xie, Jiang, & Huang, 2021), and improve colonic motor function. A number of clinical controlled observations also showed that compared with the placebo group, defecation frequency, defecation status and fecal traits of the patients in the *Aloe* group were significantly improved, and there were no obvious side effects.

Among aloe monomer components, aloe-emodin, rhein and quercetin can significantly improve constipation symptoms in mice. The mechanism may be related to the improvement of colonic myoelectric expression in constipated mice and the promotion of gastrointestinal hormone distribution and aquaporin expression. At the same time, quercetin can also regulate intestinal flora, reduce inflammatory cytokines, improve colon pathology, regulate chloride ion channels, increase intestinal mucosal secretion levels, protecting intestinal mucosa. Interstitial cells of Cajal (ICC) are widely distributed between the autonomic nerve endings of the gastrointestinal tract and the smooth muscle of the gastrointestinal tract. They are pacemaker cells for gastrointestinal motility and participate in the regulation of gastrointestinal motility by generating rhythmic electrical slow wave activity (Sanders, Koh, & Ward, 2006; Sanders, Ward, & Koh, 2014).

Exogenous glial cell line-derived neurotrophic factor (GDNF) can promote the repair of intestinal wall neurons and significantly improve the motility of the colon (Meir et al., 2021). Tomita et al. believed that the increase of nitric oxide-mediated non-adrenal non-cholinergic inhibitory nerve plays an important role in colonic motility disorders in patients with chronic transmission, controlling the expression of iNOS and effectively reducing NO content (Tomita, Igarashi, Fujisaki, & Tanjoh, 2007). In the study of the compatibility of *Aloe*, American ginseng and *Sennae Folium*, it was found that *Aloe* combined with American ginseng extract and *Sennae Folium* extract could promote intestinal peristalsis by increasing GDNF expression, promoting AchE release, inhibiting NO production. At the same time, the combination of the three can inhibit the growth of harmful intestinal flora and promote the growth of intestinal probiotics, improving the imbalance of intestinal flora structure in constipation mice and thus playing a good laxative effect.

At present, the Chinese patent medicines represented by *Aloe* used in the Chinese market can alleviate the symptoms of constipation animals or patients to a certain extent. Shouhui Tongbian Capsules is used to treat functional constipation by nourishing *yin* and replenishing *qi*, tonifying and purging simultaneously. Compound Aloe Capsules has the effects of clearing heat and moistening intestine, regulating liver and kidney, and tranquilizing heart and mind, which may be a better choice for the treatment of senile chronic constipation. Aloe Pearl Capsules has the effect of clearing heat and promoting *qi*, guiding stagnation and relaxing bowels. It can obviously promote the secretion of intestinal water in experimental animals, increase the amplitude and frequency of intestinal muscle contraction, and restore the normal motor function of intestinal tract. Other Chinese patent medicines also have good laxative effect, and no obvious adverse reactions.

As a classic TCM for the treatment of constipation, *Aloe* has the characteristics of multi-component, multi-target, multi-effect, good therapeutic effect and less toxic and side effects. *Aloe* has a broad application prospect in the treatment of constipation. For example, by extracting the active ingredients in *Aloe*, new drugs or health products for the treatment of constipation can be developed. *Aloe* is a nutritious and tasty food that can be processed into beverages and dairy products. Moreover, modern biotechnology can be used to cultivate new varieties of *Aloe* with higher medicinal value. In conclusion, *Aloe* has certain application prospects in the treatment of constipation. For research ideas for the treatment of constipation, we will focus on network pharmacology, intestinal flora and multi-omics analysis to further explore its role in the treatment of constipation. In the future, the application and development of *Aloe* in the treatment of constipation can be further promoted through in-depth research on the mechanism of *Aloe*'s laxative action, exploration of combined application with other drugs, personalized treatment and strengthening product quality control and standardization.

6. Conclusion

This article provides solid evidence and certain guidance for the rational application of *Aloe* and its prescriptions in the treatment of constipation in clinical practice, establishes an experimental basis for the development and application of constipation drugs centered on *Aloe*, and provides modern scientific basis for the treatment of constipation with TCM, so as to promote the high-quality development of TCM.

CRediT authorship contribution statement

Xianhui Shen: Data curation, Formal analysis, Visualization, Writing – original draft. **Liping Gong:** Supervision, Formal analysis, Writing – original draft. **Rongrong Li:** Writing – original draft. **Nana Huang:** Writing – original draft. **Huijie Zhang:** Writing – original draft. **Siyi Chen:** Data curation, Formal analysis. **Ying Liu:** Data curation, Formal analysis. **Rong Sun:** Conceptualization, Data curation, Project administration, Validation, Writing – review & editing.

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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