

Shengjing Runchang Decoction ameliorates spleen deficiency-induced constipation in children

An observational study

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Abstract

Traditional Chinese medicines (TCM) are often used for the treatment of spleen-deficiency (SD) syndrome in China. This study evaluated the curative effects of TCM Shengjing Runchang Decoction on SD-induced constipation children. From July 2019 to April 2020, a total of 70 children with constipation due to spleen deficiency who were admitted to our hospital were selected and randomly divided into control group ($n = 35$) and treatment group ($n = 35$). Both groups were treated with standard western medicine, and the treatment group was combined with TCM Shengjing Runchang Decoction at the same time. The clinical efficacy and neurocytokines including 5-hydroxytryptamine (5-HT), vasoactive intestinal peptide (VIP), children's colonic transit time (CTT), glial cell line-derived neurotrophic factor, colonic estrogen receptor before and after treatment were analyzed and compared between the 2 groups. The curative effect, total effective rate of TCM syndromes, CTT, 5-HT and plasma VIP levels, glial cell-derived nerve effects of trophic factor levels, immune function IgG, IgGA, CD4/CD8 in the treatment group were significantly promoted in comparison with the control group ($P > .05$). The TCM Shengjing Runchang Decoction is effective in treatment with children with SD-induced constipation, which can effectively improve immune function, reduce neurotrophic factor secretion and maintain normal secretion and improve colonic motor function.

Abbreviations: 5-HT = 5-hydroxytryptamine, CTT = children's colonic transit time, GDNF = glial cell-derived nerve effects of trophic factor, TCM = traditional Chinese medicines, VIP = vasoactive intestinal peptide.

Keywords: infantile constipation, Shengsheng Runchang Decoction, spleen deficiency type constipation, vasoactive intestinal peptide tumor

1. Introduction

Constipation, is a common problem with high prevalence and greatly affects the life quality of people, characterized by having a bowel movement <3 times a week or the necessity of using laxatives more than 3 times a week.^[1,2] Constipation in children is caused by factors such as intestinal flora imbalance, abnormal intestinal function, and weak spleen and stomach.^[3] The clinical manifestations are dry and hard stool and difficulty in excretion, accompanied by refusal to eat, irritability, vomiting and other phenomena. Relevant foreign data show that constipation in children is a common symptom in children, and long-term constipation may lead to poor concentration, large mood swings, and irregular sleep in children.^[4] Anti-constipation drugs such as montmorillonite are often used clinically to treat spleen deficiency (SD) and constipation in children to correct clinical symptoms such as electrolyte and acid-base balance disorders in children.

Traditional Chinese medicines (TCM) has been proven to have a unique advantage in treating functional constipation through approaching the disease from overall regulation, emphasizing on the root cause, and treating it in view of time, locality, and individuality.^[5-7] Domestic and foreign studies have shown that TCM has better efficacy in treating children with SD and constipation, and the incidence of adverse drug reactions is lower.^[8] For instance, TCM Yiqi Kaimi Prescription coupled with biofeedback therapy is clinically effective for treating functional SD-induced constipation.^[8] However, there are many kinds of TCM, and the selection of suitable medicines for the treatment of children with SD-induced constipation needs to be confirmed by a further research. In view of this, this study analyzed the efficacy of TCM Shengjing Runchang Decoction in our hospital in the treatment of constipation due to SD in children.

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

This study was approved by the Ethics Committee of Beijing Shunyi District Maternal and Child Health Hospital, China (No. 2021-02). Signed informed consent was also obtained from all participants.

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2. Methods

2.1. Patients collection

Through pathological classification, sorting and collection, this study selected 72 pediatric patients with constipation due to SD who were treated in our hospital from July 2019 to April 2020. Finally, a total of 70 children who met the criteria were included, and they were divided into a control group and a treatment group according to the random number of patients (35 cases in each).

Inclusion criteria: age at 6 months to 7 years old, gender was not limited; no abnormality in routine stool culture, negative bacterial culture in stool, normal blood routine examination; TCM diagnostic criteria for pediatric constipation and criteria for SD type constipation; no mild dehydration or no dehydration; the guardian was informed and signed the consent; the in-hospital Ethics Committee was informed and approved.

Exclusion criteria: children with obvious poisoning surface and severe dehydration; those who were taking antiviral or antibiotic drugs or other drugs; those who had stopped taking the drug for < 1 week; those who were allergic to this drug; those who had infectious diseases; electrolyte, acid-base balance disorder or combined with other serious diseases.

2.2. Diagnostic criteria

This study was in line with the diagnostic criteria in the "Traditional Chinese Medicine Diagnosis and Efficacy Criteria"^[9]: the syndrome was constipation of SD type; main symptoms: the stool was loose and watery, pale in color and not smelly; dry stool, constipation; feeling of fullness and stuffiness when stomach was dull; secondary symptoms: pale complexion, thin body and fatigue; tongue image: Tongue coating was reddish; pulse: weak fingerprints, weak pulse.

Western medicine diagnostic criteria^[10]: defecation frequency <3 times/week without laxative use; fecal incontinence occurred at least 2 times per week; heavy bowel movements every 7 to 30 days, twice the usual volume or dry enough obstruction of toilet; fecal mass palpable on abdominal examination or digital rectal examination.

2.3. Treatment procedure details

All children were given a list of easily digestible foods, and the food intake was gradually increased from less to more, gradually from liquid food to normal diet. After the constipation symptoms returned to normal, the children were given nutrient-rich foods to avoid restrictions and malnutrition. Nursing: the child's ward was regularly cleaned to ensure reasonable temperature, humidity, and lighting, and a comfortable environment; the child's diet, activities, rest were strictly regulated, and activities performed appropriately to improve the body's immune function; the child's buttocks skin was cleaned.

The control group was treated with western medicine, and given 420 mg of Clostridium butyric viable bacteria capsules orally which were dissolved in water. Children under 1 year old were given 1 capsule/time, 2 capsules/time for children, 3 capsules/time for children > 3 years old and ≤ 7 years old, 3 times/day. The treatment group was treated with TCM Shengjing Runchang Decoction on the basis of the control group. The formula composition included 15 g *Angelica*, 15 g *Baishao*, 15 g *Codonopsis*, 10 g *Platycodon grandiflorum*, 10 g *Citrus aurantium*, 10 g *Magnolia*, 12 g *Cistanche poria*, 10 g *Atractylodes*, 15 g *Astragalus*, and 6 g *Zhigancao*. Medicine was decocted with water, 1 days/dose, and taken twice in the morning and evening after meals.^[11] The dosage of the drug should be adjusted according to the standard age and weight of children: 1 third of the dosage of the prescription for children under 1 year old, half the dosage of the prescription for children aged 1

to 3 years, and the original dosage of the prescription for children aged 3 to 7 years. Both groups were treated continuously for 7 days.

2.4. Efficacy evaluation criteria

Evaluation criteria was referred to the "Guidelines for Diagnosis and Treatment of Common Pediatric Diseases in Traditional Chinese Medicine"^[12,13]: the curative effects of the 2 groups after treatment were compared. Clinical recovery, constipation symptoms disappeared completely, and spleen function returned to normal; markedly effective, constipation symptoms were significantly improved, stool frequency was significantly increased, and stool characteristics were basically restored; effective, constipation symptoms were improved, and defecation increased; ineffective, constipation symptoms did not improve, or even worsened. The efficacy of TCM syndromes was compared between the 2 groups: cured: the symptoms and signs of constipation in the child disappeared completely, and the symptom score was reduced by ≥ 95%; significant: the constipation symptoms of the child were significantly improved, and the symptom score was reduced by ≥ 70% to 95%; effective: the constipation symptoms of the child improved, and the symptom score decreased by ≥ 30% to 70%; ineffective: no improvement (or aggravation) of constipation symptoms in children, and symptom score reduction < 30%.

2.5. Observation indicators

After treatment, 10 mL of venous blood was collected from all the children. Following centrifugation at 3000 r/minutes at 4°C for 10 minutes, 1.5 mL of supernatant was taken with a pipette and frozen in a tube to detect serum 5-hydroxytryptamine (5-HT). A total of 3 mL of venous blood was drawn before and after treatment on the 10th day, placed in a curling pre-cooling test tube, mixed, and centrifuged at 1500 rpm for 15 minutes at low temperature to separate plasma. Then vasoactive intestinal peptide (VIP), glial cell-derived neurotrophic factor (GDNF) expression was detected by immunohistochemical staining, serum immune proteins immunoglobulin G (IgG) and IgA levels were detected by immunosingle diffusion method and CD4/CD8 was detected by immunofluorescence method.^[14] The post-treatment effects of TCM were compared between the 2 groups including the related indicators 5-HT (serum 39–361 ng/mL, normal) and VIP (plasma ≤ 60 pg/mL, normal).

2.6. Statistical methods

The data were analyzed by Statistical Product Service Solutions (SPSS) version 18.0 statistical software (IBM, Chicago, IL), the measurement data were described by mean ± standard deviation (SD), and the comparison was done by *t* test; the count data was described by the percentage (%), and the comparison was done by the χ^2 test, and *P* < .05 indicated that the difference was statistically significant.

3. Results

3.1. General information of children

The patients in the control group were 0.7 to 14 years old, with an average age of 7.25 ± 0.41 years, and the disease duration was 5 to 45 days, with an average disease duration of 25.00 ± 1.43 days. The patients in the treatment group were 0.6 to 13 years, with an average age of 6.80 ± 0.39 years, and the disease duration was 7 to 40 days, with an average disease duration of 23.50 ± 1.34 days. The general data of the 2 groups had no significances (*P* > .05). In addition, as shown in Table 1, before treatment, there was no difference in symptom scores

Table 1

Comparison of symptoms between the 2 groups before treatment.

Groups	Stool frequency	Stool character	Appetite	Mental state	Abdominal pain
Control group	4.43 ± 1.57	4.20 ± 1.80	1.49 ± 0.51	1.97 ± 0.03	1.49 ± 0.51
Treatment group	4.60 ± 1.40	4.26 ± 1.74	1.51 ± 1.49	2.03 ± 0.97	1.43 ± 0.57
<i>t</i>	0.478	0.142	0.075	0.366	0.464
<i>P</i>	.634	.888	.940	.716	.644

such as stool frequency, stool character, appetite, mental state, abdominal pain between the 2 groups ($P > .05$).

3.1.1. Clinical efficacy of TCM. After treatment, the total effective rate in the treatment group (77.14%) was higher than that in the control group (94.29%) ($P < .05$; Table 2). Before treatment, there was no difference in TCM syndrome scores between the 2 groups ($P > .05$). After treatment, the total effective rate of TCM syndromes in the treatment group was higher than that in the control group ($P < .05$; Table 3).

3.1.2. Effects of TCM on 5-HT, VIP, CTT and GDNF. There was no difference in the levels of 5-HT, VIP, colonic transit time (CTT) and GDNF between the 2 groups before treatment (all $P > .05$). After treatment, the levels of 5-HT and VIP in both groups were significantly decreased, and the treatment group was lower than those of the control group ($P < .05$; Fig. 1). Conversely, after treatment, the levels of CTT and GDNF in the 2 groups were improved (all $P < .05$). Compared to the control group, the CTT in the treatment group was increased while the level of GDNF was decreased significantly (all $P < .05$; Fig. 2).

3.1.3. Immune function. Immune function was evaluated between the 2 groups before and after TCM treatment. It was shown that there was no difference in the level of IgG, IgG, CD4/CD8 between the 2 groups before treatment ($P > .05$). After treatment, the levels of IgG, IgG, CD4/CD8 in the treatment group was significantly higher than the control group ($P < .05$; Fig. 3), indicating the improvement of immune function induced by TCM.

4. Discussion

Constipation is a common source cause for referrals to gastroenterologists and colorectal surgeons worldwide.^[3] New drugs including prokinetic and prosecretory agents, and surgical strategies, such as sacral nerve stimulation, have the potential to improve the management of children and adults with functional constipation.^[15] If the child is upset, angry, or emotionally disturbed, it will cause the liver qi to retrograde, or the liver and spleen will not be in harmony, causing the child to be constipated.^[16] TCM can be used in the treatment of constipation in children should make up for the deficiency and relieve the

excess.^[17] In clinical practice, it is advisable to take both the attack and the supplement. The principle is to strengthen the spleen and promote qi and laxatives. Oral Chinese medicine decoction or massage techniques can be used for constipation treatment.^[18] In this study, TCM Shengjing Runchang Decoction is proved to be effective in treatment of children with SD-induced constipation through effectively improving immune function and colonic motor function, reducing neurotrophic factor secretion, and maintaining normal secretion.

Clinically, Western medicine is mostly used drugs to treat constipation, such as montmorillonite powder, but the treatment effect is not good.^[15] TCM is often used in internal treatment of constipation in children, but many physicians have Dieter's opinion on the treatment of constipation due to spleen deficiency.^[19] A related study found that paying attention to the harmony of the spleen and stomach is more conducive to the recovery of constipation in children.^[20] In view of this, on the basis of spleen and stomach reconciliation, this study used TCM Shengjing Runchang Decoction consisted of *Angelica*, *Codonopsis*, *Atractylodes*, *Poria*, *Astragalus*, *Paeonia lactiflora*, *Citrus aurantium*, *Magnolia officinalis*, *Cistanche*, *Platycodon grandiflorum*, *Glycyrrhiza glabra* which can strengthen the spleen and lung qi and promote gastrointestinal motility during constipation.^[21-23] The results of this study showed that the curative effect and the total effective rate of TCM syndromes in the control group after conventional western medicine treatment were lower than those in the treatment group with Shengjing Runchang Decoction. The reason is that Shengjing Runchang Decoction can invigorate qi and help strengthen the spleen without hindering the movement, diuresis and dehumidification.^[24]

The study showed that after treatment, the levels of 5-HT, plasma VIP, and GDNF in the control group are significantly higher than those in the treatment group, and CTT is significantly lower than that in the treatment group. 5-HT, a monoamine neurotransmitter, is widely present in the central nervous system and gastrointestinal tract, and mainly involved in the regulation of gastrointestinal motility and secretion reflex.^[25] The main role of plasma VIP is to inhibit the contraction of the small intestinal annular sphincter, stimulate bile, small intestinal water-electrolyte secretion.^[26] Elevated 5-HT and VIP will accelerate gastrointestinal motility and increase intestinal water secretion, resulting in constipation.^[27] The levels of 5-HT and VIP in children with constipation treated with Shengjing Runchang Decoction are significantly reduced, indicating that this prescription can effectively regulate the gastrointestinal motility in children, maintain normal gastrointestinal motility and normal intestinal water secretion. CTT mainly reflects whether the colonic transit function is normal or not, and if the CTT level is too low, it reflects the overactive colonic transit function in children.^[28] GDNF is the most specific dopaminergic neurotrophic factor and a motor neuron trophic factor. Elevated GDNF expression indicates abnormal intestinal transport function, and decreased expression indicates improved intestinal transport function.^[29] Deficiency of GDNF will damage the intestinal mucosal barrier and the loss of nutrition or protection of intestinal neurons, resulting in inflammation. Excessive

Table 2

Comparison of treatment effects between the 2 groups [n (%)].

Groups	Clinical recovery	Remarkable effect	Effective	Invalid	Total effective rate
Control group	6 (17.14)	13 (37.14)	8 (22.86)	8 (22.86)	27 (77.14)
Treatment group	8 (22.86)	18 (51.43)	7 (20.00)	2 (5.71)	33 (94.29)
χ^2	—	—	—	—	4.200
<i>P</i>	—	—	—	—	.040

Table 3

Comparison of the efficacy of TCM syndromes between the 2 groups [n (%)].

Groups	Cured	Remarkable	Effective	Invalid	Total effective rate
Control group	5 (14.29)	13 (37.14)	10 (28.57)	7 (20.00)	28 (80.00)
Treatment group	7 (20.00)	19 (54.29)	8 (22.86)	1 (2.86)	34 (97.14)
χ^2	—	—	—	—	6.248
<i>P</i>	—	—	—	—	.012

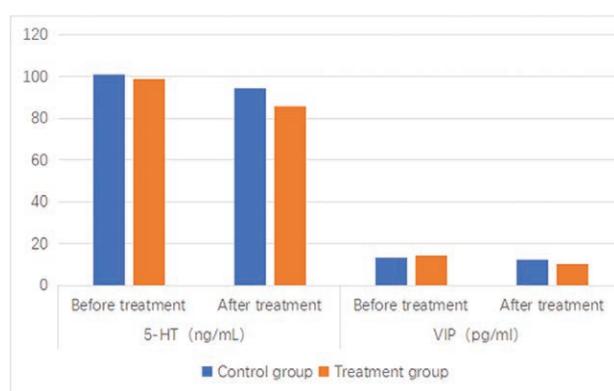


Figure 1. Comparison of 5-HT and VIP levels between the 2 groups. 5-HT = 5-hydroxytryptamine, VIP = vasoactive intestinal peptide.

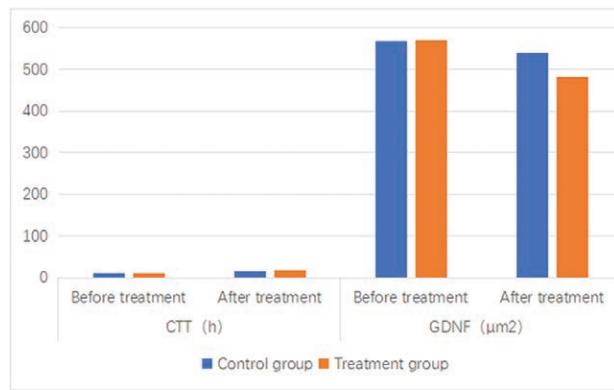


Figure 2. Comparison of CTT and GDNF levels between the 2 groups. CTT = colonic transit time, GDNF = glial cell-derived nerve effects of trophic factor.

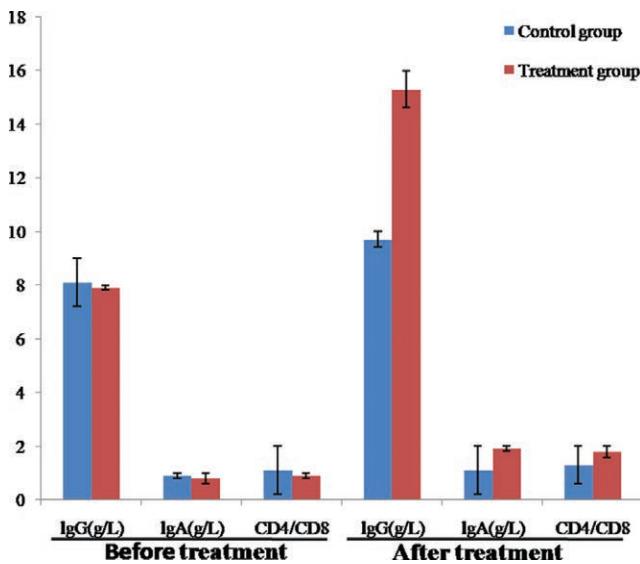


Figure 3. Comparison of immune function between the 2 groups.

secretion of GDNF will lead to abnormal intestinal function in children and promote intestinal motility.^[30,31] CTT and GDNF are effectively improved in children with constipation treated with Shengjing Runchang Decoction, suggesting that this prescription has the effect of improving and adjusting intestinal conduction, and maintaining normal intestinal motor function in children. This study also showed that after treatment of TCM,

the levels of IgG, IgG, CD4/CD8 in the treatment are significantly higher than those in the control group. It is suggested that Shengjing Runchang Decoction can improve the immunity of children.

The present study had several limitations. First, because the data of this study were only obtained from our hospital. Hence, there was a possibility of selection bias due to the single-hospital study. Second, the number of this study was limited, and a longitudinal study using more samples is required to further support the results of this study.

5. Conclusions

TCM Shengjing Runchang Decoction can regulate the gastrointestinal motility in children, restore and maintain normal, and improve the immune function of children, indicating that the application of Shengjing Runchang Decoction in children with constipation due to SS is acceptable. And it is worthy of a further clinical research and application.

Author contributions

Data curation: Huizhen Shen.
Formal analysis: Huizhen Shen.
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Writing – review & editing: Qi Li.

References

- [1] Zeyue YU, Liyu H, Zongyuan LI, et al. Correlation between slow transit constipation and spleen deficiency, and gut microbiota: a pilot study. *J Tradit Chin Med.* 2022;42:353–63.
- [2] Garrigues V, Gálvez C, Ortiz V, et al. Prevalence of constipation: agreement among several criteria and evaluation of the diagnostic accuracy of qualifying symptoms and self-reported definition in a population-based survey in Spain. *Am J Epidemiol.* 2004;159:520–6.
- [3] Vriesman MH, Koppen IJN, Camilleri M, et al. Management of functional constipation in children and adults. *Nat Rev Gastroenterol Hepatol.* 2020;17:21–39.
- [4] Paknejad MS, Motaaharifard MS, Barimani S, et al. Traditional, complementary and alternative medicine in children constipation: a systematic review. *Daru.* 2019;27:811–26.
- [5] Lee MS, Choi TY, Park JE, et al. Effects of moxibustion for constipation treatment: a systematic review of randomized controlled trials. *Chin Med.* 2010;5:28.
- [6] Yao F, Zhang Y, Kuang X, et al. Effectiveness and safety of moxibustion on constipation: a systematic review and meta-analysis. *Evid Based Complement Alternat Med.* 2020;2020:8645727.
- [7] Zhang C, Guo W, Yao X, et al. Database mining and animal experiment-based validation of the efficacy and mechanism of Radix Astragali (Huangqi) and Rhizoma Atractylodis Macrocephalae (Baizhu) as core drugs of Traditional Chinese medicine in cancer-related fatigue. *J Ethnopharmacol.* 2022;285:114892.
- [8] State Administration of Traditional Chinese Medicine. TCM Syndrome Diagnosis and Efficacy Criteria. Nanjing University Press. 1994.
- [9] Yao YB, Cao YQ, Guo XT, et al. Biofeedback therapy combined with traditional Chinese medicine prescription improves the symptoms, surface myoelectricity, and anal canal pressure of the patients with spleen deficiency constipation. *Evid Based Complement Alternat Med.* 2013;2013:830714.
- [10] Liu BH. Diagnosis and Treatment of Constipation. Military Medical Science Press. 2002.
- [11] Gao L, Pu JX, Wu LP. Prof. Wu Liping's experience in treating infantile constipation with Shengjingwuren Decoction. *J PedTradit Chin Med.* 2013;9:4–5.
- [12] Liu MY, Yang W, Wang LY, et al. Clinical application evaluation of guidelines for the diagnosis and treatment of common diseases of pediatrics in traditional Chinese medicine. *Zhongguo Zhong Yao Za Zhi.* 2017;42:3238–42.
- [13] Hu SY. Chinese Medicine Association of Pediatrics Branch, Chinese Medicine Association of Chinese Medicine Clinical Pharmacology Branch. Technical guidelines for clinical trial design and evaluation of

traditional Chinese medicine for children with functional constipation. *Drug Eval Res.* 2020;43:173–8.

[14] Wang J, Xu YQ, Liu RZ. Effects of alanylglutamine injection combined with enteral and parenteral nutrition on nutritional status and immune function in patients with intracranial infection after neurosurgery. *J Clin Surg.* 2016;24:919–22.

[15] Medina-Centeno R. Medications for constipation in 2020. *Curr Opin Pediatr.* 2020;32:668–73.

[16] Wang HD, Lin Y, Zheng JG. Efficacy observation of Xiaoshi Daozhi decoction combined with probiotics in the treatment of constipation in children with food accumulation and Qi stagnation. *Chin J Microecol.* 2021;33:87–90.

[17] Yan YB, Ding Y, Zheng HT, et al. A multi-center randomized controlled double-blind clinical study of Shenling Jianpiwei granules in the treatment of 119 children with diarrhea (spleen deficiency and diarrhea). *J Tradit Chin Med.* 2021;62:677–82.

[18] Hao HW, Wang QQ, Fang QJ, et al. Clinical observation of Zhizhu Zengye decoction in the treatment of functional constipation due to spleen deficiency and fluid deficiency in children. *Beijing Chin Med.* 2016;35:160–2.

[19] Peng SS, Yuan B. Yuan Bin's experience in treating constipation in children. *Liaoning J Tradit Chin Med.* 2021;48:49–51.

[20] Luo YJ, Wang LY, Lin XH. Introduction of Luo Xiaoxiao's experience in treating constipation in children in Lingnan area. *New Chin Med.* 2021;53:199–201.

[21] Li GH, Wang JG, Li HN, et al. Observation on the therapeutic effect of Jingu-invigorating spleen and Qi Tuina method based on the theory of "Tip is medicine" in treating infantile spleen deficiency and constipation. *Tianjin Trad Chin Med.* 2020;37:299–302.

[22] Li LF, Tong XS, Chen XY. Clinical observation of Jianpi Xiaoshi decoction in treating children with stagnation of spleen deficiency and accumulation syndrome. *China Sci Technol Trad Chin Med.* 2019;26:769–70.

[23] Luo QM, Shang JC, Gan CK, et al. Clinical study of Qizhu Runchang decoction in the treatment of habitual constipation. *Chongqing Med.* 2020;49:3244–7.

[24] Cai LW, Wang YJ, Qian WZ. Effects of Huoxue Yiqi Runchang decoction on colonic dynamics in patients with chronic intractable constipation. *Chin J Biochem Med.* 2016;36:137–9, 43.

[25] Liu N, Sun S, Wang P, et al. The mechanism of secretion and metabolism of gut-derived 5-hydroxytryptamine. *Int J Mol Sci.* 2021;22:7931.

[26] Iwasaki M, Akiba Y, Kaunitz JD. Recent advances in vasoactive intestinal peptide physiology and pathophysiology: focus on the gastrointestinal system. *F1000Res.* 2019;8:1629.

[27] Zhao DQ, Xue H, Sun HJ. Nervous mechanisms of restraint water-immersion stress-induced gastric mucosal lesion. *World J Gastroenterol.* 2020;26:2533–49.

[28] de Sillos MD, Chiba SM, Soares ACE, et al. Colonic transit time and fecal impaction in children and adolescents with cystic fibrosis-associated constipation. *J Pediatr Gastroenterol Nutr.* 2021;73:319–24.

[29] Stanga S, Boido M, Kienlen-Campard P. How to build and to protect the neuromuscular junction: the role of the glial cell line-derived neurotrophic factor. *Int J Mol Sci.* 2020;22:136.

[30] Zeng J, Yu H, Gan HT. Glial cell line-derived neurotrophic factor ameliorates dextran sulfate sodium-induced colitis in mice via a macrophage-mediated pathway. *Int Immunopharmacol.* 2021;100:108143.

[31] Meir M, Burkard N, Ungewiś H, et al. Neurotrophic factor GDNF regulates intestinal barrier function in inflammatory bowel disease. *J Clin Invest.* 2019;129:2824–40.