

Original Research Article

Efficacy of Sini SAN combined with Sijunzi decoction in tic disorder, and intestinal microbiota in children

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Abstract

Purpose: To evaluate the efficacy of Sini SAN and Sijunzi decoction in tic disorder, and intestinal microbiota in children.

Methods: This study enrolled 100 children with tic disorder from April 2020 to January 2023 in First Affiliated Hospital of Heilongjiang University of Chinese Medicine, Harbin, China. The control group ($n = 45$) was administered tiapride hydrochloride 50 mg daily, (gradually increased to thrice daily over 1 - 3 months, then reduced to once daily for 1 month, with a total treatment duration of 6 months). On the other hand, the study group ($n = 55$) received tiapride hydrochloride in addition to traditional Chinese medicine (TCM), including Sini San and Sijunzi decoction with specific herbs (*Radix pseudostellariae*, white peony), for 6 months. Efficacy, TCM syndrome scores, Yale Global Tic Severity Scale (YGTSS) scores, amino acid neurotransmitter levels, and α -diversity of intestinal microbiota were assessed in both groups before treatment and at 4th and 8th weeks after commencement of treatment.

Results: There was no significant difference in baseline characteristics between the study and control groups, indicating comparability ($p > 0.05$). The study group had a significantly higher total effectiveness/efficacy ($p < 0.05$). It exhibited greater improvements in Traditional Chinese Medicine (TCM) syndrome scores and YGTSS scores in the 4th and 8th week of treatment compared to control group ($p < 0.05$). Additionally, the study group exhibited significant decrease in glutamate and aspartate levels and a significant increase ($p < 0.05$) in α -diversity of intestinal microbiota except for Simpson index ($p > 0.05$).

Conclusion: The combination of TCM and tiapride hydrochloride improves efficacy, modulates neurotransmitter levels, alleviates symptoms, and improves α -diversity of intestinal microbiota.

Keywords: Sini SAN and Sijunzi decoction, Tic disorder, Intestinal microbiota, Amino acid neurotransmitter, Therapeutic efficacy

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INTRODUCTION

Tic disorder is a neuropsychiatric disorder that first occurs in childhood or adolescence, and is characterized by sudden motor tics or vocal tics in one or more parts of the body. Severe motor

tics may lead to cervical myelopathy, cervical disc herniation or even fracture, and it affects the emotional and psychological state of the affected children [1]. Studies suggest that an imbalance of intestinal microbiota is an important pathogenetic mechanism that causes tic disorders in children

[2]. Western medicine practice generally uses drug therapy, and psychological and behavioral interventions for treatment. Thiamphenicol, a dopamine receptor blocker, is the first-line drug for the treatment of tic disorders, but its long-term use causes dizziness, fatigue, drowsiness, breast milk overflow, amenorrhea and other adverse reactions [3]. Sini SAN and Sijunzi decoction are commonly used traditional Chinese herbal formulas in traditional Chinese medicine (TCM). Sini SAN and Sijunzi decoction are traditional Chinese herbal formulas widely recognized for their therapeutic benefits. Sini SAN, originating from the classical text 'Shang Han Lun', comprises four primary components: Bupleurum Root (*Bupleurum chinense* DC., Chai Hu), White Peony Root (*Paeonia lactiflora* Pall., Bai Shao), Immature Bitter Orange (*Citrus aurantium* L., Zhi Shi), and Licorice Root (*Glycyrrhiza uralensis* Fisch., Gan Cao).

Sijunzi decoction, detailed in the 'Pi Wei Lun', contains four key ingredients: Ginseng Root (*Panax ginseng* C.A. Mey., Ren Shen), *Atractylodes macrocephala* Rhizome (*Atractylodes macrocephala* Koidz., Bai Zhu), Poria Mushroom (*Wolfiporia extensa*, Fu Ling), and Licorice Root (*Glycyrrhiza uralensis* Fisch., Gan Cao). Both formulas are prepared by decocting the specified herbs in water for a set duration, in order to extract their medicinal properties. These compositions are lauded for their ability to harmonize the body's Qi, with Sini SAN focusing on releasing exterior conditions and moving Qi to alleviate stagnation, and Sijunzi decoction aimed at strengthening the spleen and stomach to enhance Qi and blood production. Sini San is renowned for its ability to harmonize Yin and Yang, dispel cold, and alleviate pain, hence it is often used to treat various symptoms caused by cold pathogens. On the other hand, Sijunzi decoction is well-known for its efficacy in tonifying the spleen and benefiting Qi, commonly used to address symptoms of weakness and poor appetite arising from Qi deficiency [3].

In recent years, TCM has demonstrated significant advantage in the treatment of pediatric tic disorders, thereby attracting research interest [4]. Pediatric tic disorders constitute a syndrome of movement disorders with unclear etiology, and a global prevalence of approximately 5.37%. The disorder is more common in boys compared to girls, with a male-to-female ratio of about 3.5:1 [4]. Exact pathogenesis of tic disorders is not fully understood at present. Several studies suggest a multifactorial involvement, including genetic, environmental, immunological, allergic, and neurotransmitter imbalance. Among these factors, dysfunction of the basal ganglia,

disruptions of dopaminergic transmission in the limbic system, and hypersensitivity of dopamine receptors are considered important mechanisms contributing to tic disorders [5]. Consequently, in Western medicine, dopamine receptor blockers such as thiamphenicol and tiapride are commonly used to treat pediatric tic disorders. A study has shown that the combined use of tiapride and vitamin B12 effectively treats tic disorders, improving neurological function, and alleviating anxiety [6]. Chinese medicine believes that tic disorder belongs to the category of 'liver wind, slow wind, spasm'. The spleen of tic children is often insufficient, and spleen deficiency produces phlegm and drink, marrow is not full, the essence is not solid, and so opening and closing are not in order so that the yin is not guarded internally and the yang is restless externally. The basic method of treatment is to dredge the liver and regulate the spleen [7]. Sini San is from The Treatise on Typhoid Fever and is good at dispersing the liver and regulating the spleen. Sijunzi decoction is good at benefiting qi and strengthening the spleen [8]. Therefore, this study was aimed at investigating the efficacy of Sini SAN combined with Sijunzi decoction in the treatment of tic disorder and its effect on intestinal microbiota in children.

METHODS

Baseline data

This study consecutively enrolled 100 pediatric patients with tic disorder who met the diagnostic criteria at the Pediatric Department of the First Affiliated Hospital of Heilongjiang University of Chinese Medicine from April 2020 to January 2023. The patients were divided into control and study groups. The control group (n = 45) did not receive traditional Chinese medicine (TCM) treatment, but was treated with tiapride hydrochloride, while the study group (n = 55) was administered TCM in addition to tiapride hydrochloride, specifically using the combination of Sini SAN and Sijunzi decoction. This study was approved by the ethics committee of the First Affiliated Hospital of Heilongjiang University of Chinese Medicine (no. HZYLBA2023040) and complied with the guidelines of Declaration of Helsinki [9]. Signed and written informed consent was obtained from the patient's guardians.

Inclusion criteria

Met the diagnostic criteria of tic disorder in the Expert Consensus on Diagnosis and Treatment of tic disorder in Children [6], between 4 to 14 years old, no history of relevant medications

within the past 2 weeks, which include antipsychotics such as risperidone, aripiprazole, and haloperidol, as well as medications affecting neurotransmitter systems such as clonidine and guanfacine, meet the criteria of Spleen Deficiency and Liver Exuberance Certificate in Traditional Chinese medicine Pediatrics (TCM Pediatrics) [7], long-lasting disease, often recurring, pale tongue, thin white or slightly greasy moss, thin stringy pulse with squeezing and winking of the eyebrow, wrinkled with grinning of the nose. Presence of abdominal twitching, strange noises from the throat, little food and dullness, thinness and tiredness, impatience, yellowish color, irregular bowel movements, and a signed consent form.

Exclusion criteria

Electroencephalography or cerebral nuclear magnetic examination suggests the presence of epilepsy, a serious intestinal disease that may affect the absorption of drugs, organic disease, childhood psychiatric disease or mental retardation, and allergy to the drugs involved.

Treatments

Control group received tiapride hydrochloride treatment (Tianjin Zhongxin Pharmaceutical Group Co., Ltd., Xinxin Pharmaceutical Factory, with each tablet containing 100 mg of the active ingredient). Initial treatment regimen started with a dose of 50 mg once daily. After the first month, the dose was increased to 50 mg three times daily for the next two months. Following this, the dosage was reduced to 50 mg once daily for the remaining three months, serving as maintenance therapy. Total duration of treatment was 6 months.

Study group was treated with TCM, receiving Sini San combined with Sijunzi decoction in addition to tiapride hydrochloride. The Chinese herbal formula consisted of Radix pseudostellariae 15 g, stir-fried white peony 15 g, white Rhizome 10 g, Poria 10 g, Bupleurum 15 g, Trifoliate 10 g, and grilled licorice 10 g. The dosage was adjusted based on disease symptoms. An additional 10 g of gastrodia was added for whole-body tics, 10 g of platycodon root was used for those with pronounced vocalizations, 10 g of cockscomb seed was included for patients exhibiting noticeable blinking, and 10 g of magnolia bark was added for those with evident nasal symptoms. The decoction was prepared by the Decoction Room of the First Hospital of Heilongjiang, University of Traditional Chinese Medicine, with each bag containing 150 mL. Prescribed dosage was 150 mL/day for children

aged 4 - 6 years, 200 mL/day for those aged 7 - 11 years, and 300 mL/day for those aged 12 - 14 years. Doses were administered twice daily, half an hour after meals. Both groups avoided other drugs and certain foods, maintaining regular activities without deliberately correcting tics.

Evaluation of parameters/indices

Treatment efficacy

The Yale Generalized Tic Severity Scale (YGTSS) was used to determine efficacy of treatment, and the scale was divided into three parts [8]. Vocal tics, motor tics and social function deficits. Vocal tics and motor tics were assessed in terms of quantity, frequency, intensity, complexity, and interference, with a score of 0 to 5 points. Social function deficits were assessed based on the degree of vocal or motor tics that the children's social function suffers from with the impact scored from 0 to 50 points. Total YGTSS score was 100 points, and the higher the score, the more severe the overall tic symptoms. $\geq 80\%$ of the total YGTSS score reduction was considered cured, 50% to $< 80\%$ was considered significantly effective, 30% to $< 50\%$ was considered effective, and $< 30\%$ was considered ineffective.

Traditional Chinese medicine syndrome score

A total of 9 items were used to assess severity of twitching symptoms, each scored from 0 to 3 points, where a higher score indicates more severe symptoms. The items include squeezing eyebrows, blinking, abdominal twitching, eating less, being slow, vocal tics, nose twitching, finger movement, and head jerking [10].

Serum enzyme level determination

A total of 2 mL peripheral venous blood was collected from both groups before treatment and at the 8th week of treatment, centrifuged at 4 °C for half an hour at 3000 r/min for 10 min, and the serum was frozen at - 80 °C in a refrigerator. After uniform thawing, serum glutamate (Glu) (30 - 90 $\mu\text{mol/L}$), aspartate (Asp) (10 - 30 $\mu\text{mol/L}$) and other amino acid neurotransmitter levels were determined by Agilent Bioanalyzer 2100 Bioanalyzer. Fresh fecal specimens of 5 g from children in both groups were collected before treatment and at the 8th week of treatment. The samples were placed in a closed fecal storage box and stored at - 80 °C in a refrigerator for 30 min. Total DNA was extracted uniformly using a fecal genomic DNA extraction kit, and the DNA concentration was determined. Polymerase chain

reaction (PCR) was used to amplify the V3 and V4 labeled fragments of 16SrRNA gene, and high-throughput sequencing was performed with a Qubit 3.0 Fluorometer fluorescence quantification instrument [11].

α-Diversity indices of intestinal microbiota

The α -diversity indexes of intestinal microbiota such as Chao1 index, Sobs index, Ace index and Shannon index were determined using the quantitative insights into microbial ecology (QIIME) software.

Statistical analysis

Data were processed using Statistical Packages for Social Science (SPSS 25.0, IBM, Armonk, NY, USA). Measurement data such as YGTSS scores and amino acid neurotransmitters were presented in mean \pm standard deviation (SD) and compared with t-test. Count data such as type of tic disorders and gender are presented as frequency and percentages, and compared using chi-square (χ^2). $P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

There was no significant difference in baseline characteristics between study and control groups ($p > 0.05$; Table 1).

Treatment efficacy

Total effective rate was significantly higher in study group compared to control group ($p < 0.05$; Table 2).

Traditional Chinese medicine syndrome scores

Traditional Chinese medicine syndrome scores were significantly lower in the 4th and 8th week after treatment in both study and control groups ($p < 0.05$). However, study group had significantly lower TCM syndrome scores in the 4th and 8th week compared to control group ($p < 0.05$, Table 3).

Table 1: Baseline information among two groups (N, %)

Group	N	Gender		Age (years)	Weight (kg/m ²)	Duration of illness (months)	Type of disease		
		Male	Female				Transient	Chronic movement or vocalization	Tourette syndrome
Control	45	34(75.56)	11(24.44)	7.89 \pm 1.75	29.14 \pm 4.47	20.14 \pm 4.69	26(57.78)	15(33.33)	4(8.89)
Study	55	42(76.36)	13(23.64)	7.81 \pm 1.82	28.78 \pm 5.03	19.76 \pm 5.04	27(49.09)	23(41.82)	5(9.09)
χ^2 /t		0.009		0.222	0.374	0.387	0.822		
P-value		0.925		0.824	0.709	0.700	0.663		

Table 2: Treatment efficacy of Sini SAN combined with Sijunzi decoction

Group	N	Cure	Significant effective	Effective	Ineffective	Total effective rate
Control	45	5(11.11)	19(42.22)	12(26.67)	9(20.00)	36(80.00)
Study	55	14(25.45)	27(49.09)	11(20.00)	3(5.45)*	52(94.55)
χ^2		4.959				
P-value		0.026				

Note: * $P < 0.05$ vs control group

Table 3: Traditional Chinese medicine syndrome scores (n=45)

Group	N	TCM syndrome scores		
		Pre-treatment	4 weeks of treatment	8 weeks of treatment
Control	45	19.85 \pm 2.47	13.21 \pm 2.09*	9.56 \pm 1.63*
Study	55	19.74 \pm 2.55	9.07 \pm 1.87 ^a	6.52 \pm 1.11 ^a
T-value		0.218	10.445	11.054
P-value		0.828	0.000	0.000

Note: * $P < 0.05$ vs before treatment, ^a $p < 0.05$ vs control

Yale Generalized Tic Severity Scale (YGTSS)

Motiv tic, vocal tic, social functioning deficit, and total YGTSS scores were significantly lower in the 4th and 8th week after treatment ($p < 0.05$). However, the study group exhibited significantly lower YGTSS scores at 4th and 8th week compared to control group ($p < 0.05$; Table 4).

Levels of amino acid neurotransmitters

Glutamate and aspartate levels were significantly lower in both groups after treatment at 8th of treatment ($p < 0.05$). However, the study group showed significantly lower levels in the 8th week compared to control group ($p < 0.05$; Table 5).

Alpha-diversity of intestinal microbiota

The Chao1, Sobs, Ace and Shannon indices were significantly higher in the 8th week of treatment ($p < 0.05$), but there was no significant difference in the Simpson index before and after treatment ($p > 0.05$). The alpha diversity of intestinal microbiota except the Simpson index was significantly higher in study group in the 8th week compared to control group ($p < 0.05$; Table 6).

Safety

The study population (both control and study groups) did not experience any severe adverse reactions.

Table 4: Yale Generalized Tic Severity Scale

Group	N	Motor tic scores			Vocal tic scores		
		Pre-treatment	4 weeks of treatment	8 weeks of treatment	Pre-treatment	4 weeks of treatment	8 weeks of treatment
Control	45	15.24±2.56	10.11±2.23*	8.89±2.17*	13.32±2.77	6.98±1.24*	3.71±0.86*
Study	55	15.52±2.49	8.06±1.53 ^a	5.03±1.04 ^a	12.98±3.05	4.11±0.66 ^a	2.22±0.45 ^a
T-value		0.552	5.434	11.665	0.578	14.803	11.129
P-value		0.582	0.000	0.000	0.565	0.000	0.000

Group	N	Social functioning deficit score			Total YGTSS score		
		Pre-treatment	4 weeks of treatment	8 weeks of treatment	Pre-treatment	4 weeks of treatment	8 weeks of treatment
Control	45	28.98±5.14	15.25±2.13*	8.23±1.77*	57.54±4.96	32.34±4.03*	20.83±3.47*
Study	55	30.01±4.87	11.47±1.92 ^a	5.06±0.84 ^a	58.51±5.33	23.64±3.87 ^a	12.31±2.16 ^a
T-value		1.026	9.323	11.770	0.934	10.978	15.008
P-value		0.307	0.000	0.000	0.353	0.000	0.000

Note: N (control) = 45, N s(study) = 55, * $P < 0.05$ vs before treatment, ^a $p < 0.05$ vs control group

Table 5: Amino acid neurotransmitter (mean ± SD)

Group	N	Glu (μmol/L)		Asp (μmol/L)	
		Pre-treatment	8 weeks of treatment	Pre-treatment	8 weeks of treatment
Control	45	100.14±5.28	75.23±4.26*	60.78±4.77	51.85±4.03*
Study	55	99.47±6.07	61.14±3.88*	61.39±5.02	42.17±3.68 ^a
T-value		0.582	17.286	0.618	12.537
P-value		0.562	0.000	0.538	0.000

Note: * $P < 0.05$ vs before treatment, ^a $p < 0.05$ vs control group. Glu: Glutamate; Asp: Aspartate

Table 6: Alpha diversity of intestinal microbiota

Indicator	Time	Control (n = 45)	Study (n = 55)	T-value	P-value
Chao1 index	Pre-treatment	189.96±58.47	192.07±62.34	0.173	0.863
	At 8 weeks	227.84±60.73*	274.14±68.25*	3.545	0.001
Sobs index	Pre-treatment	148.58±40.77	152.23±37.82	0.464	0.644
	At 8 weeks	175.73±45.62*	217.46±48.93*	4.373	0.000
Ace index	Pre-treatment	188.63±37.78	184.74±43.06	0.475	0.636
	At 8 weeks	236.41±47.82*	277.52±50.13*	4.165	0.000
Shannon index	Pre-treatment	2.74±0.33	2.70±0.28	0.656	0.514
	At 8 weeks	3.01±0.35*	3.45±0.41*	5.697	0.000
Simpson's index	Pre-treatment	0.08±0.02	0.09±0.03	1.914	0.059
	At 8 weeks	0.07±0.03	0.08±0.03	1.658	0.100

Note: * $P < 0.05$ vs. before treatment

DISCUSSION

Tic disorder is a group of motor disorders of unknown cause, with global prevalence of about 5.37 %, more in males than females, and a male-to-female ratio of about 3.5:1 [12]. Pathogenesis of tic disorder is still not completely clear, and some studies suggest that it is related to a variety of factors, such as genetics, environment, immunity, allergy, and neurotransmitter imbalance. Among them, dysfunction of the dopamine system in the basal ganglia, and limbic system, and hypersensitivity of dopamine receptors may be one of the important pathogenic mechanisms of tic disorder [13]. Therefore, in Western medicine, tiapride, a dopamine receptor blocker, is generally used to treat children with tic disorder. A study reported that tiapride combined with vitamin B12 improves neurological function and reduces anxiety in children [14].

According to Chinese medicine theory, the disease of liver wind is located in the liver and is closely related to the spleen's transportation failure. The spleen is often insufficient in children, and The Complete Guide to Ancient and Modern Medicine posited that the spleen and earth are weak, and the liver would take advantage of them, so the tendons are contracted and convulsions are made. This points out that deficiency of the spleen and the exuberance of the liver are the basic mechanisms of the disease [15]. *Radix pseudostellariae* is a component of Sini SAN and Sijunzi decoction. It is also known as 'baby ginseng', suitable for children and good at supplementing Qi and blood, strengthening the spleen and promoting fluid. Baizhu is good at invigorating the spleen and replenishing Qi, drying, dampness and middle. Poria is good for invigorating the spleen and dampness and calming the heart and nerves, and these two drugs strengthen the spleen. Fried white peony nourishes blood, softens liver, suppresses liver Yang; Bupleurum reconciles exterior, soothes the liver and regulates spleen; Trifoliate dispels liver-regulating qi, dissipates phlegm and disperses distention. Moxibustion with licorice moderates and balances the therapeutic properties of the decoction. For whole-body twitch, gastrodia is added to flatten the liver and extinguish wind. Cicadas are added to those who vocalize obviously to drain wind and benefit the pharynx, while for those who blink, feather seed is added to clear the liver and eyes. For obvious nasal symptoms, Xinyi is added to promote nasal orifice with the additional effect of invigorating the spleen, soothing the liver, quenching wind and relieving spasms [16,17].

This study revealed that the total effective rate of study group was significantly higher compared to control group. The two groups were found to have lower TCM syndrome scores, and total scores of motor and vocal tics and social function deficits in YGTSS at 4 and 8 weeks of treatment were significantly lower after treatment. The results suggest that Sini San combined with Sijunzi decoction reduces symptoms and improves efficacy in children with tic disorders. This is because paeoniflorin and paeonilactone contained in white peony in the formula of four reversals and four gentlemen soup regulates cellular immune function possesses anti-inflammatory and antispasmodic activities, and regulates the hyperactive hypothalamic-pituitary-adrenocortical axis [18]. Poria contains polysaccharides, choline, ergosterol and other components which possess anti-hepatic fibrosis activity improve immunity, and regulate intestinal microbiota with anti-inflammatory and other pharmacological effects [19]. Triterpenoid saponins and glycyrrhizin acid contained in licorice relieve smooth muscle spasms, protect the liver and prevent arrhythmia [20].

The occurrence of tic disorders is closely related to the neuroexcitatory amino acids such as glutamate and aspartate. Reduction of inhibitory neurotransmitter projection pathways in the brain of affected children and the insufficient inhibition of thalamocortical excitatory neurons causes an increase in levels of Glu and Asp, leading to increased excitability of cerebral cortex and the occurrence of tic disorders [21]. In this study, serum Glu and Asp decreased significantly in both groups at the 8th week of treatment. However, study group exhibited significant reduction in levels of amino acid neurotransmitters compared to control group. This result suggests that treatment of tic disorders in children by Sini San combined with Sijunzi decoction corrects the imbalance of amino acid-based neurotransmitters. This is because gastroside and gastrogenin contained in gastrodia have sedative and analgesic effects, dilate blood vessels, improve microcirculation, and protect neurons and vascular endothelial cells. In addition, gastroside relieves tic symptoms by increasing the content of gamma-aminobutyric acid and inhibiting excitatory neurons in the thalamus-cortex [22].

The intestinal microbiota is inter-regulated with the nervous system through the bacteria-gut-brain axis, and *Lactobacillus* and *Bifidobacterium intestinalis* produce gamma-aminobutyric acid, which inhibits cerebral cortex excitability. Decreased synthesis of gamma-aminobutyric

acid in dysbiosis of intestinal microbiota is associated with the development of tic disorders [23]. In this study, Chao1, Sobs, Ace and Shannon indices were significantly higher in both groups after treatment at 8th after treatment. However, there was no significant difference in the Simpson index before and after treatment. The alpha diversity of intestinal microbiota except the Simpson index was significantly higher in study group compared to control group in the 8th week. This result suggests that Sini San combined with Sijunzi decoction improves the α -diversity of intestinal microbiota in children with tic disorders. This may be attributed to the volatile oil components in TCM such as Baizhu and *Citrus aurantium* which regulate intestinal motor rhythm and reestablish intestinal microbiota balance [24]. Also, this study found that no serious adverse reactions occurred in both groups, suggesting a favorable safety profile for both treatment regimens.

Limitations of this study

This study has some limitations. A small sample size may lack statistical power, while a homogeneous sample may restrict the applicability of the findings. Issues with the reliability and validity of data collection tools and methods may affect result accuracy. Study designs that do not allow for causal inferences, inadequate control over confounding variables, and biases inherent in self-reported data may skew findings. Short follow-up periods may not adequately capture long-term effects, and specific choices in statistical analysis may impact results interpretation. Also, ambiguities in definitions and ethical restrictions may limit the scope as well as funding and resource constraints. Furthermore, study conditions may not reflect real-world settings, and as a result, limit the external validity of this study. Recognizing these limitations is fundamental for informing future studies.

CONCLUSION

Sini San combined with Sijunzi decoction improves the α -diversity of intestinal microbiota, corrects the imbalance of amino acid neurotransmitters, reduces symptoms, and improves therapeutic efficacy. Future studies to validate the outcome of these investigations would be required.

DECLARATIONS

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None provided.

Ethical approval

This study was approved by the Ethics Committee of the First Affiliated Hospital of Heilongjiang University of Chinese Medicine (HZYLLBA2023040).

Availability of data and materials

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

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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