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# Efficacy of jing Si herbal tea in functional dyspepsia: A double-blind, randomized, placebo-controlled study

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ABSTRACT

*Background:* Functional dyspepsia (FD) is prevalent worldwide and is associated with gastrointestinal inflammation, mucosal anomalies, and shifts in microbiota metabolites like short chain fatty acids. This study assesses the efficacy of Jing Si herbal tea (JSHT) in alleviating FD symptoms, psychological distress, and influencing metabolites.

*Methods:* Adults with FD based on Rome IV criteria were included. Participants underwent physical and psychological evaluations, pre-treatment blood sampling, and were randomly assigned to JSHT or placebo groups for four weeks. Post-treatment, evaluations and Liquid Chromatography-Mass Spectrometry for gut metabolites were done. Successful response was defined by a 50% symptom reduction. Symptom intensity, sleep, depression, anxiety, and stress were measured using questionnaires.

*Results:* 26 patients (median age 55.5 years, range 22–77 years, 60.6% female) were studied. Both JSHT and placebo groups were similar at baseline. JSHT showed a higher response rate (69.2%) than placebo (23.1%, $P = 0.018$). JSHT recipients experienced notable reduction in upper gastrointestinal symptoms and anxiety ($P = 0.005$; $P = 0.037$). Increased serum butyrate was observed in improved patients ($P = 0.01$), whereas no major changes were detected in the placebo group.

*Conclusion:* Four weeks of JSHT treatment ameliorated FD symptoms and anxiety, potentially linked to increased serum butyrate. This study suggests that JSHT has potential therapeutic role in patients with FD.

## 1. Introduction

Functional dyspepsia (FD) is a prevalent disease, with a global prevalence rate as high as 7.2% [1]. According to the Rome IV criteria, symptoms of FD included meal-related fullness, early satiation, epigastric pain or burning which are unexplained after routine investigation [2,3]. Currently, the mechanism of functional dyspepsia remains unclear, but it is thought to be related to the brain-gut axis, and potential mechanisms include local inflammation in the gastrointestinal tract, activation of infiltrating allergic cells, mucosal defects, changes in the microbiota, and hypersensitivity of visceral sensation [4].

In terms of the microbiota of the brain-gut axis, the gut microbiota-derived metabolites are regarded as key influences. Short-chain fatty acids (SCFAs) are considered beneficial metabolic products. After the fermentation of carbohydrates, anaerobic bacteria will produce a large amount of SCFAs in the distal small intestine and colon. They consist of 1–6 carbon atoms, and the three main metabolic compounds are acetate, propionate, and butyrate. Studies have shown that SCFAs have anti-inflammatory, antioxidant, antidiabetic, anticancer, and antimicrobial effects. When the gut microbiota is imbalanced, various detrimental metabolic products are produced: trimethylamine N-oxide (TMAO) (derived from L-carnitine or choline), indoxyl sulfate (derived from

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tryptophan), and *p*-cresyl sulfate (derived from tyrosine) [5].

Current medical treatments for FD, such as acid suppressants, prokinetics, neuromodulators, and psychosomatic therapies, fail to completely alleviate symptoms in approximately 50% of patients [6–8]. This demonstrates the need for more effective alternatives for FD treatment. Recent literature reviews suggest that Traditional Chinese Medicine may alleviate FD symptoms and associated anxiety [9,10]. A notable study tested rikkunshito, a traditional herbal medicine. In this two-month, double-blind randomized trial that included 247 FD patients, considerable improvements were reported in both epigastric pain (with an improvement ratio of 44.0% in the rikkunshito group versus 30.3% in the placebo group, $P = 0.04$) and postprandial bloating (with an improvement ratio of 50.4% in the rikkunshito group versus 37.7% in the placebo group, $P = 0.06$) [11].

Jing Si Herbal Tea (JSHT), an eight-herb formula including A. argyi leaves, has shown promise as an adjunctive treatment for COVID-19 infection [12]. The various active components of JSHT might induce an anti-inflammatory effect through different signaling pathways, thereby reducing systemic inflammation. In reducing inflammation and enhancing endothelial integrity, JSHT could potentially alleviate brain damage associated with the S protein of SARS-CoV-2. It may also provide relief from long-term depressive symptoms in COVID-19 patients [12,13]. Therefore, the primary aim of this research was to investigate if JSHT could improve symptoms of FD and reduce the associated psychological distress. Additionally, we aimed to determine whether JSHT could impact and modulate gut microbiota-derived metabolites.

## 2. Methods

### 2.1. Subjects

The study, registered under the ClinicalTrials.gov Identifier: NCT05948215, prospectively encompassed adult patients (age range 20–79 years) who demonstrated primary symptoms of FD, diagnosed per the Rome IV criteria. These patients presented at the gastrointestinal outpatient department of Hualien Tzu-Chi Hospital during the 2021–2022 period. FD is typified by chronic (at least weekly, persisting for no less than three months, with the inception of symptoms traceable to a minimum of six months prior) upper gastrointestinal symptoms, including but not restricted to meal-related fullness, early satiation, epigastric pain, or burning. Individuals meeting these criteria were, however, disqualified from the study if they exhibited any of the subsequent conditions: (1) abnormal liver or kidney function; (2) irregular blood or thyroid tests; (3) history of esophageal or gastric surgery; (4) abnormal findings in upper gastrointestinal endoscopic examinations; (5) infection with *Helicobacter pylori*; (6) current use of antibiotics for treating an infectious disease, or use of probiotics within the past six months; (7) pregnant or lactating women; (8) significant weight loss; (9) a past psychiatric history or use of psychiatric medications. The study received ethical approval from the Research Ethics Committee of Hualien Tzu-Chi Hospital, Buddhist Tzu-Chi Medical Foundation. Written informed consent was duly acquired from all participants. The study adhered to the ethical principles of the Declaration of Helsinki.

### 2.2. Protocol

Eligible participants underwent blood drawing and extensive physical and psychological symptom evaluations prior to treatment initiation. This included gastrointestinal symptom surveys, sleep habit surveys, depression and anxiety surveys, and stress surveys. Subsequently, a double-blind random allocation was executed, leveraging computer-generated random codes to designate either the JSHT concentrate or a placebo per the sequence of codes. The research assistant administered the JSHT concentrate or placebo, while the study coordinator and participants remained blinded to the allocation content.

In this randomized, placebo-controlled, parallel-group experiment, eligible FD patients received either 15 ml of JSHT or a placebo daily for a four-week duration. At the conclusion of this period, blood drawing and comprehensive physical and psychological symptom assessments were repeated. The laboratory performed pre- and post-testing analyses of the gut microbiota-derived metabolites using liquid chromatography-mass spectrometry (LC-MS). A symptom response was classified as at least a 50% reduction of dyspeptic symptoms as quantified by the visual analogue scale.

### 2.3. Questionnaires

Symptoms were evaluated at each visit and across all subjects using the Patient Assessment of Gastrointestinal Symptom Severity Index (PAGI-SYM), tailored for upper GI disorders, with the total score ranging from 0 (none) to 5 (very severe) during a 2-week recall period [14]. Sleep quality was assessed based on self-report questionnaire Pittsburgh Sleep Quality Index (PSQI) over the past month. Patients with a global score (sum of seven components, on a 0–3 scale) exceeding five were considered to have sleep disturbances [15]. Participants were guided to complete 18 questions (0–3 scale) of the culturally-adapted Taiwanese Depression Questionnaire (TDQ) [16]. In the context of our study, depression was defined as a global score surpassing 18. Anxiety was diagnosed by a global score of State-Trait Anxiety Inventory (STAI) exceeding 40. STAI comprises 20 items for trait anxiety and 20 items for state anxiety, with each item's scores ranging from 1 to 4 [17]. Perceived stress over the prior week was assessed utilizing the 10-item Perceived Stress Scale (PSS) [18].

### 2.4. Metabolites analysis by LC-MS

As previously described, gut microbiota-derived circulating metabolite levels were determined using LC-MS via a modified method [19,20]. 100 μL of plasma was transferred to a 1.5 mL centrifuge tube, to which 50 μL of 0.2 M 3-nitrophenylhydrazine hydrochloride (3NPH·HCl) and 50 μL of 0.12 M N-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride were added. Derivatization was then conducted at 40 °C for 20 min. Following this, 100 μl of 50 mM sodium phosphate dibasic heptahydrate solution was added. The stable isotopes d9-TMAO and 13C16-PA (palmitic acid) served as internal standards and were gently vortex-mixed. Extraction using the SLE column (Phenomenex, Novum®) entailed elution in 1.5 mL of ethyl acetate. The samples were subsequently dried under nitrogen gas, redissolved in 100 μl methanol, and then loaded into a sample vial for LC-MS analysis.

The Waters e2695 high-performance liquid chromatography system, integrated with a single quadrupole mass spectrometer (MS-QDa, ACQUITY QDa®, Waters Corp., Milford, MA, USA), was employed for analysis. The Phenomenex Luna® C18(2) column (5μ, 250 × 4.60 mm, 100 Å), in conjunction with a guard cartridge system (KJ0-4282, Phenomenex), was utilized for the separation of analytes. Under the hydrophobic LC-MS analysis conditions for SCFAs, the column temperature was maintained at 30 °C, the flow rate of the mobile phase was 0.6 mL/min, and the injection volume was 30 μL. Mobile phase A consisted of (60:40 acetonitrile:ddH2O) while mobile phase B comprised (90:10 isopropanol:acetonitrile). Both mobile phases A and B included 9.2 mM ammonium acetate (Sigma Aldrich, St. Louis, MO, USA). The gradient of the mobile phase initiated at 15% B, transitioning to 30% B in 8 min, increasing to 48% B over another 2 min, and then to 82% B up to 44 min. A concentration of 99% B was achieved in 2 min and sustained for another 2 min. Thereafter, 15% B commenced at 48.4 min and was maintained until 60 min. Post analysis, the column was cleansed with isopropanol and stored to forestall drying. The settings for the MS-QDa detector were: vaporization temperature 600 °C, capillary voltage 0.8 kV, and sample cone 20.0 V. The hydrophilic LC-MS analysis for TMAO, indoxyl sulfate, and p-cresyl sulfate followed the conditions outlined in our prior studies [21,22]. The single ion recording (SIR) mode targeted SCFAs, TMAO, indoxyl sulfate, and p-cresyl sulfate. The SCFAs and

long-chain fatty acids, including propionate 208.1 (73.1 + 135.0) *m/z*, butyrate 222.1 (87.1 + 135.0) *m/z*, and 13C16-PA 271.4 m/z, underwent detection in the negative ion mode. Conversely, TMAO 76.0 m/z and d9-TMAO 85.1 m/z were identified in the positive ion mode. The indoxyl sulfate 211.9 m/z and p-cresyl sulfate 187.0 m/z were detected in the negative ion mode. Data from the LC-MS were processed using the LC-MS Empower 3 software (Waters Corp., Milford, MA, USA). Detection results were quantified based on peak areas, and were compared to calibration curves derived from the standard solution.

### 2.5. Statistical analysis

Continuous data are represented as median with the interquartile range and categorical data as counts and percentages. The Pearson $\chi 2$ test was deployed to compare categorical variables, whereas the Mann-Whitney *U* test was utilized to analyze continuous variables. The therapeutic efficacy between JSHT and placebo was compared using the Pearson $\chi 2$ test, while the severity of symptoms, sleep quality, depression, anxiety, and stress in patients pre- and post-treatment were compared utilizing the Wilcoxon rank-sum test.

## 3. Results

### 3.1. Study population

During the study period, 31 FD patients were incorporated. Subsequent to the exclusion of 5 FD patients with concurrent *Helicobacter pylori* infection, therapy was initiated for the remaining 26 FD patients (median age 55.5 years, range 22–77 years, and 60.6% female). Upon the execution of randomized allocation, 13 patients underwent treatment with JSHT while the other 13 were subjected to placebo treatment. Fundamental characteristics at the outset were comparable among the two groups including parameters like age, gender, type of FD, severity of upper gastrointestinal symptoms, intensity of sleep disruption, prevalence of depression, anxiety, and perceived stress (Table 1).

### 3.2. Clinical outcomes

Table 2 encapsulates the differential response to one-month treatment between the JSHT and placebo cohorts. In the FD population, 9 out of the 13 patients demonstrated a positive response to the JSHT treatment, a marked contrast to the 3 out of 13 positive responses in the placebo group. The response rate for the JSHT group was significantly higher than the placebo cohort (69.2% versus 23.1%, $P = 0.018$). Post JSHT treatment, there were notable enhancements in the severity of upper gastrointestinal symptoms and anxiety levels (PAGI-SYM: reduced from 28.8 to 13.6, $P = 0.001$; STAI: reduced from 40.9 to 35.1, $P = 0.037$). Conversely, in the placebo cohort, variables such as the severity of upper gastrointestinal symptoms, sleep disturbances, depression, anxiety, and perceived stress maintained a steady trajectory pre and post-treatment ($P > 0.05$).

Concerning the side effects, two FD patients who received JSHT treatment experienced a mild increase in bowel movements, without the presence of diarrhea. They did not perceive this increase in bowel movements as causing any discomfort or impacting their quality of life negatively. Otherwise, none of any other side effects was observed in this study.

**Table 1**
Comparison of baseline clinical characteristics between FD patients treated with JSHT and those treated with a placebo.

| | JSHT | Placebo | *P*-value |
|---|---|---|---|
| Age | 51 (41, 65) | 57 (31, 65) | 1.000 |
| Female (%) | 7 (53.8) | 11 (84.6) | 0.089 |
| FD subtypes (%) | | | |
| PDS (%) | 8 (61.5) | 11 (84.6) | 0.185 |
| EPS (%) | 9 (69.2) | 8 (61.5) | 0.680 |
| Overlap (%) | 3 (23.1) | 5 (38.5) | 0.395 |
| PAGI-SYM | 36 (11, 41.5) | 29 (14.5, 38.5) | 0.837 |
| PSQI | 14 (7.5, 19) | 11 (7, 16) | 0.472 |
| TDQ | 12 (5.5, 18.5) | 7 (4.5, 13) | 0.247 |
| STAI | 43 (35.5, 48.5) | 35 (27.5, 44.5) | 0.237 |
| PSS | 18 (16, 19.5) | 17 (13.5, 19.5) | 0.536 |

FD, Functional dyspepsia; JSHT, Jing Si herbal tea; PDS, postprandial distress syndrome; EPS, epigastric pain syndrome; PAGI-SYM, Patient assessment of gastrointestinal symptom severity index; PSQI, Pittsburgh sleep quality index; TDQ, Taiwanese depression questionnaire; STAI, State-trait anxiety inventory; PSS, 10-item perceived stress scale. Continuous variables are reported as the median with the interquartile range, and were analyzed using the Mann-Whitney *U* test. A *P*-value of less than 0.05 was deemed statistically significant.

**Table 2**
Symptomatic and psychological burden before and after treatment with JSHT and Placebo.

| | Before | After | *P*-value |
|---|---|---|---|
| JSHT | | | |
| PAGI-SYM | 36 (11, 41.5) | 12 (5.5, 20.5) | 0.005 |
| PSQI | 14 (7.5, 19) | 12 (6.5, 17) | 0.207 |
| TDQ | 12 (5.5, 18.5) | 9 (2, 12.5) | 0.056 |
| STAI | 43 (35.5, 48.5) | 36 (31.5, 41) | 0.037 |
| PSS | 18 (16, 19.5) | 15 (11.5, 19.5) | 0.201 |
| Placebo | | | |
| PAGI-SYM | 29 (14.5, 38.5) | 18 (12.5, 21) | 0.068 |
| PSQI | 11 (7, 16) | 10 (7.5, 14.5) | 0.141 |
| TDQ | 7 (4.5, 13) | 4 (2.5, 11) | 0.135 |
| STAI | 35 (27.5, 44.5) | 34 (29, 39.5) | 0.278 |
| PSS | 17 (13.5, 19.5) | 18 (14.5, 20) | 0.532 |

JSHT, Jing Si herbal tea; PAGI-SYM, Patient assessment of gastrointestinal symptom severity index; PSQI, Pittsburgh sleep quality index; TDQ, Taiwanese depression questionnaire; STAI, State-trait anxiety inventory; PSS, 10-item perceived stress scale. Continuous variables are reported as the median with the interquartile range, and were analyzed using the Wilcoxon rank-sum test. A *P*-value of less than 0.05 was deemed statistically significant.

### 3.3. Gut microbiota-derived metabolites alterations

#### 3.3.1. Linearity

The analytes exhibited retention times of approximately 16.6 min for propionate, 23.9 min for butyrate, 35.9 min for 13C16-PA (used as internal standard 1, IS1), 1.9 min for TMAO and d9-TMAO (serving as internal standard 2, IS2), 7.8 min for p-cresyl sulfate, and 10.2 min for indoxyl sulfate. Calibration curves were subsequently established, and all yielded determination coefficients (R^2) indicating linearity of ≧ 0.992. The LC-MS SIR mode was employed for single ion analysis, and the corresponding results of the sample standards, along with their [M−H]− or [M+H]+ ions (*m/z*), are depicted in Fig. 1.

#### 3.3.2. Characteristics of the collection participants and plasma detection

Baseline characteristics related to circulating gut microbiota-derived metabolite levels are presented for both pre- and post-treatment placebo and JSHT groups. No significant differences were observed between the two groups for metabolites such as propionate, TMAO, indoxyl sulfate, and p-cresyl sulfate. Notably, a marked elevation in butyrate levels (392.4 versus 519.8 μg/L, P = 0.010) was discerned in the JSHT group compared to the placebo group, as delineated in Table 3.

## 4. Discussion

This was a double-blind, randomized, placebo-controlled study assessing the efficacy of JSHT in treating FD, as diagnosed according to the Rome IV criteria. This research illuminates that, over a one-month course of JSHT administration for FD, the therapeutic effectiveness achieved was 69.2%—a measure significantly exceeding the 23.1% observed in the placebo group. Furthermore, JSHT exerted a twofold

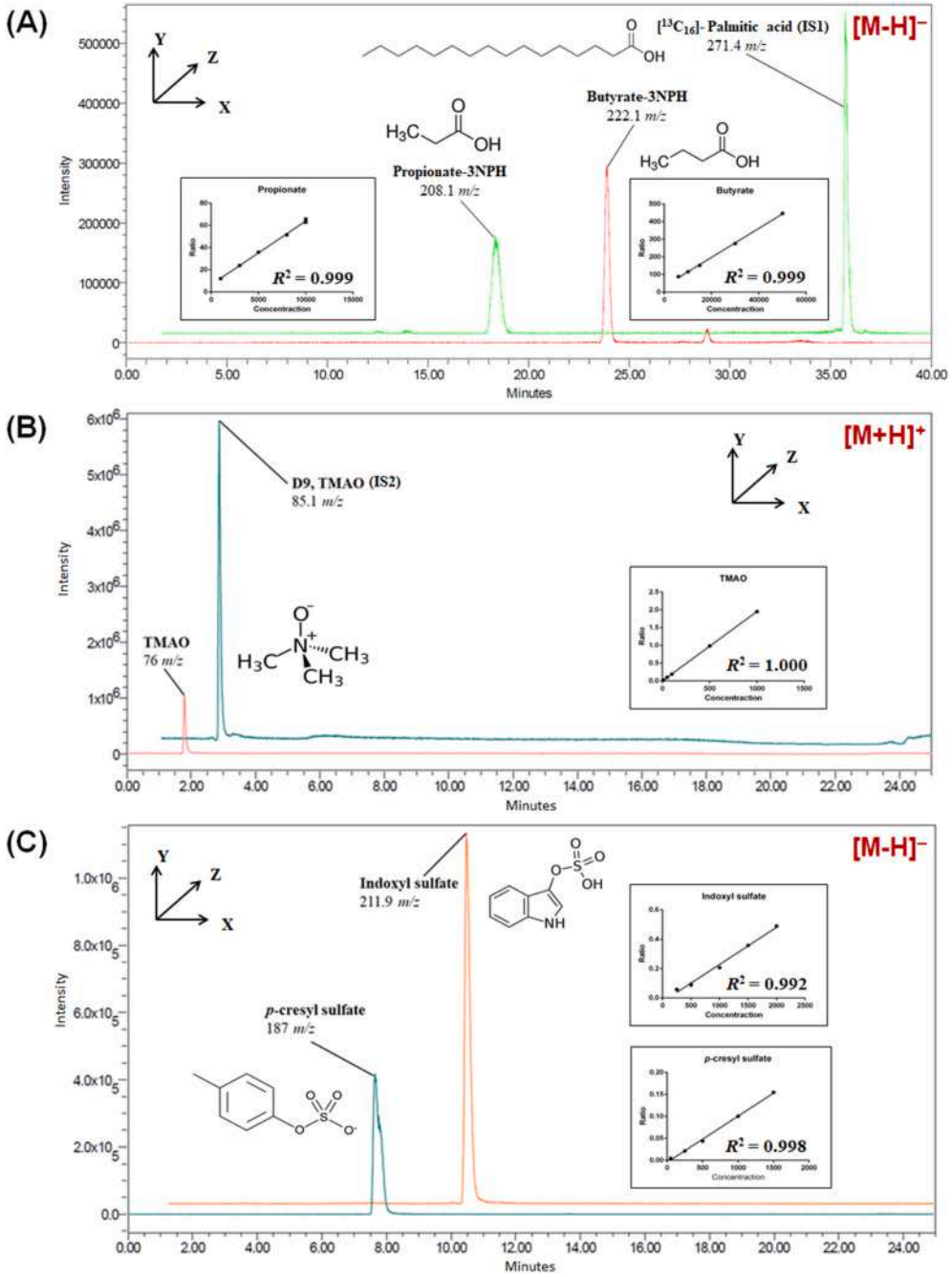


**Fig. 1.** Single ion recording (SIR) mode of liquid chromatography-mass spectrometry (LC-MS) analysis and calibration curves. **(A)** The hydrophobic LC-MS analysis condition in negative ion mode detection: propionate-3NPH (73.1 + 135.0 *m/z*), butyrate-3NPH (87.1 + 135.0 *m/z*) and $^{13}C_{16}$-PA (271.4 m/z). **(B)** The hydrophilic LC-MS analysis condition in positive ion mode detection: TMAO (76.0 *m/z*) and d9, TMAO (85.1 *m/z*). **(C)** The hydrophilic LC-MS analysis condition in negative ion mode detection: *p*-cresyl sulfate (187.0 *m/z*) and indoxyl sulfate (211.9 *m/z*). $[M-H]^-$, negative ion mode; $[M+H]^+$, positive ion mode; TMAO, trimethylamine N-oxide; $R^2$, the determination coefficients.

therapeutic effect by not only alleviating upper gastrointestinal symptoms but also diminishing anxiety levels. Notably, among the patients exhibiting FD symptom improvement, there was a discernible rise in serum butyrate levels following JSHT treatment.

FD is a prevalent and unexplained disorder with an undetermined pathophysiology, thereby hindering precise diagnosis and the advancement of efficacious medications [3]. Psychological distress, particularly anxiety, has been found to be associated with FD and may even precede the onset of the disorder in some individuals [23]. Conversely, in others, gastrointestinal symptoms appear before the onset of anxiety, suggesting that a gut-driven brain disorder may explain some cases [24]. Given the limited efficacy of most conventional medical therapies, it is unsurprising that approximately 50% of FD patients explore alternative treatment methods [25]. At least 18 pieces of literature in the Cochrane database discuss the use of herbal medicine in treating FD [10]. These studies indicate not only an improvement in FD symptoms but also suggest alleviation of patient anxiety and depression. Previous studies have also shown that JSHT, combined with standard management, may mitigate critical status and reduce mortality in patients with mild-to-moderate COVID-19, suggesting its potential as a promising complementary therapy [12]. Furthermore, by reducing inflammation and enhancing endothelial integrity, JSHT could

**Table 3**
The circulating gut microbiota-derived metabolites levels before and after treatment with placebo or JSHT.

| Metabolites | Before (μg/L) | After (μg/L) | *P*-value |
|---|---|---|---|
| *Placebo group without therapeutic effectiveness (N = 10)* | | | |
| Propionate | 810.9 (582.3, 1931.5) | 639.2 (491.6, 897.8) | 0.204 |
| Butyrate | 516.3 (400.6, 675.9) | 413.6 (370.3, 628.4) | 0.380 |
| TMAO | 165.9 (121.7, 255.0) | 179.4 (159.3, 259.3) | 0.268 |
| Indoxyl Sulfate | 3502.1 (1941.4, 4292.8) | 3101.9 (2156.1, 5117.0) | 0.677 |
| *p*-Cresyl Sulfate | 15214.8 (8719.2, 31698.3) | 10036.2 (5301.2, 28762.4) | 0.241 |
| *JSHT group with therapeutic effectiveness (N = 10)* | | | |
| Propionate | 956.5 (709.2, 1436.1) | 787.0 (588.9, 895.7) | 0.077 |
| Butyrate | 392.4 (331.1, 466.2) | 519.8 (414.3, 675.9) | 0.010 |
| TMAO | 144.1 (120.2, 274.4) | 161.5 (140.8, 239.0) | 0.557 |
| Indoxyl Sulfate | 2973.4 (1910.0, 4624.4) | 2633.4 (2124.9, 3749.0) | 0.519 |
| *p*-Cresyl Sulfate | 8145.4 (5021.1, 18157.2) | 9223.2 (5782.0, 15280.2) | 0.850 |

JSHT, Jing Si herbal tea; TMAO, trimethylamine N-oxide. Continuous variables are reported as the median with the interquartile range, and were analyzed using the Wilcoxon rank-sum test. A *P*-value of less than 0.05 was deemed statistically significant.

potentially mitigate brain damage associated with the SARS-CoV-2 S protein and provide relief to patients suffering from long-term COVID-related depression [13].

In this study, JSHT demonstrated a superior therapeutic effect on FD compared to placebo. Based on our current findings, JSHT may be effective in treating FD through multiple potential mechanisms. The anti-inflammatory properties of JSHT could act to mitigate local gut inflammation, aligning with theories that FD may be partially mediated by inflammation. Additionally, the observed anxiolytic effects may interact with the gut-brain axis, offering dual relief for both FD symptoms and associated psychological distress like anxiety. The increase in serum butyrate levels suggests that JSHT could be promoting a gut microbiota environment conducive to the production of beneficial SCFAs, which are known to have anti-inflammatory and gut health-promoting effects. These various mechanisms could offer a multifaceted approach to understanding how JSHT alleviates FD symptoms and related anxiety.

Regarding the safety JSHT, a prospective cohort study was conducted, enrolling 260 patients with mild-to-moderate COVID-19. These patients were divided into two groups: the JSHT group (n = 117) and the control group (n = 143). The investigation focused on adverse effects, liver function, and renal function to assess the safety of JSHT as complementary therapy. Notably, only 4 of the 117 patients (3.4%) in the JSHT group developed diarrhea, which resolved spontaneously within three days [12]. Additionally, in our study, only two patients receiving JSHT had a mild increase in bowel movements without any diarrhea. The small sample size might limit comprehensive observation of side effects, indicating that further research is needed to substantiate the long-term safety of JSHT.

The strengths of this study are manifold. Firstly, it is a double-blind, randomized, controlled trial in which JSHT has demonstrated superior treatment efficacy in comparison to the placebo. Secondly, this research assessed not only FD symptoms but also evaluated comprehensive psychological conditions. JSHT was observed to enhance anxiety levels. Lastly, gut microbiota-derived circulating metabolite levels evaluations were conducted before and after the treatment, and JSHT was found to increase serum butyrate concentrations in patients who responded well to the treatment.

However, there are a few limitations that merit mention. Firstly, the sample size of this pilot study, designed to investigate the efficacy of JSHT in treating FD, was relatively small. As such, further large-scale studies are worth conducting to validate the results for the application of JSHT in FD treatment. Secondly, the treatment evaluation period was only one month. Therefore, further research is required to confirm the necessity for extended observation periods for the JSHT treatment. Finally, the precise mechanism by which JSHT aids in the treatment of FD remains to be clarified. Even though we found that JSHT was able to elevate serum butyrate concentrations in patients who responded positively to the treatment, the mechanisms of butyrate may need further exploration, such as an assessment of gut microbiota alterations, to confirm these findings.

In conclusion, the four-week JSHT treatment regimen showed improvement in dyspeptic symptoms and anxiety, potentially associated with increased serum butyrate levels. These findings highlight the therapeutic potential of JSHT in the management of FD.

## Disclosure statement

The authors declare that they have no competing interests.

## Author contributions

CHL, FCT, and CLC contributed to study concept and design, analysis and interpretation of data, drafting of the manuscript. CHL and FCT contributed to statistical analysis. MWW, JSH, CHY, TTL, and WYL contributed to the acquisition of data and research performance. All authors have approved the final version of the manuscript.

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