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Treatment of Diarrhea-Predominant Irritable Bowel Syndrome with Traditional Chinese Herbal Medicine: A Randomized Placebo-Controlled Trial

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BACKGROUND: As there is no effective treatment for irritable bowel syndrome (IBS), many patients turn to traditional Chinese medicine (TCM) for possible cure. We investigated the therapeutic efficacy of an ancient herbal Chinese formula in patients with diarrhea-predominant IBS.

METHODS: This was a randomized double-blinded placebo-controlled trial. Chinese IBS patients with predominant diarrhea symptoms that fulfilled Rome II criteria were recruited. The diagnosis was verified by a TCM herbalist using TCM criteria. Eligible patients were randomized to receive a standard preparation of TCM extracts that contained 11 herbs or placebo with similar appearance and taste for 8 wk after a 2-wk run-in period. Patients were followed up for an additional 8 wk post-treatment. Primary outcome was patient's global symptom assessment. Other outcome measures included individual IBS symptom scores and health-related quality of life (short form 36).

RESULTS: One hundred nineteen patients were randomized: 60 to receive TCM and 59 to receive placebo. There was no significant difference in the proportion of patients with global symptom improvement between the TCM and placebo groups at week 8 (35% *vs* 44.1%, $p = 0.38$) and at week 16 (31.7% *vs* 33.9%, $p = 0.62$). Moreover, there was no difference in individual symptom scores and the quality-of-life assessment between the two groups at all time points.

BACKGROUND: The use of this herbal formulation for diarrhea-predominant IBS did not lead to global symptom improvement. Further controlled clinical studies may be necessary to characterize the role of TCM in the management of IBS.

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INTRODUCTION

Irritable bowel syndrome (IBS) is a common functional disorder of the digestive tract that is characterized by abdominal pain and altered bowel habits in the absence of organic disease. Epidemiological studies show that the prevalence of IBS ranged from 3% to 22% in Western populations (1, 2). We reported that about 4% of the Chinese population in Hong Kong have symptoms suggestive of IBS based on Rome II criteria (3).

Despite various advances in the understanding of functional bowel disorder, pharmacological treatment of IBS by Western medicine has so far been unsatisfactory. A review of published drug trials for IBS concluded that very few existing drug regimens could achieve a high level of therapeutic success in IBS (4). The use of loperamide has been shown to improve stool consistency, reduce defecation frequency, and reduce intensity of pain in patients with IBS (5). In a randomized trial comparing desipramine with placebo in female patients with moderate to severe functional bowel disease (6), the use of desipramine was found to be beneficial over placebo in the per-protocol analysis, particularly after excluding patients with a nondetectable desipramine level in blood. Moreover, the use of alosetron, a 5-HT3 receptor antagonist, has been shown to significantly improve the symptoms of female patients with diarrhea-predominant IBS (7). However, alosetron was withdrawn from the market because of serious adverse events. In the recent American Gastroenterological Association Medical Position Statement, it is recommended that the treatment strategy should be based on the nature and severity of symptoms, characteristics and degree of functional impairment, and the presence of psychological difficulties affecting the course of the illness (8).

With the unsatisfactory treatment response of Western medicine, many patients turn to alternative treatment for IBS. It was estimated that up to 16% of IBS patients in England had consulted alternative medicine practitioners (9). Traditional Chinese medicine (TCM) is particularly appealing to Chinese patients. In a more recent survey from Taiwan, up

to 40% of Chinese patients with chronic gastrointestinal disorders reported the use of alternative medicine and 96% of them used Chinese herbal medicine (10). However, there are very few properly designed clinical trials that examine the efficacy of TCM in IBS (11). One randomized controlled trial from Australia evaluated the role of Chinese herbal medicine in patients with IBS (12). With the use of a standard 20-herb formula or individualized herbal preparation, the investigators demonstrated a significant improvement in bowel symptoms as well as global symptoms in patients with all subtypes of IBS.

Unlike Western medicine, TCM diagnoses of IBS fall into different categories that are dependent on the patient's bowel frequency. In this regard, the diarrhea-predominant IBS subtype is caused by "stagnation of liver energy attacking the spleen resulting in dysfunction of the transportation and transformation function of the spleen" (13). Herbal drugs have therefore been used in the treatment of IBS under the general guideline of "relieving the suppressed liver and replenishing the spleen energy." It was shown in our previous study that the most common herbal regime prescribed by TCM practitioners to patients with this symptom complex was an ancient formulation called the "*Tong Xie Yao Fang,*" which dates back to the Ming Dynasty (1624 AD) (13–15). In this study, we determined the efficacy of this formulation of Chinese herbal medicine on the symptoms and quality of life of patients with diarrhea-predominant IBS.

METHODS

Patients

All IBS patients (aged 18–75 yr) who presented to the Gastroenterology Clinic of the Prince of Wales Hospital with diarrhea-predominant symptoms were eligible. Diagnosis of IBS was based on Rome II criteria (2). Because there is no objective criteria for subgrouping of IBS patients, the diarrhea-predominant type was defined if diarrhea was present for at least 75% of the time during which a patient's IBS was active (7). Patients with predominant constipation or alternating bowel habits were excluded because they are believed to represent different subgroups according to TCM criteria (14, 15). After assessment by a gastroenterologist (WKL, JW, JJYS), eligible patients were assessed by a TCM practitioner (HX, LSC, SML) to ensure their eligibility for the current TCM formulation according to TCM theories. Patients had to fulfill the TCM syndrome of "stagnation of liver energy and asthenia of spleen" before randomization (14, 15).

In addition, patients should have had a normal colonic evaluation (colonoscopy or barium enema) in the past 5 yr. Those with a history of organic disease of the gastrointestinal tract such as colorectal cancer, advanced colonic polyp, celiac disease, inflammatory bowel disease, previous gastrointestinal surgery, or systemic diseases that might cause diarrhea were excluded. Women who were pregnant, lactating, or not practicing proper contraception were not eligible. Concomitant use of medications that affect gastrointestinal motility or visceral sensation (*e.g.*, antidiarrheal agent, antidepressant, narcotic analgesic, and anticholinergic) was not allowed. Informed written consent was obtained from all eligible patients and the study protocol was approved by the Joint CUHK-NTEC Clinical Research Ethics Committee.

Trial Design

This was a prospective, randomized double-blinded placebo-controlled study. After a 2-wk run-in period, patients were randomly assigned to receive 8 wk of active herbal formulation or placebo, followed by another 8 wk of the posttreatment period. Randomization was carried out in blocks of four in a 1:1 ratio by a computer-generated list of random numbers. An independent staff member (SSLF) assigned treatments according to consecutive numbers that were kept in opaque, sealed envelopes. Treatment assignments were not revealed until the study was completed.

Herbal Preparation

The choice of the herbal formulation was based on our previous observations on Chinese patients with diarrhea-predominant IBS (14). In our previous study, most diarrhea-predominant IBS patients were found to have TCM symptoms compatible with "stagnation of liver energy and asthenia of spleen." The corresponding management of this symptom complex was to relieve the stagnant liver energy and to strengthen the spleen energy. Built on the basic composition of *Tong Xie Yao Fang*, the herbal preparation used in this study contained 11 herbs as listed in Table 1. All herbs were obtained from qualified suppliers in Hong Kong and authenticated at the School of Chinese Medicine of the Chinese University of Hong Kong on the basis of standards specified in the Chinese Pharmacopoeia (2000 edition), which included macroscopic and microscopic examination of cross sections and powders, chemical tests, and/or chromatographic analysis. Contamination screening for heavy metals, pesticides, and aflatoxins was performed to ensure their safety for human consumption. Extraction was performed in a single batch to ensure consistency of quality. Mixture of the herbs was extracted with hot water; the aqueous extract was then concentrated, spray-dried, and packed in sealed opaque aluminum bags. A placebo of similar appearance was made with starch, glucose, lactose ($<1\%$ by weight), and a bitter component, sucrose octaacetate ($<0.01\%$ by weight). They were packed in an identical manner as the active herbal preparation in opaque aluminum bags. There was no labeling outside the package to ensure blinding of patients and clinicians. All packages were dispensed by an independent research staff in a separate room after the visit. Patients were asked to dissolve the granules in each package using hot water and take them twice daily.

Assessments

Patients were seen by herbalists and gastroenterologists at the end of 4 wk (on treatment), 8 wk (end of treatment), and 16 wk (end of follow-up). During each visit, patients

Table 1. Herbal Preparation

Chinese Name	Pharmaceutical Name	Gram/ Day
Bai zhu *	*Atractylodes macrocephala* (rhizome)	15
Huang qi	*Astragalus membranaceus* (root)	15
Bai shao *	*Paeonia lactiflora* (peeled root, fried)	15
Cang zhu	*Atractylodes chinensis (*rhizome*)*	12
Chai hu *	*Bupleurum chinense* (root)	9
Chen pi *	*Citrus reticulata* (peel)	9
Fang feng	*Saposhnikovia divaricata* (root)	9
Jiu li xiang	*Murraya paniculata* (twigs)	9
Shi Liu Pi	*Punica grantum* (rind)	9
Ma Chi Xian	*Portulaca oleracea* (above-ground parts)	30
Huang Lian *	*Coptis chinensis* (rhizome)	6

*Present in Bensoussan's formula (13).

were interviewed by gastroenterologists for symptoms, compliance, and occurrence of adverse events. Data on global symptom improvement, individual bowel symptoms, stool consistency, and health-related quality of life were collected. Global symptom improvement was defined as the patient's subjective feeling of adequate relief of their symptoms by the study medication. Patients were asked the following question during each follow-up visit: "In the past 7 days, have you had adequate relief of your irritable bowel syndrome pain and discomfort?" Individual symptom scores on abdominal pain and abdominal discomfort were recorded on a 5-point Likert scale (0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe) by patients. The average bowel frequency in the past 7 days was recorded. Moreover, the Bristol scale, which is a visual descriptive stool form scale, was used to assess stool consistency during the treatment period (16). Health-related quality-of-life assessment was measured by the validated Hong Kong Chinese version of the short form 36 (SF-36) (17). To avoid multiple comparisons of the eight domains of the SF-36, the locally validated physical and mental health summary (PCS and MCS) scales were used (18). Compliance, which was defined by the use of more than 70% of study herbal medication, was checked by counting of returned TCM packages. Adverse events were monitored with a comprehensive symptom questionnaire as well as clinical laboratory evaluations including liver function, renal function, and complete blood count.

An herbalist also assessed the patients during each visit according to standard TCM practice, including enquiry on bowel symptoms, examination of the patient's tongue, and pulse. Both gastroenterologists and TCM herbalists were not allowed to alter the study medications during the study period.

The primary end point of this study was global symptom improvement at the end of the 8-wk treatment. This is based on the recent consensus that patient self-reported relief of symptoms is the most promising outcome assessment rather than ratings by investigators (19, 20). Secondary end points included global symptom improvement at other time points (4 wk, 16 wk), individual symptom scores, bowel frequency, Bristol stool scales, and the summary scales of the SF-36.

Statistical Analysis

Based on a similar study in the literature (12), we assumed that the response rate of patients treated with active TCM is 60% and the placebo response rate is 30%. Forty-nine patients would be required in each study arm to achieve a power of 0.8 and a 2-sided p-value of 0.05. We anticipated that 15% of the patients may drop out from the study follow-up. Therefore, 116 diarrhea-predominant IBS patients were needed for this study.

Analysis was based on the intention-to-treat analysis and all patients randomized were analyzed. Statistical analysis was performed using SPSS software version 13 (SPSS, Chicago, IL). Categorical data were compared using the χ^2 test or Fisher exact test where appropriate. Numerical data were compared using the Student's t-test. Comparison of individual symptom severity between the active treatment and placebo groups was computed using the the Mann-Whitney U test. The Wilcoxon signed rank test was used to compare individual symptom severity before and after treatment. Potential confounding variables including age and sex were adjusted by using binary logistic regression and linear regression where appropriate. The multiple level α for all analyses at multiple time points (weeks 4, 8, and 16) was controlled by applying a Bonferroni-Holm adjustment with a p-value of $\alpha/3$.

RESULTS

Patients

A total of 133 patients with diarrhea-predominant IBS was screened, and 119 met the inclusive criteria and was randomized. Sixty patients were assigned to receive a standard TCM herbal preparation and 59 to receive placebo. The reasons for exclusion are shown in Figure 1. Four patients were considered ineligible by a TCM herbalist according to TCM criteria. The baseline characteristics of the patients were similar between the two treatment groups (Table 2). A total of 24 (20.2%) patients withdrew from the trial during the study period: 14 (23.3%) in the active TCM group and 10 (16.9%) in the placebo group ($p = 0.49$). Six (10.2%) patients in the placebo group and 3 (5%) patients in the TCM group withdrew because of lack of symptom response ($p = 0.32$). Forty-six patients in the TCM group and 49 patients in the placebo group completed the study.

Symptoms

The proportions of patients with global symptom improvement at different time points are shown in Table 3. There was no significant difference in the proportions of patients with global symptom improvement in the two treatment groups at the end of weeks 4, 8, and 16 by the per-protocol or intention-to-treat analysis.

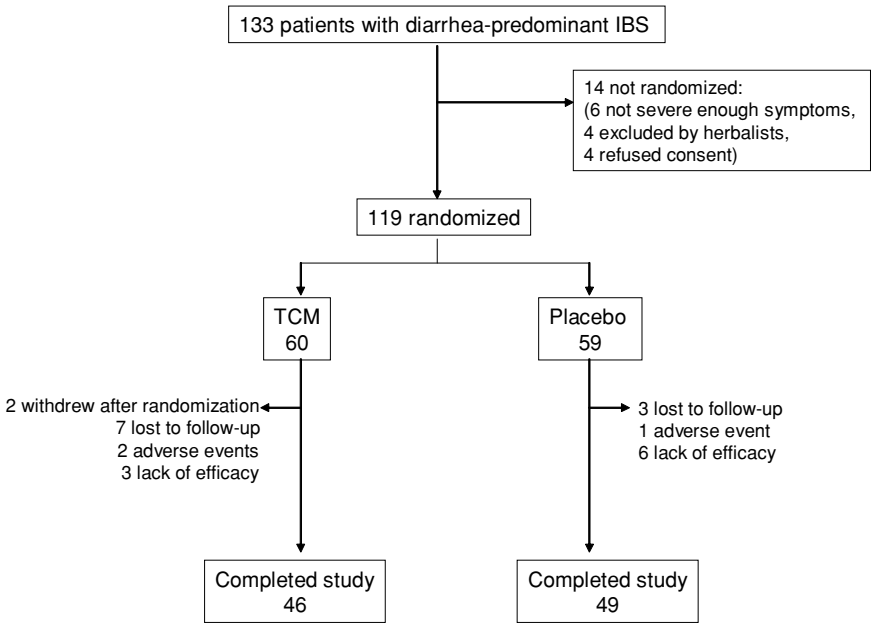

Figure 1. Trial profile.

For individual bowel symptoms, patients treated with TCM tended to have nonsignificant lower abdominal pain and abdominal discomfort scores than patients treated with placebo at week 4 but not at week 8 (Table 3). On the other hand, patients who took active TCM had significantly worsened diarrhea than patients who took placebo. The daily bowel frequency was significantly higher in the TCM group than in the placebo group both at week 4 ($p = 0.012$, Table 3) and week 8 ($p = 0.009$). There was, however, no significant difference in stool consistency (Bristol scale) between the two treatment groups at all time points.

Quality-of-Life Assessment

Quality of life was determined by SF-36 (Table 4). There was no significant difference in the physical and mental health summary scales between the two treatment groups at the end of the 8-wk treatment and at the end of the 16-wk follow-up. There was also no significant difference from baseline in both treatment groups.

Table 2. Baseline Characteristics of Patients

	TCM (N = 60)	Placebo (N = 59)
Mean age (SD)	45.4 (11.9)	43.6 (13.9)
Female	29 (48.3%)	33 (55.9%)
Mean BMI (SD)	23.5 (4.7)	23.1 (3.6)
Smoker	15 (25%)	10 (16.9%)
Alcohol use	15 (25%)	14 (23.7%)
IBS symptom duration		
<1 yr	3 (5%)	1 (1.7%)
1–5 yr	26 (43.3%)	27 (45.8%)
5–10 yr	15 (25%)	12 (20.3%)
>10 yr	16 (26.7%)	19 (32.2%)

BMI = body mass index; SD = standard deviation.

Adverse Events

Most patients tolerated the study medication well. Two patients in the TCM group developed skin rash and thyroiditis, respectively. One patient in the placebo group developed facial nerve palsy during the study period. There was no other adverse effect reported by patients.

Table 3. The Global Symptom Improvement and Individual Symptom Scores of Patients in the Two Treatment Groups

	TCM	Placebo	*p* (Adjusted *p**)
Global symptom improvement			
Intention to treat			
Week 4	27/60 (45%)	27/59 (45.8%)	1.0 (0.91)
Week 8	21/60 (35%)	26/59 (44.1%)	0.35 (0.38)
Week 16	19/60 (31.7%)	20/59 (33.9%)	0.93 (0.62)
Per protocol			
Week 4	27/55 (49.1%)	27/58 (46.6%)	0.79 (0.81)
Week 8	21/52 (40.4%)	26/53 (49.1%)	0.37 (0.53)
Week 16	19/51 (37.3%)	20/56 (35.7%)	0.87 (0.85)
Abdominal pain†			
Week 4	1 (0–3)	2 (0–3)	0.039 (0.08)
Week 8	1 (0–3)	1 (0–3)	0.45 (0.54)
Week 16	1 (0–4)	1.5 (0–4)	0.14 (0.26)
Abdominal discomfort†			
Week 4	1 (0–3)	2 (0–3)	0.06 (0.12)
Week 8	1 (0–3)	1 (0–3)	0.35 (0.32)
Week 16	1 (0–4)	2 (0–3)	0.81 (0.68)
Daily bowel frequency†			
Week 4	2 (1–8)	2 (1–6)	0.012 (0.02)
Week 8	2 (1–6)	2 (1–5)	0.009 (0.01)
Week 16	2 (1–7)	2 (1–6)	0.5 (0.67)
Bristol scale†			
Week 4	5 (1–6)	5 (2–7)	0.37 (0.8)
Week 8	5 (4–6)	5 (2–6)	0.46 (0.5)
Week 16	5 (3–6)	5 (1–6)	0.28 (0.33)

**p*-value was adjusted for age and sex.
†Median (range).

Table 4. Quality-of-Life Assessment (SF-36) in the Two Treatment Groups

	TCM	Placebo	p (Adjusted $p*$)
Physical health summary score[†]			
Week 8	37.8 (10.3)	35.3 (11.7)	0.26 (0.10)
Week 16	38.0 (10.2)	34.6 (12.0)	0.12 (0.08)
Mental health summary score[†]			
Week 8	39.8 (8.7)	38.6 (11.6)	0.57 (0.63)
Week 16	41.5 (10.2)	39.5 (12.1)	0.38 (0.38)

Higher values indicate better physical/mental health summary score.
[*] p-value was adjusted for age and sex.
[†] Mean (standard deviation).

DISCUSSION

Despite the enthusiasm on TCM, there are very few controlled clinical data on the efficacy of TCM. In this study, we evaluated the efficacy of a standard TCM formulation in treating Chinese IBS patients with predominant diarrhea symptoms. This study has several distinctive features. First, while there are considerable differences in the conceptual understandings between conventional Western medicine and TCM, we included patients with a diagnosis verified by both Western criteria of IBS (Rome II) and TCM diagnostic criteria. This design was to ensure the inclusion of patients that would potentially benefit from this particular herbal formulation. Second, unlike many published studies on TCM, this was a randomized double-blinded placebo-controlled trial. All herbal extracts and placebo were packaged in sealed aluminum bags to ensure adequate blinding of the patients and investigators. Physicians, TCM herbalists, and patients were all unaware of the treatment allocation. Third, we also monitored the patient's health-related quality of life in addition to the patient's IBS symptoms.

The results of this study, however, showed that there was no significant symptom improvement by this herbal formulation. The percentages of patients with global symptom improvement were comparable at week 4 (on study treatment), week 8 (end of treatment), and week 16 (end of study). Although about 50% of patients on herbal medicine had relief of symptoms at the end of 4 wk, a similar proportion (46.6%) of patients on placebo also reported symptomatic improvement. Based on this observation, the placebo response rate in this study appeared to be higher than most reported IBS therapeutic studies using global improvement as a primary end point (21). We speculate that the high placebo response rate in this study may be related to the anticipatory effects of our patients to TCM. The anticipatory effects of the patients could also account for the decreasing proportions of patients with symptom improvement toward the latter part of the study. It was noted that the proportion of patients with symptom improvement dropped progressively from week 4 to week 16 in both the TCM and placebo groups though the difference was not statistically significant. A similar trend of symptom deterioration toward the end of follow-up was also observed in other IBS trials (7, 12).

In this study, the proportion of patients with global symptom improvement was usually higher in the placebo group than in the active TCM group. Even in the best case scenario at week 4 on the per-protocol analysis, the therapeutic response of TCM was 49.1% as compared with 46.6% for placebo. Based on this estimation, a minimum of 6,300 patients are needed in each study arm to demonstrate a significant benefit of TCM over placebo with a statistical power of 0.8. Although we failed to demonstrate the clinical efficacy of this herbal formulation in relieving the symptoms of IBS patients, we have demonstrated the feasibility of conducting a randomized controlled trial using herbal medicine. In addition, we incorporated the use of the TCM theory and involvement of TCM practitioners in the study design as well as patient recruitment process. This platform could be used in future therapeutic trials of alternative medicine in IBS patients, which would ensure the proper translation of TCM into clinical research.

Recently, there were two randomized trials that evaluated the role of herbal medicine in patients with IBS (12, 22). Both studies included all types of IBS patients. Madisch *et al*. reported the use of a commercially available herbal preparation containing nine plant extracts and a modified research herbal preparation containing six plant extracts in German patients with IBS (22). They found that both preparations were effective in alleviating IBS symptoms. However, the plant extracts used in the German study had considerable differences from those used in traditional Chinese herbal medicine. On the other hand, a trial from Australia showed that the use of a standard formulation of Chinese herbal medicine that contained 20 herbs resulted in a significant improvement in IBS symptoms as compared with placebo (12). Notably, five of the herbs present in our formulation overlap with the previous formulation (Table 1). However, raw herbs, instead of water extracts, were used in the previous study. It is possible that some unknown yet important component may be lost in water extraction. Moreover, it is well known that the origins of the herbal materials may influence the potential therapeutic outcome of a particular herb. While the effective component(s) in the Australian's 20-herb formulation remain(s) undefined, it is difficult to determine whether the difference in outcome between these two studies lies in the difference in formulations, origin of the herbs, or method of extraction. Further studies may be necessary to characterize the effects of these two herbal formulations in patients with IBS.

The placebo used in this study contained a very small amount ($<1\%$) of lactose. Although the use of lactose may exacerbate the diarrhea symptoms of patients, we found that diarrhea was more common in patients treated with active TCM than placebo (Table 3). The bowel frequency was in fact significantly higher in patients taking TCM than for placebo, suggesting that the lactose content in the placebo was unlikely to be causing diarrhea in the placebo group.

Unlike conventional Western medicine, individualized treatment based on patients' current symptom complex is considered a very important element of TCM. Previous study

by Bensoussan *et al*. showed that both individualized and standard herbal treatments were equally effective in symptom control (12). However, because of the difficulties in standardization and adequate blinding of individualized treatment, we have not examined the efficacy of individualized treatment in this study. Further, a properly designed clinical study may be indicated to address the efficacy of individualized herbal treatment in patients with IBS.

In conclusion, the 11-herb TCM formulation did not result in significant global symptom improvement in patients with diarrhea-predominant IBS. While Chinese herbal formulations usually comprise multiple herbs, more work may have to be done to characterize the proper preparation to be used in the treatment of IBS patients. A properly controlled clinical trial is essential in this aspect because of the high placebo response of Chinese patients to TCM.

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STUDY HIGHLIGHTS:

What is Current Knowledge

- There is no effective cure for irritable bowel syndrome by conventional western medicine. Many patients resort to alternative medicine for possible cure.
- Preliminary data suggest that the use of traditional Chinese medicine (TCM) may be effective in treating IBS symptoms. However, there is evidence to suggest that there are different IBS subtypes according to TCM.
- By the integration of western and TCM approaches, we recruited diarrhea-predominant IBS patients into this randomized placebo controlled trial to evaluate the effects of a fixed formulation of TCM in relieving IBS symptoms.

What is New Here

- There was no significant improvement in global symptom assessment and quality of life assessment by this herbal formulation.
- Due to the complexity of herbal formulation, further controlled clinical studies may be necessary to characterize the role of herbal medicine in IBS patients.

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