

Treatment of Irritable Bowel Syndrome With Chinese Herbal Medicine

A Randomized Controlled Trial

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Context.—Irritable bowel syndrome (IBS) is a common functional bowel disorder for which there is no reliable medical treatment.

Objective.—To determine whether Chinese herbal medicine (CHM) is of any benefit in the treatment of IBS.

Design.—Randomized, double-blind, placebo-controlled trial conducted during 1996 through 1997.

Setting.—Patients were recruited through 2 teaching hospitals and 5 private practices of gastroenterologists, and received CHM in 3 Chinese herbal clinics.

Patients.—A total of 116 patients who fulfilled the Rome criteria, an established standard for diagnosis of IBS.

Intervention.—Patients were randomly allocated to 1 of 3 treatment groups: individualized Chinese herbal formulations ($n = 38$), a standard Chinese herbal formulation ($n = 43$), or placebo ($n = 35$). Patients received 5 capsules 3 times daily for 16 weeks and were evaluated regularly by a traditional Chinese herbalist and by a gastroenterologist. Patients, gastroenterologists, and herbalists were all blinded to treatment group.

Main Outcome Measures.—Change in total bowel symptom scale scores and global improvement assessed by patients and gastroenterologists and change in the degree of interference in life caused by IBS symptoms assessed by patients.

Results.—Compared with patients in the placebo group, patients in the active treatment groups (standard and individualized CHM) had significant improvement in bowel symptom scores as rated by patients ($P = .03$) and by gastroenterologists ($P = .001$), and significant global improvement as rated by patients ($P = .007$) and by gastroenterologists ($P = .002$). Patients reported that treatment significantly reduced the degree of interference with life caused by IBS symptoms ($P = .03$). Chinese herbal formulations individually tailored to the patient proved no more effective than standard CHM treatment. On follow-up 14 weeks after completion of treatment, only the individualized CHM treatment group maintained improvement.

Conclusion.—Chinese herbal formulations appear to offer improvement in symptoms for some patients with IBS.

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IRRITABLE BOWEL syndrome (IBS) is a common functional bowel disorder that accounts for a significant proportion of patients seen in gastroenterology offices¹ and is characterized by chronic or recurrent abdominal pain and disturbed defecation. Studies in the United States

and Australia suggest that between 10% and 20% of the population have this disorder.²⁻⁵ No single available treatment is reliably effective for this condition,^{6,7} and patients use a variety of approaches for symptom management, including drugs, dietary modifications, and counseling.

To date, no strong scientific evidence available supports the use of Chinese herbal agents in IBS.⁸ However, CHM has been used for centuries in the treatment of functional bowel disorders and is routinely used for this purpose in China. Several Chinese studies have suggested the potential effectiveness of CHM for treatment of IBS, although these have all lacked rigor in clinical trial protocol⁹⁻¹³ and have had poor randomization techniques and lack of blinding.⁸

According to the fundamental principles of traditional Chinese medicine, treatment should be tailored to the individual clinical presentation of patients, even though they all may have the same medical diagnosis.^{8,14,15} Furthermore, treatment needs to be modified at different stages of the patient's illness or recovery. In this study, we evaluated the effectiveness of CHM in the treatment of IBS. We compared individualized therapy against a standard Chinese herbal formulation for IBS and a placebo using a randomized, double-blind, placebo-controlled study design.

METHODS

Setting and Patients

Patients were recruited from gastroenterology units in 2 teaching hospitals in Sydney, Australia, and through 5 private practices of gastroenterologists. After patient screening and subsequent review in these centers, patients' conditions were further diagnosed (according to Chinese medicine principles) and treated in 3 Chinese herbal clinics by 3 Chinese medicine practitioners.

A clinical trial notification was filed with the Therapeutic Goods Administration, Commonwealth Department of Health, Housing, Local Government and Community Services, Canberra, Australia. All herbal substances used in this trial were listed with the Australian Therapeutic Goods Administration, have been acknowledged as suitable for human consumption, and were administered within standard dosage levels. All herbs used in this trial are available over-the-counter throughout Australia. No product used in this trial was a controlled substance, animal product, or endangered species. The trial protocol was approved by the ethics committee of the University of Western Sydney Macarthur and the ethics committees of the 2 participating hospitals.

Patients between the ages of 18 and 75 years (inclusive) were screened by a gastroenterologist. Screening involved a routine clinical workup for IBS with diagnostic tests as determined appropriate by the specialist. Patients were assessed according to the Rome criteria, an estab-

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Table 1.—Inclusion and Exclusion Criteria

Inclusion Criteria	
Age, 18-75 y inclusive	
Colonic evaluation (colonoscopy or barium enema) within the previous 5 years (for 18-60 y) or within the previous 3 y (for 61-75 y)	
Irritable bowel syndrome by Rome Criteria	
At least 3 mo of continuous or recurrent symptoms of:	
Abdominal pain or discomfort with at least some discomfort present within the last 2 wk; and ≥ 2 of the following on at least a quarter of occasions or days	
Abdominal distention that is visible or felt by tight clothing	
Pain relief with bowel action	
More frequent stools with onset of pain	
Looser stools with onset of pain	
Mucous in stools	
Feeling of incomplete evacuation	
At least 1 marking on the visual analog scales for IBS symptoms to be at least 20 mm from the "not present" end of the scale	
Normal liver function test and full blood cell count and urea and creatinine levels (within the last 2 wk)	
Exclusion Criteria	
Pregnancy or breast-feeding	
Liver disease	
Medications: anticholinergics, lactulose, smooth muscle relaxants, motility stimulants, and/or antidepressants. Use of these is accepted provided patient is still symptomatic for IBS, medications have been used for 3 mo, and effects of medications are stable	
Current alcoholism or drug abuse	
Current psychiatric illness or dementia	
Allergies to food additives	
Lactose intolerance—no obvious clinical indications	
Inflammatory bowel disease (ulcerative colitis, Crohn disease)	
Gastric and duodenal ulcers	
Cancers of the gastrointestinal tract	
Celiac disease	
Diabetes mellitus	

lished standard for diagnosis of IBS.^{16,17} If diarrhea was a prominent symptom, lactose intolerance was excluded by hydrogen breath testing or during a 2-week lactose exclusion period. The inclusion and exclusion criteria are shown in Table 1. Written informed consent was obtained from all patients before entering the trial. Patients were free to withdraw from the study at any time.

Treatment Schedule

After initial gastroenterological screening (week 0), all patients entered a 2-week run-in period. A Bowel Symptom Scale (BSS) was completed at the beginning and end of the 2-week period to assess measurement reliability and to account for any degree of improvement based simply on admission to the trial. Patients were seen on specified days by 1 of 3 herbalists during the trial period and were not permitted to change herbalist during the course of the treatment. The first consultation with the Chinese herbalist occurred at week 2, at which time the patient was randomized (by an assistant) to placebo, standard CHM, or individualized CHM treatment. The patient was re-evaluated by the Chinese herbalist at 2-week intervals for 2 occasions and then at

Table 2.—Standard Formula (Capsule Ingredients)*

Chinese Name	Pharmaceutical Name	Powdered Herb, %
Dang Shen	<i>Codonopsis pilosulae</i> , radix	7
Huo Xiang	<i>Agastaches seu pogostemi</i> , herba	4.5
Fang Feng	<i>Ledebourieliae sesloidis</i> , radix	3
Yi Yi Ren	<i>Coicis lachryma-jobi</i> , semen	7
Chai Hu	<i>Bupleurum chinense</i>	4.5
Yin Chen	<i>Artemisiae capillaris</i> , herba	13
Bai Zhu	<i>Atractylodis macrocephalae</i> , rhizoma	9
Hou Po	<i>Magnoliae officinalis</i> , cortex	4.5
Chen Pi	<i>Citri reticulatae</i> , pericarpium	3
Pao Jiang	<i>Zingiberis officinalis</i> , rhizoma	4.5
Qin Pi	<i>Fraxini</i> , cortex	4.5
Fu Ling	<i>Poriae cocos</i> , sclerotium (Hoelen)	4.5
Bai Zhi	<i>Angelicae dahuricae</i> , radix	2
Che Qian Zi	<i>Plantaginis</i> , semen	4.5
Huang Bai	<i>Phellodendri</i> , cortex	4.5
Zhi Gan Cao	<i>Glycyrrhizae uralensis</i> , radix	4.5
Bai Shao	<i>Paeoniae lactiflorae</i> , radix	3
Mu Xiang	<i>Saussureae seu vladimirae</i> , radix	3
Huang Lian	<i>Coptidis</i> , rhizoma	3
Wu Wei Zi	<i>Schisandrae</i> , fructus	7

*Pharmaceutical terminology from Hsu.¹⁸

monthly intervals for 2 further occasions. Continuous treatment was administered for 16 weeks. No special instructions were given to patients regarding diet, other than to continue consumption of foods they felt comfortable with and to avoid foods known to cause them gastrointestinal tract irritation. All patients were evaluated by their gastroenterologist after 8 weeks of treatment and again at the end of the 16-week treatment period. Patients were closely monitored for any adverse effects or worsening of symptoms. Liver function tests were performed after 8 weeks of treatment. Follow-up questionnaires were sent to all patients 14 weeks after completion of the treatment period. Treatment codes were broken and revealed to patients only after completion of the follow-up questionnaires.

Randomization

Randomization was done by selection of a sealed envelope from a closed bag. Seventy sealed envelopes were prepared for each of the standard and individualized groups, and 60 envelopes were prepared for the placebo group. Patients were aware that there was a greater chance of receiving active treatment. Success in blinding was evaluated using a treatment credibility scale administered during the trial.

Herbal Preparation and Dispensing

All herbs were administered in the dried powdered form and encapsulated. A period of preparation was required before commencement of the trial to develop a suitable dispensary of 81 individual dried powdered Chinese herbs for dispensing to patients in the individualized treatment group. The standard

herbal formulation was designed by Chinese herbalists and prepared by the principal supplier, Mei Yu Imports, Sydney, Australia (Table 2).¹⁸ The placebo preparation was prepared and encapsulated by a pharmaceutical contractor and was designed to taste, smell, and look similar to a Chinese herb formula. After testing on 5 independent volunteers, the placebo was deemed indistinguishable from raw powdered Chinese herbs. All herbs and the placebo formulation were supplied in the same opaque capsules. Patients in all 3 groups were required to take 5 capsules 3 times daily.

After consulting with the Chinese herbalist, all patients were required to complete a series of questionnaires and wait 30 minutes for the preparation of their capsules. The wait time was used to avoid patients identifying whether they were receiving prepared capsules (standard or placebo) or individualized formulations that were made at the treatment center. All medication preparation occurred in a closed room by assistants who were restricted from contact with the patients. Treatment codes were held by these assistants and by the chief investigator (A.B.). A blinded primary research assistant managed all the questionnaires and was responsible for giving the capsules to the patients. All patients were treated in an equivalent fashion. Compliance was assessed by an item included in the BSS and by pill count.

Measurement Instruments

The BSS was used to assess change in IBS symptoms during the course of the treatment. The BSS consists of 100-mm visual analog scales related to each symptom of IBS (pain/discomfort, bloat-

ing, constipation, and diarrhea) and an overall severity scale. Patients and gastroenterologists completed this scale independently at the beginning and end of the treatment period. Patients also were monitored during the course of the trial using this scale. The BSS also included items for assessing rate of stool passage, rating the degree to which IBS symptoms interfered with life activities, and recording changes in medications usage and fiber consumption. To assess the success of patient blinding, a brief questionnaire was administered to patients after 2, 4, 10, and 16 weeks of treatment. This 4-item scale has been used to test credibility of different forms of psychological treatment¹⁹ but also has been successfully used in acupuncture trials and shown to have good internal consistency and test-retest reliability.^{20,21}

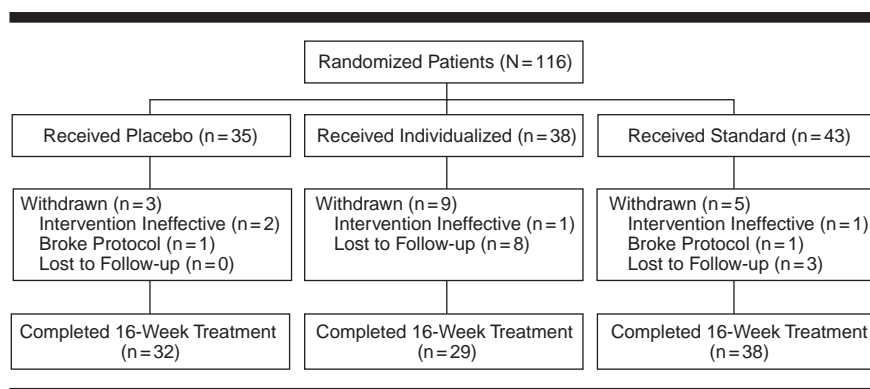
Statistical Analysis

Pearson product moment correlation was used in the analysis of reliability and validity data, and factor analysis was used to determine construct validity of the credibility scale. Outcome measures with categorical responses were analyzed using χ^2 and Fisher exact tests. For the BSS, analysis of variance was used to determine the differences among groups at baseline, end of treatment, and follow-up. All *P* values were 2-tailed, unless otherwise indicated, and the α level of significance was set at .05. Missing scale and item scores were not replaced. Data are presented according to an intention-to-treat protocol, in which patients who withdrew from the trial were recorded as having worsened (if appropriate) for categorical items only. Data for all other outcome measures are presented as per protocol analysis.

There were no reliable data that could be used to accurately predict the anticipated effect size between placebo, standard, and individualized treatment groups. We estimated that for adequate power (80%) to detect a 20% difference on the BSS scores at the $\alpha = .05$ level (1-tailed test), 35 patients were needed in each group.

RESULTS

A total of 116 subjects were recruited during an 18-month period: 35 were randomized into the placebo group, 43 into the standard group, and 38 into the individualized treatment group (Figure). Fifteen patients withdrew during the 4-month course of the trial, and 2 patients were withdrawn from the trial for commencing a variety of relevant medications during the treatment period. Patient data on study entry are shown in Table 3. Patient groups were similar in terms of age, weight, and sex distributions. There were



Patient progress through stages of the trial.

Table 3.—Patient Population Characteristics Before Treatment and Mean Total Bowel Symptom Scores*

Variables	Group, No. (SD)			<i>P</i> Values
	Placebo (n = 35)	Standard (n = 43)	Individualized (n = 38)	
Characteristic				
Weight, kg	72.1 (12.8)	66.7 (16.8)	69.1 (14.4)	.29
Age, y	45.0 (13.9)	47.6 (15.1)	47.4 (13.4)	.68
Sex ratio (male:female)	0.46	0.65	0.52	.75
Baseline data				
Gastroenterologist total BSS score	182.7 (65.4)	172.2 (72.6)	166.6 (63.6)	.59
Patient total BSS score	191.2 (69.4)	189.7 (64.8)	178.5 (69.8)	.67
End of treatment				
Gastroenterologist total BSS score	147.2 (86.6) (n = 30)	70.9 (63.2) (n = 35)	100.4 (83.6) (n = 25)	.001
Patient total BSS score	150.0 (81.6) (n = 32)	106.1 (73.7) (n = 38)	103.0 (74.7) (n = 29)	.03
At follow-up 14 weeks after study completion				
Patient total BSS score	155.7 (84.2) (n = 18)	132.6 (90.2) (n = 35)	99.4 (74.8) (n = 24)	.10

*Data are reported by patients and gastroenterologists at start and end of treatment period and at follow-up. BSS indicates Bowel Symptom Scale.

no significant differences among patients in the 3 groups in terms of total severity of symptoms as judged independently by both the patient and gastroenterologist, or in duration of the disease as reported by patients. Patients allocated to the placebo group had a higher mean score for constipation, while patients allocated to the standard treatment had a higher mean score for diarrhea. Compliance with study medication was high as measured by a questionnaire item and by random pill counts and did not differ between groups (95% for standard CHM, 94% for individualized CHM, and 95% for placebo). Fiber and nonstudy medication consumption did not change significantly for any group during the treatment period.

Reliability and Validity Testing

The reliability of the BSS (ie, consistency of the measure) was determined by a test-retest assessment during the run-in period prior to treatment commencing (week 0-2). Correlation between the BSS completed during the initial interview with the gastroenterologist and then 2 weeks later at the

clinical treatment centers was high for total score ($r = 0.7$; $P < .01$, 2-tailed) and for each individual symptom (bloating [$r = 0.8$], pain [$r = 0.6$], diarrhea [$r = 0.8$], and constipation [$r = 0.7$]).

The credibility scale also was examined for test-retest reliability. Correlation between the first and second administration of this scale was significant ($r = 0.6$; $P < .01$, 2-tailed). The correlation coefficients for each of the 4 scale items were in the range of 0.47 to 0.65. The internal consistency of the credibility scale based on interitem correlations on both occasions were uniformly high and Cronbach coefficient α (representing average interitem correlations) was .87 and .86 for the first and second occasions, respectively.

The visual analog scales within the BSS had high face validity (100-mm lines with severity marked at the extreme right and absence of symptom marked at the extreme left) and have high content validity (ie, they incorporate the key domains of interest—pain and discomfort, bloating, constipation, and diarrhea). Testing items in the scale for concurrent validity at the commencement and end of treatment showed that the gastroenterologist's assessment of the patient

correlated highly with the patient's own perception of severity of symptoms. For both, Pearson correlation coefficient was in the range of $r = 0.63$ to 0.84 for any 1 item (symptom) or for the total symptom score ($P < .01$ on all occasions).

Assessment of the credibility scale for construct validity through a principal components factor analysis based on the first administration revealed only 1 factor with an eigenvalue greater than 1 (2.89). This factor accounted for 72.2% of variance in this data set. All items had a high correlation with this first factor, suggesting satisfactory construct validity.

Main Outcome Measures

For all 5 main outcome measures—total mean BSS scores and global improvement as assessed by patients and gastroenterologists, and interference with life as assessed by patients—patients receiving the standard CHM formulation responded significantly better than patients in receiving placebo. Patients receiving individualized CHM treatment also responded significantly better on 4 of 5 scores than patients receiving placebo. Overall, patients receiving individualized CHM fared slightly worse than those receiving standard CHM treatment.

At the end of treatment, there was a significant difference between the mean total BSS scores as assessed by patients, with patients in the standard CHM group and those in the individualized CHM group responding significantly better compared with placebo (Table 3). No significant differences were noted between standard and individualized CHM treatment groups.

The BSS scores completed by the gastroenterologist at the end of treatment showed a significant difference between the mean total BSS scores for patients in each group, with patients receiving standard and individualized CHM responding significantly better compared with those taking placebo ($P = .001$). A post hoc Bonferroni test demonstrated that this difference was significant for patients in the standard group ($P = .001$) but not for those in the individualized group ($P = .08$).

Patients receiving standard herbal formulations improved by 44% (according to patients) and 59% (according to gastroenterologists), in contrast to patients in the placebo group who improved 22% (according to patients) and 19% (according to gastroenterologists). Patients receiving individualized CHM improved by 42% (according to patients) and 40% (according to gastroenterologists).

There was a significant association between the treatment groups and the change in the degree to which IBS symp-

Table 4.—Perception of Improvement by Treatment Group*

Compared With Before Trial	Group, No. (%)			P Value
	Placebo	Standard	Individualized	
Patient rating of response				
Improved	11 (33)	29 (76)	18 (64)	.007
Stayed the same	19 (57)	8 (21)	8 (29)	
Worsened	3 (9)	1 (3)	2 (7)	
Gastroenterologist rating of response				
Improved	9 (30)	29 (78)	15 (50)	.002
Stayed the same	19 (63)	7 (19)	12 (40)	
Worsened	2 (7)	1 (3)	3 (10)	

*Group differences calculated by using χ^2 .

toms caused interference with life and activities by the end of treatment ($P = .03$). Of patients receiving the standard formulation and of those receiving individual formulations, 63% and 54%, respectively, stated that treatment resulted in IBS causing less interference in their lives and activities, compared with 37% of patients in the placebo group.

At the end of the trial, the ratings of both gastroenterologists and patients who believed that the IBS symptoms had improved, stayed the same, or worsened (Table 4) showed a significant association by treatment group ($P = .007$). Of patients receiving standard CHM and of those receiving individual CHM, 76% and 64%, respectively, stated they had improved during treatment. In contrast, only 33% of patients receiving placebo stated they had improved during treatment.

The gastroenterologists' responses also demonstrated a significant association between the treatment group and how patients felt at the end of treatment ($\chi^2_4 = 17.1$; $P = .002$). Seventy-eight percent of patients receiving the standard CHM formulation, 50% of those receiving individual CHM, and 30% of those receiving placebo were judged by the gastroenterologist as having improved during treatment. There was significant correlation between patients' and gastroenterologists' assessment of global improvement and of total BSS scores at the beginning and end of the trial (all $r > 0.5$, all significant to $P \leq .01$ level, 2-tailed).

Adverse Effects

Two patients withdrew from the trial because of discomfort associated with the treatment. One patient developed upper gastrointestinal discomfort while taking the standard CHM formulation. A second patient developed headaches (although a history of headaches existed), which gradually subsided on discontinuation of therapy. Resumption of treatment caused gastrointestinal discomfort, and the patient was subsequently withdrawn from the study. No other major adverse effects were noted. Liver function tests ob-

tained after 8 weeks of treatment showed no abnormal values.

Follow-up Assessment

Results of the BSS administered to patients 14 weeks after completion of the course of treatment (but before treatment codes were revealed) demonstrated that the treatment effect weakened, with only the individualized CHM group maintaining improvement ($P < .10$) (Table 3). However, there was significant association between the treatment group and how patients felt at the 14-week follow-up ($P = .02$). Of patients who had received the standard CHM formulation and of those who had received individual CHM formulations, 63% and 75%, respectively, stated that they still felt an improvement compared with 32% of patients who received placebo.

Blinding

The success of blinding patients to treatment was tested at the beginning, end, and on 2 other occasions during the course of treatment. At 2 weeks into treatment, the overall mean on this 6-point scale was 4, indicating that patients on average viewed CHM as only moderately credible and were not a self-selected group with a bias in favor of complementary medicine. No significant difference was noted between groups at outset and at end of treatment. However, the mean credibility score decreased slightly with time for the placebo group and remained strong within the standard CHM group. Since the standard CHM treatment proved the most effective, the increased difference in credibility toward the end of the treatment may be a reflection that this group of patients was receiving the most benefit. There was a significant negative correlation between the final mean credibility score and the final patient-rated BSS score ($r = -0.43$; $P < .01$) and the final gastroenterologist-rated BSS score ($r = -0.58$; $P < .01$).

COMMENT

To our knowledge, this is the first clinical trial in CHM that fully adheres to the

traditional Chinese diagnostic and treatment processes while using a strict and accepted methodological protocol. Our study demonstrated that CHM is effective in the management of symptoms related to IBS with, in some cases, effects lasting up to 14 weeks after completion of treatment. Patients receiving standard or individualized CHM treatment demonstrated significantly better outcomes (both clinically and statistically) than patients receiving the placebo on all 5 key outcome measures. However, patients receiving individualized CHM formulations had less improvement during treatment than patients receiving the standard formula, although this difference was not statistically significant.

The first null hypothesis that CHM treatment of IBS with a standard herbal formula is of no value is rejected. The second null hypothesis that individualized treatment of IBS according to the principles of traditional CHM is of no added value to treatment with a standard formula is partially accepted. While there were no significant differences between patients receiving standard or individualized treatment at the end of the treatment period, on follow-up, patients in the individualized treatment group had maintained more substantial improvement.

Three Chinese herbalists with contrasting Chinese medicine education backgrounds participated in this trial. In theory, their degree of education in Chinese herbalism should affect their ability to successfully tailor treatment for patients. While outcome differences between practitioners were observable for this cohort of patients, sample sizes were too small to make reliable conclusions. Furthermore, the overall differences between standard and individualized CHM may be relatively small (as both

are active treatments) and require larger sample sizes. This does not, however, account for the notable improvement that was maintained in the individualized CHM group after cessation of treatment.

One plausible explanation may be that the standard CHM formulation was suitably designed to treat the complex presentations of IBS but was incapable of successfully dealing with underlying causes for most patients as viewed by Chinese medicine. The tailored formulations may have permitted the herbalists to individually address these underlying causes and deficiencies. Moreover, there may be active ingredients in the CHM formulation with properties similar to antispasmodic or anxiolytic drugs. Chinese herbal formulas are complex and viewed as a number of active ingredients working together, rather than 1 specific active substance. The standard formulation used in this study is not a sedative or anxiolytic preparation in traditional CHM terms but is a formulation considered to regulate and strengthen bowel function.

In our study, all efforts were made for the approach in the 3 treatment groups to be indistinguishable. The credibility scale was demonstrated to be a reliable and valid instrument and presents strong evidence that blinding was maintained throughout the trial. The slight decrease in credibility score seen in the placebo group toward the end of the trial was accounted for by its significant correlation with the actual treatment outcome. The authors are convinced that patients, herbalists, and gastroenterologists were all successfully blinded.

There were minimal adverse effects reported during the study. Liver function screening was included as a precaution because liver dysfunction associated

with the use of Chinese herbs has been noted in other studies.^{8,22} Liver dysfunction was not expected with the type and form of herbs used in this study. In our study, liver function was reassessed after 8 weeks of treatment. We have no data on liver function after that time, and therefore cannot comment on longer-term safety of these CHM products. Raw herbs used as starting products are partly regulated in Australia.

We conclude that Chinese herbal formulations may offer symptom improvement to some patients with IBS. In this randomized, double-blinded, placebo-controlled trial CHM was shown to be effective in the management of IBS. Patients receiving the standard CHM formulation fared best during the course of treatment, while patients receiving the individualized treatments found that the benefit gained lasted beyond the treatment period. Although not all patients responded to this therapy, our findings support the consideration of further investigation of Chinese herbal medicine as a treatment option for IBS.

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