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CLINICAL RESEARCH

Effectiveness and safety of herbal medicines in the treatment of irritable bowel syndrome: A systematic review

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Abstract

AIM: To explore the efficacy and safety of herbal medicines (HM) in the treatment of irritable bowel syndrome (IBS).

METHODS: A computer-based as well as manual literature search was performed. We reviewed randomized controlled trials on the treatment of IBS with and without HM.

RESULTS: A total of 22 studies with 25 HMs met the inclusion criteria. Four of these studies were of good quality, while the remaining 18 studies involving 17 Chinese herbal medicine (CHM) formulas were of poor quality. Eight of these reports using 9 HMs showed global improvement of IBS symptoms, 4 studies with 3 HMs were efficacious in diarrhea-predominant IBS, and 2 studies with 2 HMs showed improvement in constipation-predominant IBS. Out of a total of 1279 patients, 15 adverse events in 47 subjects were reported with HM. No serious adverse events or abnormal laboratory tests were observed. The incidence of the adverse events was low (2.97%; 95% CI: 2.04%-3.90%).

CONCLUSION: Herbal medicines have therapeutic benefit in IBS, and adverse events are seldom reported in literature. Nevertheless, herbal medicines should be used with caution. It is necessary to conduct rigorous, well-designed clinical trials to evaluate their effectiveness and safety in the treatment of IBS.

Key words: Irritable bowel syndrome; Herbal medicine; Systematic review

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INTRODUCTION

Irritable bowel syndrome (IBS) is associated with a variable combination of chronic or recurrent symptoms such as abdominal pain, bloating, constipation and diarrhea. There is generally no structural or biochemical abnormality detected by conventional laboratory tests. IBS is one of the most common functional gastrointestinal disorders accounting for 3% of all primary consultations[1]. In western countries, the prevalence of IBS is around 10%, depending upon the definition used[2]. Moreover, there is increasing prevalence of IBS in the newly developed Asian countries[3]. The potential etiological factors include stress, anxiety, visceral hypersensitivity, altered bowel motility, neurotransmitter imbalances, and inflammation.

Herbal medicines have been used in Asia for a long time. An increasing number of IBS patients are beginning to receive complementary and alternative medicines in the West, most frequently herbal remedies (43%)[4]. Patients may seek HM for symptomatic relief when conventional medicines (CM) are unsuccessful. In such situations, an important question is whether herbal medicines are effective and safe for IBS patients. In the present study, we systematically reviewed the literature and evaluated the effects of HM as well as their potential adverse events in patients with irritable bowel syndrome.

MATERIALS AND METHODS

Search strategy

We carried out a literature search using MEDLINE (1966-2005), EMBASE (1980-2005), Cochrane Database (1992-2005), TCMLARS Database (1984-2005), CJA Full-Text Database (1994-2005), and Chongqing VIP Database (1989-2005) for relevant randomized controlled clinical trials, meta-analysis and systematic reviews published in all languages until October 2005. We used MeSH terms including 'irritable bowel syndrome, functional colonic

disease, drugs, Chinese medicines, traditional medicines, herbal medicines, alternative medicines, complement medicines, plant, oriental traditional medicine' for the database search.

In addition, a hand search of reference lists, review articles, editorials and abstracts from major meetings was also conducted to supplement the electronic search. We included articles published in all languages. Titles and abstracts of all potentially relevant studies were screened before retrieval of the full articles. However, if the title and the abstract were ambiguous, the full articles were scrutinized. Two independent reviewers (J.S and H-X. L) participated in the literature search. Any disagreements were resolved by discussions in order to reach a consensus.

Inclusion and exclusion criteria

The following inclusion criteria were used: (1) Diagnostic criteria used for IBS were ROME I [5] or ROME Ⅱ [6] criteria or the 1986 National symposium on chronic diarrhea (Chengdu China) criteria[7]; (2) Study design with randomized controlled clinical trials, irrespective of blinding; (3) Studies using HM alone for treating IBS in the treatment groups; (4) Identification and description of adverse events; (5) The treatment group received orally administered HM; (5) The control groups received placebo, CM or no treatment.

We excluded studies in which HM was used in combination with CMs, in children and in control groups. Administration of HM by other routes such as injections were also excluded.

Information on HM products derived from a single herb, Chinese proprietary medicines, complex extracts of different herb preparations such as decoction, tablet, capsule, pill, powder and plaster were collected. Standardized extracts of whole plants were included, but isolated 'active' phytochemical ingredients were excluded as these are generally considered as plant chemical products.

Data extraction

Data was collected independently by the reviewers. Any disagreement between the reviewers was resolved by discussion in order to achieve consensus.

Assessment of study quality

The reviewers also assessed independently the quality of each study by Jadad scale[8] and Cochrane Handbook[9].

Statistical analysis

The relative risk (RR) and 95% confidence interval (95% CI) were calculated using raw data derived from each study. Intention-to-treat analysis was performed if possible. Meta-analyses was performed with either fixed effects model or random effects model according to the presence or absence of heterogeneity when HM was compared with control. Statistical analysis was performed with RevMan 4.2 to detect any bias in studies using the funnel plot.

RESULTS

Our initial search generated 572 citations. After analyzing the titles and abstracts, and reading the full text articles, only 22 studies[10-31] with 25 arms involving 1279 patients and 763 controls met the predefined inclusion criteria. Eighteen of the studies were conducted in China and published in Chinese, four were published in English, one each from Australia[11] and Israel[20], and two from Germany[29,31] (Table 1).

Three studies[11,20,29] used computer software and two[21,25] used random number tables to generate the allocation sequence. Four studies[11,20,29,31] used an adequate concealed allocation method of randomization. Six studies[11-12,20,27,29,31] used placebo as control, four of these studies[11,20,29,31] were considered to be adequate, while two[12,27] demonstrated an inadequate comparison between placebo and CTM decoction; Four studies[11,20,29,31] provided statistical data with intention-to-treat protocol.

Using the Jadad Score and Cochrane handbook, four studies[11,20,29,31] were judged to be of high quality, whereas the remaining reports were of poor quality.

Efficacy of herbal medicines

Global symptoms of IBS: Two studies[11,29] with 3 HMs showed significant benefit compared to placebo with respect to the global improvement of IBS symptoms: standard CHM formula[11] (RR 2.15; 95% CI: 1.26-3.65 rated by patient and RR 2.62; 95% CI: 1.44-4.78 assessed by gastroenterologist), STW5[29] (RR 1.68; 95% CI: 1.13-2.51), STW5-Ⅱ[29] (RR 1.90; 95% CI: 1.30-2.78) (Figure 1). The following seven CHMs using complex herbal formulas appeared to be effective in improving global IBS symptoms compared to CM: Lizhong huoxie decoction[10] (RR 1.40; 95% CI: 1.11-1.76), Huatan Liqi Tiaofu decoction[13] (RR 1.24; 95% CI: 1.05-1.47), Geqin Shujiang Saocao decoction[14] (RR 1.24; 95% CI: 1.05-1.47), Huanchang decoction[16] (RR 1.41; 95% CI: 1.08-1.84), Congpi Lunzhi Formula[17], (RR 1.74; 95% CI: 1.35-2.24), Xiangsha Liujunzi decoction[18] (RR 1.28; 95% CI: 1.00-1.63, $P = 0.015$), and Shunji mixture[19] (RR 1.23; 95% CI: 1.01-1.49).

By contrast, the following compounds were not effective in the treatment of global IBS symptoms compared to placebo or CM: Individualized CHM[11] (RR 1.51; 95% CI: 0.83-2.73 assessed by patients and RR 1.54; 95% CI: 0.77-3.05 assessed by gastroenterologist), Bitter candytuft[29] (RR 1.23; 95% CI: 0.78-1.92), Curcuma [31] (RR 0.97; 95% CI: 0.60-1.55), Fumitory[31] (RR 1.13; 95% CI: 0.74-1.72) (Figure 1), Changkang Capsule[21] (RR 1.03; 95% CI: 0.92-1.14), and Jiejing Yiji decoction[30] (RR 1.09; 95% CI: 0.96-1.23) (Figure 2).

Diarrhea: As shown in Figure 3, a meta-analysis of Tongxie Yaofang modified decoction[12] and Tongxie Yaofang plus Sini San decoction[27] (RR 1.14; 95% CI: 1.04-1.24) showed that compared to CM these products had antidiarrheal effects in patients with diarrhea-predominant IBS patients. We combined the data from these two studies[12,27] since their herbal ingredients and dosages were very similar. Their effects were similar to Liyiting decoction[26] (RR 1.28; 95% CI: 1.02-1.62), and Tongxie yihao capsule[28] (RR 1.22; 95% CI: 1.01-1.46).

Three studies demonstrated an insignificant improvement in diarrhea: Xianshi Capsule[15] (RR 1.20; 95% CI: 0.98-1.48), Changning Yin decoction[24] (RR 1.19; 95%

Table 1 Characteristics of studies included in the analysis

Study ID	Year	*n*	Mean age	Sex (male %)	Study quality	Herbal medicine	Type of herbs	Control	Length (wk)	Follow-up (wk)
Gao[10]	1992	111	34	39	L	Lizhong Huoxie decoction	C.F	Oryzanol, Nifedipine	4	52
Bensoussan[11]	1998	116	47	35	H	Individualized CHM Standard Formula	C.F C.F	Placebo	16	14
Zhao[12]	2000	233	39	34	L	Tongxie Yaofang modified decoction	C.F	Salazosulfapyridine Diphenoxylate, Anisodamine, Amitriptyline, Placebo	3	n.r
Lei[13]	2000	96	39	56	L	Huatan Liqi Tiaofu decoction	C.F	Smecta	3	n.r
Wang[14]	2000	96	39	49	L	Geqin Shujiang Shaocao decoction	C.F	Smecta, vitB	3	n.r
Ye[15]	2002	80	37	46	L	Xianshi Capsule	C.F	Dicetel, Smecta	8	n.r
Deng[16]	2002	62	38	35	L	Huanchang decoction	C.F	Anisodamine, Oryzanol	3-6	52
Zeng[17]	2002	98	38	46	L	Congpi Lunzhi Formula	C.F	Bacillus Licheniformis	6	n.r
Ge[18]	2002	57	40	44	L	Xiangsha Liujunzi decoction	C.F	Diazepam, Propantheline, Domperidone	2	n.r
Zhou[19]	2002	105	n.r	n.r	L	Shunji mixture	C.F	Bitinal	4	n.r
Sallon[20]	2002	80	47.9 ± 2.1[1] 46.3 ± 2.9[3]	38	H	Padma Lax (Tibetan herbal formula)	C.E	Placebo	12	n.r
Ma[21]	2003	204	36	48	L	Changkang Capsule	C.F	Amitriptyline	4	n.r
Wang[22]	2003	104	53	53	L	Wuma Simo decoction	C.F	Cisapride	2	n.r
Liu[23]	2003	77	37	36	L	Gegan Qinlian Pellet	C.F	Nifedipine	3	n.r
Li[24]	2003	101	39	68	L	Changning Yin decoction	C.F	Diphenoxylate	5	n.r
Shen[25]	2003	47	41.6 ± 12.8[1] 42.3 ± 14.7[3]	57	L	Changjitai decoction	C.F	Dicetel	8	n.r
Zhao[26]	2004	84	44	44	L	Liyiting decoction	C.F	Dicetel	6	n.r
Xiao[27]	2004	167	37	41	L	Tongxie Yaofang plus sini san decoction (similar with Tongxie Yaofang modified decoction)	C.F	Salazosulfapyridine Diphenoxylate, Anisodamine, Amitriptyline, Placebo	2	n.r
Gao[28]	2004	98	36	35	L	Tongxie yihao capsule	C.F	Dicetel, Domperidone, Loperamide, Doxepin	4	24
Madisch[29]	2004	208	47	40	H	1 STW5 2 STW5-Ⅱ 3 Bitter Candytuft	C.E C.E M.E	Placebo	4	n.r
Bo[30]	2004	92	38.8 ± 1.7[1] 41.3 ± 1.7[3]	41	L	Jiejing Yiji decoction	C.F	Cerekinon	2	4
Brinkhaus[31]	2005	106	47.2 ± 11.7[1] 49.5 ± 14.5[2] 49.0 ± 9.1[3]	37	H	1 Curcama 2 Fumitory	M.E M.E	Placebo	18	n.r

H: High quality study; L: Low quality study; C.F: Complex formulation of herbs; C.E: Complex extracts of different herbs; M.E: Mono-extract of single herb. [1]The first treatment group; [2]The second treatment group; [3]The control group; n.r: Not reported.

CI: 0.99-1.42), Changjitai decoction[25] (RR 1.14; 95% CI: 0.81-1.60) (Figure 3).

Constipation: One study[20] showed that compared to placebo Padma Lax was more effective in relieving symptoms in patients with constipation-predominant IBS (RR 7.24; 95% CI: 2.37-22.12) (Figure 4). Similarly, another study[23] demonstrated that Gegan Qinlian pellet was therapeutically effective (RR 1.28; 95% CI: 1.03-1.60). By contrast, Wuma Simo decoction[22] had no advantages over CMs in the patients with constipation-predominant IBS (RR 1.07; 95% CI: 0.91-1.25) (Figure 5).

Therapeutic period and follow-up

The duration of treatment was 8 weeks or more in five studies[11,15,20,25,31], and 5 or 6 wk in three studies[17,24,26]. In one study[16] the treatment duration was 3-6 wk, whereas the other studies[10,12-14,19,21,23,28,29] lasted 3 or 4 wk, while the shortest[18,22,27,30] period of the treatment was only 2 wk. Five studies[10-11,16,28,30] reported follow-up assessment after herbal medicine treatment. Two[10,28] reported that the symptom recurrence rates were lower in the treatment group compared to the conventional treatment group (25.5% *vs* 60%; 23.1% *vs* 50%, $P < 0.01$), after one-year and one-half-year respectively, following completion of the treatment. Another study[11] presented the result as bowel symptom scale. There was significant improvement in the individualized group (75%), and standard group (63%) compared with placebo group (32%) after 14 wk of follow-up. One study[16] reported the number of subjects that were lost to follow-up, but the reasons were not provided. Another study[30] reported symptom recurrence in 3 of 48 patients in the treatment group after 2 wk without treatment.

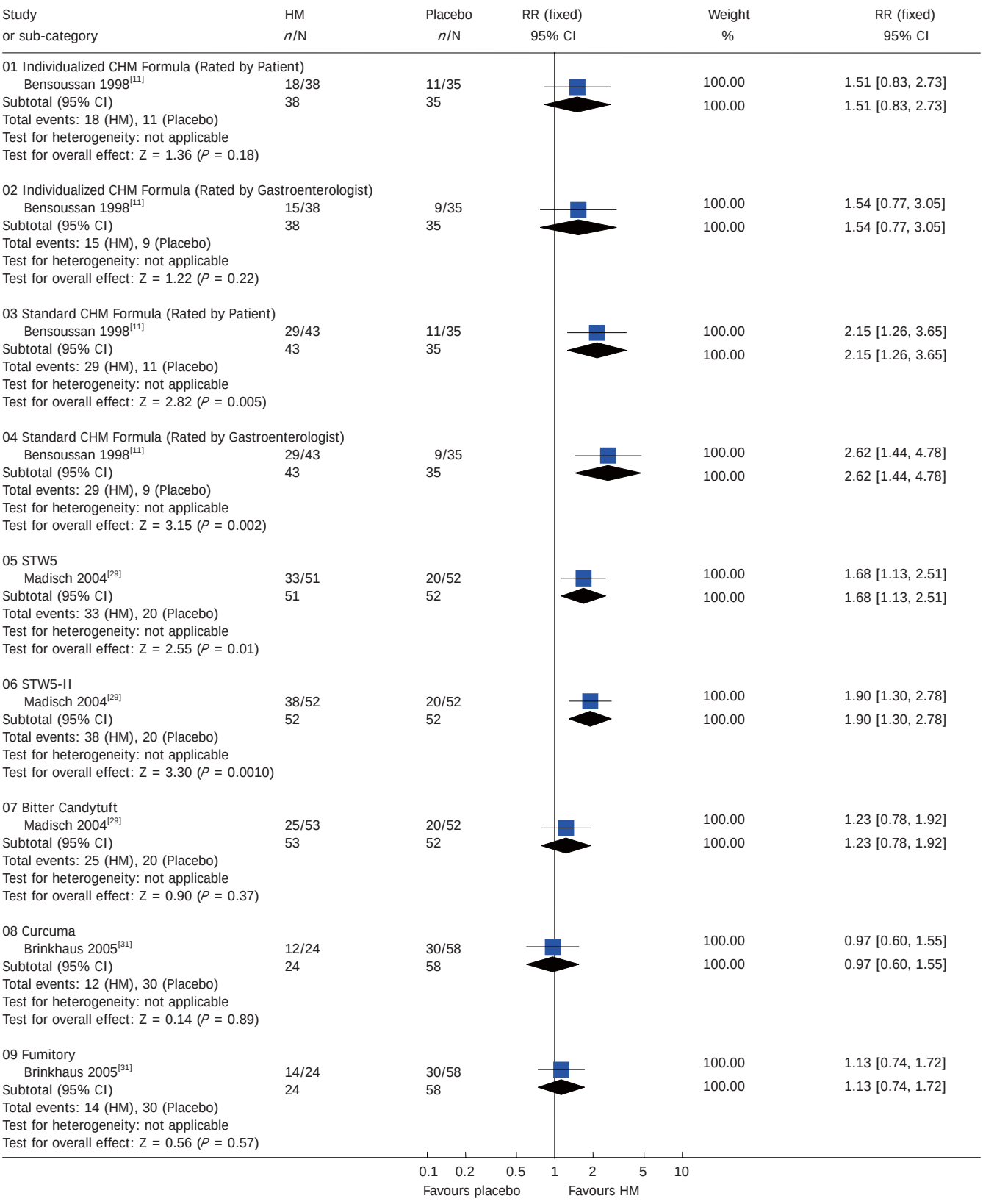

Figure 1 Comparison of herbal medicine and placebo (Outcome: global improvement of symptoms). HM: Herbal medicine; RR: Relative risk; CI: Confidence interval; Fixed: Fixed effects model.

Adverse effects of herbal medicine

In the total study group of 1279 patients, only 15 adverse events in 47 subjects were observed (Table 2). The most common symptoms were abdominal distention, constipation and abdominal pain. None of the subjects developed any serious adverse events or abnormal laboratory tests. The percentage of adverse events associated with HM was 3.67% (95% CI: 2.64-4.71%) in the 1279 patients in the different treatment groups.

Bias analysis

Funnel plots indicated an asymmetry (Figure 6).

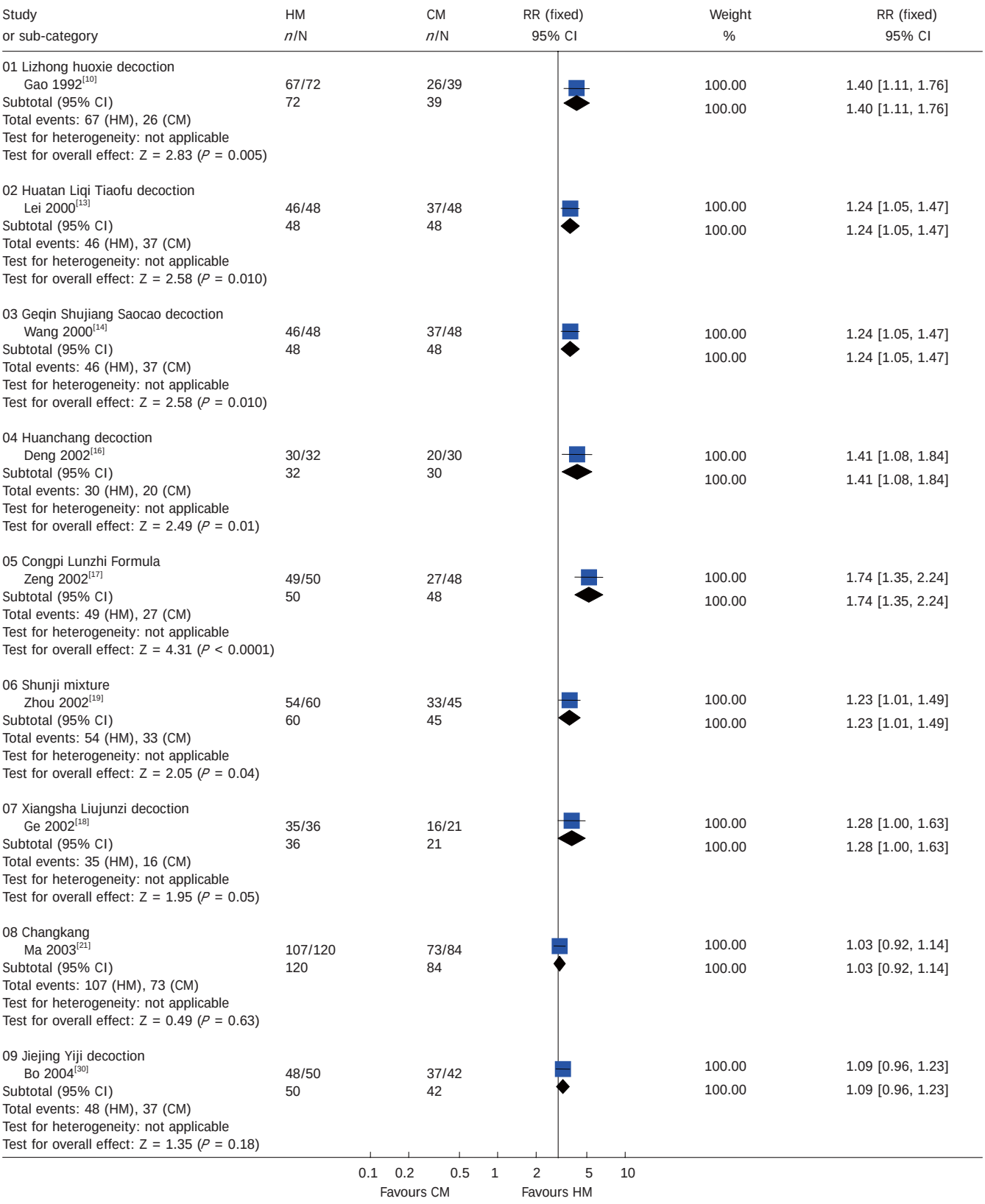

Figure 2 Comparison of herbal medicine and conventional medicine (Outcome: Global improvement of symptoms). HM: Herbal medicine; CM: Conventional medicine; RR: Relative risk; CI: Confidence interval; Fixed: Fixed effects model.

DISCUSSION

In the present review, 3 out of the 4 good quality studies[11,20,31] demonstrated 4 different herbal interventions: one Chinese herbal medicine (standard formula), one Tibetan herbal formula (Padma Lax) and two complex extracts of herbs: STW5 and STW5-Ⅱ which could potentially relieve abdominal pain, constipation, diarrhea and alternating constipation and diarrhea. Moreover, three[11,29,31] out of these four studies showed that four

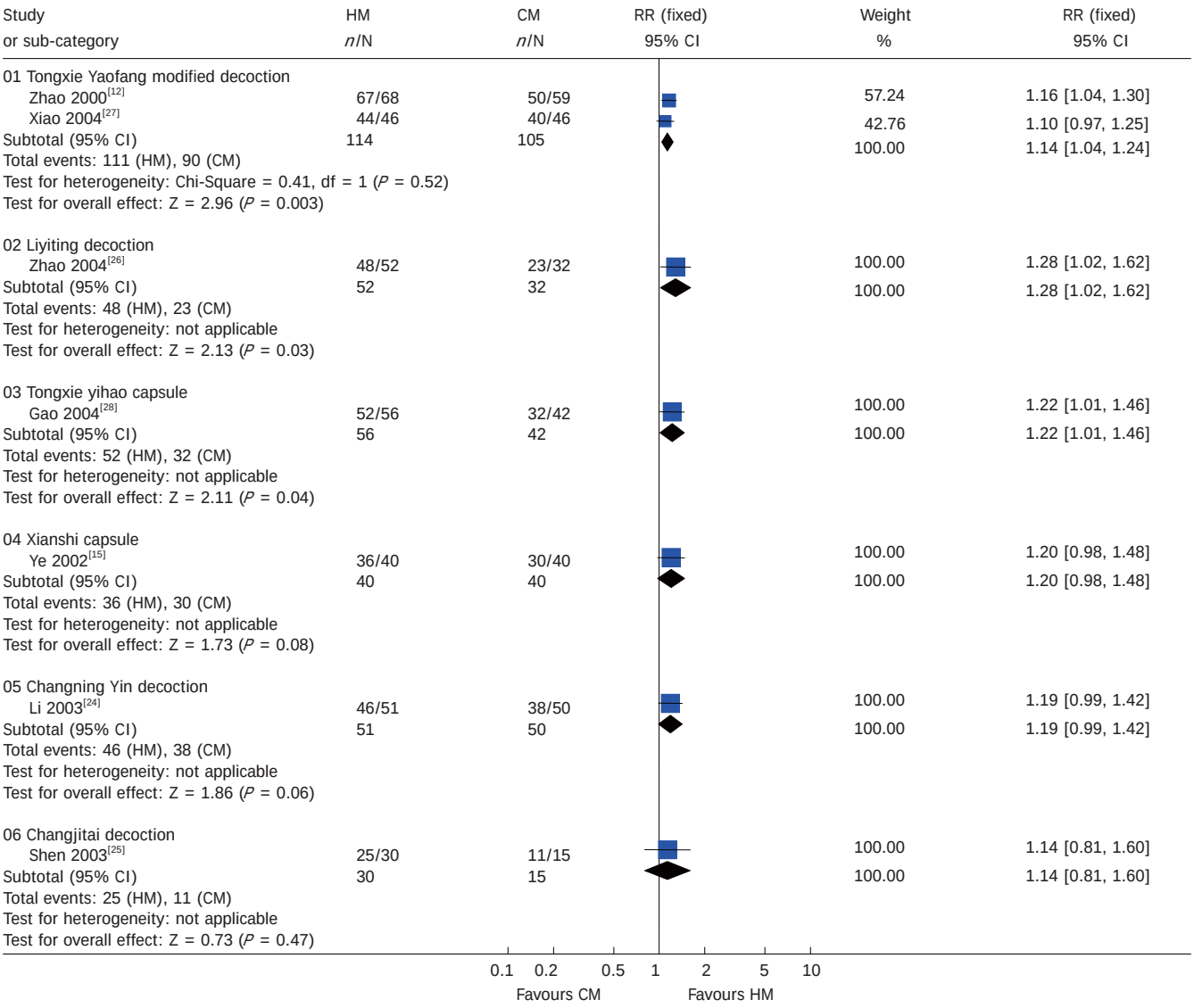

Figure 3 Comparison of herbal medicine and conventional medicine (Outcome: diarrhea). HM: Herbal medicine; CM: Conventional medicine; RR: Relative risk; CI: Confidence interval; Fixed: Fixed effects model.

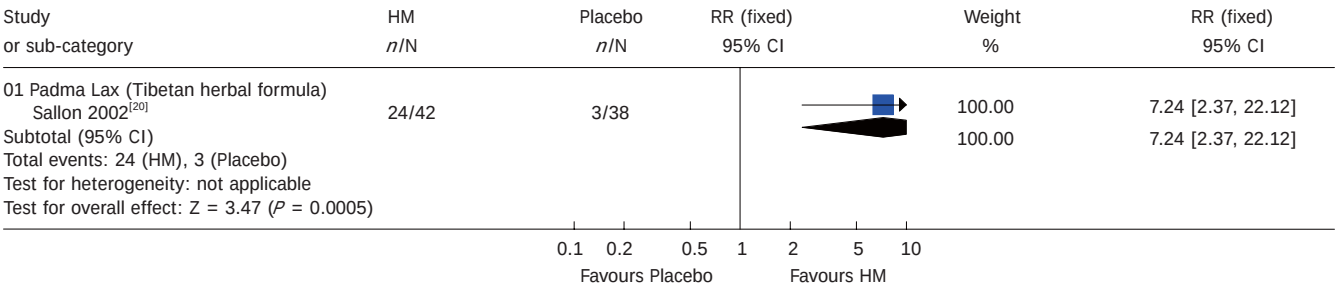

Figure 4 Comparison of herbal medicine and placebo (Outcome: constipation). HM: Herbal medicine; RR: Relative risk; CI: Confidence interval; Fixed: Fixed effects model.

interventions including one individualized formula and three mono-extracts of single herb (Bitter Candytuft, Curcama and Fumitory) were not effective in IBS. We recognized that some complex herbal formulas may improve IBS symptoms, whereas three mono-extracts of single herbs had no beneficial effect. A possible explanation for these findings is that the therapeutic effect may be enhanced by the synergic actions of compounds in a mixture of different herbs.

Twelve[10,12-14,16-19,23,26-28] out of the 18 poor quality studies showed that some Chinese herbs formulas, such as, Huatan Liqi Tiaofu decoction, Tongxie Yaofang modified and Tongxie Yaofang plus Sini San decoction, Geqin Shujiang Saocao decoction, Huanchang decoction, Congpi Lunzhi Formula, Xiangsha Liujunzi decoction, Shunji mixture, Gegan Qinlian Pellet, and Liyiting decoction were more beneficial than CMs in the treatment of IBS.

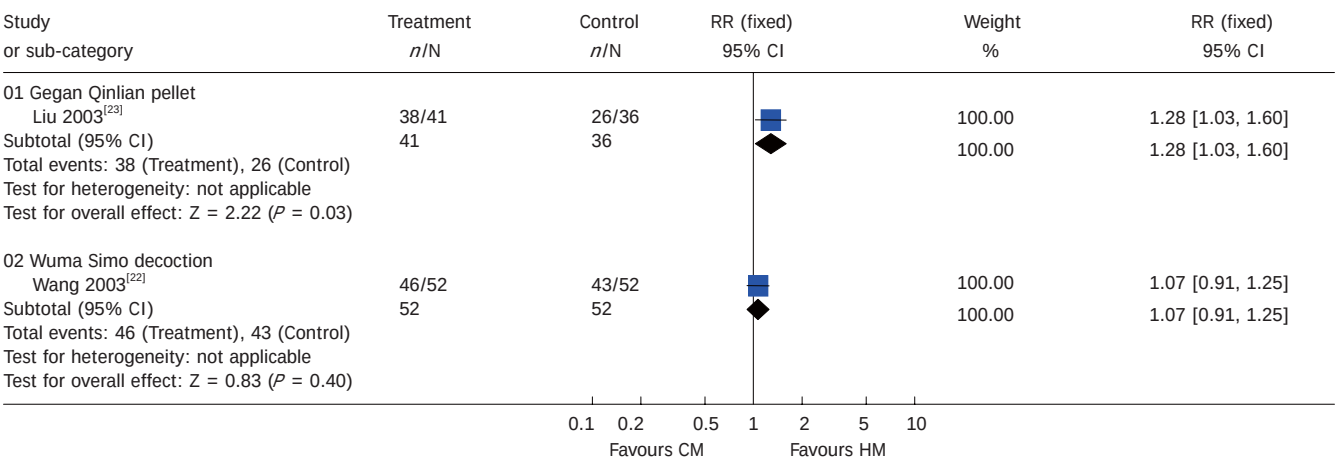

Figure 5 Comparison of herbal medicine and conventional medicine (Outcome: constipation). HM: Herbal medicine; CM: Conventional medicine; RR: Relative risk; CI: Confidence interval; Fixed: Fixed effects model.

Table 2 The type and frequency of adverse events reported in the 22 studies included in the analysis (n = 1279)

Adverse events	Number of adverse events	Percentage	95% CI
Distention	9	0.70	0.32-1.34
Diarrhea	8	0.63	0.27-1.23
Abdominal pain	6	0.47	0.17-1.02
Constipation	5	0.39	0.13-0.91
Dizziness and sleepiness	4	0.31	0.09-0.80
Headaches	4	0.31	0.09-0.80
Nausea	3	0.23	0.05-0.69
Gastrointestinal discomfort	1	0.08	0.002-0.44
Upper gastrointestinal discomfort	1	0.08	0.002-0.44
Loss of hair	1	0.08	0.002-0.44
Pruritus	1	0.08	0.002-0.44
Paraesthesia	1	0.08	0.002-0.44
Disturbance	1	0.08	0.002-0.44
Hoarseness	1	0.08	0.002-0.44
Shortness of breath and chest pain	1	0.08	0.002-0.44
Total	47	3.67	2.73-4.87

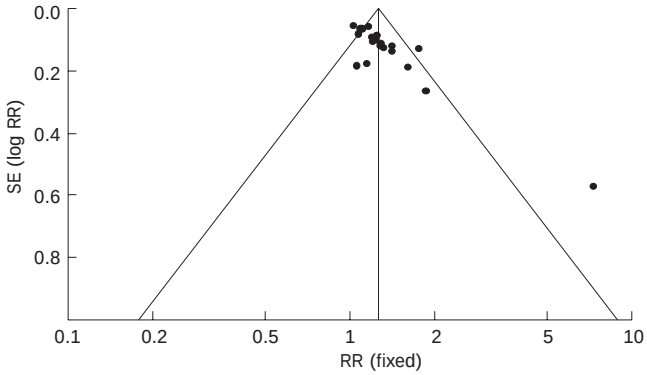

Figure 6 Funnel plot. Fixed: Fixed effects model; RR: Relative risk.

However, these studies revealed several methodological flaws. We found that the longest duration of treatment was 18 wk, while the shortest was just 2 wk, and only 5 studies lasted more than 8 wk. The most frequent treatment duration was 3-4 wk. With such a short period of treatment, it is hard to reach the therapeutic goal in IBS. Some studies reported the long-term effects of herbs and the rate of symptom recurrence. Thus, it is necessary to have a relatively long treatment duration with herbal medicines as well as the duration of the follow-up period; Funnel plot of inclusion trials indicated asymmetry, the major interpretation is the presence of publication bias and variable methodological quality. In the studies that we reviewed, 18 out of 22 were conducted in China and published in Chinese. Chinese studies more frequently showed favorable therapeutic results compared to articles in English, particularly those with a high rate of positive outcome (99%)[32]. The large number of poor quality studies is another source of bias. Furthermore, the small size of studies and the variability of the control treatment may cause asymmetry of the funnel plot. We noticed that most of the studies with Chinese herbs were of poor methodological quality and would not provide strong evidence to confirm the efficacy of CHM. However, the lack of good evidence supporting the effectiveness of CHM does not mean that these preparations are not effective in the treatment of IBS, instead we need to improve the methodological quality of trials in order to verify the efficacy of CHM as a therapeutic approach. We agree with the opinion of Liu[33] that the potential beneficial effects of CHM need to be confirmed in rigorous trials with well-designed, randomized, double blinded, placebo controlled studies. A good example is the study performed by Bensoussan and colleague[11].

There is growing interest in placebo response in patients with IBS. A systematic review of RCTs showed that global improvement in IBS symptoms with placebo was 40.2% (range 16%-71.4%)[34].Other investigators have reported placebo response rate of 57% in IBS[35]. Placebo response rate correlated with factors such as frequency of intervention, methodological quality of study, duration of the study, the patient-practitioner interaction and the diagnosis treated[34,36-38]. Since the number of studies using placebo were small, we did not explore the response effect of placebo in the present study.

In the 22 trials that we reviewed, there were only 15 adverse events associated with HM. These were abdominal distention, constipation, abdominal pain, diarrhea, dizziness and hypersomnia, headache and nausea. However, no serious side effects or abnormalities of laboratory parameters such as liver function, renal function or haematological tests were reported with the treatment. Studies conducted in the West reported more adverse events than those from China. It is possible that because of the lack of rigorous monitoring, several adverse effects including serious events may not have been reported. Similarly, because of publication bias, adverse events related to herbal medicine may not be reported properly.

In summary, the use of HM for treating IBS is increasing worldwide. Most of the studies included in our review showed a beneficial effect on IBS symptoms. However, the methodological quality of the studies was variable, with 82% being of poor quality which may have overestimated the effectiveness of treatment. Although adverse events arising from the use of herbs were mild and infrequent, HM should be used with caution because of the reasons discussed above. It is therefore necessary to conduct Level I studies in order to provide evidence for Grade A recommendations[39] and clarify whether Chinese herbal medicines are reliable and safe therapy in IBS.

COMMENTS

Background

Irritable bowel syndrome (IBS) is a common functional bowel disorder that affects the patient's quality of life. No single treatment is reliably effective, and an increasing number of patients worldwide are seeking herbal medicines to cure their illness.

Research frontiers

We assessed the efficacy and adverse events of herbal medicines in IBS.

Innovations and breakthroughs

We made a comprehensive search of studies using herbal medicines for the treatment of IBS. The studies were analyzed to determine if herbal medicines are appropriate for IBS patients.

Applications

Based on this evaluation, we concluded that herbal medicines could not be reliably recommended because of methodological flaws in the studies. Further studies of better methodological quality should be carried out to determine the efficacy of herbal medicines in IBS.

Peer review

The authors explored the efficacy and safety of herbal medicines (HM) in the treatment of IBS. It was concluded that herbal medicines have therapeutic benefit in IBS.

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