

Effects of Herbal Medicines in Patients with Irritable Bowel Syndrome

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ABSTRACT

Irritable bowel syndrome (IBS) is a common gastrointestinal (GI) disorder associated with alterations in motility, secretion and visceral sensation. Pharmacologic agents used to treat IBS include antispasmodics, 5-hydroxytryptamine-3 receptor (5-HT₃) antagonists, 5-hydroxytryptamine-4 (5-HT₄) agonists, antibiotics, probiotics, antidepressants and herbal medicines. No single therapy is reliably effective, and an increasing number of patients are taking herbal medicines worldwide. This review describes the effectiveness of herbal medicines in patients with IBS. Of single preparations, peppermint oil has shown the most evidence for efficacy, whereas, of compound preparations, most randomized controlled trials (RCTs) have been performed with *TongXieYaoFang* (TXYF). *Daikenchuto* (DKT) appears to be safe and well tolerated, and RCTs of DKT for functional constipation and IBS are now ongoing or being planned. No serious adverse events have been reported, but this may be due to publication bias or the lack of proper monitoring. Although herbal medicines may have therapeutic benefit in patients with IBS, further studies are needed to determine their efficacy and safety.

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Key words: Herbal medicine; IBS

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INTRODUCTION

Irritable bowel syndrome (IBS) is a common gastrointestinal (GI) disorder associated with alterations in motility, secretion and visceral sensation. Its symptoms include abdominal pain or discomfort associated with changes in bowel habits for which no obvious cause can be found on routine investigations, and its diagnosis is commonly dependent on the symptom based Rome criteria. The pathogenesis of IBS is considered multifactorial and includes psychosocial factors, GI dysmotility, enhanced perception of sensory stimuli, stress, corticotrophin-releasing factor, infection, microbiota, genetics and gut wall immune activation^[1].

Several ongoing clinical trials in IBS are testing agents that target visceral hypersensitivity, motility, neurotransmitters, microbiota and immune systems, acting peripherally and/or centrally. Pharmacological therapy of IBS includes antispasmodics, 5-hydroxytryptamine-3 receptor (5-HT₃) antagonists, 5-hydroxytryptamine-4 (5-HT₄) agonists, antibiotics, probiotics, antidepressants, herbal medicines^[2] and melatonin^[3]. Herbal medicines have been used to treat GI symptoms for centuries and have provided effective relief of symptoms in patients with IBS.

The multi-herbal medicine *daikenchuto* (DKT), which originated in ancient China, has been extensively modified/modernized and is now established as a pharmaceutical-grade drug for ethical use in Japan. DKT is widely prescribed for patients with gut dysfunction disorders, such as IBS, postoperative ileus and adhesive bowel obstructions following abdominal surgery^[4].

In this review, herbal medicines are defined as products derived from plants or parts of plants.

The references were collected from randomized controlled trials (RCT) recently published English manuscripts, although studies of artichoke^[5,6] and turmeric extract were case control studies.

This review describes the effectiveness of herbal medicines for IBS patients, explores the mechanisms of actions of these agents and highlights the implications of herbal medicines for understanding the management of IBS.

THERAPEUTIC EFFECTS OF HERBAL MEDICINES FOR IBS

Artichoke

Artichoke (*Cynara scolymus*) is a plant native to southern Europe

and northern Africa and is thought to be one of the oldest medicinal plants still in use. A post marketing surveillance study of 279 IBS patients treated for 6 weeks with artichoke leaf extract showed significant reductions in the severity of symptoms^[5]. Moreover, a post hoc analysis of 208 IBS patients treated with artichoke leaf extract for 2 months showed a 26.4% decrease in IBS incidence ($P<0.001$) after treatment^[6]. There was a significant shift in self-reported usual bowel pattern, from “alternating constipation/diarrhea” toward “normal”, as well as a 41% decrease in total symptom score^[6]. Furthermore, artichokes have been reported to exert a pronounced prebiotic effect on the composition of human fecal microbiota^[7].

A hydrophilic artichoke extract 36_U mainly containing luteolin-7-glycoside, luteolin-7-O-glucoside, small amounts of cynarin and luteolin increased contraction of rat ileum. This is mainly mediated by 5-HT₃ and 5-HT₂ receptors but not 5-HT₄ receptors^[8].

Fumaria officinalis

Fumaria officinalis is the most common species of the genus *Fumaria* in Western and Central Europe. One RCT showed that neither *Fumaria officinalis* nor *F. curcuma* had any therapeutic advantage over placebo in patients with IBS^[9].

Turmeric extract

Turmeric has been traditionally used to manage patients with abdominal pain and bloating. The ability of one or two tablets of a standardized turmeric extract, taken daily for 8 weeks, to improve IBS symptoms and QOL was investigated in 207 patients^[10]. Both groups showed significant improvements, between 5% and 36%, in all but one of the IBSQOL scales.

The literature showed that turmeric extract, curcuminoid produced a smooth muscle, relaxation effect on isolated guinea-pig ileum and rat uterus by acetylcholine dependent and independent mechanism^[11].

Hypericum perforatum

Hypericum perforatum (St. John's wort) has been shown effective in the treatment of patients with mild-to-moderate depression^[12]. A 12-week RCT found that *H. perforatum* was a less effective treatment for IBS than placebo^[12]. Another study showed, however, that *H. perforatum* significantly relieved intestinal symptoms, as well as improving psychological conditions and autonomic nervous system reactivity to stress, in patients with IBS^[13]. *H. perforatum* has anti-inflammatory activity^[14], but mechanism of GI motility is not certain.

Peppermint oil

Peppermint oil has been used to treat stomach upsets for thousands of years. An RCT assessing the efficacy of enteric-coated peppermint oil capsules (Colpermin) in 110 outpatients with IBS showed that symptom improvements were significantly better after Colpermin than after placebo^[15]. Another RCT in 90 IBS outpatients found that the severity of abdominal pain was significantly lower in the Colpermin than in the control group^[16]. In a trial involving 57 IBS patients, in whom small intestinal bacterial overgrowth, lactose intolerance and celiac disease had been excluded, 4 weeks of treatment with peppermint oil resulted in greater symptom improvement than in controls^[17]. An older RCT showed the opposite results, but that trial involved only 33 patients^[18]. The peppermint oil relaxes gastrointestinal smooth muscle by reducing calcium influx^[19].

Plantago psyllium

Seeds of *Plantago ovata* (psyllium) are widely used in the manufacture of bulk laxatives, as well as being added to breakfast

cereals to increase dietary fiber and reduce serum cholesterol concentrations. An RCT in patients with IBS showed that the proportion of responders was significantly greater in the psyllium than in the placebo group during the first and second months of treatment^[20].

COMPOUND PREPARATIONS

Carmint

Carmint contains total extracts of *Melissa officinalis*, *Mentha spicata*, and *Coriandrum sativum*, which have antispasmodic, carminative, and sedative effects. An RCT in 32 patients with IBS showed that the severity and frequency of abdominal pain/discomfort were significantly lower in the Carmint than in the placebo group at the end of treatment^[21]. The pharmaceutical effect of Carmint is similar to that of peppermint oil.

Tong-Xie-Yao-Fang (TXYF)

TongXieYaoFang (TXYF) is composed of four Chinese herbal medicines, *Rhizoma atractylodis Macrocephalae*, *Radix paeoniae alba*, *Pericarpium citri reticulatae*, and *Radix saposhnikoviae*. A meta-analysis of 12 RCTs, involving 1125 patients with IBS, showed that TXYF was more effective than placebo (RR 1.35, 95% CI 1.21 to 1.50), but these results were limited by the poor quality and heterogeneity of the RCTs analyzed^[22]. An RCT evaluating the effectiveness of TXYF in patients with diarrhea-predominant IBS (D-IBS) found that TXYF improved IBS symptoms, by decreasing the number of activated mast cells in the colon^[23].

Another RCT evaluated a modified version of traditional TXYF, involving 11 herbal extracts^[24]. After a 2-week run-in period, 119 patients were randomized to 8 weeks of treatment with traditional Chinese medicine (TCM) ($n=60$) or placebo ($n=59$). The proportions of patients with global symptom improvement were similar in the TCM and placebo groups at 8 (35% vs 44.1%, $p=0.38$) and 16 (31.7% vs 33.9%, $p=0.62$) weeks. Moreover, there were no between group differences in individual symptom scores and quality-of-life assessments at any time point. Pan *et al*^[23] mentioned that its mechanism of action might be through the adjustment of mast cells activation to decrease visceral hypersensitivity.

Tong-xie-ning (TXNG)

The efficacy of TXNG was evaluated in an RCT in 60 patients with D-IBS^[25]. IBS-related pain, measured using the numeric pain intensity scale, was significantly lower in the TXNG than in the placebo group by the end of therapy. Moreover, 82.7% of TXNG-treated patients reported a reduction in IBS-related pain, compared with 39.3% in the placebo group. Stool frequency at the end of treatment was significantly lower in the TXNG than in the control group, with 86.2% and 42.9% of patients, respectively, showing observable improvements in IBS-related diarrhea^[25].

Chinese herbal medicine (CHM)

An RCT in 116 IBS patients was performed to determine whether CHM is of any benefit in the treatment of IBS^[26]. Compared with patients in the placebo group, patients in the active treatment groups (standard and individualized CHM) had significant improvements in bowel symptom scores, as rated by patients ($P=0.03$) and gastroenterologists ($P=0.001$); and significant global improvement, as rated by patients ($P=0.007$) and gastroenterologists ($P=0.002$). Patients reported that treatment significantly reduced the degree that IBS symptoms interfered with activities of daily life. Although CHMs individually tailored to each patient were no more effective



Figure 1 Description of Daikenchuto (DKT), a pharmaceutical grade Japanese traditional medicine. DKT is composed of 4 ingredients, processed ginger, Zanthoxylum fruit, ginseng, and maltose. In Japan, DKT is used to treat many patients with intestinal symptoms, including abdominal pain, bloating, postoperative ileus and constipation.

than standard CHM, follow-up 14 weeks after completion of treatment showed that only the individualized CHM treatment group maintained improvement. Thus, Chinese herbal formulations appear to offer symptom improvement in some patients with IBS^[26].

Padma Lax Tibetan herbal formula

Padma Lax is a complex formula, consisting of 15 herbs and minerals, based on a Tibetan recipe used traditionally to treat constipation and as an aid to digestion. In a 3 month RCT evaluating 80 patients with constipation predominant IBS (IBS-C), with symptom severity evaluated monthly using categorical and numerical rating scales, the Padma Lax group showed significant improvements, compared with placebo, in constipation, severity of abdominal pain and its effect on daily activities, incomplete evacuation, abdominal distention and flatus/flatulence^[27]. In a rat model, cholinergic mechanisms appear to be important on the modulation of proximal colon contractility orally and directly applied Padma Lax^[28].

STW5 (Iberogast)

An RCT involving 208 patients with IBS evaluated the effectiveness of STW 5 (an extract of 9 plants) and STW-II (an extract of 6 plants)^[29]. STW and STW-II were significantly better than placebo in reducing total abdominal pain and IBS symptom scores at 4 weeks^[29]. STW 5 may be a secretagogue in the human intestine, with secretion caused by direct epithelial action and through activation of enteric neurons^[30]. The prosecretory effect is due to increased epithelial Cl⁻ fluxes via a cystic fibrosis transmembrane conductance regulator and Ca-dependent ClCa channels. Thus, STW 5 may be a novel option to treat secretory disorders associated with IBS and constipation^[30].

Clinical studies have indicated that the fixed herbal combination product STW 5 (Iberogast) has an efficacy comparable to that of metoclopramide (a 5-HT₃ antagonist) and cisapride (a 5-HT₄ agonist) in functional gastrointestinal diseases, including functional dyspepsia (FD) and IBS. In vitro data have indicated that 5-HT₄ receptors, and, to a lesser degree, 5-HT₃, muscarinic M₃, and opioid receptors, represent target sites for STW 5 in the treatment of FD and IBS^[31].

Daikenchuto (DKT; Figure 1)

DKT, a traditional herbal medicine, is composed of four medicinal herbs, Zanthoxylum fruit, processed ginger, ginseng, and maltose syrup. In Japan, DKT is widely prescribed for patients with GI obstructions, including postoperative ileus and adhesive bowel obstructions^[4]. A double-blind, placebo-controlled RCT in healthy human subjects, in which gastrointestinal and colonic transit were

measured by scintigraphy, found that DKT had promotility effects, especially in accelerating the emptying half-time of the ascending colon. DKT appears to be safe and well tolerated and is a potential treatment for patients with C-IBS and functional constipation^[32]. RCTs evaluating DKT in patients with functional constipation and IBS are now either ongoing or being planned.

In experimental studies, DKT was found to modulate gut motor function by cholinergic and serotonergic mechanisms, and to ameliorate gastrointestinal motility in patients with postoperative ileus^[33]. DKT acts by stimulating acetylcholine release from cholinergic nerve terminals, with 5-HT₄ receptors involved in this activity^[34].

CONCLUSIONS

The use of herbal medicine to treat IBS is increasing throughout the world. Most of the studies described in this review showed that herbal medicines were effective in relieving the symptoms of IBS. The single preparation with the most evidence for efficacy in IBS patients to date is peppermint oil. Limited evidence is available on the efficacy of other herbal formulas. Also the pharmaceutical mechanisms of formulas are not well evaluated yet. No serious adverse events have been reported, but this may be due to publication bias or a lack of proper monitoring. Moreover, the methodological quality of these studies was not always satisfactory. And the mechanisms of action of herbal medicines have been studied, so far cholinergic, 5-HT, Ca, and anti-inflammatory pathways are involved. Although herbal medicines likely have therapeutic benefits in IBS, further studies are required.

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