

Complementary and Alternative Medicine Modalities for the Treatment of Irritable Bowel Syndrome: Facts or Myths?

Justin C. Y. Wu, MD

Dr. Wu serves as a Professor in the Department of Medicine and Therapeutics and the Institute of Digestive Disease at The Chinese University of Hong Kong and Prince of Wales Hospital in Shatin, Hong Kong.

Address correspondence to:

Dr. Justin C. Y. Wu
Department of Medicine and Therapeutics
Prince of Wales Hospital
The Chinese University of Hong Kong
Shatin, Hong Kong;
Tel: +852 26323593;
E-mail: justinwu@cuhk.edu.hk

Abstract: Due to unsatisfactory results from conventional treatment of irritable bowel syndrome (IBS), complementary and alternative medicine (CAM) modalities are increasingly popular treatment alternatives. Unfortunately, most CAM clinical trials have been of poor quality, and the efficacies of these therapies have not been adequately elucidated, even through systematic reviews or meta-analyses. There is also a general lack of understanding of their mechanisms of action. Currently, insufficient evidence exists to support the use of traditional Chinese medicine, acupuncture, meditation, and reflexology for treatment of IBS. However, there is some evidence supporting the use of peppermint oil and gut-directed hypnotherapy for IBS treatment. Due to mounting evidence of the microbiologic and immunologic basis of IBS, probiotics and exclusion diets are also becoming promising treatment modalities. This paper will review the current literature on various CAM practices for IBS treatment and appraise their advantages and disadvantages in clinical practice.

Irritable bowel syndrome (IBS) is a chronic, recurrent, functional bowel disorder characterized by recurrent abdominal pain and disturbed bowel movements. IBS affects 10–20% of the adult population worldwide and causes significant morbidity, quality-of-life impairment, and burden on the healthcare system.¹

Despite the high prevalence of IBS, its underlying mechanism is not fully understood. Mounting evidence suggests that IBS is caused by interactions of various biological and psychosocial factors.² This “biopsychosocial” pathophysiologic model is characterized by a number of features, including visceral hypersensitivity,³ abnormal intestinal motility,⁴ a strong association with psychological disorders,⁵ abnormal neurohormonal responses to physiologic stimuli or psychological stress,⁶ and activated gut immunity.⁷

It is impossible to identify a single agent that acts on all of the mechanisms of action of IBS, due to their complexity. The use of dietary fiber, laxatives, antidiarrheal agents, and antispasmodic agents as first-line therapies has been limited by marginal therapeutic

Keywords

Complementary and alternative medicine, irritable bowel syndrome, herbal medicine, probiotics, hypnosis, acupuncture, meditation

benefits, side effects, and even exacerbation of IBS symptoms.⁸ Antidepressants have shown efficacy for improving symptoms and psychological well-being. However, their use has been limited by side effects and poor acceptance by patients.⁹ Modulators of serotonin receptors have recently been developed and initially showed promising therapeutic effects.¹⁰ Unfortunately, these modulators were withdrawn from the market due to severe adverse effects, though they were recently reapproved for use in restricted conditions with consent.¹¹

Due to disappointing results with conventional IBS treatments, CAM modalities are becoming attractive options for many patients. This paper will evaluate the efficacies of various CAM modalities for the treatment of IBS.

The Definition of Complementary and Alternative Medicine

The definition of CAM is somewhat arbitrary. According to the National Center for Complementary and Alternative Medicine (NCCAM), CAM refers to healthcare systems, practices, and products that are not considered part of conventional medicine. Western medicine, which is usually referred to as conventional or "mainstream" medicine, is comprised of medical care provided by practitioners and allied health professionals with accredited qualifications (eg, psychologists, physical therapists, and nurses). Complementary medicine refers to the use of CAM as an adjunct to conventional medicine, whereas alternative medicine refers to the use of CAM as a substitute for conventional medicine. The poorly defined boundary between CAM and conventional medicine varies among different populations and is affected by cultural, ethnic, and socioeconomic factors.

CAM practices can be classified into the following categories: natural products, mind-body medicines, and manipulative and body-based practices. Natural products include a variety of biologically-based therapies and food supplements such as herbal medicines, vitamins, minerals, peppermint oil, probiotics, and prebiotics. Although patients following an exclusion diet avoid, rather than add, certain foods, the theoretical basis—modifying biological functions—is similar to that of other treatments in this category. Mind-body medicines focus on interactions between the mind and body and involve a variety of techniques or approaches, such as hypnosis and meditation, that attempt to use the mind to affect physical functioning. Manipulative and body-based practices, which focus on applying pressure to parts of the body, include massage, reflexology, and chiropractic care. Traditional Chinese medicine (TCM), particularly acupuncture, is considered a combination of mind-body

Table 1. Complementary and Alternative Medicine Practices That Have Been Evaluated for the Treatment of Irritable Bowel Syndrome

<p>Natural products</p> <ul style="list-style-type: none"> • Herbal medicine • Peppermint oil • Exclusion diet • Probiotics • Prebiotics
<p>Mind-body medicines</p> <ul style="list-style-type: none"> • Hypnosis • Acupuncture • Meditation
<p>Manipulative and body-based practices</p> <ul style="list-style-type: none"> • Reflexology

medicine, manipulative and body-based practice, and energy-healing therapy. Acupuncture involves manipulating the energy field of the human body by stimulating specific points (acupoints) to strengthen healing energies, regulate bodily functions, and promote a healthy mind. Table 1 lists CAM treatment modalities that have been evaluated for IBS therapy.

CAM practices are generally perceived to be safe, natural treatment modalities with holistic and individualized approaches. Their use is increasingly accepted in developed countries. In the United States, alternative medicine practitioners experienced an increase of 47.3% and 45.2% in total visits and expenditure, respectively, from 1990 to 1997. Total expenditure on CAM practices during that time period was comparable to expenditure on conventional medical services.¹² In a survey of 1,409 patients in clinics or community centers in the United Kingdom, 50.9% of patients with IBS used CAM practices to treat bowel symptoms.¹³ Female patients who experienced milder bowel symptoms and less interference with work and activities were most likely to use CAM practices.¹⁴

Herbal Medicine

Herbal therapies have been extensively used to treat various gastrointestinal conditions. Of these herbal treatments, TCM formulations have undergone the most study. According to traditional Chinese medical theory, IBS is a syndrome of stagnated liver energy and dysfunction of the spleen. As a result, most traditional Chinese herbal formulations for treating IBS were developed to relieve suppressed liver function and replenish the energy of the spleen. One of the most important prototypes of

these formulations is called Tong Xie Yao Fang (this can be literally translated in English as "the essential formula for abdominal pain and diarrhea"), which contains up to 20 herbal ingredients. A number of formulations have been developed based upon Tong Xie Yao Fang, with variations in the composition and dosage of ingredients.

The efficacy of TCM formulations for the treatment of IBS remains controversial. Although a number of recent systematic reviews and meta-analyses demonstrated the efficacy of herbal medicine for treating IBS, marked heterogeneity has been noted in the literature in regard to herbal formulations, control groups, treatment course, and the definition of treatment response.¹⁵⁻¹⁷ Most studies had flawed designs and were of poor quality. Furthermore, there has been a lack of accurate documentation of adverse events and safety, and few studies have evaluated the underlying mechanisms associated with treatment response.¹⁷

Results from higher-quality randomized controlled trials were also conflicting. In a randomized controlled trial of 116 IBS patients, both standard and individualized regimens of TCM herbal capsules were equally more effective than placebo for reducing bowel symptoms and interference with daily activities. However, only patients who received individualized TCM treatment experienced sustained response 3 months after completing treatment.¹⁸ In another placebo-controlled trial using a standardized 11-herb TCM herbal extract in 119 patients with diarrhea-predominant IBS, no significant improvement was seen in bowel symptoms or quality of life.¹⁹

Apart from TCM herbal formulations, Padma Lax (Econugenics), a Tibetan herbal formulation, and STW 5 (Iberogast, Steigerwald), a commercially available 9-plant herbal preparation, have also shown efficacy for treating IBS.^{20,21} The former has been evaluated for treatment of IBS with constipation, whereas the latter has been shown to improve global IBS symptoms compared to placebo.

Many hurdles have been encountered in the development of TCM herbal formulations. First, the mechanisms of these therapies are unknown. There is a lack of physiologic data explaining the effects of TCM on biological features of IBS such as visceral sensation, gut motility, or neurohormonal function. Second, authenticating active ingredients in herbal formulations, which frequently contain more than 10 herbs, has been extremely difficult. Third, the safety of herbal medicine remains a major concern, particularly for treatment of chronic disorders such as IBS. Although toxicity or other adverse reactions may be intrinsic to an herbal formula, toxicities caused by impurities and contaminants such as heavy metals cannot be predicted or controlled in daily clinical practice. Fourth, evaluation of the individualized approach, which involves variable dosing and regimens, is difficult in a

clinical trial setting. Although TCM herbal medicines are time-honored and popular remedies, current evidence does not support their effectiveness for the treatment of IBS.

Peppermint Oil

An oil extract of the *Mentha piperita* Linnaeus plant, peppermint oil likely acts as a smooth muscle relaxant and is commercially available in an enteric-coated preparation for treatment of IBS.²² Although meta-analyses and systematic reviews of earlier randomized placebo-controlled trials have supported the effectiveness of peppermint oil, most of these trials had methodologic flaws such as heterogeneous inclusion criteria and clinical outcome measures.^{23,24} A recent placebo-controlled trial of 57 IBS patients using stringent inclusion criteria showed that 4 weeks of treatment with peppermint oil led to significantly higher response rates. However, clinical response was defined as a greater-than-50% reduction in symptom score rather than the more robust global symptom rating.²⁵ In another randomized, double-blind, placebo-controlled study of 90 outpatients with IBS, the use of peppermint oil led to a significant reduction in symptoms and improvement in quality of life compared to placebo.²⁶ A recent systematic review reported significant and consistent improvement in global IBS symptoms, with a relative risk of only 0.43 compared to placebo (95% confidence interval, 0.32-0.59).⁸

The major advantage of peppermint oil is its safety profile. Common side effects include heartburn and a perianal burning sensation, though they are generally mild and readily avoidable if patients use enteric-coated or pH-dependent capsules.²⁷ Although peppermint oil is not superior to conventional smooth muscle relaxants in terms of reducing IBS symptoms, it may be better tolerated due to the absence of anticholinergic side effects. Because of its smooth muscle relaxing properties and risk of perianal irritation, the safety of peppermint oil during pregnancy is not clear.

Exclusion Diet

IBS patients often report that intolerance to certain foods precedes symptoms; therefore, dietary exclusion is a common practice. Classically, exclusion diets initially restrict food intake and gradually rechallenge patients with foods that are potential offenders. An early study focused on the role of an exclusion diet for reducing colonic fermentation, which may account for abdominal bloating.²⁸ Milk, wheat, eggs, and foods high in salicylates and amines most frequently caused symptom exacerbation. However, based on double-blind placebo-controlled trials, response rates

to exclusion diets were highly variable, ranging from 6% to 58%. Most trials had major limitations in their designs, including inadequate patient selection, duration of the diets, and methods of food rechallenge.²⁴

Recently, more elaborate immunologic mechanisms have been implicated, and an exclusion diet has been developed guided by food-specific immunoglobulin (Ig)G antibody assays. In a study of 25 IBS patients, foods with high IgG4 titers were excluded for 6 months. Significant improvements were observed in pain, bowel motions, and quality of life. These clinical improvements were associated with increased rectal compliance, but no change in rectal sensitivity.²⁹ In another large randomized trial, 150 IBS patients were randomized for 3 months to either a diet excluding all foods associated with raised IgG antibodies or a sham diet. Food elimination has been shown to result in a significant reduction in symptom score and global rating, with a more pronounced effect among patients with high compliance.³⁰ Although these findings lend support to the therapeutic value of exclusion diets in IBS treatment, long-term application is limited by poor adherence and a negative impact on quality of life. Relaxation of the diet often leads to a recurrence of symptoms. The use of an exclusion diet for treatment of IBS inevitably impairs quality of life and may further aggravate avoidance behavior, a consequence commonly seen in patients with concomitant anxiety disorder.

Probiotics and Prebiotics

The human gastrointestinal tract harbors a complex community of bacteria known as microbiota. Through interactions with nutrients and the gut, these bacteria modulate gastrointestinal functions that may be pathogenic or beneficial to the host. Recently, altered colonic microbiota and abnormal activation of innate immunity in the gastrointestinal tract have been implicated in many gastrointestinal diseases. Recent studies suggest that the composition of colonic microbiota is disturbed and unstable in IBS patients.³¹⁻³³

Probiotics, which are defined as live microorganisms that confer a health benefit to the host, can alter colonic fermentation and stabilize colonic microbiota. Probiotics mainly include the *Lactobacillus* and *Bifidobacterium* species and have been shown to enhance gut barrier function, reduce mucosal permeability, and inhibit pathogen binding.^{34,35} They can also reduce visceral hypersensitivity through expression of mu-opioid and cannabinoid receptors in intestinal epithelial cells.^{36,37} Furthermore, probiotics attenuate gut hypercontractility induced by prior enteric infection, which leads to normalization of the ratio between anti-inflammatory and proinflammatory cytokines and is associated with bowel symptom

response.^{38,39} These findings support an immunomodulating role for probiotics in the treatment of IBS and underscore the role of microbiota and gut immunity interaction in the pathogenesis of IBS.

The therapeutic benefit of probiotics for IBS treatment is supported by a number of randomized placebo-controlled trials using certain species of *Lactobacillus* and *Bifidobacterium*, and these observations are also confirmed in meta-analyses. Probiotics have been shown to improve IBS symptoms and quality of life.^{40,41} These patient-reported clinical outcomes are associated with changes in objective markers such as abdominal girth and gastrointestinal transit.⁴² The optimal delivery mode of probiotics to the colon remains undetermined. Challenges for developing effective probiotics include degradation during gastrointestinal transit, the need for stringent quality controls during and after manufacturing, and the transient nature of bacterial colonization.

In contrast to probiotics, prebiotics are nondigestible dietary supplements fermented by host bacteria which alter microbiota of the host by selectively stimulating growth and activity of healthy bacteria in the colon. Prebiotics generally refer to polysaccharides or oligosaccharides such as fructose, galactose, and lactulose.⁴³ Galactooligosaccharide has been shown to selectively stimulate gut bifidobacteria in IBS patients and is effective for alleviating symptoms.⁴⁴

Hypnosis

Hypnosis refers to the delivery of therapeutic suggestions to patients in a state of deep relaxation and narrow focus. Gut-directed hypnotherapy is a specific technique that focuses on improving both psychological well-being and bowel symptoms. Most hypnotherapy protocols consist of up to 12 sessions in a 3-month period. Hypnosis is generally believed to improve IBS symptoms by reducing psychological distress and somatization instead of rectal sensitivity.⁴⁵⁻⁴⁷

The effectiveness of hypnosis has been supported by a number of clinical trials and systematic reviews in both adults and children,^{46,48-50} with therapeutic effects lasting for up to several years.⁵¹ An early review of 14 published studies (6 of which were controlled trials) consisting of 644 IBS patients reported consistent improvement in bowel symptoms in patients treated with hypnosis.⁵² In another systematic review of 4 controlled trials consisting of 147 patients, the therapeutic effect of hypnotherapy for abdominal pain and composite primary IBS symptoms was superior to that of a waiting list control group or patients treated with conventional medical therapies; no side effects were reported. However, these studies were limited by poor methodologic quality and small size.⁵³

Although ample evidence supports the effectiveness of hypnotherapy, this technique is usually restricted to specialist centers with expert therapists trained in gut-directed hypnotherapy. Appropriate case selection is important for treatment response. A large-scale audit reported that male IBS patients with diarrhea respond poorly to hypnotherapy.⁵⁴

Acupuncture

Acupuncture has been used in China for thousands of years to treat various medical conditions. This technique is based upon the theory that channels of internal energy (Qi), also known as meridians, run through the body. Bodily functions can be regulated by activating these meridians with needle application at acupoints. Acupuncture has been shown to be effective for treating various pain and gastrointestinal disorders, particularly nausea due to operation, chemotherapy, pregnancy, and motion sickness.^{55,56}

On the other hand, the therapeutic value of acupuncture in IBS treatment is unclear. Although several small studies have reported that acupuncture increased the threshold of rectal pain and improved bowel symptoms,^{57,58} these findings were not supported by other sham-controlled studies.⁵⁹⁻⁶² In a systematic review of 6 randomized controlled trials and quasirandomized trials of acupuncture therapy for IBS treatment, no significant differences were seen in IBS symptoms and general well-being between acupuncture and sham treatment.⁶³ Most of these trials had poor-quality heterogeneous interventions, controls, and outcome measures. In a recent randomized sham-controlled trial with a larger sample size, 230 IBS patients were randomized to 3 weeks of acupuncture or sham treatment. A third arm included a waitlist control group. No significant difference was seen in symptom response between acupuncture and sham treatment, though both groups improved significantly compared to the waitlist control group.⁶⁴ Current evidence does not support the use of acupuncture for treatment of IBS, as the apparent effect is likely attributed to placebo and may be predicted by high coping capacity and low sleep quality in individual patients.⁶¹

Several major limitations hamper the clinical use and research of acupuncture. First, acupuncture protocols are highly variable, and no consensus currently exists on optimum acupoints, type of acupuncture (electroacupuncture or manual needling), or treatment duration and frequency. Second, acupuncture shares the same individualized approach as traditional Chinese herbal medicine, and evaluation of a standardized protocol in a clinical trial setting does not reflect real-life clinical practice. Third, in clinical trials, nonacupoints, acu-

points with no stimulation, and specially designed sham needles have all been used in sham acupuncture treatments; however, the most effective blinded approach has not been defined. Further studies are required to address these limitations before breakthroughs can be achieved in clinical research.

Meditation and Reflexology

Meditation is another mind-body medicine commonly used to treat various psychological and pain disorders such as headache, fibromyalgia, lower back pain, anxiety, depression, and cancer pain. The value of meditation for treating IBS was assessed in a small pilot study in which Dr. Herbert Benson's relaxation response meditation program was tested in 16 IBS patients who were taught the technique and asked to practice it regularly at home.⁶⁵ A significant improvement was seen in flatulence, bloating, and diarrhea, and clinical responses were sustained with continued meditation at 1-year follow-up.⁶⁶ However, it is unclear whether these results demonstrate a genuine therapeutic effect or a placebo effect.

Only a small single-blind trial has been conducted on reflexology and involved 34 IBS patients in a primary care setting randomized to either reflexology foot massage or a nonreflexology foot massage control group. No significant difference was seen in bowel symptoms between the groups.⁶⁷ In a systematic review, reflexology was not effective for treating other diseases. Therefore, current evidence does not support the use of reflexology for treatment of any medical condition.⁶⁸

Conclusion

Due to unsatisfactory responses to most conventional IBS treatments, CAM practices are becoming popular alternatives. Although some CAM treatments have been evaluated in high-quality randomized controlled trials with robust methodology, most trials have been of poor quality, with efficacies that were unclear even with systematic reviews or meta-analyses. In addition, the mechanisms of action of CAM treatments in IBS are not well understood. Placebo response is generally thought to be a significant contributor to the therapeutic effect of CAM treatments.

Despite the long tradition and widespread practice of herbal medicine and acupuncture, there is insufficient evidence, based upon conventional clinical trial methodology, to support their therapeutic use in IBS. Of the many research challenges in this area, authenticating herbal formulations and standardizing acupuncture protocols are priorities.

On the other hand, other CAM treatments share similarities with conventional Western medical thera-

pies. For example, peppermint oil can be evaluated as a pharmaceutical product in randomized controlled trials. Probiotics and exclusion diets both share a strong theoretical basis in conventional medicine, with measurable microbiologic or immunologic parameters. Gut-directed hypnotherapy fits into the conceptual model of the brain-gut axis and its pathophysiologic role in the development of IBS, and it adopts the conventional psychotherapy principles of cognitive behavioral therapy. Not surprisingly, more robust scientific evidence supports its use in the treatment of IBS.

Future research directions should focus on the mechanism of the placebo effect, the use of clinical outcome measures such as patient-reported outcomes, and the physiologic mechanism of action of CAM modalities using objective tools such as functional magnetic resonance imaging and barostat.

Although conventional medical practitioners may not utilize CAM practices, these therapies are increasingly attractive treatment options for IBS patients. Even in this era of dynamic medical technology, physicians can learn from these time-honored therapies. CAM treatments focus on an individualized and holistic approach, a trustworthy patient-practitioner therapeutic relationship, and attention to the patient's psychological needs and coping difficulties. These are important core values that cannot be replaced by technology.

Dr. Wu is supported by the NCCAM (grant number 1-U19-AT003266-01) and research funds from the Department of Medicine and Therapeutics and the Li Ka Shing Institute of Health Sciences in The Chinese University of Hong Kong. The contents of this paper are his sole responsibility and do not necessarily represent official views of the NCCAM.

References

- Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology*. 2006;130:1480-1491.
- Mayer EA, Collins SM. Evolving pathophysiologic models of functional gastrointestinal disorders. *Gastroenterology*. 2002;122:2032-2048.
- Bouin M, Plourde V, Boivin M, et al. Rectal distention testing in patients with irritable bowel syndrome: sensitivity, specificity, and predictive values of pain sensory thresholds. *Gastroenterology*. 2002;122:1771-1777.
- Spiller R. Role of motility in chronic diarrhoea. *Neurogastroenterol Motil*. 2006;18:1045-1055.
- Lee S, Wu J, Ma YL, Tsang A, Guo WJ, Sung J. Irritable bowel syndrome is strongly associated with generalized anxiety disorder: a community study. *Aliment Pharmacol Ther*. 2009;30:643-651.
- Bearcroft CP, Perrett D, Farthing MJ. Postprandial plasma 5-hydroxytryptamine in diarrhoea predominant irritable bowel syndrome: a pilot study. *Gut*. 1998;42:42-46.
- Liebrechts T, Adam B, Bredack C, et al. Immune activation in patients with irritable bowel syndrome. *Gastroenterology*. 2007;132:913-920.
- Ford AC, Talley NJ, Spiegel BM, et al. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis. *BMJ*. 2008;337:a2313.
- Ford AC, Talley NJ, Schoenfeld PS, Quigley EM, Moayyedi P. Efficacy of antidepressants and psychological therapies in irritable bowel syndrome: systematic review and meta-analysis. *Gut*. 2009;58:367-378.
- Ford AC, Brandt LJ, Young C, Chey WD, Foxx-Orenstein AE, Moayyedi P. Efficacy of 5-HT₃ antagonists and 5-HT₄ agonists in irritable bowel syndrome: systematic review and meta-analysis. *Am J Gastroenterol*. 2009;104:1831-1843.
- Chang L, Chey WD, Harris L, Olden K, Surawicz C, Schoenfeld P. Incidence of ischemic colitis and serious complications of constipation among patients using alosetron: systematic review of clinical trials and post-marketing surveillance data. *Am J Gastroenterol*. 2006;101:1069-1079.
- Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990-1997: results of a follow-up national survey. *JAMA*. 1998;280:1569-1575.
- Kong SC, Hurlstone DP, Pocock CY, et al. The incidence of self-prescribed oral complementary and alternative medicine use by patients with gastrointestinal diseases. *J Clin Gastroenterol*. 2005;39:138-141.
- Koloski NA, Talley NJ, Huskic SS, Boyce PM. Predictors of conventional and alternative health care seeking for irritable bowel syndrome and functional dyspepsia. *Aliment Pharmacol Ther*. 2003;17:841-851.
- Bian Z, Wu T, Liu L, et al. Effectiveness of the Chinese herbal formula TongXieYaoFang for irritable bowel syndrome: a systematic review. *J Altern Complement Med*. 2006;12:401-407.
- Liu JP, Yang M, Liu YX, Wei ML, Grimsgaard S. Herbal medicines for treatment of irritable bowel syndrome. *Cochrane Database Syst Rev*. 2006;CD004116.
- Shi J, Tong Y, Shen JG, Li HX. Effectiveness and safety of herbal medicines in the treatment of irritable bowel syndrome: a systematic review. *World J Gastroenterol*. 2008;14:454-462.
- Bensoussan A, Talley NJ, Hing M, Menzies R, Guo A, Ngu M. Treatment of irritable bowel syndrome with Chinese herbal medicine: a randomized controlled trial. *JAMA*. 1998;280:1585-1589.
- Leung WK, Wu JC, Liang SM, et al. Treatment of diarrhea-predominant irritable bowel syndrome with traditional Chinese herbal medicine: a randomized placebo-controlled trial. *Am J Gastroenterol*. 2006;101:1574-1580.
- Sallon S, Ben-Arye E, Davidson R, Shapiro H, Ginsberg G, Ligumsky M. A novel treatment for constipation-predominant irritable bowel syndrome using Padma Lax, a Tibetan herbal formula. *Digestion*. 2002;65:161-171.
- Madisch A, Holtmann G, Plein K, Hotz J. Treatment of irritable bowel syndrome with herbal preparations: results of a double-blind, randomized, placebo-controlled, multi-centre trial. *Aliment Pharmacol Ther*. 2004;19:271-279.
- Kligler B, Chaudhary S. Peppermint oil. *Am Fam Physician*. 2007;75:1027-1030.
- Pittler MH, Ernst E. Peppermint oil for irritable bowel syndrome: a critical review and meta-analysis. *Am J Gastroenterol*. 1998;93:1131-1135.
- Spanier JA, Howden CW, Jones MP. A systematic review of alternative therapies in the irritable bowel syndrome. *Arch Intern Med*. 2003;163:265-274.
- Cappello G, Spezzaferro M, Grossi L, Manzoli L, Marzio L. Peppermint oil (Mintoil) in the treatment of irritable bowel syndrome: a prospective double-blind placebo-controlled randomized trial. *Dig Liver Dis*. 2007;39:530-536.
- Merat S, Khalili S, Mostajabi P, Ghorbani A, Ansari R, Malekzadeh R. The effect of enteric-coated, delayed-release peppermint oil on irritable bowel syndrome. *Dig Dis Sci*. 2010;55:1385-1390.
- Kline RM, Kline JJ, Di PJ, Barbero GJ. Enteric-coated, pH-dependent peppermint oil capsules for the treatment of irritable bowel syndrome in children. *J Pediatr*. 2001;138:125-128.
- King TS, Elia M, Hunter JO. Abnormal colonic fermentation in irritable bowel syndrome. *Lancet*. 1998;352:1187-1189.
- Zar S, Mincher L, Benson MJ, Kumar D. Food-specific IgG4 antibody-guided exclusion diet improves symptoms and rectal compliance in irritable bowel syndrome. *Scand J Gastroenterol*. 2005;40:800-807.
- Atkinson W, Sheldon TA, Shaath N, Whorwell PJ. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. *Gut*. 2004;53:1459-1464.
- Malinen E, Rinttila T, Kajander K, et al. Analysis of the fecal microbiota of irritable bowel syndrome patients and healthy controls with real-time PCR. *Am J Gastroenterol*. 2005;100:373-382.
- Maukonen J, Satokari R, Matto J, Soderlund H, Mattila-Sandholm T, Saarela M. Prevalence and temporal stability of selected clostridial groups in irritable bowel syndrome in relation to predominant faecal bacteria. *J Med Microbiol*. 2006;55(pt 5):625-633.
- Kassinen A, Krogius-Kurikka L, Makiuokko H, et al. The fecal microbiota of irritable bowel syndrome patients differs significantly from that of healthy subjects. *Gastroenterology*. 2007;133:24-33.
- Caballero-Franco C, Keller K, De SC, Chadee K. The VSL#3 probiotic formula induces mucin gene expression and secretion in colonic epithelial cells. *Am J Physiol Gastrointest Liver Physiol*. 2007;292:G315-G322.