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Hot Topics

Complementary Health Approaches for Irritable Bowel Syndrome

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Abstract

Purpose of review Irritable bowel syndrome (IBS) is a common functional disorder with a prevalence of up to 15% in the USA. Patients with IBS are more inclined to seek complementary treatment options for management of their conditions due to a lack of sufficient relief from conventional treatments and preference towards a more natural approach. We reviewed the most up-to-date medical literature regarding complementary health modalities for the treatment of IBS.

Recent findings Proposed mechanisms for IBS range from alterations in gut motility, intestinal permeability, intestinal microbiome, visceral hypersensitivity, and brain-gut interactions. Addressing each mechanism has helped to broaden our treatment armamentarium by introducing specific targets to different aspects of the disease mechanisms. Today, treatment options for IBS range from conventional prescription drugs for symptomatic relief, including antibiotics for IBS predominant diarrhea to complementary modalities: specific diets, probiotics, botanical herbal regimens, acupuncture, and mind-body therapies.

Summary Numerous complementary health approaches are available to patients and gastroenterologists. There is sound evidence to support the use of such modalities to augment the care and overall quality of life of patients with IBS.

Introduction

Irritable bowel syndrome (IBS) affects 15% of the population in the USA, and functional bowel disorders make up to 40% of the visits to the gastroenterologist [1, 2]. Rome IV characterizes IBS by recurrent abdominal pain weekly for at least 3 months associated with changes in bowel habits; symptoms must have started at least 6 months before establishing a diagnosis. The various subtypes of the disease include IBS-D (diarrhea

predominant), IBS-C (constipation-predominant), or IBS-M (mixed diarrhea and constipation) [3]. Over the years, the complexity and heterogeneity of the mechanisms of IBS have led to a more forward-thinking approach to a disease state than a syndrome. The complexity in the pathophysiological pathways may contribute to the challenges in treating patients with IBS successfully using conventional medicine alone. Thirty percent to 50% of patients with IBS turn to complementary health approaches to manage their condition [4–6].

Complementary health approaches include an array of modalities and products with a history of use or origins outside of conventional Western medicine. Although the words complementary and alternative are often grouped, they are distinct. A National Institute of Health (NIH) 2012 survey revealed that the majority of persons use complementary medicine to augment conventional medicine and only less than 5% use complementary medicine as a replacement [7]. In December 2014, the NIH changed the agency name from the National Center for Complementary and Alternative Medicine (NCCAM) to the National Center for Complementary and Integrative Health (NCCIH) to better align with the organization's strategic plan for public education and research.

The philosophy of complementary medicine is based on a holistic approach wherein all disease results from disturbances on physical, psychological, social, and spiritual levels. Complementary health modalities are used to restore balance and facilitate the body's healing to improve troublesome symptoms.

A significant trend in the use of complementary health approaches is observed in female gender, higher BMI, non-Hispanic whites, adults with some college degree or higher, and patients with private insurance. Patients who are more symptomatic and experience an overall feeling of dissatisfaction with conventional therapy also turn towards complementary medicine [6–8]. The most commonly used complementary health therapies are non-vitamin, non-mineral dietary supplements. Ginger, peppermint, and probiotics or digestive enzymes were predominant in this category. Following herbs and supplements were mind-body therapies, which included gut-directed hypnosis, biofeedback, meditation, yoga, and tai chi, among other guided-imagery exercises (Table 1) [7].

There are numerous challenges in study design and implementation with these modalities, particularly as it pertains to studies evaluating different diets or the incorporation of mind-body medicine to assess outcomes. IBS trials also show a strong placebo response, a recent meta-analysis finding an average placebo response rate of 37.5% [9]. Over the past 3–5 years, there has been a growing body of evidence in the form of randomized placebo-controlled trials and meta-analysis comparing the safety and efficacy of complementary health modalities therapies. This review intends to share the body of evidence for the most common modalities that are gaining wider use among our patients with functional bowel disorders, particularly IBS, an entity that can be difficult to manage and presents with significant economic health costs.

Microbiome-directed therapy

Currently, it is recognized that alterations in the gut microbiome and gut immune function are implicated, to some degree, in the development of IBS [10, 11••, 12]. Increasing research on the human microbiome highlighted the role of gut microbial dysbiosis in IBS. In the Swedish study by Tap et al., using the microbial signature for IBS, severity was associated with low microbial richness, reduced breath methane levels, and enrichment of *Bacteroides* enterotypes [11]. In a recent meta-analysis by Pittayanon et al., differences in stool microbiome in patients with IBS of different subtypes were compared to healthy cohorts. The study concluded that family Enterobacteriaceae (phylum Proteobacteria), family Lactobacillaceae, and genus *Bacteroides* are increased in patients with IBS compared with controls. In contrast, uncultured Clostridiales I, genus *Faecalibacterium*, and genus *Bifidobacterium* were decreased in patients with IBS [12]. Wang et al. in a more comprehensive analysis of 23 included

Table 1. Complementary health modalities

Biologic-based therapy	Nutritional supplements Aromatherapy	Vitamins, minerals, prebiotics, probiotics, chelation therapy, essential oils
Mind-body therapies		CBT, hypnotherapy, yoga, visualization-guided imagery meditation, biofeedback
Manipulation therapies		Osteopathy, chiropractic manipulations techniques, massage therapy
Energy therapies	Healing touch and bio electromagnetically based therapy	Reiki Qi Gong
Acupuncture		
Whole medical systems		Traditional Chinese medicine, naturopathic medicine, Ayurvedic medicine, folk medicine, tai chi

studies with 1340 subjects across the globe reported their results of a data synthesis on the stool microbiome of IBS patients. They reported that individuals with diarrhea-predominant IBS (IBS-D) have increased fecal *Enterobacter* and are deficient in *Lactobacillus* and *Bifidobacterium* species when compared to healthy controls. In a subgroup analysis of Asian studies, *Bacteroides* was increased in stool of IBS-D subjects when compared to healthy controls [13].

Studies on post infection IBS and notably the development of small intestinal bacterial overgrowth have provided etiological insights into the pathogenesis of IBS [14•, 15, 16]. In a systematic review and meta-analysis of 25 studies with 3192 patients with IBS and 3320 controls, SIBO prevalence in patients with IBS was significantly increased compared with controls (OR=3.7, 95% CI 2.3–6.0) [17]. In a cohort study of 104 included patients, herbal therapies were non-inferior to rifaximin for the induction of remission for SIBO. The odds ratio of having a negative lactulose breath test after taking herbal therapy as compared to rifaximin was 1.85 (CI=0.77–4.41, p =0.17) once adjusted for age, gender, SIBO risk factors, and IBS status [18].

Attempts to restore healthy gut microbiota through diet, prebiotics, probiotics, and antibiotics to alleviate IBS symptoms have been demonstrated [19]. Complementary health approaches that may lead to changes in the gut microbiome are continually explored in patients with IBS.

Diet: fiber, gluten elimination, and low FODMAPS

Fiber—psyllium (ispaghula)

Dietary fiber is a type of carbohydrate found in edible plant foods resistant to digestion and absorption in the small intestine. Psyllium contains 70% soluble fiber and can help improve stool viscosity, can lead to a laxation effect through stool bulking, and though poorly fermentable can increase the production of short-chain fatty acids (SCFA). SCFA, particularly

butyrate, promotes changes in the intestinal microbiota and immune and neuroendocrine systems [20, 21]. A recent meta-analysis that included 14 randomized controlled trials showed that soluble fiber, such as psyllium or wheat dextrin, had a benefit for global improvement of IBS (number needed to treat NNT 7) compared to wheat bran [22]. Similarly, a European meta-analysis concluded that soluble fiber improved global assessment of symptoms (RR 1.49; 95% CI 1.09–2.03) and abdominal pain score (mean difference: –1.84, 95% CI –2.72 to –0.97), whereas insoluble fiber did not show benefit [23]. Complex long-chain carbohydrates are recommended for patients with IBS-C and IBS-M. The fermentation process is slower, resulting in reduced abdominal distension and bloating.

Gluten elimination

Few studies have suggested that IBS patients improve on a gluten-free diet, as it reduces fructan intake, a short-chain carbohydrate, fructooligosaccharide [24]. However, a meta-analysis evaluating gluten elimination in patients with IBS found insufficient evidence to recommend this diet for IBS [25]. A systematic review and meta-analysis found an increased prevalence of celiac disease worldwide among individuals with IBS symptoms [26], therefore highlighting the importance of testing patients with IBS symptoms for celiac disease, notably before a gluten elimination challenge. However, sustained gluten elimination in all patients with IBS is not proven to be beneficial though clearly further studies are needed.

Low FODMAPS

Numerous studies have shown improvement in 50–75% of patients with IBS on the low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (LFD) diet [27–30]. The diet involves a global restriction of FODMAP intake for 4–6 weeks, followed by a gradual reintroduction of foods containing individual FODMAP to determine a patient's tolerances. This information is then used to personalize and liberalize the low FODMAPS diet for each individual patient. The physiological effects of FODMAPS include osmotic activity increasing luminal fluid volume, fermentation resulting in increased hydrogen and methane gas production [31], increased lipopolysacccharides leading to changes in gut permeability, intestinal inflammation, and visceral hypersensitivity resulting in abdominal symptoms such as pain and bloating [32]. Their fermentation by bacteria in the colon produces excess gas. The LFD improves symptoms of diarrhea, abdominal pain, distention, and bloating.

Restriction of oligosaccharides for 3–4 weeks resulted in a 6-fold reduction in Bifidobacteria in patients with IBS compared to healthy controls, along with providing symptom relief [33, 34]. However, studies evaluating gut microbiota in patients on LFD have shown inconsistent results possible due to heterogeneity in study design and protocols [35].

Data on the long-term use of an LFD diet are limited, and prolonged full dietary FODMAP restriction is not recommended. Some disadvantages of this particular diet are its complexity and high expense [36, 37]. The collaboration with a GI dietician is essential to identify which patients will

benefit most from the diet, ensure compliance, and avoid over restriction, which may lead to nutritional deficiency, orthorexia, and avoidant restrictive food intake disorder.

Prebiotics, probiotics, and fecal microbial transplantation

Prebiotics are high-fiber foods that can positively modulate gut microbiota composition. In particular, inulin and oligofructose are shown to have a bifidogenic effect. However, to date, there are insufficient clinical trials using prebiotics and symbiotics to support the efficacy and use in patients with IBS [38, 39].

Probiotics are live microorganisms that promote health benefits through alterations or interactions with the intestinal microbiome. Probiotics containing *Bifidobacterium lactis* have been shown to accelerate whole gut transit and improve symptoms in patients with IBS-C [40]. In a recent randomized, double-blind placebo-controlled study in 443 adult patients with IBS, the daily use on one capsule of non-viable *B. bifidum* for 8 weeks revealed a significant improvement in overall IBS symptoms during treatment: 34% of 221 patients in the *B. bifidum* HI-MIMBb75 group compared with 19% of 222 in the placebo group (risk ratio 1 · 7, 95% CI 1 · 3–2 · 4; p=0.0007) [41]. In recent years, several systematic reviews and meta-analysis, although limited by significant heterogenicity, have shown safety and significant benefit of using probiotics in increasing stool frequency and consistency in patients with IBS-C [42]. Similar results were noted in the most recent meta-analysis of 59 studies, including 6761 patients with IBS by Li et al. with a relative risk 1.52 (95% CI 1.32–1.76) in the improvement of symptoms in patients on probiotics versus placebo [43]. However, to date, there is insufficient data to determine which species, multistrain versus single strain, dose, and duration of therapy have significant efficacy on IBS and subtypes. In 2018, the American College of Gastroenterology Monograph on Management of IBS suggested that probiotics taken as a group may improve global symptoms as well as bloating and flatulence in IBS patients, albeit the recommendation was weak as the quality of evidence low [29]. In the recently published AGA clinical practice guidelines, the recommendation is for the use of probiotics for IBS only in the context of clinical trials until further studies bridge the knowledge gap [44].

Fecal microbiota transplantation (FMT)

FMT provides a method to restore the abnormal gut microbiome. There has been inconsistent data and the absence of large-scale, long-term endpoints of randomized controlled trials to determine the effect on FMT on IBS symptoms [45–47]. In a recent randomized double-blind, placebo-controlled of 165 patients, reduction in IBS symptoms at 3 months occurred in 23.6%, 76.9% (p <0.0001), and 89.1% (p <0.0001) of the patients who received placebo, 30 g FMT, and 60 g FMT, respectively. The findings are promising and may provide further insights into the pathophysiology and the role of the gut microbiota in IBS; however, additional studies with larger populations and subtypes of IBS are needed [48].

Biologic-based therapy

Peppermint oil (PO)

Mentha piperita L. Menthacarin is the primary component of the PO responsible for its medicinal properties. It has several mechanisms of action, including intestinal smooth muscle relaxation, modulation of transient receptor potential (TRP) channel-mediated visceral nociception, 5-hydroxytryptamine antagonism, antimicrobial and antifungal effects, and κ-opioid receptor agonism.

In a meta-analysis by Alammar et al., 835 patients concluded that the risk ratio (RR) from seven RCTs for the effect of PO (n=253) versus placebo (n=254) on global symptoms was 2.39 (95% confidence interval (CI) 1.93–2.97, I^2=0%, z=7.93, p<0.00001). The number needed to treat with the PO to prevent one patient from having persistent symptoms was three for global symptoms and four for abdominal pain [49]. A similar result was noted in the meta-analysis by Hawrelak et al. and revealed improved global IBS symptoms in PO treatment group compared with placebo groups after removal of trials with heterogeneity bias (RR=2.14, 95% CI 1.71 to 2.66, p<0.00001) [50].

A recently published Dutch RCT by Weerts et al. with 190 patients with IBS meeting Rome IV criteria randomly assigned to groups given 182 mg small intestinal release PO, 182 mg ileocolonic release PO, or placebo three times a day for 8 weeks revealed conflicting outcomes. The primary endpoint of abdominal pain response did not differ significantly between the PO and placebo groups. There was no benefit in the ileocolonic release group. There was some improvement in the small intestinal PO group when compared to the placebo group in terms of secondary outcomes of abdominal pain (p=.016), discomfort (p=.020), and IBS severity (p=.020) [51]. The differences noted may be attributed to the formulations used and the modest sample size.

Overall, there is sufficient clinical evidence to support the use of small intestinal release PO to reduce symptoms in patients with IBS. Adverse effects of high-dose PO include gastroesophageal reflux disease by decreasing lower esophageal sphincter pressure. Drug interactions for medications metabolized through cytochrome P450 have also been noted. The safety of peppermint oil with pregnancy has not been demonstrated.

STW 5

STW 5 consists of a liquid formulation of nine herbs used in clinical practice for the treatment of functional dyspepsia. It includes extracts from bitter candytuft, angelica root, milk thistle fruit, celandine herb, caraway fruit, licorice root, peppermint herb, balm leaf, and chamomile flower. These active ingredients are thought to act synergistically to ease functional gastrointestinal symptoms [52].

There is only one randomized, double-blind, multicenter placebo-controlled clinical trial on the efficacy and safety of STW 5 in patients with IBS. A total of 208 patients were randomized to receive STW 5 in 2 different

formulations or placebo over 4 weeks. It was found that STW 5 and STW 5-II significantly reduced total abdominal pain (p=0.0009) and IBS symptoms (p=0.001) compared with the placebo group [53]. In clinical practice, the benefit is seen in some patients with IBS; however, more RCTs are needed to determine dose requirements, duration, and efficacy in IBS subtypes.

Berberine

Berberine is an alkaloid obtained by extraction from *Berberis* spp. It is effective in limiting diarrhea due to its multi-factorial properties, including its antimicrobial, gut eubiotic and antisecretory actions, and its ability to slow gut motility [54]. The alkaloid is often a component of a multi-herbal herbal mixture, so its effects in isolation are difficult to know. It has been used as a component of a multi-herb antimicrobial formulation for the treatment of small intestinal bacterial overgrowth [18].
In a study by Chen et al., 132 patients were randomized to receive berberine hydrochloride 400 mg daily in two divided doses or placebo, delivered twice daily or placebo for 8 weeks followed by a 4-week washout period. The effects of berberine hydrochloride on IBS-D were significant in the berberine group with a reduction in the frequency of diarrhea (p=0.032), abdominal pain (p<0.01), and urgent need for defecation (p<0.01) compared the placebo group [55]. The exact mechanism of berberine on the gut microbiome is not clear and more studies are encouraged.

Curcumin

Turmeric is a spice from a plant of the ginger family, Zingiberaceae, and its active component is curcumin. It has antioxidant and anti-inflammatory properties with the ability to modulate gut microbiota.
In a meta-analysis by Ng et al., of 5 RCT including 326 patients, curcumin was shown to have a beneficial albeit not statistically significant effect on IBS symptoms. There was significant heterogenicity in doses of curcumin and duration of treatment [56].
A smaller non-randomized control trial has suggested some improvement in the quality of life and reduced IBS symptoms on a combined regimen of curcumin and fennel oil [57].
In conclusion, while curcumin appears to have potential clinical benefits, further studies are needed to assess IBS efficacy.

Aloe vera

Aloe vera (AV) is a plant frequently used in Ayurvedic, homeopathic, and allopathic treatments. The plant is famed for its medicinal healing properties in prevention or healing injury of epithelial tissues, and its potent laxative effect. Studies suggest that it also possesses several pharmacological actions including antioxidant, anti-inflammatory, analgesic, anti-proliferative, and anti-diabetic properties.
Several studies evaluated the use of AV in patients with IBS and found no significant benefit in symptoms than placebo groups [58–60]. In a more

recent meta-analysis by Hong et al., three RCTs with a total of 151 patients with IBS, a statistically significant difference in IBS symptoms score for patients taking AV compared to those on placebo (standardized mean difference, 0.41; 95% CI, 0.07–0.75; p=0.020). Using intention-to-treat analysis, the AV patients showed significantly better response rates of IBS symptoms than placebo (pooled risk ratio, 1.69; 95% CI, 1.05–2.73; p=0.030). No adverse events related to AV were found [61]. There may be a role for the uses of *Aloe vera* in the treatment for IBS-C, but additional randomized control trials are needed to determine dose, frequency, and duration.

Additional biologic-based nutraceuticals that have shown some potential benefit in reducing IBS symptoms include geraniol and glutamine. Geraniol (Ge-OH) is a naturally occurring acyclic monoterpene component of essential oils extracted from lemongrass, rose, and other aromatic plants. Several studies on the biological activities of Ge-OH have shown it to be a highly active antimicrobial compound with antioxidant and anti-inflammatory properties [62]. Glutamine, a nonessential amino acid, known for its role in the intestinal barrier and immune function of the gastrointestinal tract, may have some potential benefit by reducing intestinal permeability in patients with postinfectious IBS. In a randomized controlled study by Zhou et al., 54 IBS D subjects received glutamine (5 g in three divided doses) and 52 placebo subjects for 8 weeks. Reduction in Irritable Bowel Syndrome Severity Scoring System (IBS-SS) was noted in 43 (79.6%) in the glutamine group and 3 (5.8%) in the placebo group (a 14-fold difference). Glutamine also reduced all secondary endpoint means: IBS-SS score at 8 weeks (301 vs 181, p <0.0001), daily bowel movement frequency (5.4 vs 2.9±1.0, p <0.0001), Bristol Stool Scale (6.5 vs 3.9, p <0.0001), and intestinal permeability (0.11 vs 0.05; p <0.0001) [63]. Larger studies are needed to determine the therapeutic doses and sustained efficacy for use of glutamine in post infection IBS. Supplements such as ginger and CBD oil have been studied in smaller trials which have not shown any significant benefit in relieving IBS symptoms. Traditional Chinese herbal medicine (CHM) such as Tong-Xie-Yao-Fang (TXYF) has shown high rate of relief of diarrhea and abdominal in small RCT. Recent meta-analysis of RCT using an array of CHM has demonstrated superior global symptom improvement when compared with placebo [64]. However, the heterogeneity, potential for interactions, and adverse effects are not negligible. More research is necessary to determine mechanistic roles of the individual herbs as dose titrations remain unclear [65].

Conclusion

Increasing understanding of the complex multisystemic pathophysiologic pathway of IBS suggests that treatment may warrant a multidisciplinary approach, to include complementary health modalities. There is strong evidence to support the benefits of diet, cognitive behavioral therapy, gut-directed hypnotherapy,

herbal medicine acupuncture, and mindfulness-based therapies for the treatment of IBS [66–68]. Strategies to alter the gut microbiome using diet, probiotics, and biologic-based nutraceuticals have shown moderate to significant improvement with IBS global symptoms. Future studies are necessary to understand the ever-evolving etiologies and customize these treatment options for IBS subpopulations using precision medicine platforms that provide genetic, gut microbiome, and metabolomic data to refine dietary and other aforementioned interventions. Furthermore, defining treatment duration, standardizing dosage, and assessing for potential adverse effects or interactions with conventional drugs are essential.

Overall, patients with IBS contribute to high proportion of gastroenterology visits. The symptoms are chronic and recurring with significant impact on patients' quality of life and healthcare costs. Expanding our treatment armamentarium beyond conventional medicine provides a more comprehensive therapeutic approach to managing IBS. Several surveys of providers demonstrate a bias against complementary approaches despite the evidence, and IBS patients are reluctant to disclose the use of complementary health modalities. Patients also report that they take complementary therapies for additional control of their disease and that they derive benefit from them. As clinicians, we should take the totality of evidence in context and partner with our patients with the goal of improving outcomes and patient satisfaction as IBS patients benefit by improved provider relationship. In 1996 the astronomer and science educator Carl Sagan included a saying in his book "The Demon-Haunted World: Science as a Candle in the Dark," which provides insight for the IBS provider: "Keeping an open mind is a virtue—but, not so open that your brains fall out" [69].

Authors' contributions

Dr. Asamoah conducted a literature review and drafted the manuscript. Dr. Mullin provided oversight, review of drafts, and editorial contributions.

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Compliance with Ethical Standards

Conflict of Interest

Vivian A. Asamoah declares that she has no potential conflict of interest.

Gerard Mullin declares that he has no potential conflicts of interest.

References and Recommended Reading

1. Lovell RM, Ford AC. Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. Clin Gastroenterol Hepatol. 2012;10(7):712–21.e4.
2. Gan WC, Smith L, Luca EJ, Harnett JE. The prevalence and characteristics of complementary medicine use by Australian and American adults living with gastrointestinal disorders: a systematic review. Complement Ther Med. 2018;41:52–60.
3. Drossman DA, Hasler WL. Rome IV—functional GI disorders: disorders of gut-brain interaction. Gastroenterology. 2016;150(6):1257–61.
4. Hussain Z, Quigley E. Systematic review: complementary and alternative medicine in the irritable bowel syndrome. Aliment Pharmacol Ther. 2006;23(4):465–71.
5. Hung A, Kang N, Bollom A, Wolf JL, Lembo A. Complementary and alternative medicine use is prevalent among patients with gastrointestinal diseases. Dig Dis Sci. 2015;60(7):1883–8.
6. Larussa T, Rossi M, Suraci E, Marasco R, Imeneo M, Abenavoli L, et al. Use of complementary and alternative medicine by patients with irritable bowel syndrome according to the Roma IV criteria: a single-center Italian survey. Medicina (Kaunas). 2019;55(2).
7. Clarke TC, Black LI, Stussman BJ, Barnes PM, Nahin RL. Trends in the use of complementary health approaches among adults: United States, 2002-2012. Natl Health Stat Rep. 2015(79):1–16.
8. Bahrami HR, Hamedi S, Salari R, Noras M. Herbal medicines for the management of irritable bowel syndrome: a systematic review. Electron Physician. 2016;8(8):2719–25.
9. Ford A, Moayyedi P. Meta-analysis: factors affecting placebo response rate in the irritable bowel syndrome. Aliment Pharmacol Ther. 2010;32(2):144–58.
10. Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. Jama. 2015;313(9):949–58.
11.•• Tap J, Derrien M, Törnblom H, Brazeilles R, Cools-Portier S, Doré J, et al. Identification of an intestinal microbiota signature associated with severity of irritable bowel syndrome. Gastroenterology. 2017;152(1):111–23.e.

This is one of the few studies that has shown identification of an intestinal microbiota signature with the severity of IBS symptoms. This may be a path to bridging the gap in our knowledge regarding the role of the gut microbiome in IBS and customized or targeted treatment with the use of diet or probiotics.

12. Pittayanon R, Lau JT, Yuan Y, Leontiadis GI, Tse F, Surette M, et al. Gut microbiota in patients with irritable bowel syndrome-a systematic review. Gastroenterology. 2019;157(1):97–108.
13. Wang L, Alammar N, Singh R, Nanavati J, Song Y, Chaudhary R, et al. Gut microbial dysbiosis in the irritable bowel syndrome: a systematic review and meta-analysis of case-control studies. J Acad Nutr Diet. 2020;120(4):565–86.
14.• Klem F, Wadhwa A, Prokop LJ, Sundt WJ, Farrugia G, Camilleri M, et al. Prevalence, risk factors, and outcomes of irritable bowel syndrome after infectious enteritis: a systematic review and meta-analysis. Gastroenterology. 2017;152(5):1042–54.e.

Landmark systematic review of large population size for up to 10 years identifying post infectious enteritis with a significant prevalance of IBS.The study also clearly demonstrated higher risk populations emphasizing the role of immunogenicitiy, and the gut brain axis.

15. Litleskare S, Rortveit G, Eide GE, Hanevik K, Langeland N, Wensaas KA. Prevalence of irritable bowel syndrome and chronic fatigue 10 years after Giardia infection. Clin Gastroenterol Hepatol. 2018;16(7):1064–72.e4.
16. Schwille-Kiuntke J, Mazurak N, Enck P. Systematic review with meta-analysis: post-infectious irritable bowel syndrome after travellers' diarrhoea. Aliment Pharmacol Ther. 2015;41(11):1029–37.
17. Shah A, Talley NJ, Jones M, Kendall BJ, Koloski N, Walker MM, et al. Small intestinal bacterial overgrowth in irritable bowel syndrome: a systematic review and meta-analysis of case-control studies. Am J Gastroenterol. 2020;115(2):190–201.
18. Chedid V, Dhalla S, Clarke JO, Roland BC, Dunbar KB, Koh J, et al. Herbal therapy is equivalent to rifaximin for the treatment of small intestinal bacterial overgrowth. Glob Adv Health Med. 2014;3(3):16–24.
19. Pimentel M, Chow EJ, Lin HC. Eradication of small intestinal bacterial overgrowth reduces symptoms of irritable bowel syndrome. Am J Gastroenterol. 2000;95(12):3503–6.
20. El-Salhy M, Ystad SO, Mazzawi T, Gundersen D. Dietary fiber in irritable bowel syndrome (review). Int J Mol Med. 2017;40(3):607–13.
21. Muir J. An overview of fiber and fiber supplements for irritable bowel syndrome. Gastroenterol Hepatol (N Y). 2019;15(7):387–9.
22. Moayyedi P, Quigley EM, Lacy BE, Lembo AJ, Saito YA, Schiller LR, et al. The effect of fiber supplementation on irritable bowel syndrome: a systematic review and meta-analysis. Am J Gastroenterol. 2014;109(9):1367–74.
23. Nagarajan N, Morden A, Bischof D, King EA, Kosztowski M, Wick EC, et al. The role of fiber supplementation in the treatment of irritable bowel syndrome: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2015;27(9):1002–10.
24. Skodje GI, Sarna VK, Minelle IH, Rolfsen KL, Muir JG, Gibson PR, et al. Fructan, rather than gluten, induces symptoms in patients with self-reported non-celiac gluten sensitivity. Gastroenterology. 2018;154(3):529–39.e2.

25. Dionne J, Ford AC, Yuan Y, Chey WD, Lacy BE, Saito YA, et al. A systematic review and meta-analysis evaluating the efficacy of a gluten-free diet and a low FODMAPs diet in treating symptoms of irritable bowel syndrome. Am J Gastroenterol. 2018;113(9):1290–300.
26. Irvine AJ, Chey WD, Ford AC. Screening for celiac disease in irritable bowel syndrome: an updated systematic review and meta-analysis. Am J Gastroenterol. 2017;112(1):65–76.
27. Gravina AG, Dallio M, Romeo M, Di Somma A, Cotticelli G, Loguercio C, et al. Adherence and effects derived from FODMAP diet on irritable bowel syndrome: a real life evaluation of a large follow-up observation. Nutrients. 2020;12(4).
28. Ford AC, Lacy BE, Talley NJ. Irritable bowel syndrome. N Engl J Med. 2017;376(26):2566–78.
29. Ford AC, Moayyedi P, Chey WD, Harris LA, Lacy BE, Saito YA, et al. American College of Gastroenterology monograph on management of irritable bowel syndrome. Am J Gastroenterol. 2018;113(Suppl 2):1–18.
30. Werlang ME, Palmer WC, Lacy BE. Irritable bowel syndrome and dietary interventions. Gastroenterol Hepatol (N Y). 2019;15(1):16–26.
31. Ong DK, Mitchell SB, Barrett JS, Shepherd SJ, Irving PM, Biesiekierski JR, et al. Manipulation of dietary short chain carbohydrates alters the pattern of gas production and genesis of symptoms in irritable bowel syndrome. J Gastroenterol Hepatol. 2010;25(8):1366–73.
32. Zhou SY, Gillilland M 3rd, Wu X, Leelasinjaroen P, Zhang G, Zhou H, et al. FODMAP diet modulates visceral nociception by lipopolysaccharide-mediated intestinal inflammation and barrier dysfunction. J Clin Invest. 2018;128(1):267–80.
33. Staudacher HM, Whelan K. The low FODMAP diet: recent advances in understanding its mechanisms and efficacy in IBS. Gut. 2017;66(8):1517–27.
34. Staudacher HM, Lomer MCE, Farquharson FM, Louis P, Fava F, Franciosi E, et al. A diet low in FODMAPs reduces symptoms in patients with irritable bowel syndrome and a probiotic restores Bifidobacterium species: a randomized controlled trial. Gastroenterology. 2017;153(4):936–47.
35. Bellini M, Tonarelli S, Nagy AG, Pancetti A, Costa F, Ricchiuti A, et al. Low FODMAP Diet: Evidence, Doubts, and Hopes. Nutrients. 2020;12(1).
36. Hill P, Muir JG, Gibson PR. Controversies and recent developments of the low-FODMAP diet. Gastroenterol Hepatol (N Y). 2017;13(1):36–45.
37. Eswaran S, Dolan RD, Ball SC, Jackson K, Chey W. The impact of a 4-week low-FODMAP and mNICE diet on nutrient intake in a sample of US adults with irritable bowel syndrome with diarrhea. J Acad Nutr Diet. 2020;120(4):641–9.
38. Curro D, Ianiro G, Pecere S, Bibbo S, Cammarota G. Probiotics, fibre and herbal medicinal products for functional and inflammatory bowel disorders. Br J Pharmacol. 2017;174(11):1426–49.
39. Ford AC, Harris LA, Lacy BE, Quigley EMM, Moayyedi P. Systematic review with meta-analysis: the efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. Aliment Pharmacol Ther. 2018;48(10):1044–60.
40. Agrawal A, Houghton LA, Morris J, Reilly B, Guyonnet D, Goupil Feuillerat N, et al. Clinical trial: the effects of a fermented milk product containing Bifidobacterium lactis DN-173 010 on abdominal distension and gastrointestinal transit in irritable bowel syndrome with constipation. Aliment Pharmacol Ther. 2009;29(1):104–14.
41. Andresen V, Gschossmann J, Layer P. Heat-inactivated Bifidobacterium bifidum MIMBb75 (SYN-HI-001) in the treatment of irritable bowel syndrome: a multicentre, randomised, double-blind, placebo-controlled clinical trial. Lancet Gastroenterol Hepatol. 2020;5:658–66.
42. Wen Y, Li J, Long Q, Yue CC, He B, Tang XG. The efficacy and safety of probiotics for patients with constipation-predominant irritable bowel syndrome: a systematic review and meta-analysis based on seventeen randomized controlled trials. Int J Surg. 2020;79:111–9.
43. Li B, Liang L, Deng H, Guo J, Shu H, Zhang L. Efficacy and safety of probiotics in irritable bowel syndrome: a systematic review and meta-analysis. Front Pharmacol. 2020;11:332.
44. Su GL, Ko CW, Bercik P, Falck-Ytter Y, Sultan S, Weizman AV, et al. AGA clinical practice guidelines on the role of probiotics in the management of gastrointestinal disorders. Gastroenterology. 2020;159(2):697–705.
45. Ianiro G, Eusebi LH, Black CJ, Gasbarrini A, Cammarota G, Ford AC. Systematic review with meta-analysis: efficacy of faecal microbiota transplantation for the treatment of irritable bowel syndrome. Aliment Pharmacol Ther. 2019;50(3):240–8.
46. Myneedu K, Deoker A, Schmulson MJ, Bashashati M. Fecal microbiota transplantation in irritable bowel syndrome: a systematic review and meta-analysis. United European Gastroenterol J. 2019;7(8):1033–41.
47. Wang Y, Zheng F, Liu S, Luo H. Research progress in fecal microbiota transplantation as treatment for irritable bowel syndrome. Gastroenterol Res Pract. 2019;2019:9759138.
48. El-Salhy M, Hatlebakk JG, Gilja OH, Bråthen Kristoffersen A, Hausken T. Efficacy of faecal microbiota transplantation for patients with irritable bowel syndrome in a randomised, double-blind, placebo-controlled study. Gut. 2020;69(5):859–67.
49. Alammar N, Wang L, Saberi B, Nanavati J, Holtmann G, Shinohara RT, et al. The impact of peppermint oil on the irritable bowel syndrome: a meta-analysis of the pooled clinical data. BMC Complement Altern Med. 2019;19(1):21.
50. Hawrelak JA, Wohlmuth H, Pattinson M, Myers SP, Goldenberg JZ, Harnett J, et al. Western herbal medicines in the treatment of irritable bowel syndrome: a systematic review and meta-analysis. Complement Ther Med. 2020;48:102233.

51. Weerts Z, Masclee AAM, Witteman BJM, Clemens CHM, Winkens B, Brouwers J, et al. Efficacy and safety of peppermint oil in a randomized, double-blind trial of patients with irritable bowel syndrome. Gastroenterology. 2020;158(1):123–36.
52. Fifi AC, Axelrod CH, Chakraborty P, Saps M. Herbs and spices in the treatment of functional gastrointestinal disorders: a review of clinical trials. Nutrients. 2018;10(11).
53. 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(3):271–9.
54. Di Pierro F, Bertuccioli A, Giuberti R, Saponara M, Ivaldi L. Role of a berberine-based nutritional supplement in reducing diarrhea in subjects with functional gastrointestinal disorders. Minerva Gastroenterol Dietol. 2020;66(1):29–34.
55. Chen C, Tao C, Liu Z, Lu M, Pan Q, Zheng L, et al. A randomized clinical trial of berberine hydrochloride in patients with diarrhea-predominant irritable bowel syndrome. Phytother Res. 2015;29(11):1822–7.
56. Ng QX, Soh AYS, Loke W, Venkatanarayanan N, Lim DY, Yeo W-S. A meta-analysis of the clinical use of curcumin for irritable bowel syndrome (IBS). J Clin Med. 2018;7(10):298.
57. Di Ciaula A, Portincasa P, Maes N, Albert A. Efficacy of bio-optimized extracts of turmeric and essential fennel oil on the quality of life in patients with irritable bowel syndrome. Ann Gastroenterol. 2018;31(6):685–91.
58. Storsrud S, Ponten I, Simren M. A pilot study of the effect of Aloe barbadensis Mill. extract (AVH200(R)) in patients with irritable bowel syndrome: a randomized, double-blind, placebo-controlled study. J Gastrointestin Liver Dis. 2015;24(3):275–80.
59. Davis K, Philpott S, Kumar D, Mendall M. Randomised double-blind placebo-controlled trial of aloe vera for irritable bowel syndrome. Int J Clin Pract. 2006;60(9):1080–6.
60. Hutchings HA, Wareham K, Baxter JN, Atherton P, Kingham JG, Duane P, et al. A randomised, cross-over, placebo-controlled study of *Aloe vera* in patients with irritable bowel syndrome: effects on patient quality of life. ISRN Gastroenterol. 2011;2011:206103.
61. Hong SW, Chun J, Park S, Lee HJ, Im JP, Kim JS. Aloe vera is effective and safe in short-term treatment of irritable bowel syndrome: a systematic review and meta-analysis. J Neurogastroenterol Motil. 2018;24(4):528–35.
62. Rizzello F, Ricci C, Scandella M, Cavazza E, Giovanardi E, Valerii MC, et al. Dietary geraniol ameliorates intestinal dysbiosis and relieves symptoms in irritable bowel syndrome patients: a pilot study. BMC Complement Altern Med. 2018;18(1):338.
63. Zhou Q, Verne ML, Fields JZ, Lefante JJ, Basra S, Salameh H, et al. Randomised placebo-controlled trial of dietary glutamine supplements for postinfectious irritable bowel syndrome. Gut. 2019;68(6):996–1002.
64. Chen M, Tang TC, Wang Y, Shui J, Xiao XH, Lan X, et al. Randomised clinical trial: Tong-Xie-Yao-Fang granules versus placebo for patients with diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther. 2018;48(2):160–8.
65. Zhu J-J, Liu S, Su X-L, Wang Z-S, Guo Y, Li Y-J, et al. Efficacy of Chinese herbal medicine for diarrhea-predominant irritable bowel syndrome: a meta-analysis of randomized, double-blind, placebo-controlled trials. Evid Based Complement Alternat Med. 2016;2016:1–15.
66. Windgassen S, Moss-Morris R, Chilcot J, Sibelli A, Goldsmith K, Chalder T. The journey between brain and gut: a systematic review of psychological mechanisms of treatment effect in irritable bowel syndrome. Br J Health Psychol. 2017;22(4):701–36.
67. Radu M, Moldovan R, Pintea S, Băban A, Dumitrascu D. Predictors of outcome in cognitive and behavioural interventions for irritable bowel syndrome. A meta-analysis. J Gastrointestin Liver Dis. 2018;27(3):257–63.
68. Yan J, Miao ZW, Lu J, Ge F, Yu LH, Shang WB, et al. Acupuncture plus Chinese herbal medicine for irritable bowel syndrome with diarrhea: a systematic review and meta-analysis. Evid Based Complement Alternat Med. 2019;2019:7680963.
69. Sagan C The demon-haunted world: science as a candle in the dark. Quote Page 187, Ballantine Books, New York. Verified with Amazon Look Inside for 1997, Ballantine Books paperback edition.

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