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Chili Peppers, Curcumins, and Prebiotics in Gastrointestinal Health and Disease

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Abstract There is growing evidence for the role of several natural products as either useful agents or adjuncts in the management of functional GI disorders (FGIDs). In this review, we examine the medical evidence for three such compounds: chili, a culinary spice; curcumin, another spice and active derivative of a root bark; and prebiotics, which are nondigestible food products. Chili may affect the pathogenesis of abdominal pain especially in functional dyspepsia and cause other symptoms. It may have a therapeutic role in FGIDs through desensitization of transient receptor potential vanilloid-1 receptor. Curcumin, the active ingredient of turmeric rhizome, has been shown in several preclinical studies and uncontrolled clinical trials as having effects on gut inflammation, gut permeability and the brain–gut axis, especially in FGIDs. Prebiotics, the non-digestible food ingredients in dietary fiber, may serve as nutrients and selectively stimulate the growth and/or activity of certain colonic bacteria. The net effect of this change on colonic microbiota may lead to the production of acidic metabolites and other compounds that help to reduce the production of toxins and suppress the growth of harmful or disease-causing enteric pathogens. Although some clinical benefit in IBS has been shown, high dose intake of prebiotics may cause more bloating from bacterial fermentation.

Keywords Food · Chili · Curcumin · Prebiotic · Gastrointestinal sensation · Gastrointestinal motility · Functional gastrointestinal disorder

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Introduction

Between 70 and 84 % of irritable bowel syndrome (IBS) patients report aggravation of symptoms after food ingestion, and 62 % of them either limit or exclude foods from their diet [1, 2]. Food intolerance is associated with more severe IBS symptoms and this reduces the quality of life [1]. A recent study also demonstrated that high fermentable carbohydrate content or fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) were associated with more bloating, abdominal pain and unsatisfied stool form among IBS patients but not in healthy volunteers [3].

On the other hand, dietary fiber, which is described as nondigestible carbohydrates, are essential for promoting normal bowel movements, and a subgroup of nondigestible carbohydrate- prebiotics has been shown to promote health benefit through modulation of gut microbiota. In addition, chili and curcumin, which are spices commonly consumed by populations in several parts of the world, not only serve as flavor enhancers in daily food but have also long been recognized for medicinal benefits on gastrointestinal health. They have been included in folk or home remedies for treatment of abdominal pain and bloating since ancient times. In this review, we will focus on the evidence of the effects of two common spices (chili pepper and curcumin) and a subgroup of nondigestible carbohydrate-prebiotics on

gastrointestinal function in health and functional gastrointestinal disorders (FGID).

Chili Pepper and Capsaicin Receptors

Chili is a common ingredient in Asian and Latin American food. The average daily chili consumption by Asians is 2.5–8 g/person which is 10–300 times higher than by Europeans and Americans [4, 5]. Capsaicin is an active component of chili that triggers a painful and burning sensation in the human gut via transient receptor potential vanilloid-1 (TRPV1) receptors which are expressed throughout the digestive tract mucosa with variable distribution in each organ [6, 7•]. Studies in visceral hypersensitivity conditions, including non-erosive reflux disease, rectal hypersensitivity, fecal urgency and inflammatory gut mucosa including symptomatic esophagitis, have revealed more TRPV1-immunoreactive fibers or TRPV1 mRNA and protein expression than in healthy controls [8, 9]. TRPV1 receptors can also be activated by heat, acid pH, ethanol, and mechanical distension [7], and stimulate the release of several peptides, including substance P and calcitonin gene-related peptide [10]. Interestingly, repeated exposure to capsaicin can desensitize this receptor, and this not only causes the receptor to become refractory but the whole nerve fiber that subserves the receptor may also become refractory to other nociceptive and mechanical stimuli [11]. Thus, this effect provides a broader modification of painful and burning symptoms during food ingestion than the effects of specific capsaicin antagonists which inhibit only a specific group of receptors. Therefore, using chili, a natural capsaicin agonist, for providing relief to patients with chronic gastrointestinal symptoms may provide a broader effect than synthetic/specific capsaicin receptor antagonists in modifying the gut symptoms. In addition, capsaicin receptor antagonist(s) are still in development and may cause severe side effects particularly hyperthermia [12].

Effects of Capsaicin on Esophageal Sensation and Motor Function

Studies in healthy volunteers have reported that single dose intra-esophageal capsaicin infusion induced heartburn in a dose-dependent manner [13–15]. After repeated exposure, the desensitizing properties of capsaicin occurred rapidly and caused a significant decrease in heartburn intensity [16]. Desensitization to chemical stimuli may result from dephosphorylation of TRPV1 by calcium-induced calcineurin activation [17]. The recovery time from desensitization is dependent on the stimulus intensity and interstimulus interval [18].

Regarding esophageal motor function, an animal study demonstrated the role of capsaicin-sensitive neurons in esophageal myenteric plexus on controlling peristalsis [19]. In healthy volunteers, single-dose esophageal capsaicin infusion significantly increased the amplitude of distension-induced secondary peristalsis compared with placebo, and a desensitization effect on distension-induced secondary peristalsis as well as heartburn sensation were also demonstrated after repeated capsaicin infusion at the esophagus for two consecutive sessions with at least a 1-h time interval [13, 16]. A previous study also demonstrated comparable distension thresholds for secondary peristalsis as a consequence of hydrochloric acid (0.1 N) or 0.84 mg capsaicin esophageal infusion [13]. A histological study of the lower esophageal sphincter tissue in humans observed no evidence for capsaicin-sensitive axon collateral reflexes [20]. However, manometric studies on the effects of capsaicin on the lower esophageal sphincter in healthy volunteers have demonstrated conflicting results [21, 22].

Effects of Capsaicin on Gastric Sensation and Motor Function

In healthy volunteers study using the barostat technique, a single-dose capsaicin (red pepper sauce) infusion into the proximal stomach during a fasting period decreased proximal gastric tone, increased proximal stomach compliance and also increased proximal gastric distension sensitivity compared to placebo [23]. Gastric electrical activity study showed a significant increase in tachygastric activity and significantly delayed liquid gastric emptying after single-dose intraesophageal capsaicin infusion compared to placebo [21]. Regarding gastric sensation, the ingestion of capsaicin capsules induced gastric sensations of pressure, heartburn, and warmth in healthy volunteers [24]. Gastric mucosal protection of capsaicin has been demonstrated in an animal model by the release of neurotransmitters including calcitonin gene-related peptide and nitric oxide through stimulation of TRPV1 receptors. In rat and dog models, capsaicin induced calcitonin gene-related peptide release and inhibited gastric secretion [25, 26]. It was also found to induce the release of a vasodilator, nitric oxide, which may be beneficial for gastric mucosal blood perfusion [26]. Gastroprotective effects of capsaicin in human studies are limited and have not been demonstrated in a randomized trial.

Clinical Studies of Capsaicin on Gastro-esophageal Reflux Disease and Dyspepsia

Clinical studies on the efficacy of chili or capsaicin receptor antagonists on heartburn symptoms in gastro-esoesophageal reflux disease and dyspepsia are limited. Studies in Asian countries with high chili consumption rates have demonstrated a low prevalence of heartburn

symptoms in GERD [27, 28]. A small randomized cross-over study comparing chest pain, heartburn, epigastric burning, and epigastric pain symptoms induced by intraesophageal capsaicin perfusion or normal saline perfusion among 17 healthy volunteers and 31 GERD patients (10 non-erosive reflux disease, 11 erosive esophagitis and 10 Barrett's esophagus) reported significantly higher esophageal and gastric symptoms in the GERD group compared to the control group. Thirty minutes after saline or capsaicin infusion, an acid perfusion test of HCl was performed. The results showed that symptoms in response to acid perfusion in both healthy volunteers and GERD patients reduced after capsaicin infusion, especially in the Barrett's esophagus group [14]. A study from our center in NERD patients showed that a single-dose chili ingestion increased postprandial acid refluxes which were associated with increased food retention in the stomach during the first hour after ingestion compared to placebo [29]. A subsequent study confirmed these observations and showed that the chili-induced food retention resulted from exaggerated gastric accommodation which was observed only in NERD patients but not in healthy volunteers [30]. This suggests that an abnormal TRPV1 pathway may mediate gastric accommodation and this may play a role in the pathophysiology of postprandial gastroesophageal reflux. In a preliminary cross-over study that compared the therapeutic effects of chili and placebo administered in gelatin capsules to 8 NERD patients, we also showed desensitization effects after red chili capsule (2.1 mg capsaicin/day) ingestion for 6 weeks. After 6 weeks, the red chili significantly decreased total reflux symptom scores, heartburn symptom scores, and food regurgitation symptom scores when compared to placebo [31].

The effects of capsaicin on patients with esophageal motility disorders have been reported. In a randomized cross-over study of 12 mild reflux esophagitis patients with severe ineffective esophageal motility, single-dose intraesophageal capsaicin infusion increased the amplitude of esophageal contractions when compared to placebo. However, the peristalsis velocity and the lower esophageal sphincter basal tone remained unchanged [32]. Also, a study in patients with Barrett's esophagus showed no demonstrable effects on esophageal motility [33]. The effects of chronic capsaicin ingestion on esophageal motility have not been reported.

Gut hypersensitivity to capsaicin has been demonstrated in functional dyspepsia (FD) patients. Randomized double-blind controlled trials in FD patients have revealed that capsaicin ingestion induced more nausea, flutter-like sensations in the stomach, warmth and abdominal pain than placebo. This effect was not different between FD subtypes and most patients reported that these symptoms were similar to what they had experienced before the study [34•]. In a recent study on the effects of spicy meals on gastrointestinal symptoms in FD patients, a greater proportion of FD patients reported that spicy meals induced more abdominal burning symptoms in their daily life in relation to healthy controls. However, in this study, epigastric pain syndrome-subtype patients had a greater prevalence of spicy meal-induced abdominal burning symptoms compared to postprandial distress syndrome-subtype patients [35]. There is limited information regarding the effect of chronic capsaicin ingestion in FD. A randomized double-blind controlled study in 30 functional dyspepsia patients without GERD or IBS using 2.5 g red pepper powder capsules (capsaicin 1.75 mg) ingestion for 5 weeks demonstrated that red pepper significantly improved overall symptoms of epigastric pain, fullness, and nausea but not epigastric burning, bloating, and belching compared to placebo. These symptom improvements were significantly observed after chili ingestion for 3 weeks. Seven of 15 patients who received chili reported abdominal pain and/or discomfort during the first week, but these side effects improved after a few days [36].

Effects of Capsaicin on Intestinal Sensation and Motor Function

In healthy volunteers, a small intestinal capsaicin infusion induced abdominal pain, cramping, pressure, and nausea, and 3-day capsaicin ingestion increased rectal sensitivity to urgency [24, 37]. Along the small intestine, the duodenum was more sensitive to capsaicin and induced more intense symptoms compared to the distal part [24]. Desensitization after chronic capsaicin ingestion in healthy humans can also be demonstrated by capsaicin administration and balloon distension of the duodenum [11]. Regarding colonic motility, capsaicin-induced giant migrating contractions and defecation have been shown in an animal study [38], although another study reported no effect of capsaicin on colonic transit in IBS-diarrhea and healthy humans [39, 40].

Clinical Studies of Capsaicin on IBS

An increase in TRPV1-expressing nerve fibers were seen in the rectal mucosa of patients with rectal hypersensitivity [9] and significantly increased TRPV1-immunoreactive nerve fibers were seen in sigmoid mucosa of IBS patients when compared to controls [41]. Some studies have revealed that IBS patients had gut hypersensitivity to capsaicin, and that their reported symptoms included more severe abdominal burning and pain after ingestion of spicy meals than healthy volunteers [39]. Acute chili ingestion in IBS patients increased abdominal burning, pain, and discomfort as well as increased rectal sensitivity compared to placebo [39, 42]. Desensitization effects of capsaicin ingestion in IBS patients were demonstrated in two randomized controlled trials [43, 44]. The first study revealed that 6-week red pepper ingestion (capsaicin 2 mg/day), not placebo, significantly decreased abdominal pain and bloating compared to the baseline [44]. The second study

by Aniwan et al. reported that 6-week ingestion of 2.1 g. chili/day in gelatin and enteric-coated capsules in 16 IBS-diarrhea patients significantly reduced spicy meal-induced abdominal burning symptoms compared to placebo. In addition, chronic chili ingestion significantly increased rectal sensory thresholds in response to balloon distention without significant effects on rectal compliance [43]. The effects of single-dose chili administration on gastrointestinal sensation and motility are shown in Table 1. Table 2 shows studies demonstrated desensitization effects of repeated chili administration in GERD and FGIDs.

In conclusion, there has been increasing evidence to support the role of capsaicin in the pathogenesis of abdominal pain and burning symptoms in functional GI disorders. The therapeutic role of chili pepper as a natural capsaicin for the desensitization of capsaicin receptors in patients with functional dyspepsia, IBS and GERD is evolving.

Curcumin

Curcumin, the active ingredient of turmeric (*Curcumin longa*) rhizome, has been used in Asia as a herbal remedy for a variety of diseases. Like chili, turmeric is commonly used in Asian cuisine to add yellow color, as a flavor, and as a preservative. Some promising effects of curcumin have been observed including the treatment of chronic inflammatory conditions such as arthritis, uveitis, and inflammatory bowel disease, leading to improved metabolic parameters involving atherosclerosis and diabetes. In some cases, it has been found to aid in cancer prevention and treatment [45, 46]. The effects of turmeric on the gastrointestinal tract have been widely described in folk medicine including the treatment of abdominal pain and flatulence and in appetite promotion without considerable side effects. Although the molecular mechanisms of action have been studied, clinical trials on gastrointestinal conditions are limited.

Mechanisms of the Action of Curcumin on the Gastrointestinal Tract

Anti-inflammatory Effect and the Effect on Gut Permeability

Gut inflammation has been recognized in the pathogenesis of FGIDs. Curcumin has been shown in preclinical studies to modulate several inflammatory mediators. The activity of proinflammatory enzymes, including cyclooxygenase-2, 5-lipoxygenase, inducible nitric oxide synthase (iNOS) enzymes, tumor necrosis factor-alpha, interleukin (IL) -1, -2, -6, -8 and -12 have been shown to be inhibited by curcumin. It can also downregulate the expression of various cell surface adhesion molecules that have been linked with inflammation [47–49]. Recent studies have demonstrated the effects of curcumin in animal models of colitis through the suppression of Toll-like receptor (TLR) 4, nuclear factor-kappa B (NFkB), and signal transducers and activators of the transcription 3 signaling pathway [50–52]. In an animal colitis model, there was no significant difference in IL 27, TLR4, and NFkB protein expression inhibition between curcumin and sulfasalazine-treated groups, whereas curcumin significantly decreased the disease activity index faster than sulfasalazine [51]. In addition, an in vitro study demonstrated protective effects of curcumin on oxidative stress-induced intestinal barrier disruption in human intestinal epithelial cells by heme oxygenase 1 induction [53]. Since disruption of epithelial tight junctions followed by the loss of barrier function and low-grade mucosal inflammation has been described in the pathogenesis of FGIDs, particularly IBS, this might support the therapeutic role of curcumin in these patients.

Table 1 Effects of single dose chili administration on gastrointestinal sensation and motility

Esophagus	- Increase postprandial gastroesophageal reflux and induce heartburn symptom [13–15, 29]
	- Increase secondary esophageal peristalsis amplitude [13, 16]
	- Conflicting results on lower esophageal sphincter pressure [21, 22]
Stomach	- Induce epigastric burning, pressure symptom [23, 24]
	- Decrease fasting proximal gastric tone, increase proximal gastric compliance and distention sensitivity [23]
	- Increase gastric accommodation [30]
	- Increase tachygastric activity [21]
	- Delay liquid gastric emptying [21]
Intestine	- Induce abdominal cramp/pain [24, 37]
	- Decrease fecal urgency threshold [39, 42]
	- No study on colonic transit effect

Table 2 Studies showing desensitization effects of repeated chili administration in GERD and FGIDs

Disease	Study	*n*	Patients	Study design	Dosage	Study duration	Results
GERD	Jutaghokiat S, 2009 [31]	8	NERD (positive pH monitoring)	Randomized cross-over	Chili 3 g (capsaicin 2.1 mg) /day	6 weeks	Improved heartburn, food regurgitation symptoms
Functional dyspepsia	Bortolotti M, 2002 [36]	30	Functional dyspepsia	Randomized control trial	Chili 2.5 g (capsaicin 1.75 mg) /day	5 weeks	Improved epigastric pain, fullness, nausea
IBS	Bortolotti M, 2011 [44]	50	IBS	Randomized control trial	Chili 0.6 g (capsaicin 2 mg) /day	6 weeks	Improved abdominal pain, bloating
	Aniwan S, 2014 [43]	16	IBS-D	Randomized cross-over	Chili 2.1 g (capsaicin 2.5 mg) /day	6 weeks	Improved abdominal burning Increased rectal sensory threshold

Antibacterial Effect

Curcumin inhibits most metronidazole-resistant *H. pylori* growth in vitro with MIC values between 5 and 50 μg/mL irrespective of the genetic strains, and was also highly effective in the eradication of *H. pylori* from infected mice [54, 55]. The mechanism of *H.pylori* growth inhibition of curcumin may differ from antibiotics. Curcumin inhibits the assembly dynamics of FtsZ (a bacterial protofilament), which polymerizes to form a Z ring that orchestrates bacterial cell division [56] and inhibits the shikimate pathway that is necessary for the synthesis of aromatic amino acids in bacteria [57]. The effect of curcumin on gut microbiota has not been explored. Just one small study in healthy volunteers has reported that ingesting rice with turmeric significantly increased breath-hydrogen concentrations compared to rice without turmeric. This may suggest that curcumin increases carbohydrate fermentation by colonic bacteria [58].

Effect on the Brain–Gut Axis

In animal studies, curcumin significantly modulated HPA activity, up-regulated serotonin (5-HT_{1A}) mRNA and brain-derived neurotrophic factor protein levels in the hippocampus which represented a possible antidepressive effect which might be beneficial to FGIDs patients [59–61]. In regard to visceral pain perception, curcumin has been shown to have antinociceptive effects in animal models. Chronic curcumin ingestion was able to attenuate intraperitoneal acetic acid-induced visceral pain [62]. The antinociceptive mechanism was demonstrated by antagonizing TRPV1 receptors, [63•] and this may be involved in the endogenous analgesic opioid system [62].

Effect on Gastrointestinal Motility

The effect of curcumin on human gastrointestinal motility has not been clearly demonstrated, but it has antispasmodic effects in animal models. In a chemically induced colitis animal, 21-day curcumin administration significantly reduced spontaneous intestinal contractions as well as contractions in response to atropine compared to placebo, and was independent of an anti-inflammatory effect [64]. Antispasmodic mechanisms appeared as a non-competitive inhibitor through cholinergic, histaminergic, and serotoninergic receptors and showed an antispasmodic effect on potassium-induced contractions in calcium channels [65]. Effects of curcumin on gastric function were demonstrated in diabetic gastroparesis rats [66]. In this study, chronic curcumin administration significantly accelerated gastric emptying and increased ghrelin levels in a dose-dependent manner. Asummary of curcumin effects on the pathogenesis of FGIDs is shown in Table 3.

Table 3 Summary of curcumin effects on the pathogenesis of FGIDs

In vitro and animal studies

- Inhibit pro-inflammatory mediators, signaling pathways, cell surface adhesion molecules [47–52]
- Inhibit intestinal epithelial cell disruption [53]
- Accelerate gastric emptying [66]
- Increase ghrelin level [66]
- Inhibit *H. pylori* infection [54–57]
- Possible antidepressant effects by modulating HPA activity, upregulating serotonin and brain-derived neurotrophic factor protein [59–61]
- Decrease visceral pain [62, 63•]
- Inhibit intestinal contraction [64, 65]

Human studies

- Improve dyspepsia and gastric inflammation [67]
- Increase hydrogen-producing colonic microbiota [58]
- Antidepressant effect [68, 69]

Clinical Studies of Curcumin in Functional Gastrointestinal Disorders

Studies on curcumin efficacy in FGIDs patients are limited to uncontrolled and case series studies. An uncontrolled study showed a significant improvement in dyspeptic symptoms and a reduction of serologic signs of gastric inflammation at 2 months after a 7-day treatment by non-antibiotic therapy comprised of curcumin, lactoferrin, N-acetylcysteine, and pantoprazole despite the persistence of *H.pylori* infection [67].

Clinical trials of patients with major depression have shown that curcumin has antidepressant effects similar to fluoxetine [68, 69]. Although depression is prevalent among FGIDs patients, more studies are needed to elucidate the antidepressant benefits of curcumin in FGIDs.

Poor oral bioavailability is one major concern with the use of curcumin [70]. A study showed that crude turmeric, a precursor of curcumin, provided better bioavailability and had better effects on pro-inflammatory gene transcription than curcumin [71]. Structural modification, modulation of the route and medium of curcumin administration, and the blocking of metabolic pathways by concomitant administration with other agents to overcome its poor bioavailability is still being developed [72].

Regarding its safety profiles, curcumin is considerably safe with minimal side effects, which include diarrhea and nausea as well as increased serum alkaline phosphatase and lactate dehydrogenase levels [45]. Curcumin dosages of up to 8 g/day have been taken for 3 months without serious adverse events in clinical trials [73]. Nevertheless, more studies are required to evaluate its long-term toxicity.

Prebiotics

A prebiotic is defined as "a nondigestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, thusly improving host health" [74]. Although dietary fiber from fruits and vegetables are nondigestible, not all have prebiotic effects. Leeks, asparagus, chicory, garlic, artichoke, onions, wheat, bananas, oats, and soy beans contain inulin, fructo-oligosaccharides, and galacto-oligosaccharides as their major substrates and are considered prebiotics [74, 75]. They have been shown to stimulate growth of certain colonic microbiota that might benefit the host [74].

Product of Bacterial Fermentation and Effects on Host

Nondigestible carbohydrates that reach the colon are fermented to short chain fatty acids (SCFA), mainly acetate, propionate and butyrate. A number of other metabolites such as lactate, pyruvate, ethanol, and succinate as well as hydrogen, carbon dioxide, and methane gases are also produced. Of these, SCFA is considered to be beneficial to human health. It is rapidly absorbed and metabolized in muscles, kidneys, the heart and brain and serves as a tissue energy substrate [76]. Butyrate is one SCFA that is largely metabolized by colonic epithelial cells and mainly contributes to colonic tissue energy and growth of the colonic epithelium. It promotes normal colonic epithelial cell differentiation and proliferation [77]. Recent studies have demonstrated that butyrate may also play a role in gut immune homeostasis by facilitated extrathymic generation of regulatory T cells, which is the key in limiting inflammatory responses in the intestine [78, 79]. Almost all carbohydrates that reach the colon are fermented and provide substrates for colonic microbiota; however, stimulation of growth by these carbohydrates is nonspecific and they also stimulate some bacteria genera that ferment proteins and amino. The end product of these proteolyic bacteria are branch chain fatty acids, ammonia, amines and phenolic compounds which may be toxic to the host [80].

Prebiotics are non-digestible carbohydrates that selectively stimulate the growth of "specific bacteria" which prefer using saccharides as a primary substrate [81]. Lactobacillus and bifidobacterium are two colonic bacteria genera that have been widely established for the target of prebiotics. These two genera do not contain any known pathogens. They produce acetic acid and lactic acid as the major end-metabolites. An acidic luminal environment helps to reduce peptide degradation and the formation of amino acid end-product toxic compounds by other groups of bacteria and suppresses the growth of enteric pathogens. Their growth also leads to an increase in bacterial mass which consequently increases fecal mass to promote normal bowel movements. In addition, a genera *Bifidobacterium* is a dominant colonic bacteria in

Table 4 Clinical trials of prebiotics in irritable bowel syndrome (IBS)

Study	Substrate/duration	Patients	*n*	Study design	Results	Limitation
Silk DB, 2009 [86]	- Trans-galactooligosaccharide 3.5 g/day or 7 g/day vs. placebo for 4 weeks - Evaluation at the 4th week	IBS constipation, diarrhea and alternating subtype (RomeII)	60	Randomized cross-over	Increased fecal *Bifidobacterium* proportion 3.5 g/day dose - improved flatulence, bloating, composite score of symptoms, subjective global assessment of relief 7 g/day dose - improved stool consistency, subjective global assessment of relief and anxiety score - increased bloating symptom and flatulence compared to a lower dose	- high drop-out rate (16/60) - per-protocol analysis
Paineau D, 2008 [85]	- Short-chain fructo-oligosaccharides 5 g/day or placebo for 4 weeks - Evaluation at the 6th week	Mild functional bowel disorders (RomeII)	105	Randomized control trial	Decreased discomfort or pain intensity, improved disease-related quality of life and performance of daily activity	- high drop-out rate (65/105) - per-protocol analysis
Hunter JO, 1999 [87]	- Oligofructose 6 g/day or sucrose 3 g/day for 2 weeks - Evaluation at the 4th week	IBS-constipation(7), IBS-diarrhea(14)	21	Randomized cross-over	No significant difference in symptom, fecal weight and pH, whole-gut transit time and fasting breath hydrogen concentrations	Small sample size
Olesen M, 2000 [88]	- Fructooligosaccharide 10 g/day for first 2 week and 20 g/day for the following 10 weeks) or placebo - Evaluation at the 12th week	IBS (Manning criteria)	98	Randomized control trial	No significant difference on symptom at the end but treatment group showed trend to increase flatulence and stool frequency at weeks 4 and 6 of treatment	Higher dose compared to other study

exclusive breast-feeding which may play a significant role in the immune defense mechanism in newborns [82, 83].

Clinical Studies of Prebiotics on Functional GI Disorders

Among FGIDs, there is significant evidence of the effects of gut microbiota in IBS pathogenesis. Alterations of gut microbiota composition and metabolites could contribute to IBS by increasing gut permeability, activating the mucosal immune response, increasing visceral sensitivity and altering intestinal motility [84]. Previous studies based on the analysis of fecal samples have demonstrated a decreased proportion of the genera *Bifidobacterium* and *Lactobacillus* in IBS patients in comparison to healthy subjects. However, there is still a lack of consensus regarding microbiota composition changes among IBS subtypes [85] and limited evidence to sufficiently report the prebiotic effect in IBS patients. A recent randomized controlled study that included 60 constipation, diarrhea and alternating subtype IBS patients to receive either transgalactooligosaccharide 3.5 g/day, 7 g/day or placebo for 4 weeks in cross-over fashion showed that prebiotics significantly improved symptoms and increased fecal *Bifidobacterium* spp. and *Eubacterium rectal/Clostridium coccoides* proportion but decreased the proportion of the *C. perfringens–hystolyticum* subgroup and *Bactriodes/Prevotella* spp. A higher dose improved stool consistency, subjective global assessment and anxiety score but increased bloating symptoms and flatulence compared to a lower dose [86] (see Table 4). A randomized controlled study comparing 5 g short-chain fructo-oligosaccharides with placebo over 6 weeks in 105 patients with mild functional bowel disorders fulfilling the Rome II criteria of IBS, functional abdominal bloating, functional constipation or functional diarrhea showed that fructo-oligosaccharides improved symptoms, improved disease-related quality of life and the performance of daily activities compared to placebo [85]. Two other randomized controlled studies did not show prebiotic benefits in IBS patients [87, 88]. High-dose fructo-oligosaccharide (20 g/day) showed a trend to increase flatulence than placebo in the first 4–6 weeks of treatment [88]. This suggests that high doses of prebiotics should not be recommended for patients with IBS as this may cause more fermentation and bloating and could possibly worsen IBS symptoms. Natural foods such as wheat, bananas, oats, and soy beans contain prebiotics but at only trace levels [74, 75], while many other foods such as yogurt, cereal and bread are fortified with prebiotics, such as inulin, fructo-oligofructose, and galacto-oligosaccharides. Several prebiotic studies used extracted active ingredients from these food products rather than using natural food to avoid side effects from high nondigestible carbohydrate fermentation. Table 4 summarizes the clinical trials of prebiotics in IBS.

In contrast, a recent randomized controlled study showed that a low intake of FODMAPs improved overall gastrointestinal symptoms compared to a normal Australian diet which contains higher FODMAPs in IBS patients [3]. However, the low FODMAPs diet was shown to be associated with a significantly lower total fecal bacterial load by 47 % compared with a normal diet. It lowered an absolute abundance of the butyrate-producing bacteria, the prebiotic bacteria, *Bifidobacterium* spp and the mucus-associated bacterium, *A. muciniphila* which may play a role in gut barrier function. No alteration in fecal SCFA concentration or colonic transit time was shown in either group [89•]. Thus, the risk-benefit of the low FODMAPs in IBS must be elucidated because it caused a significant difference in gut microbiota with putative health benefits.

Due to the advancement of molecular biologic technology on gut microbiota, more bacteria species can be identified and a distinction between physiologic and pathologic changes in the intestinal microbiome can be made [90, 91]. Many other possible un-identified bacteria apart from *Bifidobacterium* and *Lactobacillus* could be affected when using new microbiological study techniques. In addition, it has not been clearly shown whether the colonic microbiota diversity or proportion of certain colonic bacteria may play a role in bowel function in both health and disease. Therefore, more future research is needed as previous reports may have limitations on microbiological studies on identifying the variety of gut microbiota species. This knowledge would help healthcare professionals recognize more substrates or food items that would have better prebiotic effects to improve health.

Conclusions

In summary, there has been increasing scientific evidence on GI health benefits of some food ingredients that have been previously acknowledged in traditional medicine. Chili pepper, a natural capsaicin, demonstrates the effect on TRPV1 receptor desensitization which may modify abdominal burning and pain sensation aggravated by mechanical and chemical stimulation in FGIDs including functional dyspepsia and IBS as well as GERD. Curcumin demonstrates anti-inflammatory effects and may benefit the brain–gut axis. The beneficial effects of prebiotics in FGIDs are still controversial. Low FODMAP diets, which potentially contain less prebiotic effects, significantly improved overall gastrointestinal symptoms in IBS but caused marked changes in fecal microbiota. In contrast, a higher FODMAPs intake was associated with specific stimulation of a particular gut microbiota with colonic health benefits but can produce more intestinal gas and gas symptoms. Current knowledge on the roles of gut microbiota on human health and disease is continuing with advanced techniques for gut microbiota studies. This may help identify dietary ingredients which have prebiotic effects with good fermentation profiles as well as

major health benefits in gut microbiota composition modulation. Thus, more controlled trials on these common foods or ingredients in patients with functional GI disorders are encouraged.

Compliance with Ethical Standards

Conflicts of Interest TP and SG declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent With regard to the authors' research cited in this paper, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. In addition, all applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

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