Functional Gastrointestinal Disorders

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Functional gastrointestinal disorders (FGIDs) are a common disorder characterized by persistent and recurrent gastrointestinal symptoms. This is the result of abnormal gastrointestinal function.

Keywords: irritable bowel syndrome

1. Irritable Bowel Syndrome (IBS)

Irritable Bowel Syndrome (IBS) is a common gastrointestinal condition characterized by chronic or recurrent abdominal pain associated with altered bowel habits. Despite the high prevalence of IBS, which is currently estimated at 5–20% of the population [1], the exact pathophysiology of IBS is not clear [2]. According to the updated Rome III criteria, IBS is a clinical diagnosis and presents as one of the three predominant subtypes: (1) IBS with constipation (IBS-C); (2) IBS with diarrhea (IBS-D); and (3) mixed IBS (IBS-M) Former ROME definitions referred to IBS-M as alternating IBS (IBS-A). Across these IBS subtypes, the presentation of symptoms may vary among patients and change over time. Patients report that the most distressing symptoms are abdominal pain, straining, myalgias, urgency, bloating, and feelings of serious illness [3]. Treatments that target alterations in gut microbiota may be beneficial for patients with IBS [4]. Effective pharmacological therapies for IBS exist, but the duration of most treatment trials is less than 6 months, and so the long-term efficacy of these therapies is unclear [5][6].

Dietary habits and bioactive compounds of several foods may have a positive effect on the composition of human gut microbiota. A class of bioactive compounds that are associated with the treatment of intestinal diseases are probiotics. In particular, probiotics are possible therapeutic factors associated with modification of the gut microbiome for the alleviation of IBS symptoms [7].

1.1. Efficacy of Probiotics in Irritable Bowel Syndrome

A meta-analysis of random clinical trials examined 23 randomized controlled trials to understand whether probiotics are effective therapies for IBS global symptoms. According to the inclusion criteria, the duration of therapy was at least 7 days and the diagnosis of IBS was based on either a physician's opinion or symptoms-based diagnostic criteria, supplemented by the results of investigations to exclude organic disease. Subjects were required to be followed up for at least one week. Nineteen trials used a combination of probiotics, eight trials used *Lactobacillus*, three trials used *Bifidobacterium*, two trials used *E. coli*, one trial used *Streptococcus*, one trial used *Saccharomyces*, and one trial used either *Lactobacillus* or *Bifidobacterium*. In the majority of the trials, probiotics were administered in the form of a capsule. In others, beverages enriched with probiotic strains were used. Specifically, several studies used rose hip drink, fruit drink, malted drink, fermented milk, or a milk- based drink. According to the results, probiotics had beneficial effects on global IBS symptoms (abdominal pain, bloating, and flatulence), or exclusively on abdominal pain, so they could be characterized as effective treatments for IBS. However the, individual species and strains that are the most beneficial remain unclear [8].

Results from a second meta-analysis were in accordance with the above analysis. This meta-analysis demonstrated that combinations of probiotics, or specific species and strains of probiotics, appear to have beneficial effects in IBS in terms of their effects on global IBS symptoms and abdominal pain. Specifically, the seven-strain combination of three *Bifidobacterium*, three *Lactobacillus*, and one *Streptococcus* were associated with significant improvements in global symptoms. Among individual probiotics, *Lactobacillus plantarum*, *Escherichia coli*, and *Streptococcus faecium* also had beneficial effects on global symptoms. The probiotics in the included studies were administered in the form of a drug.

Moreover, in this meta-analysis, randomized placebo-controlled trials examining the effect of at least 7 days of probiotics in adult patients (over the age of 16 years) with IBS were eligible for inclusion. The diagnosis of IBS, based on either a physician's opinion or symptoms-based diagnostic criteria, were supplemented by the results of investigations to exclude organic disease, where the studies deemed this necessary. Subjects were required to be followed up for at least 1 week [9].

Another interesting meta-analysis based on 15 independent studies came to similar conclusions. The fifteen selected trials included the use of the criteria of Rome II, Rome III, the International Classification of Health Problems in Primary Care, and the World Organization of Family Doctors. The quality score of the included trials were assessed and reported according to Jadad quality scoring and all trials had high quality, with scores ranging from 3 to 5. A total of 1793 patients

with diarrhea-predominant IBS (D-IBS), constipation-predominant IBS (C-IBS), and alternative IBS (A-IBS) were included. The probiotics in the included studies were administered in the form of a drug. According to the results, probiotics reduced the pain and symptoms of IBS disease. As in the above studies, there were results that reflected improvement in global symptoms, or exclusively in bloating or flatulence or the stability of intestinal microbiota. Moreover, the results demonstrated the beneficial effects of probiotics for IBS patients, in relation to pain assessment analyses that showed that probiotics significantly reduced pain severity after 8 weeks and 10 weeks of administration. However, the reduction rate was rather higher at week 8 than week 10, suggesting reduced effectiveness with the long-term consumption of probiotics [10].

Another meta-analysis compared the efficacy of a single probiotic, *Bifidobacterium infantis* 35624, to the efficacy of a probiotic blend in patients with irritable bowel syndrome. This included randomized controlled trials that used the Rome criteria I, II, or III for the diagnosis of IBS, and engaged adult participants. Moreover, the subjects had to be followed up for more than 1 week. The probiotics in the included studies were administered in the form of a drug and the duration of the studies was 4 weeks or 8 weeks. According to the results, treatment with the single probiotic *B. infantis* did not impact abdominal pain, bloating/distention, or bowel habit satisfaction among IBS patients. However, patients who received composite probiotics containing *B. infantis* experienced significantly reduced abdominal pain and bloating/distention. These data led to the conclusion that composite probiotics containing *B. infantis* might be an effective therapeutic option for IBS patients, significantly alleviating the symptoms of IBS without significant adverse effects [11].

Another search identified 35 studies, of which 11 met the inclusion criteria and were included. Patients were both males and females, except for one that examined only female participants. According to the inclusion criteria, studies had to be double- or triple-blinded and the diagnosis of IBS was based on the Rome III or Rome IV criteria. The probiotics in the included studies were given in the form of a drug and the examining period ranged from 60 days to 16 weeks. According to the results, seven studies (63.6%) reported that supplementation with probiotics for IBS patients, compared to a placebo, significantly improved symptoms, while the remaining four studies (36.4%) did not report any significant improvement in symptoms after probiotic supplementation. Of note, three of the trials evaluated the effect of a monostrain supplement, while the remaining eight trials used a multistrain probiotic. Overall, the beneficial effects were more distinct in the trials using multistrain supplements, with an intervention of 8 weeks or more, suggesting that multistrain probiotics supplemented over a period of time have the potential to improve IBS symptoms [12].

Finally, a randomized, placebo-controlled group focused on the efficacy of the strains *Lactobacillus paracasei* HA-196 and *Bifidobacterium longum* R0175 in alleviating the symptoms of irritable bowel syndrome. This included a 2-week run-in period, during which regular bowel habits were reported, and an 8-week intervention period, consisting of a total of four clinic visits. Participants were aged 18 years or older and were IBS-diagnosed according to the Rome III criteria. The probiotics in the included studies were administered in the form of a capsule. Each probiotic capsule contained 10×10^9 colony forming units (CFU) of either freeze-dried *B. longum* or *L. paracasei*, with potato starch and magnesium stearate as excipients. The placebo contained only potato starch and magnesium stearate. Both *L. paracasei* and *B. longum* supplementation improved the subjects' quality of life in terms of emotional well-being and social functioning. In conclusion, *L. paracasei* and *B. longum* may reduce the severity of GI symptoms and improve the psychological well-being of individuals with certain IBS subtypes [13].

1.2. Efficacy of Phytochemicals in Treating Irritable Bowel Syndrome

A meta-analysis of collected data from twenty-three randomized controlled trials examined the efficacy and safety of biophenol-rich nutraceuticals in adults with irritable bowel syndrome. Participants in the selected studies were human adults aged ≥18 years with IBS. The types of studies were parallel, or crossover randomized controlled trials (RCTs) and the studies were included if the participants in the intervention group were treated with an orally consumed biophenol-rich nutraceutical with no coadministration of any test product or therapy beyond standard care for more than 1-week. In most of the studies, biophenol-rich nutraceuticals were administered in the form of a capsule. Other studies used aloe vera gel, natural mastiha tablets, fresh juice, or blended essential oils. The studies lasted from 2 to 12 weeks. According to the results, biophenol-rich nutraceuticals may be an effective and safe adjuvant treatment for the management of IBS, with higher certainty of evidence for peppermint oil [14], as further discussed below.

A meta-analysis that specifically examined the efficacy and safety of peppermint oil in patients with IBS was in accordance with the above results. Randomized placebo-controlled trials with a minimum treatment duration of 2 weeks were included in this meta-analysis. Patients had to be IBS-diagnosed according to the criteria of Rome I or II. Specifically, nine studies that evaluated 726 patients were identified and peppermint oil was found to be significantly superior to the placebo for global improvement of IBS symptoms and improvement of abdominal pain. Although peppermint oil patients were significantly more likely to experience an adverse event, such events were mild and transient in nature. The most reported adverse event was heartburn. It is concluded that peppermint oil is a safe and effective short-term treatment for IBS [15].

2. Functional Dyspepsia (FD)

Functional dyspepsia is one of the most prevalent functional gastrointestinal disorders. Functional dyspepsia comprises three subtypes with presumed different pathophysiologies and etiologies: postprandial distress syndrome (PDS),

epigastric pain syndrome (EPS), and a subtype with overlapping PDS and EPS features [16]. Functional dyspepsia affects up to 16% of otherwise healthy individuals in the general population. The pathophysiology remains incompletely understood, but it is probably related to disordered communication between the gut and the brain, leading to motility disturbances, visceral hypersensitivity, and alterations in gastrointestinal microbiota, mucosal and immune function, and CNS processing. A genetic predisposition is probable but less evident than in other functional gastrointestinal disorders, such as irritable bowel syndrome (IBS) [17].

Eating behaviors, irregular meal patterns, and moderate-to-fast eating rates are significantly associated with functional dyspepsia [18]. Many patients recognize meals as the main triggering factor; thus, dietary manipulations often represent the first-line management strategy in this cohort of patients. Nonetheless, little quality evidence has been produced regarding the relationship between specific foods and/or macronutrients and the onset of FD symptoms, resulting in non-standardized nutritional approaches. As a result, most dietary advices are empirical and often lead to exclusion diets [19]. The role of probiotics and phytochemicals in the management of FD is currently unclear, due to the small number of RCTs available to assess the efficacy and safety of those bioactive compounds in patients with FD. However, the role of probiotics and phytochemicals is suggested as a way of treatment, due to the positive effect they may have on gut microbiota.

2.1. Efficacy of Probiotics in Functional Dyspepsia

Clinical trials have been implemented to study the efficacy of probiotics in functional dyspepsia (**Table 1**). A recent single-centered study, with a randomized, double-blind, placebo-controlled, and parallel-group design with open-label extension, showed that *Bacillus coagulans* MY01 and *Bacillus subtilis* MY02 spore-forming probiotics were efficacious and safe in the treatment of functional dyspepsia. In this exploration, scientists showed the efficacy and safety of capsules with *B coagulans* MY01 and *B subtilis* MY02 spore-forming probiotics in patients with functional dyspepsia, compared with a placebo, consumed twice a day for 8 weeks. Specifically, reduced PDS scores were noted for patients with functional dyspepsia, using probiotics versus a placebo. The effects of probiotics on PDS and EPS symptoms were corroborated for the key individual symptoms of the daily diary, compared with a placebo. Moreover, spore-forming probiotics reduced the proportion of positive glycocholic acid breath tests in patients with functional dyspepsia who were on proton-pump inhibitors, suggesting a reduction of small intestinal bacterial overgrowth. Finally, treatment with spore-forming probiotics was well tolerated. Despite the high prevalence of functional dyspepsia, participants experienced potentially beneficial immune and microbial changes, which could provide insights into possible underlying mechanisms as future predictors or treatment targets [20].

Table 1. Studies that summarize the efficacy of probiotics in treating functional dyspepsia.

Study Type	Study Sample/Duration	Participants	Diagnosis of FD	Protocol	Summary of Results	S F
Randomized, double-blind, placebo-controlled trial	68 patients/8 weeks	Adults/both male and female	Rome IV criteria	Probiotics were administered in the form of a capsule	Spore-forming probiotics *Bacillus coagulans* MY01 and *Bacillus subtilis* MY02 as treatment for two subtypes of functional dyspepsia ↓ Beneficial immune and microbial changes as potential treatment targets	
Systematic review and meta-analysis	5 Randomized Controlled Trials	Adults/both male and female	Physician's opinion or symptom-based diagnostic criteria, with a negative upper GI endoscopy excluding an organic cause of dyspepsia	Probiotics were administered in the form of a capsule	Probiotics combination or single strains of *Saccharomyces, Lactobacillus, Bifidobacterium, Escherichia coli* ↓ Probiotics seemed to be effective treatments for FD	
Pilot study	8 patients/7 days	Adults/both male and female	Rome III criteria	Probiotics were administered via extra-virgin oil enriched with probiotics	Extra-virgin oil enriched with probiotics included to patients' diet ↓ Significant improvement of dyspeptic symptoms was observed in subjects receiving	

A meta-analysis exploration examined data for 400 patients with functional dyspepsia who participated to clinical trials. The probiotic group had an improvement in functional dyspepsia symptoms compared to the placebo group. As was

stated in the first exploration, probiotics seemed to be effective treatments for FD. However, the individual species and strains that are most beneficial remained unclear [21].

Moreover, a pilot exploration was conducted in order to examine the role of probiotics in the treatment of functional dyspepsia. It was a small-scale preliminary exploration that lasted 7 days. Eight subjects with functional dyspepsia were examined. According to the protocol, the participants had to include in their diets extra-virgin oil, enriched with probiotics. Despite the short period of consumption of the enriched olive oil, a significant improvement in dyspeptic symptoms was observed in subjects receiving it [22].

2.2. Efficacy of Phytochemicals in Treating Functional Dyspepsia

Several studies aimed to investigate the association between phytochemicals consumption and functional dyspepsia. The latter pilot exploration also examined the role of probiotics in the treatment of functional dyspepsia using extra-virgin oil enriched with antioxidants. In this case, the results were encouraging. However larger studies could better elucidate the role of antioxidants in treating functional dyspepsia [22].

Another randomized, double-blind, and placebo-controlled exploration examined the efficacy of the natural antioxidant astaxanthin in the treatment of functional dyspepsia in patients with or without *Helicobacter pylori* infection. Patients with functional dyspepsia were divided into three groups, with 44 individuals in each group (placebo, 16 mg, or 40 mg astaxanthin, respectively). In general, no curative effect of astaxanthin was found in functional dyspepsia patients. A significantly greater reduction of reflux symptoms was detected in patients treated with the highest dose of the natural antioxidant astaxanthin. The response was more pronounced in *H. pylori*-infected patients [23].

3. Functional Constipation (FC)

Constipation is a heterogeneous, polysymptomatic, multifactorial disease that has several subtypes, such as acute or transient constipation, slow-transit constipation, and functional constipation [24]. Functional constipation (FC) is a very common disorder in children and adults, for which the resolution of symptoms with the currently available therapies is difficult to achieve. The symptoms of the disease vary, but mainly comprise a group of functional disorders that present difficulties in defecation. These disorders include infrequent bowel movements or seemingly incomplete evacuation, hard or lumpy stools, excessive straining, sensation of incomplete evacuation or blockage, and, in some instances, the use of manual maneuvers to facilitate evacuation. In recent years, attention has focused on the use of probiotics, which have proven to be effective in the management of various gastrointestinal disorders [25].

3.1. Efficacy of Probiotics in Treating Functional Constipation

Table 2 summarizes the recent data from clinical trials on the effect of probiotics in treating functional constipation. A randomized clinical trial studied the efficacy of *Lactobacillus paracasei*-enriched artichokes in the treatment of patients with functional constipation. Twenty constipated patients participated in the exploration and each patient was required to consume 180 g per day of ordinary artichokes, or artichokes enriched with *Lactobacillus paracasei* IMPC 2.1, for 15 days (daily dose of 2×10^{10} CFU). This trial showed a positive effect on symptoms in constipated patients after an intake of probiotic-enriched artichokes [26].

Table 2. Studies that summarize the efficacy of probiotics in treating functional constipation.

Study Type	Study Sample/Duration	Participants	Diagnosis of FC	Protocol	Summary of Results	Study Reference
Randomized controlled trial	20 patients/15 days	Adults/both male and female	Rome criteria III for constipation and constipation scoring system (CSS)	180 g probiotic-enriched artichokes	Efficacy of *Lactobacillus paracasei*-enriched artichokes in the treatment of patients with functional constipation ↓ Positive effect on symptoms in constipated patients after intake of probiotic-enriched artichokes	[26]
Randomized controlled trial	180 patients/4 weeks	Adults/both male and female	Rome IV criteria	26 gr chocolate enriched with probiotics	Chocolate enriched with probiotics *Streptococcus thermophilus* and *Lactobacillus plantarum* ↓ Probiotics significantly ameliorated stool consistency in patients with chronic constipation	[27]

Study Type	Study Sample/Duration	Participants	Diagnosis of FC	Protocol	Summary of Results	Study Reference
Randomized controlled trial	**94 patients/4 weeks**	**Adults 18–65 y/both male and female**	**Rome III**	**Probiotics were administered in the form of a capsule**	**Clinical efficacy of a multi-strain probiotic product consisting of *Lactobacillus acidophilus, Bifidobacterium animalis, Bifidobacterium longum* and *Bifidobacterium bifidum*** ↓ **Normalization of stool frequency and consistency, with most participants achieving a normalized profile after 1 week**	[28]
Systematic review and meta-analysis	**14 Randomized controlled trials/1182 patients**	**Adults/both male and female**	**Clinical symptoms, a physician's opinion, or the Rome I, II, or III criteria**	**Probiotics were administered in tablet, powder, capsule, softgel, or fortified food forms**	**Probiotics combination or single strains** ↓ **Probiotics improved whole gut transit time, stool frequency, and stool consistency, with subgroup analysis indicating beneficial effects of *B. lactis* in particular**	[29]

A exploration in a larger population took place some years later and agreed with the above results. In this randomized, double-blind, placebo-controlled exploration, the participants were 180 patients aged 18 to 75, who were required to consume chocolate enriched with probiotics (3.0×10^8 CFU/g *Streptococcus thermophilus* MG510 and 1.0×10^8 CFU/g *Lactobacillus plantarum* LRCC5193) or a placebo, daily for 4 weeks, and who were followed up for a 4-week washout period without intervention. According to the results, probiotics significantly ameliorated stool consistency in patients with chronic constipation. Moreover, the beneficial effect of *L. plantarum* on stool consistency remained after the probiotic supplementation was discontinued [27].

Another randomized controlled trial investigated the clinical efficacy of a multi-strain probiotic product on bowel habits and on the microbial profile in participants with functional constipation. The participants received a placebo or the probiotic product (1.5×10^{10} CFU/day), consisting of *Lactobacillus acidophilus* DDS-1, *Bifidobacterium animalis* subsp. lactis UABla-12, *Bifidobacterium longum* UABl-14 and *Bifidobacterium bifidum* UABb-10 over 4 weeks. According to the results, the probiotic helped to modulate bowel function earlier than the placebo. Specifically, a normalization of stool frequency and consistency was observed, with most participants achieving a normalized profile after 1 week. However, no significant differences were observed in symptomology [28].

A meta-analysis of randomized controlled trials that examined the effect of probiotics on functional constipation in adults was in accordance with the above results. That exploration examined 14 records (1182 patients), and the participants were adult populations with functional chronic constipation as defined by clinical symptoms, a physician's opinion, or the Rome I, II, or III criteria. Probiotics were administered in tablet, powder, capsule, softgel, or fortified food forms and the examining period ranged from 14 days to 8 weeks. According to the results, the probiotics significantly reduced whole gut transit time and increased stool frequency, and this was significant for Bifidobacterium lactis but not for *Lactobacillus casei* Shirota. Moreover, the probiotics improved stool consistency, and this was significant for *Bifidobacterium lactis* but not for *L. casei Shirota* [29].

Finally, several studies that used a probiotic blend or individual probiotic strains did not indicate a difference in symptomology or stool consistency between those who consumed the above probiotics and the controls. After a post hoc analysis, all studies showed improved patient outcomes after specific periods of probiotic consumption [30][31][32].

3.2. Efficacy of Phytochemicals in Treating Functional Constipation

A randomized controlled trial examined how the polyphenol-rich mango (*Mangifera indica* L.) ameliorates functional constipation symptoms in adults, beyond the equivalent amount of fiber. The 4-week consumption of mango fruit (300 g), or the equivalent amount of fiber, was investigated in otherwise healthy human volunteers with chronic constipation, who were randomly assigned to either group. Blood and fecal samples and digestive wellness questionnaires were collected at the beginning and end of the exploration. As presented in **Table 3**, the results showed that mango consumption significantly improved constipation status (stool frequency, consistency, and shape) and increased gastrin levels and fecal concentrations of short chain fatty acid (valeric acid), while lowering endotoxin and interleukin 6 concentrations in plasma [33].

Table 3. Studies that summarize the efficacy of phytochemicals in treating irritable bowel syndrome, functional dyspepsia, and functional constipation.

Study Type	Study Sample/Duration	Participants	FGID	Protocol	Summary of Results	Study Reference
Systematic review and meta-analysis	23 RCTs/ 2–5 weeks	Adults/ both male and female	IBS	Phytochemicals were administered in the form of a capsule, tablet or powder	Biophenol-rich nutraceuticals may be an effective and safe adjuvant treatment for the management of IBS; with higher certainty of evidence for peppermint oil for IBS.	[14]
Systematic review and meta-analysis	9 RCTs/ 726 patients	Adults/ both male and female	IBS/ Rome I or Rome II criteria or clinical symptoms with the exclusion of organic disease	Peppermint oil was administered in the form of a capsule or tablet	Improvement in global symptoms and abdominal pain of patients with IBS.	[15]
Pilot study	8 patients/ 7 days	Adults/ both male and female	FD/ Rome III criteria	Phytochemicals were administered via extra-virgin oil enriched with antioxidants	A significant improvement of dyspeptic symptoms was observed in subjects receiving the antioxidant enriched oil diet. ↓ Normalization of stool frequency and consistency, with most participants achieving a normalized profile after 1 week	[22]
Randomized, double-blind, and placebo-controlled study	132 patients/ 12 weeks	Males and females (non-lactating and non-pregnant) aged 18–70 years	FD/ Rome II criteria	16 mg, or 40 mg astaxanthin in the form of a capsule	Reduction of reflux symptoms was detected in patients treated with the highest dose of astaxanthin while the response was more pronounced in *H. pylori*-infected patients.	[23]
Randomized control trial	48 participants/ 4 weeks	Adults 18–65 yo/ both male and female	Self-reported	300 gr of mango fruit daily	Mango consumption improved constipation status (stool frequency, consistency, and shape) and increased gastrin levels and fecal concentrations of short chain fatty acid (valeric acid), while lowering endotoxin and interleukin concentrations in plasma	[33]

Unfortunately, no additional studies have been found that examine the role of polyphenols or phytochemicals in treating functional constipation, and that meet the inclusion criteria.

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