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# Role of Low FODMAP Diet and Probiotics on Gut Microbiome in Irritable Bowel Syndrome (IBS)

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**Abstract:** Irritable bowel syndrome (IBS) is a chronic disease prevalent in today's society and diet remains the most common aggravator of IBS symptoms. Existing literature suggest that IBS patients are dysbiotic as evidence indicates decreased levels of *Bifidobacteria*, *Bacteroidetes* and *Faecalibacterium prausnitzii* and increased levels of *Firmicutes* in comparison to healthy individuals. Studies suggest that changes in diet can modulate gut microbiota and therefore improve IBS symptoms. The two diets being investigated are the low FODMAP diet and the use of probiotics. A low FODMAP diet implements a reduction in the amount of poorly absorbed carbohydrates and probiotics are live microorganisms that have been proven beneficial when consumed appropriately. Based on the literature acquired from PubMed, a positive correlation appears to exist between the low FODMAP diet and IBS symptoms; 57% report symptom relief. There is also a notable effect on the gut microbiome after changing to low FODMAP diet, noted with a significant decrease in levels of *Bifidobacterium*, *Clostridium*, *F. prausnitzii* and *Actinobacteria*. This poses a concern as bacteria such as *Bifidobacteria* and *F. prausnitzii* are beneficial for health. When probiotics are taken amongst IBS patients a reduction in symptoms is also observed. Additionally, there is an increase in the abundance of *Bifidobacterium* and *Lactobacilli*. It is suggested that co-administration of probiotics with a low FODMAP diet may ensure beneficial levels of *Bifidobacterium* while IBS symptoms ameliorate.

**Keywords:** FODMAP; gut microbiome; probiotics; irritable bowel syndrome (IBS).

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## Introduction

Irritable bowel syndrome (IBS) is a functional bowel disorder and it is more prevalent than one may think. In fact, IBS has a global prevalence of 11% and accounts for up to 60% of outpatient appointments in gastroenterology (Figure 1)[1]. It is a disease that affects between 10–15% of individuals in Western countries, while slightly lower rates are seen in Asia, 2.3–11.5%[2]. While the prognosis for this condition is non-fatal, the impact on an individual's quality of life remains significant; IBS patients are 7.93 times more likely to experience severe pain and discomfort, 2.83 times more likely to complain of issues relating to mobility and 2.39 times more likely to experience anxiety and depression[3].

IBS requires an effective and long-term treatment and existing literature has made it abundantly clear that food is a crucial factor correlating with the presentation and severity of gastrointestinal symptoms; 80% of all IBS patients report being able to identify a minimum of one food item that aggravates their symptoms[4]. Furthermore, this disorder is also known to be influenced by a range of factors such as diet, anxiety, gastrointestinal inflammation and family history, thus may require a more holistic approach in its management. The current practice of management of IBS mainly focuses on relief of symptoms such as abdominal pain in combination with dietary modification including the introduction

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of low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet. On the other hand, some studies have unveiled the relationship between gut microbiome and IBS, suggesting that the imbalance in microbial population may aggravate IBS symptoms[5]. Therefore, these evidence then lead to the idea of probiotics intake as a means to reinstate balance in the microbial balance. Probiotics is thought to prevent bacterial overgrowth by improving gut barrier function and receptor interactions, while at the same time producing a range of protective substance include short chain fatty acids (SCFAs)[6]. Thus, the directive of the current study aims to provide an overview on the role of gut microbiome in IBS, while consolidating the data on how diet modifications, particularly low FODMAP diet and/or intake of probiotics improve IBS via actions on the gut microbiome.

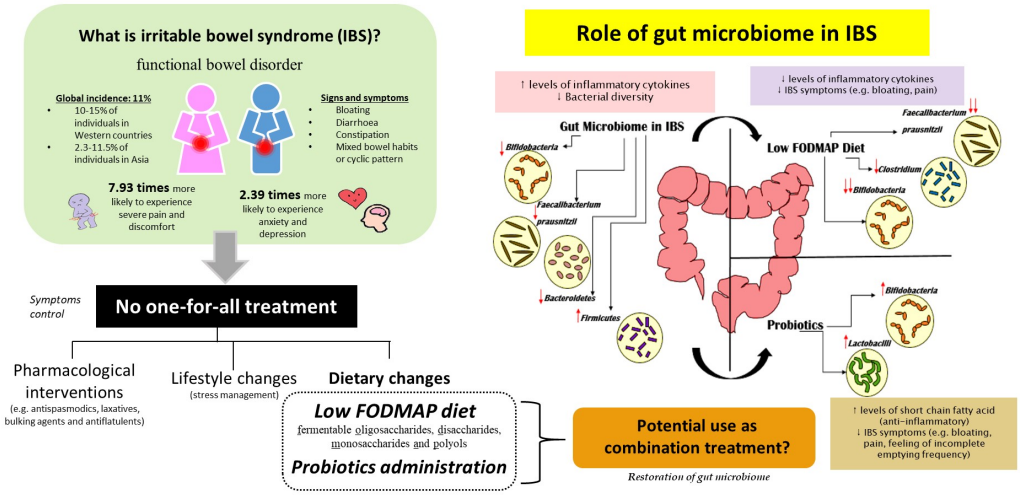


**Figure 1:** Targeting gut microbiome for the treatment of IBS.

## What is irritable bowel syndrome (IBS)?

As one of the most common functional bowel disorders (FBD), the pathogenesis of IBS remains convoluted. Based on the Rome IV criteria, IBS is defined as a FBD which is distinguished by recurrent abdominal pain accompanied with changes in bowel habits and defecation pattern, in addition to symptoms such as bloating[7]. The criteria classifies IBS into subtypes according to the Bristol Stool Scale; IBS with diarrhea (IBS-D), IBS with constipation (IBS-C) and IBS with mixed bowel habits or cyclic pattern (IBS-M)[8]. IBS has been associated with a range of intestinal and extra-intestinal presentations; there is often an overlap between the following three conditions—functional dyspepsia, gastroesophageal reflux disease and IBS[9]. Urological and gynaecological problems also arise in patients with IBS. On top of the associations made with physical health, mental health has been affected in IBS, with cases of depression and anxiety co-existing. The diagnosis of IBS is commonly suspected through extensive history taking; a pattern of intermittent or continuous abdominal pain, relief with defecation, bloating, flatulence and a lack of alarming features (loss of weight, loss of appetite or an abdominal mass) is suggestive of IBS.

The aetiology of IBS is multifactorial and the pathogenesis of the disease is not fully understood. However, some evidence showed the potential role of gut-brain axis in development of IBS. Known as the"second brain", the huge network of neurons lining the gut forms the enteric nervous system which consists of more than 100 million neuronal cells[10]. Evidence suggests that symptoms such as diarrhea and/or pain result from exaggerated responses of the intestine to food or stress and that abnormal mucosal secretions and serotonin uptake by enterocytes cause alterations in gastrointestinal motility[11,12].

Visceral hypersensitivity or pain/discomfort occurs as a result of heightened perception of mechanical triggers applied to the bowel is commonly thought to be the conditions leading to IBS; up to 50% of patients have been found to have increased visceral perception[13,14]. As a matter of fact, gut-brain axis exists as a bidirectional interaction and psychological distress can cause IBS symptoms flare-up and exaggeration[15]. Besides causing activation in immune system, stress could further enhance dysbiosis or imbalance in the microbial population residing in the gut, which then lead to the development of vicious cycle of inflammation[16–20]. Inflammation is another factor in the pathogenesis of IBS as there is increasing evidence of the association between enteric infection and the development of post infectious IBS (PI-IBS) along with studies demonstrating a greater abundance of pro-inflammatory cytokines like IL-1β and IL-8 in IBS patients[20, 21]. An eight-year follow up study conducted by Marshall *et al*. showed that 15.4% of patients (n = 488) were diagnosed with IBS using the Rome I criteria, suggesting an association between enteric infections and persistent IBS symptoms[20]. Nevertheless, the study also noted other significant risk factors for the development of PI-IBS such as anxiety and depression, which is in-line with other evidences proposing participation of gut-brain axis in IBS[21, 22]. Although the exact mechanism remains unclear, the authors suggested an association between enteric infections and persistent IBS symptoms, particularly caused by prolonged alteration in gut microbiota composition and chronic inflammation.

Above all, the current treatment for IBS patients is mainly to relieve symptoms, whereby the first line management primarily attempts to control diarrhea and constipation along with some over-the-counter medications (e.g. non-

steroidal anti-inflammatory drugs, anti-flatulent, bulking agent for diarrhea)[8,23]. On top of that, patients are often advised to change their lifestyles, including stress management and dietary modifications such as high fiber intake, probiotics administration and/or adaptation of a special diet known as the low FODMAP diet. FODMAP refers to a group of carbohydrates, with 1–10 sugars, that are poorly absorbed[24,25]. When ingested, they have an osmotic effect; drawing water into the lumen of the small intestine. In the distal ileum and colon, FODMAPs are fermented to produce short-chain fatty acids and gases such as methane, carbon dioxide and hydrogen. Such products of fermentation result in gastrointestinal symptoms in individuals with existing issues of visceral hypersensitivity and gut motility[23,26]. Another proposed mechanism through which FODMAPs generate gastrointestinal symptoms is through immune activation. Urinary metabolomic profiles of IBS patients were analysed after low and high FODMAP diets. Such an intervention indicated that patients who took a low FODMAP diet demonstrated a slight decrease in urinary histamine levels. In addition, a decrease in inflammatory cytokines IL-6 and IL-8 have also been identified in patients undergoing a low FODMAP diet[27,28]. Nonetheless, FODMAPs may act as prebiotics, inducing growth and/or activities of bacterial in the gastrointestinal tract thereby changing the composition of the gut microbiome[27,29]. So, what is the role of gut microbiome in IBS and more importantly can we tackle the symptoms of this chronic disease by targeting gut microbiome?

## Gut Health: IBS and Microbiome

Out of the 38 trillion bacterial cells living in the human body, more than one-third (33%) of them are residing in the gastrointestinal tract[30,31]. Gut microbiota has multiple functions and proves beneficial for a range of reasons. For instance, gut microbiome serves like a"physical barrier, preventing colonization by harmful pathogen[32]. In reality, gut microbiome was thought to be sterile before birth, but this dogma was challenged numerous times in the past 10 years with studies identifying bacterial DNA and/or their product present in the placenta, amniotic fluid or even meconium[33]. Having said that, the gut microbiome also plays an indispensable role in the development of the immune system; the intestinal mucosa comes in contact with external antigens, presenting antigens and "educating" immune cells on when to attack via binding on receptors (e.g. Toll-like receptor recognition) [32,34]. Several observations in rodent models showed that germ free animals (i.e. absence of microbiota) displayed immunological defects with reduced number of immune cells and abnormal functioning[35].

The connection between the gut and health has been well established for centuries; in 400 B.C. Hippocrates stated that death is in the bowels"and implied that indigestion would be the cause of all illnesses. Thousands of years have passed since then and later in 1916, Ali Metchnikoff suggested that diseases originated from the gut, when bad"bacteria can no longer be controlled. The ideal state in gut microbiome or eubiosis is achieved when there is a balance in bacterial abundance, particularly relative abundance of pathogens that may pose serious infectious risk[36]. In the gastrointestinal (GI) tract, predominant bacterial phyla comprise of *Bacteroidetes* and *Firmicutes*, along with smaller populations of *Fusobacteria*, *Actinobacteria* and *Verrucomicrobia*[37]. Typically, the complex microbial community in gut stabilizes after two to three years of age[38]. Nevertheless, it should be highlighted that variations exist between individuals as a multitude of factors contribute to the microbial composition such as age and diet to name a few[37,39,40].

Dysbiosis in the gut microbiome has been suggested to be associated with a combination of both acute and chronic diseases, or, increase the risk of its development. The different potential mechanisms on how dysbiosis and/or certain metabolites can lead to mucosal leakiness in the gut and promote inflammation milleu in entire body has been actively conversed over the past ten years[41–46]. In the recent years, many researchers have witnessed the changes in gut microbiome and its relationship to the pathogenesis of illnesses, particularly in those with IBS[30,47–51]. In patients with PI-IBS, it is simply obvious that those with history of enteric infection have a higher risk of developing IBS, given that the abundance of microbial population in the gut changed with the colonization of pathogens [51,52]. These patients have been shown to have decreased levels of *Bifidobacteria*, *Bacteroidetes* and *F. prausnitzii* and an increase in the abundance of *Firmicutes*. A 2-fold decrease in *Bifidobacteria* is found in IBS patients compared to healthy controls; *Bifidobacteria* is beneficial to the host as it produces acetic and lactic acid, thereby preventing the growth of pathogenic bacteria and maintaining the immune system[52–54].

Apart from the differences in microbial taxa, studies have also suggested a reduction in microbial diversity, richness and temporal stability. Tap *et al.* found that the severity of IBS symptoms is negatively associated with microbial richness and enterotypes enriched with *Clostridiales*/*Prevotella* species[55]. This was further emphasized by Halkjaer *et al.* whereby IBS patients have a lower stool microbial biodiversity, suggesting an association between IBS and gut microbiome[56]. In conjunction with this, there are some studies suggest that microbial composition varies according to IBS subtypes. In a study conducted by Jeffery and team, *Lactobacilli* was found in greater abundance in IBS-D patients in comparison to IBS-C patients[52]. Additionally, the luminal microbiota of patients with PI-IBS was distinguishable from non-PI-IBS patients, but like those with IBS-D. Furthermore, Kroguis-Kirikk *et al.* found a reduction in microbial diversity in IBS-D patients and this can be related to the reduction in microbial composition identified in patients with acute diarrhea[57]. Conversely, similar results were obtained in animal models of IBS, whereby fecal transplantation using stool from IBS patients induced visceral hypersensitivity in germ-free rats[58].

## Relationship between Low FODMAP Diet and Gut Microbiome

Following the diagnosis of IBS, dietary changes are often crucial steps to control unwanted symptoms such as diarrhea and bloating. The traditional IBS diet focuses a great deal on when and how to eat. Commonly, patients are told to eat 3 meals and 3 snacks a day and to reduce their intake of foods such as coffee, fatty foods, alcohol and spicy dishes[59]. Along with that, since the knowledge of saccharides causes

gastrointestinal symptoms came to light, IBS patients are introduced to a meal plan"with low composition of FODMAP content as these are considered potential triggers[25,30]. In a low FODMAP diet, the daily intake of FODMAPs in an IBS patient is reduced from 15–30 g/d to 5–18 g/d. The execution of this diet requires global restriction for 4–8 weeks followed by reintroduction of food according to a patient's tolerance. As a consequence, this diet is not only "therapeutic" food avoidance plan but can also use as a diagnostic tool to test food intolerance.

The low FODMAP diet can be deemed clinically effective as a total of 50–70% of patients with IBS reported adequate symptom relief, marked by a lower IBS symptom severity score after implementing a low FODMAP diet[1,27,60]. Evidence suggests that gastrointestinal symptoms ameliorate, with reported reductions in bloating, borborygmi, stool frequency, urgency and improvement in consistency[1,59,61]. Taking a closer look at the microbial composition, Hustoft *et al.* indicated that reduction in FODMAP intake (50%) produced a significant change in microbial composition; a 6-fold reduction was observed in those following low FODMAP diet in the relative abundance of *Bifidobacteria*, in comparison to individuals on normal diet (Table 1)[28]. Similarly, Silk *et al.* found that a significant reduction in *Bifidobacteria* abundance was seen following a 3-week implementation of a low FODMAP diet. Differing from Histoft *et al*., this study also found a 47% overall reduction in total bacterial count and a reduction in abundance of other bacterial groups[62]. A significant reduction was found in *Clostridium*, *F. prausnitzii*, *Bifidobacterium*, *Megasphaera*, *Pediococcus* and *Actinobacteria* and patients presented more dysbiotic gut microbiome. Likewise, a study by McIntosh *et al*. highlighted an increase in the relative abundance of bacteria involved in gas consumption in patients on low FODMAP diet[27]. Members of genus *Adlercreutzia* are described as hydrogen "consumers" for equol production, while reducing gas formation and eventually preventing symptoms of bloating and pain simultaneously[27,63].

**Table 1.** Effect of low FODMAP diet on IBS symptoms and gut microbiota.

| Study Design | Methods | Impact of Low FODMAP Diet on IBS symptoms | References |
|---|---|---|---|
| Randomised Controlled Trial | IBS Symptom Scoring System (IBS-SSS) | 57% had adequate pain relief vs control (38%)<br>73% achieved > 50 reduction of IBS-SSS score vs control<br>No significant difference for IBS-QOL | [61] |
| Randomised Controlled Trial | IBS Symptom Scoring System (IBS-SSS) | Mean decrease of 28% vs. control<br>High FODMAP group had a mean increase of 7% in symptoms<br>52% reduction in abdominal pain<br>Positive correlation between IBS symptom severity and level of FODMAP consumption | [27] |
| Randomised Controlled Trial | IBS Symptom Scoring System (IBS-SSS) | Symptom severity was reduced in both groups<br>There was no significant difference between the IBS-SSS scores in both groups compared to baseline.<br>The number of bowel movements reduced in the low FODMAP group compared to the traditional diet group. | [59] |
| **Study Design** | **Methods** | **Impact of Low FODMAP Diet on Gut Microbiota** | **References** |
| Randomised Controlled Trial | 16S rRNA | Increase in the number of dysbiotic patients after the low FODMAP diet (60%)<br>Reduction in *Clostridium*, *Faecalibacterium prausnizii*, *Bifidobacterium*, *Megasphaera*, *Pediococcus* and *Actinobacteria*. | [28] |
| Randomised Cross Over Controlled Trial | FISH | No difference in the relative proportion of each bacterial group at baseline and post intervention.<br>Higher proportions of *Bifidobacterium* spp.<br>Lower proportions of *C. perfingens* subgroup *histolyticum* and *Bacteroides*/*Prevotella* spp. | [62] |
| Randomised Controlled Trial | 16S rRNA<br>Operational Taxonomic Units (OTU) | No difference between α-diversity or β-diversity.<br>Higher *Actinobacteria* richness and diversity<br>IBS-M and IBS-D had higher bacterial richness (*Firmicutes*, *Clostridiales* and *Actinobacteria*).<br>*Actinobacteria* richness was increased | [27] |
| Randomised Controlled Trial | 16S rRNA | Responders had high levels of: *Bacteroidaceae*, Clostridiales (*Ruminococcaceae*, *Dorea* and *Faecalibacterum prausnitzii*) and *Erysipilotrichaceae* | [64] |
| Randomised Controlled Trial | GA-map™ Dysbiosis Test | Responders has a high level of: *Bacteriodes fragilis, Acinetobacter, Ruminiclostridium, Streptococcus* and *Eubacterium.*<br>Responders had lower levels of: Clostridials, *Shigella/Escherichia,* Unable to identify a significant change in dysbiosis. | [65] |

Even so, some researchers argued that the effectiveness of the low FODMAP diet may be dependent upon individual gut microbial composition. Chumpitazi *et al*. conducted a study among children and concluded that 24% of patients who experienced symptom response had a high abundance of *Bacteroides*, *Ruminococcaceae* and *F. prausnitzii*[64]. These findings therefore proposed that the greatest benefit of a low FODMAP diet can be seen in patients who have a high concentration of microbiota with saccharolytic potential. Amongst adults, patients who respond significantly to the diet have been found to have higher levels of *Bacteroides fragilis*, *Acinetobacter*, *Ruminiclostridium*, *Streptococcus* and *Eubacterium*[65].

## Administration of Probiotics in IBS Patients

In IBS patients, several studies have indicated a drop in abundance of certain beneficial microbes or probiotics, particularly those under the phyla *Bifidobacterium* and *Actinobacteria*[51,52,66]. Besides producing lactic acid from digested dietary sugars, some probiotics such as *Lactobacillus*, *Lactococcus*, *Bifidobacterium* and *Streptococcus* are capable of producing small chain fatty acids (SCFAs) like butyrate, propionate and acetate through fermentation of ingested food[67]. SCFAs, in particular butyrate is the primary energy source for colon cells and plays a central role in intestinal maintenance through anti-inflammatory actions[68–71]. In addition to that, one of the most traditional theory on how probiotics confer protection to the host is by displacing pathogenic GI bacteria, preventing their colonization and subsequently re-establishing the balance in gut microbiome.

In the light of current research on IBS, many researchers have reported the benefits of probiotics in IBS patients, particularly in the reduction of IBS symptoms such as abdominal pain and bloating[72–76]. A multicenter studies conducted in India by Ducrotte and team showed that 78.1% of patients consider treatment with *Lactobacillus plantarum* 299v to be effective (Table 2)[73].

**Table 2.** The effect of probiotics on IBS symptoms and gut microbiota.

| Study Design | Methods | | Probiotics intervention (Form: single/multi-strains; Dose; Duration) | Impact of Probiotics on Gut Microbiota | References |
|---|---|---|---|---|---|
| | Monitoring IBS symptoms and quality of life | Monitoring of microbiome | | | |
| Randomised Controlled Trial | Patient Diary; RAND-36 | N.R. | Capsule: *L. rhamnosus* GG, *L. rhamnosus* LC705, *B. breve* Bb99 and *P. freudenreichii* ssp. *shermanii* JS (Valio Ltd, Helsinki, Finland.<br>Equal amount of strain: each $8–9\times10^9$ CFU/day<br>Duration: 6 months | a. 42% reduction in symptom score<br>b. Probiotics appeared to be beneficial for all symptoms.<br>c. Significant reduction in scores for borborygmi | [78] |
| Randomised Controlled Trial | Patient Diary; RAND-36 | Human Intestinal Tract chip (HITChip, Agilent Technologies) | Drink: *L. rhamnosus* GG (ATCC 53103, LGG (Valio Ltd, Helsinki, Finland)), *L. rhamnosus* Lc705 (DSM 7061), *P. freudenreichii* ssp. *shermanii* JS (DSM 7067) and *B. animalis* ssp. *lactis* Bb12 (DSM 15954)<br>Equal amount of strain: each $1\times10^7$ CFU/mL<br>Duration: 5 months | a. Higher mean reduction in IBS score in the probiotic group, recorded at 37%, compared to only 9% reduction in the placebo group<br>b. Health-related quality of life analysis showed improvement in the probiotic group for the domain describing bowel symptoms | [72] |
| Randomised Controlled Trial | Visual Analogue Scale (VAS) | N.R. | Capsule: *L. plantarum* 299v (DSM 9843)<br>Amount: $1\times10^{10}$ CFU/day<br>Duration: 4 weeks | a. 45.2% reduction in mean severity of abdominal pain.<br>b. 78.1% found the treatment good/excellent compared to placebo (8.1%)<br>c. No significant side effects | [73] |
| Randomised Controlled Trial | N.R. | qPCR (Selected bacterial group only) | Capsule: *L. rhamnosus* GG (ATCC 53103), *L. rhamnosus* Lc705 (DSM 7061), *P. freudenreichii* ssp. *shermanii* JS (DSM 7067) and *B. breve* Bb99 (DSM 13692)<br>Equal amount of strain: each $8–9\times10^9$ CFU/day<br>Duration: 6 months | a. Intestinal microbiota remained stable except for *Bifidobacterium* spp.<br>b. Number of *Bifidobacterium* spp decreased | [76] |

| | | | | | |
|---|---|---|---|---|---|
| Randomised Controlled Trial | Clinical assessment at baseline and end of treatment<br><br>Telephone interview (1 month after end of treatment) | qPCR | VSL-3: 9.3 × $10^{10}$ CFU/g of *Bifidobacterium* (*B. longum* Y10, *B. infantis* Y1 and *B. breve* Y8), 2.7×$10^{9}$ CFU/g of *Lactobacillus* (*L. acidophilus*, *L. casei*, *L. delbrueckii* subsp. *bulgaricus* and *L. plantarum*) and 2× $10^{11}$ CFU/g of *Streptococcus salivarius* subsp. *thermophilus.*<br><br>Duration: 20 days | a. Significant increase in Lactobacilli, *Bifidobacteria* and *Streptococcus thermophilus*<br><br>b. No significant changes in enterococci, coliforms, *Bacteroides* and *Clostridium perfingens*. | [82] |
| Randomised Controlled Trial | N.A. | qPCR (Selected bacterial group only) | Capsule: *Lactobacillus rhamnosus* GG, *L. rhamnosus* Lc705, *Propionibacterium freudenreichii* sp. *shermanii* JS and *Bifidobacterium breve* Bb99<br><br>Equal amount of strain: each 8–9×$10^{9}$ CFU/day<br><br>Duration: 6 months | a. Group receiving probiotics appeared to be display lesser monitored IBS-related GI symptoms.<br><br>b. Significant decrease in the amount of *R. torques* 94%, increase in *C. thermosuccinogenes* 85%.<br><br>c. Increased abundance of *Ruminococcus torques* 93%.<br><br>d. *Bifidobacterium* decreased in the probiotic group | [79] |

IBS patients reported overall reductions in stool frequency, bloating and feeling of incomplete emptying frequency after 4-weeks administration of probiotics. Furthermore, there are studies emphasized that multi-strain probiotics have shown a more significant impact on improving gastrointestinal symptoms as compared to single strain probiotics. This is likely due to the fact that more niches are colonized, thus having a greater effect on gut motility[76,77]. A study using a probiotic mixture containing *Lactobacillus rhamnosus* GG*, L. rhamnosus* LC705*, Bifidobacterium breve Bb99 and Propionibacterium freudenreichii* sp. *shermanii* revealed that IBS patients experienced lesser symptoms, achieving a reduction rate as high as 42% in symptom score, whereas the placebo group only reported a 6% reduction[78]. Also, the gut microbiome of IBS patient receiving probiotics was indeed different compared to the placebo as examined using similarity index which compared the stability of the microbiota composition at baseline and post-intervention. Similar observation was obtained by Lyra and team where they observed that probiotics intake reduced amount of *Ruminococcus torques* 94%, which has been associated with gastrointestinal diseases like Crohn's Disease as well as IBS[79–81].

After all these years, the use of probiotics in IBS remains as a compelling topic as some studies did not produce obvious long-term efficacy compared to placebo. For instance, using another commercially available probiotics capsule, VSL-3 which contains *Bifidobacterium*, *Lactobacillus*, *Streptococcus salivarius* subsp. *thermophiles*, Brigidi and team observed an increase in these probiotics, but not other bacterial population such as enterococci, coliforms, *Clostridium perfringens* and *Bacteroides*[82]. The same team also noted that the gut microbial composition returned to initial values once the probiotic had been suspended, indicating that the effects do not persist long term. However, bearing in mind that most of the previous studies investigated these using conventional qPCR targeting genes like 16S–23S ribosomal RNA may not provide a full glimpse of which population changes after intervention. Additionally, most studies have also highlighted that patients can continue with their normal diet, regardless of whether they are taking probiotics or placebo, which may explain for the inconsistencies in data. There are some concerns over the form of probiotics used such as capsule, liquid or powdered form, as studies have pointed out that the delivery systems vary greatly in effectiveness[83]. Nonetheless, with the advancement in next generation sequencing and enhanced computational power, it may be easier to visualize how gut microbiome changes after probiotics intake in IBS patients, and at the same time answer the doubts on whether the observed effect is due to specific strains or a synergistic effect of these probiotics. Consequently, this method would also assist the development of biomarkers to facilitate the detection and/or diagnosis of IBS on top of classic clinical assessment.

## Conclusion and Future Recommendations

It is evident that gut microbiome plays an important role in maintenance of gut health, including IBS. Even though some medications may alleviate symptoms for IBS patients, there is still no one-for-all drug or treatment plan that would work for all of them[59,60]. The low FODMAP diet has shown to be one of the clinically effective strategy by reducing overall symptom severity in multiple studies. By adhering to the low FODMAP diet, patients may not experience symptoms flare-up but it is a challenging diet to adopt in certain regions of the world, particularly limitation of food choices as well as insufficient knowledge in delivery of the diet plan among medical practitioners[84,85]. Some clinicians may doubt its implementation in the long run as a significant reduction in carbohydrates, iron and fiber can lead to other issues like calcium deficiency. While this may be concerning, concurrent use of probiotics along with

low FODMAP diet may really help to ensure beneficial levels of *Bifidobacteria* are maintained. Theoretically, the gut microbiome patients receiving probiotics could make up for the reduced diversity following the restrictive diet, particularly by increasing the abundances of these probiotics[1,76,77]. In actual fact, there are still much to do before researchers could unravel the role of gut microbiome or even specific microbial population in IBS. Amongst existing studies, there is a lack of consistency and clarity which may be attributed by the heterogeneity between them. This heterogeneity exists in variations in individual baseline microbiota, potential microbial differences according to the IBS subtypes, study designs, the methods of analyzing the microbiota composition, the definition of clinical response and the population of selected individuals for the study[4,52]. Above and all, an innovative approach like combining probiotics and low FODMAP diet in combating IBS is clinically applicable with no or minimal side effects. Further investigations incorporating high throughput next generation sequencing technologies, analytical tools like chromatography and mass spectrometry techniques as well as improvement in delivery methods of probiotics may expedite the development of the next effective regime for the management of IBS.

## Conflict of Interest

The authors declare that there is no conflict of interest in this work.

## Author Contributions

The literature review and manuscript writing were performed by SMS and H-LS. SHW and L-HL provided vital guidance of the research and proof of the writing. L-HL and H-LS founded the research project.

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