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How can probiotic improve irritable bowel syndrome symptoms?

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Abstract

The onset and manifestations of irritable bowel syndrome (IBS) is associated with several factors, and the pathophysiology involves various central and peripheral mechanisms. Most studies indicate that the management of gut microbiota could significantly affect the improvement of subjective disorders in patients with IBS. Numerous clinical trials have assessed the efficacy of probiotics for IBS with controversial conclusions. Several clinical trials have suggested that probiotics can improve global IBS symptoms, while others only improve individual IBS symptoms, such as bloating scores and abdominal pain scores. Only a few clinical trials have found no apparent effect of probiotics on IBS symptoms. Generally, probiotics appear to be safe for patients with IBS. However, the question of which probiotics should be used for certain IBS subtypes remains unresolved. In everyday practice, the dose of the recommended probiotic remains questionable, as well as how long the probiotic should be used in therapy. The use of probiotics in the M subtype and non-classified IBS is particularly problematic, in which combination therapy should be recommended due to the change in symptoms. Therefore, new approaches are needed in the design of clinical studies that should address certain subtypes of IBS.

Key Words: Irritable bowel syndrome; Obstipation; Diarrhoea; Abdominal pain; Probiotic; Prebiotic; Symbiotic; Microbiota

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Core Tip: The onset and manifestations of irritable bowel syndrome (IBS) is associated with a number of factors, and the pathophysiology involves various central and peripheral mechanisms. The results of most studies indicate that influencing the gut microbiota could significantly affect the improvement of subjective disorders in patients with IBS. The most important open questions are the design of a clinical study in which the IBS subgroup is not initially defined and whether all IBS subtypes can be treated with the same probiotic or combination of probiotics. IBS subtype-designed clinical studies are urgently needed as a good foundation to define recommendations and guidelines for the use of probiotics in IBS.

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INTRODUCTION

Irritable bowel syndrome (IBS) is a brain-gut disorder characterised by chronic abdominal pain and discomfort that involves a change in the bowel habits and includes the absence of an organic pathological process. Other related symptoms include abdominal distension, bloating, flatulence, diarrhoea, constipation, or a combination of two symptoms. According to these bowel habit patterns, the disease is divided into subtypes: C-IBS (IBS with predominant constipation), D-IBS (IBS with predominant diarrhoea), and M-IBS (IBS with mixed bowel habits) and U-IBS (IBS unclassified). Patients with U-IBS meet the diagnostic criteria for IBS, but bowel habits cannot be accurately categorised into the above explained three subtypes[1,2].

There are no objective tests used to diagnose the disease; therefore, diagnosis is based on symptoms taken as criteria for determining IBS. These symptoms were adopted in 1988 in Rome at the World Congress of Gastroenterologists and revised several times, and based on basic science research and clinical trials, Roman IV criteria were adopted and have been in force since 2016[3,4] (Table 1).

Although the pathophysiology of IBS has not been fully elucidated, nowadays, we can claim with certainty that IBS is an unexplained brain-gut disorder (Figure 1).

The pathophysiology of IBS includes central and peripheral mechanisms. Central mechanisms involve a number of factors, including genetic (mutation of SCN5A, which belongs to a family of genes that provide instructions for making sodium channels) and altered serotonin metabolism; alterations in brain-gut function (stress and visceral hypersensitivity) and dietary influence [gluten and fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs)]. Peripheral mechanisms involve changes in gastrointestinal motility, intestinal permeability, local immune response disorder, low-grade inflammation, disordered bile salt metabolism, post-infectious changes, chronic infections and disturbances in the intestinal microbiota[5,6] (Figure 1).

CHANGES OF THE BOWEL MICROBIOTA AND IBS

Intestinal microbiota has been associated with numerous syndromes and thus, with IBS; therefore, there is a growing interest in modulating the microbiota as one of the treatment options. Because microbiota is connected with the central nervous system across the axis referred to as the gut-brain axis, additional changes in this relationship are imposed as a major factor in the pathophysiology of IBS, which acts through central and peripheral mechanisms and metabolic products of microbes in the gastrointestinal system. This, in turn, causes an altered perception of visceral events, so the individual perceives them as hyperalgesia or allodynia[7-10].

It is estimated that there are more than 100 trillion bacteria in the body of an adult; 80% of which are in the digestive system, which, in turn, contains more than 100 species of bacteria[11]. *Bacteroidetes* and *Firmicutes* predominate, and the amounts of *Proteobacteria*, *Actinomyces*, *Fusobacterium* and *Verrucomicrobia* are relatively small[12].

Table 1 Summary of diagnostic criteria used to define irritable bowel syndrome

Diagnostic criteria	Symptoms included in criteria
Rome 1 (1990)	Abdominal pain or discomfort relieved with defecation; Abdominal pain or discomfort associated with a change in stool frequency or consistency; In addition, two or more of the following on at least 5% of occasions or days for 3 mo: (1) Altered stool frequency and form; (2) Altered stool passage; (3) Passage of mucus; and (4) Bloating or distension
Rome II (1999)	Abdominal discomfort or pain that has two or three features for 1 wk (need to be consecutive) in the last year; Relieved with defecation; Onset associated with a change in the frequency of stools; Onset associated with a change in the form of stools
Rome III (2006)	Recurrent abdominal pain or discomfort three days per month in the last 3 mo associated with two or more of: (1) Improvement in defecation; (2) Onset associated with a change in the frequency of stools; and (3) Onset associated with a change in the form of stools
Rome IV (2016)	Recurrent abdominal pain on average at least 1 d/wk in the last 3 mo, associated with 2 or more of the following ¹ : (1) Related to defecation (<i>i.e.</i> , either increasing or improving pain); (2) Associated with a change in stool frequency; and (3) Associated with a change in stool form (appearance)

¹Criteria fulfilled for the last 3 mo with symptom onset at least 6 mo before diagnosis.

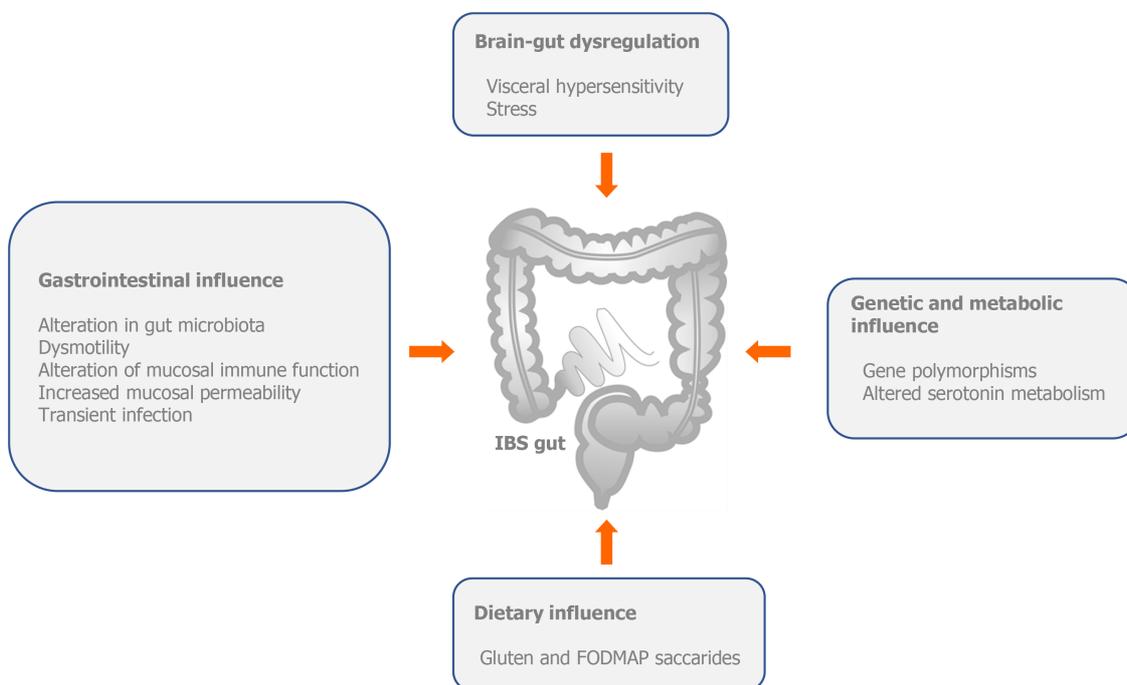


Figure 1 Pathophysiology of irritable bowel syndrome. IBS: Irritable bowel syndrome.

During life, and due to a number of environmental factors, the diversity and numerical proportion of individual strains change and there is a possibility that antibiotics and probiotics may affect the intestinal dysbiosis and microbial imbalance that may exist in IBS. Previous studies indicate a high percentage of dysbiosis in IBS patients compared to the general population[13,14]. Generally, the composition and activities of *Lactobacillus* and *Bifidobacterium* are heavily compromised in IBS patients[15]. Tap *et al*[16] reported that the severity of IBS was positively correlated with low microbial richness, absence of *Methanobacteriales* and the number of *Bacteroides* enterotypes. Pozuelo *et al* [17] found a lower abundance of butyrate-producing and methane-producing bacteria in IBS-D and IBS-M patients. Lower counts of methanogens may explain the symptoms of flatulence or excess gas in the abdomen. Dysbiosis in IBS patients is presented with an increase in abundance of *Proteobacteria* (*Veillonella*) and *Firmicutes* (*Lactobacillus* and *Ruminococcus*) and with decreased *Bifidobacterium*, *Faecalibacterium*, *Erysipelotrichaceae* and methanogens[18,19].

One of the approaches of treating IBS is the rationale use of probiotics due to their potential to correct dysbiosis (qualitative and quantitative changes in the gut microbiota) or stabilise the host microbiota (Figure 2).

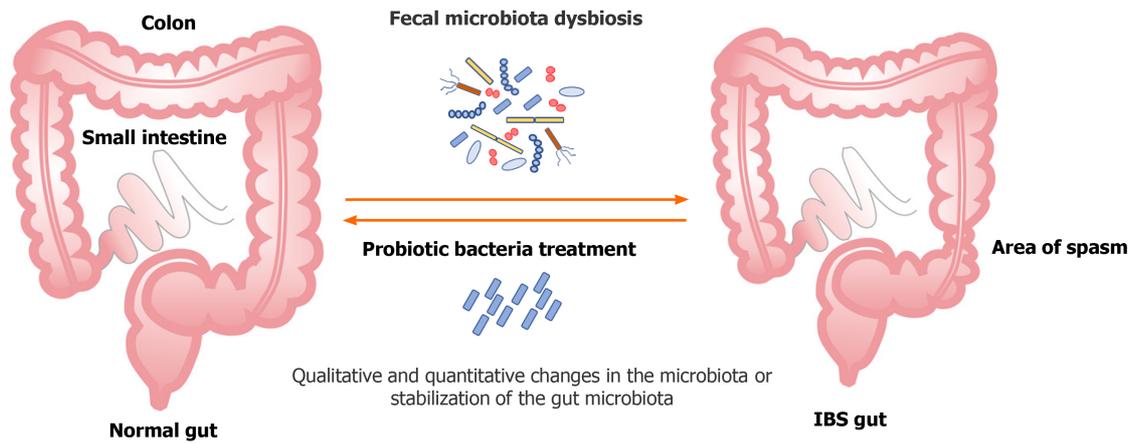


Figure 2 Probiotics in the management of irritable bowel syndrome. IBS: Irritable bowel syndrome.

There are more evidence and assumptions regarding how the gut microbiota is associated with IBS formation, either directly or indirectly. It is known that 10% of patients who develop some forms of IBS previously had an episode of infectious diarrhoea (postinfectious IBS), during which changes in the normal gut microbiota occur[20-22]. An association between broad-spectrum antibiotics and IBS is also described[23]. The microbiota interacts extensively with external factors, which occur due to some forms of diet[24].

BRAIN-GUT DYSREGULATION

Patients with IBS are more likely than healthy populations to develop depression and anxiety, and it is well known that gut microbiota even affects mood and behaviour in humans[25,26]. The microbiota is a separate variable and the axis is called the microbiota-brain axis. The most important communication pathway in this relationship is the tenth cerebral nerve, the vagus nerve. The observed benefits, which arose due to the ingestion of *Lactobacillus rhamnosus* (*L. rhamnosus*) JB-1, resulted in a reduction in anxiety and depression-like behaviour, disappeared after vagotomy in mice. At the brain level, probiotic-induced changes in GABA receptor (receptor for neurotransmitter gamma-aminobutyric acid) expression are also involved in the pathogenesis of anxiety and depression, and disappear in vagotomised mice[27].

After fecal transplantation of microbiota from depressed patients into animals, certain characteristics of depression began to manifest in the recipients (rodents), such as anhedonia and anxiety-like behaviour, and the door to a wide range of assumptions to be investigated opened[28]. An experiment was performed on healthy young students taking probiotic supplements and a reduction in cognitive response to sadness in the form of decreased aggressive thoughts was found after four weeks[29]. As a stress index in some experiments, cortisol level were considered a sign of stress, and levels decreased with improved emotional response in those taking probiotics [30]. These findings, as well as the results of many other studies in the field, were the inspiration for transferring this information to the model of patients with IBS, given the association of the gastrointestinal system, microbiota, brain, and neurotransmitters, which is formed, in part, depending on the composition of microorganisms in the intestine and disturbed axis in these patients.

The high ratio of *Firmicutes:Bacteroides* in patients with IBS correlates with depression and anxiety[31], and the result of an additional study shows that the use of prebiotics (defined as selectively fermented carbohydrate ingredients that cause specific changes in the composition and/or activity of the gut microbiota, and thus contribute to host health[32]) and galactooligosaccharides reduce anxiety for four weeks and has a positive effect on quality of life. Another study included the species *Bifidobacterium longum* (*B. longum*) and measured anxiety, depression, IBS symptoms, somatisation, and quality of life in the first, sixth, and tenth weeks. As early as the sixth week, subjects reported a reduction in depressive symptoms and improvement in quality of life, but there was no effect on IBS symptoms or anxiety. Functional magnetic resonance imaging showed a reduced response to negative emotional stimuli

in multiple areas of the brain, including the amygdala and frontolimbic area. Decreased levels of methylamine and aromatic amino acid metabolites were found in the urine of these subjects[33]. Nitric oxide (NO), carbon monoxide (CO), hydrogen sulfide (H₂S), hydrogen, methane, and ammonia may be of microbial origin and are normally created in our body, but also imported with various external factors, such as a red meat-enriched diet. H₂S gas has been recognised as a neuromodulator/neurotransmitter that influences intestinal inflammation and sensitivity and is a product of the intestinal microbiota. Therefore, it plays an important role in modulating visceral pain[34-39].

THE ROLE OF GUT MICROBIOTA IN VISCERAL SENSITIVITY

It has already been mentioned that there is evidence of direct modulation of several systems involved in visceral hypersensitivity; for example, *via* local expression of cannabinoid receptor type 2 and tryptophan hydrolase 1 isoform, and that patients with IBS, in whom hypersensitivity exists, have functional dysbiosis. Probiotics (*Lactobacillus reuteri*) directly alter the visceral perception of nociceptive stimulants[40]. *Lactobacillus reuteri* inhibits the autonomic nervous system response to colorectal distension in mice[41]. Only a few studies have been performed in humans to confirm these results in animal models. By importing unfermented dairy products containing *Bifidobacterium animalis*, *Streptococcus thermophilus*, *Lactobacillus bulgaricus* and *Lactococcus lactis*, the possibility of influencing the activity of areas of the brain, which control the central processing and processing of emotions and sensations, is opened [42].

THE ROLE OF GUT MICROBIOTA IN INTESTINAL MOTILITY

There are many variables that affect the survival of gut microbiota, especially high oxygen, pH, salt and bile contents, which are all under the influence of intestinal motility.

The change in motility in patients with IBS is manifested by stronger and faster postprandial intestinal muscle contractions in IBS-D and faster passage through the gastrointestinal system and irregular luminal contractions. *Bacteroides thetaiotaomicron* has been shown to alter the expression of a gene involved in neurotransmission and smooth muscle function[43], *Escherichia coli* Nissle 1917[44] improves contractility of colon, and *L. rhamnosus* causes a disorder of contractility stimulated by acetylcholin[45]. Therefore, we can ask ourselves whether the import of probiotics or prebiotics could affect the above mentioned functions *via* bacteria already present in our bowels.

THE ROLE OF MICROBIOTA IN EPITHELIAL BARRIER MODULATION, INTESTINAL INFLAMMATION, AND IMMUNE SYSTEM ACTIVATION

Recent findings suggest that probiotics have a good effect on the stabilisation of gut microbiota in patients with IBS[46] and modulation of the immune response in the form of normalisation of the interleukin (IL)-10/IL-12 ratio produced by mononuclear cells[47]. In patients with diarrhoeal disease, there are indications of disorders of the function of the intestinal mucosal barrier, which is measured by an increase in intestinal permeability. This leads to an increase in the number of T lymphocytes, mast cells, and enterochromaffin cells[48]. These changes indicate that IBS could have a low-grade inflammatory component in pathophysiology. Several sources report the ability of probiotics to modulate the innate and acquired immune responses with a tendency to achieve a balance between proinflammatory and anti-inflammatory cytokines[46]. A possible therapeutic option would be to use probiotics that interact with the host epithelium to resolve possible inflammation and preserve barrier function. It has been shown that, in adults, *Lactobacillus gasseri* KS-13, *B. longum* MM2 175, and *Bifidobacterium bifidum* G9-1 change the profile of cytokines by stimulating the production of less inflammatory cytokines[49]; and *Saccharomyces boulardii* reduces pro-inflammatory IL-8 and tumor necrosis factor alpha and increases the level of anti-inflammatory IL-10 [50]. The authors of one study[51] concluded that the use of probiotics resulted in reduced intestinal barrier permeability, which may be consistent with these claims.

POSSIBLE THERAPEUTIC OPTIONS AND OBJECTIVES IN THE TREATMENT OF IBS WITH PROBIOTICS

One of the generally accepted definitions of probiotics is that they are living microorganisms that contribute to the well-being and health of a host when administered in an adequate dose[52]. *Lactobacillus* and *Bifidobacterium* are the most common species that are put in the center of studies in the context of IBS because of their numerical superiority over the rest, as well as the number of aerobes *vs* anaerobes[53,54]. In 2007, Rousseaux *et al*[55] demonstrated that direct contact of certain probiotic bacteria [*Lactobacillus acidophilus* (*L. acidophilus*)] with epithelial cells induces the expression of opioid and cannabinoid receptors in the gut and contributes to the modulation and restoration of the normal perception of visceral pain. Lactic acid bacteria (LAB) are currently the most widely studied, and this group of probiotics consists of approximately 20 genera. The most common are *Aerococcus*, *Carnobacterium*, *Enterococcus*, *Lactobacillus*, *Lactococcus*, *Leuconostoc*, *Oenococcus*, *Pediococcus*, *Streptococcus*, *Tetragonococcus*, *Vagococcus* and *Weissella*. *Bifidobacterium* species does not belong to this group and has its own mode of sugar fermentation[56]. LABs are part of the gut microbiota, and they have antimicrobial action because they create an unsuitable environment for the growth of undesirable microorganisms, compete for nutrients and binding sites to the intestinal epithelium, produce products of toxic microbes for foreign microbes and prevent pathogens from settling and feeding in our bodies[57].

EFFECT OF PROBIOTICS ON OVERALL IBS SYMPTOMS

Several studies had their limitations in the form of inconsistencies in reports, variable treatment periods, small number of subjects and heterogeneous groups of patients, according to the form of the syndrome (diarrhoeal/constipation). *In vitro* and *in vivo* studies have shown that the probiotic combination VSL#3 [*L. acidophilus*, *Lactobacillus plantarum* (*L. plantarum*), *Lactobacillus casei* (*L. casei*), and *Lactobacillus delbrueckii subspecies bulgaricus* (*L. delbrueckii spp. bulgaricus*), *Bifidobacterium breve* (*B. breve*), *B. longum*, and *Bifidobacterium infantis* (*B. infantis*) and *Streptococcus salivarius ssp. thermophilus*] is likely to modulate the host immune response, intestinal microbiota, anti-inflammatory pathways, responses to visceral pain, and epithelial barrier function[58-62]. It also has different effects on different types of disease. Kim *et al*[63] found that the combination of probiotics VSL#3 slowed intestinal passage compared to placebo, indicating that the aforementioned probiotic is likely to have a better effect on the diarrhoeal form of the disease. The diversity and richness of gut microbiota has been shown to be associated with slower intestinal passage[64], whereas in softer stools, this diversity is significantly reduced[65].

Several studies have included a prepared, specific combination of eight different strains, consisting mainly of LAB and *Bifidobacterium* (including *B. longum*, *B. infantis*, *B. breve*, *L. acidophilus*, *L. casei*, *L. delbrueckii spp. bulgaricus*, *L. plantarum* and *Streptococcus salivarius*), that showed efficacy in patients with IBS in the form of reduction of bloating and abdominal symptoms[66-70].

The most commonly used probiotic bacteria in studies are *Lactobacillus*, *Bifidobacterium*, *Enterococcus* and *Streptococcus*, and in most studies that included these probiotics, there was a marked improvement in the reduction of abdominal pain and discomfort. Individual studies and the applied probiotic species/strains and the results are shown in Table 2. Diagnostic criteria of IBS were Rome III and IV, with duration of therapy of at least six weeks.

The results of several dozen examined studies showed a reduction in abdominal distension and bloating. In a meta-analysis of 42 randomised controlled trials, 34 reported improvements in at least one symptom[90]. No significant difference was observed in the individual groups of probiotics used: *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, or in a combination of the above[47,49,91,92]. The main limitation of most of the clinical studies is that the patient groups were heterogeneous; however, the overall result of all the analyses was the alleviation of general symptomatology.

A meta-analysis of the efficacy of *B. infantis* 35624 in the IBS was performed. As in the studies already mentioned, the efficacy targets were symptoms related to abdominal pain, bloating and bowel emptying habits, and respondent satisfaction with the management of these symptoms. The analysis included three studies conducted based on the use of *B. infantis* and two additional probiotics. The results showed a significant improvement in all examined parameters in terms of the mixture of probiotics together with *B. infantis*, but not equally effective if *B. infantis* was solely

Table 2 Outcomes of randomized controlled trials of probiotics versus placebo in different type of irritable bowel syndrome

Ref.	Type of IBS (%)	Sample size	Probiotic	Outcome by the type of IBS (probiotic group)	Common outcome (probiotic group)
Sinn <i>et al</i> [71], 2008	D: 20; C: 27; M: 62.5	40	<i>L.acidophilus</i> SDC 2012, 2013	Not specified	Reduction of abdominal pain (28%), bowel habit satisfaction (18.2%), reduction of straining at stool (25.4%)
Hong <i>et al</i> [72], 2009	D: 45.7; C: 20; M: 8.6; Non classified: 25.7	70	<i>Bifidobacterium bifidum</i> BGN4, <i>B. lactis</i> AD011, <i>Lactobacillus acidophilus</i> AD031, <i>L. casei</i> IBS041	Not specified	Reduction of pain score (-31.9), defecation and discomfort (-29.2), no significant change in QOL and bowel habits (defecation frequency and stool consistency)
Guglielmetti <i>et al</i> [73], 2011	D: 21.3; C: 19.7; M: 58.2; NC: 0.8	122	<i>Bifidobacterium bifidum</i> MIMBb75	Not specified	Improved global IBS symptoms by -0.88 points, reduction in pain/discomfort by -0.82 points, distention/bloating by -0.92 points, urgency by -0.76 points (Likert scale)
Cui and Hu [74], 2012	D: 48.3; C: 20; M: 11.7; NC: 10	60	<i>Bifidobacterium longum</i> and <i>Lactobacillus acidophilus</i>	Not specified	Improvement in frequency of abdominal pain (23% vs 6%), abdominal distension (27% vs 7%), bowel habits (26% vs 8%), dissatisfaction with defecation (20% vs 10%).
Dapigny <i>et al</i> [75], 2012	D: 30; C: 22; M: 34; NC: 14	50	<i>Lactobacillus casei rhamnosus</i> LCR35	D: significant reduction in abdominal pain; M: no relevant difference between groups	No clinically relevant changes overall
Ducrott��t <i>et al</i> [76], 2012	All types	214	<i>Lactobacillus plantarum</i> 299v	Not specified	Mean frequency of abdominal pain was reduced significantly by 51.9%, reductions in stool frequency, bloating and feeling of incomplete emptying, significant reduction of the daily number of stools
Amirimani <i>et al</i> [77], 2013	All types	102	<i>Lactobacillus reuteri</i>	Not specified	Increased frequency of defecation, no significant difference in bloating, urgency, abdominal pain, stool shape. Study did not classify between D and C subtype
Begtrup <i>et al</i> [78], 2013	D: 40; C: 19; M: 38; NC: 2	131	<i>L. paracasei ssp paracasei</i> F19, <i>L. Acidophilus</i> ; La5 and <i>Bifidobacterium</i> Bb12	Not specified	Adequate relief of symptoms at least 50% of the time (52% vs 41%), No difference in diarrhea, bloating and satiety
Roberts <i>et al</i> [79], 2013	D and C	179	<i>Bifidobacterium lactis</i> CNCM I-2494, <i>S.thermophilus</i> , <i>L.bulgaris</i>	Not specified	Improvements in symptoms scores, bloating, flatulence, ease of bowel movement and quality of life (48% vs 33%)
Jafari <i>et al</i> [80], 2014	All types	108	Probio-Tec [®] Quatro-cap-4	Not specified	Decrease in VAS score for abdominal pain and bloating, decrease in feeling incomplete defecation
Ludidi <i>et al</i> [81], 2014	All types	40	<i>Bifidobacterium lactis</i> W52, <i>Lactobacillus casei</i> W56, <i>L. salivarius</i> W57, <i>Lactococcus lactis</i> W58, <i>L. acidophilus</i> NCFM, and <i>L. rhamnosus</i> W71	Not specified	Decrease in visceral hypersensitivity in both groups, decreased pain in both groups, no significant difference in overall symptom improvement
Pedersen <i>et al</i> [82], 2014	D: 38; C: 17.3; M: 40.7; NC: 4	81	<i>Lactobacillus rhamnosus</i> GG	Not specified	Improvement in IBS-SSS score nad QOL score. Low FODMAP diet showed efficient in IBS-C, and probiotic in IBS-D
Sisson <i>et al</i> [83], 2014	D: 37.6; C: 21.5; M: 35.5; NC: 5.4	186	<i>Lactobacillus rhamnosus</i> NCIMB 30174, <i>L. plantarum</i> NCIMB 30173, <i>L. Acidophilus</i> NCIMB 30175, <i>Enterococcus faecium</i> NCIMB 30176	Not specified	Reduction in IBS-SSS score (abdominal pain, bloating, bowel habit satisfaction)-63.3 vs -28.3. No difference in QOL score
Yoon <i>et al</i> [84], 2014	D: 53.1; C: 40.8; M: 6.1	49	<i>Bifidobacterium bifidum</i> (KCTC 12199BP), <i>B. lactis</i> (KCTC 11904BP), <i>B. longum</i> (KCTC 12200BP), <i>L. acidophilus</i> (KCTC	Not specified	Global relief of IBS symptoms (68% vs 37.5%), reduced abdominal pain and discomfort. No difference in

			11906BP), <i>L. rhamnosus</i> (KCTC 12202BP) and <i>Streptococcus thermophilus</i> (KCTC 11870BP)		stool consistency. Changes in the fecal microbiota genome (detected by PCR test)
Pineton de Chambrun <i>et al</i> [85], 2015	D: 28.5; C: 46.9; M: 24.6	179	<i>Saccharomyces cerevisiae</i> CNCM I-3856	Not specified	Same results regarding abdominal pain and discomfort in both groups, but probiotic group showed improvement in during the second month of use
Yoon <i>et al</i> [86], 2015	D: 48.1; C: 18.5; M: 21; NC: 12.4	80	<i>Bifidobacterium bifidum</i> (KCTC 12199BP), <i>B. lactis</i> (KCTC11904BP), <i>B. longum</i> (KCTC 12200BP), <i>Lactobacillus acidophilus</i> (KCTC 11906BP), <i>L. rhamnosus</i> (KCTC 12202BP), <i>Streptococcus thermophilus</i>	Not specified	Increase in probiotic strains in stool samples, higher adequate symptom relief (but not statistically relevant), improvement in the diarrhea symptom score
Lyra <i>et al</i> [87], 2016	D: 38.9; C: 16.6; M: 44; NC: 0.5	391	<i>Lactobacillus acidophilus</i> NCFM (ATCC 700396)	Not specified	No difference in both groups in IBS-SSS score
Spiller <i>et al</i> [88], 2016	D: 20.8; C: 47.4; M: 31.7	379	<i>Saccharomyces cerevisiae</i> I-3856	Reduced abdominal pain and bloating in IBS-C	No overall benefit in all subtypes, but significant improvement in C subtype
Preston <i>et al</i> [89], 2018	D: 46.4; C: 35.7; M: 18.6	113	<i>Lactobacillus acidophilus</i> CL1285, <i>L. casei</i> LBC80R, <i>L. rhamnosus</i> CLR2	Improvement of IBS-SSS score for female D subtype by 50% to 144%. Better satisfaction with bowel habits in C subtype. Better QOL in IBS-D females. Impruvment in number of days without pain M subtype	No improvement in IBS-SSS score overall or QOL overall

IBS: Irritable bowel syndrome; IBS-SSS: Irritable Bowel Syndrome Severity Scoring System; NC: Non classified irritable bowel syndrome; D: Diarrhea irritable bowel syndrome; C: Constipation irritable bowel syndrome; M: Mixed irritable bowel syndrome; QOL: Quality of life.

used. According to that analysis, treatment with a mixture of probiotics that also contain this bacterium could have an effect in treating the disease. However, it should be considered that the number of participants in the examination was too small, and certainly, the stated claims should be further examined[50].

An interesting fact is the analysis of several studies that show that the use of one probiotic, rather than a combination of several, taken in a short period and in a low dose, proved to be better in the final general condition, general feeling of patients after treatment (testing) and improvement in their quality of life. Yoon *et al*[84] hypothesised that multi-strain-containing probiotics may result in different effects and benefits on IBS symptoms, as each bacterial species produces a different effect in the gastrointestinal system, and two or more probiotic species in combination have a synergistic effect. However, research has also shown that competition between introduced combined species or strains is possible, which can lead to negative effects. Analysis of gut microbiota before and after probiotic administration showed that different strains have different viabilities and overdoses can disturb living conditions by competition[81].

EFFECT OF PROBIOTIC DOSE ON IBS SYMPTOMS

The question of the dosage of the individual probiotics that needs to be applied to achieve the final desired effects was raised. Initially, an answer is not offered; significant is that an adequate dose is needed for the desired effect. There are several variables that could affect the effective dose of probiotics: Desired effect, specific strain, probiotic carrier, and the mode of application. In a unique study, the combination of two strains of *L. plantarum* and one strain of *Pediococcus acidilactici* (confirmed to reduce inflammation and frequency of diarrhoea in animal models of intestinal inflammation) were applied in two doses: $1-3 \times 10^{10}$ CFU (colony forming unit) per capsule and $3-6 \times 10^9$ CFU per capsule, in equal representation of each probiotic. The results are such that all patients, regardless of the dose of I.31 (as the combination of probiotics is called), indicating that the achievement effect is attained even at lower values, reported a better quality of life after three weeks of intolerance to mixtures, while reduction of anxiety was reported only after six weeks. Interestingly, the effect was achieved earlier when a higher dose was administered[93]. We must, however, emphasise that although the authors claim they tested high and low doses of

probiotics, 10^9 bacteria per capsule can in no way be considered low dose. The difference between these two doses is too small and the authors should have used a slightly lower dose to examine whether probiotic dose influences IBS.

Liang *et al*[94] analyzed several clinical trials, with a primary goal to clarify the effective dose of applied probiotics which, in this case, is a combination of *Lactobacillus* and *Bifidobacterium*. Their conclusion is comparable to previous studies, with an observed improvement in global symptoms that was achieved even at low doses. In most studies, a dose of 10^9 CFU/d to 10^{10} CFU/d of the tested strains is the recommended dose, based on comparisons of the accompanying studies.

According to Lorenzo-Zúñiga *et al*[93], probiotics do not follow pharmacological rules in achieving the effect of saturation, but this effect is attained according to the principle of synergism or antagonism, in which negative effects are caused. High doses of probiotics can cause short-term discomfort in the gastrointestinal system due to excessive fermentation of carbohydrates, which is a feature of the most studied and represented strains in patients with IBS[95].

In other medical cases, conditions and diseases, the doses of specific probiotic strains have been studied. Namely, the results of one study showed that *L. rhamnosus* GG has a greater effect in acute gastroenteritis in children when administered at a dose greater than 10^{10} CFU/d[96]. *S. boulardii* administered in patients with diarrhoea, after low and high doses, achieved an equal effect[97]. In addition, no difference was found in the dose-dependent effect for *Lactobacillus reuteri* DSM17938 on diarrhoea[98].

In 2006, in a meta-analysis of antibiotic-related diarrhoea and necrotising enterocolitis, a result based on 25 studies involving 13 probiotic products reported that probiotic doses less than 10^{10} CFU did not result in treatment success. The results were confirmed in later meta-analyses[99].

APPLICATION OF PROBIOTICS IN TREATMENT OF C-IBS

Significantly less research regarding the effectiveness of probiotics have been conducted in patients with C-IBS. Based on the Bristol stool scale, study participants described their stool as hard or lumpy ($\geq 25\%$ of all stools) and fluffy or watery ($< 25\%$ of all stools).

It is known that in these patients, there exists an increased number of bacteria that produce methane[100] and the amount of gas released is directly correlated with the severity of severe constipation[101], which is consistent with the slower passage through the intestine in these cases, with reduced segmental contraction and attenuated propulsion. Given these facts, the effect of *B. lactis* DN-173 010 on distension, bloating, and other IBS symptoms was examined[102]. Patients complained of a visible increase in abdominal volume at least twice a week and met other Roman III. The dose of *B. lactis* was 1.25×10^{10} CFU/g, and *S. thermophilus* and *L. bulgaricus* (1.2×10^9 CFU/g) were added; in fact, fermented milk and yogurts were found to contain these probiotics. The results showed that fermented dairy products reduced abdominal distension and accelerated intestinal passage. Reduced bloating was also reported, as were other IBS symptoms. There are fewer studies involving subjects who have constipation-like problems, and one of these studies was published in 2014. The results are impressive and show that probiotics have significantly reduced the passage time by 12.4 h and increased stool frequency by 1.3 wkly bowel movements. Success is related to the administration of *B. lactis* (increasing weekly bowel movements by 1.5 movements), but not to *L. casei* Shirota (recorded decreased weekly bowel movements per week to 0.2). Stool consistency was better during intake of *B. lactis*, but not *L. casei* Shirota strain[103]. Health-related quality of life was also a frequently examined aspect in patients, making it the primary subject of the study by Guyonnet *et al*[104], because they believed that the patient's perception of symptoms and the impact of difficulties on daily life are extremely important. In general, patients with more severe disease and frequent symptomatology felt relief, but were reluctant to report it. This was in contrast to those subjects who had moderate or mild disease and did not experience significant improvement, but reported a change in symptom severity. Interestingly, in a number of studies, placebo groups also reported positive effects, which is an increasingly central point of the study (Table 3).

Table 3 Outcomes of randomized controlled trials of probiotics versus placebo in the C and D type of irritable bowel syndrome

Ref.	Type of IBS	Sample size	Probiotic	Outcome by the type of IBS (probiotic group)
Agrawal et al [102], 2009	C	34	<i>Bifidobacterium lactis</i> DN-173 010	Reduction in bloating and distension (-1.52 cm), reduction of oro-caecal (-1.2 h) and colonic (-12.2 h) transit times, reduction of pain and discomfort (-0.5)
Michail et al [105], 2011	D	24	VSL#3: <i>Lactobacillus acidophilus</i> , <i>L. plantarum</i> , <i>L. casei</i> , and <i>L. delbrueckii ssp. bulgaricus</i> , <i>Bifidobacterium breve</i> , <i>B. longum</i> , and <i>B. infantis</i> and <i>Streptococcus salicarius ssp. thermophilus</i>	Significant decreases in the bloating, diarrhea, satiety and QOL in both groups (placebo and probiotic)
Ki Cha et al [106], 2012	D	50	<i>Lactobacillus acidophilus</i> , <i>L. plantarum</i> , <i>L. rhamnosus</i> , <i>Bifidobacterium breve</i> , <i>B. lactis</i> , <i>B. longum</i> and <i>Streptococcus thermophilus</i>	Symptoms (abdominal pain, abdominal discomfort, loose/watery stool, urgency, mucus in stool, bloating, and passage of gas) relief was higher (> 50%), improved stool consistency
Abbas et al [50], 2014	D	72	<i>Saccharomyces boulardii</i>	Decrease in the blood and tissue levels of proinflammatory cytokines IL-8 and TNF- α and increase in the anti-inflammatory IL-10, improvement in body image and food avoidance
Lorenzo-Zúñiga et al [93], 2014	D	84	<i>Lactobacillus plantarum</i> (CECT7484 and CECT7485), <i>Pediococcus acidilactici</i> (CECT7483)	Improved QOL score, improvement in gut-related anxiety (VSI scale)
Majeed et al [107], 2016	D	36	<i>Bacillus coagulans</i> MTCC 5856	Decrease in bloating, diarrhea, vomiting, abdominal pain, improvement in Bristol stool score
Mezzasalma et al [108], 2019	C	150	<i>Lactobacillus acidophilus</i> , <i>L. reuteri</i> , <i>L. s plantarum</i> , <i>L. s rhamnosus</i> , <i>Bifidobacterium animalis subsp. lactis</i>	QOL improved in probiotic group, increased healthier characteristic in stool samples
Hod et al [109], 2017	D	107	<i>Lactobacillus rhamnosus</i> LR5, <i>L. casei</i> LC5, <i>L. paracasei</i> LPC5, <i>L. plantarum</i> LP3, <i>L. acidophilus</i> LA1, <i>Bifidobacterium bifidum</i> , BF3, <i>B. longum</i> BG7, <i>B. breve</i> BR3, <i>B. infantis</i> BT1, <i>Streptococcus thermophilus</i> ST3, <i>L. bulgaricus</i> LG1, <i>Lactococcus lactis</i>	No difference between groups overall, no CRP and fecal calprotectin levels difference
Ishaque et al [110], 2018	D	360	Bio-Kult®	Reduced overall IBS-SSS score by 145 point in 30 d, reduced number of bowel movements, symptom free patients (33.7% vs 12.8%)
Khodadoostan et al [111], 2018	D	67	<i>Lactobacillus casei</i> , <i>L. acidophilus</i> , <i>L. rhamnosus</i> , <i>L. bulgaricus</i> , <i>Bifidobacterium breve</i> , <i>B. longum</i> , and <i>Streptococcus thermophilus</i> with prebiotic of ructooligosaccharides	Improvement in stool consistency and defecation rate after 3 mo, decrease in abdominal pain after 6 mo
Sun et al [112], 2018	D	200	<i>Clostridium butyricum</i>	Reduction in IBS-SSS score (-62.12 vs -40.74), no difference in abdominal pain and bloating, improvement in QOL, no change in Bristol stool scale.

IBS: Irritable bowel syndrome; IBS-SSS: Irritable Bowel Syndrome Severity Scoring System; D: Diarrhea irritable bowel syndrome; C: Constipation irritable bowel syndrome; QOL: Quality of life.

APPLICATION OF PROBIOTICS IN TREATMENT OF D-IBS

The symptoms of this form of the disease are similar to those in other subtypes, with more frequent bowel movements and increased peristalsis, which results in softer stools or diarrhoea. It is also characterised by the urgency for defecation. According to the Bristol stool scale, patients define this form of the disease as the presence of fluffy or watery stools ($\leq 25\%$ of all stools) and hard or lumpy stools ($< 25\%$ of all stools). When using a mixture of *L. plantarum* (5×10^7 CFU/mL) and 3.6 g of fibre, the results showed that the presence of gas/wind was significantly lower, intensity of abdominal pain was reduced and overall function of the gastrointestinal system was much better after one year of using symbiotics [113]. These effects can be explained by slowing down the passage through the intestine, facilitating the flow, electrolyte reabsorption and consequently, reducing diarrhoea. The combination of the probiotics *L. acidophilus*, *L. plantarum*, *L. rhamnosus*, *B. breve*, *B. lactis*, *B. longum* and *S. thermophilus* in a dose of 1.0×10^{10} CFU also produced promising results. The application lasted for eight weeks, and the effect manifested as alleviation of overall symptoms and improvement in stool consistency, although no specific effect on individual symptoms was observed [106]. However, regarding the primary symptom of this subgroup, diarrhoea, probiotics did not prove effective in reducing the number of diarrhoeal stools. Several studies have been conducted, testing different probiotics, but the results have not been successful [46,78,114]. Moreover, in one study, an even more significant

deterioration was reported[115]. In contrast, in this subtype of disease, *Bacillus coagulans* MTCC 5856, at a dose of 2×10^9 CFU/d for 90 d of use, proved to be quite successful. All symptoms in patients belonging to the D-IBS group were significantly alleviated, including diarrhoea[107].

The aim of one study was to evaluate the change in the frequency and intensity of abdominal pain in patients with a predominantly diarrhoeal form of the disease. A combination of strains were evaluated in the study: *Bacillus subtilis* PXN 21, *B. bifidum* PXN 23, *B. breve* PXN 25, *B. infantis* PXN 27, *B. longum* PXN 30, *L. acidophilus* PXN 35, *L. delbrueckii* spp. *bulgaricus* PXN39, *L. casei* PXN 37, *L. plantarum* PXN 47, *L. rhamnosus* PXN 54, *L. helveticus* PXN 45, *L. salivarius* PXN 57), *Lactococcus lactis* PXN 63, and *S. thermophilus* PXN 66 at 2 million colonies per capsule, twice daily for 16 wk. After this treatment, patients reported a reduction in the intensity of abdominal pain, as well as other symptoms comprising the IBS-SSS (Irritable Bowel Syndrome Severity Scoring System), including the intensity of abdominal pain, number of days of abdominal pain during the last 10 d, severity of abdominal distension, discomfort during urination, and reduced quality of life. The participants were examined every month for five months, and during these controls, the results showed an improvement in all examined elements of the disease, compared to the initial condition and results of the group of patients receiving placebo. This study included a large number of subjects (360 patients) that were relatively homogeneous with a certain subtype of the disease, resulting in a more relevant study compared to a large number of other processed analyses[110]. In Figure 3, exhibited is the effect of probiotics on different IBS type symptoms.

THE ROLE OF PREBIOTICS ON IBS SYMPTOMS

Unlike probiotics, prebiotics are not metabolised in the intestines of the host, and their ultimate purpose is to positively impact the microenvironment of the digestive system. The best known prebiotics are oligofructose, inulin, galactooligosaccharides, lactulose, and oligosaccharides from breast milk. In fact, these compounds are an integral part of the food we eat every day. Some of the positive effects include an increase in the number of bifidobacteria, calcium absorption, and fecal mass, shortening of the retention time of fecal mass in the intestines, and a possible decrease in blood lipids [32]. Several studies have investigated the effect of prebiotics[47], revealing the importance of choice of prebiotic, as well as the dose, since doses that were too small could be useless, and larger ones can stimulate gas production, which worsens symptoms[116-118].

SIDE EFFECTS OF PROBIOTICS

Most of the studies highlighted in this article did not report side effects or listed them as “unimportant”. In fact, it is an interesting that probiotics, prebiotics and symbiotics used in the treatment of IBS can sometimes cause, or even worsen, some symptoms. This phenomenon is most commonly observed in D-IBS, in which the use of prebiotics and fibre could lead to worsening of symptoms. These side effects include gas production, bloating, softer stools and abdominal pain; all of which are mostly temporary[119].

CONCLUSION

There exist several variables that affect changes in the microbiota (*i.e.*, differences in sample storage, DNA extraction, and analytical methods), as well as the diet of individuals, which were not strictly regulated in any studies. Many foods serve as prebiotics and may also contain probiotics. It has been proven that the application of multiple strains of probiotic bacteria, or even multiple species, is much more effective than the application of only one probiotic strain. It is difficult to predict which strain or species most contributed to the welfare of IBS patients. Several groups investigated the effect of a particular strain on a specific symptom, which could be considered a good research direction and a way to prove the effectiveness of a particular probiotic on the symptom that causes the most discomfort to an individual patient. A major drawback of these studies, however, is the design of clinical studies in which the types of IBS are

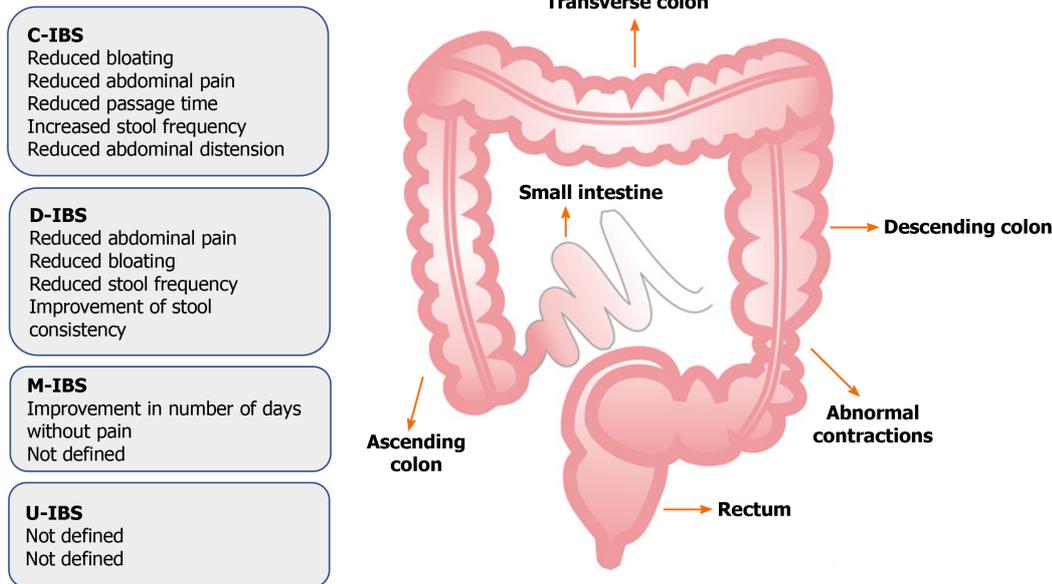


Figure 3 Effect of probiotic bacteria on different irritable bowel syndrome type symptoms. C-IBS: Irritable bowel syndrome with predominant constipation; D-IBS: Irritable bowel syndrome with predominant diarrhea; M-IBS: Irritable bowel syndrome with mixed bowel habits; U-IBS: Irritable bowel syndrome unclassified.

not clearly defined, or the analysis of IBS types is performed after the study is completed. In most of the clinical studies, a small number of patients were grouped into IBS subtypes, which made it difficult to draw conclusions. In addition, it is unlikely that the same probiotic or multispecies probiotic preparation will influence all four types of IBS. The biggest unknown remains as the mixed and unclassified types of IBS, which are present in small numbers in the conducted studies. The way to design a suitable study for mixed and unclassified types of IBS is questionable, as we do not currently have a probiotic or symbiotic that would affect the modification of the various symptoms that occur in these types of IBS. The solution may be to group patients with specific subtype and gather critical mass. Furthermore, numerous studies have shown the impact of probiotics on certain areas of the brain and their activity. Studies of this type certainly have their limitations, mostly related to the complicated interrelationships of the intestinal brain axis, such as those present in patients with IBS, which are not easy to transfer to an animal model and then map to human subjects. The need to understand the connection between the intestinal microbiota and functional diseases of the gastrointestinal system is central to the research in this field of medicine. The cognition that controlling the intake of dietary supplements can affect bowel functions, as well as the psychological manifestations of the disease, is the basis for setting new therapeutic options in the treatment of IBS and other similar disorders of the gastrointestinal system.

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