

# A Review of the Literature on the Use of Probiotics to Treat Irritable Bowel Syndrome and Inflammatory Bowel Disease

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Received: 07-06-16

Accepted: 21-04-17

## Abstract

**Introduction:** Irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) are frequent reasons for medical consultation. Usually they are treated at the first level of attention with adjustment of lifestyle and dietary changes. Pharmacological treatments have limited efficacy and significant side effects, so there is growing interest in other therapies such as the use of probiotics. **Methods:** This is literature review of studies associating nutritional supplements with IBS or IBD that have an emphasis on probiotics and which found in the Medline and Embase databases. **Results:** Of a total of 1,598 references, 43 met the final inclusion criteria. The use of probiotics in IBS and IBD suggests a therapy that helps maintain periods of disease remission, improvement of quality of life and attenuation of the pathophysiological process. **Conclusions:** The use of probiotics and prebiotics could be alternative nutritional support for selected patients.

## Keywords

Inflammatory bowel diseases, nutritional status, probiotics, irritable bowel syndrome, dietary supplements.

## INTRODUCTION

If there is a particular group of disorders that require dietary interventions, it would be diseases of the gastrointestinal tract (GIT). They are not only a reason for frequent medical consultation, but many of the most common ones respond poorly to pharmacological treatment. For this reason, there is a growing interest in using nutritional supplements for therapeutic purposes. Interest is especially strong in the use of probiotics which contain viable microorganisms in an amount sufficient to alter the intestinal microflora. (1, 2)

On the one hand, irritable bowel syndrome (IBS) is considered to be a functional gastrointestinal syndrome that has been associated with visceral hypersensitivity, impaired GIT motility, the post-infectious disease period and psychiatric comorbidities. (3, 4) Its estimated a global prevalence is 10% to 20% with a female: male prevalence ratio of 3:2. In

Colombia, its prevalence is 20% in the adult population, with a predominance of the mixed variant (diarrhea and constipation) and association with a large number of medical disabilities and restrictions on physical activity (4, 5).

There is no cure and available treatment options are palliative, supportive and aimed at the treatment of specific symptoms. They combine pharmacological, psychological and dietary approaches. (6) It has been observed that treatment with probiotics, especially lactobacilli and bifidobacteria, decreases abdominal pain and results in overall improvement of symptoms by restoring balance of the intestinal microflora, its ability to bind to the intestinal epithelium, and production of substances that inhibit invasion and adhesion of pathogenic microorganisms. (6, 7)

On the other hand, the term inflammatory bowel disease (IBD) is applied to two diseases: ulcerative colitis (UC) and Crohn's disease (CD). Both usually affect young adults, (8)

and both are related to combinations of genetic and environmental factors that alter the regulation of the immune system. (9). In UC there is continuous inflammation of the mucosa of the colon and rectum with episodes of relapse and remission. CD is characterized by transmural inflammation that can affect all of the GIT in segments which sometimes leads to luminal stenosis and obstructive symptoms. (10) These entities can result in multiple physical, nutritional and immunological disabilities which cause abdominal pain, diarrhea, rectal bleeding, fever, fatigue, weight loss. Potentially, they can result in formation of abscesses, fistulas and intestinal stenosis. (11)

The highest prevalence of IBD has been described in Canada and the United States with 26 to 198 cases of UC per 100,000 inhabitants and 38 to 229 cases of CD per 100,000 inhabitants. The lowest prevalences have been reported in Eastern Europe, Africa, South America and Asia. Although there are few epidemiological studies in Colombia, a higher frequency of UC than CD and a slight predominance of IBD in women have been reported. (9)

The intestinal microbiota is of great importance in the pathogenesis of IBD because of the relationship between bacterial flora and host immune tolerance, mucosal barrier integrity, angiogenesis and appropriate intestinal development. (12) This implies that therapeutic modification of the bacterial flora with antibiotics or probiotics, and recently with prebiotics and symbiotics, may have significant effects. (2)

The purpose of this study was to approach the consumption of nutritional supplements based on probiotics as supportive treatment in prevalent gastrointestinal diseases with an emphasis on IBS and IBD.

## MATERIALS AND METHODS

We searched the Pubmed and Embase databases for clinical studies that addressed the effect of nutritional supplements on IBD and IBS. The terms used in the Pubmed search were:

- “Dietary supplements” [MeSH] AND (“Inflammatory Bowel Diseases” [MeSH] OR “Colitis, Ulcerative” [MeSH] OR “Crohn Disease” [MeSH])
- “Dietary Supplements” [MeSH] AND “Irritable Bowel Syndrome” [MeSH]

The terms used in the Embase search were:

- ‘Dietary supplements’/exp OR ‘dietary supplements’ AND (‘inflammatory bowel diseases’/exp OR ‘ulcerative colitis’/exp OR ‘crohn disease’)
- ‘Dietary supplements’/exp AND (‘Irritable Bowel Syndrome’/exp)

Of the articles found, those referring to nutritional supplements based on probiotics were selected. The articles

selected were transferred to the Mendeley reference management program. Duplicate articles were excluded first, followed by non-systematic reviews, studies written in a language other than English or Spanish, studies of specific subgroups of patients and those whose content did not focus on the relationship between probiotics and gastrointestinal diseases of interest.

Metaanalyses, systematic reviews of the literature, clinical studies and cross-sectional studies were selected. There were no restriction of dates. After discarding the studies considered irrelevant on the bases of titles and abstracts, the full text version of the selected articles was obtained and information about intervention and exhibition, outcomes measured, the way outcomes were measured, and the most important outcome of each study was recorded. These results are shown in Figure 1.

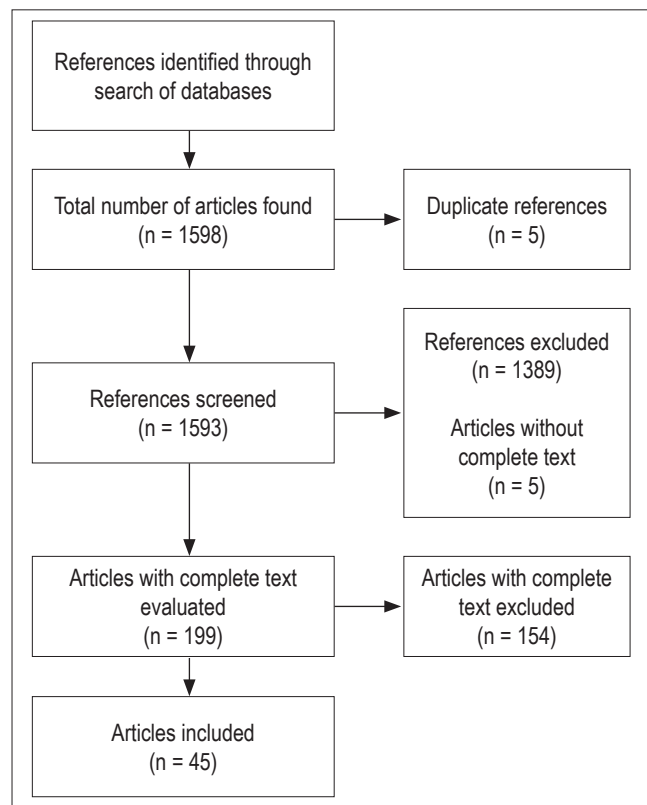


Figure 1. Schematic representation of article selection process

## RESULTS

Of the 1598 articles initially identified, the full texts of 199 were evaluated. Information was extracted from 45 articles published between 1999 and 2015. The majority of studies (n = 36) were clinical trials.

## Irritable bowel syndrome

Controlled clinical trials suggest beneficial results in relief of patients' symptoms following consumption of probiotics. It is worth noting that most studies noted improvements in abdominal pain since this is the symptom associated with greatest compromise of quality of life and the most frequent visits to the emergency department.

The Bafutto study of 53 patients in Brazil compared the use of 800 mg/day mesalazine alone with its use together with 200 mg of *Saccharomyces boulardii* for 30 days. The study reported improvement in abdominal pain and stools in patients with combined therapy ( $p < 0.05$ ). (13)

The Chambrun study compared the responses of 200 patients in France who received either 500 mg of *Saccharomyces cerevisiae* or placebos for eight weeks. It concluded that there is a slightly greater clinical improvement in abdominal pain and general discomfort in treated patients (63% vs. 47 %,  $P = 0.04$ ) with adequate tolerance and no significant adverse effects. (14). The study by Wong of 42 patients who consumed VSL # 3 (112.5 trillion lyophilized bacteria) for 6 weeks, reported significant improvement in abdominal pain in treated patients ( $p = 0.02$ ). These results are similar to those reported by Pedersen et al. in Denmark with 103 patients, Jafari et al. in Iran with 108 patients and Fan et al. in China with 74 patients. (15-18)

In addition, Lorenzo-Zuñiga's study in Spain evaluated 84 patients treated with *Lactobacillus plantarum* and *Pediococcus acidilactici* at  $3-5 \times 10^9$  colony forming units (CFU)/day. After 6 weeks they observed subjective improvement of abdominal pain with greater impact among the supplemented patients ( $p = 0.02$ ). (19) These results are similar to the Urgesi study in Italy of 52 patients treated with *Bacillus coagulans* and simethicone, the Sisson study in the United Kingdom of 186 patients treated with *Lactobacillus rhamnosus*, *Lactobacillus plantarum*, *Lactobacillus acidophilus* and *Enterococcus faecium* (1 mL/kg/day), the study by Cappello et al. in Italy of 83 patients supplemented with lactobacilli and bifidobacteria. (20-22)

In contrast, the study by Stevenson et al. in South Africa is inconclusive. It found no statistically significant difference between the use of probiotics (*Lactobacillus plantarum* 299 at doses of  $5 \times 10^9$  CFU/day) and placebos. Neither did the study by Ludidi et al. of 35 patients in the Netherlands or that of Søndergaard et al. of 52 patients in Denmark, or that of Abbas et al. of 72 patients in Pakistan. This last study administered 750 mg of *Saccharomyces boulardii* to one group of patients and placebos to a control group. However, this study did report decreased proinflammatory cytokines (interleukin 8 and tumor necrosis factor

[TNF]) in the supplemented patients as a benefit of this treatment ( $p = 0.001$ ). (23-26)

A metaanalysis by Ford analyzed 43 randomized controlled clinical trials with a total of 3,454 patients while another metaanalysis by Didari included 24 trials with a total of 1,793 patients. Both studies concluded that significantly greater clinical improvements of abdominal pain and diarrhea followed administration of probiotics consumption compared to what occurred when placebos were administered. (27-32) Table 1 summarizes the findings of the clinical studies included in these metaanalyses. These results were consistent with those of another metaanalysis by Tiequn which included 6 randomized controlled trials. (33)

## Ulcerative colitis

Overall, the studies reviewed suggest that probiotics have beneficial effects (Table 2). Lactobacilli have been shown to attenuate histological damage and to lead to remission for an important percentage of patients. (38, 39) *Saccharomyces boulardii* has also been tested as probiotic therapy since it exerts trophic effects on the intestinal mucosa and promotes the endoluminal release of immunoglobulin A (IgA). (40)

VSL # 3 is a well-known mixture of probiotic strains at it contains a high concentrations. They including  $5 \times 10^8$  cells/g of 3 strains of bifidobacteria, 4 strains of lactobacilli and 1 strain of *Streptococcus salivarius* spp. *Thermophilus*. It has been used primarily in patients who are intolerant or allergic to other treatments. (41)

Nevertheless, some randomized clinical trials suggest that the use of symbiotics may be more effective than the exclusive use of probiotics or prebiotics. The study by Ishikawa et al. in Japan demonstrated success of symbiotics for maintaining remission with significant reduction of exacerbation and possible preventive effects on relapses. The study used a 100 ML/day of bifidobacteria (symbiotic) fermented milk supplement for one year in 41 patients. This finding was reaffirmed in a new study by the same author in 2011, with colonoscopic evidence of clinical improvement and decreased myeloperoxidase levels in 21 patients ( $p < 0.05$ ) (42, 43). The Fujimori study of 31 patients, also in Japan, compared *Bifidobacterium longum*  $2 \times 10^9$  CFU and 8 g psyllium (prebiotic) with symbiotic treatment alone and found a greater impact with combined management, with remission maintained during the four weeks of treatment ( $p = 0.03$ ). (44)

In Denmark, Krag et al. studied 74 patients with moderate to severe UC who received supplements of either profermin (*Lactobacillus plantarum*  $10^8$  CFU/mL) or place-

**Table 1.** Randomized clinical trial specifications included in selected meta-analyses

Study	Sample Size	Supplement	Result
Choi, 2011 (27)	n=28	<i>L. plantarum</i> MF1289, (1 x 10 <sup>6</sup> CFU) versus placebo for 4 weeks	Greater improvement of diarrhea and general symptoms in the treated group than in the placebo group (95% confidence interval [CI] 2.3-10.9)
Drouault-Holowacz, 2008 (28)	n=100	<i>Bacillus longum</i> , <i>L. acidophilus</i> , <i>L. lactis</i> (1 x 10 <sup>10</sup> ) versus placebo for 4 weeks	Greater improvement in abdominal pain (42% vs. 24%), subjective improvement in flatulence and nocturnal awakening
Simrén, 2010 (29)	n=74	400 mL milk enriched with <i>Lactobacillus paracasei</i> , <i>L. acidophilus</i> and <i>Bifidobacterium lactis</i> versus placebo for 4 weeks	Improvement of more than 50% in the treated group in terms of abdominal pain, abdominal distension and satiety
Guglielmetti, 2011 (30)	n=122	<i>Bifidobacterium bifidum</i> (1 x 10 <sup>9</sup> ) versus placebo for 4 weeks	Prebiotic decreased overall IBS symptoms by -0.88 points (95% CI: -1.07; 0.69) compared to -0.16 points (95% CI: -0.32; 0.00) with placebo (p <0.0001)
Kruis, 2012 (31)	n=120	<i>EcN</i> 1917 (2.5-25 x 10 <sup>9</sup> CFU) versus placebo for 12 weeks	Greater response rate for abdominal pain in the treated group (20% more) after 10 weeks of treatment. Greater benefit in patients with previous intestinal infections
Roberts, 2013 (32)	n=184	Yogurt with <i>Bifidobacterium lactis</i> (1.25 x 10 <sup>10</sup> CFU) + <i>S. Thermophilus</i> y <i>L. Bulgaricus</i> (1.2 x 10 <sup>9</sup> CFU) versus placebo for 4 weeks	No significant differences with control group
Ki Cha, 2011 (34)	n=50	<i>L. acidophilus</i> , <i>L. plantarum</i> , <i>Lactobacillus rhamnosus</i> , <i>B breve</i> , <i>Bifidobacterium lactis</i> , <i>Bifidobacterium longum</i> , and <i>Streptococcus thermophilus</i> (1 x 10 <sup>10</sup> CFU) versus placebo for 10 weeks	There were more responses in the probiotic group than in the placebo group, (48% vs. 12%, P = 0.01). Stool consistency improved significantly in the treated group.
Whorwell, 2006 (35)	n=362	<i>Bifidobacterium infantis</i> (1 x 10 <sup>6</sup> , 1 x 10 <sup>8</sup> or 1 x 10 <sup>10</sup> CFU/mL) versus placebo for 4 weeks	A dosage of 1 x 10 <sup>4</sup> CFU/ml was shown to have significantly greater effects for improvement of abdominal pain, bloating, intestinal dysfunction, incomplete evacuation and flatulence than those for placebos and other doses (p <0.02)
Williams, 2009 (36)	n=52	<i>Lactobacillus acidophilus</i> , <i>Bifidobacterium lactis</i> and <i>Bifidobacterium bifidum</i> (2.5 x 10 <sup>10</sup> CFU) versus placebo for 2 weeks	The number of days of abdominal pain decreased in the probiotic group (p = 0.01)
Begtrup, 2013 (37)	n=131	<i>Lactobacillus paracasei</i> F19, <i>Lactobacillus acidophilus</i> La5 and <i>Bifidobacterium Bb12</i> (1.3 x 10 <sup>10</sup> CFU/12 h) versus placebo	52% (35/67) of the probiotic group experienced improvement of diarrhea, early satiety and abdominal distension versus 41% (26/64) of the placebo group.

EcN: Escherichia coli Nissle

bos for 8 weeks. They reported disease remission in 31% of treated patients compared with only 15 % of the untreated patients. (39)

Similarly, quasi-experimental studies have demonstrated clinical remission in patients with mild to moderate UC. In Italy, the Guslandi study of 25 patients supplemented with 250 mg/8 h of *Saccharomyces boulardii* and mesalazine for four weeks reported remission in 68% while Tsuda's study in Japan found a 45% remission rate following delivery of BIO-THREE (2 Mg of *Streptococcus faecalis* T-110, 10 mg of *Clostridium butyricum* TO-A and 10 mg of *Bacillus mesentericus* TO-A) for four weeks. (40, 45)

The non-pathogenic *EcN* 1917 probiotic strain that has been evaluated for treating UC has also been tested as

maintenance therapy for CD with evidence that it prevents and reverses symptoms in these patients by inhibiting the up to 99% of the effects of pathogens. (46) In addition, the use of symbiotics has been associated with clinical improvement and reduction of inflammatory markers. (47, 48)

The randomized clinical trial by Guslandi in Italy observed relapses in 16% of the patients treated with 1 g/day of *Saccharomyces boulardii* together with 1 g of mesalazine twice a day for 6 months, compared with relapses in 37% of the control group who only received mesalazine. (49)

Prebiotic carbohydrates such as fructooligosaccharides (FOS) have been shown to increase concentrations of fecal bifidobacteria which has immunoregulatory properties. However, a study by Benjamin in the UK found no clinical

**Table 2.** Clinical evidence for use of nutritional supplements to treat ulcerative colitis

Article	Year	Study design	Study population	Intervention	Result
Matthes, <i>et al.</i> (57)	2010	Randomized controlled clinical trial	90 patients with moderate UC	EcN ( $10^8$ CFU/ml) in enemas of 10 ml, 20 ml and 40 ml vs. placebo	Faster remission in 20 and 40 ml enemas ( $p = 0.04$ )
Borody, <i>et al.</i> (58)	2003	Quasi-experimental clinical trial	6 patients with recurrent UC	Fecal donor flora (healthy adults studied to rule out pathogens) for 5 days	Complete reversal of symptoms and colonoscopic alterations after four months
Krag, <i>et al.</i> (39)	2013	Randomized controlled clinical trial	74 patients with moderate to severe UC	Profermin (contains <i>Lactobacillus plantarum</i> ) vs. placebos	Remission in 31% of patients treated vs. 15% of placebo group
Guslandi, <i>et al.</i> (40)	2003	Quasi-experimental clinical trial	25 patients with mild to moderate UC	250 mg/8 h of <i>Saccharomyces boulardii</i> and Mesalazine	Clinical remission in 68% of patients
Tsuda, <i>et al.</i> (45)	2007	Quasi-experimental clinical trial	20 patients with mild to moderate UC	BIO-THREE (2 mg <i>Streptococcus faecalis</i> T-110, 10 mg <i>Clostridium butyricum</i> TO-A and 10 mg <i>Bacillus mesentericus</i> TO-A)	45% remission in patients with refractory UC
Fujimori, <i>et al.</i> (44)	2009	Randomized controlled clinical trial	120 patients with UC	<i>Bifidobacterium longum</i> $2 \times 10^9$ CFU (symbiotic) and 8 g Psyllium (prebiotic) or symbiotic only	Greater impact with combined management with remission maintained during the four weeks of treatment ( $P = 0.03$ )
Ishikawa, <i>et al.</i> (42)	2011	Randomized controlled clinical trial	41 patients with mild to moderate UC	1g of <i>Bifidobacterium breve</i> Yakult strain and 5.5g of galacto-oligosaccharide as symbiotic for 1 year	Clinical improvement measured by colonoscopy and decreased myeloperoxidase levels ( $P < 0.05$ )

benefit from administration of this prebiotic over administration of placebos in a four week trial with 103 patients. (50)

In Japan, Fujimori's quasi-experimental study evaluated 10 patients with active CD who received a combination of *Bifidobacterium*, 75 trillion CFU of *Lactobacillus* and 9.9 g/day of psyllium (prebiotic). Improvement of symptoms in was reported in seven patients. (47) The clinical evidence for use of nutritional supplements to treat this disease is shown in Table 3.

## DISCUSSION

There are a number of studies that have evaluated the efficacy and safety of probiotic treatment of IBS and IBD. Probiotic preparations that have been tested in animals and humans include *Lactobacilli*, *bifidobacteria*, *Escherichia coli* and *Saccharomyces*. (2) The most robust benefits found have been alterations in intestinal microflora with the use of conjugated species. This has been reported in studies by Wong, Jafari, Begtrup and Ki Cha which have demonstrated clinical improvements in up to 80% of patients treated. (15, 17, 34, 37).

Most of the articles studied that focused on IBS found associations between consumption of probiotics and subjective and objective improvements of cardinal symptoms measured by subjective questionnaires and by the Bristol scale (quality of stools). (13, 17, 32).

A diet which is low in monosaccharides, disaccharides, oligosaccharides and fermentable polyols (FODMAP) consists of reduced dietary intake of short chain carbohydrates which are difficult to digest and which are poorly absorbed in the small intestine. (51, 52) Several studies have suggested that this diet reduces functional intestinal symptoms and contributes to improvement of nutritional status in people hospitalized with diarrhea and in the control of symptoms of people with IBS. (53, 54) The Danish study by Pedersen *et al.* compared the use of this diet with probiotics and with the conventional western diet. It demonstrated the usefulness of the FODMAP diet and the used of probiotics for symptomatic control of IBS (16). However, it would be worthwhile to create studies to compare the efficacy of probiotics to that of the FODMAP diet for clinical modification of the disease.

**Table 3.** Clinical evidence for use of nutritional supplements to treat Crohn's disease

Article	Year	Study design	Study population	Intervention	Result
Boudeau, <i>et al.</i> (46)	2003	Cross-sectional	Patients with CD	Measurement of CFU of pathogenic <i>E. coli</i> in patients who received EcN	Inhibitory effect of 78-99%
Borruel, <i>et al.</i> (48)	2002	Cross-sectional	10 patients with CD and 5 controls	Intestinal biopsy cultured with non-pathogenic <i>E. coli</i> , <i>L. casei</i> , <i>L. bulgaricus</i> or <i>L. crispatus</i>	Decreased markers of inflammation in patients with either <i>L. casei</i> or <i>L. bulgaricus</i> ( $p < 0.01$ )
Fujimori, <i>et al.</i> (47)	2007	Quasi-experimental clinical trial	10 patients with active CD	Combination of Bifidobacterium, probiotic Lactobacillus (75 trillion CFU) and Psyllium prebiotic (9.9 g/day)	Symptom improvement in most patients (7/10)
Wiese, <i>et al.</i> (59)	2011	Quasi-experimental clinical trial	20 patients with CD	Nutritional formula with long chain n-3 fish oil fatty acids (1.09 g of EPA and 0.46 g of DHA), prebiotics (fructooligosaccharides and Gum Arabic) and antioxidants (vitamins and minerals)	Improved nutritional status and increased serum levels of 25-OH vitamin D ( $p < 0.01$ )

Probiotics have been associated with clinical and colonoscopic changes in IBD, and with higher percentages of patients who experience remission. The use of *E. coli* Nissle 1917 seems to be as effective as mesalazine, but there needs to be more evidence to establish whether this strain can become a probiotic alternative to the use of mesalazine alone. (46, 55, 56)

Variation in the conclusions derived from study results may be due to the heterogeneity of characteristics of the studies analyzed, especially to differences in supplement dosages, sample sizes and follow-up times. In addition, disease status, concomitant medical therapy, and factors directly related to each patient such as characteristics of intestinal lesions, histories of relapses, family histories, and smoking habits should be taken into account.

Among the limitations of this study is that the selection of articles based on the use of keywords rather than free text may have left out some studies. Keywords increase the specificity of searches but sacrifice search sensitivity.

## CONCLUSIONS

The use of probiotics appears to be beneficial for treatment of gastrointestinal diseases such as IBS and IBD. Lactobacilli and bifidobacteria have both demonstrated subjective (questionnaires) and objective (colonoscopy) improvement in treated patients.

In general, the use of these supplements has been successful in practice, especially for symptom control and maintenance of remission in these entities. However, it is necessary to take into account the specific condition of the patient and their comorbidities to make informed decisions about management.

## Conflicts of Interest

This study was sponsored by Lafranco S.A.S.

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