Journal of Food and Nutrition Research, 2018, Vol. 6, No. 11, 710-718
Available online at http://pubs.sciepub.com/jfnr/6/11/6

DOI:10.12691/jfnr-6-11-6

Meta-Analysis Study the Role of Probiotics Treatment in Irritable Bowel Syndrome (1990-2017)

Selvaganapathi G.[1], Jinat Ahmed J.A.[2,*], Mathialagan AG[2], Dinesh M.[3], Azra N.[2], Harikrishnan T.[4], Kohila J.R.[1], Fathy I.[5], Ramalinggam R.[1], Tee HY[2], Vanita S.[6]

[1]Seremban Prison, Malaysian Prison Department, Home Ministry, Malaysia
[2]Department of Post-Graduate Studies, Perdana University, Malaysia
[3]SP Care Group, Health Care, Malaysia
[4]Department of Rehabilitation Medicine, Hospital Tunku Ampuan Rahimah, Ministry of Health, Malaysia
[5]Child Health Department, Sabak Bernam District Health Department, Ministry of Health, Malaysia
[6]Klinik Sri Pulai Sdn Bhd
*Corresponding author: jinatahmedrizu@gmail.com

Received October 14, 2018; Revised November 20, 2018; Accepted December 14, 2018

Abstract Objective: To examine the relationship between Probiotics and its efficacy in reducing the symptoms of Irritable Bowel Syndrome (IBS). Methods: A meta-analysis was conducted to evaluate the quality of the clinical trials and evidence with respect to the efficacy of probiotics for the treatment of IBS. Medline, PubMed, Google Scholar, NIH registry of clinical trials, and Cochrane Central Register of Controlled Trials were reviewed from the year 1990-2017 to identify studies that fulfilled inclusion criteria and exclusion criteria. Findings: 1650 studies were found on probiotics use in IBS. From that, only 70 studies fulfilled inclusion and exclusion criteria that were defined for this study. After assessment with Linde Internal Validity Scale, around 18 clinical trials were identified for data extraction. From those studies, it was seen that probiotic use was associated with improvement in global IBS symptoms compared to placebo [pooled relative risk (RRpooled) 0.77, 95% confidence interval (95% CI) 0.62-0.94]. Probiotics were also associated with less abdominal pain compared to placebo [RRpooled = 0.78 (0.69-0.88)]. Of the 11 species and species mixtures, *Lactobacillus rhamnosus GG* was the most frequent tested probiotics. None of the 18 trials reported any serious adverse events with probiotic use. Conclusion: For management of IBS, probiotics were significantly more protective and effective than placebo.

Keywords: *irritable bowel syndrome, probiotics, placebo-controlled, randomized controlled trials, Manning criteria, Rome criteria, double blinding*

Cite This Article: Selvaganapathi G., Jinat Ahmed J.A., Mathialagan AG, Dinesh M., Azra N., Harikrishnan T., Kohila J.R., Fathy I., Ramalinggam R., Tee HY, and Vanita S., "Meta-Analysis Study the Role of Probiotics Treatment in Irritable Bowel Syndrome (1990-2017)." *Journal of Food and Nutrition Research*, vol. 6, no. 11 (2018): 710-78. doi: 10.12691/jfnr-6-11-6.

1. Introduction

Irritable bowel syndrome (IBS) is a gastrointestinal disorder that occurs with repeated pain in the abdomen and changes in the bowel movement, which may constitute diarrhoea, constipation, or both. IBS is a multifactorial disease that can be caused by autoimmune disorder, chronic inflammation or significant changes in gut microflora [1]. IBS is one of the most common gastrointestinal digestive disorders (GI) with worldwide prevalence rates generally ranging from 10-15% [2,3]. Risk factors include gender (2-3 times more common in female) occurring at age around 30-50 years old [4], acute gastrointestinal infections (eg Campylobacter or Salmonella) and psychological factors [2]. Management of IBS is big challenges as there no clear therapy that can cure IBS. Most of the time, the treatment is symptomatic whereby episodes of diarrhea are best managed with loperamide, while constipation often will respond to fiber supplements. Antispasmodics or anticholinergic agents may help relieve the abdominal pain of irritable bowel syndrome. Refractory cases are often treated with tricyclic antidepressants. Newer agents such as tegaserod and ondansetron target neurotransmitter receptors in the gastrointestinal tract. However these therapies for IBS are supportive, targeting certain symptoms, but not satisfactory [4]. While 30% of patients report a symptom resolution within one year, nearly 70% reported the symptoms repeated within five years [3].

Studies have observed modified intestinal microflora in IBS patients and elevated symptoms after enteric infection [5,6], suggesting that the recovery of intestinal microflora can be a useful therapeutic goal. A strategy to restore normal flora can be achieved by the use of probiotics [5,7]. Probiotics have been defined as "living microbes that benefit health" [8]. The group of probiotics that are most prominently studied are genera *lactobacilli* and *bifidobacteria*

[5,9]. These genera have an excellent safety profile in both fermented foods industry, where they have been used for many years, and, more recently, in probiotic foods. Thus, this group of probiotics have been investigated for its effectiveness in various gastrointestinal tracts diseases and disorders [10].

However, evidence from probiotic clinical trials for IBS have resulted in conflicting results and inadequate conclusions. This is due to a variety of factors: small sample sizes; variability in experiment design; probiotic tension heterogeneity, dose and duration of treatment; and patient characteristics. Thus, there were no real conclusive evidence on probiotic efficacy and adverse events. To address this deficit, we conducted a meta-analysis of randomized, controlled, placebo-controlled and double-blind trials published as full articles or abstract meetings for: [1] appraise the component and aspect of random clinical trials in this area and [2] orchestrate evidence across efficacy studies probiotics for IBS.

1.1. Search Strategy

PubMed, Google Scholar, and Medline was scouted from 1990-2017 for articles globally written in the English language. Two online based clinical trial registers were searched: Cochrane Central Register of Controlled Trials (www.cochrane.org) and National Institutes of Health (www.clinicaltrials.gov). Secondary and hand searches of reference lists, other studies cross-indexed by authors, reviews, commentaries, books and meeting abstracts also were performed. Search item included: irritable bowel syndrome, probiotics, placebo-controlled, randomized controlled trials, Manning criteria, Rome criteria, and double blinding. Search strategies were broad-based initially, then narrowed to the disease of interest to increase the search network. Participant-Intervention-Comparator-Outcomes (PICO) Framework was used as a baseline for inclusion and exclusion criteria and standardized data extraction. Abstracts of all citations and retrieved studies were reviewed and rated for inclusion. Full articles were retrieved if specific treatments were given for IBS. In some cases, only published abstracts from meetings were available. Published abstracts from meetings were included to lessen the potential for publication bias due to failure to publish negative findings.

1.2. Inclusion and Exclusion Criteria

This meta-analysis was conducted to deduce the overall efficacy of IBS by comparing a common outcome in treated patients with a control group. Inclusion criteria comprises of randomized, controlled, blinded efficacy trials in humans published as full articles or meeting abstracts in peer-reviewed journals. Exclusion criteria includes pre-clinical studies, safety studies, case reports or case series, reviews, duplicate reports, trials of unspecified treatments, uncontrolled studies, prebiotic treatments only, presence of antibiotics or insufficient data in article.

1.3. Assessment of Methodology Quality

Studies that met the inclusion criteria were graded for quality using the Linde Internal Validity Scale (LIVS), which includes the following six items: method of allocation to groups, concealment of allocation, baseline comparability of intervention and placebo groups, blinding of patients, blinding of evaluators, and intention to treat/handling of withdrawals and drop-outs. Authors were contacted for further information if there were no information provided for an item or if it was unclear. If the given information was still insufficient, then zero points were given to that item. Total possible scores range from 0 to 6. All trials included in the meta-analysis had a total quality score of 3 or more and those with a score less than 3 were excluded. Two independent reviewers independently assessed inclusion criteria and quality of the trials. Inconsistencies were resolved by discussion.

1.4. Intent to Treat (ITT) Analysis

Studies were considered to have adhered to intention-to-treat principles if all subjects who were randomized were analysed with the group to which they were originally assigned and if exclusions were primarily due to patient withdrawal or loss to follow-up. If the investigators excluded patients after randomization due to use of non-study medications or antibiotics, noncompliance with assigned treatment, or non-response to therapy, the analysis was not considered to be ITT.

1.5. Data Extraction

Information on study design, methods, interventions, outcomes, adverse effects and treatments was extracted from each article using a standardized extraction table. When necessary, authors were contacted for data not reported in the original article.

1.6. Outcomes and Definitions

We documented the types of outcomes for trials involving IBS and probiotic in the literature. Outcomes were reported by different studies as either the proportion of subjects reporting improvement or the change in symptom scores from baseline. We did not attempt to synthesize results from studies reporting changes in symptom scores because of numerous challenges including heterogeneity in scales and scoring systems across studies and inconsistent or incomplete reporting of numeric symptom scores. Thus, we selected the proportion of subjects with improvement in global IBS symptoms as the primary outcome for this meta-analysis. Secondary outcomes included the proportion of subjects with improvement in one of three common IBS symptoms: abdominal pain, bloating or flatulence. Documentation of the outcome was based on subject self-report and/or clinician assessment.

2. Meta Analysis Method

To estimate pooled relative risks across studies, we first evaluated heterogeneity between and within trials using s forest plot. The relative risks of responding to probiotic therapy were pooled using a random-effects model if significant heterogeneity was found or a fixed-effects model if the studies were homogenous. (The forest plot is

able to demonstrate the degree to which data from multiple studies observing the same effect overlap with one another. Results that fail to overlap well are termed heterogeneous and is referred to as the heterogeneity of the data-such data is less conclusive. If the results are similar between various studies, the data is said to be homogeneous, and the tendency is for these data to be more conclusive.) [11]. P values less than 0.05 were considered significant. Data collected were tabulated and analysed using the Statistical Package for the Social Sciences (SPSS) version 20.0.

2.1. Study Characteristics Predictive of Positive Findings

Because there is heterogeneity throughout the study, we examine the design features of the hypotheses that we hypothesize may be associated with probiotic prolapse on placebo. This analysis examines the results for major yield variables, the reduction of global IBS symptoms. We classify the study as a probiotic option if RR was unpooled 0.67 or less. The study by Whorwell [12] et al encompasses 3 different doses of probiotics but is considered a single study for the purposes of this analysis. Since one of the 3 arm shows the probiotic support results, we classify this study as a probiotic choice. Characteristics examined as possible predictors include sample size, LIVS quality score, female subject proportion, probiotic dose, treatment duration, 20% shift, ITT analysis and proprietary (commercial) and non-feasible product use. Forest plot also show strong indication probiotics are better than placebo in terms of reducing global IBS symptoms.

2.2. Literature Screening

The literature search yielded 1650 citations on probiotics, of which 401 addressed probiotics and IBS. Based on review of abstracts, 70 were selected for detailed screening.

2.3. Study Selection

The study selection process is shown in a QUOROM (Quality of Reporting of Meta-analysis) flow diagram (Figure 1) [13]. Overall, 52 studies that were screened failed to meet 1 or more of the inclusion criteria: 24 (46%) quality score<3, 2 (0.03%) meta-analysis study, 11 (21%) combine with antibiotics, 13 (25%) not related with IBS study or other disease. A total of 18 articles met inclusion criteria and provided data on probiotic treatment arms for 1515 patients with IBS (Table 1). An additional seven trials were excluded after article retrieval and screening for issues related to quality and/or study design (Table 2).

Table 1. Description of 18 randomized, controlled trials of probiotics for IBS included in systematic review

Bil	Reference	Probiotic	Type of Control	Number of subjects randomized	Number analyzed	Dose (cfu/d)	Duration of treatment (wk)
1.	Kim 2005 [14]	VSL#3 yogurt1	Placebo yogurt	48	48	8 × 109	4
2.	Bausserman 2005 [5]	*Lactobacillus rhamnosus GG*	Placebo capsules	58	50	$2x10^{10}$	6
3.	Kajander 2005 [10]	L. rhamnosus GG+L. rham LC705 +Bijfido breve Bb99+Prop. freudenreichii	Placebo capsules	103	81	8-9 × 10^9	24
4.	O'Sullivan 2000 [15]	*Lactobacillus rhamnosus GG*	Placebo tablets	24	19	$1x10^{10}$	8
5.	Maupas1983 [16]	*Saccharomyces cerevisiae boulardii lyo*	Placebo capsules	34	34	$9x10^9$	4
6.	Yoon 2014 [17]	*a mixture of Bifidobacterium longum, Bifidobacterium bifidum, Bifidobacterium lactis, Lactobacillus acidophilus, Lactobacillus rhamnosus, and Streptococcus thermophilus*	Placebo capsules/placebo powder	50	49	$5x10^9$	4
7.	WILLIAMS 2009 [18]	*Lactobacillus acidophilus Bifidobacterium lactis Bifidobacterium bifidum*	Placebo capsules	56	52	$2.5x10^{10}$	8
8.	Simren 2006 [19]	*L. plantarum* 299v in rose hip drink	plain rose hip drink	66	58	$2x10^9$	6
9.	Nobaek 2000 [20]	*Lactobacillus plantarum* DSM9843, in rose hip drink	Placebo plain rose hip drink	60	52	$5x10^7$	4
10.	Halpern 1996 [21]	*L. acidophilus* (heat killed) "Lacteol Fort"	Placebo capsules	29	18	$2x10^{10}$	6
11.	Niedzielin 2001 [22]	*Lactobacillus plantarum* 299v, "ProViva" drink	Placebo drink	40	40	$2x10^{10}$	4
12.	Bittner 2005 [23]	Prescript-assist® 29 soil strains and prebiotic "leonardite"	Placebo capsules	27	25	$2.6x10^8$	2
13.	Whorwell 2006 [12]	*Bifido. infantis* 35624 in 3 doses	Placebo capsules	362	292	1 × 10^6 1 × 10^8 $1x10^{10}$	4
14.	Kim 2003 [9]	VSL#3 (mix of 8 strains) powder packet1	Placebo powder	25	25	$9x10^{11}$	8
15.	D'haens 2007	*Bifido. longum, Lact acidophilus, Lactococcus lactis, Strept. thermophilus*	Placebo capsules	106	100	$1x10^{10}$	4
16.	Enck 2007	*E. coli+Strept* faecalis drink	Placebo drink	297	264	$4.5x10^2$	8
17.	Spiller 2016 [24]	*Saccharomyces cerevisiae*	Placebo drink	379	269	$8x10^9$	12
18.	Niv 2005 [25]	*Lactobacillus reuteri* 55730	Placebo capsules	54	39	$2x10^8$	24

IBS: Irritable bowel syndrome; cfu/d: Colony forming units per day.
Bifido: Bifidobacterium; B.: Bacillus; E.: Escherichia; L.: Lactobacillus; Prop.: Propionibacterium.
VSL#3 is a mixture of 8 probiotic strains *(Lactobacillus casei, L. plantarum, L. acidophilus, L. bulgaricus, Bifido. longum, Bifido. breve, Bifido. infantis and Streptococcus thermophilus).*

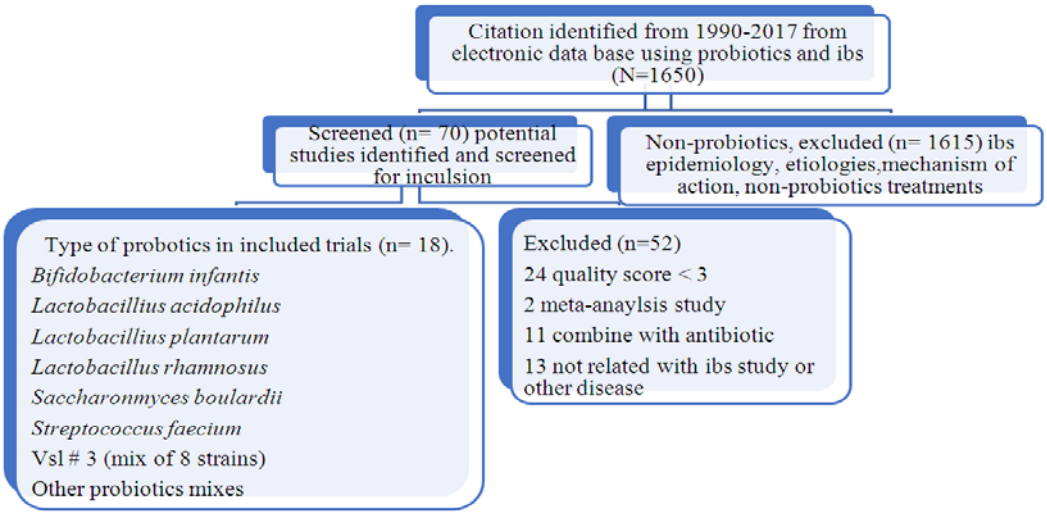

Figure 1. QUOROM flow diagram of included and excluded studies of probiotics for the treatment of Irritable Bowel Syndrome

Table 2. Examples of excluded randomized, controlled trials of probiotics for IBS

Bil	Reference	Probiotic	Number of subjects randomized	Number of subjects analyzed	Dose (cfu/mL)	Duration (wks)	Exclusion reason
1.	Evans 2016 [26]	*Lactobacillus helveticus and Lactobacillus rhamnosus*	160	80	2×10^9 (<1years) & $6\text{-}12\times10^9$ (<12 years)	8	Outcome data not provided
2.	Canai 2007 [27]	*Lactobacillus rhamnosus strain GG; Saccharomyces boulardii; Bacillus clausii; mix of L delbrueckii var bulgaricus, Streptococcus thermophilus, L acidophilus, and Bifidobacterium bifidum; or Enterococcus faecium SF68.*	600	571	6×10^9 5×10^9 7.5×10^7	36	Quality score = 1.0
3.	Sheila M 2008 [28]						Meta-Analysis
4.	Vicente Lorenzo-Zúñiga (2014) [29]	*Lactobacillus plantarum* and *Pediococcus acidilactici*.	84	84	$1\text{-}3\times10^{10}$	6	Loss follow/up or Insuffienct data/ discontinuous intevention/antibiotics
5.	Ducrotté 2012 [30]	*Lactobacillus plantarum 299v*	214	214		4	Loss follow/up or Insuffienct data/ discontinuous intevention/antibiotics
6.	JS Barrett 2008 [31]	*Lactobacillus casei*	18	14		6	Quality score = 1.0
7.	Cimperman 2011 [32]	*Lactobacillus reuteri*	31	31	1×10^8	2	Pilot Study and Antibiotic related

Table 3. Quality scoring for 11 randomized, controlled trials of probiotics for IBS (Linde Internal Validity Scale)

Bil	Reference	Total quality score [1]	Treatment allocation	Randomization method	Baseline comparison	Patients blinded	Evaluators blinded	Handling and reporting of withdrawals/use of ITT	Data source [2]
1.	Kim 2005 [14]	6	1	1	1	1	1	1	Paper
2.	Bausserman 2005 [5]	5.5	1	1	1	1	1	0.5	Paper
3.	Kajander 2005 [10]	4.5	1	1	1	0.5	0.5	0	Paper
4.	O'Sullivan 2000 [15]	4.5	1	1	0.5	1	0.5	0.5	Paper
5.	Maupas1983 [16]	5	1	1	1	1	1	0	Paper
6.	Yoon 2014 [17]	5	1	1	0.5	1	1	0.5	Paper
7.	WILLIAMS 2009 [18]	5	1	1	1	1	1	1	Paper
8.	Simren[3] 2006 [19]	4.5	1	1	1	1	1	0.5	Paper
9.	Nobaek 2000 [20]	4.5	1	1	1	1	1	0.5	Paper
10.	Halpern 1996 [21]	4	1	1	0.5	1	0.5	0	Paper
11	Niedzielin 2001 [22]	4	1	1	0.5	1	0.5	0	Paper
12	Bittner 2005 [23]	3	1	0	0	0.5	0.5	1	Paper
13.	Whorwell 2006 [12]	3.5	1	0	0.5	1	0.5	0.5	Paper
14.	Kim 2003 [9]	4	1	0	1	0.5	0.5	1	Paper
15.	D'haens 2007	4.5	1	0.5	1	1	0.5	0.5	Paper
16.	Enck 2007	4	1	0.5	0	1	0.5	1	Paper
17.	Spiller 2016 [24]	5	1	1	1	1	1	1	Paper
18.	Niv 2005 [25]	3.5	1	0	0.5	1	0.5	0.5	Paper

[1]Linde Internal Validity Scale score is based on columns 3-8; range, 0 (poor) to 6 (excellent). (Linde 1996) [33,34].
[2]Indicates whether additional contact with authors was required to obtain information needed for quality scoring.
[3]Data from published meeting abstract only.

2.4. Study Quality

The study quality of 18 studies were assessed using LIVS quality score >3.0 were included (Table 3). The median quality score was 4 (range 3-6). 0.5 marks were given to unclear data. All studies gave treatment allocation. Blinding for both patient and evaluators information were provided in all studies. 3 studies did not provide randomization method, 2 studies did not state baseline comparison, and 4 studies did not perform intention-to-treat analysis and/or did not fully describe withdrawals. Only three studies clearly documented their adherence to intention-to-treat principles. All the 5 studies did excluded participants who used prohibited/non-study medications, including antibiotics, during the treatment phase while 5 studies excluded subjects who demonstrated poor compliance with study medications. 2 studies reported that subjects either dropped out or were excluded due to inadequate response to treatment.

3. Probiotic Strain

Lactobacillus rhamnosus GG was the most frequent tested probiotics. It was tested in four trials. *Lactobacillus plantarum* and *Bifido. infitis* were both tested in three trials.

3.1. Assessment and Reporting of Outcomes

The outcomes assessed and reported varied widely across 18 studies. The effect on global IBS symptoms was reported in 66.7% of studies and was the primary outcome for 12/18 of studies. Effects on abdominal pain were reported by all studies, but only 4 studies (22.22%) used this as an outcome for primary measure.

Other symptoms were less consistently assessed (e. g. flatulence, 10/18 studies; stool frequency 13/18 mucus in stool, 4/18 studies; bloating, 15/18 studies).4 studies collected some measure of quality of life. 6 studies reported data for 3 or more symptoms or outcomes without specifying a primary outcome. Most studies reported in improvement in subjects, while others reported a change in numeric score since baseline. There were a variety of scales used to measure the severity of IBS symptoms across all studies, hence making it challenging to compare results across studies. Likert scales were used by 3 studies, and specific validated scales were used by several studies Gastrointestinal Symptom Rating Scale (GSRS) and IBS Severity Scoring System (IBS-SSS). Several studies used their own study-specific scale or scoring system. Often it was unclear whether this scale had been validated.

Although many studies assessed a wide range of IBS symptom, few reported detailed results across the spectrum of symptoms. For instance, only 5 out of 10 studies reported that they had collected data on flatulence and only 3 of 12 reporting they had collected data on stool consistency reported any such data in their paper.

3.2. Global Responders

The primary outcome selected for this analysis was the proportion of patients in each group with global IBS symptoms by the end of treatment, with ‘responders’ being a dichotomous variable defined by study investigators. Of the 18 treatment arms, all 18 (100%) had evaluable data for this outcome.

The forest plot, weighted on sample size, is shown in Figure 2. Compared to placebo, probiotics were significantly protective (less global IBS symptoms compared to placebo at the end of the study) [pooled relative risk (RR pooled)].

Table 4. Outcome assessment and reporting for 11 included clinical trials of probiotics for IBS

Bil	Reference	Global response	Abdominal pain	Bloating/distension	Flatulence	Stool frequency	Mucous	Stool consistency	Dyspepsia
1.	Kim 2005 [15]	R	R	R	R	R		R	
2.	Bausserman 2005 [5]	A	R	R	A			A	
3.	Kajander 2005 [10]	R	R	R		R	A	A	
4.	O'Sullivan 2000 [15]		R	R	A	R		A	
5.	Maupas1983 [16]	R	R	R		R		R	R
6.	Yoon 2014 [17]		R	R		R			
7.	WILLIAMS 2009 [18]	R	A	A				A	
8.	Simren 2006 [19]	R	A	A	A	A	A	A	
9.	Nobaek 2000 [20]	R	R		R	A		R	
10.	Halpern 1996 [21]	R	A	A		A	A	A	
11.	Niedzielin 2001 [22]	R	A	A		A	A	A	
12.	Bittner 2005 [23]		A		A				A
13.	Whorwell 2006 [24]	R	R	R	R	A			
14.	Kim 2003 [9]		R	A	A	A		A	
15.	D'haens 2007	R	R			A		A	
16.	Enck 2007	R	R	A		A		A	
17.	Spiller 2016 [24]	R	R	R	R				
18.	Niv 2005 [25]		R	R	R	A			
Percent of Reporting		66.70%	72.20%	50%	27.8%	27.80%	0%	16.70%	0.05%

A: Assessed; R: Reported in sufficient detail to allow extraction of data. Bold font indicates that this was the primary outcome identified by the authors for analysis. If author reported no difference between active and placebo groups for a given symptom, but did provide further details, the outcome was classified as assessed only.

Table 5. Global Improvement in IBS Symptoms in 16 probiotic/placebo treatment arm

Bil	Reference	Probiotic	Global improvement in IBS symptoms		Definition of primary outcome1
			Probiotic n/n (%)	Placebo n/n (%)	
1.	Kim 2005 [14]	VSL#3 yogurt1	4/12 (34)	5/13 (38)	Satisfactory relief of IBS symptoms
2.	Bausserman 2005 [5]	*Lactobacillus rhamnosus GG*	11/25 (44)	10/25 (40)	improvement in other GI symptoms with the use of
3.	Kajander 2005 [10]	L. rhamnosus GG+L. rham LC705 +Bijfido breve Bb99+Prop. freudenreichii	31/41 (76)	17/40 (43)	improvement in other GI symptoms with the use of
4.	O'Sullivan 2000 [15]	*Lactobacillus rhamnosus GG*	10/19 (52)	3/24 (12.5) for pain reduce and 7/24 (29) for bloating	the study was done first with blind placebo then active treatment for all subject. Final result was didn't help improvement in IBS
5.	Maupas 1983 [16]	*Saccharomyces cerevisiae boulardii lyo*	13/16 (81)	13/18 (72)	Improvement of symptoms
6.	Yoon 2014 [17]	*a mixture of Bifidobacterium longum, Bifidobacterium bifidum, Bifidobacterium lactis, Lactobacillus acidophilus, Lactobacillus rhamnosus, and Streptococcus thermophilus*	17/25 (68)	17/24 (70)	Improvement of symptoms
7.	WILLIAMS 2009 [18]	*Lactobacillus acidophilus Bifidobacterium lactis Bifidobacterium bifidum*	28/28 (100)	24/28 (85)	Improvement of symptoms
8.	Simren 2006 [19]	*L. plantarum* 299v in rose hip drink	33/37 (89)	34/37 (91)	Improvement of symptoms
9.	Nobaek 2000 [20]	*Lactobacillus plantarum* DSM9843, in rose hip drink	25/25 (100)	27/27 (100)	Known probiotic properties decreased pain and flatulence in patients with IBS.
10	Halpern 1996 [21]	*L. acidophilus* (heat killed) "Lacteol Fort"	17/18 (94)	13/18 (72)	Absence of symptoms
11.	Niedzielin 2001 [22]	*Lactobacillus plantarum* 299v, "ProViva" drink	9/20 (45)	3/20 (15)	Absence of symptoms
12.	Whorwell 2006 [12]	*Bifido. infantis* 35624 in 3 doses	33/74 (44)	32/76 (42)	Adequate relief of symptoms
13.	Kim 2003 [9]	VSL#3 (mix of 8 strains) powder packet1	45/72 (62)	32/76 (42)	Adequate relief of symptoms
14.	D'haens 2007	*Bifido. longum, Lact acidophilus, Lactococcus lactis, Strept. thermophilus*	26/71 (37)	32/76 (42)	Adequate relief of symptoms
15.	Enck 2007	*E. coli + Strept* faecalis drink	24/24 (100)	24/24 (100)	VSL# 3 reduces flatulence scores and retards colonic transit without altering bowel function in patients with IBS and bloating.
16.	Spiller 2016 [24]	*Saccharomyces cerevisiae*	20/47 (42.6)	22/52 (42.3)	Relief of discomfort

[1]Unless otherwise stated, all primary outcomes are defined based on patient report.
[2]VSL#3 is a mixture of 8 probiotic strains (Lactobacillus casei, L. plantarum, L. acidophilus, L. bulgaricus, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium infantis and Streptococcus thermophilus).

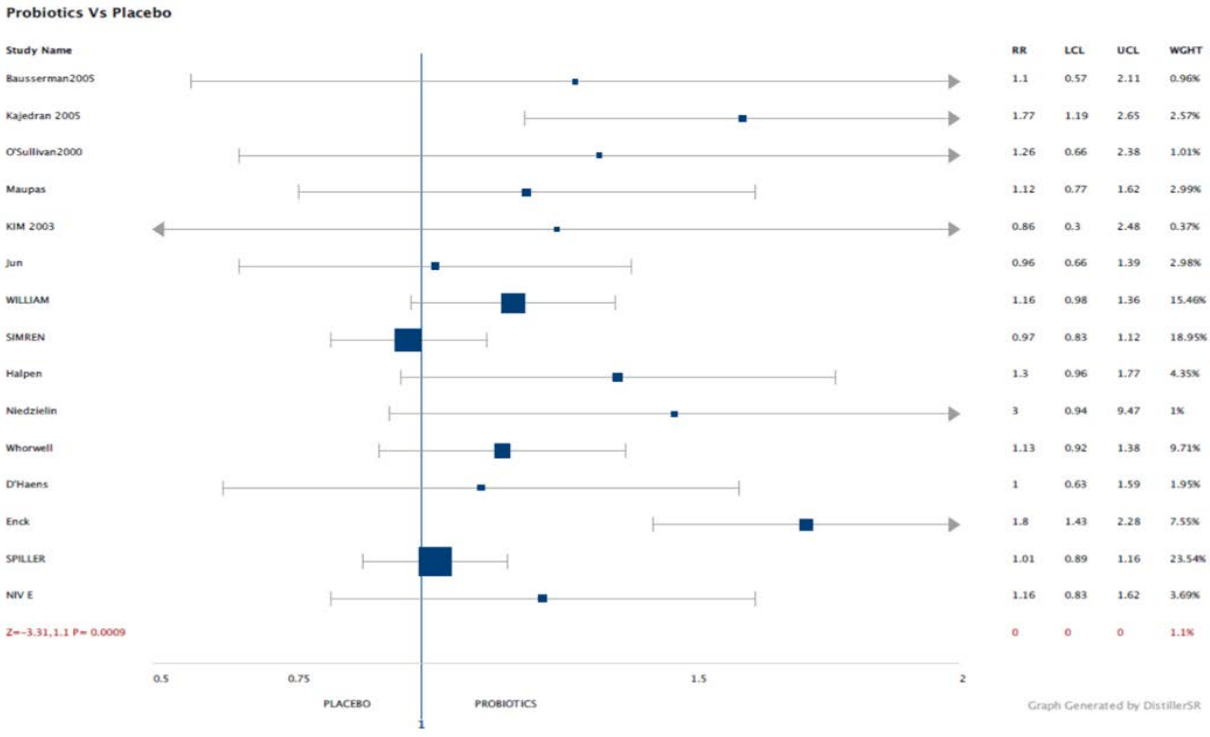

Figure 2. Forest Plot of randomized controlled trials of 18 treatment arms from 15 studies measuring relative risk of IBS symptoms after probiotic treatment compared to placebo. X-axis is relative risk; the line indicates 95% confidence interval and the size of the blue box proportional to sample size

Table 6. Adverse events associated with probiotics

Bil	Reference	Probiotic	Adverse events
1.	Kim 2005 [14]	VSL#3 yogurt1	No any adverse events
2.	Bausserman 2005 [5]	*Lactobacillus rhamnosus GG*	No any adverse events
3.	Kajander 2005 [10]	L. rhamnosus GG+L. rham LC705 +Bijfido breve Bb99+Prop. Freudenreichii	Did not update about it but by the paper didn't show any serious illness or death found
4.	O'Sullivan 2000 [15]	*Lactobacillus rhamnosus GG*	Did not update about it but by the paper didn't show any serious illness or death found
5.	Maupas1983 [16]	*Saccharomyces cerevisiae boulardii lyo*	No any adverse events
6.	Yoon 2014 [17]	*a mixture of Bifidobacterium longum, Bifidobacterium bifidum, Bifidobacterium lactis, Lactobacillus acidophilus, Lactobacillus rhamnosus, and Streptococcus thermophilus*	No any adverse events
7.	WILLIAMS 2009 [18]	*Lactobacillus acidophilus Bifidobacterium lactis Bifidobacterium bifidum*	No any adverse events
8.	Simren 2006 [19]	*L. plantarum* 299v in rose hip drink	No any adverse events
9.	Nobaek 2000 [20]	*Lactobacillus plantarum* DSM9843, in rose hip drink	No any adverse events
10	Halpern 1996 [21]	*L. acidophilus* (heat killed) "Lacteol Fort"	Did not update about it but by the paper didn't show any serious illness or death found
11.	Niedzielin 2001 [22]	*Lactobacillus plantarum* 299v, "ProViva" drink	Did not update about it but by the paper didn't show any serious illness or death found
12	Bittner 2005 [23]	Prescript-assist® 29 soil strains and prebiotic "leonardite"	No any adverse events
13.	Whorwell 2006 [12]	*Bifido. infantis* 35624 in 3 doses	Only 17 (<5%) of all subjects with-drew from the study because of an adverse event. The over-all prevalence of adverse events was not different between placebo and active treatment groups
14.	Kim 2003 [9]	VSL#3 (mix of 8 strains) powder packet1	No any adverse events
15.	D'haens 2007	*Bifido. longum, Lact acidophilus, Lactococcus lactis, Strept. thermophilus*	Did not update about it but by the paper didn't show any serious illness or death found
16.	Enck 2007	*E. coli + Strept* faecalis drink	Did not update about it but by the paper didn't show any serious illness or death found
17.	Spiller 2016 [24]	*Saccharomyces cerevisiae*	No any adverse events
18.	Niv 2005 [25	*Lactobacillus reuteri* 55730	Present with mild category adverse event with Dyspepsia (1) and Headche (1)

3.3. Adverse Reaction

Nine studies (50%) stated that no serious adverse reaction was noted but failed but failed to provide any information on how adverse events were ascertained or what types of reactions were considered (Table 6). Six studies (33%) did not provide any information on adverse effects of the intervention. All the papers also did not state regarding any serious illness or death during the studies were conducted. Two trials (11%) provided minimal data on adverse reactions. The reactions that were mentioned in one of the study were dyspepsia and headache where else the other study did not mention the symptoms of the adverse effects.

We identified 18 clinical trials that met inclusion criteria and provided relevant information about the efficacy of probiotics for IBS symptoms. These trials included 18 probiotic treatment arms and 1515 subjects. Trials were generally small and of short duration and had moderate quality. Overall, probiotic use was associated with less likelihood of global IBS symptoms compared to placebo.

4. Strength and Limitations

A comprehensive review of the literature was made to minimize the likelihood of bias by including a wider range of studies and studies that only met the criteria. PICO formatted question scores and data extraction were performed by two reviewers independently using standardized templates and differences were resolved by discussions. GRADE criteria and internal validity was also used determine the quality of the information in these articles. Studies of poor quality with usage of antibiotics were excluded. Primary outcome (global improvement in IBS symptoms) that is clinically relevant and of great concern to IBS patients were selected.

Heterogeneity was another important limitation of the published literature, including heterogeneity in the strain and dose of probiotic (which prevented analysis of effects of specific strains); sample size (smaller studies resulted in low power to detect effects in individual studies); duration of treatment and follow-up (short trials do not allow adequate follow-up given the chronic relapsing nature of IBS); and in the assessment and reporting of outcomes. All these sources of heterogeneity made it difficult to combine data from all twenty studies. Another important problem is the lack of systematic data collection and reporting about adverse effects. As a result, it is difficult to be sure that the probiotics studied have been adequately evaluated for safety.

4.1. Implications for Future Research

This systematic review showcases the possibilities for the involvement of probiotics as a treatment or preventive measure for IBS. With that being said, there is a need for a larger study to be conducted, a more specified type of probiotic stain preferably with longer duration of treatments and a smaller gap in between follow ups. Future studies should consider a better standardization tool to measure outcome. It would also be recommended that future studies examine overall relief of IBS symptom as an outcome.

4.2. Implications for Clinical Practice

Though the findings indicate that probiotics may be useful in the treatment of IBS, more research should be conducted before usage in the clinical practice. The pooled relative risks reported here are based on studies with significant methodological limitations, and bias cannot be ruled out as the explanation for these positive findings. Since we did not find any evidence of significant adverse effects from these treatments, and given the lack of available conventional treatments, clinicians should strongly consider discussing the evidence of benefits and risks of probiotics with their patients with IBS No universal quality assurance programs exist to ensure that commercial products contain the probiotic strain and concentration that are claimed, or to ensure the absence of contamination that could pose risks to consumers.

5. Conclusion

In conclusion, our meta-analysis containing 18 studies with 612 patients shows that in general, probiotics are beneficial in treatment of IBS. 18 out of the 18 studies (89%) showed that probiotics helped in symptom reduction of IBS in a duration between two up to twenty-four weeks predominantly the symptoms of abdominal pain and bloating. Future studies particularly larger studies with a more specific strain of probiotics as well as dosage need to be conducted to measure its efficacy.

Reference

[1] Definition & Facts for Irritable Bowel Syndrome|NIDDK [Internet]. National Institute of Diabetes and Digestive and Kidney Diseases. [Cited 2018 Nov 15]. Available from: https://www.niddk.nih.gov/health-information/digestive-diseases/irritable-bowel-syndrome/definition-facts

[2] Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. Clin Epidemiol. 2014 Feb 4; 6: 71-80.

[3] Spiller R, Aziz Q, Creed F, Emmanuel A, Houghton L, Hungin P, et al. Guidelines on the irritable bowel syndrome: mechanisms and practical management. Gut. 2007 Dec 1; 56(12): 1770-98.

[4] Irritable bowel syndrome: treatment and management-ProQuest [Internet]. [Cited 2018 Nov 15].

[5] Bausserman M, Michail S. The Use of Lactobacillus GG in Irritable Bowel Syndrome in Children: A Double-blind Randomized Control Trial. The Journal of Pediatrics. 2005 Aug; 147(2): 197-201.

[6] Quigley e. m. m., flourie b. Probiotics and irritable bowel syndrome: a rationale for their use and an assessment of the evidence to date. Neurogastroenterology & Motility. 2007 Mar; 19(3): 166-72.

[7] McFarland LV, Dublin S. Meta-analysis of probiotics for the treatment of irritable bowel syndrome. World J Gastroenterol. 2008 May 7; 14(17): 2650-61.

[8] Tuohy KM, Probert HM, Smejkal CW, Gibson GR. Using probiotics and prebiotics to improve gut health. Drug Discovery Today. 2003 Aug; 8(15): 692-700.

[9] Kim HJ, Camilleri M, Mckinzie S, Lempke MB, Burton DD, Thomforde GM, et al. A randomized controlled trial of a probiotic, VSL#3, on gut transit and symptoms in diarrhoea-predominant irritable bowel syndrome. Alimentary Pharmacology and Therapeutics. 2003 Apr; 17(7): 895-904.

[10] Kajander K, Hatakka K, Poussa T, Färkkilä M, Korpela R. A probiotic mixture alleviates symptoms in irritable bowel syndrome patients: a controlled 6-month intervention. Alimentary Pharmacology & Therapeutics. 2005 Sep 1; 22(5): 387-94.

[11] Forest plot. In: Wikipedia [Internet]. 2018 [cited 2018 Nov 15]. Available from: https://en.wikipedia.org/w/index.php?title=Forest_plot&oldid=858290044.

[12] Whorwell PJ, Altringer L, Morel J, Bond Y, Charbonneau D, O'Mahony L, et al. Efficacy of an Encapsulated Probiotic *Bifidobacterium infantis* 35624 in Women with Irritable Bowel Syndrome. The American Journal of Gastroenterology. 2006 Jul; 101(7): 1581-90.

[13] Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. British Journal of Surgery. 2000 Nov; 87(11): 1448-54.

[14] Kim h. j., vazquez roque m. i., camilleri m., stephens d., burton d. d., baxter k., et al. A randomized controlled trial of a probiotic combination VSL# 3 and placebo in irritable bowel syndrome with bloating. Neurogastroenterology and Motility. 2005 Oct; 17(5): 687-96.

[15] O'Sullivan M. Bacterial supplementation in the irritable bowel syndrome. A randomised doubleblind placebo-controlled crossover study. Digestive and Liver Disease. 2000 May; 32(4): 294-301.

[16] Maupas JL, Champemont P, Delforge M. Treatment of irritable bowel syndrome double blind trial of saccharomyces boulardii: 5.

[17] Yoon JS, Sohn W, Lee OY, Lee SP, Lee KN, Jun DW, et al. Effect of multispecies probiotics on irritable bowel syndrome: A randomized, double-blind, placebo-controlled trial: Probiotics in irritable bowel syndrome. Journal of Gastroenterology and Hepatology. 2014 Jan; 29(1): 52-9.

[18] Clinical trial: a multistrain probiotic preparation significantly reduces symptoms of irritable bowel syndrome in a double-blind placebo-controlled study-WILLIAMS-2009-Alimentary Pharmacology & amp; Therapeutics-Wiley Online Library [Internet]. [Cited 2018 Nov 15].

[19] Simrén M, Öhman L, Olsson J, Svensson U, Ohlson K, Posserud I, et al. Clinical trial: the effect of a fermented milk containing three probiotic bacteria in patients with irritable bowel syndrome (IBS)-a randomized, double-blind, controlled study. Alimentary Pharmacology & Therapeutics [Internet]. 2009.

[20] Nobaek S. Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. The American Journal of Gastroenterology. 2000 May; 95(5): 1231-8.

[21] EBSCOhost|16071930|Treatment of Irritable Bowel Syndrome with Lacteol Fort: A Randomized, Double-Blind, Cross-Over Trial. [Internet]. [Cited 2018 Nov 15].

[22] Niedzielin K, Kordecki H, Birkenfeld B. A controlled, double-blind, randomized study on the efficacy of Lactobacillus plantarum 299V in patients with irritable bowel syndrome: European Journal of Gastroenterology & Hepatology. 2001 Oct; 13(10): 1143-7.

[23] Bittner AC, Croffut RM, Stranahan MC. Prescript-assist™ probiotic-prebiotic treatment for irritable bowel syndrome: A methodologically oriented, 2-week, randomized, placebo-controlled, double-blind clinical study. Clinical Therapeutics. 2005 Jun; 27(6): 755-61.

[24] Spiller R, Pélerin F, Cayzeele Decherf A, Maudet C, Housez B, Cazaubiel M, et al. Randomized double blind placebo-controlled trial of *Saccharomyces cerevisiae* CNCM I-3856 in irritable bowel syndrome: improvement in abdominal pain and bloating in those with predominant constipation. United European Gastroenterology Journal. 2016 Jun; 4(3): 353-62.

[25] Niv E, Naftali T, Hallak R, Vaisman N. The efficacy of ATCC 55730 in the treatment of patients with irritable bowel syndrome-a double blind, placebo-controlled, randomized study. Clinical Nutrition. 2005 Dec; 24(6): 925-31.

[26] Evans M, Salewski RP, Christman MC, Girard S-A, Tompkins TA. Effectiveness of Lactobacillus helveticus and Lactobacillus rhamnosus for the management of antibiotic-associated diarrhoea in healthy adults: a randomised, double-blind, placebo-controlled trial. British Journal of Nutrition. 2016 Jul; 116(01): 94-103.

[27] Canani RB, Cirillo P, Terrin G, Cesarano L, Spagnuolo MI, Vincenzo AD, et al. Probiotics for treatment of acute diarrhoea in children: randomised clinical trial of five different preparations. BMJ. 2007 Aug 16; 335(7615): 340.

[28] Wilhelm SM, Brubaker CM, Varcak EA, Kale-Pradhan PB. Effectiveness of Probiotics in the Treatment of Irritable Bowel Syndrome. Pharmacotherapy. 2008 Apr; 28(4): 496-505.

[29] Lorenzo-Zúñiga V, Llop E, Suárez C, Álvarez B, Abreu L, Espadaler J, et al. I.31, a new combination of probiotics, improves irritable bowel syndrome-related quality of life. World J Gastroenterol. 2014 Jul 14; 20(26): 8709-16.

[30] Ducrotté P, Sawant P, Jayanthi V. Clinical trial: Lactobacillus plantarum 299v (DSM 9843) improves symptoms of irritable bowel syndrome. World J Gastroenterol. 2012 Aug 14; 18(30): 4012-8.

[31] Barrett JS, Canale KE, Gearry RB, Irving PM, Gibson PR. Probiotic effects on intestinal fermentation patterns in patients with irritable bowel syndrome. World J Gastroenterol. 2008 Aug 28; 14(32): 5020-4.

[32] Cimperman L, Bayless G, Best K, Diligente A, Mordarski B, Oster M, et al. A Randomized, Double-blind, Placebo-controlled Pilot Study of Lactobacillus reuteri ATCC 55730 for the Prevention of Antibiotic-associated Diarrhea in Hospitalized Adults. Journal of Clinical Gastroenterology. 2011 Oct; 45(9): 785.

[33] Linde K, Ramirez G, Mulrow CD, Pauls A, Weidenhammer W, Melchart D. St John's wort for depression-an overview and meta-analysis of randomised clinical trials. BMJ. 1996 Aug 3; 313(7052): 253-8.

[34] Linde K, Clausius N, Ramirez G, Melchart D, Eitel F, Hedges LV, et al. Are the clinical effects of homoeopathy placebo effects? A meta-analysis of placebo-controlled trials. The Lancet. 1997 Sep; 350(9081): 834-43.