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Review

The Efficacy of Probiotics Supplementation on the Quality of Life of Patients with Gastrointestinal Disease: A Systematic Review of Clinical Studies

Jalal Moludi[1,3], Amir Saber[1,3], Morteza Arab Zozani[2], Shima Moradi[3], Yasaman Azamian[3], Salimeh Hajiahmadi[4], Yahya Pasdar[1], and Fardin Moradi[3]

[1]Department of Nutritional Sciences, School of Nutritional Sciences and Food Technology and [3]Student Research Committee, Kermanshah University of Medical Sciences, Kermanshah 6719851552, Iran
[2]Social Determinants of Health Research Center (SDHRC), School of Health, Birjand University of Medical Sciences, Birjand 32048321, Iran
[4]Department of Nutrition, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd 8915173160, Iran

ABSTRACT: Patients with gastrointestinal (GI) disorders might benefit from probiotic supplementation to resolve their bowel symptoms and enhance their quality of life (QoL). This systematic review aimed to evaluate the effects of oral probiotic supplementation on improving QoL. Relevant studies were systematically searched in online databases, including PubMed, Scopus, Embase, ProQuest, and Google Scholar up to September 2022 using relevant keywords. Studies that were conducted on GI patients and presented QoL outcomes were included. The Revised Cochrane Risk of Bias 2 tool and the Risk Of Bias In Non-randomized Studies of Intervention tool were used to assess the risk of bias. Of the 4,555 results found in the systematic search of databases, only 36 studies were eligible for evaluation. According to this systematic review, 24 studies reported improvements, whereas 12 studies reported no improvements on QoL in GI patients supplemented with probiotics. We found that probiotics may improve the QoL of patients with GI diseases and related metabolic complications. Therefore, probiotics can be a useful supportive treatment strategy in these patients.

Keywords: gastrointestinal diseases, probiotics, quality of life

INTRODUCTION

Functional gastrointestinal disorders (FGIDs) are characterized by a combination of motility issues; visceral hypersensitivity; and changes in mucosal and immune function, gut microbiota, and central nervous system (CNS) processing (Drossman, 2016). Despite being poorly understood because of their complex pathophysiology, FGIDs [including irritable bowel syndrome (IBS), functional dyspepsia, and functional constipation (FC)] account for approximately 33% of all appointments at gastroenterology clinics (Shivaji and Ford, 2014). According to previous studies, more than 66% of individuals suffering from FGIDs have consulted a healthcare professional within the past year, 40% rely on medications regularly, and 33% have undergone unwarranted abdominal surgeries including hysterectomies or cholecystectomies to relieve their symptoms (Jafari et al., 2018). Aside from being costly to manage, these conditions also affect patients' quality of life (QoL), which emphasize their fundamental importance to healthcare systems and society (Jafari et al., 2018). According to previous studies, pathogenic gut microbiota may be responsible for various chronic GI disorders, including cancer and diseases involving inflammation, metabolic, cardiovascular, autoimmune, neurologic, and psychiatric components (Kataoka, 2016; Lynch and Pedersen, 2016; Cani, 2017). The human body harbors the most abundant microorganisms in the GI tract. Therefore, intestinal microflora changes have been observed as a leading mechanism in the occurrence of some GI diseases (Aziz et al., 2013; Guinane and Cotter, 2013).

Probiotics are live microorganisms found in food and dietary supplements that, when consumed, can enhance the host's health and provide nutritional value (Fuller and Gibson, 1998). These microorganisms mostly comprise bacteria and yeasts and naturally exist in fermented foods or some functional food products (Lin, 2003). The

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Correspondence to Amir Saber, E-mail: dr.saber61@gmail.com

most well-known genera of probiotics belong to *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, *Streptococcus*, *Enterococcus*, *Escherichia*, and *Bacillus*. These microorganisms exhibit different health effects based on the species and gender of the host (Marteau et al., 1993). Koretz demonstrated that various factors, including species, dosage, host's immune system, underlying pathology, and treatment duration, influence the efficacy of probiotics in the human microbiota (Koretz, 2018). Recently, many clinical trials have used different forms of probiotics to therapeutically modulate the intestinal microbiome in adults (Fuller and Gibson, 1998; Ferrario et al., 2014; Irwin et al., 2018). Because of their effectiveness in preventing and treating GI disorders, probiotics are being increasingly used in various foods or supplements to improve the microbiome (Fuller and Gibson, 1998; McFarland, 2006; McFarland and Dublin, 2008; Hoveyda et al., 2009). Moreover, several probiotic species have been used in a targeted and specific way for the prevention and treatment of specific diseases and have generally shown positive effects (Ritchie and Romanuk, 2012; Waitzberg et al., 2015; Miller et al., 2016).

In this regard, using some probiotic species can lead to a QoL improvement (Hungin et al., 2013). Research conducted in laboratory and live animal settings has demonstrated that probiotics can effectively diminish bloating, pain, and abdominal symptoms in individuals suffering from IBS (Kim et al., 2003; Aragon et al., 2010; Wong et al., 2015; Staudacher et al., 2017). In addition, studies on adults and children demonstrate the favorable effect of probiotic treatment on stool frequency, stool consistency, and constipation (Chmielewska and Szajewska, 2010). In another study, the administration of probiotics and synbiotics after surgery decreased the incidence of complications and enhanced the QoL and longevity of patients with colorectal cancer (Amitay et al., 2020). While many studies have investigated how probiotics can affect the QoL of individuals with GI diseases, no comprehensive systematic review has been conducted to reveal the potential complementary role of probiotics in patients with GI diseases and to identify existing scientific gaps. Therefore, based on available evidence, the present study investigated whether probiotic supplementation can improve the QoL of most GI patients by improving symptoms.

METHODS

This systematic review was designed based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Furthermore, the study protocol was registered in the International Prospective Register of Systematic Reviews hosted by the Center for Reviews and Dissemination (PROSPERO) (CRD42022382414).

Search strategy

Two researchers conducted a thorough systematic search in five online databases (i.e., PubMed, Scopus, Embase, ProQuest, and Google Scholar) to identify relevant studies. The keywords were carefully selected, and pre-established criteria were used for included studies. The following Medical Subject Headings (MeSH) were applied in certain combinations: "probiotics," "quality of life," "probiotics and quality of life," "probiotics and GI microbiome," "probiotics and GI disease," "probiotics and irritable bowel syndrome," "probiotics and health-related outcomes," and Medical Outcomes Study Short Form 36-Item questionnaire (SF-36).

Inclusion and exclusion criteria

Two researchers independently screened the titles and abstracts in the online database based on the inclusion and exclusion criteria. Eligible studies were required to meet the following inclusion criteria: 1) English-language articles available online (up to September 2022); 2) primary research articles and studies conducted on human individuals; and 3) all clinical trial studies on the effect of probiotics on the QoL in GI patients. Meanwhile, letters, comments, short communications, abstracts, studies on pregnant and lactating women, and *in vitro* and animal research were excluded. Additionally, all bibliographies of pertinent studies were examined to identify potentially relevant studies. After the search was completed, duplicate citations were removed.

Screening and data extraction

Two investigators independently reviewed eligible full text studies. Thereafter, data extraction was conducted using standardized forms and research questions. In case of disputes, a third researcher assessed the precision and quality of the inputted data. Next, variables including general manuscript details (author, country, location, and year), subject characteristics (age, clinical setting or population), study design and intervention characteristics (study quality, study design, sample size, QoL assessment method, probiotic strain, daily dosage, and treatment duration), and QoL summary statistics necessary for systematic review were recorded in a predetermined database. Initially, 94 studies were selected in the comprehensive search. The titles and abstracts of studies were reviewed to exclude papers published in non-English journals (six studies were excluded). Afterward, review articles, study protocols, commentaries, and case reports were removed (11 studies were excluded). Next, the full text of the remaining studies was examined and reviewed. Studies that failed to describe the QoL or those that were non-randomized, non-controlled, or otherwise irrel-

evant were further removed (four studies were excluded). Finally, studies on the population with GI diseases were isolated, and 36 studies were eligible for the final review (Fig. 1).

Quality assessment

The Cochrane Collaboration's tools were used to identify potential sources of bias in the selected studies. Two authors independently assessed each included study using the Revised Cochrane Risk of Bias 2 (RoB2) tool and the Risk Of Bias In Non-randomized Studies of Intervention (ROBINS-I) tool (Higgins et al., 2011). The methodological domains assessed for parallel and cross-over randomized controlled trials (RCTs) included the randomization process, deviation from intended interventions, missing outcome data, outcome measurement, and selection of reported results. Bias was evaluated as judgment for every criterion (indicated as "high risk of bias," "low risk of bias," or "some concerns"). Meanwhile, the methodological domains assessed for non-randomized clinical trials included bias from confounding, bias in participant selection, bias in intervention classification, bias from deviations in interventions, bias from missing data, bias in outcome measurement, and bias in the selection of reported results. Differences between these procedures were settled via agreement or seeking input from a third party, following communication with the authors of the original study for further explanation. If the trials did not provide sufficient information for assessment, we contacted the authors via email and allowed them a period of at least four weeks to reply.

RESULTS

Study selection

After applying all exclusion criteria, the final review was limited to 36 studies. Sixteen studies were related to IBS (Drisko et al., 2006; Choi et al., 2011; Dapoigny et al., 2012; Cappello et al., 2013; Abbas et al., 2014; Lorenzo-Zúñiga et al., 2014; Choi et al., 2015; Šmid et al., 2016; Giannetti et al., 2017; Nobutani et al., 2017; Pinto-Sanchez et al., 2017; Preston et al., 2018; Aroniadis et al., 2019; Catinean et al., 2019; Francavilla et al., 2019; El-Salhy et al., 2020). Eight studies were related to constipation (Ding et al., 2016; Cudmore et al., 2017; Ibarra et al., 2018; Xinias et al., 2018; Dimidi et al., 2019; Kommers et al., 2019; Riezzo et al., 2019; Olgac et al., 2020). Five studies were related to rectal cancer (Ohigashi et al., 2011; Lee et al., 2014; Theodoropoulos et al., 2016; Golkhalkhali et al., 2018; Radvar et al., 2020). One study was related to cirrhosis (Macnaughtan et al., 2020). One study was related to non-celiac gluten sensitivity disease (Di Pierro et al., 2020). One study was related to infant colic (Ahmadipour et al., 2020). One study was related to gastric bypass surgery (Chen et al., 2016). Two studies were related to FGIDs (Ringel-Kulka et al., 2011; Gomi et al., 2018). One study was related to ulcerative colitis (Fujimori et al., 2009). The details of each study are summarized in Tables 1 – 5.

Quality assessment

The risk of bias of included studies is presented in Table 6 and 7. Out of the 32 parallel and cross-over double-

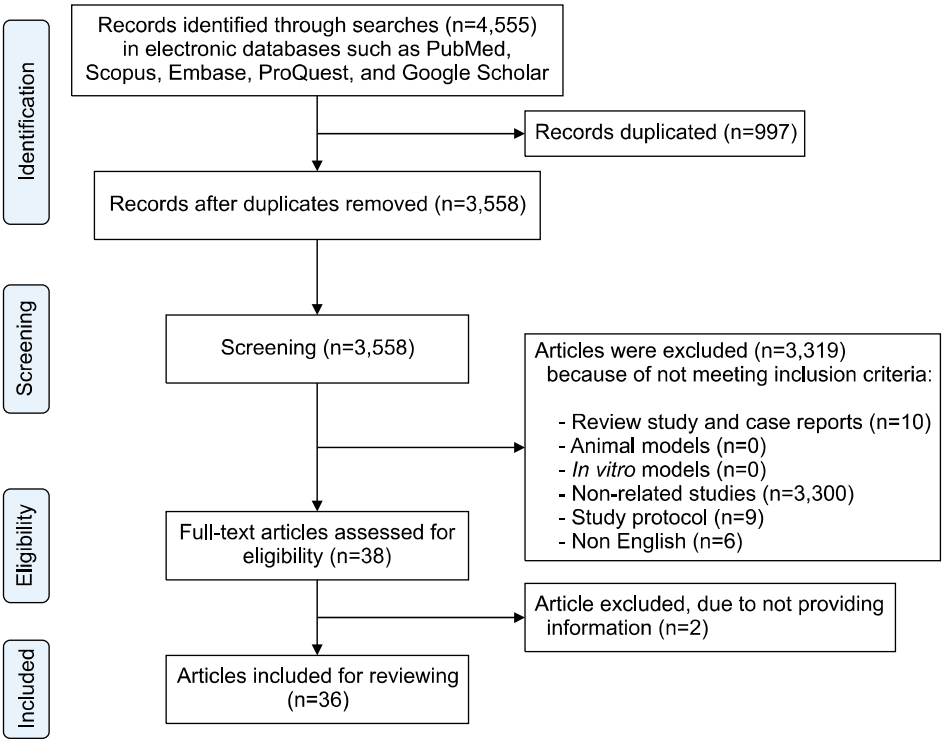

Fig. 1. Flow chart of the study selection process.

Table 1. IBS-related disease: characteristics of selected clinical trials included in the review

Reference	Type of study	Clinical setting/ population	Sample size	Age (year)	Daily dose	Probiotic species	Duration of intervention	System	Main outcomes
El-Salhy et al., 2020 (Norway)	RCT	IBS	165	39.9±9.0	30 g FMT or 60 g FMT at a ratio of 1:1:1 The material for FMT	FMT	3 months	IBS-QoL	Positive effect
Catinean et al., 2019 (Romania)	RCT	IBS	90	18-75 G1=38.77±10.96 G2=39.07±16.00 G3=40.37±11.95	G2=7 days: 1 cap 27 days: 2 cap	G1=*Bifidobacterium longum* W11 G2=five *Bacillus* spp.	34 days G1 and G3=10+24 G2=34	IBS-QoL (SF-36)	Positive effect
Preston et al., 2018 (USA)	RCT	IBS	86	Plac: 39.9 Int: 40.6	2 capsules 50×10^9 CFU	*Lactobacillus acidophilus* CL1285, *L. casei* LBC80R, and *L. rhamnosus* CLR2	12 weeks	IBS-QoL	Positive effect
Giannetti et al., 2017 (Italy)	RCT	Children with IBS and functional dyspepsia	73	8.0-17.9	3 billion (3×10^9) of *Bifidobacterium longum* BB536, 1 billion (1×10^9) of *B. infantis* M-63, 1 billion (1×10^9) of B. breve M-16V	3 *Bifidobacteria*: M-63 *breve* M-16V *longum* BB536	16 weeks: 2-week run-in phase 6 weeks Int 2-week "washout" Afterward, each patient was switched to the other group 6 weeks Int	FDI	Positive effect
Pinto-Sanchez et al., 2017 (Canada)	RCT	IBS	44	Int: 46.5 (30-58) Plac: 40.0 (26-57)	1.0E+10	*Bifidobacterium longum* NCC3001 (BL)	6-week treatment 10 week follow-up	SF-36	Positive effect
Nobutani et al., 2017 (Japan)	RCT	IBS	30	Int: 52.6±20.1 Plac: 45.9±19.5	13×10^8 CFU	*Lactobacillus gasseri* CP2305	4 weeks	IBS-QoL and PSQI-J	Positive effect
Choi et al., 2015 (Korea)	RCT	Non-diarrheal-type IBS	285	20-73 (47)	Group 1: 1.0×10^{10} CFU Groups 2 and 3: 1.5×10^{10} Group 4: 3×10^{10}	*Bacillus subtilis* and *Streptococcus faecium*	4 weeks	IBS-QoL	Positive effect
Abbas et al., 2014 (Pakistan)	RCT	IBS-D	72 64 (completed)	18-60 Int: 37.7±11.6 Plac: 33.0±12.0	750 mg/d	*Saccharomyces boulardii*	2-week run-in 6 weeks Int	IBS-QoL	Positive effect
Lorenzo-Zúñiga et al., 2014 (Spain)	RCT	IBS	73	20-70 Int: 47.5±13.1 46.3±11.6 Plac: 46.5±13.1	$1\text{-}3\times10^{10}$ CFU or $3\text{-}6\times10^9$	Two *Lactobacillus plantarum* (CECT7484 and CECT7485) and one *Pediococcus acidilactici* (CECT7483)	6 weeks	IBS-QoL	Positive effect

Table 1. Continued

Reference	Type of study	Clinical setting/ population	Sample size	Age (year)	Daily dose	Probiotic species	Duration of intervention	System	Main outcomes
Cappello et al., 2013 (Italy)	RCT	IBS	64	38.7±12.6	5×10^9 *Lactobacillus plantarum*, 2×10^9 *L. casei* subp. *rhamnosus* and 2×10^9 *L. gasseri*, 1×10^9 *Bifidobacterium infantis* and 1×10^9 *B. longum*, 1×10^9 *L. acidophilus*, 1×10^9 *L. salivarius* and 1×10^9 *L. sporogenes* and 5×10^9 *Streptococcus thermophilus* Prebiotic inulin 2.2 g	Lyophilized bacteria: *L. plantarum* *L. casei* subp. *rhamnosus* *L. gasseri* *Bifidobacterium infantis* *L. acidophilus* *L. salivarius* *L. sporogenes* *Streptococcus thermophilus* Prebiotic inulin	6 weeks (2-week run-in and 4-week treatment)	SF-36	Positive effect
Choi et al., 2011 (Korea)	RCT	IBS	67	41±13	2×10^{11}	*Saccharomyces boulardii*	4 weeks	IBS-QoL	Positive effect
Drisko et al., 2006 (USA)	Open-label pilot study Prospective outcome study	IBS	20	24-81	10 billion CFU	*Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *L. rhamnosus*, *L. plantarum*, *B. infantis*, *L. salivarius*, *L. bulgaricus*, *L. casei*, *L. brevis*, and *Streptococcus thermophilus*	1 year	IBS-QoL	Positive effect

RCT, randomized control trial; IBS, irritable bowel syndrome; FMT, fecal microbiota transplantation; QoL, quality of life; IBS-QoL, irritable bowel syndrome QoL; IBS-D, diarrhea-dominant irritable bowel syndrome; SF-36, 36-item short form survey; CFU, colony forming unit; FDI, Functional Disability Inventory; Int, intervention; Plac, placebo; PSQI-J, Pittsburgh Sleep Quality Index.

Table 2. Constipation-related disease: characteristics of selected clinical trials included in the review

Reference	Type of study	Clinical setting/population	Sample size	Age	Daily dose	Probiotic species	Duration of intervention	System	Main outcomes
Olgac et al., 2020 (Turkey)	RCT	Children with FC	49	4-16 years	1×10^8 CFU	*Lactobacillus reuteri* DSM 17938 or lactulose	4 weeks	KINDL® HRQOL	Positive effect
Kommers et al., 2019 (Brazil)	RCT	Female university students with intestinal constipation	63	20-40 years Int: 27.15±5.52 Plac: 24.38±5.41	10^9 CFU of each one	*Bifidobacterium lactis* (BL04), *B. bifidum* (Bb-06), *Lactobacillus acidophilus* (La-14), *L. casei* (Lc-11), *Lactococcus lactis* (LL-23)	45 days	PAC-QoL	Positive effect
Xinias et al., 2018 (Greece)	Non-randomized clinical trial	Infants with FC	65	3-13 weeks Int: 1.4±0.8 Plac: 1.7±0.9	Not reported	*Bifidobacterium lactis* BB12	1 month	Not reported (parents completed a QoL)	Positive effect
Cudmore et al., 2017 (Ireland)	RCT	Chronic, FC	69	18-80 years	6×10^8 CFU twice daily	*Lactobacillus rhamnosus* PXN 54 (NCIMB 30188), *Bifidobacterium bifidum* PXN 23 (NCIMB 30179), *L. acidophilus* PXN 35 (NCIMB 30184), *L. plantarum* PXN 47 (NCIMB 30187), and *L. bulgaricus* PXN 39 (NCIMB 30186) Also psyllium and inulin	4 weeks	PAC-QoL	Positive effect

RCT, randomized control trial; FC, functional constipation; CFU, colony forming unit; QoL, quality of life; KINDL® HRQOL, KINDL® Health-Related QoL; PAC-QoL, Patient Assessment of Constipation QoL.

Table 3. Functional gastrointestinal disorders (FGIDs): characteristics of selected clinical trials included in the review

Reference	Type of study	Clinical setting/population	Sample size	Age (year)	Daily dose	Probiotic species	Duration of intervention (weeks)	System	Main outcomes
Ringel-Kulka et al., 2011 (USA)	RCT	Functional bowel disorders	60	18-65 Mean age Int: 36 Plac: 37	Twice a day (2×10^{11} CFU CFU/d)	*Lactobacillus acidophilus* NCFM (L-NCFM) and *Bifidobacterium lactis* Bi-07 (B-LBi07)	8	IBS-QoL	Positive effect

RCT, randomized control trial; CFU, colony forming unit; IBS-QoL, irritable bowel syndrome-quality of life; Int, intervention; Plac, placebo.

Table 4. Colorectal cancer-related disease: characteristics of selected clinical trials included in the review

Reference	Type of study	Clinical setting/population	Sample size	Age (year)	Daily dose	Probiotic species	Duration of intervention	System	Main outcomes
Radvar et al., 2020 (Iran)	RCT	Rectal cancer	38	Int: 57.58±12.78 Plac: 62.89±13.93	2 times a day 1×10^8 CFU/g	*Lactobacillus casei* PXN 37, *L. rhamnosus* PXN 54, *Streptococcus thermophilus* 81 PXN 66, *Bifidobacterium breve* PXN 25, *L. acidophilus* PXN 35, *B. longum* PXN 30, *L. bulgaricus* PXN 39, FOS (fructooligosaccharide), magnesium stearate (source: mineral and vegetable), and vegetable capsule (hydroxypropyl methyl cellulose)	6 weeks	EORTC QLQ-C30	Positive effect
Golkhalkhali et al., 2018 (Malaysia)	RCT	Colorectal cancer	140	<18	Two sachets daily 30 billion (CFUs) per sachet	*Lactobacillus acidophilus* BCMCR 12130, *L. casei* BCMCR 12313, *Lactobacillus lactis* BCMCR 12451, *Bifidobacterium bifidum* BCMCR 02290, *B. longum* BCMCR 02120, and *B. infantis* BCMCR 02129	8 weeks	EORTC QLQ-C30	Positive effect
Lee et al., 2014 (Korea)	RCT	Colorectal cancer	60	56.18±8.86	Twice a day 2×10^9 CFU	Lacidofil (*Lactobacillus rhamnosus* R0011 and *L. acidophilus* R0052)	12 weeks	FACT	Positive effect
Ohigashi et al., 2011 (Japan)	Questionnaire-based study	Colorectal cancer	63	63±9	10 mg of *Bacillus natto* and 30 mg of *Lactobacillus acidophilus*	*B. natto* and *L. acidophilus*	3 months	SF-36 and EORTC QLQ-C30	Positive effect

RCT, randomized control trial; Int, intervention; Plac, placebo; CFU, colony forming unit; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer's 30-item QoL questionnaire version 30; FACT, Functional Assessment of Cancer Therapy; SF-36, 36-item short form survey.

Table 5. Other diseases: characteristics of selected clinical trials included in the review

Reference	Type of study	Clinical setting/ population	Sample size	Age (year)	Daily dose	Probiotic species	Duration of intervention	System	Main outcomes
Di Pierro et al., 2020 (Italy)	Non-randomized clinical trial	Non-celiac gluten sensitivity	30	Int: 46.87±17.06 Plac: 43.53±18.94	1 dose/day 1×10^9 CFU (1 billion)	Bifidobacterium longum ES1 or GFD	3 months	Document of scientific support to the protocol for the diagnosis and follow-up of celiac disease	Positive effect
Chen et al., 2016 (Taiwan)	RCT	Gastric bypass surgery	53	18-60 35.1±8.3	Twice daily A: 5×10^9 CFU (5 billion) B: 8×10^9 CFU (8 billion)	A: 1 g *Clostridium butyricum* MIYAIRI B: 300 mg *Bifidobacterium longum* BB536	2 weeks	mGIQL	Positive effect
Fujimori et al., 2009 (Japan)	RCT	Ulcerative colitis	83	Pro=36±16 Pre=37±13 Syn=35±10	2×10^9 CFU	*Bifidobacterium longum* Also prebiotic (psyllium) and synbiotic	4 weeks	IBDQ	Positive effect

RCT, randomized control trial; Int, intervention; Plac, placebo; Pro, probiotics; Pre, prebiotics; Syn, symbiotic; CFU, colony forming unit; GFD, gluten-free diet; mGIQL, modified Gastrointestinal QoL Index; IBDQ, Inflammatory Bowel Disease Questionnaire.

Table 6. Characteristics of included studies that did not find any effect

Reference	Type of study	Clinical setting/ population	Sample size	Age (year)	Daily dose	Probiotic species	Duration of intervention	System	Main outcomes
Francavilla et al., 2019 (Italy)	RCT	Patients with celiac disease and IBS	109	Age 18 years and above Int: 43.3 (18.8-62.2) Plac: 44.6 (19.3-63.4)	5×10^9 CFU/sachet+5×10^9 CFU/sachet+10×10^9 CFU/sachet+10×10^9 CFU/sachet+10×10^9 CFU/sachet	*Lactobacillus casei* LMG 101/37 P-17504 (5×10^9 CFU/sachet), *L. plantarum* CECT 4528 (5×10^9 CFU/sachet), *Bifidobacterium animalis* subsp. *lactis* Bi1 LMG P-17502 (10×10^9 CFU/sachet), *B. breve* Bbr8 LMG P-17501 (10×10^9 CFU/sachet), *B. breve* BI10 LMG P-17500 (10×10^9 CFU/sachet)	14 weeks	IBS-QoL	Without effect
Aroniadis et al., 2019 (USA)	RCT	IBS	45	18-65 Int: 33 (27-48) Plac: 42 (28-48)	25 capsules perday 0.38 g minimally	Processed donor whole stool per capsule	12 weeks	IBS-QoL	Without effect
Šmid et al., 2016 (Slovenia-Croatia)	RCT	IBS	76	18-65	(1.8×10^7 CFU/g) and (2.5×10^7 CFU/g)	*Lactobacillus acidophilus* La-5® (1.8×10^7 CFU/g) and *Bifidobacterium animalis* ssp. *lactis* BB-12® (2.5×10^7 CFU/g) *Streptococcus thermophilus*	4 weeks	IBS-QoL	Without effect
Dapoigny et al., 2012 (France)	Randomized double-blind pilot study	IBS	47	Int: 46.1±11.3 Plac: 48.0±10.8	6×10^8 CFU	*Lactobacillus casei* variety *rhamnosus* LCR35	4 weeks	GIQLI	Without effect
Riezzo et al., 2019 (Italy)	RCT	FC	56	19-65 42.4±13.8	15 days: four tablets daily Then: two tablets daily One tablet=1×10^8 CFU	*Lactobacillus reuteri* (LR) DSM 17938	105 days	PAC-QoL	Without effect
Dimidi et al., 2019 (UK)	RCT	Constipation	75	18-65 Int: 35 (12) Plac: 31 (10)	1.5×10^{10} CFU/day	*Bifidobacterium lactis* NCC2818	4 weeks	PAC-QoL	Without effect
Ibarra et al., 2018 (France)	RCT	Adults with functional constipation	224	18-70	1×10^9 or 1×10^{10} CFU	*Bifidobacterium animalis* subsp. *lactis* HN019	28 days	PAC-QoL	Without effect
Ding et al., 2016 (China)	RCT (prospective)	Slow transit constipation	93	Plac: 48.3±11.3 Int: 47.2±10.7	0.63 g	Bifid triple viable capsules (BIFICO) and 8 g of soluble dietary fiber	12 weeks	GIQLI	Positive effect
Gomi et al., 2018 (Japan)	RCT	Patients with functional GI disorders	79	20-64 Int: 41.1±10.1 Plac: 41.6±9.9	YIT 10347 = 3×10^7 CFU/mL *Streptococcus thermophilus* YIT 2021 = 1×10^7	*Bifidobacterium bifidum* YIT 10347 *Streptococcus thermophilus* YIT 2021 (in both Plac and Int groups)	4 weeks	SF-36 v2	Without effect
Theodoropoulos et al., 2016 (Netherlands)	RCT	Colectomy for cancer	67	Int: 66.8±2.17 Plac: 69±1.37	Sachets 12 g	*Pediococcus pentosaceus* 5-33:3, *Leuconostoc mesenteroides* 32-77:1, *Lactobacillus paracasei* ssp. *paracasei* 19, and *L. plantarum* 2362 and 2.5 g of each of the four fermentable fibers (prebiotics): β-glucan, inulin, pectin, and resistant starch	15 days	GIQLI and EORTC QLQ-C30	Without effect

Table 6. Continued

Reference	Type of study	Clinical setting/ population	Sample size	Age (year)	Daily dose	Probiotic species	Duration of intervention	System	Main outcomes
Macnaughtan et al., 2020 (UK)	RCT	Cirrhosis	92 (68)	18–78	6.5×10^{9} CFU	*Lactobacillus casei Shirota* (LcS)	3 times per day for 6 months	SF-36	Without effect
Ahmadipour et al., 2020 (Iran)	RCT	Infant colic	72	21–90 days old Int: 52.20±41.885 days Plac: 49.36±23.321 days	5 drops of Pedilact 10^{9} CFU	*Lactobacillus rhamnosus, L. reuteri, Bifidobacterium infantis* probiotics and fructooligosaccharide	28 days	Not reported	Without effect

RCT, randomized control trial; IBS, irritable bowel syndrome; FC, functional constipation; Int, intervention; Plac, placebo; CFU, colony forming unit; IBS-QoL, irritable bowel syndrome QoL; GIQLI, Gastrointestinal Quality of Life Index; PAC-QoL, Patient Assessment of Constipation QoL; SF-36, 36-item short form survey; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer's 30-item QoL questionnaire version 30.

blind RCTs that were included, only 14 studies had low risk of bias. The rest revealed some concerns and high risk in overall risk of bias (Table 7). Furthermore, each of the four non-randomized clinical trials showed a significant potential for bias. Confounding bias was the major concern in non-randomized clinical trials (Table 8).

Characteristics of included studies

The median age of participants across studies was 18 – 81 years, and the duration of probiotic supplementation ranged from 15 days to 16 weeks. In 36 studies, 2,942 patients with GI disease were supplemented with probiotics, and the QoL of individuals was assessed using a questionnaire. All studies were randomized trials that were published from 2006 to 2020. Five studies were conducted in Italy (Cappello et al., 2013; Giannetti et al., 2017; Francavilla et al., 2019; Riezzo et al., 2019; Di Pierro et al., 2020). Four studies were conducted in Japan (Fujimori et al., 2009; Ohigashi et al., 2011; Nobutani et al., 2017; Gomi et al., 2018). Four studies were conducted in the USA (Drisko et al., 2006; Ringel-Kulka et al., 2011; Preston et al., 2018; Aroniadis et al., 2019). Three studies were conducted in Korea (Choi et al., 2011; Lee et al., 2014; Choi et al., 2015). Two studies were conducted in France (Dapoigny et al., 2012; Ibarra et al., 2018). Two studies were conducted in the UK (Dimidi et al., 2019; Macnaughtan et al., 2020). Two studies were conducted in Iran (Ahmadipour et al., 2020; Radvar et al., 2020). One study was conducted in Norway (El-Salhy et al., 2020). One study was conducted in Canada (Pinto-Sanchez et al., 2017). One study was conducted in Romania (Catinean et al., 2019). One study was conducted in Pakistan (Abbas et al., 2014). One study was conducted in Spain (Lorenzo-Zúñiga et al., 2014). One study was conducted in Turkey (Olgac et al., 2020). One study was conducted in Brazil (Kommers et al., 2019). One study was conducted in Greece (Xinias et al., 2018). One study was conducted in Ireland (Cudmore et al., 2017). One study was conducted in China (Ding et al., 2016). One study was conducted in the Netherlands (Theodoropoulos et al., 2016). One study was conducted in Malaysia (Golkhalkhali et al., 2018). One study was conducted in Taiwan (Chen et al., 2016). One study was conducted in Slovenia-Croatia (Šmid et al., 2016).

Health-related quality of life (HRQOL) instruments

The HRQOL instruments used in the included studies were either generic or GI-specific measures. Five studies used SF-36. Thirteen studies used the IBS-QoL questionnaire (Drisko et al., 2006; Choi et al., 2011; Ringel-Kulka et al., 2011; Abbas et al., 2014; Lorenzo-Zúñiga et al., 2014; Choi et al., 2015; Šmid et al., 2016; Nobutani et al., 2017; Preston et al., 2018; Aroniadis et al., 2019; Catinean et al., 2019; Francavilla et al., 2019; El-Salhy et

Table 7. Assessment of risk of bias for randomized and cross-over clinical trials using the Cochrane Risk of Bias 2 tool

Reference	Risk domain					
	Bias arising from the randomization process	Bias because of deviations from the intended intervention	Missing outcome data	Bias in outcome measurement	Bias in the selection of reported results	Overall risk of bias
Fujimori et al., 2009	Low	High	High	Low	Some concerns	High
Chen et al., 2016	Some concerns	Low	High	Low	Some concerns	High
Ahmadipour et al., 2020	Some concerns	Low	Low	Low	Low	Some concerns
Macnaughtan et al., 2020	Low	Low	Low	Low	Low	Low
Lee et al., 2014	Low	Low	High	Low	Low	High
Theodoropoulos et al., 2016	Low	Low	Low	Low	Low	Low
Golkhalkhali et al., 2018	Low	Low	Low	Low	Low	Low
Radvar et al., 2020	Low	Low	Low	Low	Low	Low
Ringel-Kulka et al., 2011	Low	Low	Low	Low	Low	Low
Gomi et al., 2018	Low	Low	Low	Low	Low	Low
Ding et al., 2016	Low	Low	Some concerns	Low	Low	Some concerns
Cudmore et al., 2017	Low	Low	Low	Low	Low	Low
Ibarra et al., 2018	Low	Low	High	Low	Low	High
Dimidi et al., 2019	Low	Low	Low	Low	Low	Low
Kommers et al., 2019	Low	Low	High	Low	Low	High
Riezzo et al., 2019	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns
Olgac et al., 2020	Some concerns	High	Some concerns	Low	Some concerns	High
Choi et al., 2011	Low	Low	High	Low	Low	High
Dapoigny et al., 2012	Low	Low	Some concerns	Low	Some concerns	Some concerns
Cappello et al., 2013	Low	Low	Some concerns	Low	Some concerns	Some concerns
Lorenzo-Zúñiga et al., 2014	Low	Low	Some concerns	Low	Some concerns	Some concerns
Abbas et al., 2014	Low	Low	Some concerns	Low	Some concerns	Some concerns
Choi et al., 2015	Low	Low	Low	Low	Low	Low
Šmid et al., 2016	Low	Low	Low	Low	Low	Low
Nobutani et al., 2017	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Pinto-Sanchez et al., 2017	Low	Low	Low	Low	Low	Low
Giannetti et al., 2017	Low	Low	Low	Low	Low	Low
Preston et al., 2018	Some concerns	Low	Low	Low	Low	Some concerns
Aroniadis et al., 2019	Low	Low	High	Low	Low	High
Francavilla et al., 2019	Low	Low	Low	Low	Low	Low
Catinean et al., 2019	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
El-Salhy et al., 2020	Low	Low	Low	Low	Low	Low

Table 8. Assessment of risk of bias for non-randomized clinical trials using the Cochrane Risk of Bias 2 tool

Reference	Risk domain							
	Bias because of confounding	Bias because of the selection of participants	Bias in the classification of intervention	Bias because of deviations from the intended intervention	Bias because of missing outcome data	Bias in outcome measurement	Bias in the selection of reported results	Overall risk of bias
Drisko et al., 2006	High	Low	Some concerns	Low	Some concerns	Low	Low	High
Xinias et al., 2018	High	Low	Low	Low	Low	Low	Low	High
Ohigashi et al., 2011	High	Low	Some concerns	Low	Some concerns	Low	Some concerns	High
Di Pierro et al., 2020	High	Low	Low	Low	Low	Low	Low	High

al., 2020). Three studies used the Gastrointestinal Quality of Life Index (GIQLI) (Chen et al., 2016; Ding et al., 2016; Theodoropoulos et al., 2016). Four studies used the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) (Ohigashi et al., 2011; Theodoropoulos et al., 2016; Golkhalkhali et al., 2018; Radvar et al., 2020). One study used the Functional Disability Inventory (FDI) (Giannetti et al., 2017). One study used the Pittsburgh Sleep Quality Index-Japanese version (PSQI-J) (Nobutani et al., 2017). One study used the Functional Assessment of Cancer Therapy (FACT) (Lee et al., 2014). One study used the modified Gastrointestinal QoL (mGIQL). One study used the Inflammatory Bowel Disease Questionnaire (IBDQ) (Fujimori et al., 2009). One study used the KINDL® Health-Related Quality of Life (KINDL® HRQOL) (Olgac et al., 2020). One study used the "Document of scientific support to the protocol for the diagnosis and follow-up of celiac disease" (Di Pierro et al., 2020). Two studies did not report the method used to measure the QoL (Xinias et al., 2018; Ahmadipour et al., 2020).

Probiotics

Among the 36 studies, eight different bacterial genera were used as probiotic supplements: a) *Lactobacillus*, b) *Bifidobacterium*, c) *Streptococcus*, d) *Saccharomyces*, e) *Bacillus*, f) *Enterococcus*, g) *Pediococcus*, and h) *Clostridium*. *L. gasseri* species were used as a supplement in two studies (Cappello et al., 2013; Nobutani et al., 2017). *L. acidophilus* was used in nine studies. *L. plantarum* was used in five studies (Drisko et al., 2006; Cappello et al., 2013; Lorenzo-Zúñiga et al., 2014; Theodoropoulos et al., 2016; Cudmore et al., 2017). *B. bifidum* was used in five studies (Drisko et al., 2006; Cudmore et al., 2017; Golkhalkhali et al., 2018; Gomi et al., 2018; Kommers et al., 2019). *L. casei* was used in seven studies (Drisko et al., 2006; Dapoigny et al., 2012; Cappello et al., 2013; Golkhalkhali et al., 2018; Kommers et al., 2019; Macnaughtan et al., 2020; Radvar et al., 2020). *L. salivarius* and *L. sporogenes* were used in one study (Cappello et al., 2013). *L. brevis* (Drisko et al., 2006), *L. paracasei* (Theodoropoulos et al., 2016), *Leuconostoc mesenteroides* (Theodoropoulos et al., 2016), *B. breve* (Radvar et al., 2020), *Bacillus subtilis* (Choi et al., 2015), *B. natto* (Choi et al., 2015), *E. faecalis* (Ohigashi et al., 2011), *P. pentosaceus* (Ohigashi et al., 2011), and *C. butyricum* (Chen et al., 2016) were each used in one study. Meanwhile, *Lactobacillus bulgaricus* (Drisko et al., 2006; Cudmore et al., 2017; Radvar et al., 2020), *Bifidobacterium animalis* (Cappello et al., 2013; Šmid et al., 2016; Ibarra et al., 2018), and *L. reuteri* (Riezzo et al., 2019; Ahmadipour et al., 2020; Olgac et al., 2020) were each used in three studies. *L. rhamnosus* was used in five studies (Drisko et al., 2006; Lee et al., 2014; Cudmore et al., 2017; Ahmadipour et al., 2020; Radvar et al., 2020). *Lactococcus lactis* (Golkhalkhali et al., 2018; Kommers et al., 2019), *Saccharomyces boulardii* (Choi et al., 2011; Abbas et al., 2014), and *P. acidilactici* (Drisko et al., 2006; Ibarra et al., 2018) were each used in two studies. *B. longum* was used in eight studies (Drisko et al., 2006; Fujimori et al., 2009; Cappello et al., 2013; Chen et al., 2016; Golkhalkhali et al., 2018; Ahmadipour et al., 2020; Di Pierro et al., 2020; Radvar et al., 2020). *B. lactis* (Ringel-Kulka et al., 2011; Xinias et al., 2018; Dimidi et al., 2019; Kommers et al., 2019) and *Streptococcus thermophilus* (Drisko et al., 2006; Šmid et al., 2016; Gomi et al., 2018; Radvar et al., 2020) were each used in four studies. Most probiotic species that were used as supplements in the RCT studies included *Lactobacillus acidophilus*, *B. longum*, and *L. casei*. *Lactobacillus* and *Bifidobacterium* are the two most commonly studied probiotic genera in clinical GI studies. The details of this section are summarized in Table 9.

Overall, the investigation of the effect of different types of probiotic supplementation on the QoL of GI patients in RCT studies showed that 23 studies reported improvement in the QoL of patients (Drisko et al., 2006; Fujimori et al., 2009; Choi et al., 2011; Ringel-Kulka et al., 2011; Ohigashi et al., 2011; Cappello et al., 2013; Abbas et al., 2014; Lee et al., 2014; Lorenzo-Zúñiga et al., 2014; Choi et al., 2015; Chen et al., 2016; Cudmore et al., 2017; Giannetti et al., 2017; Nobutani et al., 2017; Pinto-Sanchez et al., 2017; Golkhalkhali et al., 2018; Preston et al., 2018; Ringel-Kulka et al., 2011; Xinias et al., 2018; Kommers et al., 2019; Di Pierro et al., 2020; El-Salhy et al., 2020; Olgac et al., 2020; Radvar et al., 2020), whereas 12 studies reported no improvement in the QoL of patients after probiotic supplementation (Dapoigny et al., 2012; Ding et al., 2016; Šmid et al., 2016; Theodoropoulos et al., 2016; Gomi et al., 2018; Ibarra et al., 2018; Aroniadis et al., 2019; Dimidi et al., 2019; Riezzo et al., 2019; Ahmadipour et al., 2020; Francavilla et al., 2019; Macnaughtan et al., 2020) (Table 6).

Irritable bowel syndrome (IBS)

Based on evidence provided by the included studies, supplementation with the following probiotic species has been reported to be effective in IBS: *Bifidobacterium longum* W11 and *Bacillus* spp. (Catinean et al., 2019); bifidobacteria (Giannetti et al., 2017); *Bifidobacterium longum* (Pinto-Sanchez et al., 2017); *Bacillus subtilis* and *Streptococcus faecium* (Pinto-Sanchez et al., 2017); *Saccharomyces boulardii* (Abbas et al., 2014); *Lactobacillus plantarum*, *L. casei* subp. *rhamnosus*, *L. gasseri*, *Bifidobacterium infantis*, *L. acidophilus*, *L. salivarius*, *L. sporogenes*, and *Streptococcus thermophilus* (Cappello et al., 2013); *L. plantarum* and *Pediococcus acidilactici* (Lorenzo-Zúñiga et al., 2014); *Saccharomyces boulardii* (Choi et al., 2011); *L. acidophilus*, *B. bifidum*,

Table 9. Genus and species of probiotic supplementation in the included studies

Genus	Species	Studies wherein probiotic supplements were effective	Studies wherein probiotic supplements were ineffective
Lactobacillus	*Lactobacillus gasseri*	Cappello et al., 2013	Nobutani et al., 2017
	Lactobacillus acidophilus[1)]	Cappello et al., 2013, Kommers et al., 2019, Cudmore et al., 2017, Ringel-Kulka et al., 2011, Radvar et al., 2020, Golkhalkhali et al., 2018, Lee et al., 2014, Ohigashi et al., 2011	Šmid et al., 2016
	Lactobacillus plantarum	Lorenzo-Zúñiga et al., 2014, Cappello et al., 2013, Drisko et al., 2006, Cudmore et al., 2017, Theodoropoulos et al., 2016	-
	Lactobacillus casei[1)]	Cappello et al., 2013, Drisko et al., 2006, Kommers et al., 2019, Radvar et al., 2020, Golkhalkhali et al., 2018	Dapoigny et al., 2012, Macnaughtan et al., 2020
	Lactobacillus salivarius	Cappello et al., 2013	-
	Lactobacillus sporogenes	Cappello et al., 2013	-
	Lactobacillus brevis	Drisko et al., 2006	-
	Lactobacillus bulgaricus	Drisko et al., 2006, Cudmore et al., 2017, Radvar et al., 2020	-
	Lactobacillus salivarius	Drisko et al., 2006	-
	Lactobacillus rhamnosus	Drisko et al., 2006, Cudmore et al., 2017, Radvar et al., 2020, Lee et al., 2014	Ahmadipour et al., 2020
	Lactobacillus reuteri	Olgac et al., 2020	Riezzo et al., 2019, Ahmadipour et al., 2020
	Lactococcus lactis	Kommers et al., 2019, Golkhalkhali et al., 2018	-
	Lactobacillus paracasei	Theodoropoulos et al., 2016	-
	Leuconostoc mesenteroides	Theodoropoulos et al., 2016	-
Bifidobacterium	*Bifidobacterium bifidum*	Drisko et al., 2006, Kommers et al., 2019, Cudmore et al., 2017, Abbas et al., 2014	Gomi et al., 2018
	Bifidobacterium longum[1)]	Cappello et al., 2013, Drisko et al., 2006, Radvar et al., 2020, Golkhalkhali et al., 2018, Di Pierro et al., 2020, Chen et al., 2016, Fujimori et al., 2009	Ahmadipour et al., 2020
	Bifidobacterium animalis	Cappello et al., 2013	Šmid et al., 2016, Ibarra et al., 2018
	Bifidobacterium lactis	Kommers et al., 2019, Xinias et al., 2018, Ringel-Kulka et al., 2011	Dimidi et al., 2019
	Bifidobacterium breve	Radvar et al., 2020	-
Streptococcus	*Streptococcus thermophilus*	Drisko et al., 2006, Radvar et al., 2020	Šmid et al., 2016, Gomi et al., 2018
Saccharomyces	*Saccharomyces boulardii*	Abbas et al., 2014, Choi et al., 2011	-
Bacillus	*Bacillus subtilis*	Choi et al., 2015	-
	Bacillus natto	Ohigashi et al., 2011	-
Enterococcus	*Enterococcus faecalis*	Choi et al., 2015	-
Pediococcus	*Pediococcus pentosaceus*	Theodoropoulos et al., 2016	-
	Pediococcus acidilactici	Drisko et al., 2006	Ibarra et al., 2018
Clostridium	*Clostridium butyricum*	Chen et al., 2016	-

[1)] *Lactobacillus* and *Bifidobacterium* were the most common genera of probiotics that were used to study the effects of probiotic supplementation in clinical gastrointestinal investigations.
-, not available.

L. rhamnosus, *L. plantarum*, *B. infantis*, *L. salivarius*, *L. bulgaricus*, *L. casei*, *L. brevis*, and *Streptococcus thermophilus* (Drisko et al., 2006). Despite these results, no differences were observed with regard to the effects of supplementation with probiotics or placebos among patients with IBS when using the following probiotic species: *L. casei*, *L. plantarum*, *B. animalis* subsp. *lactis* Bi1 LMG P-17502, *B. breve* Bbr8 LMG P-17501, and *B. breve* Bl10 LMG P-17500 (Francavilla et al., 2019); *L. acidophilus* CL1285, *L. casei* LBC80R, and *L. rhamnosus* CLR2 (Francavilla et al., 2019); *L. acidophilus*, *B. animalis* ssp, and *S. thermophilus* (Šmid et al., 2016); and *L. casei* and *L. casei rhamnosus* LCR35 (Dapoigny et al., 2012).

Rectal cancer

Based on evidence provided by the included studies, the following probiotic species have been demonstrated to improve overall health status and QoL and minimize

certain side effects of chemotherapy in patients with cancer: *Lactobacillus casei* PXN 37, *L. rhamnosus* PXN 54, *Streptococcus thermophilus* PXN 66, *Bifidobacterium breve* PXN 25, *L. acidophilus* PXN 35, *B. longum* PXN 30, and *L. bulgaricus* PXN 39 (Radvar et al., 2020); *L. acidophilus* BCMCR 12130, *L. casei* BCMCR 12313, *L. lactis* BCMCR 12451, *B. bifidum* BCMCR 02290, *B. longum* BCMCR 02120, and *B. infantis* BCMCR 02129 (Golkhalkhali et al., 2018); and *Bacillus natto* and *L. acidophilus* (Ohigashi et al., 2011). However, no significant changes in cancer-related QoL were observed in patients with cancer receiving supplementation with probiotics or placebo when using the following probiotic species: *Pediococcus pentosaceus* 5-33:3, *Leuconostoc mesenteroides* 32-77:1, *L. paracasei* ssp. *paracasei* 19, and *L. plantarum* 2362 (Theodoropoulos et al., 2016) and Lacidofil (*L. rhamnosus* R0011, *L. acidophilus* R0052) (Lee et al., 2014).

Functional gastrointestinal disorders (FGIDs)

According to several studies, probiotic supplementation with the following species had no effect on the QoL of patients with FGIDs: *Bifidobacterium bifidum* YIT 10347 and *Streptococcus thermophilus* YIT 2021 (in both placebo and intervention groups) (Gomi et al., 2018) and *L. acidophilus* NCFM (L-NCFM) and *B. lactis* Bi-07 (B-LBi07) (Ringel-Kulka et al., 2011).

Functional constipation (FC)

Based on evidence provided by the included studies, supplementation with the following probiotic species could improve FC and the QoL of patients: *Lactobacillus reuteri* DSM 17938 or lactulose (Olgac et al., 2020), *Bifidobacterium lactis* (BL04), *B. bifidum* (Bb-06), *L. acidophilus* (La-14), *L. casei* (Lc-11), and *Lactococcus lactis* (LL-23) (Kommers et al., 2019); *B. lactis* NCC2818 (Dimidi et al., 2019); *B. lactis* BB12 (Xinias et al., 2018); and *Lactobacillus rhamnosus* PXN 54 (NCIMB 30188), *B. bifidum* PXN 23 (NCIMB 30179), *L. acidophilus* PXN 35 (NCIMB 30184), *L. plantarum* PXN 47 (NCIMB 30187), and *L. bulgaricus* PXN 39 (NCIMB 30186) (Cudmore et al., 2017). However, *B. animalis* subsp. *lactis* HN019 (Ibarra et al., 2018), *L. reuteri* DSM 17938 (Riezzo et al., 2019), and Bifid triple viable capsules (Ding et al., 2016) could not improve the QoL of these patients. The various methods used to assess gut microbiota and other key clinical findings for GI diseases are shown in Table 10.

Table 10. Notable outcomes of selected RCT studies assessing the effects of probiotics on GI diseases

Reference	Gut microbiota assessment	Outcomes of GI symptoms
Macnaughtan et al., 2020, UK	-	-
Giannetti et al., 2017, Italy	-	In IBS, *Bifidobacteria* supplementation resulted in a complete resolution of abdominal pain in a significantly higher proportion of children
Cappello et al., 2013 Italy (Rome)	-	-
Cudmore et al., 2017, Ireland	-	Symptoms of constipation improved
Fujimori et al., 2009, Japan	-	Emotional function increased in the probiotic and synbiotic groups
Gomi et al., 2018, Japan	-	The YIT10347 group had significantly higher relief rates of overall gastrointestinal symptoms, upper gastrointestinal symptoms, flatus, and diarrhea than the placebo group
Francavilla et al., 2019, Italy	· Using plate counts and 16S rRNA gene-based analysis · Fecal samples (5 g) were mixed with 45 mL of sterilized physiological solution and homogenized. Viable bacterial cells were counted as described by De Angelis et al. · To determine the identities of bacteria, sequences were first queried using a distributed BLASTn.NET algorithm24 against 16S bacterial sequences derived from NCBI.	-
Radvar et al., 2020, Iran	-	Body weight decreased in the synbiotic and placebo groups
Aroniadis et al., 2019, USA	16S rRNA sequencing	-
Chen et al., 2016, Taiwan	-	Complaints of abdominal pain, abdominal bloating, excessive passage of gas, foul smell of flatulence, belching, abdominal noises, and heartburn were significantly improved in the entire sample

Table 10. Continued

Reference	Gut microbiota assessment	Outcomes of GI symptoms
Dapoigny et al., 2012, France	Extraction of total bacterial DNA (QIAamp Fast DNA Stool Mini Kit, QIAGEN), the presence of *Lactobacillus casei* variety *rhamnosus* was specifically determined by qualitative polymerase chain reaction (PCR – primer pairs hyb-21) – cycles of amplification.	A decrease in the abdominal pain severity score was observed with LCR35
Choi et al., 2015, Korea	-	The abdominal pain/discomfort score in treatment group 4 was more prominently improved compared with that of the placebo group In patients with constipation-predominant IBS, the improvements in stool frequency and consistency were significantly higher in treatment groups 4 and 1, respectively, than those in the placebo group There were more favorable tendencies of effects on bloating in all treatment groups than in the placebo group
El-Salhy et al., 2020, Norway	16S rRNA gene sequencing	-
Ding et al., 2016, China	-	During the intervention period, patients who were treated with the synbiotic exhibited increased stool frequency, improved stool consistency, decreased colonic transit time, and improved constipation-related symptoms
Ohigashi et al., 2011, Japan	-	Defecation frequency, anal pain, and Wexner score were significantly poorer in the rectal group than in the colonic group
Ringel-Kulka et al., 2011, USA	Quantitative real-time polymerase chain reaction of fecal samples	Abdominal bloating improved in the probiotic group compared with the placebo group at 4 and 8 weeks
Dimidi et al., 2019, UK	Quantitative polymerase chain reaction	-
Šmid et al., 2016, Slovenia & Croatia	-	Significant improvements in bloating severity, satisfaction with bowel movements
Golkhalkhali et al., 2018, Malaysia	-	Nausea, vomiting, and diarrhea significantly improved in the treatment group
Theodoropoulos et al., 2016, Netherlands	-	Differences in the EORTC QLQ-C30 "diarrhea" domain score from baseline were better after synbiotic administration after 3 (P=0.04) and 6 months (P=0.003)
Nobutani et al., 2017, Japan	· Purified DNA was used as a template for the following two-step polymerase chain reaction. · Fecal microbiota was measured using fecal bacterial 16S rDNA V4-V6 region-targeted pyrosequencing.	CP2305 favorably changed the fecal characteristics compared with placebo among patients with IBS with either diarrhea or constipation subtypes
Drisko et al., 2006, USA	-	Significant improvements in pain were observed (P=0.05)

RCT, randomized controlled trial; GI, gastrointestinal; IBS, irritable bowel syndrome; NCBI, National Center for Biotechnology Information; QoL, quality of life; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer's 30-item QoL questionnaire version 30; -, not available.

DISCUSSION

To the best of our knowledge, this study is the first systematic evaluation examining how different probiotic species affect the QoL of patients with GI disorders. According to the 10 different QoL assessment systems used in recent clinical studies (SF-36, IBS-QoL, GIQLI, EORTC QLQ-C30, FDI, PSQI-J, FACT, mGIQL, IBDQ, and KINDL® HRQOL), different probiotic species (especially *Lactobacillus acidophilus*, *Bifidobacterium longum*, and *L. casei*) significantly improved the QoL of GI patients. Moreover, the clinical trial studies included in this systematic review did not report any side effects of probiotic supplementation. Generally, based on the studies reviewed in this article, different bacterial strains effectively improved the QoL of patients with IBS, rectal cancer, and FC; however, they did not improve the QoL of FC and related diseases. There is a direct relationship between QoL and psychological and physical parameters. Moreover, psychological pathways are responsible for every benefit of probiotics. The combined delivery of *Bifidobacterium* and *Lactobacillus* species in humans reduces responses to stress and negative stimuli, suggesting that probiotics indirectly affect QoL through perception and mood (Messaoudi et

al., 2011; Steenbergen et al., 2015; McKean et al., 2017).

Probiotic supplementation and IBS

After the idea linking the gut microbiome with human illnesses was put forward, researchers have investigated whether microbiome changes could be found in GI diseases (Pimentel and Lembo, 2020). Several studies have identified less microbial diversity or richness in individuals with IBS than in those without (Codling et al., 2010; Carroll et al., 2012; Jeffery et al., 2012; Ng et al., 2013; Giamarellos-Bourboulis et al., 2015; Maharshak et al., 2018). However, one study did not (Ponnusamy et al., 2011). The majority of trials have assessed how well probiotics work in patients with IBS, many of whom have significant cognitive impairments (Quigley, 2009). The results from a meta-analysis of 15 controlled studies discovered that probiotics decreased pain levels and symptom severity in IBS (Didari et al., 2015). However, the best strain, dose, formulation, and length of treatment remain unknown (Pimentel and Lembo, 2020).

When probiotics were utilized for treating IBS, *Bifidobacterium infantis* 35624 demonstrated a notable enhancement in alleviating abdominal discomfort/pain, bloating/distention, and/or bowel movement difficulties compared with placebo (O'Mahony et al., 2005). Moreover, fecal consistency was significantly improved by probiotic supplementation compared with placebo, which could indirectly improve patients' QoL (Cha et al., 2012). Hollister et al., examined how bacterial families are linked to daily GI symptoms and additional forms of pain including heartburn, joint pain, muscle aches, back pain, and headache. They found that various families under Firmicutes (*Dehalobacteriaceae*, *Oscillospiraceae*, *Mogibacteriaceae*, *Ruminococcaceae*) are associated with lower extra-intestinal pain (Hollister et al., 2020). Moreover, *in vitro* and *in vivo* studies demonstrated that probiotics can effectively decrease bloating and abdominal symptoms in patients with IBS (Kim et al., 2003; Aragon et al., 2010; Wong et al., 2015; Staudacher et al., 2017).

Probiotic supplementation and cancer

Cancer and its treatments are commonly accompanied by fatigue. Several studies have demonstrated intestinal microbiome changes in patients with cancer, chronic fatigue syndrome, and other neuropsychiatric disorders (Hajjar et al., 2021). Hajjar et al., revealed that cancer patients with varying levels of fatigue may exhibit diverse gut microbiome compositions. Because of the significance of the microbiome in mucosal immunity and the growing understanding of the link between the gut-brain axis and fatigue and other symptoms, disruption in intestinal microbiota may play a key role in these conditions. On the other hand, improving the microbiome can reduce fatigue severity in patients with cancer and improve their QoL. This research indicates the necessity for further studies on how adjusting the gut microbiome can affect fatigue and enhance QoL in individuals with cancer (Hajjar et al., 2021).

To date, the exact mechanisms behind the effect of gut microbiota on cancer remain unknown. Nevertheless, the gut microbiome could have a significant impact on cancer development through various mechanisms (Grivennikov et al., 2012). First, there are differences in the gut microbial content between individuals with cancer and those without, which may have carcinogenesis effects and contribute to cancer development. For instance, research on the human microbiome revealed notable variations in the prevalence of certain microbes in the cancer group compared with the control group (Bultman, 2014). The second mechanism is the well-known link between inflammation and intestinal microbiota and metabolism, which are cancer characteristics (Tlaskalova-Hogenova et al., 2014). In the metabolic pathway, plant-derived foods are metabolized by intestinal microbiota to biologically active compounds that may be carcinogenic (Tlaskalova-Hogenova et al., 2014). Some studies suggested that the perioperative administration of probiotics/synbiotics reduces the prevalence of side effects and improves the QoL and survival of patients with colorectal cancer (Amitay et al., 2020).

Probiotic supplementation and FC

The prevalence of FC is high in the elderly and is associated with poor QoL. According to previous studies, the most common symptoms of FC that significantly affect the health-related QoL of adults include stool stiffness, squeezing, and feeling of anal obstruction (Norton, 2006; Arco et al., 2022), wherein patients with FC scored lower in all dimensions of the EQ5D3L than those without. European Quality of Life 5 Dimensions 3 Level Version (EQ5D3L) is recognized as an effective and useful assessment tool for comparing QoL in different conditions. However, some researchers also recommend the use of FC-specific QoL measurements, such as assessing a patient's QoL in constipation (Marquis et al., 2005). Moreover, FC has been reported to be associated with serious mental illness (Merkel et al., 1993; Towers et al., 1994). One study showed that patients with FC are more likely to experience depression and anxiety, according to the corresponding EQ5D3L subscale. Thus, primary care teams and specialists should take into account the impact of FC on the QoL of the elderly, considering the wide range of factors to enhance the overall health of this group (Arco et al., 2022). Additionally, evidence indicated that probiotic therapy has a positive impact on defecation frequency, stool consistency, and constipation condition in adults and children (Chmielewska and Szajewska, 2010).

Mechanism of action of probiotics in improving the QoL of GI patients

Age, health conditions, and food choices play a significant role in shaping the microbiota composition. A previous study showed that the microorganisms found in individuals between the ages of 65 and 96 years are distinct from those in younger adults, showing elevated levels of cluster IV of *Bacteroides* and *Clostridium*, as well as specific sequences unique to older individuals (Claesson et al., 2011). Various illnesses are linked to alterations in microflora (known as dysbiosis), ranging from GI conditions such as IBS and inflammatory bowel disease to non-GI conditions such as obesity and diabetes (Shanahan, 2013). In dysbiosis, the diversity of commensal microbiota is decreased, and the interaction between the immune system and the gut microbiota is disturbed. In fact, some gut bacteria increase the production of proinflammatory factors, whereas others cause the production of proinflammatory factors (de Oliveira et al., 2017). Probiotic consumption ensures the effect of healthy microbiota homeostasis in the intestinal mucosa by modulating systemic immune responses and seems to be effective as supportive treatment in GI disorders. The mechanism of action of probiotics in improving dysbiosis includes the following: improving mucus secretion, producing antimicrobial peptides, maintaining the function of the gastric-intestinal-epithelial barrier, and ensuring proper interaction between intestinal microbiota and mucosal immune cells (Bron et al., 2017; López-Moreno et al., 2020). Moreover, probiotics can reverse dysbiosis by preventing the colonization of pathogenic bacteria in the gut and maintaining the intestinal mucosa through the production of short-chain fatty acids (Dazıroğlu and Yıldıran, 2023).

With regard to nutrition, the impact of eating on the microbiome has been thoroughly researched. A habitual long-term diet is strongly associated with enterotypes. Animal fat/protein is linked to enterotype 1, whereas carbohydrates are linked to enterotype 2. On the other hand, acute feeding with diets containing different fats and non-starch polysaccharides alters the human microbial phase, indicating that the manipulation of major dietary nutrients is responsible for most changes in microbiota (Faith et al., 2011; Wu et al., 2011). Some approaches for regulating GI flora, especially the use of probiotic organisms, have been sought as ways to promote health and, in some cases, treatment of diseases (Whelan and Quigley, 2013).

In addition, the gut microbiota is associated with many GI-related syndromes, including IBS. Hence, there is an increasing focus on controlling the microbiota as a treatment alternative. Since microbial flora is connected to the CNS via the cerebrointestinal axis, additional changes in this relationship have been identified as the mechanisms of IBS, which function in the intestines through central and peripheral pathways and microbial metabolites (Distrutti et al., 2004; Parkes et al., 2008; Bhattarai et al., 2017).

Limitations and future directions

This review has some limitations. First, there may be language bias as our search only used English sources. Second, the evidence level of the systematic review is restricted by included studies' evidence level. Third, we did not exclude studies that used unreliable HRQOL tools. Finally, systematic studies on probiotic formulations did not find enough evidence to explain how each species in the combination works. In future studies, the effects of supplementation with different types of probiotics in combination and alone need to be studied to determine the exact mechanisms of each probiotic species.

This systematic review provides a new overview of how probiotic supplementation affects QoL in patients with GI diseases and outlines potential areas for future research. Based on our review of available clinical trial studies, we found that patients with GI diseases reported significant improvement in HRQOL after probiotic supplementation. However, more *in vitro* and *in vivo* studies and clinical trials on probiotics are needed to investigate the precise ways in which probiotics affect GI diseases.

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The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept and design: JM, AS. Analysis and interpretation: MAZ. Data collection: MAZ. Validation: YA, SM, SH. Writing the article: YA, JM, SM, SH. Critical revision of the article: YP, SM, FM. Statistical analysis: FM, YA. Obtained funding: FM, YA, SH, MAZ. Final approval of the article: all authors. Overall responsibility: AS.

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