Journal of Applied Microbiology

Journal of Applied Microbiology ISSN 1364-5072

REVIEW ARTICLE

The effects of probiotics, prebiotics and synbiotics on the reduction of IBD complications, a periodic review during 2009–2020

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Keywords
probiotics, inflammatory bowel disease, synbiotic, ulcerative colitis, Crohn's disease, 5-ASA compounds.

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2020/1852: received 1 September 2020, revised 15 October 2020 and accepted 20 October 2020

doi:10.1111/jam.14907

Abstract

Aims: To perform a systematic review on randomized controlled trials to examine the efficacy of probiotics, prebiotics and synbiotics in the treatment of IBD.

Methods and Results: PubMed, Web of science, Scopus and Google Scholar were systematically searched from January 2009 to January 2020 using the following keywords: 'Inflammatory Bowel Disease', 'Probiotics' and 'Clinical trial'. The statistical analysis was performed using SPSS software version 24.0. A total of 1832 articles were found during the initial search and 21 clinical trials were eligible. Studies comparing the effects of probiotics and placebo among patients with active ulcerative colitis (UC) showed a significant difference in clinical outcomes. Moreover, probiotics improved the overall induction of remission rates among patients with Crohn's disease (CD). Probiotics significantly decreased the IL-1β, TNF-α and IL-8 levels. Also, the need for systemic steroids, hospitalization, surgery, as well as histological score and disease activity index significantly decreased in patients who used probiotic or pro-/synbiotics.

Conclusions: The use of probiotics, as food supplements, can induce anti-inflammatory reactions, balance the intestinal homeostasis and induce remission in IBD. The efficacy of probiotics on remission induction is more reported in UC rather than CD. Larger well-designed clinical trials are needed to further determine whether probiotics are of clear benefits for remission in IBD.

Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing inflammatory disorder which comprises the two conditions: ulcerative colitis (UC) and Crohn's disease (CD) (Matsuoka and Kanai 2015). CD and UC differ by the intestinal localization and features of the inflammation. Totally, CD inflammation occurs in the gastrointestinal tract, whereas UC inflammation starts in the rectum, and is restricted to the colon (Dobre*et al.*2018).

It is generally accepted that IBD is the result of overactive response of mucosal immune system to the food, environmental or infectious antigens in a genetically susceptible host (Manuc*et al.*2016). Evidence from patients and animal models have shown that both the innate and cell-mediated immunities are activated by the commensal

enteric bacteria which play crucial roles in the progression and maintenance of IBD (Mizoguchi and Mizoguchi 2010).

IBD treatment often involves induction of remission and prevention of relapse. Corticosteroids have been initially used to induce remission, but their effectiveness is limited, and patients under long-term corticosteroid treatment have shown complications such as growth failure or osteopenia (Tsampalieros*et al.*2014). Many studies have recommended aminosalicylates as a maintenance treatment for IBD. Although the clinical treatment of patients with IBD has been well established with aminosalicylates (Nielsen and Munck 2007), there are some possible side effects such as infection, hepatitis, leukopenia and pancreatitis associated with this medication (Gisbert*et al.*2011; Meczker*et al.*2019). Using probiotics to modify and improve the bacterial population of the intestine, and thereby reducing inflammation, is another treatment method to induce or maintain remission in IBD. It is also possible to use antibiotics to eliminate the bacteria that potentially cause inflammation in the bowel, but there are limitations and complications associated with the use of antibiotics (Lewis 2014).

According to the definition of the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations (FAO), probiotics are living micro-organisms which, when administered in adequate amounts, confer a health benefit on the host (Hotel and Cordoba 2001). Probiotics can have positive effects on the treatment of traveller's diarrhoea (Bae 2018), diarrhoea caused by human immunodeficiency virus (Carter*et al.*2016) and recurrence of difficile colitis (Mills*et al.*2018). Probiotics can also inhibit the overgrowth of potentially pathogenic bacteria in the bowel (Zhang*et al.*2015). Despite some conflicting results on the therapeutic efficacy of probiotics, several studies have shown the beneficial effects of the probiotics *Escherichia coli* Nissle 1917 (EcN), *Saccharomyces boulardii* and VSL # 3 on the treatment of IBD (Currò*et al.*2017; Mills*et al.*2018). Prebiotics are defined as non-digestible food components that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in gastrointestinal tract, and thus improve the host's condition against IBD complications (Gibson and Roberfroid 1995). The main characteristics of prebiotics are their resistance to digestive enzymes produced by the human body while remaining susceptible to colonic micro-flora fermentation (Cummings and Macfarlane 2002). Recent studies have shown the beneficial effects of prebiotics, and immune-nutrients such as polyunsaturated fatty acids (PUFAs) in the remission of IBD in human (Bernstein 2014; Ferguson 2015).

The term synbiotic refers to a product that contains both probiotics and prebiotics. The probiotic component of synbiotics helps the development of beneficial intestinal microflora, whereas the prebiotic component inhibits the growth of pathogenic bacteria. Synbiotics help decrease the concentration of undesirable metabolites, including nitrosamines, inactivate carcinogens, and prevent constipation and diarrhoea in the host (Bengmark 2005; Bengmark and Martindale 2005).

The aim of this study was to review the overall efficacy of probiotics, prebiotics and their combination (synbiotics) in the treatment of IBD.

Materials and Methods

The keywords 'Inflammatory Bowel Disease', 'Probiotics' and 'Clinical trial' were searched in the data banks; PubMed, Web of Science, Scopus and Google Scholar. The papers published from January 2009 to January 2020 were further assessed for their relevance based on their title, abstract and the main text. The data extraction was conducted by two independent researchers, and the papers indexed in two or more databases were considered only once. References list of all the related articles were investigated to identify any ignored articles. A third researcher checked the results to ensure that all the eligible articles were evaluated.

The extracted data were organized based on the authors' name, country, date of publication, type of clinical trial, sample size, diagnostic criteria, patient's characteristics, time period of the study, genus, and species of probiotics, probiotic dose, side effects of probiotics and the treatment outcomes. Chi-squared test was used to analyse the qualitative variables. Data were analysed using SPSS software version 24.0 (IBM, Armonk, NY, USA) and $P < 0{\cdot}05$ was considered as statistically significant.

Inclusion criteria

- Articles from January 2009 to January 2020.
- Clinical trial studies.
- Clinical trial studies on patients with IBD.

Exclusion criteria

- Animal experiments
- Congress papers
- Reviews, meta-analyses, case reports, letters to the editor and correspondences
- Clinical feature summary
- Non-English articles
- Studies with no clear information

Results

The initial search of the keywords generated a total of 1832 articles. Search strategy and selection of the studies are described in Fig. 1. A total of 1519 articles were excluded through evaluating the titles and abstracts, following which 74 articles were retained for detailed full-text evaluation. Following the full-text evaluation, 21 studies, investigating the efficacy of the probiotics on IBD treatment, fulfilled the inclusion criteria and were considered for further analysis.

Table 1 shows the summary of the characteristics and disease distribution of the participants from articles included in this review. The outcomes of different clinical trials assessing the efficacy of the probiotics on the treatment of IBD are shown in Table 2. Most of the studies, which examined the effects of probiotics on the remission of IBD, were carried out in Italy (6 out of 21 studies and 532 out of 1478 participants), followed by Iran and the UK, respectively. The specimens including blood, serum, stool, urine, rectal tissue biopsies and histopathology samples were obtained from both males (54%) and females (46%) with the mean age of 35·2 ± 14·8 (ranging from 1 to 78 years) (Fig. 2). Among the 21 studies, 19 examined the effect of probiotics, 1 assessed the effect of synbiotics and 1 examined the effects of both probiotics and synbiotics on the treatment of IBD. A total of 31 different probiotic species were administered once, twice or three times daily at doses of 1×10^{6} to $3{\cdot}6 \times 10^{12}$ colony forming units (CFUs). The average dose of probiotics was $2{\cdot}6 \times 10^{13}$ CFUs. The frequency of probiotic bacteria administrated in different trials for patients with IBD is shown in Fig. 3. The most common probiotics used by different studies were *Lactobacillus acidophilus* (15·7%), *Brevibacterium breve* (9%) and *Bifidobacterium longum* (7·9%). The majority of participants had Pancolitis (15·7%), left-sided colitis (14·9%) and ulcerative left colitis (14%). The detailed characteristics of individual trials are shown in Table 2.

As shown in Table 2, among the 21 clinical trials, 16 trials used a combination of multi-strain probiotic bacteria. One of the trials used nine types of probiotic bacteria, and five trials used eight types, one trial used six types of probiotics in combination, while one study used four types of probiotic bacteria. Also, two clinical trials used three types of probiotic bacteria in combination.

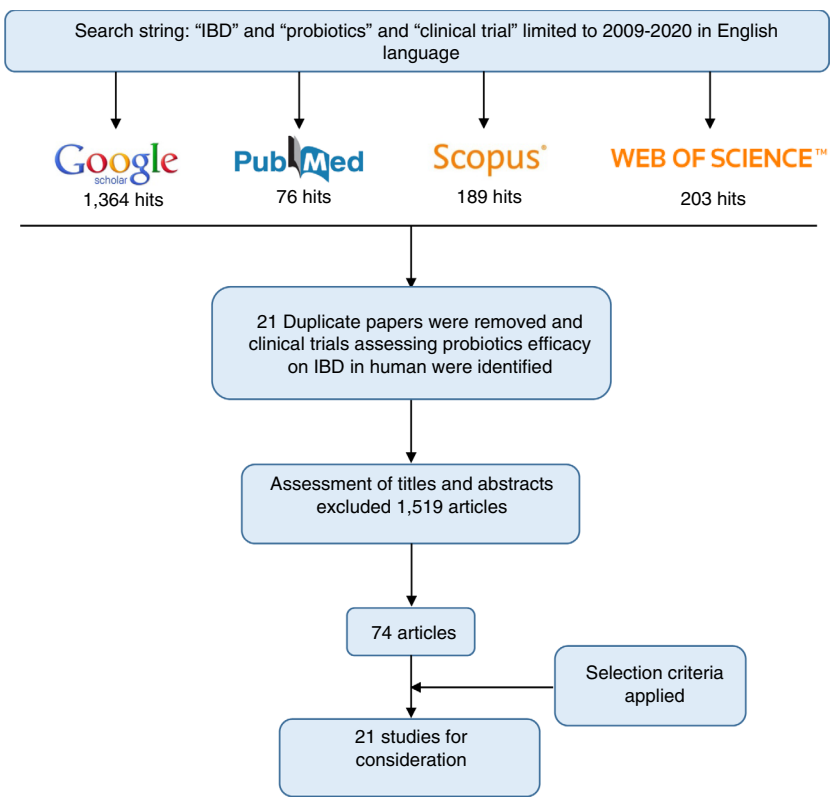

Figure 1 Flow diagram of evaluation of the studies selected for consideration in this review.

Table 1 Background characteristics of the patients in studies included in this review

Disease distribution	*n*	%	Previous treatment	*n*	%
Small bowel disease	91	6·1	Prednisone	48	3·2
Colonic disease	109	7·3	Prednisolone	8	0·5
Ileal disease	22	1·4	Azathioprine/6-mercaptopurine	38	2·5
Ileocolonic disease	66	4·4	Methotrexate	2	0·1
Distal proctitis	5	0·3	Infliximab	2	0·1
Ulcerative left colitis	220	14	Mesalamine	145	9·8
Pancolitis	233	15·7	Mesalazine	151	10·2
Proctosigmoid disease	203	13·7	Balsalazide	4	0·2
Left-sided colitis	221	14·9	Sulphasalazine	20	1·3
Ileocolic Crohn's	59	4	Tacrolimus	191	13
Colic Crohn's	9	0·7			
Crohn's with fistulae	10	0·6			

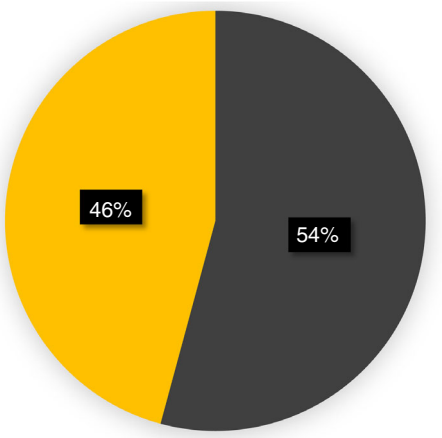

Figure 2 Percentage of IBD among male and female patients. (■) Male; (■) Female.

Moreover, four clinical trials utilized a double probiotic agent, and four trials used only a single strain of probiotic bacteria. Another study used kefir to evaluate the effect of probiotics on patients with IBD.

Generally, cases in these trials were randomly divided into two or three groups (probiotics, placebo and/or 5-ASA) using a random numbers sequence or by computer-generated random numbers. Treatment allocation concealment by sealed opaque envelopes was implemented in one single-blinded study, and physicians were blinded to treatment options.

Efficacy of probiotics in inducing remission in active UC

Four out of the 13 eligible trials compared probiotics with 5-ASA compounds for remission induction of active UC, and the other 9 trials were placebo-controlled. Detailed study characteristics are provided in Table 2. The four trials that compared probiotics with 5-ASAs, for their effect in inducing remission of active UC, contained 157 patients.

Six of the trials, containing 503 patients, used VSL#3 (Ferring Pharmaceuticals Ltd.), which is a combination of *Lactobacillus*, *Bifidobacterium* and *streptococcus* bacteria. In one trial (Dore*et al.*2020), the need for systemic steroids, hospitalization and surgery decreased to zero events per person-year among UC patients. In another study, VSL#3 resulted in a remission rate of 56% and a combined remission/response rate of 61% (Huynh*et al.*2009). Miele*et al.*investigated the effects of VSL#3 on children with UC and they found that remission was achieved in 13 (92·8%) patients treated with VSL#3 and 5-ASAs and in four (36·4%) patients treated with placebo and 5-ASAs ($P < 0·001$). In total, 3 of 14 (21·4%) patients treated with VSL#3 and 5-ASAs and 11 of 15 (73·3%) patients treated with placebo and 5-ASAs relapsed within 1 year of follow-up ($P = 0·014$) (Miele*et al.*2009). Wildt *et al.* reported the higher efficacy of probiotics over placebo in terms of reducing relapses ($P = 0·37$) and longer remission periods ($P = 0·683$). In this study, no significant clinical benefit was seen for probiotics compared to placebo for maintaining remission in patients with left-sided ulcerative colitis (Wildt *et al.* 2011). Amiriani *et al.* examined the effects of the probiotics on mitigating the UC symptoms in patients with UC. In this trial, a significant decrease was seen in the intervention group ($4·56 \pm 2·56$) vs. the placebo group ($6·54 \pm 2·47$) ($P < 0·05$). Response to treatment was seen in 64·3% of the treatment group vs. 47% in the placebo group ($p = 0·18$). Also, response to treatment was observed in 90·9% of patients with UC for more than 5 years compared to 44·4% of the individuals in the control group ($P = 0·01$) (Amiriani *et al.* 2020). The diagnosis of UC in three trials (Huynh *et al.* 2009; Wildt *et al.* 2011; Amiriani *et al.* 2020) was based on the Simple Clinical Colitis

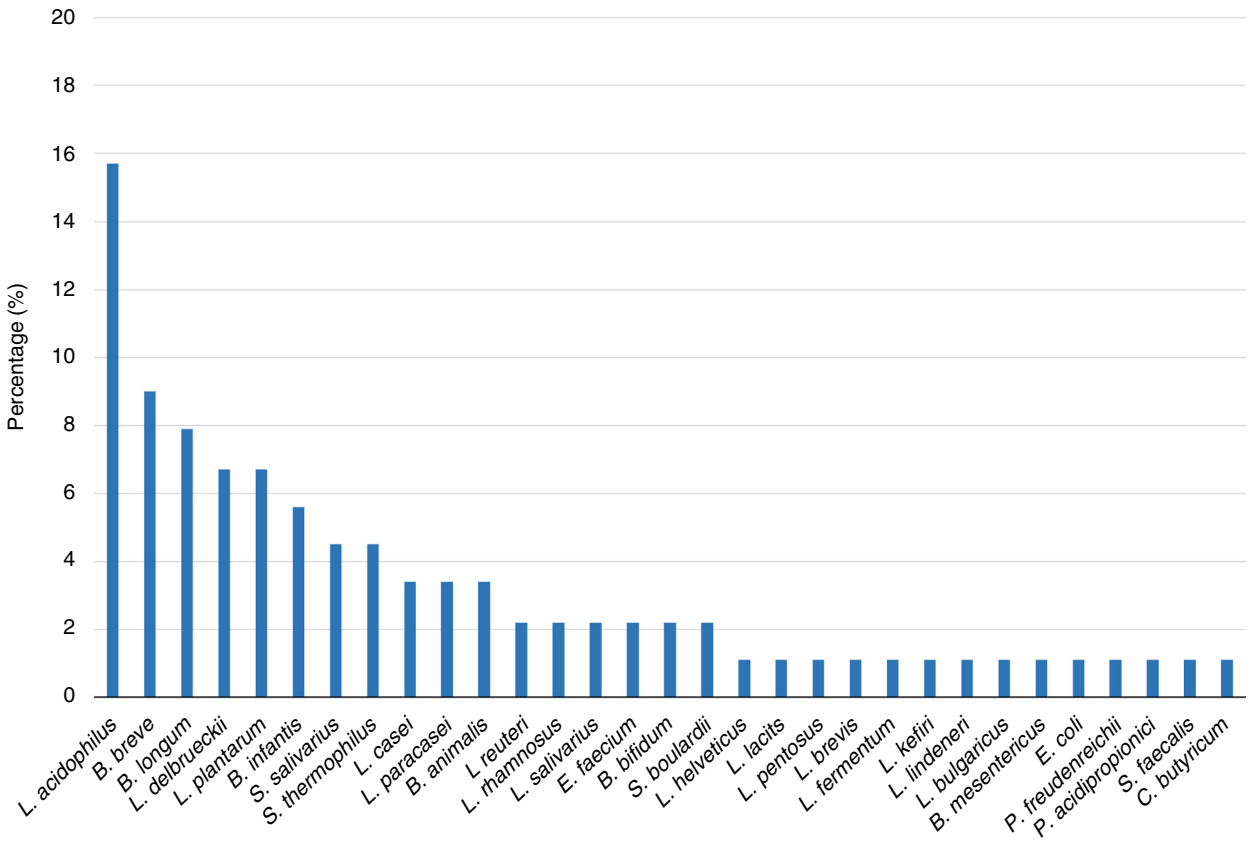

Figure 3 The frequency of probiotics used in different trials for patients with IBD.

Activity Index (SCCAI) score. Olivia *et al.* examined the efficacy of enema solution containing 10^{10} CFU of *Lactobacillus reuteri* ATCC 55730 on remission induction in children with active distal UC. Disease activity was assessed using the Mayo Disease Activity Index (DAI), endoscopic and histological analysis. Moreover, RT-PCR was carried out to check IL-1β and β-actin mRNA expression. Mayo score, including clinical and endoscopic features, was decreased significantly in the *L. reuteri* group compared with placebo ($P < 0{\cdot}01$). Furthermore, histological score significantly dropped only in the *L. reuteri* group ($P < 0{\cdot}01$). In the post-trial evaluation of mucosal cytokine expression levels, IL-10 significantly increased ($P < 0{\cdot}01$) only in the *L. reuteri*-treated group, whereas IL-1β, TNF-α and IL-8 significantly decreased ($P < 0{\cdot}01$) (Oliva *et al.* 2012).

In the trials that were conducted on UC patients, the criteria such as quality of life (QOL) Questionnaire and full blood counts, renal, and liver function, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), faecal calprotectin (FCAL), serum cytokine profiling, rectal tissue microbial profiling, PCR and qPCR, haemoglobin (Hgb), white blood cell (WBC) count, albumin and faecal organic acids were measured.

Two, out of 21, trials (Bourreille *et al.* 2013; Matsuoka *et al.* 2018) showed no significant effect for probiotics regarding the remission of UC and CD among patients. In addition, no major adverse events were reported among patients, assigned to probiotics or 5-ASAs. In one trial (Matsuoka *et al.* 2018), individuals had avascular necrosis of bilateral femoral head (one patient in the placebo group), surgical removal of granuloma in the throat (one patient in the probiotics group) and pulmonary thromboembolism (one patient in the placebo group).

Efficacy of probiotics in inducing remission in active CD

In our literature search, we found four trials, totally containing 370 patients, which reported the efficacy of probiotics vs. placebo and/or 5-ASAs on inducing remission of active CD. In these studies, the CD Activity Index (CDAI) scores and European Crohn's and Colitis Organization (ECCO) were used as diagnostic criteria. Detailed study characteristics are provided in Table 2.

Table 2 The outcome of different clinical trials assessing the efficacy of probiotics, prebiotics and synbiotics vs. 5-ASAs or placebo on the treatment of IBD patients

Reference	Country	Study design	Participants characteristics	No. of participants, mean age (SD)	Probiotics	Dose	Intervention	Control used and duration of therapy	Outcomes
Amiriani *et al.* (2020)	Iran	RDBPCT	Mild-to-moderate UC	60, Not reported	*Lactobacillus casei Lactobacillus acidophilus Lactobacillus rhamnosus* *Lactobacillus bulgaricus* *Bifidobacterium breve* *Bifidobacterium longum* *Streptococcus thermophilus*	1×10^9 CFU	1 capsule/b.i.d/8wks	Identical placebo 1 capsule/b.i.d/ 8 weeks	Probiotics mitigate symptoms in patients with UC
Bjarnason *et al.* (2019)	UK	MC, RDBPCT	CD and UC	500, 42·7 (13·1)	*Lactobacillus rhamnosus* NCIMB 30174 *Lactobacillus plantarum* NCIMB 30173 *Lactobacillus acidophilus* NCIMB 30175 *Enterococcus faecium* NCIMB 30176	10^{10} CFU	1 mg kg^{-1} d^{-1} 4 weeks	Identical placebo 1 mg kg^{-1} d^{-1} 4 weeks	Probiotics decreased intestinal inflammation in patients with UC, but not in CD
Bourreille *et al.* (2013)	France	RPCT	On remission during steroid or aminosalicylates therapy with CD	196, 36·9	*Saccharomyces boulardii*	1 g	1 g/day 52 weeks	Identical placebo 1 g/day 52 weeks	*S. boulardii* did not have any beneficial effects on patients with CD in remission after steroid or salicylate therapies
Dore *et al.* (2020)	Italy	RCT	CD and UC	200, 39·7 (15·2)	*Lactobacillus reuteri* *Streptococcus thermophiles Lactobacillus acidophilus* *Bifidobacterium breve* *Bifidobacterium animalis* subsp. *Lactis*	10^8 CFU 5×10^{10} CFU	1 tablet per day 1 week 1 packet per day 1 wk	Not reported	Probiotics reduced adverse events and the need for systemic steroids, hospitalization and surgery in UC and CD patients
Huynh *et al.* (2009)	Canada	Open-label study	Mild-to-moderate acute UC	18, 12·2 (1·03)	*Lactobacillus casei* *Lactobacillus plantarum* *Lactobacillus acidophilus* *Lactobacillus delbrueckii* subsp. *Bulgaricus* *Bifidobacterium longum* *Bifidobacterium breve* *Bifidobacterium infantis* *Streptococcus salivarius* subsp. *Thermophilus*	$4{\cdot}5 \times 10^{11}$ CFU	2–4 years: 1/2 sachet 5–8 years: 1 sachet 9–13 years: 1 + 1/2 sachets 14–18 years: 2 + 1/2 sachets b.i.d 8 weeks	Not reported	Probiotics were safe in the treatment of children with UC
Joeres-Nguyen-Xuan *et al.* (2010)	Germany	Prospective, RDBPCT	Healthy volunteers	48, 30·4 (6·5)	*Escherichia coli* strain Nissle 1917 (EcN)	$2{\cdot}5–25 \times 10^9$ CFU	2 capsules per day 17 days	Mesalamine 1500 mg/b.i.d Identical placebo 7 days	The combination of EcN and mesalamine had no considerable effect on the survival of EcN in healthy volunteers

(Continued)

Table 2 (Continued)

Reference	Country	Study design	Participants characteristics	No. of participants, mean age (SD)	Probiotics	Dose	Intervention	Control used and duration of therapy	Outcomes
Marushko (2013)	Ukraine	RCT	Children with chronic non-specific non-UC (CNNC)	92, 1·6	*Bifidobacterium bifidum* *Bifidobacterium longum* *Lactobacillus acidophilus* *Lactobacillus delbrueckii* subsp. *Bulgaricus* *Lactobacillus helveticus* *Lactococcus lactis* *Propionibacterium freudenreichii* subsp. *Shermanii* *Propionibacterium acidipropionici* *Streptococcus salivarius* subsp. *Thermophilus*	Not less than 10^8 CFU Not less than 10^9 CFU Not less than 3×10^7 CFU	Not reported	5-ASA and steroids	DAI score, disease activity and mucosal inflammation in infants with CNNC decreased. The probiotics improved the clinical manifestation of the disease, and positive changes were seen in the expression of pro- and anti-inflammatory cytokines
Matsuoka *et al.* (2018)	Japan	RDBPCT, multicentre	UC	195, 41·8	*Bifidobacterium breve* strain Yakult *Lactobacillus acidophilus*	1×10^{10} CFU 1×10^9 CFU	o.d 48 weeks	Identical placebo o.d 48 weeks	Probiotics had no effect on the relapse time in UC patients compared to the placebo group
Miele *et al.* (2009	Italy	Prospective, DBPCT,MC	Children with newly diagnosed UC	29, 9·8	*Lactobacillus paracasei* *Lactobacillus plantarum* *Lactobacillus acidophilus* *Lactobacillus delbrueckii* subsp. *bulgaricus* *Bifidobacterium longum* *Bifidobacterium breve* *Bifidobacterium infantis* *Streptococcus salivarius* subsp. *thermophilus*	4·5-18 $\times 10^{11}$ CFU	4–6 years; 1/2 packet 7–10 years; 1 packet 11–14 years; 1 + 1/2 packet 15–17 years; 2 packet o.d/1 yr	Identical placebo o.d/1 yr Methylprednisolone1 mg kg^{-1} d^{-1} Max 40 mg/day/4 weeks Mesalamine 50 mg kg^{-1} d^{-1}	Probiotics were efficient and safe in remission of UC
Oliva *et al.* (2012	Italy	Prospective, RPCT	Children with mild-to-moderate Distal active UC	40, 12·7	*Lactobacillus reuteri* ATCC 55730	10^{10} CFU	Enema solution/o.d/8 weeks	Identical placebo o.d/8 wks Oral mesalazine 50–75 mg kg^{-1} d^{-1} during the last 12 weeks	*L. reuteri* was effective in improving mucosal inflammation and changing mucosal expression levels of some cytokines
Palumbo *et al.* (2016)	Italy	CS	Moderate-to-severe UC	60, 44·5	*Lactobacillus salivarius* *Lactobacillus acidophilus* *Bifidobacterium bifidum* subsp. BGN4	Not reported	b.i.d/2 years	Mesalazine 1200 mg/o.d/2 years	Long-term treatment of anti-inflammatory drugs and probiotics could be an alternative to corticosteroids in mild to moderate UC

(Continued)

Table 2 (Continued)

Reference	Country	Study design	Participants characteristics	No. of participants, mean age (SD)	Probiotics	Dose	Intervention	Control used and duration of therapy	Outcomes
Shadnoush *et al.* (2013	Iran	RDBCT	IBD patients in remission	305, 37·7	Bifidobacterium Lactobacillus	10^6 CFU per g	Probiotic yoghurt 250 g/o.d/8 weeks	Plain yoghurt 250 g/o.d/8wks	Use of the probiotic yoghurt decreased serum levels of IL-1β, TNF-α and CRP but increased the serum levels of IL-6 and IL-10
Shadnoush *et al.* (2015	Iran	RDBPCT	IBD patients with no manifestation of acute inflammation during histological examination	210, 59·2	*Lactobacillus acidophilus* La-5 *Bifidobacterium* BB-12	106 CFU per g of yogurt	250 g/d/8 weeks	Identical placebo 250 g/d/8 weeks	Probiotic yoghurt in patients with IBD improve intestinal function by increasing the number of probiotic bacteria in the intestine and colon
Ng *et al.* (2010)	UK	DBPCT, multicentre	Mild-to-moderately active UC and healthy controls	28, 43	*Lactobacillus casei* *Lactobacillus Plantarum* *Lactobacillus acidophilus* *Lactobacillus delbrueckii* subsp. *Bulgaricus* *Bifidobacterium longum* *Bifidobacterium breve* *Bifidobacterium infantis* *Streptococcus salivarius* subsp. *Thermophilus*	$3{\cdot}6 \times 10^{12}$ CFU	2 sachets b.i.d/8 weeks	Identical placebo b.i.d/8 weeks Prednisolone 40 mg/8 weeks and reduced by 5 mg/week	Treatment of UC patients with probiotic and corticosteroids induced favourable intestinal DC
Sood *et al.* (2009)	India	RDBPCT, multicentre	Mild-to-moderate UC	84, 40·3 (12·7)	*Lactobacillus paracasei* *Lactobacillus plantarum* *Lactobacillus acidophilus* *Lactobacillus delbrueckii* subsp. *Bulgaricus* *Bifidobacterium longum* *Bifidobacterium breve* *Bifidobacterium infantis* *Streptococcus thermophilus*	9×10^{11} CFU	4 sachets/b.i.d/12 weeks	Identical placebo b.i.d/12weeks	Probiotics were safe and effective in achieving clinical responses and remissions in patients with mild-to-moderately active UC
Steed *et al.* (2010)	UK	RDBPCT	Active CD	35, 47·6	*Bifidobacterium longum*	2×10^{11} CFU	1 capsule/b.i.d/6 months	Identical placebo b.i.d/6 months	Synbiotic consumption was effective in improving clinical symptoms in patients with active CD

(Continued)

Table 2 (Continued)

Reference	Country	Study design	Participants characteristics	No. of participants, mean age (SD)	Probiotics	Dose	Intervention	Control used and duration of therapy	Outcomes
Tomasello *et al.* (2015)	Italy	Prospective study	IBD with extraintestinal involvement	59, 43·4	*Lactobacillus salivarius* *Lactobacillus acidophilus* *Enterococcus faecium* *Saccharomyces boulardii*	Not reported	1 tablet/b.i.d/52 weeks	Mesalazine For mild forms 800 mg/b.i.d For moderate forms 800mg/t.i.d	Probiotics improved the clinical response to standard therapy and reduced the need for corticosteroids use
Tursi *et al.* (2010)	Italy	RDBPCT	UC patients with relapsing disease of mild-to-moderate severity	144, 47 (14·2)	*Lactobacillus paracasei* *Lactobacillus plantarum* *Lactobacillus acidophilus* *Lactobacillus delbrueckii* subsp. *bulgaricus* *Bifidobacterium longum* *Bifidobacterium breve* *Bifidobacterium infantis* *Streptococcus thermophilus*	9×10^{11} CFU	2 Sachets b.i.d/8 weeks	Identical placebo b.i.d/8weeks	Probiotics reduced UCDAI scores in patients with mild-to-moderate UC who were under treatment with 5-ASA and/or immunosuppressant. Probiotics improved rectal bleeding and re-induced remission in relapsing UC patients
Wildt *et al.* (2011)	Denmark	RDBPCT	Left-sided UC in remission including proctitis and at least one relapse within the last year	32, 37·5	*Lactobacillus acidophilus* strain LA-5 *Bifidobacterium animalis* subsp. *lactis* strain BB-12	$1{\cdot}5 \times 10^{11}$ CFU	2 capsules/t.i.d/ weeks	Identical placebo 2 capsules/t.i.d/52 wks	Probiotics reduced relapses and longer remission periods
Yilmaz *et al.* (2019)	Turkey	Open-label, prospective RCT, MC	IBD	45, 33	*Lactobacillus pentosus* *Lactobacillus brevis* *Lactobacillus plantarum* *Lactobacillus fermentum* *Lactobacillus kefiri* *Lactobacillus lindneri*	2×10^{10} CFU	Kefir 200 ml/b.i.d/4 weeks	Not reported	Kefir modulated gut microbiota, and improve the patient's quality of life in the short term
Yoshimatsu *et al.* (2015)	Japan	RDBPCT, MC	Inactive UC	60, 43·8 (14·8)	*Streptococcus faecalis* T-110	2 mg	3 tablets/t.i.d/1y	Identical placebo t.i.d/1y	Probiotic was effective in maintaining clinical remission in patients with quiescent UC

RCT, randomized controlled study; MC, monocentric; DB, double-blind; RPCT, randomized placebo control trial; RDBPCT, randomized double-blind placebo-controlled trial; RDBCT, randomized double-blind controlled trial; DBPCT, double-blind placebo-controlled trial; CS, clinical study; UC, ulcerative colitis; CD, Crohn's disease; o.d, Once daily; b.i.d., twice daily; t.i.d., three times daily; d, days; wk, week; y, year; SD, standard deviation

In one study (Steed *et al.* 2010), the consumption of *B. longum* and Synergy 1 (as a synbiotic) improved clinical outcomes with reductions in both CDAI ($P = 0{\cdot}020$) and histological scores ($P = 0{\cdot}018$). On the other hand, the use of probiotics alone had no significant changes in CD patients ($P > 0{\cdot}05$) (Bjarnason *et al.* 2019). In another trial (Bourreille *et al.* 2013), *S. boulardii* was introduced as a safe and well-tolerated probiotic, but did not have any beneficial effects on CD remission after steroid or salicylate therapies. Moreover, CRP, ESR, FCAL, microbiological analysis of tissue biopsies and histopathology indexes, as well as ELISA and qPCR of the pro-inflammatory cytokines in mucosal tissue were investigated for further understanding of the probiotics and synbiotics effects. One trial conducted by Marushko *et al.* on children with chronic non-specific non-UC (CNNC), compared the effects of immuno-nutrients, as well as probiotics, prebiotics and PUFAs, with conventional therapy (including 5-ASAs and steroids) on remission induction of CNNC. Prebiotics used in this study were inulin-type prebiotics that contains fructans. DAI score, as well as mucosal inflammation, decreased in infants treated with immune-nutrients and conventional therapy. Furthermore, immuno-nutrients improved the clinical manifestation of the disease, reduced disease activity index and mucosal inflammation in infants with CNNC, decreased the expression levels of pro-inflammatory cytokines while decreased the levels of anti-inflammatory cytokines involved in the mechanisms of IBD. The immuno-nutrients also increased the indigenous bacterial count. No serious adverse events were observed in these trials.

Efficacy of probiotics in inducing remission in patients with IBD

In five studies, containing 667 patients, effects of probiotics were compared with 5-ASA compounds on the remission of types of IBD. The diagnosis of IBD in these studies was made according to the DAI and the Western Ontario, and McMaster Universities Arthritis (WOMAC) index. One of these studies used EcN on 48 healthy volunteers and showed that the combination of EcN and mesalamine has no considerable effects on the survival of EcN, and the difference between the two groups was not statistically significant ($P > 0{\cdot}05$). Only one serious adverse event was reported in a volunteer in the mesalamine group, who developed diarrhoea, fever and haematochezia on the day 7 of the investigational phase, when the administration of EcN plus mesalamine was ended. Tomasello *et al.* investigated the effects of a combination of *Lactobacillus* spp., *Enterococcus faecium* and *S. boulardii* in IBD patients with extra-intestinal involvement and they found that probiotics improved the clinical response to standard therapy and reduce the need for corticosteroids ($P < 0{\cdot}05$) (Tomasello *et al.*2015).

Shadnoush *et al.*(2013) investigated and compared the serum levels of different pro-inflammatory cytokines following the administration of probiotic yoghurt. They found that probiotic yoghurt consumption significantly decreased the serum levels of IL-1β, TNF-α and CRP among patients with IBD in comparison to the healthy control group ($P < 0{\cdot}05$). Also, in another study, conducted by these same authors (Shadnoush *et al.*2015), the mean numbers of *Lactobacillus* ($P < 0{\cdot}001$), *Bifidobacterium* ($P < 0{\cdot}001$) and *Bacteroides* ($P < 0{\cdot}01$) significantly increased in the intestine and colon of individuals consuming probiotic yoghurt, compared to the group consuming plain yoghurt. Yilmaz *et al.* reported that kefir modulates gut microbiota, and regular consumption of this product improves the patient's QOL in the short term. They found that the faecal load of *Lactobacillus* spp. was between 10^4 and 10^9 CFU per g among all the participants in the treatment group Furthermore, the *Lactobacillus kefiri* load in the stool of 17 cases was measured to be between 10^4 and 10^6 CFU per g. In this study, there was a significant decrease in the ESR and CRP levels, a significant increase in the Hgb level, and for the last 2 weeks of treatment, there was a significant decrease in the bloating scores ($P = 0{\cdot}012$), and a significant increase in feeling good scores ($P = 0{\cdot}032$) (Yilmaz *et al.*2019). In these studies, Hgb, CRP and ESR were calculated before and after the probiotic treatment and some laboratory indexes such as TNF-α, IL-6, IL-1β, IL-10 and CRP were measured by Taqman real-time PCR to the estimate the effect of the probiotic bacteria on IBD. Moreover, culture and Vitek® MS MALDI-TOF mass spectrometry were performed on the bacterial isolates for the *Lactobacillus* spp. identification.

Discussion

At the present moment, there are no standard medical therapies that can cure the two main types of IBD, UC and CD. However, there are treatments that can reduce and/or control the associated risk of cancer in the bowel (van Bodegraven and Mulder 2006). Unfortunately, several studies have reported side effects for the medicals used in the management of IBD after long time follow-up (Frandsen *et al.*2002). Researchers are looking for alternative therapy or supplement to improve remission in IBD. In recent years, the interest in microbiota-based IBD therapy has gained more popularity, due in part to having fewer adverse effects than traditional therapies (Khan *et al.*2019). This systematic review was undertaken to evaluate the consequences of clinical trials, assessing the efficacy of probiotics on IBD treatment over the past several years (Ghouri *et al.*2014). In the last years, several

studies have shown beneficial effects of different probiotic preparations in inducing and maintaining remission in adults and children with IBD, although there are two studies which have shown no beneficial effects for probiotics in this regard, either alone or in combination with synbiotics (Miele *et al.*2009; Sood *et al.*2009; Bourreille *et al.*2013; Matsuoka *et al.*2018). A Cochrane review has shown that there is no evidence to support the beneficial effects of probiotics over placebo in inducing remission in IBD (Kaur *et al.*2020). Discrepancies in the responsiveness to probiotic treatments might be due to differences in the characteristics of the hosts (age, gender, lifestyle), dosing regimens, duration of use, disease severity, single or multi-strain formulation, delivery modes, etc. involved in each study, which require further detailed investigations to match these variables and conclude a more comprehensive result. Among the 21 clinical trials, 16 applied multi-species probiotics and 4 trials used mono-species probiotics. Many properties of probiotics are strain-specific, and it is possible that multi-species probiotics be more efficient than mono-species in the treatment of certain clinical conditions due to, for example, enhanced chance of colonization, symbiosis and synergy between different strains and variety diverse production of antimicrobial compounds (Mezzasalma *et al.*2016). Although there are conflicting data regarding the effects of probiotics on IBD treatment (Joeres-Nguyen-Xuan *et al.*2010; Iheozor-Ejiofor *et al.*2020), several studies have shown that combination of probiotics with conventional therapies such as mesalamine or 5-ASA, significantly enhance the overall outcome on IBD treatment, improve the beneficial effects on the gut function, reduce the need for occasional corticosteroid therapy and induce IBD remission through synergy with the anti-inflammatory effect of 5-ASA compounds (Marushko 2013; Tomasello *et al.*2015; Palumbo *et al.*2016). 5-ASA compounds inhibit the production of inflammatory mediators such as leukotrienes, prostaglandins, platelet-activating factor and free radicals, all of which have roles in the pathogenesis of IBD (Wallace *et al.*1999).

The six extensive studies in our review (Huynh *et al.*2009; Miele *et al.*2009; Sood *et al.*2009; Ng *et al.*2010; Tursi *et al.*2010; Amiriani *et al.*2020) showed that the probiotic cocktail VSL#3 could successfully induce IBD remission among patients. Moreover, two trials (Sood *et al.*2009; Tursi *et al.*2010) supported the idea that the use of VSL#3 in conjunction with mesalamine or immunosuppressant improves symptoms among patients who have not responded to mesalamine alone. Several clinical studies have shown the efficacy of VSL#3 in inducing and maintaining remission among IBD patients (Bibiloni *et al.*2005; Park *et al.*2011). It is possible that VSL#3 may act in synergy with, or perhaps augment, the action of standard therapies due to the strain-specific properties of its probiotic mixture which might influence the efficacy of treatment in different cases and situations. In addition, probiotics are considered as useful nutritional supplements and their continuous ingestion might stably improve the QOL among patients with IBD. In a clinical trial in 2018, Yilmaz *et al.* assessed the effects of kefir consumption on the QOL of IBD patients. Compared to the control group, abdominal pain score ($P = 0{\cdot}049$) and feeling good score ($P = 0{\cdot}019$) were improved in the probiotic consuming group (Yılmaz *et al.*2019). However, a similar analysis by Zocco *et al.*(2006) showed no significant differences between the probiotic and placebo-treated IBD patients.

The optimal probiotic combination and dose for the treatment of different disease conditions have not been specified yet. However, it is generally accepted that 10^8–10^9 CFU per g probiotic should be consumed daily to deliver the minimum concentration of 10^6 viable cells into the intestine to exert positive effects on the host (Knorr 1998; Neffe-Skocińska *et al.*2018). In different trials assessed in this review, probiotics were administered once, twice or three times daily at doses of 1×10^6 to $3{\cdot}6 \times 10^{12}$ CFU. Overall, according to the treatment results among IBD patients, the best-recommended dose was an average of $\geq 10^9$ CFU per g, showing efficacy in remission induction and a decrease in relapse and complication rate. Some studies have shown that a higher or lower probiotic dose than 10^9 CFU per g is only effective in increasing the QOL and response to general symptoms (Lorenzo-Zúñiga *et al.*2014). On the other hand, all the probiotics' effects on human health do not seem to be associated with the viability of the bacteria, since even the dead cells or the probiotic-derived DNA have shown the ability to ameliorate significant health problems (Lammers *et al.*2003; Rachmilewitz *et al.*2004; Lahtinen 2012).

It is difficult to discuss the supremacy of different probiotic species/strains since, due to the strain-specific properties of probiotics and different categories of patients, a specific probiotic might not be appropriate in all patients (Zocco *et al.*2006; Darbandi *et al.*2020). Most probiotic products contain species from *Lactobacillus* and *Bifidobacterium* genera which modulate the gut microbial population and increase intestinal barrier function (Kleerebezem and Vaughan 2009; Li *et al.*2016). The effect of probiotics on the gut microbiota of patients has been reported (Marushko 2013; Shadnoush *et al.*2015; Yılmaz *et al.*2019). Shadnoush, in 2015, indicated that the consumption of the probiotic yogurt by IBD patients increases the number of helpful bacteria such as of *Bifidobacterium* and *Lactobacillus*, and decreases the stool load of *Bacteroides* (Shadnoush *et al.*2015). It is believed that probiotics can induce changes in the intestinal

microbiota and stabilize the beneficial microbial population by competition with pathogenic bacteria for nutrients and adhesion sites, and production of different metabolites. Yoshimatsu *et al.* demonstrated that probiotic therapy was potentially most beneficial for patients that initially had cluster I microflora rather than cluster II. It has been demonstrated that specific cluster types of intestinal microbiota influence the responsiveness to probiotic therapy (Yoshimatsu *et al.*2015). It is shown that the interaction between probiotics and toll-like receptors (TLRs) of enterocytes exerts its avails predominantly on the innate immune system (Llewellyn and Foey 2017). The imunomodulatory properties of probiotics may be due to the bioactive compounds and secondary metabolites produced during the fermentation process (Braat *et al.*2006). Moreover, probiotics can reduce or repair intestinal permeability leading to a reduced interaction between the antigens of pathogenic bacteria and the intestinal lumen of the host, which reduce the inflammatory response in the lumen (Santos *et al.*2003). It has been reported that probiotics can modulate the function of immune cells such as T and B cells, dendritic cells (DCs) and cytokines which have a direct influence on human health and immune-mediated diseases (Ng *et al.*2010; Dargahi *et al.*2019). One study has reported that probiotics significantly reduce TLR-4 and IL-1β levels and significantly increase mucosal IL-10 levels (D'Incà *et al.*2011). Since probiotics' effects are strain-specific, each specific probiotic induces a unique profile of cytokines secreted by immune cells such as lymphocytes, enterocytes or DCs (Azad *et al.*2018). Several randomized clinical trials (RCTs) have evaluated the effects of administering probiotics on the clinical scores of IBD patients (Sood *et al.*2009; Marushko 2013). According to the literature search, two trials showed side effects for probiotic consumption (Huynh *et al.*2009; Matsuoka *et al.*2018). Probiotic administration has shown a good safety profile among patients with only a low rate of bacteraemia associated with the *Lactobacillus* and *Bifidobacterium* (approximately 0·05–0·4%) which has been seen in elderly/non-elderly patients with concomitant immunosuppressive therapy (Borriello *et al.*2003). Probiotics, specifically VSL#3 and *Lactobacillus* spp., are shown to have significant health effects among children with an age range 2–21 years who have been diagnosed with IBD (CD and UC) ($P < 0·01$) (Ganji-Arjenaki and Rafieian-Kopaei 2018). Huynh *et al.* demonstrated a decrease in the SCCAI score, ESR, CRP, serum interferon levels, Mayo endoscopy score for UC, as well as a decreasing trend for TNF levels with a corresponding increase in the Hgb and HCT levels among patients who responded to VSL#3 treatment. Sixty-seven per cent of the IBD patients in remission demonstrated a change in their microbial profile with a Dice's similarity coefficient (Huynh *et al.*2009). Considering the occurrence of IBD in infants and very young children, it is noted that genetic factors are basic and important elements in this event (Kelsen *et al.*2015; Chandrakasan *et al.*2017). Despite extensive studies showing the effects of probiotics on the induction and maintenance of remission in UC, the benefits of probiotics in CD are less convincing. Shen *et al.*(2005) published a systematic review with meta-analysis of RCTs that showed therapeutic benefits associated with the use of probiotics among UC, and pouchitis patients, but no such effects were noted in CD. Among the four clinical trials reporting the efficacy of probiotics vs. placebo and/or 5-ASAs in terms of inducing remission of active CD, two trials used a single probiotic agent and the other three trials used multi-species probiotics or a combination of probiotics and synbiotics (Steed *et al.*2010; Bourreille *et al.*2013; Bjarnason *et al.*2019; Dore *et al.*2020). Many studies have shown that a mixture of probiotics or probiotic–synbiotic combinations could improve remission in CD and clinical symptoms among patients receiving the therapy. For example, Steed *et al.* showed that the co-administration of synbiotics and probiotics induce a significant reduction in both CD activity index ($P = 0·02$), and histological scores ($P = 0·018$), as well as an increase in the proliferation of mucosal Bifidobacteria (Steed *et al.*2010).

Conclusions

According to the literature review, the use of probiotics as food supplements can induce anti-inflammatory reactions, balance the intestinal homeostasis, improve the individuals' QOL, and induce and maintain remission in patients with IBD. The efficacy of probiotics in remission induction is more extensively reported by different studies in UC rather than CD. Small study populations, a short length of patients' follow-up and the lack of dose-response analyses are significant limitations in interpreting the effects of probiotics in inducing remission in CD. Larger well-designed RCTs are needed to further determine whether probiotics and/or synbiotics are of clear benefit for remission in both UC and CD. Understanding the aetiology of IBD, the cellular and molecular mechanisms of its development, as well as the functions of different probiotic strains can help the selection of appropriate probiotic strains for specific IBD patients.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Author contributions

Atieh Darbandi initiated the idea of this study. Amir Darb Emamie and Mohammadreza Rajabpour contributed to data collection, interpretation and final approval of data for the work. Roya Ghanavati and Sorour Farzi developed the first and final draft of the manuscript. Behnam Sobouti developed the second draft of the manuscript. All figures and tables were designed and checked by Amir Darb Emamie and Atieh Darbandi. Parisa Asadolahi critically reviewed and revised the manuscript. All authors reviewed and contributed to the revisions and finalized the drafts.

Conflict of Interest

The authors declare that they have no competing interests.

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