Probiotics in the Treatment of Inflammatory Bowel Diseases in Adulthood: A Systematic Review

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ABSTRACT

Background & Aims: Crohn’s disease (CD) and ulcerative colitis (UC) are inflammatory bowel diseases (IBD) characterized by chronic uncontrolled inflammation with an increasing prevalence in western countries. Standard medications are often associated with adverse side effects. Thus, alternative therapies such as probiotic treatment are of great interest. We aimed to review the effect of probiotics in IBD patients.

Methods: A systematic search strategy was carried out in PubMed in June 2021 and 22 studies published from 1997 to 2019 were included; they analyzed the influence of probiotics in adult IBD patients both in active and inactive stage of disease.

Results: Probiotic treatment in CD patients had no effect in 6 of 7 studies. Only in one study a positive effect of an adjunctive probiotic treatment next to standard treatment in CD patients was reported. In patients with active UC, a combination of standard treatment with probiotics resulted in improvement of the disease in 5 of 9 studies. Three of 7 studies among UC patients in remission demonstrated that probiotic treatment could be as effective as standard treatment. No clear evidence was found in studies comparing probiotics to placebo in inactive UC patients with ongoing standard medication.

Conclusion: There is no clear evidence of the benefit of probiotic treatment in CD patients. In contrast, combining standard treatment with probiotics might be an option to achieve remission in active UC patients.

Key words: inflammatory bowel diseases - Crohn’s disease - ulcerative colitis – probiotics - systematic review.

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic disorders that affect people worldwide which are mostly apparent in industrialized and developed countries of Europe and North America [1, 2]. In fact, 2-2.5 million Europeans are estimated to be living with these diseases [1, 3]. Inflammatory bowel diseases are subdivided into two main clinical entities: Crohn's disease (CD) and ulcerative colitis (UC) [4]. In Europe, the incidence of UC varies from 0.9-24.3 per 100,000 person-years, while the incidence of CD varies from 0.5-10.6 per 100,000 person-years [2]. Overall, an increasing number of IBD cases can be seen in westernized countries since 1950 [5]. The pathological hallmark of IBD is chronic uncontrolled inflammation of the intestinal mucosa, causing IBD specific gastrointestinal and extra-gastrointestinal manifestations [6-8].

Current therapeutic strategies comprise lifestyle changes, medical treatment and surgical interventions and the overall aim is to induce and maintain remission and improve the disease's secondary side effects [4, 9, 10]. Conventional medical drug treatment includes aminosalicylates (mesalazine, mesalamine, 5-aminosalicylic acid etc.) [11], budesonide, systematic corticosteroids, immunosuppressants and monoclonal...
antibodies e.g. anti-tumor necrosis factor (TNF)-α, mainly targeting effector immune responses [10, 12]. Mesalazine is the first-line standard treatment for IBD patients and several oral as well as rectal agents of this anti-inflammatory drug are available [13]. Its prodrug is called basalazide [14]. The mechanism of action of mesalazine include the inhibition of mediators of lipooxygenase and cyclooxynase, interleukin (IL)-1, IL-2 and TNF-α [13, 15]. It also appears to act as a potent antioxidant and free-radical scavenger [13, 15].

However, standard treatment is often associated with adverse events [16]. That is the reason why new approaches and alternative therapies in IBD treatment are needed. Unbalanced gut microbiota profiles are a common characteristic in IBD [17] and the diversity of bacteria is significantly decreased in IBD patients [18, 19]. As a consequence, approaches targeting the manipulation of the enteric bacteria through probiotics are moving more into the researchers’ focus [20]. One common worldwide accepted definition of the term “probiotics” is “live microorganisms which when administered in adequate amounts confer a health benefit on the host” [21]. In general, three main mechanisms are associated with probiotics [22].

First, some probiotics might be able to modulate the hosts’ immune response. Second, probiotics may act directly on other microorganisms, and third, some probiotics might act via microbial products [22]. Due to these postulated mechanisms of action of probiotics, many studies have been performed to investigate the association between IBD and probiotic treatment, to modulate the gut microbiota and the host’s immune response. However, studies identified contradictory outcomes. The following overview provides an up-to-date systematic review of the present literature on interventional studies.

**METHODS**

The manuscript was written according to the PRISMA 2020 statement [23].

**Data Sources and Search Strategy**

A systematic search was conducted in PubMed up until the end of June 2021. Results were limited to full-text articles written in English, using the following search key words: “inflammatory bowel disease”, “inflammatory bowel diseases”, “IBD”, “Crohn’s disease”, “CD”, “ulcerative colitis”, “UC”, both as all fields terms and medical subject headings (MESH). These keywords were cross-referenced with studies identified with the terms “probiotic”, “probiotics”, both as all field terms and as MESH, in all given combinations. There was no year of publication limitation and only interventional studies were selected for this review.

**Study Selection and Eligibility Criteria**

All potentially relevant studies were screened by abstract and title, removing those among minor patients (age <18), studies in vitro and in animals, studies using only prebiotically or symbiotically treatment and studies not relating to IBD. Next, full-text screening was performed on the remaining studies with further eligible criteria: studies both in patients in an active or an inactive stage of disease were eligible for inclusion, studies only reported about UC patients with pouchitis were excluded. Inflammatory bowel diseases had to be confirmed via endoscopic and/or histological and/or radiological diagnostics. Interventions had to assess the influence of probiotics via clinical outcome either with the assessment of various disease activity scores or/and through histological or endoscopic scores or/and time of relapse/recurrence.

**Data Extraction**

The following clinical data were extracted from eligible studies to a Microsoft Excel spreadsheet: country of origin, year of publication, number and age of patients, dosage and duration of treatment, diagnosis of IBD, concomitant medication, adverse events and general clinical outcome.

**Quality Assessment**

For quality assessment selected studies were assessed for potential risk of bias and the overall quality of methodology using “The Cochrane risk-of-bias tool for randomized trials” [24]. Studies were assessed via five different categories and then ranked into an overall risk of bias: “low”, “some concerns” and “high”.

**RESULTS**

Database search identified 2,708 records. After removing non-clinical trials (n=2,560), 148 records were screened on title and abstract. Ninety-seven records were excluded for not meeting the above-mentioned eligible criteria. Full text assessment was performed on the remaining 51 records, among them 29 were ineligible. Finally, this overview identified a total of 22 studies (Fig 1). Overall, seven studies about patients with CD (Table I), nine studies with patients in an active state of UC (Table II), and seven studies with patients in an inactive state of UC (Table III). Studies were conducted in Europe (n=16), Asia (n = 5) and Europe/America (n = 1).

**Quality assessment**

All 22 included studies were considered as “low risk of bias” after using “The Cochrane risk-of-bias tool for randomized trials” (Supplementary file, Fig. S1) [24]. Two of the included studies were identified as open-labeled studies [25, 26]. However, A.L. and L.M. agreed that this fact did not cause significant disruption to the results. One study was considered as “high risk of bias” and had to be removed due to several limitations: low quality in statistical analysis, poor result presentation, non-blinding-methods and different diets between control and observational group. Also, in this certain trial both CD and UC patients were analyzed, but clinical recurrence rates were not differentiated between the two diseases, the outcome was only demonstrated as one variable for all IBD patients [27]. Due to those concerns, the study was not included in this review.

**Impact of Probiotic Treatment on Crohn’s Disease**

Table I provides an overview of studies with probiotics in patients with CD. The effect of orally administered probiotic agents compared to placebo was analyzed in six studies [28-33].
Overall, none of these studies in CD patients could identify beneficial effects by probiotic treatment. In two studies, capsules were used for applying probiotics [28, 33]. Schultz et al. [33] performed a randomized-controlled clinical trial (RCT) with eleven patients in remission who were treated with Lactobacillus rhamnosus strain GG (LGG) or placebo. After six months, no difference in relapse rates between the two groups could be seen [33]. Bourreille et al. [28] investigated active CD patients who received randomly either Saccharomyces (S.) boulardii or placebo for 52 weeks. Relapse rates did not differ between the two groups after the intervention time [28].

Probiotic agents dissolved in different liquids were used in four studies [29-32]. One study group [32] compared LGG with placebo and analyzed the effect on post-operative recurrence in CD patients. After 52 weeks, clinical recurrence occurred in 16.6% in the LGG group compared to 10.5% in the placebo group [32]. Marteau et al. [29] also investigated the influence of probiotics on post-operative recurrence, by orally administering L. johnsonii LA1 strain (LA1) dissolved in water or placebo for six months. The study group did not find a significant benefit of LA1. Clinical recurrence was identified in 8.3% in the probiotic group compared to 6% in the placebo group [29]. In the RCT by Van Gossum et al. [31] orally administered LA1 to patients after ileo-caecal resection was analyzed. Patients were randomized to either receive LA1 or placebo, both dissolved in 120 ml enteral formula. After the three-months intervention, severe recurrence and mean endoscopic score did not differ significantly between the two groups [31]. In 2019, a RCT was performed to analyze the effect of treatment with the liquid multi-strain probiotic Symprove, a mixture of L. rhamnosus, L. plantarum, L. acidophilus and Enterococcus (E.) faecium dissolved in water-based suspension of barley extract [30]. Sixty-one patients were randomized to take either liquid Symprove or liquid placebo for one month. After intervention, the CD activity index (CDAI) did not differ significantly between CD patients in the probiotic and placebo group. Four patients experienced clinical relapse, all belonging to the placebo group [30].

In one study the effect of probiotics in combination with standard treatment compared to standard treatment alone was investigated [34]. In the study by Guslandi et al. [34] 32 patients were randomized to receive either S. boulardii plus mesalazine or mesalazine alone for six months. Significantly fewer clinical relapses occurred in the combination group compared to the group only receiving mesalazine. The authors suggest that S. boulardii beneficial effects might be through its trophic effect on the intestinal mucosa and by triggering release of secretory immunoglobulin A [34].

Impact of Probiotic Treatment on Ulcerative Colitis

Overall, nine eligible studies with patients in an active stage of UC were included (Table II) [26, 35–42]. A specific probiotic agent was compared to placebo in active UC patients
**Table I.** Characteristics and results of studies with probiotics in adult patients with Crohn’s disease

<table>
<thead>
<tr>
<th>Reference; Country; Year;</th>
<th>Probiotic used</th>
<th>Form and quantity of administration</th>
<th>Study design; duration</th>
<th>No. of patients; disease activity</th>
<th>Effects of probiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guslandi et al.[34]; Italy; 2000</td>
<td><em>S. boulardii</em></td>
<td>via 2 x capsules/d (à 500 mg)</td>
<td>pro + mesalazine vs mesalazine; 6 months</td>
<td>32; inactive</td>
<td>↓ clinical relapse (CDAI &gt; 150) (p = 0.04); pro + mesalazine 6.25 % mesalazine 37.5 %</td>
</tr>
<tr>
<td>Prantera et al.[32]; Italy; 2002</td>
<td><em>L. rhamnosus GG</em></td>
<td>via 2 x packets/d (à 6 x 10^9 cfu) dissolved in water</td>
<td>pro vs pl; 12 months</td>
<td>45; inactive, after curative resection</td>
<td>↔ clinical recurrence (CDAI &gt; 150): pro 16.6 % pl 10.5 % ↔ endoscopic recurrence (p = 0.297)</td>
</tr>
<tr>
<td>Schultz et al.[33]; Germany, USA; 2004</td>
<td><em>L. rhamnosus GG</em></td>
<td>via capsules (2 x 10^8 cfu/d)</td>
<td>pro vs pl; 6 months</td>
<td>11; inactive</td>
<td>↔ clinical relapse (CDAI + 100): pro (2/4) pl (3/5) ↔ CDAI</td>
</tr>
<tr>
<td>Marteau et al.[29]; France; 2006</td>
<td><em>L. johnsonii LA1</em></td>
<td>via 2 x packets/d (à 2 x 10^8 cfu) dissolved in water</td>
<td>pro vs pl; 6 months</td>
<td>98; inactive, after curative resection</td>
<td>↔ clinical relapse (CDAI &gt; 200): pro (4/48) pl (3/50) ↔ endoscopic recurrence (ITT; p = 0.15); pro 49 % pl 64 %</td>
</tr>
<tr>
<td>Van Gossum et al.[31]; Belgium; 2007</td>
<td><em>L. johnsonii LA1</em></td>
<td>via packets (à 10^10 cfu/d) + 120 ml/d enteral formula</td>
<td>pro vs pl; 3 months</td>
<td>70; inactive, after curative resection</td>
<td>↔ mean endoscopic score (ITT; p = 0.48) ↔ CDAI ↔ severe recurrence (ITT; p = 0.33); pro 21 % pl 15 %</td>
</tr>
<tr>
<td>Bourreille et al.[28]; France; 2013</td>
<td><em>S. boulardii</em></td>
<td>via capsules 1g/d</td>
<td>pro vs pl; 12 months</td>
<td>165; inactive</td>
<td>↔ clinical relapse (p = 0.5): pro 47.5 % pl 53.2 % ↔ median time to relapse (p = 0.78)</td>
</tr>
<tr>
<td>Bjarnason et al.*[30]; UK; 2019</td>
<td>Symprove</td>
<td>via bottles pro in water-based suspension of barley extract 1 ml/kg/d (10^9 cfu/50 ml dose)</td>
<td>pro vs pl; 1 month</td>
<td>61; quiescent or mild</td>
<td>↔ clinical disease activity (p = 0.66)</td>
</tr>
</tbody>
</table>

No.: number; pro: probiotic group; pl: placebo group; cfu: colony forming unit; B.: *Bifidobacterium*; L.: *Lactobacillus*; S.: *Saccharomyces*; E.: *Enterococcus*; CDAI: Crohn’s disease activity index; sign.: significant; ITT: intent-to-treat; *: studies investigating ulcerative colitis and Crohn’s disease patients.

In six trials [35,37-40,42]. It should be noted that ongoing standard medication was allowed in all groups throughout the studies. In two large, double-blinded RTC trials the effect of the oral treatment either with VSL#3 - administered in cold water/ yoghurt - or placebo was analyzed [37, 39]. VSL#3 is a combination of four *Lactobacillus* strains (*L. plantarum, L. acidophilus, L. delbrueckii subs bulgaricus*), two *Bifidobacteria* strains (*B. longum, B. breve, B. infantis*) and *S. salivarius*. After twelve weeks of intervention, Sood et al. [39] observed significantly higher clinical remission rates in patients in the VSL#3 group (42.9%) compared to patients in the placebo group (15.7%). In addition to that, the mean decrease in UC disease activity index (UCDAI) from baseline to week twelve was significant higher in the VSL#3 group compared to the placebo [39]. After eight weeks of intervention, Tursi et al. [37] observed no difference in achieving remission between patients in the VSL#3 group (47.7%) compared to patients in the placebo group (32.4%). Despite that, significantly more patients in the probiotic group achieved an improvement in their UCDAI score of at least 50% after eight weeks than patients in the placebo group [37].

Tamaki et al. [42] performed a RCT on the effect of orally administered *B. longum* 536 compared to placebo in 56 UC patients. After eight weeks of intervention, clinical remission rates did not differ significantly between the *B. longum* group (62.5%) and the placebo group (52.2%). Also, no differences in UCDAI scores were seen [42].

In the RCT performed by Kato et al. [38] clinical remission was identified in 40% patients in the probiotic group compared to 33% in the placebo group, after the twelve weeks treatment either with placebo or 100 ml/d bifidobacterial-fermented milk (BFM), containing *B. breve, B. bifidum* and *B. acidophilus*. The clinical activity index (CAI) score was significantly lower in UCDAI scores were seen [42]. Furthermore, significantly higher amount of total short chain fatty acids (SCFA), butyrate and propionate, in the BFM group compared to the placebo group could be observed. Also, the numbers of *B. pseudocatenulatum* and *B. breve*
were significantly increased in the BFM group, but not in the placebo group. SCFA, especially butyrate, are energy sources for enterocytes and appear to inhibit NF-κB activation [38]. In the study by Petersen et al. [35] 50 active UC patients were randomized to either receive *Escherichia coli* Nissle 1917 (EcN) or placebo for 7 weeks. After treatment time, significantly fewer patients in the EcN group reached remission (54%) compared to the patients in the placebo group (89%). Authors also observed that significantly more patients in the EcN group withdrew from the study. In one trial the effect of EcN by either administering enemas in different quantities of bacteria or placebo was investigated [40]. Overall, 57/90 patients achieved remission [40].

| No.: number; pro: probiotic group; pl: placebo group; cfu = colony forming unit; B: *Bifidobacterium*; L: *Lactobacillus*; S: *Saccharomyces*; E: *Enterococcus*; BFM: bifidobacterial-fermented milk; UCDAI: ulcerative colitis disease activity index; UCAI: ulcerative colitis activity index; PP: per-protocol; ITT: intent-to-treat; MMDAI: modified mayo disease activity index; *: studies investigating ulcerative colitis and Crohn’s disease patients; **VSL#3: *L. praceaei, L. plantarum, L. acidophilus, L. delbrueckii subs bulgaricus, B. longum, B. breve, B. infantis, S. salivarius.*

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Table II. Characteristics and results of studies with probiotics in adult patients with active ulcerative colitis

<table>
<thead>
<tr>
<th>Reference; Country; Year</th>
<th>Probiotic used</th>
<th>Form and quantity of administration</th>
<th>Study design; duration</th>
<th>No. of patients; disease activity</th>
<th>Effects of probiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tursi et al.[36]; Italy; 2004</td>
<td>VSL#3**</td>
<td>via 3x packets/ d 3g/ d (3 x 10^8/g) no further specification</td>
<td>pro + basalazide vs mesalazine; 2 months</td>
<td>90; mild-to-moderate</td>
<td>↑ achieving remission (ITT; p &lt; 0.02); pro+basalazide 80.0 % basalazide 70.0 % mesalazine 53.33 %</td>
</tr>
<tr>
<td>Kato et al.[38]; Japan; 2004</td>
<td>BFM: - <em>B. breve</em> - <em>B. bifidum</em>, - <em>B. acidophilus</em></td>
<td>via 100 ml/d (10 x 10^9 bacteria/100 ml)</td>
<td>pro vs pl; with ongoing standard medication; 3 months</td>
<td>20; mild-to-moderate</td>
<td>←→ achieving remission: pro 40 % pl 33 % ←→ clinical activity index (p &lt; 0.05)</td>
</tr>
<tr>
<td>Sood et al.[39]; India; 2009</td>
<td>VSL#3**</td>
<td>via 4 x packets/d (3.6 x 10^8 cfu) in cold water or yoghurt</td>
<td>pro vs pl; with ongoing standard medication; 3 months</td>
<td>147; mild-to-moderate</td>
<td>↑ achieving remission (ITT; p &lt; 0.001); pro 42.9 % pl 15.7 %</td>
</tr>
<tr>
<td>Tursi et al.[37]; Italy; 2010</td>
<td>VSL#3**</td>
<td>via 4 x packets/d (3.6 x 10^8 cfu/d) in cold water or yoghurt</td>
<td>pro vs pl; with ongoing standard medication; 2 months</td>
<td>144; mild-to-moderate</td>
<td>←→ achieving remission (ITT; p = 0.132); pro 47.7 % pl 32.4 % ↑ improvement in clinical activity (PP; p = 0.010)</td>
</tr>
<tr>
<td>Matthes et al.[40]; Germany; 2010</td>
<td><em>E. Nissle 1917</em></td>
<td>via enema (10^9 bacteria/ml)</td>
<td>pro (10 ml, 20 ml, 40 ml) vs pl; with ongoing standard medication; 2 months</td>
<td>90; mild-to-moderate</td>
<td>←→ remission rates (ITT; p = 0.4430) pro (40 ml) 43.5 % pro (20 ml) 47.8 % pro (10 ml) 36.4 % pl 35.0 % ↑ remission rates (PP; p = 0.0446) - significant dose-dependence pro (40 ml) 52.9 % pro (20 ml) 44.4 % pro (10 ml) 27.3 % pl 18.2 %</td>
</tr>
<tr>
<td>D’Incà et al.[41]; Italy; 2011</td>
<td><em>L. casei DG</em></td>
<td>via enema or oral (1.6 x 10^8 cfu)</td>
<td>pro (oral) + mesalazine vs pro (rectal) + mesalazine; 2 months</td>
<td>26; left-sided-UC mild</td>
<td>←→ clinical activity in pro groups (p &gt; 0.05) ↑ improvement in histological disease severity in both pro groups (p &lt; 0.05)</td>
</tr>
<tr>
<td>Petersen et al. [35] Denmark; 2014</td>
<td><em>E. Nissle 1917</em></td>
<td>via capsules 1x100 mg/d for 4 days, 2 x 100 mg/d for rest (2.5 - 25 x 10^9 bacteria/capsule)</td>
<td>pro vs. pl; with ongoing standard medication; 7 weeks</td>
<td>50; active</td>
<td>←→ achieving remission: (PP) pro 54 % pl 89 %</td>
</tr>
<tr>
<td>Palumbo et al.[26]; Italy; 2016</td>
<td><em>L. salivarius, L. acidophilus, B. bifidus strain</em> BGN4</td>
<td>via 2 x capsules/d</td>
<td>pro + mesalazine vs mesalazine; 24 months</td>
<td>60; moderate-to-severe</td>
<td>↑ improvements in MMDAI (p = 0.0001)</td>
</tr>
<tr>
<td>Tamaki et al.[42]; Japan; 2016</td>
<td><em>B. longum</em></td>
<td>via 3 x packets/ d 2 - 3 x 10^8 no further specification</td>
<td>pro vs pl; with ongoing standard medication; 2 months</td>
<td>56; mild-to-moderate</td>
<td>←→ achieving remission (ITT; p = 0.63); pro 62.5 % pl 52.2 % ←→UCDAI (p = 0.50)</td>
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</table>

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The effect of probiotics in combination with standard treatment vs. standard treatment alone in patients in an active stage of UC was analyzed in three studies [26, 36, 41]. In 2004, Tursi et al. [36] compared VSL#3 in combination with standard treatment vs standard treatment alone. After treatment time, symptomatic remission rates were significantly higher in the VSL#3 plus balasazide group (80%) compared to the balasazide group (70%) and the mesalazine group (53.3%) [36]. In one study, 60 moderate-to-severe active patients were randomly divided into two groups either receiving oral mesalazine or mesalazine plus the probiotic mixture of L. salivarius, L. acidophilus and B. bifidus strain BGN4 for two years [26]. Both groups showed improvement in the general clinical condition which was measured by modified Mayo disease activity index (MMDAI). However, results in the combination group showed greater improvements in MMDAI than mesalazine [26]. All three groups showed a reduction in their disease activities compared to baseline; however the reduction was only significantly different in the mesalazine group. In contrast to the mesalazine group, significantly more Lactobacillus spp. and significant fewer Enterobacteriaceae spp. could be found in the UC patients receiving rectal L. casei plus mesalazine. Histological disease severity improved in both probiotic groups (p<0.05). Moreover, a significant reduction of toll-like receptor (TLR) 4 mRNA levels, IL-1β mRNA levels and a significant increase of mucosal IL-10 mRNA levels were seen in patients receiving rectal L. casei plus mesalazine [41].

Overall, seven studies have been included that evaluated the use of probiotics in the treatment of inactive UC (Table III) [25, 30, 43–47]. A specific probiotic agent was compared to an identical appearing placebo in four studies [30, 45–47]. It should be noted that ongoing standard medication was allowed in all groups throughout the studies. Cui et al. [45] evaluated the effect of treatment with a specific probiotic called Bifico compared to placebo, both applied via capsules. The two-month follow-up analyses identified 20% relapses in the Bifico group and 93.3% relapses in the placebo group (p<0.01) [45]. After treatment time, concentration of fecal Lactobacillus...
spp. and Bifidobacteria spp. was significantly increased, as well as significantly decreased levels of TNF-α and IL-1β in the Bifico group. Additionally, NF-κB was significantly less activated after treatment in the Bifico group [45]. In 2011, Wildt et al. [46] studied the effect of a multi-strain probiotic called Probio-Tec AB-25, containing L. acidophilus LA1 and B. animalis subsp. lactis, compared to placebo. After treatment, analysis revealed no differences in maintaining remission and in median time to relapse between the two groups [46]. As mentioned above, Bjarnason et al. [30] evaluated the effect of the multi-strain probiotic Symprove. Eighty-one UC patients were randomized to take either liquid Symprove or liquid placebo for one month. After intervention, no difference in clinical disease activity between the probiotic and the placebo group was identified. However, there was a small signal that the probiotic might be anti-inflammatory in quiescent UC patients, due to decreased calprotectin levels in UC patients in the probiotic group after four weeks [30]. In one trial, 198 UC patients were treated either with one pack of 100 ml BFM, containing B. breve and L. acidophilus, or placebo for 48 weeks [47]. Generally, relapse-free time of UC patients during trial was not significantly different between the two groups and no remission-maintaining effect of BFM compared to placebo was seen. Time to relapse and clinical disease activity were also not statistically significant between groups [47].

One hundred and eighty seven patients in quiescent UC were randomly divided into three groups either receiving LGG or mesalazine or LGG plus mesalazine for twelve months [25]. No significant difference in clinical, endoscopic and histological score could be identified between the three groups. Also, relapse rates did not differ significantly. The authors suggested that probiotics might have the same efficacy as standard treatment on one-year treatment [25].

Furthermore, in two of the included trials orally applied EcN with mesalazine in UC patients in remission was analyzed. These investigations were performed by Kruis et al. in 1997 [44] and in 2004 [43]. Their results are leading to the conclusion that orally given EcN is as effective as standard treatment with mesalazine [43, 44]. In 1997, Kruis et al. [44] identified no significant difference in clinical activity index between groups after the twelve-week intervention with EcN vs mesalazine in a total of 103 randomized patients (p=0.12). Relapse was observed in 16% in the EcN group and 11.3% in the mesalazine group [44]. Later in 2004, Kruis et al. [43] identified similar outcomes on the use of EcN compared to mesalazine. This time in a larger, long-term, double-blinded, RCT. After twelve months of treatment, relapse occurred in 45.1% in patients in EcN group compared to 37% in patients in the placebo group, meaning that treatment with EcN showed the same efficiency like treatment with mesalazine (ITT; p=0.013) [43].

**DISCUSSION**

Overall, probiotic treatment in CD patients had no effect in 6 of 7 studies. In patients with active UC, a combination of standard treatment with probiotics resulted in an improvement of the disease in 5 of 8 studies. Three of 7 studies among UC patients in remission demonstrated that probiotic treatment could be as effective as standard treatment. No clear evidence was found in studies comparing probiotics to placebo in inactive ulcerative colitis patients with ongoing standard medication.

A comparison of the six studies analyzing probiotic agents vs. placebo in CD patients is difficult due to major inconsistencies in study design, probiotic strains used, applied dosage and the form of administration. However, as a general conclusion, no study found a positive effect of probiotics when compared to placebo in the treatment of CD patients. All study groups applied their probiotic agents orally and probiotic treatment was well tolerated. In two studies, the effect of treatment with LGG was analyzed; once applied via capsules and once applied dissolved in water [32, 33]. Still, by using different forms of application, both studies did not find a lower clinical relapse in the probiotic group compared to the placebo group [32, 33].

Bourreille et al. [28] and Guslandi et al. [34] both used orally applied S. boulardii in their interventions. However, in both studies contrary outcomes were observed. In contrast to Guslandi et al. [34], Bourreille et al. [28] did not allow other IBD medication during trial and could not identify a clinical benefit of S. boulardii in CD patients. This indicates that the probiotics might show beneficial effects when combined with standard treatment.

Remarkably, clinical relapse rates in the mesalazine group in the study by Guslandi et al. [34] were higher compared to other investigations done on mesalazine. In other studies lower relapse rates were reported during mesalazine treatment [48, 49]. Higher relapse rates in mesalazine groups, as reported in Guslandi et al. [34], could be the cause of significant difference between probiotic plus mesalazine group vs mesalazine alone.

A meta-analysis by Doherty et al. [50] in 2010 on post-operative CD patients concluded that probiotics do not show clinical benefits in that group of CD patients. Since there is no more research published on that topic, this statement still applies today.

It should be noted that the studies about CD patients included in this review had significant limitations: small cohorts [32-34], short follow-up times [30] or high drop-out [29, 31, 32]. There is still a lack of studies about probiotic treatment with CD patients in an active stage disease or about analyzing the use of enema for probiotic application. Overall, studies on more controlled conditions, patients in same disease activities, placebo-controlled, blinded settings and larger sample sizes are required to obtain more confirmation on the benefit, if any, of probiotic treatment in CD patients.

The application of probiotics in combination with standard medication might be a choice in active UC patients for achieving remission. Five studies comparing probiotic to placebo showed superior outcomes in their probiotic group relating to disease activity in UC patients in active stage of disease. Only one study identified no beneficial effects by probiotic treatment [35]. Importantly, in each trial concomitant medication on stable dosage was allowed during intervention [35, 37-40, 42]. This might indicate the possible synergistic effect of probiotics and standard treatment in combination. In 4 of 6 studies probiotics were applied orally dissolved in by-products of yoghurt or cold water [37, 39], in fermented milk [38] or not further specified [42]. Only in one study
probiotics were applied via capsules [35] and in one via enemas in different quantities [40]. Kato et al. [38] used BFM for administration and did not find significant differences in the endoscopic score between probiotic and placebo groups after intervention. Nevertheless, patients had better improvements in CAI and higher remission rates in the probiotic group compared to placebo group [38]. The studies of Sood et al. [39] and Tursi et al. [37] were well-designed but had to report high drop-out rates and a respectively short intervention period. Both groups used VSL#3 in the same amount and administered the probiotic orally in yoghurt or cold water and both could find significant differences in disease activity after treatment, but only Sood et al. [39] demonstrated significant differences in remission rate between groups. In contrast to that, Tursi et al. [37] did not; the authors believe that their non-significant outcomes might be due to a type II error and a study with more patients could have had enough power to identify significant differences.

Studies comparing probiotics and standard treatment vs. standard treatment alone could all find significant differences in disease activity after treatment time [26, 27, 36], except one, in which _L. casei_ was given rectally [41]. In all four studies different strains of bacteria were used.

However, _Lactobacillus_ spp. was part of all probiotics used. _Lactobacillus_ genus is generally associated with healthier mucosa, and UC patients often show fewer _Lactobacillus_ species associated to the sigmoid mucosa than healthy controls [51]. In supplying more of this bacterium genus through probiotic treatment, this lack of bacteria could be overcome. _Lactobacillus_ spp. seem to be able to resist to acid and bile, adherence to intestinal cells and to attain bowel colonization [25, 52]. Furthermore, LGG might increase the secretion of the cytokines IL-10 and IL-4, as well as decreasing the secretion of pro-inflammatory cytokines TNF-α and IL-6 [53].

Concerning the selection of probiotics, VSL#3 seemed to be efficient in achieving benefits on disease activity and remission rates. In total, VSL#3 was the most applied probiotic in the reviewed studies on active UC patients (3/8) and found to have superior effects on disease activity compared to standard treatment or placebo [36, 37, 39]. VSL#3 seems to be able to increase levels of the anti-inflammatory cytokine IL-10 and decreases levels of pro-inflammatory cytokines TNF-α, IL-1 and interferon-γ [54, 55]. A systematic review and meta-analysis published by Derwa et al. [56] in 2017 analyzed seven placebo controlled RCTs on the efficiency of probiotics in inducing remission in active UC. These seven studies contained a total of 535 patients with active UC and 56.3% of patients assigned to probiotics failed to achieve remission, compared to 66.3% assigned to placebo failed to achieve remission. In contrast to that, when only studies on treatment with VSL#3 were considered, 56.2% of patients receiving VSL#3 failed to achieve remission, compared to 75.2% of patients receiving placebo who failed to achieve remission. Therefore, the authors suggested that the probiotic VSL#3 might have beneficial effects in terms of inducing remission in active UC [56]. Furthermore, a pilot study among children with mild-to-moderate active UC showed positive outcomes on achieving remission following VSL#3 treatment [57]. Additionally, in a RCT it was demonstrated that higher doses of 6 g basalazide showed better results on clinical activity than lower doses of 3 g basalazide [58]. However, when looking at the results of Tursi et al. [36] in 2004, it is interesting to see that low doses of basalazide in combination with VSL#3 showed better results in obtaining remission than high doses of basalazide. This leads to the conclusion that the combination of basalazide with VSL#3 might reduce the intake of standard treatment. Thus, this could lead to fewer experiences of side effects relating to standard treatment. Indeed, Tursi et al. in 2004 [36] reported fewer side effects in their basalazide plus VSL#3 group than in both mesalazine and basalazide groups. However, this difference was not significant. Despite that, they concluded that patient's strong compliance in the combination group could have been influenced by fewer side effects experienced.

Moreover, results have led to the conclusion that oral treatment with probiotics might be an efficient form of application and the use of capsules or probiotics dissolved in different liquids were overall associated with positive outcomes.

Probiotic treatment seems to be as effective as standard treatment in patients which are in an inactive stage of UC. However, a general conclusion of probiotic treatment in inactive UC patients is proving difficult. In no study - each comparing a different probiotic to placebo - were significant effects found except from Cui et al. [45], who had to report a small sample size and a short follow-up time. Thus, these results have to be viewed with caution. Zocco et al. [25], Kruis et al. 1997 [44] and 2004 [43] suggested that LGG/ EcN might be as effective as standard treatment with mesalazine in preventing relapse in patients in remission. These studies might indicate that there could be a role of probiotics in the treatment of UC patients in maintenance therapy. The effects of EcN might result through a reduced secretion of pro-inflammatory cytokines IL-2, TNF-α and an upregulation of the secretion of IL-10 [59].

The most used application format was capsules, but due to different results, no comment on the efficiency of that application form can be drawn. In a systematic review published in 2012 on probiotic treatment in IBD patients a conclusion is reached that there might be benefits in the application of EcN agents in inactive UC patients. Nevertheless they also conclude that there is still a need for further research on that topic [60]. Until now, this statement is still valid. To sum up, no conclusive benefit could be found in studies analyzing the use of probiotics compared to placebo in inactive UC patients. Also, studies often reported several limitations such as small cohorts [45, 46], short follow-up times [30, 44, 45], or open-labeled study designs [25].

The role of the combination of prebiotics and probiotics, known as synbiotics, is also an important topic in this context, since recently published studies found beneficial effects of synbiotic treatment in combination with standard treatment in UC patients. In the study by Amiriani et al. [61] 60 mild-to-moderate UC patients taking standard medication were treated either with a specific synbiotic mixture called Lactocare or placebo. The disease activity index was significantly decreased in the synbiotic group compared to the placebo group after treatment time [61]. In the 8-week RCT by Altun et al. [62] 40 mild-to-moderate UC patients on standard medication were treated either with a specific synbiotic mixture or placebo. Improvement in clinical activity was significantly higher in the
symbiotic groups compared to the placebo group. However, changes in laboratory parameters and endoscopic score did not differ between groups [62]. Next to that, in a study done by Furrie et al. [63] symbiotic or placebo was applied to 18 active UC patients for four weeks. They found a significant reduction in mucosal inflammatory markers after treatment time, but no significant differences in CAI scores between the placebo and the symbiotic group [63]. When searching the studies about CD patients analyzing symbiotic treatment, different results occur. Cheremsh et al. [64] analyzed a specific symbiotic on its effects to prevent post-operative recurrence in CD patients. In this study, symbiotic treatment showed no clinical benefits when compared to placebo [64]. On the other hand, one RCT by Fujimori et al. [65] identified better improvements in the quality of life in patients treated with symbiotics than in patients treated with probiotics or prebiotics. Hence, authors suggested that symbiotics treatment might have a synergistic effect compared to probiotics alone [65]. To this end, the role of symbiotic treatment in IBD is still unclear, and more studies are required to obtain conclusive evidence; however, potential benefits of symbiotic treatment compared to standard treatment tend to be with active UC patients.

Overall, comparison between the studies often proved difficult due to rather high heterogeneity between their probiotic strain applied, form of application and dosage used, as well as concomitant medication allowed. Thus, well-designed, larger, double-blinded RCT’s under more controlled conditions are required to gain conclusive confirmation. With regards to limitations of the review itself, study selection was only conducted using Pubmed and studies about pouchitis were not included. Also, no meta-analysis was carried out. However, this systematic review was written according to the standard guidelines and provides insights into the current available data on probiotics in the treatment of IBD.

**CONCLUSIONS**

We have no clear evidence of the benefit of probiotics in CD patients. In contrast to that, the application of probiotics in combination with standard medication might be a good choice in active UC patients for achieving remission. In terms of interventions in inactive UC patients, studies demonstrated that probiotic treatment might be as effective as standard treatment. When probiotics were compared to placebo in UC patients with ongoing standard medication, no conclusive benefit could be found. The use of probiotics in IBD therapy could be an option for patients allergic to standard treatment or patients looking for a more natural treatment. Also, side effects relating to high doses of standard treatment could be avoided or reduced by combining probiotic agents with lower amounts of standard medication. Despite that, probiotics seemed to be well tolerated. Taking this into consideration, probiotics could play a not insignificant role as a harmless adjunctive agent next to standard treatment in the therapy of UC patients.

**Conflicts of interest:** None to declare.

**Authors’ contributions:** L.M. and A.L. designed the study and conducted the search strategy. L.M. performed the electronic search. Data were extracted by L.M. and checked by A.L. for appropriateness. L.M. wrote the paper, A.L. had primary responsibility for final content. All authors have read and approved the final manuscript.

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