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Review article

Systematic review: does the use of probiotics generate benefits for patients treating inflammatory intestinal disease?

Revisão sistemática: o uso de probióticos gera benefícios para pacientes em tratamento de doenças inflamatórias intestinais?

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ABSTRACT: Objectives: To review the literature that assesses whether the use of probiotics generates benefits for individuals with IBD and to describe the mechanisms of action of probiotics in the pathogenesis of inflammatory bowel disease. Methods: This is a study classified as a systematic review. The selected publications were submitted to the Jadad Scale criteria to assess methodological quality. 17 articles were selected. Results: Of the five clinical trials that used placebo, only 1 did not show benefits from the use of probiotic therapy. The remainder showed a reduction in signs and symptoms and acute phase reagents or induction of remission in the groups treated with probiotics compared to placebo. Conclusion: The present systematic review suggests that the use of probiotics is beneficial in patients with IBD.

KEYWORDS: Probiotic. Treatment of inflammatory bowel disease. IBD. Lactobacillus. Bifidobacterium.

RESUMO: Objetivos: Revisar a literatura que avalia se o uso de probióticos gera benefícios para indivíduos com DII e descrever os mecanismos de ação dos probióticos na patogênese da doença inflamatória intestinal. Métodos: Trata-se de um estudo classificado como revisão sistemática. As publicações selecionadas foram submetidas aos critérios da Escala de Jadad para avaliação da qualidade metodológica. Foram selecionados 17 artigos. Resultados: Dos cinco ensaios clínicos que utilizaram placebo, apenas 1 não apresentou benefícios com o uso da terapia probiótica. O restante apresentou redução de sinais e sintomas e reagentes de fase aguda ou indução de remissão nos grupos tratados com probióticos em relação ao placebo. Conclusão: A presente revisão sistemática sugere que o uso de probióticos é benéfico em pacientes com DII.

PALAVRAS CHAVES: Probiótico. DII. Tratamento de DII; Lactobacillus. Bifidobacterium.

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INTRODUCTION

Inflammatory Bowel Disease (IBD) preferentially affects young people and progresses with frequent relapses, assuming highly severe clinical forms, which are: Crohn's Disease (CD) and Ulcerative Colitis (UC)[1]. CD and UC can occur at any age, with the peak incidence of CD between 15 and 30 years, with a second peak in the seventh decade of life[2]. CU, on the other hand, affects young people between 20 and 40 years[2]. Both CD and UC are products of a dysregulation of the immune system.

The impact of the association of probiotics in the treatment of IBD can be found in different pharmaceutical presentations, such as in milk-derived and fermented foods such as yogurt [4]. The microorganisms contained in these drugs can be diverse, but the most common are lactic acid-producing bacteria such as Lactobacillus sp and Bifidobacteriumsp and yeasts of the Saccharomyces genus[3,4].

Thus, it is important to verify the relationship between the use of probiotics in the treatment of IBD (CD and UC). These medications can improve and maintain the general well-being of patients, maintaining steroid-free remissions and maintain a good nutritional status. Therefore, we aim to assess the level of scientific evidence, through a systematic review and describe the findings and reported in the literature, about the benefits of using probiotics in individuals with IBD.

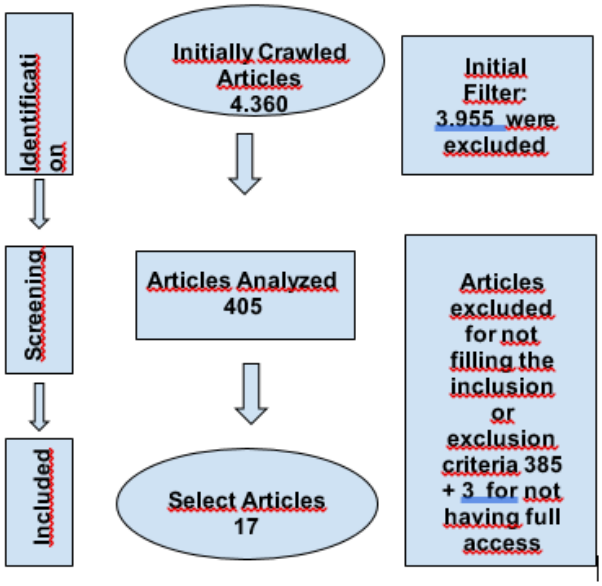
METHODOLOGY

The present systematic review presented as an initial search strategy the formulation of the question: "Does the use of probiotics generate benefits for individuals undergoing treatment for inflammatory bowel disease?". The database used to select the articles was MEDLINE and the keywords used were "probiotic"; "inflammatory bowel disease", "Lactobacillus" AND "Bifidobacterium" from then on, were selected in the initial filter: the full texts published in the last 5 years. The following inclusion criteria were applied: Studies that used patients older than 13 years, articles in Portuguese, English and Spanish that fully answer the central question of the study. The next step was to apply the exclusion criteria: repeated articles, studies with systematic review methodology and publications that used experimental models.

The selected studies were evaluated by 2 reviewers who needed a consensus to select a suitable article, and in cases of disagreement, a third reviewer evaluated the publications. At this stage, the researchers analyzed the titles and abstracts independently. The publications selected for review were submitted to methodological quality analysis considering the criteria of the Jadad Scale (Jadad et al., 1996)[6] studies with a score lower than 3 had low methodological quality, so they were excluded[5,6]. To ensure confidence in the information used in the current systematic review, in support of a given recommendation, the GRADE system (Grading of Recommendations, Assessment, Development and Evaluation). The highlighted review has high quality of evidence by the GRADE system. The present review follows PRISMA principles[7].

RESULTS

The initial selection resulted in 4.360 articles and after applying the initial filter of the MEDLINE search platform, 405 eligible articles remained. When applying the inclusion criteria and exclusion criteria were applied 385 articles were excluded. 3 articles were excluded due to the impossibility of reading it in its entirety. After applying the criteria, there were then 17 scientific papers eligible for systematic review (Figure 1).



The 17 selected articles were analyzed for their quality using the Jadad scale.[6] The high quality of the articles was present in 10 of them, and the low quality in 7 articles, which were excluded from the present study (Table 1).

Table 1 - Quality of articles by item according to the Jadad scale.

Criteria	Was the study described as randomized?	Was the method for generating the randomization sequence described and appropriate?	Was the study described as double-blind?	Was the double-blind method described and appropriate?	Was there a description of exclusions and losses?	Total of points*
Fernández-Tomé et al.	YES	NO	NO	NO	NO	1
Coman et al.	NO	NO	NO	NO	NO	0
Fan et al.	YES	YES	NO	NO	YES	3
Bjarnason et al.	YES	YES	YES	YES	YES	5
FangHsu et al.	NO	NO	NO	NO	NO	0
Altun et al.	YES	YES	NO	NO	YES	3
Yılmaz et al.	YES	YES	NO	NO	YES	3
Matsuoka et al.	YES	YES	NO	NO	YES	3
Sasaki et al.	NO	NO	NO	NO	NO	0
Palumbo et al.	YES	YES	NO	NO	YES	3
Sheikhi A et al.	YES	NO	NO	NO	NO	1
Guslandi et al.	YES	YES	NO	NO	NO	2
Yoshimatsu et al.	YES	YES	YES	YES	YES	5
Tamaki et al.	YES	YES	YES	YES	YES	5
Geirnaert et al.	YES	NO	NO	NO	NO	1
Caviglia et al.	YES	YES	NO	NO	YES	3
Nakamura et al .	YES	YES	YES	YES	YES	5

*YES = represents 1 point and NO = 0.

Most studies were carried out in Japan (4) and Turkey (3), followed by the United Kingdom (1) and Italy (2). All studies have clinical trial methodology, being 1 from 2022, 1 from 2021, 5 from 2019, 1 from 2016 and 2 from 2015. 10 articles included a total of 690 individuals, the most used probiotic among the articles was lactobacillus, being studied in 6 of the 10 selected articles, followed by bifidobacterium, which was analyzed in 6 of the 10 studies; the outcome was positive in 9 articles, and the only study that showed a negative result evaluated only 2 probiotic strains (Table 2).

To emphasize the impact of the use of probiotics, the symptoms and imaging tests were considered. Five of these articles had as a comparison group the use of placebo and the use of probiotics[3,4,6,8,9]. Only one[8] did not show benefits from the use of probiotic therapy to the detriment of the other four that demonstrated its effectiveness[9,10,1,12].

In the article Altun et al.[9], a total of 40 patients with UC were randomized into two groups: the probiotic group and the control group. When both groups were compared, there was a significant improvement in the clinical activity of the symbiotic group ($p < 0.05$). The small sample of patients and the absence of more specific inflammation markers were the main limitations of this study[9].

On the other hand, in the study Bjarnason et al.[10], in order to assess the efficacy of a multi-strain probiotic related

to quality of life and intestinal inflammation in patients with asymptomatic UC and CD, the important fecal calprotectin (FCAL) was analyzed. The differences in FCAL between patients with UC before and after probiotics approached statistical significance (p = 0.076), thus revealing that the probiotic can be anti-inflammatory in these patients. However, there was no significant change in patients with CD. The deficiency presented by the study was that the selected group of patients with IBD were asymptomatic[10].

Following the same line of analysis, the study Yoshimatsu et al.[11], with the objective of defining factors related to the effectiveness of the probiotic for the prevention of relapse in patients with inactive UC, used the T-RFLP grouping to analyze the fecal flora of patients and the fecal concentration of short chain fatty acids. At 12 months, the remission rate was 69.5% in the probiotic group (p=0.248). Probiotics, therefore, have been shown to be effective in maintaining clinical remission in patients with quiescent UC[11].

In the Yılmaz et al.[12] article, the aim was to determine the effects of kefir on the flora of patients with CD and UC, investigating symptoms and quality of life. A statistical analysis was performed to obtain data from the symptom diary using the SPSS 23.0 program. For the control group, a yoghurt similar to the fermented drink was used, but which also had Lactobacillus. There was a statistically significant improvement in abdominal pain (p=0.049), bloating and quality of life when compared to the control group. The small sample size and the short time are the main weaknesses of the study[12].

The articles in this literature review emphasizes the effectiveness of probiotics in relation to IBD[9,10,11,12]. However, the study carried out by Matsuoka et al.[8], indicated the absence of a significant effect with the use of probiotic therapy. The aim of this study was to investigate the potential effect of bifidobacteria in maintaining the relapse status in patients with UC by comparing the placebo group and the probiotic group. The outcome was not significantly different between the two groups (P = 0.803). Furthermore, there were also no statistically significant differences in clinical deterioration (P = 0.803). The article brings as a limitation for the absence of a significant treatment effect the amount of bifidobacteria administered[8].

In the article Fan et al.[13], the CD activity index (CDAI) and the UC activity index (UCAI) were used. When compared to the recurrence rate, the observation group had significantly less impact compared to the control group ($p < 0.05$). It was also observed that the association between pentasa and probiotics can effectively readjust the composition of the intestinal microflora by reducing intestinal lactoferrin, 1-antitrypsin and β2-microglobulin levels. The short follow-up time was the weaknesses of this study[13].

Palumbo et al.[14] recruited patients with UC for clinical and endoscopic evaluation over a period of 2 years, according to the. The use of probiotics plus standard therapy improves the quality and life expectancy of patients, significantly reducing symptoms and side effects through the evolution of the response to anti-inflammatory[14].

In the article H. Tamaki et al.[15] Both groups used 5-ASA, prednisolone, azathioprine and 6-mercaptopurine. During the study period of the article, the UCDAI score (already mentioned above) was used, showing that the group that received the BB536 had a significant reduction in rectal bleeding (p = 0.038) and in mucosal findings (p = 0.017). Endoscopic evaluation was performed using the EI score and the Mayo subscore, seven patients (29.2%) in the probiotic group achieved mucosal healing compared to four patients (17.4%) in the placebo group; however, this difference was not statistically significant[15].

In the Claviglia et al.[16] article, the control group was treated with 5-ASA alone and the case group was treated with 5-ASA plus FEEDColon® (Bifidobacterium *longum* BB536; calcium butyrate, Bifidobacterium *bifidum*, Bifidobacterium lactis and FOS). The study noted that 95% of patients treated with combination therapy maintained remission compared with 57% of those treated with 5-ASA alone. The article also showed that the case group achieved a significant improvement in subjective symptoms[16].

Nakamura et al.[17] analyzed the microbiome and metabolome profiles of fecal samples collected during the experimental study period. This study showed that some of the bacterial genera were different in the test intervention group from those in the other groups ($p < 0.05$, uncorrected). Overall, the results indicate that the effect of B. *longum* BB536 ingestion on the gut microbiome and metabolome was small relative to the effect of individual differences in the gut environment. However, this study indicated that some individuals had increased bowel movements as a result of taking the B. *longum* BB536 supplement; these individuals were defined as "intestinal responders'' and had an abundance of propionate and butyrate, which are the main metabolites produced by the intestinal microbiota (p = 0.0361 for butyrate, p = 0.0118 for propionate; Jonckheere-Terpstra trend test)[17].

DISCUSSION

IBD is an inflammatory condition of the colon and small intestine, which has two types: CD and UC. UC mainly affects the colon, while CD can affect the entire digestive tract. They have a multifactorial etiology and are related to the intestinal microbiota and changes in the immune system. It is known that patients with IBD have dysbiosis, that is, their intestinal microbiota is deregulated[18]. In these cases, there is usually a reduction in diversity and an increase in inflammatory bacteria. In view of this, the use of probiotics has been researched as a possible way to balance the intestinal flora in IBD,

contributing to drug therapy and maintaining disease remission, because probiotics are living microorganisms that help to balance the intestinal microbiota, inhibiting the growth of pathogenic bacteria, stimulating intestinal immunity and increasing anti-inflammatory agents. The time, dose and form of administration of probiotics were different in each of the studies, but the shortest time observed to demonstrate some benefit was 4 weeks and most articles used probiotics about 2 or 3 times a day[9-18]. Furthermore, the only study that did not demonstrate benefit in its use, it used only 01 dose a day, however, it did so for 48 weeks[8]. As for the form of presentation, some studies used tablets, others liquids, however, regardless of this, they obtained benefits from their use[9-18].

All studies show positive results on the use of probiotics associated with traditional treatments for patients with IBD. Except Matsuoka et al.[8], it is also worth emphasizing that this article still has gaps to be understood, such as: the type of probiotic that would be most effective for the pathophysiology of IBD, its ideal dosage and administration scheme, and the small sample space. This study looked at the use of Bifidobacterium breve and Lactobacillus acidophilus. This study looked at the use of Bifidobacterium breve and Lactobacillus acidophilus. However, other studies[9,10,14]. studied the same bacteria and obtained a positive result.

Considering the above, it is known that the standard treatment for IBD is immunosuppression by corticosteroids and biological agents, which act to relieve symptoms in the short term[13]. By addressing the use of traditional therapy plus probiotics, the present study points to this therapeutic combination as promising[9-16]. The association with these live microorganisms seems to guarantee that, in addition to reducing the symptoms of the active disease, there is a prolongation of the clinical remission, improving the quality of life of patients with the present pathology in question[13,14,15]. However, it was not possible to observe a positive endoscopic remission[9].

The present study has as a possible limitation the number of articles available in full and free of charge that answered the proposed key question. In addition, the articles claim that the use of probiotics can be beneficial in the treatment of IBD, but none can consistently demonstrate that their use should be done routinely.

Table 2 - General characteristics of selected studies.

					COMPARISON		
Select articles	**Kind of study**	**Year**	**Local**	**Sample**	**Comparision groups**	**Probiotic used**	**Clinical acticity**
Fan et al.	Clinical trial	2019	Turkey	40	A total of 40 patients with IBD were randomized: 19 patients received pentasa and 21 patients received probiotics together with pentasa.	Bifidobacterium and Lactobacillus. 2 probiotics tablets once and three times a day .	Positive
Bjarnason et al.	Clinical trial	2019	United Kingdom	142	81 and 61 patients with UC and CD, respectively, were randomized and completed the study.	Lactobacillus rhamnosus, Lactobacillus plantarum NCIMB 30173, Lactobacillus plantarum NCIMB 30173, Lactobacillus acidophilus NCIMB 30175 and Enterococcusfaecium. 50 ml/dose containing about 10 billion live bacteria.	Positive
Altun et al.	Clinical trial	2019	Turkey	40	40 patients with UC were randomized between symbiotic and placebo groups.	Six probiotic strains: Enterococcusfaecium, Lactobacillus plantarum, Streptococcus thermophilus, Bifidobacteriumlactis, Lactobacillus acidophilus, Bactoidobacterium longum. One tablet after breakfast and dinner. Was composed of six probiotic strains (3×109 CFU) and fructooligosaccharide (225 mg/tablet).	Positive
Yılmaz et al.	Clinical trial	2019	Turkey	45	45 patients: 25 treatment groups and 20 control groups participated in this study.	Lactobacillus is the dominant flora of kefir, a fermented milk that has probiotic properties. The Lactobacillus kefiri is the characteristic microorganism from kefir. 400 mL/day was administered twice a day which contains a total of 2.0×1010 CFU/mL viable Lactobacillus bacteria.	Positive
Matsuoka et al	Clinical trial	2019	Japan	195	195 patients with inactive UC were randomized to receive a package of fermented milk and matching placebo.	Bifidobacterium breve and Lactobacillus acidophilus.100 mL of an opaque white liquid that contained B. breve strain Yakult (10 billion bacteria) and Lactobacillus acidophilus (1 billion bacteria).	Negative

continue

contination

COMPARISON							
Select articles	**Kind of study**	**Year**	**Local**	**Sample**	**Comparision groups**	**Probiotic used**	**Clinical acticity**
Palumbo et al.	Clinical trial	2016	Italy	60	Group A: treated with 1200 mg of mesalazine (anti-inflammatory) orally once/day. Group B: was treated with daily administration of oral mesalazine 1200 mg + double administration of a probiotic mixture.	Lactobacillus salivarius, Lactobacillus acidophilus and Bifidobacterium Bifidum. Single daily administration of oral mesalazine 1200 mg and a double administration of a probiotic blend.	Positive
Yoshimatsu et al.	Clinical trial	2015	Japan	46	Treatment was started in 23 patients in the probiotic group and 23 in the placebo group.	Streptococcus faecalis, Clostridium butyricum, Bacillus mesentericus. Three tablets. Each tablet contains 2 mg of lactomin (Streptococcus faecalis T-110), 10 mg of Clostridium (Clostridium butyricum TO-A), and 10 mg of Bacillus (Bacillus mesentericus TO-A).	Positive
Tamaki et al.	Clinical trial	2015	Japan	56	Probiotic group: 28 patients and in the group placebo: 28 patients.	Bifidobacterium longum 536 (BB536). 2-3 × 10^{11} freeze-dried viable BB536.	Positive
Caviglia et al.	Clinical trial	2021	Italy	42	The control group there are 21 patients and there are 21 patients in the case group.	*Bifidobacterium bifidum*, *Bifidobacterium lactis*, and fructooligosaccharides (FOS). 2 tablets/day (1 tablet at breakfast and dinner).	Positive
Nakamura et al.	Clinical trial	2022	Japan	24	12 patients allocated to control food intervention and in the B.longum food intervention group 12 patients.	*Bifidobacterium longum* BB536. 01 acid-resistant seamless capsule per day.	Positive

CONCLUSION

Finally, based on the results found in this systematic review and analysis of articles on the association between IBD and probiotics, strong evidence was found regarding the benefit of using probiotics in the treatment of IBD, especially when associated with standard therapy. It is therefore relevant to the need for future research using quantitative techniques as meta-analysis to answer the main limitations present in this article.

Author contribution

MTM: Project administration, Conceptualization, Data curation, Formal analysis, Investigation, and writing the original draft.
SOM: Project administration, Conceptualization, Data curation, Formal analysis, Investigation, and writing the original draft.
ACLAC: Project administration, Writing the original draft, Translate, Review and Editing.
ICF: Supervision, Visualization, validation, and formal analysis.

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