Japanese Journal of Gastroenterology and Hepatology

Review Article ISSN 2435-1210 |Volume 6

The Role of Prebiotics on Inflammatory Bowel Disease: A Systematic Review

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Received: 12 May 2021
Accepted: 04 Jun 2021
Published: 12 Jun 2021

Citation:

Barbalho SM. The Role of Prebiotics on Inflammatory Bowel Disease: A Systematic Review. Japanese J Gstro Hepato. 2021; V6(15): 1-9

Keywords:

Ulcerative colitis; Crohn's disease; Inflammatory bowel disease; Prebiotics; Non-digestible oligosaccharides

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1. Abstract

1.1. Background: Inflammatory Bowel Diseases (IBD) are a set of disorders of idiopathic and multifactorial etiology, composed of two main entities: Ulcerative Colitis (UC) and Crohn's Disease (CD). The pathophysiology relies on inflammatory responses of the intestinal wall. Modern western dietary habits lack fibers and short-chain fatty acids (SCFAs), contributing to dysbiosis and malnutrition. Prebiotics are non-digestible oligosaccharides present in foods with a high amount of fiber and depend on microorganisms' action to be metabolized. This paper aimed to build a systematic review of the effects of IBD.

1.2. Methods: This review included studies available in MEDLINE–PubMed, EMBASE, and Cochrane databases, and the final selection included ten studies performed in humans. Our results show that ten studies investigated the use of prebiotics in humans. Therapies with prebiotics could improve and correct the microbiome imbalance caused by gut diseases, dietary habits, and drug administration. Thus, they could be considered as adjuvant therapy for IBD. However, the included studies were performed with a low number of patients, with different doses, different types of prebiotics, and therapy duration.

1.3. Conclusion: We suggest that more clinical trials are needed to elucidate the correct doses, types of prebiotics, and treatment duration to reach beneficial results for IBD patients.

2. Introduction

Inflammatory Bowel Diseases (IBD) are a set of disorders of idiopathic and multifactorial etiology, composed of two main entities: Ulcerative Colitis (UC) and Crohn's Disease (CD). It is postulated that its pathogenesis permeates genetic predisposes, which, in association with environmental factors and imbalance of intestinal immunity, become generators of an exacerbated immune response that culminate in the intestine's inflammation [1, 2].

IBD are clinically presented with periods of remission and recurrence that involve intestinal (diarrhea, possibly bloody and with the presence of pus, or even constipation) and extraintestinal manifestations (uveitis, ankylosing arthritis, aphthous stomatitis, erythema nodosum, psoriasis, sclerosing cholangitis, bronchiolitis, granulomatous interstitial lung disease, and glomerulopathies). A relevant consequence is an intestinal malabsorption, which can lead to anemia and malnutrition. Besides that, recent evidence demonstrates interference of IBD in the nervous system due to damage to the gut-brain axis [3-6].

The conventional treatment for IBD is based on the use of immunomodulators and corticosteroids. However, these medications may present limitations, such as high costs, adverse effects, and in some cases, the loss of effectiveness. Moreover, the use of immunosuppressant's requires a closer look, especially in periods of vulnerability associated with pandemics, as in the current circumstance of COVID-19, to prevent IBD patients from being a potential target [7-10].

The intestinal microbiota has great importance in the organism's defense mechanisms since it interposes the contact between the gastrointestinal tract and pathogens coming from the external environment. Nevertheless, a mucus barrier, located between the microbiota and the mucous layer's cells, contributes to preventing the interaction between the intestinal flora components and innate immunity, namely M cells sub epithelial dendritic cells, avoiding the triggering of inappropriate and uncontrolled immune responses. Thus, changes in these defense systems, such as dysbiosis, can contribute to IBD's installation and recurrence. The aging process, diet, host immune response, use of antibiotics, and other environmental factors are responsible for modulating and modifying intestinal biota [11-13].

Prebiotics are non-digestible oligosaccharides, present abundantly in foods with a high amount of fiber, and therefore depend on the action of microorganisms from the intestinal biota to be degraded and absorbed. Thus, these dietary components serve as a substrate for the microbiota's development and maintenance, which maintains balance and symbiosis with the host [14-15].

Many studies have focused on the therapeutic use of prebiotics in the treatment of IBD. For this reason, this work aims to perform a Systematic Review of the effects of prebiotics in IBD and their possible therapeutic use.

3. Methods

3.1. Focal Question

This systematic review was built to answer the focused question: Can prebiotics promote beneficial effects on Inflammatory Bowel Diseases?

3.2. Language

Only studies in English were selected.

3.3. Databases

This review has included studies in MEDLINE–PubMed (National Library of Medicine, National Institutes of Health), EMBASE, and Cochrane databases.

The Mesh terms used were "Prebiotics or conjugated linoleic acid or polyunsaturated fatty acid or fructooligosaccharides or galactooligosaccharides or mannanoligosaccharide or xylooligosaccharide and Inflammatory Bowel Disease or Ulcerative Colitis or Crohn's Disease." The use of these descriptors helped identify studies related to prebiotics and their beneficial effects on Inflammatory Bowel Disease treatment. We have followed PRISMA (Preferred Reporting Items for a Systematic Review and Meta-Analysis) guidelines [16].

3.4 Study Selection

This review included studies that reported the potential beneficial role of prebiotics in patients with Inflammatory Bowel Disease. The inclusion criteria were studies performed in humans, including Randomized Clinical Trials (RCTs), primary and interventional studies, open-label, and case-control articles.

The exclusion criteria were reviews, studies not in English, editorials, and poster presentations. Reviews were consulted but were not included.

3.5 Eligible Criteria

The eligible criteria for this review followed the PICO (Population, Intervention, Comparison, and Outcomes) format for RCT. The outcomes were a reduction in IBD scores, reduction of proinflammatory biomarkers, and improved quality of life. Only full studies published in the consulted databases were selected.

3.6 Data Extraction

Two independent reviewers performed the search for the studies to identify the RCT in the databases. The articles' abstracts were evaluated, and only full-text studies were retrieved to support the decision-making process. Disagreements between the judges were evaluated and decided by two other reviewers.

The selected articles included studies from 2011 to 2021 and, after identifying the available articles, only the studies presented at the end of the flow chart (Figure 1) filled the objectives of this review. These studies are described in (Table 1).

Table 1:

Reference	Country	Type of Study	Patients	Intervention	Comparison	Outcomes
Valcheva et al. [51]	Canada	Randomized, dose-response study.	25 patients with an endoscopic confirmed diagnosis and mild to moderately active UC; 18-65y (11 men; 14 women)	7,5g (n=12) or 15g (n=13) of oligofructose-enriched inulin/day, orally/ 9w.		Fructans significantly reduced colitis in the high-dose group and increased colonic butyrate production. Fecal butyrate levels were negatively correlated with Mayo score. High-dose of fructan increased *Bifidobacteriaceae* and *Lachnospiraceae.*

Anderson et al. [17]	United Kingdom	Case-control study.	303 patients with active CD (n=98), inactive CD (n=99) and healthy controls (n=106); 18-65y (124 men; 179 women)	Observational (questionnaire) – Measure of intake of inulin-type fructan from habitual diet.	-	Patients with active CD presented lower fructan and lower oligofructose intakes than inactive CD or control groups. Negative correlation between HBI wellbeing score and fructan and oligofructose intakes, as good as the HBI abdominal pain score was noted.
Benjamin et al. [20]	United Kingdom	Randomized double-blind placebo-controlled trial.	103 patients with active CD; mean ages: 40±14.8 (intervention group, n=54) and 39±13.7 (control group, n=49) (40 men; 63 women).	15 g/day of FOS, orally/4w.	Non-prebiotic placebo	No significant differences in clinical response between FOS and placebo. Subjects that received FOS showed reduction of IL-6-positive and increased IL-10 in *lamina propria* dendritic cells. No significant changes in IL-12p40 production. No notable differences in fecal concentration of *bifidobacteria* and *F prausnitz*ii.
Wiese et al. [18]	USA	Open-label study.	28 patients with CD; 20-75 y (6 men; 22 women).	Two 8-oz cans/day of IBDNF orally/ 4m.		Significant decrease in plasma phospholipid levels of arachidonic acid with an increase in EPA and docosahexaenoic acid. There was also improvement in fat-free and fat mass.
Faghfoori et al. [21]	Iran	Randomized, controlled study.	41 patients with UC in remission; mean ages: 33.90±11.76 (GBF group) and 33.04±12.41 (control group) (26 men; 15 women).	30g/3 times day of GBF, orally/ 2m.	Standard drug treatment	There was a decrease of TNF-α, IL-6, and IL-8 in the GBF group, while in the control group, all values were increased.

CD: Crohn's Disease; EPA: eicosapentaenoic acid; FOS: fructooligosaccharides; GBF: Germinated Barley Foodstuff; HBI: Harvey-Bradshaw Index; IBD: Inflammatory Bowel Disease; IBDNF: Inflammatory Bowel Disease Nutrition Formula; IL: interleukin; TNF: tumor necrosis factor; UC: ulcerative colitis.

Table 2: Descriptive Table of the Biases of the Included Randomized Clinical Trials.

Study	Question focus	Appropriate randomization	Allocation blinding	Double-blind	Losses (<20%)	Prognostics or demographic characteristics	Outcomes	Sample calculation	Adequate follow-up
Valcheva et al. [51]	No	NR	NR	No	Yes	Yes	Yes	NR	Yes
Anderson et al. [17]	No	NR	No	No	No	Yes	Yes	Yes	NR
Benjamin et al. [20]	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Wiese et al. [18]	No	NR	No	No	No	Yes	Yes	NR	Yes
Faghfoori et al. [21]	No	NR	No	No	NR	Yes	Yes	NR	Yes

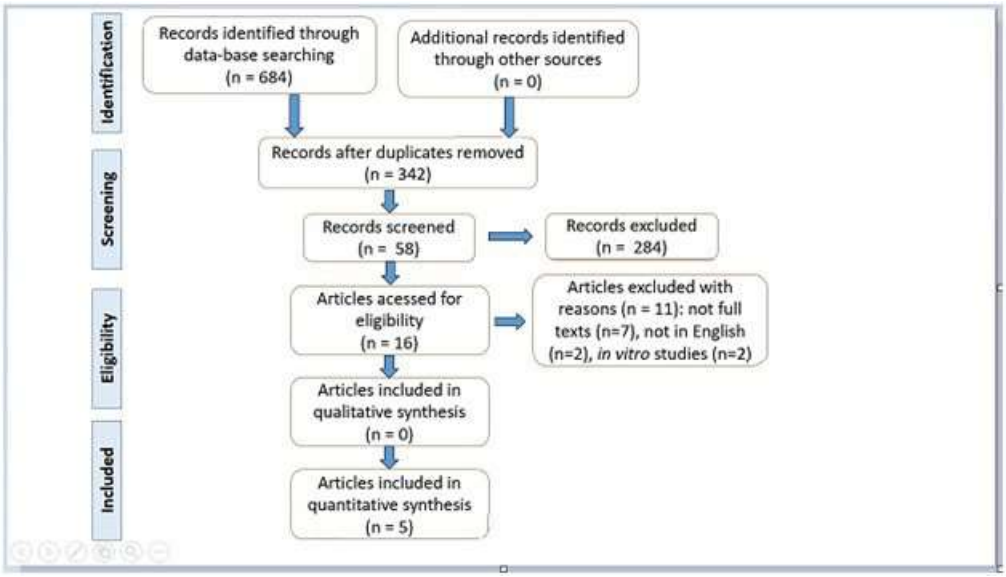

Figure 1: Literature search flow diagram [52]

4. Results

The flow diagram (Figure 1) shows the selection of the articles and the inclusion and exclusion criteria. Five studies were selected to build this review. Among these studies, one was an open-label trial, one was a case-control study, and three were randomized clinical trials. Altogether, 500 individuals were enrolled in the selected studies, 18-75 years old, 207 men, and 293 women.

From the five articles (one from Canada, two from the United Kingdom, one from the USA, and one from Iran), one was a case-control study [17], one an open-label [18], one a randomized dose-response study [19], one a randomized double-blind placebo-controlled [20] and one was a randomized controlled study [21].

One of the studies was performed with patients with UC in remission [21], one with active CD patients [20], one with active and inactive CD patients, and also healthy controls [17]. Another study was performed with patients with mild to moderately active UC confirmed by endoscopy [19]. One study enrolled patients with CD but failed to specify the disease activity status [18].

One study used oligofructose-enriched inulin [19], another measured the inulin intake [17], one used FOS (fructooligosaccharides) [20], another used GBF (germinated barley foodstuff) [21], and one used IBDNF (Inflammatory Bowel Disease Nutrition Formula) [18] as interventions. The doses administered had a wide variation range from 7, 5g per day to 8-oz per day, and the period of intervention ranged from 4 weeks to 9 weeks.

The studies showed that the use of prebiotics reduced colitis and increased colonic butyrate production [19], reduced IL-6 and increased IL-10 [20], decreased TNF-α, IL-6, and IL-8 [21], and also decreased plasma phospholipid levels of arachidonic acid with an increase in EPA (eicosapentaenoic acid), and docosahexaenoic acid [18]. We also observed that patients with active CD presented a lower intake of prebiotics when compared to patients with inactive CD [17] (Table 1).

5. Discussion

5.1. Inflammatory Bowel Disease: Pathophysiology

IBD consist of multifactorial diseases, whose pathophysiological architecture is based on predisposing genetic factors added to environmental factors and the intestinal microbiota, as illustrated in (Figure 2). However, studies still seek to elucidate better these elements and how they participate in the development of an exacerbated and extremely harmful inflammatory response [22-24].

CD is characterized by intramural lesions capable of affecting the entire gastrointestinal tract, from the mouth to the anus, with a predominance of discontinued lesions and a granulomatous pattern. It is related to a TH1 and TH17 immune pattern, whereas UC is more related to the TH2 response, with a predominance of ulcerative lesions and inflammatory hemorrhage. Besides, UC differs from CD in terms of the lesion site since it is more restricted to the rectum, continuously reaching segments of the colon, only in the mucous layer. Both are related to an exacerbated response, with reduced regulatory T cell activity, and have classic manifestations such as abdominal discomfort and pain, diarrhea, vomiting, and even bleeding of the gastrointestinal tract [25-27] [28].

Predisposing genetic factors are related to changes in alleles of proteins and receptor genes present in immune cells. These changes in epithelial cell and lymphoid tissue proteins are closely associated with stimulating nuclear factors, such as the Nuclear Factor kB (NFkB). In turn, the activation of these factors is linked to the development of a proinflammatory secretory pattern, with increased secretion of cytokines such as TNF-α, IL-1β, IFN-γ, IL-12, IL-6 [29] [30].

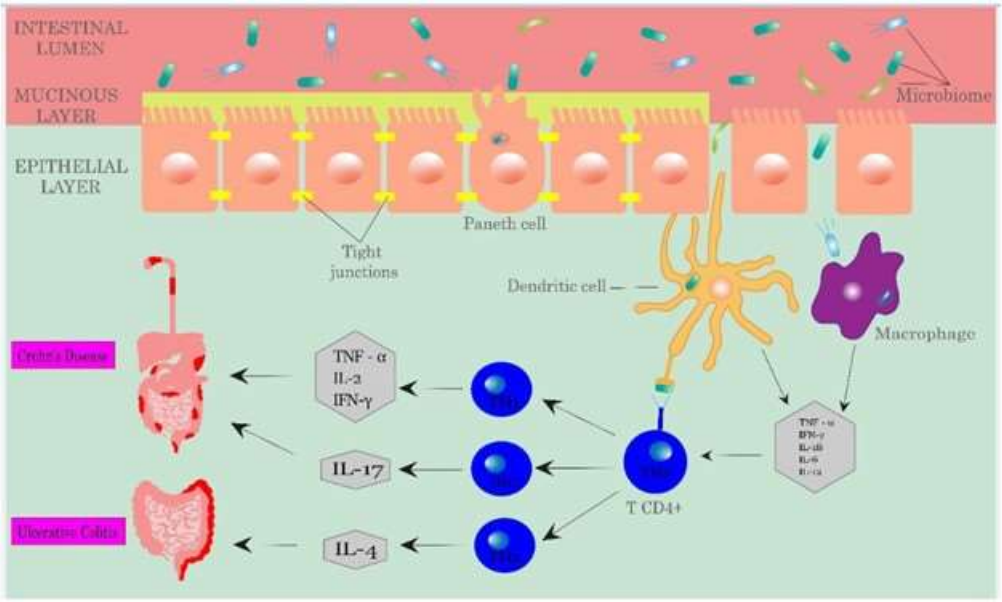

Figure 2: In the pathophysiology of IBD, there is an imbalance in intestinal microbiota, with disruption of tight junctions and mucinous layer, which leads to the inflammatory response. In CD, the primary response is mediated by TH1 and TH17, resulting in proinflammatory cytokines. In UC, the primary immune response is mediated by TH2. TH: T helper cell; IL: Interleukin; IFN: Interferon; TNF: Tumor necrosis factor.

As environmental factors, it is noteworthy to mention the lifestyle. The increase in consumption of xenobiotics rich in preservative dyes to the detriment of the consumption of natural products leads to a lack of essential nutrients. Also, excess sugar intake, smoking, and alcohol consumption are attributed to harmful factors since they damage the intestinal epithelial barrier. The indiscriminate use of antibiotics, which have a significant negative impact on the intestinal microbiota, may also be associated with the pathogenesis of the condition [30-33].

Several studies have shown the participation of the intestinal microbiota in the trigger process for an exacerbated immune response. The dysbiosis added to the greater permeability of the intestinal wall favors the presentation of pathogens to trigger inflammatory and oxidative secretory patterns [33-35]. (Figure 2) shows the pathophysiology of IBD.

5.2. Prebiotics

In the last decade, there was a significant development in research about the intestinal microbiome dynamics and the emergence and progression of several diseases. It is known that dysbiosis plays an essential role in the pathophysiology of IBD [36-39]. It has been proposed that therapies with probiotics, prebiotics, and symbiotics could improve and correct the microbiome imbalance caused by gut diseases, dietary habits, and drug administration, such as antibiotics. Thereby, several studies have focused on providing evidence that prebiotics administration is a viable alternative for treating a significant number of diseases related to dysbiosis [14] [40].

The definition of 'prebiotic' has changed since its creation in the late 1990s, by Gibson and Roberfroid. It was considered that a prebiotic is a non-digestible food ingredient that reaches the lower gut system and enables the growth and activity of healthy, nonpathological bacteria [41]. The current definition is given by The International Scientific Association for Probiotics and Prebiotics (ISAPP), as a consensus that a prebiotic is a substrate that is selectively utilized by host microorganisms conferring a health benefit. Therefore, a prebiotic is not limited to stimulation of bifidobacterial and lactobacilli only. By the current definition, it is needed that a prebiotic requires utilization by host microbiota, which is not narrowed to the gastrointestinal tract but also sites such as vaginal and skin. Although, it is implied that a prebiotic for gut beneficial health must be non-digestible. Furthermore, substrates that alter the microbiota by mechanisms other than its utilization by host's microorganisms are not prebiotics [42].

Some of the most widespread and common prebiotics are fructooligosaccharides (FOS), present in fibers from fruits and vegetables; galactooligosaccharides (GOS), present in dairy and infant formulas; Human Milk Oligosaccharides (HMOs); Polyunsaturated Fatty Acid (PUFA); Mannanoligosaccharide (MOS); Xylooligosaccharide (XOS) and Conjugated Linoleic Acid (CLA) [42]. These prebiotics act as a substrate to various bacteria genera, such as Bifidobacterium and Lactobacillus, producing substances like butyrate and Short-Chain Fatty Acids (SCFAs), which play a role in reducing inflammatory responses [43].

According to these definitions, some substracts affect the host microbiome but do not act as prebiotics, such as antibiotics, proteins and fats, probiotics, vitamins, and less fermentable dietary fibers [42].

Due to these findings, it is possible to suggest that introducing prebiotics on modern western diets could be of great importance to lowering and better conducting a vast majority of diseases, not only restricted to the gastrointestinal tract.

5.3 Use of Prebiotics on Inflammatory Bowel Disease

In the past few years, it is seen an increase in the number of studies proposing various prebiotic therapies to patients suffering from different diseases. Since IBD is an idiopathic disease which pathophysiology relies on an exacerbated inflammatory and dysbiosis, it is possible that the imbalance can be corrected by improving the microbiome. The decrease of pathological bacteria in the gut and providing commensal bacteria with substrates capable of being metabolized into substances that contribute to the production and secretion of anti-inflammatory cytokines is more than an ever valid path to follow [11].

Standard clinical treatment for IBD consists of drugs that modulate the gastrointestinal tract's inflammatory patterns, such as mesalamine, azathioprine, anti-TNF, and glucocorticoids. However, these drugs often appear to have significant side effects, and to some patients, higher doses are to be needed throughout the treatment period. Hence, these drugs are not always specific to either CD or UC, which are used due to their potential in diminishing and ameliorating symptoms, but not without critical adverse effects [44]. For these reasons, prebiotics could be considered since they have may be effective in decreasing pathological gut bacteria, such as Escherichia and Shigella species, improving the growth of healthy commensal bacteria, especially within the Bifidobacterium and Lactobacillus genera, diminishing inflammatory cytokines, such as IL-1α, IL-1β, IL-6, IL-12, TNF-α, IFN-γ, and improving the natural intestinal barrier by increasing mucinous layer and tight junctions between epithelial cells [45-46].

Prebiotics are relatively easy to be found and consumed. Most daily foods, such as fruits and vegetables, contain a wide variety of fibers, fatty acids, and carbohydrates that can act as prebiotics. Nevertheless, it has been noticed that modern western dietary habits lack fibers, SCFAs, and other nutritional vitamins and minerals. Therefore, prebiotic supplementation could provide these important food components [47-48].

Prebiotics are not digested and remain in the gut lumen and serve as a substrate to many bacteria. These microorganisms often produce butyrate, acetate, and SCFAs from the prebiotic formulas and improve healthy bacteria by controlling intestinal populations. Therefore, they correct the imbalance in the intestinal microbiota [49], as shown in (Figure 3).

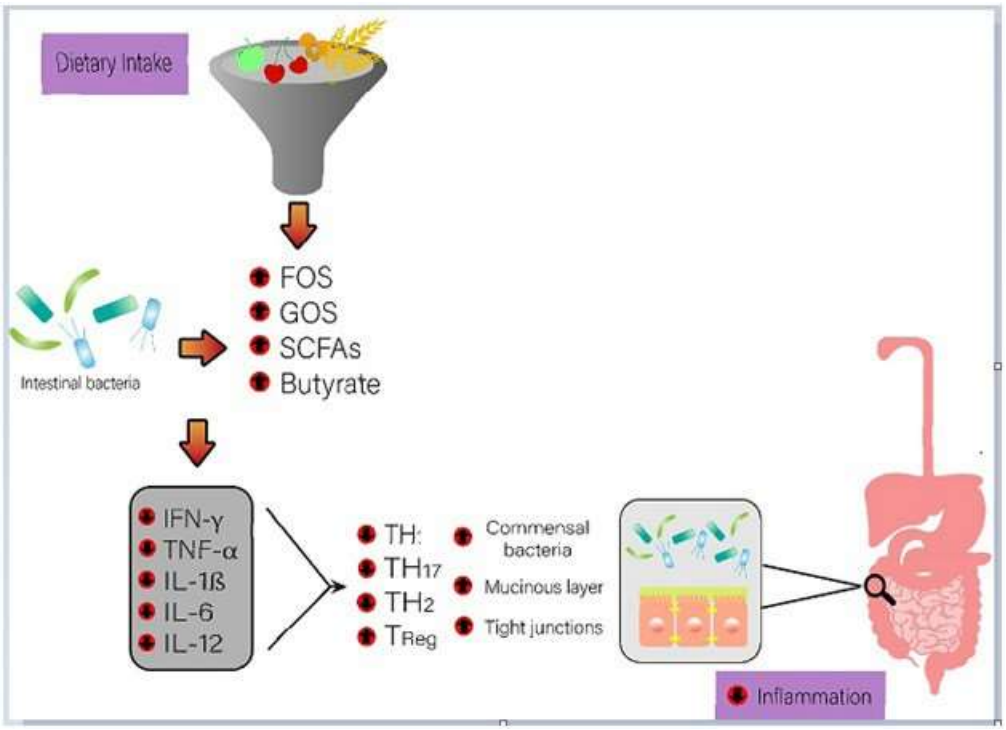

Figure 3: Prebiotics are obtained from dietary intake and act in the intestinal lumen as a substrate to the microbiome. The homeostasis of intestinal microbiota, improved by the intake of prebiotics, corroborates the development of an anti-inflammatory pattern and reduction of inflammation. Also, prebiotics help in the maintenance of tight junctions and mucinous layer. FOS: Fructooligosaccharide; GOS: galactooligosaccharide; SCFAs: Short-chain fatty acids; TH: T helper cells; IFN: Interferon; IL: Interleukin; Treg: T regulatory cells.

Due to the pathogenesis of IBD, it is apparent the importance of discussing the role of the prebiotics in the therapeutic approach of these conditions. Furthermore, the use of prebiotic, besides showing potential to ameliorate inflammation and immune responses, is not associated with relevant adverse effects [50] [25]. (Figure 3) shows some effects of prebiotics in the gut.

Below we briefly discuss the studies included in Table 1, and Table 2 shows the biases of the studies.

Valcheva et al. [51] performed a randomized dose-response study to evaluate clinical scores and fecal calprotectin levels in patients with active mild-to-moderate endoscopically diagnosed UC. Patients received different doses of oligofructose-enriched inulin daily, orally. At baseline and post nine weeks of treatment, patients were clinically evaluated to determine remission in the UC activity. Changes in the fecal calprotectin, the composition of fecal and mucosal microbiota, the fecal short-chain fatty acids (SCFA's) production, and butyrate metabolism were also analyzed at both times. There was a significant improvement in clinical response, determined as a decrease of total Mayo score by 3 at the end compared to baseline, or total Mayo score of 2 or less, which characterizes clinical remission. There was a significantly greater clinical improvement on patients in the 15g inulin group than the 7.5g inulin group. However, patients in the 15g inulin group reported flatulence at the beginning of the treatment. Therefore, significant adverse effects are causing transitional flatulence and bloating. Furthermore, fecal butyrate levels were negatively correlated with Mayo score. High-dose of fructan increased Bifidobacteriaceae and Lachnospiraceae, but these shifts were not correlated with improved disease scores and inflammation markers, which shows that the tested prebiotic enhances the activity of nonpathological bacteria in UC. Beyond that, there was a significant improvement in the SCFA's production in the high dose group, but not in the low dose one. Finally, it is possible to notice that the administration of high-dose fructan as prebiotic in patients with active UC is beneficial despite some transient adverse effects.

Anderson et al. [17] carried out a case-control study using questionnaires on the correct intake of inulin-type fructan in active and inactive CD patients. The study showed that patients with active CD had less fructan and oligofructose intake than the group of patients with inactive CD. Indeed, a negative correlation between HBI wellbeing score and fructan and oligofructose intakes was noted, as good as the HBI abdominal pain score (Table 2).

In another study, Benjamin et al. [20] investigated the CDAI and interleukin levels after FOS intervention in CD patients. Their results showed improvement in IL in the intervention group. Nevertheless, there were no statistical differences regarding the clinical response in both groups. Moreover, no relevant changes were noted in the production of IL-12p40 and the fecal concentrations of Bifidobacteria and F. prausnitzii. The change in cytokines' pattern may demonstrate a potential effect of FOS on the disease's inflammatory activity.

Wiese et al. [18] performed a study with active CD and investigate the fatty acids composition and micronutrients plasma levels, such as vitamin D after four months of treatment with 16 oz per day of a nutritionally balanced Inflammatory Bowel Disease Nutrition Formula (IBDNF), enriched with fish oils, prebiotic fibers with fructooligosaccharide, and gum Arabic; and vitamins and minerals antioxidants. This formula enables alteration in inflammatory patterns by increasing the levels of ω-3 polyunsaturated fatty acids and decreasing the arachidonic acid levels. At baseline, all patients had plasma phospholipid EPA levels <2%. At the end of the trial, there was a significant decrease in plasma phospholipid levels of arachidonic acid with an increase in EPA and docosahexaenoic acid and an increase in ω-3 PUFA and a decrease in ω-6 PUFA. There was also improvement in fat-free and fat mass and vitamin D levels. Furthermore, there was an improvement in the IBDQ and CD activity index in patients who showed this increase in EPA levels after the four-month trial. Although it is not sufficient to determine clinical improvement in patients with active CD, this study demonstrates that changes in nutrition and fatty acid composition can ameliorate and induce changes in inflammatory patterns in patients who suffer from CD.

Faghfoori et al. [21] performed a trial to evaluate immune cytokine levels in patients with UC in remission before and after treatment with Germinated Barley Foodstuff (GBF), a prebiotic fiber resulted from the scutellum and aleurone fractions of germinated barley. Twenty patients were included in the GBF group and were treated with 30g of prebiotic fiber per day. In the control group, 21 patients were treated with their standard UC drug therapy. After the treatment period, there was a non-significant increase in the TNF-α values in the control group and a non-significant decrease in the prebiotic group. However, there was a statistical reduction in the other inflammatory cytokines IL-6 and IL-8 in the prebiotic group. Hence, this prebiotic fiber administration may ameliorate the inflammatory pattern in patients who suffer from UC.

It is important to highlight that we included Faghfoori's study in this review, despite some objections to the use of GBF as a prebiotic, because of our understanding that, as a fiber, it has the potential to modulate the growth of specific genera of bacteria in the gut and promote beneficial effects to the human host. Furthermore, the ISAPP definition supports that some fibers can be considered prebiotics (ISAPP, 2017).

Among the selected studies, one showed a reduction in inflammatory cytokines levels such as IL-6 and improvement in IL-10. The other three studies presented modulation of the microbiota and levels of butyrate, but none showed improvement in clinical or wellbeing scores. Another study associated FOS with fish oils, minerals, and vitamins, and the results improved the fat-free serum levels and decreased plasma phospholipid levels, although it is not possible to assess whether those results are due to the prebiotic individually, or to the whole compound.

6. Conclusion

The included studies showed relevance in the use of prebiotic as a potential therapy for IBD, especially at positively modifying the composition of the gut microbiome, since its imbalance is implied

in IBD pathogenesis. However, the studies included a small number of patients using different types of prebiotics at different doses and therapy duration. For these reasons, more clinical trials are needed to elucidate the correct types of prebiotics, doses, and treatment duration to reach clinically beneficial results for IBD patients.

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