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Review

Effects of dietary fiber on inflammatory bowel disease

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The chronic idiopathic inflammatory bowel diseases (IBDs), namely Crohn's disease and ulcerative colitis, appear to be derived from an inappropriate reaction towards a luminal agent, most probably driven by the intestinal microflora, which upregulates the synthesis and release of different pro-inflammatory mediators, thus contributing to tissue damage that characterizes these intestinal conditions. Several studies have reported that IBD is associated with impairment in short-chain fatty acid (SCFA) production, mainly acetate, propionate, and butyrate. They are produced in the large bowel by anaerobic bacterial fermentation of undigested dietary carbohydrates and fiber polysaccharides, with butyrate being considered as the major fuel source for colonocytes. These SCFAs have been proposed to play a key role in the maintenance of colonic homeostasis. Therefore, it is reasonable to consider therapeutic approaches that increase colonic SCFA production, as it can be achieved by administration of dietary fiber to IBD patients. Unfortunately, there is quite limited documentation of efficacy of dietary fiber in properly designed trials. This review discusses the rationale, available evidence for the use of dietary fiber and its mechanisms of action in the treatment and prevention of IBDs.

Keywords: Dietary fiber / Experimental colitis / Inflammatory bowel disease / Prebiotic / Review / Short-chain fatty acid

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Contents

1 Introduction

The term inflammatory bowel disease (IBD) comprises two closely related pathologies, ulcerative colitis (UC) and Crohn's disease (CD), which are characterized by chronic and spontaneously relapsing inflammation of the gut. UC affects only the large bowel, and the inflammatory process is confined to the mucosa. CD may affect any part of the bowel, from the mouth to the anorectum, and it is not confined to the lining of the bowel but affects all the bowel wall to form abscesses and fistulas (abnormal connections between the lumen of the bowel and other organs or the surface of the skin) and it may also present with bowel obstruction. Although much progress has been made in the understanding of human IBD pathogenesis, its precise etiology still remains unknown and involves a great number of factors, including genetic, environmental, microbial, and immunological factors [1]. Thus, an exacerbated inflammatory response of the intestine results from an inappropriate reaction towards a luminal agent, most probably driven by the intestinal microflora [2], which upregulates the synthesis and release of different pro-inflammatory mediators, including reactive oxygen and nitrogen metabolites, eicosanoids, platelet activating factor, and proinflammatory cytokines [3]. All these mediators actively contribute to the pathogenic cascade that initiates and perpetuates the inflammatory response in the gut. In fact, the intestinal epithelium acts as a defense against invasion by luminal toxins and bacteria but, as a consequence of the inflammation, the barrier function of the epithelium is impaired, and the subsequent translocation of endotoxins and antigens further upregulates the immune response [4].

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Abbreviations: CD, Crohn's disease; **GBF**, germinated barley foodstuff; **IBD**, inflammatory bowel disease; **SCFA**, short-chain fatty acid; **UC**, ulcerative colitis

Moreover, there is an alteration of the intestinal functions, both motility and mucosal hydroelectrolytic transport, responsible for some of the symptoms that characterize these intestinal conditions, *i.e.*, diarrhea and malnutrition [5]. Therefore, it is speculated that an improvement on the mucosal integrity may contribute to a reduction of the intestinal inflammation [6, 7].

Short-chain fatty acids (SCFAs), mainly acetate, propionate, and butyrate, have been attributed an important role in the maintenance of colonic homeostasis. They are produced in the large bowel by anaerobic bacterial fermentation of undigested dietary carbohydrates and fiber polysaccharides, and butyrate is considered as the major fuel source for colonocytes [8]. For this reason, a relationship between IBD and impairment of the colonic SCFA production and/or metabolism has been proposed to happen. In fact, previous studies have reported decreased SCFA concentrations in the colonic lumen of UC patients, in comparison with normal subjects [9], as well as in the cotton-top tamarin model of idiopathic colitis [10]. Theoretically, this could be attributed to a lower intake of dietary fiber, which, in turn, would result in an alteration of the colonic flora and the homeostasis between bacteria and colonocytes, driving to intestinal inflammation [11]. However, colonocytes incubation studies have shown impaired butyrate metabolism in patients [12 – 14], and diminished β-oxidation of luminal butyrate to CO_2 and ketones, resulting in energy deficiency within colonic epithelial cells. For this reason, an impairment of the colonocyte metabolism could effectively contribute to the pathogenesis of ulcerative colitis. This suggestion is supported by the experimental model of intestinal inflammation developed by Roediger and Nance [15], in which mitochondrial ß-oxidation of butyrate is blocked after intracolonic instillation to rats of sodium-2-bromooctanoate, and displays some similar features to those observed in human UC, including weight loss, bloody diarrhea, and histological lesions, such as ulceration, mucus cell depletion, and inflammatory cell infiltration. However, controversial results have been reported in subsequent studies, which did not show butyrate metabolism impairment in colonocytes isolated from UC patients [16, 17]. The methodological aspects of colonocyte incubations seem to be crucial and might explain the contradictory findings of the different investigators. In order to solve this problem, Den Hond *et al.* [18] measured *in vivo* butyrate metabolism in UC patients, and concluded that patients with active extensive disease had a decreased colonic butyrate oxidation, whereas remission was associated with normal oxidation. The latter suggests that UC mucosa does not intrinsically alter butyrate oxidation, making this unlikely to be a primary defect in UC.

All these facts promoted the use of butyrate enemas to alleviate the symptoms of ulcerative colitis, by restoring luminal levels of butyrate and thus facilitating the mucosal recovery from inflammation, as it has been reported [19, 20]. However, other studies have described the lack of effectiveness of the treatment with SCFA enemas (or only butyrate enemas) [21, 22], most probably due to the short-lived contact of SCFAs with the mucosal surface. Considering that SCFAs are derived from bacterial degradation of indigestible carbohydrates in the colonic lumen, *e.g.*, dietary fiber, the potential of regulating colonic butyrate production by dietary means is highly attractive.

2 Studies in humans

Dietary fiber consists of plant substances that resist hydrolysis by small bowel digestive enzymes. It is an extremely complex group of substances, including non-starch polysaccharides, resistant starch (that is starch that escapes digestion in the small intestine), cellulose and hemicellulose, oligosaccharides, pectins, gums, lignin, and waxes [23]. From a practical point of view, these components can be divided into soluble, which are highly fermentable by colonic bacteria and thus producing SCFAs and promoting bacterial growth, and insoluble, which are barely fermentable. The proportions of these components of a particular dietary fiber will determine its physiological and physical functions, and its diverse effects, both in the gastrointestinal tract and systemically.

Probably, the first approach to dietary fiber as a potential therapeutic option in human IBD was performed in 1978 by Davies and Rhodes [24], who evaluated the impact of dietary oat bran supplementation to UC patients in maintaining remission. Unfortunately, the main conclusion in this study was that this dietary fiber did not extend the time of remission. However, the lack of any beneficial effect in this clinical trial may be attributable to the type of fiber used, since oat bran is mainly composed of nonsoluble and nonfermentable components, and, in consequence, its ability to increase colonic butyrate production is very limited. On the contrary, the bulking effect of this type of fiber, which increases stool volume and causes colonic propulsion, predominates and is not beneficial for these patients.

A subsequent study reported by Hallert *et al.* in 1991 [25] tested the effects exerted by *Plantago ovata* husk in UC patients in remission. The authors concluded that this dietary fiber supplementation resulted in alleviation of the symptoms in these patients, mainly due to the normalization of the altered intestinal transit, which was probably attributed to the effect of the fiber on gastrointestinal motility. It is important to note that *Plantago ovata* husk is mainly composed of soluble and fermentable components; for this reason, and in addition to its effects on the normalization of the intestinal transit, its administration would

result in a significant increase in the SCFA luminal contents, mainly in the ascending colon, which could be responsible for the beneficial effects observed in these patients.

More recently, Fernandez-Bañares *et al.* [26] carried out a controlled investigation of daily oral administration of 10 g dietary fiber from *Plantago ovata* seeds in UC patients. This study reported the efficacy and safety of this kind of fiber as compared with mesalamine, a 5-aminosalicylate derivative commonly used in human IBD therapy, in maintaining remission in these patients. The results suggested that *Plantago ovata* seeds were well tolerated by the patients throughout the study, and this dietary manipulation resulted in an equivalent efficacy when compared with mesalamine in preventing relapse of the disease over a 12-month period. Furthermore, the beneficial effect exerted by long-term *Plantago ovata* oral administration was associated with increased butyrate concentrations in the distal colon. This was probably due to the fact that *Plantago ovata* seeds are composed of both soluble and nonsoluble fiber components, thus being slowly fermented along the colon, which may enable SCFA production and butyrate delivery in the distal parts of the colorectum, and not only in the proximal colon, as occurred when *Plantago ovata* husk was used, mainly composed of soluble fermentable fiber. In the same study, the authors also report the effects exerted by the combination of *Plantago ovata* seeds plus mesalamine in these patients. Although there were no statistical differences among groups, a trend to increase the mean time of treatment failure in the association group was observed [26].

In a later study, Hallert *et al.* [27] described a pilot trial in which patients with quiescent UC were instructed to add 60 g oat bran (corresponding to 20 g dietary fiber) to the daily diet for three months. They observed that these patients could safely take the diet, which specifically increases the fecal butyrate level, without showing signs of colitis relapse or an increase in gastrointestinal complaints during the trial, thus supporting the potential benefits of raising fecal butyrate by the oral route.

Since 1998, several studies have reported the beneficial effects of germinated barley foodstuff (GBF) in human UC [28 – 32]. GBF is derived from the aleurone layer and scutellum fractions of brewer's spent grain, and consists mainly of dietary fiber and glutamine-rich protein. The fiber fractions of GBF are mainly composed of low-lignified hemicellulose, which was shown to be utilized efficiently by colonic bacteria, including *Bifidobacterium* and *Lactobacillus*, thus promoting the increase of SCFA production, especially butyrate, in the colonic lumen. The different studies have concluded that this dietary fiber fraction actively contributes to the intestinal anti-inflammatory effects attributed to GBF. Thus, GBF administration to patients with mild to moderate active UC, concurrently with conventional treatment (5-ASA compounds and/or steroids), resulted in a significant decrease in the clinical activity index of the disease and mucosal damage compared with the control group of patients who received only the standard treatment [30, 31]. In addition, when the efficacy of GBF in patients with UC during the remission stage was assessed, the conclusions of the study revealed that the recurrence rate in the group of patients that received GBF with steroid tapering treatment was significantly lower compared with the control group without GBF [32]. Of note, no side effects related to GBF were observed in any of the clinical trials reported.

3 Mechanisms of action of dietary fiber in animal models of IBD

The different studies performed in experimental models of colitis have provided valuable information about the mechanisms involved in the intestinal anti-inflammatory effects of dietary fiber, supporting its potential role in the treatment of human IBD. Thus, it has been reported that dietary supplementation to rats with *Plantago ovata* seeds, inulin, or GBF resulted in an amelioration in the development of the inflammatory status in several models of experimental colitis, including those induced after intracolonic administration of trinitrobenzenesulfonic (TNBS) acid [33], or by incorporating dextran sulfate sodium (DSS) in the drinking water [34, 35], or in HLA-B27 transgenic rats [36, 37], being all of them well-established experimental models of intestinal inflammation with some resemblance to human IBD [38 – 40].

A common feature of all these experimental studies with dietary fiber was a therapeutic effect associated with an increased SCFA production in the colonic lumen, including butyrate, propionate, and acetate, thus counteracting the compromised colonocyte energy supply as a consequence of the intestinal inflammatory process [33 – 37], similarly to that reported in human IBD [9, 18]. However, it is important to note that not all the dietary fiber components that are able to promote SCFA production exert a beneficial effect in experimental colitis. Thus, whereas administration of short-chain fructo-oligosaccharides (FOSs), rapidly fermented in the caeco-colon, was devoid of any beneficial effect in the DSS model of rat colitis [41], the dietary supplementation to laboratory animals of resistant starch resulted in the improvement of the damaged intestinal mucosa in both the DSS and TNBS models of rat colitis [41, 42]. All these studies confirm the interest of promoting the generation of SCFA, and especially butyrate, in the management of IBD; however, the type of dietary substrate in achieving this is crucial because all the substrates suscep-

tible to be fermented and produce a high proportion of SCFA are not equivalent. It seems that the selection of slowly fermented dietary fiber along the colon may be of interest for a beneficial effect in these chronic intestinal conditions.

Furthermore, these experimental studies have revealed that the dietary fiber supplementation not only resulted in an increased colonic production of butyrate, but it promoted its use by colonic epithelial cells [33, 42], which was also impaired in experimental colitis [33], similarly to what has been described in human IBD [12, 18]. The result is the conversion of the predominating anaerobic adenosine triphosphate (ATP) production by glycolysis that characterizes intestinal inflammation into aerobic ATP production after butyrate oxidation by colonocytes [42]. The restoration of the metabolic function of these intestinal cells accelerates the regeneration of the inflamed colonic tissue in comparison with nontreated animals, and preserved the integrity of the colonic mucosa, a key process necessary to downregulate the exacerbated immune response that characterizes the intestinal inflammatory process [4].

In addition to its effect on the metabolic function of the epithelial cells, the increased production of SCFAs associated to dietary fiber intake may exert other different actions that also contribute to the intestinal anti-inflammatory effect evidenced both in human IBD and in experimental models. One such mechanism could be the inhibition in the production and release of inflammatory mediators, such as cytokines [33, 36, 43 – 46]. They participate in the exacerbated immune response that takes place and are responsible for the recruitment and/or activation of the different cells that play a key role in the intestinal inflammatory process, including neutrophils, macrophages, lymphocytes [47], intestinal epithelial cells [48], and dendritic cells [49]. Indirectly, this inhibitory effect can result in the preservation of the intestinal tissue from the damage exerted by other mediators, like reactive oxygen and nitrogen metabolites, once they are produced in high amounts by the different cell types participating in the inflammatory process [50].

Different i*n vivo* studies in experimental models of colitis have reported the ability of dietary fiber to attenuate the production of proinflammatory cytokines, including interleukin-6 (IL-6), IL-8, and tumor necrosis factor α (TNFα) [33 – 37]. Furthermore, i*n vitro* studies performed in HT-29 cells, as a model of intestinal epithelium, have revealed that both butyrate and propionate, at concentrations easily reached after dietary fiber supplementation (1–8 mM), are able to inhibit the production of the chemokine IL-8 in these cells when stimulated by lipopolysaccharides (LPSs) [33]. The inhibition of IL-8 production by SCFAs could contribute to a lower leukocyte infiltration and collaborate in the intestinal anti-inflammatory activity shown by dietary fiber supplementation [51], since margination and extravasation of circulating granulocytes markedly contribute to the chronic injury in these experimental models as well as in human IBD [52]. It is evident that the lower granulocyte infiltration would also result, subsequently, in downregulation of the production of most of the proinflammatory cytokines. In addition, and similarly to that previously described for IL-8, SCFAs can directly inhibit the production and/or release of other cytokines, like TNFα or IL-1β, thus contributing to the intestinal anti-inflammatory activity ascribed to dietary fiber. In this sense, it has been reported that butyrate (2 – 10 mM) decreases TNFα production by intestinal biopsies and by isolated lamina propria mononuclear cells [43], as well as in the human monocytic cell line THP-1 [36]. This inhibitory effect on TNFα production is very interesting since agents that block the actions of TNFα, such as infliximab (a humanized monoclonal antibody to TNFα) have showed to be highly effective in the treatment of CD [53 – 55]. In addition, butyrate has been reported to suppress the biological effects of TNFα in different intestinal epithelial cell lines, *i. e.*, HT-29, T_{84}, and Caco-2, probably *via* inhibition of nuclear factor-κB (NF-κB) activation [56, 57]. In fact, NF-κB is a transcription factor, described to be activated in human IBD [58]. It is composed of two polypeptide units termed p50 and p65, and at rest state is normally sequestered in the cytosol by the proteins IκBs (IκBα, β, and ε) which tightly block NF-κB transport into the nucleus. Upon cell activation, IκB is phosphorylated by two IκB kinases (IKKs), cleaved from NF-κB and then degraded by proteasomes. NF-κB then enters the nucleus where it binds to DNA regulatory sites and initiates the transcription process.

In vitro studies performed in human adenocarcinoma cells (SW480, SW620, and HeLa229) have shown that butyrate treatment (4 mM) for up to 48 h is able to inhibit TNFα-mediated phosphorylation and degradation of IκBα and effectively block NF-κB translocation [59]. It has been proposed that the inhibitory effect of butyrate on NF-κB activation is derived from the ability to inhibit histone deacetylase activity *via* histone hyperacetylation, an activity also described for propionate [60, 61]. Supporting the role of NF-κB inhibition in the beneficial effect of SCFA in human IBD, it has been recently reported that treatment of UC patients with butyrate enemas, for 4 and 8 weeks, resulted in a significant inhibition of NF-κB activation in the lamina propria macrophages from these patients. This effect was associated with a reduction in both the number of neutrophils in the crypt and surface epithelia and of the lamina propria lymphocytes/plasma cells, and correlated with minor mucosal inflammation in these patients [44].

The inhibitory effect of SCFAs on NF-κB activation can also explain the downregulation of the increased expression

of genes encoding inducible nitric oxide synthase (iNOS) as well as vascular cell adhesion molecule-1 (VCAM-1) and intracellular cell adhesion molecule-1 (ICAM-1), which have been described to play an important role in the pathogenesis of different inflammatory conditions, including IBD [62, 63]. During the last decade, it has become increasingly clear that chronic colonic inflammation is associated with enhanced NO production, mainly *via* iNOS activity, in humans and experimental models [36, 62, 64, 65]. Thus, inhibition of NO overproduction has been reported to be beneficial in IBD [66, 67]. In fact, the intestinal anti-inflammatory effects exerted by dietary fiber in experimental colitis were associated with a significant inhibition of colonic NOS activity when compared to untreated control rats [33, 36], and this could prevent, at least partially, the deleterious activity ascribed to NO when it is produced in high amounts by iNOS under these conditions. Since it has been established the relationship between NF-κB activation and upregulation of iNOS expression [68], the inhibition of this signaling cascade may justify the inhibitory effects of SCFA after dietary fiber ingestion on the augmented colonic iNOS expression in intestinal inflammation. Similarly, it has been recently reported that pretreatment of human umbilical vein endothelial cells (HUVEC) with butyrate (10 mM) inhibited TNFα-induced expression of the adhesion molecules VCAM-1 and ICAM-1 [69], which play a crucial role in leukocyte recruitment in inflammatory processes. Consequently, this can be considered as an additional mechanism to the inhibitory effect of SCFA on the IL-8 production, both responsible for the inhibition of leukocyte infiltration under these intestinal inflammatory conditions. In the same study, the authors found that butyrate was able to inhibit effectively NF-κB activation, but they also involved in the mechanism of action of butyrate, the ability of this SCFA to enhance peroxisome proliferator-activated receptor α (PPARα) expression in HUVEC [69]. In fact, previous *in vitro* studies had already reported that PPARγ expression was increased after butyrate incubation in the human adenocarcinoma cell line Caco-2 cells in a dose- and time-dependent manner, thus promoting cell differentiation [70]. Activation of PPARs by butyrate appears to be relevant to the intestinal anti-inflammatory properties of this fatty acid, considering the fact that there is increasing interest in considering PPARs as a crucial target to control inflammation associated with IBD [71, 72].

Finally, although the etiology of IBD remains unknown, there is increasing experimental evidence to support a role for luminal bacteria in the development of IBD and its chronicity; probably related to an imbalance in the intestinal microflora, relative predominance of aggressive bacteria and an insufficient amount of protective species [73]. Consequently, the modulation of the colonic luminal environment may play an important role in the treatment and prolongation of remission in IBD. Indeed, probiotic therapy, considering probiotic as 'live nonpathogenic organisms that confer health benefits by improving the microbial balance', has been effective for the attenuation of experimental colitis [74 – 76], prevention of pouchitis, and maintenance of remission of pouchitis, CD, and UC [77 – 79]. Since dietary fiber is fermented in the colon by different species of intestinal anaerobic microflora, in addition to its ability to increase luminal SCFA production as commented before, its administration may beneficially affect the host by selectively stimulating the growth and/or the activity of particular bacteria species in the colon, especially *Bifidobacteria* and *Lactobacillus*, as it has been reported to occur after dietary supplementation of inulin to DSS colitis rats [35]. This would further support the beneficial role of dietary fiber in human IBD. This hypothesis has been confirmed in human studies performed by Kanauchi *et al.* [30], who reported that after oral GBF therapy to UC patients, the beneficial effects exerted by this dietary intervention were associated with increased fecal concentrations of *Bidifobacterium* and *Eubacterium limosum*.

4 Conclusions

Dietary fiber exerts clinical benefits in patients with IBD, since it has been shown to maintain remission effectively and reduce colonic damage. This is achieved by promoting changes in the colonic lumen of the host; first, by facilitating the production of SCFAs, which are able to modulate the immune response in the different cell types residing the inflamed intestine, and second, by actively modifying the intestinal microbial balance towards nonpathogenic bacteria. At present, it is difficult to establish which of both mechanisms predominates in the beneficial effects exerted by dietary fiber in IBD. Although this dietary strategy holds great promise and appears to be helpful in some settings, more clinical studies are needed to firmly establish the relevance of this therapy.

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