Journal of Functional Foods 93 (2022) 105073

Contents lists available at ScienceDirect

Journal of Functional Foods

journal homepage: www.elsevier.com/locate/jff

Feed your gut: Functional food to improve the pathophysiology of inflammatory bowel disease

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ARTICLE INFO

Keywords:
Ulcerative colitis
Crohn's disease
Microbiota
Food intake
Prebiotic
Probiotic

ABSTRACT

The incidence of inflammatory bowel diseases (IBD) has increased and its etiology remains unknown. Many risk factors are associated with developing IBD, among them is food intake. Damage in the epithelial mucosa is the focus of IBD, and the gut microbiome is associated with the immune system response. Therefore, environmental stimulus or substrate ingested in diet can alter the microbiota composition, impacting this response. So, functional foods (FF) can be used as a health promoter protecting the microbiome and the intestinal epithelial cells. FF can modulate the microbiota and produce many beneficial metabolites. Furthermore, fermented foods can contribute to the microbiota and intestinal mucosa because, in general, the nutrients and non-nutrient present in its food matrix become more accessible. This graphical review encompasses the etiology of IBD, its associated risk factors, and the impact of FF to prevent the disease activity (recurrent inflammatory periods) and improve patients' health quality.

1. Graphical Review

Fig. 1. In the inflammatory bowel diseases' (IBD) etiology, intrinsic factors are inherent to the organism; these factors include, genetics, immunological status, and the gut microbiome. The genetic factors and immunological status are related, as more than 200 IBD risk loci correlate to the innate and adaptive immune responses of individuals, autophagy mechanisms, endoplasmic reticulum stress, changes in intestinal epithelial barrier function, and microbial defense pathways that can contribute to IBD pathogenesis (Kaplan & Ng, 2017). The gut microbiota plays a substantial role in maintaining intestinal health, and perturbations in its composition, function, and structure (dysbiosis) were reported in patients with IBD, which can contribute to gut inflammation, as well as render them more susceptible to colonization with pathogens and impact IBD status (Ananthakrishnan et al., 2017). The extrinsic factors can induce or modify disease expression through their interaction with genetic and microbial factors (Ananthakrishnan et al., 2017; Kaplan & Ng, 2017). Breastfeeding is an early factor in life that positively impacts gut health, influencing the microbiota development and improving the infant immune system conferring tolerance to dietary and microbial antigens. Although infant formulas also contribute to microbiota development, breastfeeding has a more noticeable impact; therefore, its replacement with infant formula use might represent a risk factor for IBD (Ananthakrishnan et al., 2017). Diet is another extrinsic factor that begins in early life and impacts health throughout the years. The mechanisms underlying its contribution to these diseases comprehend the pro-inflammatory effects of low fiber consumption and high contents of animal protein, trans and saturated fats, and simple sugars, which can also lead to changes in the intestinal microbiome. Besides that, the composition of processed food, including additives, emulsifiers, pollutants such as pesticides, and heavy metals, may serve as triggers for IBD (Ho et al., 2019). Alongside diet, smoking and physical inactivity are modifiable extrinsic factors that affect IBD etiology. Smoking increases toxins exposure and, despite the mechanisms are not completely elucidated, it appears to have opposite effects on IBD, being protective against ulcerative colitis (UC) and a risk factor for Crohn's disease (CD) development, flares occurrence, surgery need, and postoperative recurrence (Ho et al., 2019). Being physically active

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https://doi.org/10.1016/j.jff.2022.105073
Received 11 February 2022; Received in revised form 2 April 2022; Accepted 9 April 2022
Available online 26 April 2022

benefits the mucosal immune function and the gut microbiome, and a regular exercise regimen may improve the disease course as it positively impacts inflammatory parameters, psychological status, and quality of life in patients with IBD (Hashash & Binion, 2017). Another factor contributing to IBD pathogenesis and flare occurrence is disturbed sleep, as it has been linked to exacerbation of pro-inflammatory responses, dysbiosis, and increased intestinal permeability (Canakis & Qazi, 2020). Regarding medication, antibiotics exposure can negatively affect the gut microbiota, leading to changes in diversity and abundance of bacterial species, even with a short use, which can predispose the dysbiosis observed in IBD patients (Ananthakrishnan et al., 2017). In addition to antibiotics, the frequent consumption of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with a higher risk of CD and UC incidence and a greater risk of flares (Ho et al., 2019). Nonetheless, air pollution is a factor over which individuals have no direct control, but it also affects gut health. Components of air pollution such as CO, NO_2, SO_2, and particulate matter can penetrate the gastrointestinal tract barrier leading to oxidative stress, DNA damage, and alterations in immune responses that have been associated with IBD (Ananthakrishnan et al., 2017; Ho et al., 2019). Created with BioRender.com.

Fig. 2. IBD encompasses several chronic inflammatory conditions, most significantly ulcerative colitis (UC) and Crohn's disease (CD) (Ramos & Papadakis, 2019). UC mainly affects the final portion of the colon and usually involves only the mucosa, manifesting itself as continuous areas of inflammation and ulceration. It can be insidious, with a gradual onset of symptoms; A) the milder ones include several episodes of evacuation throughout the day, intestinal cramps, and abdominal pain. As the severity of the disease progresses, the patient may also experience fatigue, loss of appetite, and consequent weight loss, which can result in nutrient deficiencies, in addition to mucus in the stool, severe rectal bleeding, anemia, and fever (Porter et al., 2020). On the other hand, the CD is a chronic, recurrent inflammation that affects all layers of the intestine. In addition, B) it can affect any part of the gastrointestinal tract from the mouth to the anus, but it is predominantly seen in the colon. The signs and symptoms of CD are similar to those of UC, differing in the presence of arthritis and erythema nodosum lesions in the extremities (Roda et al., 2020). Different profiles of cytokines and other inflammatory mediators in both diseases were identified and involved the mucosa with epithelial damage, consequent infiltration of neutrophils and abscesses in the intestinal villi, generating an inflammatory response. In this sense, the immune system permeates the pathogenesis of IBD's as the intestinal epithelial cells recruit leukocytes to the intestinal mucosa. The narrowing of the intestine (luminal opening) results from the inflammatory process. The main hypothesis that elucidates the pathophysiology of IBD's is that there is a misleading immune system response to host microbiota in general and not to a single microorganism (Pittayanon et al., 2020). Several changes occur in the intestinal mucosa of patients with active IBD's compared to healthy individuals, dysbiosis being one of them and the reduction of tight junction proteins and the mucus layer. Furthermore, CD appears to have a more pronounced dysbiosis than UC, with less diversity, altered composition, and a more unstable microbial community (Parada Venegas et al., 2019). In addition, a diet rich in saturated and *trans*-fatty acids (STFA), refined sugars, and deficient dietary fiber can induce dysbiosis and intestinal inflammation. These nutrients stimulate the production of pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6) from binding to the Toll-like receptors (TLR), thus activating the transcription of necrosis factors, such as nuclear factor-κB (NF-κB) in the colonocytes, which is an important biomarker in IBD's (Basson et al., 2021). Contrarily, the ingestion of a diet rich in fiber increases the production of short-chain fatty acids (SCFA) due to microbiota's fermentation, especially butyrate, which helps maintain intestinal epithelial cells' homeostasis. It also inhibits NF-κB activation pathways reducing the production of pro-inflammatory cytokines and adhesion molecules that can cause tissue damage from IBD (Couto et al., 2020). Created with BioRender.com.

Fig. 3. The search for functional foods (FF) has become more popular among consumers, the food industry, and research groups. The aim of FF

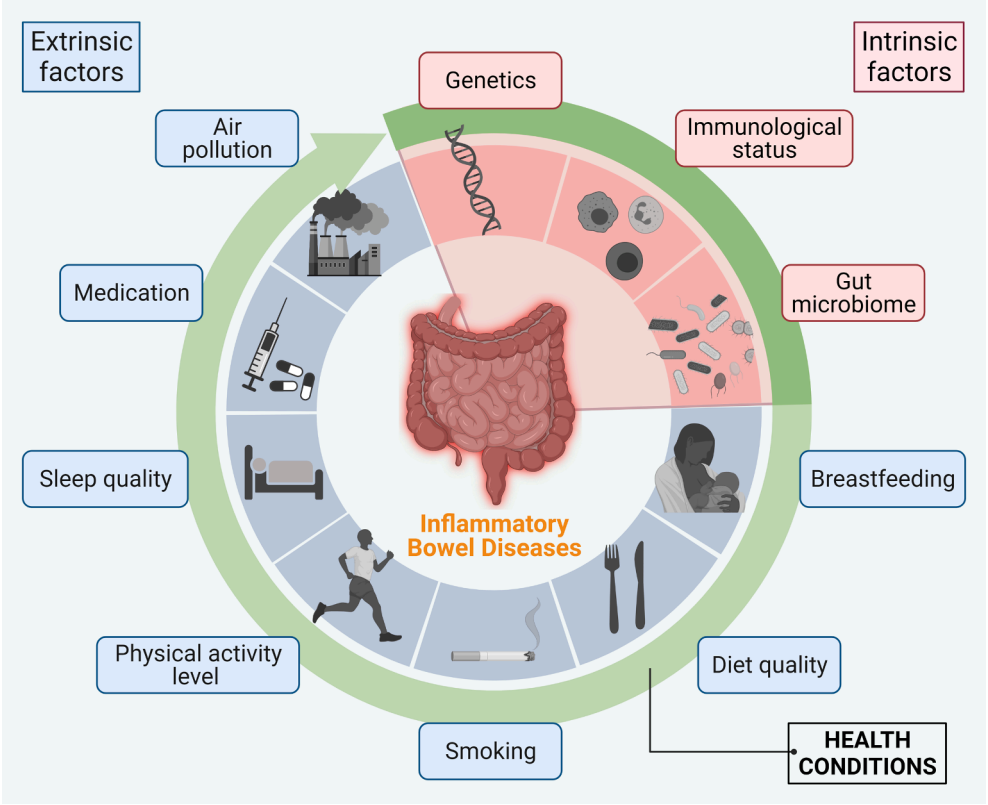

Fig. 1. Factors affecting inflammatory bowel diseases' etiology.

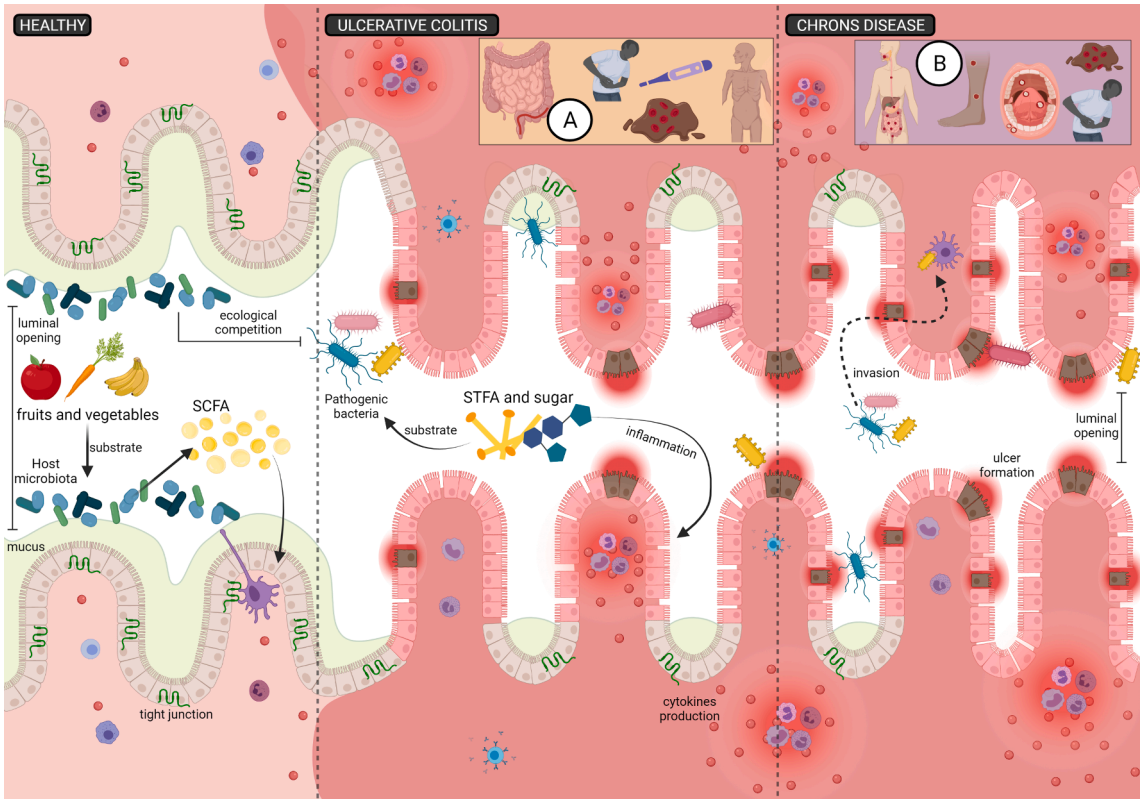

Fig. 2. Pathophysiology of inflammatory bowel disease (IBD) related to food consumption.

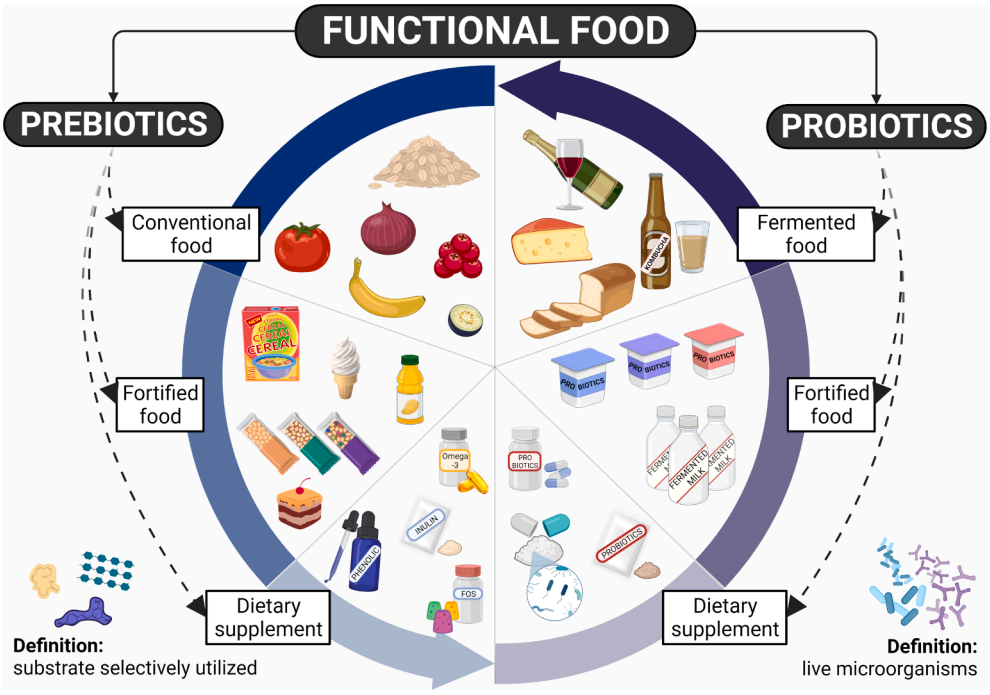

Fig. 3. Common worldwide functional foods to treat inflammatory bowel disease (IBD).

is beyond nurturing; it is to present a bioactive compound that could bring a health benefit to the consumer (Min et al., 2019). Prebiotics or candidates (PREC) and probiotics (PRO) are well consolidated as to their technological advantages in food products; additionally, their effects on consumer's health are facts. PREC are substrates selectively utilized by host microorganisms conferring a health benefit, such as oligosaccharides (inulin, fructooligosaccharides, and galactooligosaccharides), polyunsaturated fatty acids (especially omega 3), phytochemicals (resveratrol, catechins), and others (Gibson et al., 2017). These substrates naturally occur in conventional foods and are parts of a regular diet, such as fruits and vegetables. Due to its chemical properties (alternative sweeteners, emulsifiers, natural antioxidants,

etc.), some PREC can be incorporated into food products, thus enhancing desirable sensory aspects and nutritional quality. The isolated form of PRE is considered a dietary supplement; their presentation varies depending on the characteristics of the PREC, aiming to offer a therapeutic dosage to treat IBD's (Cunningham, et al., 2021; Cunningham, et al., 2021a). A key point in developing a FF is its chemical stability of PRE, or cell viability from PRO, throughout the product's shelf life. Thus, PRO food must present viable cells up to its expiration date since PRO is, by definition, live microorganisms that confer a health benefit to the consumer when administered in adequate amounts (Hill et al., 2014). When isolated, probiotic bacteria (PROB) presentation can vary depending on where it should be delivered along the gastrointestinal tract and its adequate dosage. Regarding food products, dairy products are the leaders in the industry applicability of PRO. The interactions between the PRO strains and the food matrix generate chemical and sensory modifications that attribute particular characteristics to each product, challenging the food industry in terms of consumer acceptance. Recently food products derived from cereals, fruits, vegetables, and meats are being researched as vehicles of PRO strains (mainly from *Lactobacilli* and *Bifidobacterium* genera) (Min et al., 2019). Although not considered PRO, fermented foods may contain traces of non-viable microorganisms that might interact in the gastrointestinal tract. However, the benefits of the fermented food in treating IBD's is the fermentation process *per se*, where chemical compounds from the food matrix, e.g., phenolic compounds, peptides, and (poly)saccharides, become more bioaccessible and bioactive; in addition, this process assigning texture, taste, aroma, and color expected from classical fermented foods (Melini et al., 2019). Created with BioRender.com.

Fig. 4. 1) The consumption of prebiotics (PRE) from dietary sources improves pathological parameters, including those from IBD, especially ulcerative colitis (UC) (Guarino et al., 2020). The main compounds in PRE are non-digestible fibers, such as fructooligosaccharides (FOS) and galactooligosaccharides (GOS). 2) On the luminal gut, those fibers will be fermented by the host microbiota and increase their abundance. 3) Thus, the gut microbiota can regulate immune responses, pathogen bacteria growth and produce many metabolites (mainly short-chain fatty acids - SCFA) (Lavelle & Sokol, 2020). These mechanisms will be described further. 4) Some phenolic compounds (PRE candidates) undergo the biotransformation (deglycosylation) by the gut bacteriota (*Lactobacilli* and *Bifidobacterium*), thus becoming more biologically active (aglycone form) being capable of suppressing inflammation directly on the colonocytes (Danneskiold-Samsøe et al., 2018). For example, once uptaken by colonocytes, resveratrol regulates anti- and pro-inflammatory mediators, mainly cyclooxygenase-2 enzyme, IL-6, and −10, TNF-α, and NF-kB (Guarino et al., 2020). Through this pathway, resveratrol contributes to alleviating the clinical symptoms and pathophysiological mechanisms of the IBD condition. Dietary omega-3 polyunsaturated fatty acids (ω3FA) are partially metabolized by anaerobic bacteria, modulating the gut bacteriota towards a healthier composition, reducing *Enterobacteria*, and increasing *Bifidobacterium* growth (Fu et al., 2021). In addition, ω3FA molecules exert beneficial effects, mainly on the active phase of UC through the inhibition of metabolite production from arachidonic acids (AA), an omega-6 fatty acid (ω6FA) present in the cell's phospholipids membrane. When activated, ω6FA will be added to one oxygen molecule by COX-1 or −2 enzymes, and the main products derived from this reaction are prostaglandin and leukotrienes, which are directly related to inflammatory processes (Barbalho et al., 2016). A decrease in those pro-inflammatory mediators will reduce pain, tumor, platelet aggregation, local temperature, redness, immune cells recruitment, and consequently, modulate local inflammation and promote cell recovery (Innes & Calder, 2018). 5) Furthermore, after transposing the colonocytes, ω3FA reduces $CD4^+$ cells function and, consequently, TLR expression and inflammasome NLR family pyrin (NLRP) activation, counteracting tissue inflammation and improving IBD pathological conditions (Barbalho et al., 2016). 6) In the intestine, probiotic bacteria (PROB) play several roles that influence each phase of IBD, such as reducing tissue inflammation and improving the disease's clinical and pathophysiological parameters. 7) Mainly

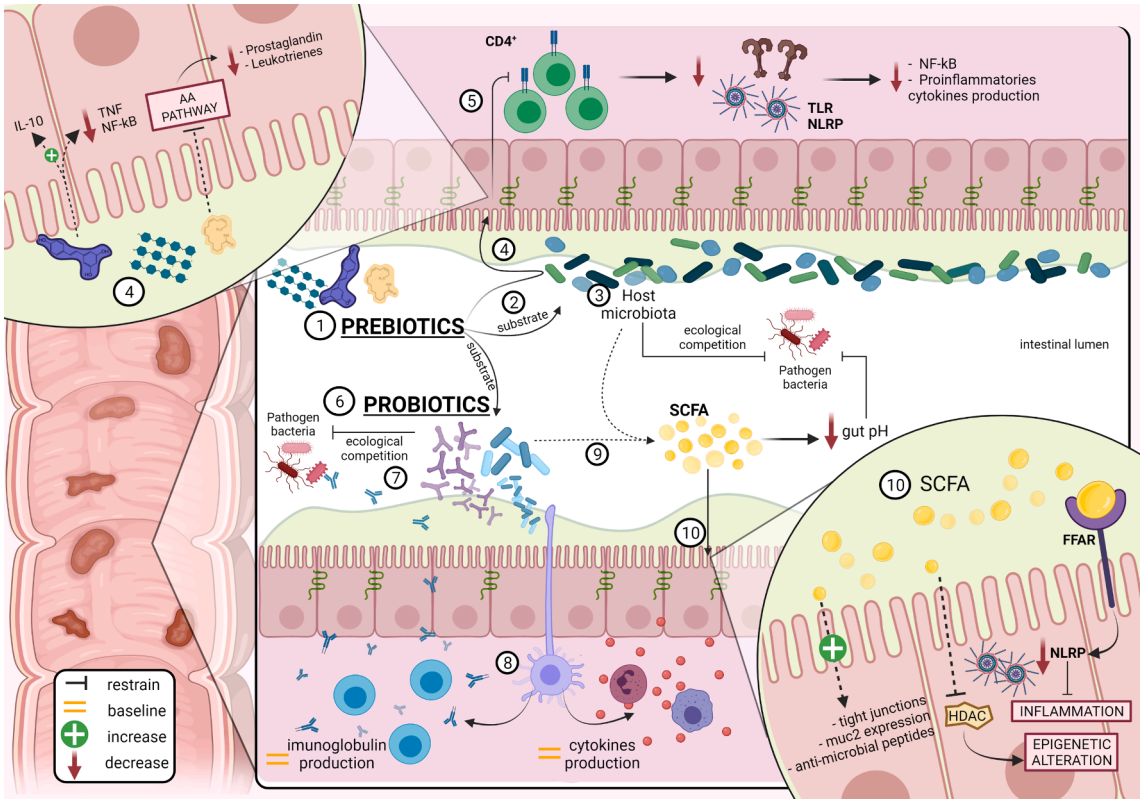

Fig. 4. Prebiotics and Probiotics: mechanisms of action in inflammatory bowel disease (IBD).

through the ingestion of *Lactobacillus* and *Bifidobacterium* strains, there is an increase in the PROB relative abundance, and proportionally the population of pathogenic bacteria (PATB) present in the gut reduces. So, ecological competition for available nutrients to the gut microbiota intensifies, thus restricting the proliferation of PATB (Plaza-Diaz et al., 2019). 8) Also, in the lumen, PROB modulates the immune response through their interaction with dendritic cells, which are responsible for the recognition of infectious agents and the development of innate (inflammatory cytokines) and adaptive (antibodies) immune responses at the basal level (Lavelle & Sokol, 2020). 9) In addition to these direct mechanisms of actions of PROB, there are indirect actions that stimulate the regression of UC through the metabolites produced by PROB. SCFA are the main metabolites from gut bacteriota, responsible for acidifying the intestinal lumen, inhibiting pathogenic microorganisms, and increasing the uptake of nutrients by colonocytes (Plaza-Diaz et al., 2019). 10) By binding to the G-protein coupled free fatty acid receptor (FFAR)-2 and 3, propionate and butyrate (SCFA) counteract tissue inflammation via reduced activation of the inflammasome NLRP-3 (Lavelle & Sokol, 2020). Once taken up by colonocytes, SCFA can inhibit the activity of histone deacetylases (HDAC), improving the expression of zonula occludens-1, occludin protein, and muc2, and stimulating the production of antimicrobial peptides, thus enhancing the barrier integrity of the colonocyte, and preventing the invasion of PATB, improving the IBD (Plaza-Diaz et al., 2019). Created with BioRender.com.

CRediT authorship contribution statement

Paulo Sérgio Loubet Filho: Conceptualization, Writing and creation of figures. **Thaís Otranto Dias:** Writing and creation of figures. **Vitória Helena de Oliveira Teixeira Reis:** Writing and creation of figures. **Amanda Maria Tomazini Munhoz Moya:** Writing and creation of figures. **Elisvânia Freitas dos Santos:** Reviewing, editing, and guiding to the final manuscript. **Cinthia Baú Betim Cazarin:** Reviewing, editing, and guiding to the final manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

This study was supported by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES - finance code 001), and support from the Universidade Federal de Mato Grosso do Sul (UFMS). CBBC is grateful to the National Council for Scientific and Technological Development - CNPQ for the financial support and research productivity scholarship grant (421857/2018-8; 306891/2021-2).

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