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Non-pharmacologic strategies for the management of intestinal inflammation

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ABSTRACT

Inflammatory bowel diseases, irritable bowel syndrome, and mucositis are characterized by intestinal inflammation, but vary according to their pathological mechanisms, severity, location, and etiology. Significant intestinal inflammation that occurs in these diseases induces weight loss, nutritional depletion, and gastrointestinal tract dysfunction. Nutritional support is important in alleviating symptoms and improving patients' quality of life. In this review, we summarize some nutritional components used to manage intestinal disorders. These include fatty acids, probiotics, parabiotics, postbiotics, prebiotics, synbiotics, and low FODMAP (LFD) diets. These components and LFD diets have been studied and clinical trials have been designed to develop new strategies to alleviate intestinal inflammation and improve the quality of life. Clinical trials on their use in intestinal inflammation do not allow firm conclusions to be drawn mainly because of the heterogeneity of the dose used and the study design or their inconclusive results. However, in the majority of cases, the use of omega-3, probiotics, parabiotics, postbiotics, prebiotics, synbiotics, and LFD improve the health.

1. Introduction

The intestine is a complex organ that extends from the end of the stomach to the anus. It allows the passage of digested food and facilitates nutrient absorption and elimination of feces. To facilitate this process, the intestine is approximately 7–9 m long with approximately 300 m^2 of contact area, and it is divided into small and large intestines [1]. It is considered the largest contact surface with the external environment and harbors the most complex immune system [2]. Approximately 10^{12} colony forming units (CFU)/cm^3 commensal bacteria, fungi, and viruses inhabit the human intestinal lumen, and the number of bacteria increases in the most distal parts [3]. Continuous contact with food proteins, microbiota antigens, pathogenic microorganisms, and toxic agents requires a constant balance between inflammation and intestinal regulation [4].

In this sense, the upregulation of the inflammatory immune response to antigens presents in the gut and decrease in the immune regulatory mechanism triggers various disorders. The breakdown of this fine balance between inflammation and immune regulation, induced by several factors that include genetic, pharmacologic, psychiatric, nutritional status, and microorganisms, leads to the development of some diseases such as inflammatory bowel diseases (IBDs), irritable bowel syndrome (IBS), and mucositis.

The incidence of these gut disorders is variable. The incidence of IBD has increased in the twentieth century, mainly in the Western world, affecting approximately 1% of the total population [5,6]. IBS has a global prevalence of 11% and is more prevalent in women of working age. It is important to consider the economic impact of such prevalent conditions in terms of the loss of workdays and the substantial costs to patients, healthcare system, and the society. Considerable benefits can

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be obtained from effective interventions and nutritional care [7,8]. Unlike other gut disorders, mucositis is considered a side effect of cancer treatment. Its prevalence follows that of cancer, reaching 40% of cancer patients receiving chemotherapy or radiotherapy, and approximately 80% when administered in combination with chemotherapy or radiotherapy.

IBD, IBS, and mucositis are completely different in etiology. However, all three lead to intestinal irregularity, pain, nutritional status disruption, poor quality of life, and direct high cost to the health care system [8]. In this regard, we aimed to identify common non-pharmacological tools to manage these intestinal diseases.

There are no definitive treatments or cures for IBD, IBS, and mucositis. However, some compounds and nutrients have positive effects on the immune system and intestinal microbiota composition. These findings have prompted researchers to consider that nutritional strategies can contribute to the improvement of these conditions.

In this review, we have aimed to synthesize the benefits of some non-pharmacological components, such as omega-3 fatty acids, probiotics, synbiotics, parabiotics, postbiotics, prebiotics, and fermentable oligo-, di-, and monosaccharides and polyols (FODMAP); low FODMAP diet (LFD) as therapeutic strategies for people with intestinal problems including IBD, IBS, and mucositis.

2. Molecular events involved in the pathogenesis of different types of intestinal disorders

2.1. IBDs

The main causes of IBDs include genetic background, inflammatory immune response, changes in the gut microbiota, and food intake [9,10]. The individual genetic backgrounds lead to variations in disease severities. A healthy host is tolerant to microbiota and food antigens [11,12]. Breakdown of this immune tolerance due to dysbiosis or altered immune response to food antigens leads to the loss of gut homeostasis, which favors the development of IBDs [13]. IBDs comprise a spectrum of idiopathic human syndromes marked by unrestrained gastrointestinal inflammation that drives ulcerative colitis (UC) and Crohn's disease (CD) [10]. Symptoms including diarrhea, abdominal pain, weight loss, and nausea, in addition to UC and CD, are marked by episodes of relapse and remission, which interfere with the quality of life of the affected individuals [14]. Thus, an important role of nutritional therapies is to maintain the patient as long as possible in the non-active phase of the disease, through dietary interventions and with the use of immunomodulators. UC is characterized by inflammation in the large intestine and is restricted to the mucosal layer. In contrast, CD occurs anywhere in the gastrointestinal tract and can disrupt all associated tissue layers [15,16].

The immune response related to IBDs is initiated by the activation of antigen-presenting cells, such as macrophages and dendritic cells (DCs), by the recognition of microorganisms and food antigens. These antigens interact with Toll-like receptors (TLRs) and inflammasomes that culminate in the activation of inflammatory signaling. The inflammatory cytokines that are secreted are interleukin (IL)−6 and tumor necrosis factor-alpha (TNF-α). After secretion of these compounds, there was an increase in T helper cell (Th)1 and Th17 immune responses consistent with the increased levels of interferon-gamma (IFN-γ), IL-17, and IL-22 observed in the chronically inflamed intestine, decreased activity of regulatory cells, and decreased secretion of transforming growth factor-beta (TGF-β) and IL-10 (reviewed in [16]). These changes characterize the inflammatory environment in the gut mucosa that contributes to disease severity. In healthy conditions, intestinal Th17 cells and innate lymphoid cell (ILC) 3 are important components of mucosal homeostasis. However, in patients with IBD, Th17 cells produce high levels of cytokines that include IL-17, IL-22, and IL-26, which increase in the gut mucosa and plasma. On the other hand, ILC3 expands in response to IL-23 via IL-23R signaling, expresses RAR-related orphan-receptor-gamma-t-isoform (RORγt), and produces more IL-17, IL-22, and TNF-α [17]. Thus, Foxp3^{+} cells, and consequently TGF-β and IL-10 production, decrease [18]. Genetic variants of the IL-10 gene in humans are associated with clinical manifestations of CD because the absence of IL-10 function disrupts gut homeostasis and increases inflammatory pathways [19,20].

In addition to changes associated with the immune system, the gut microbiota is an important component of environmental stimuli in the pathogenesis of intestinal disorders. Dysbiosis (defined as decreased ratios of beneficial microorganisms and increased potential pathogenic bacteria) has been observed in IBD [21,22]. IBDs feature a reduction in the α-diversity of microbiota in patients with CD when compared with healthy controls [23]. Increase in the *Veillonellaceae* and *Fusobacteriaceae* population and decrease in the *Bacteroidales, Erysipelotrichales*, and *Clostridiales* population has been previously suggested as IBD biomarkers [24]. In addition, some gut bacteria may have protective roles in IBD. *Bacteroides fragilis* increases the suppressive capacity of regulatory T cells Foxp3 + and *Faecalibacterium prausnitzii* induces the secretion of IL-10 [25]. Both can reduce the inflammatory profile and alleviate IBD symptoms.

The foregoing indicates that, beyond therapy, there is a need for improved nutritional or probiotic aspects to activate anti-inflammatory responses.

2.2. IBS

IBS is a functional gastrointestinal disorder and is more common in females. Its pathogenesis involves changes in gastrointestinal motility, intestinal secretion, visceral hypersensitivity, intestinal permeability, and gut microbiota [26,27]. In addition, IBS symptoms are affected by previous intestinal infection, food intolerance, host genetics, psychosocial aspects, and environment, which modulate human gut homeostasis [28,29]. The most common symptoms are abdominal pain and disturbances in bowel habits that include diarrhea (IBS-D), constipation (IBS-C), or a mixture of both (IBS-M), as well as extra-intestinal symptoms, including anxiety, depression, headache, and fatigue [30].

Patients with IBS present increased frequency of peripheral blood T cells expressing the gut-homing integrin β7, which favors the migration of effector cells to the intestinal mucosa [31], decreased tight junction expression in gut epithelial cells [32], altered expression of TLR9 and cells from the lamina propria [33,34] and an increased percentage of cells expressing the gut-homing integrin that also co-expresses the intestinal resident chemokine receptor (CCR) 9 [35] and CCR5 [36]. IBS also features higher infiltration of inflammatory cytokine-producing cells that increase the concentration of IL-4, IL-6, or TNF-α, pro-inflammatory mediators, and mast cells in the colonic mucosa, which contribute to impaired tight junction expression [37]. All these alterations can contribute to the pathogenesis of IBS, which includes leukocyte accumulation in the mucosal layer and low-grade inflammation. Surprisingly, IBS does not feature tissue destruction. This could reflect the absence of neutrophils and the impaired secretion of the CXCL9 and CCL2 chemokines [38]. IBS patients present a dysregulated mucosal inflammatory profile with increased levels of the TH1, TH2, and TH17 markers, with increased secretion of IL-5 upon fructose stimulation [39]. Importantly, the Th17 response in IBS is involved in the aggravation of psychiatric symptoms [40]. There is also a correlation between IL-5 and IL-4 secretion, which is also correlated with mast cell activation.

The inflammatory profile observed in IBS is linked to mast cell accumulation and activation in the gut. These cells can produce mediators, such as prostaglandin E2, histamine, tryptases, and dopamine, which can activate the inflammatory response and also the mesenteric afferent nerve [41,42].

Regarding antibody secretion, the production of IgA in the gut mucosa is increased in IBS patients. The secreted IgA presents more affinity to the bacteria in the gut. This IgA response is linked to IBS severity and

altered bacterial microbiota profile [43]. The gut microbiome is altered in patients with IBS. Specific findings in IBS patients include lower levels of Lactobacillus, Bifidobacterium, and *Faecalibacterium prausnitzii*. Small intestinal bacterial overgrowth is associated with IBS-D, whereas increased levels of methanogenic archaea, specifically *Methanobrevibacter smithii*, are associated with IBS-C [28,31]. IBS is also frequently characterized by a reduction in *Bifidobacterium* spp [26]. A higher relative abundance of more than 20 *Lactobacillus* spp. was observed in patients with severe IBS compared to mild and moderate IBS. Moreover, IBS symptoms are directly associated with bacterial metabolite concentrations in the gut, mainly reduction in short-chain fatty acids (SCFAs) [44].

Improvement of intestinal homeostasis due to nutrients, probiotics, and their derivatives, or even by avoiding FODMAPs, could be an interesting strategy to control IBS.

2.3. Mucositis

Mucositis occurs due to chemotherapy or radiation therapy that directly injures DNA and RNA, and causes strand breaks. This results in the death of basal epithelial cells, in turn resulting in inflammation and tissue damage [45]. The clinical manifestations of mucositis are noticeable when the integrity of the mucosa and submucosa is compromised by ulceration. This disruption enables the contact of microorganisms, resulting in increased inflammation and tissue damage. Mucositis can cause pain when swallowing, loss of appetite, vomiting, abdominal distension, and diarrhea, in addition to changes in the intestinal barrier, mucositis leads to an increased susceptibility to opportunistic infections [46]. These symptoms can compromise the nutritional status of the patient, decrease the ability to tolerate cancer treatment, extend the length of stay, and increase hospital costs [47].

The inflammatory profile observed during mucositis is driven by cytokines that include TNF-α, IL-1β, and IL-6 [45]. There is also a Th2 inflammatory response involved in disease development and severity. IL-4 and ST2 deficient mice do not develop mucositis [48,49]. DNA and RNA damage to cells due to chemotherapy induces apoptosis by caspase activity. This increases the production of reactive oxygen species and activates nuclear factor kappa B (NF-κB) pathways that drive inflammatory cytokines and cyclooxygenase liberation, and promote intestinal inflammation [50,51]. Mucosal toxicity includes the loss of extracellular matrix and epithelial tight junctions, with decreased mucus secretion [52,53]. These events enable the direct contact of bacterial content with the mucosal cells activating the TLR, which further exacerbates inflammation [50,54].

The gut microbiota are fundamental for the severity of mucositis [55]. Pathologic derangement of the microbiota is associated with a reduction in the quantity and diversity of the enteric microbiota caused by chemotherapy. Mucositis is also related to microbiota alterations and commensal bacteria translocation to lymphoid organs. These vents are associated with the drug used [56]. Cyclophosphamide and doxorubicin treatment can reduce the abundance of lactobacilli and enterococci. These bacteria are necessary to induce an adequate immune response needed for tumor reduction. Methotrexate reduces their diversity and shifts in relative abundance associated with chemotherapy-induced diarrhea [57]. Therefore, the use of probiotics can improve cancer therapy and manage mucositis [58].

Considering the above information and unknown effective and definitive treatment for intestinal pathologies, all the described diseases are related to increased inflammatory profiles in the intestine, weight loss, nutritional depletion, and overall health disturbance. Dietary orientation and nutritional support are important in maintaining a patient's quality of life. Nutritional therapy has been used to compliment drug treatments since the 1980 s. Despite this history, evidence of the benefits of nutritional therapy remain controversial. This largely reflects the low number of clinical trials, as well as the wide variations in doses and times used [59–61]. In seeking some clarity, this review provides clinical insights into different strategies with omega-3 fatty acids, probiotics and other compounds, with the aim of alleviating intestinal inflammation and improving the quality of life of individuals affected by these diseases.

3. Omega-3 fatty acids and their role in gastrointestinal inflammation

Growing evidence suggests that fatty acids are involved in the symptom relief of inflammation in several gastrointestinal diseases and clinical conditions, such as IBDs, IBS, and mucositis [62–64]. Polyunsaturated fatty acids (PUFAs) have an important impact on the inflammatory process through their metabolism and incorporation into cells and membrane phospholipids, especially in immune cells [64–66]. Among these, it is important to highlight omega-3 fatty acids, which is a series of essential fatty acids that humans obtain from diet and have potential benefits in different inflammatory diseases [62,67].

Omega-3 PUFAs include alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Vegetable oils, walnuts, flax seeds, canola, and soy products are rich in ALA [67]. EPA and DHA are mainly derived from seafood and marine fish, such as salmon, sardines, and mackerel [68]. These fatty acids cannot be synthesized by the human body and must be obtained directly from the diet or converted from ingested ALA. However, in human the endogenous conversion of ALA to EPA and DHA is limited. Therefore, dietary supplements or consumption of DHA and EPA sources are essential to provide sufficient omega-3 fatty acids [69]. Their mechanism of action involves antagonization of inflammatory eicosanoid mediators derived from arachidonic acid, control of inflammatory cytokine production, and downregulation of expressed genes involved in inflammatory cascades, fibrinolysis, leukocyte adhesion, and blood coagulation [70]. In addition, omega-3 fatty acids are further converted into a series of bioactive lipid mediators through the action of cyclooxygenases, lipoxygenases, and cytochrome P450 enzymes (CYPs) [62].

Several studies have shown the important roles of omega-3 and their lipid mediators in the modulation of cell membrane fluidity, regulation of inflammation, and gut microbiota through a series of metabolic pathways [67,71,72]. Among lipid metabolites, resolvin, protectin, maresin, and 17,18-epoxy-eicosatetraenoic acid (17,18-EpETE) have been highlighted [62]. The anti-inflammatory pathways that fatty acids often act are the blockage of NF-κB activation and modulation of peroxisome proliferator-activated receptor-alpha (PPAR-α) and -gamma (PPARγ), which are important pathways in the derived regulatory immune response [73]. Importantly, intestinal commensal bacteria metabolize lipids and yield unique lipid metabolites, including hydroxyl, oxo, and conjugated fatty acids. Thus, the quality of all dietary lipids influences the production of lipid mediators by the intestinal microbiota and by enzyme competition, which can be a determinant in the regulation of gut inflammation [62].

Experimental evidence supports the use of omega-3 in IBDs and other intestinal disorders. However, clinical data are still controversial and conflicting, especially for CD [74,75]. Discussion about daily doses, time of administration, and mechanism of action in the human gut might be performed to clarify and define the correct supplementation of omega-3. Some clinical trials have attempted to identify the correct protocol for omega-3 administration to control gut inflammation.

In a placebo-controlled trial, Scaioli et al. observed that supplementation with EPA (2 g/day) for 6 months reduced fecal calprotectin levels, an important inflammatory biomarker in active UC, and maintained histological remission in UC patients [63]. In addition, an open-label randomized controlled trial evaluated the effects of a 12-week diet supplementation with ground flaxseed (30 g/day) and flaxseed oil (10 g/day) in patients with active, mild-to-moderate UC. The researchers described that both ground flaxseed and flaxseed oil reduced fecal calprotectin and inflammatory cytokines (IL-6 and IFN-γ), increased TGF-β concentrations, and improved IBD symptoms as

Table 1
Description of the main clinical trials that evaluated omega 3 supplementation in intestinal inflammation in the last years.

Study	Study Design	Supplement/diet	Dose and period of treatment	Outcome
Omega-3				
Scaioli et al. [63]	RCT, double-blind, placebo-controlled, 60 patients (active UC Mayo score under 2)	EPA	2 g/d or placebo 6 months	Reduction of calprotectin level on treated groups with no serious adverse events
Morshedzadeha et al. [76]	RCT, open-label, 75 UC patients	Grounded flaxseed and Flaxseed oil	Grounded flaxseed 30 g/day Flaxseed oil 10 g/day12 weeks	Attenuate inflammatory markers, disease severity, blood pressure, and waist circumference.
Abhari et al. [77]	RCT, placebo-controlled, 70 UC Patients	Omega-3	4800 mg of omega-3 (4 capsules of 1200 mg/day) 2 months	Reduce the levels of inflammatory and oxidative markers and increase in antioxidant markers in the serum.
Laing et al. [81]	RCT 30 participants (15, healthy and 15 CD)	DHA, EPA, vitamin D3, co-Enzyme Q10, zeaxanthin, leutin, astaxanthin	2 capsules/day containing- DHA (255 mg), EPA (170 mg), vitamin D3 (500 IU), co-Enzyme Q10 (50 mg), zeaxanthin (0.82 mg), leutin (3 mg), and astaxanthin (500 mcg) each capsules. 4 weeks for Healthy6 weeks for CD	Increase serum EPA, DHA and vitamin D levels in healthy and CD groups. No evidence on reducing the inflammation was found.
Feagan et al. [80]	2 RCT, double-blind, placebo-controlled, quiescent CD363 patients: EPIC-1375 patients: EPIC-2	EPA e DHA	4 g/d of omega-3 free fatty acids or placebo50% to 60% EPA and 15–25% DHA58 weeks	No beneficial effect was observed for the prevention of relapse over 1 year of follow-up.
Boisselier et al. [88]	Phase III multicentre study180 head and neck cancer patients treated with chemotherapy and radiotherapy	Arginine and omega-3	3 sachets/day - Formula enriched with L-arginine and omega-3 (1.3 g EPA+DHA /sachet)5 days before each chemotherapy session	No changes in the severity of mucositis and increase in overall survival after 3 years

CD: Crohn's disease; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; EPIC: Epanova Program in Crohn's Study; RCT: randomized control trial; UC: ulcerative colitis.

determined by increased inflammatory bowel disease questionnaire-short form (IBDQ-9) score. A higher IBDQ-9 score indicated a better quality of life [76]. Abhari et al. also observed beneficial effects in a placebo-controlled trial. They observed a reduction in the serum levels of malondialdehyde (MDA), advanced glycation end-products, oxidized low-density lipoprotein (oxidized LDL), and TNF-α. In addition, they reported improvements of antioxidant catalase copper markers in patients with mild or moderate UC [77]. In addition to clinical data, several epidemiologic studies have suggested that omega-3 PUFAs may protect against the development of UC [78,79].

In patients with CD, two randomized, double-blinded, placebo-controlled studies evaluated whether the oral administration of omega-3 was more effective than placebo in preventing CD relapse. In the Epanova Program in Crohn's Study (EPIC)−1 and EPIC-2 trials, administration of a high dose of omega-3 (4 g/day) did not reduce the rate of relapse in patients with quiescent CD [80]. In addition, a randomized control trial [81] measured the bioavailability and impact of a supplement containing omega-3 and other nutrients on inflammation. The patients received two supplements containing DHA (255 mg), EPA (170 mg), vitamin D3 (500 IU), coenzyme Q10 (50 mg), zeaxanthin (0.82 mg), leucine (3 mg), and astaxanthin (500 mcg) for 6 weeks. The supplement significantly increased the serum levels of EPA, DHA, docosapentaenoic acid, and vitamin D in the CD group. However, plasma C-reactive protein and stool calprotectin measures showed no evidence of treatment of inflammation [81]. Further research is required to better elucidate the effects of these inflammatory markers.

A controlled study revealed that subjects with IBS presented decreased serum concentrations of docosapentaenoic acid (22:5 n-3) and DHA (22:6 n-3), which are long-chain PUFAs of the omega-3 family. The supply of long-chain fatty acids is inadequate in IBS patients [82]. The same result was observed by Chua et al. in Asian women [83]. These findings indicate that omega-3 supplementation for IBS patients could be an alternative to control low-grade inflammation. In an experimental model of IBS, rats treated with fish oil showed reduced colon distention and pro-inflammatory cytokine reduction in colon tissue [84]. However, no clinical trials have evaluated the role of PUFA supplementation in patients with IBS.

The effect of omega-3 supplementation on cancer and mucositis has also been studied. The positive effects of omega-3 supplementation have been observed in mucositis experimental models [85,86]. Generoso et al. observed that omega-3 reduced weight loss, damage to the intestinal mucosa, and apoptosis caused by 5-fluorouracil (5-FU)-induced mucositis [85]. A clinical trial indicated the potential role of omega-3 in reversing cancer cachexia and suggested that clinically relevant achievements could be obtained in terms of enhanced efficacy of anticancer drugs, reduced toxicity, and enhanced quality of life of patients [87].

In a double-blinded phase III trial, Boisselier et al. evaluated the efficacy of immune-nutrient supplements containing omega-3 and arginine during chemotherapy and radiotherapy in patients with head and neck cancer. The patients received 1.3 g EPA + DHA three times daily for 5 days before each chemotherapy session. The supplementation was not able to reduce the incidence of mucositis, but overall survival was increased after three years [88]. More clinical trials are needed to further investigate the efficacy and safety of omega-3 supplements in patients with mucositis.

Table 1 summarizes the main clinical trials that have evaluated omega-3 supplementations in intestinal inflammation in recent years.

4. Functions of prebiotics, probiotics (paraprobiotics and postbiotics) and synbiotics in intestinal inflammation

The association between intestinal inflammation, the microbiota, and the immune system has been studied in the past few decades. The findings suggest that probiotics, prebiotics, and synbiotics could be used to alleviate intestinal inflammation because their action influences intestinal ecology, intestinal homeostasis, and homeostasis of the immune system [89,90]. However, many species and products are still being studied to clarify their mechanisms of action and their influence on gut disturbances. The use of these products to replace or augment conventional therapies to treat or decrease the symptoms of intestinal inflammation is still challenging.

4.1. Prebiotics

The current consensus of the International Scientific Association of Probiotics and Prebiotics is that a prebiotic is "a substrate that is used selectively by host microorganisms that confers a health benefit." This concept, in addition to contemplating non-digestible carbohydrates, also includes other substances, such as polyphenols and PUFAs. However,

recent findings still indicate that the most widely documented dietary prebiotics that have health benefits in humans are non-digestible oligosaccharides, such as fructooligosaccharides (FOS) and galactooligosaccharides (GOS). This seems to be related to the structure of these carbohydrates, which are easily and characteristically degraded by *Bifidobacteria* [91].

The presence of these compounds triggers increased functionality and intestinal microbial growth, especially of bifidogenic bacteria, by increasing the production of SCFAs. Despite the selectivity previously demonstrated for *Bifidobacteria* and *Lactobacillus*, the influence of probiotics on the growth of other bacterial genera, such as *F. prausnitzii* and *Anaerostipes* spp., has already been described [91–93]. Bacterial changes can vary according to host ecology. Thus, the production of SCFAs is influenced by several factors that include the diversity of the microbiota, source of the substrate, and speed of intestinal transit [89].

SCFAs, propionate, acetate, and butyrate are energetic substrates for intestinal cells. These compounds stimulate differentiation and proliferation of colonocytes [94]. In addition, SCFAs can decrease colonic pH and inhibit the growth and activity of pathogenic bacteria [89]. The production of these compounds can also be enhanced by the presence of chemical signals (quorum sensing), which are termed autoinducers. These activate specific receptors and induce bacterial phenotypic changes correlated with adherence, motility, and intestinal density of bacteria [95,96]. These events influence the competition for binding sites, inhibition of adhesion, and bacterial translocation, and improve the function of the intestinal barrier by strengthening the tight junctions and reducing intestinal permeability [95,96].

Despite this evidence, the benefits of prebiotics in intestinal inflammation remain controversial and scarce. For patients with IBD, studies have suggested an improvement in the relief of gastrointestinal symptoms, reduction in disease activity, and consequently improved the quality of life with the use of prebiotics [97–99].

In a pilot clinical study, Valcheva et al. demonstrated that supplementing 15 g of inulin for nine weeks increased the production of butyrate in the colon and the abundance of *Bifidobacteriaceae* and *Lachnospiraceae* in patients with mild/moderately active UC. However, these observed effects were not able to change the disease score [98]. A randomized placebo-controlled clinical trial evaluated the supplementation of 15 g of FOS for four weeks in patients with active CD. After this period, no modulation benefits were observed in the intestinal microbiota associated with the group that received the prebiotic, despite the positive impact on the active CD, with reduced interleukin IL-6 and increased IL-10 *lamina propria* dendritic cells [99]. Due to the heterogeneity of the studies, the researchers concluded in a review article that the existing results are not sufficient evidence to support the use of prebiotics in UC [100].

Likewise, Ford et al. performed a systematic review and meta-analysis of three studies that evaluated the efficacy of prebiotics in IBS. These studies showed that only the use of 3.5 g or 7 g of transgalactooligosaccharide for four weeks significantly reduced the mean global symptom scores after prebiotic use [101].

Relating to mucositis, to date few clinical studies have investigated prebiotics. A double-blinded clinical study with women diagnosed with gynecological cancer evaluated the benefits of a prebiotic mixture (50% inulin and 50% FOS) on the intestinal mucosa during abdominal radiotherapy. The administration of 6 g of the mixture twice daily for one week before and after three weeks radiotherapy treatment resulted in higher counts of *Lactobacillus* and *Bifidobacterium* in the treated group than in the placebo group. These findings indicated that supplementation with inulin and FOS can improve the recovery of microbiota after radiotherapy [102]. A recent experimental study found that prophylactic treatment and therapeutic supplementation with FOS improved the damage caused to the intestinal mucosa by 5-FU chemotherapy in mice [103]. In addition, our research group showed that treatment with FOS in mice increased the production of SCFAs and prevented an increase in intestinal permeability due to mucositis caused by chemotherapy [104].

4.2. Probiotics

The current definition of a probiotic *is "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host"* [105]. For a microorganism to be considered a probiotic, certain criteria must be fulfilled. Probiotic cultures should be recognized as safe for human consumption, stay viable during preparation, and be resistant to gastric and intestinal enzymes. In addition, probiotics should adhere to human intestinal cells and intestinal mucins, and induce the production of antimicrobial substances against pathogens. Their clinical use, safety, and efficacy should be established through randomized and placebo-controlled clinical trials [106].

Several studies attempted to elucidate how probiotic microorganisms can counteract inflammatory processes in the gastrointestinal tract [96,107]. Depending on the type of probiotic strain, they either induce immune activation signaling by producing IL-12, IL-1β, and TNF-α, or trigger tolerance signaling by stimulating anti-inflammatory cytokines, such as IL-10 and TGF-β levels [108]. They also improve mucus secretion and secretory IgA production and modulate the immune system by regulating cytokine production and immune cell activation. Probiotics interact with intestinal epithelial cells, mucosal DCs, and macrophages in diverse ways [96].

The use of probiotics has been indicated as an adjuvant therapy in the treatment of dysbiosis, commonly identified in intestinal inflammation [107]. However, the benefits are strain- and dose-dependent [109].

Several probiotics have been investigated in intestinal inflammation. Bacteria belonging to the genera *Lactobacillus, Bifidobacterium*, and the yeast *Saccharomyces boulardii* have been extensively explored for their applications in probiotics. In addition, strains including *Streptococcus* spp., *Lactococcus* spp., and *Enterococcus* spp. are also commonly used. More recently, probiotics described as a new generation, such as *Faecaliumbacterium prausnitzii*, *Akkermansia muciniphila* and *Clostridium* IV, XIVa and XVIII, have also shown beneficial effects in preclinical trials [107,110].

A double-blind, placebo-controlled clinical study evaluated the efficacy of administering a probiotic composed of 10^9 CFU of four bacterial strains (L. *rhamnosus* NCIMB 30174, L. *plantarum* NCIMB 30173, L. *acidophilus* NCIMB 30176 NCIMB 30175 and Enterococcus) in adult patients with asymptomatic UC and DC. After weeks of supplementation, no significant differences in the quality of life were observed. However, a significant reduction in fecal calprotectin was identified in patients with UC who received probiotics compared to the placebo group [111]. In a recent review, Silva et al. also concluded that the use of probiotics seems to be a considerable alternative in the treatment of active UC, especially with the use of *Escherichia coli* Nissle 1917 and VSL #3. However, the same benefits were not observed in patients with active CD [112].

Due to dysbiosis and the characteristic gastrointestinal clinical changes in IBS, the promising applications of probiotics are also represented in this functional disease. Previous studies have demonstrated that some strains can contribute to the relief of gastrointestinal symptoms and psychiatric manifestations commonly observed in patients with IBS [113]. A placebo-controlled, double-blind, randomized controlled trial included 251 adults with IBS and identified that supplementation with L. *paracasei* HA-196 and *Bifidobacterium longum* R0175 (10×10^9 CFU for 8 weeks) reduced the severity of gastrointestinal symptoms and improved the emotional well-being of patients with some subtypes of IBS [113]. Similar findings were reported after evaluating the supplementation of 113 individuals with IBS for 12 weeks with 50×10^9 CFU of a probiotic suspension (L. *acidophilus* CL1285, L. *casei* LBC80R, and L. *rhamnosus* CLR2) compared to placebo. Interestingly, women showed better results for the evaluated outcomes. In addition, a significant improvement was seen in stool frequency and

Table 2
Main clinical trials that evaluated pre pro and symbiotic supplementation in intestinal inflammation.

Prebiotics				
Valcheva et al. [98]	RCT with 25 patients with mild/moderately active UC	Oligofructose-enriched inulin (Orafti®Synergy1)	7.5 or 15 g for 9 weeks	Supplementation at a dose of 15 g increased the production of colonic butyrate and produced functional changes in patients with UC
Benjamin et al. [99]	RCT, double masked with 103 patients with active Crohn's disease	FOS	15 g for 4 weeks	No clinical benefits were seen after supplementation. However, there was a reduction in positive interleukin (IL)−6 lamina propria DC and increased IL-10 DC staining in patients receiving FOS
García-peris et al.	RCT, double masked with 31 patients with gynaecological cancer who received radiotherapy after surgery	50% inulin and 50% FOS	6 g of the mixture, twice daily, for one week before and three weeks after radiotherapy treatment	Increase in Lactobacillus and Bifidobacterium three weeks after radiotherapy
Probiotics				
Bjarnason et al. [111]	RCT, double masked with 81 and 61 patients with UC and CD, respectively	L. *rhamnosus* NCIMB 30174, L. *plantarum* NCIMB 30173, L. *acidophilus* NCIMB 30176 in NCIMB 30175 and *Enterococcus*	10^9 CFU for 4 weeks	There were no significant differences in IBD-QOL scores and laboratory data between the placebo and probiotic groups.
Lewis et al. [113]	RCT, double masked with 251 patients with either constipation (IBS-C), diarrhea (IBS-D), or mixed-pattern (IBS-M)	L. *paracasei* HA-196 and *B. longum* R0175	10×10^9 CFU for eight weeks	Improve the quality of life in patients with IBS
Preston et al. [114]	RCT, double masked with 113 patients with IBS	L. *acidophilus* CL1285, L. *casei* LBC80R and L. *rhamnosus*	50×10^9 CFU twice daily for 12 weeks	Increase in quality of life. Women with IBS-D who received the probiotic showed greater and more consistent effects
Symbiotics				
Ishikawa et al. [123]	RCT, with 41 with mild to moderate UC	*B. breve* Yakult strain and GOS	Probiotic (10^9 CFU) three times a day and 5.5 g of GOS once a day for one year	Improvements in clinical conditions
Furrie [124]	RCT, double masked with 18 patients with active UC	*B. longum* and a prebiotic (Synergy 1) inulin/oligofructose	Probiotic (2×10^{11}) and 6 g of prebiotic, twice daily for one month	Clinical improvement and reduction of inflammation
Altun et al. [125]	RCT, with 40 patients with mild-to-moderate UC	*E. faecium*, L. *plantarum*, *S. thermophilus*, *B. lactis*, L. *acidophilus*, *B. longum* and FOS	3×10^9 CFU of probiotic and 225 mg of FOS for 8 weeks	Significant clinical improvement
Skrzydło-radomańska et al. [127]	RCT, double masked in 68 adult patients with moderate and severe diarrhea-dominant IBS (IBS-D)	L. *rhamnosus* FloraActive ™ 19070–2, L. *acidophilus* DSMZ 32418, *B. lactis* DSMZ 32269, *B. longum* DSMZ 32946, *B. bifidum* DSMZ 32403 and FOS	Probiotic (5×10^9) and 947 mg of FOS, twice daily for 8 weeks	Significant improvement in symptoms such as feeling of incomplete bowel movements, flatulence, pain, fecal pressure and diarrhea.

consistency between the supplemented and placebo groups [114]. Although several studies have demonstrated efficacy and significant improvement in IBS symptoms, especially in general scores and abdominal pain, there is still no established recommendation on probiotic strains and specific doses for the management of IBS [115].

The benefits of probiotics have also been described in the context of intestinal mucositis. Recently, a mixture of probiotics containing *Lactobacillus* spp. and *Bifidobacterium* spp. demonstrated the ability to modulate inflammation, oxidative stress, intestinal permeability, and cytokine production in mice with 5-FU-induced mucositis, evident as normalization of the homeostasis of the intestinal microbiota [116]. Positive results in experimental trials were also described in a systematic review and meta-analysis, indicating that probiotics reduce weight loss and intestinal permeability. Furthermore, they can suppress the production of pro-inflammatory cytokines and inhibit apoptosis pathways [117]. However, clinical investigations are still scarce and the results are controversial. There is a concern about bacterial translocation in immunosuppressed patients and whether the use of live probiotics would be detrimental is unresolved [118]. A meta-analysis that included five clinical studies concluded that probiotics could reduce the incidence and severity of mucositis. However, the studies showed moderate heterogeneity due to different study designs, strains, supplementation time, and conflicting results [119].

4.3. Synbiotics

The combination of prebiotics and probiotics is a synbiotic. The combination can influence the composition of the microbiota, increase the production of SCFAs, and modulate the immune system [120]. A synbiotic is defined as "a mixture of live microorganisms and their substrate(s) selectively utilized by host microorganisms that confer a health benefit on the host" [121]. Synbiotic formulations can potentiate the ecological effects of microorganisms and the prebiotic substrate through the joint operation and synergism of the combination. This mechanism contributes to the alteration of the intestinal microbiota, resulting in benefits for the host [121]. For this reason, the use of synbiotics has been studied in some diseases, especially intestinal disorders.

Few clinical studies have investigated the efficacy of synbiotics in IBDs. However, most of these studies showed beneficial effects [122]. Ishikawa et al. conducted a randomized controlled study with 41 patients with mild-to-moderate active or inactive UC who received *Bifidobacterium breve* strain and GOS for one year. At the end of this period, the clinical characteristics assessed by colonoscopy were significantly improved as the concentration of myeloperoxidase decreased [123]. However, in a double-blind, randomized controlled trial with 18 patients with active UC who received *B. longum* and a prebiotic (Synergy 1) inulin/oligofructose for one month, the researchers did not observe differences in clinical activity index score or histopathology score compared to placebo [124]. The effects of synbiotic therapy using six probiotic strains combined with FOS for 8 weeks were also evaluated in 40 patients with mild-to-moderate active UC. A synbiotic suspension containing 3×10^9 CFU of *Enterococcus faecium*, L. *plantarum*, *Streptococcus thermophilus*, *B. lactis*, L. *acidophilus*, *B. longum*, and 22 mg of FOS was administered twice a day before lunch. After treatment, a significant reduction in C-reactive protein values and clinical improvement were observed in the group that received the synbiotic compared to the placebo group. However, there were no differences in the level of endoscopic activity [125].

IBS generates a dysbiosis that activates the immune system. The resulting low-grade inflammation of the intestine disrupts the gut-brain axis [126]. Strategies with the use of synbiotics are also therapeutic means associated with the modification of the intestinal microbiome for the relief of symptoms of IBS and have been the focus of recent research. The efficacy of a synbiotic preparation was also investigated in a randomized placebo-controlled clinical trial involving 80 adults diagnosed with IBS with moderate and severe dominant diarrhea. After 8 weeks, patients who received the synbiotic (containing L. *rhamnosus* FloraActive ™ 19070–2, L. *acidophilus* DSMZ 32418, *B. lactis* DSMZ 32269, *B. longum* DSMZ 32946, *B. bifidum* DSMZ 32403, and FOS) showed significant improvement in intestinal symptoms, including flatulence and pain, compared to subjects who received placebo [127]. These findings illustrate the benefits of the use of synbiotics in IBS patients.

Currently, the use of synbiotics in the treatment of intestinal mucositis is promising and has become a research target [90]. Trindade et al. observed that synbiotic treatment of mice with mucositis induced by 5-FU prevented mucosal damage, attenuated weight loss, intestinal permeability, and inflammation of mucosal tissue, increased the mucus layer, and production of SCFAs [128]. To the best of our knowledge, no clinical studies have assessed the use of synbiotics for intestinal mucositis.

4.4. Paraprobiotics and postbiotics

In recent years, concepts related to probiotics have emerged as new therapeutic frontiers. Paraprobiotics or phantom probiotics are "non-viable microbial cells (intact or broken) or bacteria-free extracts capable of providing benefits to the host" [129,130]. Postbiotics, refer to the free fraction of cells, as metabolic products secreted by microorganisms or released after cell death [131]. Several aspects of the mechanisms of action of paraprobiotics and postbiotics remain unknown. However, their clinical application is promising, especially concerning the safety of the administration of these products [132]. Evidence supports that bacterial viability is not essential to achieve the beneficial effects of probiotics. These benefits are directly or indirectly related to antimicrobial, antioxidant, anti-inflammatory, antiproliferative, and immunomodulatory functions [90,132,133].

Pretreatment with *E. coli* Nissle 1917 and L. *rhamnosus* GG cell-free supernatants can also prevent or inhibit enterocyte apoptosis, in addition to maintaining a barrier function after 5-FU-induced damage [134,135]. Gao et al. observed increased mucin secretion and reduced intestinal permeability after administration of a soluble protein (HM0539) secreted from L. *rhamnosus* GG in mice with colitis [136].

Although potential results for the application of prebiotics, probiotics, synbiotics, parabiotics, and postbiotics in intestinal inflammation have been obtained, only a few randomized clinical trials have assessed the efficacy and safety of use of these formulations. Discrepancies in study design, administration time, dose, and probiotic combinations limit supplementation in clinical practice.

The main findings of these studies are summarized in Table 2.

5. FODMAPs and intestinal inflammation

Although some prebiotic fibers demonstrate beneficial effects on intestinal inflammation, other fermentable short-chain carbohydrates, such as oligo-, di-, monosaccharides, and polyols, also known as FODMAPs, have the opposite effects. Throughout the digestive process, carbohydrates are poorly absorbed in the small intestine. The presence of these compounds in the intestinal lumen promotes bacterial fermentation in the colon and secretion of water by osmosis, leading to excessive gas production and abdominal distension, especially in patients with IBD [137,138]. However, there is evidence that LFD diets can reduce the functional gastrointestinal symptoms commonly seen in IBD [138].

A recent study demonstrated the safety and efficacy of an LFD diet consumed for four weeks. Intestinal symptom control in patients with quiescent IBD was described, with a significant improvement in quality of life compared to the group that received a control diet [139]. Similar results were described by Bodini et al. who evaluated the effect of a six-week LFD diet intervention in patients with IBD that was in remission or mild in activity. After the dietary intervention, reductions in disease activity index (Harvey-Bradshaw index and Mayo partial score) and fecal calprotectin dosages were observed in patients who consumed the LFD diet. In addition, in the short term, the LFD diet was safe and contributed to improving the quality of life of patients with IBD in remission or mild in activity [140]. Few studies have evaluated the impact of long-term use of the LFD diet on bowel symptoms. Orlando et al. investigated changes in symptoms and inflammatory markers after 90 days of an LFD diet in patients with IBS-D. The patients showed improved bowel symptoms and reduced inflammatory markers [141].

Table 3
Diet with low in FODMAPs diet and intestinal inflammation.

FODMAPs				
Cox et al. [139]	RCT, single-blind in 52 patients with quiescent Crohn's disease or ulcerative colitis and persistent gut symptoms	Diet low in FODMAPs	Restriction of dietary fructans, GOS, lactose, fructose in excess of glucose, and polyols, including sorbitol and mannitol for 4 weeks	After 4 weeks of treatment there was no difference in disease score, but improvements in persistent bowel symptoms
Bodini et al. [140]	RCT, with 55 patients with IBD in remission or with mild disease activity	Diet low in FODMAPs	Restriction of dietary fructans, GOS, lactose, fructose in excess of glucose, and polyols for 6 weeks	Reduced disease activity index and fecal calprotectin. In addition to the improvement in quality of life after 6 weeks
Orlando et al. [141]	Clinical trial, with 20 Patients suffering from IBS-D in accordance with the Rome IV criteria	Diet low in FODMAP	Personalized LFD for 90 days	Improvement in bowel symptoms and reduced inflammatory markers

GOS: galactooligosaccharides; IBD: Inflammatory Bowel Disease; IBS-D: irritable bowel syndrome – with diarrhea; LFD: low FODMAPs; RCT: randomized control trial.

The benefits of low consumption of FODMAPS have also been demonstrated to reduce diarrhea in cancer patients during chemotherapy treatment. One study followed 55 patients with colorectal cancer during chemotherapy. Scrutiny of the food diaries that were maintained by the patients revealed that the high consumption of lactose and other fermentable carbohydrates was associated with a higher prevalence of diarrhea. The researchers suggested that the LFD diet may be a strategy to prevent or alleviate the occurrence and severity of diarrhea resulting from cancer treatment [142].

Table 3 describes the main clinical trials described above. The adoption of an LFD diet in inflammatory bowel conditions is beneficial for gastrointestinal symptoms and quality of life of patients. Further studies are needed to assess the safety and efficacy of FODMAP restriction in the long term.

6. Final consideration

Intestinal inflammation, such as IBDs, IBS, and mucositis, often leads to increased recruitment of immune cells and production of

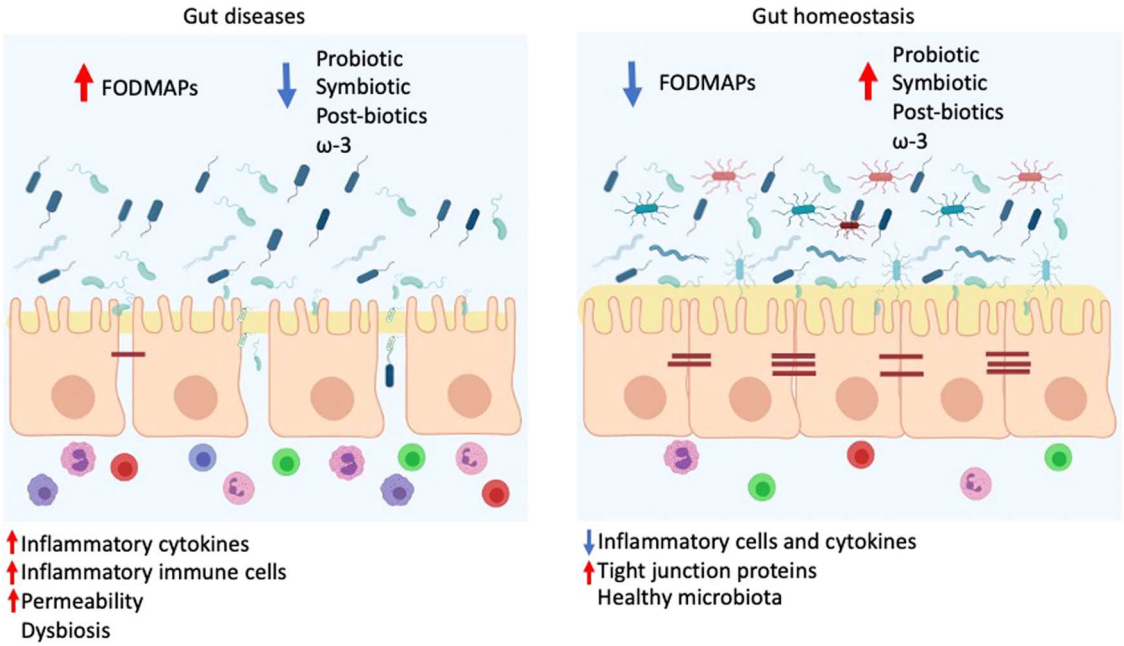

Fig. 1. Non-pharmacological alternatives to restore gut homeostasis. Excessive consumption of FODMAPs, low consumption of polyunsaturated fatty acids, and absence of beneficial bacteria or synbiotics increase the chance of developing inflammation in the intestine in susceptible individuals. In such cases, there is an increased accumulation of immune cells and gut permeability, as well as decreased microbiota diversity and tight junction synthesis. Gut homeostasis can be restored by the low consumption of FODMAPs, increased consumption of polyunsaturated fatty acids and synbiotics, and supplementation with probiotics.

inflammatory cytokines. These recruitments lead to changes in the intestinal microbiota and increased intestinal permeability and are mainly responsible for the symptoms presented by patients. Supplementation with omega 3, prebiotics, probiotics, symbiotics and low FOMAPS diet seems to act on these changes, which improves the symptoms of patients. (Fig. 1).

Omega 3 fatty acid acts on specific receptors, such as GPR120, which drives immunoregulation and decreases the synthesis of inflammatory mediators by activating PPARγ and decreasing NF-κB translocation to the nucleus. Supplementation with omega 3 fatty acid can attenuate inflammation in patients with UC; however, the optimal dose is not defined in the guidelines. Information is scant regarding omega 3 fatty acid supplementation in CD patients. For mucositis, the benefits of the supplementation of omega 3 fatty acid remain controversial, because the published data are mainly experimental.

The mechanism of action of probiotics and prebiotics involve different pathways, such as inducing the differentiation of regulatory T cells and production of IgAs by B cells. The presence of probiotics and prebiotics in the gut stimulates mucous secretion and proliferation of enterocytes. Regarding prebiotics, administering FOS and inulin at a dosage of 15 g for longer than 4 weeks can significantly improve the quality of life of patients with IBD and mucositis. The consumption of probiotics, especially strains belonging to the *Lactobacillus* and *Bifidobacterium* genera, can contribute to the well-being of patients with IBD. However, these benefits have not been demonstrated in IBS and mucositis. Regarding therapy with synbiotics, supplementation with bacteria (*Lactobacillus* and *Bifidobacterium*) combined with FOS and GOS for 8 weeks has reduced pain and the levels of inflammatory markers in patients with UC and IBS. However, the same benefits have not been observed in individuals with CD.

Finally, the low fermentative capacity of LFM diets can reduce functional gastrointestinal symptoms that are commonly observed in intestinal inflammation. Consumption of the LFD diet for 4–6 weeks has improved the quality of life of patients diagnosed with IBD and IBS by reducing diarrhea and abdominal bloating. The mechanism might be related to better digestion of food and decreased gas formation during metabolism by bacteria.

There is some evidence indicating the benefits of non-pharmacological intervention for managing intestinal inflammation. However, the evidence from clinical trials on their use in intestinal inflammation remains inconclusive, mainly because of the heterogeneity of the dosages and study design and variable results. However, the present knowledge concerning the results of these strategies and their mechanisms indicates the potential value of the future clinical use of these substances.

Authors' contributions

Statement of authors' contributions to manuscript: TUM, LMT, AS, LT, and MERA analyzed and summarized the published data and wrote the draft version of the manuscript. TUM, VNC, and SBG critically revised the article for important intellectual content. All authors read and approved the final version of the manuscript.

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Conflict of interest statement

All the authors declare no conflict of interest.

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