Prebiotic selection influencing inflammatory bowel disease treatment outcomes: a review of the preclinical and clinical evidence

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ABSTRACT
Inflammatory bowel disease (IBD) is characterised by chronic inflammation in the gastrointestinal tract, with unclear aetiology but with known factors contributing to the disease, including genetics, immune responses, environmental factors and dysbiosis of the gut microbiota. Existing pharmacotherapies mainly target the inflammatory symptoms of disease, but recent research has highlighted the capacity for microbial-accessible carbohydrates that confer health benefits (ie, prebiotics) to selectively stimulate the growth of beneficial gut bacteria for improved IBD management. However, since prebiotics vary in source, chemical composition and microbiota effects, there is a clear need to understand the impact of prebiotic selection on IBD treatment outcomes. This review subsequently explores and contrasts the efficacy of prebiotics from various sources (β-fructans, galacto-oligosaccharides, xyl-oigosaccharides, resistant starch, pectin, β-glucans, glucamannans and arabinoxylans) in mitigating IBD symptomatology, when used as either standalone or adjuvant therapies. In preclinical animal colitis models, prebiotics have revealed type-dependent effects in positively modulating gut microbiota composition and subsequent attenuation of disease indicators and proinflammatory responses. While prebiotics have demonstrated therapeutic potential in animal models, clinical evidence for their precise efficacy remains limited, stressing the need for further investigation in human patients with IBD to facilitate their widespread clinical translation as microbiota-targeting IBD therapies.

INTRODUCTION
Inflammatory bowel disease (IBD), encompassing Crohn’s disease (CD), ulcerative colitis (UC) and IBD-unclassified, represents a group of chronic and severely debilitating disorders.1 These diseases share common initiating factors, including abnormal immune responses, alterations in the gut microbiota and various environmental triggers. IBD results in chronic inflammation and damage to the gastrointestinal (GI) tract. CD can affect any part of the GI tract and is characterised by skip lesions, while UC typically involves localised inflammation that begins in the rectum and extends proximally in a continuous manner.2 Roughly half of all patients with IBD develop extraintestinal manifestations (eg, peripheral arthritis, erythema nodosum and anaemia) or complications including strictures (abnormal intestinal narrowing), fistulas (aberrant intestinal connections with other organs/skin) and an increased risk of cancer, ultimately requiring surgical interventions.3,4 The global impact of IBD is substantial, with the European Federation of Crohn’s Disease and Ulcerative Colitis Associations estimating around 10 million people affected worldwide. The financial burden associated with IBD is significant, with annual costs reaching up to $31 billion, highlighting the need for effective management strategies.5

The aetiology of IBD is multifactorial and complex, involving a combination of genetic susceptibility, gut microbiota composition, altered immune responses and various environmental factors.6 Individuals who are genetically predisposed to IBD can develop the disease as a result of abnormal immune reactions directed towards the gut microbiota.7 This microbiota, primarily consisting of obligate anaerobic bacteria in the colon (ie, large intestine), plays a crucial role not only in the fermentation of indigestible components in the diet but also in maintaining overall host health.8 It achieves this by modulating the immune system, producing anti-inflammatory metabolites and regulating the integrity of the gut mucosal barrier.9 These interconnected roles of the gut microbiota highlight its importance in the pathophysiology of IBD, underlying its significance in both the onset and progression of the disease. An altered balance between beneficial commensal and pathobiont species, along with diminished
bacterial diversity, commonly known as dysbiosis, has been linked with the aberrant phenotypes seen in patients with IBD. Current pharmacotherapeutic approaches for IBD primarily target the downstream inflammatory symptoms rather than addressing the underlying dysbiosis.

Recognising the profound influence of the gut microbiota in the development and progression of IBD, treatment strategies targeting the microbiota have begun to emerge. Among these, carbohydrate-type prebiotics have attracted significant recent attention for their potential role in the management of IBD. Defined by the International Scientific Association for Probiotics and Prebiotics as ‘a substrate that is selectively used by host microorganisms conferring a health benefit’, prebiotics have shown promise in conjunction with traditional IBD pharmacotherapies in improving disease outcomes.

Most prebiotics are indigestible dietary fibres derived from various food and nutritional sources. They are distinct from probiotics and synbiotics (combinations of probiotics and prebiotics) in that they are not significantly impacted by the oral transit through the GI tract. This contrasts with the viability challenges faced by certain oral probiotics, which can be hindered by the acidic gastric environment before they colonise the intestine. Subsequently, the limitations of oral probiotics and synbiotics in maintaining a long-term presence within the GI tract highlight the potential of prebiotics as a more effective therapy in the management of IBD. Recent research has also explored the combination of prebiotics with other innovative treatments, such as faecal microbial transplant (FMT) or encapsulated oral delivery systems.

However, it is clear from both preclinical and clinical studies that the source and type of prebiotics are crucial to their effectiveness. Prebiotics vary based on their monomeric and linkage type, polymer or oligomer length, and these differences result in unique responses in the host and shifts in the gut microbiota. This review aims to provide a comprehensive overview of fibre-type prebiotics, derived from various food and nutritional sources, and their demonstrated efficacy as either standalone or adjuvant therapies in the management of IBD in both preclinical and clinical settings. It will also explore the challenges and future directions in the development and translation of effective prebiotics to enhance clinical outcomes in IBD management, including the potential use of an integrative adjuvant approach for improved disease management. Ultimately, this review presents novel strategies and directions for effectively treating the underlying dysbiosis associated with IBD, which is expected to facilitate improved clinical outcomes for patients with IBD.

**PHARMACOTHERAPIES FOR IBD MANAGEMENT**

The management of IBD is multifaceted, with the primary focus on symptom alleviation via controlling inflammation and the induction and maintenance of remission, as well as the prevention of disease-related complications. These therapies encompass pharmacological therapies, as well as the surgical removal, resection or widening of the diseased intestine when patients fail to respond to therapeutics or to address complications such as strictures and fistulas.

Existing literature highlights the tailored approach to current IBD pharmacotherapies, with treatment selection influenced by factors including age, comorbidities, extraintestinal manifestations, disease subtype and severity. For instance, a guideline published for the management of adult IBD suggests an initial treatment of aminosalicylates (eg, mesalamine, sulfasalazine) for mild to moderate adult UC. Conversely, paediatric IBD treatment regimens often deviate significantly from those employed for adults. For example, the European Crohn’s and Colitis Organisation recommends children with mild to moderate CD to be prescribed with an exclusive enteral nutrition diet therapy initially. For severe cases, the use of biologics (eg, anti-tumour necrosis factor (TNF)-α agents) is commonly preferred.

Despite the wide array of available interventions, up to 46% of patients with IBD never experience response or lose response to primary therapies after 12 months, necessitating therapy modification or the implementation of concomitant strategies. While existing IBD therapies primarily aim to improve symptoms, they mainly target the downstream effects of the disease rather than addressing its pathogenesis, likely as aetiology remains poorly understood. As such, there is a growing interest in microbiota-targeting prebiotics that aim to have an additive effect when concomitantly dosed with pharmacotherapeutics, with the potential of serving as the next frontier of IBD therapies. The therapeutic potential of fibre-type prebiotics has been highlighted in recent reviews, gaining attention in the management of IBD. These studies suggest that while certain soluble fibres like β-fructans show promise in reducing disease activity and improving symptoms, there is still a degree of inconsistency in the effects of various fibres, particularly during IBD flares. As such, this review highlights the impact of existing and emerging fibre-type prebiotics as standalone or concomitants to pharmacotherapies, in both animal colitis and human IBD studies. The efficacy of each prebiotic will provide a more informed perspective on the selection of prebiotics in future IBD management strategies.

**PREBIOTIC FIBRES FOR THE PRECLINICAL AND CLINICAL MANAGEMENT OF IBD**

**Therapeutic mechanisms of prebiotics in treating IBD**

Prebiotics’ therapeutic action in IBD can depend on the prebiotics’ food-derived sources and polymeric structures (figure 1). Studies highlight the variability in response to prebiotics, yet most studies continue to evaluate prebiotic-based diets in a holistic manner. This knowledge is essential for creating effective dietary guidelines and treatments to foster a healthy microbiota and boost short-chain fatty acid (SCFA) production.
SCFAs, generated by the microbiota’s fermentation of prebiotics, are critical in this context and extensively reviewed by Keshteli et al.29 30 These metabolites activate receptors like free fatty acid receptors, on various cells, including intestinal and immune cells, leading to either inflammatory or anti-inflammatory responses, crucial for maintaining gut homeostasis.29 31–35 Figure 2 summarises the multifaceted effects of prebiotics on animal models of colitis. Given these mechanisms are dependent on the prebiotic type, the subsequent section delves into different prebiotics and their impact on animal colitis and clinical IBD management.

Impact of prebiotic selection on preclinical colitis and clinical IBD outcomes

β-fructans
β-fructans are β-(2→1) linked polysaccharides and oligosaccharides commonly found in plant-based foods such as chicory root, garlic, Jerusalem artichoke, and bananas and are commonly referred to as fructo-oligosaccharides (FOS), oligofructose or inulin, depending on their average degree of polymerisation (DPn: 2–4 for FOS, <10 for oligofructose and 2–60 for inulin).36 Tables 1 and 2 highlight the preclinical and clinical findings for the use of β-fructans in IBD. In a pilot study involving patients with active CD, β-fructans supplementation led to a notable decrease in the Harvey Bradshaw Index, a tool used for quantifying the severity and presence of symptoms and complications associated with CD activity.37 Furthermore, in patients with mild to moderately active UC, a combination of short and long-chain β-fructans at a dosage of 15 g/day led to a reduction in the Mayo score, a clinical tool that evaluates stool frequency, rectal bleeding, endoscopic findings and a physician’s global assessment of UC severity.38
Histopathological analysis revealed that β-fructans play a vital role in mitigating the structural damage associated with IBD.39–42 In preclinical models of colitis induced by dextran sodium sulfate (DSS) or trinitrobenzene sulfonic acid (TNBS), β-fructan administration led to decreased colonic histological scores. This decrease implies less tissue damage and ulceration, reduced thickening of the mucosa and lower incidences of diarrhoea, collectively contributing to improved overall colonic health.43 The prebiotic effects of β-fructans have been demonstrated, in part, due to their promotion of beneficial SCFA metabolites in both rodent colitis and clinical IBD trials.38 41–43 Inflammatory biomarkers of IBD, colonic myeloperoxidase (MPO), and dialysate eicosanoids, prostaglandin E2, thromboxane B2 and leukotriene B4 have all been demonstrated to be reduced by β-fructans in a rodent model of colitis.39 Similarly, β-fructans diminished colonic interleukin (IL)-1β, nitric oxide synthase and cyclo-oxygenase-2 in TNBS-treated rats.42 Supplementation with β-fructans has been shown to increase anti-inflammatory mucosal IL-10-positive dendritic cells in patients with active CD.45 Moreover, the prebiotic intervention notably elevated the expression of Toll-like receptor 4 (TLR-4) on colonic dendritic cells, a key receptor in the detection of microbial-associated microbial patterns including lipopolysaccharide and initiation of the innate immune response.46 However, a counterpoint to these findings emerged from a recent study that assessed cultured ex vivo colonic biopsies from a paediatric cohort of patients with IBD, who were exposed to unfermented β-fructans.45 This study observed that in patients whose gut microbiota were unable to ferment β-fructans, the prebiotics led to a proinflammatory response through the activation of NLR family pyrin domain containing (NLRP)-3 and TLR-2 pathways. The team further validated their findings in a randomised controlled trial of adult patients with UC in remission that consumed 15 g/day of β-fructans over 6 months, demonstrating a 14-fold reduction in faecal calprotectin compared with the placebo group.46 However, a subset of patients with UC who present with flares following β-fructan supplementation exhibited increased proinflammatory cytokines, IL-1β, IL-23 and IL-5.45 These results thereby suggest that although β-fructan supplementation commonly yields advantageous outcomes in healthy individuals possessing a robust microbial fermentative capacity, interactions between unfermented β-fructans and host immune cells may be deleterious in a subset of patients with IBD, mediated by altered immunity and diminished gut microbiota fermentative potential.

**Galacto-oligosaccharides**

Galacto-oligosaccharides (GOS) are carbohydrates that are commonly found naturally in legumes such as lentils and chickpeas.47 The structure of GOS typically consists of β-(1→4) and β-(1→6) linked galactose units, with a DPn ranging from 2 to 9, capped with a terminal glucose molecule. The impact of GOS on the gut microbiota and the consequent implications for IBD have been evaluated in various preclinical studies, as shown...
Table 1: The impact of β-fructans on preclinical models of IBD

<table>
<thead>
<tr>
<th>Dose</th>
<th>Dosing duration</th>
<th>Experimental model</th>
<th>Outcomes</th>
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<tr>
<td></td>
<td></td>
<td>Histopathology</td>
<td>Inflammation indicators</td>
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<tr>
<td>1.0% (m/v) or 0.4 g/day</td>
<td>14 days</td>
<td>↓ Colonic histological scores</td>
<td>↓ Dialysate prostaglandin E2, thromboxane B2, leukotriene B4, ↓ Colonic MPO</td>
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<td>↓ Colonic luminal pH</td>
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<td>5.0 g/kg of bodyweight/day</td>
<td>49 days</td>
<td>↓ Caecal and colonic tissue damage</td>
<td>↓ Caecal IL-1β and TGF-β</td>
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<td>8.0 g/kg of bodyweight/day</td>
<td>84 days</td>
<td>↓ Colonic histological scores</td>
<td>↓ Caecal IL-1β</td>
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<td>63 g/kg of diet</td>
<td>14 days</td>
<td>↑ Distal colon butyrate concentration</td>
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<tr>
<td>0.5 g/kg of bodyweight/day</td>
<td>8 days</td>
<td>↑ Colon weight, extent of necrosis</td>
<td>↓ Colonic RNA expression of IL-1β, NOSs, COX-2</td>
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</table>

↑, increase; ↓, decrease.

COX-2, cyclo-oxygenase-2; DSS, dextran sodium sulfate; IBD, inflammatory bowel disease; IL, interleukin; MPO, myeloperoxidase; NOSs, nitric oxide synthases; SCFA, short-chain fatty acid; TGF-β, transforming growth factor-β; TNBS, trinitrobenzene sulfonic acid.
<table>
<thead>
<tr>
<th>Table 2</th>
<th>The impact of β-fructans on clinical trials of IBD</th>
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<tbody>
<tr>
<td>Concomitant drugs</td>
<td>Dose</td>
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<tr>
<td>Mesalamine, corticosteroids, azathioprine or none (unspecified dose)</td>
<td>15g/day</td>
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<tr>
<td>Mesalamine or none (unspecified dose)</td>
<td>7.5–15g/day</td>
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<tr>
<td>Biologics, aminosalicylates, immunomodulators, prednisone</td>
<td>5.0g/L in vitro; 15g/day for 6 months</td>
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†, increase; †, decrease.
CD, Crohn’s disease; HBI, Harvey Bradshaw Index; IBD, inflammatory bowel disease; IL, interleukin; SCFA, short-chain fatty acid; TLR-4, Toll-like receptor 4; UC, ulcerative colitis.
in Table 3. Immunodeficient rat models of colitis demonstrate that GOS protects against *Helicobacter hepaticus*-induced colon weight reduction, indicative of a positive effect on disease activity.48 The inflammatory status of the system, as assessed by serum levels of TNF-α, IL-1β and interferon (IFN)-γ, was also found to be reduced,

<table>
<thead>
<tr>
<th>Dose</th>
<th>Dosing duration</th>
<th>Experimental model</th>
<th>Outcomes</th>
<th>Histopathology</th>
<th>Inflammation indicators</th>
<th>Microbial and metabolic profiles</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0 g/kg bodyweight/day</td>
<td>14 days</td>
<td><em>Helicobacter hepaticus</em>-induced colitis on immunodeficient rats</td>
<td>Protection against <em>H. hepaticus</em>-induced colon weight reduction</td>
<td>↓ Serum TNF-α, IFN-γ and IL-1β</td>
<td>↓ Diarrhoea score</td>
<td>48</td>
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</tr>
<tr>
<td>0.5 g/kg bodyweight/day</td>
<td>7 days</td>
<td>DSS-induced colitis in mice</td>
<td>1. Protection against DSS-induced colon length reduction</td>
<td>↓ Disease Activity Index</td>
<td>↓ Colonic IL-6, IL-18, IL-13 and IL-33 (mRNA expression also reduced)</td>
<td>↓ Faecal Verrucomicrobia and Proteobacteria phyla</td>
<td>49</td>
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<td>2. ↓ Colon tissue histological score</td>
<td></td>
<td>↓ Mesenteric lymph node Th17, ↑ Treg cells</td>
<td>↑ Faecal <em>Bacteroides fragilis</em></td>
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<tr>
<td>0.4 g/kg bodyweight/day of α-GOS/GOS</td>
<td>21 days</td>
<td>DSS-induced colitis in mice</td>
<td>1. Protection against DSS-induced colon length reduction</td>
<td>↓ Disease Activity Index</td>
<td>↓ Colonic mRNA expression of ZO-1, occludens and claudin-1</td>
<td>↓ Faecal phylum Bacteroidetes</td>
<td>50</td>
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<td></td>
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<td>2. ↓ Colonic tissue damage</td>
<td>↓ Colonic and serum TNF-α, IL-1β and IL-6</td>
<td>↓ Faecal phylum Proteobacteria</td>
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<td>3. ↓ Colonic mRNA expression NLRP-3 and caspase-1</td>
<td>↓ Faecal phylum Proteobacteria</td>
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<tr>
<td>0.5% w/v in drinking water of α-GOS</td>
<td>14 days</td>
<td>DSS-induced colitis in mice</td>
<td>1. Protection against DSS-induced colon length reduction</td>
<td>↓ Colitis score</td>
<td>↓ Colonic mRNA expression of IL-6, COX-2, macrophage colony-stimulating factor, IL-1β and TNF-α</td>
<td>↓ Faecal haemoglobin content</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. ↓ Colonic NF-κB p65 activation</td>
<td>↓ Faecal haemoglobin content</td>
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↑, increase; ↓, decrease.

COX-2, cyclo-oxygenase-2; DSS, dextran sodium sulfate; GOS, galacto-oligosaccharides; IBD, inflammatory bowel disease; IFN-γ, interferon-γ; IL, interleukin; NF-κB, nuclear factor-κB; NLRP-3, NLR family pyrin domain containing-3; Th, T helper; TNF-α, tumour necrosis factor-α; Treg cells, regulatory T cells; ZO, zonula occludin.
hinting at a potential anti-inflammatory role for GOS. In the context of DSS-induced colitis in mice, both GOS and α-GOS (α-1→6 linkages) offered protection against DSS-induced reduction in colon length and lowered disease activity. Simultaneously, GOS downregulated mRNA expression of colonic inflammatory markers, including IL-6, IL-18, IL-13 and IL-33 in mice. The study concluded that the reduction in proinflammatory cytokines may, in part, be due to GOS inhibiting nuclear factor-κB (NF-κB) signalling pathways. Moreover, GOS triggered an imbalance of T helper (Th)17 cell/regulatory T cell (Treg) in the mesenteric lymph node through the regulation of the gut microbiota. As Tregs play a suppressive function on the immune system by secreting anti-inflammatory cytokines (ie, IL-10, IL-35), its down-regulation can improve IBD disease outcomes. Interestingly, GOS and α-GOS enhanced the mRNA expression of tight junction proteins in the colon, namely zonula occludin (ZO)-1, occludens and claudin-1, which were reduced, indicating its regulation of gut barrier function. Alongside this, a reduction of colonic and serum TNF-α, IL-1β and IL-6 was observed, as well as the inhibition of nucleotide oligomerisation domain-like receptor-P3 inflammasome-mediated inflammation. These outcomes further establish the anti-inflammatory potential of GOS in animal models of colitis.

Clinically, in an open-label study spanning 42 days and involving 18 patients with active UC, the impact of GOS supplementation at a dose of 2.8 g/day was assessed. Notably, patients on GOS experienced an increase in the proportion of normal stools and a significant reduction in stool urgency, highlighting its potential in ameliorating disease symptoms. Moreover, there was an increase in the faecal genus Bifidobacterium and family Christensenellaceae, specifically in patients who had a clinical Colitis Activity Index of 2 or less. Alongside these observations, there was an elevated presence of colonic IL-1β in proinflammatory responders as opposed to non-responders, and an increase in colonic IL-23 in patients experiencing flares in contrast to those in remission. While the effects of GOS as a standalone or adjuvant therapy for IBD lacks extensive clinical validation, the existing preclinical evidence highlights its potential in enhancing health outcomes for patients with colitis.

β-glucans

β-glucans are a class of naturally occurring, non-digestible polysaccharides with either linear or branched chains of glucose residues, typified by either β-(1→3) or β-(1→4) glycosidic bonds. Several preclinical studies have highlighted the relevance of β-glucans in the context of colitis, as shown in table 4. For example, yeast-derived β-glucans administered for 14 days were found to significantly reduce the colonic histopathological score in rats. Similarly, mushroom-derived β-glucans were associated with a decrease in colon length and colonic histological scores in a similar colitis model. Oat-derived β-glucans administered at varying doses and duration also demonstrated a reduction in the Disease Activity Index, colon length reduction and protection against epithelial cell apoptosis in mouse models. These findings underline the efficacy of β-glucans, irrespective of glycosidic linkage type, in ameliorating the deleterious histopathological changes associated with colitis in mice.

Supplementation of β-glucans further influenced an array of inflammatory biomarkers associated with IBD. A reduction in the mRNA expression of proinflammatory markers such as colonic IL-6, IL-17, IFN-γ, TNF-α and IL-1β was observed alongside an increase in serum anti-inflammatory IL-10 following the administration of yeast-derived β-glucans. Interestingly, however, yeast-derived β-glucans also appear to stimulate an increase in the expression transforming growth factor-β (TGF-β), a key mechanistic driver of intestinal fibrosis in IBD. These findings demonstrate a dualistic effect of β-glucan supplementation. The study evaluating mushroom-sourced β-glucans found that when added to the apical side of in vitro cultured colonic cell lines, the prebiotics suppressed inflammation-induced NF-kB activation, further substantiating the anti-inflammatory role of β-glucans prebiotics. β-glucans appear to promote intestinal barrier integrity, with oat-derived β-glucans increasing the mRNA expression of ZO-1, occludens, claudin-1 and claudin-4, demonstrating the role of the prebiotics in the reinforcement of the epithelial barrier. Changes in faecal microbiota were also discerned, with an increase in mucin-degrading Akkermansia muciniphila, as well as the Bacteroidetes and Verrucomicrobia phyla, taxa that have shown to be depleted in clinical IBD. Despite these findings, the benefits of pure β-glucans (ie, non-whole food source) on patients with IBD remain limited, lessening the significance of these preclinical outcomes in colitis models.

Xylo-oligosaccharides

Xylo-oligosaccharides (XOS) are polymers of two to seven xylose molecules connected by β-1,4 glycosidic bonds that can be produced from either chemical, physical or enzymatic degradation of xylan fractions in sugarcane, corn cob and rice husk. There are a limited number of available preclinical studies exploring the use of XOS in mitigating colitis, complemented by an explorative study conducted on patients with UC. A 28-day study on rats with peptidoglycan-polysaccharide-induced colitis demonstrated a protective effect of a fibre diet with equal parts of XOS and gum Arabic (at 1.5% w/v of drinking), evident in the mitigation of colonic weight increases, crypt damage and inflammatory MPO activity. It is important to note, however, that these outcomes may also have been influenced by the co-dosed gum Arabic.

In a similar study, mice with induced colitis were given XOS at a dose of 0.23 g/kg of bodyweight/day. Within 21 days, a notable decline in Disease Activity Index was observed. XOS not only counteracted the DSS-induced reduction in colon length but also markedly decreased the pathological scores linked to inflammation, mucosal damage and crypt damage. Additionally, there was a
reduction in the overall lesion score. The therapeutic benefits of XOS were further evident as it decreased levels of proinflammatory TNF-α and IL-1β markers in colonic tissues. There was also a marked reduction in the mRNA expression of proinflammatory markers, including TNF-α, IL-1β, NLRP-3 and caspase-1. Concurrently, an upregulation in the expression of tight junction proteins, ZO-1, occludens and claudin-1 was observed. These findings highlight the potential of XOS in treating histopathological disturbances and proinflammatory mediators in small animal models with colitis.

A small explorative study evaluated the effects of XOS on the faecal microbiota of five UC remission patients. Using an in vitro culture medium supplemented with 0.8 g/L of XOS, the study used a fermentation chamber seeded with samples from patients with UC and healthy patient faecal samples to simulate GI conditions. The results indicated a significant increase in the abundance of Faecal Akkermansia muciniphila, Bacteroidetes and Verrucomicrobia genera and a decrease in Faecal Allobaculum, Bacteroides and Ruminococcus genera.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>The impact of β-glucans on preclinical models of IBD</th>
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<tbody>
<tr>
<td><strong>Dose</strong></td>
<td><strong>Dosing duration</strong></td>
</tr>
<tr>
<td>0.5 g/kg bodyweight/day (yeast)</td>
<td>14 days</td>
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<td>50–100 µg/day (mushroom)</td>
<td>14 days</td>
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<td>0.5 and 1.0 g/kg bodyweight/day (oat)</td>
<td>14 days</td>
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<td>0.8 g/kg bodyweight/day (oat)</td>
<td>8 days</td>
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<td>95 g/kg of diet (oat)</td>
<td>14 days</td>
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↑, increase; ↓, decrease.

DSS, dextran sodium sulfate; IBD, inflammatory bowel disease; IFN-γ, interferon-γ; IL, interleukin; MPO, myeloperoxidase; nNOS, neuronal nitric oxide synthase; TNF-α, tumour necrosis factor-α; ZO, zonula occludin.
of *Bifidobacterium* and *Lactobacillus* genera when exposed to XOS. These genera, well-regarded for their beneficial properties such as butyrate production and immune modulation, underscore the potential capability of XOS in modulating the gut microbiota. Crucially, other clinical studies offer differing perspectives on the benefits of *Bifidobacterium* and *Lactobacillus* genera in active IBD phases. Despite this, the benefits of XOS are limited by insufficient evidence in clinical IBD studies.

**Pectin**

Pectin is a complex polysaccharide abundantly present primarily in the pith of citrus fruits, with lesser amounts found in a variety of other fruits and vegetables. The structure of pectin consists of α-1,4-linked D-galacturonic acid residues, varying in esterification levels depending on the plant species, thereby influencing its effects on fermentation, SCFA production and immune modulation. Two key preclinical studies have demonstrated the potential therapeutic efficacy of pectin in animal models of colitis. For instance, a 17-day study evaluating the side chain content of pectin (5% of orange pectin w/w of diet) on colitis-induced mice found that a high side chain content pectin (orange pectin) ameliorated TNBS-induced colitis. These findings support the structure specificity of pectin as an anti-colitis agent, as low side chain content (citrus pectin) did not modulate disease outcomes in the study. Similarly, in a 21-day study using DSS-induced colitis in mice, orange pectin (200mg/kg of bodyweight/day) led to a reduction in disease activity, protection against TNBS-induced colonic length reduction and tissue damage.

Pectin supplementation also modulated the levels of several key inflammatory biomarkers. In the TNBS-induced colitis model, orange pectin resulted in immune modulation by increasing the number of colonic Th1 cells while decreasing the levels of proinflammatory cytokines TNF-α and IL-17A. In the DSS-induced colitis model, orange pectin downregulated serum levels of MPO, TNF-α, IL-1β and IL-6, while upregulating the expression of anti-inflammatory cytokine IL-10 and enhancing the colonic expression of SCFA receptors, GPR43 and GPR109A. Colonic mRNA and protein expression of tight junction proteins occludens, ZO-1 and claudin-1 was also improved by orange pectin following DSS-colitis.

In subsequent in vitro studies with orange pectin on macrophage-like cells sourced from mice, production of IL-6 was inhibited with the introduction of pectin when the cells were stimulated by TLR agonists or intestinal endotoxins. This demonstrates the anti-inflammatory potential of pectin administration in animal colitis studies. Alterations in faecal and caecal biomarkers further emphasise the potential therapeutic benefits of pectin. Orange pectin increased faecal propionic and butyric acid levels in the TNBS-induced colitis model. Moreover, the DSS-induced colitis model showed a significant enhancement of caecal butyrate, acetate, propionate and total SCFA concentration alongside increased populations of beneficial bacteria including *Akkermansia* and *Lactobacillus*, the families Lachnospiraceae NK4A136, Ruminococcaceae UCG-014 and Prevotellaceae UCG-001, as well as decreased *Bacteroides* genus. Despite promising results from preclinical studies, there is a significant gap in pectin’s effects on clinical IBD. The lack of clinical trials highlights the necessity for further investigation into pectin’s potential therapeutic role in IBD.

**Resistant starch**

Resistant starch (RS) is a complex carbohydrate that resists digestion and has been linked to improvements in gut microbiota composition and its metabolomic profile in patients. Principally consisting of amylose, amylopectin or retrograded amylose molecules, RS is often categorised into four types based on its inherent structure and response to enzymatic digestion. Notably, RS2, the most prevalent form of RS in dietary staples like unripe bananas, potatoes and high-amylose maize starchy, has been the focus of two preclinical colitis models of disease. In a study using DSS-induced colitis in mice, a diet supplemented with 10% w/w RS2 resulted in a decreased Disease Activity Index. Histopathological benefits were observed in a TNBS-induced colitis in rats, where diets supplemented with 15% or 30% w/w RS2 led to reduced Disease Activity Index, colon weight and colon length, and decreased colonic permeability. Although different models (ie, TNBS-rats and DSS-mice) of disease limit the extrapolation from these studies, these results may suggest that RS2 has a dose-dependent protection against rodent colitis.

Assessing the effect of RS2 supplementation on other biomarkers, populations of beneficial commensal *Bifidobacterium* and *Enterococcus* spp genera, along with butyrate-producing *Faecalibacterium prausnitzii*, were promoted in the rat caecum. Conversely, levels of pathobiont *Escherichia coli*, as well as *Ruminococcus* spp, were reduced. However, the butyrate-producing *Clostridium cocoides*, which is often negatively associated with UC, was lowered in the same animal model. In the TNBS-induced colitis model, RS2 supplementation resulted in reduced colonic MPO levels and an increase in colonic mucin density, particularly notable at 30% w/w supplementation. This supplementation also resulted in increased concentrations of caecal acetate, propionate and butyrate, decreased caecal pH and elevated mucin levels in both the caecal region and faeces. As such, particularly at higher doses between 15% and 30% w/w RS2 can protect against colitis damage to the colon, while enhancing the concentration of SCFA metabolites. However, the prebiotic effects have yet to be validated in a human model of IBD.

**Glucomannan**

Glucomannan (GM) is primarily found in the konjac root and is a polysaccharide formed by glucose and mannose monomers connected via β-(1→4) linkages and branching α-(1→6) linkages. GM supplementation
can influence the outcomes of limited preclinical colitis models, as well as a preliminary clinical study on patients with IBD. GM (0.2 g/kg of bodyweight/day) administered over 18 days in a DSS-induced mouse colitis model led to a decrease in the Disease Activity Index and reduced colonic crypt damage. Another study using a DSS-induced model with GM supplementation (25 g/kg of the diet) for 29 days showed protection against inflammatory cell infiltration in the colon.

Inflammatory biomarkers are also modulated by the administration of GM, leading to increased colonic goblet cell numbers and subsequent mucin content. GM upregulated colonic IL-6, IFN-γ, TGF-β, IL-10 and TNF-α, and restricted colonic mRNA expression of TLR-2, TLR-4, TLR-6 and TLR-9 in mice with colitis. The second colitis model observed a decrease in the colonic mRNA expression of TNF-α, IL-6 and IL-10, and an increase in the mRNA expression of ZO-1 and occludens. Hence, GM administration in colitis-induced mice reduced both proinflammatory cytokines and upregulated tight junction protein expression, and these properties of GM may be TLR mediated.

The prebiotic effects of GM are evident in murine models, as indicated by an increase in beneficial faecal Lactobacillus and Bifidobacterium, and a reduction of pathobiont Clostridium genera. Moreover, an increase in total SCFA concentration, and increased levels of acetate, butyrate and propionate were also observed with GM use in the model. A small clinical study investigating GM hydrolysates in patients with CD and UC who are presented with constipation and diarrhoea found that 3.3 g/day over 14 days led to reductions in bowel movement, stool consistency, diarrhoea, blood in faeces, abdominal pain, flatulence and vomiting. These results display the promising effects of GM against GI symptoms in clinical IBD.

Arabinoxylnans

Arabinoxylnans (AX), primarily found in the cell walls of cereal grains, are hemicellulose polysaccharides primarily comprised of xylose units interconnected by β-(1→3) linkages, while arabinose moieties frequently extend from the xylose backbone via O-2 and O-3 atoms. In a murine colitis model induced by DSS, the oral administration of AX (0.2 g/kg bodyweight) over a 2-week period resulted in an increased prevalence of Akkermansia and Coprobacillus genera, concomitant with a reduction in the Clostridium XIVa cluster within the murine gut microbiota. Another study highlighted the anti-inflammatory attributes of AX (0.6 g/kg bodyweight) in a T cell transfer model of chronic mice colitis. AX intervention induced the production of TNF-α from Th1 cells, concurrently mitigating colonic damage and reducing colitis scores when compared with a cellulose-controlled group. Like the previous study, AX supplementation fostered the proliferation of multiple microbial taxa, prominently those affiliated with the butyrate-generating Lachnospiraceae family, further affirming AX’s anti-inflammatory efficacy in murine colitis.

To date, no current study has measured the effects of pure AX in patients with IBD. However, an in silico study investigated the potential of microbiota communities of patients with CD to metabolise AX. Using metagenome-assembled genomes (MAGs), the study revealed that MAGs responsible for the enzymatic degradation of AX are present in both healthy individuals and those with CD. However, the cross-feeding interaction of these MAG degraders with other beneficial bacterial species was diminished in patients with CD. Consequently, the study postulated that AX supplementation within this cohort might replenish such microbial communities, potentially ameliorating dysbiosis in individuals with CD. Hence, AX may hold promise as a therapeutic avenue in the context of IBD.

LIMITATIONS OF PREBIOTIC ADJUVANTS FOR IBD

Prebiotics show promise in modulating gut microbiota for IBD treatment yet face significant translational challenges from preclinical models to human conditions. Notably, the differences in physiological processes and gut microbiota compositions between rodents and humans limit the applicability of these findings. Recent studies have further suggested the notable difference between a healthy microbiota composition and that of IBD in remission, suggesting that humanised animal models are necessary for the study of the fermentable dietary factors, at the very least. Moreover, the selection of prebiotics has a variable effect on the microbiota. For example, β-fructans can preferentially promote Lactobacillus and Bifidobacterium genera, while pectins have been shown to target Bacteroides genus. Furthermore, the metabolites produced by prebiotic fermentation, such as butyrate from β-fructans and a mix of acetate, propionate and butyrate from AX degradation, vary, affecting the therapeutic response.

Human IBD studies on prebiotics also have limitations, particularly in prebiotic selection altering clinical outcomes. Most studies focus on β-fructans or whole food mixed prebiotics, which may not comprehensively represent different prebiotics’ effects on host cells and microbiota. Additionally, the co-administration of prebiotics with pharmacotherapies is often not controlled or disclosed, obscuring the adjuvant effects of prebiotics. Importantly, many studies overlook the inability of some patients with IBD to ferment prebiotics. Recent efforts include using germ-free or humanised animal models and subdividing patients with IBD based on their fermentation capacity in human studies. The regulatory status of prebiotics as dietary supplements has played a significant role in their rising adoption in the Western diet. However, the accessibility of prebiotics to patients presents other limitations, including issues related to their palatability, the acceptability of the dosage form and sustainability concerns related to sourcing natural prebiotic
supplements. Industries are facing challenges to meet these demands, due to limited sources to manufacture prebiotics at a low cost. Moreover, the long-term effect of prebiotic therapy is an area of interest, especially given the intolerability to high-prebiotic diets within specific IBD cohorts that lack a fermentative microbiota.

Despite these challenges, prebiotics remain a promising area for IBD treatment, as research continues to bridge gaps between preclinical and human studies. Emerging strategies, such as combining prebiotics with FMT and their metabolites (eg, SCFAs), suggest a multifunctional approach targeting gut microbiota modulation could enhance therapeutic outcomes. While these integrative strategies show promise, further exploration is beyond the scope of this manuscript and is supported by ongoing clinical and translational studies.

CONCLUSION
In summarising the insights from eight prebiotic types studied in animal models of colitis, it becomes evident that while these compounds show promise, their efficacy varies. A critical limitation in translating these findings to clinical practice is the gap between rodent-based preclinical models and the multifaceted physiological nature of human IBD. To date, most clinical investigations have demonstrated the benefits of β-fructans as an adjunct therapy for IBD, yet emerging evidence suggests that other prebiotics, including GM and β-glucans, mitigate rodent colitis symptoms and may offer beneficial effects on clinical IBD. We recommend that future prebiotic efforts are dedicated to conducting a larger number of clinical trials to offer an alternative avenue for advancing human IBD management.

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