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Review

Current Research on the Role of Isomaltooligosaccharides in Gastrointestinal Health and Metabolic Diseases

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ABSTRACT: The intestinal epithelium plays an important role in maintaining the intestinal barrier and facilitating nutrient absorption. It also serves as a critical physical barrier against the infiltration of foreign substances from the intestinal lumen into the circulation. Intestinal barrier dysfunction has been implicated in the development of several diseases. Isomaltooligosaccharides (IMOs), which are a type of dietary fiber, possess multiple health benefits. However, there is limited information regarding their efficacy against gastrointestinal diseases. This review explores the therapeutic potential of IMOs in obesity, diabetes mellitus, inflammatory bowel disease (IBD), hyperlipidemia, and constipation. High-fat diet (HFD)-induced obesity models have shown that IMOs, administered alone or in combination with other compounds, exhibit potent antiobesity effects, making them promising agents in the treatment of obesity and its associated complications. Moreover, IMOs exhibit preventive effects against HFD-induced metabolic dysfunction by modulating gut microbiota and short-chain fatty acid levels, thereby ameliorating symptoms. Furthermore, IMOs can reduce IBD and alleviate hyperlipidemia, as indicated by the reduced histological colitis scores and improved lipid profiles observed in clinical trials and animal studies. This review highlights IMOs as a versatile intervention strategy that can improve gastrointestinal health by modulating gut microbiota, immune responses, and metabolic parameters, providing a multifaceted approach to address the complex nature of gastrointestinal disorders.

Keywords: diabetes mellitus, dietary fiber, intestinal barrier function, metabolic diseases, prebiotics

INTRODUCTION

The gastrointestinal tract has the largest surface area of the body that is in contact with the external environment; it relies on the intestinal epithelium to serve as a critical physical barrier against harmful substances, including pathogens, toxins, and antigens, and to absorb nutrients (Peterson and Artis, 2014). An intact intestinal barrier plays a critical role in preventing and mitigating intestinal and metabolic diseases, including obesity, type 2 diabetes mellitus (T2DM), inflammatory bowel disease (IBD), food allergies, and alcoholic liver disease (Parlesak et al., 2000; Ventura et al., 2006; Cani et al., 2007; Camilleri et al., 2012). Several studies have highlighted the beneficial effects of various dietary components on intestinal homeostasis. Among these components, dietary fiber (DF) has received considerable attention. Because it is resistant to digestive enzymes and economically advantageous, DF has emerged as a promising candidate for new technofunctionalities and easier dietary incorporation (He et al., 2022). In the food industry, isomaltooligosaccharides (IMOs), which are a well-developed DF in Asian countries, stand out because of their favorable properties (Goffin et al., 2011). For example, IMOs exhibit prebiotic properties that stimulate the growth of beneficial bacteria. In addition, they can modulate immune responses, enhance disease resistance, and improve lipid metabolism and liver and kidney functions (Mizubuchi et al., 2005; Sorndech et al., 2018).

Therefore, this review discusses current research on the impact of IMOs on the incidence of gastrointestinal disorders, including obesity, diabetes, and IBD, with particular emphasis on elucidating the mechanisms by which the physical and fermentation properties of IMOs inter-

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act within the gastrointestinal tract.

INTESTINAL EPITHELIAL BARRIER FUNCTION

The gastrointestinal tract serves as a critical interface between the external environment and the body's internal milieu, with the intestine acting as a barrier to various stimuli. The integrity of the intestinal epithelium plays a primary defensive role against harmful microorganisms and antigens and facilitates the proper absorption of nutrients, water, and ions (Peterson and Artis, 2014). This critical balance is achieved through the orchestrated interplay of crucial components, including the mucus layer, commensal bacteria, epithelial cells, and immune cells (e.g., dendritic and plasma cells, macrophages, and lymphocytes) within the lamina propria (Fig. 1) (Maldonado-Contreras and McCormick, 2011). Five distinct cell lineages are contained in the intestinal epithelium: absorptive enterocytes, goblet cells, tuft cells, enteroendocrine cells, and Paneth cells. Among them, absorptive enterocytes play a central role in nutrient absorption, microvillus formation, and enzyme secretion during digestion. Tuft cells actively contribute to luminal sensing and modulate the immune response. Meanwhile, goblet cells secrete mucus glycoproteins and form a protective barrier, preventing direct microbial contact with colonocytes. In contrast, enteroendocrine cells regulate various physiological functions by releasing hormones in response to luminal stimuli, thereby influencing critical processes such as digestion, nutrient absorption, and intestinal motility. With their distinct antimicrobial properties, Paneth cells secrete bactericidal proteins, thereby contributing to defense mechanisms (Allaire et al., 2018).

The intestinal epithelium plays a dual role by facilitating nutrient absorption and acting as a protective barrier against proinflammatory substances, such as pathogens, toxins, and antigens. The transcellular pathway, which is characterized by specific transporters or channels on cell membranes responsible for nutrient transport, and the paracellular pathway, which is regulated by tight junctions (TJs) and adherence junctions (AJs), are two distinct pathways that achieves selective permeability. TJs, which comprise transmembrane proteins such as claudins and occludin, control selective permeability to solutes, whereas AJs form strong adhesive junctions between epithelial cells (Suzuki, 2013). The dynamic adjustment of the barrier function and paracellular permeability of TJs is intricately linked to external stimuli and plays a pivotal role in maintaining overall health and influencing disease susceptibility (Di Tommaso et al., 2021). The interactions among these cellular components orchestrate the intricate functions of the gastrointestinal system, ensuring delicate yet robust homeostasis.

Gut microbiota, which are bacteria that reside in the intestine, steadily increase along the length of the intestine, reaching their highest density in the colon. The duodenum, jejunum, ileum, and colon have a microbiota density of 10^3 bacteria/g, 10^4 bacteria/g, 10^7 bacteria/g, and 10^{12} bacteria/g, respectively (Dieterich et al., 2018). Gut microbiota help to maintain intestinal homeostasis in several ways. For example, they oppose pathogen colonization and promote the differentiation of regulatory T (T_{reg}) cells, which induce tolerance to luminal antigens (Kosiewicz et al., 2014). In the lumen, microbe-associated molecular patterns, including flagellin, lipopolysaccharide

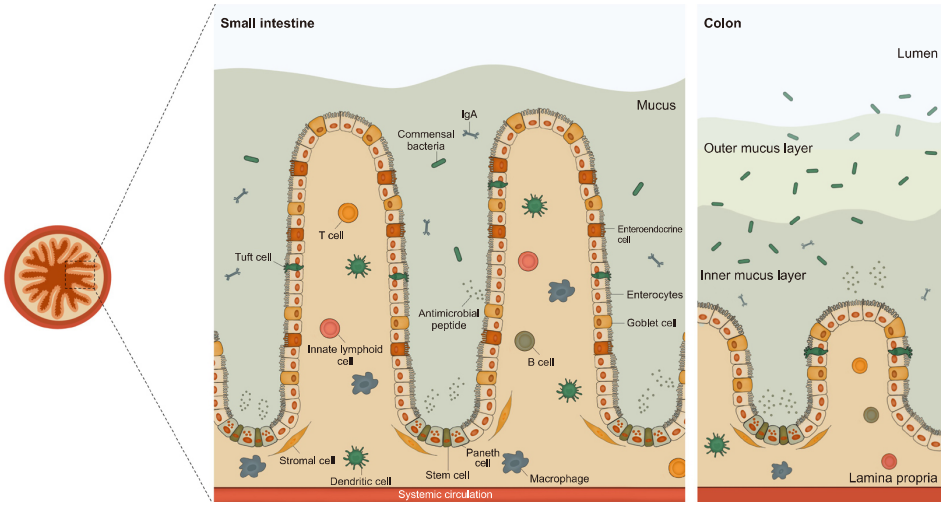

Fig. 1. Components of the intestinal epithelial barrier. Intestinal homeostasis is maintained by a coordinated interplay of essential components, including the mucus layer, commensal bacteria, epithelial cells, and various immune cells (e.g., dendritic cells, plasma cells, macrophages, and lymphocytes) that reside within the lamina propria. The intestinal epithelium comprises five different cell lineages: absorptive enterocytes, goblet cells, tuft cells, enteroendocrine cells, and Paneth cells. The intricate interactions among these cellular components regulate the complex functions of the gastrointestinal system, ensuring a finely tuned yet resilient homeostasis.

(LPS, a component of the wall of gram-negative bacteria), and peptidoglycan (a component of the wall of gram-positive bacteria), induce the production of antimicrobial proteins by binding to Toll-like receptors on intestinal cells' apical surface (Allaire et al., 2018). In goblet cells, gut microbiota can induce mucus production by activating the secretion of interleukin (IL)-22 by innate lymphoid cells (Stefka et al., 2014). Gut microbiota convert DF into short-chain fatty acids (SCFAs), which protect the intestinal barrier by providing energy to colonocytes and stimulating the production of mucus, antimicrobial proteins, and T_{reg} cells (Allaire et al., 2018). The reduction in beneficial gut microbiota, termed dysbiosis, and their replacement with pathogens called symbionts can consequently disturb intestinal barrier function (Fan and Pedersen, 2021).

Intestinal barrier dysfunction has been implicated in the pathogenesis of intestinal (e.g., celiac disease, IBD, irritable bowel syndrome, and colon carcinoma) and extraintestinal diseases (e.g., chronic liver disease, diabetes, and obesity) (Turner, 2009). Intestinal barrier dysfunction facilitates the entry of antigens, harmful substances, and microorganisms or their components into the lamina propria, which leads to the subsequent activation of the immune system, triggering inflammatory responses and potentially resulting in a vicious cycle. In a previous study, mice lacking mucin-2, a major mucus glycoprotein, exhibited intestinal barrier dysfunction and spontaneously developed colitis and colon cancer, illustrating the role of mucus in maintaining homeostasis (Van der Sluis et al., 2006). Decreased goblet cells, mucus production, and secretory IgA levels and increased translocation of bacteria or bacterial products to the pancreatic lymph nodes indicate a disruption in intestinal barrier function, which precedes the onset of type 1 diabetes mellitus (Miranda et al., 2019). Animal studies have shown that elevated LPS levels induce systemic and tissue inflammation, similar to that observed in studies using a high-fat diet (HFD) model. Circulating LPS serves as a useful biomarker of impaired intestinal barrier function. In patients with obesity and diabetes, elevated LPS levels are commonly reported (Riedel et al., 2022). In addition, the early disruption of the TJ-mediated paracellular barrier in the duodenum and jejunum is observed at the onset of prediabetes, independent of detectable endotoxemia or inflammation, which may contribute to the increased intestinal permeability induced by HFD (Nascimento et al., 2021).

In the context of metabolic diseases, several biomarkers, including leptin, adiponectin, leptin:adiponectin ratio, plasminogen activator inhibitor-1 (PAI-1), uric acid, IL-6, tumor necrosis factor-α (TNF-α), pro-oxidized low-density lipoprotein (OxLDL), ghrelin, IL-10, and paraoxonase-1 (PON-1), serve as critical indicators for early detection and targeted treatment approaches (Srikanthan et al., 2016). Specifically, individuals with metabolic syndrome have elevated levels of proinflammatory cytokines (e.g., IL-6 and TNF-α), pro-oxidant status markers (e.g., OxLDL and uric acid), and prothrombic factors (e.g., PAI-1) (Kraja et al., 2007; Kelly et al., 2010; Aroor et al., 2013; Weiss et al., 2013). Metabolic syndrome is associated with decreased levels of anti-inflammatory cytokines (e.g., IL-10), ghrelin, adiponectin, and antioxidant factors (e.g., PON-1). Decreased levels of these biomarkers are correlated with specific manifestations within the metabolic syndrome cluster, suggesting their potential utility in identifying and characterizing metabolic disorders (Tschöp et al., 2001; Matsuzawa et al., 2004; Aroor et al., 2013).

IMOs

IMOs are oligosaccharides comprising less than 10 glucose monomers linked by α-(1→4) and α-(1→6) glycosidic linkages. In fermented foods such as miso, sake, soy sauce, beer, and honey, minimal concentrations of naturally occurring IMOs can be observed (Tungland and Meyer, 2002). Because of the high market demand for products containing IMOs, obtaining a sufficient supply of naturally occurring IMOs for commercial use is not economically feasible. Consequently, IMOs are being commercially produced through the enzymatic modification of starch (Sorndech et al., 2018).

Starches, which are homopolysaccharides of glucose units, are the primary form of carbohydrates stored in higher plants. The two primary types of starches are amylose and amylopectin, and their ratios vary depending on the source and type of starch. Typically, starch molecules contain approximately 20%～30% amylose and 70%～80% amylopectin. Amylose starch is a linear homopolysaccharide that comprises hundreds of glucose units linked by α-(1→4) glycosidic linkages. Conversely, amylopectin starch is a branched homopolysaccharide that comprises thousands of glucose units in the main chain linked by α-(1→4) glycosidic linkages. Branching points occur every 25～30 glucose units, with one glucose unit forming a branch through α-(1→6) glycosidic linkages (Fig. 2) (Ibrahim, 2018).

Liquefaction and saccharification are involved in the production of IMOs. These processes convert starch into small soluble molecules. Glycosidase enzymes such as α-amylase and pullulanase are used to liquefy starch. The liquefied starch is then converted into uniform chains by β-amylase, yielding maltose, dextrin, malt-pentose, and malt-triose. This process is followed by transglycosylation, which converts the α-(1→4) glycosidic linkages in starch to indigestible α-(1→6) glycosidic linkages, producing pure forms of IMOs with varying degrees of glucose polymerization, including isomaltose, panose, iso-

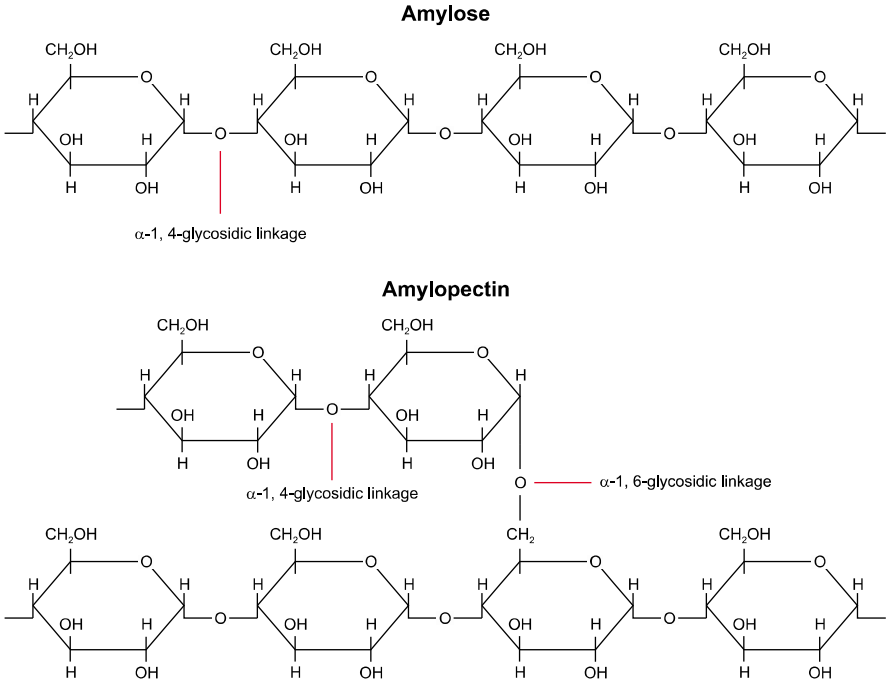

Fig. 2. Structures of amylose and amylopectin.

maltotriose, and other higher oligosaccharides (Panesar et al., 2022). Novel enzymes are used to generate different degrees of polymerization (DP) for IMOs, and their respective structures are shown in Fig. 3.

Human digestive enzymes such as isomaltase and maltase/glucoamylase partially hydrolyze IMOs. The manufacturing process determines the DP and α-(1→4):α-(1→6) linkage ratio in IMOs and the digestibility by brush border enzymes in the small intestine. IMOs that contain a component with higher DP and α-(1→6) linkages are less digestible by human digestive enzymes (Goffin et al., 2011). Consequently, these indigestible IMOs enter the colon and are metabolized by gut microbiota to produce SCFAs, which are largely responsible for the beneficial effects of fibers (Tan et al., 2023). In contrast, a recent study demonstrated that IMOs are fully hydrolyzed by mammalian α-glucosidases at a slow pace, suggesting the recharacterization of IMOs from prebiotic or colon-health-promoting substances to slowly digestible carbohydrates (Song et al., 2022).

IMOs were originally developed in Japan for use in the Asian market. At present, they are now available worldwide in syrup or powder form and are characterized by low calories and a mildly sweet taste. IMOs are used as bulking agents to increase the fiber content of food. Additionally, they are blended with intense zero-calorie sweeteners to mitigate their unpleasant taste. These sweeteners, including saccharin, aspartame, stevia, sucralose,

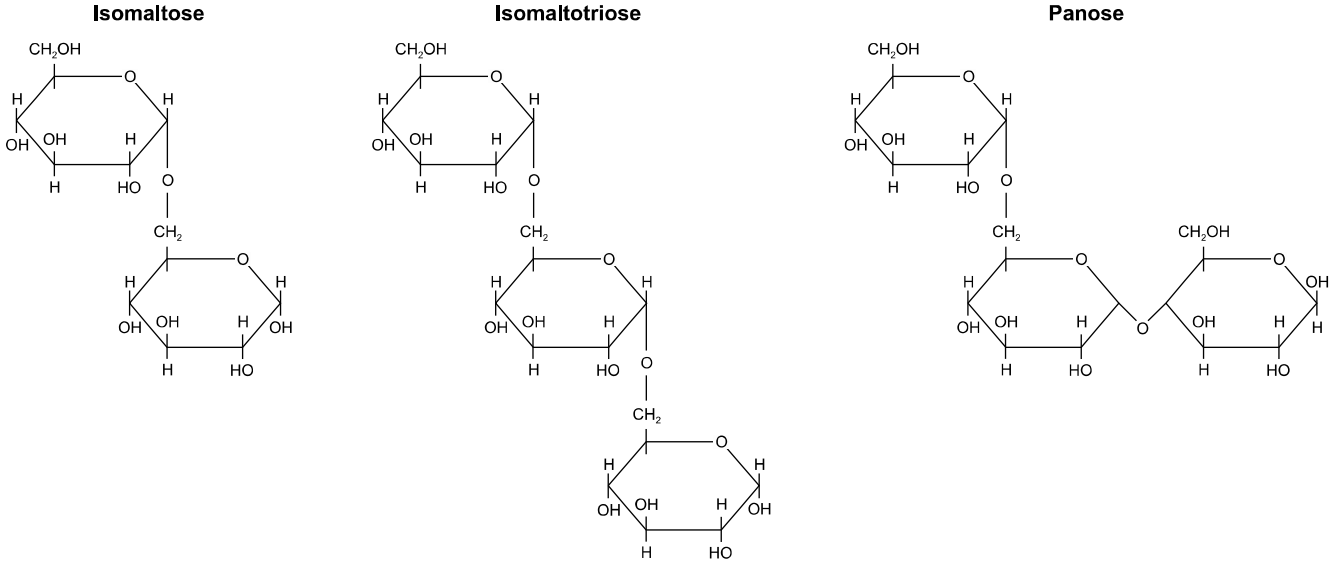

Fig. 3. Chemical structures of isomaltooligosaccharides.

and acesulfame K, serve as artificial sweeteners and sugar substitutes in dietary and functional foods. Currently, the US Food and Drug Administration and other global regulatory agencies have generally recognized IMOs as safe, with a maximum daily intake of 30.0 g/d (Ibrahim, 2018).

IMOs IN AMELIORATING GASTROINTESTINAL DISORDER

IMOs when administered alone or in combination with other dietary factors can remarkably alleviate gastrointestinal disorders and related diseases (Table 1). Their specific roles in different diseases are described below.

Obesity

Obesity is defined by a body mass index (BMI) of 30 kg/m^2 or greater. It is intricately linked to several health complications, acting independently or synergistically with other diseases, such as T2DM, coronary heart disease, and cancer (Piché et al., 2020). The prevalence of obesity has a consistent inverse relationship with DF intake from different sources (Waddell and Orfila, 2023). In a previous study, the co-administration of IMOs and cinnamaldehyde (an antiobesity agent) mitigated HFD-induced obesity and associated metabolic symptoms in mice. The co-supplementation of IMO (1 g/kg) and cinnamaldehyde (10 mg/kg) for over 12 weeks decreased HFD-induced intestinal permeability, LPS upregulation, histological and inflammatory changes in the colon, hepatic inflammatory markers, peripheral hormones, and lipid metabolism-related parameters. Moreover, it decreased the levels of LPS-producing bacteria, including Enterobacteriaceae, *Escherichia coli*, *Cronobacter* spp., *Citrobacter* spp., *Klebsiella* spp., and *Salmonella* spp., and prevented the HFD-induced reduction in the levels of beneficial bacteria such as *Bifidobacteria* and *Roseburia* spp. (Singh et al., 2017a). These results provide compelling evidence that the combination of IMO and cinnamaldehyde exerts enhanced antiobesity effects by modulating gut microbiota. However, this study did not elucidate the effects of IMO alone.

In a separate investigation by another research group, the antiobesity effects of IMO alone and their potential relationship to diabetes were investigated. Animal studies have shown that the co-administration of IMOs (1 g/kg body weight) with green tea extract (GTE, 200 mg/kg body weight) for 12 weeks exhibited antiobesity effects by attenuating HFD-induced adiposity and lipid accumulation in the liver and muscle. Moreover, the co-administration of IMOs and GTE normalized the levels of diabetes-related markers including fasting blood glucose, insulin, glucagon, and leptin. Furthermore, it prevented intestinal barrier damage and HFD-induced elevation of circulating LPS and proinflammatory markers such as resistin, adiponectin, TNF-α, IL-1β, and IL-6. The administration of IMO alone attenuated HFD-induced body weight gain, BMI, serum insulin levels, and ileal permeability. IMOs reportedly increased the levels of cecal propionate and normalized the levels of liver TNF-α and IL-1β (Singh et al., 2017b). The co-administration of IMOs with cranberry extract also decreased systemic obesity-associated metabolic changes in adipose tissue and liver of mice (Singh et al., 2018). Thus, the consumption of IMOs, with or without other dietary factors, is emerging as a viable strategy for decreasing obesity and its associated disorders.

Diabetes mellitus

The interplay between metabolic diseases and obesity is bidirectional, with the former influencing the development of the latter, and vice versa. Metabolic diseases including T2DM are characterized by energy metabolism, insulin sensitivity, and lipid profile disturbances, which result in weight gain and excess body fat accumulation, thereby promoting obesity (Zatterale et al., 2020; Kosmas et al., 2023). Simultaneously, obesity also significantly increases the risk of metabolic diseases, mainly because of the association between excess visceral fat and insulin resistance, inflammation, and dyslipidemia, which are critical factors in the pathogenesis of metabolic diseases (Wondmkun, 2020). This complex relationship involves intricate interactions that are influenced by lifestyle factors, genetic predispositions, and environmental exposure (Smith and Ryckman, 2015). Thus, a comprehensive treatment approach that includes lifestyle modifications, dietary interventions, and in certain cases medications is needed (Wondmkun, 2020).

The relationship between IMO intake and T2DM has been investigated clinically. A previous study evaluated the glycemic and insulin responses of healthy subjects to whey protein bars containing IMOs as a carbohydrate source. A randomized crossover study with 10 participants showed that the glycemic response was significantly lower in the first 60 min after the ingestion of whey protein bars compared with a dextrose reference (Grubic et al., 2018). In an animal study, IMOs and their co-supplementation with fructooligosaccharide (FOS) ameliorated T2DM induced by poloxamer 407 in Wistar rats. Moreover, this co-supplementation decreased glycemic and lipid dysmetabolism, as indicated by the decreased levels of oxidative markers and increased glucagon-like peptide-1 levels and *Bifidobacteria/Lactobacilli* population in the cecum compared with FOS or IMO treatment alone. Meanwhile, 10% of IMOs alone suppressed the increase in blood glucose in the oral glucose tolerance test and fasting blood glucose at 2, 4, and 6 weeks of treatment (Bharti et al., 2015).

Table 1. Effect of IMOs on gastrointestinal disorders and related diseases

Type	Model	Dosage	Duration	Related disease	Physiological effect	Reference
IMOs and lycopene	Mice	5~10 mg/kg lycopene 0.5~1 g/kg IMOs	12 weeks	Metabolic diseases	IMOs and the combination of IMOs and lycopene: ↓weight gain, adiposity, insulin resistance, prevent NAFLD-like symptoms, improve adipose tissue fat mobilization, glucose homeostasis, selective gut microbial abundance, SCFA	Singh et al., 2016
IMOs, FM-AX, *Bifidobacterium longum* Bif10 and *Bifidobacterium breve* Bif11	Mice	1×10^9 CFU/mouse probiotic 1 g/kg body weight IMOs and FM-AX	25 days	Colitis	IMOs alone and its synbiotic mix: ↓DAI score, histological damage to the colon, gut dysbiosis, and inflammation Synbiotic mix more potent in ↓TNF-α, lipocalin, and ↑IL-10, IL-22, cecal SCFA	Sharma et al., 2023
IMOs	Mice	20% IMOs in drinking water	8 weeks	Colonic mucosal disruption	↓Mucosal damage and pathological alteration in colonic mucosa	Kumar et al., 2023
IMOs and *Latilactobacillus curvatus* MS2	Mice	1% IMOs 1×10^9 CFU/mL *L. curvatus*	5 weeks	Hyperlipidemia	↓Blood cholesterol	Kim et al., 2021
IMOs and FOS	Rats	8 kg/kg body weight	12 weeks	IBD	IMOs and FOS: ↓histological score of colitis, IL-1β in cecum and colon, ↑specific but divergent microbiota changes	Koleva et al., 2014
IMOs and CRX	Mice	200 mg/kg CRX 1 g/kg IMOs	12 weeks	Metabolic diseases	Co-supplementation of IMOs and CRX improves cecal SCFA, gut beneficial bacterial abundance, glucose intolerance, systemic obesity-associated metabolic changes in adipose tissue and liver	Singh et al., 2018
IMOs and cinnamaldehyde	Mice	1 g/kg IMOs 10 mg/kg cinnamaldehyde	12 weeks	Obesity, metabolic diseases	Co-supplementation of IMOs and cinnamaldehyde improves HFD-induced changes in serum LPS, LPS-producing bacteria, gut permeability, histological and inflammatory changes in colon, hepatic inflammatory markers, peripheral hormones, and lipid-metabolism-related parameters	Singh et al., 2017a
IMOs	Mice	0.8, 4, and 8 g/d/kg body weight	17 days	Constipation	↑Water content of feces, small intestinal transit rate, and SCFA concentration in feces Medium dose of IMOs is the most effective to treat constipation	Wang et al., 2017a
IMOs and inulin	Rats	20 g/kg	7 days	Constipation	↑Gastrointestinal motility-related hormones (ACTH, MTL, SP), SCFA and ↓CORT, VIP, CGRP in the colon	Lan et al., 2020
IMOs	Human	10 g	30 days	Constipation	↑Defecation frequency, wet and dry stool output, fecal acetate and propionate ↓Serum sodium concentration	Chen et al., 2001
IMOs	Human	86 g cookies daily	4 weeks	Hyperlipidemia	↓Cholesterol, triglycerides, and cardiac risk ratio scores	Sunarti et al., 2022
IMOs	Human	13 g whey protein bars	7~10 days	Diabetes	↓Glycemic response	Grubic et al., 2018
IMOs	Rats	5% IMOs (2 mL/d)	2 weeks	IBD	Improved intestinal transit rate, fecal microbiota, and serum cytokine in WAS model ↓AWR score, ileal epithelial damage ↑Pain threshold	Wang et al. 2017c
IMOs from rice starch	Rats	1.5 g/kg	19 weeks (3 times/ week)	Colon cancer	↓DSS-induced colonic polyps and histological changes ↑Gut barrier function Improve DSS-induced ↓beneficial bacteria and butyric production and ↑harmful bacteria	Plongbunjong et al., 2019

Table 1. Continued

Type	Model	Dosage	Duration	Related disease	Physiological effect	Reference
IMOs	Human	8.1 g active IMOs	8 weeks	Chronic constipation	↓Dose of laxative for peritoneal dialysis patients ↓Constipation-related symptoms ↑Quality of life of peritoneal dialysis patients	Tung et al., 2018
IMOs and GTE	Mice	1 g/kg body weight IMOs, 200 mg/kg body weight GTE	12 weeks	Obesity, diabetes	Combination of GTE and IMOs: ↓HFD-induced adiposity and lipid accumulation in liver and muscle. Normalizing fasting blood glucose, insulin, glucagon, and leptin levels. Prevents leaky gut phenotype and HFD-induced increase in LPS, resistin, adiponectin, TNF-α, IL-1β, IL-6. ↑Beneficial gut microbiota, ↓pathogen bacteria, ↑butyric acid IMOs alone are able to ↓body weight gain, BMI, serum insulin, ileal permeability, ↑cecal propionic acid, normalize TNF-α and IL-1β in liver	Singh et al., 2017b
IMOs from rice starch	Rats	5% IMOs	12 weeks	Colon cancer	↑Inflammatory response, intestinal microecological environment ↓The development of 1,2-dimethylhydrazine-induced early colon cancer	Chen et al., 2022
IMOs	Human	10 g/d IMOs	4 weeks	Constipation	↑Daily fecal excretion of acetate and propionate, colonic microbiota ↑Spontaneous defecation, wet fecal mass ↓Plasma total and low-density lipoprotein cholesterol levels	Yen et al., 2011
IMOs, FOS	Rats	10% IMOs 10% FOS 5% IMOs+5% FOS	6 weeks	Diabetes	IMOs alone, and combination of IMOs with FOS: ↓glycemic and lipid dysmetabolism, oxidation markers ↑GLP-1 content, cecal beneficial bacteria	Bharti et al., 2015
IMOs, FOS, GOS	Mice	0.8, 4, and 8 g/d/kg body weight	2 weeks	Constipation	↑Cecal microbiota in constipated mice.	Wang et al., 2017b
Lactiplantibacillus pentosus GSSK2, IMOs	Rats	1×10^9 CFU/0.1 mL 1 g/kg body weight IMOs	12 weeks	Metabolic diseases	Ameliorate HFD-induced weight gain, abdominal circumference, Lee's index, BMI, visceral fat. ↑Fecal *Lactobacillus* spp., *Akkermansia* spp., *Faecalibacterium* spp., *Roseburia* spp. and decreased Enterobacteriaceae, Bacteroidetes:Firmicutes ratio ↓Glucose, lipid biomarkers, oxidative stress, leaky gut phenotype, serum LPS, inflammation, lipid and glucose metabolism genes Restore histomorphology of adipose tissue, colon, and liver	Khanna et al., 2021
IMOs, RS, FOS, Inulin	Rats	8% mix dietary fiber	9 days	Colon cancer	↓CPT-11 toxicity, ↑cecal butyrate, bacterial butyril-CoA gene, MCT1	Lin et al., 2014
IMOs	Human	30 g	4 weeks	Chronic constipation, hyperlipidemia	↑Bowel movement, HDL-C level ↓Constipation, total cholesterol and triglycerides	Wang et al., 2001

IMOs, isomaltooligosaccharides; NAFLD, nonalcoholic fatty liver disease; SCFA, short-chain fatty acid; FM-AX, finger millet arabinoxylan; CFU, colony-forming unit; DAI, disease activity index; TNF-α, tumor necrosis factor-α; IL, interleukin; FOS, fructooligosaccharide; CRX, cranberry extract; HFD, high-fat diet; LPS, lipopolysaccharide; ACTH, adrenocorticotropic hormone; MTL, motilin; SP, substance; CORT, corticosterone; VIP, vasoactive intestinal peptide; CGRP, calcitonin gene-related peptide; WAS, water avoidance stress; AWR, abdominal withdrawal reflex; DSS, dextran sodium sulfate; GTE, green tea extract; BMI, body mass index; GLP-1, glucagon-like peptide-1; GOS, galactooligosaccharide; RS, resistant; CPT-11, irinotecan; MCT1, monocarboxylate transporter-1; HDL-C, high-density lipoprotein cholesterol.

However, the mechanism by which IMOs suppress T2DM development remains unknown. Most studies support the hypothesis that soluble fibers with viscous properties can reduce postprandial glucose and cholesterol levels by delaying gastric emptying, decreasing the accessibility of digestive enzymes, and slowing the absorption of intestinal nutrients (Davison and Temple, 2018). Delayed gastric emptying contributes to increased satiety, which reduces energy intake and increases fat oxidation, thereby reducing body weight (Slavin, 2005). However, closer examination revealed conflicting findings. IMO feeding increases, rather than decreases, gastrointestinal peristalsis (Lan et al., 2020). However, the fermentability of soluble fibers in the gut results in the production of metabolites, particularly SCFAs, and gut microbiome changes may be involved in this mechanism (Tan et al., 2023). The absorbed SCFAs that are metabolized through the GPR41/43 pathway serve as an energy source, increase satiety, decrease fat accumulation, and improve glucose tolerance by modifying lipid metabolism and insulin sensitivity (Xiong et al., 2022). Consequently, the consumption of soluble fiber reduces T2DM risk and contributes to the expansion of a healthy gut microbiome, thereby reducing inflammation and strengthening the immune system against various diseases, including T2DM (Slavin, 2005). IMOs exhibit prebiotic activity by promoting the growth of beneficial gut microbiota and the production of SCFAs (Chen et al., 2001; Plongbunjong et al., 2017; Lan et al., 2020). In a clinical study, older men who were fed a diet supplemented with 10 g of active IMOs for 30 days showed significantly increased concentrations of fecal acetate and propionate (Chen et al., 2001). In another study, supplementation with 20 g/kg of IMO increased the abundance of *Lactobacillus reuteri* and *Lactobacillus intestinalis* in male rats (Lan et al., 2020). Moreover, an *in vitro* fermentation study showed that IMOs derived from rice starch increased the abundance of *Bifidobacteria* and *Lactobacilli* and decreased the abundance of pathogenic bacteria such as *Clostridia* and *Bacteroides* (Plongbunjong et al., 2017). Song et al. (2022) demonstrated that mammalian α-glucosidases completely hydrolyze IMOs, resulting in the gradual release of glucose. This observation underscores the function of IMOs as slowly digestible substrates that may play a regulatory role in modulating glycemic response and energy supply in the mammalian physiological milieu. However, further studies are needed to elucidate the precise mechanisms underlying this phenomenon.

Metabolic diseases

The association between IMOs and metabolic diseases, particularly obesity- and diabetes-related indicators, has been studied extensively. In mice, the combination of IMOs and lycopene has demonstrated preventive effects against HFD-induced metabolic disorders, including weight gain, adipose tissue fat mobilization, insulin resistance, and nonalcoholic fatty liver disease (NAFLD)-like symptoms. Moreover, this combination modulated hypothalamic orexigenic and anorectic genes, which are appetite-stimulating and suppressing genes, respectively (Singh et al., 2016). In another study, the co-administration of IMOs (1 g/kg) and cranberry extract (200 mg/kg) for 12 weeks showed preventive effects against HFD-induced systemic and tissue inflammation, glucose intolerance, and systemic obesity-associated metabolic changes in the adipose tissue and liver of male Swiss albino mice (Singh et al., 2018). Synbiotics can effectively alleviate obesity-related symptoms; improve glucose clearance and lipid biomarkers; attenuate oxidative stress; prevent leaky gut phenotypes; reduce serum LPS; and modulate genes associated with inflammation, lipid metabolism, and glucose metabolism. A previous study found that the administration of synbiotics restored the histomorphology of adipose tissue, colon, and liver compared with HFD groups (Khanna et al., 2021).

While the precise mechanisms underlying the impact of IMOs in mitigating metabolic diseases remain to be elucidated, existing literature highlights the pivotal role of gut microbiota in this context. According to studies, IMOs contribute to an increased abundance of *Lactobacillus* and *Bifidobacteria* and increased levels of SCFAs, which are associated with reduced systemic inflammation and metabolic endotoxemia and improved ileal and colonic health (Singh et al., 2016). Furthermore, the co-administration of cranberry extract and IMOs in HFD-fed mice increased cecal levels of SCFAs, particularly butyrate, and stimulated the proliferation of butyrate-producing bacteria (Singh et al., 2018). In addition, compared with HFD-fed mice, the administration of synbiotics was associated with an increased Bacteroidetes:Firmicutes ratio in fecal samples; increased abundance of *Lactobacillus* spp., *Akkermansia* spp., *Faecalibacterium* spp., and *Roseburia* spp.; and decreased abundance of Enterobacteriaceae (Khanna et al., 2021).

IBD

IBD, most notably Crohn's disease (CD) and ulcerative colitis (UC), are persistent and chronic conditions characterized by inflammation of the gastrointestinal tract. The increased prevalence of IBD in specific global populations suggests a significant genetic influence on the development of this disease. However, emerging epidemiological patterns also highlight the pivotal role of environmental factors in the pathogenesis of CD and UC (Baumgart and Carding, 2007). Thus, the complex interplay between genetic predisposition and environmental exposure within the microbiome results in a compromised intestinal barrier, which contributes to aberrant

immune activation, and underlies the clinical and endoscopic manifestations observed in patients with IBD (Antoni et al., 2014). Patients with IBD who are exposed to environmental factors experience microbial dysbiosis, which is characterized by a decreased abundance of SCFA-producing bacteria and an increased prevalence of *Proteobacteria* (Vester-Andersen et al., 2019). The downregulation of TJ proteins, mucus layer alterations, and dysfunctional Paneth cell-associated processes are some of the disruptions in intestinal barrier mechanisms (Turner, 2009). In addition, the IBD mucosa exhibits defects in the innate immune system, including reduced levels of colonic macrophages, impaired antigen presentation by dendritic cells, and disturbances in leukocyte migration, leading to an imbalanced activation of different T cell lineages (Antoni et al., 2014).

Animal studies have found that the combination of IMOs and FOS reduced intestinal inflammation in rats by decreasing the histologic score of colitis and IL-1β levels. Although IMOs and FOS induced specific changes in microbiota, they were not directly correlated with colitis reduction, suggesting that their protective effects involve the modulation of microbiota metabolic activity rather than stimulation of specific bacterial groups (Koleva et al., 2014). Colitis is associated with the increased production of branched-chain SCFAs; thus, successful dietary interventions for IBD are characterized by increased carbohydrate fermentation and production of straight-chain SCFAs in the colon (Wong et al., 2006; Koleva et al., 2012). In a previous study, IMOs and a synbiotic mixture comprising IMOs, finger millet arabinoxylan, *Bifidobacterium longum* Bif10, and *Bifidobacterium breve* Bif11 ameliorated dextran sodium sulfate (DSS)-induced UC in BALB/c mice. In mice fed with DSS diet, all dietary interventions improved the disease activity index and immune parameters, promoted the restoration or regeneration of specific intestinal bacterial populations, enhanced SCFA production, strengthened the intestinal barrier, prevented intestinal inflammation, and reduced the colitis histology index score. The synbiotic mixture suppressed TNF-α and lipocalin levels and increased IL-10, IL-22, and cecal SCFA levels (Sharma et al., 2023). Moreover, in a rat water avoidance stress model, IMOs have demonstrated efficacy in alleviating visceral hypersensitivity, a phenomenon that is characterized by increased pain perception in response to internal organ stimuli commonly associated with gastrointestinal disorders such as IBD. IMOs can also reduce the abdominal withdrawal reflex, mitigate ileal epithelial damage, and increase the pain threshold (Wang et al., 2017c).

Persistent inflammation in IBD can lead to intestinal lining changes, which may increase the risk of colorectal cancer development over time. In contrast, colorectal cancer is a broader term that includes several cancers that can originate in the colon or rectum. Although not all colorectal cancers are directly related to IBD, individuals with a history of IBD, especially those with extensive and prolonged inflammation, have a higher risk of developing colorectal cancer compared with the general population. Rats fed with rice-derived IMOs (1.5 g/kg) for three times a week for 19 weeks showed decreased DSS-induced colonic polyps and histological changes and increased intestinal barrier function (Plongbunjong et al., 2019). Moreover, feeding rats with 5% IMOs for 12 weeks reduced the incidence of early colon cancer induced by 1,2-dimethylhydrazine. IMOs increase the inflammatory response and the intestinal microenvironment to reduce the development of colon cancer (Chen et al., 2022). In a previous study, a DF mixture comprising IMOs, resistant starch, FOS, and inulin decreased the toxicity of irinotecan and increased the levels of cecal butyrate, bacterial butyryl-CoA gene, and monocarboxylate transporter-1 in rats with Ward colon carcinoma (Lin et al., 2014). According to Plongbunjong et al. (2019), IMOs can enhance colonic peristalsis by inducing the production of SCFAs, thereby accelerating the transit of food through the colon and reducing the duration of exposure to carcinogens. Moreover, IMOs may play a role in regulating intestinal dysbiosis by enhancing the integrity of TJs and promoting the growth of *Akkermansia muciniphila*. Consequently, this mechanism may contribute to the prevention of intestinal leakage, alleviation of mucosal inflammation, modulation of immune responses, and potential reduction of colon cancer risk.

Dyslipidemia

Dyslipidemia is characterized by an imbalance in the levels of low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides. Elevated levels of LDL cholesterol and triglycerides and reduced levels of HDL cholesterol are typical manifestations of hyperlipidemia (Ballantyne et al., 2000). This condition is associated with gastrointestinal function, particularly in the liver and digestive system. NAFLD, which is characterized by excessive lipid accumulation in the liver, is often associated with hyperlipidemia, thereby affecting liver function (Pouwels et al., 2022). Lipids, including dietary fats, are absorbed in the small intestine after digestion. However, hyperlipidemia can affect this process of absorption, potentially leading to elevated levels of circulating cholesterol and triglycerides (Ko et al., 2020).

A clinical trial showed that the daily consumption of IMO-fortified cookies over 4 weeks reduced the levels of cholesterol and triglycerides and decreased the cardiac risk ratio scores (Sunarti et al., 2022). Similarly, in another clinical trial, treatment with 30 g of IMOs for 4 weeks significantly reduced total cholesterol and triglyc-

eride levels in patients requiring hemodialysis (Wang et al., 2001). Furthermore, an animal study showed that the administration of a synbiotic combination of IMOs and *Latilactobacillus curvatus* MS2 for 5 weeks reduced blood cholesterol levels in healthy mice (Kim et al., 2021). Hyperlipidemia often coexists with metabolic syndrome, which refers to a cluster of conditions that includes abdominal obesity, insulin resistance, hypertension, and elevated blood glucose levels. Metabolic syndrome can contribute to gastrointestinal complications, including NAFLD and dysbiosis (Fonseca, 2005). As mentioned previously, IMOs have shown efficacy in reducing obesity- and diabetes-related symptoms and subsequently preventing NAFLD-like symptoms (Bharti et al., 2015; Singh et al., 2017b; Khanna et al., 2021).

Although the literature consistently supports the idea that IMOs can control hyperlipidemia, their underlying mechanisms remain unknown. Based on current knowledge, DF uses five key mechanisms (i.e., low energy, bulking, viscosity, binding capacity, and fermentation) to counteract hyperlipidemia. Insoluble DF contributes to bulking, whereas soluble DF has a significant water-holding capacity, resulting in increased stool weight and nutrient dilution. The intrinsic properties of DF influence bulking and viscosity, prolong satiety, and reduce food intake, thereby facilitating lipid reduction. Moreover, DF binds to bile, inhibits reabsorption in the small intestine, and stimulates the synthesis of new bile acids from cholesterol, thereby lowering blood cholesterol levels. The fermentation process produces SCFAs, such as propionate and acetate, which play a complex role in lipid metabolism by inducing satiety and inhibiting cholesterol synthesis (Nie and Luo, 2021). In summary, DF may play a beneficial role in suppressing hyperlipidemia through multiple mechanisms. However, further studies are needed to clarify the mechanism by which IMOs suppress hyperlipidemia.

Constipation

Constipation is a symptom or clinical condition that is characterized by difficult and infrequent bowel movements. It usually occurs three times or less per week and can be caused by several factors, including metabolic disorders (Rao et al., 2016). Therefore, the effective management of constipation is important in metabolic disorders such as diabetes and obesity as it promotes optimal gut health, aids nutrient absorption, and mitigates the factors inherent to these conditions.

Several clinical trials have systematically investigated the associations between IMOs and constipation. A previous study found that 30 days of IMO supplementation resulted in a twofold increase in defecation frequency, wet stool volume, and dry stool weight in a group of healthy participants (Chen et al., 2001). Similarly, constipated patients who received 10 g/d of IMOs for 4 weeks experienced an increase in defecation frequency and output of wet and dry stools. Moreover, the fecal acetate and propionate levels of participants were elevated (Yen et al., 2011). Animal studies have elucidated the potential mechanisms underlying the efficacy of IMOs in relieving constipation. In a previous study, the co-administration of IMOs, FOS, and galactooligosaccharides effectively treated loperamide-induced constipation in mice by increasing fecal water content and small intestine transit rate and modulating gut microbiota (Wang et al., 2017a, 2017b). Another study suggested that the modulation of gastrointestinal motility-related hormones is involved in the alleviation of constipation. The combined administration of inulin and IMOs improved diphenoxylate-induced constipation in rats, as evidenced by higher serum levels of adrenocorticotropic hormone, motilin, and substance P and lower levels of corticosterone, vasoactive intestinal peptide, and calcitonin gene-related peptide compared with untreated rats (Lan et al., 2020). These findings highlight the multifaceted effects of IMOs on constipation, including their clinical efficacy, gut microbiota modulation, and hormonal regulatory mechanisms.

CHALLENGES AND FUTURE PERSPECTIVES

Accumulating evidence suggests that IMOs have potential clinical application as a broad therapeutic and preventive strategy for several gastrointestinal diseases. Moreover, IMOs may serve as a diverse intervention strategy that fills critical gaps in current therapeutic approaches, particularly in the context of obesity, diabetes mellitus, IBD, hyperlipidemia, and constipation. Because of their effects in modulating gut microbiota, immune response, and metabolic parameters, they may play a promising role in promoting gut health, providing a multifaceted approach to addressing the complex nature of gastrointestinal disorders. The compelling results from animal and clinical studies, which demonstrate the efficacy of IMOs in alleviating disease symptoms and improving overall gastrointestinal well-being, provide a solid foundation for further exploration of IMOs in clinical settings and in the food industry.

While existing literature provides promising insights into the therapeutic potential of IMOs, there are specific challenges and limitations that need to be considered. More comprehensive mechanistic studies are needed to elucidate the precise pathways through which IMOs exert their effects. In addition, future studies should prioritize in addressing knowledge gaps regarding the specific mechanisms underlying the effects of IMOs on diseases. The key findings from various studies converge on

the pivotal role of IMOs in maintaining intestinal barrier function and ameliorating gastrointestinal disorders. The central mechanisms contributing to the observed therapeutic effects include the modulation of gut microbiota, SCFA production, and regulation of metabolic parameters, revealing a comprehensive understanding of the molecular and physiological aspects of the impact of IMOs on gastrointestinal health (Fig. 4). The implications of these findings extend beyond disease-specific contexts and suggest a broader impact on systemic health and homeostasis. The potential of IMOs to attenuate inflammation, improve metabolic profiles, and prevent complications associated with obesity and diabetes underscores their importance in integrative approaches to gastrointestinal health.

In conclusion, the compelling evidence discussed in this review suggests that IMOs are promising candidates for maintaining intestinal barrier function and treating gastrointestinal diseases. The diverse beneficial effects of IMOs underscore their versatility as a promising intervention strategy for treating obesity, diabetes mellitus, IBD, and hyperlipidemia. However, considering the gut microbiome's complexity and the bidirectional relationship between metabolic diseases and gastrointestinal disorders, further well-designed clinical trials and mechanistic studies are required. As researchers have delved deeper into understanding the complex interactions of IMOs within the gastrointestinal milieu, the potential for refining clinical applications and advancing personalized interventions has become increasingly apparent. The journey toward exploring the full therapeutic potential of IMOs in gastrointestinal health continues, promising a future wherein these oligosaccharides may play pivotal roles in optimizing human health.

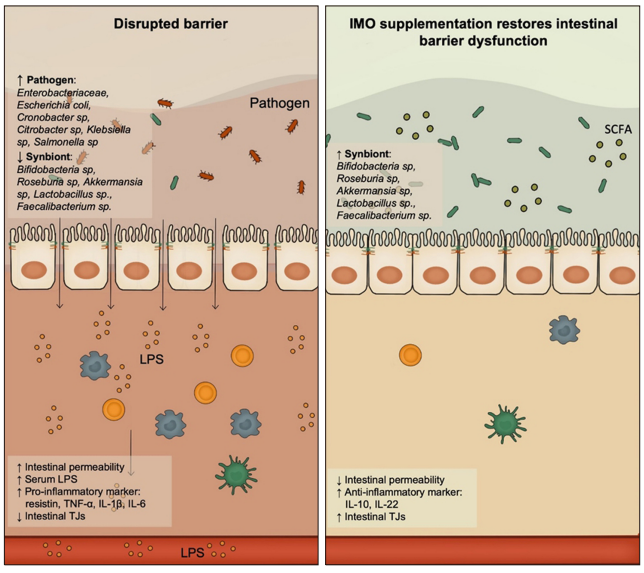

Fig. 4. Supplementation with isomaltooligosaccharides (IMOs) restores intestinal barrier integrity. Intestinal barrier disruption leads to disordered tight junctions (TJs), allowing the translocation of bacteria or bacterial products, such as lipopolysaccharide (LPS), into the lamina propria. This process triggers an immune response and increases the levels of proinflammatory cytokines. LPS entering the systemic circulation results in heightened systemic inflammation, resulting in intestinal dysbiosis and contributing to the development of various diseases. Supplementation with IMO normalizes intestinal microbiota composition, reduces intestinal permeability, enhances short-chain fatty acid (SCFA) production, and strengthens intestinal TJs. Collectively, these effects attenuate gastrointestinal-related diseases. TNF-α, tumor necrosis factor-α; IL, interleukin.

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The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept and design: DMR. Analysis and interpretation: DMR, TS. Data collection: DMR, WX, TS. Writing the article: DMR, WX, TS. Critical revision of the article: DMR, TS. Final approval of the article: all authors. Overall responsibility: DMR, WX, TS.

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