Functional Oligosaccharides: The Preparation Methods and Therapy Mechanism Related to Inflammatory Bowel Disease

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Abstract: The incidence of inflammatory bowel disease has increased substantially in recent decades. Some studies have found that oligosaccharides have anti-inflammatory, antioxidant and other physiological activities. This article summarizes the research progress in the preparation of oligosaccharides and the treatment of colitis in recent years. The preparation methods of oligosaccharides mainly focus on enzymatic degradation and acid degradation. In addition, this article summarized the mechanisms of oligosaccharides in IBD, including the regulation of inflammatory factors, regulation of oxidative stress, regulation of intestinal microbes, and influence on inflammatory signal pathways. In summary, oligosaccharides have the potential to treat inflammatory bowel disease, which provides new ideas for the clinical treatment of IBD.

1 INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC) are two dominant forms of Inflammatory bowel disease (IBD). In UC, the inflammatory process affects only the mucosa and extends continuously from the rectum. The typical symptom of colitis is bloody diarrhea, which may be accompanied by abdominal pain or fever(Besednova, Zaporozhets et al. (2020). The prevalence of IBD is increasing every year worldwide. Epidemiological studies show that in North America more than 1.2 million people and 2 million people in Europe suffer from IBD, and it exceeds 0.3% of the population in many countries in Oceania, North America and Europe. It is predicted that in 2025, the total number of patients with IBD in the world would be equal to the total population of Western countries, and the treatment of IBD is imminent (Zhang, Huang et al. (2019).

From the current point of view, IBD is thought to be the result of the interaction of a number of factors. NF-κB is an important signaling pathway in inflammatory response, regulation of inflammatory cytokine expression. Activation by NF-κB induces the production of immune mediators. In intestinal immunity in IBD, cytokines are important mediators between activated cells and non-immune cells.

The intestinal barrier facilitates the separation of substances and prevents the invasion of pathogenic antigens(Dong, Li et al. 2020). Intestinal microbe is a kind of microorganisms that live on the surface of intestinal mucosa and intestinal lumen for a long time. Patients with colitis were found to have less diversity and a change in their gut flora composition. Intestinal microorganisms can induce regulatory and protective immune responses(Belkaid and Harrison 2017).

Studies have shown that reactive oxygen and nitrogen are significantly associated with

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inflammatory bowel disease as they regulate the associated oxidative stress and redox(Korenaga, Takesue et al. 2002). Oxidative stress in IBD not only produces excessive ROS/RNS, damages cell lipids and other components, but also leads to mucosal damage, dysfunction and inflammation, directly leading to intestinal injury, and redox signaling disorders, promoting the overexpression of inflammatory factors and adhesion molecules(Grisham and Granger 1988).

Currently, the drugs used in clinical treatment of IBD include glucocorticoids, immunosuppressants and biological agents. The main purpose is to relieve the acute onset of inflammation, but personalized treatment plans are still adopted in clinical practice(Ramos de Mattos, Gracindo Garcia et al. 2015). However, their use is often harmful and has side effects. Amino Salicylates can cause patients to experience nausea and vomiting or other intestinal side effects. Glucocorticoids can lead to osteoporosis, hypertension, obesity, type 2 diabetes. Glucocorticoids should not be used as long-term treatment(Ramos de Mattos, Gracindo Garcia et al. 2015). Methotrexate in the treatment of IBD showed a good anti-inflammatory effect, but nausea, vomiting, and certain renal toxicity. Some heart conditions, allergic or infectious complications and skin lesions are side effects of anti-TNF-alpha drugs(Nielsen 2014).

Because of the severe side effects of traditional drug therapy, an important way to improve the clinical symptoms of IBD is to find new sources of drugs. Oligosaccharides are attracting more and more attention as prebiotics functional food ingredients. Methods of obtaining include extraction from various biological sources, or obtaining by enzymatic and acid digestion of polysaccharides, or synthesis by enzymatic transfer reactions using simple oligosaccharides(Rastall 2010). Recently, other physiological functions of oligosaccharides have been found. For example, short-chain fatty acids, a metabolite that provides energy to cells in the intestine, can also accelerate cell renewal(Courtois 2009).

Many oligosaccharides in recent studies, including fructo-oligosaccharides(Winkler, Butler et al. 2007) and lacto-oligosaccharides(Algieri, Rodriguez-Nogales et al. 2014), can alleviate damage to the intestinal barrier. This article summarizes the possibility of using oligosaccharides extracted from natural substances or degraded by polysaccharides as drugs or functional food products to prevent and treat inflammatory bowel disease.

2 TYPES AND PREPARATION OF OLIGOSACCHARIDES

2.1 Oligosaccharides Derived from Plants

2.1.1 Oligogalacturonic Acid

Oligogalacturonic acid (OGA) is a polymer consisting of 2~10 galacturonic acids attached by α-1, 4-glycosidic bond(Huang, Huang et al. 2018). Oligomeric isomalturonic acid esters (OGA) from citrus pectin hydrolysed by microbial pectinases can be used as food emulsifiers and have shown antioxidant capacity and the ability to inhibit lipid oxidation., and had bactericidal effect on foodborne pathogens(Huang, Lu et al. 2011). The literature reports that OGA fragments can prevent the multiplication of human cancer cells (Wu, Li et al. 2014).

2.1.2 Xylo-oligosaccharides

Xyloglucan (XOS) is a common oligosaccharide consisting of xylose(Seesuriyachan, Kawee-ai et al. 2017). XOS is mainly obtained by physical, chemical and enzymatic degradation of xylan in corn cob, bagasse and other agricultural Enzymatic method is the main method for industrial production of xylo-oligosaccharide due to its mild reaction conditions, easy control, high conversion rate and environmental friendliness(Chapla, Pandit et al. 2012). Adding XOS to the diet to show the effect of XOS probiotics(Karlsson, Schmitz et al. 2018). They can significantly increase beneficial intestinal bacteria and thus relieving the damage to the intestinal tract(Christensen, Licht et al. 2014).

2.1.3 Fructose-oligosaccharides

FOS is an indigestible carbohydrate, chemically composed mainly of a fructose unit chain and a glucose unit connected by the glycoside bond beta -(2-1) (Table 1). Their structure is formed by the repeated combination of disaccharides such as sucrose(Flores-Maltos, Mussatto et al. 2016). A few articles have proposed new bioprocesses that can integrate the production of inulin endosynthesis, FOS fermentation and impurity removal into a single reactor, left-handed disaccharide, which can significantly improve the yield of FOS(Wang, Li et al. 2016). Fructo-oligosaccharides have low calorific value, help intestinal absorption of ions, reduce lipid and cholesterol levels, and stimulate Bifidobacteria.

Because of its potential health benefits, purified linear fructose oligomers are added to a variety of foods(Bali, Panesar et al. 2015).

Table 1: Types and molecular structure of functional oligosaccharides.

Oligosaccharide	Structure
Xylooligosaccharides (XOS)	(Xylβ-1,4)n Xyl; n =1 ～ 4
Fructooligosaccharides (FOS)	Glcα-1,2(Fruβ-1,2/β-1,6)n Fru; n =1 ～ 3
Isomaltooligosaccharides (IMO)	Glcα-1,6 Glcα-1,6 Glc; Glcα-1,4 Glcα-1,6 Glc
lactosucrose	Galβ-1,4Glcα-1,2Fru
lactulose	Galβ-1,4Fru

2.1.4 Oligomeric Mannose

Mannan oligosaccharide (MOS) consists of mannose residue fragments attached by beta-1,4-mannose, and is further characterized as galactomannan, galactomannan, and galactomannan. They are usually found in the endosperm of legumes(Singh, Singh et al. 2018). At present, it mainly adopts physical method, chemical method and enzyme method MOS was prepared by degradation of mannan(Malgas, van Dyk et al. 2015).

2.1.5 Oligomeric Maltose

Isomalto Oligosides (IMO) are functional oligosaccharides with a degree of 2-10, consisting of glycosylated units with α-1,6-glucosidic bonds(Zhang, Wang et al. 2019). In general, IMO is produced by the conversion of starch hydrolysates by α -glucosidase in conventional industrial processes(Huang, Li et al. 2018). IMO is a natural functional oligosaccharide that regulates the intestinal flora. For example, after using IMO, the levels of *Bifidobacteria* and *Lactobacilli* are increased(Shi, Hou et al. 2016).

2.1.6 Alginate Oligosaccharides

Alginic acid consisting of alpha-1, 4-glycosidic bonds between manuronic acid and guluronic acid. AOS is the depolymerization of alginate by enzymolysis (Table 2), acid hydrolysis and oxidative degradation. Alginate lyase is an important tool enzyme in the production of AOS(Zhu, Ni et al. 2021). Alginate oligosaccharide treatment can regulate intestinal microbial community and significantly reduce the expression of inflammatory markers, which has good anti-inflammatory effect(Wang, Li et al. 2020).

2.1.7 Agarose Oligosaccharides

Agarose oligosaccharides (AGOs) are produced by the hydrolysis of agarose. The structure and biological activity of AGO have been extensively studied(Chen and Yan 2005). AGOs has repeated agarose units consisting of non-reducing d-galactose and reducing 3, 6-dehydrogen-L-galactose (Higashimura, Naito et al. 2014).

2.2 Oligosaccharides from Animals

2.2.1 Galactose Oligomeric

Galactosyl oligosaccharides (GOS) are formed by 1 to 10 galactosyl units connected to a terminal glucose(Dai, Lyu et al. 2017), or formed from galactose-based units only. β-galactosidase can catalyze galactose acylation to produce galactose oligosaccharides(You, Zhang et al. 2017). GOS reduces the incidence of intestinal diseases and a significant increase in the SCFAs concentration was found. One study found that GOS has significant potential to improve intestinal health and body immunity(Wang, Zhu et al. 2020).

2.2.2 Oligo-chitosan

Chitosan is a polysaccharide with varying degrees of n-acetylation. It is obtained from the degradation of chitosan and is the n-deacetylated form of chitin. Chitosan has been prepared by various enzymatic and acid hydrolysis methods. In contrast, COS, the hydrolysis product of chitosan, consisting of beta-1,4-glycosidic bonds linking 2-amino-2-deoxy-D-glucopyranose. The short chain of D-glucosamine units in COS and the small number of free amino groups make it more soluble under physiological conditions(Lodhi, Kim et al. 2014).

3 ANTI - INFLAMMATORY EFFECT AND MECHANISM OF OLIGOSACCHARIDES

3.1 Effects on Cytokines

Inflammatory bowel disease (IBDs) is a debilitating condition in which chronic inflammation leads to intestinal damage. The cytokines produced by the immune cells are involved in colitis due to the large number of immune cells that infiltrate the colon(Francescone, Hou et al. 2015). Tumour

necrosis factor (TNF) has been reported to influence cell proliferation, differentiation and apoptosis, and has also been associated with inflammation and cancer development(Liu 2005). Different target cells are triggered by Il-6, to affect pro-inflammatory functions(Kim, Keku et al. 2008). Studies have shown that Il-1 β indirectly activates endothelial cells and angiogenesis by regulating pro-inflammatory and pro-angiogenic molecules(Carmi, Dotan et al. 2013). Ferulic acid oligosaccharides can significant reduction IL-23 and IL-6 in dendritic cells (DCs) in vivo and in vitro, enhance the secretion of TGF-β1, and regulate colitis in mice(Xia, Zhu et al. 2019). Glucosamine oligomers reduced pro-inflammatory factors in mouse serum and effectively alleviated clinical signs of colitis in mice(Azuma, Osaki et al. 2015).

3.2 Effects on Inflammatory Signaling Pathways

3.2.1 Effects on NF-κB Signaling Pathway

One way in which gene expression of inflammatory cytokines is elevated is through NF-κB signaling pathway(Atreya, Atreya et al. 2008). In the DSS-induced mouse colitis model, NF -κB p65 protein expression was suppressed because of galactose intervention(Dai, Feng et al. 2018). Sucrose (LS) significantly reduced the levels of TLR-2 protein and NF-κB pathway protein. Therefore, LS has potential as a nutritional intervention for colitis(Zhou, Ruan et al. 2015).

3.2.2 Influence on MAPK Signaling Pathway

A variety of serine and threonine kinases make up the mitogen-activated protein kinase (MAPK)(Wang, Pan et al. 2019). It was found that fructose-oligosaccharides can down-regulate the expressions of Jun and JNK proteins in d-galactose induced rat aging model, suggesting that fructose-oligosaccharides may improve lung inflammation and fibrosis in aging rats by inhibiting the activation of JNK/Jun pathway, and has obvious anti-inflammatory effect(Yeh, Wu et al. 2014).

3.3 Regulation of Oxidative Stress

Oxidative stress injury was significantly correlated with the onset and severity of IBD(Rezaie, Parker et al. 2007). Infiltrates of immune cells, especially neutrophils, are histologic features of IBD. The excessive production of ROS in host tissues exacerbates oxidative damage and may damage the mucosa of the intestine. Neutrophil-myeloperoxidase (MPO), a granulocyte enzyme, increases the levels of more potent ROS. Biomarkers of intestinal mucosal damage appear significantly increased in patients (Chami, Martin et al. 2018). Lactulose can prevent and suppress intestinal inflammation, which can significantly reduce myeloperoxidase activity, TNF-α and leucotriene B4 concentration in colon(Algieri, Rodriguez-Nogales et al. 2014). Hame oxygenase-1 (HO-1) has a significant antioxidant effect. A mouse macrophage inflammation model (RAW264.7 cells) was constructed with LPS and HO-1 expression was upregulated by chitosan (COS) intervention(Hyung, Ahn et al. 2016).

Table 2: Common preparation methods of oligosaccharides.

Polysaccharide	Method	Oligosaccharide	Mechanism
Xylan	Xylanase	Xylo-oligosaccharides	The endonuclease cleaves the xylan chain at specific cleavage sites to produce different oligosaccharides (Karlsson, Schmitz et al. 2018).
Pectin	Polygalacturonase	Oligogalacturonic acid	Polygalacturonase catalyzes the cleavage of pectin molecule poly-α-(1,4)-polygalacturonic acid and participates in the degradation of pectin(Li, Coffman et al. 2015).
Mannan	Mannanase	Mannose oligosaccharides	β-Mannanase randomly cleaves the backbone to produce shorter beta-1,4-mannan oligomers. It is very important in the preparation of mannans(Liu, Ning et al. 2020).
Sucrose	α-amylase、α-glucosidase	Isomalt oligosaccharide	The receptor reaction catalyzed by glucose glucosidase can generate branched imo or glucose oligosaccharides (GOSs) from sucrose(Goffin, Delzenne et al. 2011).

Alginate	Alginate lyase	Alginate oligosaccharide	Glycosidic bonds within alginate polymers are cleaved by alginate lyase to produce unsaturated oligosaccharides, while exonuclease can degrade the oligosaccharides again to become monomers(Zhu, Ni et al. 2021).
Agar	Agarase	Agaro oligosaccharides	Breakage of the alpha-1,3-glycosidic bond of agarose by alpha-agarase(Jiang, Cheng et al. 2021).
Lactose	β-galactosidase	Galacto oligosaccharide	Galacto oligosaccharides are produced by the conversion of lactose through glycosylation and can be catalyzed by many enzymes. It includes two processes: glycosylation and deglycosylation(Gao, Wu et al. 2019).
Chitosan	Chitosanase	Chitosan-oligosaccharide	Chitosanase can hydrolyze the bata-(1-4)-sugar-silicic acid bond of chitosan(Liu, Jiang et al. 2009).

3.4 Repair of the Intestinal Barrier

There are many factors that affect intestinal health and the intestinal barrier is a very significant part. The composition of the intestinal barrier includes the mucus layer and the intestinal epithelium. The mucosal barrier consists of gel formation and transmembrane mucin. It prevents the entry of pathogens. Therefore, the intestinal barrier is implicated in IBD(Johansson, Sjovall et al. 2013). It was found that in mice with acetic acid-induced colitis, COS infusion reduced the inflammatory response and restored intestinal barrier damage(Yousef, Pichyangkura et al. 2012). Interestingly, another study showed that COS can promote T84 cell tight-knit assembly(Muanprasat, Wongkrasant et al. 2015).

3.5 Influence on Intestine Flora

Intestinal microbe is a kind of microorganisms that live on the surface of intestinal mucosa and intestinal lumen for a long time. It was found that altered intestinal flora diversity in UC patients, and the group was transformed(Frank, Amand et al. 2007). In the colon, AG and FOS exhibit different fermentation properties (FOS in the proximal end, AG in the distal end). These two fibers can repair the intestinal barrier and effectively reduce inflammation(Daguet, Pinheiro et al. 2016). Konjac oligosaccharide can significantly relieves inflammatory symptoms of experimental acute colitis induced by TNBS, and improve intestinal flora structure. Therefore, the mechanism is at least involved in the improvement of intestinal microflora structure and anti-inflammatory effect(Liu, Li et al. 2016).

4 CONCLUSIONS

In recent decades, the research on oligosaccharides has been the focus of research at home and abroad. The preparation methods of functional oligosaccharides mainly include chemical method, enzymatic method and physical method. Among them, enzymatic preparation is green, efficient, and the most promising method for application. Oligosaccharides have a positive impact on the relief of other intestinal disorders, but they are effective in the intervention of oligosaccharides. With further research into the mechanism of action of oligosaccharides in reducing inflammation, high-efficiency and non-toxic oligosaccharide anti-inflammatory drugs will be screened.

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