Functional Oligosaccharides in the Treatment of Inflammatory Bowel Disease

Ping Zhang*, Xiuyu Ji, Le Su, Qiulin Yue, Chen Zhao, Song Zhang, Xin Sun, Lin Zhao

State Key Laboratory of Biobased Material and Green Papermaking, School of Bioengineering, Qilu University of Technology, Shandong Academy of Sciences, Jinan, 250353, China

*Corresponding Author

Keywords: Ibd, Intestinal flora, Functional oligosaccharides

Abstract: Nowadays, a growing number of people suffer from enteritis. Good treatments are needed to relieve the intestinal illness. The medicines used for enteritis are in limited efficacy with side effects. More and more research has reported that functional oligosaccharides have numerous health benefits, including regulating the immune response of body and alleviating the allergic inflammatory, stimulate the growth of intestinal flora and inhibit the reproduction of harmful microorganisms. Therefore, Functional oligosaccharides have become a hot spot in the treatment of enteritis. In this review, we addressed the researches of functional oligosaccharide in the treatment of enteritis.

1. Introduction

Functional oligosaccharides are small complexes composed of 2-10 monosaccharide units connected bonds (Rastall, 2010). They are intermediate between monosaccharides and highly polymerized polysaccharides. It has good physical and chemical properties such as low heat, stability, safety and no side effect (Varki, 1993). A large number of studies have shown that oligosaccharides can not only improve the digestive tract microflora of animals, promote the growth of beneficial bacteria and inhibit the reproduction of harmful bacteria (Muanprasat and Chatsudthipong, 2017). It could be used as carbohaydrate to promote the probiotic reproduction. Common functional oligosaccharides in recent study mainly included Galacto-oligosaccharide (GOS), Konjac-oligosaccharide (KOS), chitooligosaccharides (COS), Fructo-oligosaccharides (FOS), and manno-oligosaccharides (MOS).

Inflammatory Bowel Disease (IBD) is a group of chronic, recurrent and inflammatory disease, mainly including Crohn's disease (CD) and ulcerative colitis (UC). IBD originated from western developed countries, the incidence and prevalence of IBD have been on the rise around the word, and it has become a global disease (Kaplan, 2015). IBD is a recurrent epidemic disease that could seriously affect patient's quality of life. The colon and ileum likely are most likely to be affected by IBD, which can lead to colitis, abdominal pain, diarrhea, rectal bleeding, and weight loss(Gearry, 2016). Aminosalicylates, immunosuppressants and hormones are commonly used for IBD. These traditional drugs on IBD are relatively limited and come with more side effects. Therefore, safety and effective method are needed to cure IBD. With the deepening of large number of researches, functional oligosaccharide therapy for IBD has been proposed gradually (Tozlu *et al.*, 2021). In this review, we addressed the use of functional oligosaccharides would provide an effective method to improve the symptom.

2. Inflammatory Bowel Disease (Ibd)

Inflammatory bowel disease is one of the most common diseases of the digestive system. IBD is combined with Ulcerative colitis (UC) and Crohn's disease (CD)(Wehkamp *et al.*, 2016). UC is characterized by a continuous inflammatory response in the mucosa and sub mucosa of the colon, which begins in the rectum and spreads throughout the colon (Flynn and Eisenstein, 2019). CD has a wider range of lesions, involving the whole digestive tract. The primary manifestations of UC are bloody stools accompanied by diarrhea and abdominal pain (Ordás *et al.*, 2012). The main

  DOI: 10.25236/icbcme.2021.034

symptoms of CD are intestinal obstruction and diarrhea (Fig.1). At present, the incidence of rate is increasing among young people in china. It has gradually become a serious digestive tract disease affecting the health of Chinese people (Kaplan and Ng, 2017). Although the etiology of IBD is not yet clear, its formation is influenced by environmental, genetic, immune and intestinal microbiome factors (Lavelle and Sokol, 2020). The mainly treatments are aminosalicylates, immunosuppressants and hormones (Pithadia and Jain, 2011). Mesalazine is a kind of aminosalicylic, mainly regulating the local arachidonic acid metabolism of intestinal mucosa, scavenging oxygen free radicals, therapy reducing intestinal inflammation, which could be used for mild to moderate UC and CD (Nielsen *et al.*, 2014). Hormone and immunosuppressants could control the development of disease in the short period term (Sairenji *et al.*, 2017). More and more studies have shown that many functional oligosaccharides could regulate the intestinal flora and have anti-inflammatory effects. The high safety of functional oligosaccharides is expected to be an important strategy for the prevention adjuvant treatment of IBD (Mentella *et al.*, 2020).

3. Functional Oligosaccharides

Functional oligosaccharides are non-starch polysaccharides of medium molecular, which could be produced by incomplete hydrolysis of macromolecule non-starch polysaccharides with corresponding enzymes. It could selectively promote the proliferation of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus* and inhibit the colonization of harmful bacterium such as *Escherichia coli* in the posterior segment of intestinal tract, thus optimizing the intestinal microecosystem (Astó *et al.*, 2019). Commercial functional oligosaccharides include Galacto-oligosaccharide (GOS), Konjac-oligosaccharide (KOS), chitooligosaccharides (COS), Fructo-oligosaccharides (FOS), and Manno-oligosaccharides (MOS) (Fig.2).

4. Functional Oligosaccharide Relieve Ibd

4.1 Functional Oligosaccharide Regulate the Intestinal Flora

Intestinal flora imbalance is one of the important factors in the occurrence and development of IBD. In IBD patients, the diversity of intestinal flora decreased. However, the total number of pathogenic intestinal bacteria increased, such as *Escherichia coli* and *Bacteroidetes*. The proportion of beneficial bacteria such as Bifidobacterium and Lactobacillus decreased significantly and the total number is lower than that of pathogenic bacteria. The results of the study show that GOS could promote the growth of *Bifidobacteria* and *Lactobacillus* in the ascending colon and transverse colon (Yazbeck *et al.*, 2019). FOS could stimulate the number of Bifidobacteria by increasing SCFs and lowing PH in intestinal. In addition, the proportion of Bifidobacteria in the gut could be increased in the combination of FOS with GOS (Pan *et al.*, 2018). Moreover, GOS could improve the abundance of intestinal flora in patients (Tingirikari, 2018). Besides, functional oligosaccharides promote the colonization of probiotic in the intestinal by producing bacteriocins, antimicrobial substances and inhibiting the growth of pathogenic bacteria.

4.2 Functional Oligosaccharide Improve Intestinal Barrier Function

Intestinal mucosal inflammation is associated with impaired intestinal barrier function in IBD patients. Functional oligosaccharides could improve intestinal barrier function in patients with IBD through mechanisms. COS could directly affect epithelial cells, restore the integrity of the intestinal mucosal barrier in TLR4/NF-κB signaling pathway (Shi *et al.*, 2019). And FOS could correct the decrease of transmembrane resistance, reduce interferon gamma signal and repair epithelial barrier defect (Johnson-Henry *et al.*, 2014, Tu *et al.*, 2016). It is speculated that FOS is a therapeutic for restoring intestinal barrier function.

4.3 Functional Oligosaccharide Reduce Mucosal Inflammation

Functional oligosaccharide could suppress intestinal disease and restore the function of intestinal barrier by promoting T lymphocyte differentiation and secrete cytokine IL-2, IFN-γ, IL-10, TGF-β

to participate in cellular and humoral immunity. According to the report of *Wan Jin et*, Alginate oligosaccharide (AOS) could alleviate inflammatory injury in intestinal epithelial cells by decreased the expression levels of cytokine (interleukin-6 and TNF-α) (Wan *et al.*, 2020). Besides, the levels of inducible nitric oxide synthase (iNOS), TNF-α and interleukin-1β are decreased in UC colitis model under Konjac oligosaccharide (KOS) treatment (Liu *et al.*, 2016). These results indicate that Functional oligosaccharide could be a useful method to mitigate inflammatory disease.

5. Future Prospects

Functional oligosaccharide has great potential in the treatment of IBD. It plays an important role in regulating intestinal flora balance, enhancing intestinal mucosal barrier function, and alleviates intestinal mucosal immunity. The discovery of the therapeutic effect of functional oligosaccharide is a breakthrough in the field of clinic treatment of IBD. Targeted clinic studies should be carried out in the future to explore the mechanism and best dosage of specific functional oligosaccharide for patients with IBD.

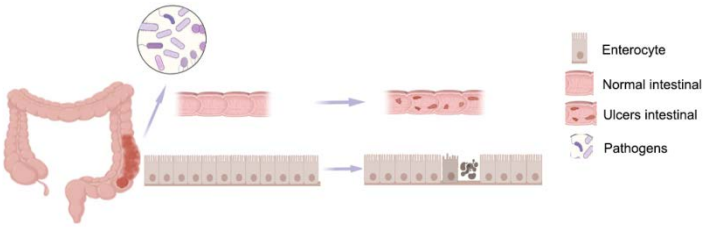

Fig.1 Pathogenesis of Inflammatory Bowel Disease.

Clinical Condition	Treatment	Result	*Refs.*
Ulcerative colitis	Fructo-oligosaccharide(FOS)	Altered the response of mice DSS-induced diarrhea.	Haruka Goto *et al.* 2010. Petya T Koleva *et al.* 2012.
Ulcerative colitis	Galacto oligosaccharides(GOS)	GOS against UC by inhibiting NF-κB pathway.	Roger Yazbeck *et al.* 2019. Jung Il Kwon *et al.*2018.
Ulcerative colitis	Mannooligosaccharides(MOS)	Repaire damaged small intestinal mucosa.	Roger Yazbeck *et al.* 2019. En Yu *et al.*2020.
Ulcerative colitis	Soybean oligosaccharides(SBOS)	Promote diversity of intestinal flora to improve the symptom of UC.	Ma Yan *et al.*2020.
IBD	Alginate oligosaccharide(AOS)	Alleviate TNF-α-induced inflammatory injury in intestinal epithelial cells	Wan Jin *et al.2020.*
Ulcerative colitis	Chitosan oligosaccharide (COS)	Alleviate DSS-induced inflammatory disease in IPEC-J2 cells.	Xianghong Ju *et al.* 2019. Chatchai Muanprasat at al.2015.

Fig.2 Summary of Oligosaccharide Effect in Ibd Studies.

6. Conclusion

IBD is epidemic and important disease that is closely related to the imbalance. A large number of studies have proved that FOS, GOS, COS, KOS and MOS have good effects in the cure of IBD. Compared with other traditional drugs, functional oligosaccharide has the advantage of safety and effective. It has made significantly progress in promoting intestinal health. More research is needed to explore the effects of functional oligosaccharide in the treatment of IBD.

References

[1] Astó, E., I. Méndez, S. Audivert, A. Farran-Codina, and J. Espadaler. 2019. The Efficacy of Probiotics, Prebiotic Inulin-Type Fructans, and Synbiotics in Human Ulcerative Colitis: A Systematic Review and Meta-Analysis. Nutrients 11.

[2] Flynn, S., and S. Eisenstein. 2019. Inflammatory Bowel Disease Presentation and Diagnosis. Surg Clin North Am 99:1051-1062.

[3] Gearry, R. B. 2016. IBD and Environment: Are There Differences between East and West. Digestive diseases (Basel, Switzerland) 34:84-89.

[4] Johnson-Henry, K. C., L. J. Pinnell, A. M. Waskow, T. Irrazabal, A. Martin, M. Hausner, and P. M. Sherman. 2014. Short-chain fructo-oligosaccharide and inulin modulate inflammatory responses and microbial communities in Caco2-bbe cells and in a mouse model of intestinal injury. The Journal of nutrition 144:1725-1733.

[5] Kaplan, G. G. 2015. The global burden of IBD: from 2015 to 2025. Nat Rev Gastroenterol Hepatol 12:720-727.

[6] Kaplan, G. G., and S. C. Ng. 2017. Understanding and Preventing the Global Increase of Inflammatory Bowel Disease. Gastroenterology 152:313-321 e312.

[7] Lavelle, A., and H. Sokol. 2020. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. Nat Rev Gastroenterol Hepatol 17:223-237.

[8] Liu, R., Y. Li, and B. Zhang. 2016. The effects of konjac oligosaccharide on TNBS-induced colitis in rats. International immunopharmacology 40:385-391.

[9] Mentella, M. C., F. Scaldaferri, M. Pizzoferrato, A. Gasbarrini, and G. A. D. Miggiano. 2020. Nutrition, IBD and Gut Microbiota: A Review. Nutrients 12.

[10] Muanprasat, C., and V. Chatsudthipong. 2017. Chitosan oligosaccharide: Biological activities and potential therapeutic applications. Pharmacology & therapeutics 170:80-97.

[11] Nielsen, O. H., C. Maxwell, and J. Hendel. 2014. IBD medications during pregnancy and lactation. Nat Rev Gastroenterol Hepatol 11:116-127.

[12] Ordás, I., L. Eckmann, M. Talamini, D. C. Baumgart, and W. J. Sandborn. 2012. Ulcerative colitis. The Lancet 380:1606-1619.

[13] Pan, L., M. H. Farouk, G. Qin, Y. Zhao, and N. Bao. 2018. The Influences of Soybean Agglutinin and Functional Oligosaccharides on the Intestinal Tract of Monogastric Animals. International journal of molecular sciences 19.

[14] Pithadia, A. B., and S. Jain. 2011. Treatment of inflammatory bowel disease (IBD). Pharmacological reports : PR 63:629-642.

[15] Rastall, R. A. 2010. Functional oligosaccharides: application and manufacture. Annual review of food science and technology 1:305-339.

[16] Sairenji, T., K. L. Collins, and D. V. Evans. 2017. An Update on Inflammatory Bowel Disease. Primary care 44:673-692.

[17] Shi, L., B. Fang, Y. Yong, X. Li, D. Gong, J. Li, T. Yu, R. Gooneratne, Z. Gao, S. Li, and X. Ju. 2019. Chitosan oligosaccharide-mediated attenuation of LPS-induced inflammation in IPEC-J2 cells is related to the TLR4/NF-κB signaling pathway. Carbohydrate polymers 219:269-279.

[18] Tingirikari, J. M. R. 2018. Microbiota-accessible pectic poly- and oligosaccharides in gut health. Food & function 9:5059-5073.

[19] Tozlu, M., B. Cash, M. Younes, and A. Ertan. 2021. Dilemma in post-IBD patients with IBS-D symptoms: A 2020 overview. Expert review of gastroenterology & hepatology 15:5-8.

[20] Tu, J., Y. Xu, J. Xu, Y. Ling, and Y. Cai. 2016. Chitosan nanoparticles reduce LPS-induced inflammatory reaction via inhibition of NF-κB pathway in Caco-2 cells. International journal of biological macromolecules 86:848-856.

[21] Varki, A. 1993. Biological roles of oligosaccharides: all of the theories are correct. Glycobiology 3:97-130.

[22] Wan, J., J. Zhang, H. Yin, D. Chen, B. Yu, and J. He. 2020. Ameliorative effects of alginate oligosaccharide on tumour necrosis factor-α-induced intestinal epithelial cell injury. International immunopharmacology 89:107084.

[23] Wehkamp, J., M. Gotz, K. Herrlinger, W. Steurer, and E. F. Stange. 2016. Inflammatory Bowel Disease. Dtsch Arztebl Int 113:72-82.

[24] Yazbeck, R., R. J. Lindsay, M. S. Geier, R. N. Butler, and G. S. Howarth. 2019. Prebiotics Fructo-, Galacto-, and Mannan-Oligosaccharide Do Not Protect against 5-Fluorouracil-Induced Intestinal Mucositis in Rats. The Journal of nutrition 149:2164-2173.