

Review

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Review

The Role of Indigestible Oligosaccharides in Alleviating Human Chronic Diseases by Regulating Gut Microbiota: A Review

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Abstract: The gut has been a focus of chronic disease research. The gut microbiota produces metabolites that act as signaling molecules and substrates, closely influencing host health. Indigestible oligosaccharides (NDOs), as a common dietary fiber, play an important role in regulating the structure and function of gut microbiota. Their mechanism of action is mainly attributed to their carbon source as specific probiotics, producing related metabolites, and regulating the gut microbial community. However, due to the selective utilization of oligosaccharides, some factors such as the types and structures of oligosaccharides have different impacts on the composition of microbial populations and the production of metabolites in the colon ecosystem. This review systematically describes the key factors influencing the selective utilization of oligosaccharides in microorganisms and elaborates how oligosaccharides affect the host's immune system, inflammation levels and energy metabolism by regulating microbial diversity and metabolic function, which in turn will affect the onset and progress of chronic diseases, especially diabetes, obesity, depression and intestinal inflammatory diseases, constipation. In this review, we re-examine the interaction mechanisms between gut microbiota and its associated metabolites and diseases, and explore new strategies for promoting human health and combating chronic diseases through dietary interventions.

Keywords: nondigestible oligosaccharides; gut microbiota; short-chain fatty acids; constipation; diabetes; obesity; depression; inflammatory bowel disease

1. Introduction

Chronic diseases refer to diseases that have a slow onset, slow progression, long course, and usually cannot be completely cured. In the past few years, the role of gut microbiota in related diseases has been extensively studied, such as ulcerative colitis [1], irritable bowel syndrome [2], diabetes [3], Alzheimer's disease [4], non-alcoholic fatty liver disease [5], obesity [6]. In this case, the role of probiotics becomes particularly important. By regulating the balance of gut microbiota, it is possible to maintain the stability of the gut environment, enhance intestinal barrier function, reduce gut inflammation levels, and help regulate energy metabolism and insulin sensitivity [7–9]. For example, in obese individuals, the diversity of the gut microbiota is decreased, which is usually accompanied by changes in key species [6,10–13], like *Firmicutes* and *Bacteroidetes* [14,15]. Diabetes mellitus type 2 (T2DM) is characterized by an impaired gut microbiota [16,17], and *Akkermansia* and *Enterobacter* have been found to have a causal role in the onset and progression of T2DM [18]. Nonalcoholic fatty liver disease (NAFLD) is regarded as a typical metabolic disorder at the intersection of obesity, metabolic syndrome and T2DM [19], often with a proliferation of *Enterobacteriaceae* and *Escherichia coli* [20]. Dysbiosis of the gut microbiota has also been associated

with inflammatory bowel disease (IBD), including encompassing three main phenotypes-Crohn disease (CD) and ulcerative colitis (UC) and IBD unclassified (IBDU) [21]. There are common microbial patterns among IBD patients, manifested at the phylum level as a loss of *Firmicutes* [22–24], an increase in *Proteobacteria* and potential pathogenic bacteria [25–28]. At the genus level, *Clostridium* and *Escherichia coli* were significantly increased in IBD, whereas *Phascolarctobacterium*, *Faecalibacterium*, and *Roseburia intestinalis* were significantly decreased [27,29–32]. The gut-brain axis plays an important role in neurological diseases including Alzheimer's disease (AD), anxiety, and depression. The gut microbiota is linked to central nervous system in a variety of ways, including regulation of immune responses, formation of metabolites (e.g., short-chain fatty acid), and synthesis of neurotransmitters (e.g., serotonin and dopamine). Now some studies have shown that some microorganisms can regulate intestinal homeostasis and hinder the progression of neurological diseases [33–41]. In fact, diet is the main determinant that drives the growth of gut microbiota and regulates its interaction with the host. The lack of sufficient functional microbiota and accessible carbohydrates (MAC) is the main reason for the disappearance of important species that regulate intestinal homeostasis [42,43]. Indigestible oligosaccharides (NODs) are typical MAC that are easily broken down by *Bacteroides* and *Lactobacillus* containing metabolic enzymes. The use of oligosaccharide fermentation to improve intestinal health is a widespread and current focus [44,45]. The beneficial effects and promising prospects of NODs on the host by targeting the gut microbiota and microbial metabolites are now generally accepted [46–50], including improvement of bowel movements, suppression of appetite, enhancement of postprandial glycemic response and promotion of mineral absorption. This article describes the structure and sources of NODs, as well as the factors affecting the microbial fermentation of NODs, and then elucidates the important role of oligosaccharides in chronic diseases by regulating the gut microbiota.

2. Classification and Sources of Oligosaccharides

Oligosaccharides are a class of carbohydrates that consist of 2 to 10 monosaccharide molecules, typically consisting of two or more different monosaccharides that are linked together in various ways through glycosidic bonds [51], classified as digestible or indigestible [52]. In some dietary oligosaccharides, the anomeric C atom (C1 or C2) of the mono-saccharide units has a configuration that makes their glycosidic bounds nondigestible to the human digestive enzymes [52]. In addition to α -1,4 glycosidic bonds, the chemical bonds between monosaccharides in NDOs also contain α -1,6 glycosidic bonds or β -1,2 glycosidic bonds that cannot be degraded by human digestive enzymes. It belongs to prebiotics along with fiber polysaccharides, which are selectively fermented and cause specific changes in the composition and/or activity of gastrointestinal microbiota, thereby benefiting the well-being and health of the host [53,54].The source and structural characteristics of main functional oligosaccharides are listed in Table 1.

Table 1. Basic information of the main nondigestible oligosaccharides (NDOs).

Name	Glucosidic linkage	Monosaccharides	DP	Preparation	Natural source	Reference
FOS	β -1,2	Fructose	2-5	Enzyme	Onions,	[55]
		Glucose		degradation, Microbial Fermentation	chicory, Wheat	[56]

IMO	α -1,3	Glucose	2-5	Enzyme synthesis 、 Enzymatic hydrolysis、 Enzymatic conversion	Starch,	[57]
	α -1,4				Corn milk,	[58]
	α -1,6				Wheat bran	
XOS	β -1,4	Xylose	2-7	Enzymatic conversion	hoots,	[59]
					corncob, wheat straw	[60]
MOS	α -1,2	Mannose	2-	Enzymatic hydrolysis	Carrageenan	[61]
	α -1,6	Glucose	10		Konjaku Flour	[57]
GOS	β -1,4	Galactose	3-6	Enzymatic conversion	Lactose	[55]
	β -1,6	Glucose				[62]
SOS	α -1,2 α -1,6	Galactose, Glucose Fructose	2-5	Extracted	Soybean	[57]
COS	β -1,4	D-glucosamine	—	Enzymatic hydrolysis	Shell of crustaceans	[63]

3. The impact of Different NODs on the Diversity of Gut Microbiota

Non digestible oligosaccharides (NODs) are mainly fermented by Bifidobacteria, Lactic acid bacteria (LAB), and other symbiotic bacteria, which typically contain various enzymes related to carbohydrate metabolism in the large intestine [64,65]. For example, LAB can degrade FOS and GOS by encoding β -FFase and β -galactosidase [66]. Different NODs often have many differences, such as source, degree of polymerization, glycosidic bonds and overall structural complexity (e.g., side chains) [67–69]. These differences result in a diverse microbiota for fermenting NDOs, manifested in varying degrees of beneficial bacterial proliferation, inhibition of harmful bacteria, and differences in acid and gas production [70].

3.1. Degree of Polymerization (DP)

In fact, NODs with different DP can be utilized by different strains. For example, DP3 oligofructose (FOS) promoted the growth of Bifidobacterium species in vitro while inhibiting the proliferation of Clostridia, and it showed superior selective stimulatory activity compared to other FOS [71]. In previous work, Gopal et al. [72] demonstrated that Bifidobacterium lactis DR10 consumes

oligosaccharides (GOS) with higher DP, while *Lactobacillus rhamnosus* DR20 prefers to use galactose disaccharides. In general, oligosaccharides with higher DP are more resistant to digestion when passing through the upper digestive tract and are therefore more likely to reach the colon to be utilized by the gut microbiota. However, high DP may also inhibit selective fermentation by microorganisms. Zhao et al. [73] evaluated the prebiotic ability of Bamboo Shoot Shells Xylo-Oligosaccharide (XOS) with different DP, and showed that XOS with a high DP ($>X5$) led to an increase in the abundance of beneficial bacteria such as *Phascolarctobacterium* and *Bacteroides*, while low DP XOS with more X2-X3 components promoted the proliferation of other beneficial bacteria, including *Lachnospirillum*. Immerzeel et al. [74] and Falck et al. [75] demonstrated that *Bifidobacterium adolescentis* and *Lactobacillus acidophilus* predominantly utilize the X2-X3 fractions. In fact, low DP NODs has a stronger ability to support the growth and proliferation of gut microbiota [76]. When high DP XOS exists, the microbial community consumes more energy to secrete xylanase, preferentially degrading high DP XOS to low DP XOS, thereby limiting the metabolic capacity of gut microbiota [77]. Another study on oligomeric dextran showed that the component with DP 3-4 ($\geq 80\%$) was utilized by all probiotic strains, the portion with DP 5-6 was utilized by some strains, and the portion with DP ≥ 7 was only utilized by LAB and *Bifidobacteria* [78]. Similarly, isomaltose from DP 3-5 is more indigestible than DP 2, and although it has a higher chance of reaching the colon, its fermentation selectivity for beneficial probiotic species is lower [79–81].

3.2. Glycosidic Bond

Different structures of NODs have different effects on gut microbiome, including glycosidic bond types and connection modes. For example, α -(1 $\rightarrow$ 3) and α -(1 $\rightarrow$ 2)-linked glucose oligosaccharides (GlcOS) formed during isomaltooligosaccharides (IMOs) production promote the growth of *Bifidobacterium* spp. and *Lactobacillus* spp. [82], and their fermentation selectivity (against probiotic species in gut bacteria) is higher than that of only α -(1 $\rightarrow$ 6)-linked IMOs [83]. Zeng et al. [84] studied the effect of NODs with different disaccharide bonds on selected *Lactobacillus*, and most of the species had low growth rates on IMOs with α -(1 $\rightarrow$ 6), except *L. fermentum* FUA 3589, where β -(1 $\rightarrow$ 4)-linked fibrous disaccharides and β -(1 $\rightarrow$ 6)-linked gentian disaccharides were able to significantly promote the proliferation of *L. brevis* ATCC 8287, *L. rhamnosus* ATCC 53103, *L. plantarum* WCFS1, and *L. gasseri* ATCC 33323. Similarly, Sanz et al. [70] investigated the prebiotic index (PI) of disaccharide, which was higher for α -glucose disaccharides than for β -types, except for α , α -alginose. Djouzi Z et al. [85] compared the effects of β -oligofructose, β -oligogalactose and α -oligosaccharides (non-disaccharides) on the metabolism of gut microbiota, and compared to α -oligosaccharides, oligofructose and oligogalactose containing β -glycosidic bonds were the preferred substrates for the growth of *Bifidobacteria*, which have a great impact on microbial composition, which has been found in several studies [86,87]. More importantly, it has been reported that intake of GOS containing β -1, 3, β -1, 4 and β -1, 6 glycosidic bond showed better prebiotic effects in healthy volunteers [88]. In addition, Kittibunchakul et al. [89] concluded that the fermentation activity of *Bifidobacterium* and *Lactobacillus* as well as *E. faecium* on GOS (mainly containing β -1, 3 and β -1, 6 glycosidic bonds) showed better fermentative activity than those GOS which contain a single β -1, 4 glycosidic bond. This is similar to the conclusion of Cardelle Cobas [90], who found that *Bifidobacteria*, LAB and *Streptococcus* preferred galactose containing β -1, 6 glycosidic bond, but not β -1, 4 glycosidic bond. In conclusion, the growth ability of probiotics is related to the type of glycosidic bond. Therefore, it is important to understand the structure-activity relationship of NODs.

3.3. Linear and Branching Structures

The type, number and branching complexity of substituents in NODs will affect the microbial fermentation rate and composition. It has been reported that the presence of substituents on XOS can affect *Bifidobacterium* fermentation, resulting in different amounts of lactic acid [91]. In addition, Kabel observed that the lactic acid content in unsubstituted XOS was higher than that in substituted XOS [92], that is, the XOS with linear structure was fermented by more gut microorganisms. When

fermented in vitro with human feces, the fermentation speed of linear XOS and arabinose substituted XOS (AXOS) was faster than acetylated XOS (AXOS), and XOS containing 4-O-methylglucuronic acid group (GlcAmeXOS) was the slowest [93], which indicated that the presence of substituents delayed or completely hindered the fermentation. On the other hand, Bacteroidetes showed superior growth performance when XOS was used as the sole carbon source compared to AXOS [94]. Bacteroidetes was able to utilize AXOS and released ferulic acid [95–97]. The process of XOS degradation by Bacteroidetes involves extracellular degradation and debranching of the skeleton, followed by intracellular hydrolysis of the oligomers, which ultimately produces acetate, propionate, and butyrate as the major metabolic end products [98]. It has been proved that microbial degrading enzymes are not easy to contact NODs with high content of branches, resulting in the reduction of microbial fermentation rate [99]. In addition, the chain length and shape of NODs are equally important. For example, long-chain IMO has stronger resistance to the hydrolysis and degradation of the upper intestine, and is more effective than short-chain IMO in stimulating the growth of Bifidobacterium, Prevotella and Lactobacillus. Bifidobacteria have selective specificity in utilizing FOS with different chain lengths. Generally, short-chain FOS are preferentially fermented, followed by long-chain FOS [100]. Cyclic IMO have been shown to inhibit Streptococcus [80,101–103].

From the above viewpoints, the degree of polymerization, substituents, glycosidic bond types have a significant impact on the fermentation activity of probiotics. However, the reasons for the preference of probiotics for oligosaccharides are lack of in-depth investigation, and the metabolic mechanism of microorganisms for oligosaccharides with different structures needs further study.

4. The Impact of Different NODs on the Diversity of Gut Microbiota

4.1. T2DM

Diabetes is a chronic disease characterized by hyperglycemia, caused by absolute or relative insufficiency of insulin secretion and impaired utilization. At present, increasing dietary fiber intake is one of the recommendations for patients with T2DM [104]. In recent years, many studies have shown that, including in vivo and in vitro experiments, NODs can effectively improve diabetes by regulating gut microbiota to enrich or decrease specific flora. For example, in T2DM rats, the abundance of Firmicutes increased at the phylum level, while the abundance of Bacteroidetes, Actinobacteria, and Verrucomicrobia decreased [105]. At the genus level, Bifidobacterium, Roseburia, Faecalibacterium, Bacteroides, and Akkermansia decreased, while Desulfovibrio, Oscillibacter, Fusobacterium, Ruminococcus, and Blautia increased [106,107]. Weninger et al. [107] showed that FOS reduced the species α -diversity after 16 weeks of treatment in T2DM rat, that the relative abundance of Bifidobacterium increased and the relative abundance of Ruminococcus decreased significantly. This result was also found in the later study of FOS and GOS [108], with the difference that Phascolarctobacterium, Coprococcus and Oscillospira were also decreased.

In addition, NODs can regulate insulin sensitivity, blood glucose and lipid metabolism by influencing microorganisms to produce beneficial metabolites, such as short-chain fatty acids (SCFAs), amino acid metabolites, and bioactive polypeptides, thereby alleviating the onset and progression of diabetes. 1) SCFAs are currently the most studied metabolites. Gobinath et al. [109] demonstrated that the decrease of plasma cholesterol in diabetic rats fed XOS or FOS was due to the inhibition of cholesterol synthesis by increased propionate or altered bile acid metabolism. In addition, the reduction of butyrate producing bacteria is associated with impaired glucose control [17,110]. SCFAs act as signaling molecules to maintain host energy homeostasis by activating G protein-coupled receptors GPR41 and GPR43 to regulate insulin levels and inhibit hepatic gluconeogenesis [111]. It also promotes the secretion of glucagon-like peptide-1 (GLP-1) and peptide YY (PYY). GLP-1 participates in glucose homeostasis primarily by reducing blood glucose levels and improving insulin secretion and resistance. PYY, as a hormone mediating satiety, is secreted from endocrine L cells in the distal intestine after the body intakes enough food. SCFAs play a crucial role in the development of T2DM and can be used as markers of metabolic disorders or homeostasis [112]. 2) Amino acids and their metabolites: The intake of NODs can produce a variety of amino acid metabolites, which have an impact on blood glucose levels and insulin sensitivity. It has been

reported that fecal metabolic profiling showed the content of glycogen amino acids such as proline, serine, and leucine increased after NODs intervention in T2DM rats [113]. This result was also confirmed by Chen et al. [114], who found that an increase in serine and glutamine can reduce the risk of T2DM progression. In addition, the expression of glucose transporter (GLUT4) was decreased in STZ induced diabetic rats, whereas Rice husk oligosaccharides (RH-XOS)-treated T2DM rats significantly regulated total GLUT4 protein expression [115].

In conclusion, NODs can influence glucose metabolism (especially glucose metabolism), lipid metabolism, protein and carbohydrate metabolism by regulating the gut microbiota and fecal metabolites [113,114]. Specifically, they can improve insulin sensitivity by regulating AMPK pathway and INS-R/IRS/Glut4 insulin signaling pathway to achieve the goal of treating T2DM [116,117]. On the other hand, hundreds of metabolites of gut microbiota can be fed back to the brain, which plays a key role in influencing many gastrointestinal processes through the autonomic nervous system and the hypothalamus-pituitary-adrenal axis [118] (Figure 1).

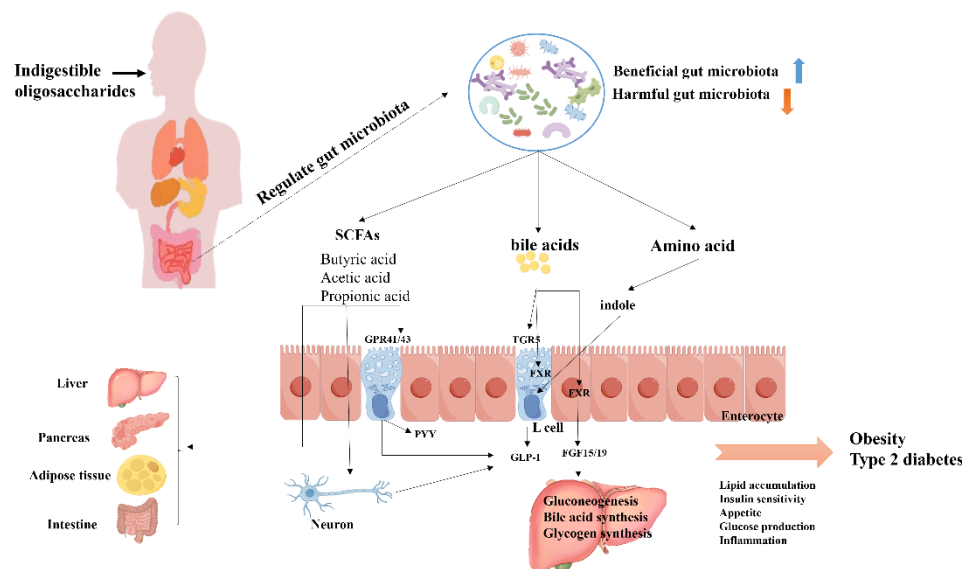


Figure 1. The effect of NODs on T2DM and Obesity by regulating gut microbiota composition and metabolites. 1) SCFAs: SCFAs can promote the release of PYY and GLP-1 from intestinal endocrine L cells, increase energy consumption of adipose tissue, reduce lipid accumulation and inflammation. In the liver, SCFAs affect the generation of fat and glucose. In the pancreas, SCFAs promote insulin secretion. SCFAs can transmit neural signals to maintain homeostasis of systemic functions. 2) Amino acids: amino acids are converted by intestinal bacteria into other bioactive metabolites, such as indole, which can stimulate L cells to secrete GLP-1, thereby promoting insulin secretion and inhibiting glucagon secretion. 3) Bile acids (BAs): BAs is converted to secondary bile acids through uncoupling, dehydroxylation and epimerization by intestinal bacteria. BAs act on two receptors (FXR and TGR5) to regulate glucose homeostasis. In addition, the activation of FXR by BAs promotes the release of FGF15/19, which promotes hepatic glycogen synthesis and reduces BAs synthesis and gluconeogenesis in the liver.

4.2. Obesity

Several studies have revealed the role of gut microbiota in host physiology, behavior and metabolism, providing new insights into the pathogenic mechanism of obesity.

Firstly, gut microbial dysbiosis is a common feature in obese patients and obese animal models. Studies have shown that prebiotic oligosaccharides, such as FOS, XOS, GOS, and COS, have an anti-obesity effect by regulating the gut microbiota[49]. Generally, obese individuals have a higher proportion of Firmicutes and Bacteroidetes. A study on obese mouse model showed that the administration of NODs increased the abundance of Bacteroidetes, decreased the abundance of Firmicutes, and changed more than 100 bacterial taxa [119]. Long et al. [120] demonstrated that XOS

diet reduced visceral fat in mice, which was associated with changes in gut microbiota. In addition, the increase in Proteobacteria containing gram negative lipopolysaccharide (LPS) is also a microbial signature of intestinal dysbacteriosis in mice fed a high-fat diet (HFD) [121]. HFD leads to a sustained increase in plasma LPS levels (i.e., metabolic endotoxemia), as well as a systemic inflammatory response, which play a promoting role in the development of insulin resistance in obese patients. In a study of obese women, *Bifidobacterium* and *Faecalibacterium prausnitzii* were increased after intervention with FOS, it was proved that the changes of gut microbiota were related to the changes of fat mass, serum LPS level and metabolism (hippuric acid, lactate, and plasma protein C) [122]. Similarly, Thiennimitr et al. [121] demonstrated that consumption of XOS reduced metabolic endotoxemia in obese mice. The results indicate that NODs can inhibit the growth of pro-inflammatory bacteria and promote the growth of beneficial bacteria, thereby helping to alleviate intestinal inflammation and reduce the risk of obesity. In summary, manipulation of the composition of the gut microbiota through NODs has been considered as a possible approach for the prevention and treatment of obesity.

The direct cause of obesity is that the rate of fat synthesis exceeds the rate of fat consumption. Therefore, blocking fat synthesis and increasing energy consumption is the most effective strategy to combat obesity. The impact of NODs on weight loss is mainly attributed to the production of SCFAs by the gut microbiota [123], as they play an important role in regulating food intake and energy metabolism [124]. Research has shown that GOS improves lipid metabolism in mice by regulating the synthesis of SCFAs [125]. Dietary supplementation of MOS can inhibit appetite and systemic insulin resistance in obese mice by remodeling gut microbial composition and enhancing the formation of SCFAs [126]. Chen et al. [127] found that XOS changed the gut microbiota and affected the levels of SCFAs. After removing the gut microbiota, SCFAs levels were significantly decreased, indicating that XOS indirectly affected the generation of SCFAs by regulating the metabolic activities of the microbiota. In addition, acetate is catalyzed to acetyl-CoA and butyrate is converted to butyryl-CoA, both of which act as inhibitors of fatty acid synthesis by acetyl CoA carboxylase (ACC) to prevent obesity [127]. Butyrate is enriched by the intake of oligosaccharides, and regulating the ratio of butyrate to acetate in the gut microbiota is a potential strategy for the treatment of obesity. For example, specific enrichment of butyrate producing bacteria may be beneficial for obesity treatment.

NODs can regulate the synthesis and release of bile acids by affecting gut microbiota associated with bile acid (BA) metabolism, such as *Clostridia*, *Bacteroidetes*, *Bacteroides*, *Lactobacillus*, and *Bifidobacterium* [49]. The G-protein-coupled bile acid receptor (TGR5) is one of the key receptors for BA. Under the action of *Clostridia*, bile acids can be converted to deoxycholic acid (DCA) and lithocholic acid (LCA), which activate TGR5 and enhance the cyclic adenosine monophosphate/protein kinase A (cAMP-PKA) signaling pathway. Activation of TGR5 also promotes conversion of glucagon to GLP-1. Lun et al. [128] revealed the dynamic balance relationship between gut microbiota and bile acids.

The study found that after COS intervention, gut microbiota can promote the release of bile acid, and then activate TGR5, enhance brown fat thermogenesis and TGR5 dominated fatty acid oxidation signaling pathway, thus playing a role in weight loss and lipid reduction. Farnesoid X receptor (FXR) is another key receptor for BA, and several studies have shown that activation of FXR promote adipose tissue browning and reduce obesity in mice [129]. Mechanistically, activation of FXR induces the release of fibroblast growth factor 15 (FGF15) or FGF19, which reach hepatocytes through the portal vein, thereby inhibiting BA synthesis in the liver [130]. In addition, FGF19 promotes hepatic glycogen synthesis and inhibits hepatic gluconeogenesis. Other studies have shown that GOS significantly reduced the concentration of bile acids in the small intestine, improved glucose metabolism, and influenced lipid absorption by regulating lipid digestion [131,132]. Pectin oligosaccharides have also been shown to mediate cholesterol metabolism through the gut microbiota and their metabolites [133].

The gut microbiota can utilize NODs to generate nutritional metabolites that act as "messengers" for the bacterial community, influencing host energy homeostasis and regulating host metabolism, thus contributing to the fight against obesity (Figure 1).

4.3. Depression

NODs may influence the development of depression by regulating gut microbiota. For example, FOS inhibits depression-associated bacteria such as *Anaerostipes*, *Lachnospiraceae* incertae sedis, *Oscillibacter*, *Proteobacteria*, and *Streptococcus*, while effectively promoting the growth of beneficial bacteria with antidepressant properties [134,135]. The combination of FOS and GOS has been shown to reduce depressive symptoms [136]. At the microbial level, there is evidence that the combination of the two can prevent the change of the ratio of *Actinomycetes* and *Proteobacteria*, which is a typical feature of patients with major depression [137]. Chi et al. [134] conducted a comparative analysis of FOS and the standard antidepressant fluoxetine, noting that they had similar effects and that both FOS and fluoxetine promoted the growth of *Dialister* spp. A recent cohort study reported that *Dialister* was not found in depressed patients [138]. In other words, FOS and fluoxetine may improve depressive symptoms by regulating the presence of *Dialister*. In addition, *Eubacterium* [139], *Lactobacillus* [139,140] and *Oxalobacter* [141] are also considered beneficial. Overall, NODs showed antidepressant activity, and part of this effect was achieved by regulating of functional gut microbiota, although the exact mechanism in depressed patients requires further investigation.

The microbiota-gut-brain axis (MGBA) has been considered as a potential pathway for the treatment of neurodegenerative diseases [142] involving the autonomic nervous system (ANS), the enteric nervous system (ENS), and the hypothalamic-pituitary-adrenal axis (HPA). Gut microbes can affect the brain through a variety of pathways, including neural, immune, endocrine pathways and microbial metabolites, and even stimulate the vagal nerve endings of the gut through neurotransmitters produced by microbes themselves [143]. Neurotransmitters known to be affected by gut microbiota include SCFAs [144], γ -aminobutyric acid (GABA) [145], tryptophan (Trp) [146], and serotonin (5-HT) [147]. For example, valeric acid can alleviate intestinal injury, protect neurons, and regulate neurotransmitters [148]. And the increase of butyrate may directly affect the central nervous system [149–151]. This view was validated in a pig model, where oral butyrate was found to affect brain metabolism and hippocampal neurogenesis [152]. Therefore, NODs supplementation may inhibit the development of depression by enhancing the formation of SCFAs, including improving cognitive functioning and alleviating anxiety behaviors. Another important pathway is tryptophan $\rightarrow$ 5-hydroxytryptophan $\rightarrow$ serotonin. Gut microbiota plays an indispensable role in intestinal tryptophan metabolism. Tryptophan is the only precursor for the synthesis of the neurotransmitter 5-HT, which influences the development of depression [153]. Kelly et al. [154] found that transplantation of feces from depressed patients into recipient animals resulting in these recipient animals showing behavioral and physiological characteristics of depression, and the metabolic pathway of tryptophan was changed. Deng et al. [155] demonstrated that feruloylated oligosaccharides (FO) exhibited antidepressant and anxiolytic effects by regulating 5-HTP, suggesting that the gut microbiota and microbial metabolism were key mediators supporting FO to protect the nervous system. Similarly, Zhang et al. [156] revealed that *Morinda officinalis* oligosaccharide (MOO) regulates the 5-HT synthesis pathway (Trp $\rightarrow$ 5-HTP $\rightarrow$ 5-HT) in the gut microbiota, so that the elevated 5-HTP from the gut microbiota is absorbed into the blood, and then crosses the blood-brain barrier to improve the 5-HT level in the brain. These findings suggest that microbiota can regulate neurotransmitter levels to affect the development of depression.

Gut microbial dysbiosis may lead to physiological and behavioral disorders by inducing neuroinflammation in the central nervous system. NODs alters neural function by manipulating the gut microbiota. Currently, the exact mechanisms by which NODs play a role in depression are unknown, and it is difficult to definitively show how many or which key pathways are responsible for the pathophysiology of depression. However, it is still a very important research direction to regulate the gut microbiota and its metabolites to affect host metabolic pathways, thereby alleviating depressive symptoms (Figure 2).

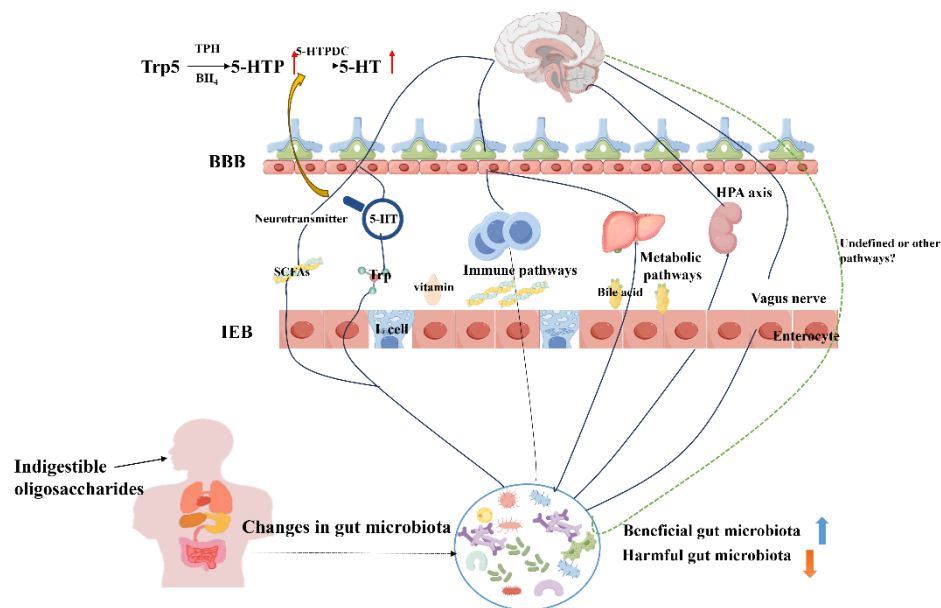


Figure 2. Gut microbiota and the brain communicate in both directions through the immune system, intestinal endocrine signals, neurotransmitters, amino acids, BAs, SCFAs, the hypothalamic-pituitary-adrenal axis, etc.

4.4. Inflammatory Bowel Disease (IBD)

Inflammatory bowel disease (IBD) is a common non-specific chronic gastrointestinal inflammatory disease, including crohn's disease (CD) and ulcerative colitis (UC). The mechanisms by which oligosaccharides alleviate IBD by regulating gut microbiota mainly include: 1) enriching the diversity of the gut microbiota; 2) protecting the intestinal barrier; and 3) regulating T-cell differentiation and related signaling pathways (Figure 3). Recent studies have verified that breast milk oligosaccharides (HMOs) alleviated sodium disulfide (DSS)-induced ulcerative colitis by improving intestinal barrier function and regulating gut microbiota [48]. The gut microbiota of colitis mice treated with unsaturated alginate oligosaccharides (UAOS) was altered, with increased abundance of Firmicutes and Actinomycetes and decreased abundance of Bacteroidetes and the results showed that the protective effect of UAOS treatment was attributed to the maintenance of mucosal barrier function and suppression of immune injury by regulating gut microbiota [157].

Increasing evidence shows that functional oligosaccharides as natural active substances can effectively improve IBD [100,158]. 1) NODs can alleviate intestinal inflammation in animals by regulating the gut microbiota. Gut microbial dysbiosis will lead to ecological imbalance of intestinal mucosa, increase the production of pro-inflammatory cytokines and reduce the production of anti-inflammatory cytokines. It was found that the levels of *Escherichia coli* and *Enterococcus faecalis* in the feces of patients with IBD were significantly higher than those of normal people, while the abundance of *Lactobacillus* and *Bifidobacterium* were significantly lower [159]. In addition, FOS alleviated intestinal inflammation by promoting the growth of LAB [157]. SCFAs can be absorbed by intestinal epithelial cells (IEC) and inhibit the production of pro-inflammatory cytokines IL-8 and IL-6, thereby alleviating the inflammatory response of colonic epithelial cells. In conclusion, NDOS can alleviate the symptoms of IBD by reducing pro-inflammatory bacteria, increasing anti-inflammatory bacteria, and promoting the production of SCFAs [160].

2) Protecting the intestinal barrier. In animal models of IBD, alterations in tight junction proteins (e.g., Claudin1, Occludin, ZO-1) and adhesion junction proteins (e.g., E-cadherin, β -catenin) are usually accompanied by increased intestinal permeability and disruption of intestinal structure. In fact, it helps to restore the integrity of the mucosal barrier by regulating gut microbiota diversity [161]. For example, HMOs restored the expression of tight junction proteins and MUC-2, inhibited the production of LPS and LBP, and restored the integrity of the intestinal barrier in colitis mice [48]. SCFAs may provide energy for IEC, promote epithelial cell proliferation and differentiation, and

enhance intestinal barrier function, which may be related to their regulation of the AP-1 signaling pathway [162]. In addition, konjac oligosaccharides increased the concentration of SCFAs in the mice colon, which could promote IL-18 and repair the integrity of IEC [163]. Essential aromatic amino acids (e.g., Trp) can be metabolized into indoles and their derivatives, and these metabolites can activate the aryl hydrocarbon receptor (AhR), which is closely associated with the pathogenesis of IBD [164]. Consistent with the findings of Xia et al. that three microbial metabolites of Trp alleviate IBD by improving tight junctions [165].

3) Regulation of immune homeostasis. Toll-like receptors (TLRs) in intestinal epithelial cells and immune cells recognize and respond to different microbial structural motifs. When pathogens invade, macrophages recognize pathogen-associated molecular patterns (PAMPs) through TLRs and secrete various proinflammatory cytokines (such as TNF- α , IL-1 β , IL-6, IL-12, etc.). TLR-4 plays a crucial role as a receptor for LPS in the pathogenesis of UC. The number of Tregs cells decreases in patients with IBD. SCFAs can induce the differentiation of T cells into Treg cells, promote the synthesis of the anti-inflammatory cytokine to regulate the immune response, and restore the balance of Th1/Th2 and Th17/Treg cells. A study showed that XOS were metabolized into SCFAs, and propionate and butyrate can promote the differentiation of CD4+ T cells into Treg cells, thereby slowing down inflammatory bowel disease [166]. Similarly, feruloylated oligosaccharides (FOs) promoted the percentage of Treg cells and the production of corresponding specific cytokines, thereby regulating the immune homeostasis of Th17/Treg cell in IBD mice [167]. In addition, gut microbiota can also stimulate B cells (Breg) to produce inhibitory cytokines (e.g., IL-10 and TGF- β) that affect other immune cells and immunoglobulins (e.g., sIgA). Nowadays, numerous studies have confirmed the effectiveness of oligosaccharides in improving IBD by modulating the gut microbiota, both in animal models and in human experiments [168].

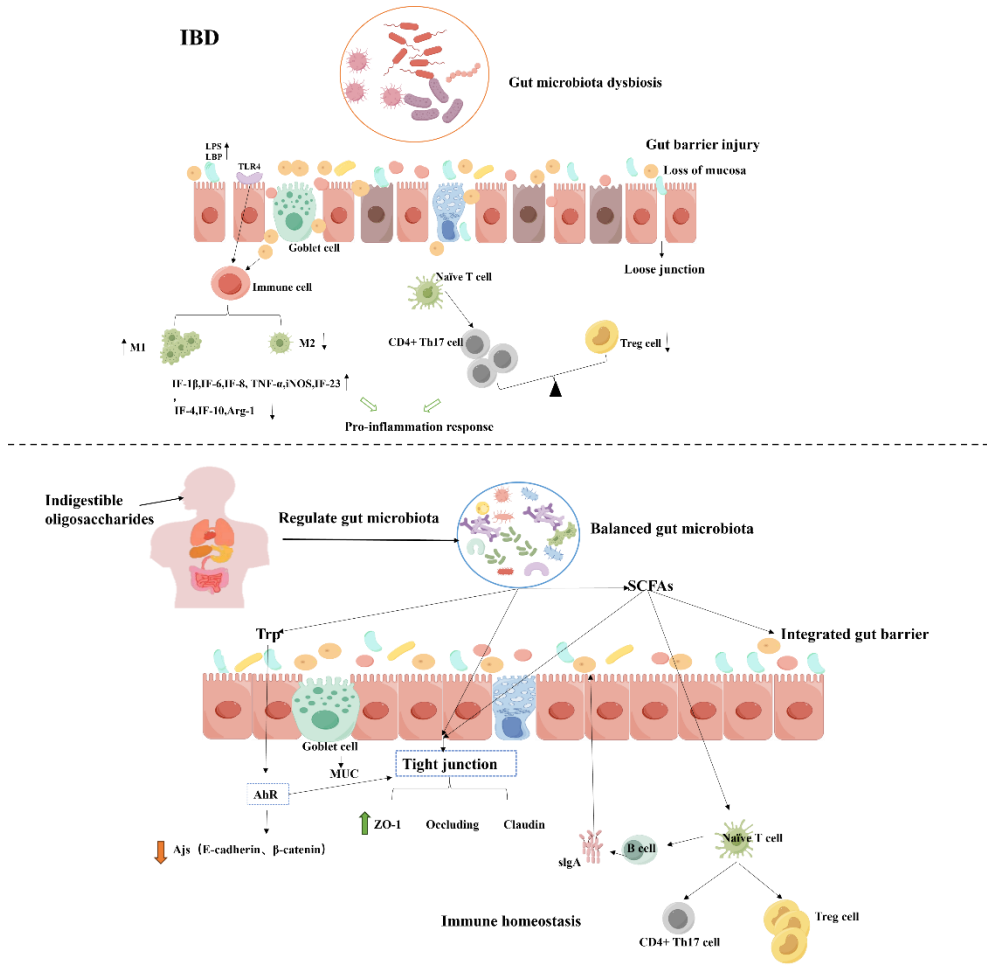


Figure 3. NODs alleviate IBD progression by regulating the gut microbiota. 1) NODs promote the proliferation of beneficial bacteria and corrects intestinal dysbiosis in IBD patients. 2) SCFAs can improve the barrier function and reduce the permeability of intestinal barrier by affecting the maturation of intestinal epithelial cells (IECs) and regulating the expression of tight junction proteins (Claudin1, Occludin, ZO-1). SCFAs also affect the interaction between immune cells (T cells, B cells), regulate the expression of pro-inflammatory/anti-inflammatory cytokines, and reduce intestinal inflammation. 3) Microbial metabolites of Trp regulate the expression of adhesion junction proteins (E-cadherin, β -catenin) and maintain the integrity of the intestinal barrier.

4.5. Constipation

Intestinal motility is regulated by the interaction of the intestinal immune system, intestinal secretions, intestinal microbiota and their fermentation products, and impaired intestinal motility can lead to constipation [169]. The increase in the abundance of beneficial bacteria such as *Bifidobacterium* and *Alistipes*, as well as the decrease in colonic transport-associated bacteria (*Oscillospira*, *Odoribacter*), contributes to the relief of constipation [170]. NODs can significantly improve defecation frequency and shorten colonic transit time, with few side effects, such as FOS, IMO, and GOS [171]. In addition to the fact that NODs themselves occupy intestinal volume to increase fecal volume and promote intestinal motility, several studies have shown that NODs also have significant benefits in alleviating constipation in terms of microbiota remodeling [84,172–175]. Specifically, Lactic acid bacteria utilize FOS to improve fecal consistency and reduce defecation time [176]. IMO effectively improves fecal consistency and frequency of defecation of subjects, which may be attributed to increased abundance of some microorganisms after colonic fermentation [174,175]. Lotus seed oligosaccharides alleviate constipation by stimulating the growth of beneficial bacteria in the host intestine to promote intestinal motility and defecation [177]. In addition, Zhang et al. demonstrated that COS could improve constipation by regulating the production of intestinal metabolites. This regulatory effect is mainly achieved by reshaping the structure of the gut microbiota in constipated mice [178].

The intake of NODs increases the substrate for probiotic fermentation and promotes the production of SCFAs, which stimulate the growth of colonic epithelial cells, thereby restoring intestinal morphology and increasing intestinal motility to alleviate constipation [179]. Current research suggests that butyrate improves intestinal motility by affecting water and electrolyte metabolism. Similarly, COS relieves constipation by restoring deteriorated water-electrolyte metabolism, including AQP3/4 and ENaC- β/γ expression. Among them, AQP3/4 transports water from the intestinal lumen to the colonic epithelium, ENaC- β/γ mediates the uptake of Na^+ into colonic epithelial cells [178,180].

In the current literature, the improvement of constipation by NODs may be related to the regulation of some metabolic pathways, including lipid metabolism (e.g., sphingolipid metabolism, glycerophospholipid metabolism and arachidonic acid metabolism), bile acid metabolism, and tryptophan metabolism [169,180]. Sphingolipid metabolism and glycerophospholipid metabolism have been proved to be associated with inflammatory responses to intestinal disorders. Inflammation will damage the integrity of intestinal epithelium, which reduces the secretion of neurotransmitters and hormones, affects gastrointestinal motility, and induces constipation [181]. Tryptophan generation has a significant accelerating effect on gastrointestinal motility. In this pathway, L-tryptophan, 5-HTP and other intermediate metabolites are substrates produced by neurotransmitters and neuromodulators, which can enhance the sensitivity of visceral nerves in the gastrointestinal tract and stimulate gastrointestinal motility. Several studies have shown that NODs can relieve constipation by activating the 5-HT signaling pathway [179,182]. In addition, it is equally important that bile acids regulate constipation through the metabolism of intestinal bacteria, such as *Bacteroides* [178].

In conclusion, NODs can effectively relieve constipation through a variety of mechanisms, such as promoting intestinal motility, enhancing intestinal barrier function, and regulating immune response (Figure 4). These findings indicate the potential value of NODs in the treatment of

constipation, further supporting the direction of research to improve constipation by targeting the gut microbiota and its metabolic functions.

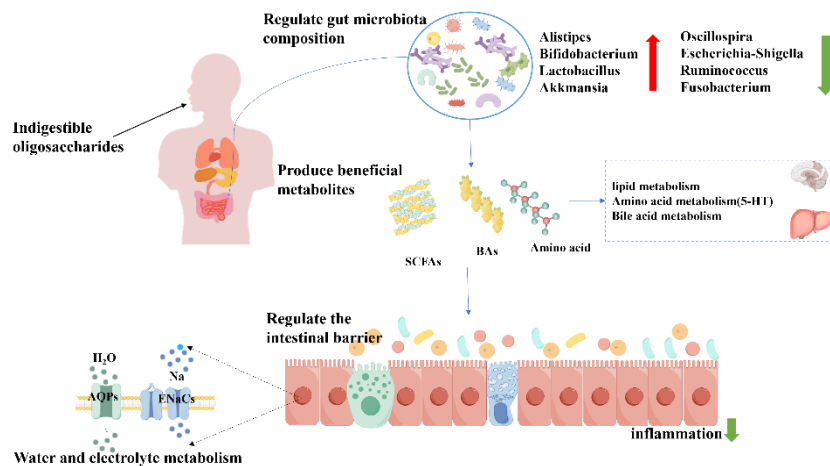


Figure 4. Schematic diagram of the mechanism of action of NODs in relieving constipation.

5. Conclusions and Perspectives

NODs, as prebiotics, show remarkable potential in alleviating a variety of human chronic diseases, such as diabetes, depression, constipation, colitis, and obesity, by modulating the gut microbiota to produce beneficial metabolites. However, the relationship between the precise structure of oligosaccharides and their fermentation state in the gut remains unclear, which limits their application.

In the future, it is necessary to study the interaction between the structure of NODs and gut microbiota, further explore the specific mechanism of NODs in different chronic diseases, and compare the effects of different oligosaccharide types. The efficacy and safety of NODs have been demonstrated in multi-center, large-scale human clinical trials. We can make better use of NODs to develop new dietary supplement and functional foods, to provide effective prevention and treatment strategies for chronic diseases.

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