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Effects of Nondigestible Oligosaccharides on Obesity

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Abstract

Obesity is a major public health concern that has almost reached the level of pandemic and is rapidly progressing. The gut microbiota has emerged as a crucial regulator involved in the etiology of obesity, and the manipulation of it by dietary intervention has been widely used for reducing the risk of obesity. Nondigestible oligosaccharides (NDOs) are attracting increasing interests as prebiotics, as the indigestible ingredients can induce compositional or metabolic improvement to the gut microbiota, thereby improving gut health and giving rise to the production of short-chain fatty acids (SCFAs) to elicit metabolic effects on obesity. In this review, the role NDOs play in obesity intervention via modification of the gut microecology, as well as the physicochemical and physiological properties and industrial manufacture of NDOs, is discussed. Our goal is to provide a critical assessment of and stimulate comprehensive research into NDO use in obesity.

INTRODUCTION

Obesity is one of the greatest challenges of the twenty-first century in public health and is characterized by excess body weight and adipose tissue accumulation due to a long-term energy imbalance. Obesity is generally defined as a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or higher (Heymsfield & Wadden 2017). Obesity and overweight (BMI $\geq$ 25) cause profound psychological and physical distress in humans and are major risk factors for several chronic diseases, including diabetes, nonalcoholic fatty liver, cancer, and cardiovascular disease (Thaiss 2018). The prevalence of obesity has increased from 3.2% to 10.8% in men and 6.4% to 14.9% in women during the past four decades. Furthermore, the number of adolescents with obesity has risen more than tenfold during the same time period (Smith 2016).

Obesity and overweight were once considered problems in developed countries only, but their rates have now reached pandemic levels in low- and middle-income countries as well. This rise in their rates has been driven by multiple factors, including age, medication, genetic factors, decreased exercise frequency, and increased food (higher caloric) intake, which interact with each other and the environment to drive the complex pathogenesis of obesity (Blüher 2019). Furthermore, the primary cause of obesity is a long-term energy imbalance with increased energy consumption and decreased energy expenditure. Foundational to any weight-loss effort is lifestyle change, which includes diet regulation and increased physical activity. Over the past few decades, human lifestyles around the world have changed. Societal shifts have dramatically reduced the requirements for physical activity and have increased processed/animal-based food consumption (Imamura et al. 2015, Sallis et al. 2012). Human intervention and prospective studies have demonstrated that dietary interventions with bioactive food components (e.g., prebiotics, probiotics, synbiotics) are inversely correlated with the risk of obesity and its comorbidities, indicating the potential capacity of dietary strategy in limiting body-weight gain (Brahe et al. 2016, Makki et al. 2018).

Oligosaccharides are defined as molecules that contain a small number of monosaccharide residues with degrees of polymerization (DPs) between 2 and 10, with molecular weight intermediate in nature between simple sugars and polysaccharides; molecules with DPs ranging from 11 to 19 are generally also considered as oligosaccharides because of their similar physiological properties (Delzenne et al. 2007, Wang et al. 2019). Oligosaccharides can be divided into digestible or nondigestible oligosaccharides (NDOs) on the basis of their physicochemical and physiological properties (Delzenne et al. 2007). NDOs are characterized as resistant to gastric acidity and mammalian enzymes but are partially or completely fermented in the large intestine by the gut microbiota. Several NDOs have been used as functional food ingredients in, e.g., beverages, dairy products, synbiotic products, desserts, confectionary products, sweeteners, and breads and pastries (Wang et al. 2019). Health benefits of NDOs, such as improved defecation, reduction of appetite and postprandial glycemic response, regulation of lipid metabolism, and improvement of mineral absorption, have been discovered (Verspreet et al. 2016). NDOs are attracting increasing interest as prebiotics, as the indigestible ingredients can induce compositional or metabolic improvement in the resident microorganisms; for example, the increase of health-promoting bacteria during fermentation is considered beneficial for the host (Verspreet et al. 2016). Additionally, fermentation of NDOs can promote the production/absorption of certain essential micronutrients and short-chain fatty acids (SCFAs; primarily acetate, propionate, and butyrate), with the latter possibly exerting beneficial effects such as appetite and glycemic control, anti-inflammation, immune regulation, and gut microecology modification (Bindels et al. 2015, Fernandes et al. 2017, Zmora et al. 2019).

On the basis of the modulating effects on metabolic disorders and gut microbiota in the hosts, NDOs are generally considered conducive to reducing obesity, not only because of their fermentability but also their stimulating effects on beneficial colonic bacteria. This review provides an

overview of NDO physicochemical and physiological properties, production methods, and structural confirmation. The beneficial effects of NDOs on obesity and potential mechanisms are also discussed.

SOURCES AND PRODUCTION OF NONDIGESTIBLE OLIGOSACCHARIDES

NDOs have been used extensively as food ingredients, prebiotic supplements, animal and fishery feeds, drug-delivery and immune-stimulating agents, cosmetics, and agrochemicals. Because of their multiple beneficial health effects, their use as food ingredients is attracting increasing interest from the food industry (Wang et al. 2019). Food oligosaccharides can be obtained from natural sources or via enzymatic/chemical processing. Natural NDOs [e.g., fructooligosaccharides (FOS), galactooligosaccharides (GOS), isomaltooligosaccharides (IMO), xylooligosaccharides (XOS)] are typically edible constituents of whole grains (rye, barley, wheat), fruits (banana, yacon), vegetables (onion, tomato, asparagus, sugar beet, artichoke, chicory, garlic, bamboo shoots), and other foods (milk, honey, sugarcane juice, pulses) as well as some plant-based materials (**Table 1**), with concentrations ranging between 0.3% and 20% (Mussatto & Mancilha 2007). The amount of natural NDOs is generally insufficient for scientific research or industrial application. Thus, the development of efficient technologies to improve the production of NDOs has become a new challenge in glycoscience. In addition to direct extraction from naturally available materials by water, methanol, or other alcoholic media with ultrasonic or microwave assistance, many commercial NDOs can be industrially produced from saccharide-based substrates using polysaccharide hydrolysis or enzymatic synthesis.

Depolymerization

Obtaining NDOs from the depolymerization of polysaccharides can be achieved by acidic, physical, or enzymatic hydrolysis. The acidic (e.g., sulfuric, hydrochloric, trifluoroacetic) and physical (e.g., high temperature with gamma radiation, ultrasonication, microwave, ultraviolet light assistance) hydrolysis reactions are relatively simple and easy to control via neutralization of the medium or regulation of physical conditions in industrial production. These procedures generally involve depolymerization, debranching, and/or deesterification of the polysaccharides, leading to low yield and the possible formation of some undesirable or toxic substances (e.g., monosaccharides, hydroxymethylfurfural, melanoidins, furfural) (de Moura et al. 2015). Thus, refining steps, such as solvent precipitation, ion exchange, freeze-drying, and solvent extraction, are necessary (Coelho et al. 2014, Rose & Inglett 2010). Enzymatic hydrolysis is a better choice for large-scale NDO production [such as FOS, XOS, maltooligosaccharides (MOS), and chitosan oligosaccharides (COS)] because of the high conversion rate and minimum adverse chemical modifications in the end products. Enzymes (endoenzymes or exoenzymes) produced by microorganisms can be highly regio- and stereoselective; thus, these enzymes can be exploited for the production of bioactive NDOs. Although efficient, enzymatic hydrolysis is highly dependent on the adaptive capacity of the microorganism to the substrate and the hydrolysis conditions should also be optimized to eliminate the potential microbiological contaminants (de Moura et al. 2015).

Several factors, including yield, cost, purity, environmental waste, and applicable material and reagents, should be considered during hydrolysis method selection. Because acidic and physical hydrolysis are random, the length of chains of the resulting oligosaccharides is generally varied. However, the different enzymes (e.g. source and type) in enzymatic hydrolysis can determine the outcome, including yield and type of product. For example, amylose hydrolysis under acidic and

Table 1 Basic information about different nondigestible oligosaccharides (NDOs)

Type of NDO	Monosaccharides	Glycosidic linkage	Natural occurrence	Industrial production process
Fructooligosaccharides	Fructose, glucose	β-2,1	Onions, chicory, banana, garlic, sugar beet, wheat, asparagus, barley, rye	Inulin hydrolysis, transfructosylation from sucrose
Galactooligosaccharides	Galactose, glucose	β-1,3; β-1,4; α-1,6	Cow milk, human milk, soybean, legumes	Enzymatic process from lactose
Soybean oligosaccharides	Galactose, glucose, fructose	α-1,6; α-1,3	Soybean	Extracted from soybeans whey
Isomaltooligosaccharides	Glucose	α-1,2; α-1,3; α-1,4; α-1,6	Honey, beer, fermented food (miso, soy sauce, sake)	Transgalactosylation of maltose
Maltooligosaccharides	Glucose	α-1,4	ND	Enzymatic process from starch
Xylooligosaccharides	Xylose	β-1,4	Wheat bran, bamboo shoots, corncob, wheat and barley straw	Hydrolysis from xylans
Lactulose/lactosucrose	Galactose, fructose	β-1,4	ND	Alkali isomerization of lactose
Chitosan oligosaccharides	D-glucosamine	β-1,4	ND	Depolymerized products of chitosan or chitin
Arabinooligosaccharides	Arabinose	α-1,5	ND	Enzymatic degradation of sugar-beet arabinan
Arabinoxylan oligosaccharides	Arabinose, xylose	β-1,4; α-1,2; α-1,3	ND	Arabinoxylan degradation
Glucooligosaccharides	Glucose	α-1,2; α-1,3; α-1,4; α-1,6	ND	Fermentation by *Leuconostoc mesenteroides*
Human-milk oligosaccharides	Glucose, galactose, GlcNAc	α-1,2; α-1,3; α-1,4; α-2,3; β-2,6; β-1,3; β-1,4	Human milk	Enzymatic and whole-cell microbial biotransformation
Cyclodextrins	D-glucopyranose	α-1,4	ND	Synthesis from starch
Gentiooligosaccharides	Glucose	β-1,6	Gentian plants	Enzymatic synthesis by β-glycosidases
Isomaltulose (or palatinose)	Glucose, fructose	β-1,6	Honey, cane juice	Produced from sucrose by α-glucosidase reaction of *Protaminobacter rubrum*

Abbreviation: ND, no data.

physical (microwave irradiation) conditions generates carbohydrates with a DP range of 1–37 (with monosaccharides as the most abundant component) (Warrand & Janssen 2007). Enzymes from different species influence the type of generated products. For example, endo-inulinases from *Xanthomonas oryzae* and *Pseudomonas* sp. result in the production of FOS with a DP $\geq$ 5 and DP2 and DP3, respectively (Martins et al. 2019). In addition, the purity of the raw materials used in enzymatic hydrolysis influences the composition of NDOs.

Synthesis

The chemical synthesis of NDOs is generally a laborious multistep endeavor using hazardous/expensive chemical reagents under harsh conditions and with low yields and is currently adopted only to prepare some special oligosaccharides in the laboratory. A combination of enzymes, including glycosyltransferases (which catalyze the transfer of an activated saccharide moiety to a nucleophilic glycosyl acceptor) and glycoside hydrolases (which cleave glycosidic bonds in complex oligosaccharides), are generally used in commercial NDO synthesis (Benkoulouche et al. 2019). Enzymatic synthesis can be applied in virtually any oligosaccharides under the transglycosylation reactions. Glycosyltransferases and glycoside hydrolases are regio- and stereoselective and therefore circumvent the tedious protection/deprotection steps (Zhao et al. 2017). The reaction conditions of enzymatic synthesis are generally mild, strongly controllable, environmentally friendly, highly efficient, and specific to the substrates, which at present can be economically produced at considerable yields (Díez-Municio et al. 2014). Enzymatic synthesis is commercially available for the production of various NDOs, including FOS, GOS, and IMO (**Table 1**). For example, FOS produced from sucrose by glycosyl transfer reactions with fructosyltransferase have a much lower DP range (2–4) than inulin-derived FOS (Rastall 2010). Because the end products after NDO production generally contain monosaccharides, initial substrates, and undesirable or toxic substances, purification of NDOs to homogeneity is necessary. Several methods, including evaporation, ion exchange, chromatographic separation, use of immobilized yeast cells, physical absorption, ultrafiltration, and high-shear rotating disk filtration, have been employed to purify NDOs from sugar mixtures (Kothari et al. 2014).

PHYSICOCHEMICAL PROPERTIES AND STRUCTURE CONFIRMATION OF NONDIGESTIBLE OLIGOSACCHARIDES

In NDOs, the anomeric C atoms (C1 or C2) of the monosaccharide units have a configuration that makes their glycosidic bonds nondigestible to human digestive carbohydrases (Fontana et al. 2017, Roberfroid & Slavin 2000). Food oligosaccharides in the diet are structurally different, which is reflected by the type of hexose moieties (glucosyl-, fructosyl-, galactosyl-, xylosyl-), the DP, and the position of links between the hexose moieties and their conformation (α-, β-). These characteristics determine the physicochemical properties of NDOs, such as solubility, viscosity, particle size, and water-holding capacity, and further influence their physiological effects and industrial application (Delzenne et al. 2007). NDOs are typically regarded as low-calorie (~1.5 kcal per gram) and low-cariogenic sweeteners (0.3–0.6 times as sweet as sucrose) that are readily water-soluble (Delzenne et al. 2007). The sweetness of NDOs depends on the chemical structure and DP of the oligosaccharides, whereas water-binding and gelling properties increase with the number of hexose molecules and reticulation (Mussatto & Mancilha 2007). The viscosifying properties of NDOs in solution depend not only on structure and molecular weight but also on the processing conditions (such as shear rate and temperature) (Verspreet et al. 2016). The stability of NDOs is associated with the number of sugar residues and their ring form, anomeric configuration, and

linkage types. Generally, β-linkages are stronger than α-linkages, hexoses are more strongly linked than pentoses, and hydrolyzation of oligosaccharides occurs under unfavorable conditions such as low pH, elevated temperatures, or prolonged preservation time at room temperature (Mussatto & Mancilha 2007).

The physiological effects of oligosaccharides are associated with their structural characteristics, such as molecular weight, glycosidic linkages, and monomer constituents, and the overall structural complexity (e.g., the presence of decorated side chains) (Sarbini & Rastall 2011). For example, low DP oligosaccharides with more nonreducing ends favor attack by *Bifidobacterium* spp.–produced exo-glycanase (Wang et al. 2019). As some bacteria (e.g., *Bifidobacterium*) are beneficial to human health, it is important to elucidate the structure of NDOs for the investigation of structure–function relationships. Most of the naturally occurring and industrially produced oligosaccharides are generally presented as mixtures, and these fractions can be monitored by either high-performance size-exclusion chromatography coupled with refractive index detector (HPSEC-RI) or high-performance anion-exchange chromatography coupled with a pulsed amperometric detector (HPAEC-PAD) (Wang et al. 2019). The introduction of mass spectrometry allows rapid determination of accurate mass and structural information on oligosaccharides, especially the widely used matrix-assisted laser desorption ionization (MALDI) and electrospray ionization (ESI), both of which are important ionization methods for the production of less fragmentation. Importantly, MALDI–time-of-flight mass spectrometry (TOF/MS) has been used to characterize carbohydrate composition, including information on the linkage and branching patterns as well as fragmentation spectra. And the technique also possesses higher resolution and more favorable ionization effects without derivatization compared with other MS-based techniques (Harvey 1999, Kailemia et al. 2014). Furthermore, the building blocks and corresponding linkage patterns of the oligosaccharides can be elucidated by monosaccharide composition combined with methylation analysis, as these procedures qualify and quantify building blocks of the oligosaccharides after hydrolysis of the fully methylated sugar. The detailed sequencing information, as well as the configuration (α- or β-) of each sugar residue, can be obtained with the help of 1D and 2D nuclear magnetic resonance spectroscopy analyses (Wang et al. 2019).

EFFECTS OF NONDIGESTIBLE OLIGOSACCHARIDES ON OBESITY

Dietary strategy is favored by medical practitioners because it is low cost and has fewer side effects and safety issues. It has been proven that NDOs contribute to weight loss, fat-mass reduction, and improved metabolic parameters in obese humans and rodents. Furthermore, obese individuals had increased satiety and levels of satiety peptides, reduced energy and food intake, and an increase in bifidobacteria and lactobacilli after consumption of NDOs. In the below sections, we describe and discuss the anti-obesity effects of NDOs (animal and human studies). A variety of NDOs have been studied for their potential anti-obesity effects, of which FOS and GOS are the most widely studied and commercially available on the global market.

Effects of Fructooligosaccharides on Obesity

FOS is a generic term for a series of homologous oligosaccharides in plants, composed of linear chains of fructose units linked by β-2,1 bonds (Guo et al. 2016). Humans lack digestive enzymes to break down the β-2,1 covalent bonds of fructans. *Lactobacillus* and *Bifidobacterium* species specifically possess dedicated transporters and intracellular β-fructofuranosidase for the catabolism of mainly low-DP FOS substrates (Delzenne et al. 2011, Goh & Klaenhammer 2015), leading to the improvement of composition and metabolic activity of gut microbiota (Kim et al. 2017).

Supplementation with FOS increases the secretion of satiety hormones, decreases hepatic de novo lipogenesis, eventually decreases food intake and fat-mass development, and improves glucose and lipid metabolism. Furthermore, SCFAs produced from FOS fermentation could reach the circulation to improve host homeostasis (Bindels et al. 2015).

Animal studies. Anti-obesity effects of FOS have been observed in several genetically obese and diet-induced obese animals (**Table 2**). The researchers found that FOS supplementation markedly reduced body weight, fat mass, and serum lipids; increased muscle mass; and improved glucose and lipid metabolism in genetically and diet-induced obese mice (Everard et al. 2011, Frederique et al. 2013). A meta-analysis showed that the consumption of FOS could significantly improve glucose homeostasis, especially via a greater reduction in fasting blood glucose for those with obese/high-fat-diet (HFD) status (−22%) (Le Bourgot et al. 2018). Obesity is associated with the loss of beneficial bifidobacteria and the increase of some key proinflammatory species (e.g., *Peptococcaceae rc4–4* sp., *Peptostreptococcaceae* sp.), leading to the progression of insulin resistance and systemic inflammation. FOS showed favorable bifidogenic effects and inhibition effects of pathogenic or detrimental gut bacteria in genetically and diet-induced obese animals, which in turn decreased the inflammatory markers and reduced adiposity (Everard et al. 2011, Dahiya et al. 2017, Gibson et al. 2017). Along with increased levels of bifidobacteria, a change in proportion of more than 100 taxa and decreased Firmicutes:Bacteroidetes ratio (F:B) were observed after FOS feeding, and the modification of gut microbiota has been proposed to improve leptin sensitivity and glucose and lipid metabolism in obese mice (Everard et al. 2011). Everard et al. (2014) further analyzed the effects of FOS on gut microecology during obesity development. In addition to the gut microbiota modification, FOS also increase the production of organic acids (SCFAs, succinate) and the expression of intestinal antimicrobial peptides, eventually promoting intestinal homeostasis to attenuate obesity. Additionally, the production of SCFAs by FOS fermentation promotes gut hormone secretion, contributing to appetite control and energy metabolism regulation (Huazano-García et al. 2017, Liu et al. 2016).

Maternal obesity is associated with an increased risk of developing gestational diabetes mellitus as well as obesity and insulin resistance in their offspring (Menting et al. 2019). Dietary supplementation with FOS during pregnancy or lactation may normalize body weight, energy metabolism, and the metabolomic signature of insulin resistance in diet-induced obese female Sprague-Dawley rats, ultimately preventing the increase of adiposity in offspring (Dennison et al. 2017, Hallam et al. 2014, Paul et al. 2016). Infants with an increased abundance of *Bifidobacterium* spp. were more likely to maintain a healthy weight as they entered childhood (Collado et al. 2010). Thus, the FOS-induced modification of gut microbiota (such as increased *Bifidobacterium* spp., *Clostridium coccoides*, and *Bacteroides/Prevotella* spp. and decreased *Clostridium leptum* and *Clostridium* cluster XI) may play an important role in the colonization of offspring gut microbial profiles, which ultimately reduce the incidence of obesity (Paul et al. 2016).

Clinical trials. The heterogeneity and differences in dose and duration of FOS may contribute to the limited anti-obesity effects in clinical trials in comparison to animal studies. However, intervention with FOS improved gut microbiota, satiety, energy intake, postprandial glucose, insulin resistance, and low-grade inflammation in obese humans (**Table 3**) (Delzenne et al. 2011, Parnell & Reimer 2009, Reimer et al. 2017). In a randomized controlled trial, 12 weeks of FOS intake (21 g/day) significantly decreased body weight and food intake, serum lipopolysaccharide (LPS), and plasminogen activator inhibitor-1 (PAI-1), and improved glucose metabolism and satiety hormone profiles [suppress ghrelin and enhance peptide YY (PYY)] in overweight and obese adults (Parnell et al. 2017, Parnell & Reimer 2009). Although there was no significant

Table 2 Effect of nondigestible oligosaccharide (NDO) interventions on obesity (animal studies)

NDO	Dosage	Duration (weeks)	Subjects	Indexes for pathological improvement	Change of gut microbiota profiles	Involved therapeutic mechanisms	References
FOS	0.3 g/day	8	Genetically/ diet-induced obese mice	↓Plasma glucose, adipose tissue weight, adipose tissue oxidative stress, inflammation, TG ↑Glucose tolerance, L-cell number, plasma GLP-1, leptin sensitivity	↑*Bifidobacterium* spp., *Akkermansia muciniphila Eubacterium rectale/Clostridium coccoides* group ↓F:B, *Desulfovibrio*, *Roseburia* spp.	Gut microbiota modulation improves glucose homeostasis, leptin sensitivity, and enteroendocrine cell activity	Everard et al. 2011
FOS	0.38 g/day	5	Diet-induced obese mice	↓Cecal content pH, body weight ↑Cecal SCFAs	↑*Prevotella*, *Faecalibacterium*, *Allobaculum* ↓F:B, *Desulfovibrio*, *Lactobacillus*, *Enterococcus*, *Odoribacter*, *Adlercreutzia*, *Ruminococcus*	FOS led to partial microbiota restoration and SCFA production, resulting in body-weight loss	Huazano-García et al. 2017
FOS	10% FOS	7	Diet-induced obese mice	↓Fat mass, body weight, food intake ↑Cecum weight	↑*Bifidobacteria*, *C. coccoides*, *Ruminococcus torques*, *Dorea longicatena* ↓*Bacteroides–Prevotella/ C. coccoides* ratio, *Clostridium leptum*	FOS induced metabolic changes by modulating the composition and activity of the gut microbiota	Frederique et al. 2013
FOS	10% FOS	6	Diet-induced obese rats	↓Body weight, energy intake, fat mass, plasma glucose, and GIP ↑Plasma PYY	↑*Bifidobacterium* spp., *Lactobacillus* spp., *Roseburia* spp. ↓*C. leptum*, *Clostridium* cluster I, *Clostridium* cluster XI, F:B	Improvement of gut hormones and gut microbiota profile contributes to energy intake and adiposity reduction	Cluny et al. 2015
FOS	10% FOS	8	Diet-induced obese rats	↓Energy intake, weight gain, fat mass, insulin and leptin levels, liver TG, glycemic response ↑GLP-1, PYY, cecum weight, insulin sensitivity	↑*Bacteroides–Prevotella* spp., *Bifidobacterium* spp., *Lactobacillus* spp., *Bifidobacterium animalis* ↓F:B, *C. coccoides*, *C. leptum*, *Clostridium* cluster XI and I, *Enterobacteriaceae*	FOS reduced adiposity and modified gut microbiota, improved glucose tolerance	Bomhof et al. 2014

(*Continued*)

Table 2 (*Continued*)

NDO	Dosage	Duration (weeks)	Subjects	Indexes for pathological improvement	Change of gut microbiota profiles	Involved therapeutic mechanisms	References
GOS	0.083, 0.42, 0.83 g/kg	6	Diet-induced obese mice	↓Blood glucose, TC, TG, LDL-C, liver lipid deposition ↑HDL-C, SCFAs	↑*Bifidobacterium*, *Lactobacillus*	GOS positively affected the metabolic disorders and gut bacterial ecosystem	Dai et al. 2017
MOS	6 g/kg	11	Diet-induced obese mice	↓Body-weight gain, adipose size, serum TC and TG, insulin resistance	↑*A. muciniphila*, *Bacteroides acidifaciens*, *Lactobacillus gasseri*, *Bifidobacterium pseudolongum* ↓F:B, *Desulfovibrionaceae*, *Oscillospira*, *Mucispirillum*	MOS corrected the gut microbial dysbiosis related to the improvement of HFD-induced obesity	Wang et al. 2018
AXOS	5% AXOS	4	Diet-induced obese mice	↓Steatosis, hepatic lipids, fat mass, insulin and leptin levels, insulin resistance, hyperglycemia, hypercholesterolemia, GIP	↑*B. animalis*, *B. pseudolongum*	AXOS improved lipids and glucose homeostasis	Neyrinck et al. 2018
COS	200 mg/kg	21	Diet-induced obese mice	↓Blood glucose, TG, LPSs, adipose inflammation ↑Glucose tolerance, insulin secretion, HDL-C, intestinal integrity	↑*Bifidobacterium*, *Lactobacillus*, *Akkermansia*, *Bacteroides* ↓*Desulfovibrio*	COS rebuilt the microbial community and improved metabolic syndrome	Zheng et al. 2018a
BMO	6% BMO	6	Diet-induced obese mice	↓Body weight, LBP, hepatic steatosis, gut permeability, total fat mass, adipocyte cell size ↑Propionate and butyrate levels	↑Ileum α-diversity, *Bifidobacterium*, *Lactobacillus*	Improvement of gut permeability and microbial dysbiosis was related to the anti-obesity effects of BMO	Hamilton et al. 2017
BMO	6% BMO	2	Diet-induced obese rats and mice	No significant improvement was observed	↑Cecum and colon α-diversity, *Lactobacillus* ↓*Ruminococcus*, *Allobaculum*	BMO may provide promising prebiotics to modulate gut microbiota and intestinal barrier function	Boudry et al. 2017

Abbreviations: AXOS, arabinoxylan oligosaccharides; BMO, bovine-milk oligosaccharides; COS, chitosan oligosaccharides; F:B, Firmicutes:Bacteroidetes ratio; FOS, fructooligosaccharides; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; GOS, galactooligosaccharides; HDL-C, high-density lipoprotein cholesterol; HFD, high-fat diet; LBP, lipopolysaccharide binding protein; LDL-C, low-density lipoprotein cholesterol; LPSs, lipopolysaccharides; MOS, maltooligosaccharides; PYY, peptide YY; SCFAs, short-chain fatty acids; TC, total cholesterol; TG, total triglycerides.

Table 3 Effect of nondigestible oligosaccharide (NDO) interventions on obesity (clinical trials)

Type	Dosage	Duration (weeks)	Object	BMI	Indexes for pathologicalimprovement	Change of gut microbiota profiles	References
Fructans (75% FOS)	8 g/d	12	Obese adults	31.6	↓Hunger, desire to eat, energy intake ↑Satiety	↑*Bifidobacterium*, *Akkermansia*, *Lactobacillus*	Reimer et al. 2017
Yacon flour (FOS enriched)	0.1 g/kg	6	Overweight adults	30.4	↓Body weight, waist circumference, waist-to-height index, sagittal abdominal diameter, body fat	Not studied	Machado et al. 2019
FOS	21 g/d	12	Overweight and obese adults	30.4	↓Body weight, fat mass, PAI-1, LPSs	Not studied	Parnell et al. 2017
Inulin:FOS (1:1)	16 g/d	12	Obese women	36.1	Tends to decrease metabolic endotoxemia	↑*Bifidobacterium* spp., *Faecalibacterium prausnitzii*, *Lactobacillus* spp. ↓*Bacteroides intestinalis*, *Bacteroides vulgates*, *Propionibacterium*	Dewulf et al. 2013
FOS-enriched inulin	8 g/d	16	Obese children	26.3	↓Body-weight z-score, fat mass, IL-6, serum triglycerides	↑*Bifidobacterium* spp., *Collinsella* ↓*F. prausnitzii*, *B. vulgates*, *Ruminococcus gauvreauii*	Nicolucci et al. 2017
trans-GOS mixture	5.5 g/d	12	Obese adults	30.7–32.1	↓Plasma CRP, insulin, TC, TG, TC:HDL ratio, fecal calprotectin	↑*Bifidobacterium* spp. ↓*Clostridium histolyticum*, *Desulfovibrio*, *Bacteroides* spp.	Vulevic et al. 2013
GOS	5.5 g/d	10	Normal and overweight elderly adults	22–31	↑NK cell activity, IL-10 production ↓IL-6, IL-1-β, TNF-α production	↑*Bifidobacterium* spp., *Lactobacillus–Enterococcus* spp., *Clostridium coccoides–Eubacterium rectale* ↓*Bacteroides* spp., *Desulfovibrio* spp., *Escherichia coli*, *C. histolyticum* group	Vulevic et al. 2008
α-GOS	6, 12, or 18 g/d	2	Overweight adults	26.3–26.6	↓Satiety, food intake, LPSs, CRP, BMI, variation of body-fat mass, body weight	↑*Bifidobacteria*	Morel et al. 2015
GOS	5 g/d	3	Obese adults	30.0–40.0	↓Colonic permeability	↑*Bifidobacterium* ↓*Bacteroides*, *Lachnobacterium*	Krumbeck et al. 2018
GOS	15 g/d	12	Obese prediabetic individuals	28–40	No significant improvement was observed	↑*Bifidobacterium*, *Prevotella oralis*, *Prevotella melaninogenica* ↓*Bacteroides stercoris*, *Sutterella wadsworthia*	Canfora et al. 2017a
XOS	2 g/d	8	Obese prediabetic individuals	32	No significant improvement was observed	↑*Blautia hydrogenotrophica* ↓*Howardella*, *Enterorhabdus*, *Slackia*	Jieping et al. 2015

Abbreviations: BMI, body-mass index; CRP, C-reactive protein; FOS, fructooligosaccharides; GOS, galactooligosaccharides; HDL, high-density lipoprotein; LPSs, lipopolysaccharides; MOS, maltooligosaccharides; NK, natural killer; PAI-1, plasminogen activator inhibitor-1; SCFAs, short-chain fatty acids; TC, total cholesterol; TG, total triglyceride; XOS, xylooligosaccharide.

improvement in the anthropometric parameters, controlled clinical trials indicated that supplementation with FOS-enriched prebiotics (50/50 inulin/FOS; 16 g/day) plays a beneficial role in the modulation of microbiota and causes modest changes in host metabolism in obese women (Dewulf et al. 2013). An increase in *Faecalibacterium prausnitzii* and *Bifidobacterium* spp. with prebiotics administration was negatively correlated with levels of serum endotoxin (LPS). Furthermore, *Bacteroides intestinalis*, *Bacteroides vulgatus*, and *Propionibacterium* were decreased, with effects on slight decreases in fat mass and other markers (lactate, phosphatidylcholine) of obesity (Dewulf et al. 2013). In a study in obese children, supplementation with FOS-enriched inulin (8 g/day) for 16 weeks significantly decreased body-weight z-score (by 3.1%), percent body and trunk fat (by 2.4% and 3.8%, respectively), serum IL-6, and triglycerides, and corrected obesity-related gut microbiota dysbiosis compared with placebo (Nicolucci et al. 2017). By contrast, Reimer et al. (2017) found that only appetite control was affected by fructans supplementation (75% FOS, 8 g/day) in overweight/obese adults, but the fructans showed favorable bifidogenic effects together with increased abundance of Actinobacteria phylum, *Akkermansia*, and *Lactobacillus* genus. Generally, naturally occurring or industrially produced FOS or FOS-enriched materials used in human studies are presented as mixtures, and a lack of detailed information about the structure and distribution of DP hinders the further analysis of structure–function relationships. Also, intake of less than 10 g/day of NDOs might not affect satiety or food intake in humans, and a higher dose of FOS (16 g/day) for a longer duration (12–16 weeks) is recommended to investigate its effects on appetite control and subsequent energy intake (Korczak & Slavin 2018).

Effects of Galactooligosaccharides on Obesity

GOS are another type of NDO with prebiotic activities and can be divided into two categories: β-GOS, which is derived by enzymatic synthesis from lactose using bacterial galactosidases, and α-GOS, which is isolated from natural sources (Meyer 2015). β-GOS (*trans*-GOS) consists of β-1,6-linked galactosyl residues that terminate in a β-1,4-linked glucose unit, with a mixture of other bond types presented. α-GOS, including raffinose, stachyose, and verbacose, consists of galactosyl residues, which are α-1,6-linked to the glucose moiety of sucrose (Meyer 2015, Mitmesser & Combs 2017). Anti-obesity effects of GOS may be associated with the improvement of metabolic disorders, gut-barrier function, inflammation, and lipid metabolism as well as modification of the gut microbiota (Fernandes et al. 2017, Nath et al. 2018, Overduin et al. 2012).

Animal studies. The positive effects of GOS on obesity are mainly involved in the improvement of metabolic dysregulation, especially the favorable regulatory effects on hyperlipidemia and metabolic endotoxemia, leading to the improvement of host homeostasis. Supplementation with GOS in the diet (7%, w/w) for 18 weeks significantly decreased body weight, FBG (fasting blood glucose), and mRNA expression levels of liver gluconeogenesis, increased the concentration of GLP-1 (glucagon-like peptide-1), and improved insulin resistance in HFD-induced obese mice (Kavadi et al. 2017). Consistent with the effects on body weight and fat-mass reduction, GOS (0.5% in drinking water) also attenuated obesity-associated lipid dysregulation, including decreasing liver steatosis, low-density lipoprotein (LDL) cholesterol, and total cholesterol (TC) levels as well as downregulating the hepatic fatty-acid synthesis gene *ACC-α* on obese mice. Additionally, an increased abundance of gut *Bifidobacterium* and decreased abundance of *C. leptum* were observed after GOS supplementation (Dai et al. 2019). Although some studies showed no significant reduction in body weight, effects of GOS on the improvement of obesity-related inflammation, hyperlipidemia, metabolic endotoxemia, and gut microecology dysbiosis were widely reported (Chappuis et al. 2017, Dai et al. 2017), suggesting a beneficial role of GOS on host homeostasis.

Obesity-associated inflammation and metabolic endotoxemia are generally related to disrupted gut-barrier integrity. GOS can prevent the elevation of HFD-induced CB1R binding density, stimulating synthesis and secretion of mucin by intestinal goblet cells and eventually reinforcing the gut-barrier function to counter obesity-associated inflammation (Bhatia et al. 2015, Yu et al. 2018). Furthermore, GOS fermentation can produce more SCFAs and reduce the formation of putrefactive metabolites compared to apple fiber and sugar-beet pectin in vitro (Aguirre et al. 2014) as well as improve metabolic/bacterial dysbiosis by stimulating the production of SCFAs and growth of health-promoting bacteria (e.g., *Bifidobacterium*, *Lactobacillus*, *Blautia*, and *Akkermansia*) in vivo (Chen et al. 2019, Dai et al. 2017). GOS are structurally similar to the cell surface glycoconjugates (adherent sites for pathogens) in the gastrointestinal tract, which can protect against bacterial colonization and invasion to improve gut microecology (L. Pan et al. 2018).

Clinical trials. The association between consumption of NDOs (FOS and GOS) and incidence of overweight had been evaluated by the Seguimiento Universidad de Navarra project, which showed that subjects in the highest quartile of GOS consumption (>0.45 g/day) had a 17% lower risk of being overweight (Perez-Cornago et al. 2015). However, some of the beneficial effects of GOS demonstrated in animal studies, including improvement of body composition, insulin sensitivity, and lipid profile, are not always duplicated in clinical trials, but the alleviative effects in obese individuals seem to be enhanced with dosage increase (Morel et al. 2015). Consumption of GOS (6, 12, and 18 g/day) for 14 days has been found to dose-dependently reduce appetite, food intake, and inflammation in overweight adults (Morel et al. 2015). Obese prediabetic individuals (15 g/day) and obese adults (5 g/day) whose diets were supplemented with GOS did not show significant improvement in anthropometric parameters or host metabolism (Canfora et al. 2017a, Krumbeck et al. 2018). The high heterogeneity of human obese prediabetics and the relatively low dose and short duration (3 weeks) may be responsible for the variations between studies, and effects of GOS on obese individuals with different status (overweight, obese, obese prediabetic) should be investigated in the future. Consistent with results from animal studies, in obese individuals, GOS administration improved in inflammation and immune function, such as reduction of proinflammatory cytokine levels and increased levels of phagocytosis, NK cell activity, and anti-inflammatory cytokines (Vulevic et al. 2008, 2013). Intake of GOS has been reported to attenuate stress-induced gastrointestinal dysfunction in university students (Hughes et al. 2011). Supplementation with GOS (5.5 or 10 g/day) in overweight or obese diabetic individuals is associated with positive effects on the composition of the gut microbiota (promote the growth of beneficial bacteria and inhibit the growth of opportunistic pathogens) and enhancement of gastrointestinal health (Gonai et al. 2017; Vulevic et al. 2008, 2013). Therefore, GOS-induced improvement of the gut microecology could alleviate metabolic syndrome, lipid homeostasis, and low-grade systemic inflammation in obesity (Fernandes et al. 2017). Furthermore, differential structures and DP might influence the effects of GOS on obesity. Probiotic strains such as *Bifidobacterium lactis* DR10 preferentially utilize GOS with DP3 and DP4, whereas *Lactobacillus rhamnosus* DR20 prefers sugars with DP1 and DP2 (Gopal et al. 2001). β-GOS possesses better bifidogenic effects in comparison with α-GOS in germ-free rats inoculated with a human fecal flora, and the profiles of increased SCFAs were markedly different between the two GOS treatments (Djouzi & Andiueux 1997). These results indicated that GOS with a different structure might have different physiological functions, even regarding the anti-obesity effects.

Effects of Xylooligosaccharides on Obesity

Administration of 10% XOS to HFD-induced obese rats for 12 weeks could improve body composition, dyslipidemia, gut dysbiosis, and inflammation (Thiennimitr et al. 2018, Tunapong

et al. 2018). XOS significantly reduced body and visceral fat weight, dyslipidemia, and food and calorie intake, and attenuated cardiac mitochondrial dysfunction and insulin resistance in obese rats (Tunapong et al. 2018). Furthermore, gut dysbiosis in obese rats, including increased F:B and *Enterobacteriaceae* (LPS-containing bacteria) levels and decreased bifidobacteria levels, was significantly reversed by XOS supplementation (Thiennimitr et al. 2018). Also, XOS reduced adiposity through downregulating both gene expression associated with markers of adipogenesis and fat synthesis and mRNA expression of colon proinflammatory cytokine and circulation of LPS, leading to the improvement of obesity-associated systemic inflammation and peripheral insulin sensitivity (Chunchai et al. 2018, Long et al. 2019).

Effects of Chitosan Oligosaccharides on Obesity

COS have been demonstrated to be effective in reducing calorie intake, body-weight gain, levels of serum glucose, triglycerides, and cholesterol (TC and LDL-c), and alleviating lipid accumulation in the liver and adipose tissues in obese rodents with doses of 25–1,000 mg/(kg·day) (Kumar et al. 2009, Muanprasat & Chatsudthipong 2017, H. Pan et al. 2018). Among these improved parameters related to anti-obesity, COS showed favorable lipid-lowering effects in a number of studies, as COS intake inhibited cell differentiation, triglyceride accumulation, and the expression of adipogenic markers in 3T3-L1 adipocytes and suppressed adipogenesis in rat and mouse models of obesity (Cho et al. 2008, Muanprasat & Chatsudthipong 2017). Also, downregulation of gene expressions for adipose tissue peroxisome proliferator-activated receptor gamma (PPAR-γ), TNF-α, and IL-6; upregulation of adiponectin in adipocytes; and activation of hepatic JAK2-STAT3 signaling pathway in obese rodents by COS treatment are beneficial for lipid metabolism (Kumar et al. 2009, H. Pan et al. 2018). Several lines of evidence have also shown that COS inhibit pancreatic lipase activity and binds with bile acids, leading to the reduction of intestinal fat absorption and an increase in fecal fat excretion (Muanprasat & Chatsudthipong 2017). In addition, obesity-related microbial community dysbiosis and metabolic syndrome may be partly improved by COS treatment, as NDO feeding may maintain the stability of intestinal homeostasis via enhanced gut integrity and the increased abundance of beneficial bacteria and a reduced number of proinflammatory bacteria (Zheng et al. 2018a).

Effects of Arabinoxylan Oligosaccharides on Obesity

Anti-obesity effects of arabinoxylan oligosaccharides (AXOS) were tested in HFD-fed mice for eight weeks. AXOS supplementation increased the levels of circulating satietogenic peptides produced by the colon (GLP-1 and PYY) and coherently counteracted HFD-induced body-weight gain and fat-mass development (Neyrinck et al. 2012). Also, the anti-obesogenic effect of AXOS is associated with a bloom in the genus *Bifidobacterium* and increased fermentation capacity, along with decreased inflammation through the improvement of gut-barrier and endocrine function (Neyrinck et al. 2012). A recent study investigated the differential anti-obesity effect between crude wheat bran and AXOS (extracted from crude wheat bran). Interestingly, AXOS were found to be more efficient in reducing body-weight gain and adiposity than the two fractions of wheat bran with different particle sizes (Suriano et al. 2017). AXOS has profound effects on gut microbiota and goes beyond the bifidogenic effect on obese animals. For example, AXOS significantly increased gut-barrier-protecting bacteria such as *Butyricicoccus* and wholly blunted taxa related to bacteria associated with colitis and inflammatory disorders (*Turicibacter*, *Clostridium*, and Proteobacteria) and related to endotoxin-producing opportunistic pathogens (*Desulfovibrionaceae*) (Suriano et al. 2017). In the MyNewGut project, AXOS were proven to be the best fiber to stimulate the growth of the symbiont *Bacteroides uniformis* CECT 7771. An animal study also

demonstrated that the combination of AXOS and the bacteria could reduce body-weight gain and fat mass to a greater extent than the bacterial strain or the AXOS alone (Delzenne et al. 2019).

Effects of Other Nondigestible Oligosaccharides on Obesity

The HFD-induced gut microbial profile was associated with increased gut permeability linked to increased endotoxemia and a dramatic increase in cell number in the stroma vascular fraction from visceral white adipose tissue; most of the physiological characteristics and gut dysbiosis of the HFD-fed mice could be improved by glucooligosaccharides (Matteo et al. 2012). Another study found that IMO could potentiate the metabolic health benefits of polyphenols on obesity via beneficial modulation of intestinal health, including decreased F:B and an increase in LPS-producing bacteria, together with increased numbers of bifidobacteria, *Akkermansia* sp., and some butyrate-producing bacteria. This modification eventually contributes to the improvements of metabolic endotoxemia, systemic inflammation, and obesity-related parameters as well as increased gut-barrier integrity and higher concentrations of SCFAs (Singh et al. 2018). MOS combined with metformin also showed synergistic effects in ameliorating insulin resistance and augmenting hypoglycemic effects, with the modulation of gut microbiota via the increased abundance of *Akkermansia muciniphila* and *Bifidobacterium pseudolongum* (Zheng et al. 2018b).

MECHANISMS OF NONDIGESTIBLE OLIGOSACCHARIDES IN OBESITY

The gut microbiota play a critical role in the maintenance of host health (e.g., energy harvest, immune regulation, nutrient/xenobiotic metabolism, vitamin production). Unique microbial composition in obese subjects is associated with a higher presence of enzymes targeting complex carbohydrate degradation (e.g., glycoside hydrolase, carbohydrate esterase, glycosyltransferase) for effective energy extraction (Bäckhed et al. 2004, Cox et al. 2015, Muñiz Pedrogo et al. 2018). An obesogenic diet shapes the microbiome prior to the development of obesity. The aberrant gut microbiota profiles (e.g., increased F:B, reduced bacterial diversity and richness, change of some specific bacteria) then contribute to the increased intestinal permeability, LPS translocation, and metabolic endotoxemia as well as disordered host metabolism. All these variations interact with each other to influence the host epigenome and eventually contribute to the pathogenesis of obesity (Cani & Jordan 2018, Qin et al. 2018). Importantly, gut microbiota evolutionarily codevelop with the host and coproduce a large number of small molecule metabolites during the metabolism of food/xenobiotics; many of these metabolites play critical roles in shuttling information between the host and microbial symbionts (Nicholson et al. 2012, Nie et al. 2019a). NDOs have fewer calories in comparison with digestible carbohydrates, and the nondigestible ingredients are mainly fermented in the intestine to induce compositional or metabolic improvement of gut microbiota on obesity, making microbes a link between diet and physiological states via bacterial metabolite generation and gut microecology regulation (**Figure 1**).

Modulating Gut Microbiota

Improving human health by modulation of gut microbiota is a promising strategy that is part of a comprehensive approach to lifestyle wellness. Supplementation with NDOs associated with modulation of the composition and metabolic function of gut microbiota makes microbes a link between NDOs and physiological states.

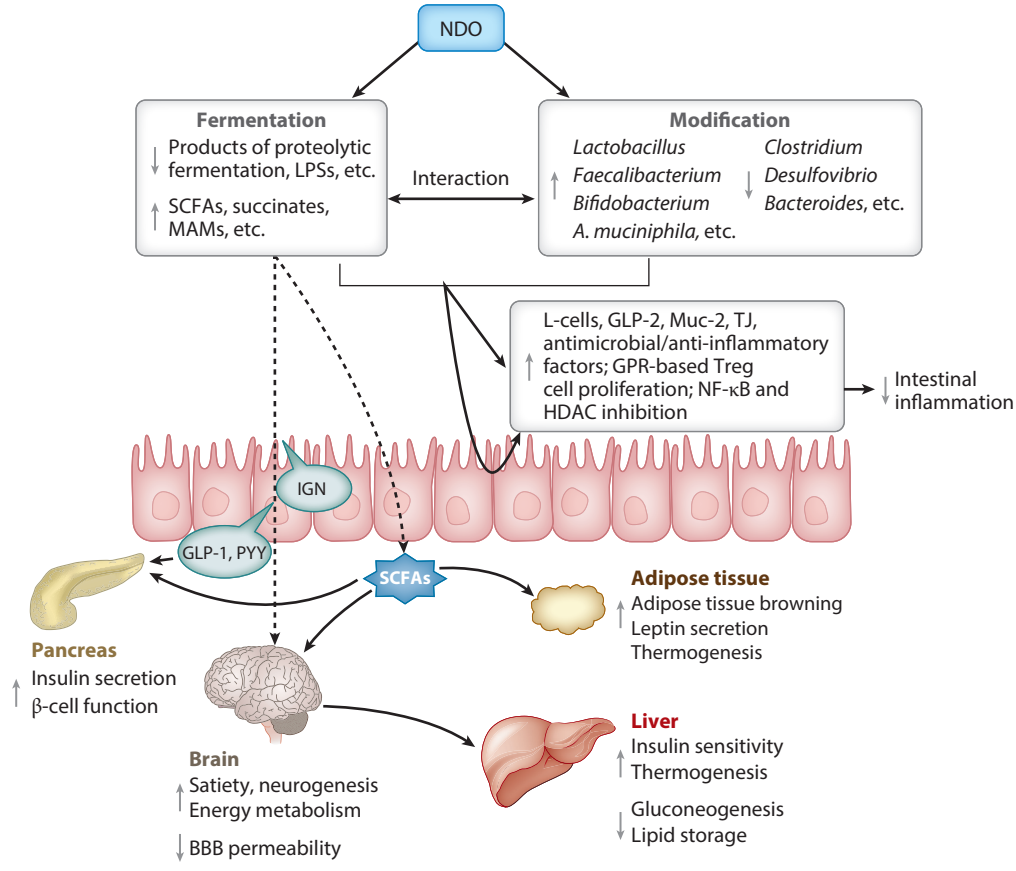

Figure 1

Potential mechanism of nondigestible oligosaccharides (NDOs) on obesity. Intervention with NDOs associated with the modification of the gut microbiota composition confers health benefits to the host via the promotion of saccharolytic fermentation and growth of beneficial bacteria and inhibition of proteolytic fermentation and overgrowth of pathogenic or detrimental gut bacteria. Supplementation with NDOs contributes to the production of short-chain fatty acids (SCFAs) and bacteria/host-derived antimicrobiota/anti-inflammatory components, along with decreased levels of lipopolysaccharides (LPSs) and detrimental catabolites. The fermentation and modification procedures contribute to the reinforcement of the gut-barrier function to decrease the leakage of bacteria, LPSs, and toxins and regulation of SCFAs-GPR (G protein–coupled receptor)-based Treg cell expansion/generation, NLRP3 inflammasome activation, and histone deacetylase (HDAC) inhibition, eventually reducing intestinal inflammation and metabolic endotoxemia caused by obesity. Furthermore, SCFAs stimulate the secretion of gut hormones (PYY and GLP-1) and can be converted into glucose by intestinal gluconeogenesis (IGN), leading to satiety, thermogenesis, and decreased hepatic glucose production, thereby improving glucose and energy homeostasis. Small amounts of SCFAs that reach the circulation can also directly affect the adipose tissue, brain, liver, and pancreas, counteracting hepatic steatosis, insulin resistance, and adiposity by modifying gene expression at the tissue level, inducing overall beneficial metabolic effects. All of these improvements may be associated with the management of obesity. Abbreviations: *A. muciniphila*, *Akkermansia muciniphila*; BBB, blood–brain barrier; MAMs, microbial anti-inflammatory molecules; TJ, tight junction.

Promotion of probiotic microbes. The accumulating bacterial genomic data and application of molecular-based methods have made it evident that a broad range of members of the gut microbial community, especially *Lactobacillus* and *Bifidobacterium* species—which are the prototypical groups of probiotic microbes that have beneficial physiological effects on obesity via NDO administration—are endowed with a wide range of NDO-degrading abilities (Goh &

Klaenhammer 2015). Lactobacilli and bifidobacteria are positively correlated with weight loss and negatively correlated with the development of fat mass, glucose intolerance, and LPS level (Dewulf et al. 2013, Vinke et al. 2017). Universal mechanisms of the two microbes, including the normalization of perturbed microbiota, production of useful metabolites or enzymes, and reinforcement of gut barrier, are observed across taxonomic groups. Other beneficial effects, such as endocrinological effects or immune modulation, that improve host homeostasis and inflammation are more likely to be strain specific (Hill et al. 2014). Furthermore, NDOs fermented by bifidobacteria and lactobacilli stimulate the production of lactate and acetate, which in turn can be converted into butyrate via microbial cross-feeding (Rivière et al. 2016). However, concentrations of SCFAs displayed limited growth after NDO administration in some clinical cases, which may be associated with the heterogeneity of host and metabolic status (such as obese prediabetic) (Canfora et al. 2017a, Salazar et al. 2015).

It is important to recognize that fermentation of oligosaccharides does not selectively influence only one or two probiotic species based on the new definition of prebiotics. The selective effect of NDOs could extend to several microbial groups to evoke health benefits. Other commensals with beneficial attributes toward obesity (especially on metabolic endotoxemia), such as *F. prausnitzii* and *A. muciniphila*, were also found to be increased by different NDOs (e.g., FOS, IMO, MOS, COS) in both animal studies and human clinical trials (Dewulf et al. 2013, Huazano-García et al. 2017, Reimer et al. 2017, Santacruz et al. 2010, Zheng et al. 2018a,b). *F. prausnitzii* is negatively correlated with serum LPS and positively correlated with body compositional changes. In metabolic aspects, utilization of complex carbohydrates, simple sugars, or acetate to produce butyrate, formate, and D-lactate by *F. prausnitzii* is strain specific (Hiippala et al. 2018). In addition to the health benefits of butyrate production, *F. prausnitzii* is well known by its anti-inflammatory effects through secreted microbial anti-inflammatory molecules (MAMs; peptides or protein) to inhibit the NF-κB pathway and IL-8 production as well as promote regulatory T-cell production (Breyner et al. 2017, Lopez-Siles et al. 2017). Furthermore, *F. prausnitzii* is also important in epithelial homeostasis, as this bacterium is metabolically complementary to *Bacteroides thetaiotaomicron* and modulates the intestinal mucus barrier by modifying goblet cells and mucin glycosylation (Wrzosek et al. 2013).

Decreased levels of *A. muciniphila* (a mucin-degrading bacterium) have been reported in both obese animals and human; the species is inversely linked with the symptoms of obesity, especially plasma glucose, triglycerides, body-fat distribution, and metabolic endotoxemia (Dao et al. 2016, Shanahan et al. 2017). Reduced mucus layer thickness and increased bacterial-to-epithelium distance lead to microbiota encroachment, whereas the integrated gut barrier is associated with mucus layer thickness, epithelial cell renewal, and tight-junction (TJ) protein expression (Chassaing et al. 2017). Some NDOs (e.g., FOS) seem to act through distinct mechanisms that result in an intestinal environment propitious for the growth of *A. muciniphila* (Nie et al. 2019a). SCFAs (especially butyrate) produced by NDO fermentation promote the expression of mucin 2 mRNA, resulting in a mucus secretion by goblet cells that creates a favorable environment for *A. muciniphila*. *A. muciniphila* also degrades mucins to generate SCFAs, which in turn stimulates mucus secretion for the development of the integrated and impenetrable mucus layer (Anhê et al. 2016, Nie et al. 2019a). Additionally, *A. muciniphila*–derived extracellular vesicles can also improve gut permeability through the regulation of TJs by the AMPK pathway (Chelakkot et al. 2018). However, fiber deprivation results in the excessive degradation of the colonic mucus layer by *A. muciniphila*, which promotes epithelial access and lethal colitis by the mucosal pathogen, suggesting detrimental or beneficial potential is also dependent on the specific circumstance (Desai et al. 2016).

In addition to the probiotic microbes from NDO supplementation that help reduce obesity, other species with anti-obesity effects should also be considered. In a recent study, researchers

found disturbed gut microbiota composition (increased *Desulfovibrio* and decreased Clostridia) contributes to driving the obesogenic phenotype in mice with impaired immune systems, and Clostridia could function to reduce lipid uptake through downregulation of lipid sensor CD36 and exert anti-obesity effects (Petersen et al. 2019). Clostridia was found to be influenced by NDO treatment in obese rodents and humans (**Tables 2** and **3**); therefore, the function and strain-specific effects of Clostridia on obesity should be considered in the future. In the MyNewGut project, growth of the symbiont *B. uniformis* CECT 7771 can be stimulated by AXOS and may have anti-obesity effects, especially when combined with AXOS (Delzenne et al. 2019). Furthermore, *Christensenella minuta*, a cultured member of the *Christensenellaceae*, was also reported to negatively correlate with the BMI (Goodrich et al. 2014). Notably, neither of the clinical trials assessed the function of these microbes on obesity. This emphasizes a need for not only in vitro/in vivo studies assessing the role of NDOs in the growth of these potential probiotic microbes but also clinical trials assessing the potential mechanistic roles of these gut microbes.

Inhibition of pathogenic or detrimental gut bacteria. Administration of NDOs (or enrichment of *Bifidobacterium* spp.) decreases the amount of *Bacteroides* in human clinical trials (**Table 3**), but the phenomenon seems to rarely appear in animal studies (**Table 2**). Differences in obesogenic dietary patterns, such as protein-enriched diets in humans and fat-/sucrose-enriched diets in animals, might be responsible for this phenomenon because bacterial groups such as *Bacteroides* and Clostridia are recognized as having proteolytic fermentation ability (Bindels et al. 2015). The decrease of these commensals by NDOs also represents the inhibition of proteolytic fermentation. *Desulfovibrio* damages the gut barrier and promotes inflammation by inhibiting butyrate oxidation and decreasing energy supply to colonocytes (Roediger et al. 1993, Singh & Lin 2015). Furthermore, *Enterobacteriaceae*, *Desulfovibrio*, and *Bacteroides* are major LPS producers (Xie et al. 2016). The expansion of *Desulfovibrio* could upregulate the lipid sensor CD36, leading to the uptake of more long-chain fatty acids (Petersen et al. 2019). Overall, the decrease of these species by NDOs reinforces gut-barrier function and attenuates intestinal/systemic inflammation in obesity.

Improvement of Gut Health

Gut health is influenced by a variety of interactions between host, intestinal bacteria, and external factors that affect the physiological functions of the intestine and host metabolism. Increased animal-based food consumption (rich in dietary fat and protein) may induce dysbiosis of the gut microbial community, leading to the accumulation of detrimental metabolites that have been postulated as major triggers of metabolic impairments associated with obesity. High-fat diets induce a reduction in the loss of individual and total SCFAs as well as an increase in host-microbiota cometabolites (fat-derived fatty acids and induced bile acids) that are associated with host metabolic disorders (Salonen & de Vos 2014, Wan et al. 2019, Zou et al. 2018). Unlike the dietary fat absorbed in the small intestine, fermentation of undigested protein in the distal colon yields a variety of metabolites, including branched-chain amino acids (BCAAs), aromatic amino acids (AAAs), ammonia, gases, indolic/phenolic compounds derived from AAAs, and branched-chain fatty acids derived from BCAAs, depending on the amino acid composition and protein contents. Many of these metabolites are detrimental to gut health and are associated with obesity and insulin resistance (Canfora et al. 2019, Koh et al. 2018, Pedersen et al. 2016).

Improvement of gut health is associated with the prevention of pathogenic infection and inhibition of detrimental compound production. In addition to the inhibitory effects of some specific bioactive NDOs [such as COS and HMO (human milk oligosaccharides)] on gut pathogens,

SCFAs fermented from NDOs may lower intestinal pH to inhibit the overgrowth of pH-sensitive pathogenic bacteria (Nie et al. 2019b, L. Pan et al. 2018, Zou et al. 2016). NDO fermentation stimulates the growth of beneficial bacteria that antagonize the colonization of detrimental bacteria through competitive exclusion and production of compounds with antibiotic or immunomodulating effects (Verspreet et al. 2016). Furthermore, NDOs such as FOS were found to increase the expression of antimicrobial factors (e.g., Reg3g, Pla2g2, and Lyz1) in obese candidates, leading to the production of antimicrobial peptides for the improvement of gut microbiota homeostasis and physical segregation of commensal microorganisms from host tissue (Everard et al. 2014). Additionally, the selective stimulation of bifidogenic bacteria by saccharolytic pathways can suppress proteolytic fermentation in the colon, which further improves the intestinal environment through inhibiting the production of toxic catabolites (Singh et al. 2015).

Successful prevention of infections by pathogens/toxic components requires appropriate actions from the host's defense system. Mucins (mainly mucin 2) secreted from goblet cells within the mucosa and TJs between the mucosal epithelial cells constitute the primary physical intestinal barrier (Brahe et al. 2016). Leakiness of detrimental components can be caused by epithelial damage or dysregulation of TJ proteins triggered by proinflammatory cytokines. The SCFAs, especially butyrate, which is the preferred substrate for the colonocytes, have beneficial effects on gut-barrier function because of their ability to modulate the expression of mucins and TJ proteins. Translocated LPSs can trigger host defense response by initiating the release of the gut peptide glucagon-like peptide-2 (GLP-2) on enteroendocrine L cells to promote intestinal repair (Gribble & Reimann 2019). In contrast, SCFAs can positively stimulate expression and secretion of GLP-2 to maintain the gut-barrier function and reduce LPS translocation under obese conditions (Verspreet et al. 2016). Furthermore, it has also been suggested that some NDOs associated with increased expression of intectin, which accelerates apoptosis of intestinal epithelial cells to promote epithelial cell renewal, lead to the reinforcement of barrier function (Everard et al. 2014, Hidefumi et al. 2004). Other mechanisms, including antioxidant activities of fructan and butyrate, promote intestinal epithelial O_2 consumption (epithelial metabolism of butyrate) to stabilize the hypoxia-inducible factor for barrier protection and have also been reported for the reinforcement of gut-barrier integrity and inhibition of protein oxidation (Kelly et al. 2015, Pasqualetti et al. 2014). Collectively, the promotive effects of NDOs on gut health can be attributed to the inhibition of pathogenic colonization, stimulation of mucin production, reinforcement of the gut barrier, and reductions in the levels of toxic catabolites in the intestine. All these improvements ultimately protect the intestinal epithelium against chemical/biological hazards and boost immunoregulatory signal delivery.

Improvement of Energy Metabolism

Improvement of energy metabolism by regulation of energy intake and energy expenditure through fermented products (SCFAs and succinate) by gut microbiota is crucial to body-weight control. Supplementation with fermentable NDOs, SCFAs, or SCFA-containing materials has been observed to reduce body weight in both rodent and human studies (Canfora et al. 2019, Chambers et al. 2015). NDOs increased the number of endocrine L-cells (e.g., FOS) and levels of SCFAs to stimulate the secretion of satiety hormones (GLP-1 and PYY) via the dependent manner of G protein–coupled receptors (GPR41 and GPR43), especially those hormones found at the highest density in the ileal and colonic epithelium. GLP-1 and PYY could inhibit/delay gastric emptying and gastric acid secretion via the gut–brain axis by neuropeptide Y suppression and proopiomelanocortin neuron activation in the hypothalamic arcuate nucleus, resulting in eating behavior modification and postprandial glycemia regulation (Canfora et al. 2015). SCFAs can

also directly target central nervous system–related pathways for appetite and energy regulation; for example, butyrate suppresses the activity of orexigenic neurons that express neuropeptide Y, and acetate induces an anorectic signal by increasing the glutamate–glutamine cycle and γ-amino butyric acid neuroglial cycle in the hypothalamus (Frost et al. 2014, Li et al. 2018). However, although acetate can promote the secretion of the insulin through parasympathetic nervous system activation, the hunger hormone (ghrelin) also increases simultaneously and thus facilitates food intake, suggesting that further research is required to investigate the role of acetate/SCFAs on energy regulation (Perry et al. 2016). In addition, SCFAs may also promote the secretion of the adipose-tissue-derived satiety hormone leptin via activation of GPR41 to improve insulin sensitivity and satiety control through multiple mechanisms, including molecular and neural regulation (Canfora et al. 2019, Pan & Myers 2018).

In an interesting animal study, improved glucose tolerance, insulin sensitivity, and body weight via SCFAs or dietary fiber were completely abolished in mice deficient in intestinal gluconeogenesis (IGN) (De Vadder et al. 2014). Unlike the increased hepatic glucose production positively related to insulin resistance, IGN contributing approximately 20–25% of total endogenous glucose is associated with inhibition of hepatic glucose output and improvement of glucose homeostasis (Kim et al. 2017). Propionate can be used as a substrate and activates gene expression (GPR41) of IGN through the gut–brain neural circuit, whereas butyrate can directly activate IGN-related gene expression in enterocytes via the cAMP-dependent mechanism (De Vadder et al. 2014). Furthermore, microbiota-produced succinate can improve glucose homeostasis and body weight via IGN (De Vadder et al. 2016). Glucose produced by IGN is sent to the portal vein, at which point the periportal neural system can sense glucose and send a signal to the brain, thus improving glycemic control and energy homeostasis (Mithieux 2014).

In addition to the regulation of energy intake, SCFAs (acetate and butyrate) may also beneficially affect body-weight control by increasing lipid oxidation and energy expenditure (Canfora et al. 2017b, Gao et al. 2009). This effect might be partly related to the increased expression of thermogenesis-related genes and proteins, such as PPAR-γ coactivator (PGC)-1α, uncoupling protein (UCP)-1, UCP-2, acetyl-CoA oxidase, and carnitine palmitoyltransferase-I in liver and brown adipose tissue (Gao et al. 2009, Kondo et al. 2009). Furthermore, supplementation with sodium butyrate increased the proportion of type 1 oxidative muscle fibers (associated with fat oxidation for ATP biosynthesis) and PPARδ (associated with fatty-acid oxidation) expression in skeletal muscle, which suggests the beneficial roles of butyrate are related to the promotion of energy expenditure and the induction of mitochondrial function (Gao et al. 2009). Although human trials indicated that SCFA supplementation increased the resting energy expenditure and fasting lipid oxidation in both obese and healthy individuals (Chambers et al. 2018, van der Beek et al. 2016), further studies such as tissue biopsy and stable isotope tracers are warranted to provide mechanistic insight into the association between the SCFAs and the energy metabolism.

Reduction of Intestinal Inflammation

Obese individuals are characterized by lower bacterial alpha diversity and gene counts that carry a higher proportion of potentially proinflammatory *Bacteroides* as well as by the accumulation of LPSs and proinflammatory factors (Emmanuelle et al. 2013, Wan et al. 2019). From a molecular point of view, microorganism-associated molecular patterns (MAMPs; e.g., LPSs, flagellin, peptidoglycan) derived from gut microbiota engage in complex signaling cascades by pattern recognition receptors (PRRs) such as transmembrane surface receptors or endosome Toll-like receptors (TLRs). Under normal situations, MAMPs typically induce secretion of anti-inflammatory cytokines (e.g., TSLP, IL-33, IL-25, TGF-β) by intestinal epithelial cells. TGF-β also suppresses

NF-κB-dependent proinflammatory signaling in intestinal macrophages and dendritic cells (DCs) (Maynard et al. 2012, Winer et al. 2016). In contrast, upon LPS accumulation, barrier breach, or pathogen invasion, LPSs bind TLR-4 to activate NF-κB, eventually triggering the transcription of various cytokines and chemokines by MYD88-dependent pathways (Cani & Jordan 2018). Indeed, patients with obesity generally have higher circulating levels of inflammatory markers (such as IL-6, IL-1, TNF-α, and MCP-1) and LPSs (by leaky intestinal TJs or infiltrating chylomicrons), suggesting inflammation and metabolic endotoxemia.

Certain bacterial taxa, including *Bifidobacterium* and *F. prausnitzii*, are inversely correlated with levels of LPSs, high-sensitivity C-reactive proteins, and some proinflammatory cytokines (van den Munckhof et al. 2018). SCFAs fermented from NDOs may be responsible for the anti-inflammatory effects. Because of the inhibition effects of the NF-κB pathway and reduction of LPSs, TNF-α and IFN-γ were observed in both in vitro and in vivo studies (Canfora et al. 2015). The main anti-inflammatory effects of SCFAs are mainly involved in SCFA-GPR-based Treg cell expansion/generation, NLRP3 inflammasome activation, and histone deacetylase (HDAC) inhibition. In addition to the activation of GPR43 on Treg cell proliferation by SCFAs, butyrate can induce production of IL-10 and retinoic acid by DCs through activation of the GPR109A. These DCs further stimulate the conversion of naive T cells into Treg cells and suppress the generation of Th17 cells (Singh et al. 2014, Sivaprakasam et al. 2016). Meanwhile, SCFAs either induce transcription of IL-18 (through GPR109A) or stimulate potassium efflux that drives activation of the NLRP3 inflammasome to produce mature IL-18 and IL-1β on enterocytes (through GPR43), thus contributing to the suppression of colonic inflammation (Macia et al. 2015, Man 2018). Also, SCFAs (mainly butyrate and propionate) are known to act as HDAC inhibitors, which exert anti-inflammatory effects; for example, butyrate downregulates proinflammatory effectors in lamina propria macrophages and regulates cytokine expression in T cells (Liu et al. 2018, van den Munckhof et al. 2018). Other mechanisms, such as inhibition of NF-κB and IFN-γ signaling pathways and activation of PPAR-γ by butyrate to exert anti-inflammatory effects, were reported previously (Liu et al. 2018).

CONCLUSIONS AND PERSPECTIVES

NDOs have been used extensively in the fields of food, pharmaceuticals, and cosmetics as a result of their various specific properties and multiple beneficial health effects. The majority of NDOs are commercially available via industrial production through depolymerization or synthesis. However, drawbacks such as a wide DP range, the presence of toxic/undesirable substrates, and low final product yields are still challenges to scientific research and industrial application. NDOs are generally mixtures of oligosaccharides with different DPs. Their physicochemical and physiological properties are strongly associated with their compositions, which in turn affect the production process. For this reason, enzymatic synthesis might have more advantages for investigating structure–function relationships because of cost-effective substrates (such as glucose, sucrose, and lactose) and relatively higher homogeneity in comparison with products with a wide range of DPs obtained by hydrolysis/extraction.

The effects of NDOs on obesity have been well investigated in the past decade. There is no doubt that administration of NDOs can improve obesity if the dosage and duration time are appropriate, and improvement of body composition, hyperlipidemia, inflammation, energy intake, and gut microbiota are observed in obese individuals. As NDOs are fermented by gut microbiota in the intestine, the modification of gut microbiota and production of SCFAs are fundamental for NDOs to exert anti-obesity effects. Yet the heterogeneity and complexity of the hosts and gut microbiome, type of NDO, and differences in dose and duration, as well as the

contradictory results in mechanism research, made it difficult for the scientific community to prove the anti-obesity effects of NDOs. For instance, supplementation with FOS led to a decrease in abundance of SCFA-producing bacteria (e.g., *F. prausnitzii*, *Propionibacterium*) (**Table 3**), and SCFAs/succinate produced by gut microbiota may contribute to the increased risks of obesity/diabetes (e.g., acetate on ghrelin secretion, propionate on increased risk of T2D, activation of SUCNR1/GPR on inflammation) (Ang & Ding 2016, Perry et al. 2016, Sanna et al. 2019, Serena et al. 2018, van Diepen et al. 2017). Although the decrease of some specific bacteria is inversely associated with host homeostasis, it is important to keep the diversity and abundance of these bacteria by dietary intervention (e.g., NDOs).

The structure of NDOs may impact their anti-obesity effects and gut microbiota modification. For example, low-molecular-weight COS (≤1,000 Da) reduced more body weight than did high-molecular-weight COS (≤3,000 Da); probiotic strains such as *B. lactis* DR10 preferentially utilizes GOS with DP3 and DP4, whereas *L. rhamnosus* DR20 prefers sugars with DP1 and DP2 (Gopal et al. 2001, Huang et al. 2015). Research focused on understanding the structure–function relationships contributes to the development of the functional food market toward specific health needs. Furthermore, the role of gut microbiota and their metabolic activities during the onset and progression of obesity must be elucidated. Microbiome-based themes during dietary intervention, e.g., (*a*) gut microbiota responds rapidly to significant changes in diet, (*b*) long-term dietary habits are a dominant force in the composition of gut microbiota, and (*c*) phenotypes can be influenced by the individualized nature of their gut microbiota, should also be considered. Finally, future studies should focus on the dynamic gut microbiota changes in composition and metabolic activity during NDO supplementation and may provide detailed information about the gut microecology, which may help in designing novel dietary strategies for preventing and/or treating obesity.

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