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INVITED REVIEW

Non-digestible oligosaccharides-based prebiotics to ameliorate obesity: Overview of experimental evidence and future perspectives

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Abstract

The diverse populations reportedly suffer from obesity on a global scale, and inconclusive evidence has indicated that both environmental and genetic factors are associated with obesity development. Therefore, a need exists to examine potential therapeutic or prophylactic molecules for obesity treatment. Prebiotics with non-digestible oligosaccharides (NDOs) have the potential to treat obesity. A limited number of prebiotic NDOs have demonstrated their ability as a convincing therapeutic solution to encounter obesity through various mechanisms, viz., stimulating beneficial microorganisms, reducing the population of pathogenic microorganisms, and also improving lipid metabolism and glucose homeostasis. NDOs include pectic-oligosaccharides, fructo-oligosaccharides, xylo-oligosaccharides, isomalto-oligosaccharides, manno-oligosaccharides and other oligosaccharides which significantly influence the overall human health by different mechanisms. This review provides the treatment of obesity benefits by incorporating these prebiotic NDOs, according to established scientific research, which shows their good effects extend beyond the colon.

Keywords Prebiotics · Non-digestible oligosaccharides · Obesity · Beneficial microorganisms · Lipid metabolism and Glucose homeostasis

Introduction

Obesity, an accumulation of abnormal fat that leads to detrimental health effects (Cerdó et al., 2019) and currently believed to be a global pandemic that affects over 1 in 3 people (Mazloom et al., 2019). The pervasiveness of obesity is continuously increasing worldwide, and the world health organization (WHO) estimates that about 39% of today's people in society will be affected by obesity in 2035 (WHO Consultation on Obesity (1999: Geneva and Organization, 2000). Efforts to control obesity has made slow progress in the last decades, but have identified the various factors or its complex interactions which play a distinct role in the effect of obesity (Mazloom et al., 2019). Among the array of factors, gut microbiota is reported to influence obesity. A large body of evidence has described the association of gut microbiota (composition and their metabolic functions) in obesity development (Abenavoli et al., 2019).

The trillions of microorganisms that constitute the human gut significantly contribute to host energy homeostasis through symbiotic relationships (Dahiya et al., 2017). Gut dysbiosis has been reported to cause disequilibrium in energy homeostasis leading to obesity and other metabolic syndromes (Abenavoli et al., 2019). Gut-residing beneficial microorganisms called "Probiotics" are demonstrated to offer anti-obesity effects through the degradation of "Prebiotics/dietary fibers". Probiotics which are characterized as live microorganisms that, when delivered to a host in sufficient quantities, confer various health benefits. Prebiotics are a class of NDOs that bacteria can biotransform to have health effects potentially. Though the prebiotics utilized directed initially to treat various gastrointestinal ailments, since the past decade, the prebiotics efficacy to combat obesity via the production of SCFAs, increasing the beneficial bacteria abundance (Liu et al., 2019) and by decreasing the abundance of Firmicutes/Bacteroidetes (F/B) ratio (Turnbaugh et al., 2006).

The mechanism through which they offer anti-obesity effect is detailed in the below section and is via reducing adipose fat mass (Long et al., 2019) and inflammatory

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responses (Yan et al., 2019), suppression of the peroxisome proliferator-activated receptor γ (PPARγ) gene expression, activation of the leptin signal pathway, and reduction of lipid accumulation (Huang et al., 2015). Considering the therapeutic prebiotic's potential, it is now significant to understand its anti-obesity functions for its integration into various health solutions and inclusive wellness. In this review, numerous prebiotic NDOs are discussed with the reported therapeutic benefits which help to explain the evidence that they have anti-obesity properties at the pre-clinical and clinical stages. In a separate section, the putative mechanism through which the anti-obesity impact is shown is highlighted. The concluding section of the analysis the obvious knowledge gaps and potential research directions.

Prebiotic oligosaccharides

Oligosaccharides are organic molecules made up of monosaccharide units with a degree of polymerization ranging from 2 to 10 (Nie et al., 2020). Oligosaccharides are grouped into digestible and non-digestible oligosaccharides (NDOs) based on their physiological and physicochemical properties (Delzenne et al., 2011). NDOs are categorized as prebiotics based on their ability to resist digestion to mammalian enzymes and gastric acidity and their ability to get fermented completely in the colon by probiotics (Nie et al., 2020). Prebiotic NDOs are widely used as supplements, food ingredients, fishery, and animal feeds, immune-stimulating and drug-delivery agents, agrochemicals and cosmetics. The food industry is increasingly paying attention to their utilization as food additives due to their abundance of beneficial health effects (Wang et al., 2020).

Nutritional modulation of probiotics by NDOs promotes short-chain fatty acids (SCFAs) production, propionate, primarily butyrate, and acetate, with the latter reported to exert anti-obesity effects, including glycemic control and appetite, anti-inflammation, and immune regulation via modification of gut microecology) (Zmora et al., 2019). Prebiotic NDOs can be found in various natural sources and could be synthesized using different enzymes commercially (Lockyer and Stanner, 2019). Prebiotic NDOs includes fructo-oligosaccharides (FOS), xylo-oligosaccharides (XOS), isomalto-oligosaccharides (IMO), pectic-oligosaccharides (POS), manno-oligosaccharides (MO) are the edible ingredients found in fruits (yacon, banana), grains (wheat, rye, and barley), vegetables (tomato, asparagus, garlic, chicory, onion, sugar beet, bamboo shoots) and other foods viz., sugarcane juice, milk, and honey (Nie et al., 2020) with their concentrations in the range of 0.3–20% (Mussatto and Mancilha, 2007). Due to their insufficient attention in natural sources, their production at an industrial scale for scientific research and to offer prebiotic activity has gained considerable interest in glycoscience. Few NDOs are extracted naturally via microwave and ultrasound assistance using water or alcoholic solvents, whereas other NDOs are produced industrially via the enzymatic synthesis process (Nie et al., 2020).

Fructo-oligosaccharides

Fructo-oligosaccharides (FOS) are commercially produced via enzymatic synthesis using fructosyltransferase from the substrate, sucrose by glycosyl transfer reactions (Rastall, 2010). The synthesized FOS will consist linear chain of fructose units linked by the β-2,1 bond (Guo et al., 2016). The specific digestive enzymes lacking in humans to hydrolyze β-2,1 covalent bonds of FOS which make them better substrates for gut-residing probiotics as they possess intracellular β-fructofuranosidase to catabolize low-degree of polymerization of FOS (Goh and Klaenhammer, 2015). SCFAs produced from FOS fermentation are reported to offer an anti-obesity effect by enhancing the concentration of satiety hormones secretion by decreasing food intake and fat mass accumulation (Bindels et al., 2015).

Galacto-oligosaccharides

Galacto-oligosaccharides (GOS) is another prebiotic NDOs type, classified as α-GOS and β-GOS or trans-GOS. α-GOS is made up of 1,6 connections and is isolated from natural sources. Bacterial galactosidases are used in the enzymatic manufacture of β-GOS, which is made up of terminally connected glucose and internal β -1,6-linked galactosyl residues (Meyer, 2015; Mitmesser and Combs, 2017). The ability of GOS to alter gut microbiota, lipid metabolism, and gut-barrier function is considered to have an anti-obesity impact (Canfora et al., 2017).

Isomalto-oligosaccharides

Isomalto-oligosaccharides (IMO)s are the oligosaccharide mixture typically consisting of mainlyα-1,6 glucosidic bonds between glucose units and lesser extent by α-1,2, α-1,3, α-1,4 linkages (Sorndech et al., 2018). Production of IMO is through a 2-step process using an initial substrate, starch. Starch has been hydrolyzed thermally, and the concomitant action of α-amylase and pullulanase, hydrolyzed into maltose (Vera et al., 2021). In the next stage, α-glucosidase produces IMO from maltose with a degree of polymerization ranging from 2 to 6 by transglucosylation (Divyashri et al., 2021). IMO offers anti-obesity benefits by improving

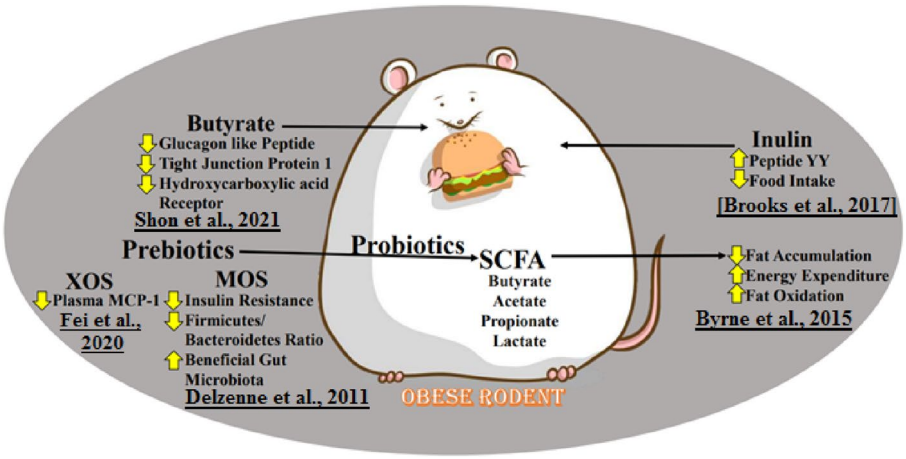

Fig. 1 Relationship between intestinal microbiota, prebiotics and obesity

adipose tissue fat mobilization and reducing gut inflammation (Singh et al., 2017a, 2016).

Xylo-oligosaccharides

Lignocellulosic materials (LCMs) rich in xylan embodies as a source to produce Xylo-oligosaccharides (XOS) (Jain et al., 2015). On an industrial scale, enzymatic, chemical, or a combination of enzymatic and chemical operations will hydrolyze LCMs to generate XOS (Jain et al., 2015). Chemically synthesized XOS using dilute solutions of alkali, mineral acids, or steam results in the monosaccharides generation along with XOS, with a broad degree of polymerization (Divyashri et al., 2021). Exo-xylanase, β-xylosidase and endo-xylanase, and debranching enzymes are employed in the commercial production of pharmaceutically significant and food-grade XOS by the enzymatic method from LCMs (Aachary and Prapulla, 2011; Mamo et al., 2013). Prior to this step, xylan extraction from LCMs is achieved by pre-treating them with alkaline solution. This method has proven to be the most efficient for xylan extraction from LCMs degradation (Rico et al., 2018). Anti-obesity effect of IMO is reported through the modulation of renal Oat 3 function and plasma MCP-1 levels (Fei et al., 2020; Wanchai et al., 2018).

Pectic-oligosaccharides

Pectic-oligosaccharides (POS) is enzymatically synthesized using pectinase from pectin. Pectin is a naturally occurring complex polymer made up of covalently linked homogalacturonan, rhamnogalacturonan I (RG I), and rhamnogalacturonan II (RG II) (Holck et al., 2014). Production of POS from pectin is conventionally a two-step process: (i) extraction of pectin from raw material; (ii) hydrolysis of pectin to POS using commercially available hydrolytic enzymes. Conversely, A1 step approach has also been developed by Babbar et al., (2016) for the direct production of POS from pectin-rich raw material. They were able to produce POS-rich hydrolysate from pectin-rich sugar beet pulp in a single step.

Chitosan oligosaccharides

Chitosan oligosaccharides (COS) are prepared from the degradation of chitosan and they compose of β-(1–4)-linked D-glucosamine, and N-acetyl-D-glucosamine with the degree of polymerization ranging from 2 to 10 (Li et al., 2019).

Manno-oligosaccharides

Manno-oligosaccharides (MOS) is commercially produced via mannan hydrolysis using β-mannanase (Singh et al., 2018). Below section details the probable mechanisms through which various NDOs offer anti-obesity effects. Indications in human and rodent models are elucidated with monitored therapeutic benefits. Anti-obesity effect is detected is described in an isolated section mechanism. The latter section recognizes the noticeable research gap, and for future investigation.

Anti-obesity effect of NDOs: Experimental evidence on mechanisms

Evidence in animal model

Significant evidence have identified the relationship between intestinal microbiota, prebiotics, and obesity (Fig. 1). SCFA produced by probiotics via the prebiotic fermentation has shown a beneficial effect by reducing the accumulation of body fat via modulation of energy expenditure and increasing fat oxidation (Byrne et al., 2015). A day's production

of SCFAs ranges from 500 to 600 nmol, with the molar ratios of propionate, butyrate, and acetate being 20:20:60, respectively (Dalile et al., 2019). Colonocytes rapidly absorb the produced SCFAs, and the un-metabolized SCFAs will get transported to portal circulation. Moreover, only a relatively low concentration of SCFAs from the colon penetrates the peripheral tissues and central nervous system (Boets et al., 2017).

Pre-clinical studies have determined the ability of SCFAs to exert numerous beneficial effects on mammalian energy metabolism and ameliorate obesity (Table 1) (Besten et al., 2013; Fang et al., 2019; Shon and Park, 2021). Among SCFAs, butyrate has shown the potential to offer beneficial effects in alleviating obesity and other metabolic comorbidities (Coppola et al., 2021). Fang et al., (2019) investigated the sodium butyrate (0.1 M in the drinking water) ability to regulate obesity in an increased fat diet fed C57BL/6 J male mice. Chronic administration of sodium butyrate for 12 weeks could lower high-fat diet-induced increase in weight gain and further reduce hepatic triglyceride levels with the decrease in serum Tumour necrosis factor α (TNF-α) and interleukin-6 levels. On similar lines, the administration of sodium butyrate (3% w/w, 14 weeks) to increased fat diet, which induced obese male Sprague–Dawley ratson lipid metabolism to prevent diet-induced obesity was assessed (Shon and Park, 2021).

The results demonstrated that the administrated butyrate was recognized by free fatty acid receptor 2 (FFAR2) and suppressed the stimulation of glucagon-like peptide-1 (GLP-1), which involved suppression of appetite in the colon. Furthermore, the down-regulation of tight junction protein 1 and hydroxycarboxylic acid receptor 2 proved the anti-obesity effects of butyric acid. Interestingly, chronic treatment of 5% w/w sodium butyrate for 12 weeks attenuated hepatosteatitis in the western-style obese C57BL/6 female mouse model caused by food and reduced body weight gain with a decrease in hepatic and plasma triglyceride levels (Beisner et al., 2021). In addition, butyrate supplementation could effectively restore matrix metalloproteinase-7 and paneth cell α-defensins expression hampered through a western-style diet. Thus, this result proves the ability of sodium butyrate as a fascinating therapeutic agent in improving diet-induced obesity by inducing the expression of paneth cell antimicrobials. In line with this, the ability of propionic acid to modulate obesity was evaluated (Tengeler et al., 2020). The efficacy of propionic acid to lessen non-alcoholic steatohepatitis and obesity caused by high-fat diets was studied by the researchers.

In addition, propionic acid effects on liver and adipose tissue pathology, brain function and structure were also evaluated. Leiden mice (low-density lipoprotein receptor knockout) were incorporated into a higher-fat diet almost for 16 weeks to stimulate obesity. The obese Leiden mice supplemented with propionic acid (2.55 w/w) for 12 weeks revealed that it can reduce high fat-induced increased body weight and liver function, macrovesicular steatosis with a concomitant decrease in collagen content, and inflammation levels. Furthermore, propionic acid reduced hepatic steatosis by decreasing hepatic cholesterol ester content and stimulating β-oxidation. The pronounced effects of propionic acid on collagen content and hepatic inflammatory aggregates proved its ability to treat NASH and liver fibrosis. However, propionic acid failed to restore a high fat diet and induce a decline in motor coordination.

Furthermore, propionic acid-treated mice were found to be more anxious than the mice group fed with normal chow diet. Results revealed diminished synaptogenesis and glutamate regulator activity in the hippocampal area. Therefore, extra caution should be taken while administering propionic acid even though positive metabolic effects is observed. A study by Tirosh et al., (2019) showed the adverse metabolic effects of propionic acid consumption. The effect of propionic acid (15 mg/kg in drinking water for 6 weeks) on hyperglycemia was evaluated using C57BL/6 J male mice. Their results revealed that administered propionic acid could activate the sympathetic nervous system, thereby leading to the secretion of hormones viz., norepinephrine, glucagon, and fatty acid-binding protein 4. Enhancement in the above said hormones induced significant glucose production from liver cells causing hyperglycemia. Furthermore, chronic treatment with a single dose of propionic acid (150 µg/mL) led to a significant gain in weight and impaired glucose homeostasis compared to the group of mice (control). Thus, all the above-mentioned research findings necessities further in-depth evaluation of the adverse metabolic consequences of propionic acid consumption.

MCP-1, a protein that differentiates adipocytes and is present in white adipose tissue, is overexpressed in obese individuals (Panee, 2012). The ability of XOS to gut microbiota modulation and regulate high fat diet induced inflammation through MCP-1 was evaluated (Fei et al., 2020). Sprague Dawley rats were randomly divided into three groups and given three different diets: a regular diet, a high-fat diet, and a high-fat diet + XOS (2 g/kg BW/d). The duration of the experiment was for almost 12 weeks. At the conclusion of the study, XOS supplementation prevented body weight gain caused by a high-fat meal by lowering plasma MCP-1 levels. Furthermore, the proportion of *Bacteroidetes*/*Firmicutes* increased significantly at the end of the study.

An excessive level of free radicals is reported to abrupt cell function, thereby enhancing fatty acid oxidation, over action of NADPH oxidase with dysfunction in renal organic anion transporters (Oats), causing obesity (Fernández-Sánchez et al., 2011). Wanchai et al. (2018) investigated the XOS effect on renal Oat 3 function and the possible mechanisms involved. Male Wistar rats fed on high-fat diet

Table 1 Studies of in vivo conducted in a preclinical level demonstrating the anti-obesity effects of prebiotics/probiotics and its metabolites

Prebiotics/Probiotics /SCFA	Duration of feeding	Model organism	Observation	References
Sodium butyrate (0.1 M)	12 weeks	C57BL/6 J male mice	Lower body weight gain Reduction in hepatic triglyceride Decrease in TNF-α and interleukin-6 levels	Fang et al. (2019)
Sodium butyrate (3% w/w)	14 weeks	Male Sprague–Dawley rats	Suppression of GLP1 stimulation Down-regulation of tight junction protein 1 and hydroxycarboxylic acid receptor 2	Shon and Park (2021)
Sodium butyrate (5% w/w)	12 weeks	Female C57BL/6 mice	• Reduction in body weight gain • Decrease in hepatic and plasma triglyceride levels • Restoration of matrix metalloproteinase-7 and paneth cell α-defensins expression	Beisner et al. (2021)
Propionic acid (2.55 w/w)	16 weeks	Leiden mice	• Reduction in high fat diet induced body weight gain and liver macrovesicular steatosis • Decrease in collagen content and hepatic cholesterol ester content	Tengeler et al. (2020)
XOS (2 g/kg BW/d)	12 weeks	Sprague Dawley rats	• Supplementation of XOS counteracted increased higher fat diet stimulate body weight gain • Reduction in plasma MCP-1 levels	Fei et al. (2020)
XOS (1000 mg/kg BW/d)	12 weeks	Male Wistar rats	• Restoration of renal Oat3 function • Reduction in apoptosis and oxidative stress • Activation of AT1R-PKCα-NOXs	Wanchai et al. (2018)
Probiotic, *L. paracasei* (1×10^8 CFU/ml/d) Prebiotic, XOS (10% w/v) Synbiotics, *L. paracasei* + XOS	12 weeks	Male Wister rats	• Reduction in the *Firmicutes*/*Bacteroidetes* ratio • Decrease in metabolic endotoxemia (low LPS levels) and gut inflammation	Thiennimitr et al. (2018)
XOS (5 & 10% w/w)	12 weeks	C57BL/6 J mice	• Improvement in glucose intolerance and slow downed body weight gain • Increased beneficial microbial levels • 31 metabolic molecules alteration in the plasma (including ceramide and diacylglycerol)	Zhang et al. (2020)
XOS (2 & 7% w/w)	3 weeks	MaleC57BL/6 J mice	• Significant change in gut microbial composition • Increase in cecum SCFAs levels • Reduction in adipose fat mass • Reduction in the levels of *Firmicutes* & *Bacteroidetes*	Long et al. (2019)
MOS (1% w/v)	12 weeks	C57Bl/6 J male mice	• Significant change on final body weight and visceral fat	Smith et al. (2010)
MOS (6 g/kg BW/d)	7 weeks	C57BL/6 J male mice	• MOS supplementation attenuated high fat induced metabolic syndrome • Decrease in insulin resistance was observed by lowering body weight gain and serum lipid levels • Reduction in Firmicutes/ Bacteroidetes ratio	Delzenne et al. (2011)
MOS (100 and 200 mg/kg BW/d)	4 weeks	Male ICR mice	• Reduction in insulin resistance and body weight gain • Obese mice had reduced inflammatory reactions and fatty livers • Inhibition of lipogenesis in the adipose tissue	Yan et al. (2019)
COS capsules (150, 300 and 600 mg/kg BW/d)	8 weeks	Sprague–Dawley rats	• Reduction in lipid accumulation • Activation of leptin signal pathway	Pan et al. (2018)

Table 1 (continued)

Prebiotics/Probiotics /SCFA	Duration of feeding	Model organism	Observation	References
Inulin (7.5% w/w)	12 weeks	Male free fatty acid receptor 2 (FFAR2)$^{-}$deficient C57BL6 mice	• Regulation of metabolism via binding to FRAR2 • Increase in cell density to increase appetite-suppressing hormone peptide YY (PYY) levels to reduce food intake	Brooks et al. (2017)
IMO (0.5 & 1 g/kg BW/d) Lycopene (5 & 10 mg/kg BW/d) IMO (1 g/kg BW/d) + Lycopene (10 mg/kg BW/d)	12 weeks	Male Swiss albino mice	• Increased body weight growth was caused by a reduction in high-fat diet • Improvement in adipose tissue fat mobilization • Alteration in selected gut microbial abundance	Singh et al. (2016)
IMO (1 g/kg BW/d) Green tree extract (200 mg/kg BW/d) IMO (1 g/kg BW/d) + Green tree extract (200 mg/kg BW/d)	12 weeks (5 times/week)	Male Swiss albino mice	• IMO supplementation improved gut health through the production of SCFAs and encouraging beneficial gut microbial growth • Green tree extract prevented gut inflammation by suppressing oxidative stress • Combinational treatment prevented gut dysbacteriosis and endotoxemia	Singh et al. (2017a)
Cinnamaldehyde (10 mg/kg BW/d) Cinnamaldehyde (10 mg/kg BW/d) + IMO (1 g/kg BW)	12 weeks	Male Swiss albino mice	• Improved metabolic profile through the prevention of high fat diet induced weight gains • Combinational treatment showed significant anti-obesity effect by improving gut health, gut barrier function and mucin synthesis • Reduction in colonic and hepatic inflammation	Singh et al. (2017b)
Cranberry extract (200 mg/kg BW/d) cranberry extract (200 mg/kg BW/d) + IMO (1 g/kg BW/d)	12 weeks	Male Swiss albino mice	• Improvement in cecal SCFAs with enhancement in butyrate producing bacteria • Improvement in the metabolic alterations in adipose tissue linked to diet-induced systemic obesity	Singh et al. (2018)
COS (250, 500 and 1000 mg/kg BW/d)	6 weeks	MaleSprague-Dawley rats	• Reduction in body weight gain • Inhibition of adipocyte differentiation • Reduction in the expression of PPARγ	Huang et al. (2015)
COS (0.1 g/kg BW/d)	6 weeks	Male obese Sprague–Dawley rats	• COS administration lowered body weight gain • Enhancement in serum adiponectin levels • Reduction in serum total cholesterol and triglycerides levels	Lee et al. (2021)
FOS (45 g/d)	6 weeks	Arabian geldings horses	• Improvement in insulin sensitivity	Respondek et al. (2011)
Synbiotics comprising of *L. acidophilus* ATCC 4962 with 1 g/d and prebiotics viz., FOS with 1.25 g/d, mannitol with 1.56 g/d and inulin with 2.2 g/d	8 weeks	White male Landrace pigs	• Decrease in total cholesterol, low-density lipoprotein (LDL)-cholesterol and triacylglycerol levels	Liong et al. (2007)

(12 weeks) to induce obesity were divided at random into 4 groups: rats receiving normal diet; rats receiving normal diet plus XOS (1000 mg/kg BW/d for 12 weeks), rats receiving high-fat diet, and rats receiving high-fat diet plus XOS (1000 mg/kg BW/d for 12 weeks). Rats fed a high-fat diet showed a significant rise in obesity and insulin resistance at the conclusion of the trial, along with reduced Oat3 activity. In obese insulin-resistant mice, reducing oxidative stress and apoptosis as well as controlling the activation of AT1R-PKC-NOXs, may indirectly improve kidney Oat3 function. Thus, XOS can be used in obesity treatment caused by altering renal Oat3 functions.

The relationship between obesity and gut dysbiosis, an imbalance in intestinal microbiota, and persistent low-grade gut inflammation has been strongly supported by scientific research (Cox and Blaser, 2015; Festi et al., 2014). The beneficial role of a probiotic strain, *Lactobacillus paracasei* HII01; XOS and a synbiotic product (*L. paracasei* HII0I and XOS) in improving metabolic parameters via modulation of gut dysbiosis and inflammation in obese-insulin resistant rats was evaluated (Thiennimitr et al., 2018). Male Wister rats were distributed at random to one of four treatment groups after consuming a high-fat diet for 12 weeks: probiotic (1×10^8 CFU/ml/d), prebiotic (10% w/v, 1 mL), synbiotic (1×10^8 CFU, 1 mL + 10% w/v XOS, 1 mL) and vehicle (saline) treated. Normal diet-fed rats were used as control. Authors quantified metabolic parameters viz., serum lipopolysaccharides (LPS), gut proinflammatory cytokine gene expression, and fecal *Firmicutes/Bacteroidetes* ratio at the end of the study. Reduction in the *Firmicutes/Bacteroidetes* ratio, metabolic endotoxemia (low LPS levels), and gut inflammation in the groups administered probiotic, prebiotic, and synbiotics, demonstrated their capacity for reversing metabolic dysfunction in obese and insulin-resistant mice.

The role of important metabolites in the origin of obesity which determined and demonstrated by a body of research (Wen et al., 2019). Accumulation of sphingolipids (particularly ceramide) is reported to play a major role in the progression of obesity (Chavez and Summers, 2012). Zhang et al., (2020) demonstrated the anti-obesity effect of XOS in the mice model. Male C57BL/6 J mice randomly divided into 4 groups were fed with one of the four diets, high fat plus 5% XOS, high fat plus 10% XOS and low fat for 12 weeks. XOS supplementation (both 5% and 10%) could significantly improve glucose intolerance and slow down body weight gain. Analysis of lipidomic profile and gut microbiota showed that the XOS supplementation could alter 31 metabolic molecules (including diacylglycerol and ceramide) in the plasma and increase the levels of beneficial microbes (genus *Bifidobacterium*, *Roseburia,* and *Lachnospiraceae*). Hence, by significantly altering the gut microbiota composition and plasma lipid profile, XOS supplementation may reduce obesity and improve glucose intolerance. A considerable increase in adiposity and a decrease in coccyx mass have been observed in mice fed a diet high in refined carbohydrates and AIN93 diet or low in soluble fibers (LSFD).

In line with this, metabolic regulatory XOS effects in the mice fed with AIN93 diet was evaluated. MaleC57BL/6 J mice fed with LSFD for 3 weeks were randomly assigned into two groups: mice receiving LSFD plus 2% XOS and mice receiving LSFD plus 7% XOS. The duration of the study was for 3 weeks. A significant change in gut microbial composition was reported with both doses of XOS supplementation, with an increase in cecum SCFAs levels. The presence of the microbial phyla Bacteroidetes and Firmicutes associated with obesity in the gut, as well as the reduction in adipose fat mass with visceral fat depots and the inflammatory cytokine MCP-1, were only seen with larger XOS doses. Thus, XOS supplementation could reduce adiposity by changing intestinal microbial composition. A similar line of experiments made using Male C57Bl/6 J mice was fed either 1% (w/v) MOS or a high-fat western diet supplement for 12 weeks showed that MOS supplementation failed to show significant change in final body weight and visceral fat in comparison to a control group (Smith et al., 2010). Thus, this result challenges the potentiality of MOS in obesity treatment.

Ability of MOS to attenuate high-fat diet-induced metabolic syndrome and obesity was investigated (Delzenne et al., 2011). The division of male C57BL/6 J mice into six treatment groups at random. The first group of mice received a normal chow diet for 11 weeks; the second group received a higher fat diet; mice (third group) were fed a normal diet and received 6 g/kg BW/d of MOS for 11 weeks; the fourth group of mice was incorporated with higher fat diet and got MOS (6 g/kg BW/d) for 11 weeks; fifth group of mice were fed with normal chow diet and MOS for 4 weeks and later shifted to high-fat diet for 7 weeks; sixth group of mice received normal chow diet and MOS for 4 weeks and later shifted to high-fat diet plus MOS for 7 weeks. The outcomes clearly showed that MOS supplementation might reduce insulin resistance and attenuate high fat-stimulated metabolic syndrome by preventing body weight increase and serum lipid levels.

Further decrease in *Firmicutes*/*Bacteroidetes* ratio establishes that MOS has the potential to regulate obesity-related metabolic disorders by modulating gut microbiota. Furthermore, a study by Yan et al., (2019) studies the MOS ability in down-regulating appetite-causing genes and up-regulating appetite-related hormones expression viz., neuropeptide Y, cocaine- and amphetamine-regulated transcript (CART), leptin and proopiomelanocortin. Male ICR mice were used in the study, and they were given an 8-week diet heavy in fat and fructose to cause obesity. Then the diet-induced obese mice were orally supplemented with two doses of MOS

(100 and 200 mg/kg BW/d, 4 weeks). The findings show that in obese mice, MOS supplementation could reduce body weight increase, insulin resistance, fatty liver, and inflammatory responses. MOS supplementation was effective in restructuring gut microbiota by increasing the abundance of genus *Bifidobacterium* and *Lactobacillus* and stimulated lipolysis through inhibiting lipogenesis in the adipose tissue. On similar lines, administration of COS capsules (150, 300, and 600 mg/kg BW/d) to obese Sprague-Dawleyrats for eight weeks demonstrated anti-obesity effects by activating the leptin signal pathway to conquer leptin resistance. Furthermore, COS capsules could reduce lipid accumulation by suppressing adipogenesis (Pan et al., 2018).

Significant evidence also demonstrate the ability of prebiotic polysaccharides in obesity treatment. The role of inulin against diet-induced obesity was investigated (Brooks et al., 2017). Male free fatty acid receptor 2 (FFAR2)$^{-}$deficient C57BL6 mice were fed with high-fat diet and high-fat diet plus inulin (7.5% w/w). Inulin supplementation for 12 weeks provided mechanistic insights on how inulin regulates metabolism via binding to FRAR2, thereby increasing cell density to increase the levels of appetite-suppressing hormone peptide YY (PYY) to decrease calorie intake and minimize diet-stimulated obesity.

A leaky gut barrier is reported to induce metabolic endotoxemia, low-grade systemic inflammation with ectopic fat deposition (Singh et al., 2017a). Antioxidants (lycopene, grape tree extract, cranberry extract) and prebiotic/probiotics per se have been reported to prevent high-fat induced obesity-related comorbidities (Singh et al., 2016, 2017b). In line with this, various research groups have evaluated the effectiveness of combinational treatments for their application against high fat induced obesity associated-metabolic alterations. Lycopene, a naturally carotenoid, is found to confer beneficial effects in obesity-related conditions (Arora et al., 2014). Singh et al., (2016) evaluated the combination of lycopene and IMO preventing of gut derangements and high-fat induced adiposity. Male Swiss albino mice fed on high fat diet were supplemented with lycopene (5 and 10 g/kg BW/d), IMO (0.5 g/kg and 1 g/kg BW/d) or their combination [IMO (1 g/kg BW/d) + Lycopene (10 mg/kg BW/d)] for 12 weeks.

Lycopene, IMO and their combination were found effective in decreasing high-fat diets stimulating an increase in body weight gain with improvement in adipose tissue fat mobilization and selected gut microbial abundance. Interestingly, combinational treatment synergistically improved metabolic endotoxemia, and ileal and colonic health, thereby proving that combinational therapy (antioxidant + prebiotic) could be used to produce unique functional foods to prevent the effects of an obesity-causing high-fat diet. Male Swiss albino mice fed on high-fat diet were supplemented 5 days a week with either IMO (1 g/kg BW), green tree extract (200 mg/kg BW), or both for 12 weeks. IMO supplementation improved gut health by producing SCFAs and encouraged beneficial gut microbial growth. On the other hand, supplementation of green tree extract prevented gut inflammation by suppressing oxidative stress.

Furthermore, combinational treatment was found effective over individual supplementations by preventing gut dysbacteriosis and resultant endotoxemia (Singh et al., 2017a). Cinnamaldehyde, an organic compound from Cinnamon, is monitored to offer anti-hyperglycemic and anti-obesity properties (Camacho et al., 2015). However, due to its bacteriostatic action, it is known to decrease the levels of significant microbes in the gut (Khare et al., 2016). Thus, in line with this observation, same group of authors evaluated the ability of IMO to augment the metabolic health benefit of cinnamaldehyde by improving the levels of gut-associated beneficial microbes (Singh et al., 2017b). Four sets of male Swiss albino mice were created at random. The first group of mice received their standard chow diet, the second group a high-fat diet, the third group a high-fat diet with cinnamaldehyde (10 mg/kg BW/d), and the fourth group a high-fat diet with cinnamaldehyde (10 mg/kg of BW/d) and IMO (1 g/kg of BW).

After 12 weeks of supplementation, cinnamaldehyde showed an anti-obesity effect by improving metabolic profile through the minimization of higher fat diet stimulated weight gains. Yet, no enhancement in beneficial gut bacterial abundances was observed in the mice supplemented with cinnamaldehyde. Furthermore, a combination of IMO and cinnamaldehyde displayed significant anti-obesity effects by improving gut health, gut barrier function, and mucin synthesis, and by reducing colonic and hepatic inflammation. Thus, this research highlights the prebiotic potential of IMO in obesity, which is related to the enhancement of the gut health. Male Swiss albino mice fed with high-fat diet and supplemented with either cranberry extract (200 mg/kg BW/d) individually or in combination with IMO (1 g/kg BW/d) for 12 weeks demonstrated the ability of combinational treatment in improving cecal SCFAs with enhancement in butyrate-producing bacteria in high-fat diet treated mice. Furthermore, combinational therapy showed improved beneficial bacterial abundance in the gut in comparison to the individual agents. The effectiveness of IMO and cranberry extract in preventing high fat diet-induced gut imbalances was demonstrated by the fact that it reduced metabolic alterations in adipose tissue that are related to systemic obesity and are caused by high fat diets (Singh et al., 2018).

Anti-obesity effect of COS was evaluated on male Sprague–Dawley rats (Huang et al., 2015). COS has been given to obese rats fed a higher-fat diet in three doses with the concentration of 250, 500, and 1000 mg/kg BW/d for six weeks. Diet-induced increase in body weight gain was prevented effectively by COS supplementation through

the inhibition of adipocyte differentiation and by reducing the peroxisome proliferator-activated receptor γ (PPARγ) expression. This key adipogenic transcription factor which present in white adipose tissue. Male obese Sprague–Dawley rats supplemented with COS (0.1 g/kg BW/d) for 6 weeks were assessed for their anti-obesity effects (Lee et al., 2021). COS administration lowered body weight gain by enhancing serum adiponectin levels (Low levels are linked to metabolic problems brought on by obesity) and decreasing serum total cholesterol and triglycerides. Thus, this finding suggests COS's ability to prevent diet-induced body weight gain and its anti-obesity effects are mediated through the inhibition of adipogenesis and enhancing adiponectin levels.

Several research has assessed the potential of NDOs to reduce obesity using systems other than the rodent system. Respondek et al., (2011) evaluated the ability of FOS to improve insulin sensitivity in obese horses. Supplementation of FOS (45 g/d, 6 weeks) to mature Arabian gelding horses demonstrated that FOS can moderately improve insulin sensitivity in obese horses, thereby showing its ability in the dietary management of insulin-resistant, obese horses. Supplementation of synbiotic formulation comprising of *L. acidophilus* ATCC 4962 (1 g/d) and prebiotics viz*.,* FOS (1.25 g/d), inulin (2.2 g/d) and mannitol (1.56 g/d) for 8 weeks to hypercholesterolemic pigs (white male Landrace pigs) could reduce obesity associated levels of low-density lipoprotein (LDL)-cholesterol, total cholesterol and triacylglycerol levels (Liong et al., 2007).

Evidence in humans

Evolving clinical studies recommend the use of prebiotic NDOs for managing obesity and associated metabolic complications (Table 2). NDOs were proven to function differently depending on gender regarding fat loss (Jana et al., 2021). A study in 60 overweight men and women found that consumption of MOS containing beverages (4 g/d for 12 weeks) in addition to dietary weight-loss counseling helped only men to lose significant adipose tissue and body weight loss, thereby suggesting the potential of MOS in body weight management and adipose tissue distribution. To support the apparent gender difference in reaction to MOS consumption, however, an in-depth investigation is necessary (St-Onge et al., 2021). The positive probiotics effects on humans have been confirmed by a considerable number of research findings. Supplementation of a probiotic strain, Lab4P (50 million/day), in 220 participants aged between 30 and 62 years resulted in significant weight reduction by decreasing low-density lipoprotein-cholesterol levels (Michael et al., 2020). This research group also evaluated the weight modulation capability of Lab4p in free-living overweight adults for 9 months. The study findings supported their previous outcome and proved the efficiency of Lab4p in reducing body weight in obese participants (Michael et al., 2021).

Grembi et al. (2020) demonstrated the importance of gut microbiota for sustained weight loss, and proved that maintaining gut microbiota plasticity is crucial for weight loss. Attempts have also been made to enhance the functionality and performance of prebiotics by combining them with probiotics. Variability of gut microbiota supplementation of *Bifidobacterium adolescentis* IVS-1 (1×10^9 CFU/d), GOS (5 g/d), and a synbiotic product (*B. adolescentis* IVS-1 and GOS) to healthy obese volunteers (114) for 3 weeks was investigated on the clinical outcomes on improving intestinal barrier function in obese adults.

Probiotic and prebiotic treatment decreased intestinal inflammation and improved intestinal permeability, thereby suggesting their use in the obesity associated pathogenies of leaky gut barrier. However, no supplementary advantage is reported in the synbiotic-treated group (Krumbeck et al., 2018). A randomized control of trials to assess the effect of probiotics, *B. animalis*ssp. *lactis* 420 and prebiotic fiber, Litesse® Ultra polydextrose, on obesity-related clinical outcomes were measured (Stenman et al., 2016). A total of 225 healthy volunteers were randomly assigned into a prebiotic group (Litesse® Ultra: 12 g/d), probiotic group (*B. animalis*ssp. *lactis* 420: 10^{10} CFU/d); synbiotic group (Litesse®Ultra + *B. animalis*ssp. *lactis* 420: 12 g/d + 10^{10} CFU/d) and a placebo group.

Probiotic and synbiotic supplementation for 6 months could significantly improve weight management with the reduction in waist circumference and food intake. However, prebiotic supplementation failed to show any impact on the evaluated outcomes (Stenman et al., 2016). A study using obese prediabetic men and women (44 no.) found that consumption of GOS (15 g/d) administered for 12 weeks significantly enhanced the fecal abundance of *Bifidobacterium* spp. However, no noticeable changes in the insulin sensitivity of adipose tissue were observed, suggesting that GOS supplementation failed to establish significant changes in insulin sensitivity in overweight or obese subjects (Canfora et al., 2017). Similar research was made by Smiljanec et al., (2017). Inulin supplementation (10 g/d) to overweight or obese middle aged and older adults (7 no., mean age 60 years and BMI 32.9 ± 4.3 kg/m^2) showed no impact on energy intake and failed to suppress appetite in older obese adults. The effect of oligofructose (10 & 16 g/d, for 13 days) on energy intake, appetite profiles and satiety hormone concentration were evaluated in 32 healthy subjects (21 women & 10 men).

Higher dose of oligofructose significantly reduced energy administration with a concomitant increase in the levels of GLP-1 and PYY (Verhoef et al., 2011). Sergeev et al., (2020) investigated the association of synbiotic (*L. acidophilus, B.*

bifidum, B. longum, B. lactis (59×10^9 CFU/d) and GOS mixture (5.5 g/d)) combination on obesity biomarkers in humans. A study plan consisted of human subjects (20 no.) participating in a weight loss program. Supplementation of a synbiotic product for 3 months enhanced the gut abundance of beneficial microbes and reduced obesity-related biomarker *i.e.,* blood glucose levels. The influence of 8-week supplementation of a synbiotic capsule (500 mg comprising of *L. acidophilus, L. casei, B. bifidum* and inulin) on glycemic and lipid profile, psychological status and anthropometric indices were evaluated in 60 obese adults.

Synbiotic treatment could reduce body weight gain by lowering lipoprotein cholesterol of low density and triglyceride levels. Furthermore, effectively reduced anxiety and stress in obese subjects (Hadi et al., 2019). Chaiyasut et al., (2021) also observed the similar effect on administering probiotics comprising of *L. paracasei* (2×10^{10} CFU), *B. longum* (1×10^{10} CFU), *B. breve* (2×10^{10} CFU) and prebiotics (FOS and inulin each 5 g) for 12 weeks in Thai obese individuals (72 no., 18–65 years). The results demonstrated the synergetic ability of pro and prebiotics in treating obesity by significantly altering obesity-associated biomarkers viz., reduction in cholesterol, gut permeability, and oxidative stress.

Beneficial effects of prebiotic supplements on obesity in infants, children, and adolescents are examined with a smaller experimental window. On the BMI of overweight and obese children, the effects of oligofructose supplementation for 12 weeks were assessed (Liber et al., 2014). Children who were overweight or obese were randomly assigned to receive oligofructose (8 g/d for subjects aged of 7 to 11 and 15 g/d for individuals aged 12 to 18) or a placebo (97 no., aged between 7 and 18 years, BMI > 85th percentile) (maltodextrin). Results revealed that oligofructose supplementation was ineffective in reducing body weight in obese and overweight children. A study by Alderete et al., (2015) employing mother-infant dyads (25 no.) supplemented with human milk oligosaccharides (through breast milk) for 6 months showed a reduction in the risk of developing childhood obesity. Safety consideration and digestive tolerance of human milk oligosaccharides in obese children are investigated (Fonvig et al., 2021).

Obese children (75 no., 6–12 years) underwent randomized, double-blind trial and received either 2′-fucosyllactoseor a mixture of 2′-fucosyllactose and lacto-N-neotetraose for 8 weeks. Both 2′-fucosyllactose or a mixture of 2′-fucosyllactose and lacto-N-neotetraose were found to be well tolerated at the tested doses in obese children with significant enhancement in the levels of *Bifidobacterium* spp. The research was demonstrated by Kianifar et al., (2018) wherein administration of synbiotic capsule (FOS, vitamin A, vitamin C, and vitamin E, and 100 million CFU of *Bifidobacterium breve, Streptococcus thermophilus, B. infantis, L. casei, L. rhamnosus, L acidophilus* and *L bulgaricus*) for 12 weeks decreased waist circumference in obese children (46 no., 7–13 years) with enhancement in gut abundance. Obese boys and girls (7–12 years, BMI ≥ 85th percentile) receiving inulin-rich oligofructose with the concentration of 8 g/d administered for 16 weeks improved over lower energy intake in older but not in younger children (2017). The effect of inulin type fructans (2 g inulin from chicory root and 6 g oligofructose, 12 weeks) on appetite and gut microbiota composition was analyzed in a double-blind study employing 125 obese subjects (BMI > 25, age 18–75). Supplementation of inulin-type fructans enhanced the abundance of *Bifidobacterium* spp. with an improvement in appetite control (Reimer et al., 2017). A parallel-research was made by Nicolucci et al., (2017) in which supplementation of inulin-rich oligofructose with the concentration of 8 g/d for 16 weeks to 22 obese children showed considerable reduction in body fat with significant alterations in the beneficial intestinal microbiota. All these studies warrant the link of gut microbiome dysregulation to obesity and how dietary supplements (probiotics, prebiotics, and symbiotic) can be utilized as adjunctive therapy in the treatment of health problems caused by obesity.

Mechanism-based studies

Regulating energy consumption and energy expenditure equilibrium in the human body could be one of the finest approaches for obesity therapy (Coppola et al., 2021). SCFAs are known to regulate body weight by decreasing energy intake and promoting energy expenditure (Table 3). More specifically, butyrate is proven promising in obesity treatment. Butyrate action's mechanism in obesity treatment is regulating genes implicated in the oxidation of fatty acids and lipolysis and increasing ATP consumption by activating AMP kinase (Den Besten et al., 2015; Hong et al., 2016). Sodium butyrate was added as a supplement to high-fat diet-induced obese C57BL/6 J mice (80 mg/d, on alternate days for 10 days), fatty acid oxidation enzymes, adiponectin receptors, and AMP kinase expression are all upregulated (Hong et al., 2016). Den Besten et al., (2015), through their investigation using male C57Bl/6 J mice supplemented with SCFAs (5% w/w) demonstrated that SCFAs could reverse high-fat diet-stimulated metabolic abnormalities via switching PPARγ from lipid synthesis to utilization.

Adipose tissue plays major role in energy homeostasis, and butyric acid is reported to regulate thermo genesis and energy homeostasis in brown adipose tissue (Wang et al., 2020). Wang et al., (2020) found that the antibiotic treatment for 2 weeks (200 µL of ampicillin with 1 mg/mL, neomycin with 1 mg/mL, metronidazole with 1 mg/mL, and vancomycin with 0.5 mg/mL, oral gavage) to wild-type C57BL/6 J

Table 2 In vivo studies at a clinical level demonstrating the anti-obesity effects of prebiotics alone and prebiotics combined with probiotics

Probiotics and Prebiotics	Duration	Subjects	Results	Reference
Prebiotics				
MOS (4 g/d) containing beverage	12 weeks	60 overweight men and women	MOS supplementation caused significant reduction in body weight adipose tissue loss in men than women. However, further studies are required to investigate the gender difference in response to MOS supplementation	St-Onge et al. (2012)
GOS (15 g/d)	12 weeks	44 obese prediabetic men and women	Supplementation of GOS resulted in selective enhancement of fecal *Bifidobacterium* species. However, no significant alterations in adipose and peripheral tissue insulin sensivity was observed with no change in substrate and energy metolism	Canfora et al. (2017)
Oligofructose (10 & 16 g/d)	13 days	32 healthy subjects	Supplementation of oligofructose stimulated satiety hormone secretion (GLP-1 and PYY) thereby causing reduction in body weight	Verhoef et al. (2011)
Human milk oligosaccharides (through breast milk)	6 months	25 mother-infant dyads	Supplementation of human milk oligosaccharides positively influenced infant growth and body composition and thereby reduced the risk for developing childhood obesity	Alderete et al. (2015)
Human milk oligosaccharides (2′-fucosyllactose or a mixture of 2′-fucosyllactose and lacto-N-neotetraose)	8 weeks	75 obese children	Supplementation of human milk oligosaccharides resulted in significant enhancement in the levels of *Bifidobacterium* spp. Dose was also well toleratred in children	Fonvig et al. (2021)
Oligofructose-enriched inulin (8 g/d)	16 weeks	obese boys and girls	Supplementation of oligofrustice improved feeling of fullness in older children	Hume et al. (2017)
Inulin type fructans (+2 g inulin from chicory root + 6 g oligofructose)	12 weeks	125 obese subjects	Supplementation of inulin type fructans resulted in enhancement in the abundance of *Bifidobacterium* spp. with improvement in appetite control	Reimer et al. (2017)
Oligofructose-enriched inulin with concentration of 8 g/d	16 weeks	22 obese children	Supplementation resulted in reduction in body fat with significant alterations in the beneficial intestinal microbiota (*Bifidobacterium* spp.)	Nicolucci et al. (2017)
Prebiotics combined with probiotics				
Probiotic (*B. adolescentis* IVS-1: 1×10^9 CFU/d) Prebiotic (GOS: 5 g/d) Synbiotic (*B.adolescentis* IVS-1 and GOS)	3 weeks	114 healthy obese volunteers	Probiotic and prebiotic supplementation resulted in reduction of intestinal inflammation; improved obesity associated intestinal permeability. However synbiotic combination failed to offer functional synergism	Krumbeck et al. (2018)
Probiotic (*B. animalis* ssp. *lactis* 420: 10^{10} CFU/d) Prebiotic (Litesse® Ultra polydextrose: 12 g/d) Synbiotic (*B. animalis* ssp. *lactis* 420 + Litesse®: 10^{10} CFU/d + 12 g/d)	6 months	225 healthy volunteers	Probiotic, prebiotic and synbiotic supplementation resulted in significant improvement in weight management with reduction in waist circumference and food intake	Stenman et al. (2016)
Synbiotic (*L. acidophilus, B. lactis, B. longum, B. bifidum* (59×10^9 CFU/d)and GOS mixture (5.5 g/d))	3 months	20 healthy subjects	Synbiotic supplementation caused significant enhancement in the gut abundance of beneficial microbes and brought reduction in the obesity related biomarker (blood glucose)	Sergeev et al. (2020)

Table 2 (continued)

Probiotics and Prebiotics	Duration	Subjects	Results	Reference
Synbiotic capsule (500 mg comprising of *L. acidophilus, L. casei, B. bifidum* and inulin)	8 weeks	60 obese adults	Supplementation of symbiotic capsule caused reduction in the body weight gain by lowering low-density lipoprotein cholesterol and triglyceride levels	Hadi et al. (2019)
Probiotics (*L. paracasei* (2×10^{10} CFU), *B. longum* (1×10^{10} CFU), *B. breve* (2×10^{10} CFU) • Prebiotics (FOS and inulin each 5 g)	12 weeks	72 thai obese individuals	Probiotic and prebiotic supplementation altered obesity associated biomarkers viz., reduction in cholesterol, gut permeability and oxidative stress	Chaiyasut et al. (2021)
Synbiotic capsule (FOS, vitamin A, C, and E, and 100 million CFU of *L. casei, L rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, L acidophilus, B infantis* and *L bulgaricus*)	12 weeks	46 obese children	Synbiotic capsule caused reduction in waist circumference with enhancement in gut abundance with beneficial microbiota	Kianifar et al. (2018)

male mice was effective in inducing microbiota depletion in the gut and impaired thermo genesis through the decrease in expression of lysine-specific demethylase 1 (LSD1, main factor in regulation of thermo genesis) in adipose tissues. Administration of butyrate for 2 weeks (1000 mg/kg BW, oral gavage) to antibiotic-treated mice could attenuate thermo genesis by up-regulating LSD1 expression. Prior to this, the ability of sodium butyrate in alleviating diet-induced obesity was evaluated (Jia et al., 2017). Three-week-old male mice (C57BL/6 J) were grouped randomly: a control group receiving control diet (10% energy from fat); high-fat diet group (45% energy from fat) receiving sodium butyrate (80 mg/ml in water every other day for 10 days) and high-fat diet group (45% energy from fat) receiving vehicle (water).

Their research showed that stimulating-adrenergic receptors in white adipose tissue by short-term administration of sodium butyrate significantly reduced diet-induced obesity. Thus, this result proved that the butyrate induces lipolysis/fat burning *via*β-adrenergic receptor activation in mice white adipose tissue. Furthermore, butyrate is also associated with obesity treatment by inhibiting the body weight gain via suppression of food intake (Li et al., 2018). Administration of sodium butyrate (5% w/w, 9 weeks) to APOE*3-Leiden CETP mice fed on high-fat diet (60% kcal derived from lard fat and 0.25% cholesterol (w/w)) resulted in a reduction of cumulative food intake by inducing satiety. Sodium butyrate-induced suppression in the orexigenic neurons activity in the hypothalamus demonstrates the mechanism connecting the gut-brain neural circuit.

Mechanism of prebiotic NDOs administered with butyrate, acetate and propionate towards the neural, metabolic, hormonal and inflammatory system (Fig. 2). Another validated mechanism through which SCFAs offer anti-obesity effects is through the modulation of gut hormone release and hypophagic (reduction in food intake and eating behavior) effects (Lin et al., 2012). The effect of SCFAs on diet-induced obesity was evaluated using free fatty acid receptors 3-deficient C57BL/6N male mice. Acute administration of sodium salts of butyrate, acetate, and propionate (6 mL/kg BW each in saline, oral gavage for 3 weeks) revealed that SCFAs suppress food intake and regulate gut hormone (glucagon-like peptide-1) release to offer protection against diet-induced obesity. Propionate decreased food intake, nevertheless, butyrate and acetate prevented mice from becoming obese due to food without inducing hypophagia. Thus, food intake inhibition and stimulation of gut hormones by SCFAs represent a novel mechanism by which SCFAs regulate host metabolism.

Rectal administration of SCFA mixtures (200 mmol/L) to 12 normoglycaemic men (BMI 25–35 kg/m^2) for 4 days showed that obese males, colonic infusions of SCFA combinations enhanced postprandial plasma peptide YY

concentrations along with energy expenditure, fat oxidation, and reduced lipolysis (Canfora et al., 2017). Inflammation (vascular wall) and atherosclerosis are metabolic complications caused by obesity (Coppola et al., 2021). Cleophas et al., (2019) studied the effect of sodium butyrate (4 g/d for 4 weeks) in lean (09 no.) and obese (10 no.) men to slow down atherosclerosis development and irritation of vascular walls. According to this study, butyrate supplementation may reduce the trained immunity caused by ox-LDL for LPS-stimulated Pam3CSK4-stimlated TNF responses and IL-6 responses, providing a positive immunomodulatory and anti-inflammatory effect to reduce inflammation and atherosclerosis.

Systemic regulation of SCFAs is via inhibiting histone deacetylase (HDAC) activity (Divyashri et al., 2021). HDAC catalyzes acetyl group exclusion that results in the interaction of histones with DNA forming more compacted and transcriptionally repressive conformation of chromatin (Licciardi et al., 2011). SCFAs, particularly butyrate, inhibit the activity of HDAC (Dalile et al., 2019). Signaling inhibition of intracellular HDAC is reported in the remote organs and gut (Stilling et al., 2016). In line with this, Henagan et al., (2015) explored the anti-obesity property of sodium butyrate by inhibiting HDAC activity and chromatin remodeling. Five-week-old male C57BL/6 J mice were assigned randomly to one of three groups: those receiving low-fat, high-fat, or high-fat plus sodium butyrate (5% w/w) diets. After 10 weeks of treatment, sodium butyrate could prevent body weight increase caused by high-fat diet without altering energy expenditure and food intake. The mechanism through which it does is attributed to the induction of beneficial skeletal muscle mitochondrial adaptations (enhancement in type 1 fiber with an increase in acylcarnitine concentrations and chromatin modeling through the induction of nucleosome repositioning). Thus, sodium butyrate can be used as an effective pharmacological approach for obesity treatment.

SCFA suppressing fasting-induced adipocyte factor (angiopoitein-like protein 4, Fiaf/ANGPTL4) to enhance lipoprotein lipase and to inhibit fatty acid synthase activity in adipocyte tissue from reducing fat accumulation is yet another mechanism of SCFA-induced host adiposity (Khan et al., 2016). In addition, peripheral infusions of anorectic gut hormones viz., GLP-1 and PYY has been the focus of anti-obesity therapy and is connected to decreased energy intake (Byrne et al., 2015). This is further supported by Jiao et al., (2021). The authors have investigated the SCFA effect on the levels of PYY, and GLP-1, lipid metabolism and appetite regulation using 49 C57BL/6 J male mice. Mice fed on high-fat diet and receiving sodium butyrate (5% w/w), sodium propionate (5% w/w) and sodium acetate (5% w/w) for 35 days showed that SCFA could reduce free fatty acid levels with an increase in GLP-1 and PYY levels. SCFAs also down regulated the mRNA expression of Fiaf and LPL, thereby underlying their effects on lipid homeostasis.

Intracolonic administration of propionate (180 mmol/L) on PYY and GLP-1 in suppressing appetite and the role of FFA2 in facilitating these effects in wild-type (male C57BL6 mice) and FFA2 knockout mice was investigated by Psichas et al., (2015). Their results showed the ability of propionate to enhance the levels of GLP1 and PYY in wild-type mice. However, the lack of stimulation of these gut hormones in FFA2 knockout mice demonstrates that FFA2 deficiency weakens SCFA-induced secretion of both GLP1 and PYY. Supplementation of arabinoxylan oligosaccharides (AXOS 7.5% w/w, 8 weeks) to high-fat diet-induced obese mice (male C57bl6/J mice) could improve the levels of circulating hormones (GLP1 and PYY) and counteracted diet fat mass development and body weight gain (Neyrinck et al., 2012).

Mammalian coupled receptors of G protien viz., G protein couple receptor 41 (GPR41) and GPR43in adipocytes and colon are reported to mediate the interaction between host and gut microbiome via SCFA (Ang and Ding, 2016). Propionate mediates the effects by binding to GPR41 and GPR43, while acetate and butyrate are more selective for GPR43 and GPR41, respectively (Den Besten et al., 2015). In line with this, a study by Lu et al., (2016) demonstrated that 12-week supplementation of sodium butyrate (5% w/w), sodium acetate (5% w/w), sodium propionate (5% w/w) or their mixtures in a ratio of 1:3:1 to C57BL/6 J male mice causing significant alterations in the G-protein coupled receptor 41 (GPR41) and GPR43 expressions. Furthermore, they found the effectiveness of SCFA in reducing body weight via enhancing triglycerides hydrolysis and free fatty acids oxidation in the adipose tissue, thereby promoting adipogenesis. Supplementation of inulin type fructans (4 weeks, 0.2 g/d) to high-fat diet-induced obese male C57bl6/J mice, significantly regulated higher fat diet stimulated GPR43 overexpression in the adipose tissue by reducing PPARγ levels (Dewulf et al., 2021).

Delannoy-Bruno et al (2021) integrative multi-species transposon mutagenesis and meta-proteomics research showed that natural dietary fibers with varied glycan compositions encourage the proliferation of bacteriodetes (expresses glycan catabolic enzymes viz., CAZymes and carbohydrate-active enzymes). The authors were successful used machine learning approach to identify bacterial taxa, CAZymes and associated microbial pathways. Natural fibres (pea and orange) enhanced the abundance of genes associated with arabinan and galacturonan metabolism by increasing the levels of *Bacteroides* sp. These research findings in germ-free mice model was further validated in humans. The study enrolled 26 participants (maintained on a diet low in vegetables and fruits and heavy in saturated fats) were divided to two groups. For three weeks, the 12 participants in Group 1 received a pea fiber snack. Group 2 (consisting of

Table 3 Prebiotics, Probiotics and/or their metabolites mechanism according to evidences (SCFA) in offering anti-obesity effects

Proposed mechanism		Prebiotics, Probiotics and its metabolites (SCFA)	Model/Subjects	Reference
Metabolic	Upregulation of enzymes involved in fatty acid oxidation and activation of AMP kinase	Sodium butyrate (80 mg/d, alternate days for 10 days)	Male C57BL/6 J mice	Hong et al. (2016)
Metabolic	Switching PPARγ from lipid synthesis to utilization	SCFAs (5% w/w)	Male C57BL/6 J mice	Den Besten et al. (2015)
Metabolic	Reduction in the expression of lysine specific demethylase 1	Butyrate for 2 weeks (1000 mg/kg BW)	Wild-type C57BL/6 J male mice	Wang et al. (2020)
Metabolic	Activation of β-adrenergic receptors in white adipose tissue and induces lipolysis/fat burning	Sodium butyrate (80 mg/ml in water very other day for 10 d)	Male C57BL/6Jmice	Jia et al. (2017)
Neural	Suppression in the orexigenic neurons activity in the hypothalamus and gut-brainneural circuit	Sodium butyrate (5% w/w, 9 weeks)	APOE*3-Leiden.CETPmice	Li et al. (2018)
Hormonal	Increase in GLP1 and suppression of food intake	Sodium salts of SCFAs (6 mL/kg BW each in saline, 3 weeks)	Free fatty acid receptors 3-deficient C57BL/6N male mice	Lin et al. (2012)
Metabolic Hormonal	An increase in fat oxidation and energy expenditure. Reduction in lipolysis and increase in PYY	SCFA mixtures (200 pg/mL, 4 d)	Normoglycaemic men	Canfora et al. (2017)
Inflammatory	Decrease in TNF-α and IL-6 levels	Sodium butyrate (4 g/day, 4 weeks)	Lean and obese men	Cleophas et al. (2019)
Metabolic Neural	Induction of beneficial skeletal muscle mitochondrial adaptations and inhibiting HDAC activity	Sodium butyrate (5% w/w, 10 weeks)	Male C57BL/6 J mice	Henagan et al. (2015)
Hormonal	Increase in GLP-1 and PYY levels and suppression of Fiaf and LPL	Sodium butyrate (5% w/w), sodium propionate (5% w/w) and sodium acetate (5% w/w) for 35 days	Male C57BL/6 J mice	Jiao et al. (2021)
Hormonal	Enhancement in the levels of GLP1 and PYY in wild type mice	Propionate (180 mmol/L)	Wild type (male C57BL6 mice) and FFA2 knockout mice	Psichas et al. (2015)
Hormonal	Enhancement in the levels of GLP1 and PYY	AXOS (7.5% w/w, 8 weeks)	Male C57BL/6 J mice	Neyrinck et al. (2012)
Metabolic	Increase in fatty acid oxidation and promoting adipogenesis	Sodium butyrate (5% w/w), sodium acetate (5% w/w), sodium propionate (5% w/w) or their mixtures in a ratio of 1:3:1	Male C57BL/6 J mice	Lu et al. (2016)
Metabolic	Reduction in PPARγ levels	Inulin type fructans (4 weeks, 0.2 g/d)	Male C57BL/6 J mice	Dewulf et al. (2021)

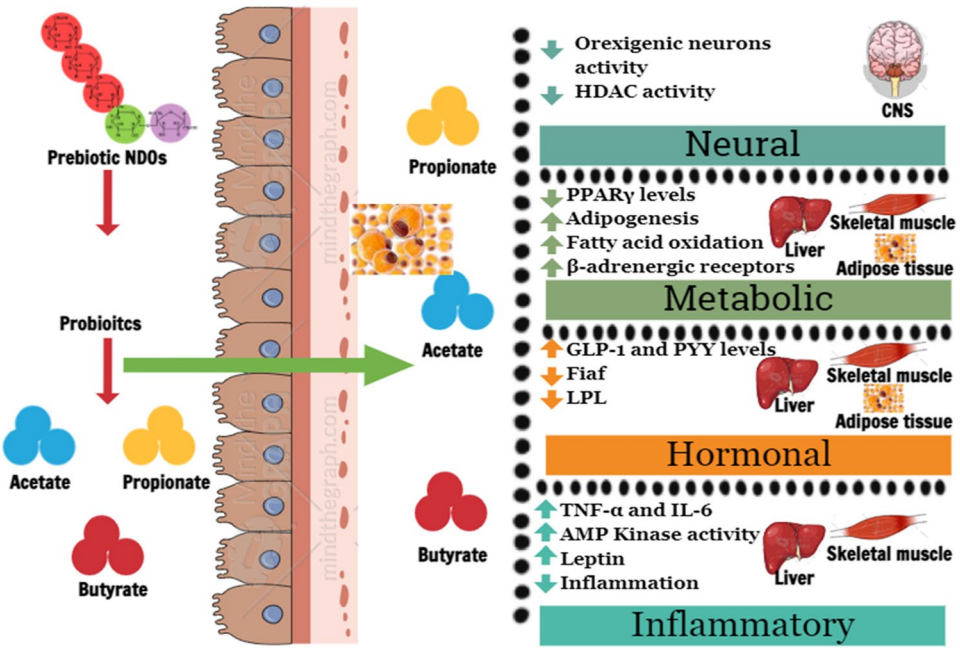

Fig. 2 Mechanism of prebiotic NDOs converted into probiotics towards the application of neural, metabolic, hormonal and inflammatory systems

14 participants) first received a 2-fiber (pea plus inulin) shot for 2 weeks before receiving a 4-fiber (pea + orange + barley inulin) shot for 2 additional weeks. Supplementation of natural fibre resulted in a significant increase in *Bacteroidetes* sp. and also altered metabolic and immune functions by enhancing the activity of CAZymes. This study demonstrates the fact that prebiotic fibres are capable of enriching specific beneficial bacteria in obese individuals.

Current limitation and future prospective

Obesity prevalence is rising worldwide, and its impact on society has major health and economic issues. Energy imbalance leads to obesity, which is mostly influenced by bad lifestyle choices, cognitive function, hormonal responses, genetic and epigenetic factors (Cerdó et al., 2019). This multi-component factor explains the clinical need for obesity treatment. Evolving evidence has acknowledged the clear association between beneficial intestinal microbiota (probiotics) and the onset of obesity. Dietary inclusion of prebiotic NDOs has proven beneficial in obesity treatment. However, the minute quantities of NDOs naturally present in food are found ineffective in conferring healthiness (Divyashri et al., 2021). As a result, methods are being developed for the synthesis of NDOs on an industrial scale as well as fortifying their inclusion into designer foods and/or additional goods for greater health advantages. There are reports that SCFAs generated from NDOs fermentation have various anti-obesity benefits. SCFAs exert numerous beneficial effects on mammalian energy metabolism and ameliorate obesity (Shon and Park, 2021).

Research advances to date have identified metabolic (activation of β-adrenergic receptors in white adipose tissue and AMP kinase, switching PPARγ from lipid synthesis to utilization, etc.), neural (suppression in the orexigenic neurons activity in the hypothalamus via gut-brain neural circuit), hormonal (increase in PYY and GLP-1 levels by suppression of LPL and Fiaf) and inflammatory (decrease in IL-6 and TNF-α levels) mechanisms that are associated with NDOs to confer anti-obesity benefits. Among SCFAs, butyrate has shown the potential to offer beneficial effects in alleviating obesity and related metabolic comorbidities (Coppola et al., 2021). The available literature has indicated the binding ability of butyrate to FFAR2 receptors and down-regulation of tight junction protein 1 and hydroxycarboxylic acid receptor 2 has proven its anti-obesity effects (Shon and Park, 2021).

Other SCFAs, viz., propionic acid, has failed to restore high-fat diet induce decline in motor coordination (Tengeler et al., 2020), and reported adverse metabolic effects of propionic acid consumption (Tirosh et al., 2019). Therefore, extra caution should be taken while administering propionic acid even though limited evidence suggests their positive metabolic effects. However, additional research is still needed to assess whether propionic acid could be used as an anti-obesity treatment. NDOs have demonstrated only modest clinical efficacy in the treatment of obesity, despite encouraging preclinical results. Also, the clinical investigations are restricted to young, healthy, middle-aged obese adults and obese children, and they tend to be shorter in duration (13 days to 16 weeks). MOS has shown gender-specific activity in fat reduction (Jana et al., 2021).

MOS supplementation was found beneficial only to men to lose significant body weight and adipose tissue loss.

Therefore, additional study is necessary to support the gender difference in MOS consumption responses (St-Onge et al., 2012). It is worth noting that NDO's beneficial effect on obesity has been strongly supported by animal models observations obtained from clinical trials are contradictory. In obese children, oligofructose supplementation has dubious benefits on body weight and composition. Obese youngsters supplemented with oligofructose-enriched inulin for 16 weeks significantly reduced body weight and body fat (Nicolucci et al., 2017). However, oligofructose supplementation for 12 weeks to obese children, combined with healthy lifestyle habits was ineffective in reducing body weight and total body fat (Liber and Szajewska, 2014).

Even though daily supplementation of oligofructose-enriched inulin (Hume et al., 2017) or inulin-type fructans (Reimer et al., 2017) for 12–16 weeks showed improvement in satiety, substantial weight reduction was not related to their impact on satiety. Thus, this necessitates further investigations to implement NDOs as an effective tool to prevent and treat obesity and related metabolic diseases. Clinical studies focusing on long-term obesity-associated parameters encompassing high sample size will enable to the development of better nutritional and clinical guidelines for the use of NDOs in obesity therapy (Cerdó et al., 2019). In addition, the incorporation of probiotics with NDOs to use synbiotics for obesity management should answer questions about the type of probiotic strains, their dosage, and the duration of the treatment. NDOs have become a distinctive dietary intervention in the management and prevention of obesity despite all the shortcomings.

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Author's contribution GD prepared original draft, performed visualization and investigation. KRR conceived and designed the analysis, methodology and conceptualization. AVR and VVK contributed to the final version of the manuscript by editing and supervision. All authors read and approved the final manuscript.

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Declarations

Conflict of interest The authors declare no competing interests.

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