International Food Research Journal 29(2): 236 - 247 (April 2022)
Journal homepage: *http://www.ifrj.upm.edu.my*

Review

Biological functions of nutraceutical xylan oligosaccharides as a natural solution for modulation of obesity, diabetes, and related diseases

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Article history

Received:
24 November 2020
Received in revised form:
18 May 2021
Accepted:
11 August 2021

Keywords

xylooligosaccharides, obesity, diabetes, dyslipidaemia, related diseases

Abstract

Natural compounds have been used to regulate numerous metabolic dysfunctions such as obesity, diabetes, and dyslipidaemia. Xylan oligosaccharides (XOS) alleviate obesity, diabetes, and dyslipidaemia via the regulation of glucose and lipid metabolisms, and the modification of gut microbiota. Moreover, XOS is also shown to inhibit obesity, diabetes, and related metabolic disorders such as inflammation and oxidative stress, by regulating the related genes and enzymes that contribute to the respective disorders. The information currently available does not offer in-depth elucidation regarding the molecular mechanisms of action of XOS in controlling obesity, diabetes, and related metabolic disorders, thus remain to be elucidated. The present review discusses XOS and its mechanisms of action, and key roles in regulating obesity, diabetes, and related metabolic disorders, highlighting the potential use of this compound in the improvement of novel therapeutic approaches for the treatment of the aforementioned diseases.

Introduction

Accumulating evidences indicate that the consumption of natural compounds ameliorates metabolic disorders such as diabetes, obesity, and dyslipidaemia (Lim *et al*., 2016; 2018). The study of natural compounds over the years has demonstrated their therapeutic potentials and preventive effects in the management of the aforementioned diseases. Some studies even suggested that bioactive compounds influence the metabolism of the whole body via the regulation of food intake, glucose, and lipid metabolism (Samanta *et al*., 2015).

Xylooligosaccharides (XOS) constitute a group of naturally occurring molecules with increasing interest in the nutrition field. XOS are obtained from natural sources by the hydrolysis of lignocellulosic materials (LCMs) (Brienzo *et al*., 2016). Due to low molecular weight (MW) and water solubility, LCMs are often used in large-scale commercial applications, especially XOS, which are essential for human healthcare. The biological effects of XOS include anti-obesity, antidiabetes, and dyslipidaemia modulation (Lim *et al*., 2016; 2018; Long *et al*., 2019), anticancer (Aachary *et al*., 2015), anti-inflammatory, enhancement of calcium availability (Singh *et al*., 2015), antioxidant (Jagtap *et al*., 2017), immunoregulatory (Patel and Prajapati, 2015), anticoagulant, antihypertensive, and anti-Alzheimer activities (Zhang *et al*., 2018). In general, XOS that have two units of xylose or more have been shown to possess greater biological activities such as anti-obesity, as compared to xylose monosaccharide. Furthermore, the biological activities of XOS are highest as compared to the other oligosaccharides (Saville and Saville, 2018). Although several studies have confirmed the anti-obesity, antidiabetic, and related effects of XOS, the underlying mechanisms are yet to be elucidated. Based on the efficacy of XOS in relieving diabetes, obesity, and related diseases, the search for their natural sources is rapidly becoming a goal for the treatment of diabetics and obese patients.

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DOI:
https://doi.org/10.47836/ifrj.29.2.02

Herein, we summarised the efficacy of XOS in the management of obesity, diabetes, and related diseases.

XOS preparation

XOS are prepared from a variety of agricultural residues such as corncobs and sugarcane bagasse (Carvalho *et al*., 2013), wheat waste (Faryar *et al*., 2015), mahogany and mango wastes (Gobinath *et al.*, 2017), rice waste, and cotton and sunflower stalks (Kiran *et al*., 2013), and green coconut husks (Jayapal *et al*., 2014). Corncobs, barley straws, cotton stalks, and sugarcane bagasse are considered rich sources of XOS (Carvalho *et al*., 2013).

The preparation of XOS is divided into two steps. The first step or pre-treatment step involves xylan (hemicellulose) extraction, while the second step involves the hydrolysis of xylan into XOS. The pre-treatment step can be conducted by ultrasound (Antov and Đorđević, 2017), microwave extraction (Panthapulakkal *et al*., 2013), steam explosion (Álvarez *et al*., 2017), and alkaline extraction (Carvalho *et al*., 2013). In the second step, the xylans can be hydrolysed using autohydrolysis, chemical methods, or enzymatic methods. The autohydrolysis method involves the conversion of xylan to XOS at 140 - 220°C in the presence of water (Samala *et al.*, 2012; Samanta *et al*., 2015) and slightly acidic conditions (Qing *et al*., 2013). In chemical methods, XOS are produced by hydrolysis of xylan using mineral acid solutions such as sulphuric acid, acetic acid, and hydrochloric acid. Typically, chemical methods may yield toxic substances and monosaccharides in the final product, in addition to XOS, with a broad degree of polymerisation (DP) (Jain *et al*., 2015). The enzymatic method is performed using xylanases (Samanta *et al*., 2015), with endo-1,4-β-xylanase being the common enzyme acting on the hydrolysis bond in internal xylan polymers (β-1,4-linked backbone) (Chapla *et al*., 2012). In contrast to the previous methods, this method exhibits numerous advantages such as is easy to control and specialised. In addition, it operates under moderate conditions, environmentally friendly, and generates fewer undesirable substances as compared to the other methods. Moreover, it does not require special equipment, and is common in XOS production, although it is expensive as compared to the chemical methods (Chapla *et al*., 2012). XOS preparation from LCMs is summarised in Figure 1A.

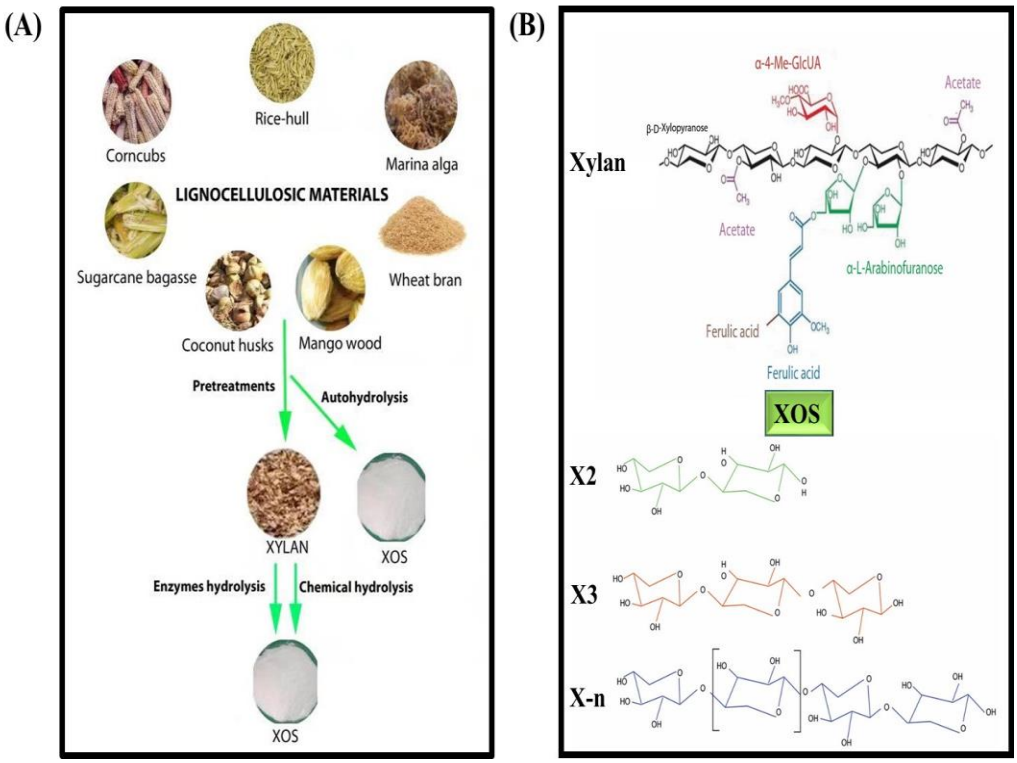

Figure 1. (A) Preparation of XOS from lignocellulosic materials, and **(B)** structures of xylan and XOS, modified from Brienzo *et al.* (2016) and Dodd and Cann (2009). α-4-Me-GluUA: α-4-methyl-glucuronic acid, XOS: xylooligosaccharides, X2: xylobiose, and X3: xylotriose.

Chemical structure and physicochemical properties of XOS

XOS consists of two to ten molecules of xylose linked by β-(1→4)-glycosidic bonds, namely xylobiose, xylotriose, or xylotetraose (Figure 1B) (Samanta *et al*., 2015), and the presence of other side groups such as acetyl groups, arabinofuranosyl residues, α-D-glucopyranosyl uronic acid, or its 4-O-methyl derivative associated with xylan (Figure 1B) (Aachary and Prapulla, 2011). XOS are obtained through the hydrolysis of xylan, which is extracted from LCMs that are produced from agricultural sources, and consist of three main components: hemicellulose, cellulose, and lignin (Samanta *et al*., 2015). Hemicellulose percentage in common LCMs is 14 - 36% (Ruiz *et al*., 2013). Xylan is the most common type of hemicellulose, consisting of β-1,3-linked xylose units in marine organisms (Konishi *et al*., 2012) or β-1, 4-linked xylose unit in plants (Samanta *et al*., 2015). The structure and function of xylan depend on the extraction method and its source (Jensen *et al*., 2013). Therefore, XOS activity varies according to the different sources of xylan. XOS are also naturally present at low concentrations in fruits, vegetables, bamboo, honey, and milk. Xylan is water-soluble with low caloric value and a sweet taste, *i.e.*, about 40% sweetness as compared to sucrose. In food application, XOS are incorporated in a wide variety of food products such as beverages, dairy products, acid products, salad dressings, alcoholic beverages, functional foods, and sugarless or low-sugar confectionaries. XOS are generally recognised as safe (GRAS) by the Food and Drug Administration (FDA), and approved by other worldwide organisations for application in foods and pharmaceutical product formulations (Ibrahim, 2018).

Effects of XOS on obesity, diabetes, and related diseases

Effects of XOS on obesity

Obesity is a major public health concern, and considered an epidemic hazard (Mohamed *et al.*, 2014). In April 2020, the World Health Organization (WHO) reported that the number of overweight and obese people reached 1.9 billion and > 650 million, respectively, globally. In addition, > 340 and 41 million children, aged > 5 and < 5 years, are overweight or obese, respectively (WHO, 2020; Paciência *et al*., 2021). These numbers are expected to increase by 33% over the next two decades as compared to the past three decades, which represents 51% of the population, incurring a healthcare cost of $549.5 billion (Finkelstein *et al*., 2012). The phenomenon is restricted to increased body weight, and linked to numerous comorbidities such as diabetes mellitus (DM), hypertension, dyslipidaemia, cardiac alterations, metabolic syndromes, cancers, neurological disorders, and lung diseases (Mohamed *et al*., 2014). Although several probable targets have been recently identified for obesity control, the search for new, cost-effective, and safe therapeutic approaches remains essential.

The anti-obesity properties of XOS have attracted the attention of the scientific community in recent years. Data from both human and animal studies indicated that XOS are effective in regulating body and adipose fat tissue weights via several mechanisms such as improving in the inhibition of fat deposition and gene expression of adipogenesis markers, inducing changes in the composition of gut flora, and regulating food intake and body lipids (Lim *et al*., 2016; 2018; Zhang *et al*., 2018; Saville and Saville, 2018; Long *et al*., 2019; De Freitas *et al*., 2019). The inconsistent effects in these experiments may be due to the differences in the XOS compositions, sources, and protocol treatments used.

The regulation of body weight is influenced via the impact of XOS on the intestinal microflora, which in turn influences the extraction of energy from the diet. The intestinal microflora mainly comprise of three phyla: Actinobacteria (*Bifidobacteria*), Firmicutes (*Ruminococcus*, *Clostridium*, *Lactobacillus*, and *Eubacteria*), and Bacteroidetes (*Porphyromonas*, *Prevotella*, and *Bacteroides*) (Azad *et al*., 2018). Firmicutes and Actinobacteria in intestinal microflora contain the majority of obesity-linked genes (Turnbaugh *et al*., 2009; Hansen *et al*., 2013). The proportion of Firmicutes in obese individuals is higher as compared to that of Bacteroidetes; moreover, the increase in Firmicutes/Bacteroidetes ratio was also observed in obese individuals (Kasai *et al*., 2015; Koliada *et al*., 2017). The growth promotion of *Bifidobacterium* also plays a crucial role in inhibiting the development of obesity (Zhang *et al*., 2020). *Roseburia* spp. and members of the Lachnospiraceae family are characterised as typical short-chain fatty acids (SCFAs)-producing bacteria (Jefferson and Adolphus, 2019). Hansen *et al.* (2013) noted that 10% XOS supplementation into diet promoted SCFAs production in the gut of mice. It was speculated that

SCFAs protect against obesity by promoting the release of gut hormones such as glucagon-like peptide-1 (GLP-1) and peptide YY (PYY), and influence lipid metabolism (Canfora *et al*., 2015; Zhao *et al*., 2017). Several experiments suggested that XOS alleviate obesity-related phyla such as Firmicutes and Firmicutes/Bacteroidetes ratio; correspondingly, XOS augmented *Bacteroidetes*, *Bifidobacterium*, *Lachnospiraceae NK4A136* group, and *Roseburia* (Long *et al*., 2019; Zhang *et al*., 2020). *In vitro* and *in vivo* studies showed that XOS from different sources and structures regulated the bacteria related to obesity, especially the *Bifidobacterium* genus, with increasing SCFA production (Faryar *et al*., 2015; Gobinath *et al*., 2017; Jagtap *et al*., 2017). On the other hand, the decreased food intake due to XOS could be attributed to improved circulating leptin release from adipocytes that promotes satiety. In addition, XOS treatment enhanced adiponectin hormone (Lim *et al*., 2018) which is inversely associated with obesity via lipid metabolism. XOS also suppressed fat accumulation, adipose tissue weights (mesenteric, subcutaneous, and perirenal deposits), and fat mass in the liver by regulating the expression of genes associated with adipogenesis and lipogenesis (Lim *et al*., 2018; Long *et al*., 2019). Furthermore, XOS also attenuated obesity via the reduction of ceramide and diacylglycerol in the plasma due to lipogenesis regulation by XOS (Boini *et al*., 2018; Zhang *et al*., 2020). Similar results were observed by wheat-bran arabinoxylan-oligosaccharides that reduced the plasma ceramide levels in overweight human subjects (Benítez-Páez *et al*., 2019). Therefore, these findings indicated that XOS could be used as a nutraceutical for obesity treatment. The potential mechanisms of XOS against obesity are summarised in Figure 2.

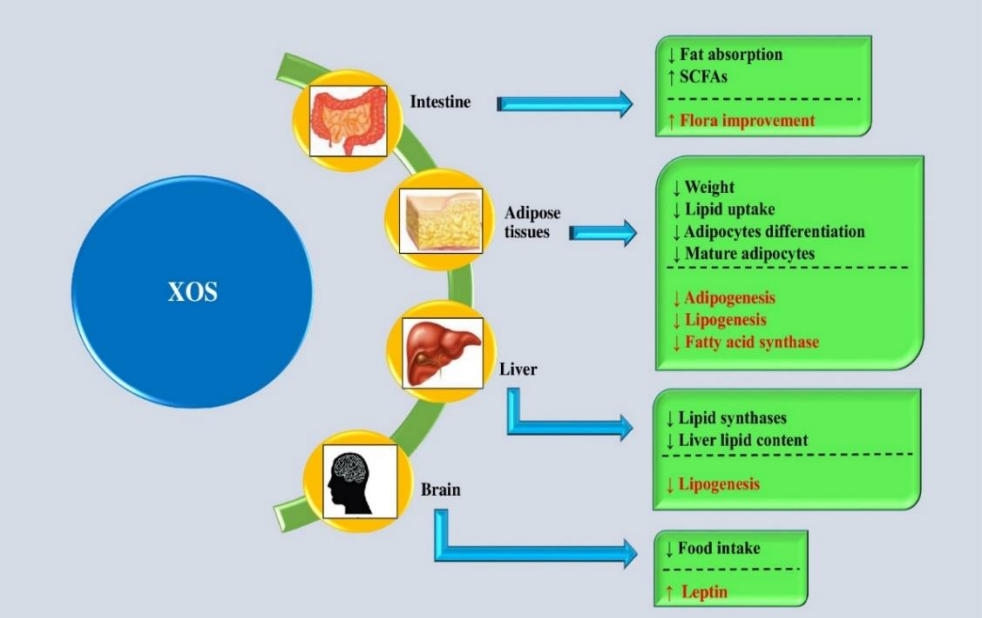

Figure 2. Probable mechanism of anti-obesity action of XOS in obesity models. SCFAs: short-chain fatty acids, and XOS: xylooligosaccharides.

Effects of XOS on diabetes

DM is a metabolic disorder characterised by high plasma glucose levels caused by inappropriate secretion of insulin (type 1 DM or T1DM) or action of insulin (type 2 DM or T2DM). Currently, DM is a critical health problem worldwide, and the main risk for hypertension, cardiovascular diseases, respiratory diseases, and other complications that lead to mortality (Lee *et al*., 2016).

The application of XOS in the management of diabetes has been studied using several types of diabetic models. Currently, there are several reports on the antidiabetic activity of XOS. A study showed that XOS fed for six weeks attenuated hyperglycaemia in streptozotocin-induced diabetic rats by reducing nephromegaly, and lowering the advanced glycation end products (AGEs) (Gobinath *et al*., 2010). Another study unveiled that XOS attenuated the peripheral insulin resistance in obese-insulin resistant rats through the gut-brain axis (Chunchai *et al*., 2018). Furthermore, the consumption of XOS (DP 2 - 4) for 12 weeks alleviated glucose intolerance in mice fed a high-fat diet (HFD). This alleviation was due to the ability of

XOS in modifying gut flora and ceramide rise (Zhang *et al*., 2020). Previous studies also reported an association between impaired homeostasis of glucose and escalated ceramide levels in T2DM (Benítez-Páez *et al*., 2019).

The antidiabetic effect of xylobiose (a major disaccharide in XOS) has also been assessed in normal mice and diabetic db/db mice (the most extensively used mice model of T2DM) throughout six weeks. This administration of xylobiose successfully suppressed the improvement of hyperglycaemia in db/db mice. The antidiabetic action of xylobiose in this study regulated plasma glucose (Lim *et al*., 2016). In addition, the antidiabetic effect of xylobiose in obese mice also increased the insulin levels (Lim *et al*., 2018). Furthermore, the administration of D-xylose, a monosaccharide of XOS, also influenced insulin and blood glucose levels in obese mice; the mechanism by which D-xylose alleviated DM was the suppression of sucrase activity (Lim *et al*., 2015; 2016; 2018). The same mechanism was observed using the human models (Bae *et al*., 2011), proposing that the antidiabetic influence of XOS was also conferred to their monosaccharides. The efficiency of XOS in managing plasma glucose has also been evaluated in humans. A dosage of 2 gm/d XOS for eight weeks altered the intestinal microflora and insulin levels in pre-diabetic subjects (Yang *et al*., 2015). Furthermore, XOS consumption by T2DM subjects lowered the glucose, and managed the abnormal lipid metabolism (Zhu *et al*., 2019). In another study, XOS derived from rice husk exhibited antidiabetic efficacy by attenuating endotoxemia, and reducing the level of lipopolysaccharide (LPS) in diabetes plasma; whereas the presence of LPS in plasma was recognised as metabolic endotoxemia, which is linked to numerous diseases, specifically T2DM and obesity. Moreover, paracellular transport is a key function of several diseases, such as DM. XOS lessened the impaired intestinal paracellular permeability by decreasing the levels of fluorescein isothiocyanate-dextran in rat plasma. Furthermore, the glucose uptake surged in skeletal muscle (Khat-udomkiri *et al*., 2019). Together, these findings proposed that XOS could be used as a natural agent for the management of DM. Figure 3 shows the summary of the mechanisms of action of XOS against diabetes.

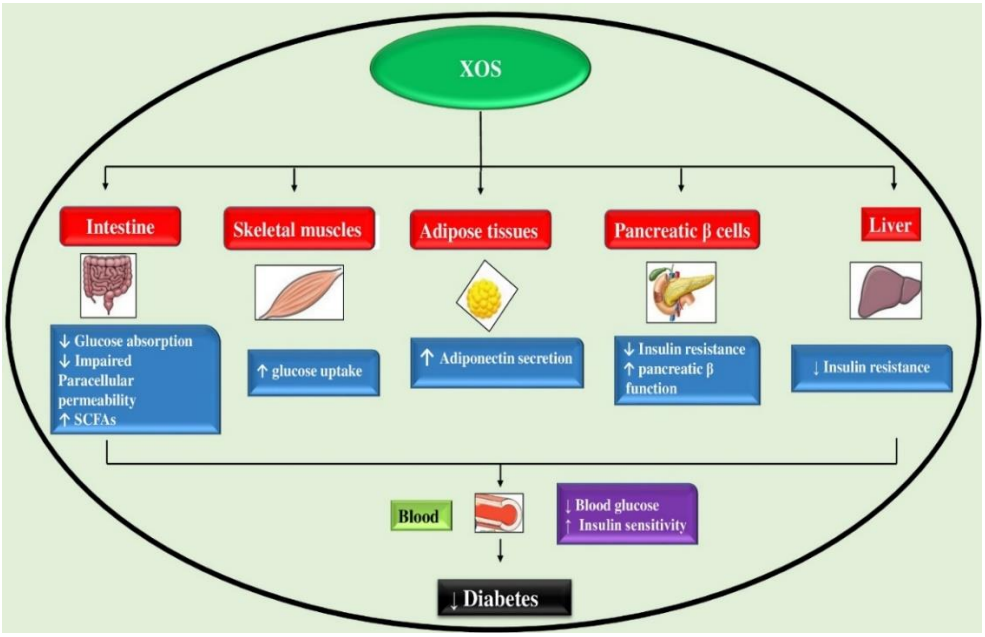

Figure 3. Potential principal mechanisms of anti-diabetes action of XOS in diabetes models. SCFAs: short-chain fatty acids, and XOS: xylooligosaccharides.

Effects of XOS on obesity- and diabetes-related diseases

Effects of XOS on dyslipidaemia

An upsurge in the levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) or high-density lipoprotein cholesterol (HDL-C) is defined as dyslipidaemia or hyperlipidaemia (He *et al*., 2011; El-Tantawy and Temraz, 2018), which is responsible for an increased risk of heart diseases, atherosclerosis, and

cardiovascular diseases (Dake and Sora, 2016). Overall, a healthy diet has beneficial effects on regulating the profiles of serum lipid: reducing the TC, TG, and LDL-C (the bad cholesterol), while enriching the HDL-C (good cholesterol). A healthy diet may include decreased intake of dietary cholesterol and saturated and trans-fatty acids, and increased intake of functional foods and nutraceuticals (Chen *et al*., 2014).

The mechanism of dyslipidaemia modulation by XOS is to regulate lipid metabolism. XOS demonstrated TG- and cholesterol-lowering activities by enhancing mRNA expression of cholesterol 7-alpha-hydroxylase (*CYP7A1*), sterol 12-alpha-hydroxylase (*CYP8B1*), and ATP-binding cassette transporter G5/G8 (*ABCG5/8*) enzymes that enhance bile acid synthases from cholesterol (Li *et al*., 2013; Lim *et al*., 2016). In contrast, XOS suppressed sterol regulatory element-binding protein (SREBP) that leads to the formation of enzymes involved in the synthesis of cholesterol such as HMG-CoA reductase (HMGCR) and hydroxyl-methylglutryl-coenzyme A (HMG) synthase. XOS also suppresses the expression of *SREBP-2* mRNA via liver X receptor alpha (LXR-α), an oxysterol receptor that stimulates ATP-binding cassette transporter (*ABCG1/5/8*), thus diminishing the level of HMGCR to yield less free cholesterol and other lipogenic genes including fatty acid synthase (FAS), sterol regulatory element-binding protein-1C (SREBP), acetyl-CoA carboxylase (ACC), and peroxisome proliferator-activated receptor gamma (PPAR-γ); all were regulated by XOS feeding (Lim *et al*., 2016; 2018). Another study found that XOS attenuated dyslipidaemia in obese-insulin resistant rats through the gut-brain axis (Chunchai *et al*., 2018). In obese mice, XOS supplementation levels alleviated plasma ceramides and diacylglycerol (DAG) levels via lipogenesis (Zhang *et al*., 2020). In human studies, HDL-C levels were increased in healthy subjects by feeding 8 gm/day XOS (Childs *et al*., 2014). The atherogenic index (AI) values were associated with atherogenic profiles, namely apolipoprotein B (ApoB), containing small LDL particles and lipoproteins. However, plasma TG and HDL-C independently represent risk factors for coronary diseases, whereas the AI formula that uses both the aforementioned factors, for example, log (TG/HDL-C), is useful and precise in predicting the atherogenicity of plasma. XOS decreased the AI values in obese mice (Lim *et al*., 2018). The mechanisms of the XOS action on dyslipidaemia regulation are depicted in Figure 4.

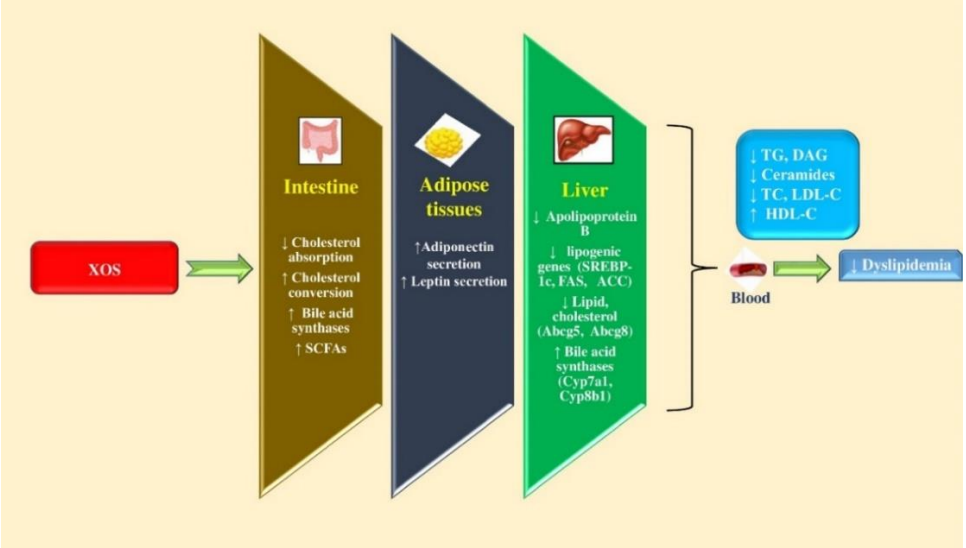

Figure 4. Mechanisms of the XOS action on dyslipidaemia regulation in obesity or diabetes models. *ABCG5/8*: ATP-binding cassette transporter G5/G8, ACC: acetyl-CoA carboxylase, *CYP7A1*: cholesterol 7 alpha-hydroxylase, *CYP8B1*: sterol 12-alpha-hydroxylase, DAG: diacylglycerol, FAS: fatty acid synthase, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, SCFAs: short-chain fatty acids, SREBP-1c: sterol regulatory element-binding protein, TC: total cholesterol, TG: triglycerides, and XOS: xylooligosaccharides.

Effects of XOS on inflammation

Obesity or diabetes induces pro-inflammatory cytokine production and low-grade chronic systematic inflammation. The adipose tissues are a major source of interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α), and resistin; these cytokines are

driven by HFD or lipid infusion. TNF-α levels are higher in the serum of obese individuals, thus releasing fatty acids into circulation by boosted adipose tissue lipolysis than in non-obese controls (Lim *et al*., 2018). Various concentrations and structures of XOS have anti-inflammatory effects. Long *et al*. (2019) showed a decrease in monocyte chemoattractant protein-1 (MCP-1) in obese mice after 2 and 7% doses of XOS, respectively. On the other hand, a 10% XOS (DP 2 - 6) consumption by male C57BL/6NTac mice for ten weeks downregulated interferon-gamma (IFN-γ) and the low-grade inflammatory cytokine IL-1β, thereby decreasing systemic inflammation. The underlying mechanism is an increase in SCFA concentrations by XOS supplementation (Hansen *et al*., 2013). Furthermore, D-xylose and xylobiose treatments lowered the pro-inflammatory cytokine expressions including MCP-1, TNF-*α*, and IL-1β (Lim *et al*., 2018). Under diabetic conditions, the increased production of inflammatory cytokines led to insulin resistance, which is linked to diabetes; XOS addition inhibits the levels of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, and MCP) and other genes related to inflammatory response including cyclooxygenase-2 (COX-2) and nitric oxide synthase (iNOS) (Lim *et al*., 2016). Moreover, mitogen-activated protein kinases (MAPKs) are triggered in response to various stimuli including inflammatory signals, stress, and ultraviolet irradiation (Tarantino and Caputi, 2011). p38MAPK phosphorylation is shown to stimulate the pro-inflammatory cytokines (TNF-α, IL-1β, and MCP). Thus, it could be hypothesised that XOS inhibited MAPKs phosphorylation in the liver of db/db mice, and also inactivated the MAPK pathway. Additionally, the inhibition of inflammatory response was consistent with the reduced blood glucose level (Lim *et al*., 2016). The mechanisms of inflammation regulation by XOS are summarised in Figure 5.

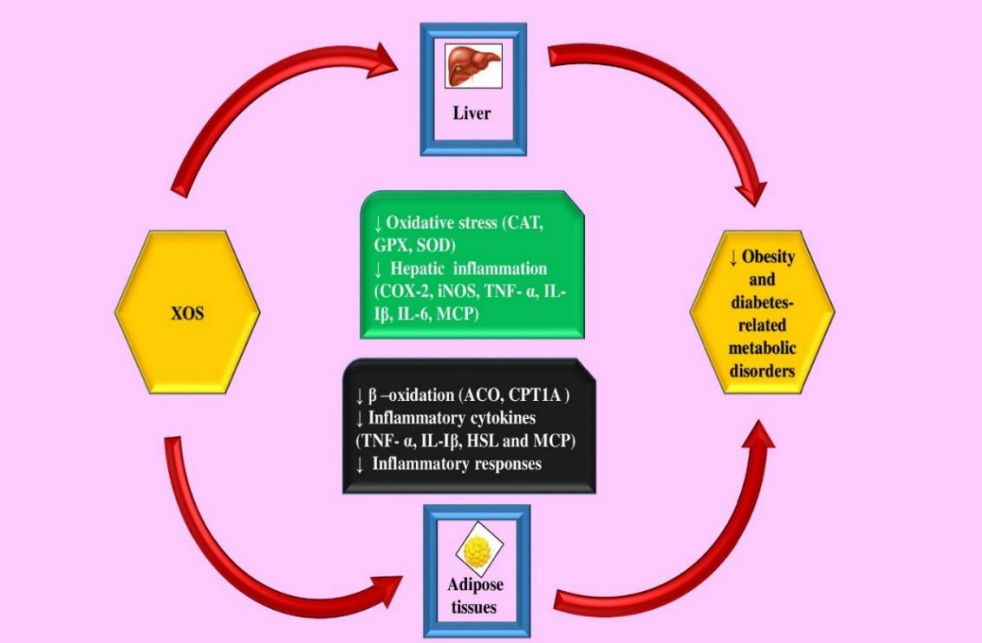

Figure 5. Mechanisms of the role of XOS in attenuating inflammation and oxidative stress in obesity or diabetes models. ACO: acyl CoA oxidase, CAT: catalase, COX-2: cyclooxygenase-2, CPT1A: carnitine palmitoyltransferase 1-A, GPX: glutathione peroxidase, HSL: hormone-sensitive lipase, IL-1β: low-grade inflammatory cytokine interleukin-1β, IL-6: interleukin-6, iNOS: nitric oxide synthase, MCP: monocyte chemoattractant protein, SOD: superoxide dismutase, TNF-α: tumour necrosis factor-α, and XOS: xylooligosaccharides.

Effect of XOS on oxidative stress

In diabetes, both blood glucose elevation and glucose oxidation give rise to large amounts of free radicals, thus resulting in enhanced activities and expression levels of antioxidant enzymes including superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT). The increased levels of blood glucose in diabetes are accompanied by an escalation in expression levels of these antioxidant enzymes, which may be associated with an increase in oxidative stress (Lim *et al*., 2016). Under diabetic conditions, oxidative stress also produces AGEs

(Gobinath *et al*., 2010). The addition of XOS significantly improved the antioxidant enzymes and AGEs in the diabetic model (Gobinath *et al*., 2010; Samanta *et al*., 2015; Lim *et al*., 2016; De Freitas *et al*., 2019). Fascinatingly, the lipid oxidation-related gene, *PPAR-γ*, was downregulated by XOS treatment (Lim *et al*., 2016). XOS alone or amalgamated with probiotics attenuated hippocampal oxidative stress of HFD-fed rats (Chunchai *et al*., 2018). In addition, XOS administration significantly improved GPX and CAT levels in diabetic rats' blood (Gobinath *et al*., 2010). Remarkably, 5% XOS supplementation to rats fed HFD alleviated malondialdehyde (oxidative stress biomarker) levels in the heart, liver, and serum. In contrast, glutathione (GSH), a major antioxidant, glutathione disulphide, and primary antioxidant enzymes (SOD, CAT, and GPX) were augmented in the above organs (Wang *et al*., 2011). Overall, the activity of XOS against free radicals also depends on the bound phenolic content in the former structure, which was affected by their sources (Singh *et al*., 2015). For example, the antioxidant activity of XOS prepared from ragi was stronger than that prepared from rice, wheat, and maize (Jagtap *et al*., 2017). Furthermore, the antioxidant activity of garlic straw xylan XOS was equal to that presented by XOS derived from rice (Kallel *et al*., 2014). The regulatory mechanisms of XOS-mediated oxidative are summarised in Figure 5.

Conclusion

The present review proposed that XOS could be beneficial for the prevention of obesity, diabetes, and the related diseases, without the side effects often caused by chemical therapies. However, some future studies need to address, including but not limited to, multiple concentrations of XOS to assess the concentration-response results, separation of individual XOS and compare the effect for short and long study durations, and combination of XOS with various oligosaccharides that may provide synergistic effects on disease regulation. Furthermore, additional studies are needed to examine the effect of XOS on microbiota under diabetes. Also, animal studies are needed to understand the capacity of short-chain XOS in energy metabolism regulation, while clinical studies are needed to confirm the animal results and examine the long-term health consequences.

Acknowledgement

The present review was financially supported by the National Key Research and Development Program of China (grant no.: 2017YFD040020601); the National Natural Science Foundation of China (grant no.: 31830069, 31671798, 31701592); the Science and Technology Program of Beijing Municipal Education Commission (grant no.: KM202010011007); and the Science and Technology Innovation Service Ability—Construction of Provincial-level Scientific Research Platforms, Beijing Food Nutrition and Human Health Advanced Innovation Centre (grant no.: 19008020101).

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