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Review Article

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Effects of Natural Alternative Sweeteners on Metabolic Diseases

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ABSTRACT

The rising prevalence of obesity and diabetes is a significant health concern both in globally and is now regarded as a worldwide epidemic. Added sugars like sucrose and high-fructose corn syrup (HFCS) are a major concern due to their link with an increased incidence of diet-induced obesity and diabetes. The purpose of this review is to provide insight into the effects of natural sweeteners as alternatives to sucrose and HFCS, which are known to have negative impacts on metabolic diseases and to promote further research on sugar consumption with a focus on improving metabolic health. The collective evidences suggest that natural alternative sweeteners have positive impacts on various markers associated with obesity and diabetes, including body weight gain, hepatic fat accumulation, abnormal blood glucose or lipid homeostasis, and insulin resistance. Taken together, natural alternative sweeteners can be useful substitutes to decrease the risk of obesity and diabetes compared with sucrose and HFCS.

Keywords: Sugars; Sugar substitutes; Metabolic diseases; Obesity; Diabetes mellitus

METABOLIC DISEASES

Obesity

The rising prevalence of obesity is a significant health concern both in the United States (US) and globally and is now regarded as a worldwide epidemic. Data from the Centers for Disease Control and Prevention shows that 40% of Americans are currently impacted by obesity [1]. In May 2022, the World Health Organization published a report on the status of the obesity pandemic in Europe, which revealed that approximately 60% of individuals residing in the region are either overweight or obese [2]. Obesity can result in metabolic dysregulation, which can interfere with the proper functioning of key metabolic organs, including the liver, adipose tissue, pancreas, muscles, and intestines [3-5]. Studies on the distribution and determinants of diseases in populations have shown that there is a connection between high body mass index (BMI) and various chronic conditions such as non-alcoholic fatty liver disease (NAFLD) [6], cardiovascular disease [7,8], diabetes [7,9], multiple cancers [10-12], musculoskeletal diseases [13,14], and chronic kidney disease [7].

Type 2 diabetes mellitus (T2DM)

T2DM is significantly associated with overweight and obesity, as high BMI and waist circumference ratios have been confirmed as risk factors for the disease. Obesity is a triggering factor for DM related to insulin resistance. Insulin resistance is a common factor associated with obesity, which is a pathological condition in the development of T2DM [15]. T2DM is a major type of DM that results from imbalanced glucose homeostasis due to insulin resistance in peripheral tissues, such as the pancreas, liver, adipose tissue, and muscle. Furthermore, DM is a complex chronic disease characterized by high blood glucose levels or hyperglycemia, which results from a deficiency in insulin secretion, action, or both [15,16]. Obesity-related insulin resistance is associated with a range of metabolic abnormalities related to obesity, including dyslipidemia, NAFLD, hypertension, heart disease, and stroke [15,17,18]. Insulin resistance triggered by inflammation can increase lipolysis in adipose tissue, leading to the release of free fatty acids (FFAs) into the bloodstream. This, in turn, can contribute to other metabolic dysfunctions, such as hepatic steatosis [19,20].

NAFLD

The liver plays a significant role in regulating numerous metabolic pathways. NAFLD is the most frequent liver disease worldwide, and is a general type of chronic liver disease that is associated with obesity and T2DM [18,19]. For example, NAFLD shows dyslipidemia, abdominal adiposity, and glucose intolerance. Increased of visceral adipose tissue is associated with NAFLD, which raises FFAs and accumulate fat in the liver [21]. NAFLD is a condition that includes 2 forms: hepatic steatosis, which is characterized by the accumulation of fat within the liver cells, and nonalcoholic steatohepatitis, which is a more severe form that can lead to liver cirrhosis and failure [22]. Furthermore, hyperglycemia led to insulin resistance could worsen the condition of NAFLD. According to a study conducted in Japan, the occurrence of hepatic steatosis in lean adults was 62% among newly diagnosed T2DM patients and 43% among individuals with impaired fasting glucose levels, whereas it was only 27% in those with normal fasting glucose levels [23]. Insulin resistance in adipocytes can lead to the failure of suppressing hormone-sensitive lipase through insulin and result in the release of FFAs into the bloodstream, mainly from visceral adipose tissue [24]. The release of FFAs from visceral adipose tissue is particularly problematic, as they are processed first in the liver [25,26]. These FFAs can travel to the liver and contribute to lipid accumulation within the organ such as the liver. The triglyceride (TG) accumulation in the liver comes from 3 sources including FFAs, de novo lipogenesis, and diet. FFAs that enter the portal circulation can be classified into one of 3 types: i) undergo β-oxidation, ii) get re-esterified to form TG and are exported as very low-density lipoprotein, or iii) get re-esterified and stored in the liver [27]. The conversion of carbohydrates into lipids, known as de novo lipogenesis, also plays a role in the accumulation of lipids in the liver and is elevated in cases of insulin resistance [27]. Furthermore, inflammation can increase proinflammatory cytokines-mediated upregulation of hepatic fatty acid translocase and also exacerbate the accumulation of FFAs in the liver, leading to steatosis [28]. These feature of NAFLD can cause an increase gluconeogenesis and hyperglycemia in the liver [29].

The balance between energy intake and expenditure is crucial for metabolic processes, and diet plays a significant role in this regard. Maintaining a balanced macronutrient intake is important to prevent excess energy storage in adipose tissue, which can lead to obesity [16]. Additionally, controlling body weight is therefore important in both preventing and treating metabolic disease such as diabetes and obesity. In diabetic and obesity patients, a high intake of diets containing red meats, refined grains, and sugars has been shown to increase the risk

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of diabetes and exacerbate glycemic control and blood lipids, emphasizing the importance of individual dietary behavior in the prevention and management of metabolic diseases [30,31]. High intake of fats and sugars-rich foods are major factors of obesity [31,32]. Therefore, the management of health conditions such as obesity and diabetes, as well as related liver diseases, heavily relies on the implementation of proper diet control as an essential preventive and therapeutic manners.

ADDED SUGARS AND METABOLIC DISEASES

The consumption of high levels of dietary sugars has become a global concern due to its association with increased risk for metabolic disorders such as obesity, T2DM, and NAFLD [33-35]. The Food and Drug Administration (FDA) strongly recommends that people should limit their intake of added sugars to no more than 10% of their total daily calorie consumption [36]. In 2016, although the American Heart Association advised people to consume no more than 6–9 teaspoons of sweeteners per day [37], the average per-person consumption of sweeteners in the US was approximately 22 teaspoons per day [38]. The consumption of added sugar has notably increased the glycemic index (GI) and overall energy intake of various food and beverage products. Excessive consumption of high-calorie and high-GI foods can lead to elevated glucose levels, which in turn can contribute to the accumulation of body fat and metabolic alterations [39,40]. Added sugars in the human diet come mainly from sucrose (which is composed of 50% fructose and 50% glucose) and high-fructose corn syrup (HFCS). There are 2 types of HFCS commonly used, HFCS-55 (which consists of 55% fructose and 45% glucose or glucose polymers) and HFCS-42 (which is composed of 42% fructose and 58% glucose or glucose polymers) [41,42]. In recent years, there has been significant scientific evidences surrounding the metabolism, endocrine response, and potential health impacts of sucrose, HFCS, and fructose [43-45]. Therefore, decreased intake of added sugars such as sucrose and HFCS is an important way in the prevention and treatment of various diseases.

Sucrose

Sucrose is a type of disaccharide consisting of fructose and glucose, linked by an O-α-D-glucopyranosyl-(1→2)-β-D-fructofuranoside bond, which are 2 types of monosaccharides, in a 1:1 ratio. This covalent bond between monosaccharides in sucrose is easily broken down by the sucrase enzyme in the gastrointestinal tract [46]. It is commonly used as a sweetener in the food industry and cooking due to its standard sweetness [47]. It is also used for energy source due to quick absorption in small intestine after breaking down into fructose and glucose by the enzyme sucrase in the small intestine [48] and increases blood glucose level [49,50]. Various studies have shown that a high sucrose diet can lead to a range of metabolic diseases, including hyperlipidemia and hyperglycemia. Within 10 weeks of intake, sucrose has been demonstrated to have a negative impact on the metabolic profile of overweight individuals [51]. Sucrose feeding in the rats produces impair insulin action, predominantly in the liver, compared to starch feeding rats [52]. Rats fed equienergetic high sucrose diets show significantly higher body weights compared to rats fed a control diet, similar to rats fed equienergetic high-fat diets (HFDs). These findings suggest that sucrose may contribute to weight gain as much as fat, even when calorie intake is the same [53]. Furthermore, High-sucrose diets elevated plasma TG by increasing hepatic TG secretion which is symptom of liver steatosis in both human and animals [54,55] and up-regulated visceral fat in bilateral ventromedial hypothalamic-lesioned obese rats-lesioned obese rats [56]. In fruit fly, high

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sucrose diet decreased fruit fly development and promotes obesity phenotype accompanied by elevated steady-state insulin-like peptide 3 mRNA level [57]. Taken together, numerous studies have shown that high sucrose intake is associated with the development of obesity, diabetes, and NAFLD by up-regulating blood glucose and lipid levels, insulin resistance, and hepatic lipid accumulation.

HFCS

It is not uncommon for the public and media to have difficulty distinguishing between studies that use pure fructose or glucose, which are not commonly consumed in the human diet, and studies that use more commonly consumed sweeteners such as HFCS, which contain both fructose and glucose. HFCS-42 and HFCS-55 have similar monosaccharide compositions to sucrose, but unlike sucrose, their monosaccharides are not chemically bonded. They are instead free in solution. The main difference between sucrose and HFCS-42 and HFCS-55 is their moisture content, with sucrose having a lower percent moisture content (5%) compared to HFCS-42 and HFCS-55 (29% and 23%, respectively) [46]. In the US, HFCS has become a common replacement for refined sugar (sucrose) in various food items and almost all sweetened drinks [58]. Different types of HFCS have specific uses in the food industry. HFCS-42 is commonly used in baked goods, canned fruits, and condiments, whereas HFCS-55 is primarily used in regular carbonated soft drinks, other sweetened beverages like fruit drinks and ades, as well as ice cream and frozen desserts [58]. It is important to comprehend the behavioral and physiological impacts of consuming dietary HFCS, considering its widespread consumption in the American diet. This has led to considerable scientific researches over the past decade regarding the metabolism, endocrine response, and potential health effects of these sweeteners [59]. Previous studies insisted that the rapid rise in obesity in the US was closely linked to the increased consumption of HFCS [35,44] as well as T2DM [60]. Teff et al. [43] demonstrated that consumption of meals with a high fructose content can decrease circulating of insulin and leptin levels in the bloodstream of women. Rats fed a diet high in HFCS for a period of 6 to 7 months displayed signs of obesity, including abnormal weight gain, increased levels of circulating TG, and increased fat deposition [61]. Research indicates that consuming HFCS may not provide the same level of satisfaction and feelings of fullness as consuming sucrose, leading to overeating. These studies have found that consuming pure fructose can result in higher levels of various factors such as plasma FFAs, leptin, adiponectin, abdominal adipose tissue, and reduced insulin sensitivity [62-64]. Moreover, rats fed a HFD with consuming high-fructose showed increased resistance to leptin and worsened weight gain [64].

Consumption of HFCS results in higher levels of fructose in the body and causes acute metabolic effects that differ significantly from those caused by other sweeteners [65]. Metabolism of fructose and glucose in the liver differs significantly. The liver regulates glucose metabolism through glycolytic pathways, which can be influenced by the enzyme 6-phosphofructo-2 kinase isoform 1. However, fructose is metabolized differently in the liver, as it is first phosphorylated by fructokinase and then cleaved into trioses by aldolase B, bypassing the regulation of glycolytic pathways [66]. Fructose can enter the glycolytic/gluconeogenetic pathway continuously and uncontrollably, leading to the production of glucose, glycogen, lactate, and pyruvate [67], which suggests the importance of fructose in regulating metabolism in the liver. Thus, excessive intake of fructose from HFCS has been proposed as a potential factor contributing to epidemics of various health conditions such as T2DM, insulin resistance, obesity, dyslipidemia, hypertension, and heart disease [68-70]. In addition, one previous study discovered that people who consumed a quarter of their energy in fructose had higher levels

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of visceral fat, which is a risk factor for metabolic syndrome, compared to obese diabetic individuals who consumed a quarter of their energy in glucose [71].

Taken together, excessive consumption of sucrose and HFCS may be a significant contributor to the rise in metabolic disorders such as overweight, insulin and leptin resistance, hyperglycemia and hyperlipidemia in plasma, liver, etc. Recent researches indicate that using natural alternative sweeteners as a substitute of sucrose and HFCS may improve metabolic disease symptoms including high blood sugar, insulin resistance, hyperlipidemia, and liver steatosis [72-74]. The aim of this review article is to promote research into better sugar consumption by providing insights into the effects of natural sweeteners as substitutes for sucrose and HFCS, which are known to have negative impacts on metabolic diseases. These natural sweeteners are explored for their potential to mitigate the adverse effects of added sugars and ultimately improve metabolic health.

NATURAL LOW-INTENSITY ALTERNATIVE SWEETENERS

Monosaccharides and disaccharides

With the emerging use of added sugars around the world, natural alternative sweeteners have become very popular, especially for the diabetic population. There has been a rise in the availability of products sweetened with sugar alcohols (polyols), which are commonly marketed to individuals with diabetes [75]. Xylitol is a sugar alcohol with 5 carbon atoms that has a lower GI and fewer calories than sucrose, making it an appealing option for those with diabetes [76]. Erythritol is a polyol with 4 carbon atoms and is about 60%–80% as sweet as sucrose. Both sugars are naturally found in fruits and vegetables and have gained popularity as alternative sweeteners [77]. In particular, xylitol has demonstrated its efficacy as a viable alternative for diabetic patients. It can help reduce visceral fat, which is one of the leading factors contributing to insulin resistance and the further progression of T2DM [78]. After feeding animals with xylitol (1–2 g/100 kcal) for 8 weeks, there was a decrease in visceral fat mass, and lipid metabolism was impacted [79]. In addition, xylitol taken orally was found to decrease plasma insulin levels and increase insulin sensitivity, while also increasing the production of adiponectin. The impact of xylitol on adipose tissue is still unclear as it is mainly metabolized by the liver, but there was a noticeable increase in the expression of peroxisome proliferator-activated receptor gamma (PPARγ) in the adipose tissue. This increase in PPARγ upregulated the expression of adiponectin and lipolysis [79].

D-Xylose is a type of monosaccharide that acts as an inhibitor of sucrase, which prevents the conversion of sucrose into glucose and fructose [80,81]. D-Xylose is only partially broken down in the intestine and can undergo fermentation by bacteria [82,83]. Administering a sucrose solution (2 g/kg) with D-xylose (0.1 g/kg) in normal rats resulted in significantly lower levels of blood glucose compared to rats that only received a sucrose solution [84]. In animal studies, D-xylose has been found to regulate blood glucose levels by promoting the regeneration of damaged pancreas and liver tissues and by regulating the expression of phosphoenolpyruvate carboxykinase, a key enzyme involved in the process of gluconeogenesis. In addition, in vitro studies have demonstrated that D-xylose can induce the uptake of glucose by muscle cells and stimulate insulin secretion by β-cells [85]. Bae et al. [80] demonstrated that the levels of blood glucose in healthy individuals were reduced at different time intervals (15 minutes, 30 minutes, and 45 minutes) after consuming a sucrose solution containing 5 g or 7.5 g of D-xylose. In addition, supplementing with D-xylose was

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discovered to decrease in weight gain, the weight of adipose tissue, and blood glucose levels, as well as an improvement in blood lipid profiles, and a reduction in hepatic lipogenesis and adipogenesis in mice were fed HFD with 5% or 10% of the total sucrose content supplemented with D-xylose, respectively, compared to HFD fed control mice [86].

Recently, rare sugars that occur naturally have been recognized as a new type of sweeteners. These sugars and their derivatives are naturally present in small amounts [87]. Four more naturally occurring monosaccharides, namely D-allulose, D-tagatose, D-sorbose, and D-allose, have gained attention due to their palatability, lack of unpleasant aftertaste, and low-calorie content when compared with sugar. These monosaccharides are either not fully metabolized or partly metabolized by humans [87]. D-Allulose (D-psicose, a C-3 epimer of D-fructose) is a sweetener that is structurally similar to D-fructose and has about 70% of the sweetness of sucrose, exhibiting almost zero calories. It is highly soluble and possesses antioxidant properties, making it a desirable ingredient for use in food manufacturing [88-90]. Diets containing 5% D-allulose, normalizes the metabolic state of dietary-induced obesity by improving lipid-regulating enzyme activity and gene expression levels related with lipid metabolism [91]. The use of D-allulose in Otsuka Long-Evans Tokushima Fatty rats or Wistar rats was found to protect and maintain pancreatic β-islets by preventing fat accumulation and maintaining hyperglycemia [92,93]. In a clinical trial with a limited number of participants, it was found that 5 g of D-allulose could decrease plasma glucose and insulin levels after consuming 75 g maltodextrin. D-Allulose can act as an inhibitor of sucrase and maltase in the intestine, thereby potentially improving postprandial hyperglycemia [94]. D-Tagatose has a similar structure to D-fructose, except for the reversal of an optically active center, and has received significant attention and interest due to its advantageous properties, particularly since it was approved as a food additive by the US FDA [95]. D-Tagatose has been shown to help regulate glucose levels and insulin secretion during a glucose tolerance test in rats. It does this by promoting the conversion of blood glucose to glycogen in the liver through the movement of glucokinase from the nucleus to the cytoplasm [96].

Xylobiose is a type of xylo-oligosaccharide that consists of 2 xylose molecules linked by a β-1,4 bond. It is a major component of xylo-oligosaccharides and has only 30% sweetness compared to sucrose [97]. Xylobiose has been shown to have anti-obesity properties by regulating metabolic changes associated with obesity such as fat accumulation and inflammation by down-regulating pro-inflammatory cytokines, fatty acid uptake, lipolysis, and β-oxidation-related gene expression levels in mesenteric fat in the mice received a 60% HFD supplemented with 15% xylobiose as part of the total sucrose content of the diet compared to HFD control. In addition, xylobiose supplementation has been shown to protect against HFD-induced steatosis by regulating the expression of hepatic lipogenesis-related genes [98]. Furthermore, xylobiose exhibits anti-diabetic, hypo-lipogenic, and anti-inflammatory effects through down-regulating de novo synthesis of FFAs and cholesterol and restoring miR-122a/33a axis in the liver in *db*/*db* mice [99].

Sucrose isomers

There are sucrose isomers, including trehalulose α (1→1), turanose α (1→3), maltulose α (1→4), leucrose α (1→5), and palatinose α (1→6) [100]. Recently, interest in functional evaluation studies for these sweeteners has increased as sugar substitutes.

Daily supplementation of palatinose (isomaltulose) up to 7.0 and 8.1 g/kg body weight in both male and female rats did not show adverse effects in 13-week subchronic toxicity study [101].

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Palatinose is a dietary carbohydrate that serves as a source of energy and imparts sweetness to food products. Its energy content is similar to that of sucrose, but it has only about half the sweetness [102]. Palatinose is a famous disaccharide as a low-calorie and low-glycemic substance [102]. The GI of palatinose is 32, as indicated in the Sydney University GI database, which is significantly lower than the GI of sucrose (67) and glucose (100), thereby classifying palatinose as a low-GI carbohydrate with a GI of less than 55 [103]. Several studies have confirmed that palatinose has a low glycemic response in various populations, including healthy individuals, overweight or obese individuals, or T2DM [104-106]. These studies consistently show that palatinose leads to lower blood glucose responses compared to other sugars and also results in a reduction in blood insulin response. In addition, research has established the involvement of the incretin hormone GLP-1, which is released in response to distal carbohydrate absorption and plays a role in limiting the rise in blood glucose levels after a meal [104,105]. The diet that includes palatinose and has immune-modulating properties was found to reduce inflammation by decreasing the presence of pro-inflammatory cytokines in the bloodstream. Additionally, it was able to improve blood glucose levels in a gut ischemia-reperfusion model [107].

Leucrose which is composed of D-glucosyl-α(1-5)-D-fructopyranose is a naturally occurring sucrose isomer that can be found in sources such as honey and pollen [108,109], having 40%–50% sweetness compared to sucrose [108]. Toxicological studies (13-week sub-acute) in rats and dogs have shown no toxic side effects [110]. Leucrose, similar to sucrose, can be hydrolyzed into glucose and fructose. However, it is digested more slowly than sucrose [110]. Previous studies have reported that leucrose has demonstrated potential to reduce obesity and lower lipid accumulation [111,112]. Lee et al. [112] showed that replacing glucose with 50%, 75%, and 100% leucrose led to a reduction in lipid content in 3T3-L1 adipocytes, likely due to the down-regulation of adipogenic genes, when compared to cells treated with high glucose (25 mM). According to Lee et al. [111], when mice were given a HFD supplemented with leucrose replacing 25% or 50% of the total sucrose content, there was a reduction in fat accumulation in the liver. This effect was attributed to the suppression of lipogenesis and fat oxidation in obese mice.

Turanose, which is a sucrose isomer and found in honey, has a sweetness level of less than 50% compared to sucrose. It is composed of 3-O-α-D-glucosyl-D-fructose [113]. Studies on the toxicity of turanose have shown that the no-observed-adverse-effect-level for turanose is 7 g/kg/day. This suggests that turanose is a safe sugar for both short-term and long-term consumption [114]. The hydrolysis rate of turanose was found to be 54% of sucrose and 6% of maltose in a rat intestinal enzyme mixture, indicating that it is slowly digested in the small intestine. This slow digestion suggests that turanose may be a suitable low GI sweetener for individuals with metabolic disorders [100,115,116]. In the presence of high amounts of glucose in cell media, turanose substitution attenuated lipid accumulation in 3T3-L1 preadipocytes in a dose-dependent manner. Treatment with turanose at concentrations representing 50%, 75%, and 100% of total glucose concentration in cell media significantly reduced lipid accumulation by 18%, 35%, and 72%, respectively, compared to high glucose control [117]. Studies have demonstrated that substituting glucose with turanose at concentrations representing 50%, 75%, and 100% in macrophage cells led to a reduction in lipopolysaccharide- and glucose-induced inflammation. This was achieved by down-regulating the production of inflammatory cytokines and nitric oxide [118].

Taken together, these natural alternative sweeteners can play functional sweeteners as sucrose substitutes for preventing and treating metabolic diseases (**Table 1**). Generally,

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Table 1. Summary of the effects of natural low-intensity alternative sweeteners on metabolic diseases

Types	Sweeteners	Effects on metabolic diseases	References
Monosaccharides	Xylitol	· Reduced visceral fat mass and improved insulin resistance in SD rats	[78,79]
		· Increased in PPARγ upregulated the expression of adiponectin and lipolysis in SD rats	[79]
	D-xylose	· Regulated blood glucose by regulating glucose uptake in muscle cells from human skeletal muscle and gluconeogenesis in the liver in Wistar rats	[84,85]
		· Induced glucose update in the skeletal muscle and stimulated insulin by β-cell in Wistar rats	[85]
		· Decreased weight gain and hepatic lipogenesis and adipogenesis in HFD-fed obesity mice	[86]
	D-allulose (D-psicose)	· Normalized the metabolic state of dietary-induced obesity by improving lipid-regulating enzyme activity and gene expression levels related to lipid metabolism in HFD-fed obesity mice	[91]
		· Maintain pancreatic β-islets by preventing fat accumulation and maintaining hyperglycemia in vivo rat model	[92,93]
		· Inhibited of sucrase and maltase in the intestine, thereby potentially improving postprandial hyperglycemia in twenty human subjects aged 20–39 yr	[94]
	D-tagatose	· Regulated glucose levels and insulin secretion by promoting the conversion of blood glucose to glycogen in the liver in Wistar rats	[96]
Disaccharides	Xylobiose	· Decreased fat accumulation and inflammation by down-regulating pro-inflammatory cytokines, fatty acid uptake, lipolysis, and β-oxidation-related gene expression levels in HFD-fed mice	[98]
		· Reduced de novo synthesis of FFAs and cholesterol and restoring miR-122a/33a axis in the liver in *db/db* mice	[99]
Sucrose isomers	Palatinose (isomaltulose)	· Low glycemic response in ten healthy non-obese subjects, eleven patients with T2DM, and twenty overweight subjects	[104-106]
		· Decreased blood glucose and insulin levels in ten healthy non-obese subjects, eleven patients with T2DM	[104,105]
		· Reduced inflammation by decreasing the presence of pro-inflammatory cytokines in the bloodstream in ICR mice	[107]
	Leucrose	· Diminished lipid accumulation in 3T3-L1 cells by down-regulating adipogenic genes compared to high glucose condition	[112]
		· Reduced fat accumulation in the liver in HFD-fed mice	[111]
	Turanose	· Diminished lipid accumulation in 3T3-L1 cells by down-regulating adipogenic genes compared to high glucose condition	[117]
		· Reduced inflammation induced by LPS and glucose in Raw 264.7 macrophage cells	[118]

SD, Sprague-Dawley; PPARγ, peroxisome proliferator-activated receptor gamma; HFD, high-fat diet; FFA, free fatty acid; T2DM, type 2 diabetes mellitus; ICR, Institute of Cancer Research; LPS, lipopolysaccharide.

natural alternative sweeteners appear to have more positive effects on glucose metabolism, lipid homeostasis, steatosis, and inflammation.

CONCLUSIONS

The use of natural alternative sweeteners as functional substitutes for sucrose can be beneficial in preventing and treating metabolic diseases. These sweeteners have been found to have varying effects on body weight, blood glucose, lipid metabolism, and anti-inflammatory pathways. It is important to note that the effects of natural alternative sweeteners may depend on the dose used. In general, natural alternative sweeteners appear to have more positive effects on glucose metabolism, lipid homeostasis, steatosis, and inflammation than sucrose. However, it is important to consider that there are some limitations to the current evidence, such as small sample sizes, short study durations, and a lack of clinical studies. While the available research provides valuable insights from cellular and animal models, the direct impact of these sweeteners on metabolic disease patients and their efficacy in clinical settings remain to be fully explored. The inclusion of well-designed clinical studies is necessary to provide more definitive evidence and establish the effectiveness of natural alternative sweeteners in managing metabolic diseases. Therefore, further research is needed to fully understand the long-term effects of natural alternative sweeteners on metabolic diseases, including glucose homeostasis, lipid metabolism, and inflammation. Future studies should involve larger sample sizes of individuals with and without obesity or diabetes, and long-term evaluation of the effects of natural alternative sweeteners on metabolic disease. This will provide more robust evidence and contribute

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to a better understanding of the potential benefits and limitations of natural alternative sweeteners as a substitute for sucrose in the prevention and treatment of metabolic diseases.

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