Review

Hypoglycemic Health Benefits of D-Psicose

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ABSTRACT: Diabetes is an emerging health problem worldwide. The incidence of type 2 diabetes has dramatically increased and is expected to increase more rapidly in the future. Most patients with type 2 diabetes suffer from obesity and diabetes-related complications, including cardiovascular disease and hepatic steatosis. It has been proposed that simple sugar consumption is one of the major risk factors in the development of diabetes. Hence, the replacement of sugars with a low glycemic response would be an effective strategy to prevent type 2 diabetes. Accumulating evidence demonstrates that D-psicose, which has 70% the sweetness of sucrose and no calories, is a functional sugar exerting several health benefits preventing the development of diabetes. Although D-psicose presents in small amounts in natural products, a recent new technique using biocatalyst sources enables large-scale D-psicose production. More importantly, several clinical and animal studies demonstrated that D-psicose has hypoglycemic, hypolipidemic, and antioxidant activities, which make it an ideal candidate for preventing diabetes and related health concerns. This review will summarize the protective effects of D-psicose against type 2 diabetes and its complications, suggesting its potential benefits as a sucrose substitute.

KEYWORDS: D-psicose, type 2 diabetes, cardiovascular diseases, steatosis

INTRODUCTION

Diabetes is a global health crisis affecting approximately 285 million people worldwide, and it is expected that the diabetic population will increase to 438 million by 2030.[1] Although a number of pharmacological and surgical treatments have been developed for treating diabetes, several lines of evidence strongly suggest that diet and/or lifestyle modifications are the basic therapeutic strategies to prevent the development of type 2 diabetes.[2] Therefore, the identification of effective and easily implemented dietary modifications to mitigate diabetes is needed.

The consumption of foods with a high glycemic index as well as excess calorie intake is an important predisposing factor in the development of type 2 diabetes.[3] A recent meta-analysis provided evidence that greater amounts of sugar-sweetened beverage intake are associated with increased risk of type 2 diabetes.[4] After ingestion, the sucrose contained in sugar-sweetened beverages rapidly raises blood glucose and insulin levels, increases insulin demand, and subsequently exhausts pancreatic β-cells, which are implicated in the pathogenesis of type 2 diabetes.[2] Fructose from high-fructose corn syrup or other sugars also causes hepatic de novo lipogenesis, dyslipidemia, and subsequent insulin resistance.[5] Hence, the intake of sugars with a low glycemic response would be an effective strategy to prevent type 2 diabetes.

Recently, a rare sugar has gained great attention because of its increasing use as a noncaloric sweetener[6] or as a raw material for the production of rare sugars.[7,8] In particular, D-psicose is known to have a low glycemic response,[9] but is found in small amounts in commercial carbohydrate and agricultural products.[10] Because of its scarcity, few studies have been conducted to investigate the biological functions and physiological implications of D-psicose. However, mass production of D-psicose has recently become

feasible. Using a new technique, D-psicose can be produced from D-fructose by the action of D-tagatose 3-epimerase (Figure 1) in a
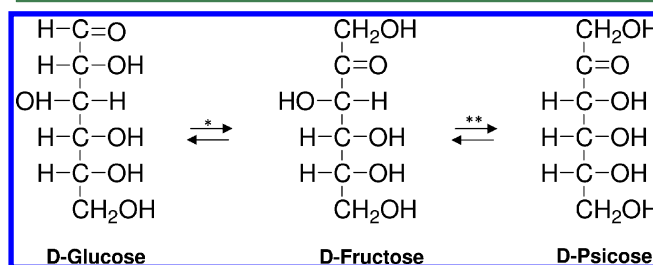

Figure 1. D-Psicose can be enzymatically produced from D-glucose via D-fructose. *, D-xylose isomerase; **, D-tagatose 3-epimerase.

simple and cost-effective manner.[11] This has enabled investigations of D-psicose to be extended into a variety of research fields. Therefore, this review will summarize the properties, absorption, and excretion of D-psicose, followed by its biological production and functions, as well as the potential benefits of D-psicose on type 2 diabetes, and its safety and possible use as a sucrose substitute.

PROPERTIES OF D-PSICOSE

D-Psicose (D-ribo-2-hexulose; molecular formula, $C_6H_{12}O_6$; molecular weight, 180.156) originates from processed cane and beet molasses.[12] It was identified to occur naturally as the

sugar moiety of the antibiotic psicofuranine and exists in wheat[13] and *Itea* plants[14] as a free sugar. D-Psicose is also formed during cooking processes from fructose or fructose-containing foods, such as fruit juice, fruit cereal, Worcestershire sauce, and Coke.[12,15] The concentrations of D-psicose in various food products have been measured[15] using high-performance liquid chromatography (HPLC) with pulsed amperometric detection, which is a highly sensitive method to measure sugar levels.[16] As shown in Figure 2 (modified from ref 15), D-psicose is widely found in daily foods.[17]
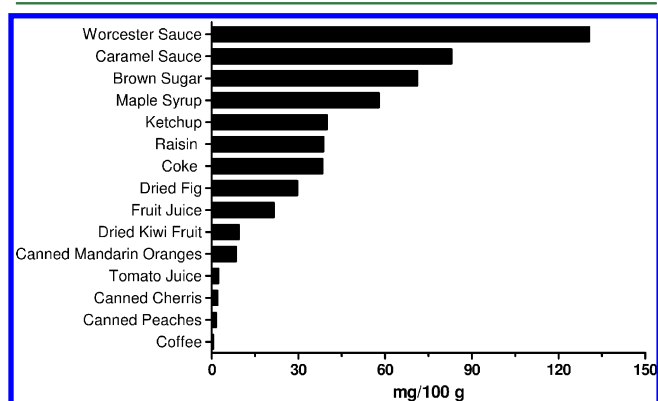

Figure 2. D-Psicose contents in food products (mg/100 g).

■ ABSORPTION AND EXCRETION OF D-PSICOSE

A study of oral administration of D-psicose (5 g/kg body weight) in rats demonstrated that up to 25% of absorbed D-psicose is excreted in the urine,[18] suggesting that D-psicose is absorbed by the small intestine.[19] Moreover, it has been shown that approximately 98% of D-psicose is excreted in the urine within 6 h with intravenous administration. Thus, absorbed D-psicose is likely excreted in the urine via bloodstream without significantly being metabolized.[20] Unabsorbed D-psicose transfers into the large intestine, where it is fermented to produce short-chain fatty acids (SCFA). Whereas D-psicose levels in the serum, stomach, and small intestine were significantly decreased 3 and 7 h after oral D-psicose administration (5 g/kg body weight), a significant amount of D-psicose was detected in the cecum content at these later time points.[18] A large portion of D-psicose is likely fermented by rat intestinal bacteria to produce SCFA following oral administration of D-psicose [5 g/kg body weight (BW)].[18]

The absorption and excretion of D-psicose are likely different in humans compared to those in rats. The metabolism of D-psicose has been examined in humans who consumed a typical dose of D-psicose (0.35 g/kg BW in a 100 mL solutions, which corresponds to 20 g of D-psicose ingestion for humans with average body weight).[19] The intestinal absorption of D-psicose was estimated to range between 66.2 and 80% of the orally ingested dose (0.33 and 0.17 g/kg BW, respectively). This could be comparable with the intestinal absorption rate of erythritol, which has about 90% intestinal absorption rate, and the no-observed-effect level (NOEL) is 0.66 g/kg BW for males and 0.8 g/kg BW for females. For D-psicose, the NOEL is 0.5 g/kg BW for males and 0.6 g/kg BW for females.[17,21] These also suggest that a large quantity of the ingested D-psicose is likely absorbed in the human small intestine.

Unlike glucose, which stimulates insulin secretion and subsequently is used as energy following absorption in the small intestine, D-psicose does not increase carbohydrate energy

expenditure within 3 h of D-psicose ingestion (0.35 g/kg BW).[19] This indicates that D-psicose is not metabolized to produce energy following intestinal absorption. Furthermore, net blood glucose or insulin levels was unaffected after D-psicose ingestion.[22] Several studies reported that a small part of D-psicose likely passes into the human large intestine, where D-psicose is not readily fermented by intestinal bacteria at a daily consumption of 10 g of D-psicose.[22]

■ BIOLOGICAL PRODUCTION OF D-PSICOSE

Although D-psicose is found naturally in small quantities, a recently developed new technique enables its large-scale production. D-Psicose can be chemically produced from D-fructose by using a molybdate ion catalyst,[23] by synthesis from 1,2,4,5-di-*o*-isopropylidene-*β*-D-fructopyranose,[24] and by boiling in ethanol and triethylamine.[25] However, these chemical processes have disadvantages, such as complex purification steps, chemical waste, and byproduct formations. Hence, biological production of D-psicose from D-fructose has been investigated using biocatalyst sources, including D-psicose 3-epimerase from *Agrobacterium tumefaciens*,[26−28] and D-tagatose 3-epimerases from *Pseudomonas cichorii* [11,29] and *Rhodobacter sphaeroides*.[30]

D-Psicose, D-tagatose, and D-fructose act as substrates with highest specificity for *A. tumefaciens* D-psicose 3-epimerase, *P. cichorii* D-tagatose 3-epimerase, and *R. sphaeroides* D-tagatose 3-epimerase, respectively. Although these enzymes belong to the ketose 3-epimerase family, D-psicose 3-epimerase exhibits higher D-fructose epimerization activity compared to D-tagatose 3-epimerases. Indeed, *A. tumefaciens* D-psicose 3-epimerase has produced 230 g/L of D-psicose, which is 1.53- and 1.95-fold higher than the D-psicose concentration obtained from D-tagatose 3-epimerases of *P. cichorii* (150 g/L) and *R. sphaeroides* (118 g/L), respectively. This suggests that D-psicose 3-epimerase is a potential D-psicose producer.[26,29,30] As described in Table 1, the addition of Mn^{2+} to the enzymes, as metal-dependent enzymes, significantly increases the epimerization rate from D-fructose to D-psicose. The optimal temperatures of *A. tumefaciens* D-psicose 3-epimerase, *P. cichorii* D-tagatose 3-epimerase, and *R. sphaeroides* D-tagatose 3-epimerase are 50, 60, and 40 °C, respectively.[26,29,30] In particular, thermostability is important for the industrial production of D-psicose. Recently, the thermostable I33L-S213C variant of D-psicose 3-epimerase from *A. tumefaciens*, in which serine at position 33 and isoleucine at position 213 were replaced with cysteine and leucine, respectively, was obtained from random and site-directed mutagenesis.[31] The double-site variant showed increases of 7.5 °C and 26.5-fold in optimal temperature and half-life at 55 °C, respectively.

D-Psicose can be produced from D-fructose by several biocatalysts, including cells and free and immobilized enzymes, and wild-type and variant enzymes (Table 2). Borate reacts with carbohydrates to form complexes, which interact with enzyme systems and change the equilibrium of any reaction involving *cis*-diol carbohydrates by the difference of binding affinities for sugars.[32] It has been demonstrated that D-psicose has a high complexing capacity for borate, contributing to yield greater formation of D-psicose from D-fructose.[28] The borate of the D-psicose−borate complex is easily removed using Amberite IRA-743 and Dowex 50 resins.[33] D-Psicose production using a packed-bed bioreactor containing immobilized D-psicose producing-enzyme has been used for the commercial manufacture of D-psicose. The immobilized enzymes of *A. tumefaciens* D-psicose 3-epimerase I33L-S213C variant and *P. cichorii* D-tagatose 3-epimerase produced

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Table 1. Biochemical Properties of *A. tumefaciens* D-Psicose 3-Epimerase, *P. cichorii* D-Tagatose 3-Epimerase, and *R. sphaeroides* D-Tagatose 3-Epimerase

	A. tumefaciens D-psicose 3-epimerase	*P. cichorii* D-tagatose 3-epimerase	*R. sphaeroides* D-tagatose 3-epimerase
molecular mass (kDa)	132 (tetramer)	68 (dimer)	64 (dimer)
metal ion requirement	Mn^{2+}	Mn^{2+}	Mn^{2+}
optimal pH	8.0	7.5	9.0
optimal temperature (°C)	50 (wild-type) 57.5 (I33L-S213C variant)	60	40
half-life at 55 °C (min)	10 (wild-type) 265 (I33L-S213C variant)	not reported	15
substrate with highest specificity	D-psicose	D-tagatose	D-fructose
equilibrium ratio between D-psicose and D-tagatose	32:68 (30 °C) 33:67 (40 °C) 64:36 (40 °C with borate)	20:80 (30 °C)	23:77 (40 °C)
refs	26, 28, 31	63 and 64	30

D-psicose without decreases of activities during 30 and 60 days. However, as illustrated in Table 2, the productivity of the *A. tumefaciens* D-psicose 3-epimerase I33L-S213C variant was 14-fold higher than that of *P. cichorii* D-tagatose 3-epimerase. Thus, the double-site variant may be useful for the commercial manufacture of D-psicose using an enzymatic process.

■ BIOLOGICAL FUNCTIONS OF D-PSICOSE

Hypoglycemic Activity. The most well studied biological function of D-psicose is its ability to suppress hyperglycemia. A clinical study has demonstrated that acute consumption of D-psicose (>5 g/day) suppresses increased plasma glucose and insulin levels ($P < 0.05$) by simultaneous intake of maltodextrin

(75 g) in healthy individuals.[22] However, 7.5 g of D-psicose administration without maltodextrin did not affect blood glucose and insulin levels in an oral glucose tolerance test.[22] This study suggests that D-psicose at 5 g, which is approximately 6.7% of carbohydrate intake, is likely to be the minimum effective level for suppressing postprandial glucose elevation. They also suggested that 5 g of D-psicose would be an attainable dose for suppressing plasma glucose levels by consuming one slice of toast, which corresponds to about 50 g carbohydrate.[22] Moreover, long-term ingestion of D-psicose (5 g, three times/day, for 12 weeks) significantly suppressed postprandial glucose elevation ($P < 0.01$) after standard meal consumption in borderline diabetic patients, whereas no D-psicose effects have been found in normal healthy subjects.[34]

The glucose-lowering effect of D-psicose was further evaluated using various animal models of type 2 diabetes.[35,36] In 4-week-old male OLETF rats, 5% D-psicose intake (prepared as a drink) for 13 weeks significantly decreased blood glucose levels by 32−38% ($P < 0.01$) and insulin levels by about 2 times ($P < 0.01$) compared to control LETO and OLETF rats.[35] In *db/db* mice, another animal model of diabetes, oral administration of D-psicose (200 mg/kg BW) for 4 weeks significantly decreased body weight gain by 37% compared to diabetic controls ($P < 0.05$) without affecting food consumption. Interestingly, no significant reductions in body weight were observed by D-glucose and D-fructose supplementation ($P > 0.05$) compared to diabetic controls. During intervention, only the D-psicose supplementation group showed lower blood glucose levels compared to other diabetic groups supplemented with D-glucose, D-fructose, or nothing ($P < 0.05$). Furthermore, in a glucose tolerance test, the area under the curve (AUC) for plasma glucose in D-psicose group was 22.8 and 20% lower compared to D-glucose- and D-fructose-supplemented groups, respectively, and it was 15% lower compared to diabetic controls.[36] These studies indicate that D-psicose has antidiabetic effects by reducing plasma glucose and insulin concentrations and also attenuates body weight gain, unlikely with D-glucose and D-fructose in diabetic animal models.

Another line of evidence suggests that 5% D-psicose (prepared as a drink) protects against chronic hyperglycemia-induced pancreatic β-cell failure,[35] thereby contributing to improve insulin

Table 2. D-Psicose Production from D-Fructose by D-Psicose 3-Epimerase and D-Tagatose 3-Epimerase

enzyme source	process mode	biocatalyst	fructose (g/L)	psicose (g/L)	productivity (g L^{-1} h^{-1})	reaction time[a] (h)	refs
Sinorhizobium sp.	batch	cells	540	41	3.4	12	65
R. sphaeroides	batch	free enzyme	700	118	39	3	30
P. cichorii	continuous	immobilized enzyme at 0.4 h^{-1}	500	90	36	240	66
	continuous	immobilized enzyme at 0.28 h^{-1}	600	150	42	1440	11
A. tumefaciens	batch	free enzyme	700	230	115	2.0	26
		free enzyme with borate	700	436	174	2.5	28
		immobilized enzyme	700	195	130	1.5	27
		immobilized enzyme with borate	700	435	174	2.5	27
	continuous	immobilized enzyme at 4.15 h^{-1}	500	146	606	384	27
		immobilized enzyme at 4.15 h^{-1} (I33L-S213C variant)	500	145	602	720	31
		immobilized enzyme at 1.62 h^{-1} with borate	500	325	527	236	27
		immobilized enzyme with borate at 1.62 h^{-1} (I33L-S213C variant)	500	324	525	720	31

[a]The reaction time that psicose productivity does not decrease in continuous mode.

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sensitivity in a genetically obese animal model of type 2 diabetes. Whereas diabetic rats with D-glucose supplementation and diabetic controls showed irregular pancreatic islets with disrupted cell architecture and extensive fibrosis, D-psicose administration led to smaller islets with a large number of normal, round, or oval islets and almost no fibrosis.[35] The defect of pancreatic β-cells is a key event in the development of diabetes. Indeed, improvements in glucose intolerance were apparent in OLETF rats after treatment with high doses of ramipril that can directly protect against pancreatic islet defects and subsequent fibrosis.[37] Therefore, improved pancreas islet morphology by D-psicose likely contributes to attenuate insulin resistance.

Although the mechanisms by which D-psicose suppresses blood glucose levels and protects against diabetes are yet to be fully understood, potential mechanisms may involve the suppression of intestinal α-amylase and α-glucosidase activities.[38] Matsuo et al.[38] demonstrated that D-psicose significantly decreases the elevation of plasma glucose after ingestion of sucrose or maltose, and these suppressions were not observed upon coadministration with fructose in rats. D-Psicose also inhibited the activities of intestinal α-glucosidases, including maltase and sucrase, and slightly decreased the activities of intestinal and salivary α-amylase.[38] Collectively, these data indicate that D-psicose can delay or inhibit carbohydrate digestion by suppressing the activities of intestinal α-glucosidases, thereby suppressing postprandial hyperglycemia.

A recent study also suggested that D-psicose improves hyperglycemia by increasing hepatic glucose uptake after a glucose load, which may be attributed to increased glucokinase translocation from the nucleus to the cytoplasm in diabetic rats.[35] Glucokinase is predominantly found in the nucleus under static metabolic conditions, and increased demand of glucokinase triggers its translocation toward the cytoplasm, where it regulates hepatic glucose metabolism.[39] The translocation of glucokinase from the nucleus to the cytoplasm has been reported to be elevated by postprandial rises in plasma glucose and insulin in rat livers.[40] D-Psicose-mediated increases in glucokinase translocation toward the cytoplasm contribute to enhance glucose uptake, therefore improving insulin resistance.

Collectively, D-psicose may be an effective therapeutic strategy in lowering postprandial glycemic elevations and improving pancreatic β-cell failure. These are attributed to the suppression of intestinal α-glucosidase activity and enhancement of glucokinase translocation from the nucleus to the cytoplasm. D-Psicose-mediated attenuation in postprandial glucose elevation has not been studied in in vitro condition; thus, its molecular signaling mechanisms have yet to be clearly understood. Whether D-psicose regulates insulin binding with its receptors and/or insulin-mediated signaling pathways and subsequent increases in glucose uptake into the cells needs to be further investigated.

Hypolipidemic Activity. Evidence suggests that D-psicose has hypolipidemic activity. A recent study conducted by Hossain et al.[35] found lowered abdominal fat accumulation in OLETF rats following 5% of D-psicose (prepared as a drink) consumption for 13 weeks. D-Psicose decreased intra-abdominal fat accumulation by 3.5% compared to OLETF control rats, thereby reducing body weight gain. Another study using male Wistar rats evaluated the same levels of D-psicose.[41] In Wistar rats, 5% D-psicose also significantly reduced abdominal adipose tissue mass ($P < 0.05$) without affecting food consumption, compared to rats fed D-fructose and D-glucose diets.[41] The hypolipidemic action of D-psicose can possibly be explained by a reduction in lipogenic enzymes activity. Indeed, D-psicose

significantly attenuated the activities of hepatic fatty acid synthase (FAS) by 17−24%, compared to glucose and fructose groups, and also reduced the hepatic glucose-6-phosphate dehydrogenase activity by 24%, compared to the fructose group ($P < 0.05$).[41] This was consistent with reductions in adipocyte fat accumulation in these D-psicose-fed rats, compared to rats fed D-fructose and D-glucose.[41]

An aforementioned hypoglycemic action of D-psicose may indirectly improve hyperlipidemia. Insulin resistance leads to decreased glucose uptake and increases of circulating free fatty acid, which is partly attributed to the inability of insulin to prevent adipocyte lipolysis.[42] In this regard, D-psicose-mediated hypoglycemia indirectly contributes to decrease circulating free fatty acids and increase glucose uptake to improve hyperglycemia and subsequent hepatic lipid accumulation.

Antioxidant Activity. Considerable evidence exists that D-psicose exerts non-antiobesity activities.[43,44] It has been demonstrated that high glucose facilitates monocyte chemotactic protein (MCP)-1 gene expression, which was suppressed by p38-mitogen-activated protein kinase (p38-MAPK) specific inhibitor in monocytic cells[45] and human umbilical vein endothelial cells (HUVECs).[46] In addition, Murao et al.[43] demonstrated that D-psicose inhibits the elevation of MCP-1 mRNA expression induced by high glucose in HUVECs in part by suppressing p38-MAPK phosphorylation. Likewise, a study conducted by Suna et al.[44] showed that D-psicose reduced di(2-ethylhexyl) phthalate-induced testicular injury in rats by inhibiting lipid peroxidation, evidenced by a decreased testicular malondialdehyde (MDA) level, which was not decreased by D-glucose administration. Taken together, D-psicose may have antioxidant activity by reducing the expression of MCP-1 mRNA and MDA levels.

Although the mechanisms by which D-psicose exerts antioxidant activity have not been fully elucidated, possible mechanisms may involve D-psicose-mediated reactive oxygen species (ROS) scavenging and glutathione restoration. An in vitro study found greater scavenging activity by D-psicose compared to D-glucose and D-fructose.[47] In zymosan-stimulated rat neutrophils, ROS production was also lowered by D-psicose compared to D-glucose and D-fructose, although there was no statistical significance.[47] In addition, simultaneous treatment of D-psicose (50 mM) and a neurotoxin, 6-OHDA, significantly enhanced intracellular glutathione levels in neurotoxin-induced PC12 cells, thereby protecting against oxidative stress-mediated apoptosis.[48] However, the antioxidant activities of D-psicose have been evaluated under in vitro conditions only. Therefore, further in vivo and clinical studies are warranted to investigate the mechanism regulating the antioxidant activity of D-psicose.

■ ROLE OF D-PSICOSE IN THE PREVENTION OF DIABETES AND ITS COMPLICATIONS

A number of clinical and animal studies have suggested that D-psicose may protect against type 2 diabetes and its complications, such as cardiovascular diseases (CVD) and liver steatosis. Although the underlying mechanisms by which D-psicose exerts its protective effects are under investigation, the aforementioned hypolipidemic, hypoinsulinemic, hypoglycemic, and antioxidant activities likely contribute to its protection against disease progression.

There has been much scientific interest in finding effective dietary therapies in the prevention and treatment of type 2 diabetes. Given that impaired glucose metabolism is a critical risk factor for type 2 diabetes,[42] the glucose-lowering effect of

D-psicose can be beneficial for preventing and/or treating diabetes. Indeed, D-psicose has lowered hyperglycemia-induced elevations in blood glucose and insulin in diabetic animals[35,36] and in prediabetic patients,[34] as well as in healthy subjects.[22] The hypoglycemic action of D-psicose is likely mediated by suppressing intestinal α-glucosidase, increasing glucokinase translocation, and improving pancreatic β-cell failure.[35,38]

Impaired glucose tolerance increases susceptibility to CVD and CVD-related mortality.[49] Given that at least 65% of type 2 diabetic patients die from CVD,[50] D-psicose-mediated improvements in insulin resistance may indirectly contribute to protect against CVD.[49] It is well-known that oxidative modification in the vascular wall is a major event in atherosclerosis.[51] Therefore, it is also possible that the known antioxidant properties of D-psicose, mediated by ROS scavenging and restoring glutathione, may contribute to decrease the susceptibility for vascular oxidation. Furthermore, increased pro-inflammatory regulator MCP-1 is one of the key events contributing to the development of atherosclerosis.[52] More importantly, hyperglycemia induces MCP-1 by activating the p38-MAPK pathway,[53,54] emphasizing the greater risk of atherosclerosis in the hyperglycemic state. D-Psicose has been shown to decrease MCP-1 gene expression by inhibiting p38-MAPK phosphorylation,[43] thereby protecting against the development of atherosclerosis. Whether D-psicose-mediated inhibition of p38-MAPK phosphorylation possibly down-regulates other pro-inflammatory cytokines requires further investigation.

Hepatic steatosis, an initial stage of nonalcoholic fatty liver disease, is characterized by insulin resistance, excess hepatic lipid accumulation and injury, and dyslipidemia.[55,56] Supplementation of 5% D-psicose significantly reduced hepatic fat accumulation in diabetic rats.[35] This was likely mediated by the hypolipidemic action of D-psicose, evidenced by decreased hepatic FAS and glucose-6-phosphate dehydrogenase activities.[35,41] Taken together, D-psicose may protect against type 2 diabetes and its complications including CVD and liver steatosis by suppressing blood glucose and insulin levels and further regulating oxidative stress and inflammation. Nevertheless, because the mechanisms underlying its protective effects remain unclear and clinical evidence is not sufficient, continued studies are certainly warranted.

■ SAFETY OF D-PSICOSE

A study conducted by Matsuo et al.[57] found that extremely high levels of oral D-psicose intake (>20% of the dietary intake for 34 days) may be harmful to the intestinal tract, causing diarrhea in rats. However, the dosage selected by Matsuo et al.[57] was likely too high because their observation is contradicted by the findings of recent animal and clinical studies. The recent study indicates that chronic D-psicose ingestion (3%; 12−18 months) was relatively safe without any adverse effects in young rats.[58] In addition, long-term ingestion of D-psicose (5 g) with meals (3 times) for 12 weeks did not induce any toxicity issues (i.e., hepatic function and physical symptoms) in healthy humans with normal blood glucose levels.[34]

The maximum noneffective levels of D-psicose for inducing diarrhea were later estimated as 0.5 and 0.6 g/kg BW for healthy males and females, respectively.[17] Furthermore, the LD_{50} value of D-psicose is 16 g/kg in rats, which is similar to the LD_{50} of D-sucralose at doses of 16 g/kg for mice and 10 g/kg for rats.[59] Hence, D-psicose is generally regarded as safe, although the upper safety level of D-psicose needs to be investigated.

■ D-PSICOSE AS AN IDEAL SUGAR SUBSTITUTE

It is believed that D-psicose could be an ideal substitute for sucrose. Increased sucrose consumption causes adverse health effects due to excess calorie intake and a relatively high glycemic response. Although other alternative artificial sweeteners containing almost zero calories, such as aspartame, sucralose, saccharin, and cyclamate, have been developed, their function is only to provide sweetness.[60] In addition to acting as a functional rare sugar, D-psicose has about 70% the sweetness of sucrose, high solubility,[15] clean taste, smooth texture, desirable mouthfeel,[60] and no calories with a low glycemic response.

Moreover, it has been reported that the addition of D-psicose to foods improves gelling characteristics and flavor and provides great antioxidant activity. Particularly, the antioxidant property of D-psicose is partly attributed to the increased production of antioxidant substances, including Maillard reaction products (MRP). The MRPs are produced through nonenzymatic reaction between reducing sugars and amino acids[61] through the Maillard reaction, which occurs during the processing, cooking, and storge of food.[61] Increased production of MRP contributes to delay the initiation of lipid autoxidation and an extended storage period for food products.[60,62] In this regard, D-psicose can be used as an effective functional sucrose substitute for food products with no calories.

■ CONCLUSION

D-Psicose is a relatively nontoxic monosaccharide that lowers glycemic responses after carbohydrate consumption. It has been demonstrated to contribute to improve insulin resistance and reduces hepatic lipogenesis and body weight gain in humans and animals. Despite the lack of evidence from clinical studies, several in vitro and animal studies have supported the protective activities of D-psicose against type 2 diabetes and its complications, including CVD and liver steatosis via hypoglycemic, hypoinsulinemic, and antioxidant mechanisms. Because maintaining appropriate blood glucose and insulin levels is a key step in preventing diabetes and its complications, the replacement of D-psicose as a noncalorie sugar substitute would be an ideal strategy to aid diabetic patients and/or numerous obese individuals who are at high risk for developing diabetes. Further investigations are warranted to examine molecular signaling pathways and to evaluate the potential health benefits of D-psicose in obese humans.

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■ ABBREVIATIONS USED

CVD, cardiovascular diseases; FAS, fatty acid synthase; MCP-1, monocyte chemotactic protein-1; MDA, malondialdehyde; MRP, Maillard reaction products; NOEL, no-observed-effect

level; ROS, reactive oxygen species; SCFA, short-chain fatty acids.

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