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Review Article

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Metabolism and Health Impacts of Dietary Sugars

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ABSTRACT

Consumption of excessive amounts of added sugars and their effects on human health has been a major concern in the last several decades. Epidemiological data suggest that the incidence of metabolic disorders, such as obesity, nonalcoholic fatty liver disease, cardiovascular disease and diabetes, has increased due to chronic surplus consumption of these sugars. While many of these sugars have been isolated and studied for centuries, their health impacts and exact underlying mechanisms are still unclear. In this review, we discuss the pathophysiological role of 6 major simple sugars present in the human diet and the biochemical and molecular pathways related to their metabolism by different organs and gut microbiota, with a focus on the most recent investigations.

Keywords: Glucose; Fructose; Mannose; Galactose; Xylose; Arabinose

INTRODUCTION

Changes in food consumption patterns towards diets richer in sugar and fats have contributed to the rising trends in obesity and metabolic disease on a global scale, but especially in the US.[1-3] A person with metabolic syndrome is classified as having at least 3 of the following: obesity, low high-density lipoprotein cholesterol, elevated blood triglycerides and glucose, and high blood pressure.[4,5] A recent study surveyed >17,000 individuals representative of the US population relative to their race, gender, and ethnicity found an increase in the overall prevalence of metabolic syndrome from 2011–2016.[6] Notably, they reported a significant increase in the prevalence of metabolic syndrome among women (31.7% to 36.6%), adults ages 20 to 39 (16.2% to 21.3%), Asian (19.9% to 26.2%) and Hispanic (32.9% to 40.4%) adults. Trends continued to rise with increasing age, from 19.5% among those aged 20 to 39 years to 48.6% among those aged above 60 years. This is a worthwhile cause for concern given the aging population and parallel increase in comorbidities, with diabetes prevalence estimated at 10.5% of the entire US population in 2018, according to the Centers for Disease Control (CDC). Without a significant push for change, it is reasonable to assume these trends will continue to tend towards adverse health effects at an alarming rate.

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Conflict of Interest

The authors have no conflicts of interest to declare.

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Excessive intake of sugars, especially fructose and sucrose (a dimer of glucose and fructose monomers), are highly correlated with metabolic disease including obesity, diabetes, fatty liver, and cardiovascular disease. According to the CDC, Americans are consuming a large amount of added sugars. The Dietary Guidelines for Americans 2020–2025 recommends that Americans keep their added sugar intake to less than 10% of their total daily calories (CDC, 2021). Specifically, the guidance suggests no more than 200 calories of added sugar per day (about 60 g). However, in 2017–2018, the average daily intake was about 85 g of sugar (CDC, 2021). This excessive fructose consumption decreases satiety and increases adipogenesis, leading to fat accumulation, insulin resistance, inflammation, and elevated blood pressure to cause vascular damage.[7] The current aims of the field involve the pursuit of a better understanding of how high-fructose intake relates to dietary habits of other sugars and whether some common signaling pathways and mechanisms contribute to the development of metabolic disease.

Though the cellular and biochemical breakdown of dietary sugars have been known for decades, it is only recently that their organismal metabolism and its relationship with pathological effects have been studied. In this review, we describe the major characteristics of the 6 abundant, key dietary sugars important for many biological processes. These 6 sugars (glucose, fructose, mannose, galactose, xylose, and arabinose) were selected based on their relative abundance in diet and disease relevance. The recent findings highlighted here emphasize the variable effects that dietary hexose and pentose sugar metabolism has on human health. Together, they provide new insights into the measures that should be taken to improve the quality of life across human populations.

DIETARY HEXOSE AND PENTOSE SUGARS

Chemically, a hexose or a pentose sugar is a simple monosaccharide with the chemical formula $C_6H_{12}O_6$ or $C_5H_{10}O_5$, respectively. These naturally occurring sugars can be classified according to their functional groups and the number of carbon atoms (**Fig. 1**). Those that contain an aldehyde functional group on their first carbon are called aldoses, while those containing a ketone functional group on the second carbon are ketoses. Among the most abundant 6-carbon monosaccharides in diet, fructose is uniquely a ketohexose, while glucose, mannose, and galactose are aldohexoses. Arabinose and xylose are 5-carbon sugars with an aldehyde group granting them the term: aldopentoses. While these chemical structure differences seem to be small, their metabolic pathways and biological effects are remarkably different, as discussed below.

1. Absorption

Ingested hexose or pentose sugar requires interaction with several key transporters to cross through the intestinal epithelial cell membrane. For some sugars, these transporters are shared or remain unidentified (**Fig. 1**). The transport of monosaccharides across the membranes of eukaryotic cells is mediated by members of the glucose transporter family (GLUTs) encoded by SLC2 genes.[8] Since the transport and metabolism of dietary sugars have been extensively reviewed elsewhere,[9-15] a brief outline will be described here.

In addition to the availability of transporters, absorption efficiency and kinetics of sugars are also determined by several factors, including maturity and location of the gut epithelial cells, and doses/forms (liquid vs. solid) of dietary carbohydrates ingested. Because the epithelial cells are continuously differentiating, the absorptive function is dependent upon the degree

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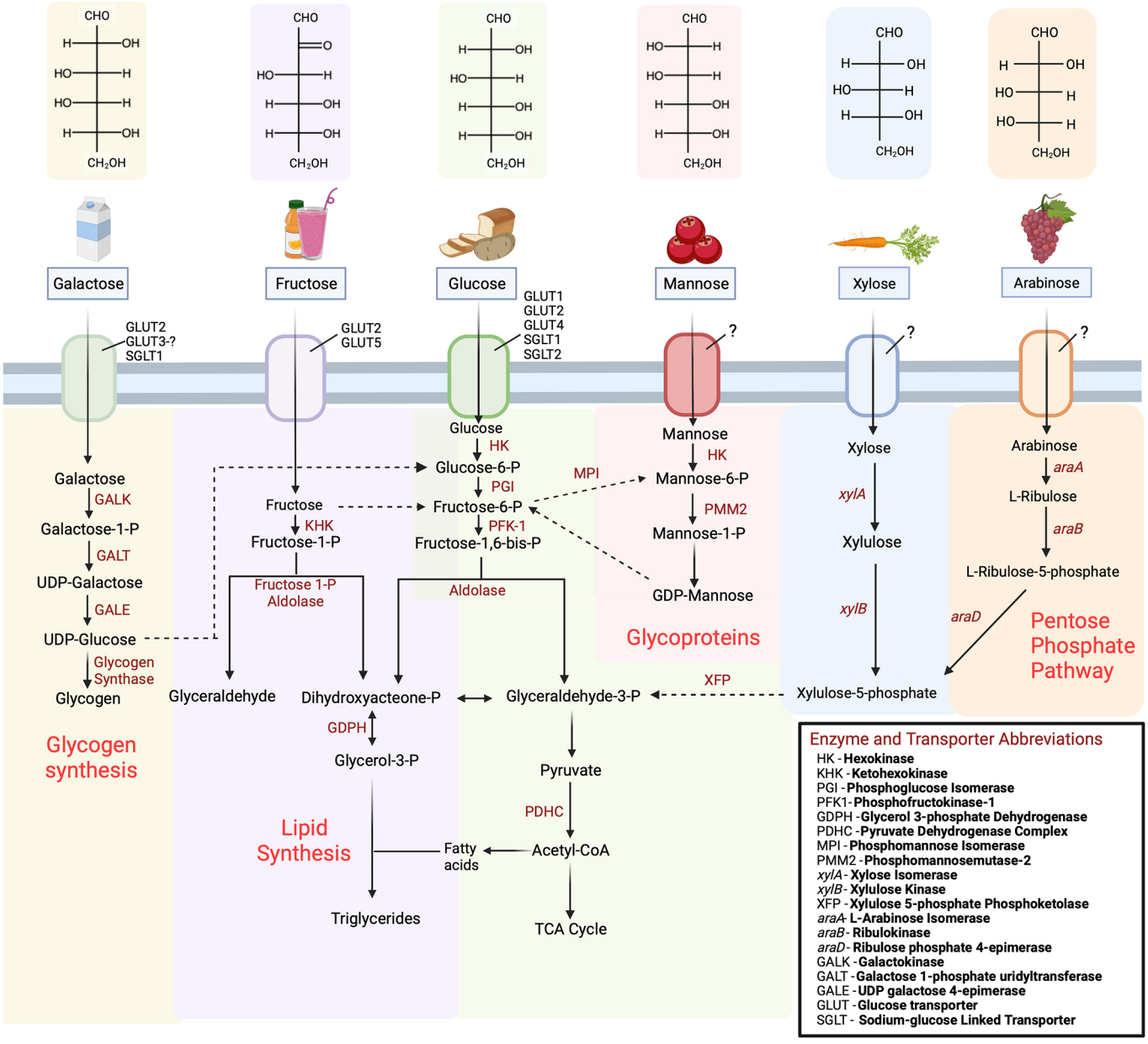

Fig. 1. Simplified metabolic pathways of dietary sugars. Different dietary sugars are abundant in different food sources. Once they are transported into the cells, they initially undergo specific catabolic pathways and merge into the common pathways such as glycolysis, glycogenesis, pentose phosphate pathway, TCA cycle, or fatty acid and lipid synthesis. While such biochemical pathways are well-known, our understanding of the relative carbon fluxes in each pathway, regulation, and interactions between pathways in different cell types are still rudimentary. Unidentified transporters are indicated with a question mark. Bacterial enzymes for xylose and arabinose catabolism, which do not exist in mammals, are indicated as italic.
HK, hexokinase; KHK, ketohexokinase; PGI, phosphoglucose isomerase; PFK1, phosphofructokinase-1; GPDH, glycerol-3-phosphate dehydrogenase; PDHC, pyruvate dehydrogenase complex; MPI, phosphomannose isomerase; PMM2, phosphomannomutase-2; xylA, xylose isomerase; xylB, xylulose kinase; XFP, xylulose-5-phosphate phosphoketolase; araA, L-arabinose isomerase; araB, ribulokinase; araD, ribulose phosphate 4-epimerase; GALK, galactokinase; GALT, galactose-1-phosphate uridyltransferase; GALE, UDP galactose-4-epimerase; GLUT, glucose transporter; SGLT, sodium-glucose linked transporter.

of maturation and activity of these cells.[16] Poor differentiation due to chronic inflammation or tumor formation can impair intestinal sugar absorption.

Glucose and galactose share the sodium-glucose linked transporters (SGLTs), specifically SGLT1.[17] SGLTs located in the apical membrane of intestinal epithelial cells consume ATP to

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transport substrates against their concentration gradients. SGLT1 couples the transport of one glucose or galactose molecule with 2 sodium ions, generating a concentration gradient that drives the accumulation of the sugar in the intestinal enterocyte. Na+/K+-ATPase then transports the sodium out into the blood, enabling the passive diffusion of the sugar out of the cell through GLUT2 on the basolateral membrane. Importantly, under settings of high luminal sugar concentrations, GLUT2 is transiently localized on the apical membrane to increase uptake.[18,19] In the pathological context of obesity and diabetes, GLUT2 becomes permanently localized to the apical membrane, leading to unregulated sugar transport into the blood. Of note, galactose is mostly coming from dietary lactose breakdown by lactase enzyme. Thus, this upstream process is critical for galactose absorption efficiency. Individuals with lactase deficiency, for example, cannot absorb galactose and exhibit lactose intolerance due to its accumulation in the gut lumen.

Dietary fructose uses a different transporter to enter enterocytes, mainly via an ATP-independent, facilitative transporter, GLUT5, on the apical border of intestinal cells. Then, fructose is subsequently transported to the portal blood by GLUT2, the same transporter for glucose and galactose.[17] GLUT5 has been reported as the only GLUT protein with high specificity for fructose.[20] Animals lacking GLUT5 exhibit fructose intolerance and even death due to their inability to absorb fructose.[21] Specifically, Barone et al.[21] showed that GLUT5 knockout (KO) mice maintained normal healthy phenotypes without dietary fructose consumption. However, they developed severe hypovolemic shock and died after 7–10 days of increased dietary fructose intake. Notably, fructose absorption is augmented by glucose co-ingestion.[13] This is worth noting because dietary fructose is rarely consumed alone but mostly consumed with glucose.

Mannose, a less abundant hexose in the diet, has been much less studied than glucose or fructose. Some reports suggest that mannose is transported by shared hexose transporters while others suggest mannose-specific transport systems.[22-24] For example, a competitive inhibitor of SGLT1 and SGLT2 blocked glucose reabsorption in the kidney but 78% of mannose was still reabsorbed, suggesting the existence of a mannose-specific transporter.[23] Meanwhile, the rate of mannose uptake by Caco-2 cells increased by fructose but decreased by glucose,[25] suggesting that mannose transporters are regulated by other hexose sugars. Durán et al.[22] reported that mannose is taken up by enterocytes isolated from the chicken small intestine via 2 mannose transport systems: a concentration and Na+-dependent system and a passive Na+-independent system. Much is thus left to be discovered regarding mannose transport mechanisms, likely affected by other dietary sugars co-ingested in the diet. Interestingly, unlike other hexoses, studies have revealed several beneficial health effects of mannose, as discussed below.

2. Catabolism

After absorption, different dietary sugars undergo cellular catabolism via specific upstream enzymes and common downstream pathways (**Fig. 1**). Once glucose is transported into the cell, it is quickly phosphorylated into glucose-6-phosphate (G6P), which is a central molecule in several metabolic pathways, including glycolysis, gluconeogenesis, glycogenesis, and the pentose phosphate pathway. The addition of this phosphate group to glucose by hexokinase renders the molecule captured by the cells. Additionally, this chemical modification creates a glucose gradient between the cytoplasm and extracellular space, which can further increase the transport of glucose into cells. Isomerization of G6P into fructose-6-phosphate followed by additional phosphorylation into fructose-1,6-bisphosphates commits the glycolytic pathway. This second phosphorylation by phosphofructokinase (PFK) is the most heavily

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regulated process by many allosteric metabolites and signaling pathways to avoid excessive glycolysis. Glycolysis occurs in most living organisms in the presence or absence of oxygen, though the fate of its end products, either complete oxidation to CO_2 or fermentation to lactate, depends on the levels of oxygen in the environment.[26]

Fructose catabolism, on the other hand, lacks such complex regulated enzymes. Once inside the cell, fructose is rapidly phosphorylated by ketohexokinase (KHK) to form fructose-1-phosphate (F1P). Importantly, the specificity of this phosphorylation on the 1-position allows for the unique bypassing of the PFK-dependent control step. Without such negative feedback regulation, F1P is further catabolized into the glycolytic intermediate, dihydroxyacetone phosphate, and glyceraldehyde, enabling further incorporation into downstream pathways such as the TCA cycle and fatty acid synthesis pathways.[13,27] Uncontrolled fructose catabolism activates cellular signaling cascades that stimulate the conversion of excessively generated acetyl-CoA into fatty acids, especially in the liver.[7] Also, when KHK-mediated rapid ATP consumption overwhelms ATP regeneration, AMP accumulates and initiates its breakdown pathway, resulting in high uric acid production. High circulating uric acid levels have been linked to oxidative damage, inflammation, and several metabolic disorders.[28] In summary, the difference in unique enzymes of early fructose metabolism as compared to glucose metabolism causes a much faster and unregulated catabolism, leading to metabolic complications such as ATP depletion, excess uric acid production, and other whole-body metabolic consequences.[29]

Another important difference between glucose and fructose is their catabolic organs. While most dietary glucose bypasses intestinal or hepatic metabolism (except when portal glucose levels are high enough to trigger glucokinase in the liver), fructose is almost completely catabolized by the intestines and liver.[30] There are also some reports of fructose metabolism by the kidney,[31] with evidence of increased expression of fructose transporters in the kidney following fructose consumption. This key difference in glucose and fructose catabolism, enables glucose (but not fructose) tolerance tests by sampling systemic blood. Glucose released into systemic circulation feeds many peripheral tissues, including the brain, muscle, and adipose tissues. Glucose accumulation in the blood is highly toxic (e.g., in diabetes), and thus, to prevent such organ damages, its circulating levels are tightly controlled by the actions of hormones, including insulin and glucagon. This homeostatic regulation mechanism of circulating glucose is unique among dietary sugars because others, such as mannose, fructose, or galactose do not circulate much in the systemic bloodstream due to their low dietary intake and negligible amounts of endogenous production.

Galactose is primarily converted to glucose for glycogen storage in the liver. On the other hand, mannose is converted into glucose for further catabolism, or it can be used for biosynthesis of glycans, polymers of monosaccharides linked by glycosidic bonds.[32] More details in galactose and mannose catabolism will be discussed separately below. Altogether, there are some similarities in dietary sugar absorption and metabolism while distinct biochemical pathways and organ distribution likely contribute to their different biological impacts on organ health.

3. Glucose: the relationship between different forms and glycemic response

Glucose is the most abundant sugar in nature. It is derived from the biochemical breakdown of most dietary carbohydrates. Glucose is central to the production, storage, and regulation of energy. Its homeostasis is maintained by intestinal glucose absorption following a meal, hepatic and renal glucose production, and glucose usage by many organs.[30] Additionally,

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glucose is responsible for controlling hormone secretion in the endocrine pancreas and neuronal signaling in the regulation of feeding processes, energy expenditure, and overall homeostasis.[33-36] A detailed description of glucose metabolism, regulation, and health effects was reviewed by many others.[37,38] Thus, we will briefly emphasize the most recent findings regarding the different forms of dietary glucose and whole-body glycemic response, a key parameter for insulin release, the pathogenesis of insulin resistance and diabetes.

The postprandial glycemic response of a carbohydrate-rich meal is determined by the amount of glucose absorbed, rate of entry into circulation, rate of tissue uptake, and regulation of liver glucose production.[39] It also varies according to the type of carbohydrate that is present in the meal besides glucose itself. Recently, a large number of studies have been evaluating unique starch diets on postprandial glycemic response. For instance, Tan et al.[40] compared the effects of a soluble corn fiber drink (containing 25 g of corn fiber + 25 g of glucose powder) and glucose only drink (containing 50 g of glucose powder) on glycemic and insulin response over a 130 minutes time course in 22 healthy human subjects. The blood glucose area under the curve (AUC) was 20% lower in the corn fiber-fed subjects compared to glucose-only-fed subjects. The AUC for blood insulin was also 33% lower in the corn fiber-fed subjects. Thus, the slower digestion of glucose as starch with compact and complex structure efficiently decreased glycemic response.

A similar study examining low and high amylose wheat content also determined glycemic and insulin responses in 20 human subjects.[41] The study found a 39% lower AUC glycemic response and a 24% lower AUC insulin response in participants who consumed high amylose wheat content compared to those who ate low amylose wheat content. Similarly, consumption of compact bread compared to porous bread showed slower initial rates of blood glucose excursions as well as lower peak glucose.[42] These studies highlight the critical impact of chemically diverse glucose forms in the diet in determining glycemic response, an often-overlooked factor in many animal and human dietary intervention studies.

4. Fructose: the critical balance between liver and gut catabolism matters

Given the wide consumption of fructose worldwide and increasing incidence rates of various metabolic diseases, an understanding of their causal relationship has become a priority in the field. Here, we focused on highlighting the most recent findings of organ-specific fructose metabolism and its pathophysiological relevance.

As previously mentioned, fructose catabolism is initiated by the phosphorylating enzyme, KHK, which is the key determinant of fructose organ metabolism. Two isozymes of KHK exist, encoded by alternatively spliced mRNAs.[43,44] KHK-A isoform is ubiquitously expressed across organs, while KHK-C, the more active and high-affinity isoform, is solely expressed in the intestine, liver, kidney, and pancreas.[43-47] A recent report revealed that triokinase, another key enzyme in fructose metabolism that converts glyceraldehyde into glyceraldehyde-3-phosphate, is required to prevent fructose carbon assimilation toward *de novo* serine synthesis. By stimulating lipogenic metabolism, triokinase in hepatocytes drives energy storage as fat, reduces oxidative stress, and distributes fructose carbons to a variety of downstream pathways, including gluconeogenesis, glycogenesis, and lactate secretion.[27]

The primary assumption in the field for a long time was that dietary fructose catabolism occurs solely in the liver because of the strongest expression of KHK-C in hepatocytes.[43-45] However, recent studies have highlighted that fructose catabolism in the gut prior to liver

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plays a key role in determining the pathological effects of fructose. Because the small intestine is the first organ that encounters dietary fructose before the liver, intestinal fructose catabolism acts as a shield to protect the liver from excessive fructose exposure.[48] While low doses of dietary fructose are efficiently cleared by the small intestine, high doses overwhelm the intestinal capacity, resulting in fructose spillover to the liver and colonic microbiota.[49,50] In this case, fructose that is excessively assimilated by the liver becomes fat while fructose that is catabolized by the gut microbiota can lead to composition changes and dysbiosis of gut microbiota.[50,51]

This altered view of organismal fructose metabolism led to studies regarding its relevance in human diseases. Andres-Hernando et al.[52] aimed to address the effect of tissue-specific differences in fructose catabolism in obesity and fatty liver development by generating tissue-specific KHK-A/C deficient mice. The study found that liver-specific KO mice were completely protected from metabolic syndrome whereas intestinal KO mice were more likely to develop metabolic syndrome due to greater fructose delivery from the gut to the liver. For example, the intestinal KO mice showed 50% higher body weights and triglyceride levels after fructose feeding, whereas the liver-specific KO mice were lower on average in both measurements. Further, GLUT5 expression in the gut is lower in sugar-exposed intestinal KO mice. Such downregulated GLUT5 levels suggest the overall decrease in fructose absorption by the gut yet still higher fructose delivery to the liver. Thus, the study shows how fructose catabolism in different organs can have differential impacts on the development of metabolic diseases.

While intestinal fructose catabolism seems to protect the liver, its excessive catabolism can cause other consequences. A recent report by Taylor et al.[53] showed that dietary fructose improves intestinal cell survival and increases intestinal villus length in several mouse models. Mice were fed a control diet with no fructose, a standard high-fat diet (HFD), or an HFD with dextrose replaced by sucrose. Mice fed the sucrose-based HFD gained significantly more weight and fat mass and longer intestinal villus length as compared to the standard HFD group. The authors further confirmed that increased intestinal epithelial cell survival in response to dietary fructose is the major determining factor of these phenotypes. Additionally, inhibition of the M2 isoform of pyruvate kinase (the final rate-limiting enzyme of glycolysis) by F1P accumulation mediates this increased epithelial cell survival in a hypoxic gut environment. This was a notable finding that may explain the increase in fructose-derived adiposity and the related rise in obesity as a result of the Western style diet.[1,2,54,55]

Recently, Todoric et al.[56] also suggested that excessive intestinal fructose catabolism can be detrimental. While it has been previously shown that fructose causes gut microbiota dysbiosis and barrier deterioration,[57-60] how fructose triggers these impairments and induces nonalcoholic fatty liver disease (NAFLD) is unclear. To obtain deeper mechanistic insights, the authors fed mice a chronic high-fructose diet and Toll-like receptor (TLR) agonists.[56] They found that inhibition of N-glycosylation by F1P in the intestine triggers endoplasmic reticulum stress and inflammation that affects barrier function and results in endotoxemia (i.e., the increased delivery of lipopolysaccharide endotoxins of gut bacteria to the liver). This, in turn, engages TLR4 on macrophages to initiate an inflammatory response that prompts the liver to increase fatty acid synthesis and decrease mitochondrial fat oxidation. Whether this is the key mechanism in human NAFLD requires further investigation.

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5. Mannose: uniquely health-beneficial dietary hexose?

While less abundant than fructose, mannose is also plentiful in vegetables and fruits. It is produced by microbes, plants, and animals[32] and is ubiquitously found in mammalian plasma at reasonably high concentrations of 35–120 μM.[25] Mannose is an epimer of glucose and is primarily used in glycation, which attaches sugars to a protein or lipid. It has been reported that mannose is 5 times more active than glucose in the glycation process. This may suggest why mannose did not evolve to be favored as a biological energy source.[32]

Mannose is the major monosaccharide component of N-glycans, most commonly linked in a precursor oligosaccharide chain that becomes a glycoprotein upon attachment to amino acid side chains of proteins. In addition to dietary sources, endogenous production of mannose through phosphomannose isomerase (MPI) can be physiologically significant (**Fig. 1**).[61] Hydrolysis of the dietary oligosaccharides also liberates copious free mannose that can be subsequently phosphorylated to produce mannose-6-phosphate (M6P) for the glycation reaction.[62] Therefore, MPI activity and dietary mannose intake are the 2 major sources of mannose for glycation.[63]

Strict regulation of mannose-derived metabolites like M6P is necessary, as deficiency or excess can be detrimental to cells and the whole organism. Notably, Ichikawa et al.[62] found that mannose-derived from glycoprotein degradation does not contribute to N-glycans and therefore exogenous mannose is required as a therapeutic for treating glycosylation disorders. Studies on glycosylation-deficient cells,[63] mice,[64] or humans[65,66] showed that small amounts of dietary mannose rescued the deficiency.

More recently, mannose has been considered as more than a supplement for congenital disorders of glycosylation. Sharma et al.[67] found that mannose supplementation prevents weight gain, fat accumulation, and liver steatosis in HFD-fed mice. Interestingly, these effects only occurred when mannose supplementation was initiated early in life. Also, such effect was mannose-specific because the same dose galactose supplementation did not show any effects. The authors also identified changes in gut microbial compositions and energy metabolism after mannose treatment, but this was again only observed when mannose was introduced early in life. Notably, these phenotypes were reversed after mannose removal.

Mannose has also been highlighted as a novel treatment strategy to suppress inflammation and autoimmunity. Mannose supplementation suppressed immune cell hyperactivation via induction of regulatory T (Treg) cells in non-obese diabetic mice.[68] This increase in Treg cells showed suppressive functions in type 1 diabetes and airway inflammation.[68] Furthermore, mannose suppresses effector T cells and inflammatory macrophages and increases anti-inflammatory gut microbiota. Meanwhile, Torretta et al.[69] showed that mannose impairs IL-1β production and reduces activation of lipopolysaccharide-induced macrophages *in vitro*. This impairment relies on the low MPI expression since MPI can otherwise support glycolysis and allow the macrophages to continue functioning efficiently. Finally, mannose treatment blocks glucose uptake and glycolysis of cancer cells *in vitro* and suppresses tumor growth in mice by starving tumors.[70]

6. Galactose: a milk-derived hexose with controversial health impacts

Galactose is abundant in many dairy products and has been occasionally used as an alternate sugar to reduce the effects of metabolic syndrome. Galactose has also gained clinical attention due to an inborn error of galactose metabolism such as galactosemia, the inability to break down galactose. Recently, galactose has been reported to accelerate

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neurodegeneration and cardiac dysfunction in animal models. However, some other studies have found that galactose can improve cognitive functions. This section will discuss such controversies of galactose's effect on health.

Galactose typically comes in the form of lactose, a disaccharide composed of one glucose and one galactose monomer. Upon ingestion, lactose is broken down into glucose and galactose by the enzyme lactase on the brush border of the small intestine (**Fig. 2A**). As discussed previously, intestinal SGLT1 is known to mediate galactose uptake. Subsequently, galactose passes through the basolateral membrane into the portal bloodstream by GLUT2. Galactose that reaches the liver is then transported through GLUT2 and converted into various metabolites including glycolytic intermediates through the Leloir pathway (**Fig. 2B**).[71]

Galactose has been a popular molecule of interest in many fields, particularly immunology and neuroscience. For example, a link has been recently suggested between increased immunoglobulin E (IgE) blood levels and atherosclerotic plaque risk through α-Gal, an antigen containing 2 unique galactose sugars at the end of the N-terminus of various molecules.[72] The α-Gal molecule is present in glycolipids as well as in a myriad of human

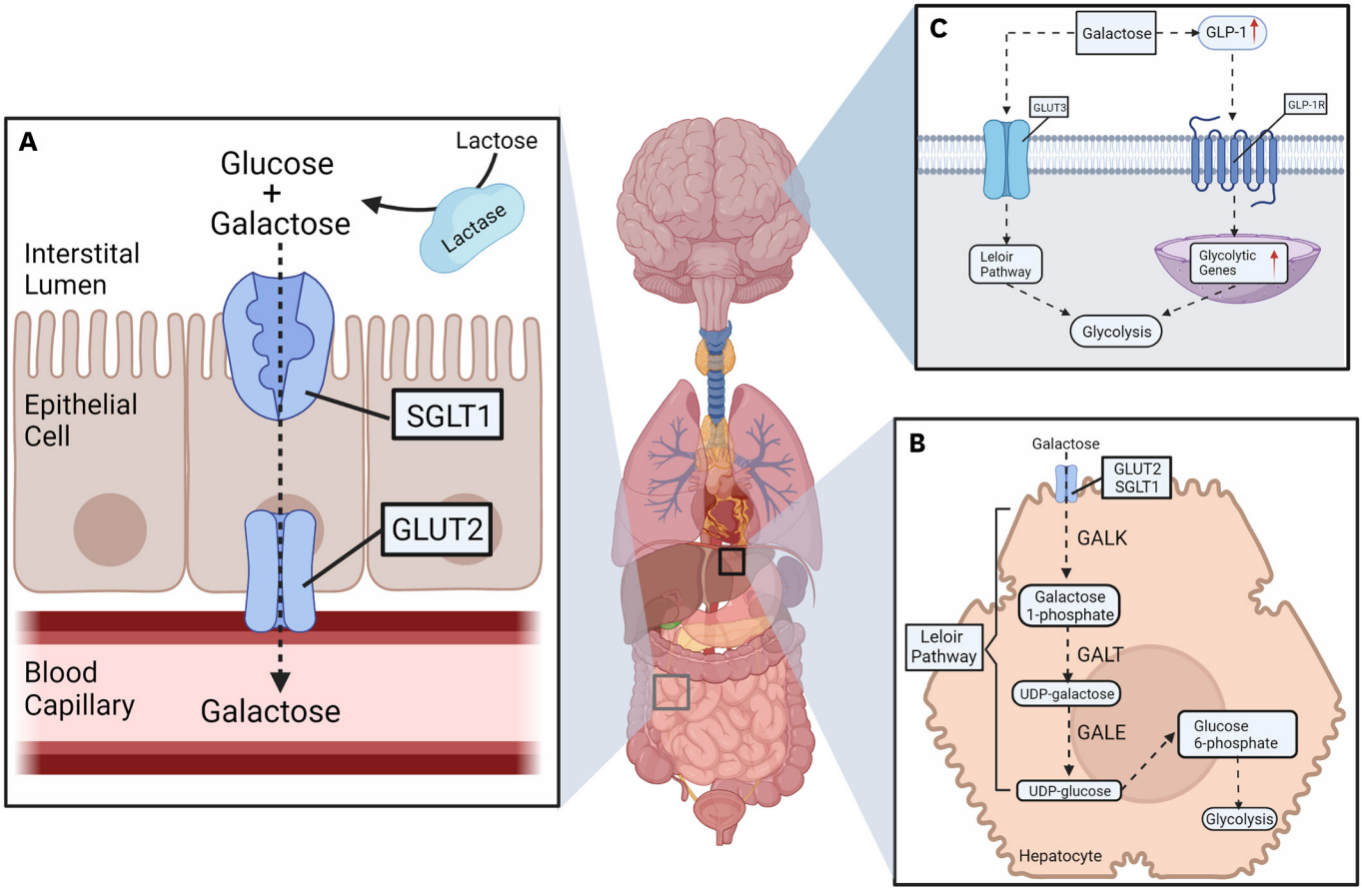

Fig. 2. Metabolism of galactose. (A) Galactose is a component of lactose that is broken down by lactase, a brush border enzyme of the small intestines. Upon transport through SGLT1 and GLUT2 into the enterocytes, galactose is translocated to the liver via the portal circulation. (B) Galactose is then internalized in the liver by GLUT2 and metabolized via the Leloir pathway. The final product, UDP-glucose, becomes glucose-6-phosphate to enter the glycolysis. (C) In brain neurons, it is hypothesized that galactose is taken up by the insulin-independent transporter, GLUT3, thereby feeding neurons even when glucose uptake is impaired by insulin deficiency or resistance. Galactose can also activate GLP-1R signaling to stimulate neuronal glycolysis to support energy metabolism. SGLT, sodium-glucose linked transporter; GLUT, glucose transporter; GLP-1R, glucagon-like peptide 1 receptor.

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remedies such as medications, vaccines, and milk products. It is speculated that the α-Gal would increase IgE production and cause atherosclerotic plaque build-up by upregulating mast cell activation.

Meanwhile, several studies have proposed the potential neurotoxic effects of galactose. Galactose induces neurodegeneration by increasing the production of reactive oxygen species, resulting in symptoms related to Alzheimer's disease and dementia.[73-76] Cui et al.[77] investigated the effect of increased systemic galactose levels on the brain by comparing mice given a normal saline control or galactose via subcutaneous injection for 7 weeks. Mice that received galactose showed accelerated neurological dysfunction with increased oxidative stress and neuronal senescence. Enzymatic activities of the oxidative stress marker, malondialdehyde (MDA), increased while the activities of antioxidant proteins such as super-oxidase dismutase and glutathione peroxidase decreased in the galactose-treated group. Further, histological analysis of the hippocampus revealed that pyknotic nuclei and caspase-3-positive cells, the 2 indicators of cellular apoptosis, were significantly increased in the galactose-treated group. These data suggest that systemic elevation of galactose can accelerate neurodegeneration via cellular senescence.

In support of the neurodegenerative effects of galactose, Ali et al.[78] analyzed the chronic effect of galactose on the neuronal synaptic functions in mice after intraperitoneal administration of galactose for 60 days. When compared to control mice injected with saline, there was a 25% decrease in the number of synaptic proteins in the hippocampus in mice given galactose. Further, immunofluorescence staining also showed large increases of 8-oxoguanine in the cortex and hippocampus, an oxidative stress marker known to cause age-related neuronal disorders such as dementia. These studies suggest that chronic galactose exposure may result in memory impairment and a decrease in cognitive function, though the relevance of these findings in humans remains unknown.

Besides neuronal consequences, it has also been shown that galactose can elicit harmful effects on the cardiovascular system. Bo-Htay et al.[79] found that galactose worsened cardiac dysfunction in HFD-fed obese, insulin-resistant rats. Rats administered with galactose further increased cardiac MDA levels elevated by HFD feeding. This is also accompanied by increased reactive oxygen species and mitochondrial swelling in cardiac tissue.

In contrast, a few recent studies have suggested that galactose may have some health benefits. Salkovic-Petrisic et al.,[80] showed that oral galactose administration induces beneficial effects on improving cognitive defects in streptozotocin (STZ)-induced Alzheimer's disease rat model. Through the Morris Water Maze swimming test, 3 different concentrations of galactose (100–300 mg/kg/day) were administered upon STZ injection and compared to the STZ only control. The rats that received the highest galactose dosage (300 mg/kg) had twice the lower number of mistakes on the swimming test compared to the STZ controls. Mechanistically, the study proposed that galactose can be converted into glucose and directly used by the neurons via the insulin-independent GLUT3, which showed 67% increased levels upon galactose administration (**Fig. 2C**). The same group also investigated cognitive improvement in STZ-treated rats by evaluating glucagon-like peptide molecules (GLP-1) in the brain after oral galactose administration.[81] Galactose provision for 2 months significantly increased active GLP-1 in the plasma as well as in the hippocampus. This GLP-1 activates signaling cascades to induce glycolytic genes, which may support galactose usage by neurons (**Fig. 2C**).

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Overall, galactose's impact on health remains controversial. One possible explanation is that galactose elicits beneficial effects only in the absence of insulin such as in STZ-treated animals. Because galactose, unlike glucose, can be taken up by cells without insulin signaling (via insulin-independent GLUT3), it can serve as an alternative energy source especially when glucose uptake is impaired. Another important consideration is the different routes of administration utilized in various studies. Salkovic-Petrisic et al.[80] orally administered galactose whereas the studies that showed detrimental neuronal effects of galactose used subcutaneous or intraperitoneal injections that bypass galactose metabolism in the digestive system. As the gut-brain axis via intestinal hormones and gut microbiota plays key roles in a variety of human pathophysiology, further studies may need to focus on the effect of orally administered galactose.

DIETARY PENTOSES

With the associated chronic illnesses that result from excessive intake of fructose and glucose in the human diet, research has been targeted towards alleviating health complications by using substitute sugars. One such alternative is the use of aldopentoses as dietary supplements, which are derived from hemicellulose, abundant in plant-based food including corns, potatoes, and coconuts. In this section, we review recent findings on the 2 most-studied aldopentose sugars, D-xylose and L-arabinose, both of which are potential candidates to alleviate metabolic syndromes.

1. Xylose: potentially beneficial sugar to combat against metabolic diseases

In general, the relative sweetness of xylose (5%–11% in solution) was determined to be 0.63 sweeter than 5% sucrose solution.[82] Despite its lower relative sweetness, xylose makes an attractive sweetening supplement for humans without providing calories. It is prevalent in its reduced form, xylitol, in many sweets such as chewable vitamins and gums. While humans lack the enzyme to break down xylose, gut bacteria may have enzymes and transporters for the uptake and catabolism of xylose or xylitol, thereby affecting host metabolism (**Fig. 3A**). Indeed, a recent study has shown that gut microbiota produces more propionate, one of the short-chain fatty acids (SCFAs), when exposed to xylitol,[83] although it does not indicate that xylitol is directly catabolized by microbiota.

SCFAs are known to regulate host metabolism in a variety of ways. One such effect includes an increased release of gut hormones such as leptin, which reduces appetite and enhances satiety. Thus, xylitol consumption may improve insulin sensitivity through SCFAs.[84] Consistent with this notion, xylitol consumption has been shown to exert metabolically beneficial effects in mice. Amo et al.[85] fed 3 groups of mice with differing amounts of xylitol (0, 1 or 2 g per 100 kcal) with an HFD. They found that visceral fat was decreased by 15.5% in the 2 g xylitol supplemented group compared to the HFD alone group. Moreover, xylitol feeding increased the expression of genes involved in fatty acid oxidation, such as *Acyl-CoA oxidase* and *Uncoupling protein 2* in the hepatocytes.[85] It is unclear how xylose stimulates these genes, but xylitol catabolism by gut microbiota and increased SCFA production may be involved. Another possible mechanism may be through xylitol-mediated direct activation of unknown signaling pathways in the host organs.

In a similar context, Lim et al.[86] showed that xylose suppresses lipid metabolism genes in mice fed a HFD. Compared to the HFD control group, the 10% xylose supplemented group

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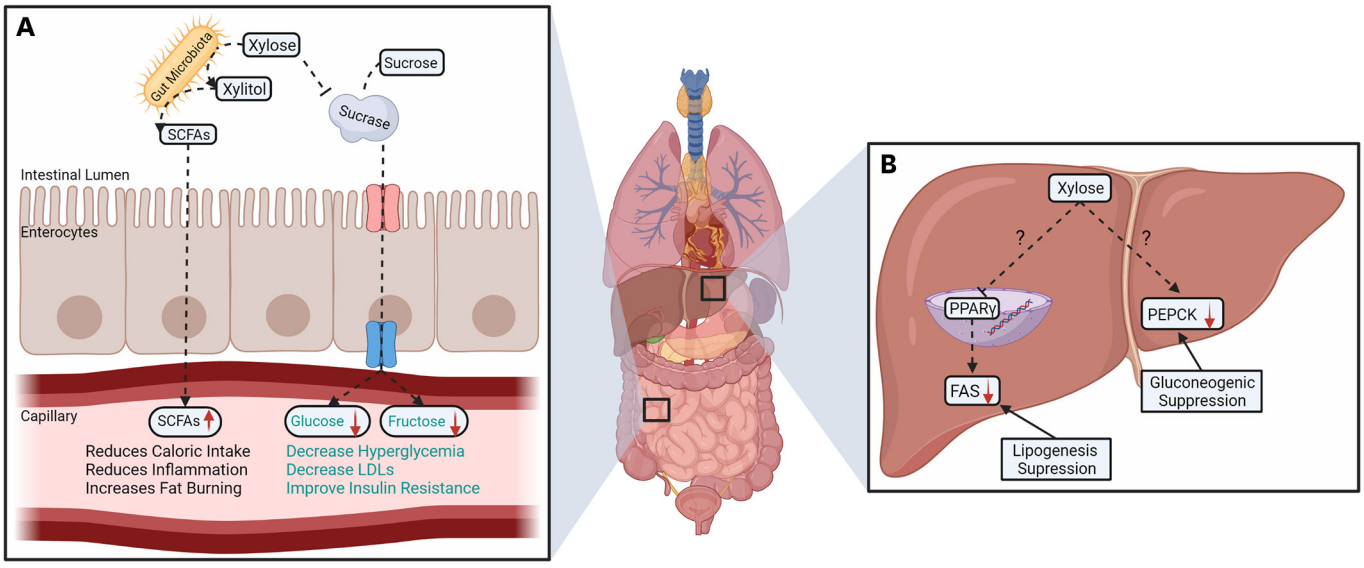

Fig. 3. Metabolism of xylose. (A) Xylose is hypothesized to be catabolized by the gut microbiota to produce SCFAs and other metabolites, potentially exerting various effects on the host organs. Moreover, xylose has been shown to inhibit sucrase, a small intestinal brush border enzyme that catalyzes the hydrolysis of sucrose into glucose and fructose. This effect can alleviate fructose-related pathologies. (B) Xylose has been suggested to regulate glucose and fat metabolism through diverse mechanisms in the liver, including suppression of lipid synthesis or gluconeogenesis via regulating key transcription factors and enzymes.
SCFA, short-chain fatty acid; LDL, low-density lipoprotein; PPARγ, peroxisome proliferator-activated receptor γ; PEPCK, phosphoenolpyruvate carboxykinase; FAS, fatty acid synthase.

showed significantly lower expression levels of *peroxisome proliferator-activated receptor γ* and its downstream enzyme, *fatty acid synthase*. This effect potentially reduces lipogenesis and lipid storage to promote liver health. In a separate study,[87] the same group analyzed the effect of xylose on gluconeogenesis using the same experimental groups. The 10% xylose supplemented group showed a 28.2% reduction in *phosphoenolpyruvate carboxykinase* (*PEPCK*) expression levels compared to the control group, which likely mediated the reduced blood glucose levels by suppression of hepatic gluconeogenesis (**Fig. 3B**). These studies suggest that xylose may be a potential candidate in combating metabolic syndrome by substituting other dietary sugars, such as glucose and fructose.

Notably, xylose was also found to inhibit the small intestinal sucrase, an essential enzyme for cleaving sucrose to glucose and fructose (**Fig. 3A**). Seri et al.[88] investigated the inhibition of sucrase activity in the small intestinal brush border upon xylose administration in mice. Four groups of mice were orally administered with small amounts of xylose (0, 12.5, 25, and 50 mg/kg) along with a large bolus of 1 g/kg sucrose. After normalization to the control group, the authors found that 44 mg/kg of xylose inhibited sucrase activity by 20% and significantly reduced blood glucose excursion after sucrose feeding. This study identified xylose as a potential dietary supplement to alleviate sucrose-induced metabolic disruptions.

To validate such findings, human studies were conducted. A randomized experiment was performed to determine the effects of xylose supplementation in a sucrose test solution (50 g of sucrose in 130 mL water) on blood glucose and insulin levels.[89] The authors examined 3 different xylose concentrations (0 g: control, 5 g: low, and 7.5 g: high) over a 2-hour time course. Intriguingly, xylose-treated groups showed a 30%–50% decrease in both glucose and insulin levels during early time points (0–60 minutes) after sucrose feeding. Similar findings were established by Jun et al.[90] where 25 healthy subjects and 50 hyperglycemic subjects were recruited in a double-blind experiment. Along with glucose and insulin levels,

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the authors found that C-peptide levels, an indicator of endogenous insulin production, decreased considerably by xylose supplementation. Although this beneficial effect of xylose on postprandial glycemic response is promising, the study period of these experiments was short. Thus, further studies are needed to evaluate the long-term effects of xylose consumption.

2. Arabinose: a poorly understood, yet promising sugar for diabetes treatment

L-arabinose, whose sweetness is about a half of sucrose and common in the human diet (e.g. wheat cereal), was found to have similar anti-diabetic effects as xylose.[91] Arabinose is especially abundant in cherries, apples, and coffee. Interestingly, arabinose inhibits sucrase more potently than xylose: 18.5 mg/kg of arabinose was needed to inhibit 20% of sucrase activity, while 44 mg/kg of xylose was needed to achieve the same effect.[88] This suggests that arabinose may be another potential candidate in combating sucrose-related human pathologies.

One recent finding showed that arabinose can suppress gluconeogenesis.[92] When arabinose was added to the high-fat, high-sucrose diet, the expression levels of key hepatic gluconeogenesis enzymes such as *PEPCK* and *Glucose-6-phosphatase* (*G6Pase*) decreased by 23.9% and 26.1%, respectively. To examine whether this effect is direct on hepatocytes, the authors treated human liver cells (HepG2) with 100 μg/mL of arabinose and found that arabinose significantly decreased expression of *Forkhead Box O1* and *peroxisome proliferator-activated receptor-γ coactivator 1α*, both of which are known to stimulate gluconeogenic enzymes under normal fasting conditions. On the other hand, arabinose treatment increased phosphorylated AMP-activated protein kinase levels, which may also mediate improved insulin sensitivity and glucose uptake in arabinose-treated animals.

Another study also supported the effects of arabinose on having key anti-diabetic properties *in vivo*.[93] Mice were fed either a normal chow diet or a high-carbohydrate and high-fat (HCHF) diet, supplemented with or without arabinose. In the arabinose-supplemented HCHF group, expression levels of inflammatory cytokines such as tumor necrosis factor-α and leptin decreased by 2-fold in adipose tissues. Symptoms related to metabolic syndrome also decreased. *Acetyl-coenzyme A carboxylase α*, the rate-limiting step of the fatty acid synthesis, decreased by 80% while *carnitine palmitoyltransferase 1 α*, a rate-limiting enzyme of the β-oxidation of fatty acids, increased by 30%. Together, these studies suggest that arabinose can alleviate metabolic syndromes by regulating genes related to insulin sensitivity and lipid metabolism both in the liver and white adipose tissue (**Fig. 4**).

CONCLUSION REMARKS

As the world population continues to abuse sweeteners and increase consumption of dietary sugars, a call for understanding the metabolic consequences and potential risks for the disease has become a priority for global health. The 6 simple monosaccharides, abundant in our diet and discussed here, are the foremost examples of dietary sugars highly relevant in metabolic health. Though much is known about glucose and fructose metabolism, mannose, galactose, and the dietary aldopentoses (xylose, and arabinose) remain poorly understood. Further clinical studies, as well as detailed mechanistic studies using genetically modified animal models with metabolic tracing and multi-omics techniques, will be the valuable future frontier that can disclose biochemical mechanisms underlying the effects of these dietary sugars on human health and disease.

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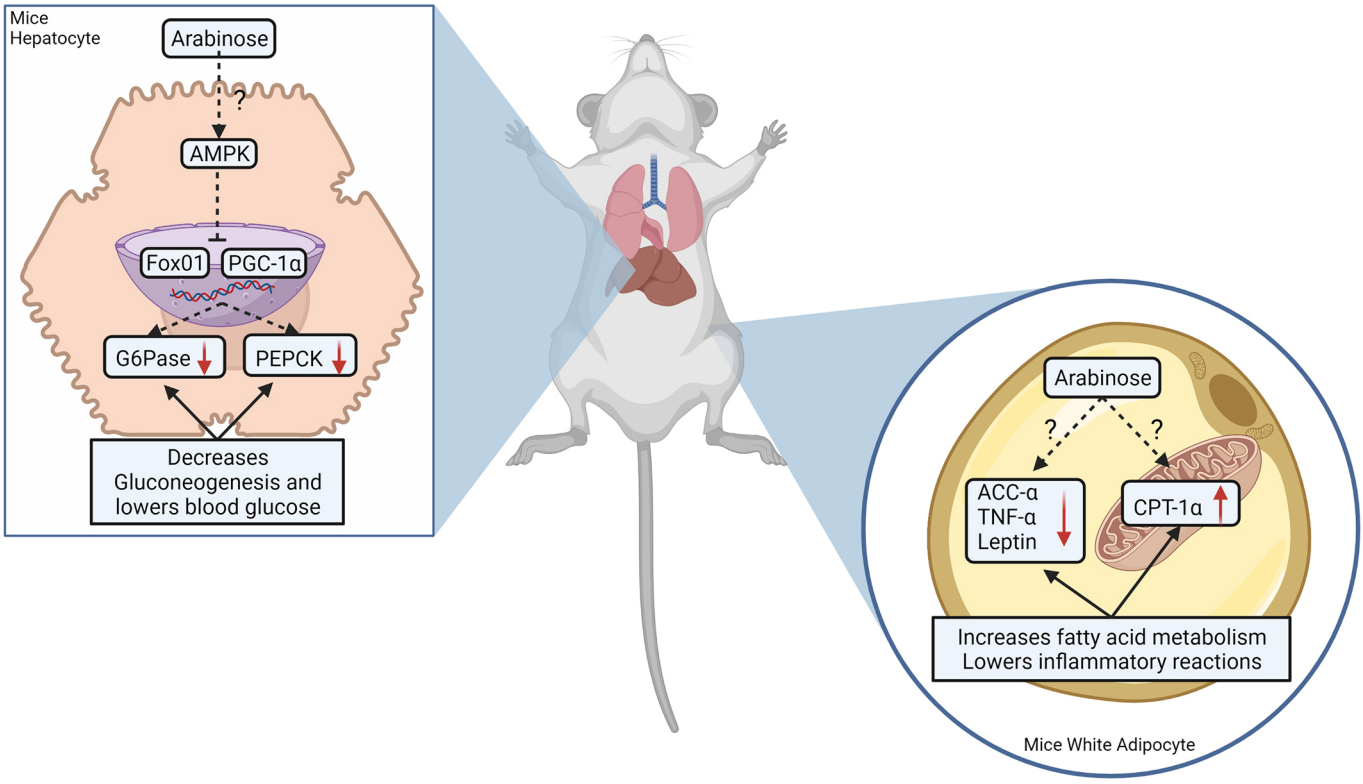

Fig. 4. Effects of arabinose on key metabolic genes in the liver and adipose tissues. Arabinose has been shown to have anti-diabetic effects such as reduced hepatic gluconeogenesis and increased fat oxidation in adipose tissues.
PGC1α, peroxisome proliferator-activated receptor-γ coactivator 1α; G6Pase, glucose-6-phosphatase; PPARγ, peroxisome proliferator-activated receptor γ; PEPCK, phosphoenolpyruvate carboxykinase; ACCα, acetyl-coenzyme A carboxylase α; CPT-1α. carnitine palmitoyltransferase 1 α; TNF-α, tumor necrosis factor α.

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