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REVIEW

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Fructose metabolism and its roles in metabolic diseases, inflammatory diseases, and cancer

Zhenhong Li[1,2], Xinzou Fan[1], Fan Gao[1], Shengguang Pan[1], Xiao Ma[1], Hao Cheng[1], Hiroko Nakatsukasa[3], Wei Zhang[1,2*] and Dunfang Zhang[1,2*]

Abstract

Fructose, a prevalent hexose, has become a widely used food additive, with its usage rising significantly because of socio-economic advancements and shifts in human dietary habits. Excessive fructose intake has been implicated in obesity, cardiovascular disease, metabolic syndromes, inflammation, and cancer, among other disorders. This review discusses the absorption, distribution, and metabolism of fructose and the links between fructose metabolism and major metabolic pathways. The role of fructose in metabolic diseases, including metabolic dysfunction-associated fatty liver disease, hyperinsulinemia, and hyperuricemia, is also highlighted. Furthermore, the role of fructose in the development of chronic inflammation, including gut inflammation, liver inflammation, and neuroinflammation, is discussed. Lastly, in the context of cancer development, this review summarizes the dual role of fructose in tumors, both pro- and anti-tumor effects. Future studies on the role of fructose in cancer should focus on the complexity of physiological and pathological conditions, such as the specific tumor microenvironment and metabolic status. Fructose has been shown to induce metabolic reprogramming of multiple immune cells and increase pro-inflammatory immune responses; therefore, inhibiting or promoting its metabolism may regulate immune responses. And targeting fructose metabolism may be a promising approach to treating metabolic diseases, inflammation, and cancer.

Keywords Fructose, Fructose metabolism, Inflammation, Tumor metabolism, Glycolysis

Introduction

Humans have a natural preference for sweet foods, which induce strong sensory pleasure and can increase the chances of survival of individuals in extreme environments, leading to a stronger evolutionary advantage [1]. Fructose is the sweetest known hexose in nature, often considered a healthy sugar primarily owing to its low glycemic index and impact on blood glucose fluctuations [2, 3].

Moderate fructose consumption increases energy availability without significantly impacting insulin levels, making it a great long-term energy source, especially for physically active individuals [4]. Short-term or appropriate doses of fructose can help lower blood pressure and body mass index, improve glucose tolerance,

*Correspondence:
Wei Zhang
zwvivian111@126.com
Dunfang Zhang
izdf@163.com
[1] Department of Biotherapy, State Key Laboratory of Biotherapy and Cancer Center, Collaborative Innovation Center of Biotherapy, West China Hospital, Sichuan University, Sichuan, Chengdu 610041, China
[2] Center for Immunology and Hematology, Department of Biotherapy and Cancer Center and State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Sichuan, Chengdu 610041, China
[3] Laboratory of Microbiology and Immunology, Graduate School of Pharmaceutical Sciences, Chiba University, Chiba 260-8675, Japan

and be a valuable nutrient [5, 6]. However, extensive research has highlighted the hazards of fructose to human health. Indeed, high fructose intake can lead to obesity, metabolic disorders, and cardiovascular and cerebrovascular diseases [3, 7–11], and has been linked to inflammation, as excessive intake induces the secretion of various pro-inflammatory cytokines [12–14]. Also fructose is inextricably associated with cancer occurrence and development [7, 15, 16].

The increasing prevalence of metabolic disorders in modern society and their association with excessive fructose intake emphasize the importance of fructose in metabolic dysregulation [17–19]. Inflammatory diseases often coincide with metabolic disorders, illustrating the systemic effects of fructose on human health [12, 20]. Additionally, the emerging link between fructose and cancer biology, both beneficial and detrimental, has made fructose a hot research topic in oncological studies [21, 22]. Therefore, herein, we reviewed the recent research on fructose metabolism and its contribution to metabolic diseases and inflammatory responses, focusing on the association between fructose intake and cancer.

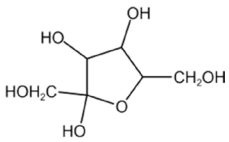
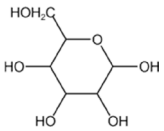
First, this review outlines the absorption, transportation, and metabolic pathways of fructose, highlighting its differences from glucose metabolism. Subsequently, it analyzes the mechanism underlying the role of fructose in metabolic disorders, such as obesity and metabolic dysfunction-associated fatty liver disease (MAFLD; also known as nonalcoholic fatty liver disease, NAFLD). This review also explores how fructose triggers systemic inflammation by disrupting the intestinal barrier and inducing endoplasmic reticulum (ER) and oxidative stress. This review provides insights into the dual role of fructose in cancer in promoting tumor cell proliferation and metabolic reprogramming and potentially potentiating immune anti-tumor responses under specific conditions. A summary of the current preventative strategies for fructose-related health risks and key directions for future research are finally proposed to provide a theoretical basis for the prevention and treatment of fructose-related diseases.

Fructose and fructose metabolism

Fructose, an isomer of glucose and the most common type of ketohexose, is found in high concentrations in honey, fruits, and vegetables. It combines with glucose in equal quantities to form sucrose, a major cyclic disaccharide in plants. In industrial food production, fructose is essential owing to its high sweetness, ease of storage, and low cost, hence, it is added to several beverages and manufactured foods as sugar in sucrose or high-fructose syrup to increase food palatability [23]. With the continuous increase in pre-made foods and drinks, the global consumption of fructose has significantly increased by an estimated 1,000% over the past 50 years [24].

The absorption and metabolism of fructose differ from those of glucose (Table 1). Glucose relies on transporter proteins such as Na^+- and glucose-linked transporter 1

Table 1 Metabolic differences between fructose and glucose

	Fructose	Glucose
Chemical Structure		
Absorption Pattern	Fructose is absorbed in the intestine via GLUT5, then transported to the liver by GLUT2 and possibly GLUT8	Glucose is absorbed in the intestine via SGLT1 and transported into the bloodstream by GLUT2
Initial Phosphorylation	Phosphorylated by Ketohexokinase to form fructose-1-phosphate	Phosphorylated by hexokinase to form glucose-6-phosphate
Key Enzyme	Ketohexokinase, Aldolase B	Hexokinase, Phosphofructokinase-1,
Rate-limiting Steps	Bypasses glucokinase and phosphofructokinase	Controlled by hexokinase and phosphofructokinase
Glycolysis	Directly catalyzed to glyceraldehyde 3-phosphate and dihydroxyacetone phosphate, thus entering glycolysis	Phosphorylated by hexokinase and enter glycolysis
TCA Cycle	Pyruvate from glycolysis enters the mitochondria, converted to acetyl-CoA, entering the TCA cycle	

GLUT5 glucose transporter 5, *GLUT2* glucose transporter 2, *GLUT8* glucose transporter 8, *SGLT1* Sodium-Glucose Cotransporter 1, *TCA Cycle* Tricarboxylic Acid Cycle, *Acetyl-CoA* Acetyl Coenzyme A

(SGLT1) for absorption active transport, whereas fructose primarily relies on glucose transporter 5 (GLUT5), which facilitates its absorption via passive diffusion [25]. The key rate-limiting enzymes involved in the metabolism of glucose and fructose also differ. This allows fructose to bypass some key rate-limiting steps and directly enter the metabolic pathways. The absorption and metabolism of glucose are strictly regulated, which makes glucose a stable source of energy, while the unregulated metabolic characteristics of fructose make it more likely to cause harm. The following sections provide an overview of fructose absorption, transport mechanisms, and metabolic pathways in different tissues.

Fructose absorption and transport

Typically, fructose concentration in human peripheral blood plasma is 0.04 mM. Following oral administration of large amounts of fructose (0.5 g/kg), serum fructose levels surge 50–100-fold [26–28]. Despite this initial spike, the body reaches fasting levels within 2 h [29–31] as fructose metabolism differs from that of glucose in that the site of fructose metabolism is centralized in the intestine and liver [32, 33]. Fructose was first believed to be metabolized primarily in the liver; however, fructose enters the intestine first and is passively transported across the cell membrane from the intestinal lumen into intestinal epithelial cells via GLUT5 (also known as hexose transporter receptor, SLC2A5) localized at the brush border of intestinal epithelial cells, highlighting the intestinal role in fructose metabolism. GLUT5, a fructose-specific transporter with a greater affinity for fructose than glucose, is important for the intestinal absorption of dietary fructose. *GLUT5*-deficient mice have approximately 90% lower serum fructose levels and 75% lower levels in the jejunum than their wild-type counterparts [34]. In hepatocytes, as GLUT5 is poorly expressed in the liver, it may not be the primary transporter of fructose; rather, GLUT2 may be [35, 36]. Additionally, GLUT8 has an affinity for fructose that may contribute to fructose transport in hepatocytes [37, 38].

Metabolism of fructose in specific organs or tissues

Fructose entering intestinal epithelial cells is phosphorylated by ketohexokinase (KHK) and converted into glucose, lactate, glycerate, and other organic acids [19]. Fructose-derived metabolites enter the liver via the portal vein [39]. If ingested at relatively low doses and rates of intake, fructose is readily cleared by the intestines [40]. However, on exceeding the intestinal absorption capacity, fructose reaches the liver, where it is metabolized [32, 41]. Reportedly, 90% of normal dietary fructose is processed primarily in the intestine [32, 42, 43]. However, if excess fructose is consumed, it will be transferred to the liver for metabolism [39, 44, 45]. Particularly, excess fructose is excreted from the intestinal epithelium via GLUT2 and enters the portal vein, reaching the liver [46]. In hepatocytes, fructose is first phosphorylated to fructose 1-phosphate by KHK, and this reaction is rapid and irreversible. The high affinity of KHK for fructose and the fact that KHK is not regulated by its end products or denaturation allows fructose to enter the liver for rapid extraction and metabolism, with negligible escape into circulation. Subsequently, fructose 1-phosphate is cleaved by aldolase B into dihydroxyacetone phosphate and glyceraldehyde (Fig. 1).

Shared similarities exist between the metabolisms of fructose in the intestine and liver; however, the ability of intestinal epithelium to metabolize fructose is very limited. Only GLUT5 transports fructose in the small intestine compared to the liver; the ability of GLUT5 to transport fructose is limited despite its increase in expression upon fructose intake [46, 47]. However, other proteins that transport fructose are expressed in the small intestine at much lower levels than GLUT5, yet are not regulated by fructose [37, 48]. Conversely, in the liver, the expression of proteins and enzymes associated with the transport and metabolism of fructose is high. In contrast, the small intestine is more inclined to rapidly translocate fructose than to metabolize it, and the expression of its associated proteins and enzymes is inducible. Considering the harmful effects of excess fructose, restricting fructose metabolism in the small intestine may be a potential protection strategy for intestinal cells [49, 50]. Therefore, the small intestine is the site of fructose transport and the initial site of metabolism, whereas the liver is the primary site of fructose metabolism. This strategy of different division of labor can be attributed to evolutionary selection.

In addition to the small intestine and liver, the remaining organs can also metabolize fructose. Indeed, previous studies have reported that the kidney can metabolize fructose [51, 52]. In healthy kidneys, the proximal tubule is the primary site of fructose metabolism, which takes up urinary fructose *via* GLUT5 and metabolizes it in the cytoplasm [53, 54]. Moreover, Na^+- and glucose-linked transporter 5 (SGLT5), expressed only in the kidney, is also an essential transporter protein for fructose reabsorption [55–57]. Notably, the kidney produces endogenous fructose, which characterizes the metabolism of this fructose as an important risk factor for kidney injury [54, 58, 59]. Along with the liver, intestine, and kidney, which metabolize most of fructose, adipose tissues and muscles can also metabolize the remaining fructose [60–62]. Adipocytes and muscles take up fructose through GLUT5; however, they metabolize fructose primarily with hexokinase [63, 64]. As fructose is metabolized in

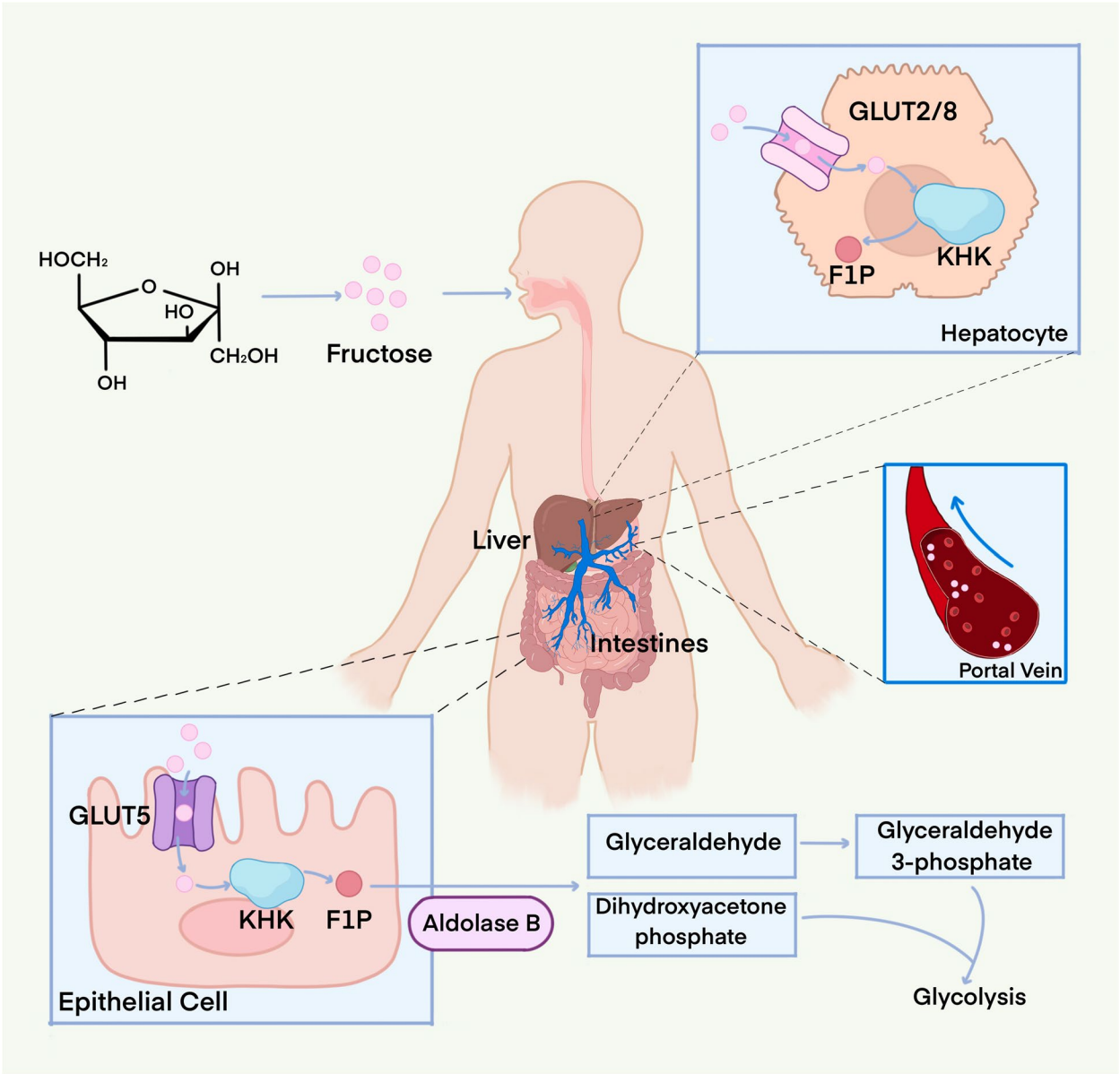


Fig. 1 Fructose metabolism. Fructose first enters the intestine and is passively transported from the intestinal lumen across the cell membrane to the intestinal epithelial cells by glucose transporter 5 (GLUT5). Excess fructose reaches the liver through the portal vein for further metabolism. After entering hepatocytes, glucose transporter protein 2/8 (GLUT2/8) facilitates the transport of fructose, which is rapidly phosphorylated by KHK to fructose 1-phosphate and further metabolized to glucose, lactate, glycerate, and other organic acids

various tissues or organs, excessive fructose intake can be harmful.

Fructose in relationship to central carbon metabolism

Fructose is mostly phosphorylated by fructokinase to generate fructose-1-phosphate, unlike glucose, which enters glycolysis via phosphorylation by hexokinase to form glucose-6-phosphate (Table 1). Consequently, fructose-derived glyceraldehyde and dihydroxyacetone phosphate bypass glucokinase and phosphofructokinase, the key rate-limiting enzymes, and enter the glycolysis/gluconeogenic carbon pool. Glyceraldehyde is catalyzed by glyceraldehyde kinase to form 3-phosphoglyceraldehyde, which enters the glycolytic pathway. In contrast, glyceraldehyde can form dihydroxyacetone phosphate catalyzed by alcohol dehydrogenase, glycerol kinase, and glycerol phosphate dehydrogenase. Dihydroxyacetone phosphate is then converted to 3-phosphoglyceraldehyde

by phosphoglycan isomerase and enters the glycolytic pathway.

The metabolic pathways are complex and overlap. Fructose is closely linked to glycolysis and impacts other metabolic pathways. For example, fructose-derived dihydroxyacetone phosphate or fructose-6-phosphate can enter the pentose phosphate pathway (PPP) through hexose phosphate isomerase [65]. Lodge et al. observed fructose labeled with C13 in PPP, specifically ribose-5-phosphate [66]. While ribose-5-phosphate and its derivatives can be used to synthesize DNA, RNA, and other important biomolecules, this shows the important role of fructose in the PPP.

Furthermore, fructose can be converted to glucose through gluconeogenesis, which occurs frequently in the kidneys [54, 67], maintaining glucose homeostasis. In contrast, glucose can be converted to fructose via the polyol pathway [68, 69]. This highlights the close relationship between fructose and glucose.

The complicated biochemical processes of fructose metabolism include intestinal absorption, liver transport, and integration into the central metabolic pathways [70]. Consuming fructose more than the body can digest induces metabolic disturbances. The liver is an essential organ for this process. Understanding these metabolic pathways and their health effects is essential, especially considering the increasing global fructose consumption.

Role of Fructose in metabolic diseases

Several studies have linked consuming large amounts of fructose to the development of obesity and metabolism-related diseases, such as abnormal lipid metabolism, MAFLD, and gout [71–77]. In this section, the review summarizes several metabolic diseases associated with fructose and briefly describe their causal mechanisms (Table 2 and Fig. 2).

Fructose consumption promotes obesity

The prevalence of obesity has been steadily increasing, with the same trend seen for the consumption of fructose, potentially linking fructose and obesity [2]. In a study, participants who consumed soda with high-fructose corn syrup for three weeks experienced notable weight gain, with similar outcomes observed with sucrose [86, 87]. These early studies used only mixtures containing fructose and ignored whether fructose alone had a corresponding effect. In later experiments, researchers realized that fructose did not appear to have a direct effect on weight [88–90]. In a recent test of sugary beverages involving 131 participants, those who consumed glucose and high-fructose corn syrup gained significantly more weight, whereas no significant difference was observed in weight among those who consumed only fructose [91]. These findings indicate that fructose did not cause weight gain under equal caloric intake [92] and may indirectly increase body weight by increasing energy intake [93]. In animal studies, long-term fructose intake induced leptin resistance, which, in turn, promoted energy intake and led to obesity [71, 94]. It has also been claimed that fructose intake reduces leptin concentrations but does not have a significant effect on weight [91]. In addition, fructose may also promote the survival of intestinal cells and increase the length of intestinal villi, which in part enhances nutrient absorption and contributes to obesity [95]. Interestingly, fructose mediates a survival switch in organisms that aids in storing energy when resources are lacking (similar to the state of animals preparing for hibernation) [93]. But in the present resource-rich world, this protective mechanism has harmed organisms. Thus, the obesity caused by fructose may not be a direct effect, but rather an indirect promotion of the energy intake of the body through other pathways.

Fructose impacts lipid metabolism and MAFLD

MAFLD, a chronic liver disease closely related to metabolic disorders, has become a major public health challenge, the risk of which can be significantly increased by high-fructose intake [78, 96, 97].

Enhanced de novo lipogenesis (DNL) is a major cause of MAFLD [98]. Fructose promotes DNL through several mechanisms. Fructose is metabolized in the liver to the DNL substrates dihydroxyacetone, phosphate, and glyceraldehyde. In the presence of α-phosphoglycerol dehydrogenase, dihydroxyacetone phosphate produces glycerol phosphate. The reduced glycerophosphate produces 1,2-diacylglycerol (DAG) through various enzymatic reactions.

In a process catalyzed by acyltransferases, DAG interacts with acyl-coenzyme A to form triacylglycerol (TAG), whose levels are associated with DNL [99, 100]. In contrast, TAG is involved in steatosis via binding to lipid droplets or in the formation of very low-density lipoprotein conjugates secreted from the liver into circulation. Glyceraldehyde is a fructose derivative phosphorylated to 3-phosphoglyceraldehyde by triphosphate kinases and enters the glycolytic process [19]. Following glycolysis, 3-phosphoglyceraldehyde is metabolized to pyruvate, which is then oxidized and decarboxylated by the pyruvate dehydrogenase complex to form acetyl-coenzyme A (acetyl-CoA). Under energy-deficient conditions, acetyl-CoA enters the tricarboxylic acid cycle (TCA cycle) and is metabolized to release energy. Under energetic conditions, acetyl-CoA acts as a substrate and participates in DNL. Acetyl-CoA can also be carboxylated to form malonyl-CoA, which inhibits the transfer of fatty acids from carnitine palmitoyl transferase (CPT1A) to mitochondria

Table 2 Summary of fructose-induced metabolic diseases

Studies	Species	Methods	Results
Lanaspa et al. [9]	Sprague–Dawley rats	15% fructose fed to rats for 10 days	Fructose induces fatty liver and is dependent on xanthine oxidase
Ouyang X et al. [78]	Humans	Dietary history and paired serum and liver tissues were compared between 49 patients with MAFLD and matched with samples from 24 normal individuals	Fructose intake was nearly 2- to threefold higher in patients with MAFLD than in controls
Stanhope et al. [79]	Humans	Participants received fructose-sweetened beverages for 10 weeks at an intake of 25% of energy requirements	In overweight/obese adults, dietary fructose specifically increases de novo lipogenesis (DNL), promotes dyslipidemia, reduces insulin sensitivity, and increases visceral fat
Galderisi et al. [80]	Humans	Participants received 75 g of glucose or fructose, and plasma was collected every 10 min for 60 min	After fructose intake, insulin and GLP-1 increased more in obese adolescents than in lean adolescents
Kyriazis et al. [81]	Mice	Mice were injected intravenously with fructose (1.0 g/kg) and monitored for plasma glucose and insulin	Fructose and glucose synergistically promote insulin release
Meeprom et al. [82]	Wistar rats	Rats were fed either a normal diet or a high-fructose diet for 8 weeks; the diet in two of the treatment groups was supplemented with either 0.5% or 1.0% grape seed extract	High-fructose diet reduces insulin receptor, IRS-1, Akt, GLUT4, and adiponectin, AdipoR1, AMPK-α mRNA in skeletal muscle, causing insulin resistance
Li et al. [83]	Sprague–Dawley rats	Rats were given normal drinking water or water contain 10% fructose for 8 weeks	Fructose-fed rats exhibit obesity, fasting hyperinsulinemia, and hyperleptinemia, but no fasting or postprandial hyperglycemia
Cabral et al. [84]	Sprague–Dawley Rats	Both groups of rats were fed 20% fructose in the drinking water for 14 days. One group was started on a high-salt diet (8% NaCl) after 7 days of fructose treatment	20% fructose in the diet and high salt synergistically contribute to higher blood pressure
Johnson et al. [85]	Humans	Researchers analyzed a previously published randomized controlled study that included 33 healthy male adults who ingested 200 g of fructose daily for 2 weeks	Fructose intake leads to increased serum UA levels, decreased serum ionized calcium, mildly increased PTH, decreased urinary pH, increased urinary oxalate and decreased urinary magnesium

MAFLD Metabolic dysfunction-associated fatty liver disease, *GLP-1* glucagon-like peptide-1, *IRS-1* insulin receptor substrate-1, *Akt* protein kinase B, *GLUT4* glucose transporter 4, *AdipoR1* adiponectin receptor R1, *AMPK* AMP-activated protein kinase, *UA* uric acid, *PTH* parathyroid hormone

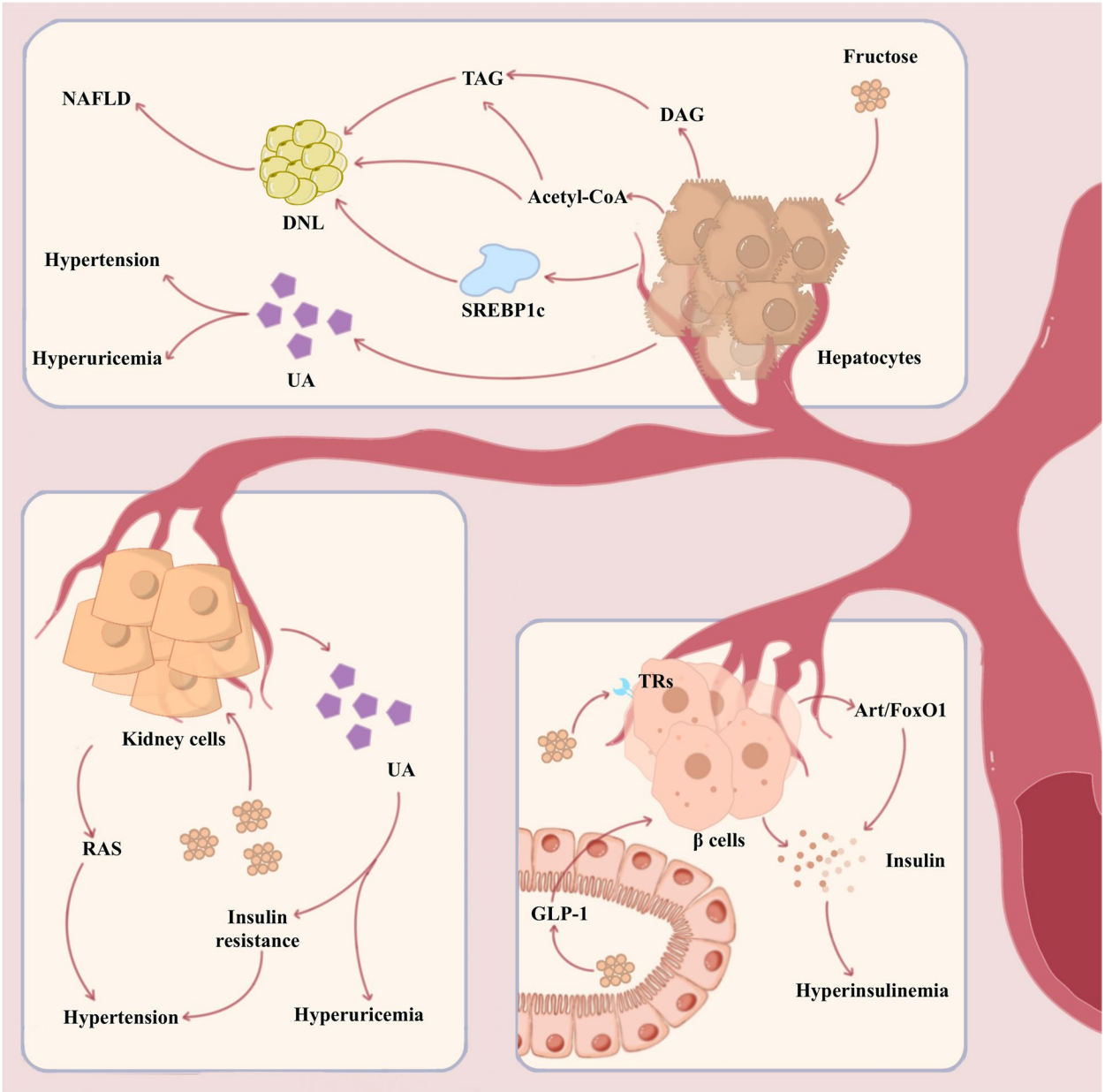


Fig. 2 Fructose metabolism in metabolic diseases. Fructose is metabolized in the liver to form 1,2-diacylglycerol (DAG) and triacylglycerol (TAG), which ultimately contribute to de novo lipogenesis (DNL), as does acetyl-coenzyme A (Acetyl-CoA). Fructose intake also activates a key transcription factor, sterol regulatory element binding protein 1c (SREBP1c), which increases DNL levels. Dysregulation of lipid metabolism in hepatocytes because of high fructose intake ultimately causes metabolic dysfunction-associated fatty liver disease (MAFLD). High intake of fructose also causes hyperinsulinemia and reduces insulin sensitivity. Indirectly, fructose stimulates the secretion of glucagon-like peptide-1 (GLP-1) from L-cells, leading to increased insulin secretion. Fructose activates sweet taste receptors (TRs) and the protein kinase B/forkhead box protein O1 (Akt/FoxO1) pathway on β-cells, stimulating insulin secretion. In addition, fructose causes liver and kidney cells to accumulate more uric acid (UA), leading to hyperuricemia. Fructose can also contribute to hypertension by affecting the renal renin–angiotensin–aldosterone system (RAS), as well as insulin resistance caused by elevated UA

for oxidation, increasing the fatty acid stocks available for TAG production [101].

In addition, fructose intake increases DNL levels by activating key transcription factors [102]. Sterol regulatory element-binding protein 1c (SREBP1c) is a regulator of adipose synthase, whose activity increases upon fructose intake. Dihydroxyacetone phosphate is a fructose metabolite that activates the mTORC1 pathway

and promotes SREBP1c activation [103]. However, SREBP1c is regulated at the transcriptional and post-translational levels by nutrients and hormones [19, 45]. In summary, fructose promotes DNL and is an important factor in MAFLD [17, 104, 105]. A high-fructose diet increases the rate of fasting DNL from 2 to 9% [106]. In abdominally obese men on a habitual diet for over 12 weeks, 75 g/day fructose intake significantly increased DNL in the fasting state and 4 to 8 h following a meal [107, 108]. Similarly, nine days of isocaloric fructose restriction as part of a normal diet resulted in a significant decrease in DNL in 37 of 40 children with obesity [109].

Fructose contributes to hyperinsulinemia and insulin resistance

Insulin regulates blood glucose levels, which are secreted by pancreatic beta cells [110]. When insulin is overproduced or not removed promptly, it may manifest as hyperinsulinemia [111–115]. Insulin resistance is defined as the inability of a given amount of insulin to promote normal glucose uptake and utilization and can also be understood as reduced sensitivity and responsiveness to insulin action [116, 117]. Studies have shown a strong link between hyperinsulinemia and insulin resistance, a precursor to the development of diabetes mellitus [118–120].

Insulin resistance co-occurs with hyperinsulinemia because of defective insulin action [119, 121]. Fructose intake can trigger hyperinsulinemia and insulin resistance [80, 122–124]. Indeed, high fructose intake reduces insulin sensitivity and glucose tolerance in rats [125, 126]. Fructose also directly activates sweet taste receptors on beta cells, promoting glucose-stimulated insulin secretion in humans and mice [81]. The authors also found that this mechanism only occurs in the presence of glucose, suggesting a synergistic interaction between fructose and glucose [81, 127]. However, fructose cannot directly promote insulin secretion because of the absence of GLUT5 in beta cells, and fructose intake stimulates glucagon-like peptide-1 (GLP-1) secretion via GLUT5-containing L-cells in the gut, thereby increasing insulin secretion, an effect more pronounced in individuals with obesity [80, 128, 129]. Furthermore, Li et al. found that fructose activates the protein kinase B/forkhead box protein O1 (Akt/FoxO1) pathway in beta cells, which mediates the action of leptin on beta cells and promotes insulin secretion [83, 130–132]. High fructose intake can reduce the expression of insulin receptors, insulin receptor substrate-1, protein kinase B (Akt), and glucose transporter 4 (GLUT4), directly inducing insulin resistance [133, 134]. Fructose intake also decreases mRNA expression of adiponectin, adiponectin receptor R1 (AdipoR1), and AMP-activated protein kinase (AMPK)-α [134, 135] and reduces adiponectin, which correlates with insulin sensitivity [82, 136, 137]. Evidently, fructose intake has persistent adverse effects in individuals with hyperinsulinemia [123].

Fructose causes hyperuricemia and hypertension

Uric acid (UA) is the end product of purine metabolism, not further degraded as the body lacks the enzyme uric acid oxidase [138–141]. Under normal conditions, UA acts as an antioxidant that provides several benefits [142–144]. However, an abnormal increase in UA can lead to hyperuricemia, negatively affecting human health [145–148]. Examples include fat accumulation and steatosis [149, 150]. Fructose intake is associated with elevated fasting UA levels [85, 151–153] because of the unique metabolic processes of fructose. After ingestion, fructose is rapidly extracted from the liver and phosphorylated to fructose 1-phosphate by KHK. This reaction is rapid, not controlled by negative feedback regulation, and consumes a large amount of adenosine triphosphate (ATP) in a short period [154]. ATP exhaustion is accompanied by a large production of adenosine monophosphate (AMP) [155, 156]. The large amount of AMP produced is catalyzed by adenosine deaminase, yielding hypoxanthine. Hypoxanthine is eventually hydrolyzed to UA by two oxidations of xanthine oxidase, which increases UA levels in the body. Fructose intake reduces water loss by stimulating pressin secretion, reducing urine volume [157]. Moreover, large amounts of UA produced by fructose metabolism are not readily excreted through the urine, elevating UA levels. Furthermore, fructose-induced insulin resistance increases UA levels by decreasing UA excretion and upregulating inflammation [158, 159].

Hypertension is an extremely complex disease with unclear predisposing factors [84, 160–162]. Although hypertension is a multifactorial disease, fructose intake may be an important factor in regulating hypertension [3, 163–166]. Previous findings indicated that fructose intake increased blood pressure compared to glucose intake, along with oxygen consumption and respiratory quotient [79, 167, 168]. One study showed that four weeks of continuous fructose feeding increased the mean arterial blood pressure in rats [169]. Similarly, another study reported that rats developed hypertension after three weeks of a fructose diet [170]. Furthermore, the offspring of rats exposed to a 60% high-fructose diet during pregnancy and lactation showed an increased risk of hypertension [171]. How does fructose increase blood pressure? Interestingly, fructose has been shown to regulate blood pressure through UA [3, 163, 172, 173]. Fructose intake can increase UA levels, which may cause endothelial dysfunction by contributing to insulin

resistance, which increases the risk of hypertension [174, 175]. UA can also stimulate the renal renin–angiotensin–aldosterone system, inducing the proliferation of vascular smooth cells and endothelial dysfunction [176]. For every 1 mg/dL increase in serum UA levels, the prevalence of hypertension increases by 13% [177]. Pharmacological intervention studies have shown that febuxostat, a xanthine oxidase inhibitor, prevents fructose-induced hypertension by reducing the UA levels [178, 179]. Furthermore, fructose increases blood pressure through several other pathways, such as sodium handling, activation of the renal sympathetic nervous system, and synergy with salt [72, 180–182].

Role of fructose in systemic chronic inflammation

Increased fructose intake is associated with several inflammatory diseases [183–185]. Fructose is metabolized and absorbed in various body parts, triggering an inflammatory response, including gut inflammation, liver inflammation, and neuroinflammation (Table 3 and Fig. 3) [186–189].

Excessive fructose intake leads to intestinal damage and inflammation

The gut, the body's largest barrier to the external environment, is important in protecting the organism from harm and the primary site of fructose absorption [196]. Excess fructose intake can cause intestinal barrier damage and endotoxemia [197–200]. Damage to the intestinal barrier increases the exposure to various metabolites, triggering an inflammatory response [201]. Excess fructose intake has also been shown to cause nitration of intestinal tight junction and adherent junction proteins, which can lead to an increased leaky gut [202, 203]. A large influx of antigens and other macromolecules into the barrier causes local or systemic inflammation [204, 205].

In addition, dysregulation of the gut microbiota promotes gut barrier damage and inflammatory responses [206]. The gut microbiota is the "second genome" and plays a significant role in the body's metabolism and immunity [190]. Tan et al. reported elevated levels of *Bacteroides*, *Akkermansia*, *Lactobacillus*, and *Ruminococcus* in the intestines of rats after fructose feeding, which may be associated with inflammation [190]. Similar studies have shown that a fructose diet increases the abundance of *Bacteroides*, *Bifidobacterium*, and *Marvinbryantia* [20, 198]. In contrast, one study showed that mice fed a high-fructose diet had a lower proportion of *Bacteroidetes* and an increased proportion of *Proteobacteria* [88]. Despite the differences between the results of previous studies, alterations in the gut microbiota do influence intestinal inflammation and damage to the intestinal barrier.

Metabolites of the gut microbiota, such as lipopolysaccharides (LPS) and short-chain fatty acids (SCFAs), are important signaling mediators [207]. Dysbiosis of the gut microbiota promotes the release of LPS (Parabacteroides is the main source of LPS), which in turn activates the Toll-like receptor 4 (TLR4) and exacerbates intestinal inflammation by inducing the release of pro-inflammatory cytokines [208–210]. At the same time, because of the altered intestinal permeability, LPS circulates through the portal vein to the liver and induces secretion of the inflammatory factor tumor necrosis factor-alpha (TNF-α) by activating TLR4 on macrophages [40, 211, 212]. SCFAs are important signaling molecules for metabolic and immune regulation [207, 213, 214]. Acetate, an SCFA, induces retinoic acid production in dendritic cells, which further promotes the intestinal IgA response and protects the gut from inflammatory damage [215–217]. Similarly, n-butyrate, another SCFA, induces intestinal macrophages to reduce the secretion of pro-inflammatory mediators such as nitric oxide (NO), interleukin-6 (IL-6), and IL-12 by inhibiting histone deacetylases [218, 219].

SCFAs also affect other immune cells in the gut. For example, Sun et al. demonstrated that SCFAs activate Th1 cell STAT3 and mTOR and upregulate transcription factor B lymphocyte-induced maturation protein 1 (Blimp-1), which can induce the production of IL-10 [220]. Notably, SCFAs can induce the differentiation of intestinal regulatory T cells, which maintain intestinal homeostasis [221–224]. Overall, SCFAs have a positive effect on gut homeostasis and immunity; however, fructose intake appears to reduce SCFAs in the gut [192]. And indirectly, fructose intake affects gut stability and induces inflammation.

Excessive fructose intake induces inflammation, resulting in liver injury

Excessive fructose intake leads to MAFLD and contributes to metabolic dysfunction-associated steatohepatitis (MASH), which may progress to liver fibrosis, cirrhosis, or even liver cancer [191, 225]. Recently, several studies have revealed fructose-induced inflammation in the liver [66, 226–229]; however, the induction mechanism is complex. Hepatocytes are particularly vulnerable to ER stress. A chronic fructose diet affects lipid metabolism and the production of very low-density lipoproteins, which leads to ER stress and the unfolded protein response (UPR). ER stress induces inflammation, oxidative stress, and apoptosis [230–232]. Oxidative stress induced by fructose can induce inflammation via the accumulation of oxygen reactive species (ROS) as it can activate some inflammatory pathways, including nuclear factor kappa B (NF-κB) and C-Jun amino terminal kinase

Table 3 Overview of fructose-induced inflammatory responses

Studies	Species	Methods	Results
Wang et al. [20]	Sprague–Dawley rats	Rats were administered pure fructose at a dose of 0, 2.6, 5.3, and 10.5 g/kg/day for 20 weeks	High intake of fructose increased UA, pro-inflammatory cytokines, intestinal permeability, and lipid accumulation in the liver and induced an inflammatory response in the pancreas and colon
Lodge et al. [66]	C57BL/6 J mice	Mice were supplemented with 30% fructose, glucose or no supplementation in their drinking water for 24 or 32 weeks	Chronic fructose exposure caused liver injury and increased anti-inflammatory and resolution associated genes in KC
Tan et al. [190]	Balb/c mice	Mice were fed either a high-fructose diet (60%), a high-fat (60 kcal%), or a normal diet for 8 weeks	Abnormalities in the intestinal structure were found in both the high-fructose and high-fat groups, and infiltration of inflammatory cells was observed
Seki et al. [191]	Fisher 344 rats	Rats were fed either CSAA diet + water, CDAA diet + water, and CDAA + water containing 20% fructose for 10 weeks	Fructose exacerbates liver fibrosis through increased intestinal permeability and contributes to the progression of MASH
Li et al. [192]	C57BL/6N mice	Mice were fed a standard diet (3.4 kcal/g) or a high-fructose diet (35% fructose-derived calories) for 4 or 8 weeks	High-fructose diet caused the hippocampal neuroinflammatory response, reactive gliosis, and neuronal loss in rats
Xu et al. [193]	ICR mice	Fructose-fed mice were given drinking water with 30% fructose solution and control mice were given normal drinking water for a total of 56 days	Fructose feeding induced hippocampal microglia activation with neuroinflammation through the activation of the TLR4/NF-κB signaling
Chen et al. [194]	ICR mice	Mice were given ordinary drinking water or 10% fructose solution for 8 weeks	The rats fed fructose showed a significant decrease in epithelial cell brush border and renal tubules, with tubulointerstitial infiltration primarily involving mononuclear cells and macrophages
Kovačević et al. [195]	Wistar rats	For 9 weeks, rats in the control group were fed standard food and drinking water, and rats in the fructose group were fed the same food and a 10% fructose solution	Rats fed fructose showed enhanced VAT mass, elevated nuclear accumulation of NF-κB, and elevated IL-1β expression, but not TNFα expression

KC Kupffer cells, *CSAA* choline-supplemented/L-amino acid, *CDAA* choline-deficient/L-amino acid, *MASH* Metabolic dysfunction-associated steatohepatitis, *TLR4* Toll-like receptor 4, *VAT* visceral adipose tissue, *NF-κB* nuclear transcription factor κB

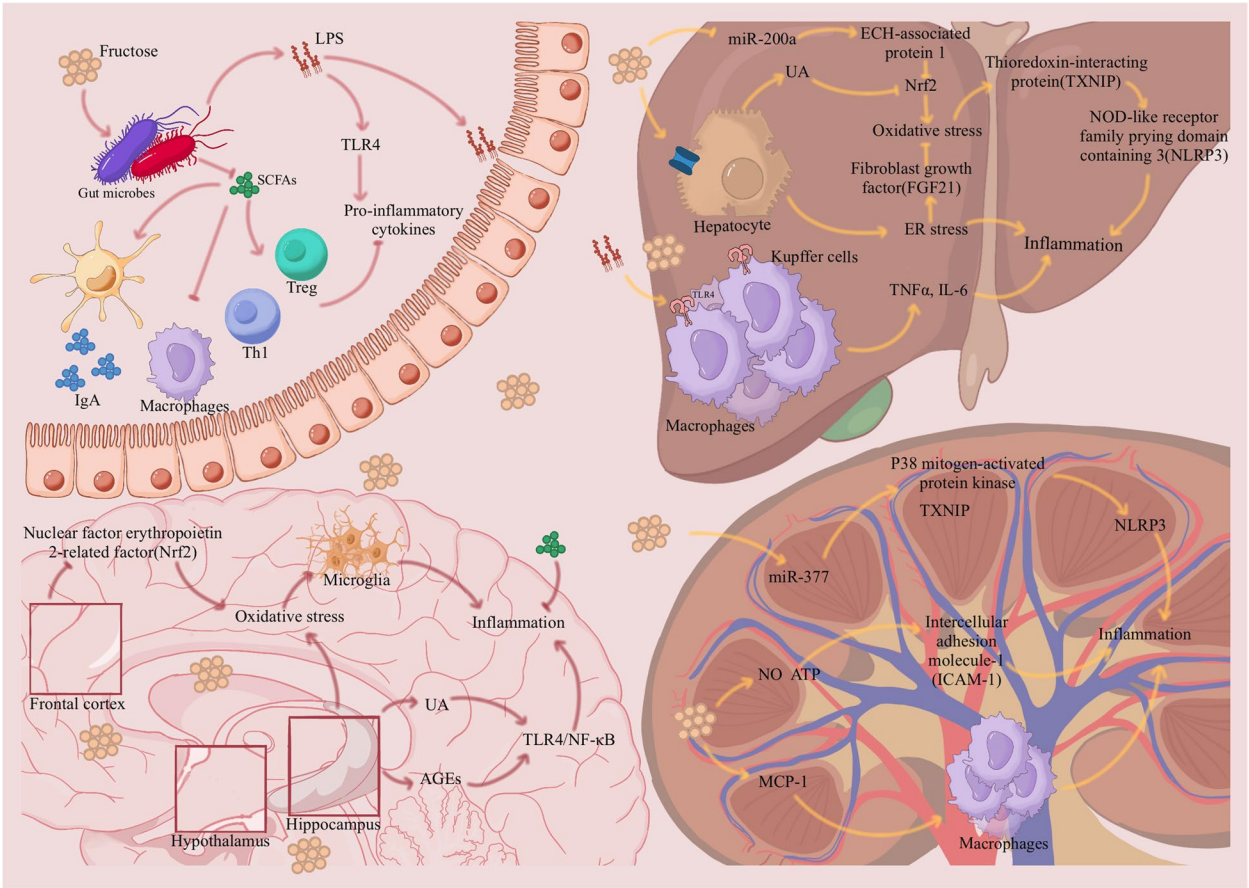


Fig. 3 Fructose promotes systemic chronic inflammation. High fructose intake leads to a leaky gut, which in turn induces an inflammatory response. Abnormal gut microbiology reduces the secretion of short-chain fatty acids (SCFA) and promotes the release of lipopolysaccharides (LPS), which further activates the Toll-like receptor 4 (TLR4), thereby mediating various inflammatory effects. In the liver, fructose induces oxidative stress and endoplasmic reticulum (ER) stress in hepatocytes, ultimately triggering inflammation, in a variety of ways, including by promoting uric acid (UA) accumulation, while fructose also activates secretion of inflammatory factors by hepatic macrophages. In addition, fructose intake results in elevated levels of UA and advanced glycation end products (AGEs) in mouse hippocampi, which in turn induces hippocampal inflammation via the TLR4/NF-κB pathway. Fructose also activates resident microglia and secretes inflammatory factors by causing oxidative stress in the brain. At the same time, SCFA relieves the inflammatory response in the brain. Fructose in the kidney ultimately mediates inflammation through elevated microRNA-377 (miR-377) and reduced nitric oxide (NO) and ATP levels while recruiting monocytes or macrophages by inducing monocyte chemotactic protein 1(MCP-1)

(JNK) [233, 234]. A high-fructose diet can inhibit the ER stress-induced production of fibroblast growth factor 21 (FGF21), reducing oxidative stress [235]. In addition to cellular stress, UA is an important inflammatory trigger [236]. UA in the liver contributes to oxidative stress and inflammation by inhibiting nuclear factor erythroid 2-related factor (Nrf2) and the production of thioredoxin, leading to the activation of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome [237, 238]. Furthermore, a more in-depth study showed that fructose intake reduced microRNA-200a (miR-200a), targeting Kelch-like ECH-associated protein 1 (Keap1) and inhibiting the Nrf2 antioxidant pathway, thereby triggering the thioredoxin-interacting protein (TXNIP)-activated NLRP3 inflammasome, ultimately inducing liver inflammation [239]. The liver also contains various macrophages, including Kupffer cells (KC) and other recruited monocytes or macrophages, which typically exhibit a pro-inflammatory phenotype [240–242]. It has also been reported that a fructose diet can activate TLR4 on KC, which elevates ROS, induces inflammation, and induces hepatocyte necrosis by increasing the expression of TNF-α and IL-6 [243–245]. This process may involve the fructose-induced increase in fatty acids, such as acylcarnitine and palmitate [245–248].

Fructose triggers neuroinflammatory responses in key brain regions

Fructose-induced inflammation has been widely reported in various tissues, including nervous tissue. Fructose-induced neuroinflammation has attracted attention [193, 249–251]. Cells in the brain can directly metabolize fructose; GLUT5 expression has been detected in the hippocampal microglia [252, 253]. The hippocampus, the memory center of the brain, is vital for learning and memory. Recent studies have found that excessive fructose intake damages hippocampal function [254, 255]. Indeed, excessive fructose intake blunts hippocampal plasticity and reduces hippocampal weight, which reflects functional changes in brain cells [256–260]. Fructose intake causes an increase in CLUT5 in the hippocampus of mice and an increase in UA levels; UA can induce hippocampal inflammation via the TLR4/NF-κB pathway [261, 262]. Additionally, accumulation of toxic compounds and advanced glycation end products (AGEs) because of fructose intake has been linked to inflammation [12, 263–265]. Mastrocola et al. reported that in mice fed a 60% fructose diet for 12 weeks, carboxymethyl lysine, an AGE that accumulates in hippocampal neurons, is induced and activates NF-κB signaling [266]. Fructose-induced hippocampal inflammation is associated with oxidative stress in the brain, which activates the resident microglia and secretes inflammatory factors [267–270]. Cigliano et al. found an increase in lipid peroxidation and nitro-tyrosine in the hippocampus of rats after 2 weeks of fructose feeding, suggesting the presence of oxidative stress damage. The author also detected an increase in TNF-α levels, with a positive correlation with oxidative stress [270]. Indirect mechanisms have also been reported in the hippocampus. Li et al. found that high fructose-induced intestinal dysregulation induces hippocampal neuroinflammation in mice, which can be alleviated by SCFA supplementation [192]. What is surprising is that excessive maternal fructose intake can damage the hippocampus of the offspring, an effect linked to reduced expression of the brain-derived neurotrophic factor (*BDNF*) gene [271].

In addition to the hippocampus, fructose-induced inflammation has also been observed in other brain parts. The hypothalamus, a component of the mesencephalon, is the center for regulating visceral and endocrine activity, where astrocytes play an important role. Inflammatory responses in this region cause various metabolic disorders [272–275].

Li et al. revealed that fructose intake induced hypothalamic astrocytosis and inflammation by activating the TLR4/NF-κB pathway, resulting in neurological damage in the hypothalamus [276]. Similarly, fructose-induced inflammatory responses have been observed in the frontal cortex. As the frontal cortex is the latest area of the brain to mature, its development is susceptible to dietary influences [277–280]. Indeed, a fructose diet for two weeks has been shown to negatively affect the nuclear factor (erythroid derived 2)-like 2 (Nrf2) pathway in the frontal cortex of rats, impairing the brain's antioxidant defense system and causing oxidative stress and synaptic dysfunction in the frontal cortex [281].

Inflammatory effects of fructose in other body parts

Fructose induces inflammation in various tissues and organs [206]. The kidney is primarily responsible for filtering impurities and metabolic waste from blood. Various studies have demonstrated a strong correlation among fructose intake, kidney damage, and inflammation [178, 194, 282–284]. Wang et al. showed that a fructose diet increased microRNA-377 (miR-377) expression in the kidney and miR-377-induced p38 mitogen-activated protein kinase phosphorylation and TXNIP expression, which in turn activated the NLRP3 inflammasome, ultimately leading to inflammation [285]. Another study showed that fructose induced the synthesis of monocyte chemotactic protein 1 (MCP-1), recruitment of monocytes or macrophages, and oxidative stress in proximal tubular cells; this effect depends on KHK [178, 286]. Furthermore, fructose-induced decreases in renal endothelial NO and ATP levels upregulates the inflammatory molecule intercellular adhesion molecule-1 (ICAM-1) expression [287].

Similarly, a comparable mechanism has been reported in adipocytes. Excessive fructose intake induces the expression of MCP-1 and ICAM-1 in adipocytes, leading to an increase in macrophage infiltration, further contributing to inflammation [287–289]. Furthermore, fructose increases leptin levels, inducing inflammation in adipocytes by releasing ROS [94, 290, 291]. Additionally, a fructose diet increases visceral adipose tissue mass, NF-κB accumulation, and elevated IL-β in rats [195]. A fructose-rich diet can also affect pancreatic islet cells, leading to hyperinsulinemia and insulin resistance. Moreover, fructose induces an inflammatory response in the pancreatic islet cells, and its intake increases the size and number of pancreatic islets; fructose-induced UA stimulates inflammatory mediators and oxidative stress in pancreatic islet cells [89, 292, 293].

Co-mechanisms of fructose in metabolic diseases or inflammation

Previous sections have detailed fructose's role in various metabolic diseases; the corresponding studies are summarized in Table 2. Although a direct causal relationship between fructose and obesity remains to be confirmed, it has been shown to play an important role in the

development of lipid metabolic disorders, MAFLD, and metabolic syndromes (including hyperinsulinemia, insulin resistance, hyperuricemia, and hypertension) (Fig. 2) [17, 91, 294, 295].

Hyperuricemia is a key contributor to various metabolic diseases. Fructose metabolism induces the production of uric acid, which directly causes gout, exacerbates insulin resistance, and participates as an inflammatory factor in the occurrence of MAFLD and hypertension [149, 179, 236].

Inflammation is an important mechanism via which fructose exposure leads to metabolic diseases. Excessive fructose can induce inflammatory responses in organs, such as the gut, liver, brain, and kidneys (Table 3). Activation of the TLR4/NF-κB pathway is a common mechanism of inflammatory responses. In the gut, fructose promotes intestinal flora dysregulation, increases LPS production, activates the TLR4/NF-κB pathway, and triggers intestinal inflammation [208, 210]. In the liver, factors such as disordered fructose metabolism, elevated uric acid, and fatty acid accumulation can activate TLR4 in KC, which in turn activates the NF-κB pathway and releases pro-inflammatory cytokines [244]. Similarly, in brain regions such as the hippocampus, the fructose metabolite UA can induce neuroinflammation through the TLR4/NF-κB pathway [261].

In conclusion, fructose plays a complex role in various metabolic diseases, with inflammation being an important contributing pathogenic mechanism. A deeper understanding of fructose metabolism and the inflammatory responses it triggers could help develop more effective strategies to prevent and treat related metabolic diseases. Further studies remain warranted to elucidate the mechanisms underlying fructose action in different organs and tissues and develop targeted interventions.

Complex relationship between fructose and cancer

The link between fructose and tumor has also attracted extensive attention in recent years. Long-term high fructose consumption is implicated in a range of cancers, and its role varies depending on the type of cancers [296–298]. This section collects epidemiological evidence on the relationship between fructose and tumors and discusses the role of fructose in tumor development.

Epidemiological studies on high-fructose diets and cancer risk

Excessive fructose intake is linked to various metabolic disorders, as confirmed by epidemiological studies [299–301]. The relationship between fructose and cancer has been a research focus. A previous investigation included approximately 1.2 million participants and over 3000 pancreatic cancer cases to investigate the relationship between fructose, carbohydrates, glycemic index, and pancreatic cancer risk [302]. The authors revealed for the first time the links between fructose intake and pancreatic cancer risk [302]. Another study investigated the relationship between fructose from diet and colorectal cancer and reported a higher incidence of colorectal cancer among those consuming fructose at higher levels [303]. Likewise, a 12-year epidemiological study involving a cohort of Canadian women reported that a high intake of sugar-sweetened beverages was associated with a significantly elevated risk of endometrial and ovarian cancer [304]. Although the authors did not specifically identify fructose, most sugary drinks contain fructose as an ingredient. Fructose also appears to be associated with poor patient prognosis. For example, a study analyzed the relationship between the intake of different types of carbohydrates and breast cancer-specific mortality in patients diagnosed with breast cancer [305]. The data from 8,932 breast cancer patients followed for more than a decade showed a highly significant positive association between higher fructose intake and the risk of breast cancer-specific mortality [305].

Nevertheless, not all studies have reported a positive association between fructose and cancer risk. For instance, in a survey of 3,184 adults aged 26–84 years, no significant correlation was found between fructose intake and the incidence of obesity-related cancers, nor an association with the risk of any site-specific cancer [306]. Following the same trend, a meta-analysis pooled multiple prospective cohort studies and found that while excessive total sugar and fructose intake were associated with all-cause and cardiovascular disease mortality, no association was found with cancer mortality [307].

These conflicting results highlight the degree of complexity in the fructose-cancer relationship. Fructose significantly influences people's diets, and its effects may vary based on age, geography, or dietary habits. [303, 304, 306]. Conversely, fructose may involve multiple mechanisms in its effects on cancer in the body.

Role of fructose in tumors

Fructose plays complex and diverse roles in tumors (Table 4 and Fig. 4). Tumor metabolism favors aerobic glycolysis, a process through which ample energy is supplied to the tumor to support the rapid proliferation of tumor cells.

Several intermediates produced during glycolysis can act as biomolecule synthesis precursors for the rapid expansion and metastasis of tumor cells. Tumor metabolism is highly plastic, enabling the utilization of available carbon sources to adapt to nutrient-stressed environments [157, 308, 309]. Abnormalities in glycolytic metabolism may disturb glucose levels in the tumor

Table 4 Complex role of fructose in tumor development

Studies	Role in tumors	Specific Mechanism
Jeong S et al. [16]	Directly Promotion	High fructose enhances SSP, increasing α-ketoglutarate production, which supports leukemia cell proliferation
Goncalves MD et al. [21]	Directly Promotion	Fructose promotes glycolysis and DNL, increasing fatty acid synthesis for tumor cell growth
Bu P et al. [22]	Directly Promotion	Upregulated aldolase B enhances fructose metabolism, promoting liver metastasis of colorectal cancer
Taylor S R et al. [95]	Indirectly Promotion	Fructose improves intestinal cell survival and increases the length of intestinal villi. The increase in the length of intestinal villi enlarged the surface area of the mouse intestines, which increased the rate of nutrient absorption and thus promoted tumor growth
Kuehm LM et al. [313]	Indirectly Promotion	Melanoma tumors in mice on the high-fructose diet were resistant to immunotherapy and showed increased expression of the cytoprotective enzyme HO-1
Fowle-Grider R [314]	Indirectly Promotion	fructose supplementation increases circulating nutrients such as LPCs, which can enhance tumor growth through a cell non-autonomous mechanism
Yan H et al. [315]	Indirectly Promotion	Fructose inhibits M1 macrophage polarization, reducing anti-tumor activity by altering calcium ion signaling
Chen WL et al. [316]	Directly Promotion	AML cells are prone to fructose utilization with an upregulated fructose transporter GLUT5, which compensates for glucose deficiency
Fang J H et al. [298]	Directly Promotion	Fructose activates AMPK, enhancing tumor angiogenesis and growth in liver cancer
Kang Y L et al. [317]	Directly Promotion	Polyol pathway increases endogenous fructose, activating KHK-A and inducing epithelial-mesenchymal transition, promoting cancer metastasis
Zhang Y et al. [318]	Inhibition	Fructose activates mTORC1 in adipocytes, inducing leptin, which enhances $CD8^+$ T cell anti-tumor activity
Dewdney B et al. [319]	Inhibition	Fructose promotes apoptosis and inhibits proliferation of hepatoma cells

SSP the serine synthesis pathway, *DNL* de novo lipogenesis, *HO-1* heme oxygenase-1, *LPCs* lysophosphatidylcholines, *AML* acute myeloid leukemia, *GLUT5* glucose transporter 5, *AMPK* AMP-activated protein kinase, *KHK-A* ketohexokinase-A, *mTORC1* mTOR Complex 1

microenvironment. Fructose is a potential alternative carbon source that tumor cells use to maintain metabolism. After simple metabolism, fructose metabolites can directly enter glycolysis and bypass the key rate-limiting step of glycolytic phosphofructokinase to satisfy the demand for energy and biomolecule synthesis substrates in tumor cells and facilitate tumorigenesis and development. Under specific conditions, fructose can be phosphorylated to fructose 6-phosphate by hexokinase and directly enter glycolysis [16, 310]. Similar to glucose, fructose affects the survival, growth, and proliferation of tumor cells [311, 312].

The indirect tumor-promoting effect of fructose

Excessive fructose intake is associated with the development of gastrointestinal cancers and drives tumor growth and metastasis in mice with colorectal cancer [21, 22, 320–322]. Dietary fructose positively affects the survival and nutrient absorption of small intestinal cells in mice. Feeding mice with high-fructose syrup for four weeks increased the length of the small intestinal villi by 15–40%, increased the relative surface area of the intestine, improved nutrient absorption, and significantly increased body weight. The growth of mouse small intestinal villi is attributed to the extraction and metabolism of fructose by intestinal epithelial cells, which is rapidly converted to fructose 1-phosphate by KHK. In mice, fructose 1-phosphate was found to inhibit pyruvate kinase M2 activity—which protects intestinal epithelial cells—and promoted small intestinal epithelial cell survival, which ultimately increases intestinal tumor load [95]. A high-fructose diet upregulates heme oxygenase-1 (HO-1) expression, which makes mouse melanoma immune checkpoint inhibitor treatment resistant, and the use of HO-1 small-molecule inhibitors is effective in alleviating resistance [313].

In addition, fructose supplementation increases the amount of nutrients in the blood, which supports tumor development. According to a recently published study [314]. Because tumor cells lack the necessary enzymes to directly metabolize fructose, they are therefore less likely to use fructose for nutrition. The liver metabolizes most excess fructose. In co-culture studies, hepatocytes were found to have transformed fructose carbon into nutrients, which promoted the growth of cancer cells. The most noticeable alteration was observed in lysophosphatidylcholines (LPCs), in which cancer cells ingested and utilized phosphatidylcholine, the primary phospholipid found in cell membranes. Additionally, high-fructose corn syrup feeding in animal studies increases the number of LPC species in the blood of mice. These results imply that fructose indirectly stimulates tumor growth by increasing the levels of nutrients such as LPC in the blood.

Moreover, fructose may indirectly promote tumor growth by affecting the polarization of relevant immune

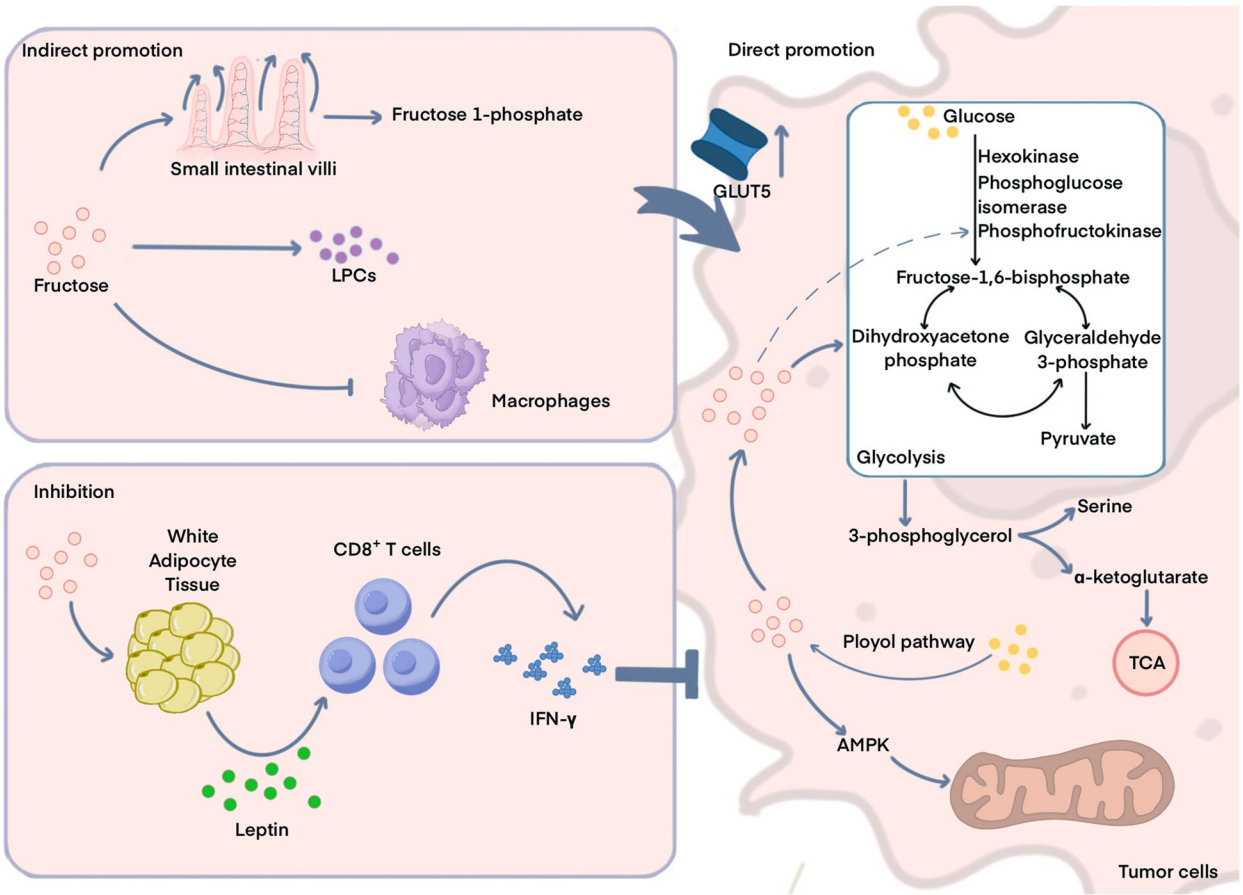


Fig. 4 The dual role of fructose in cancer. The relationship between fructose and cancer is complex. Fructose promotes the growth of small intestinal villi, enhancing their absorption capacity. Fructose is rapidly converted to fructose 1-phosphate by ketohexokinase (KHK), and upregulates the expression of glucose transporter 5 (GLUT5). In addition, the metabolism of fructose through the liver leads to a large increase in circulating nutrients such as lysophosphatidylcholines (LPCs). These processes indirectly provide appropriate substrates for central carbon metabolism during tumor proliferation, and fructose also inhibits the polarization of tumor-associated macrophages, further promoting tumor growth. Because of the special metabolic process of fructose, fructose enhances tumor metabolism through glycolysis, the serine synthesis pathway, polyol pathway and so on. fructose also enhances the function of mitochondria through the AMP-activated protein kinase (AMPK) after absorbed by tumor cells, and enhances fatty acid synthesis by up-regulating the expression of glucose transporter 5 (GLUT5). These processes will directly promote tumor growth. On the contrary, fructose can induce adipocytes to secrete leptin, which can act on $CD8^+$ T cells and enhance the anti-tumor activity of $CD8^+$ T cells

cells. Fructose also promotes cancer cell growth by affecting the polarization of tumor-associated macrophages (TAMs) [315]. The interaction between hexokinase 2 and inositol-1,4,5-trisphosphate receptor 3 was improved by fructose treatment. This, in turn, affects intracellular calcium ion flow and signaling and finally inhibits the polarization of M1-type macrophages, which are known to have anti-tumor capabilities, thereby indirectly promoting the development of cancer.

The direct tumor-promoting effect of fructose

Some tumor cells upregulate the transcription of the GLUT5-encoding gene SLC2A5 to increase fructose utilization. Acute myeloid leukemia (AML) is metabolically characterized by SLC2A5-mediated high fructose utilization, which correlates with patient prognosis. The use of the small-molecule drug 2,5-anhydro-D-mannitol to block fructose transmembrane transport in a mouse AML model resulted in a significant improvement in leukemia symptoms and prolonged the survival of mice. The use of fructose transmembrane transport blockers in AML cells cultured in vitro were found to have significantly inhibited malignant proliferation and infiltration of cancer cells [316]. Glioma cell lines show high levels of GLUT5 expression, and the upregulation of GLUT5 expression in the glioma tissues of patients is usually associated with poor prognosis. Under glucose-poor culture conditions, the survival and proliferation of glioma

cells (in vitro cultures) were found to be promoted by upregulating GLUT5 expression [323]. The glioma cell line LN229 was used to study subcutaneous tumor formation in mice fed 15% fructose water. The results showed that mice administered fructose water had larger tumor volumes and smaller foci of tumor necrosis. However, the knockdown of GLUT5 in LN229 cells was followed by the inoculation of mice with tumors, and mice in the fructose-fed group did not show any of these conditions [323]. The authors of the study reported that the analysis of clinical samples revealed that the expression of the fructose transporter proteins GLUT5 and GLUT9 was upregulated in patients with prostate cancer, and that their serum fructose levels were higher than those in normal subjects. In another study, fructose treatment of in vitro cultured prostate cancer cells PC3 revealed that fructose promoted the proliferation and invasion of prostate cancer cells. Based on the transcriptome analysis of the PC3 cell line, fructose activates the proliferation-related pathway of prostate cancer cells and up-regulates the expression of transforming growth factor-β, wingless-type MMTV integration site family-4, and other genes; the authors concluded that fructose-fed prostate cancer cell xenograft tumor model mice promotes prostate tumor growth and proliferation [324]. In addition, fructose accelerates lung cancer cell growth in vivo by upregulating GLUT5 protein expression and inhibiting AMPK, which activates mTORC1 activity and promotes fatty acid synthesis and palmitoleic acid production [325].

KHK, a key enzyme in fructose metabolism, is involved in fructose utilization by glioma cells and promotes tumor progression. Analysis of clinical samples revealed that high KHK expression was associated with poor prognosis. Silencing KHK in glioma cells significantly inhibited their proliferation and migration. Glioma cells cultured in fructose medium for four weeks show upregulated *KHK* gene expression, increased protein stability, and upregulated KHK expression, which accelerated the malignant progression of tumors [326].

In primary hepatocellular carcinoma, the downregulation of aldolase B expression correlates with increased tumor aggressiveness and is usually associated with poor prognosis. Stable expression of aldolase B in primary hepatocellular carcinoma promotes the expression of DNA demethylase Ten-Eleven Translocation 1, which reduces the migratory ability of hepatocellular carcinoma cells in vitro and their metastatic potential in vivo [327]. In contrast, in colorectal cancer liver metastasis, aldolase B expression is upregulated and fructose metabolism is enhanced, allowing colorectal cancer cells to rapidly adapt to the high-fructose environment of the liver. Enhanced fructose metabolism increases gluconeogenesis, glycolysis, and the pentose phosphate pathway, which provides the corresponding substrates for central carbon metabolism during tumor proliferation and promotes the growth of metastatic liver tumors from colorectal cancer. Targeting aldolase B or its upstream regulator GATA6 may be effective, and reducing fructose intake is important for controlling liver metastasis [22].

In a study by Goncalves et al. an intestinal tumorigenesis model using adenomatous polyposis coli mutant mice ($APC^{-/-}$ mice) that were administered by gavage high-fructose syrup water equivalent to the daily dose of one can of soda consumed by a human. Eight weeks later, $APC^{-/-}$ mice did not show a significant increase in body weight, but they had an increased tumor load. This is most likely because daily intake of high-fructose syrup creates a high-fructose environment in the intestinal lumen of mice. Excessive fructose is metabolized through the consumption of a large amount of ATP, and low levels of ATP activate phosphofructokinase, which increases glucose metabolism flux and directs fatty acid synthesis. Fatty acids are important for tumor growth and are biomolecular substrates used by tumor cells to synthesize cytosolic or signaling molecules. The authors of the study concluded that fructose promotes intestinal tumorigenesis in mice by promoting glycolysis and DNL [21].

Serine is an essential nutrient specific to tumor cells, and the serine synthesis pathway (SSP) is important for tumor metabolism. In SSP, 3-phosphoglycerol derived from glycolysis is converted to serine by various enzymes to provide the metabolic precursors for one-carbon metabolism [328]. Meanwhile, α-ketoglutarate produced during SSP enters the TCA cycle, providing substrates for nucleotide synthesis and to maintain redox balance among tumor cells [328–332]. High fructose levels can drive SSP in AML cells and exacerbate tumor burden. Acute myeloid leukemia cells are more SSP-dependent in high-fructose environments. These cells mediate their proliferation in the presence of glucose deficiency by upregulating SSP flux and producing α-ketoglutarate from glutamine. Targeting the rate-limiting enzyme phosphoglycerol dehydrogenase in SSP in a high-fructose environment significantly reduced tumor load and slowed leukemia progression in mice [16]. Moreover, fructose promotes mitochondrial respiration by activating AMPK, which increases the proliferation and migration capacity of tumor endothelial cells and promotes tumor angiogenesis, growth, and metastasis in hepatocellular carcinoma xenografts and Myc/sgp53-induced hepatocellular carcinoma mouse models [298]. An SLC2A5 inhibitor was hsown to have effectively inhibited fructose-induced tumor angiogenesis and suppresses tumor growth in mice [298].

The polyol pathway facilitates the production of endogenous fructose. Glucose is reduced to sorbitol by

NADPH and aldose reductase. Sorbitol is oxidized by NAD^+ and catalyzed by sorbitol dehydrogenase to produce endogenous fructose and NADH [333]. Endogenous fructose production coupled with KHK, which is commonly highly expressed in tumors, bypasses the rate-limiting step in glycolysis and rapidly meets the energy and substrate requirements of tumor cell growth, thereby promoting tumor cell growth. Schwab et al. reported a direct correlation between the polyol pathway activity and tumor development [334]. Aldo–keto reductase family 1 member B1 (AKR1B1) encodes a specific member of the Aldo–keto reductase superfamily that catalyzes the reduction of glucose to sorbitol and has an important role in the polyol pathway [335]. AKR1BA is associated with epithelial mesenchymal transition in lung cancer patient samples. Inhibition of epithelial-to-mesenchymal transition was found to occur after in vitro knockdown of AKR1B1 in mesenchymal-like cancer cells [334]. There is a link between the polyol pathway and gastric cancer progression. In gastric cancer cell lines, hyperglycemia induces endogenous fructose formation by increasing the flux of the polyol pathway, which in turn activates the KHK-A signaling pathway and inhibits CDH1 expression, thus inducing epithelial mesenchymal transition and promoting gastric cancer metastasis [317].

When taken together, fructose induces metabolic stress in tumor cells, leading to metabolic reprogramming. Fructose promotes tumor development mainly by upregulating the expression of the fructose transporter, GLUT5, and metabolism-related enzymes to meet the energy and substrate requirements of tumors. The metabolic reprogramming of tumor cells increases fructose metabolism, glycolysis, DNL, and polyol pathway fluxes through multiple pathways, providing synthetic precursors for tumor development, regulating functional gene expression, and promoting tumor progression [336, 337]. Thus, the fructose transporter protein GLUT5 or the key enzymes of fructose metabolism, KHK and aldolase B, are potential targets for anticancer treatment.

The tumor-suppressing effect of fructose

Although the mainstream view among researchers is that fructose promotes cancer, some epidemiological studies have shown that fructose is protective against oral and lung cancers in men, and against lung and ovarian cancers in women [318, 321, 338]. Recently, Zou et al. published their latest research on fructose and tumors [318]. In contrast to the generally held view, the authors reported that that fructose inhibited tumor growth and induced leptin secretion from adipocytes by activating mTORC1 in white adipose tissue cells. Adipocyte-derived leptin acts on $CD8^+$ T cells to enhance the anti-tumor activity of $CD8^+$ T cells to control transplanted lung tumors. Transcriptome analysis of $CD8^+$ T cells revealed that tumor-infiltrating $CD8^+$ T cells in high-fructose-fed mice were predominantly early stage $CD8^+$ T cells, whereas tumor-infiltrating $CD8^+$ T cells in fructose-free control mice were predominantly exhausted. Therefore, fructose treatment can reduce the number of exhausted $CD8^+$ T cells, downregulate the overall exhaustion rate of $CD8^+$ T cells, and increase the proliferation rate and IFN-γ production of $CD8^+$ T cells, thereby achieving anti-tumor effects (Fig. 4) [318]. Currently, it is not clear how fructose and leptin inhibit $CD8^+$ T cell exhaustion. One possible mechanism is that fructose and leptin reorganize T cell metabolism and maintain T cell stemness. Moreover, the in-depth mechanism of the fructose-leptin axis in the regulation of the tumor immune microenvironment and its application in tumor immunotherapy warrant further study. In addition to fighting tumors by regulating the immune microenvironment, fructose was found to significantly inhibit the proliferation of cultured hepatoma cells Huh7 and promote cell apoptosis [319], indicating that fructose may have a direct anti-tumor function in some tumors.

Given the positive role of fructose in $CD8^+$ T cell-mediated antitumor immunity, the use of fructose as a nutritional supplement or in combination of fructose supplementation with adoptive T cell therapy may be a promising avenue for cancer treatment. However, further clinical evidence is still required to determine whether this effect occurs in humans. In addition to affecting adipocyte metabolism, the direct role of fructose in regulating T-cell metabolism and function has not yet been identified. When considering the opposing effects of fructose on tumors, fructose may exert different regulatory effects on different tumors. Therefore, the complex regulatory mechanisms of fructose in specific tumors and the tumor immune microenvironment require further investigation.

Therapeutic modulation of fructose metabolism

In modern society, human consumption of fructose is increasing, and the adverse effects of fructose on humans are becoming increasingly clear. Today, regulating the metabolism of fructose has become a key area in the investigation of metabolic diseases and inflammation, and is a highly promising field for cancer treatment.

Intervention of fructose metabolism through the GLUT5-KHK axis

GLUT5 expression is linked with numerous metabolic syndromes and tumors. GLUT5 inhibition lowers the total fructose in the body, which may have beneficial implications in slowing metabolic disorders, reducing inflammation, and even interfering with tumor

development [339, 340]. Only a few GLUT5 inhibitors are currently available; one study yielded a small molecule inhibitor, N-[4-(methylsulfonyl)−2-nitrophenyl]−1,3-benzodioxol-5-amine (MSNBA), which blocks fructose uptake by specifically binding to the fructose site of GLUT5 [341]. Identifying it may aid in studying fructose and its related health issues.

KHK is a crucial enzyme in the metabolism of fructose and the first to act on it. KHK catalyzes the conversion of fructose to fructose 1-phosphate, and hence is a very vital target for controlling the metabolism of fructose. KHK inhibition markedly decreases hepatic fat deposition, enhances glucose tolerance, and reverses MAFLD [342–344]. Recently, the synthesis of the inhibitors of KHK has been accomplished; one such inhibitor, PF-06835919, has drawn much interest [345]. In a phase 2 randomized clinical trial, 300 mg of PF-06835919 reduced the whole liver fat mass in MAFLD patients and inflammatory markers. This offers a novel therapeutic approach for managing metabolic disorders caused by fructose and inflammatory reactions [346]. Other efficient KHK inhibitors have also been reported; however, clinical studies remain warranted to test these drugs [347]. KHK expression in several tumor cells is abnormally high, and fructose can drive tumor growth and metastasis through the activity of KHK [297, 310, 348]. This suggests that targeting KHK may be a potential cancer treatment strategy.

Intervention of fructose metabolism through modulation of gut microbes

Fructose is directly linked to gut flora dysbiosis. Fructose feeding has been shown to modify the gut flora composition to induce an inflammatory response and metabolic abnormalities; regulating the gut microbiota to correct fructose metabolism may counteract fructose-induced illness [349–351]. Broad-spectrum antibiotics can suppress the hippocampal neuro-inflammation in fructose-fed mice by regulating gut microbiota; however, the effectiveness of antibiotics needs to be verified through more definitive studies, considering their safe use in humans [192]. Certain natural antioxidants isolated from plants and animals have therapeutic properties. For instance, the water extract of *Lycium ruthenicum* Murray ameliorates neuroinflammation and cognitive deficits induced by a high-fructose diet by modifying the gut-liver-brain axis. Furthermore, it can alter the composition of the intestinal microbiota, increasing the abundance of beneficial bacteria [352]. Anthocyanins from *Lycium ruthenicum* Murray can effectively reduce the ecological dysbiosis of the intestinal microbiota and preserve the integrity of the intestinal barrier, lowering neuroinflammation caused by a high-fructose diet in rats [353].

Individuals seem to respond more readily to the therapeutic advantages of these bioactive compounds than to antibiotics. These substances exhibit significant biological activities, particularly antioxidant activities, and have numerous health benefits, in addition to their role in treating fructose-induced disorders. Furthermore, most of these compounds are safe and nontoxic; therefore, developing therapeutic drugs based on these biologically active substances is promising. Current research on reversing and preventing the side effects of fructose is still limited because of unclear mechanisms and the complexity of its effects, particularly in targeted therapy.

Conclusion and future perspectives

Fructose, the sweetest hexose in nature, is a popular additive in processed foods and beverages, the metabolism of which plays a key role in the response of organisms to extreme environmental conditions (such as food, water, and oxygen shortages). Fructose is metabolized differently from glucose, leading to its rapid absorption in the liver. However, high consumption of fructose is frequently linked to obesity and several metabolic disorders, particularly in nations experiencing greater economic development and greater access to processed foods [7]. The relationship between fructose and obesity remains debatable: some studies suggest that fructose directly causes obesity, whereas others indicate that fructose does not appear to have a direct impact on obesity [86, 92]. The intricacy of fructose metabolism in the body is reflected in this side, and further research is necessary to determine whether fructose induces obesity directly. Also, the triggers of metabolic diseases are extremely complex and involve various biological processes, such as dysregulation of adipose synthesis, activation of specific cellular receptors, and aberrant expression of related pathways (Fig. 2). Although several studies have revealed that fructose can induce a wide range of metabolic diseases, including MAFLD, hyperinsulinemia, hyperuricemia, and hypertension, the underlying mechanisms remain obscure and require further investigations. Because of different experimental conditions and testing standards, conflicting views exist among researchers [26, 354–357]; therefore, when investigating the connection between metabolic diseases and fructose consumption, the association must be confirmed from various aspects.

Moreover, inflammation is a detrimental effect of fructose, with substantial evidence indicating that excessive fructose intake drives inflammatory effects via various mechanisms (Fig. 3). In the intestine, fructose damages the intestinal barrier and causes dysbiosis of the intestinal bacterial flora, directly or indirectly, inducing inflammatory responses [201, 206]. When fructose enters the liver, it induces ER and oxidative stress in liver cells,

activating relevant inflammatory pathways [232]. Macrophages in the liver are negatively affected by fructose. Indeed, excessive fructose intake induces an inflammatory response in the brain, affecting the hippocampus, hypothalamus, and parts of the cerebral cortex. Additionally, fructose induces a systemic inflammatory response, and its harmful effects cannot be ignored. Therefore, future research should focus on the latent targets of these induction mechanisms to identify relevant therapeutic approaches.

Fructose increases tumor risk (Table 4). Tumor cells exhibit abnormally high glycolytic metabolic activity and rapidly consume glucose [309]. Fructose is the second most abundant blood sugar in the body, and a high-quality alternative carbon source for tumor cells to support survival and growth when glucose is scarce [310]. Fructose provides energy for tumor cells and biomolecular precursors for tumor cell proliferation by increasing the flux of glycolysis, the PPP, and the polyol pathway. Even if tumor cells do not directly metabolize fructose, they still produce large amounts of circulating nutrients through liver cells to promote tumor growth. In turn, fructose affects anti-tumor-related immune cells to promote tumor development.

However, a recent study has confirmed that fructose promotes cancer by demonstrating that fructose enhances the anti-tumor response of $CD8^+$ T cells by promoting leptin secretion from adipocytes (Fig. 4) [318]. Currently, it appears that the effect of fructose on tumor cells is a "double-edged sword." Research on the role of fructose should be based on the specific tumor microenvironment involved in fructose metabolism, tumor metabolism, and other complex and precise regulatory mechanisms.

Multilevel targeted fructose metabolism or targeted fructose metabolism in combination with current chemotherapeutic and immunosuppressive drugs may provide novel cancer treatments. Current research on the role of fructose in tumors tends to focus on metabolic changes in tumor cells in a high-fructose environment, whereas research on the influence of fructose on immune cells in the tumor microenvironment is scarce. Future research should explore the metabolic and behavioral changes in immune cells in the tumor microenvironment in a high-fructose environment. Several studies investigating the effects of fructose on the immune cells indicate that fructose induces metabolic reprogramming of multiple immune cells and increases immune cell inflammation. Whether future cell therapies can specifically target immune cells to deliver fructose and enhance the anti-tumor activity of immune cells remains to be determined.

Preliminary studies on intervention strategies for fructose-induced diseases have been conducted. GLUT5 is the primary fructose transporter. Although targeting it has therapeutic potential, GLUT5 has several physiological roles; therefore, side effects associated with blocking its expression must be considered. The effectiveness of PF-06835919, a small-molecule inhibitor of KHK, has been demonstrated in clinical trials, the results of which confirmed the therapeutic utility in targeting KHK [358]. However, KHK with aberrantly high-level expression in cancer is KHK-A and not KHK-C, indicating that the development of KHK inhibitors must address the problem of selectivity to mitigate side effects [310]. In regulating gut microbiota, the exploration and application of biologically active substances have attracted interest. These substances might offer numerous undiscovered advantages for humans, with alleviating fructose-induced diseases being just one of many effects. Therefore, this class of substances has great potential for future drug development. In addition, substances that modulate the gut microbiota (e.g., probiotics and prebiotics) may have similar effects and should, therefore, be explored [11]. Interventions targeting the gut microbiome may need to consider differences among various populations. [349]. Overall, intervention via fructose metabolism requires targeting multiple pathways and individualized approaches. However, more simply, reducing fructose intake may be the most straightforward strategy.

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Authors' contributions
Z.L. drafted the manuscript. X.F. drafted part of the manuscript. F.G., S.P., X.M., H.C. and H.N. edited the manuscript. W.Z. edited and revised the manuscript. D.Z. supervised the work and edited the manuscript. All the authors contributed to the work and approved the manuscript for publication.

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Declarations

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