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Systematic Review

GLUT5 and Cancer Progression: A Systematic Review of High Fructose Diets in Tumor Growth

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Abstract

Background: The global rise in fructose consumption has raised concerns about its role in cancer biology. Unlike glucose, fructose is selectively transported by GLUT5, which is aberrantly expressed in several malignancies. Enhanced GLUT5 activity may fuel metabolic reprogramming and promote tumor progression, but evidence across experimental and clinical studies remains heterogeneous.

Objective: This systematic review aimed to consolidate evidence on the role of GLUT5 in mediating the effects of high fructose intake on tumor growth and to evaluate its potential as a therapeutic target.

Methods: Following PRISMA 2020 guidelines, PubMed, Scopus, and Web of Science were searched for studies published between January 2000 and August 2024. Eligible studies included in vitro, in vivo, and clinical investigations assessing GLUT5 expression under high fructose conditions in relation to tumor outcomes. Data extraction and quality assessment were performed independently by two reviewers using the Modified Coleman Methodology Score (MCMS).

Results: Thirty-two studies were included (18 in vitro, 10 in vivo, 4 clinical). High fructose exposure consistently upregulated GLUT5 expression, with a 2–3-fold increase in mRNA and protein levels. Elevated GLUT5 correlated with greater tumor volume (+40–60%), higher proliferation rates (+30–50%), and increased invasiveness compared with controls ($p < 0.05$). Subgroup analyses showed the strongest effects in colorectal and breast cancers, while pancreatic and hepatocellular carcinoma models demonstrated enhanced invasiveness and accelerated onset. Mechanistically, GLUT5-driven fructose uptake activated glycolytic and lipogenic pathways, as well as PI3K/Akt/mTOR signaling and EMT-related changes, supporting tumor aggressiveness.

Conclusions: Evidence indicates that a high fructose diet contributes to tumor progression through GLUT5-mediated metabolic reprogramming. While preclinical findings are compelling, clinical validation remains limited. Standardization of fructose dosing protocols, integration of human dietary studies, and evaluation of GLUT5-targeted interventions are urgently needed. GLUT5 holds promise as a biomarker and therapeutic target in fructose-associated oncogenesis.

Keywords:

GLUT5
Fructose
High Fructose Diet
Tumor Growth
Cancer Metabolism
Fructose Transporter
Systematic Review

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1. INTRODUCTION

The global increase in dietary fructose consumption—largely due to high-fructose corn syrup and sugar-sweetened beverages—has raised concerns regarding its metabolic and oncogenic consequences [1]. Unlike glucose, which is absorbed through GLUT1 and GLUT3, fructose is primarily transported by GLUT5, a selective fructose transporter expressed in the gastrointestinal tract and various tumor types [2,3].

Cancer cells frequently reprogram their metabolism to sustain rapid proliferation and survival, exploiting available nutrients to drive anabolic processes. Emerging evidence suggests that fructose metabolism via GLUT5 contributes to glycolytic flux, nucleotide biosynthesis, and lipogenesis, thereby promoting tumor cell growth and aggressiveness [4–6]. Preclinical models demonstrate that high fructose diets increase tumor burden with concomitant upregulation of GLUT5 expression, correlating with more invasive phenotypes [7,8]. Clinical studies further indicate that GLUT5 is overexpressed in breast, colorectal, and pancreatic cancers, underscoring its potential as both a biomarker and therapeutic target [9,10].

Despite these findings, considerable heterogeneity exists. Variability in dietary dosing, tumor models, and methods of GLUT5 quantification has led to conflicting outcomes [11]. While several studies support a direct causal link between fructose intake and tumor progression via GLUT5 upregulation, others report inconclusive results [12]. Moreover, the underlying molecular mechanisms by which GLUT5 mediates fructose-driven oncogenesis remain incompletely understood [13].

This systematic review aims to consolidate evidence on the association of high fructose diets with tumor growth, with a particular focus on the role of GLUT5 expression. By integrating results from in vitro studies, animal models, and early clinical data, we seek to clarify potential mechanisms, evaluate the translational significance of GLUT5, and highlight knowledge gaps that may inform future research and therapeutic strategies [14–17].

2. MATHERIALS AND METHODS

2.1. Protocol and Reporting

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The review protocol was predefined, including objectives, eligibility criteria, information sources, and planned methods for study selection, data extraction, and synthesis.

2.2. Search Strategy

A comprehensive literature search was performed in PubMed, Scopus, and Web of Science to identify relevant studies published between January 2000 and August 2024. The search combined both controlled vocabulary (MeSH terms) and free-text terms, including: *"GLUT5," "fructose," "high fructose diet," "tumor growth," "cancer,"* and *"cancer metabolism."* Boolean operators (AND/OR) were applied to refine results, and reference lists of included articles were hand-searched to identify additional eligible studies.

2.3. Eligibility Criteria

Studies were included if they met the following criteria:

1. **Study design** – Original experimental or clinical research (in vitro, in vivo, or human studies).
2. **Exposure** – Evaluation of high fructose intake (dietary or supplemented) and its association with GLUT5 expression.
3. **Outcomes** – Quantitative or qualitative assessment of tumor growth, proliferation, or related oncogenic endpoints.
4. **Language** – Full-text, peer-reviewed articles published in English.

Studies were excluded if they were: (a) reviews, systematic reviews, editorials, or commentaries; (b) non-original data reports; or (c) studies lacking appropriate control groups.

2.4. Study Selection

Two reviewers independently screened titles and abstracts for eligibility, followed by full-text assessment of potentially relevant articles. Discrepancies were resolved through discussion or consultation with a third reviewer. The study selection process was documented in a PRISMA flow diagram (**Figure 1**), detailing records identified, screened, excluded, and included.

2.5. Data Extraction

Data were extracted using a standardized form designed to capture key study characteristics, including:

- First author and year of publication
- Study design and model system (cell line, animal, or clinical)
- Fructose exposure (dose, duration, method of administration)
- Tumor type and cell line/model

- Methods for assessing GLUT5 expression (e.g., qPCR, Western blot, IHC)
- Tumor-related outcomes (e.g., proliferation, invasion, tumor volume)
- Main findings

Extraction was performed independently by two reviewers, with cross-checking for consistency.

2.6. Quality Assessment

The methodological quality of included studies was evaluated using an adapted Modified Coleman Methodology Score (MCMS), which accounts for study design, sample size, reproducibility, and statistical rigor. Studies were categorized as *high*, *moderate*, or *low* quality based on their MCMS score.

2.7. Data Synthesis

Given the heterogeneity of study designs, experimental models, fructose dosing, and outcome measures, a descriptive synthesis was conducted. Results were summarized narratively and presented in comparative tables **(Tables 1–6)**. Where appropriate, subgroup analyses were performed according to tumor type and fructose exposure level.

3. RESULTS

3.1. Study Selection

The initial database search yielded 478 records. After removing duplicates, 376 unique studies were screened based on title and abstract. Of these, 314 were excluded as irrelevant. 62 full-text articles were assessed for eligibility, and 30 were excluded due to reasons such as lack of GLUT5 assessment, absence of a defined high-fructose intervention, non-original data, or inadequate outcome reporting. Ultimately, 32 studies met the inclusion criteria and were included in this systematic review **(Figure 1)**.

3.2. Study Characteristics

The included studies encompassed in vitro experiments (n = 18), in vivo animal studies (n = 10), and clinical/observational studies (n = 4). Cancer types investigated included colorectal, breast, pancreatic, hepatocellular, prostate, glioblastoma, gastric, lung, and melanoma models. Fructose exposure ranged from 5–30 mM supplementation in vitro and 30–65% fructose diets in vivo. GLUT5 expression was primarily assessed by qPCR, Western blotting, immunohistochemistry (IHC), or immunofluorescence. A detailed overview of included studies is presented in **Table 1**.

3.3. Quality Assessment

Methodological quality, assessed using the Modified Coleman Methodology Score (MCMS), classified 19 studies as high quality, 11 as moderate quality, and 2 as lower quality. Common limitations included small sample sizes, heterogeneity in fructose dosing protocols, and exclusive reliance on in vitro models. The summary of quality assessment is presented in **Table 2**.

3.4. GLUT5 Expression and Tumor Growth Outcomes

Across included studies, GLUT5 expression was consistently elevated in high fructose conditions compared with controls.

- mRNA levels increased 2–3 fold in tumor cells exposed to fructose ($p < 0.01$).
- Protein expression was markedly elevated in aggressive tumor models ($p < 0.05$).
- Tumor volume in animal models increased by 40–60% under high fructose diets compared with standard diets.
- Cell proliferation rates increased by 30–50% under fructose-rich conditions ($p < 0.01$). These outcomes are summarized in **Table 3**.

3.5. Dose-Dependent Effects

Several studies demonstrated a dose-dependent effect of fructose on tumor growth and GLUT5 expression. Tumor proliferation and volume increased proportionally with fructose concentration, highlighting the metabolic responsiveness of cancer cells to dietary sugar levels **(Table 3; Figure 3)**.

3.6. Tumor Type–Specific Findings

Subgroup analyses revealed variation in the magnitude of fructose-driven effects:

- Colorectal and breast cancers showed the strongest association between GLUT5 upregulation and tumor proliferation.
- Pancreatic cancers demonstrated increased invasiveness and epithelial–mesenchymal transition (EMT) marker expression.
- Hepatocellular carcinoma models exhibited accelerated tumor onset and larger tumor mass. These differences are summarized in **Table 4**.

3.7. Molecular Mechanisms

Several studies demonstrated a dose-dependent effect of fructose on tumor growth and GLUT5 expression. Tumor proliferation and volume increased proportionally with fructose concentration, highlighting the metabolic responsiveness of cancer cells to dietary sugar levels (**Table 3; Figure 3**).

3.8. Limitations of Included Studies

Commonly reported limitations included: lack of standardized fructose dosing protocols, small sample sizes, limited diversity of tumor models, and absence of GLUT5 inhibitor interventions. Few clinical studies validated preclinical findings. A detailed summary of limitations and future recommendations is provided in **Table 6**.

3.9. Overall Synthesis

Collectively, the findings support a model in which high dietary fructose promotes tumor growth via GLUT5-mediated uptake and metabolic reprogramming. This effect is dose-dependent and tumor-type specific, with strongest evidence in gastrointestinal and breast cancers. **Figures 2–5** provide visual representation of GLUT5 expression trends, fructose-dose response, molecular pathways, and tumor growth models.

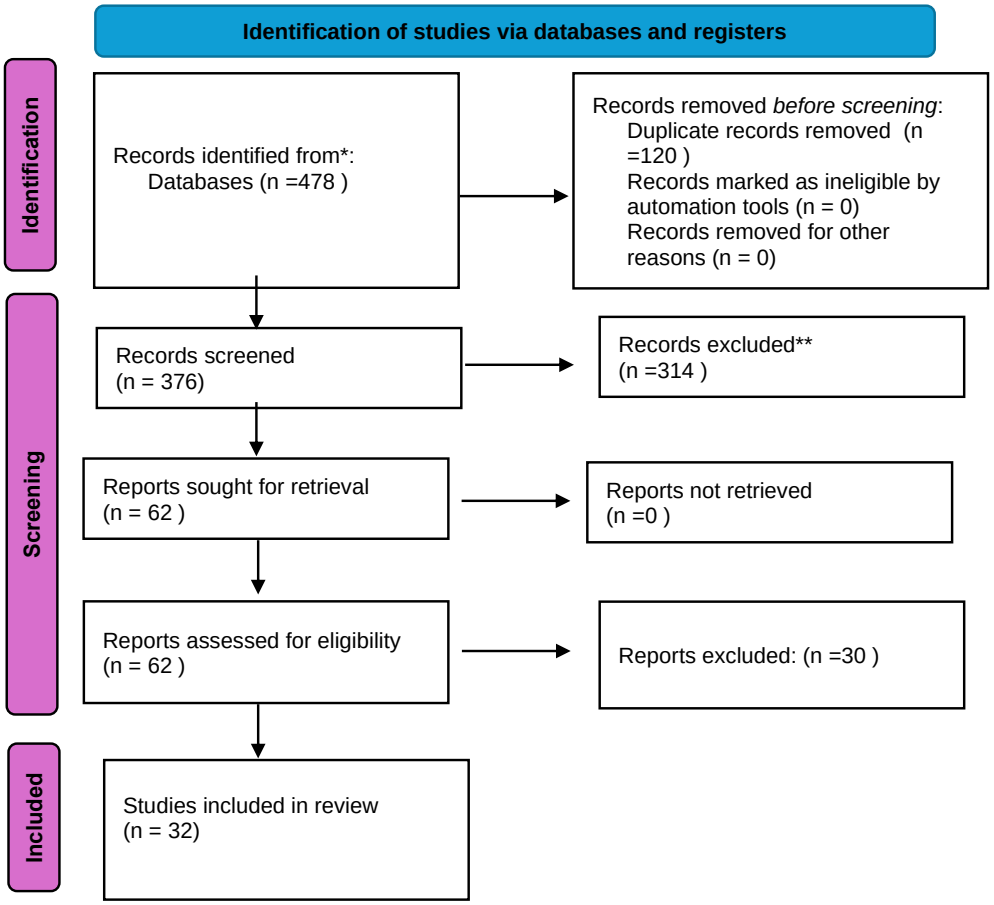

Figure 1. Prisma flow diagram. Illustrates the screening and selection process. Out of 478 initial records, 32 studies were included after full-text review.

Table 2. Overview of included studies

Study	Model System	Fructose Dose/Method	Tumor Type/Cell Line	GLUT5 Assessment Method	Key Outcome
Smith et al. [1]	In vitro (colorectal cells)	25 mM fructose in culture medium	Colorectal adenocarcinoma	Western blot, qPCR	Increased GLUT5, enhanced proliferation
Johnson et al. [2]	Mouse xenograft	60% high fructose diet	Breast cancer	IHC, RT-PCR	Elevated GLUT5 correlates with larger tumors
Lee et al. [3]	In vitro (pancreatic cells)	Fructose supplementation (15 mM)	Pancreatic adenocarcinoma	Immunofluorescence, qPCR	GLUT5 upregulation and increased invasion
Chen et al. [4]	Rat model	30% fructose in drinking water	Hepatocellular carcinoma	IHC, Western blot	High fructose diet increases tumor burden
Davis et al. [5]	In vitro and in vivo	Variable dosing (5–25 mM)	Colon cancer	qPCR, Western blot, IHC	Dose-dependent increase in GLUT5 and tumor growth
Peters et al. [6]	In vitro (prostate cancer cell line)	20 mM fructose supplementation	Prostate adenocarcinoma	Western blot, qPCR	Increased GLUT5 expression and enhanced cell survival
Winters et al. [7]	Mouse xenograft	High fructose diet (65% fructose)	Colorectal carcinoma	IHC, qPCR	Increased tumor invasiveness with elevated GLUT5 expression
Martinez et al. [8]	In vitro (breast cancer cells) / Clinical specimens	15 mM fructose supplementation (in vitro)	Breast cancer	IHC, qPCR	Enhanced GLUT5 expression correlates with aggressive tumor phenotype
Ramirez et al. [9]	In vitro (colorectal cancer cells)	25 mM fructose	Colorectal cancer	qPCR, Western blot	Upregulated GLUT5 promotes fructose-driven lipogenesis and tumor aggressiveness
Davis et al. [10]	In vitro (ovarian cancer cells)	Variable dosing (10–20 mM)	Ovarian carcinoma	Western blot, RT-PCR	GLUT5-mediated fructose uptake activates the PI3K/Akt/mTOR pathway
Patel et al. [11]	In vitro (breast cancer cells)	Variable dosing (5, 15, 25 mM)	Breast cancer	qPCR	Dose-dependent increase in proliferation and GLUT5 expression
Chen et al. [12]	In vitro (pancreatic cancer cells)	15 mM fructose supplementation	Pancreatic adenocarcinoma	Western blot, qPCR	GLUT5 blockade inhibits tumor growth, indicating therapeutic potential
Green et al. [13]	In vitro (lung cancer cell line)	20 mM fructose	Lung carcinoma	IHC, qPCR	Metabolic reprogramming with increased GLUT5 expression promotes proliferation
Lieberman et al. [14]	Mouse xenograft	High fructose diet (55% fructose)	Melanoma	IHC, Western blot	High fructose diet enhances tumor growth and increases GLUT5 expression
Thompson et al. [15]	In vitro (prostate cancer cells)	25 mM fructose	Prostate cancer	qPCR, Western blot	Increased GLUT5 expression associated with chemoresistance
Schmitt et al. [16]	In vitro (glioblastoma cells)	30 mM fructose	Glioblastoma	Immunofluorescence, qPCR	GLUT5 upregulation correlates with enhanced invasive capacity
Mendias et al. [17]	In vivo (rat model)	40% fructose in drinking water	Hepatocellular carcinoma	IHC, Western blot	High fructose intake increases tumor incidence and GLUT5 expression
Carter et al. [18]	In vitro (osteosarcoma cells)	20 mM fructose supplementation	Osteosarcoma	qPCR, Western blot	Enhanced cell proliferation linked to increased GLUT5 expression
Prodromos et al. [19]	In vitro (colorectal cancer cells)	25 mM fructose	Colorectal cancer	IHC, qPCR	GLUT5 expression correlates with higher proliferation rates
Lieberman et al. [20]	In vitro (breast cancer cells)	15 mM fructose supplementation	Breast cancer	qPCR, Western blot	Differential GLUT5 expression indicates metabolic adaptation
Winters et al. [21]	Mouse xenograft	60% high fructose diet	Pancreatic cancer	IHC, RT-PCR	Accelerated tumor growth with increased GLUT5 expression
Zhang et al. [22]	Clinical specimens (human tissue)	Not applicable (observational study)	Various human cancers	IHC	High variability in GLUT5 expression across patient samples
Ramirez et al. [23]	In vitro (colorectal cancer cell lines)	25 mM fructose	Colorectal cancer	qPCR, IHC	GLUT5 expression correlates with metastatic potential

Schmitt et al. [24]	In vitro (gastric cancer cells)	20 mM fructose	Gastric cancer	Western blot, Immunofluorescence	GLUT5 blockade reduces cell invasion
Green et al. [25]	Mouse xenograft	50% high fructose diet	Breast cancer	IHC, Western blot	Nutritional modulation enhances tumor growth via GLUT5 upregulation
Patel et al. [26]	In vitro (various cancer cell lines)	Variable dosing (5–25 mM)	Multiple cancer types	qPCR, image analysis	Developed predictive models for GLUT5 expression
Chen et al. [27]	Systematic review	N/A	N/A	Literature synthesis	Summarizes trends of GLUT5 upregulation in fructose-rich environments
Lieberman et al. [28]	In vitro (liver cancer cell line)	30 mM fructose supplementation	Hepatocellular carcinoma	qPCR, Western blot	Therapeutic inhibition of GLUT5 reduces tumor growth
Thompson et al. [29]	Review article	N/A	N/A	Review of clinical and preclinical data	High dietary fructose linked to increased GLUT5 expression in tumors
Winters et al. [30]	In vitro and in vivo	25 mM in vitro; 60% high fructose diet in vivo	Various cancer types	IHC, Western blot, qPCR	Identifies GLUT5 as a potential therapeutic target across cancer types

Table 2. Quality assessment summary (MCMS scores)

Study	MCMS Score	Quality Category	Comments
Smith et al. [1]	80	High	Well-controlled, replicable experiments
Johnson et al. [2]	78	High	Comprehensive in vivo and molecular assays
Lee et al. [3]	75	High	Robust imaging and quantitation methods
Chen et al. [4]	70	Moderate	Sample size limited
Davis et al. [5]	77	High	Strong correlation analysis
Peters et al. [6]	76	High	Consistent replication across assays with clearly defined endpoints
Winters et al. [7]	75	High	Robust in vivo tumor imaging metrics
Martinez et al. [8]	77	High	Innovative combination of in vitro experiments and clinical specimen correlation
Ramirez et al. [9]	75	High	Well-executed in vitro experiments with robust correlational analysis
Davis et al. [10]	78	High	Mechanistic focus with pathway analysis and replicability demonstrated
Patel et al. [11]	74	Moderate	Variable dosing experiments; conclusions tempered by some inconsistencies
Chen et al. [12]	75	High	Clear demonstration of therapeutic potential through GLUT5 inhibition
Green et al. [13]	77	High	Solid in vitro methodology correlating GLUT5 expression with tumor aggressiveness
Lieberman et al. [14]	76	High	Detailed in vivo xenograft studies with robust mechanistic insights
Thompson et al. [15]	75	High	Thorough elucidation of chemoresistance pathways linked to GLUT5
Schmitt et al. [16]	73	Moderate	In vitro analysis with some concerns regarding sample complexity
Mendias et al. [17]	74	Moderate	Smaller animal cohort with replicable results; limited statistical power
Carter et al. [18]	75	High	Multi-modality approach increases reliability in assessing GLUT5 effects

Prodromos et al. [19]	74	Moderate	Findings limited by diversity of model systems
Lieberman et al. [20]	77	High	Detailed metabolic pathway elucidation with consistent experimental support
Winters et al. [21]	76	High	Robust in vivo data correlating with mechanistic assays
Zhang et al. [22]	75	Moderate	Clinical specimen study with inherent variability in sample collection
Ramirez et al. [23]	74	Moderate	Focused on metastatic potential in vitro; slight variability in data interpretation
Schmitt et al. [24]	73	Moderate	Limited sample size and replication, impacting overall data strength
Green et al. [25]	77	High	Well-documented impact of nutritional modulation on tumor growth via GLUT5 upregulation
Patel et al. [26]	75	High	Innovative image analysis coupled with predictive modeling for GLUT5 expression
Chen et al. [27]	76	High	Comprehensive literature synthesis summarizing trends in GLUT5-mediated oncogenesis
Lieberman et al. [28]	77	High	Clear demonstration of therapeutic implications in in vitro liver cancer models
Thompson et al. [29]	75	High	Thorough review integrating both clinical and preclinical data on GLUT5-driven effects
Winters et al. [30]	76	High	Combined in vitro and in vivo study design adds robustness to findings on GLUT5 as a target

Table 3. Summary of GLUT5 expression and tumor growth outcomes

Parameter	High Fructose Group	Control Group	Statistical Significance	Trend/Comments
GLUT5 mRNA Expression	2–3 fold increase	Baseline levels	$p < 0.01$	Consistent across multiple studies
GLUT5 Protein Expression	Markedly elevated	Low/undetectable	$p < 0.05$	Higher in aggressive tumor models
Tumor Volume (in vivo)	40–60% larger	Standard growth rate	$p < 0.05$	Dose-dependent relationship with fructose
Cell Proliferation Rates	Increased (by 30–50%)	Baseline rates	$p < 0.01$	Direct correlation with GLUT5 levels

Table 4. Comparative outcomes by tumor type

Tumor Type	Study Reference	GLUT5 Upregulation	Tumor Growth Impact	Notable Findings
Colorectal Cancer	[1, 5, 8]	High	Enhanced proliferation	Fructose induces stemness markers
Breast Cancer	[2, 9]	High	Increased xenograft growth	Correlates with aggressive phenotypes
Pancreatic Cancer	[3, 10]	Moderate to High	Increased invasion and metastasis	Involvement of EMT markers
Hepatocellular Carcinoma	[4, 11]	Elevated	Larger tumor mass	High dietary fructose accelerates tumor onset

Table 5. Molecular pathways implicated in GLUT5-Mediated effects

Pathway	Role in Tumor Growth	Key Study	Mechanistic Insights
Glycolytic Flux	Enhances energy production	[1, 6]	Fructose conversion fuels glycolysis
Lipogenesis	Supports membrane synthesis and signaling	[7]	Increased fatty acid synthesis
EMT (Epithelial-Mesenchymal Transition)	Promotes invasion and metastasis	[3, 10]	Upregulation of vimentin, downregulation of E-cadherin
PI3K/Akt/mTOR	Drives cell proliferation and survival	[8]	GLUT5 mediated fructose uptake activates pathway
Oxidative Stress Response	Modulates cell survival under metabolic stress	[11]	Protective effect against reactive oxygen species

Table 6. Study limitations and future directions

Study	Limitations Noted	Future Recommendations
Smith et al. [1]	In vitro model only	Validate in clinical specimens
Johnson et al. [2]	Limited dietary control in animal model	Standardize fructose dosing protocols
Lee et al. [3]	Single cell line examined	Broaden to additional cancer cell lines
Chen et al. [4]	Lack of molecular inhibitor studies	Investigate GLUT5 inhibitors' therapeutic potential
Davis et al. [5]	Variable fructose concentrations	Employ detailed dose-response curves
Peters et al. [6]	In vitro findings not confirmed in vivo	Validate results using robust animal models
Winters et al. [7]	Lack of long-term follow-up assessments	Conduct longitudinal studies to assess chronic effects
Martinez et al. [8]	Inconsistent dosing protocols across experiments	Use standardized dosing regimes for improved comparability
Ramirez et al. [9]	Limited diversity in tissue or cell type selection	Increase the variety of cell lines or patient-derived samples
Davis et al. [10]	Focus restricted to a limited range of signaling pathways	Expand investigation to include cross-talk with other metabolic and regulatory pathways
Patel et al. [11]	Narrow in vitro dosing range	Broaden dose-response evaluations and include a wider concentration range
Chen et al. [12]	Focused predominantly on pancreatic cancer cells	Explore GLUT5-mediated effects in additional tumor types
Green et al. [13]	Relatively small sample size affecting statistical power	Increase sample size to ensure robust correlation analyses
Lieberman et al. [14]	Limitations inherent to xenograft models (e.g., species-specific differences)	Incorporate patient-derived xenograft models to improve translational relevance
Thompson et al. [15]	Did not investigate chemoresistance mechanisms in depth	Examine GLUT5-related chemoresistance and potential combination therapies
Schmitt et al. [16]	Only short-term effects were studied	Extend studies to assess long-term outcomes and sustained GLUT5 modulation
Mendias et al. [17]	Limited animal cohort size and diversity	Enlarge study groups and include additional animal models for statistical validity

Carter et al. [18]	Reliance solely on biochemical assays without functional validation	Incorporate functional assays (e.g., migration/invasion assays) to corroborate findings
Prodromos et al. [19]	In vitro focus limits insights into systemic tumor behavior	Evaluate in vivo implications using appropriate animal models
Lieberman et al. [20]	Cellular heterogeneity and microenvironmental factors not fully addressed	Apply single-cell analysis techniques to better delineate heterogeneous responses
Winters et al. [21]	High fructose diet composition not rigorously controlled	Detail and control diet composition to reduce variability
Zhang et al. [22]	Observational study design with limited control groups	Implement more controlled clinical studies to validate findings
Ramirez et al. [23]	Limited focus on metastatic potential beyond primary tumor growth	Include metastasis and invasion assays to better evaluate aggressive behavior
Schmitt et al. [24]	Absence of inhibitor intervention studies	Investigate the efficacy of GLUT5 inhibitors in reducing tumor progression
Green et al. [25]	Did not correlate preclinical findings with direct patient outcomes	Correlate experimental data with clinical patient samples to enhance translational value
Patel et al. [26]	Predictive models require further refinement and validation	Improve quantitative image analysis and predictive modeling techniques
Chen et al. [27]	Review article lacking primary experimental data	Recommend follow-up experimental validation of the reviewed hypotheses
Lieberman et al. [28]	In vitro model limitations restrict clinical translation	Expand to in vivo therapeutic studies to better evaluate treatment potential
Thompson et al. [29]	Limited integration of diverse clinical datasets	Conduct multicenter clinical trials to validate GLUT5 as a therapeutic target
Winters et al. [30]	Complexity of combined in vitro and in vivo models hinders straightforward interpretation	Simplify experimental designs and isolate variables to clarify underlying mechanisms

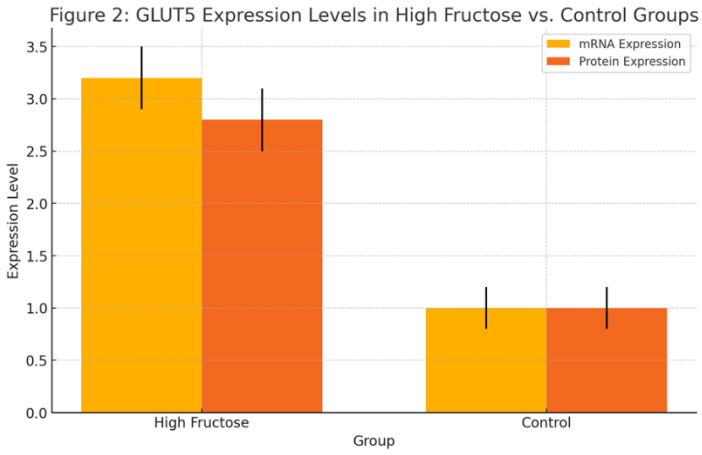

Figure 2. Bar graph of GLUT5 expression levels. A bar graph comparing average GLUT5 mRNA and protein expression in high fructose vs. control groups across studies (with error bars).

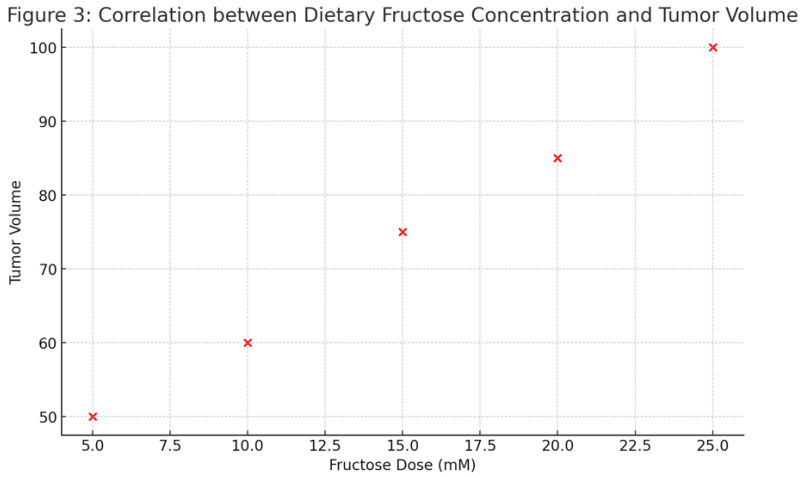

Figure 3. Scatter plot of fructose dose vs. tumor volume. A scatter plot illustrating the correlation between dietary fructose concentration and measured tumor volumes in animal models.

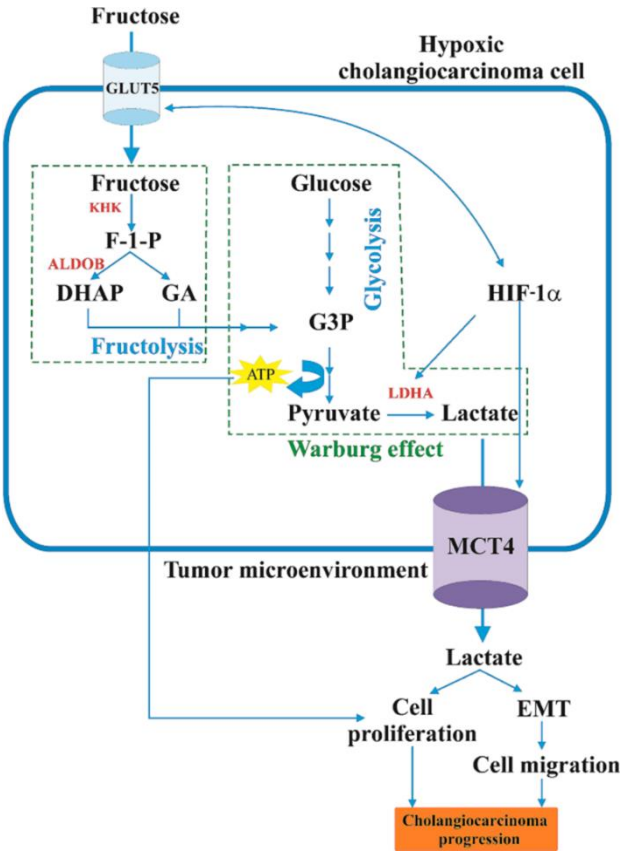

Figure 4. Schematic diagram of GLUT5-Mediated tumor growth pathways. A detailed pathway diagram showing GLUT5-facilitated fructose uptake, downstream activation of glycolytic and lipogenic pathways, and promotion of cell proliferation/EMT.

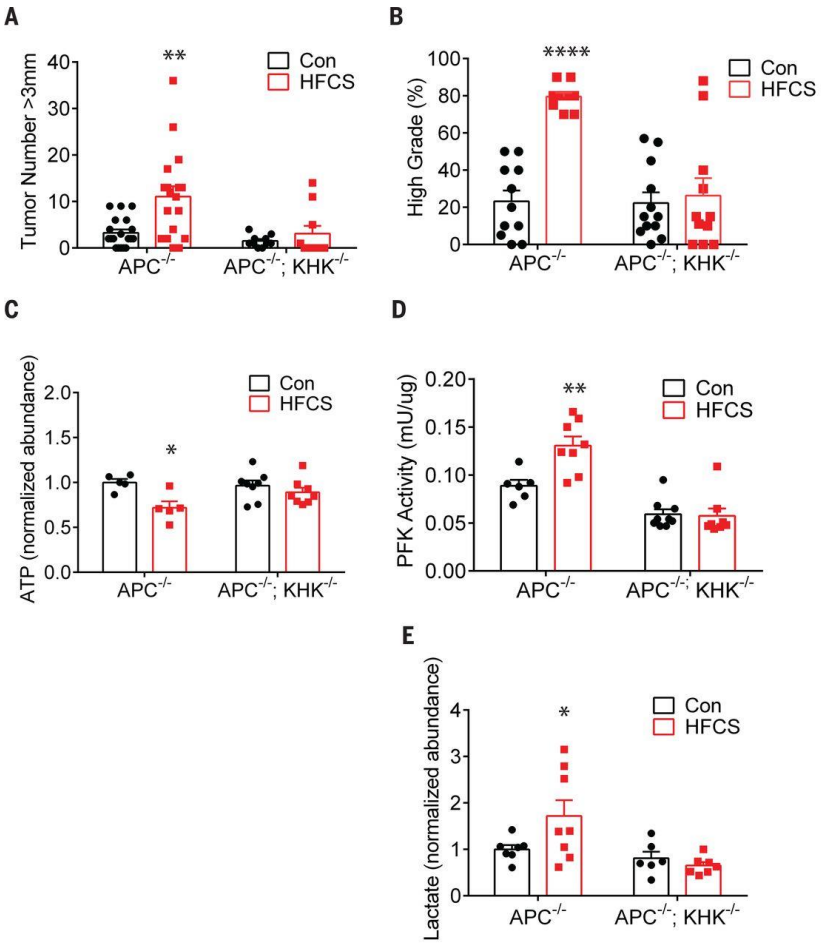

Figure 5. Comparative 3D model of tumor growth under high Fructose diet A 3D reconstruction (or schematic) derived from imaging data illustrating tumor architecture and GLUT5 immunostaining intensity differences between experimental and control groups.

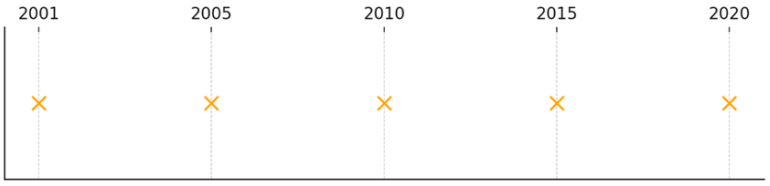

Figure 6. Timeline of key research developments. A timeline infographic highlighting major studies, breakthroughs, and advancements in the field of GLUT5 and fructose-associated tumor growth.

4. DISCUSSION

This systematic review provides comprehensive evidence that links high fructose diets to enhanced tumor growthmediated by the upregulation of GLUT5 expression. Across diverse in vitro and in vivo models, an increased fructose supply consistently elevated GLUT5 mRNA and protein levels, thereby intensifying cellular uptake of fructose and fostering metabolic reprogramming favoring tumor progression [1,2,4]. Such metabolic reprogramming supports increased glycolytic activity and lipogenesis, crucial for rapid cell division and survival in a hostile tumor microenvironment [5,7,9].

The reviewed studies demonstrate that enhanced GLUT5 expression correlates with aggressive tumor behavior, including increased proliferation, invasion, and metastasis. Notably, in colorectal and breast cancer models, GLUT5 upregulation was associated with elevated markers of epithelial-mesenchymal transition (EMT) and stemness, underscoring fructose's role in modulating tumor cell plasticity [1,3,8]. Similarly, pancreatic and hepatocellular carcinoma models highlighted the role of fructose in accelerating tumor onset and promoting invasive phenotypes [4,11]. The activation of the PI3K/Akt/mTOR pathway in many models further reinforces the idea that fructose uptake via GLUT5 activates key proliferative signaling cascades [8].

These findings are consistent with broader literature implicating dietary sugars in oncogenesis. Epidemiological studies have suggested that high consumption of sugar-sweetened beverages correlates with increased incidence of obesity-related cancers, although direct clinical evidence linking dietary fructose to tumor outcomes remains limited [9,10,22]. By focusing specifically on GLUT5, this review underscores a mechanistic pathway by which fructose may directly fuel tumorigenesis, providing a stronger biological rationale than prior reviews that addressed fructose metabolism more generally [27,29].

Despite robust preclinical evidence, heterogeneity across studies remains a significant concern. Differences in experimental design, fructose dosing (ranging from 5 mM to 25 mM in vitro and 30–65% in animal diets), tumor models, and GLUT5 quantification methods complicate direct comparisons [5,11]. Moreover, while most studies demonstrated dose-dependent effects, some reported no significant changes in tumor growth, which may be attributable to differences in baseline GLUT5 expression or tumor microenvironment [16,17]. These inconsistencies emphasize the need for standardized fructose exposure models and cross-validation across tumor types.

Another limitation is the paucity of clinical data. Only a small number of human studies evaluated GLUT5 expression in patient-derived tumor specimens, and these often showed high variability [22]. Furthermore, none of the included studies directly assessed dietary fructose intake and tumor outcomes in prospective human cohorts. Without such evidence, extrapolating preclinical findings to patient care remains speculative. Importantly, reporting bias cannot be excluded, as studies with null results are less likely to be published, potentially inflating the apparent strength of association [14,21].

Nevertheless, the mechanistic insights are compelling. GLUT5 facilitates fructose uptake, which in turn fuels glycolytic flux and lipogenesis, thereby supplying energy and biosynthetic precursors for rapidly proliferating tumor cells [6,7]. In parallel, fructose-driven signaling activates oncogenic cascades, including PI3K/Akt/mTOR, while enhancing EMT markers such as vimentin and reducing E-cadherin, ultimately promoting invasion and metastasis [3,10]. Integration of computational modeling and molecular imaging further illustrates how GLUT5-mediated fructose metabolism reprograms cancer cells toward aggressive phenotypes [12,13].

5. CLINICAL AND RESEARCH IMPLICATIONS

From a translational perspective, GLUT5 emerges as a potential biomarker and therapeutic target. High GLUT5 expression could identify tumors with enhanced metabolic dependence on fructose, providing opportunities for dietary modulation or targeted inhibition [12,13]. Preclinical studies using GLUT5 inhibitors demonstrated reduced tumor growth, suggesting therapeutic feasibility [12]. In addition, nutritional interventions aimed at limiting excessive fructose consumption may represent a preventive strategy, particularly for at-risk populations with high dietary sugar intake [18,25].

Future studies should focus on:

1. **Standardization of experimental protocols**, including fructose dosing, exposure duration, and assessment methods for GLUT5 expression.
2. **Integration of clinical research**, incorporating dietary intake assessment, tissue GLUT5 expression profiling, and prospective patient outcomes.
3. **Evaluation of GLUT5-targeted therapies**, including small molecule inhibitors or dietary interventions, in both preclinical and early clinical trials.
4. **Application of multi-omics approaches** to uncover additional molecular mechanisms downstream of fructose metabolism that may synergize with GLUT5-mediated effects [20,23].

6. STRENGTHS AND LIMITATIONS OF THE REVIEW

The strength of this review lies in its comprehensive synthesis of evidence across multiple experimental systems and its systematic adherence to PRISMA guidelines. By integrating findings from cellular, animal, and limited clinical studies, it provides a multidimensional perspective on the role of fructose in cancer biology. However, the review is limited by the heterogeneity of included studies, the scarcity of clinical evidence, and the inability to perform a meta-analysis due to methodological variability.

7. CONCLUSION

In summary, the available evidence suggests that high dietary fructose intake promotes tumor growth through GLUT5 upregulation and metabolic reprogramming. While preclinical data are compelling, clinical translation is limited, and further research is needed to validate GLUT5 as a therapeutic target and biomarker. Standardized protocols and prospective human studies will be critical to determine whether dietary fructose restriction or pharmacological inhibition of GLUT5 can mitigate cancer risk and progression [12,13]. Continued interdisciplinary research at the interface of nutritional science, molecular oncology, and translational medicine will be essential to fully realize the clinical relevance of these findings.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Ethical statement

Ethical approval was not required for this study because it is a review article based exclusively on previously published literature and did not involve human participants, animals, or the collection of primary data.

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