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Warburg Effect and Type II Glucose Transporter Inhibitors as a Potential Targeted Therapy for Liver Cancer: A Review

Dhassida Sooksawat[1,2], Worarat Boonpech[3,4] , Varomyalin Tipmanee[4,5], Chaitong Churuangsuk[6], Pemikar Srifa[4,7] and Kantida Juncheed[3,4,5,*]

[1]Division of Physical Science and Center of Excellence for Innovation in Chemistry, Faculty of Science, Prince of Songkla University, Songkhla 90110, Thailand
[2]Center of Excellence for Trace Analysis and Biosensor, Prince of Songkla University, Songkhla 90110, Thailand
[3]Institute of Biomedical Engineering, Faculty of Medicine, Prince of Songkla University, Songkhla 90110, Thailand
[4]Department of Biomedical Sciences and Biomedical Engineering, Faculty of Medicine, Prince of Songkla University, Songkhla 90110, Thailand
[5]Center of Biological Activities Testing, Department of Biomedical Sciences and Biomedical Engineering, Faculty of Medicine, Prince of Songkla University, Songkhla 90110, Thailand
[6]Clinical Nutrition and Obesity Medicine Unit, Division of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Songkhla 90110, Thailand
[7]Translational Medicine Research Center (TMRC), Department of Biomedical Sciences and Biomedical Engineering, Faculty of Medicine, Prince of Songkla University, Songkhla 90110, Thailand

([*]Corresponding author's e-mail: kantida.j@psu.ac.th)

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Abstract

Cancer cells demonstrate enhanced survival owing to the underlying metabolic changes that accelerate tumor growth. Hepatocellular carcinoma (HCC) cells exhibit the Warburg effect, a hallmark of cancer metabolism associated with aberrant proliferation. This review critically assesses the existing obstacles in developing selective type II glucose transporter GLUT-2 inhibitors, examining the inhibition of GLUT-2 by natural extracts and synthesized compounds. Liver cells regulate glucose uptake and release via GLUT-2. Dysregulated GLUT-2 expression in HCC increases glucose absorption and metabolism, thereby fueling tumor growth. Targeting inhibition of GLUT-2 may delay tumor development and improve therapeutic sensitivity by preventing glucose uptake by cancer cells. Natural and synthetic chemicals that specifically limit GLUT-2 activity are promising GLUT-2 inhibitors. GLUT-2 inhibitors must be engineered with precision to specifically target GLUT-2 while avoiding interference with other GLUT functions. Targeted therapy is complicated by difficulties in determining the mechanisms underlying GLUT-2 dysregulation in various malignancies. New HCC treatments require a deep understanding of GLUT-2 and cancer metabolism as well as advances in pharmacological research and development. Conclusively, the targeting of GLUT-2 is a novel therapeutic strategy for HCC. Understanding the intricate role of GLUT-2 in the pathophysiology of HCC may lead to the development of tailored therapies for patients with HCC.

Keywords: GLUT-2 inhibitor, Glucose transporters, Targeted therapy, Liver cancer, Small molecule synthesis

Introduction

Glucose is a vital component of human physiology and acts as a fundamental energy source for the metabolic processes of mammalian cells. Under normal cellular metabolism, glucose undergoes complete breakdown to produce energy in the presence of oxygen through the Krebs cycle and oxidative phosphorylation [1].

Cancer cells derive energy from glucose via distinct metabolic pathways. In the presence of oxygen, cancer cells prefer glycolysis for energy production. The phenomenon is referred to as the "Warburg effect", which is characterized by the occurrence of "aerobic glycolysis" [2]. Owing to the lower adenosine triphosphate (ATP) production during glycolysis compared to that observed during the oxidative breakdown of glucose, cancer cells require a higher quantity of glucose than normal cells to meet their high

metabolic demands for growth. Increased glucose uptake in cancer cells has been observed with overexpression of the glucose transporter **(**GLUT**)** family, and an association between GLUT overexpression and the aggressiveness and invasiveness of cancers has been established [3].

Among class I glucose transporter isomers, glucose transporter protein type 2 **(**GLUT-2**)** is highly expressed in the hepatocytes, intestinal cells, kidney cells, and pancreatic ß-cells [3]. The expression of GLUT-2 is upregulated in liver cancer cells compared to that in healthy liver tissue [3-5]. The rate of glucose uptake and subsequent utilization in glycolysis can be decreased with the use of GLUT-2 inhibitors to suppress GLUT-2 protein function. This could potentially deprive cancer cells of the energy and resources required for accelerated growth. Consequently, targeting GLUT-2 protein emerges as a promising therapeutic approach for liver cancer [6,7]. However, the development of GLUT-2 inhibitors is limited.

Current therapies for hepatocellular carcinoma **(**HCC**)** have several limitations, hindering their effectiveness. Despite several advancements, current therapies fail to adequately address the complexities of HCC, particularly in advanced stages. A comprehensive solution necessitates further advancements in targeted therapies and the development of innovative treatment approaches tailored to the unique characteristics of HCC. Enhancing treatment efficacy while minimizing damage to healthy liver tissues remains a critical goal in improving patient outcomes.

In this review, we aimed to highlight the limitations of conventional treatments for HCC and emphasize the potential of targeted GLUT-2 therapy by developing GLUT-2 inhibitors as a treatment option. Furthermore, we demonstrate the correlation between the distinguishing characteristics of cancer and the Warburg effect. Moreover, we provide a comprehensive analysis of the progress made in the development of class I GLUT inhibitors, the outcomes of *in vitro* cytotoxicity tests, and the suppression of glucose uptake. Finally, this review critically evaluates the current barriers to the development of selective GLUT-2 inhibitors, focusing on their inhibition by natural extracts and synthesized compounds.

HCC treatment

HCC is a significant global health concern. Curative and palliative methods form the core of traditional liver cancer therapies [8]. The standard methods of treating liver cancer include surgery, radiation therapy, and chemotherapy [9-11]. Despite considerable advances made in treatment via these approaches, a significant gap persists in comprehending the unique characteristics of liver cancer [12]. The limitations of the traditional treatments are discussed in this section.

First, surgical interventions such as liver resection and liver transplantation are considered curative treatments for HCC because they aim to remove the tumor or replace the diseased liver with a healthy liver. Nevertheless, surgery is typically reserved for patients with early-stage HCC and healthy liver function [13]. Consequently, a significant treatment gap exists for many patients with advanced-stage HCC or underlying liver cirrhosis, who may not be suitable candidates for surgery.

Second, radiation therapy and chemotherapy are used as primary or adjuvant therapies for HCC treatment. Commonly employed techniques include external beam radiation therapy (EBRT) and internal radiation therapy (brachytherapy) [14,15]. However, the effectiveness of radiation therapy is restricted by the radiation tolerance of the liver and the proximity of HCC tumors to vital structures [16,17]. In addition, the heterogeneous nature of HCC renders targeting all tumor sites difficult. Nevertheless, the limited efficacy of systemic chemotherapy for HCC is predominantly due to the inherent resistance of liver cancer cells to chemotherapeutic agents. Standard chemotherapy regimens have demonstrated modest response rates, and the associated adverse effects can be severe [18,19].

In recent years, immunotherapy, specifically with immune checkpoint inhibitors, such as nivolumab and pembrolizumab, has demonstrated significant efficacy in the treatment of numerous types of cancers [20]. Despite these advancements, the response rates observed in patients with HCC remain low, and immunotherapy does not benefit everyone. To maximize the efficacy of immunotherapy for the treatment of HCC, it is essential to identify predictive biomarkers and enhance patient selection criteria. This will boost treatment outcomes and increase the efficacy of immunotherapy in patients with HCC [21].

Traditional treatments have assisted in the management of HCC; however, they fail to sufficiently tackle its complications, particularly in advanced stages. Consequently, a comprehensive solution is required. The development of targeted therapies is promising for minimizing the gap in traditional liver cancer treatments. These therapies specifically target molecular aberrations or signaling pathways involved in the development and progression of liver cancer [22]. Consequently, by attacking cancer cells more selectively, targeted therapies have the potential to improve treatment efficacy while minimizing damage to healthy liver tissues.

Targeted therapy is a promising treatment option for HCC. Recently, major advances have been made in the development of HCC-specific targeted therapies. Sorafenib, lenvatinib, and regorafenib specifically

target the molecular pathways involved in tumor growth and angiogenesis, whereas other drugs focus on inhibiting the expression of specific genes, utilizing antibodies, or disrupting the functions of proteins involved in the disease [23]. Commonly targeted molecules in HCC including Tumor Protein p53 (TP53), Catenin Beta 1 (CTNNB1), Catenin Beta Interacting Protein 1 (CTNNBIP1), Myelocytomatosis Oncogene (MYC), Vascular Endothelial Growth Factor (VEGF), Epidermal Growth Factor Receptor (EGFR), and Programmed Death-Ligand 1 (PD-L1). These targeted therapies have demonstrated efficacy in improving overall survival in patients with advanced HCC [24].

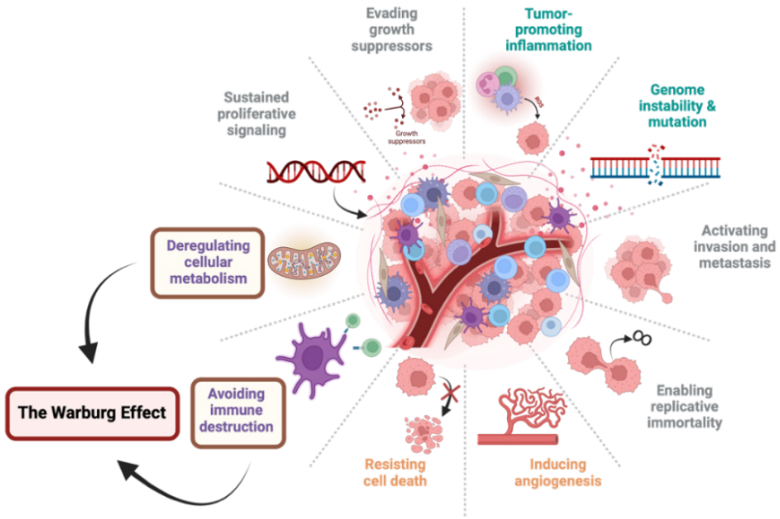


Figure 1 The hallmarks of cancer. **(**Created with BioRender.com**)**

The Warburg effect is related to cancer hallmarks

Cancer cells exhibit an uncontrollable proliferative ability driven by oncogenic mutations and epigenetic alterations that disrupt the signals governing cell growth and division. This increase in proliferation necessitates increased uptake of sugar by cancer cells, which serves as both an energy source and building blocks for macromolecules, to sustain their accelerated growth [25-27]. This phenomenon was first reported by Otto Warburg. He discovered that human and animal cancer cells prefer to convert glucose to lactate for energy production rather than utilizing mitochondrial metabolism or the oxidative phosphorylation chain, even in the presence of oxygen [28]. This observation was further confirmed by the high levels of lactate dehydrogenase identified in many tumors [27,29]. **Figure 1** demonstrates the hallmarks of cancer, illustrating how the Warburg effect promotes cancer cell proliferation by increasing the energy required for aberrant proliferative activity, which disrupts cellular metabolism (deregulating cellular metabolism). In addition, elevated levels of lactate dehydrogenase within tumor cells may indicate increased lactic acid production, resulting in an acidic environment in malignant tissues [30-32]. This phenomenon is one of the cancer hallmarks that helps cancer cells escape immune destruction (avoiding immune destruction) [31,32].

Cancer cells demonstrate altered metabolism of all nutrient substrates. However, carbohydrate metabolism has been extensively studied because cancer cells produce energy via glucose metabolism. Targeted therapies are currently being studied as potentially effective methods for the treatment of HCC. These therapies focus on the relevant biochemical pathways involved in tumor growth and angiogenesis and address the consequences of the Warburg effect.

While healthy cells use pyruvate in the tricarboxylic acid (TCA) cycle and oxidative phosphorylation in the presence of oxygen to generate approximately 36 mol ATP per mol absorbed glucose, cancer cells use aerobic glycolysis, or the Warburg effect, to produce only 4 mol ATP per mol glucose under conditions involving adequate oxygen supply, as shown in **Figure 2** [5,33-36]. High levels of lactate dehydrogenase found in tumors also corroborate this finding [27,29]. Cancer cells consume more glucose than normal cells, leading to an increased expression of GLUTs. Thus, the Warburg effect is especially crucial in the development of HCC, as malignant cells exhibit increased glucose uptake and metabolism owing to the dysregulation of GLUTs, most notably GLUT-1 and GLUT-2. Overexpression of GLUT, notably GLUT-2, promotes enhanced glucose absorption and supplies energy for tumor growth. The inhibition of the overexpression and modulation of the functions of GLUTs have been examined as strategies for disrupting

the Warburg effect and inhibiting HCC growth [3]. By interfering with GLUT-2 functions, it is possible to impede enhanced glucose uptake and metabolic reliance of cancer cells, offering potential opportunities in HCC treatment.

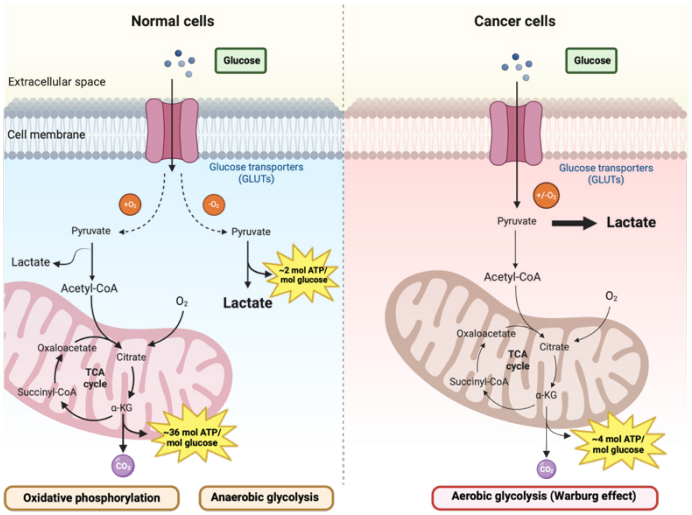


Figure 2 The Warburg effect: Contrasts in glucose uptake and lactate production in cancer cells versus normal cells. **(**Created with BioRender.com**)**

Biochemical characteristics and clinical relevance of the Warburg effect

The use of aerobic glycolysis in cancer cells, a metabolic pathway that yields less ATP per cycle than oxidative phosphorylation, may be explained by various molecular mechanisms. A potential consequence of the Warburg effect, characterized by inefficient ATP synthesis, is the likelihood of a disparity in the rates of aerobic glycolysis and oxidative phosphorylation. Cancer cells may exhibit an increase in aerobic glycolysis. Demetrios *et al.* found that the Warburg effect promotes glucose-to-lactate conversion 100 times faster than the tricarboxylic acid (TCA) cycle. Enhanced glycolysis produces comparable amounts of ATP within the same timeframe [37]. Despite continued oxidative phosphorylation, aerobic glycolysis leads to a significantly greater influx of glucose [38].

It is necessary to critically evaluate the fundamental attributes of cancer that are characterized by accelerated proliferation and intense anabolic processes. This will improve our understanding of the mechanisms by which cancer cells undergo aerobic glycolysis. Tumor cells require anabolic metabolism in conjunction with ATP to accumulate a substantial quantity of biomass, which is essential for sustaining their proliferation. The Warburg effect facilitates the provision of carbon to several pathways involved in the synthesis of nucleotides, fatty acids, and amino acids with several types of glycolytic intermediates [39].

The tendency of cancer to metastasize to other parts of the body and its ability to avoid apoptotic cell death, both of which are exploitable traits in cancer treatment, may elucidate why aerobic glycolysis is prevalent in cancer. The production of reactive oxygen species (ROS) occurs as a result of anoikis, a type of programmed cell death caused by the dissociation of cells from the extracellular matrix [40,41]. In an environment with cancer cells, anoikis ceases when the cells dissociate. This is primarily due to the Warburg effect [40,42]. This effect is characterized by a decrease in the production of mitochondrial ROS, which is mediated by a reduction in the pyruvate flux into oxidative phosphorylation [43]. The ability of tumor cells to resist apoptosis during matrix detachment is vital for metastatic dissemination.

The Warburg effect is also advantageous for medical applications. One significant application is positron emission tomography (PET) in the context of cancer diagnosis. PET imaging has become a valuable tool for the identification of malignancies and assessment of therapeutic response in confirmed cancer cases. PET is based on the increased glycolytic activity observed in cancer cells when utilizing [^{18}F]fluoro-2-deoxy-D-glucose (FDG), a glucose analog tagged with a radioactive isotope. This radiotracer accumulates in tumor cells because of increased glucose uptake. Warburg effect can also be leveraged to examine glycolysis-related gene expression patterns to predict outcomes in various contexts. The presence of glycolytic phenotypes has often been linked to reduced patient mortality in conditions such as triple-negative breast cancer and lung adenocarcinoma, as evidenced by many investigations [46-48].

GLUT-2 as a targeted therapy for liver cancer

Because of the hydrophilic nature of glucose, specific carrier proteins are required for its translocation across the cell plasma membrane. The transport of glucose into cells is mediated by 2 families of membrane-associated transporters: facilitative GLUT and sodium-coupled glucose co-transporter (SGLT). GLUT transporters, unlike SGLT proteins that require energy to transport glucose, transport sugars down a concentration gradient [27,47-49]. This section focuses on facilitative GLUT-2.

GLUT-2 is a member of the class I facilitative GLUT family, along with GLUT-1, GLUT-3, and GLUT-4, which exhibit similar amino acid sequences and structures [50]. Among GLUT isoforms, class I GLUTs consist of GLUT type I-IV, which are mainly expressed in the hepatocytes, pancreatic ß-cells, intestinal cells, and renal cells. These isoforms are vital for facilitating the glucose transport into the blood circulatory system. GLUT-2, a prominent member of class I GLUTs, plays a pivotal role in maintaining glucose homeostasis in various human tissues including the intestines, liver, and kidneys [3,27,49]. It regulates glucose sensing and signaling and facilitates the first step in glucose-stimulated insulin secretion [3,27].

GLUT-2 is encoded by the *SLC2A* gene. It is composed of 496 amino acids and has a molecular weight of 58 kDa. GLUT-2 exhibits 80 % homology and 55 % identity with GLUT-1, showing a high similarity among humans, mice, and rats. It has a low affinity for glucose but can utilize other substrates, such as mannose, galactose, fructose, and glucosamine. The structure of GLUT-2 includes transmembrane domains and a cytosolic loop that facilitates substrate selection (**Figure 3**). GLUT-2 plays a crucial role in maintaining glucose homeostasis in various human tissues, including the intestine, liver, kidneys, and brain. Overexpression of GLUT-2 has been associated with poor health outcomes in diseases like HCC and colorectal cancer [51-53]. Therefore, the development of GLUT-2 inhibitors could result in an alternative and potentially more effective approach to treating liver cancer.

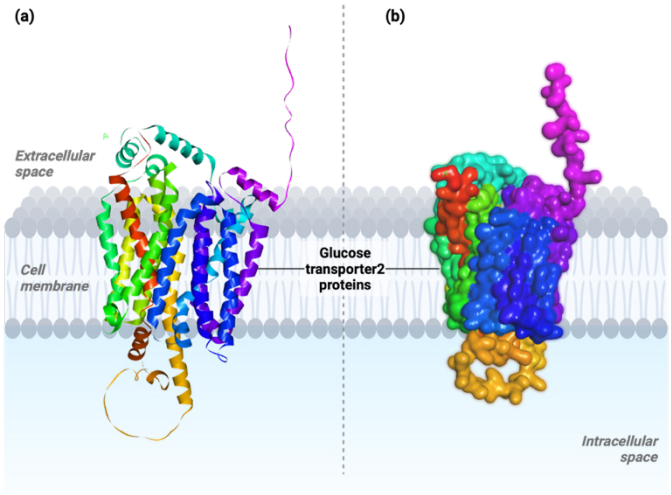


Figure 3 Structural features of GLUT-2, including a) the ribbon structure and b) the surface view of the GLUT-2 protein. (Created with BioRender.com)

Upregulation of class I GLUTs has been observed in various cancer cell types compared to that in healthy tissues or cells, as shown in **Figure 4** [27,49]. Based on the Warburg effect, tumor cells are more susceptible to alterations in glucose concentration than normal cells and are more vulnerable to death when the glucose supply is limited and glycolysis is disrupted [4,39]. To date, many specific GLUT inhibitors, such as fasentin (GLUT-1 and GLUT-4 inhibitor) and apigenin (GLUT-1 inhibitor), have been assessed *in vitro* and *in vivo*. These selective agents act by suppressing the glucose uptake from tumor cells. They induce cellular apoptosis and restrain the normal activation of the PI3K/Akt/mTOR intracellular pathway [54-56].

Notably, upregulation of GLUT-2 has been detected in HCC compared to that in healthy liver tissue [3,5,57]. Kim *et al.* recently used data from The Cancer Genome Atlas (TCGA) to analyze the expression patterns of class I GLUTs in tumor tissues and how they relate to the progression of HCC. It demonstrated that GLUT-2 expression was higher in HCC than in other members of the class I GLUTs [53,58]. Therefore, GLUT-2 could be considered a promising target for alternative therapies against HCC compared to other

member of class I GLUTs [59]. Hence, GLUT-2 inhibitors are key players in suppressing glucose uptake in HCC cells. Inhibition of GLUT-2 function can effectively improve HCC treatment by reducing cancer cell proliferation [60]. Furthermore, the characterization of selective GLUT-2 inhibitors may offer an alternative approach for determining substrate specificity among GLUT members [54]. Targeting glucose metabolism specifically via GLUT-2 inhibition has emerged as a promising avenue for therapeutic intervention in liver cancer. Inhibition of GLUT-2 has the potential to disrupt energy metabolism in cancer cells, impairing their ability to proliferate and survive.

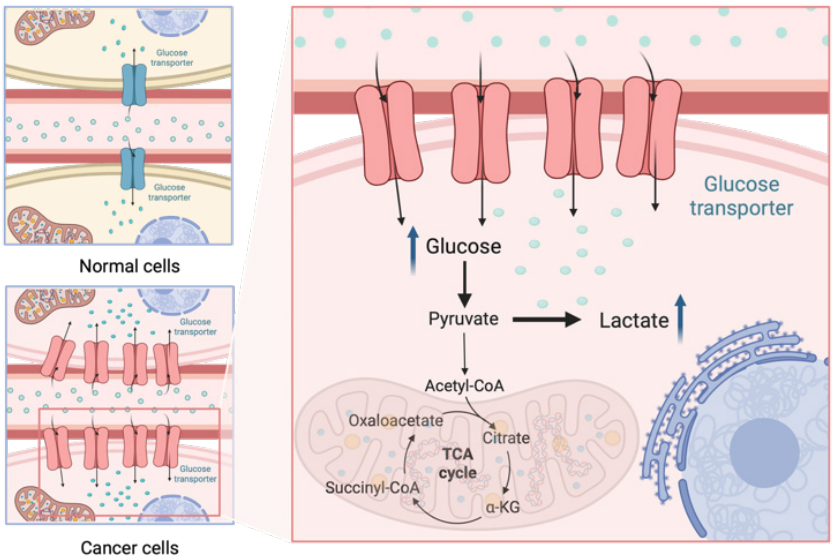


Figure 4 Changes in GLUT expression in cancer cells: Transition from physiological to elevated levels of GLUTs. (Created with BioRender.com)

GLUT-2 inhibitors

GLUT-2 inhibitors are characterized by their ability to block or reduce the function of GLUT-2, thereby affecting the glucose uptake and metabolism in cells expressing this transporter. By inhibiting GLUT-2, these compounds effectively interfere with the utilization of glucose by cancer cells, potentially leading to impaired cell growth, proliferation, and survival [53,57,61]. Additionally, GLUT-2 inhibitors may disrupt glucose sensing and signaling mechanisms, further contributing to their anticancer effects.

Several natural and synthetic substances have been identified in recent years owing to their potential to impact GLUT-2 activity and demonstrate anticancer properties. Among these, the fungal metabolite Cytochalasin B, as illustrated in **Figure 5** is an example. It significantly diminishes glucose uptake in various cells, exerting a notable effect on GLUT-2 and other class I GLUT. This inhibition occurs through a noncompetitive mechanism [62]. Its ability to suppress actin polymerization is well recognized [63]. However, its development as a GLUT inhibitor was discontinued owing to its concurrent actin-inhibitory effects. Inhibition of actin polymerization or disruption of actin filaments can lead to significant adverse effects on cellular functions, potentially affecting cell viability and overall physiological processes [63,64]. Subsequently, numerous other GLUT inhibitors, ranging from GLUT-specific to pan-GLUT inhibitors, have been investigated. These ongoing studies reflect continuous efforts to identify effective strategies for targeting GLUT-2 and modulating its activity for cancer therapy.

A large class of natural products that reduce glucose uptake include flavonoids and polyphenol compounds found in foods, especially fruits and vegetables [65]. GLUT-2 inhibition activity has been observed with several flavonoids, including phloretin, quercetin, isoquercitrin, myricetin, fisetin, apigenin, luteolin, hesperetin, hesperidin, and tiliroside [66]. Phloretin, a potent inhibitor, is commonly found in apples and apple-derived products [67], while quercetin is abundant in foods like onions, citrus fruits, and leafy greens [68,69]. Similarly, myricetin, fisetin, and apigenin are present in berries, nuts, and vegetables [55,70]. Their potential as GLUT-2 inhibitors highlights the diverse sources from which these compounds can be derived, thereby offering prospects for the development of novel anticancer therapeutics.

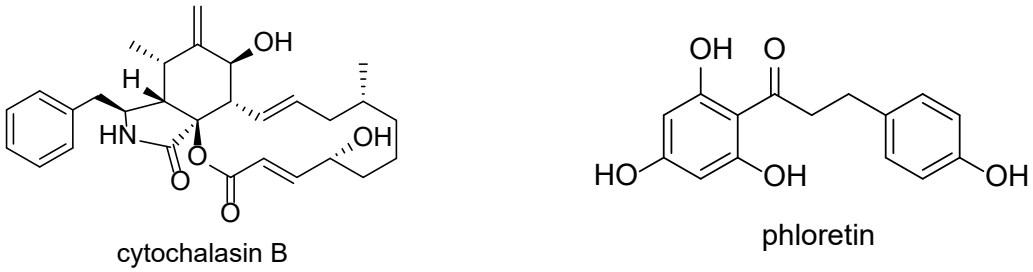


Figure 5 Structures of natural GLUT inhibitors.

Sappanin-type homoisoflavonoids isolated from the fibrous roots of *P. odoratum* have shown potent GLUT-2 inhibitory effects [61]. However, the effectiveness of these flavonoids is within the micromolar range, and in certain instances, they do not selectively inhibit GLUT-2. Although phloretin competitively inhibits GLUT1 in tumor cells, it also induces apoptosis in human liver cancer cells **(**HepG2**)**. Additionally, RT-PCR results of HepG2 and Hep3B cells showed that downregulation of GLUT-2 using siRNA led to reduced GLUT-2 expression [57]. Phloretin was used as a positive control for GLUT-2 inhibition [52,61,71]. The low affinity of GLUT-2 for glucose and fructose renders the determination of its function in the physiology or pathology of cells challenging, as other GLUT isoforms are present within 1 tissue or cancer cell line[79-81]. GLUT-2-selective inhibitors have rarely been reported.

The discovery of GLUT-specific inhibitors and substrates with therapeutic potential has been facilitated by the elucidation of GLUT crystal structures**.** Notably, Class I GLUTs, such as GLUT-1, have been successfully crystallized [82-84]. Crystallographic studies of GLUT-1 and GLUT-3 have revealed that glucose interacts with GLUTs in the deep binding cleft, which is consistent with the binding of GLUT-5 and homologous bacterial glucose transporters [78,79]. However, the core chemical structure of GLUT inhibitors is less important than the interaction points between the compounds and transporter**s** [76]. Schmidl *et al.* recently reported the results of an *in silico* ligand screening for GLUT-2-selective inhibitors [53]. The GLUT-2 inward-facing conformational structural model was selected based on the crystal structure of GLUT-1. G2iA and G2iB are the 2 most potent noncompetitive GLUT-2 inhibitors that bind at a site different from that of glucose. Their structures are displayed in **Figure 6**. These can be used as tools to identify and understand GLUT-2 expression.

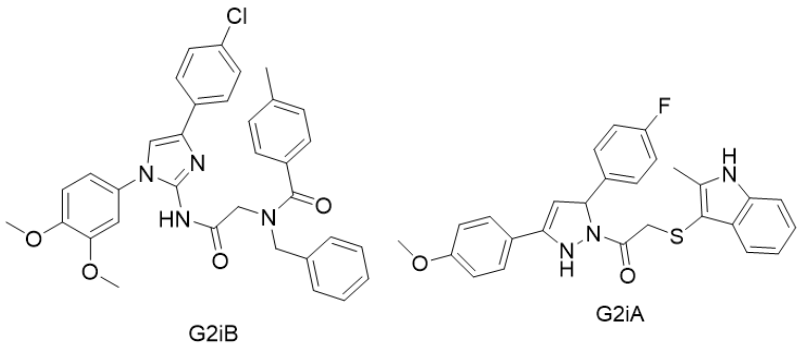


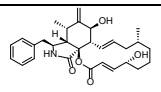
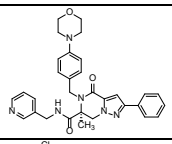
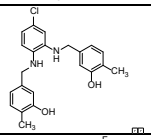
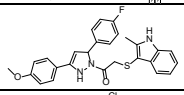
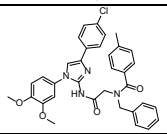
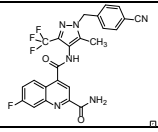
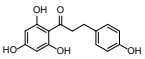
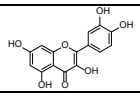
Figure 6 Structures of GLUT-2 inhibitors, G2iA and G2iB.

Studying the effects of GLUT inhibitors on cancer cells is an interesting approach to understanding the regulation of glucose uptake in cancer cells. This is in addition to the aforementioned examples. Some compounds act as class I GLUT inhibitors in certain cancer cell types **(Table 1**). The inhibition of GLUTs can control cancer cell growth by reducing the crucial glucose uptake, which is essential for cancer cell proliferation. Various methods have been employed to observe decreases in glucose uptake by cancer cells. Glutor, a piperazine-2-one derivative, is a newly reported pan-GLUT inhibitor and has the potential to treat cancer**.** Treatment with glutor modulated the expression of cell survival regulatory molecules p53, Hsp70, IL-2 receptor CD25, and C-myc along with mitochondrial membrane depolarization, increased intracellular ROS expression, and altered Bcl-2/BAX ratio [80]. Furthermore, the toxicity of glutor has been scrutinized *in vitro* in more than 94 cell lines. The results have shown notable toxicity against cancer cells at IC_{50} levels

in the nanomolar range. However, no apparent toxicity toward normal cells has been observed [81]. DRB18 is a potent inhibitor of glucose transport via GLUT pan-class I proteins in cancer cells. Experiments using 2-deoxy-d-[^{3}H] DRB18 revealed a reduction in glucose uptake mediated by GLUT1-4, each with a distinct IC_{50}. These results highlight the potential of DRB18 to reduce the growth of cancer cells by inhibiting glucose transport [82]. The recently discovered BAY-876 showed potent inhibition of tumor-associated glycolysis and growth in ovarian cancer cells *in vitro* and *in vivo* [83]. Notably, it exhibited exceptional specificity with a unique single-digit nanomolar potential and more than 100-fold selectivity for GLUT-1 compared to that for GLUT-2, GLUT-3, and GLUT-4 [84]. Additionally, when used in combination with DBI-1, a replacement isoflavonoid, dia BAY-876 effectively inhibits the growth of colorectal cancer cells both *in vitro* and *in vivo* [85].

Table 1 presents potential GLUT-2 inhibitors of interest**.** The column labeled **'**Glucose Uptake Assay**'** indicated whether each compound was examined for its effect on glucose uptake. The decision to mark 'Yes' was based on a variety of analysis methods, including direct measurements like 2-DG, 2-NBDG, and ^{18}F-FDG, as well as indirect assessments such as H_2O_2 production. Hence, the decision stemmed from the use of diverse analytical approaches in studying the effects of GLUT-2 inhibitors.

Table 1 Glucose transporter inhibitors and their cytotoxicity tested against different cell lines.

Compound name	Chemical structure	Class	Target	Mode of action	Cells line	Assayed for Glucose Uptake (Yes /No)	IC_{50}	Ref
Cytochalasin B		Natural compounds	GLUTs class I	Non-competitive	Colorectal cancer (DLD-1 cell lines)	Yes	0.01 µM	[62,63,76]
Glutor		Small molecule	GLUTs class I	Competitive	94 different cell lines	Yes	0.004-30 µM	[80,86,87]
DRB18		Small molecule	GLUTs class I	N/A	Lung cancer (A549, H1299 cell lines) Cervical cancer (Hela cell lines) Kidney cells (HEK293 cell lines)	Yes	< 10 µM	[82]
G2iA		Small molecule	GLUT-2	Non-competitive	hxt^0 yeast cells	Yes	N/A	[53]
G2iB		Small molecule	GLUT-2	Non-competitive	hxt^0 yeast cells	Yes	N/A	[53]
BAY-876		Small molecule	GLUT-1* and GLUT-2,-3, and-4	Competitive	Ovarian cancer (SKOV-3, OVCAR-3, HEY, A2780, OVCA-429 cell lines) Colorectal cancer (LS174 cell lines)	Yes N/A for colorectal cancer	75 nM-2 µM	[83,85,88]
Phloretin		Natural compound	GLUT-1 and GLUT-2*	Competitive	Breast cancer (MDA-MB-231 cell lines) Breast cells (MCF-10A cell lines) Liver cancer (HepG2 cell lines) Colorectal cancer (COLO 205, HCT-116, SW-480 cell lines)	Yes N/A for colorectal cancer	100-200 µM	[57,89-91]
Quercetin		Natural compound	GLUT-2, SGLT-1	Non-competitive	Colorectal cancer (Caco-2E, Caco2 cell lines)	Yes	< 20 µM	[92,93]

Note; The asterisk (*) signifies a higher specificity to GLUT compared to that toward other GLUTs.

Development of a limited number of selective GLUT-2 inhibitors

Although pan-class I GLUT inhibitors and several mixed inhibitors inhibit cancer cell proliferation, their side effects and safety issues remain unknown. The scarcity of *in vitro* and *in vivo* studies on the adverse effects, efficacy, and toxicity is of particular concern. Furthermore, overuse of GLUT inhibitors can lead to toxic effects on healthy cells that contain similar GLUT forms. Therefore, specific GLUT-2 inhibitors are required to overcome these challenges.

Moreover, the in-depth understanding of GLUT-2 as a target protein in liver cancer is limited. Promising targets are the initial step in the development of anticancer drugs; however, the results can be disappointing for several reasons. First, many targets are involved in the intricate signaling pathways that are altered in cancer. Because of the upstream or downstream components, modifying the target may not have a significant impact. Second, the value of the overexpression of a target is frequently overestimated, which can result in therapeutic resistance and occasional inaccurate prediction of treatment response. Finally, genetic changes lead to susceptibilities that influence the development of malignant tissues by altering the microenvironment, indicating that cancer involves more than just cancer cells. For effective treatments, including the investigation of the function of cancer stem cells, it may be essential to understand and disrupt these interdependencies among cellular components.

Conclusions

Overexpression of GLUT-2 in liver cancer cells has made it an attractive target for the development of novel therapies. Inhibition of the expression or function of GLUT-2 has been proposed as a potential approach to limit the glucose supply to cancer cells, thereby impeding their growth and survival. Although the targeting of GLUT-2 is a promising therapeutic strategy, significant challenges persist. The development of selective inhibitors that specifically target cancer cells without affecting healthy cells is crucial. Further research is needed to understand the precise mechanisms underlying the role of GLUT-2 in liver cancer progression and validate its potential as a therapeutic target in preclinical and clinical studies. In conclusion, GLUT-2 presents a promising avenue for targeted therapy in liver cancer owing to its overexpression and role in facilitating glucose uptake in cancer cells. However, further studies are required to translate these findings into effective and safe treatments for patients with liver cancer.

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