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# An appraisal of the current status of inhibition of glucose transporters as an emerging antineoplastic approach: Promising potential of new pan-GLUT inhibitors

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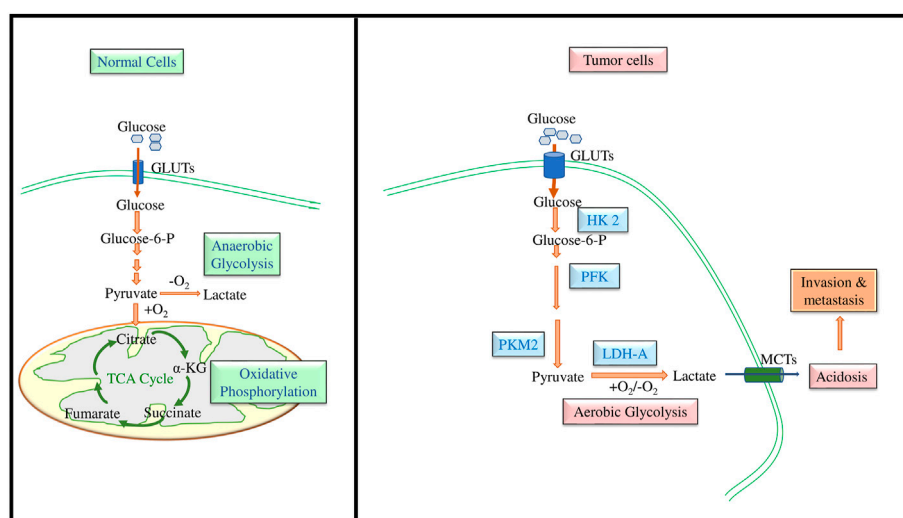
Neoplastic cells displayed altered metabolism with accelerated glycolysis. Therefore, these cells need a mammoth supply of glucose for which they display an upregulated expression of various glucose transporters (GLUT). Thus, novel antineoplastic strategies focus on inhibiting GLUT to intersect the glycolytic lifeline of cancer cells. This review focuses on the current status of various GLUT inhibition scenarios. The GLUT inhibitors belong to both natural and synthetic small inhibitory molecules category. As neoplastic cells express multiple GLUT isoforms, it is necessary to use pan-GLUT inhibitors. Nevertheless, it is also necessary that such pan-GLUT inhibitors exert their action at a low concentration so that normal healthy cells are left unharmed and minimal injury is caused to the other vital organs and systems of the body. Moreover, approaches are also emerging from combining GLUT inhibitors with other chemotherapeutic agents to potentiate the antineoplastic action. A new pan-GLUT inhibitor named glutor, a piperazine-one derivative, has shown a potent antineoplastic action owing to its inhibitory action exerted at nanomolar concentrations. The review discusses the merits and limitations of the existing GLUT inhibitory approach with possible future outcomes.

## KEYWORDS

GLUT, neoplastic cells, pan-GLUT inhibitors, glutor, tumor metabolism

## Introduction

Neoplastic cells display altered carbohydrate metabolism, which has emerged as one of the targetable hallmarks of cancer (Hanahan and Weinberg, 2011; Senga and Grose, 2021; Hanahan, 2022). One of the prominent features of the reprogrammed metabolism in cancer cells concerns the predominance of glycolysis irrespective of the availability of O<sub>2</sub>, a phenomenon designated as the “Warburg effect.” Accelerated glycolysis helps



**FIGURE 1**

Role of GLUTs in the accelerated glycolysis of neoplastic cells. Neoplastic cells display an upregulated expression of GLUTs for increased glucose uptake, which is rapidly metabolized to lactate leading to the production of a high amount of ATP and biosynthetic precursors.

neoplastic cells rapidly produce ATP and precursors of the anabolism (Warburg et al., 1927; Warburg, 1956; Lopez-Lazaro, 2008; Cassim et al., 2020). Mathematical models of accelerated glycolysis suggest that it lets the neoplastic cells produce a much higher amount of ATP than that derived from the normal Krebs cycle (Gillies and Gatenby, 2007). To maintain the unhindered supply of glucose for fueling glycolysis, cancer cells overexpress several nutrient transporters on their cell surface, among which one of the most prominent ones are the glucose transporters (GLUTs) (Ancey et al., 2018; Szablewski, 2022). Thus, irrespective of their etiologies, most neoplastic cells overexpress GLUT1 and GLUT3 isoforms, which have high efficiency for glucose transport (Ancey et al., 2018; Suwabe et al., 2021). Consequently, several upcoming anticancer therapeutic strategies are focused on designing effective approaches to achieve inhibition of one or more GLUT isoforms to interfere with the glucose uptake of cancer cells. Given the background mentioned above, the following review of literature discusses the current status of knowledge concerning: 1) the importance of sugars in carbohydrate metabolism of neoplastic cells; 2) the biochemistry of the functioning of glucose transporters; and 3) Emerging approaches for therapeutic targeting of GLUTs.

## The necessity of glucose for neoplastic cells

It has remained a hot and debated topic if sugars feed cancer. Among the diverse types of sugars, glucose is the

simplest one, the most assimilable form of carbohydrates (Parker, 2020). Cancer cells metabolize glucose at a comparatively faster rate for which they need to have a high uptake of glucose. This feature of neoplastic cells was initially recognized by a well renowned German scientist Sir Otto Heinrich Warburg, Nobel laureate of 1931 in Physiology or Medicine, who noted that neoplastic cells consume a relatively higher amount of glucose (20 times more) than normal healthy counterparts (Warburg et al., 1927; Warburg, 1956). Further, Warburg also presented evidence demonstrating that cancer cells metabolized most of their consumed glucose *via* lactate fermentation instead of utilizing glucose metabolism through the TCA cycle. Figure 1 depicts the typical pathway of glucose metabolism in cancer cells in which glucose is metabolized to lactate compared to normal cells, which metabolize it through the TCA cycle. The role of glycolysis in neoplastic cells is accelerated on an average by 100 times (range: 20–300 times) (Vaupel and Multhoff, 2021). Though the glycolysis is inferior compared to the Krebs cycle for the generation of ATP, cancer cells still evolved to opt for glycolysis even in the presence of  $O_2$  owing to two possible reasons: 1) The rate of ATP production in cancer cells is approximately 100 times faster than normal cells and 2) glycolysis provides precursors for biosynthetic machinery (Lunt and Vander Heiden, 2011; Zhou et al., 2018). The metabolic switching of cancer cells is mainly attributed to HIF and its downstream signaling pathways (Semenza, 2010; Zhao T et al., 2014; Masoud and Li, 2015; Nagao et al., 2019; Lee et al., 2021).

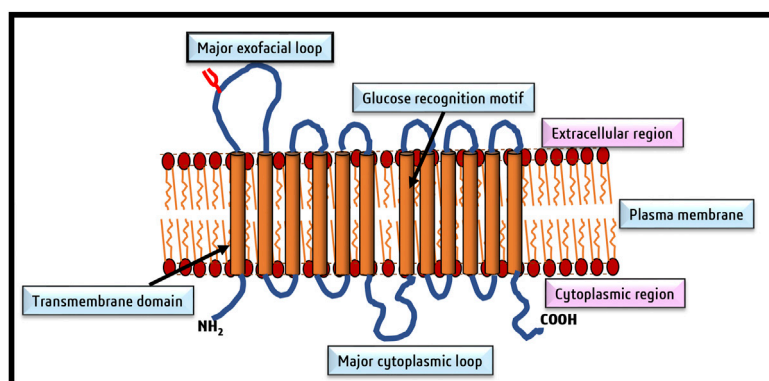


FIGURE 2

A typical topographical representation of GLUT (GLUT1). The figure shows the organization of the N and C termini, linker regions, and the 12 transmembrane domains of GLUT, which form an aqueous channel for glucose transport across the membrane.

## Glucose transporters (GLUTs)

Glucose uptake of cancer cells is facilitated by glucose transporters which belong to the solute carriers (SLC) family. The most prominent GLUTs are highly overexpressed in cancer cells and encoded by the SLC2A gene family (Thorens and Mueckler, 2010; Mueckler and Thorens, 2013; Navale and Paranjape, 2016; Galochkina et al., 2019; Echeverría et al., 2021). In addition, another group of membrane-associated glucose transporters belongs to the Na<sup>+</sup>/glucose cotransporters (SGLT) gene family designated as the SLC5A, which carries out the active transport of glucose (Wright et al., 2011).

The credit for discovering glucose transporters goes to LeFevre (1948), followed by advanced research to decipher their structure and functions primarily in the erythrocyte membranes (Widdas, 1952). Fourteen members now constitute the GLUT family with different affinities for glucose transport (Uldry and Thorens, 2004; Thorens and Mueckler, 2010; Mueckler and Thorens, 2013). Figure 2 depicts the typical structural organization of GLUT as downloaded from PDB Data Bank. A GLUT molecule is a glycoprotein with N-linked oligosaccharides composed of 500 amino acids arranged in an array of 12 transmembrane alpha-helices. Depending on the sequence differences, the nomenclature of the various members of the GLUT family was proposed (Joost and Thorens, 2001; Joost et al., 2002; Holman, 2020). According to the Heidelberg Unix sequence analysis, GLUTs are grouped into three classes: Class I, II, and III. Class I comprises GLUT1, GLUT2, GLUT3, GLUT4 and GLUT14. The class II members are GLUT5, GLUT7, GLUT9, and GLUT11. Class III constitutes GLUT 6, GLUT8, GLUT10, GLUT12, and GLUT13/HMIT-1 (Ancy et al., 2018). The GLUT isoforms also display tissue-specific need-based variations in their expression pattern (Boado et al., 1994; Uldry and Thorens, 2004; Calvo et al., 2010). As

neoplastic cells display essential dependency on glucose, they are reported to overexpress various isoforms of GLUTs (Table 1), particularly GLUT1, GLUT3, GLUT4, and GLUT12 (Martell et al., 1997; Szablewski, 2013; Barbosa and Martel, 2020; Pliszka and Szablewski, 2021). However, the expression of GLUT1 and GLUT3 is most ubiquitous in all cancers (Krzeslak et al., 2012; Barron et al., 2016); hence the following description of the literature review is focused on GLUT1 and GLUT3.

The GLUT1 and GLUT3 display about 64% resemblance of amino acid composition. Deng and Yan (2016) have elegantly described the crystal structure-dependent details of GLUT1 and GLUT3. GLUT1 comprises 492 amino acids from aa 9–455 GLUT constitutes prominent canonical facilitator super family (MFS) protein folds (Deng et al., 2014; Galochkina et al., 2019; Drew et al., 2021). Twelve transmembrane  $\alpha$  helices are linked with extracellular and cytoplasmic linker amino acids. The structural organization of GLUT1 and GLUT3 has been reported to exist in three conformational states.

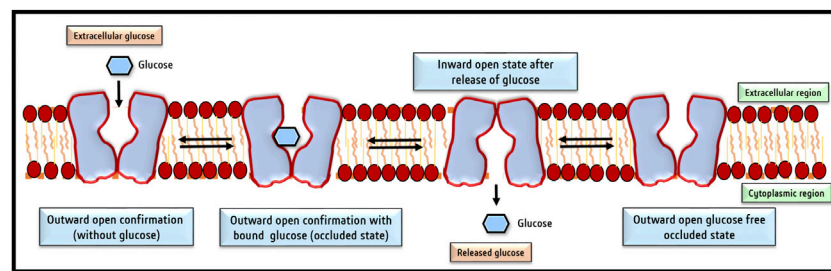
Despite amino acid differences, all GLUT isoforms possess a similar group structure, The central aqueous channel of GLUT1, through which glucose is passaged, comprises transmembrane domains 3,5,7, 8 and 11 with amphipathic helices (Mueckler et al., 1985). Groups of Alvarez et al. (1987), Jung (1996), and Heinze et al. (2004) aided in the understanding of the structural organization of GLUT1 using specialized techniques like circular dichroism and Fourier transform infrared spectroscopy, mass spectroscopy, and scanning glycosylation mutagenesis (Alvarez et al., 1987; Jung, 1996; Heinze et al., 2004). Subsequently, the chemically predicted structures were reconfirmed using computer modeling techniques (Deng et al., 2014), followed by final corroboration of the predicted structures of GLUT1 by X-ray diffraction of crystal structures, with 12 transmembrane domains clustered into two units of six helical units (Deng et al., 2014; Holman, 2020).

TABLE 1 Cancer genome-based representative distribution of GLUTs in various cancer cells.

Name of GLUT isoform	Representative neoplastic cells	Name of normal cells/tissues	References
GLUT1	Head and neck, brain, thyroid, pancreatic, breast, esophageal, gastric, renal, lung, cutaneous, adenocarcinoma, hepatocellular cholangiocellular carcinoma (HCCC), colorectal, bladder, endometrial, prostate, ovarian and cervical cancer, penile and hematological malignancies, sarcomas, laryngeal carcinomas	Erythrocytes, endothelial and epithelial cells, glandular cells, placenta, astrocytes, and cardiac muscles	Ancey et al. (2018); Barron et al. (2016); Carvalho et al. (2011); Ding et al. (2016); Gaber et al. (2021); Pliszka and Szablewski, (2021); Pragallapati and Manyam, (2019); Shim et al. (2013); Heydarzadeh et al. (2022); Zhao T et al. (2014)
GLUT2	Hepatocellular carcinomas, cholangiocellular carcinoma, breast, gastric cancers	Pancreatic islet cells	Godoy et al. (2006); Lin et al. (2016); Mueckler, (1994); Schmidl et al. (2021b, 2021a)
GLUT3	Non-small cell lung cancer, breast cancer, brain tumors, bladder, laryngeal, prostate, gastric, head and neck, ovarian, oral squamous cancer, astrocytoma, choriocarcinoma, retinoblastoma, rhabdomyosarcoma, pancreatic cancer, endometrial carcinoma	The brain, especially in neurons, testis, uterus, prostate, pancreas	Boado et al. (1994); Burant and Bell, (1992); Krzeslak et al. (2012); Meneses et al. (2008); Yamamoto et al. (1990)
GLUT4	Breast, lung, gastric, and pancreatic cancer	Insulin-sensitive tissue adipocytes and skeletal muscle	Adekola et al. (2012); Chadt and Al-Hasani, (2020); Richter and Hargreaves, (2013); Stuart et al. (2009); Torrance et al. (1997)
GLUT5	Liver carcinoma, lung cancer, renal cell carcinoma, breast and prostate cancer	Plasma membranes of small intestinal epithelial cells, kidney, testis, muscle	Chan et al. (2004); Godoy et al. (2006); Li et al. (2011); Phay et al. (2000); Yamamoto et al. (1990)
GLUT6	Several cancers, including endometrial cancer	Brain, spleen, and leukocytes	Godoy et al. (2006); Nualart et al. (2009); Pyla et al. (2013); Uldry and Thorens, (2004)
GLUT7	Not determined in cancer cells	Colon epithelium, prostate	Mueckler, (1994)
GLUT8	Multiple myeloma	Testis, adrenal gland, liver, spleen, lung	Maria et al. (2015); Shikhman et al. (2001)
GLUT9	Hepatocellular carcinoma, melanoma	Liver, kidney, lung, leukocytes, small intestine	Godoy et al. (2006); Phay et al. (2000)
GLUT10	Gastric cancer	Adipose tissue	Pyla et al. (2013)
GLUT11	Multiple myeloma	Several cell types, including heart, muscle, kidneys	McBrayer et al. (2012)
GLUT12	Breast and prostate cancer cells	Heart, small intestine, skeletal muscles	Bakht et al. (2020); Barron et al. (2012); Stuart et al. (2009); White et al. (2018)

GLUT1 contains a single glucose binding site near the C terminal (Deng et al., 2015). Glutamine residues form the glucose binding site at 161, 282, 283, and 288 and tryptophan at 412 positions (Mueckler and Makepeace, 2009). The *in silico* structure and docking prediction tools have greatly added to deciphering the binding sites of glucose and inhibitors on GLUT and predicting the ‘Modus Operandi’ of the transport process (George Thompson et al., 2015). The two most acceptable models predict the transport of glucose by GLUT1. In the first model, it is predicted that glucose binding sites are located on two sides of the aqueous channel; one is located towards the exterior and the other towards the cytoplasmic side. Hence named as two site/flexed site transport model (Custódio et al., 2021). The glucose transport depends on a simple ligand exchange at these two binding sites. However, GLUT1 is demonstrated to transport glucose unidirectionally at a given time and hence is a uniporter. The second popular glucose transport model by GLUT1 is named the “alternating access model” (Lloyd et al., 2017). According to this model, GLUT1 undergoes transformational oscillations by alternatively opening on either side. Hence, GLUT1 is predicted

to be an antiporter in this model (Chadt and Al-Hasani, 2020). The pioneering study of Deng et al. (2014) published in ‘Nature’ demonstrated the existence of four conformational states of GLUT1 based on its crystal structure. These four conformational states are designated as 1) outward open conformation with one substrate; 2) a ligand-bound state and occluded state; 3) an inward open state; and 4) a ligand-free and occluded state (Deng and Yan, 2016). A recent review by Galochkina et al. (2019) has summarized the current state of knowledge on the mechanism of glucose transport by GLUT1 by molecular dynamic simulation studies. According to the model proposed by this study, glucose transport by GLUT1 comprises three stages of a highly cooperative process. The movement of glucose involves its transition *via* a rotational movement with H-bonds (Galochkina et al., 2019), which is followed by the transformation of the outside open conformational state to the ‘inside open’ conformational state, through which the queued glucose molecule is released in the cytoplasm (Galochkina et al., 2019). The cytoplasmic glucose gets phosphorylated immediately by the action of hexokinase; hence, the concentration of free



**FIGURE 3**

Conformational changes of GLUT facilitate glucose transport across the cell membrane. The four conformational changes oscillate between 1) Outside open conformation facilitating loading of glucose; 2) outward open conformation with bound glucose (occluded state); 3) inward open state following release of glucose and 4) shifting back to the outward open glucose-free state to capture of glucose. So basically, there are two main conformations the outside open (OOP) and inside open (IOP) states.

glucose in the cytoplasm remains at a very low concentration, which in turn becomes the driving force for the passive transport of glucose by GLUT (Medina and Owen, 2002). Figure 3 depicts various conformational changes which facilitate glucose transport across the cell membrane. This mode of glucose transport by GLUT is also designated as gated pore and rocker switch mechanism (Nomura et al., 2015), membrane phospholipids associated cell signaling has been reported to play a crucial role in regulating the signaling events responsible for the oscillation of GLUT conformational states (Hresko et al., 2016).

Nevertheless, in addition to glucose transport, GLUT1 also mediates the uptake of mannose, galactose, glucosamine, and ascorbic acid by cells (Uldry et al., 2002; Pliszka and Szablewski, 2021), which also work through the same operating system of altered conformational states (Pragallapati and Manyam, 2019). Moreover, the expression of GLUT on cell membrane displays clustered and focal distribution patterns, in which cell junctions and cytoskeletal elements play an essential role, as revealed by direct stochastic optical reconstitution microscopy (Yan et al., 2018). Almahmoud et al. (2019) performed a series of *in silico* studies to comprehend the mechanism of the aforementioned conformational changes in GLUT1. Their systemic molecular docking investigation revealed that the Phe291, Phe379, Gln380, Trp388, and Trp412 amino acid residues mediate the binding of glucose with GLUT1 and determine its conformational oscillation (Almahmoud et al., 2019). Further, the 12 transmembrane domains of GLUT1 are clustered in a replicated trimeric organization, as revealed by crystallographic studies (Holman, 2020). Crystallographic studies on GLUT1 have also revealed additional insight into the conformational states (Holman, 2020). Some amino acids are crucial in maintaining various conformational states, particularly the hydrophobic residues at 291, 292, 293, 294, 386, and 387 positions (Holman, 2020).

The expression of GLUTs in normal healthy cells and transformed cells is a highly regulated process, depending on the glucose needs of specific cell types (Navale and Paranjape, 2016). However, the precise mechanism of the gene expression and membrane transporters of GLUT1 and GLUT3 have still not been fully deciphered. Neoplastic cells largely depend on cAMP-dependent secondary messenger signaling for regulating the expression of GLUT1 and GLUT3 (Meneses et al., 2008). In addition, PI3K/Akt pathway has also been demonstrated to facilitate GLUT1 expression (Hoxhaj and Manning, 2020).

## Regulation of GLUT expression

A survey of literature strongly indicates the involvement of multiple signaling messengers in the regulation of GLUT expression in cancer cells in which the prominent ones include  $\text{Ca}^{2+}$  (Diaz-Ruiz et al., 2011; Echeverría et al., 2021), CAMK (White et al., 2018), PI3K/Akt (Hoxhaj and Manning, 2020), mTOR (Shin and Koo, 2021), HIF1- $\alpha$ , p53 (Monde, 2018; Schwartzenberg-Bar-Yoseph et al., 2004), Matrix metalloproteinases (MMP) (Ito et al., 2002), RAS, PKC (Lee et al., 2015), NF- $\kappa$ B (Zha et al., 2015), AMPK (Zambrano et al., 2019), Phosphate and Tensin Homolog (PTEN) (Ancy et al., 2018), and Thioredoxin-interacting protein (TxNIP) (Ancy et al., 2018). Many of these critical signaling and regulatory molecules are integrated into a specific loop to regulate the expression of various GLUT isoforms. Zhao and Zhang (2016) have elegantly described critical regulatory and canonical pathways regulating GLUT expression: GLUT-PI3K, GLUT-mTOR, GLUT-HIFs, GLUT-RAS, GLUT-MMP, and GLUT-p53 (Zhao and Zhang, 2016). Upstream to these cell-associated signaling mediators regulating GLUT expression, several extrinsic factors are also key players in modulating GLUT expression. Among these, proinflammatory cytokines have been reported to play a crucial role in regulating the



expression of GLUT1 and GLUT3. GLUT regulatory cytokines include TNF $\alpha$  (Shikhman et al., 2001; Straus, 2013), IL-1 $\beta$  (Phillips et al., 2005), TGF- $\beta$  (Andrianifahanana et al., 2016), IFN- $\gamma$  (Freemerman et al., 2014), IGF1 (Actis Dato et al., 2021), and IL-13 (Wieman et al., 2007). These cytokines indirectly regulate GLUT expression *via* their ability to modulate one or more signaling pathways. For example, IL-1 $\beta$  regulates GLUT expression by modulating PKC, PI3K, p38, and cJUN activation. Likewise, proinflammatory cytokines like IL-13 and IFN- $\gamma$  modulate GLUT1 expression *via* NF- $\kappa$ B activation (Freemerman et al., 2014; Tan et al., 2018). In addition to cytokines, several regulatory RNAs are also reported to regulate GLUT expression. Non-coding RNAs, including several miRNAs, have been demonstrated to regulate GLUT expression (Kong et al., 2016; Hu et al., 2019). Long non-coding RNA, HOTAIR, has been shown to regulate GLUT by its ability to modulate NF $\kappa$ B (Obaid et al., 2021). Extrinsic factors like iron availability also affect GLUT expression (Potashnik et al., 1995).

Importantly several hormones also play a crucial role in regulating GLUT expression. Gender-specific hormones like estrogen (Medina et al., 2004; Nualart et al., 2009), testosterone (Wilson et al., 2013; Mitsuhashi et al., 2016), and progesterone (Medina et al., 2003; Medina et al., 2004; Frolova et al., 2009; Nualart et al., 2009) whereas non gender-specific hormones like thyroid hormone (Torrance et al., 1997; Brunetto et al., 2012; Ding et al., 2016), insulin (Brosius et al., 1992; Stuart et al., 2009; Maria et al., 2015), and pituitary hormones (growth hormone, gonadotropin releasing hormone (GnRH), luteinizing hormone (LH), follicle stimulating hormone (FSH), and somatotropins) (Kilgour et al., 1995; Harris et al., 2012; De Los Santos, 2013; Kim and Park, 2017; Nicholas et al., 2020) have been implicated in the regulation of GLUT expression. However, like cytokines, the modulatory effect of hormones in GLUT expression is mediated *via* the involvement of one or more aforementioned signaling mediators and pathways (Kilgour et al., 1995; Shikhman et al., 2001; Phillips et al., 2005; Freemerman et al., 2014; Santos et al., 2014; Maria et al., 2015; Ding et al., 2016; Takaguri et al., 2016; Kim and Park, 2017). Nevertheless, the blend of cytokines, hormones, and specific signaling mediators is also likely to manifest cancer cell-specific differences in the expression of various GLUTs. Nevertheless, physical activities like exercise also modulate GLUT expression *via* CAMK and AMPK-associated signaling pathways (Röckl et al., 2007; Richter and Hargreaves, 2013).

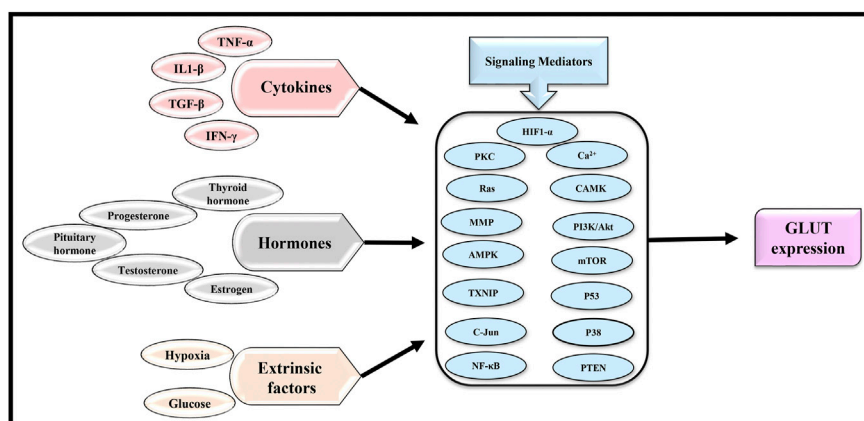
Further, the role of hypoxemic conditions and HIF1 $\alpha$  in regulating GLUT expression needs a little more attention as HIF1 $\alpha$  is the master regulator of tumor metabolism (Nagao et al., 2019). Experimental reports strongly indicate a correlation of HIF1 $\alpha$  to the expression of various GLUT isoforms (Semenza, 2010; Mattmiller et al., 2011; Semenza, 2013; Sadlecki et al., 2014; Seleit et al., 2017; Kierans and Taylor, 2021). The modulation of GLUT expression by HIF1 $\alpha$  is also mediated by the co-

involvement of other signaling messengers like RAS (Moldogazieva et al., 2020; Ghanavat et al., 2021; Shin and Koo, 2021). Hypoxic conditions of the tumor microenvironment also regulate GLUT gene expression *via* modulation of HIF1 $\alpha$  and its downstream signaling events (Roy et al., 2020; Li et al., 2021). Nevertheless, even glucose levels in the external milieu serve as essential triggers of GLUT1 and GLUT3 expression *via* HIF1 $\alpha$  mediated regulation of GLUT gene expression (Hayashi et al., 2004; Yang et al., 2014; Zhao and Zhang, 2016; Seleit et al., 2017). Hypoxia and glucose levels have been reported to modulate mRNA levels of GLUT1, GLUT3, GLUT8, GLUT9, GLUT10, and GLUT12 (Frolova et al., 2009; Frolova and Moley, 2011; Kido et al., 2020), indicating the importance and central role of these extrinsic factors on pan-GLUT expression in which HIF1- $\alpha$  has a central role. Nevertheless, some evidence also indicates HIF1- $\alpha$  independent regulation of GLUT expression (Macheda et al., 2005). Such variations could be dependent on the etiology of various cancer cells. Figure 4 shows the primary regulators of GLUT expression and their downstream signaling mediators.

## Inhibition of GLUT as a promising anti-cancer approach

Considering the crucial role of glucose supply for sustaining accelerated tumor metabolism and most malignant cells' overexpression of GLUT1 and GLUT3, strategies are being devised to effectively inhibit GLUTs in a neoplastic cell-specific manner. Nevertheless, as discussed earlier in this literature review, many cancer cells also overexpress other isoforms of GLUTs, SGLT1, and SGLT2 for sugar uptake (Szablewski, 2013; Wright, 2020; Pliszka and Szablewski, 2021; Szablewski, 2022). Thus, several approaches are envisaged for targeted inhibition of such transporters, particularly the GLUTs. Significantly, the effectiveness of any GLUT inhibition strategy will depend on the strength of the binding of a given inhibitor. Availability of the molecular structures of GLUT inhibitors and *in silico* tools has significantly helped to characterize GLUT inhibition.

Moreover, the availability of the crystal structure of GLUT1 and GLUT3 has further strengthened the approaches for exploring their effective inhibitors. In this context, searching and developing such inhibitors will be desirable, which can cause a pan-GLUT inhibition. This approach will help overcome the adaptability of neoplastic cells to recruit additional GLUTs for glucose uptake. Moreover, it is also essential to explore inhibitors that can inhibit GLUTs at minimal concentrations; this will aid in avoiding toxicity to normal cells with a low level of GLUT expression. In addition to the ongoing search for ideal small molecule inhibitors for GLUTs, other approaches mainly focused on inhibiting GLUT expression at the gene level are also under active investigation. These approaches include anti-GLUT



**FIGURE 4**  
Regulation of GLUT expression in cancer cells. Indicated extrinsic and intrinsic factors can regulate the expression of GLUTs via the mediators of a plethora of signaling messengers, the blend of which could vary in a cancer-specific manner.

antibodies, antisense DNA, shRNA, miRNAs, long non-coding (LNC), and Hox antisense intergenic RNA (HOTAIR) (Rastogi et al., 2007; Liu et al., 2018; Hu et al., 2019; Liu et al., 2021). Given the rapid progress in this field, the current status of GLUT inhibition strategies is discussed in the following section of the literature review.

## GLUT inhibitors of natural origin

Small molecule GLUT inhibitors mainly belong to natural, seminatural and synthetic chemical origins (Shriwas et al., 2020). have elegantly summarized the GLUT inhibitors of herbal origin. Vick et al. (1973) introduced the first herbal GLUT inhibitor named “Phlorizin,” which was followed by a series of discoveries of several other GLUT inhibitors of plant origin which belong to various chemical categories, including alkaloids, flavonoids, and other oxygen heterocyclic and phenolic compounds (Shriwas et al., 2020). Among these diverse categories of GLUT inhibitors of plant origin, those identified with antineoplastic action include more than 25 compounds, to name a few of them: apigenin (Gonzalez-Menendez et al., 2014), curcumin (Gunnink et al., 2016; Soni et al., 2021), genistein (Vera et al., 1996; Pérez et al., 2011), naringenin (Memariani et al., 2021), oridonin (Yao et al., 2017), phloretin (Wu et al., 2018; Wang et al., 2022), phlorizin (Vick et al., 1973; Kwon and Levine, 2007; Shriwas et al., 2020), quercetin (Schmidl et al., 2021a), resveratrol (Jung et al., 2013; Gwak et al., 2015; Zambrano et al., 2019; Samec et al., 2020), silybin (Zhan et al., 2011), and vinblastine (Shriwas et al., 2020). Although many of these GLUT inhibitors display a

promising antineoplastic potential, the precise mechanism of the inhibitory action of most remains elusive, which needs to be deciphered for their optimal utilization in antineoplastic therapeutics.

## Cytochalasin B

A cell-permeable mycotoxin named cytochalasin B, which is also a microfilament poison and used to regulate cytoskeletal elements is yet another GLUT inhibitor of natural origin that is extensively investigated for its mechanism of GLUT inhibition and utility for antineoplastic applications (Jung and Rampal, 1977; Devés and Krupka, 1978; Klip and Pâquet, 1990; Granchi et al., 2016; Kapoor et al., 2016). Kapoor et al. (2016) published an elegant article regarding the mechanism of the GLUT-1 inhibitory action of cytochalasin B along with two phenylalanine amides. This study also showed that the GLUT-1 inhibitory action of cytochalasin B could be manifested in mM concentration ranges. The study utilized crystallography and *in silico* docking tools to decipher the mechanism of GLUT1 inhibition and identified the amino acids and binding sites through which cytochalasin B exerted its inhibitory action. However, being a blocker of microfilament polymerization, its utility for antineoplastic application *in vivo* needs to be verified vis à vis validation of safety for other organs and tissues. Moreover, the cytoskeleton plays a crucial role in the functioning of many tumor-infiltrating cells like macrophages and dendritic cells, where microfilament poisoning by cytochalasin B needs to be controlled while utilizing it for anticancer therapeutic approaches.

## Glucopiericidin A

Glucopiericidin A is yet another highly potent GLUT inhibitor of natural origin with an IC<sub>50</sub> value of 22 nM compared to 500 nM for cytochalasin B (Kitagawa et al., 2010). The group of glucopiericidin A members are produced by *streptomyces* of the actinomycetes family. Glucopiericidin A has been remarkable for its low LD<sub>50</sub> values and is predicted to have less toxicity (Zhou and Fenical, 2016). Though initially discovered as a filopodia protrusion inhibitor (Kitagawa et al., 2010), it was later discovered that glucopiericidin A could simultaneously inhibit both mitochondrial respiration (Hall et al., 1966) and glycolysis (Kitagawa et al., 2010) by its ability to inhibit GLUT leading to declined ATP production. Moreover, glucopiericidin A is also shown to interfere with tyrosine kinase-based signaling (Zhou and Fenical, 2016). It has been demonstrated that glucopiericidin A synergies with low glucose levels for inducing cell death in the pancreatic, lung, and other cancer cells (Palorini et al., 2013). However, the precise mechanism of GLUT inhibition by glucopiericidin A remains elusive. Moreover, its antineoplastic action needs to be assessed in a broader spectrum of targets, and its specificity on cancer cells remains undetermined. It remains elusive whether it can directly inhibit GLUT from interfering with glycolysis or *via* glucose phosphorylation. The GLUT inhibiting potential of glucopiericidin A solely depends on maiden experiments displaying its ability to inhibit the uptake of 2-deoxyglucose (2DG) (Imoto, 2019). Thus, the antineoplastic potential of glucopiericidin A needs further validation.

## Polyphenols

Polyphenols are a group of natural compounds found in many plants with reported antineoplastic potential (Keating and Martel, 2018). Polyphenols like apigenin, silibin, kaempferol, gossypol, naringenin, phloretin, genistein, resveratrol, herpentin, quercetin, myricetin, and catechin are reported to inhibit glucose uptake in several neoplastic cell lines, by their ability to inhibit GLUTs at both gene and protein expression level (Keating and Martel, 2018; Ji et al., 2019; Kang et al., 2019). On the other hand polyphenols like quercetin are reported to competitively inhibit GLUT1 (Hamilton et al., 2018; Salehi et al., 2020), whereas for some other polyphenols the mechanisms of GLUT inhibition remain unclear. Johnston et al. (2005) and Farrell et al. (2013) reported that dietary polyphenols decrease glucose uptake in the Caco-2 cell line, possibly depending on their ability to inhibit GLUT and SGLT1. Moreover, polyphenols like curcumin, genistein, and quercetin can improve the antineoplastic action of glycolytic inhibitors in cell lines of myeloid leukemia origin (de Blas et al., 2016). Moreover, phloretin, a polyphenol

derived from apple, was shown to inhibit the proliferation of colorectal cancer cell lines by inhibiting GLUT2 and activating the p53-dependent signaling pathway (Lin et al., 2016). *In vitro* experiments on Caco-2 cells revealed that exposure to anthocyanin-rich plant extract inhibited the expression of SGLT1 and GLUT2 (Alzaid et al., 2013). However, for many polyphenols, the precise mechanism of their inhibitory action on GLUTs remains to be clarified. Among the most worked out polyphenols, apigenin and resveratrol are known to inhibit GLUT1 (Melstrom et al., 2008; Gwak et al., 2015), whereas phloretin, and quercetin are reported to inhibit GLUT1, and GLUT2 (Schmidl et al., 2021a) on the other hand silybin inhibits GLUT4 (Zhan et al., 2011). These studies on polyphenols also corroborate that eating fruits and a vegetable-rich diet abundant in polyphenols decreases cancer risk. It can be attributed mainly to the GLUT inhibitory potential of several dietary polyphenols. In addition, polyphenols manifest their anticancer action through other mechanisms, including modulation of cell signaling, cell survival, angiogenesis, immunopotential, hormonal regulation, and enzyme modulation (Niedzwiecki et al., 2016). The target cancers investigated for the anticancer action of polyphenols include prostate, colon, breast, lung, bladder, pancreas, spleen, and leukemia (Niedzwiecki et al., 2016; Montané et al., 2020).

## Small inhibitory molecules

The main group of small inhibitory molecules of various GLUTs are principally aromatic compounds with unique imidazole, pyridine and pyrazole rings and most of them have a common overall structural organization with minor differences as depicted in Figures 5A–F.

### WZB 117

WZB 117 (Figure 5A) is a polyphenol-derived small molecule inhibitor of GLUT1 (Liu et al., 2012; Ojelabi et al., 2016; Chen et al., 2017). It exerts antineoplastic action with an IC<sub>50</sub> value in the 10 μM concentration range on HeLa, RKO, A549, and MCF7 cells of the cervix, endometrial carcinoma, lungs, and breast origin, respectively (Liu et al., 2012), accompanied by enhanced radio-sensitization (Zhao et al., 2016). Some mechanisms of the antineoplastic action of WZB117 have also been worked out, showing the implication of a declined GLUT1 expression along with a decrease in ATP levels and glycolytic enzymes (Liu et al., 2012). Moreover, WZB117 triggers an increase in the ATP sensing AMPK and a decline in cyclin E2 (Liu et al., 2012). The antineoplastic activity of WZB117 has also been evaluated *in vivo* (Liu et al., 2012). Interestingly WZB117 is



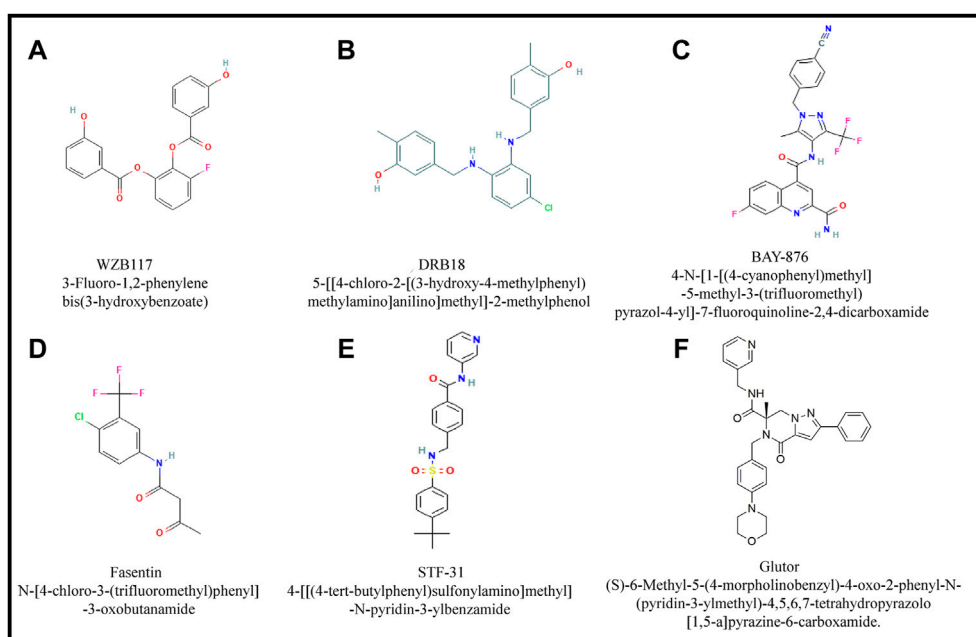


FIGURE 5

Major small inhibitory molecules of GLUTs. Figures (A–F) show structural details of small GLUT inhibitory molecules. Most of these molecules have overall common structural organization except few alterations in ring structure, constituent elements and their arrangement.

also reported to inhibit cancer stem cells (Shibuya et al., 2014). However, one of the disadvantages of WZB117 is its instability owing to its ester bonds under aqueous physiological conditions, potentially the most significant limiting factor in its use in cancer therapeutic strategies. Moreover, it is described as inhibiting only GLUT1, which can be another limitation of its use for antineoplastic applications.

## DRB18

In a recent study, another promising GLUT inhibitor named DRB18 (Figure 5B), which belongs to a synthetic small inhibitory molecule, has been reported with the ability for GLUT inhibition as evaluated on A549 tumor-bearing nude mice and HER293 cell lines (Shriwas et al., 2021). One of the reported advantages of DRB18 is its relative stability compared to WZB117 (Roberts et al., 2020). So far, DRB18 has been shown to exert cytostatic action on around 60 cancer cell lines of diverse origins. The primary mechanism of the antineoplastic action of DRB18 was shown to be *via* increased endoplasmic reticulum oxidative stress (Shriwas et al., 2021). The pan-GLUT inhibitory ability of DRB18 was verified through *in silico*-based studies. The cytotoxic ability of DRB18 accompanied by inhibitory action on glucose uptake showed IC<sub>50</sub> in the concentration range of 900 nM–9.0 μM (Shriwas et al., 2021). Moreover, DRB18 treatment caused a remarkable inhibition of

glucose-dependent metabolic pathways like glycolysis, TCA cycle, purine, and pyrimidine synthesis (Shriwas et al., 2021). However, the GLUT inhibitory and antineoplastic action of DRB18 has not been reported for any hematological malignancies. The wide range of low to high IC<sub>50</sub> values indicates the need for testing its efficacy and safety for antineoplastic applications against a wider variety of preclinical cancer models. It is also unclear if DRB18 can modulate the cytotoxic action of other antineoplastic agents. Safety issues on normal tissues and organs of the tumor-bearing host also remain largely unverified. Moreover, DRB18 is water insoluble, which could be another limitation of its use in anticancer strategies.

## BAY-876

A quinoline derivative named BAY-876 (Figure 5C) was initially identified for its highly selective GLUT1 inhibitory potential by (Siebeneicher et al., 2016b), which also exerts its actions in nM ranges but has limited ability to inhibit other GLUT isoforms like GLUT2, GLUT3, and GLUT4. Additional advantages of BAY-876 include its aqueous stability *in vitro* and adequate bioavailability upon administration through the oral route (Siebeneicher et al., 2016b). BAY-876 manifests antineoplastic action mainly *via* its ability to inhibit GLUT1 leading to multiple actions on neoplastic cells, including suppression of

proliferation, drug-resistance, EMT, and metabolism (Yang et al., 2021). BAY-876 was reported to manifest increased NADP<sup>+</sup>/NADPH simulating glucose starvation conditions (Chen et al., 2022). However, the antineoplastic activity of BAY-876 needs to be validated on a broader range of neoplastic cells. However, docking studies have been performed on BAY-876 for binding to GLUT1 (Ojelabi, 2017), and its exclusive binding to only GLUT1 limits its therapeutic applications. Moreover, the safety of its *in vivo* applications needs further verification.

## Fasentin

Fasentin N-(4-chloro-3-(trifluoromethyl)phenyl)-3-oxobutanamide (Figure 5D) is a small molecule inhibitor of GLUT that was initially reported as a sensitizer to induction of cell death *via* FAS and TNF (Kraus et al., 2018; Ocaña et al., 2020) later it was reported that Fasentin leads to glucose deprivation by its ability to bind to GLUT1 and GLUT4 as revealed by docking studies (Wood et al., 2008). However, despite the promising GLUT1 inhibitory potential alongside sensitization of cells to death stimuli, not much has been worked out concerning its antineoplastic potential. A recent study reported that fasentin could inhibit the proliferation of endothelial cells and hence may have an implication in antiangiogenic therapeutic strategies. However, its effect on other normal healthy cells must be explored to predict safety issues (Ocaña et al., 2020). Moreover, the effect of fasentin is apparent in about 100 μM range (Ocaña et al., 2020) which is on the higher side than that desired for an effective and safe therapeutic agent.

## STF-31

Another promising GLUT1 inhibitory agent with antineoplastic potential is STF-31 (Figure 5E) (Chan et al., 2011; Adams et al., 2014; Xintaropoulou et al., 2015; Kraus et al., 2018). It was shown initially to manifest renal cell carcinoma (RCC) specific cytotoxic action (Chan et al., 2011). Additionally, STF-31 has been shown to modulate HIF and target NAMPT to manifest its antineoplastic action (Adams et al., 2014; Xintaropoulou et al., 2015). Moreover, Kraus et al. (2018) reported that the anticancer action of STF-31 is apparent only at higher concentrations, and hence there is a need for further optimization and testing on a broad range of neoplastic target cells both *in vitro* and *in vivo* to explore its dual inhibitory action on GLUT1 and NAMPT. However, the utility of the same will depend on the expression levels of GLUT1 and NAMPT, which may vary in a tumor-to-tumor manner. Moreover, it is also reported that if cancer cells express GLUT2, they can overcome the inhibitory action of STF-31 and that it does not harm normal cells (Chan et al., 2011).

## Glutor, a Pan-GLUT inhibitor

Recently a pan-GLUT inhibitor named glutor has been demonstrated to exhibit a potent antineoplastic action in the nanomolar concentration range against cancer cells of diverse origins (Reckzeh and Waldmann, 2020a; Reckzeh and Waldmann, 2020b; Temre et al., 2022). Glutor is (S)-6-Methyl-5-(4-morpholinobenzyl)-4-oxo-2-phenyl-N-(pyridin-3-ylmethyl)-4,5,6,7-tetrahydropyrazolo [1,5-a] pyrazine-6-carboxamide, with the empirical formula C<sub>3</sub>H<sub>32</sub>N<sub>6</sub>O<sub>3</sub>, and molecular weight of 536.62 (Figure 5F) (Reckzeh et al., 2019).

Glutor was identified to inhibit GLUT1, GLUT2 and GLUT3 in HCT116 cells (Reckzeh et al., 2019). The inhibition of the uptake of 2DG was determined to have an IC<sub>50</sub> value of 11 nM in most sensitive cell lines, including urinary cancer-derived cell lines, which are most glucose-addicted (Lea et al., 2015). Interestingly glutor was found to impart no cytotoxicity on normal healthy peripheral blood mononuclear cells and Institute for medical research-90 (IMR-90) embryonic lung cells (Reckzeh et al., 2019). Further, the elegant study of Reckzeh et al. (2019) also screened the antineoplastic action of glutor on a battery of about 94 cancer cell lines of diverse origins, and it was observed that the antineoplastic action was exerted with IC<sub>50</sub> values of less than 100 nM. Moreover, the inhibitory action of glutor was also evaluated in multicellular spheroids of HCT-116 cells (Reckzeh et al., 2019). Interestingly glutor treatment minimized glucose deprivation in a dose-dependent manner. Hence, glutor displays the potential for effectively inhibiting glucose uptake in solid tumors. However, it was also reported that some cell lines like BxPC-3 exhibit resistance to glutor. The sensitivity or resistance to glutor depends on the cancer cells' metabolic background (Reckzeh et al., 2019). The glutor resistance cell lines can stitch between glycolytic and OXPHOS phenotypes (Reckzeh et al., 2019). Depending on the metabolic make-up of the target cells and selected dose, glutor could usher a complete glucose deprivation condition, even leading to upregulation of GLUT1 and GLUT3 expression due to hypoglycemia. Moreover, it is also likely that by its ability to cause inhibition of GLUT1, GLUT2, and GLUT3, glutor possesses an extraordinary capacity to overcome the rescue and compensatory mechanisms of highly adaptive neoplastic cells. It is also noteworthy that the study of Reckzeh et al. (2019) also indicated that neoplastic cells' cytostasis and cytotoxicity could be synergistically upregulated by using glutor along with glutaminase inhibitor CB-839.

Thus, the results obtained based on screening of glutor for its antineoplastic action on 94 cancer cell lines derived from highly malignant cancers revealed the extraordinary ability of glutor to inhibit glucose uptake, glycolytic flux, and cell survival (Pliszka and Szablewski, 2021).

However, despite the evaluation and certification of the antineoplastic action of glutor on cancer cell lines of diverse origins, the same has not been evaluated in any *in vivo* tumor

model, which will be necessary to assess the translational value of glutor's antineoplastic potential for therapeutic applications. Moreover, the issues of bioavailability and ideal administration routes also need to be assessed in an appropriate *in vivo* model.

Glutor treatment of tumor cells inhibited cell survival and increased cell death. It also caused a decrease in glucose uptake associated with altered expression of GLUT1 and GLUT3. HIF-1 $\alpha$ , HK-2, LDH-A, and MCT1 also decreased with diminished lactate production and deregulated pH homeostasis. Moreover, the expression of cell survival regulatory molecules p53, Hsp70, IL-2 receptor CD25, and C-myc was modulated upon treatment with glutor. Additionally, glutor treatment triggered mitochondrial membrane depolarization, accompanied by high ROS generation and the modulated ratio of Bcl-2/BAX. Chemosensitivity of tumor cells increased following exposure to glutor and decreased MDR1 expression (Temre et al., 2022). Hence, these observations indicate that glutor has the potential to be used in antineoplastic therapeutic applications.

## Other inhibitors

Other crucial small molecule inhibitors of GLUT include GLUTi1 and GLUTi2 (Kapoor et al., 2016), compound 3 (Siebeneicher et al., 2016a), compound 15b (Liu et al., 2020), PUG1 (Ung et al., 2016), KL-11743 (Olszewski et al., 2022), and NV5440 (S. A. Kang et al., 2019) which belong to diverse families of chemicals and exert limited GLUT isoform inhibitory potential and have high IC<sub>50</sub> values, so the possibilities of *in vivo* toxicity remains a concerning issue. Further, the neoplastic cell inhibitory potential in most of these remains limited to only a few targets investigated. Tuccinardi et al. reported the GLUT1 inhibitory potential of oxime-based inhibitors with compatibility to inhibiting the growth of the H1299 lung cancer cell line (Tuccinardi et al., 2013). However, not much has been reported further on the anticancer potential of this category of inhibitors except for their utility in developing novel GLUT inhibitory agents.

## Combinatorial approaches

Studies have indicated the promising potential of a combinatorial approach for GLUT inhibition instead of a single inhibitor approach (Tilekar et al., 2020). Such approaches mainly involve a combination of agents with 1) the ability to directly bind to GLUT isoforms and cause their inhibition; 2) approaches to inhibit expression of GLUT, and 3) use of agents which compete with glucose for binding to GLUTs and hence cause inhibited glucose transport. Further to achieve success in such approaches, GLUT inhibitors with pan-GLUT inhibitory potential can be of great use to usher the inhibition of

multiple GLUT isoforms. Moreover, a combination of multiple GLUT inhibitors of natural and synthetic origin can also be considered and has shown hope during *in vitro* experiments on cancer cell lines of various origins ((Kast et al., 2016; Sawayama et al., 2019; Tilekar et al., 2020). However, adding several inhibitors together may cause toxicity and can likely lead to certain harmful effects on normal healthy cells, which also use GLUT isoforms for glucose uptake. Further, most of such combinations still lack the much-required *in vivo* testing for evaluating efficacy and safety parameters. Moreover, WZB117 (Chen et al., 2017), 2DG (Lee et al., 2016), and BAY876 (Mori et al., 2019) have also been sporadically used in combination with chemotherapeutic agents under *in vivo* experimentation. Moreover, several studies have been conducted to evaluate the outcome of combining various GLUT inhibitors for achieving optimum inhibition of glucose uptake (Tilekar et al., 2020). The most promising of such combinations with successful antineoplastic outcomes include combination of GLUT inhibitors like cytochalasin B, WZB117 and its derivatives, BAY-876, silibinin, glutor, STF-31 and phloretin with other conventional anticancer drugs like doxorubicin, curcumin, etoposide, cisplatin, 5-fluorouracil, vincristine, cytarabine, oxaliplatin, paclitaxel and antimycin A (Liu et al., 2012; Tsakalozou et al., 2012; Li et al., 2019; Trendowski, 2015; Trendowski, 2015; Kapoor et al., 2016; Chen et al., 2017; Reckzeh et al., 2019; Zambrano et al., 2019; Barbosa and Martel, 2020; Joly et al., 2020; Tilekar et al., 2020; Wu et al., 2020; Shriwas et al., 2021; Olszewski et al., 2022; Temre et al., 2022; Weng et al., 2022) to name a few such representative anticancer drugs in cancers of diverse origins. Nevertheless, inhibitors of other molecules and/or pathways have also been combined with GLUT inhibitors to achieve fruitful antineoplastic effects (Tsakalozou et al., 2012; Tilekar et al., 2020; Weng et al., 2022). For example, the combination of glutor with glutaminase inhibitor CB-839 resulted in successful antineoplastic manifestations (Reckzeh et al., 2019). Additionally, combination with GLUT inhibitors with radiotherapeutic strategies had also displayed improved antineoplastic potential (Zhao et al., 2016). Moreover, GLUT inhibitors, combined with other antiglycolytic agents, also result in superior inhibition of tumor cell metabolism, compared to such action of these agents when applied alone (Raez et al., 2013; Barbosa and Martel, 2020; Tilekar et al., 2020). These studies are also limited in their long-lasting impact in designing novel therapeutics due to the lack of extensive *in vivo*-based investigations to assess safety and toxicity issues on normal healthy cells and tissues. However, despite the limitations above, combinatorial approaches hold promise for formidable antineoplastic therapeutic applications to overcome drug- and radio-resistance and synergize with the anticancer action of individual agents. Importantly, a combination of GLUT inhibitors with chemotherapeutic agents will also aid in reducing the cytotoxic dose of

chemotherapeutic agents and hence minimize their side effects, which need experimental validation. Moreover, combining GLUT inhibitors with other antineoplastic therapeutic agents to manifest a robust and multifaceted inhibition of tumor metabolism could also be a promising antineoplastic strategy. However, such possible combinations are yet to be fully explored. The combinatorial approach of multiagent strategies must be carefully explored to optimize anticancer action while minimizing the side effect. These promising results are also being explored for translational therapeutic potential in clinical trials.

## Additional approaches

### GLUT antibodies

For a long, attempts have been made to make the best utilization of anti-GLUT antibodies to block glucose transport by GLUT. Anti-GLUT1 antibodies have been demonstrated to inhibit glucose uptake in resealed erythrocyte membrane ghosts (Afzal et al., 2004). Nevertheless, a study using Cal27 cells showed that anti-GLUT1 antibodies could inhibit proliferation, induce apoptosis, and chemosensitization for cisplatin (Wang et al., 2013). A study by Rastogi et al. (2007) reported that anti-GLUT1 antibodies could arrest cell growth accompanied by induction of apoptosis in cell lines derived from breast and non-small cell lung cancer (NSCLC). Additionally, anti-GLUT1 antibodies also chemosensitized MCF7 cells to cisplatin, paclitaxel, and gefitinib (Rastogi et al., 2007). Further, anti-GLUT1 antibodies have also been explored for the targeted delivery of chemotherapeutic agents (Barbosa and Martel, 2020). However, a literature search reveals that the spectrum of cancers against which anti GLUT1 antibodies have been tested is limited to realizing their therapeutic potential.

### miRNAs in anti-GLUT strategies

There have been attempts to use the potential of miRNAs to target various aspects of tumor metabolism, including GLUTs (Chen et al., 2012; Pedroza-Torres et al., 2019; Shiah et al., 2021). miRNAs like miR-133 and miR-195-5P have modulated gene transcription of various GLUT isoforms (Macheda et al., 2005; Krüger et al., 2008). In this quest, miRNA to GLUT1, GLUT3, and GLUT4 has shown promising antineoplastic potential in prevalent cancers like lung, prostate, breast, colorectal carcinoma, bladder cancer, and pancreatic adenocarcinoma (Lu et al., 2010; Chen et al., 2012; Fei et al., 2012; Chen et al., 2015; Zhao et al., 2017; Pedroza-Torres et al., 2019; Azizi et al., 2021; Shiah et al., 2021). Moreover, a direct inverse correlation has been reported between miRNA-144 and GLUT1 in breast

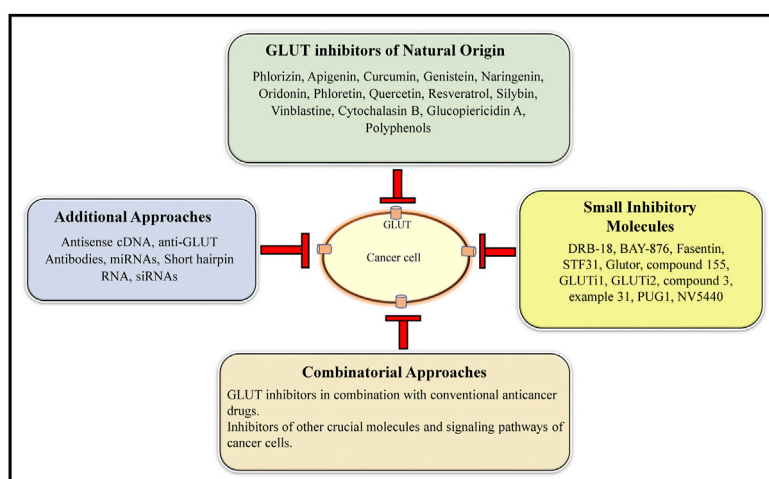
and non-small cell lung cancer (NSCLC) (Azizi et al., 2021). Similarly, the role of miR-22, miR1291, and miR-195-5P have been associated with GLUT1, and GLUT3 in breast, RCC, and T24 cells, respectively (Fei et al., 2012; Yamasaki et al., 2013; Chen et al., 2015; Alamoudi et al., 2018). Given such intimacy between various miRNAs and GLUT isoforms, there is a strong logic to utilize them in therapeutic applications. Similarly, a study on the role of MiR-218 and MiR340 in the expression of GLUT1 is demonstrated in oral squamous cell carcinoma (OSCC) (Xu et al., 2018; Wang et al., 2020; Shiah et al., 2021). Combinatorial use of miRNAs with other conventional GLUT1 inhibitors is also needed to be explored to circumvent GLUT at both gene expression and protein function levels.

### Short hairpin RNA

Short hairpin RNA (shRNA) to GLUT1 has shown a promising inhibitory effect on M.D. Anderson - Metastatic Breast 231 (MDA-MB-231) and *Homo sapiens*-578 tumor cells (HS578T) triple-negative breast cancer (TNBC) cell lines (Oh et al., 2017; Shriwas et al., 2018; Wu et al., 2020). Similarly, the use of shRNA to GLUT1 was observed to show promising outcomes in colon cancer cells (Bai et al., 2019). Wang et al. (2020) demonstrated that shRNA inhibits the survival of laryngeal carcinoma HEP2 cells *via* beclin-1-associated autophagy. shRNA to GLUT1 is also reported to effectively block glucose uptake in various cancer cell lines (Pliszka and Szablewski, 2021). Thus, the shRNA approach is also promising for effective combat against GLUT expression and function in neoplastic cells by silencing gene expression of various isoforms of glucose transporters.

### Antisense cDNA

Approaches to transfecting neoplastic cells with GLUT1 antisense cDNA have been demonstrated to usher in a decline in the gene expression of GLUT1 and an increase in radiosensitivity of neoplastic cells (Chan et al., 1999; Ito et al., 2000; Yan et al., 2013; Pliszka and Szablewski, 2021). The common cancers used to test this approach include leukemia, gastric, rhabdosarcoma, breast, and glioblastoma (Ito et al., 2002; Chan et al., 2004; Yang et al., 2019; Pliszka and Szablewski, 2021). However, not much breakthrough is yet reported using this approach, and its clinical applications need to be evaluated. The approaches mentioned above of 'nipping in the bud' of GLUT expression level have still not come into vogue for preclinical and clinical trials as more basic data needs to be collected before embarking further. However, the most popular and explored approaches are still to identify the best pan-GLUT inhibitor, as other approaches to gene intervention can have potentially harmful outcomes. In this quest, a newly recognized



**FIGURE 6**

A collation of the current GLUT inhibitory approaches. The main GLUT inhibitors belong to both natural and small inhibitory molecule categories. In addition, antisense cDNA, anti-GLUT antibodies, miRNAs, shRNA, and siRNAs constitute additional GLUT inhibitory approaches. GLUT inhibition can be further potentiated by combining the GLUT inhibitors of natural origin and small inhibitory molecule categories.

pan-GLUT inhibitor named glutor is emerging with the hope of effective GLUT1 and GLUT3 inhibition.

## Epilogue

The review above shows that inhibition of GLUT can be a promising antineoplastic therapeutic approach, which needs to be vigorously approached at preclinical and clinical levels. Figure 6 shows a summary of the various GLUT inhibition strategies holding a strong supporting experimental evidence. Since many of these strategies have been explored only on cell lines, their further validation in appropriate *in vivo* animal models is essential before exploring the clinical potential. As stated above, selecting those GLUT inhibitors with a pan-GLUT inhibitory potential at low concentrations will be necessary to avoid toxicity on normal healthy cells and organs. Assessing safety on crucial physiological parameters, including blood profile, renal and hepatic function, will also be essential. The half-life of the GLUT inhibitors and their renal clearance needs to be determined for dose optimization. As GLUT plays a critical role in neurological functions, the ability of GLUT inhibitors to cross the blood-brain barrier must be critically evaluated.

It will be essential to consider the safety of the combinatorial approach of GLUT inhibitors. As a massive fraction of the human population is coming under various metabolic disorders, including diabetes, GLUT inhibitors' impact must be carefully evaluated in such patients. However, overcoming these lacunas and unaddressed issues

indicates a bright future for using GLUT inhibition approaches in anticancer regimens.

Based on the criteria for selection of GLUT inhibitors, it emerges that glutor is one of the best to choose for further investigations owing to the following points in its favor:

- 1) It is worked out to be a Pan-GLUT inhibitor and hence is supposed to exert a more potent inhibitory action on glucose uptake
- 2) It has been screened against 94 cancer cell lines and is found to be effective in more than half of cell lines for its cytostatic action, and no other small molecule inhibitor has been tested on such a broad range of target cancer cells of diverse etiology.
- 3) Its antineoplastic action is exerted in the nanomolar concentration range and has been shown to have the least toxic effect on normal cells.
- 4) Its easy accessibility at the commercial level for further investigation.

Therefore, based on our evaluation glutor has an edge over other pan-GLUT inhibitors for further investigations at preclinical and clinical level.

## Author contributions

MT: conceiving the idea, a survey of the literature, writing, and preparation of the manuscript. AK: conceiving the idea and writing the manuscript. SS: conceiving the idea and writing the manuscript.



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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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