



Glucose and antidiabetic therapy in temozolomide resistance in glioblastoma

Emir Begagić, Amina Džidić-Krivić, Hakija Bečulić, Ragib Pugonja, Adnana Ljevaković, Binasa Bašić, Adem Nuhović, Elma Milanović, Semir Hadžić, Emir Bećirović, Lemana Buljubašić, Minela Bećirović, Mirza Pojskić

Specialty type: Oncology

Provenance and peer review:

Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade B

Novelty: Grade B, Grade B

Creativity or Innovation: Grade B, Grade C

Scientific Significance: Grade B, Grade B

P-Reviewer: Wang N

Received: April 8, 2025

Revised: April 25, 2025

Accepted: June 25, 2025

Published online: August 24, 2025

Processing time: 136 Days and 11.9 Hours



Emir Begagić, Hakija Bečulić, Department of Neurosurgery, Cantonal Hospital Zenica, Zenica 72000, Bosnia and Herzegovina

Amina Džidić-Krivić, Department of Neurology, Cantonal Hospital Zenica, Zenica 72000, Bosnia and Herzegovina

Ragib Pugonja, Department of Otorhinolaryngology, Cantonal Hospital Zenica, Zenica 72000, Bosnia and Herzegovina

Adnana Ljevaković, Binasa Bašić, Department of Neurology, General Hospital Travnik, Travnik 72270, Bosnia and Herzegovina

Adem Nuhović, Department of Infective Diseases, University Clinical Center Sarajevo, Sarajevo 71000, Bosnia and Herzegovina

Elma Milanović, Department of Neurology, University Clinical Center Sarajevo, Sarajevo 71000, Bosnia and Herzegovina

Semir Hadžić, Department of Endocrinology, University Clinical Center Tuzla, Tuzla 75000, Bosnia and Herzegovina

Emir Bećirović, Department of Intensive Care, University Clinical Center Tuzla, Tuzla 75000, Bosnia and Herzegovina

Lemana Buljubašić, Department of Rehabilitation, University Clinical Center Tuzla, Tuzla 75000, Bosnia and Herzegovina

Minela Bećirović, Department of Nephrology, University Clinical Center Tuzla, Tuzla 75000, Bosnia and Herzegovina

Mirza Pojskić, Department of Neurosurgery, University Hospital Marburg, Marburg 35037, Hesse, Germany

Corresponding author: Emir Begagić, MD, Academic Editor, Department of Neurosurgery, Cantonal Hospital Zenica, Crkvice 67, Zenica 72000, Bosnia and Herzegovina.

begagicem@gmail.com

Abstract

Glioblastoma (GBM) remains a major clinical challenge due to limited therapeutic success despite standard treatments including surgery, radiotherapy, and temozolomide (TMZ). Recent evidence links hyperglycemia to cancer progression, and altered glucose metabolism has emerged as a key factor in GBM development. Metformin, an antidiabetic drug, has shown promise in improving survival in GBM patients, possibly due to its ability to cross the blood-brain barrier and target metabolic pathways involved in tumor growth. Preclinical studies suggest metformin may enhance TMZ efficacy by acting on glioma stem cells and overcoming resistance mechanisms. Its activation of AMPK and modulation of Wnt signaling further support its therapeutic potential. However, while early studies and clinical trials have explored metformin's safety and efficacy, its direct impact on GBM survival remains unclear. Ongoing research aims to clarify its mechanisms and identify responsive patient subgroups. Novel strategies, including PPAR γ agonists and nanoerythrocyte-based drug delivery systems, are also under investigation to improve metformin's therapeutic profile. Rigorous clinical trials and mechanistic studies are essential to determine the role of metformin as adjunct therapy in GBM treatment.

Key Words: Drug resistance; Glioblastoma multiforme; Neoplasms; Glucose metabolism; Antidiabetic drugs

©The Author(s) 2025. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Metformin shows promise as an adjunct therapy in glioblastoma by modulating glucose metabolism, enhancing temozolomide efficacy, and targeting glioma stem cells. Its ability to cross the blood-brain barrier and influence pathways such as AMPK and Wnt highlights its potential. However, its impact on survival remains unclear, requiring further clinical validation.

Citation: Begagić E, Džidić-Krivić A, Bečulić H, Pugonja R, Ljevaković A, Bašić B, Nuhović A, Milanović E, Hadžić S, Bećirović E, Buljubašić L, Bećirović M, Pojskić M. Glucose and antidiabetic therapy in temozolomide resistance in glioblastoma. *World J Clin Oncol* 2025; 16(8): 108112

URL: <https://www.wjgnet.com/2218-4333/full/v16/i8/108112.htm>

DOI: <https://dx.doi.org/10.5306/wjco.v16.i8.108112>

INTRODUCTION

Cancer is a cellular-level disease characterized by alterations in cell cycle control mechanisms, involving uncontrolled cell division and avoidance of programmed cell death marked as apoptosis[1,2]. Damage to cellular DNA by endogenous or exogenous factors hinders DNA repair mechanisms, leading to insufficient control over programmed cell growth and promotes cancer development[3]. Cancer cells adapt metabolically to survive in the tumor microenvironment, relying on a constant nutrient and energy supply in unfavorable conditions[4]. Recently, hyperglycemia has been recognized as one of oncogenic factors for certain cancers, the direct impact of glucose on cancer cell behavior remains unclear[5]. The role of glucose metabolism has also been researched in the development of primary brain tumors. Classified under gliomas, primary brain tumors include astrocytic tumors like glioblastoma (GBM), oligodendrogliomas, ependymomas, and mixed gliomas[6,7]. GBM is a grade IV glioma that remains one of the most prevalent and severe solid tumors among primary brain tumors. Around 6 cases per 100000 people are diagnosed each year, accounting for approximately 45.2% of all brain cancers[1,2]. It is the most common and malignant astrocytoma with poor prognosis and an average survival of 14 to 15 months from initial diagnosis[8,9].

Predominantly affecting the elderly and men, GBM symptoms include persistent headaches, nausea, vomiting, vision disturbances, and seizures[10]. The treatment of GBM, despite numerous researches, has very limited success. It still remains the most demanding task in clinical oncology, as the treatment of patients with GBM requires a multidisciplinary approach in terms of symptomatic treatment, surgical treatment, radiotherapy, and chemotherapy[10,11]. Although advances in surgical intervention, radiotherapy, and adjuvant chemotherapy have led to incremental improvements in survival and quality of life among patients with GBM, the overall prognosis remains poor. The current therapeutic standard comprises symptomatic management, including corticosteroids, along with surgical resection followed by radiotherapy and adjuvant chemotherapy with temozolomide (TMZ).

TMZ currently represents the gold standard chemotherapeutic agent for the treatment of GBM. Its cytotoxic effect is primarily mediated through DNA methylation at the N7 and O6 positions of guanine residues, as illustrated in Figure 1. This modification disrupts the DNA mismatch repair (MMR) system's ability to locate a complementary base, resulting in persistent DNA strand breaks. These lesions trigger cell cycle arrest at the G2-M transition and ultimately induce apoptosis[12]. Elevated activity of O6-methylguanine-DNA methyltransferase (MGMT) in tumor cells has been associated with decreased responsiveness to TMZ. By repairing the DNA damage caused by TMZ, MGMT plays a critical role in decreasing the cytotoxic effects of TMZ and creating resistance. This is also influenced by other DNA repair processes,

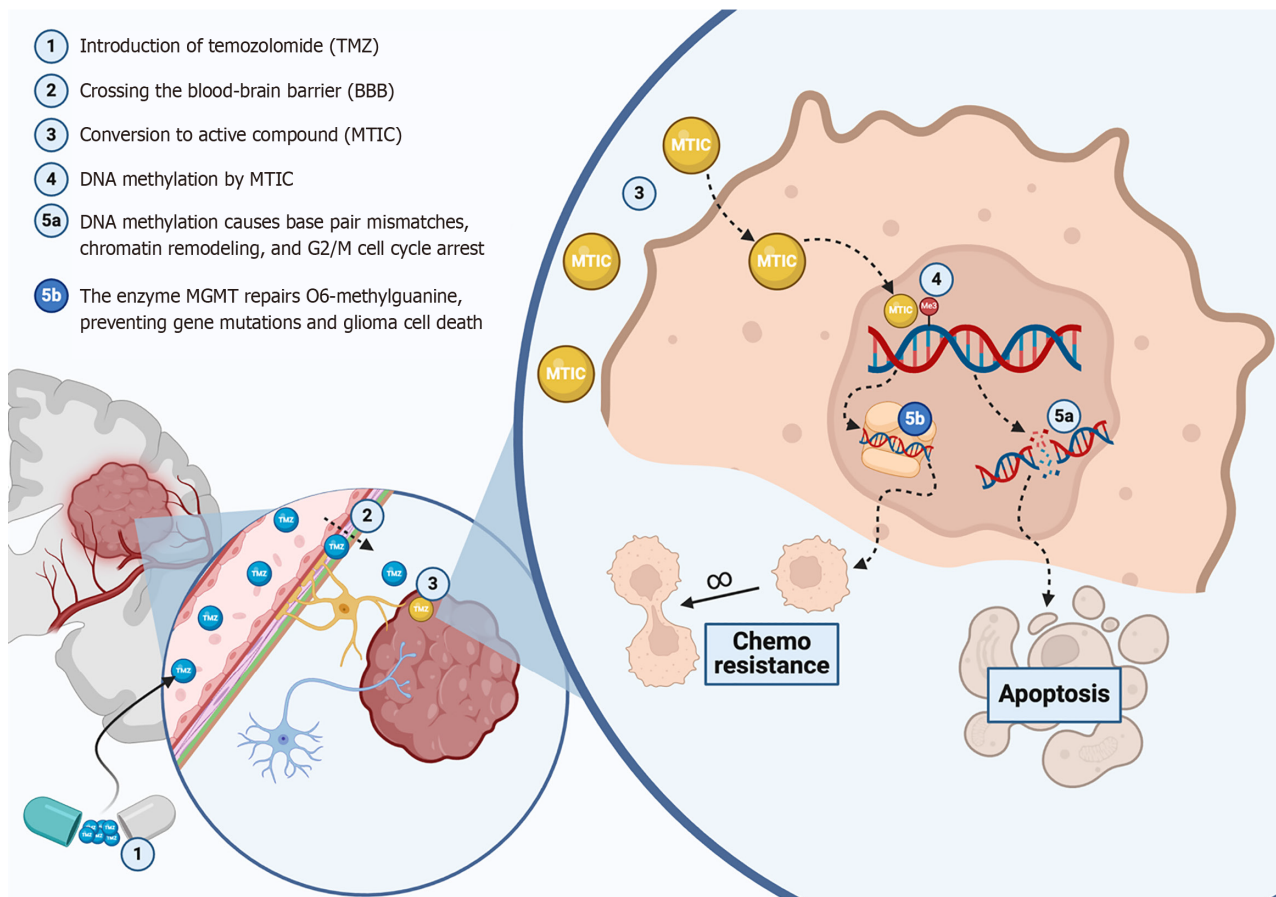


Figure 1 The basic mechanism of action of temozolomide in the treatment of gliomas. Temozolomide reaches high-grade glioma cells after passing through the blood–brain barrier. The active molecule (MTIC), which methylates DNA bases, splits double-strand DNA, and triggers apoptosis. O6-methylguanine-DNA methyltransferase and other DNA repair pathways are in opposition to MTIC action. MTIC: 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide; TMZ: Temozolomide; MGMT: O6-methylguanine-DNA methyltransferase; BBB: Blood-brain barrier. This figure was created by BioRender.com (Supplementary material).

including base excision repair and MMR. MGMT is a key DNA repair enzyme that protects tumor cells against the cytotoxicity of alkylating agents such as TMZ by reversing O6-methylguanine lesions. The methylation status of the MGMT gene promoter serves as a predictive biomarker of treatment response, with promoter hypermethylation correlating with increased TMZ sensitivity. Overall, various factors, such as improved DNA repair, altered cellular signaling, mitochondrial malfunction, and metabolic alterations contribute to the complexity of TMZ resistance in GBM [13–16].

The main aim of this review is to investigate the association between glucose metabolism, antidiabetic therapy and TMZ resistance in GBM. As GBM remains largely incurable despite various common therapeutic approaches, understanding how glucose levels and antidiabetic medications influence resistance to TMZ is crucial. According to the findings of recent studies, influencing the metabolism and microenvironment of GBM cells is a potential novel treatment approach for GBM. Maintaining low physiological glycemia levels and regularly controlling glycemia in GBM patients could help to modulate the efficiency of anticancer medications like dexamethasone (DXM) and TMZ. This highlights the urgent need for larger clinical trials aiming to decipher mechanisms of action of the different antidiabetic medications, such as metformin. Therefore, recent studies investigated the synergistic effects of combining TMZ with drugs that control glucose uptake and metabolism. Further studies should confirm that targeting glucose metabolism and its related pathways could offer novel therapeutic methods to overcome TMZ resistance in GBM.

COMPLEX RELATIONSHIP BETWEEN ALTERED GLUCOSE METABOLISM AND GBM DEVELOPMENT

Recent evidence suggests that disrupted glucose metabolism significantly contributes to the invasiveness and proliferation of hypoxic tumors such as GBM[9–12]. DXM, commonly administered to manage cerebral edema in GBM patients, appears to enhance cellular energy metabolism by promoting viability and proliferation under low-oxygen conditions. This metabolic support may facilitate the development of resistance to TMZ, thereby contributing to tumor recurrence in this highly aggressive malignancy[13]. Glucose serves as the principal energy substrate for cancer cells, and variations in its concentration are critical to sustaining their tumorigenic potential. This metabolic reprogramming is often described by the Warburg effect, which denotes the preferential shift of GBM cells toward aerobic glycolysis. Aerobic glycolysis is highly dependent on glucose metabolism, as shown in Figure 2, and this metabolic change promotes GBM cells' fast

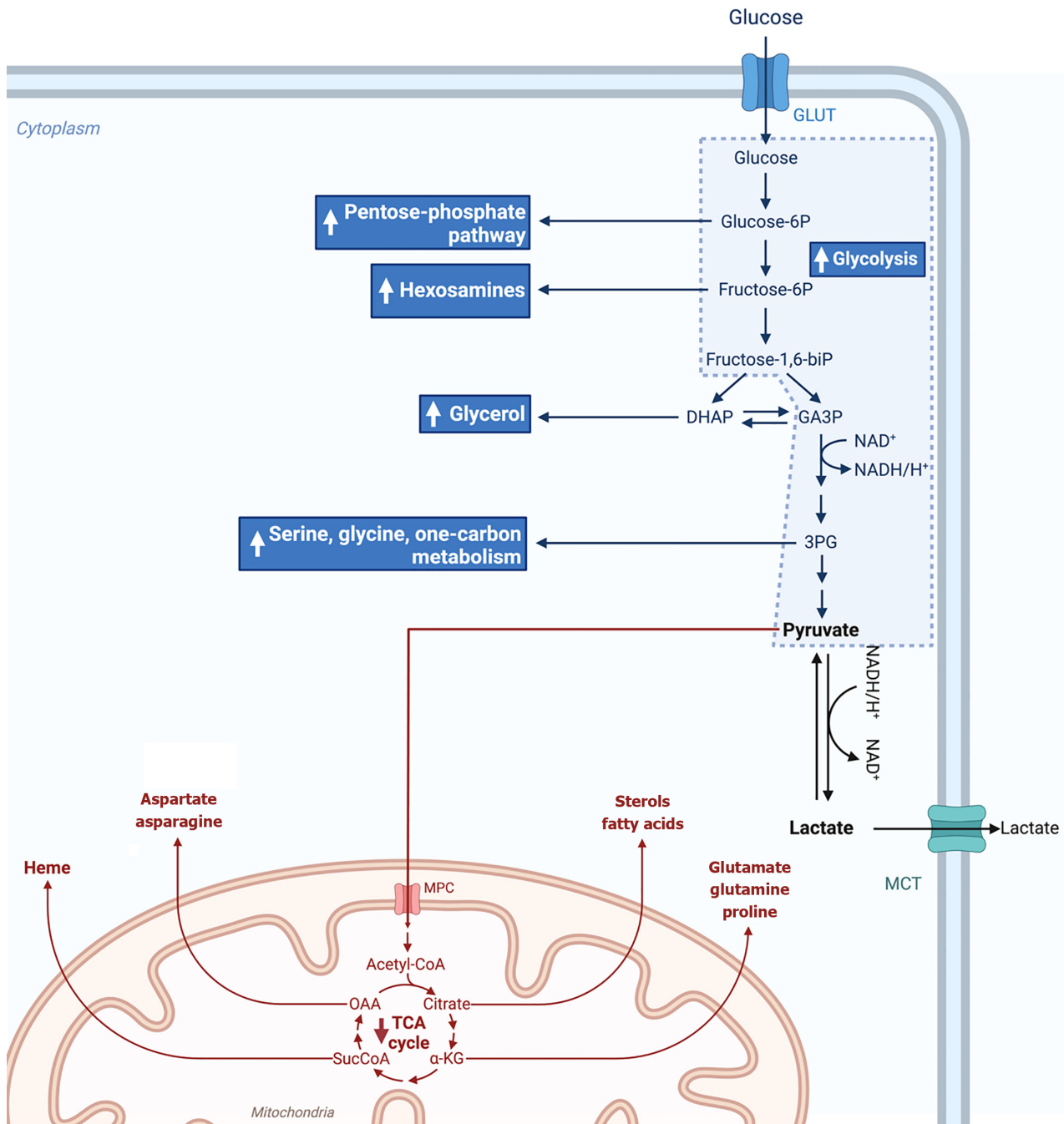


Figure 2 Illustration of glucose metabolism metabolized in a tumoral cell. The Warburg effect, also known as aerobic glycolysis, marks the process of glucose conversion to pyruvate and then to lactate, despite cancer cells having a fully functional respiratory chain. In addition to increasing the amount of lactate and protons secreted into the extracellular space, an enhanced glycolytic pathway also makes glycolysis intermediates more readily available. This enables the increased flow of substrates to the one-carbon cycle and pentose phosphate pathway, which supports lipid and nucleotide synthesis and preserves redox homeostasis. 1,3-biPG: 1,3-biphosphoglycerate; 2-PG: 2-phosphoglycerate; 3-PG: 3-phosphoglycerate; ADP: Adenosine diphosphate; αKG: Alpha-ketoglutarate; ALDO: Aldolase; ATP: Adenosine triphosphate; DHAP: Dihydroxyacetone phosphate; ENO: Enolase; FAD+: Flavin adenine dinucleotide; G6PD: Glucose-6-phosphate dehydrogenase; GA3P: Glyceraldehyde 3-phosphate; GAPDH: Glyceraldehyde 3-phosphate; GDP: Guanosine diphosphate; GLUT1: Glucose transporter 1; GSH: Glutathione; GTP: Guanosine triphosphate; Hcy: Homocysteine; HK: Hexokinase; LDH: Lactate dehydrogenase; MCT4: Monocarboxylate transporter 4; Met: Methionine; NAD+: Nicotinamide adenine dinucleotide; NADP: Nicotinamide adenine dinucleotide phosphate; OAA: Oxaloacetic acid; PEP: Phosphoenolpyruvate; PFK: Phosphofructokinase; PGAM: Phosphoglycerate mutase; PGI: Phosphoglucoisomerase; PGK: Phosphoglycerate kinase; PK: Pyruvate kinase; SucCoA: Succinyl-coA; THF: Tetrahydrofolate. This figure was created by BioRender.com (Supplementary material).

growth and survival, which strengthens their resistance to TMZ[10].

In various *in vivo* models and clinical studies, it has been shown that limited availability of glucose with increased production of ketone bodies prolongs survival of cancer patients[9,11]. According to a study by Bielecka-Wajdman *et al*[4] that investigated the effect of hyperglycemia on human GBM cell growth, it was concluded that high glucose (HG) levels promote the progression of GBM. The proposed mechanism underlying this phenomenon involves the enhanced activity of chemoattractant and growth factor receptors, alongside increased proliferation and reduced apoptosis in U87 GBM

cells under HG conditions[3]. Mechanistically, HG has been shown to upregulate both the expression and function of the G-protein-coupled receptor formyl peptide receptor 1 (FPR1) and the epidermal growth factor receptor (EGFR), thereby facilitating GBM cell migration and proliferation in response to their respective agonists[3]. Furthermore, HG promotes the invasiveness of U87 cells and augments vascular endothelial growth factor production, effects largely mediated through FPR1 and EGFR signaling. A range of *in vitro* models, preclinical animal studies, and clinical observations support a positive association between elevated glucose levels and GBM aggressiveness[3,6]. Additional evidence includes enhanced tumorigenic potential and the accelerated growth of xenograft tumors derived from GBM cells in diabetic nude mice models[5]. Although prior investigations have largely concentrated on the molecular characteristics of GBM, the influence of the tumor microenvironment, particularly metabolic factors such as glucose, on its malignant behavior remains insufficiently explored[13-17]. However, based on the results of recent studies, it can be assumed that influencing the metabolism and microenvironment of GBM cells can be a universal therapeutic strategy for all GBM tumors. This area necessitates further investigation to elucidate the mechanisms of action of antidiabetic agents, particularly in the context of GBM. Moreover, consistent glycemic monitoring and the maintenance of low physiological blood glucose levels have been shown to influence the efficacy of anticancer therapies such as TMZ and DXM[18]. Accordingly, glycemic assessment and its appropriate modulation should be considered essential components of standard oncologic treatment strategies in GBM management.

POTENTIAL ROLE OF ANTIDIABETIC THERAPY IN GBM TREATMENT

Type 2 diabetes mellitus (T2DM) is a disease associated with insulin resistance, hyperglycemic state, impaired levels of insulin-like growth factor-1 (IGF-1), as well as chronic inflammation, which can promote the growth of cancer[19]. Many studies suggest that T2DM has an important role in carcinogenesis, especially in GBM[4,20]. The limited success of standard therapies in newly diagnosed GBM multiforme has stimulated interest in exploring alternative therapeutic strategies. Current treatment is largely based on the Stupp protocol, which involves maximal surgical resection of the tumor, followed by adjuvant radiotherapy in combination with TMZ, and subsequent maintenance chemotherapy with TMZ and DXM. Therefore, the potential use of antidiabetic therapy for GBM treatment has been supported by recent studies that noted its inhibitory effects on the growth of cancer cells[21,22]. Pharmacologic treatment options for T2DM encompass several classes of antidiabetic agents, including thiazolidinediones (*e.g.*, rosiglitazone), biguanides (*e.g.*, metformin), sulfonylureas, meglitinides, α -glucosidase inhibitors, amylin analogs, dipeptidyl peptidase-4 inhibitors, incretin-based therapies such as exenatide, and various insulin formulations[19]. However, biguanides and thiazolidinediones are currently the most investigated drugs with potential use for GBM treatment, which was recently shown in *in vitro* and animal models[23-32].

For example, thiazolidinediones have anti-tumor effects and up-regulate PTEN, thus promoting apoptosis in cancer cells[33]. Thiazolidinediones demonstrate antitumor potential through the activation of multiple signaling cascades, including peroxisome PPAR γ , MAPK, inflammatory mediators, and transforming growth factor-beta pathways[22]. Recent study conducted by Zander *et al*[34] investigated the effects of the ligand-activated nuclear receptor PPAR γ on the proliferation and growth of GBM cells, as well as their potential to promote apoptosis of tumor cells. Authors noted that three PPAR γ agonists, LY171 833, ciglitazone, and prostaglandin-J₂, promoted apoptosis in human and rat glioma cells. This was connected with the up-regulation of Bax and Bad protein levels. Therefore, the PPAR γ agonists have the potential to be used as a part of the therapeutic regimen for GBM. Insulin functions not only as a key metabolic hormone but also as a growth factor that can facilitate tumor progression, including in colorectal cancer, where it has been shown to enhance tumor growth, reduce CD8⁺ T cell infiltration, and diminish the efficacy of anti-PD1 immunotherapy. Hyperinsulinemia has been implicated in the development of multiple malignancies, such as pancreatic, hepatic, renal, gastric, pulmonary, breast, and colorectal cancers. Further clinical studies are required to establish clear guidelines regarding the use of insulin in GBM patients undergoing immunotherapeutic interventions[35].

Nevertheless, control of glycemia levels in the blood is desirable due to enhancing the effectiveness of chemotherapy [19]. Glimepiride, a third-generation sulfonylurea, is an oral hypoglycemic agent commonly prescribed for the management of T2DM[36]. However, its impact on tumor biology remains a subject of ongoing debate. Some recent studies suggest that glimepiride increases the risk of the development of tumors, such as colorectal carcinoma and hepatocellular carcinoma[37]. On the other hand, in the orthotopic xenograft mouse model, the combination of radiotherapy and glimepiride in GBM was shown to effectively decrease the growth of GBM cells[38,39]. Kang *et al*[40] reported the potential effect of glimepiride for radio resistance and overcoming recurrence. Larger clinical trials are necessary to further elucidate these findings.

Also, it is well-known that increased levels of circulating insulin/IGF1 and an increase in the insulin/IGF receptor signaling can promote the progression of many types of cancer, including GBM[41,42]. It is noted that increased food consumption promotes the production of IGF-1 in the liver, which acts similarly to insulin and binds to the insulin receptor and IGF-1 receptor. Downstream of insulin receptor activation, signaling is relayed *via* insulin receptor substrate to PI3K and subsequently to Akt/protein kinase B, which in turn indirectly stimulates mTOR complex 1 (mTORC1). In parallel, the insulin receptor also engages growth factor receptor-bound protein 2, leading to activation of the Ras/Raf/ERK signaling cascade. Collectively, these pathways drive oncogenic processes by enhancing cancer cell proliferation[43-47]. Metformin is the antidiabetic drug from the group of biguanides that has the potential ability to reverse these metabolic alterations and carcinogenic pathways[20,23]. However, these findings need further clarification and investigation in larger clinical trials.

Role of metformin in GBM treatment

Current research demonstrates antidiabetic therapy's inhibitory effects on cancer cell proliferation, which has enabled the investigation of its possible application in the treatment of GBM. Novel studies, as noted in Table 1, noted the potential impact of metformin and other antidiabetic drugs on the treatment of tumors, especially GBM.

As illustrated in Figure 3, metformin exerts anticancer effects through multiple mechanisms, including modulation of the PI3K, mTOR, AMPK, and MAPK signaling pathways. Takhwifa *et al*[32] demonstrated that the combination of metformin treatment and glucose deprivation exerts a lethal effect on cancer cells. Systemically, metformin reduces circulating insulin and IGF-1 levels, attenuates insulin/IGF-related signaling, and alters metabolic activity in both normal and malignant cells[32]. Also, recent studies demonstrate that metformin modulates anabolic metabolism, resulting in cell cycle arrest and apoptosis[48], enhances glioma cell responsiveness to TMZ therapy by counteracting MGMT activity[49], and diminishes glioma stem cell populations, thereby increasing treatment sensitivity[50].

Moreover, the therapeutic efficacy of metformin may vary depending on GBM molecular subtypes and patient-specific metabolic profiles[51-54]. For example, IDH-wildtype tumors, characterized by high glycolytic activity, may be more vulnerable to metformin-induced AMPK activation and mTOR suppression. The MGMT promoter methylation status, already known to influence TMZ sensitivity, may also modulate metformin's effectiveness by altering DNA repair capacity[55]. Laviv *et al*[46] reported that insulin resistance is associated with gemistocytes (GCs), a histological feature indicating metabolically active GBM with poor prognosis. These cells were observed more frequently in patients with long-standing hyperglycemia, suggesting that metformin might have enhanced effects in these subpopulations[46]. Further biomarker-driven studies are warranted to clarify and personalize metformin's role in GBM management.

Laviv *et al*[46] also demonstrated that various metabolic factors found in insulin resistance and health conditions such as T2DM and obesity, are connected with the occurrence of specific histologic GBM phenotypes that show the presence of special forms of reactive astrocytes marked as GCs. These cells are frequently observed in GBM, especially in higher-grade or more aggressive types. They are larger, contain more cytoplasm, and are frequently linked to more invasive or metabolically active parts of the GBM. GCs are usually found in GBM's with a poor prognosis and can serve as an indicator for tumor aggressiveness. These cells were also detected in patients with long-term increased glucose levels who were not using insulin as a part of their therapy, thus indicting that GCs could respond to metabolic dysfunction in the GBM. Montemurro *et al*[3] proved that patients with GBM who have diabetes mellitus (DM) and are being treated with metformin, have a longer overall survival (OS) when compared to other antidiabetics. Another proposed mechanism of metformin's antineoplastic potential is its antiproliferative effect, as well as the decrease in angiogenesis due to the promotion of AMPK activity[46,47]. Therefore, metformin's metabolic effects promote the death of tumor cells by taking away their main source of energy, which is glucose.

Zander *et al*[34] conducted an *in vitro* study showing that PPAR γ agonists induce apoptosis and redifferentiation in glioma cells, while sparing healthy astrocytes. This mechanism might support metformin's antineoplastic role through shared pathways.

Potential effects of metformin on TMZ resistance in GBM treatment

The option of combining metformin with TMZ in the treatment of GBM has been recently investigated[48-53]. Furthermore, research indicates that the combined use of TMZ and metformin significantly inhibits glioma cancer stem cells more than either agent alone[54]. Yang *et al*[55] noted that metformin decreased the occurrence of resistance to TMZ therapy in GBM cells. Metformin also inhibited the growth of GBM xenografts *in vivo*, suggesting that metformin and TMZ have synergistic effects.

On the other hand, Seliger *et al*[41] conducted a study on 1731 patients with GBM to investigate the connection between metformin and OS. However, they found no association between DM or increased glucose levels and differences in OS or progression-free survival (PFS) in GBM patients. Similarly, Maraka *et al*[50] and Yoon *et al*[51] did not observe significant clinical benefits, despite the safety of metformin being confirmed. These findings may be influenced by several factors: Lack of stratification by MGMT methylation status (a known predictor of TMZ efficacy), variable metformin doses (from 1000 to 2250 mg/day), short treatment durations, and absence of glycemic monitoring or body mass index (BMI) data. Additionally, steroid-induced hyperglycemia could mask metformin's benefit in real-world use. Therefore, further studies should account for these biological and clinical heterogeneities and emphasize the design of biomarker-guided prospective trials to assess metformin's true efficacy in GBM.

For example, Bielecka-Wajdman *et al*[4] explored the relationship between glucose concentration and TMZ resistance in GBM. In an *in vitro* model employing glucose concentrations of 0.6, 1.0, and 4.5 g/L, the investigators found that only the highest glucose level-mimicking hyperglycemic conditions-promoted a more aggressive GBM phenotype in the T98G cell line as well as in primary GBM cultures HROG02 and HROG17. This enhancement was evident through increased cell viability, proliferation, density, dispersal, chemoresistance, and elevated expression of insulin receptor[4]. The findings also align with previous research on hyperglycemia in patients and elevated glucose concentrations in experimental models. Moreover, the combined administration of TMZ and DXM enhanced TMZ-induced cytotoxicity in cells cultured under low glucose conditions (0.6 and 1.0 g/L), whereas this synergistic effect was absent in HG environments. Although TMZ and DXM together reduced cell viability in a glucose-dependent manner, the observed cytotoxicity was less pronounced than with TMZ monotherapy. However, limitations of the study include the use of a flat bottom plate *in vitro* model without representation of normal human astrocytes, oligodendrocytes, or neurons, a restricted hypoxic condition (2.5%), a brief exposure duration (48 hours) to TMZ/DXM, and the lack of information on BMI.

The authors[4] also performed a retrospective analysis involving 40 patients with GBM who received TMZ and DXM as part of their treatment. The cohort consisted of 17 female and 23 male patients, with a mean age of 54.3 years, all of whom underwent radiochemotherapy (RTM) in combination with prophylactic corticosteroid therapy. The study id-

Table 1 Important studies investigating the potential benefits of antidiabetic drugs in glioblastoma therapy

Ref.	Type of study	Number of patients	Follow-up	Drugs	Mechanisms of resistance	Outcome
Yang <i>et al</i> [55]	Experimental <i>in vitro</i>	Temozolomide (TMZ)-resistant glioblastoma cell lines named U87R and U251R	N/A	Metformin and TMZ	N/A	TMZ resistant cell lines were treated with metformin for 2 weeks and then exposed to TMZ, causing survival rate of glioblastoma cells to drop significantly
Seliger <i>et al</i> [41]	Matched case-control analysis	2005 glioma cases and 20 050 matched controls. 55.2% were men. The mean age was 55.5 (+18.7) years	N/A	Sulfonylurea, metformin and insulin	N/A	A study found an inverse relationship between diabetes and the risk of glioma, most pronounced among those with long-term and poorly controlled diabetes. Antidiabetic medications were unrelated to gliomas
Bielecka-Waldman <i>et al</i> [4]	Experimental <i>in vitro</i> and clinical retrospective analysis	Commercial T98G cell line and two primary GBM lines (HROG02, HROG17) treated with TMZ and/or DXM were combined with clinical analysis on 40 patients, 17 women and 23 men	N/A	TMZ, Dexamethasone (DXM)	High glucose concentrations, MGMT methylation, oxygen conditions, gene mutations (IDH 1 and 2, B-Raf)	For higher glucose concentrations, primary GBM cell lines have shown resistance to TMZ. Simultaneous administration of TMZ and DXM enhanced the cytotoxic action of TMZ in cells cultured in the lower glucose medium (0.6 and 1 g/L glucose) but not in the high glucose medium (4.5 g/L). In clinical analysis in patients with glioblastoma, increased glucose level are positively correlated with an increased expression of Ki-67 proliferation index
Zander <i>et al</i> [34]	Experimental <i>in vitro</i>	Cell lines used: Human U87MG and A172, and rat C6 glioma cells	N/A	PPAR γ agonists (ciglitazone, LY171833, prostaglandin-J2), PPAR α agonist (WY14643), synthetic receptor-antagonists (BADGE)	PPAR γ agonist-induced apoptosis is inhibited by BADGE	PPAR γ agonists induce apoptosis and redifferentiation in glioma cells; primary murine astrocytes are unaffected
Moezzi <i>et al</i> [57]	Experimental <i>in vitro</i> and <i>in vivo</i>	Not applicable (the study focuses on <i>in-vitro</i> and <i>in-vivo</i> experiments, not on patients)	The study includes long-term stability tests over 100 days	Metformin	The study focuses on overcoming resistance through the use of nanoerythrocytes to deliver metformin effectively to glioma cells by protecting the drug from metabolizing enzymes in the blood-brain barrier and extending its presence in circulation	The nanoerythrocytes successfully encapsulated metformin, maintained its stability, and released the drug in a controlled manner. The study concludes that nanoerythrocytes can be a suitable drug delivery system for therapeutic amounts of metformin to treat glioma
Valtorta <i>et al</i> [58]	Experimental <i>in vitro</i>	Two cell lines, U251 and T98G	N/A	Metformin (MET), TMZ and their combination	Combined-treatment modulated apoptosis by increasing Bax/Bcl-2 ratio and reducing reactive oxygen species (ROS) production	MET enhances TMZ effect on TMZ-sensitive cell line (U251) and overcomes TMZ-resistance in T98G GBM cell line
Feng <i>et al</i> [59]	Experimental <i>in vitro</i>	Glioblastoma cell lines (U87MG, LN2308, and LN229)	N/A	Temozolomide, Metformin	MGMT expression, epithelial-mesenchymal transition, mitochondrial biogenesis	Metformin decreased cell viability, proliferation, migration, increased apoptosis and ROS in glioblastoma cell lines; combined treatment with TMZ varied (synergistic in U87, antagonistic in LN2308, and additive in LN229)
Ohno <i>et al</i> [60]	Multicenter single-arm phase I/II study	Phase I included seven patients, between 20 and 74 years of age with newly diagnosed supratentorial GBM to determine MET tolerability, phase II comprised 22 patients	12 months after initial surgery	MET and TMZ combination	Metformin could induce the differentiation of stem-like glioma-initiating cells and suppress tumor formation through AMPK-FOXO3 activation	Phase I study demonstrated that 2250 mg/day MF combined with TMZ appeared to be well tolerated, phase II is ongoing

GBM: Glioblastoma; MGMT: O6-methylguanine-DNA methyltransferase; MF: Metformin.

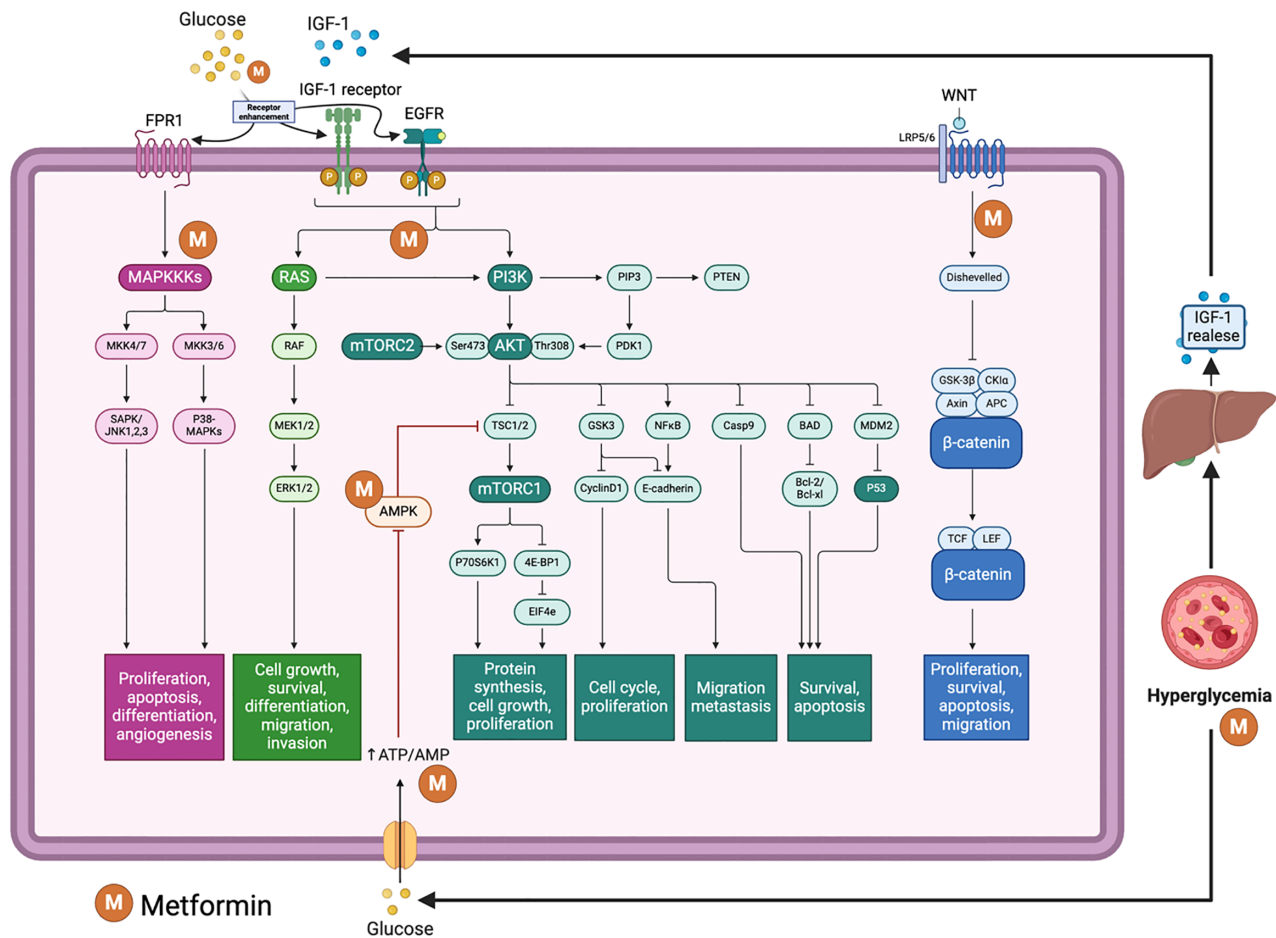


Figure 3 Pathways related to glucose and metformin effects on glioblastoma. Figure illustrates the complex signaling pathways influenced by glucose and metformin in the context of glioblastoma, a type of aggressive brain tumor. Glucose enters the cell and contributes to hyperglycemia, which can indirectly promote tumor growth. Hyperglycemia stimulates the release of insulin-like growth factor 1 (IGF-1) from the liver, which binds to the IGF-1 receptor (IGF-1R) on the cell membrane, activating downstream signaling pathways that include the RAS/MAPK and PI3K/AKT/mTOR pathways. Epidermal growth factor receptor (EGFR) is another receptor that activates similar downstream signaling cascades, further promoting cell growth and survival. The MAPK pathway, activated by both IGF-1R and EGFR, involves several kinases (MAPKKK, MAPKK, MAPK) and leads to cell proliferation, differentiation, and angiogenesis. The PI3K activation leads to the phosphorylation of AKT, which in turn activates mTORC1 and mTORC2 complexes; mTORC1 promotes protein synthesis, cell growth, and proliferation, while mTORC2 supports cell survival and cytoskeletal organization. AKT activation also influences cell cycle regulation and apoptosis through various downstream targets. WNT signaling leads to the stabilization and nuclear translocation of β-catenin, which influences gene expression related to proliferation, survival, and migration. Metformin, a common diabetes medication, activates AMPK, inhibiting mTORC1, thus reducing protein synthesis and cell growth, and promotes glucose uptake, counteracting hyperglycemia. Metformin directly inhibits mitochondrial complex I, leading to increased AMP/ATP ratio and subsequent AMPK activation. It also inhibits IGF-1R and EGFR signaling, reducing the downstream effects on cell growth and survival pathways, and impacts the WNT/β-catenin pathway by reducing β-catenin levels, which may suppress tumor proliferation and survival. This figure was created by BioRender.com (Supplementary material).

entified a correlation between serum glucose levels and Ki-67 expression in tumor specimens, indicating that elevated glycemia was associated with increased tumor cell proliferation. Notably, the highest Ki-67 indices were observed in patients who developed hyperglycemia as a consequence of steroid therapy (post-steroid diabetes). These findings suggest that glucose may play a role in modulating the biological behavior of GBM, as evidenced by the positive correlation between hyperglycemia and Ki-67 expression. The greatest proliferation rates were recorded in patients with post-steroidal diabetes and T2DM, both conditions marked by glycemic instability and transient glucose surges[4,56]. Therefore, this study proposed a connection between *in vitro* results and clinical data, suggesting that HG levels may influence GBM progression[4].

Also, Stepanenko *et al*'s study[18] revealed that extended treatment with TMZ in GBM cell lines resulted in heightened chromosomal instability in tumor cells, which can lead to genetic diversity within the tumor and the promotion of adaptability and resistance to standard therapies. Interestingly, cells subjected to TMZ treatment displayed a unique reaction to decreased glucose concentration, demonstrating increased resistance to TMZ the ability of GBM cells to adapt metabolically during TMZ treatment[57,58]. Valtorta *et al*[58] also observed that during the treatment with metformin, a reduction in aggressiveness and a decrease in SOX2 expression in TMZ-resistant GBM cells occurred, when compared to

untreated-resistant cells. A growing body of evidence suggests that metformin selectively targets CSCs and counteracts multidrug resistance, which should be further investigated by additional pre-clinical and clinical studies.

In addition, Feng *et al*[59] found that these encouraging results from *in vitro* studies led researchers to design clinical studies evaluating the clinical benefits of metformin and TMZ for GBM, which ultimately showed synergistic, antagonistic, and additive effects depending on the cell line. An ongoing phase I dose-escalation trial in Japan, led by Ohno *et al*[60], is assessing the safety and optimal dosing of metformin in combination with maintenance TMZ for patients with newly diagnosed GBM, in preparation for a phase II study. The investigators reported that a daily dose of 2250 mg of metformin was well tolerated, with manageable side effects including appetite loss, nausea, and diarrhea. Tumor progression occurred in two patients at 6.0 and 6.1 months, while one patient died 12.2 months postoperatively. The remaining five patients showed stable disease at last follow-up. Based on these findings, the study advanced to a phase II trial using 2250 mg/day of metformin[60]. Also, a systematic review conducted by Takhwifa *et al*[32] noted that the combination of metformin, with TMZ after the radiotherapeutic treatment, resulted in better OS and PFS in patients with primary tumors of the brain. They also proposed that one of the main highlights of metformin's use is its ability to cross the blood-brain barrier (BBB), which is a large obstacle for commonly used antineoplastic agents. However, the exact mechanism of action that promotes metformin's potential in the treatment of GBM is still being investigated[41]. Soritau *et al*[47] conducted a study that researched metformin's effects on tumor tissue cultures and compared these effects with the effects of other antineoplastic agents, such as epidermal growth factor and TMZ. They noted that a significant statistical difference between monotherapy with TMZ monotherapy and dual therapy with TMZ plus metformin. A study conducted by Sesen *et al*[48] also noted that metformin decreased the synthesis of ATP in the mitochondria, and increased the production of lactate and glycolytic ATP. This led to the induction of tumor cells autophagy, as well as to the inhibition of cell proliferation and apoptosis. They have also proven that metformin slows down the growth of the glioma cell lines *in vivo* by the use of xenografts in mice, especially when combined with TMZ and/or irradiation[48].

In addition, Seliger *et al*[41] conducted a retrospective cohort study noted that metformin monotherapy was associated with improved survival rates, but this was not observed in patients receiving metformin combined with RTM. Other antidiabetic drugs were associated with poorer survival outcomes, suggesting that the benefits might be specific to metformin. Tseng *et al*[49] noted that metformin use significantly reduced the overall risk of developing malignant brain tumors and highlighted the importance of long-term metformin therapy, with a minimal duration of 2-5 years required for significant risk reduction. Maraka *et al*[50] explored the safety and efficacy of combining metformin with TMZ and other drugs in a Phase 1 randomized controlled trial and noted that metformin (850 mg twice daily) could be safely administered alongside TMZ, mefloquine, and memantine, with gastrointestinal issues being the primary side effect. Despite the promising safety profile, the study did not show a marked improvement in OS, which was 21 months for the cohort. This indicates that while metformin is safe in combination therapy, its direct impact on survival may be limited. Yoon *et al*[51] conducted a Phase II randomized controlled trial that showed that despite the good tolerance of the metformin regimen, metformin use did not have significant clinical benefit for patients with recurrent or refractory GBM. This underscores the complexity of GBM treatment and the necessity for further research to fully understand the potential synergistic effects of metformin when combined with conventional therapies.

Limitations and future directions

Although recent research demonstrates its ability to decrease GBM cell resistance to TMZ, further studies are needed to clarify metformin's impact on outcomes in patients with GBM. This will also help to overcome obstacles regarding metformin's use for GBM treatment, such as metformin being a hydrophilic drug that has trouble penetrating through the BBB and in the tumor cells, as well as the reaching of the GBM cells in sufficient concentrations. Additionally, systemic drug administration often comes with a non-specific distribution and required effective doses of metformin are often too high for clinical use, which limits its clinical everyday application. Recently, the use of nanoerythroosomes as a transport vehicle for metformin to GBM cells has been researched[57].

Nanoerythroosomes are drug carriers engineered from the cellular membrane of red blood cells that can prevent the degradation of metformin before its delivery to the targeted cells. Understanding the interplay between metabolism and treatment response, as well as exploring novel delivery methods like nanoerythroosomes, could improve GBM therapy[58-60]. They can load and transport hydrophilic medications, including metformin, preventing enzymatic breakdown at the BBB and prolonging their half-life. Therefore, the prolonged and regulated release of metformin made possible by its encapsulation in nanoerythroosomes may improve its therapeutic effectiveness against GBM cells. Also, their use could be beneficial for solving the TMZ resistance and DXM impact on the effectiveness of treatment for GBM. Although this needs more research, the use of nanoerythroosomes could maximize metformin delivery and possibly mitigate some of the metabolic changes brought on by DXM[58]. Another limitation of metformin's use in GBM treatment is that it shows potential benefits as a monotherapy and in long-term preventive use, but its role in combination with standard GBM treatments like TMZ remains inconclusive. The varying results across studies underscore the necessity for more extensive research to elucidate the precise mechanisms and optimal conditions under which metformin could contribute to improved GBM outcomes.

Table 2 summarizes the key challenges and corresponding research needs to provide a more precise and structured overview of the current limitations regarding metformin use in GBM and facilitate future research planning.

CONCLUSION

GBM remains a formidable challenge in clinical oncology, demanding a multifaceted treatment approach involving

Table 2 Summary of current limitations and directions for future research on metformin in glioblastoma		
Limitation	Underlying issues	Proposed solutions /future directions
Heterogeneous trial designs	Inconsistent patient selection (MGMT status, IDH mutation)	Stratify future trials by molecular subtypes and metabolic profiles
Variable dosing and exposure	Metformin doses ranged from 1000 to 2250 mg/day; durations varied	Standardize dosing protocols; consider longer duration studies
Inadequate CNS penetration	Metformin is hydrophilic, and the blood-brain barrier limits delivery	Explore alternative delivery systems (nanoerythroosomes, liposomal carriers)[58,60]
Lack of metabolic data	Poor glycemic control and steroid use are often unreported	Integrate glycemic monitoring and steroid adjustment protocols in trial design
Biomarker absence	No validated predictors of response	Identify and validate predictive biomarkers (AMPK activity, gemistocyte index, insulin resistance)

MGMT: O6-methylguanine-DNA methyltransferase; CNS: Central nervous system; IDH: Isocitrate dehydrogenase.

surgery, radiotherapy, and chemotherapy with TMZ. While TMZ serves as the standard chemotherapeutic agent, the emergence of resistance mechanisms, including elevated MGMT activity, presents significant hurdles in treatment efficacy. Recent research underscores the intricate relationship between impaired glucose metabolism, the tumor microenvironment, and GBM pathogenesis, highlighting the potential therapeutic role of antidiabetic drugs like metformin in overcoming TMZ resistance. However, further investigation is needed to elucidate the underlying mechanisms and optimize treatment strategies. Additionally, the exploration of novel therapeutic modalities, such as innovative drug delivery systems like nanoerythroosomes, offers promising avenues for improving GBM outcomes.

FOOTNOTES

Author contributions: Begagić E, Džidić-Krivić A and Bečulić H designed the research study; Pagonja R, Ljevaković A, Bašić B, Nuhović A, Milanović E, Hadžić S, Bećirović E, Buljubašić L and Bećirović M performed the research; Bečulić H and Pojskić M supervised the research; Begagić E, Džidić-Krivić A and Bečulić H, Nuhović A, Milanović E, Hadžić S, Bećirović E, Buljubašić L and Bećirović M wrote the manuscript; All authors have read and approved the final manuscript.

Conflict-of-interest statement: There is no conflict of interest associated with any of the senior author or other coauthors contributed their efforts in this manuscript.

Open Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country of origin: Bosnia and Herzegovina

ORCID number: Emir Begagić 0000-0002-3988-8911.

S-Editor: Qu XL
L-Editor: A
P-Editor: Zhao YQ

REFERENCES

1 Shah S. Novel Therapies in Glioblastoma Treatment: Review of Glioblastoma; Current Treatment Options; and Novel Oncolytic Viral Therapies. *Med Sci (Basel)* 2023; **12**: 1 [RCA] [PMID: 38249077 DOI: 10.3390/medsci12010001] [FullText]

2 Begagić E, Bečulić H, Đuzić N, Džidić-Krivić A, Pagonja R, Muharemović A, Jaganjac B, Salković N, Sefo H, Pojskić M. CRISPR/Cas9-Mediated Gene Therapy for Glioblastoma: A Scoping Review. *Biomedicines* 2024; **12**: 238 [RCA] [PMID: 38275409 DOI: 10.3390/biomedicines12010238] [FullText]

3 Montemurro N, Perrini P, Rapone B. Clinical Risk and Overall Survival in Patients with Diabetes Mellitus, Hyperglycemia and Glioblastoma Multiforme. A Review of the Current Literature. *Int J Environ Res Public Health* 2020; **17**: 8501 [RCA] [PMID: 33212778 DOI: 10.3390/ijerph17228501] [FullText] [Full Text(PDF)]

4 Bielecka-Wajdman AM, Ludyga T, Smyk D, Smyk W, Mularska M, Świderek P, Majewski W, Mullins CS, Linnebacher M, Obuchowicz E. Glucose Influences the Response of Glioblastoma Cells to Temozolomide and Dexamethasone. *Cancer Control* 2022; **29**: 10732748221075468 [RCA] [PMID: 35225010 DOI: 10.1177/10732748221075468] [FullText] [Full Text(PDF)]

5 Agnihotri S, Burrell KE, Wolf A, Jalali S, Hawkins C, Rutka JT, Zadeh G. Glioblastoma, a brief review of history, molecular genetics, animal

- models and novel therapeutic strategies. *Arch Immunol Ther Exp (Warsz)* 2013; **61**: 25-41 [RCA] [PMID: 23224339 DOI: 10.1007/s00005-012-0203-0] [FullText]
- 6 **Bao Z**, Chen K, Krepel S, Tang P, Gong W, Zhang M, Liang W, Trivett A, Zhou M, Wang JM. High Glucose Promotes Human Glioblastoma Cell Growth by Increasing the Expression and Function of Chemoattractant and Growth Factor Receptors. *Transl Oncol* 2019; **12**: 1155-1163 [RCA] [PMID: 31207546 DOI: 10.1016/j.tranon.2019.04.016] [FullText] [Full Text(PDF)]
- 7 **Begagić E**, Bečulić H, Džidić-Krivić A, Kadić Vukas S, Hadžić S, Mekić-Abazović A, Šegalo S, Papić E, Muchai Echengi E, Pugnja R, Kasapović T, Kavgić D, Nuhović A, Juković-Bihorac F, Đuričić S, Pojskić M. Understanding the Significance of Hypoxia-Inducible Factors (HIFs) in Glioblastoma: A Systematic Review. *Cancers (Basel)* 2024; **16**: 2089 [RCA] [PMID: 38893207 DOI: 10.3390/cancers16112089] [FullText]
- 8 **Rock K**, McArdle O, Forde P, Dunne M, Fitzpatrick D, O'Neill B, Faul C. A clinical review of treatment outcomes in glioblastoma multiforme--the validation in a non-trial population of the results of a randomised Phase III clinical trial: has a more radical approach improved survival? *Br J Radiol* 2012; **85**: e729-e733 [RCA] [PMID: 22215883 DOI: 10.1259/bjr/83796755] [FullText]
- 9 **Begagić E**, Pugnja R, Bečulić H, Čeliković A, Tandir Lihčić L, Kadić Vukas S, Čejvan L, Skomorac R, Selimović E, Jaganjac B, Juković-Bihorac F, Jusić A, Pojskić M. Molecular Targeted Therapies in Glioblastoma Multiforme: A Systematic Overview of Global Trends and Findings. *Brain Sci* 2023; **13**: 1602 [RCA] [PMID: 38002561 DOI: 10.3390/brainsci13111602] [FullText]
- 10 **Barba I**, Carrillo-Bosch L, Seoane J. Targeting the Warburg Effect in Cancer: Where Do We Stand? *Int J Mol Sci* 2024; **25**: 3142 [RCA] [PMID: 38542116 DOI: 10.3390/ijms25063142] [FullText]
- 11 **Poff AM**, Ari C, Arnold P, Seyfried TN, D'Agostino DP. Ketone supplementation decreases tumor cell viability and prolongs survival of mice with metastatic cancer. *Int J Cancer* 2014; **135**: 1711-1720 [RCA] [PMID: 24615175 DOI: 10.1002/ijc.28809] [FullText] [Full Text(PDF)]
- 12 **Giotta Lucifero A**, Luzzi S. Against the Resilience of High-Grade Gliomas: The Immunotherapeutic Approach (Part I). *Brain Sci* 2021; **11**: 386 [RCA] [PMID: 33803885 DOI: 10.3390/brainsci11030386] [FullText] [Full Text(PDF)]
- 13 **Das A**, Banik NL, Patel SJ, Ray SK. Dexamethasone protected human glioblastoma U87MG cells from temozolomide induced apoptosis by maintaining Bax:Bcl-2 ratio and preventing proteolytic activities. *Mol Cancer* 2004; **3**: 36 [RCA] [PMID: 15588281 DOI: 10.1186/1476-4598-3-36] [FullText] [Full Text(PDF)]
- 14 **Shields LB**, Shelton BJ, Shearer AJ, Chen L, Sun DA, Parsons S, Bourne TD, LaRocca R, Spalding AC. Dexamethasone administration during definitive radiation and temozolomide renders a poor prognosis in a retrospective analysis of newly diagnosed glioblastoma patients. *Radiat Oncol* 2015; **10**: 222 [RCA] [PMID: 26520780 DOI: 10.1186/s13014-015-0527-0] [FullText] [Full Text(PDF)]
- 15 **Deutsch MB**, Panageas KS, Lassman AB, Deangelis LM. Steroid management in newly diagnosed glioblastoma. *J Neurooncol* 2013; **113**: 111-116 [RCA] [PMID: 23462855 DOI: 10.1007/s11060-013-1096-4] [FullText]
- 16 **Inskip PD**, Tarone RE, Hatch EE, Wilcosky TC, Shapiro WR, Selker RG, Fine HA, Black PM, Loeffler JS, Linet MS. Cellular-telephone use and brain tumors. *N Engl J Med* 2001; **344**: 79-86 [RCA] [PMID: 11150357 DOI: 10.1056/NEJM200101113440201] [FullText]
- 17 **Scott J**, Tsai YY, Chinnaiyan P, Yu HH. Effectiveness of radiotherapy for elderly patients with glioblastoma. *Int J Radiat Oncol Biol Phys* 2011; **81**: 206-210 [RCA] [PMID: 20675068 DOI: 10.1016/j.ijrobp.2010.04.033] [FullText]
- 18 **Stepanenko AA**, Andreieva SV, Korets KV, Mykytenko DO, Baklaushev VP, Huleyuk NL, Kovalova OA, Kotsarenko KV, Chekhonin VP, Vassetzky YS, Avdieiev SS, Dmitrenko VV. Temozolomide promotes genomic and phenotypic changes in glioblastoma cells. *Cancer Cell Int* 2016; **16**: 36 [RCA] [PMID: 27158244 DOI: 10.1186/s12935-016-0311-8] [FullText] [Full Text(PDF)]
- 19 **Feng YH**, Velazquez-Torres G, Gully C, Chen J, Lee MH, Yeung SC. The impact of type 2 diabetes and antidiabetic drugs on cancer cell growth. *J Cell Mol Med* 2011; **15**: 825-836 [RCA] [PMID: 20455996 DOI: 10.1111/j.1582-4934.2010.01083.x] [FullText] [Full Text(PDF)]
- 20 **Daugan M**, Dufay Wojcicki A, d'Hayer B, Boudy V. Metformin: An anti-diabetic drug to fight cancer. *Pharmacol Res* 2016; **113**: 675-685 [RCA] [PMID: 27720766 DOI: 10.1016/j.phrs.2016.10.006] [FullText]
- 21 **Wang LW**, Li ZS, Zou DW, Jin ZD, Gao J, Xu GM. Metformin induces apoptosis of pancreatic cancer cells. *World J Gastroenterol* 2008; **14**: 7192-7198 [RCA] [PMID: 19084933 DOI: 10.3748/wjg.14.7192] [FullText]
- 22 **Guarnaccia L**, Navone SE, Masseroli MM, Balsamo M, Caroli M, Valtorta S, Moresco RM, Campanella R, Schisano L, Fiore G, Galiano V, Garzia E, Appiani GC, Locatelli M, Riboni L, Marfia G. Effects of Metformin as Add-On Therapy against Glioblastoma: An Old Medicine for Novel Oncology Therapeutics. *Cancers (Basel)* 2022; **14**: 1412 [RCA] [PMID: 35326565 DOI: 10.3390/cancers14061412] [FullText] [Full Text(PDF)]
- 23 **Hirsch HA**, Iliopoulos D, Tschlis PN, Struhl K. Metformin selectively targets cancer stem cells, and acts together with chemotherapy to block tumor growth and prolong remission. *Cancer Res* 2009; **69**: 7507-7511 [RCA] [PMID: 19752085 DOI: 10.1158/0008-5472.CAN-09-2994] [FullText]
- 24 **Jones RG**, Plas DR, Kubek S, Buzzai M, Mu J, Xu Y, Birnbaum MJ, Thompson CB. AMP-activated protein kinase induces a p53-dependent metabolic checkpoint. *Mol Cell* 2005; **18**: 283-293 [RCA] [PMID: 15866171 DOI: 10.1016/j.molcel.2005.03.027] [FullText]
- 25 **Isakovic A**, Harhaji L, Stevanovic D, Markovic Z, Sumarac-Dumanovic M, Starcevic V, Micic D, Trajkovic V. Dual antiglioma action of metformin: cell cycle arrest and mitochondria-dependent apoptosis. *Cell Mol Life Sci* 2007; **64**: 1290-1302 [RCA] [PMID: 17447005 DOI: 10.1007/s00018-007-7080-4] [FullText]
- 26 **Fenner MH**, Elstner E. Peroxisome proliferator-activated receptor-gamma ligands for the treatment of breast cancer. *Expert Opin Investig Drugs* 2005; **14**: 557-568 [RCA] [PMID: 16004588 DOI: 10.1517/13543784.14.6.557] [FullText]
- 27 **Lyles BE**, Akinyeke TO, Moss PE, Stewart LV. Thiazolidinediones regulate expression of cell cycle proteins in human prostate cancer cells via PPARgamma-dependent and PPARgamma-independent pathways. *Cell Cycle* 2009; **8**: 268-277 [RCA] [PMID: 19164938 DOI: 10.4161/cc.8.2.7584] [FullText]
- 28 **Dong YW**, Wang XP, Wu K. Suppression of pancreatic carcinoma growth by activating peroxisome proliferator-activated receptor gamma involves angiogenesis inhibition. *World J Gastroenterol* 2009; **15**: 441-448 [RCA] [PMID: 19152448 DOI: 10.3748/wjg.15.441] [FullText] [Full Text(PDF)]
- 29 **Papageorgiou E**, Pitulis N, Manoussakis M, Lembessis P, Koutsilieris M. Rosiglitazone attenuates insulin-like growth factor 1 receptor survival signaling in PC-3 cells. *Mol Med* 2008; **14**: 403-411 [RCA] [PMID: 18475308 DOI: 10.2119/2008-00021.Papageorgiou] [FullText]
- 30 **Cantini G**, Lombardi A, Piscitelli E, Poli G, Ceni E, Marchiani S, Ercolino T, Galli A, Serio M, Mannelli M, Luconi M. Rosiglitazone inhibits adrenocortical cancer cell proliferation by interfering with the IGF-IR intracellular signaling. *PPAR Res* 2008; **2008**: 904041 [RCA] [PMID: 18670617 DOI: 10.1155/2008/904041] [FullText] [Full Text(PDF)]
- 31 **Teresi RE**, Shaiu CW, Chen CS, Chatterjee VK, Waite KA, Eng C. Increased PTEN expression due to transcriptional activation of

- PPARgamma by Lovastatin and Rosiglitazone. *Int J Cancer* 2006; **118**: 2390-2398 [RCA] [PMID: 16425225 DOI: 10.1002/ijc.21799] [Full Text]
- 32 **Takhwifa F**, Aninditha T, Setiawan H, Sauriasari R. The potential of metformin as an antineoplastic in brain tumors: A systematic review. *Heliyon* 2021; **7**: e06558 [RCA] [PMID: 33869859 DOI: 10.1016/j.heliyon.2021.e06558] [FullText] [Full Text(PDF)]
- 33 **Bowker SL**, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. *Diabetes Care* 2006; **29**: 254-258 [RCA] [PMID: 16443869 DOI: 10.2337/diacare.29.02.06.de05-1558] [FullText]
- 34 **Zander T**, Kraus JA, Grommes C, Schlegel U, Feinstein D, Klockgether T, Landreth G, Koenigsknecht J, Heneka MT. Induction of apoptosis in human and rat glioma by agonists of the nuclear receptor PPARgamma. *J Neurochem* 2002; **81**: 1052-1060 [RCA] [PMID: 12065618 DOI: 10.1046/j.1471-4159.2002.00899.x] [FullText]
- 35 **Wu W**, Wang Y, Xie J, Fan S. Empagliflozin: a potential anticancer drug. *Discov Oncol* 2023; **14**: 127 [RCA] [PMID: 37436535 DOI: 10.1007/s12672-023-00719-x] [FullText]
- 36 **Hendriks AM**, Schrijnders D, Kleefstra N, de Vries EGE, Bilo HJG, Jalving M, Landman GWD. Sulfonylurea derivatives and cancer, friend or foe? *Eur J Pharmacol* 2019; **861**: 172598 [RCA] [PMID: 31408647 DOI: 10.1016/j.ejphar.2019.172598] [FullText]
- 37 **Long L**, Hu X, Li X, Zhou D, Shi Y, Wang L, Zeng H, Yu X, Zhou W. The Anti-Breast Cancer Effect and Mechanism of Glimepiride-Metformin Adduct. *Oncotargets Ther* 2020; **13**: 3777-3788 [RCA] [PMID: 32440146 DOI: 10.2147/OTT.S240252] [FullText] [Full Text (PDF)]
- 38 **Kang H**, Lee H, Kim D, Kim B, Kang J, Kim HY, Youn H, Youn B. Targeting Glioblastoma Stem Cells to Overcome Chemoresistance: An Overview of Current Therapeutic Strategies. *Biomedicines* 2022; **10**: 1308 [RCA] [PMID: 35740330 DOI: 10.3390/biomedicines10061308] [FullText] [Full Text(PDF)]
- 39 **McAleavey PG**, Walls GM, Chalmers AJ. Radiotherapy-drug combinations in the treatment of glioblastoma: a brief review. *CNS Oncol* 2022; **11**: CNS86 [RCA] [PMID: 35603818 DOI: 10.2217/cns-2021-0015] [FullText] [Full Text(PDF)]
- 40 **Kang H**, Lee S, Kim K, Jeon J, Kang SG, Youn H, Kim HY, Youn B. Downregulated CLIP3 induces radioresistance by enhancing stemness and glycolytic flux in glioblastoma. *J Exp Clin Cancer Res* 2021; **40**: 282 [RCA] [PMID: 34488821 DOI: 10.1186/s13046-021-02077-4] [Full Text] [Full Text(PDF)]
- 41 **Seliger C**, Ricci C, Meier CR, Bodmer M, Jick SS, Bogdahn U, Hau P, Leitzmann MF. Diabetes, use of antidiabetic drugs, and the risk of glioma. *Neuro Oncol* 2016; **18**: 340-349 [RCA] [PMID: 26093337 DOI: 10.1093/neuonc/nov100] [FullText]
- 42 **Lu VM**, Goyal A, Vaughan LS, McDonald KL. The impact of hyperglycemia on survival in glioblastoma: A systematic review and meta-analysis. *Clin Neurol Neurosurg* 2018; **170**: 165-169 [RCA] [PMID: 29803727 DOI: 10.1016/j.clineuro.2018.05.020] [FullText]
- 43 **Liu EK**, Vasudevaraja V, Sviderskiy VO, Feng Y, Tran I, Serrano J, Cordova C, Kurz SC, Golfinos JG, Sulman EP, Orringer DA, Placantonakis D, Possemato R, Snuderl M. Association of hyperglycemia and molecular subclass on survival in IDH-wildtype glioblastoma. *Neurooncol Adv* 2022; **4**: vdacl63 [RCA] [PMID: 36382106 DOI: 10.1093/oaajnl/vdac163] [FullText] [Full Text(PDF)]
- 44 **Tieu MT**, Lovblom LE, McNamara MG, Mason W, Laperriere N, Millar BA, Ménard C, Kiehl TR, Perkins BA, Chung C. Impact of glycemia on survival of glioblastoma patients treated with radiation and temozolomide. *J Neurooncol* 2015; **124**: 119-126 [RCA] [PMID: 26015297 DOI: 10.1007/s11060-015-1815-0] [FullText] [Full Text(PDF)]
- 45 **Adeberg S**, Bernhardt D, Foerster R, Bostel T, Koerber SA, Mohr A, Koelsche C, Rieken S, Debus J. The influence of hyperglycemia during radiotherapy on survival in patients with primary glioblastoma. *Acta Oncol* 2016; **55**: 201-207 [RCA] [PMID: 25990634 DOI: 10.3109/0284186X.2015.1043397] [FullText]
- 46 **Laviv Y**, Sapirstein E, Kanner AA, Berkowitz S, Fichman S, Benouaich-Amiel A, Yust-Katz S, Kasper EE, Siegal T. Significant Systemic Insulin Resistance is Associated With Unique Glioblastoma Multiforme Phenotype. *Clin Pathol* 2023; **16**: 2632010X231207725 [RCA] [PMID: 37920781 DOI: 10.1177/2632010X231207725] [FullText] [Full Text(PDF)]
- 47 **Sorिताu O**, Tomuleasa C, Aldea M, Petrushev B, Susman S, Gheban D, Ioani H, Cosis A, Brie I, Irimie A, Kacso G, Florian IS. Metformin plus temozolomide-based chemotherapy as adjuvant treatment for WHO grade III and IV malignant gliomas. *J BUON* 2011; **16**: 282-289 [RCA] [PMID: 21766499] [FullText]
- 48 **Sesen J**, Dahan P, Scotland SJ, Saland E, Dang VT, Lemarié A, Tyler BM, Brem H, Toulas C, Cohen-Jonathan Moyal E, Sarry JE, Skuli N. Metformin inhibits growth of human glioblastoma cells and enhances therapeutic response. *PLoS One* 2015; **10**: e0123721 [RCA] [PMID: 25867026 DOI: 10.1371/journal.pone.0123721] [FullText] [Full Text(PDF)]
- 49 **Tseng CH**. Chronic Metformin Therapy is Associated with a Lower Risk of Hemorrhoid in Patients with Type 2 Diabetes Mellitus. *Front Pharmacol* 2020; **11**: 578831 [RCA] [PMID: 33664665 DOI: 10.3389/fphar.2020.578831] [FullText] [Full Text(PDF)]
- 50 **Maraka S**, Groves MD, Mammoser AG, Melguizo-Gavilanes I, Conrad CA, Tremont-Lukats IW, Loghin ME, O'Brien BJ, Puduvalli VK, Sulman EP, Hess KR, Aldape KD, Gilbert MR, de Groot JF, Alfred Yung WK, Penas-Prado M. Phase 1 lead-in to a phase 2 factorial study of temozolomide plus memantine, mefloquine, and metformin as postradiation adjuvant therapy for newly diagnosed glioblastoma. *Cancer* 2019; **125**: 424-433 [RCA] [PMID: 30359477 DOI: 10.1002/encr.31811] [FullText]
- 51 **Yoon WS**, Chang JH, Kim JH, Kim YJ, Jung TY, Yoo H, Kim SH, Ko YC, Nam DH, Kim TM, Kim SH, Park SH, Lee YS, Yim HW, Hong YK, Yang SH. Efficacy and safety of metformin plus low-dose temozolomide in patients with recurrent or refractory glioblastoma: a randomized, prospective, multicenter, double-blind, controlled, phase 2 trial (KNOG-1501 study). *Discov Oncol* 2023; **14**: 90 [RCA] [PMID: 37278858 DOI: 10.1007/s12672-023-00678-3] [FullText]
- 52 **Sato A**, Sunayama J, Okada M, Watanabe E, Seino S, Shibuya K, Suzuki K, Narita Y, Shibui S, Kayama T, Kitanaka C. Glioma-initiating cell elimination by metformin activation of FOXO3 via AMPK. *Stem Cells Transl Med* 2012; **1**: 811-824 [RCA] [PMID: 23197693 DOI: 10.5966/scem.2012-0058] [FullText]
- 53 **Wang J**, Li G, Wang Y, Tang S, Sun X, Feng X, Li Y, Bao G, Li P, Mao X, Wang M, Liu P. Suppression of tumor angiogenesis by metformin treatment via a mechanism linked to targeting of HER2/HIF-1α/VEGF secretion axis. *Oncotarget* 2015; **6**: 44579-44592 [RCA] [PMID: 26625311 DOI: 10.18632/oncotarget.6373] [FullText] [Full Text(PDF)]
- 54 **Yu Z**, Zhao G, Li P, Li Y, Zhou G, Chen Y, Xie G. Temozolomide in combination with metformin act synergistically to inhibit proliferation and expansion of glioma stem-like cells. *Oncol Lett* 2016; **11**: 2792-2800 [RCA] [PMID: 27073554 DOI: 10.3892/ol.2016.4315] [FullText] [Full Text(PDF)]
- 55 **Yang SH**, Li S, Lu G, Xue H, Kim DH, Zhu JJ, Liu Y. Metformin treatment reduces temozolomide resistance of glioblastoma cells. *Oncotarget* 2016; **7**: 78787-78803 [RCA] [PMID: 27791206 DOI: 10.18632/oncotarget.12859] [FullText] [Full Text(PDF)]
- 56 **Zuccoli G**, Marcello N, Pisanello A, Servadei F, Vaccaro S, Mukherjee P, Seyfried TN. Metabolic management of glioblastoma multiforme

using standard therapy together with a restricted ketogenic diet: Case Report. *Nutr Metab (Lond)* 2010; **7**: 33 [RCA] [PMID: 20412570 DOI: 10.1186/1743-7075-7-33] [FullText] [Full Text(PDF)]

- 57 **Moezzi SMI**, Javadi P, Mozafari N, Ashrafi H, Azadi A. Metformin-loaded nanoerythrocytes: An erythrocyte-based drug delivery system as a therapeutic tool for glioma. *Heliyon* 2023; **9**: e17082 [RCA] [PMID: 37484272 DOI: 10.1016/j.heliyon.2023.e17082] [FullText] [Full Text (PDF)]
- 58 **Valtorta S**, Lo Dico A, Raccagni I, Gaglio D, Belloli S, Politi LS, Martelli C, Diceglie C, Bonanomi M, Ercoli G, Vaira V, Ottobrini L, Moresco RM. Metformin and temozolomide, a synergic option to overcome resistance in glioblastoma multiforme models. *Oncotarget* 2017; **8**: 113090-113104 [RCA] [PMID: 29348889 DOI: 10.18632/oncotarget.23028] [FullText] [Full Text(PDF)]
- 59 **Feng SW**, Chang PC, Chen HY, Hueng DY, Li YF, Huang SM. Exploring the Mechanism of Adjuvant Treatment of Glioblastoma Using Temozolomide and Metformin. *Int J Mol Sci* 2022; **23**: 8171 [RCA] [PMID: 35897747 DOI: 10.3390/ijms23158171] [FullText] [Full Text (PDF)]
- 60 **Ohno M**, Kitanaka C, Miyakita Y, Tanaka S, Sonoda Y, Mishima K, Ishikawa E, Takahashi M, Yanagisawa S, Ohashi K, Nagane M, Narita Y. Metformin with Temozolomide for Newly Diagnosed Glioblastoma: Results of Phase I Study and a Brief Review of Relevant Studies. *Cancers (Basel)* 2022; **14**: 4222 [RCA] [PMID: 36077758 DOI: 10.3390/cancers14174222] [FullText] [Full Text(PDF)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: office@baishideng.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

