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Review

Glioblastoma multiforme: an updated overview of temozolomide resistance mechanisms and strategies to overcome resistance

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Abstract
Glioblastoma (GBM) is an aggressive primary brain tumor with high lethality. The typical treatment regimen includes post-surgical radiotherapy and temozolomide (TMZ) chemotherapy, which helps extend survival. Nevertheless, TMZ resistance occurs in approximately 50% of patients. This resistance is primarily associated with the expression of O6-methylguanine-DNA methyltransferase (MGMT), which repairs O6-methylguanine lesions generated by TMZ and is thought to be the major mechanism of drug resistance. Additionally, the mismatch repair and base excision repair pathways play crucial roles in TMZ resistance. Emerging studies also point to drug transport mechanisms, glioma stem cells, and the heterogeneous tumor microenvironment as additional influences on TMZ resistance in gliomas. A better understanding of these mechanisms is vital for developing new treatments to improve TMZ effectiveness, such as DNA repair inhibitors, inhibitors of multidrug transporting proteins, TMZ analogs, and combination therapies targeting multiple pathways. This article discusses the main resistance mechanisms and potential strategies to counteract resistance in GBM patients, aiming to broaden the understanding of these mechanisms for future research and to explore the therapeutic effects of traditional Chinese medicines and their active components in overcoming TMZ resistance.

Keywords Glioblastoma · Temozolomide · Resistance · Combination therapy · Traditional Chinese medicine

Abbreviations

GBM	Glioblastoma
TMZ	Temozolomide
CNS	Central nervous system
BBB	Blood-brain barrier
BBTB	Blood-brain tumor barrier
CCNU	Lomustine
MTIC	5-(3-Methyl-triazine) imidazole-4-carboxamide
MGMT	O6-methylguanine-DNA methyltransferase

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MLH1	MutL homologue 1
MSH2	MutS homologue 2
PMS2	Postmeiotic segregation 2
EXO1	Exonuclease 1
LIG1	DNA ligase I
APE1	Apurinic/apyrimidinic endonuclease 1
HTATIP2	HIV-1 Tat interactive protein 2
MPG	N-Methylpurine DNA Glycosylase
PARP1	Poly (ADP-ribose) polymerase 1
BTB	Brain tumor barrier
TPSA	Topological polar surface area
PSA	Polar surface area
GLUT-1	Glucose transporter-1
MMPs	Matrix metalloproteinases
VEGF	Vascular endothelial growth factor
SLC	Solute carrier
GSCs	Glioma stem cells
SHH	Sonic hedgehog
HIF-1	Hypoxia-inducible factor 1
CQ	Chloroquine
HCQ	Hydroxychloroquine
DAS	Daurisoline
TME	Tumor microenvironment
MDSCs	Myeloid-derived suppressor cells
GAMs	Glioma-associated macrophages
EVs	Extracellular vesicles
PARPi	PARP inhibitors
CAXII	Carbonic anhydrase II
ADC	Apparent diffusion coefficient
ADAM	A Disintegrin and Metalloprotease
KDM1A	Lysine-specific histone demethylase 1A
BiA	6′-Bromoindirubin-3′-acetoxime
IDO1	Indoleamine 2,3-dioxygenase 1
THC	Δ^9-Tetrahydrocannabinol
PD-L1	Programmed cell death 1 ligand 1
TSN	Toosendanin
GM-CSF	Granulocyte-macrophage colony-stimulating factor
RFA	RTK-fatty acid-gene signature
TCM	Traditional Chinese Medicine
WDR1	WD repeat domain 1
PDCs	Patient-derived glioma cells
ORI	Ornithogalum officinale

1 Introduction

Glioblastoma (GBM) is categorized as a grade IV glioma and is one of the deadliest adult brain tumors, comprising about 49% of all malignant brain tumors [1]. It is a highly invasive condition with a median survival time of approximately 12–15 months post-diagnosis, and less than 5% of patients live longer than 5 years [2]. While the precise etiology and mechanisms behind GBM pathogenesis are not yet fully elucidated, several tumorigenic processes have been pinpointed as contributing factors to its development and progression. These intracellular events mainly include growth factor overexpression, cell cycle deregulation, angiogenesis, invasive migration, genetic instability and disrupted apoptosis [3]. Exposure to ionizing radiation is also considered to be the most significant risk factor linked with GBM and is the

only known potentially modifiable risk factor [4]. At present, the conventional treatment for GBM comprises maximal surgical resection, succeeded by radiation and chemotherapy administered with temozolomide (TMZ), which is the primary chemotherapeutic drug for GBM treatment endorsed by the FDA. However, due to challenges like incomplete tumor removal and emerging resistance to TMZ, 90% of cases recur at the original tumor site, leading to limited survival improvements for patients [5].

A substantial challenge impacting the development and effective utilisation of any anticancer agent targeting the central nervous system (CNS) is the blood–brain barrier (BBB). The BBB comprises the outermost layer of blood vessels within the brain and spinal cord, limits the efficacy of therapeutic drugs for GBM by hampering their delivery to the CNS [6]. Up to this point, the most effective chemotherapeutic drugs that exhibit improved penetration across the BBB/blood–brain tumor barrier (BBTB) for the treatment of GBM include TMZ, Lomustine (CCNU), procarbazine, and carboplatin [7]. Notably, when compared to other chemotherapeutic agents like carmustine (BCNU), CCNU, and platinum-based drugs, TMZ stands out as the optimal choice, having demonstrated the most significant improvement in median survival time for GBM patients [8, 9]. Additionally, TMZ is frequently utilized in conjunction with radiotherapy. This combination not only facilitates the spontaneous transformation of TMZ into its active form within the brain but also enhances its permeability across the BBB [10]. Despite this, the effectiveness of TMZ is still limited by both intrinsic and acquired resistance mechanisms. Additionally, the genetic diversity and extensive infiltration capacity of GBM allow it to evade standard radiotherapy and chemotherapy treatments. This review discusses TMZ's primary cytotoxic mechanisms, explores advanced strategies to enhance its effectiveness, and considers future directions for both basic investigations and clinical utilization in GBM treatment.

2 Mechanism of TMZ action

The TMZ, a lipophilic prodrug (molecular weight: 194.154 g/mol), exhibits stability exclusively under acidic conditions [11, 12]. As a second-generation alkylating agent, TMZ can be administered orally and has a bioavailability close to 100%. It is a prodrug of imidazotetrazine that does not require hepatic activation. Under physiological pH conditions, TMZ rapidly becomes its active form, 5-(3-methyl-triazine) imidazole-4-carboxamide (MTIC), which is unstable and quickly hydrolyzes to form highly reactive methyl diazo cations [13]. These cations transfer their methyl groups to DNA, inducing cytotoxicity by methylation at specific sites: the N7 position of guanine (70%), the N3 position of adenine (10%), and the O6 position of guanine (5%) [14, 15]. Methylation at the O6 position of guanine is primarily responsible for TMZ-related toxicity, leading to DNA replication errors that may cause G2/M phase arrest, potentially resulting in apoptosis, autophagy, or cellular senescence [16].

3 Mechanisms of TMZ-resistance in GBM

Resistance to TMZ and other anticancer drugs poses a significant challenge in treating GBM. TMZ resistance involves various molecular pathways, as illustrated in Fig. 1. Potential mechanisms include the overactivation of DNA repair pathways, prevention of TMZ accumulation by multidrug transporters, and mediation by the heterogeneous tumor microenvironment, which includes factors like glioma stem cell phenotypes, hypoxia, and protective autophagy, as illustrated in Fig. 1. Appreciating these mechanisms is fundamental for advancing new anticancer methods.

3.1 Overactivation of DNA repair mechanisms

3.1.1 MGMT-mediated DNA repair

O6-methylguanine-DNA methyltransferase (MGMT) is vital for maintaining cellular genome stability by removing O6-MeG cytotoxic lesions caused by TMZ [17]. The MGMT promoter, which is rich in CpG sites, shows that methylation of these sites is inversely related to MGMT expression in GBM patients [18]. Approximately 45% of GBM cases exhibit MGMT promoter methylation [19], which is more common in gliomas with isocitrate dehydrogenase (IDH) mutations [20]. Studies in vitro have linked high MGMT expression to TMZ resistance, suggesting that GBM cells with high MGMT expression are more resistant to TMZ cytotoxicity than those without MGMT activity[21]. In GBM xenograft models, tumors with unmethylated MGMT promoters may show reduced response to long-term TMZ treatment

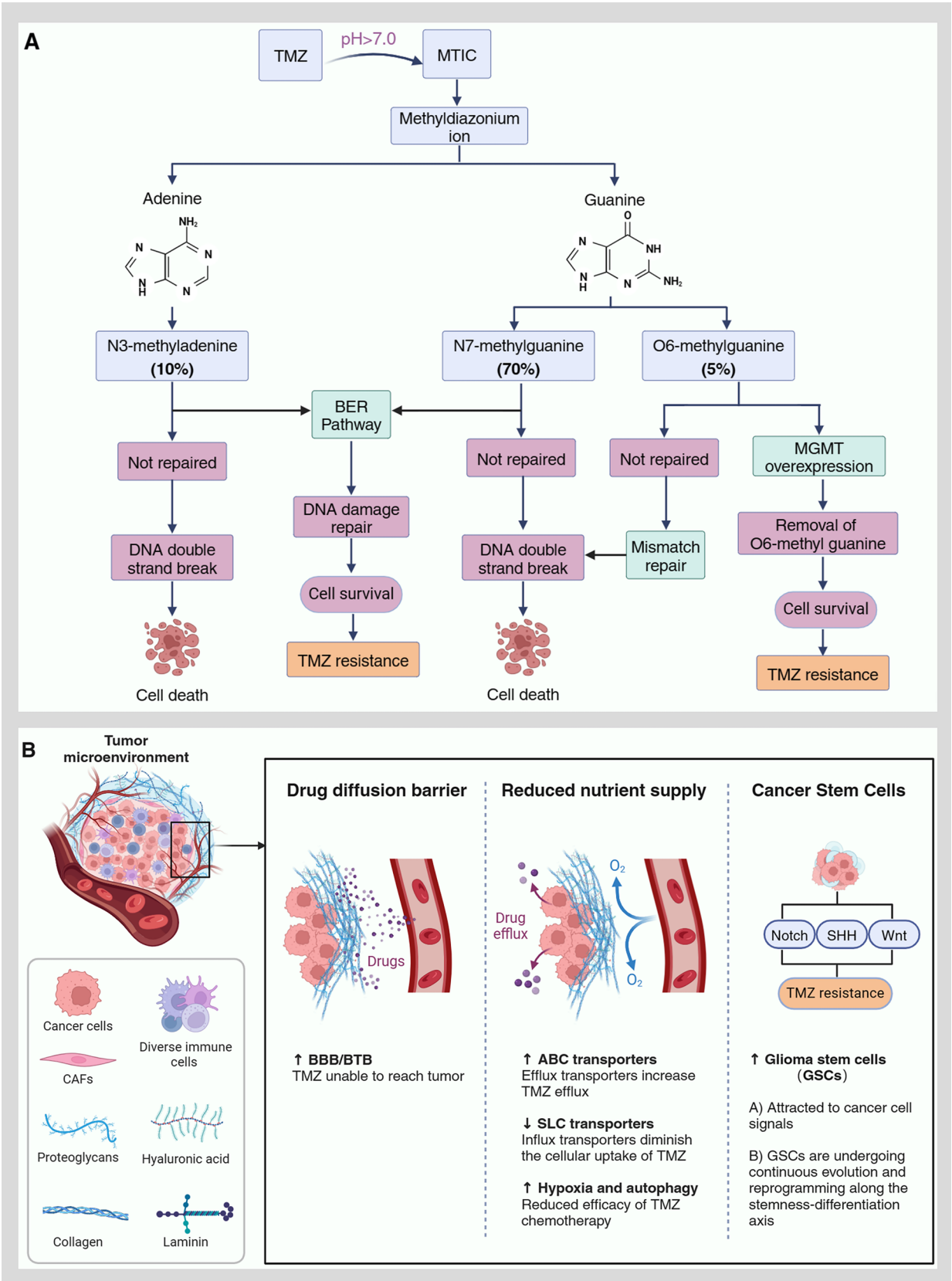
Fig. 1 Potential mechanisms underlying resistance to TMZ in GBM. **A**: DNA repair mechanisms and TMZ resistance. At physiological pH, TMZ ▶ undergoes hydrolysis to form its active metabolite (MTIC), which is further converted into the pharmacologically active methyl diazonium. This alkylating agent engages in the methylation of the O6 and N7 positions of guanine and the N3 position of adenine residues in DNA, resulting in DSBs that subsequently activate apoptotic pathways in tumor cells. **B**: Barriers to BBB and BTB permeability and the heterogeneous tumor microenvironment. The BBB/BTB limits the delivery and infiltration of TMZ into tumor-infiltrated areas. Abnormal expression of membrane transporters, coupled with microenvironmental factors such as hypoxia and autophagy, reduces drug availability, thereby compromising the effectiveness of chemotherapy. Glioblastoma stem cells (GSCs) activate intrinsic signaling pathways essential for GBM proliferation, maintenance, and progression, contributing to TMZ chemoresistance. Moreover, GSCs can persist following treatment, resulting in tumor recurrence. TMZ, temozolomide; GBM, glioblastoma; BER, base excision repair; MGMT, methylguanine methyltransferase; MTIC, 5-(3-Methyl-1-triazeno) imidazole-4-carboxamide; DSBs, DNA double strand breaks; BBB, blood–brain barrier; BTB, brain tumor barrier; ABC transporters, ATP-binding cassette transporters; SLC transporters, solute carrier transporters; SHH, Sonic hedgehog

[22]. Therefore, demethylation of the MGMT promoter serves as a crucial regulator of MGMT gene expression and a significant predictor of TMZ treatment outcomes. However, recent studies have revealed that in a subset of recurrent glioma, genomic rearrangements of the MGMT can lead to MGMT overexpression, independent of promoter methylation status [23]. Furthermore, the combination of IDH mutation and MGMT promoter methylation has been shown to be directly associated with the best response rate to TMZ and is independently linked to favorable survival outcomes [24]. These findings indicate that the combination of IDH mutation status and MGMT promoter methylation may serve as a suitable clinical stratification factor for glioma patients, potentially guiding personalized treatment strategies.

3.1.2 Mismatch repair (MMR)

The MMR system, a highly conserved molecular pathway, serves to identify and repair errors including insertions, deletions, and nucleotide misincorporations that arise during DNA replication, recombination, and damage response processes [16]. The MMR system comprises various subunits of mismatch repair proteins, including MutL homologue 1 (MLH1), MutS homologue 2 (MSH2), MSH3, MSH6, and the mismatch repair endonuclease postmeiotic segregation 2 (PMS2), which associate to form heterodimers [25]. MutL homologs (MLH/PMS) and MutS homologs (MSH) are conserved across biological processes [26, 27]. Both MLH/PMS and MSH proteins possess ATP-binding and hydrolysis activities, which are essential for orchestrating downstream MMR excision events that ultimately remove the error-containing DNA strand [28–30]. Among them, MLH1 serves as the central component of the MMR pathway, functioning through its formation of a heterodimer (MutLα) with PMS2. MutLα can recognize mismatched DNA identified by MutSα (MSH2-MSH6) or MutSβ (MSH2-MSH3) and coordinates downstream repair processes. These repair processes involve exonuclease 1 (EXO1), DNA ligase I (LIG1), and proliferating cell nuclear antigen, which collectively correct replication errors that result in mismatched nucleotides or insertion-deletion loops in DNA [31–33]. Specifically, the MMR DNA repair process progresses through several sequential phases. In the initial stage, the recognition and attachment to mismatches are carried out by either the MSH2-MSH6 or MSH2-MSH3 subunits, contingent on the specific nucleotide base mismatch. The heterodimer subsequently interacts with the MLH1-PMS2 complex to establish a tertiary complex, which facilitates the recruitment of necessary proteins for gap repair. The second stage is carried out by the EXO1 exonuclease, while the third stage involves repair and ligation by LIG1 [9].

Studies indicate that the MMR system holds significant importance in managing DNA damage triggered by DNA-alkylating agents such as TMZ. If TMZ-induced O6-MeG adducts are not repaired by MGMT, they can incorrectly pair with thymine during DNA replication. The MMR system attempts to remove the mismatched thymine, leaving the methylated guanine, which leads to DNA double-strand breaks, disruption of the cell cycle, and induction of programmed cell death [16, 34]. As previously mentioned, the identification of TMZ-induced O6-MeG:T mismatches is initiated by the multiprotein complex MutSα, which consists of the heterodimer formed by MSH2 and MSH6. However, inactivation of MSH2 and MSH6 genes might fail to respond to TMZ-induced mismatches, associated with the cytotoxic effects of TMZ [35]. Yip et al. demonstrated that MSH2 suppression could lead to TMZ resistance in xenograft models [36]. Clinically, reduced expression and functionality of MSH6 are linked with tumor progression during TMZ therapy [37]. Nonetheless, Maxwell et al. [38] observed no correlation between MMR defects and TMZ chemoresistance at the clinical level, suggesting other pathways may also contribute to TMZ resistance in GBM.


A
TMZ
pH>7.0
MTIC
Methyldiazonium ion
Adenine
Guanine
N3-methyladenine (10%)
N7-methylguanine (70%)
O6-methylguanine (5%)
BER Pathway
Not repaired
Not repaired
Not repaired
MGMT overexpression
DNA damage repair
DNA double strand break
DNA double strand break
Mismatch repair
Removal of O6-methyl guanine
Cell survival
Cell survival
TMZ resistance
TMZ resistance
Cell death
Cell death
B
Tumor microenvironment
Cancer cells
Diverse immune cells
CAFs
Proteoglycans
Hyaluronic acid
Collagen
Laminin
Drug diffusion barrier
Drugs
↑ BBB/BTB
TMZ unable to reach tumor
Reduced nutrient supply
Drug efflux
O2
O2
↑ ABC transporters
Efflux transporters increase TMZ efflux
↓ SLC transporters
Influx transporters diminish the cellular uptake of TMZ
↑ Hypoxia and autophagy
Reduced efficacy of TMZ chemotherapy
Cancer Stem Cells
Notch
SHH
Wnt
TMZ resistance
↑ Glioma stem cells (GSCs)
A) Attracted to cancer cell signals
B) GSCs are undergoing continuous evolution and reprogramming along the stemness-differentiation axis

3.1.3 Base excision repair (BER)

Most cytotoxic lesions caused by TMZ, including N7-MeG and N3-MeA, is efficiently resolved through the base excision repair mechanism, a process that is vital for maintaining the viability of GBM cells [39]. The restoration process commences with the recognition and elimination of defective bases by a specific DNA glycosylase enzyme. Then, apurinic/apyrimidinic endonuclease 1 (APE1) processes the abasic sites, making a cut at the DNA's 5′-end. DNA ligase and DNA polymerase subsequently complete the repair [16]. DNA glycosylases, as the initiating enzymes of the base BER pathway, exert their function in BER by mediating the removal of methylated purine adducts. The specific recognition capacity of DNA glycosylases determines the accuracy and efficiency of BER [33]. Moreover, elevated DNA glycosylase expression in GBM typically correlates with unfavorable outcomes and TMZ resistance. Recent investigations have revealed that HIV-1 Tat interactive protein 2 (HTATIP2), also called TIP30 or CC3, functions as a negative regulator of importin β-mediated cytoplasmic-nuclear protein translocation [40–42]. In gliomas, epigenetic silencing or functional loss of HTATIP2 correlates with poor clinical prognosis [43, 44]. Analysis of the DNA methylome in GBM has identified recurrent epigenetic silencing of HTATIP2. This silencing may augment the capacity of GBM cells to repair treatment-induced lesions by promoting the nuclear localization of BER enzyme N-Methylpurine DNA Glycosylase (MPG), thereby fostering treatment resistance [45].

Among the BER components, poly (ADP-ribose) polymerase 1 (PARP1) serves a critical function in identifying and signaling the presence of DNA damage. It repairs single-strand DNA breaks during BER and assists in recruiting MGMT proteins to fix O6-methylguanine residues. Overexpression of PARP1 is generally linked with enhanced resistance to TMZ chemotherapy and lower survival prospects in individuals with glioma [46]. Additionally, inhibiting PARP leads to an increase in DNA double-stranded breaks, making PARP-deficient cells more susceptible to carcinogens [47]. Thus, targeting BER could potentially enhance the response to TMZ and manage resistance in GBM.

3.2 Increase drug efflux and decrease uptake, impede intracellular TMZ accumulation

3.2.1 Brain/brain tumor permeability barriers: drug efflux transporters

Despite TMZ, an alkylating agent, having a good clinical effect on newly diagnosed GBM patients, up to 50% of patients still have a poor response to TMZ treatment. Mechanistically, the presence of these two barriers further limits the delivery and penetration of TMZ into the tumor-infiltrating area: the BBB and the brain tumor barrier (BTB) [2]. The topological polar surface area (TPSA) has been extensively employed as a predictive indicator for BBB/BTB permeability in pharmaceutical research [48]. Studies have unveiled a linear relationship between brain penetrability and dynamic polar surface area (PSA), indicating that the efficiency of BBB penetration declines as PSA values rise [49]. CNS drugs typically demonstrate significantly lower TPSA values compared to non-CNS therapeutics, with the optimal range for BBB penetration generally falling below 76 $Å^2$ (25–60 $Å^2$) [50]. Notably, although multiple studies have demonstrated favorable CNS penetration of TMZ [51, 52], its TPSA (106 $Å^2$) [53] substantially exceeds the estimated threshold for BBB permeability (76 $Å^2$), suggesting potential challenges in traversing both the BBB and BTB. GBM tumors are shielded by the BBB, which functions as a preliminary filter in their resistance mechanisms. A healthy BBB features continuous tight junctions consisting of astrocytes and pericytes. This characteristic permits the passive diffusion of selective substances, including small molecules (< 500 Da) and lipophilic compounds, across the BBB into the CNS, thereby maintaining homeostasis [54]. In contrast, larger or hydrophilic molecules rely on specialized transporters for penetration, including the glucose transporter-1 (GLUT-1) or members of the ABC transporter protein family [55]. The ABC transporter proteins are located on the luminal side (blood side) of the BBB endothelium and are capable of excreting foreign substances out of cells, reducing drug accumulation in the brain and rendering treatment ineffective[56]. These transporters include 48 genes across 7 subfamilies, from ABCA to ABCG [57]. Notably, only three ATP-driven efflux pumps, ABCB1 (P-gp/MDR1), ABCG2 (BCRP), and ABCC1 (MRP1), are actively involved in chemoresistance in vivo [58]. Research has demonstrated that P-gp identifies and transports approximately 60% of anticancer agents out of cells, decreasing intracellular drug levels and reducing therapeutic efficacy. Increased expression of P-glycoprotein (P-gp), which is encoded by the MDR1 gene, is linked to unfavorable prognoses and chemoresistance in glioma cases [59]. Furthermore, TMZ is recognized as a substrate for P-gp and BCRP, with the expression of these transporters is commonly upregulated following exposure to chemotherapeutic agents. TMZ penetrates the brain 1.5-fold more effectively in P-gp and BCRP knockout mice than in wild-type mice [60]. Consequently, the upregulation of ABC transporters is associated with the emergence of acquired resistance, making these efflux transporters promising candidates for overcoming TMZ resistance.

GBM has been demonstrated to induce aberrations in the blood–brain barrier, leading to the formation of blood-tumor barrier, which is typically characterized by a disorganized structure and non-uniform permeability [6]. Moreover, GBM cells release vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs), scatter factor/hepatocyte growth factor (SF/HGF), and certain chemokines and cytokines, all of which contribute to the formation of the BTB. Due to the heterogeneity of BTB, cancerous cells typically have hypoxic regions where therapeutic delivery is limited, thus exacerbating drug resistance in GBM [61–63]. Some studies suggest that the tight junction integrity among brain endothelial cells may be impaired in both primary and metastatic brain tumors, attributed to the expansion of the perivascular space and BBB dysfunction. As a result, the BTB seems to impose fewer osmotic restrictions than the BBB. However, the complexity in these tumors is compounded by the overexpression of drug efflux transporters at the BTB, which might mitigate the effects of increased passive diffusion [35]. Both the blood–brain barrier and blood-tumor barrier vasculature may exhibit P-gp expression, facilitating the expulsion of drugs from cells [64]. The protective function of P-gp is greatly weakened in tumor necrotic regions due to a compromised BTB. In contrast, P-gp activity is apparent at the tumor margins where the BBB remains intact [65]. This finding has significant clinical relevance for the successful treatment of GBM patients post-surgical resection, as the overexpression of tumor-specific P-gp impedes the penetration of chemotherapeutic drugs into the brain [66]. Inhibiting ABC transporters, particularly through agents like P-gp inhibitors and small interfering RNAs (siRNAs), is being explored to reduce drug efflux and improve TMZ effectiveness against glioma.

Taken together, the BBB/BTB impedes the arrival of multiple chemotherapeutic agents, including TMZ, to the GBM tumor infiltration areas in the brain, presenting a significant challenge to effective GBM treatment. Despite multiple strategies having been investigated to boost intracerebral drug delivery efficiency to the brain—such as drug chemical modifications, efflux transporter suppression, and direct intra-tumoral injection—the mechanisms governing the pathological changes in the BBB that affect drug delivery to the CNS remain incompletely understood. Continued efforts are needed to elucidate the complexities of the BBB and BTB, and to conduct comprehensive and precise preclinical assessments of drug efficacy in GBM.

3.2.2 Low expression of solute carrier (SLC) transporters inhibits drug uptake

The SLC transporter superfamily, comprising 439 transmembrane transporters divided into 65 subfamilies—60 of which are found in the brain [67]—plays a vital role in anticancer drug resistance by regulating drug concentrations at target sites in both normal tissues and tumor-infiltrated areas. Specifically, the influx transporters primarily involved in cellular uptake of anticancer drugs, such as members of the SLCO and SLC22 families, are typically down-regulated in tumor cells concerning both expression and function. This limits the accumulation of anticancer agents within tumor cells, thereby leading to ineffective drug therapy [68]. Clinically relevant is the observation that SLC22A18 protein expression downregulation may serve as a predictive tumor biomarker for glioma patients receiving TMZ treatment. Research by Yang et al. demonstrated that silencing SATB1 increases SLC22A18 expression in human GBM cells, countering TMZ resistance [69]. Furthermore, high SLC22A18 expression has been shown to enhance the chemosensitivity of malignant glioma cells to the antitumor agent 1,3-bis(2-chloroethyl)-1-nitrosourea and improve glioma's radiosensitivity by inhibiting DNA damage repair capacity, both in vitro and in vivo experiments [70].

To summarize, the inadequate expression and abnormal function of influx SLC transporters in malignant glioma cells are a key driver of therapeutic resistance. On the other hand, attempts to augment the limited efficacy of TMZ by increasing the dosage might lead to systemic toxicity. To address this, various strategies to enhance drug uptake into cancer cells, such as using prodrugs and targeting nanocarriers at transporter proteins, have been proposed and are currently under investigation.

3.3 Heterogeneous tumor microenvironment

3.3.1 Glioma stem cells (GSCs)

GSCs represent a distinct subset of GBM cells, defined by their strong tumorigenic properties and remarkable cellular plasticity. These cells exhibit unlimited proliferative potential, sustained self-renewal, and the ability to differentiate into multiple lineages [71]. Although they constitute only 3%–5% of GBM tumors [72], GSCs are crucial in driving treatment resistance and maintaining GBM cellular heterogeneity [73]. Stem cell niches consist of specific dynamic microenvironments that support the survival of stem cells throughout a lifetime [74]. Numerous in vitro experiments

have shown that cells expressing GSC markers are more resistant to TMZ exposure [75]. Major surface molecular markers of GSCs include CD133, SSEA1, ALDH1A3, nestin and SOX2. Nevertheless, the continuous evolution and reprogramming of these cells along the stemness-differentiation axis render it challenging to precisely recognize and target the whole GSC subpopulation within tumor tissues from a functional perspective [76, 77]. Additionally, GSCs activate intrinsic signaling pathways related to GBM growth, renewal, and development, such as Notch, Sonic hedgehog (SHH), and Wnt/β-catenin signaling pathways, which contribute to TMZ chemotherapy resistance [78]. Targeting these GSC-specific signal transduction pathways offers a promising direction for effective GBM treatment.

3.3.2 Hypoxia and autophagy

Tumor hypoxia is frequently associated with unfavorable outcomes in multiple aggressive cancers, such as GBM. Hypoxia-inducible factor 1 (HIF-1) serves as an essentia transcription factor under hypoxic conditions, modulating the expression of numerous genes to orchestrate the adaptive response of tumor cells to hypoxia. As cancer and stromal cells expand, they decrease oxygen availability, leading to hypoxia through HIF-1α, which promotes cancer progression and treatment resistance [79]. Studies suggest that targeting HIF-1α, particularly in combination with other anticancer drugs or therapies, can suppress tumorigenesis and significantly enhance chemosensitivity. Ding et al. conducted in vivo studies using anti-PD-L1 antibody in combination with HIF-1α inhibitor (PX-478), finding that the combination therapy has a more significant anti-cancer effect in terms of both tumor proliferation and survival compared to each therapy alone [60]. Notably, PX-478 also enhances the intracranial efficacy of anti-PD-L1 antibody in a glioma model (Luci + GL261), suggesting that inhibiting HIF-1α expression, in conjunction with immunotherapies, could be a promising strategy to advance glioma treatment.

Autophagy is a protective mechanism triggered by hypoxia, enabling the degradation of unnecessary proteins and damaged organelles. It often activates following cytotoxic treatments to maintain mitochondrial function and minimize DNA damage, thereby playing a crucial role in developing drug resistance [80]. For instance, acute TMZ treatment inhibits PI3K/AKT/mTOR signaling and transiently induces autophagy, leading to resistance in GBM therapy [81]. Current clinical trials are exploring autophagy inhibitors, including chloroquine (CQ) and hydroxychloroquine (HCQ) to suppress protective autophagy in GBM cells, potentially enhancing the efficacy of TMZ treatment [82, 83]. Recent studies indicate that Daurisoline (DAS) disrupts TMZ-triggered autophagy by targeting the PI3K/AKT/mTOR signaling pathway effectively, enhancing TMZ chemosensitivity [84]. Consequently, regulating autophagy offers a promising strategy against glioma.

3.3.3 Immuno-suppressive tumor microenvironment

The therapeutic resistance to immunotherapy in GBM patients is mainly attributed to the augmented acquired immunosuppressive capacity of tumor cells and the alteration of the immunosuppressive tumor microenvironment (TME). Elucidating the mechanisms of immunosuppressive TME-mediated therapy resistance is essential for minimizing GBM recurrence. The immunosuppressive microenvironment in GBM exhibits a complex composition, encompassing immunosuppressive cytokines, extracellular vesicles, chemokines secreted by glioma cells and glioma-initiating cells, as well as various immunosuppressive cell populations [85]. In particular, recent investigations have emphasized the involvement of immunosuppressive cells, including M2-polarized macrophages and myeloid-derived suppressor cells (MDSCs), in mediating immune suppression and tumor resistance in the GBM microenvironment [86–88]. GBM tumor cells are known to 'hijack' the immune microenvironment to facilitate their growth and evade immune surveillance. Several studies have noted that glioma-associated macrophages (GAMs) promote the transition to a mesenchymal-like state, correlating with heightened resistance to chemo- and radiotherapy [89, 90]. Additionally, genes responsible for detecting tumor cells and signals, as well as initiating immune responses, were found to be downregulated in microglia from GBM mice, whereas genes facilitating tumor progression were upregulated [91]. Studies indicate that adjuvant immunotherapy targeting specific antigens can decrease survival in TMZ-resistant GBM cells, highlighting the role of GBM's immune microenvironment in evading TMZ-induced cell death [92, 93]. However, despite the success of immune-targeting therapies like monoclonal antibodies in other cancers, their efficacy in GBM clinical trials has been limited, hindering their progress [94]. Emerging evidence has revealed that the intercellular trafficking of lipids, nucleic acids, and proteins through extracellular vesicles (EVs) can facilitate chemoresistance. A notable example is the EV-mediated transfer of MGMT mRNA from tumor-associated regulatory astrocytes to GBM cells, which has been shown to confer a TMZ-resistant phenotype [95]. Moreover, EVs harboring miR-3591-3p [96] and miR-1246 [97] are capable of inducing

M2 macrophage polarization, thereby exacerbating immunosuppression under hypoxic conditions. Studies have also demonstrated that exosomes derived from TMZ-resistant GBM cells can enhance the survival of TMZ-sensitive cells, confirming that EVs promote tumor progression and therapeutic resistance by altering cellular functions [98].

Collectively, the immunosuppressive TME of GBM facilitates TMZ resistance through a variety of mechanisms, including the infiltration of immunosuppressive cells, the secretion of immunosuppressive factors, defects in antigen presentation, and metabolic reprogramming. Targeting these mechanisms with novel therapeutic strategies, such as immune checkpoint inhibitors, oncolytic virus therapy, and the reprogramming of tumor-associated macrophages (TAMs), may effectively overcome TMZ resistance, enhance tumor cell death, and ultimately improve therapeutic efficacy.

4 Approaches to Overcome TMZ-resistance in GBM

4.1 DNA-targeting agents

Based on the aforementioned molecular mechanisms, researchers have identified several compounds targeting the MGMT, MMR, and BER systems to improve TMZ's therapeutic effects. High MGMT gene expression in glioma is connected with resistance to TMZ treatment. Novel compounds, EPIC-0307 [99] and EPIC-0412 [100], discovered through high-throughput screening, inhibit DNA damage repair responses and reduce MGMT expression in GBM cells via an epigenetic pathway, enhancing TMZ's efficacy. Clinically, their combination with TMZ has been demonstrated to enhance survival benefits in GBM patients. Additionally, PARP inhibitors (PARPi), including olaparib and veliparib, reinstate chemosensitivity to TMZ in MSH6-null MMR-deficient GBM cells [101]. This PARPi-induced effect does not involve BER inhibition and cannot be replicated by knocking out PARP1 [101]. Combining PARPi and TMZ is seen as an innovative strategy to counteract chemoresistance in glioma. Promising PARP inhibitors, including niraparib, veliparib, olaparib, and pamiparib, are currently being evaluated in combination with TMZ in clinical trials for GBM patients [102].

Multiple studies highlight the role of APE-1 enzyme activity in regulating resistance to TMZ in glioma. Across in vitro and in vivo experiments, Cho et al. illustrated that NTX reduces APE-1 expression, thereby inhibiting tumor growth and inversely correlating with the apparent diffusion coefficient (ADC) of TMZ-resistant GBM [103]. Furthermore, Demple et al. [104] observed in several cancer cell lines that significant downregulation of APE-1 is associated with reduced growth and invasion in resistant cells, while having limited cytotoxic effects on TMZ-sensitive cell lines. These studies suggest that APE-1 is a promising target for malignant glioma treatment, and the design of small molecule inhibitors targeting APE-1 could offer extensive therapeutic benefits for glioma patients.

4.2 Inhibitors of multidrug transporting proteins

Higher expression of MRP1 and P-gp in glioma and their role in active transport across the BBB identify these drug efflux transporters as potential targets to enhance TMZ's effectiveness in GBM. Reversan, a pyrazolopyrimidine compound discovered from a systemic compound library, significantly enhances TMZ chemosensitivity both in primary and recurrent GBM tumor cells as a novel MRP1 inhibitor [105]. Additionally, the well-known dual P-gp and BCRP inhibitor elacridar (GF120918) increased the BBB permeability of TMZ by 1.5-fold and enhanced its anticancer effects in intracranial tumor-implanted mice [60]. An alternative strategy involves targeting carbonic anhydrase II (CAXII), which regulates intracellular/extracellular pH to efficiently facilitate P-gp function. Salaroglio et al. [106] observed co-expression of CAXII and P-gp in glioma neurospheres, noting that Psammaplin C, a CAXII inhibitor, suppressed P-gp-driven TMZ efflux and enhanced TMZ's anticancer efficacy in glioma. These findings suggest that inhibiting efflux transporter proteins may increase intracellular TMZ bioavailability and re-sensitize GBM cells to TMZ.

As an alternative strategy, drug repurposing—also known as drug repositioning or therapeutic switching—has gained traction as an innovative strategy for identifying effective modulators of drug efflux transporters in clinical settings [107]. One of the outstanding advantages of this new strategy is that it circumvents the lengthy timelines and high expenses associated with the new drug development process, thereby delivering novel therapeutic agents against gliomas in a relatively short period of time. During the past few years, drug repurposing has contributed to approximately 30% of new drug and vaccine approvals by the FDA [108]. These repurposed therapeutic agents exhibit well-defined pharmacological mechanisms, proven administration strategies, and extensively researched pharmacological and toxicological profiles. This allows for theoretical predictions regarding their pharmacokinetics and adverse effects at both preclinical and clinical levels [109]. Erlotinib, a tyrosine kinase inhibitor (TKI) targeting EGFR, is approved for treating locally advanced or

metastatic non-small cell lung cancer (NSCLC) in patients who have not responded to at least one previous chemotherapy treatment. Evidence suggests that erlotinib not only exerts anti-tumor effects by inhibiting EGFR but also modulates the transmembrane transport function of specific ABC transporters, reversing ABCB1- and ABCB2-mediated multidrug resistance (MDR) in cancer cells [110]. Jessian et al. demonstrated that erlotinib, an EGFR kinase inhibitor, reduced P-gp levels and sensitized GBM cells to TMZ. Combination therapies using EGFR inhibitors and the alkylating agent TMZ may provide additional clinical benefits for overcoming chemoresistance. Additionally, cediranib is an investigational small molecule oral multi-receptor TKI that has undergone evaluation in a Phase III clinical trial for managing recurrent GBM patients (NCT00777153) [107]. Cediranib effectively overcomes chemoresistance driven by ABCC1 and ABCB1 through directly suppressing the drug efflux function and expression levels of both transporters [111]. In conclusion, repurposing existing drugs for assessment in clinically relevant GBM models, together with advanced technologies to predicting, validating, and improving CNS penetration, is anticipated to boost the number of effective GBM treatments that advance to clinical arena.

4.3 Targeting the tumor microenvironment

The TME encompasses both organismal milieu and tumor-specific ecological niche, which collectively regulate the growth and invasion of GBM [112]. Existing studies confirm that TMZ chemoresistance can be effectively reversed by targeting and modulating the TME. Tumor-associated macrophages and microglia (TAMs), as major immune cell populations within the TME, are potential regulators of the response to TMZ. Members of the metzincin superfamily, such as MMPs and A Disintegrin and Metalloprotease (ADAM), play crucial roles in mediating cellular communication within the TME. ADAM8 has been shown to activate the HB-EGF/EGFR signaling pathway, upregulate CCL2 expression and promote TAM recruitment in GBM. This process further induces ADAM8 expression in GBM cells to mediate TMZ chemoresistance [113]. Therefore, modulating the ADAM8-dependent positive feedback loop between TAMs and GBM cells can help sensitize GBM to TMZ chemotherapy. GSCs effectively repair DNA damage induced by standard therapies, thereby contributing to resistance. The epigenetic modifier lysine-specific histone demethylase 1A (KDM1A/LSD1), which is highly expressed in GBM, is crucial for the DNA double-strand break repair capacity of GSCs. Inhibition of KDM1A impairs both homologous recombination and non-homologous end-joining repair pathways, thereby sensitizing cells to TMZ. Additionally, the KDM1A inhibitor NCD-38 exhibits good BBB permeability and knockdown of KDM1A enhances the efficacy of TMZ both in vitro and in vivo. The combination of TMZ with KDM1A inhibitors may emerge as a novel therapeutic strategy for GBM [114].

Notably, certain active ingredients of TCM and their derivatives can precisely target the TME and exert anti-tumor effects by modulating therapeutic resistance. Indirubin, a natural product present in indigo plants and is also an active ingredient in the TCM formula Dang Gui Long Hui Wan. Sean et al. [115] discovered that the chemical derivative of indirubin, 6′-bromoindirubin-3′-acetoxime (BiA), can slow the growth of GBM in mice. In vitro and animal experiments have demonstrated that indirubin and its derivatives possess broad anti-inflammatory and anti-tumor effects. A nanoparticle formulation of BiA, PPRX-1701, has been developed. Intravenous administration of PPRX-1701 can reduce the expression of the key enzyme indoleamine 2,3-dioxygenase 1 (IDO1) in the immunosuppressive tumor microenvironment of GBM, thereby blocking the growth of brain tumors in GBM mouse models and improving survival rates [116]. Previous studies have shown the presence of endocannabinoid receptors within the tumor microenvironment, suggesting that these receptors may serve as promising therapeutic targets for GBM [117]. Subcutaneous or intracranial implantation of human-derived or syngeneic glioma cells into immunodeficient murine models or immunocompetent rats have confirmed the anti-glioma efficacy of Δ^9-Tetrahydrocannabinol (THC) and other cannabinoid receptor agonists [118, 119]. These preclinical studies provide compelling evidence supporting the therapeutic potential of combining TMZ and oral cannabinoids to target the TME in the treatment of GBM.

4.4 Immunotherapy

The immunosuppressive TME, blood–brain barrier, and both intratumoral and intertumoral heterogeneity collectively impede the application of immunotherapy in GBM. To reverse immunosuppression and augment the immune response against GBM, a variety of immunotherapeutic strategies have been employed, including immune checkpoint inhibitors, chimeric antigen receptor (CAR) T-cell therapy, multiantigen vaccines, oncolytic viruses, and retroviruses [120, 121]. Yong et al. [122] demonstrated that the small-molecule compound toosendanin (TSN) effectively reverses macrophage-mediated tumor immune suppression, thereby promoting T-cell infiltration, activation, and reducing T-cell exhaustion,

which collectively enhance antitumor immunity in GBM in mouse models. Furthermore, the combination of TSN treatment with immune checkpoint blockade successfully induces regression of syngeneic GBM tumors in mice. These results indicate that TSN may serve as a promising therapeutic compound for blocking tumor immune suppression and circumventing resistance to T cell-based immunotherapy in GBM. The upregulation of immunosuppressive molecules secreted by GBM, including indoleamine 2,3-dioxygenase (IDO) and programmed cell death 1 ligand 1 (PD-L1), has been implicated in the initiation of immune suppression. Siglec-9 has been identified as a novel macrophage immune checkpoint molecule that can be targeted to potentiate the efficacy of anti-PD-1/PD-L1 immunotherapy in GBM [123]. This study further demonstrates that integrating single-cell analysis of human samples with translational studies in mice can effectively uncover novel immune checkpoint-based immunotherapies. Another line of evidence demonstrates that MS4A4A inhibition attenuates M2-polarized TAM infiltration, modulates ferroptosis-related gene expression, and enhance the responsiveness of PD-1 immunotherapy via remodeling of the immunosuppressive microenvironment [124]. Furthermore, Liu et al. [125] reported that the nano-co-delivery of TMZ and small interfering PD-L1 (siPD-L1) significantly suppressed the growth of orthotopic TMZ-resistant GBM and prolonged survival in rat models by reversing TMZ resistance and remodeling the immunosuppressive tumor microenvironment. The TMZ/siPD-L1@GLPN/dsb nanocomplex demonstrated promising therapeutic potential for treating orthotopic TMZ-resistant GBM.

Novel immunotherapeutic approaches have been extensively investigated in various preclinical and clinical trials, with combination therapies emerging as an innovative strategy to enhance treatment efficacy. Oncolytic viruses exert anti-glioma effects by directly lysing tumor cells, subsequently releasing tumor antigens that activate systemic immune responses. This therapeutic pathway may be further potentiated through synergistic combinations with dendritic cell vaccines and immune checkpoint inhibitors [126]. Viruses can serve as vectors to transduce genes encoding cytokines and other suicide genes to damage glioma cells. However, rational design of combination immunotherapy requires thorough mechanistic understanding. While granulocyte–macrophage colony-stimulating factor (GM-CSF) demonstrates potential for cytokine therapy, CSF inhibitors offer targeted modulation of TAMs. Importantly, these two immunotherapeutic approaches may exhibit antagonistic effects when combined [127], highlighting the need for careful therapeutic strategy optimization. Future research endeavors should focus on elucidating the optimal combinations of immunotherapies, optimizing the timing of treatment administration, and identifying novel therapeutic targets and strategies. Such advancements are crucial for mitigating adverse side effects and enhancing the antitumor immune response against GBM.

4.5 Combination drug therapy

Currently, combining TMZ with other anti-tumor agents or therapies is a prominent strategy for treating drug-resistant glioma. The addition of common chemotherapeutic agents to TMZ enhances patient survival and introduces new possibilities for effective GBM treatment. For example, the efficacy of TMZ combined with statins is being explored in both in vivo and clinical trials, and attempts are being made to elucidate their synergistic mechanisms in treating GBM [25, 128]. Numerous preclinical studies have demonstrated that statins have unique anticancer properties and are safe, non-toxic, and well-tolerated, suggesting that statins are suitable for investigation in well-designed prospective clinical trials [129]. However, these medications can occasionally lead to neuromuscular side effects, constituting approximately two-thirds of all reported adverse events. The spectrum of muscle-related adverse events encompasses spasticity, weakness, myalgia, immune-mediated necrotizing myopathy, and, in less common instances, rhabdomyolysis [130]. A study reported that the combinatorial therapy of TMZ, EGFR-TKI, and atorvastatin significantly inhibited GBM growth and reversed the immunosuppressive microenvironment, thereby extending the survival duration of GBM patients exhibiting high RTK-fatty acid-gene signature (RFA) scores [131]. The findings revealed the metabolic reprogramming mechanism in EGFR-activated GBM and provided a predictive marker-guided, precise combination therapeutic program for the clinical management of GBM [131]. Notably, although statins have proven effective in tackling some of the disadvantages and toxic side effects of standard cancer therapies, the molecular mechanisms behind these improvements necessitate additional investigation to support the rational use of statins in combination with anticancer drugs [132]. Furthermore, therapeutic combinations of TMZ with other innovative compounds have been designed to enhance chemosensitivity. Dey et al. demonstrated through in vitro and in vivo studies that the co-administration of an atypical PKC inhibitor with TMZ synergistically promotes apoptosis in GBM tumor cells, reduces tumor invasion and abnormal proliferation, and enhances GBM cells sensitivity to TMZ [133]. Thus, combination chemotherapy may offer more effective anti-tumor activity and help prevent the development of chemo-resistance (Table 1).

Table 1 Combination therapy used to overcome GBM's resistance to temozolomide

Type	Drug	In vitro/in vivo	Therapeutic effects	References
Common chemo-therapy agents	Cyclotides	In vitro	Enhance chemosensitivity to TMZ by inducing cell death	[140]
	Valproic Acid	In vitro	Improve the anti-GBM effect of TMZ through the p53-PUMA apoptosis pathway	[141]
	NCD38	In vivo	As a KDM1A inhibitor, KDM1A inhibition combined with TMZ improved survival in orthotopic GBM mouse models	[114]
	CDDP	Both	In vitro: Reduce MGMT activity to attenuate DNA damage repair In vivo: Inhibit GBM tumor growth and extend the lifespan of mice	[142]
	Regorafenib	Both	In vitro: Improve GBM sensitivity to TMZ by inducing lethal autophagy arrest In vivo: Inhibit tumor growth in orthotopic GBM models	[143]
	Levetiracetam	Both	In vitro: Suppress MGMT expression and promote apoptosis In vivo: Inhibit tumor growth and increase mice survival rate	[144]
	Riluzole	Both	In vitro: Attenuate TMZ-induced upregulation of MGMT In vivo: Suppress tumor growth in the intracranial MGMT-positive GBM model	[145]
	Mifepristone	Both	In vitro: Increase the intracerebral concentration of TMZ by decreasing P-gp levels In vivo: Significantly diminish tumor proliferation	[146]
	Chloroquine	Both	In vitro: Inhibit protective autophagy and induce apoptosis In vivo: Inhibit tumor growth rate and reduce the tumor volume	[147]
	SurVaxM	Clinical trial	SurVaxM plus TMZ was well tolerated with no serious adverse events (NCT02455557)	[148]
	Depatuxizumab mafodotin	Clinical trial	Demonstrated positive anticancer efficacy and manageable side effects in EGFR-amplified rGBM patients (NCT01800695)	[149]
	Veliparib	Clinical trial	The combination of TMZ and Veliparib showed good tolerability, with manageable grade 3 or 4 hematologic toxicity (NCT02152982)	[150]
	DSF/Cu	Clinical trial	Extended remission occurred in 3 BRAF-mutant GBM patients	[151]
	DCvax	Clinical trial	Improve progression-free survival in patients with GBM and well tolerated	[152]
	Olaparib	Clinical trial	Olaparib reliably penetrates recurrent GBM at radiosensitizing concentrations	[153]
	Nivolumab	Clinical trial	The combination therapy did not improve survival in newly diagnosed GBM patients with methylated or unmethylated MGMT promoters (NCT02667587)	[154]
Traditional Chinese Medicine	Resveratrol	In vitro	Inhibit tumor growth and improve TMZ chemosensitivity by targeting STAT3 signaling	[155]
	Naringenin	In vitro	Inhibit cell proliferation and migratory	[156]
	Tubeimoside-I	In vitro	Induce apoptosis via reducing MGMT expression and inhibit the EGFR induced PI3K/Akt/mTOR/NF-κB signaling pathway	[157]
	Osthole	In vitro	Down-regulation of Bcl-2/ Beclin 1 expression and inhibit the migration phenotype of GBM cells	[158]
	Methanolic extract of *C. foetida*	In vitro	Induction of cell cycle arrest, autophagy, apoptosis and inhibition of metastasis	[137]
	Muscone	In vitro	Suppress TOP2A expression via the EGFR/Integrin β1/FAK signaling pathway	[138]
	Oridonin	Both	In vitro: Suppress the growth of GBM cells via inhibiting Hippo/YAP axis In vivo: Repress the tumor growth in a mouse xenograft, inhibit tumor cells proliferation and promotes apoptosis	[139]

Table 1 (continued)

Type	Drug	In vitro/in vivo	Therapeutic effects	References
	Paclitaxel	Both	In vitro: Suppress tumor growth via hydrogel encapsulation In vivo: Regulation of MGMT expression and enhanced survival in U87 MG xenografted mice	[159]
	Artesunate	Both	In vitro: Alleviate DNA damage repair by inhibiting the Wnt/β-catenin pathway In vivo: Decrease U251-TR glioma burden and improve the survival of mice	[160]
	β-Elemene	Both	In vitro: Slow the metabolic rate of TMZ in plasma and lengthen the mean residence time of TMZ in the brain In vivo: Inhibit tumor growth in glioma xenografts	[161]
	Cannabinoids	Both	In vitro: Induce lethal mitophagy via the ATF4-DDIT3-TRIB3-AKT-MTOR axis In vivo: Suppress glioma growth and prolong survival of mice	[162]
	Berberine	Both	In vitro: Reduce TMZ resistance by inducing autophagy via the ERK1/2 signaling pathway In vivo: Reduce tumor weights and tumor growth rates	[163]

Traditional Chinese Medicine (TCM), a key element of complementary and alternative medicine, raises concerns regarding its therapeutic toxicity and safety. Nevertheless, standardized application and optimal treatment strategies can minimize the toxic side effects associated with TCM [134]. Combining active ingredients from TCM with TMZ shows potential for enhancing sensitization, creating synergistic effects, and reducing adverse effects caused by TMZ. Previous research indicates that active components like ginsenoside Rg3 can reduce proliferation and induce apoptosis by activating the AKT and MEK signaling pathways [135]. Gambogic amide (GA-amide), an analogue of gambogic acid (GAC), is a principal active constituent of the traditional Chinese medicine gamboge. Qu et al. revealed that the tumor-enriched small molecule GA-amide inhibits glioma growth by targeting WDR1-dependent cytoskeletal remodeling. Mechanistically, GA-amide directly interacts with WD repeat domain 1 (WDR1), accelerates the depolymerization of F-actin, inhibits the invasion of patient-derived glioma cells (PDCs), and induces apoptosis in PDCs via the mitochondrial apoptotic pathway [136]. This study not only identifies GA-amide as a safe and effective therapeutic agent for glioma but also elucidates its underlying mechanisms from the perspective of cytoskeletal homeostasis. A recent study reported that CF-ME, an methanolic extract of the traditional Chinese medicine Cimicifuga foetida, induced G1-phase cell cycle arrest, promoted apoptosis via caspase activation, and triggered autophagy. Additionally, CF-ME also inhibited GBM cell invasion, migration and adhesion. In combination with TMZ, CF-ME further reduced GBM cell viability in a synergistic manner [137]. Muscone, one of the pharmacologically active components of Moschus, exhibits BBB permeability and has emerged as a potential antitumor agent. Recent work by Zou et al. [138] revealed that muscone suppresses TOP2A, a critical DNA repair enzyme, via the EGFR/integrin β1/FAK signaling axis, ultimately resensitizing TMZ-resistant GBM cells to anoikis. These findings position muscone as a promising adjunctive therapy for TMZ-resistant GBM, particularly in tumors with aberrantly high TOP2A expression. Ornithogalum officinale (ORI), a bioactive compound purified from the traditional Chinese herb Rabdosia rubescens, exhibits potent anticancer properties. Wang et al. [139] demonstrated that ORI significantly inhibits cell proliferation and induces apoptosis in a dose-dependent manner in U87MG glioblastoma cells, primarily by suppressing the Hippo/YAP signaling pathway. Furthermore, in a glioma xenograft mouse model, ORI effectively reduced both tumor weight and volume, confirming the antitumor efficacy. Therefore, this multi-level, multi-targeted pathway could introduce new opportunities for treating or providing adjunct therapy for GBM. Here, we list various active components and derivatives from TCM that have been leveraged to optimize the therapeutic response to TMZ in GBM patients (Table 1).

4.6 Novel TMZ analogs

Several analogs share a similar mode of action with TMZ but are immune to the resistance mechanisms associated with TMZ. Kingson et al. [164] leveraged the low MGMT expression in glioma cells to develop KL-50, a compound structurally akin to TMZ. KL-50 demonstrates a more potent specific effect on GBM cells without causing drug resistance, positioning it as a potential candidate for clinical GBM treatment. Additionally, TMZ analogs such as C8-imidazolyl and C8-methylimidazolotetrazine exhibited strong anticancer effects on MGMT-overexpressing T98G glioma cell lines by inducing G2/M cell cycle arrest, DNA double-strand breaks, and apoptosis [165]. Furthermore, Rai et al. synthesized an N,N-dimethyl carboxamide analog of TMZ that has a brain/plasma (B/P) ratio 30 times higher than that of TMZ, enhancing DNA alkylation activity and brain permeability. However, these promising in vitro results did not translate into tumor suppression in in vivo studies [166]. Future research will thus focus on evaluating the in vivo efficacy in orthotopic GBM xenograft models and further defining the toxicity and therapeutic window of these agents.

5 Conclusions and Future Perspectives

TMZ functions by inducing apoptosis via DNA damage and is a mainstay drug in treating GBM patients. However, GBM's chemoresistance to TMZ is driven by various molecular mechanisms, presenting a multifaceted challenge. Given the genomic heterogeneity of GBM and the involvement of multiple signaling pathways, monotherapy often falls short. Consequently, an effective therapeutic strategy for GBM will require combination therapies targeting several pathways. Additionally, developing novel TMZ analogs holds promise for improving clinical management of GBM.

TCM active ingredients and derivatives show a wide range of pharmacological activities in glioma. Nonetheless, most current studies of TCM for TMZ-resistant GBM focus on mouse ectopic tumor models and glioma cell lines, which may not adequately represent the tumor microenvironment's complexity. Consequently, the current focus for medical

practitioners is on effectively integrating and applying TCM preparations in clinical settings, which necessitates thorough research to discover and leverage innovative approaches. Future investigations into GBM's molecular biology and the optimization of drug delivery strategies are expected to uncover new therapeutic targets and compensatory mechanisms. Particularly, combining immunotherapy and nanomedicine could provide valuable insights into managing TMZ-resistant GBM effectively.

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Declarations

Competing interests The authors declare no competing interests.

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