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Review

Challenges and Perspectives of Standard Therapy and Drug Development in High-Grade Gliomas

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Abstract: Despite their low incidence rate globally, high-grade gliomas (HGG) remain a fatal primary brain tumor. The recommended therapy often is incapable of resecting the tumor entirely and exclusively targeting the tumor leads to tumor recurrence and dismal prognosis. Additionally, many HGG patients are not well suited for standard therapy and instead, subjected to a palliative approach. HGG tumors are highly infiltrative and the complex tumor microenvironment as well as high tumor heterogeneity often poses the main challenges towards the standard treatment. Therefore, a one-fit-approach may not be suitable for HGG management. Thus, a multimodal approach of standard therapy with immunotherapy, nanomedicine, repurposing of older drugs, use of phytochemicals, and precision medicine may be more advantageous than a single treatment model. This multimodal approach considers the environmental and genetic factors which could affect the patient's response to therapy, thus improving their outcome. This review discusses the current views and advances in potential HGG therapeutic approaches and, aims to bridge the existing knowledge gap that will assist in overcoming challenges in HGG.

Keywords: high-grade glioma; glioblastoma; anaplastic astrocytoma; anaplastic oligodendroglioma; oligodendroglioma; chemotherapy; radiotherapy; immunotherapy; phytochemicals; nanoparticles

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1. Introduction

Cancer is categorized by the World Health Organization (WHO) as the second deadliest disease, with an estimated death of 9.6 million globally in 2018 [1]. According to Siegel et al., in the United States alone, the number of newly diagnosed cancer patients shows an increment of around 8.94%, with an increase of 2.90% in mortality rate in the last five years [2,3]. According to the WHO classification, glioblastoma (GBM) is a grade IV glioma and the most aggressive form of diffuse glioma belonging to the astrocytic lineage. Out of all gliomas and primary brain tumors, GBM makes up the majority of it. This makes it the most common primary brain tumor [4].

Gliomas are neuroepithelial CNS tumors that can be classified into low-grade gliomas (LGG) and high-grade gliomas (HGG) [5]. Gliomas are characterized by the grade of malignancy, morphological characteristics, and molecular markers alteration based on the 2016 WHO classification [6]. Grade II–IV glioma includes astrocytoma, oligodendrogliomas, and glioblastoma (GBM) [6–8]. Although the prevalence of HGG (4.55%) is low compared to other cancers, it remains a fatal and aggressive type of primary brain tumor based on the CBTRUS statistical report from 2009–2013 in the US population [2,3,9]. LGG patients often respond better to treatment and have a better prognosis though patients may experience relapse with more aggressive glioma features [10,11]. GBM is the most aggressive adult form of HGG, accounting for 60–80% of all incidence among elder individuals (median age of diagnosis of 62 years old) with a median survival of 15 months [4,12,13]. However, many

HGG patients are not well suited for oncological treatment and are referred for palliative care instead [4,13–15].

The recommended standard of care for newly diagnosed HGG includes surgical resection, radiotherapy, and chemotherapy. Despite the optimal primary treatment, the patients' prognoses remain abysmal. According to the Central Brain Tumor Registry of the United States, the median overall survival is between 15–23 months and a low five-year survival rate (between 2007–2011) [4,13,16]. This can be due to surgical resection's inefficacy to fully resect the tumor and lack of effective therapeutic approaches to exclusively target HGG tumors that often have high tumor heterogeneity with complex tumor microenvironment [17]. Currently, there are no curative treatment options available for HGG, especially in GBM, and the current therapeutic leads to adverse side effects. Recent clinical trials utilize targeted treatment like immunotherapy and gene therapy as an adjuvant to counter the impact of immune dysregulation by stimulating the patient's immune system [18]. Recent breakthroughs in unraveling the molecular pathogenesis in HGG would improve the classification of gliomas, determine a patient's prognosis, and develop a therapeutic regimen based on each patient's requirement.

Additionally, research has looked into the potentiality of natural products as nutraceutical-based adjuvants [19–21]. Hence, this present review aims to discuss the current views of drug development and therapy in HGG. Additionally, this review discusses the therapeutic potential and the challenges associated with each of the different treatment modalities. The highlights and discussion in this review aim to improve the existing knowledge and bridge the gap in HGG research and advancement, particularly in the last decade. We hope this will provide a more comprehensive understanding of the development of more precise, effective, and personalized therapy in HGG patients.

2. Overview of Standard Therapy in HGG

2.1. Surgical Resection

Surgical resection is regarded as the benchmark to alleviate symptoms due to tumor mass. It decompresses the bulk of the tumor, reduces the elevated intracranial pressure, and provides a sufficient histological analysis of the tissue sample [22]. GBM's residual presence is often seen in tumor recurrence cases due to their highly infiltrative and proliferative nature. Therefore, maximizing the tumor removal, which includes excising the margins with minimal impacts on the healthy surrounding tissue, is crucial to improve the life expectancy of GBM patients [23]. The average survival for patients who have undergone surgical resection only instead of biopsy is significantly higher (7 months vs. 3.5 months), according to Lara-Velazquez et al. [24]. Thus, the degree of tumor resection influences GBM patients' prognoses. Although radical extirpation is usually the aim, this is not attainable due to the infiltrative nature of GBM cells [8,24,25]. Hence, every neurosurgeon's realistic aim is to resect up to a 90% threshold without causing surgery-related neurological deficits. The innovations in the field of neurosurgical oncology which can aid in ensuring maximum cytoreduction are summarized in Table 1.

Table 1. Innovations in neurosurgical oncology.

Innovation	Description
Awake Craniotomy	• Allows identification of eloquent areas of tumor in the subcortical and cortical regions, especially tumors which would otherwise be regarded as inoperable [24,26]. • Allows monitoring of patient while awake during surgery, thus increasing the degree of resection. • Better Karnofsky Performance Score post-operatively, local anesthesia usage, and decrease hospitalization [24,27,28]. • Patients generally had better resections than patients under general anesthesia (25.9% vs. 6.5%) [24,27].

Table 1. *Cont.*

Innovation	Description
5-Aminolevulinic acid (5-ALA)	• Used in fluorescence-guided surgery, allowing to determine the tumor location, investigate MRI findings pre and post-operatively, and identify the eloquent areas involved in surgery [29,30]. • Exhibits promising results in increasing the patient's survival with gross total resection more achievable than without 5-ALA (65% vs. 35%, respectively) [24,29–31]. • Adverse effects—increased liver enzymes, neurological impairment and photosensitivity [24,32].
Intraoperative mass spectrometry (MS) and Desorption electrospray ionization (DESI)	• Used to determine how molecules are arranged spatially in biological tissues [24]. • Integration of MS allows surgeons to distinguish tumors by acquiring the complex molecular data in real-time [33–35]. • DESI allows biological tissues to be directly sampled and analysis of molecules that are intact [34,36,37]. • 83% and 93% value for specificity and sensitivity respectively of surgical demarcation when estimating the percentage of high tumor cell using DESI-MS [33].
Carmustine (BCNU) wafers (Gliadel®)	• During surgery, carmustine (BCNU) is implanted at the tumor site. This enables carmustine (BCNU) to diffuse across the adjacent tissues and supply therapeutic doses locally [38,39]. • The combination of Gliadel wafers with systemic Tmz and radiotherapy prolonged the overall survival [38,39].

2.2. Chemotherapy

The common alkylating agents used in HGG are temozolomide (Tmz, 8-Carbamoyl-3-(2-chloroethyl)imidazo (5, 1-d)-l,2,3,5-tetrazin-4(3 H)-one) (Figure 1) and lomustine (chloroethyl-cyclohexyl-nitrosourea, CCNU) [40–42]. Before Tmz, CCNU was the first-line of treatment in GBM patients (110 mg/m^2 orally every six weeks) [43]. Currently, CCNU is administered in recurrent GBM patients [41,42,44]. CCNU is highly lipophilic, enabling BBB penetration, making it an ideal candidate in GBM and treating other HGGs [40,44]. CCNU induces alkylation of DNA and RNA strands resulting in the formation of O6-chloroethylguanine lesions [44]. CCNU inhibits the enzymatic function of key enzymes involved in the carbamoylation process of amino acids, interfering with transcription and translation processes [45–47]. CCNU efficacy in GBM relies on *MGMT* and mismatch repair status, which repair the interstrand links form via CCNU toxicity [44,48]. Although GBM patients with methylated *MGMT* and deficient mismatch repair often have a better prognosis with CCNU, the six-months progression-free survival (19%) and median overall survival (7.1 months) remains low, particularly in recurrent GBM patients as demonstrated in phase III clinical trial [49].

Tmz had become the major game-changer in HGG, replacing nitrosourea-based chemotherapy following a phase II randomized trial for recurrent GBM [50]. Tmz is hydrophilic and small in size (194 Da) with BBB's efficient penetration. Oral administration of Tmz is accompanied by 100% bioavailability in the blood flow [51–53]. However, in brain tumor tissue, the concentration of Tmz is around 20% of the plasma level [54,55]. The cerebrospinal fluid concentrations are similar, but the levels can rise to 35% of plasma levels [54,56]. Tmz is stable in acidic conditions and labile in an alkaline state with a plasma half-life of 1.8 h at pH 7.4 [57]. Moreover, brain tumors have a higher alkaline pH compared to the surrounding healthy tissue, a condition that favors Tmz prodrug activation [57]. Moreover, Tmz demonstrates an acceptable safety profile with mild or moderate adverse effects making it a standard treatment in recurrent HGG while CCNU being the second-line therapy [50]. However, Tmz is associated with side effects such as nausea, fatigue, significant myelosuppression, thrombocytopenia, severe infections, and myelodysplastic syndrome [54,58].

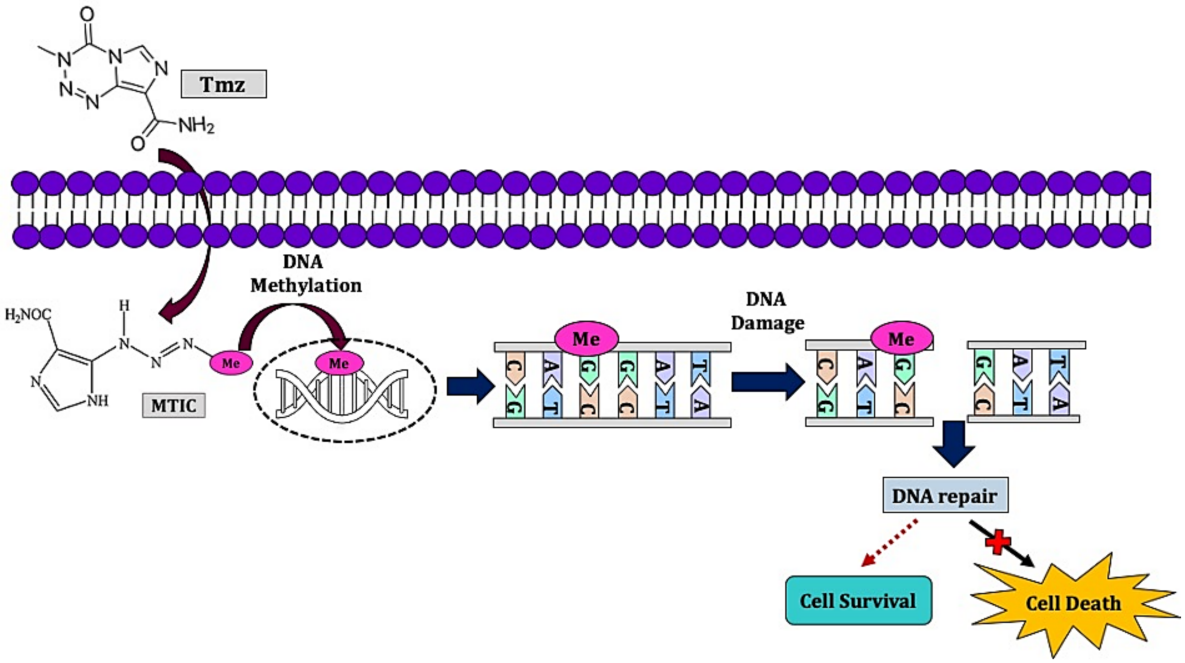

Figure 1. Schematic depiction of Tmz mode of action. Tmz undergoes spontaneous hydrolysis intracellularly to form monomethyl triazene 5-(3-methyltriazen-1-yl)-imidazole-4-carboxamide (MTIC). MTIC then hydrolyzed to form 5-aminoimidazole- 4-carboxamide, which later converts into methylhydrazine [52]. Methyldiazonium, an active cation, then methylates the nucleobases, preferentially N^7 position of guanine (N^7-MeG; 70%), guanine rich site and to a certain extend at N^3 adenine (N^3-MeA; 9%) and O^6 guanine residues (O^6-MeG; 6%) [59,60]. This results in the formation of nicks in the DNA resulting in apoptosis and cell cycle arrest at the G_2/M phase [60,61].

The standard dose (75 mg/m^2/day) and concurrent administration of Tmz in recurrent anaplastic astrocytoma patients demonstrated 6-month progression-free survival and overall survival of around 46% and 13.6 months, respectively [62–64]. The continuous dose-dense Tmz for recurrent anaplastic astrocytoma can help overcome the drug resistance by decreasing *MGMT* activity with anti-angiogenic properties [62,65,66]. In contrast, anaplastic oligodendroglioma patients are responsive to various chemotherapy such as PCV (procarbazine, vincristine, lomustine) and Tmz [62,67]. Although PCV administered prior or after radiotherapy did not improve the overall survival among newly diagnosed low-grade anaplastic oligodendroglioma patients, significant improvement was observed in the progression-free survival when PCV administered following radiotherapy (24.3 months vs. 13.2 months) [67–69]. This improvement, however, demonstrated significant toxicity and patients' low quality of life. Interestingly, high-grade anaplastic oligodendroglioma patients with 1p/19q co-deletion treated with radiotherapy only or a combination of radiotherapy and PCV exhibited improvement in the overall survival [70–73]. Tmz is more tolerable than PCV, and recent clinical trials supported its use for anaplastic oligodendroglioma patients with intact 1p/19q and wild-type *IDH1* [68,71]. Tmz demonstrated a positive response in anaplastic oligodendroglioma patients and is used as the first line treatment in progressive or recurrent anaplastic oligodendroglioma who are CT-naïve [74,75]. Previously, in a prospective GICNO study, it was reported that co-deletion of 1p/19q is associated with Tmz responses, and *MGMT* methylation is correlated with co-deletion of chromosome 1p/19q in anaplastic oligodendroglioma [76]. Hence, *MGMT* methylation and 1p/19q co-deletion could confer a favorable prognosis in patients with HGG. Thus, a complex model integrating 1p/19q co-deletion, *MGMT* methylation, *IDH1* mutations while taking into consideration the patient's age and histopathological diagnosis should be integrated to validate this [77]. The univariate analysis of the NRG Oncology/RTOG 0424 trial also validated *MGMT* promoter methylation as an independent prognostic biomarker, particularly in LGG patients receiving a combination of Tmz and radiotherapy [78]. This analysis

demonstrated a significantly reduced OS association with unmethylated *MGMT* promoter status. Additionally, this study highlighted *MGMT* promoter methylation as a potential prognostic tool besides *IDH1/2* mutation for LGG [78]. Anaplastic oligodendroglioma patients treated with radiotherapy and PCV obtained an approximately objective response rate of 44% towards Tmz with the median overall survival of 10 months [74,75,79,80].

Typically, the standard treatment for newly diagnosed GBM involves a four-pronged approach. Following surgery and histopathological and molecular diagnosis, patients are subjected to radiotherapy with concurrent administration of Tmz [81]. Stupp and coworkers [82] showed that patients who received radiotherapy with concomitant daily Tmz followed by six cycles of adjuvant Tmz recorded an improved median survival (14.6 months) as compared to control groups (12.1 months). Additionally, the patients showed a 26.5% improvement in the two-year survival rate compared to the traditional approach (10.4%). For patients over 70, where surgery is not an ideal option, less aggressive radiation or Tmz treatments are prescribed [83]. Nevertheless, due to tumor resistance over time, extreme neurological deterioration, and the high risk of relapse, these therapies are frequently proven ineffective [60,84].

2.3. Radiotherapy

Although radiotherapy following surgical resection does not offer complete curative effects in most HGG cases, it offers progression-free survival benefits compared with chemotherapeutic agents [16,69]. In a prospective study (NOA-04 study), initial chemotherapy (Tmz or Vincristine) combined with deferred radiotherapy was equivalent to using radiotherapy alone [85]. Additionally, the study showed no significant difference in progression-free survival between patients who received chemotherapy versus initial radiotherapy. This study also indicated that *IDH1* mutation has a favorable prognosis than the methylation of *MGMT* promoter or 1p/19q co-deletion. Hence, anaplastic astrocytoma with *IDH1* wild-type and *MGMT* methylation patients may be more suitable treated with chemotherapy and if the *MGMT* is unmethylated, they are better treated by radiotherapy only. This is because *MGMT* encodes for a DNA repair enzyme that interferes with DNA alkylation by Tmz [86]. Additionally, when the CpG islands located in the promoter regions of *MGMT* are methylated, it suppresses *MGMT* transcription. Hence, individuals with methylated *MGMT* HGG exhibit a favorable response when given Tmz [86]. Re-irradiation is also useful in providing palliative benefit and is considered safe in recurring anaplastic astrocytoma patients [62,87,88].

In three clinical trials, a combination of radiotherapy with PCV in anaplastic oligodendroglioma patients (EORTC 26955 and RTOG 9402) and LGG (RTOG 9802) demonstrated an improvement in overall survival [62]. In another study, PCV addition to radiotherapy in anaplastic oligodendroglioma patients is not restricted to tumors with 1p/19q co-deletion but also to *ATRX* and *IDH* mutations [89]. Anaplastic astrocytoma patients may share similar molecular traits with anaplastic oligodendroglioma patients having 1p/19q co-deletion and low-grade astrocytoma with *IDH* mutations. The results from these clinical studies can be extrapolated for all diffuse gliomas, including anaplastic astrocytoma. The efficacy of Tmz in combination with radiotherapy in treating anaplastic astrocytoma with 1p/19q co-deletion yielded superior results as opposed to radiotherapy only [63,90]. In 2017, the European Union of Neuro-Oncology suggested maximal safe resection followed by radiotherapy only or chemotherapy only (Tmz or PCV) for individuals with newly diagnosed anaplastic astrocytoma lacking 1p/19q co-deletion [40]. Postoperative radiotherapy (total dose of 60 Gy across 30 fractions) is commonly given in anaplastic oligodendroglioma patients [91–93]. However, there are different views that radiotherapy is unnecessary for anaplastic oligodendroglioma patients with 1p/19q co-deletion due to neurocognitive impairment. Nevertheless, there is no substantial scientific evidence of this opinion, and therefore, radiotherapy is still considered the standard therapy for all malignant gliomas until further evidence is made available.

3. Challenges in HGG Standard Therapy

Though HGG therapy gives the patients an extended overall survival, it comes with an actual impedance [94]. For example, in oligodendroglioma, ~4% of the cancer stem cells (CSC) are cycling stem cells that promote tumor growth and recurrence. In comparison, the remaining 96% are non-cycling cancer cells that are resistant to chemotherapy and radiotherapy [94–96]. Mutation of *IDH* renders cells incapable of fully utilizing the citric acid cycle, which creates ATP deprivation, leading to a low cell cycle performance [94]. Although chemo-radiotherapy has substantial benefits in prolonging the median overall survival (>14 years), even after the prescription has been repealed by six rounds and the dose has been lowered, the mortality rate remains high. In RTOG 9402 and EORTC 26951 clinical trials, patients prescribed with lesser cycle therapy and lower dose exhibited significant hematological toxicities (56% and 46%, respectively) [97]. These toxicities further necessitate the development of more effective therapy that selectively targets tumor cells while maintaining patient quality of life.

In anaplastic oligodendroglioma patients, radiation is included as post-surgery initial treatment. However, the PCV regime has been added as part of disease management (based on EORTC 26951 and the RTOG 9402 trials), which demonstrated prolonged survival and better radiographic response rate (93–100%) in 1p/19q co-deletion gliomas than Tmz (35–82%) [98]. However, the combination of PCV with radiotherapy has been associated with cognitive deterioration and brain damage due to prolonged irradiation. In the hope of sparing and delaying such damage, the possibility of including only PCV chemotherapy has been suggested as an alternative option [98]. Although PCV was suggested as the potential standard care chemotherapy based on the EORTC/RTOG (phase III) trial (PCV + radiotherapy) in patients with 1p/19q codeletion, there is still an ongoing debate on Tmz use as a replacement for PCV due to its lower toxicity and easy administration mode [98–100]. Although PCV demonstrated better effects than Tmz, the NOA-04 trial demonstrated no difference between PCV and Tmz in combination with radiotherapy. Suggesting neither regimen is superior to the other [101]. An ongoing two-arm phase III clinical trial (NCT00887146) is looking into the direct comparison between PCV- radiotherapy combination against concomitant and adjuvant Tmz with radiotherapy anaplastic oligodendroglioma patients with 1p/19q co-deletion [102].

Anaplastic astrocytoma patients with 1p/19q co-deletion and *IDH* mutation often have a better prognosis. In contrast, patients with only *IDH* mutation and intact 1p/19q have moderate prognoses [62]. Although wild-type *IDH* anaplastic astrocytoma patients tend to have poorer prognoses, they share similar molecular alterations with GBM patients, including *EGFR* amplification, gain in chromosome 7, and loss in chromosome 10 [103]. In *IDH*-wild type astrocytoma, the high tumor heterogeneity further under defined treatment strategy [104]. Hence, patients are diagnosed and treated on a case-to-case basis based on age, Karnofsky Performance Status (KPS), loss in chromosome 10, and gain in chromosome 7 along with the clinical and radiological course, and *MGMT* methylation status [104]. Although *IDH*-mutated diffuse glioma patients have better prognoses and higher sensitivity to chemotherapy, the IDH protein may represent a druggable antigen [105]. IDH catalyzes the conversion of α-ketoglutarate into 2-HG, causing D-2-HG accumulation, which can inhibit numerous histone demethylases. The D-2-HG acts as a competitive inhibitor towards α-KG-dependent histone demethylases [106]. Additionally, D-2-HG also competitively inhibits the function of ten-eleven translocation methylcytosine dioxygenase 1 and 2 (TET 1 and TET2). TET functions as a catalyst for 5-methylcytosine (5-mC) demethylation process through a series of conversions. However, when D-2-HG is present, it limits the ability of cytosine to demethylate. Hence, this causes 5-mC to accumulate in the genome, which induces cytosine demethylation [107]. Increased histone methylation associated with D-2-HG can restrict cell differentiation which is vital in gliomagenesis and cell maintenance [108]. Furthermore, D-2-HG may affect numerous pathways involved in DNA repair. It inhibits the α-KG-dependent alkB homolog (ALKBH) enzyme, which sensitizes cancers with *IDH* mutations to DNA alkylating agents [109]. Moreover, mutation to *IDH1* downregulates

the ataxia-telangiectasia-mutated (ATM) signaling pathway via an alteration to histone proteins' methylation [110], resulting in enhanced sensitivity towards agents that damage the DNA. Moreover, *IDH* mutation causes a reduction in NAD+, affecting the poly (ADP-ribose) polymerase-1 (PARP1)-associated DNA repair pathways [107].

The current standard protocol of treating HGG can be improved using immunotherapy or gene therapy to target the DNA repair pathways. Furthermore, decreased glutamate and enhanced glutaminolysis are commonly seen in cancers with *IDH* mutation. Hence, inhibiting glutaminases, would suppress *IDH* mutant cancers from growing as decreased glutamate and dependence on glutaminolysis are important characteristics of *IDH* mutant cancers [107].

Up-to-date chemotherapy of either PCV or Tmz, depending on physicians/patients' preference for residual tumor patients after initial surgery, is recommended either with radiotherapy for diffuse astrocytomas (*IDH* mutated or wild type) or alone for oligodendrogliomas [111]. Although prolonged survival of oligodendroglial patients over anaplastic astrocytomas was reported, the differences were not statistically significant [112]. The lack of details on possible allelic losses on chromosomes 1p/19q and *IDH* mutation status in the patient population prevents a full assessment of observing survival disparity after radiotherapy [112].

Tmz efficacy within a tumor can be affected by DNA repair systems (Figure 2) such as base excision repair, mismatch repair, and notably, the methylation status of *MGMT* [54]. *MGMT* encodes O6-alkylguanine-DNA alkyltransferase (AGT) protein that removes the alkyl genotoxic O6-meG adducts leading to chemoresistance [113]. In GBM, the therapeutic advantage is most effective in 50% of patients whose tumors exhibit *MGMT* promoter methylation [54,113]. GBM patients who initially respond to Tmz eventually experience a relapse before or after treatment termination [114]. Cysteine-phosphate-guanine (CpG) is the DNA methylation site of the *MGMT* gene that renders its inactivation leading to reduced gene expression. Within this promoter region, 97 CpG loci are present with two different methylation domains. However, not all the methylation site of CpG loci regulates *MGMT* expression [115–117]. An unmethylated promoter region corresponds to an active *MGMT* gene leading to an increased expression commonly associated with Tmz resistance [117–121]. However, *MGMT* accounts for only 8–10% of Tmz resistance in GBM [119,122]. Although *MGMT* promotes Tmz resistance, additional factors such as post-translational modifications on histones proteins [123] and miRNAs deregulation [124] are also involved.

The mispairing of O^6-methylguanine (O^6-MeG) with thymine induced by Tmz is seen during the replication of DNA in unmethylated *MGMT* cells (Figure 2) [125,126]. This mispairing results in the mismatch repair system's activation to excise thymine from the newly synthesized daughter strand, leaving O6-MeG the parental strand intact. This restorative process undergoes repetitive cycles by reinsertion and removal of thymines leading to cell cycle arrest and apoptosis [125,126]. Impairment in mismatch repair system contributed by gene mutations such as *melanocyte-stimulating hormone 2* (*MSH2*), *MSH6*, *mutL homolog 1* (*MLH1*), and *post-meiotic segregation-increased Saccharomyces cerevisiae 2* (*PMS2*) [57,59,122]. In a study by McFaline-Figueroa and colleagues [127], Tmz showed modest deregulation in the expression of MutS ∝ MMR recognition complex components with MSH6 (50%) and MSH2 (70%) proteins. The observation is correlated with the diminished mismatch repair activity and accounted for Tmz resistance. However, these mutations are predominant among recurrent patients with methylated *MGMT* GBM than primary GBM, suggesting that initial Tmz sensitivity may exert selective pressure to alter mismatch repair protein expression [57,59,122].

Base excision repair system is involved in repairing DNA damage caused by oxidizing, ionizing radiation, or alkylating agents [119]. The methylation of N7-guanine (60–80%) and N3-adenine (10–20%) represents more than 90% of the methylation by Tmz and is rapidly repaired by base excision repair [119,122]. When one or more base excision repair components are mutated, its ability is deficient and contributes to Tmz cytotoxicity [128,129].

Notably, N3 lesions are lethal if not repaired, as opposed to N7 lesions, which leads to inhibition of PARP-1. Such inhibition results in the accumulation of DNA nicks, which is removed via the cell death mechanism. DNA damage causes hyper-activation of PARP-1, resulting in NAD+ and ATP depletion, leading to cell death [59,122]. Although N7-guanine and N3-adenine methylation are higher than that of O6-guanine, base excision repair role in Tmz resistance is reportedly less critical than that of *MGMT* and MMR mutation [59,122]. Current studies have found that ferroptosis, a novel cell death mechanism, has been linked to cancer progression and drug resistance in GBM [130,131]. Although ferroptosis's role in Tmz resistance may serve as a potential therapeutic avenue in sensitizing GBM cells to Tmz, further studies are needed to fully understand its mechanism.

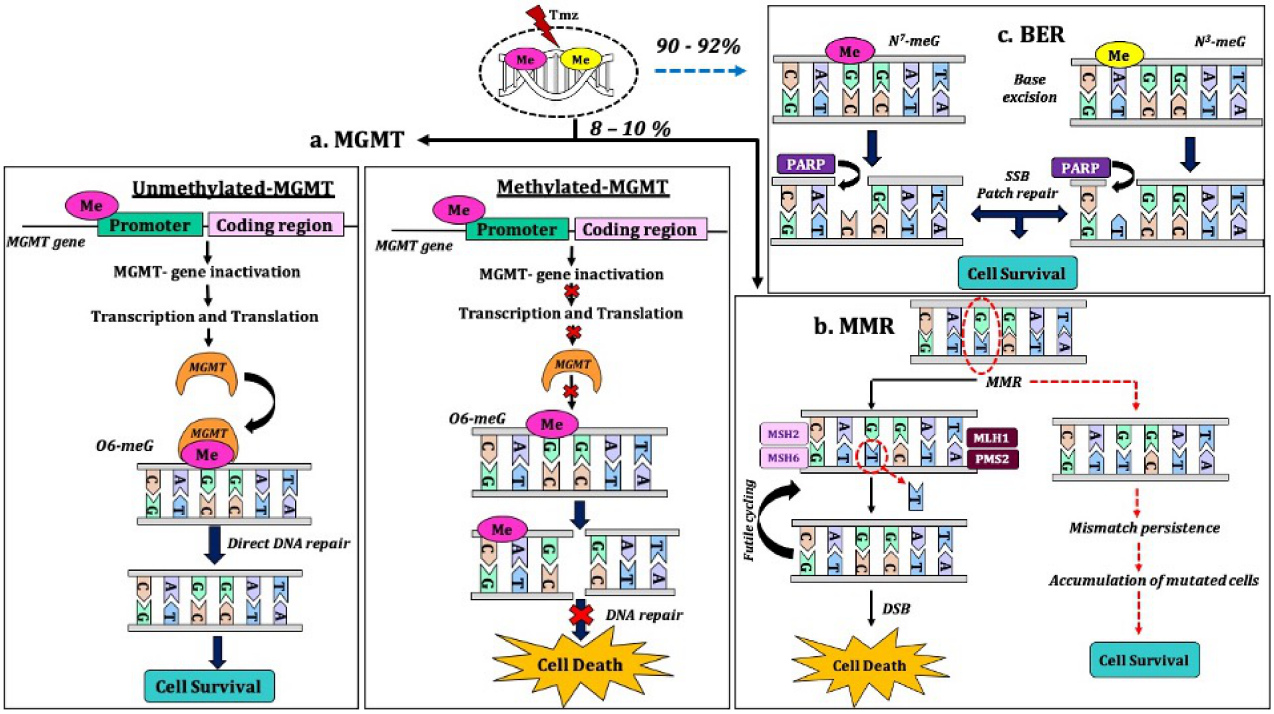

Figure 2. Mechanisms of Tmz resistance. (**a**) The expression of *MGMT* along with successful DNA repair mechanisms: (**b**) mismatch repair; (**c**) Base excision repair resulting in survival as GBM tumors leading to chemoresistance.

Generally, Tmz can induce cell cycle arrest and apoptosis via DNA damage in tumors that lack *MGMT*. However, in glioma, such as U87 cell line, they can develop a response against Tmz-induced apoptosis and arrestment of the cell cycle at the G_2/M phase [119,132]. Such finding suggests the possible involvement of other cell death mechanisms. Recent studies have shown Tmz treatment induces autophagy in GBM cells. Chemotherapeutic agents and radiations are known to activate autophagic pathways in cancer cells [119,133]. However, autophagic cell death is controversial as its dual effect includes pro-survival or pro-death response [134,135]. Autophagy is a cytoprotective mechanism that can provide cells with energy, prolonging their survival and evading apoptosis [134]. In cancer cells, such a process can be detrimental as it favors the survival of cancer cells contributing to chemoresistance. For instance, oxidative stress induced by chemotherapeutic drugs enables cancer cells to survive, even in hypoxic and nutrient-deficient environments [134]. Autophagy through ATM/AMPK pathway can result in the formation of acidic vesicular organelles and aggregation of LC3, which are vital for cytoprotective and cell survival [136,137]. Additionally, the hypoxic microenvironment in HGG tumors is a vast challenge in radiotherapy as it induces radioresistance [138,139]. In GBM, the hypoxic conditions can induce stemness and upregulate *MGMT* expression [59,140–142]. This hypoxic condition elevates HIF-1, which increases glycolysis, pentose phosphate pathways, and serine production pathways, heightening antioxidant production, thereby buffering

ROS's actions induced by radiation. Furthermore, the hypoxic state increases ROS production, stimulating an antioxidant generation loop [143–145]. Hyperbaric oxygen is used to counteract the tumors' hypoxia [146,147]. GBM tumors subjected to hyperbaric oxygen displayed reversal/reduced radioresistance, chemoresistance, and radiation-enhanced tumor motility [147–151]. Radiation from radiotherapy can adversely affect the patients' neurocognitive ability [152–154]. Hence, the application of fractionated radiotherapy or interstitial brachytherapy is thought to be safer and well-tolerated among HGG patients [155–159]. In a retrospective study, 59 recurrent GBM patients demonstrated prolonged median survival by eight months when given a median dose of 36 Gy radiotherapy with 2 Gy given each day [160]. However, there are insufficient data for fractionated radiotherapy to be used routinely in the setting of recurrent GBM. Like fractionated radiotherapy, brachytherapy also enables a sharp dose gradient by placing a radiation source within the tumor volume to be treated [161]. This is usually carried out postoperatively, and it is offered to patients with a good performance status and more resectable small tumor in volume. One of the approaches in which brachytherapy can be utilized is by placing permanent iodine 125 (I-125) seeds in the resection cavity [161]. In a retrospective study by Darakchiev et al. in 2008, utilizing brachytherapy in patients with GBM reported a favorable result with the median survival of 15.9 months [162]. However, the disadvantage of brachytherapy is the high incidence of radionecrosis. Hence, brachytherapy has to be used with caution [161].

4. Drug Development for HGG: Advancements and Challenges

4.1. Gene Therapy

Alterations in various genes largely drive tumorigenesis. Thus, gene therapy can be utilized to inhibit the oncogenic properties of tumor cells [163,164]. Gene therapy in cancer involves introducing a tumor-suppressing or growth-regulating gene into the tumor [163]. Since conventional treatment modalities are incapable of overcoming resistance, the genetic component of tumor cells may be manipulated by utilizing gene therapy to acquire a therapeutic benefit. To improve the delivery of these therapies, delivery vectors such as viral vectors, polymeric nanoparticles, and non-polymeric nanoparticles have been studied [163,165–167]. Although the use of these viral and non-viral vectors offers therapeutic advantages, their utilization in HGG possesses some challenges (Tables 2 and 3).

Viruses target specific cells and hijack the cell's replicative properties. In doing so, this leads to the release of numerous copies of the virus and the host cell's death [168]. This specific capacity of viruses allows them to selectively attack and overwhelm a particular tumor cell population while sparing the other surrounding cells in its vicinity, making viral therapy a potential candidate for the treatment of HGG [168]. Various trials have been conducted to assess their efficacy, summarized in Table 4 [168]. According to a meta-analysis carried out by Artene et al. in 2018 (Table 4), viral therapy improved the overall-survival among newly diagnosed HGG patients (HR = 0.72, 95% CI: 0.54–0.97) [168]. However, the meta-analysis findings stated these studies were not statistically significant (p = 0.13). Additionally, viral therapy did not statistically improve the progression-free survival [168]. Hence, gene therapy using viral agents alone may not be a feasible treatment modality in HGG.

Glioma cells secrete immunosuppressive factors that prevent them from being detected and eliminated by the immune system. Additionally, glioma cells can express CD95 ligand on their surface, which allows them to trigger apoptosis and subsequently reduce T-cells' infiltration in the tumor microenvironment [169,170]. Therefore, researchers focus on developing multitarget therapies that enhance tumor detection and clearance, promoting cell death such as apoptosis, while reducing processes such as angiogenesis and chemoresistance. Such therapies include the use of immune therapy, electric field therapy, nanoparticles and phytochemicals that can further enhance Tmz and radiotherapy efficacy.

Table 2. Example of viral vectors in HGG studies.

Vector	Findings
Herpesvirus and Retrovirus	The use of herpes simplex virus as suicide gene therapy by converting antiviral drugs which prolonged prodrug treatment, improved survival and inhibited proliferation as well as tumor growth [171–173].
	TOCA 511 resulted in the promotion of T cell expansion (Th1, Th2 in $CD4^{+,}$ $CD8^{+}$), mediated antitumor immune response, and concentrated the effect of drugs at the tumor site which increased direct tumor cell death, alterations in immune cell infiltration, and improved survival [174–178].
	Retroviral replicating vectors (RRV) based on gibbon ape leukemia virus enabled high-efficiency gene transfer and persistent expression of *E. coli* nitroreductase prodrug activator genes, resulting in efficient cell killing, suppression of tumor growth, and prolonged survival upon CB1954 administration [166].
	Semi- and pseudotyped-RRV system harboring two suicide genes—HSV1 thymidine kinase and yeast cytosine deaminase and prodrug demonstrated high oncolytic capability against extremely heterogeneous and treatment-refractory GBM which promoted the inhibition of cell proliferation, angiogenesis, increased apoptosis, and the depletion of tumor-associated macrophages in orthotopic GBM [179].
Adenovirus	The replication-deficient adenovirus mutant thymidine kinase (ADV-TK) in combination with ganciclovir improved recurrent patients' survival, integrin antagonist cRGD (EMD121974) promoted adenovirus-mediated REIC/Dkk-3 reduction of cell proliferation and mice survival. Adenovirus is also used to transfect *p53* gene, mediated cytotoxic immune therapy of prodrug and PTEN, PI3K inhibitors [180–183].

Table 3. Benefits and challenges of viral and non-viral vectors in HGG [163].

Vector	Benefits	Challenges
Adenovirus	• Deliver large amounts of DNA	• The gene expression is transient • Elicits an immune response against the tumor cells
Adeno-associated virus	• Can transfer genetic material to non-dividing and dividing cells	• Producing vectors is difficult • The transgene capacity is limited • Elicits an immune response
Retrovirus	• Can transfer genetic material to cells that are dividing • The expression of the vector is sustained	• Elicits an immune response • Unable to transfect non-dividing cells • Low transfection efficiency in vivo • Risk of insertion at the wrong location
Gold nanoparticles	• Can be used to treat and image the tumor • Can be functionalized for targeting	• Non-biodegradable
Polymeric micelles	• Can be functionalized for targeting • It is self-assembled with nucleic acids	• Increased the cytotoxic effects for poly(ethylenimine) as well as other cationic polymers. • Low loading ability
Dendrimer and Dendrigraft	• It is self-assembled with nucleic acids • Can be functionalized for targeting • Non-immunogenic	• Increased cytotoxicity for cationic dendrimers • Limited release of therapeutics
Poly(β-amino ester)	• Biodegradable • Compared to other cationic polymers, it has a lower cytotoxic level • Its efficiency to transfect is high	• It has limited control when releasing the therapeutic agent.

Table 4. Studies that utilized viral therapy in the treatment of HGGs. (AA—anaplastic astrocytoma, AO—anaplastic oligodendroglioma, GBM—glioblastoma, OS—overall survival, PFS—progression-free survival) [168].

Study Reference	WHO Classification of Tumor	Phase of the Clinical Trial	Total Patients		Outcome
			Experimental Group	Placebo Group	
Rainov et al. [184]	IV (GBM)	III	111	103	OS, PFS
Stragliatto et al. [185]	IV (GBM)	I/II	22	20	OS, PFS
Westphal et al. [186]	IV (GBM)	III	119	117	OS
Wheeler et al. [187]	III (AA,AO), IV (GBM)	Ib/IIb	48	134	OS, PFS

4.2. Immunotherapy

Immunotherapy is used to treat many cancers, such as melanoma, renal cell carcinoma, lymphoma, and non-small lung cancer [188]. Immunotherapy research is still ongoing to explore potential newer target sites in HGG (Table 5) [18]. The treatment modalities that can render tumors more vulnerable to one's immune system are considered strong candidates. Dendritic cell (DC) vaccine can serve as a mediator between the innate and adaptive immune systems by processing and presenting the antigens to either B or T-cells. This will then trigger an immune response via T or B-cells [168]. Thus, this makes them an appealing vaccine candidate that can induce an immune response against tumors [168]. Various trials have been conducted to assess their efficacy, summarized in Table 6 [168].

According to a meta-analysis by Artene et al. (Table 6), DC therapy prolonged the overall survival of newly diagnosed (HR = 0.65, 95% CI: 0.45–0.93, $p = 0.02$) and recurrent HGG patients (HR = 0.63, 95% CI: 0.46–0.88, $p = 0.006$) [168], Also, the newly diagnosed HGG patients had a 51% chance of having a longer progression-free survival period between treatment initiation and the confirmation of tumor recurrences via MRI. Despite this, the results were insignificant ($p = 0.10$) [168]. In conclusion, the meta-analysis by Artene et al., exhibited that DC therapy provided significant improvement in the overall survival among both groups of patients (newly diagnosed and recurrent HGG) [168]. However, all the studies included are in Phase I or II, which have limited value statistically. Hence, larger phase III trials are required to justify this treatment modality further. In a randomized phase III clinical trial (NCT00045968), the addition of DCVax to regular therapy (Tmz) in newly diagnosed GBM patients prolonged the two and three-year survival rate by 66.7% and 46.4% respectively in patients with methylated *MGMT*, whereas in patients with unmethylated *MGMT,* the two and three-year survival rate is 32.1% and 11% respectively [189]. The authors concluded that the addition of DCVax-L to standard therapy is safe and feasible for patients with GBM and may prolong their survival.

Monoclonal antibodies (Mabs) have high affinity and specificity in targeting growth factor receptors such as PDGFR, VEGFR, and EGFR. One challenge of utilizing Mabs is that they may not easily cross the BBB due to their large molecular size. Hence, to overcome this, Mabs can be attached to a nanocarrier surface via a pre-adsorption process and prevent biomolecular corona formation [190,191]. The nature of HGG, mainly GBM cells, which are incredibly heterogenic, makes the usage of monovalent vaccines inadequate to control tumor progression [192–194]. For example, some peptide vaccines are vastly restricted towards the $EGFR_VIII$ variant, which is only present in 23–33% of GBM patients [195,196]. Thus, in GBM patients without this variant, the peptide vaccines may be futile. Moreover, even if some patients have the $EGFR_VIII$ variant, the natural evolution of the GBM tumor could result in a loss of this variant subtype, thus, causing peptide vaccines to be ineffective, as seen in phase III of the ACT IV trial [197]. One strategy is to use a polyvalent vaccine so that a larger population of tumor cells can be targeted.

CAR T cell therapy, which utilizes engineered T cells to kill tumors by targeting cell surface-specific antigens, has gained emerging interest in preclinical and clinical GBM studies [198–202]. Moreover, single use of CAR T cell therapy has demonstrated tolerable safety profiling and feasibility in glioma. For instance, the use of CD70-specific CAR T cells, which recognize CD70 positive GBM in vitro, promotes tumor regression in the

xenograft and syngeneic GBM models [203]. CD70 expression is generally associated with poor survival among *IDH* wild-type primary LGGs, the mesenchymal GBM subtypes, and the recurrent GBM patients. In a study by Tang and coworkers, CAR T cells' construction, which targets B7-H3 was delivered using lentivirus in preclinical primary and GBM cell lines [204]. B7-H3 is highly expressed in glioma patients as it is linked to tumor malignancy and poorer survival. Using the constructed CAR-T-cell-B7-H3 targeting, they demonstrated antitumor and cytotoxic activities, which promoted longer median survival in the orthotropic GBM models.

A number of phases I and II clinical trials have shown the efficacy of CAR T cell therapy in GBM patients (targeting IL-13Rα2, *EGFRvIII*, EphA2, and HER2) [199]. However, these molecular targets are more prone to antigen escape since they are not homogenously expressed in GBM tumors. Additionally, the high tumor heterogeneity and complex GBM tumor microenvironment serve as limitations. These situations may impede the CAR T cell migration towards the GBM tumor site and affect its persistence. Thus, a one-fit-target approach may not be suitable. Additionally, combining immunotherapy such as CAR T cell therapy with other therapeutic approaches could confer greater efficacy. In a recent study, the addition of TGFβ-trap into *EGFRvIII*-specific CAR T cell further prolonged the survival of mice [205]. The authors also observed the elevated expression of M1 polarization markers of GBM-infiltrated microglia, which may be responsible for disrupting the immunosuppressive tumor microenvironment. In a study by Bielamowicz and colleagues [206], the use of trivalent CAR T cells (UCAR T cells) could be beneficial in overcoming antigenic heterogeneity in GBM. In this cohort study, co-targeting HER2, IL13Rα2, and EphA2 overcomes the interpatient variability and activates the immune synapses to improve cytotoxicity and release of cytokines when compared to monospecific and bispecific CAR T cells. Additionally, the low concentration of the UCAR T cells enhances the control of established autologous GBM patient derived xenografts and promotes animal survival. In a different study, the local GBM tumor irradiation resulted in a synergistic antitumor of natural killer group 2-member D (NKG2D) CAR T cell therapy in immunocompetent GBM mice [207]. The tumor irradiation enhances the NKG2D CAR T-cell activity, tumor recognition, and better trafficking of the intravenous injected NKG2D CAR T cells.

The therapeutic efficacy of immunotherapy such as CAR T cell, peptide vaccine, or monoclonal antibodies can be improved by (i) combining them with the existing conventional therapy, (ii) the use of multitarget agent such as natural products, and (iii) the construction of multi-target CAR T cells. In a study by Suryadevara and coworkers [208], preexposure of GBM tumors to Tmz promotes *EGFRvIII* CAR T cells' efficacy. The authors demonstrated that the *EGFRvIII* CAR T cell's engraftment would benefit from Tmz-induced lymphopenia, which extended the survival of the animal models. Their study suggested using standard therapy such as TMZ as a first-line approach or preconditioning before the systemic infusion of *EGFRvIII* CAR T cell. Following these observations, the authors conducted a phase I trial on 12 newly diagnosed GBM patients subjected to Stupp regimen and three cycles of dose-intensified Tmz before administering *EGFRvIII* CAR T cell (NCT02664363).

However, the combination of immunotherapy with other therapeutic approaches may also heighten the toxicity and adverse effects. Therefore, such an approach of combining CAR T cells, immune checkpoint blockades, monoclonal antibodies, conventional therapy, and natural products still requires phase I and II clinical trials (which some are undergoing) to provide important safety information. Additionally, these clinical trial data are essential in limiting or superimposing the toxicities while justifying the efficacy and potential pitfalls. To date, most of the studies of CAR T cell and its combination with other therapies are mostly focusing on preclinical and xenograft of immunocompromised GBM models. This does not represent the complex tumor microenvironment of GBM. Thus, it will be important to evaluate CAR T cells and other therapy combinations in immune-competent GBM models. Additionally, the use of 3D culture and patient-derived xenografts would be beneficial as they closely mimic the tumor microenvironment and phenotypic of GBM.

Table 5. Immunotherapy in HGG.

Immunotherapy	Description
Bevacizumab	• Promotes survival, enhances standard therapy, and inhibits neoangiogenesis by binding with VEGF [209–212]. • A systematic review exhibited that when used alone or when combined with a cytotoxic drug, it prolonged the overall survival in patients with recurrent GBM by four months [209]. • Bevacizumab in anaplastic astrocytoma, anaplastic oligodendroglioma, and oligodendroglioma improved overall survival, progression-free survival, and standard therapy in patients. The common toxicities are hypertension, thromboembolic events, and hypophosphatemia [213–215].
Depatuxizumab mafodotin (ABT-414)	• Inhibits wild type *EGFR* or *EGFRVIII*, thus preventing polymerization of microtubules which is important for vesicular trafficking and mitosis of cancer cells. Modest improvement in progression-free survival among recurrent GBM patients [216–218].
Peptide vaccine	• Peptide vaccines act against *EGFRvIII*, which is an active protein that is only expressed in GBM and not healthy tissues; rindopepimut (CDX-110) is used in clinical trials to target *EGFRvIII* in recurrent GBM patients [219–222]. • Rindopepimut used in recurrent GBM patients showed a significant improvement in progression-free survival when combined with Bevacizumab [219,220]. • In the ACT IV trial, whereby peptide vaccine was used for newly diagnosed GBM patients, it failed to show survival benefits when used in combination with Tmz [197].
Heat Shock Protein (HSP) vaccine	• Patients treated with the HSPPC-96 vaccine in a phase-II trial showed median overall survival that is comparable to phase-I, an improvement compared to their benchmark, with or without bevacizumab (42.6 weeks vs. 14.6 months) [223,224]. • HSPPC-96 demonstrated median overall survival with a high tumor-specific immune response above 40.5 months (95% CI) as compared with 14.6 months (95% CI) for patients with low tumor-specific immune response. The HSPPC-96 in combination with standard therapy, was safe in newly diagnosed GBM patients [225].
Dendritic cell (DC) vaccine	• DC vaccine can immunologically present the antigens on glioma, activate $CD8^+$ cells, prevent angiogenesis, and trigger tumor cell death [226–228]. • In newly diagnosed GBM, patients treated with DCs with or without adjuvant therapy resulted in an improved median overall survival, progression-free survival, and higher survival rate of three years [189,195,229–231]. • In Phase I/II, the use of DC-type multipeptide vaccine in patients with HGG (GBM, anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma) demonstrated clinical efficacy in as nine patients who were vaccinated (41%) remained free of progression for more than 12 months [197].

Table 6. Studies carried out that utilized DC vaccine in the treatment of HGGs. (AA—anaplastic astrocytoma, AO—anaplastic oligodendroglioma, GBM—glioblastoma, OS—overall survival, PFS—progression-free survival) [168].

Study Reference	WHO Classification of Tumor	Phase of the Clinical Trial	Total Patients		Outcome
			DC Vaccine	Placebo	
Wheeler et al. [232]	IV (GBM)	IA/IB/II	13	13	OS
Yu et al. [233]	III (AA), IV (GBM)	I	8	26	OS
Batich et al. [234]	IV (GBM)	I	11	23	OS
Der-Yang Co et al. [231]	IV (GBM)	II	18	16	OS, PFS
Chang et al. [235]	III (AA, AO), IV (GBM)	I/II	16	63	OS
Yamanaka et al. [236]	IV (GBM)	I/II	18	27	OS
Jie et al. [237]	IV (GBM)	I/II	13	12	OS
Vik-Mo et al. [238]	IV (GBM)	I/II	7	10	OS, PFS

4.3. Tumor-Treating Field (TTF)

Tumor-treating field (TTF) is an anti-mitotic electric field therapy that tampers with cell division and assembly of organelle via the delivery of low-intensity alternating electric field to GBM tumor [239]. Initial clinical studies in recurrent GBM patients (n = 10), shows that TTF prolonged the median time of disease progression (26.1 months), 6 months progression-free survival rates (50%) and median overall survival (>62 weeks) [240,241] TTF can enhance Tmz therapeutic efficacy by delaying the repair of damaged DNA in newly diagnosed or recurrent GBM [242–245]. TTF in combination with Tmz increases overall survival (about four months) and progression-free survival (approximately three months) with reported improvement in patients' quality of life and low incidence of adverse effects as opposed to Tmz only (Table 7) [242,246,247]. Optune, a clinical TTF device commercialized by Novocure, has demonstrated statistically significant survival rates in recurrent GBM patients [248]. The minimally invasive nature, decreased systemic toxicity and side effects are some of the attractive properties of TTF therapy [241,248]. This is particularly important in recurrent illness, where patients undergo a variety of treatments from chemotherapy to additional surgery and/or re-irradiation [248]. Despite significant improvement with minimal adverse effects on physical and social functioning, TTF is a costly option with an average cost of 185,476 euros per patient [243,249–251]. Additional drawbacks include lifestyle restrictions as the device must be continuously worn due to the correlation between device compliance and overall survival [251].

Table 7. Tumor-treating field (TTF) and adjuvants in HGG.

	Study Design	Treatment Intervention	Outcomes
Dendritic cell (DC) vaccine	Phase II—randomized, double-blind, controlled study (n = 124 newly diagnosed GBM without chemoradiation) NCT01280552	Patients ratio, 2:1 • ICT-7 (n = 81) • Placebo DC (n = 43)	18.3 months overall survival for ICT-7 group vs. 16.7 months control group [252].
	Phase III—a randomized trial (n = 331 GBM post-surgery and chemoradiation) NCT00045968	Patients ratio, 2:1 • Tmz + DCVax-L (n = 232) • Tmz + placebo (n = 99)	Median overall survival of methylated *MGMT*—34.7 months, with 3 years OS (46.4%) [189].
Tumor-treating fields (TTF)	Phase III—randomized, open label-trial (n = 695 GBM with resected tumors and completed chemoradiation)	Patients ratio, 2:1 • Tmz + TTFields (n = 466) • Control: Tmz alone (n = 229) TTF—18 h/day followed with Tmz (150–200 mg/m^2/day) for 5 days (28 cycles).	TTF with chemoradiation increased overall survival from 16 months (Tmz alone) to 20.9 months [242].
Nanoparticles	In vitro SF-763, and U-118MG cell lines	Iron Oxide Nanoparticle conjugated with Cyclodextrin and Chlorotoxin and loaded with fluorescein and paclitaxel	Selectively targeted GBM cell line, effectively killing *MGMT*-resistant GBM cells [253].
	In vivo Wild type mice IV administration	Gemcitabine + Chlorotoxin Conjugated Iron Oxide Nanoparticle + Hyaluronic acid	Increased half-life (blood) 2.8 h, 10-folds higher than free GEM mice [254].

5. Repurposing Drugs for HGG

Quinoline-based antimalarial drugs such as chloroquine and hydroxychloroquine have gained the potential to be repurposed alongside Stupp therapy. Both chloroquine and hydroxychloroquine have been studied in preclinical and clinical trials as chemo-radiosensitizer. Chloroquine promotes Tmz sensitivity by promoting apoptotic cell death while inhibiting autophagosome fusion and mitochondrial autophagy [255]. Hydroxy-

chloroquine (5 μg/mL) synergizes Bevacizumab (100 μg/mL) inhibition of autophagy by increasing LC3-II/LC3-I ratio and p62 that causes Beclin1 degradation [256]. The formation of GSCs and the highly hypoxic HGG tumors may hinder current therapy efficacy in HGG. Chloroquine (20 nmol/L) synergistically radiosensitizes irradiation-induced apoptotic death and autophagy suppression in U87 glioma-initiating cells. The addition of chloroquine further reduced the number and diameter of glioma-initiating cells tumorsphere [257]. Chloroquine also promotes the histone deacetylation induced by histone deacetylase inhibitor, suberoylanilide hydroxamic acid, in combination with Tmz [258]. Interestingly, chloroquine cotreatment with radiation suppresses the malignancy characteristic of GBM cells by inhibiting TGF-β [259]. This inhibits matrix metalloproteinase-2, cell invasion, clonogenic formation and enhances cell death. Both chloroquine (200 mg, daily) and hydroxychloroquine (200 to 800 mg, daily) have been tested in a clinical trial to enhance the efficacy of Tmz and radiation in improving median overall survival, particularly in newly diagnosed *EGFRvIII*- and *EGFRvIII*+ GBM patients [260,261].

Repurposing older drugs such as metformin and antipsychotics is beneficial as they are relatively cheap while capable of promoting standard therapy. For instance, in response to specific Tmz concentrations, Akt activity can be activated, heightening tumorigenicity, stemness, and cancer cells' invasiveness [262]. Hence, by down-regulating Akt activation, the cytotoxic effects of Tmz can be enhanced. Metformin showed the ability to inhibit Akt activation, thus enhancing TMZ cytotoxicity [263,264]. Additionally, antipsychotics can also be repurposed to counter the neoplastic activity of human gliomas, as reviewed extensively by Kamarudin and Parhar [265]. For instance, perphenazine, in combination with Tmz, demonstrated significant antiproliferative activity. Moreover, antipsychotic drugs such as perphenazine can cross the BBB and antagonize the dopamine receptors, namely D2 and D3, which are implicated in glioma formation [266,267].

Although the repurposing of drugs shares an adjuvant commonality in improving HGG therapy, several issues may limit their therapeutic use. Although their repurposing may offer therapeutic advantages in HGG therapy, most drugs can elicit cytotoxicity with severe side effects. For instance, most studies reported the effective concentration of hydroxychloroquine as an adjuvant to be ∼20 μM, significantly higher than its acceptable dose of ∼5 μM. Even though the current empirical evidence supports their potentiation of current therapy, it is generally accepted that such combinations would also equally enhance the side effects. Hence, it is imperative to determine the clinically acceptable range dose of these drugs, particularly in phase I/II clinical trial. Alternatively, the sequential treatment of Tmz with hydroxychloroquine and BH3 mimetic, AT101, demonstrated a higher cytotoxic effect toward GBM tumor growth but with lesser cytotoxicity in normal astrocytes as compared to treatment with Tmz alone [268]. This sequential approach may be beneficial as a clinical approach to reducing long-term treatment side effects. One of the significant problems is their capability to cross the BBB since most of these commercially available drugs have not been proven to cross the BBB.

Additionally, their bioavailability in the brain and pH stability, particularly within the HGG tumor surrounding, remains unanswered. As compared to metformin and quinolone-based antimalarial drugs, anti-psychotics agents such as selective serotonin reuptake inhibitors, tricyclic antidepressants, lithium chloride, and valproic acid are more commonly prescribed with glioma patients following the standard therapy. These antipsychotic drugs' ability to cross the BBB further highlights their potential to be prioritized as a repurposed drug-based adjuvant in the clinical setting, as reviewed by us previously [269]. Additionally, these anti-psychotic drugs are well-studied in brain-related disorders and cancer studies. Moreover, in clinical and population-based studies, retrospective, and case-report, this group of drugs demonstrated safety profiling and promoted standard therapy. However, more conclusive data from a larger cohort and Phase III trial are still required to justify using these antipsychotic drugs towards the standard treatment.

6. Phytochemicals and Nanoparticles in HGG

6.1. Flavonoids

Flavonoids are a group of bioactive polyphenolic agents structurally diverse with low toxicity [269,270]. They have been studied for their anti-cancer properties in glioma models [271–274]. Galangin (3, 5, 7-trihydroxyflavone), a natural flavonoid from roots of *Alpinia officinarum Hance*, *Alnus pendula Matsum*, *Plantago major* L, and *Scutellaria galericulata* L. *(S.scrodifolia Fisch.*), honey, and propolis [275,276]. Interestingly, galangin is cytotoxic to tumor cells but non-cytotoxic to normal cells, making it a potential anti-neoplastic agent [276]. Galangin's anti-cancer effects include induction of autophagy, cell cycle arrest at the G_0/G_1 phase, promotion of ROS-induced apoptosis, anti-angiogenesis, and anti-proliferation [275,277]. Galangin, in combination with chloroquine, suppresses tumor growth, promotes apoptosis, pyroptosis, and prolonged survival in vitro and in vivo GBM models compared to galangin monotherapy [276].

Curcumin [1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione] has been reported with anti-proliferative, anti-angiogenesis and induction of apoptosis in numerous cancer models [20,278]. For instance, curcumin enhances inhibition of angiogenesis, cell invasion and promotes apoptosis when combined with paclitaxel in GBM cells [20,279]. Curcumin augments nimustine (ACNU) anti-tumor activity by enhancing the inhibition of P13K/Akt and NF-κB/COX-2 in GBM cells [20]. In another study, curcumin potentiated paclitaxel cytotoxicity in rat C6 glioma cells by inhibiting NF-κB activation [280]. In patient-derived GSCs, curcumin (25 μM) significantly reduces Glio 3 and Glio 9 cells' viability via induction of ROS, activation of MAPK pathway, and downregulation of STAT3 and IAPs [281].

miRNA can play a role in treatment resistance in GBM [282–285]. Curcumin can increase miRNA expression in GBM, overcoming Tmz resistance. Li and coworkers showed that curcumin (60–120 mg/kg) induced miR-378 expression significantly inhibited tumor growth (30–60%) of xenografted U87-miR-378 in SCID mice [285]. The study also demonstrated curcumin (50 μM) significantly suppressed cell proliferation and enhanced apoptosis via p38 signaling in U87-miR-378 [285].

Although curcumin is useful in various cancers, its bioavailability and absorption are low, resulting in rapid metabolism and systemic elimination. The use of formulated nanoparticles such as poly(lactic-co-glycolic acid) [286], poly(butyl)cyanoacrylate [287], and tripalmitin-oleic acid [288] enhance curcumin distribution in vitro and in vivo models. For instance, poly(lactic-co-glycolic acid) demonstrated an increased half-life in male Sprague–Dawley rat (210 ± 10 g body weight) brain tissue from 9 to 15 min [286]. Additionally, a significant increase in curcumin retention time was reported in the hippocampus (83%) and cerebral cortex (96%). Curcumin loaded in tripalmitin-oleic acid [288] showed an IC_{50} reduction (80 μg/mL to 20 μg/mL) in A172 cells and further reduced tumor volume (82%) in subcutaneous flank tumor-bearing female nude mice.

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) can promote apoptosis and cell cycle arrestment at G_1 phase via cyclin-dependent kinase (CDK)-4 and cyclin D1 through p53 activation [274,289]. Additionally, quercetin targets the P13K/Akt/mTOR, IL-6/STAT, and apoptotic protein modulation [274,290–292]. Quercetin (30 μmol/L) in combination with Tmz (100–200 μmol/L) promoted Tmz-induced growth inhibition in U87 and U251 via Hsp27 inhibition [293]. Quercetin combination with chloroquine (CQ) induced caspase-dependent apoptosis, autophagic inhibition, and lysosomal suppression in T98G cells [294]. Additionally, quercetin (50 μM) and CQ (20 μM) induced ER stress in T98G cells. In another study, quercetin (25 μM) in combination with sodium butyrate (1 mM) induced apoptosis in rat C6 and T98G cells by modulating Bax, Bcl-2, and survivin proteins that led to caspase-3 activation and PARP [295].

Resveratrol (3,4′,5-trihydroxy-trans-stilbene) anti-cancer effects include anti-proliferation, cell cycle arrestment, and apoptosis promotion through multiple signaling pathways such as EGFR, p53, P13K/AKT/mTOR, STAT3, NF-κB, and oncogenic miRNAs [296,297]. Resveratrol suppresses tumor growth and prolongs survival in rats bearing

intracranial C6 glioma [296,298,299]. Wang and coworkers showed a longer mean survival in C6-xenograft rats treated with resveratrol (29.75 ± 9.27 days) than the control group (15.8 ± 0.93 days) [296]. Resveratrol administration decreased the expression of EGFR, MMP-9 NF-κB, PCNA, COX-2, and VEGF while increasing GFAP expression compared to the control group. Resveratrol also enhances Tmz efficacy by reducing ROS/ERK-mediated autophagy and promoting apoptosis [297,299,300]. Resveratrol in combination with Tmz suppresses the cell growth and induces apoptosis in RG-2 cell (>20%, 17%), LN-18 (62.3%, 12%), and LN-428 cells (28.6%, 8%) [297]. The co-treatment also reduce MGMT protein expression RG-2 (44.9%), LN-18 (38.7%), and LN-428 (33.5%) compared to the Tmz-treated group only. Additionally, resveratrol administration via lumbar puncture effectively suppresses intracranial tumor growth in orthotopic rats and prolonged survival [299,301,302]. Combination therapy with neurosurgery and lumbar-punctured resveratrol demonstrated significant improvement of survival post-operation in orthotopic rats by inhibiting tumor growth, promoting apoptosis, and inactivation of STAT3 [299,303]. The use of resveratrol-loaded polyethylene glycol-polylactic acid nanoparticles with transferrin moieties (Tf-NP-RES) reduced tumor volume and prolonged the survival in C6 orthotopic rats and U87MG-xenograft mice [304,305]. The use of liposomal TriCurin (TrLp; curcumin: epicatechin gallate: RES 4:1:12.5) synergistically enhanced resveratrol anticancer effects through the upregulation of p53 proteins in GL261 cells and C57BL/6 male mice implanted with GL261 cells [306].

6.2. Polysaccharides

Polysaccharides possess immunomodulatory properties and are often referred to as "biological response modifiers" [304,305], contributing to their therapeutic value as anticancer agents. Polysaccharides modulate transcription factors and transcription of genes associated with cell proliferation, angiogenesis, metastasis, cell cycle arrest, and apoptotic induction [307–309]. Schizophyllan is a (1→3)-β-D-glucan rich polysaccharide found in the fungus *Schizophyllum commune.* Zhou and coworkers showed that schizophyllan reduced tumor growth in a dose-dependent manner in male Sprague Dawley rat models implanted with the intracranial tumor in situ (20 mg/kg: 30.8 ± 4.1%, 40 kg/mg: 38.3 ± 3.5%, 60 mg/kg: 55.3 ± 5.1%) compared to control group [310]. In vitro study on CNS-1 rat glioma treated with 40 and 60 mg/L schizophyllan showed a reduction in cell number, increased apoptosis, and cell cycle arrestment at G_0/G_1 phase [310]. Fucoidan is a sulfated polysaccharide, commonly found in brown algae (*Laminaria digitata, Ascophyllum nodosum*, and *Fucus vesiculosus*) and brown seaweeds [249,311]. Its bioactivities include anti-tumor, immunoregulatory, and anti-inflammatory effects [311,312]. Oligo-fucoidan, a glycolytic cleavage product fucoidan (brown seaweed, *Laminaria japonica)* inhibits the cell proliferation of U87MG and GBM8401 cells compared to SVGp12 cells [249]. The study also demonstrated oligo-fucoidan ability to inhibit the expression of DNA methyltransferases 1, 3A, and 3B, induce differentiation of cell markers (MBP, OLIG2, S100, GFAP, NeuN, and MAP2), and decrease methylation of p21 (DNMT3B target gene). Additionally, the addition of decitabine (DNMT inhibitor) to oligo-fucoidan promoted inhibition of U87MG cell growth and induced myelin basic protein [249].

Ganoderma lucidum, commonly known as "Reishi" in Japan and "Lingzhi" in China, is a mushroom used in Asian countries for its medicinal values [313,314]. *G. lucidum* polysaccharides (GL-PS) are the bioactive component of the fungus, which possess immunomodulatory and anticancer properties [315]. GL-PS inhibited U251 cell proliferation by blocking cell cycle at G_0/G_1 and promoted apoptosis via caspase-3 activation [316]. In a separate study, the authors demonstrated an increase in the concentration of IL-2, TNF-α, and IFN-γ following GL-PS administration in Male Fischer rats (F344) bearing RG2 glioma [314]. The abdominal injection promoted functional maturation of dendritic cells leading to inhibition in tumor growth (101.93 ± 53.58, 113.56 ± 39.76, 161.28 ± 56.69 mm^3) and increased median survival (27.67 ± 2.87, 31.78 ± 6.38, 27.33 ± 4.97 days) compared to control rats (162.99 ± 48.34 mm^3, 24.44 ± 2.55 days) [314].

Lentinan (*Lentinus edodes,* also known as the shiitake mushroom), is an attractive polysaccharide with reported minimal toxicity and pharmacological properties, including antitumor, immunomodulatory, antioxidant, and blood lipid reduction [317]. Lentinan elicits its immunomodulatory properties by activating macrophages and dendritic cells via Dectin-1 receptor binding, resulting in the elevation of cytotoxic T lymphocytes and natural killer (NK) cells [318,319]. Lentinan as a monotherapy or in combination with chemotherapy has been extensively studied in osteosarcoma [320], breast [321], and ovarian cancer [322]. However, to date, lentinan has only been studied on C6 glioma cells, demonstrating anti-proliferative, cell cycle arrestment at G_0/G_1 phase and apoptosis induction [323]. Such findings propose lentinan as a potential phytochemical that should be explored more in preclinical HGG models.

6.3. Cannabinoids

Cannabinoids from *Cannabis* possess anti-cancer properties and are primarily used in cancer patients as part of palliative care to relieve pain, relieve nausea, and stimulate appetite [324,325]. Nabiximols trademarked as Sativex®, which contains equal parts Δ^9-Tetrahydrocannabinol (THC) and cannabidiol (CBD) (1:1) is formulated as an oromucosal spray that allows slow absorption through the mucus, with rapid and direct access to the circulation, where plasma concentration plateaus more rapidly [326–328]. The combination of phytocannabinoids inhibited tumor growth via anti-angiogenesis and induction of apoptosis [326–328] in vitro (U87 and T98G) and orthotopic glioma murine models [329,330]. The phytocannabinoids combinations (THC and CBD (1:1 ratio)), when co-administered with Tmz, demonstrated strong synergistic reduction of glioma initiating cell growth in orthotopic xenograft nude mice [331]. Sativex has been explored in a clinical setting combined with Tmz (NCT01812603) in placebo-controlled phase II clinical trials involving recurrent GBM patients [328]. In a study conducted by GW Pharmaceuticals, GBM patients with 60% or greater Karnofsky performance who received dose-intense Tmz (100 µL of solution containing 27 mg/mL THC and 25 mg/mL CBD (12 sprays) reported a one-year survival rate of 83% and a median survival over 662 days compared to control group (44% and 369 days) who received Tmz only [328,332].

6.4. Thymoquinone

Thymoquinone (2-methyl-5-isopropyl-1, 4-benzoquinone) from *Nigella sativa* (black seed) [333] possesses anti-angiogenesis, anti-invasion, and anti-metastasis in various cancers with minimal effect on normal cells [334–336]. Thymoquinone also enhances the efficacy of chemotherapeutic drugs when used in combination in cancer models [337]. Thymoquinone (3.6 µM) addition to chloroquine (4.4 µM) suppresses autophagic flux, inhibits cell proliferation in T98G and Gli36ΔEGFR cells independent of the p53 status [338]. Thymoquinone (50 µM) synergized Tmz (100 µM) effects by enhancing the inhibition of U87MG cell migration and invasion, significantly more significant than Tmz or thymoquinone alone [334]. However, thymoquinones' lipophilicity hinders its pharmacokinetics resulting in low membrane permeability, solubility, and bioavailability [333,337].

6.5. Potential and Challenges of Phytochemicals and Nanoparticles

The discovery of plant-derived bioactive compounds as novel therapeutics may provide therapeutic advantages in HGG research (Figure 3, Table 8). Around 60 percent of commercially available clinically approved anti-cancer medications are derived from medicinal plants [339,340]. Their multitarget, high selectivity against cancer cells, capable of reducing multidrug chemoresistance, inexpensive and marginal side effects make them valuable potential therapeutics, especially when combined with current therapy advancement [341]. Phytochemicals such as thymoquinone, cannabinoids, and resveratrol have proven to enhance the anti-cancer effect in pre-clinical models when combined with Tmz [297,328,334]. Such development in pre-clinical findings further necessitates clinical studies to fully assess phytochemicals efficacy in combination with current standard

therapy. Although Sativex (THC:CBD, 1:1) clinical trial (NCT01812603) demonstrated an increase in 1-year survival rates in combination with Tmz (83%) over standard therapy with Tmz alone (44%), the clinical trial did not progress any more than phase II. Hence further clinical inspection should be considered for further validation [328]. Although various phytochemicals demonstrated pre-clinical potential, their use in the animal or actual clinical setting is still not convincing and well-studied. Thus, incorporating these phytochemicals with nanoparticles delivery systems may be of interest to researchers.

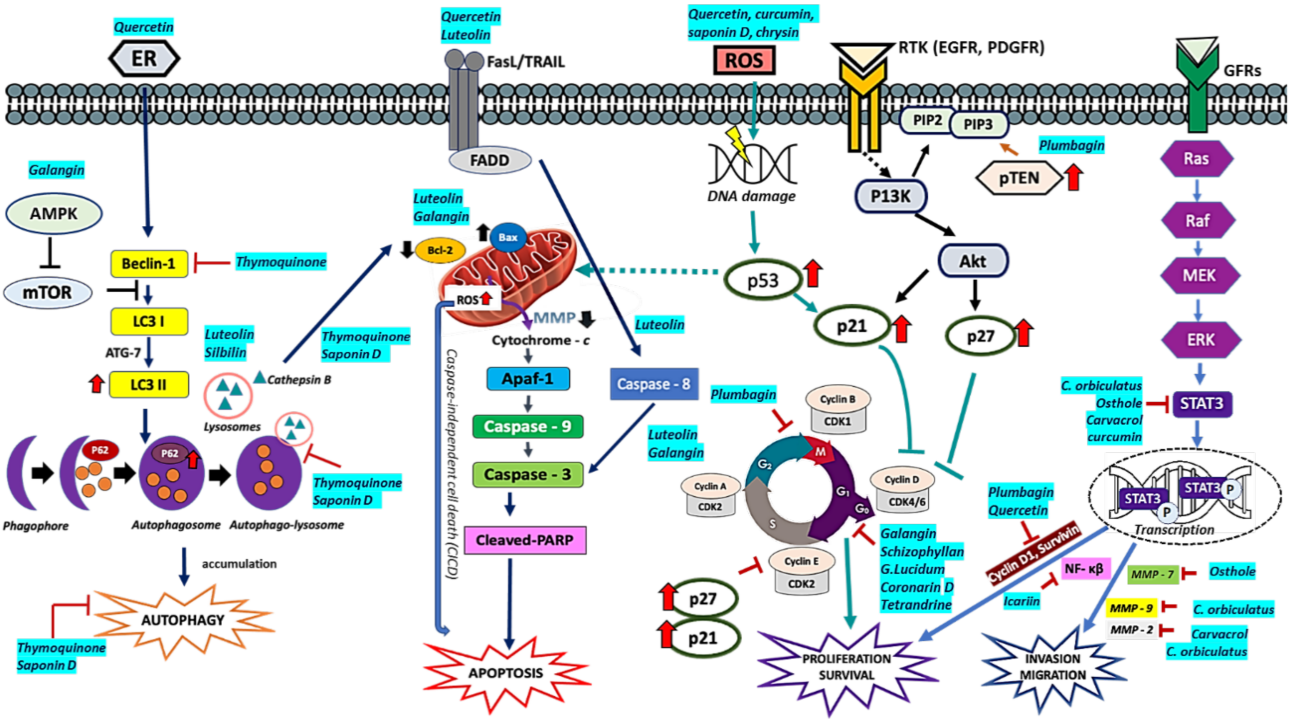

Figure 3. Phytochemicals as potential adjuvants in HGG. Phytochemicals from different classes modulate various signaling pathways in human HGG tumor cells that promote cell cycle arrestment, inhibit cell proliferation, invasion, migration, and promote cell death.

Cancer nanomedicine has emerged as a revolutionary approach in cancer research, changing cancer therapeutics' paradigm [342]. The recent rapid development of nanomaterials brings an exciting opportunity to deliver various therapeutics to sites of interest in patients while preserving healthy tissues and organs [343]. This therapeutic approach has also been approved in the ovarian and breast cancer model by the United States Food and Drug Administration and the European Medical Agency due to lesser side effects and better safety profile than the conventional therapeutic [343]. Nanomaterials such as liposomes, nanoemulsion, polymeric micelles, and iron oxide nanoparticles have been investigated as therapeutics carriers to treat HGG (Table 6). These materials demonstrated a favorable effect, enhanced permeability, and retention through positive targeting that allows nanomaterials to retain tumor tissues. Nanoparticles can cross the BBB and maintain in GBM tissue due to the "leaky" BBB caused by necrosis and microvascular proliferation of GBM cells [344]. Such properties have enabled nanoparticles to be explored in clinical settings. In early-phase clinical trials, liposome-based nanomedicines using single-agent therapy of nanoliposomes containing doxorubicin (NCT02766699) and irinotecan are currently in development (NCT02022644) [345,346]. The current status of these clinical trials is still ongoing with active recruitment.

The use of nanoparticles also faces challenges such as immune response, blood flow, red blood cells hemolysis, and substantial tissue resistance, preventing nanoparticles from being internalized cellularly, particularly in the nano-drug diffusion in vivo model [347]. In

phase II clinical trial, postoperative GBM patients who underwent chemoradiation did not show statistically significant benefit in the overall survival and 6-month progression-free survival when subjected to the combination of Tmz and pegylated liposomal doxorubicin [348]. Similarly, intraperitoneal administration of pegylated liposomal Tmz in glioma bearing male Lewis rats and in vitro study (CNS-1 glioma cancer cells) demonstrated prolonged survival and decreased tumor volume. However, such effects were not statistically significant [349]. These unsuccessful events could be due to the mode of delivery, non-specific, non-targeted, and reduced drug availability impeded by the BBB and tumor heterogeneity. Therefore, a more precise and target-specific nano therapy is required. The use of doxorubicin as a standard drug in this in vitro study demonstrated ITGα-2 expression in GBM to be significantly higher than EGFR [350]. Doxorubicin delivered by GBM-induced angiogenesis selectively via ITGα-2 antibody-directed liposome improved anti-tumor efficacy and penetrated BBB (cells A172 and U87), which highlights ITGα-2 as a potential strategy.

Table 8. Pre-clinical and clinical studies on the use of natural products in GBM treatment.

Phytochemical	Study Design	Observations
Curcumin	U118, U87, U251MG-100 μM nimustine hydrochloride + 20 μM curcumin	Enhanced anti-proliferation, anti-migration, and proapoptotic activities of nimustine hydrochloride [20].
	Patient-derived GSCs (Glio 3, Glio 9)—25 μM curcumin	Reduced cell viability of GSCs via ROS-dependent mechanism, MAPK-pathway activation and downregulation of STAT3 and IAPs [281].
	U87-miR-378-50 μM c SCID mice-30, 60, 120 mg/kg	miR-378 sensitized GBM toward curcumin, inhibited tumor growth, cell proliferation, and induce apoptosis [285].
Thymoquinone	U87MG-50 μM TQ + 100 μM Tmz	Decreased cell migration and invasion [334].
Plumbagin	A172, U251-5.5 μM (IC_{50})	Cell cycle arrestment at G_2/M phase. Apoptotic induction with minimal necrotic cell death. PTEN overexpression and downregulation of E2F1, MDM2, cyclin B1, surviving, Bcl-2 protein, and PARP-1. Inhibition of telomerase activity [351].
Sativex	NCT01812603 Phase I and Phase II (n = 21 GBM) with Karnofsky performance scale ≥60% 100 μL (12 spray/day) Sativex (27 mg/mL THC + 25 mg/mL CBD) orally + Tmz Control: Tmz alone	83% of one year survival rate in Sativex + Tmz group compared to 44% in Tmz alone [328].
Quercetin	T98G-50 μM quercetin + 20 μM chloroquine	Induced autophagy and ER stress [294].
	C6, T98G-25 μM quercetin + 1mM NaB	Promoted apoptosis via increased expression of Bax, caspase 3, downregulation of Bcl-2, surviving and PARP degradation [295].
Resveratrol	C6-50,100,150 μM	Inhibited cell proliferation, cell cycle arrestment at s-phase, apoptotic induction, downregulation of miR-21, miR-19 and miR30a-5p [296].
	RG-2-25 μM Resveratrol + 250 μM Tmz LN18, LN428-75 μM Resveratrol + 750 μM Tmz	Inhibition of MGMT expression, downregulation of STAT3/Bcl-2/surviving, apoptosis and cell cycle arrestment (G1 or S-phase) [297].
Galangin	U87MG and U251-100 μM	Apoptosis, cell cycle arrest G_0/G_1 pytoptosis, and protective autophagy. Enhanced chloroquine-suppressed tumor growth compared to galangin monotherapy [276].
	Male BALB/c athymic mice, 4 weeks old; 14–17 g) (orthotopic U87MG xenograft) 100 mg/kg/day GG + 25 mg/kg/day chloroquine; control: DMSO	

Table 8. *Cont.*

Phytochemical	Study Design	Observations
Schizophyllan	CNS-1-40 and 60 mg/L Schizophyllan	Apoptosis and cell cycle arrest at G_0/G_1 phase. Tumor growth inhibited [310].
	Sprague Dawley male rats (n = 40) (in situ intracranial tumors, CNS-1) 20, 40, 60 mg/kg; control 0.9% NaCl	
Icariin	U87MG-10 μM ICA + 200 μM Tmz	Synergistically decreased cell proliferation, sensitized GBM cell by enhanced apoptosis by increased caspase-3 and cleaved PARP expression. Inhibited cell migration, invasion via suppression of NF-κB activity [352].
Silbinin (*Silybum*)	A172, SR-50, 100, 150 μM s	Apoptotic induction via caspase-3 activation and PARP-1 cleavage. Enhanced autophagic flux via LC3-I to LC3-II conversion and P62 degradation. Inhibition of mTOR and downregulation of YAP [353].
Luteolin	U251, LN229-10, 20 30 μM	Inhibited cell proliferation. Apoptotic induction via MAPK by activation of FADD, upregulation of cleaved PARP, cleaved caspase-8, and cleaved caspase-3. Increased expression of Bax to Bcl_2 ratio. Autophagy induction promoting miR-124-3p expression [354].
Silbinin + Luteolin	U87, T98G-50 μM SIL + 20 μM	Synergistically inhibited cell proliferation, invasion, and migration. Apoptosis induction and inhibition of rapamycin (RAPA)-induced autophagy via iNOS downregulation, PKCα suppression, and miR-7-1-3p upregulation [355].
	Female nude mice (nu/nu) (subcutaneous U87MG, T98G xenografts) Silbinin (200 mg/kg/day) + Luteolin (10 mg/kg/day)	
Oligo-fucoidan	GBM8401, U87MG-50, 100, 200 μg/mL	Cell cycle arresting at G_1/S phase induced cell differentiation, inhibited DNA Methyltransferases, and decreased p21 methylation [249].
G. lucidum polysaccharides (GL-PS)	U251- 50, 100, 200, 400 or 800 μg/mL	Inhibited cell proliferation, cell cycle arrestment at G_0/G_1 phase, promote apoptosis via caspase 3 activation. Increased IL-2, TNF-α, INF-γ. Enhanced cytotoxicity of NK and T cells. Inhibited tumor growth and prolonged rat survival [316].
	Male Fischer rats (200-250G)- 50, 100, and 200 mg/(kg d) GL-PS; control: saline	
Saponin D (*Pulsatilla koreana*)	U87 MG-10 μM SB365	Inhibited cell proliferation. Alteration in mitochondrial membrane potential (MMP), neutralization of lysosomal pH Increased ratio of LC3-II/I and p26 in cell indicating Inhibition of autophagic influx mediated by cathepsin B and mainly ROS. Co-treatment of SB365 and Tmz exerted an additive effect. Suppression of tumor growth in xenograft model [356].
	Nude mice-SB365 (5 mg/kg/every other day, intratumoral) + Tmz (2.5 mg/kg/day, i.p., U87 xenograft)	
Toosendanin	U87, C6, T98G-10 nM	Inhibited cell proliferation and induced apoptosis in vitro and in vivo. Reduce tumor progression via apoptosis. Reduced tumor weight. Increased expression of Bax, cleaved caspase-3, and reduction in Bcl-2 expression. No cytotoxic effect in T98G. Apoptosis induced via increased expression of estrogen receptor β and p53 [357].
	Athymic nude mice—6 weeks old (n = 10), (U87-Luc xenograft, subcutaneous) 1 mg/kg qd (orally)	

Table 8. *Cont.*

Phytochemical	Study Design	Observations
Coronarin D	U251-10, 20, 40 μM	Cell cycle arrest at G_1 phase, induced caspase-dependent mitochondrial-mediated apoptosis by increasing phosphorylated ERK, p-H2AX histone, and overexpression of p21 [358].
Carvacrol	U87-500 μM	Inhibition of TRPM7. Reduction in cell viability, migration, invasion, and MMP-2. Promotion of cofilin phosphorylation and inhibition of Ras/MEK/MAPK and PI3K/Akt. TRPM7 [359].
Lentinan	C6- 20, 40, 80 mg/L SD male rats-20, 40, 80 mg/kg/d; control: 0.9% Nacl	Inhibited tumor growth, cell proliferation, cell cycle arrestment at G_0/G_1 phase, and promoted apoptosis [323].
Ficus carica	U138 MG, T98G, U87 MG-0.25 mg/mL U138 MG, T98G-0.25 mg/mL + 450 μM Tmz U87 MG-0.25 mg/mL + 25μM Tmz	Inhibited GBM cell proliferation, and stimulated apoptosis. Inhibit cell invasion via reduction in VEGF expression. Synergistic inhibition in GBM cell proliferation. The co-treatment increased miRNA expression (let-7d) in T98G cells modulating GBM progression via miRNA [360].
Celastrus orbiculatus	U87, U251-20, 40, 80 μg/mL	Inhibition of cell adhesion, migration, and invasion. Reduction in N-cadherin, vimentin, MMP-2, and MMP-9 expression. Upregulation of E-cadherin. Inhibition in actin assembly. [361].
Tetrandrine (*Stephania tetrandra*)	U87, U251-4 μM Tet + 2 Gy	Enhanced radiosensitivity of the cell. Inhibited cell proliferation by decreasing phosphorylated ERK expression. Cell cycle arrestment at G_0/G_1 phase [362].
Osthole	U87-50, 100, 200 μM	Inhibited cell proliferation and enhanced apoptosis in cells. Increased expression of miR-16 precursor and decreased expression of MMP-9 [363].
Trichosanthin	U87, U251-10, 20 μM	Inhibited cell proliferation, invasion and migration. Induced apoptosis and inhibited LGR5 expression suggesting repression in Wnt/β - catenin signaling pathway [364].

7. Precision Medicine

Precision medicine is a type of customized treatment that can be used to treat patients with HGG according to their specific molecular profile [365,366]. One example is using the novel 3D brain cancer chip, which utilizes GBM cells to form 3D cancer tissues for drug screening, therapy resistance, and tumor cell motility [367–370]. For instance, the use of poly(ethylene glycol) diacrylate (PEGDA) hydrogel, thereby making it permeable to biomolecules and water, allows "smart release" of the chemical transported on the chip to study the response of the drug in the adjacent 3D environment [367]. Utilizing the concept of PEGDA hydrogel, this can be applied in the polyvalent vaccine, which may confer better advantages than monovalent vaccines. However, its large molecular size may pose a challenge to cross the BBB. Hence, by integrating PEGDA hydrogel in it, this challenge could be overcome. The ability of induced neural stem cells (iNSCs) derived from patients' skin cells to cross the BBB makes it an ideal candidate to be used for personalized therapy in GBM treatment [22]. iNSCs are genetically engineered to have the ability to undergo differentiation while triggering apoptosis in co-cultured human GBM cells [22,196]. In a study by Bago et al. in 2016, the authors proved that the delivery of TNF-

α-related apoptosis-inducing ligand (TRAIL) via iNSCs in murine GBM models resulted in a decreased growth of diffused and solid GBM xenografts by 20 and 230-fold respectively.

Additionally, it also prolonged the median survival in these murine models [371]. The data support the potential of iNSC being a highly efficient drug-delivery vehicle for the treatment of both invasive and solid brain tumors [371] Hence, more preclinical studies are required to determine the efficacy and potentiality of iNSCs before considering it in GBM treatment. Moreover, molecular genetic tools would help to determine a patient's prognosis and the best therapeutic regimen for each patient. For instance, patients with triple-positive mutations (1p/19q codeletion, *IDH* mutation, and *TERT* promoter mutation) have a favorable prognosis, while patients with triple-negative mutation often have poorer prognoses [372–375]. This information can be used to ensure the patients whose prognosis is favorable are not treated too aggressively at the onset of the disease to prevent treatment-induced neurological deficits. Hence, in precision medicine, a prognostic marker can be determined, which could be used to plan the treatment mode, eventually improving the patients' prognoses.

In an article by Prados et al. [376], to illustrate the principles of molecular profiling of GBM, the authors carried out genome and exome-wide sequencing of 13 samples of recurrent GBM. They mapped the identified genomic alterations to possible CNS-active treatment modalities. One of the recurrent GBM samples exhibited *CDKN2A* gene deletion, *EGFR* gene amplification, and *EGFRvIII* expression [376]. The therapeutic agents which served as strong candidates for GBM with amplification of the *EGFR* gene include afatinib, dacomitinib, and propranolol. Afatinib is an irreversible EGFR/ERBB2 inhibitor [376]. In preclinical trials, it has been shown to have activity against the *EGFRvIII* variant. However, afatinib's efficacy in GBM is not demonstrated yet [376]. Dacomitinib is also an EGFR inhibitor and is currently tested in GBM clinical trials (NCT01112527). It is reported that dacomitinib have improved penetration of the BBB [376]. Propranolol, commonly used in hypertension, migraine prophylaxis, angina pectoris, and various other conditions, has recently exhibited the ability to control EGFR trafficking. However, its efficacy in clinical trials remains to be seen [376]. For *CDKN2A* deletion, the therapeutic agent of choice includes cyclin-dependent kinase (CDK) 4/6 inhibitors. One example is PD-0332991, which is currently in phase II of GBM clinical trials (NCT01227434), as mentioned in an article by Prados et al. [376]. Using this GBM sample as an example, if an EGFR inhibitor that has activity against *EGFRvIII* and can penetrate the BBB is coupled with a CDK 4/6 inhibitor, it may serve as a potentially effective treatment strategy in this case. Another recurrent GBM sample exhibited mutation of *BRAF* V600E gene, deletion of *TSC2, FANCA* and *RECQL5* genes [376]. These deletions and mutation can cause the activation of both the MAPK and P13K/mTOR signaling pathways. In this context, if an mTOR inhibitor coupled with a BRAF/MEK pathway inhibitor is utilized, it could be a potentially effective treatment mode in this case [376]. These two examples exhibit the importance of precision medicine in HGG.

One way precision medicine could be applied is by acquiring multiple biopsies of the tumor mass during surgery, which includes both the enhancing and the non-enhancing regions of the particular HGG [376]. Then, extensive profiling of the genome is performed, and the drugs which are considered the most probable candidates to serve as the therapeutic agent of choice are selected. All the drug selections can be individualized to tackle the various genetic alteration of the HGG. Additionally, some samples of the tumor are also collected for future xenograft testing. Blood samples are also acquired over time so that tumor DNA that is circulating can be assessed. This may help for the future development of non-invasive biomarkers [376]. In short, precision medicine will help to combat the heterogeneity and complex nature of GBM strategically.

8. Conclusions

The introduction of newer therapies like immunotherapy or gene therapy has provided some improvement in HGG patients. However, prolongation of overall survival does not translate into the eventual prospect of curing this disease. Immunotherapy, although promising, is yet to demonstrate anti-tumor efficacy in human HGG. This may be due to the complex immune mechanisms and tumor heterogeneity that have not been fully understood. These approaches should be pursued, perhaps by trying to reactivate the tumor-immune system several times until the tumor has completely disappeared. The different subtypes of GBM (neural, proneural, mesenchymal, and classical) have made the disease even more complicated. Thus, how each different subtype responds with the other immunotherapies remains unclear. Another challenge is to ensure that immunotherapy and chemoradiation are used strategically when used in combination. The side effects of chemotherapy and radiotherapy may pose an obstacle to immunotherapy efficacy; thus, timing is crucial when used in combination.

Although fascinating, the current therapeutic approaches, such as immunotherapy, are accompanied by many drawbacks such as time-consuming, materials used, and complexity of the experimental design. Therefore, a more cost-friendly with high specificity towards tumors with marginal side effects such as the use of phytochemicals and the repurposing of older drugs should be further considered in HGG treatment. Moreover, repurposing older drugs with the innovations mentioned above provides a multitarget molecular approach while being cost-effective in HGG management. Although these phytochemicals and older drugs' bioavailability is a major problem, formulation and combination therapy have shown as a solution to address such issues. Studies focusing on the use of novel nanoformulations to improve the bioavailability and efficacy of flavonoids and other lipophilic compounds are vital. Moreover, the co-administration of phytochemicals, immunotherapy, and older drugs with standard chemotherapeutic drugs mainly results in modulating multiple signaling pathways. Thus, the use of nano targeted delivery may provide a clinical perspective in HGG therapy. Hence, precision medicine with the integration of the discussed therapeutic advancements may be the future trend to find a cure via extensive genetic profiling. In short, a multimodal approach is required to treat HGG as no single method is considered adequate, with surgical resection being an integral part of this approach. More importantly, the current established use of chemotherapy, surgical resection, and radiotherapy do not guarantee a complete remission or tumor resection in HGG patients. Therefore, the combination of various therapeutic approaches may provide a better alternative to exclusively treat and target HGG tumor with different subtypes while delivering a safer toxicity profile in patients with HGG.

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Abbreviations

DESI—Desorption electrospray ionization; *EGFRvIII*—Epidermal growth factor receptor variant III; GBM—Glioblastoma; GSC—Glioma stem cell; HGG—High-grade glioma; LGG—Low-grade glioma; *MGMT*—O6-methylguanine–DNA methyltransferase.

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