OVERVIEW ON GLIOBLASTOMA TREATMENT

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ABSTRACT:

Glioblastoma is the most prevalent malignant brain tumor. Due to the GBM microenvironment, it is challenging to obliterate the tumor with surgery, chemotherapy, and radiation. It is difficult to increase the survival rate with these therapies, and it also has various adverse effects. Moreover, the resistance developed by the GBM to current treatment is also high. In recent years, numerous therapies have developed to achieve target specificity and minimize side effects. This review summarized various treatment approaches like adjuvant therapy, phytotherapy, immunotherapy, gene therapy, Oncolytic virotherapy, intranasal drug delivery, nanotherapy, and synthetic therapy.

Keywords: Glioblastoma, surgery, chemotherapy, radiation, resistance, various treatment approaches.

1. INTRODUCTION

Glioblastoma is the most aggressive neoplasm of the brain and CNS. It is previously known as glioblastoma multiforme (GBM) [1]. About 50% of primary brain tumors are GBMs. Every year around seven in one lakh people develop this disease [2].GBMs are immensely seen in the brain; conversely, they can also emerge from the spinal cord, brain stem, and cerebellum [3-4]. As per WHO 2017 classification, it is considered a grade IV glioma. GBM has an abysmal prognosis with a median survival of about only 15 months. Based on the response to therapy, disease prognosis, age, and genetic variability, GBM is of two types primary and secondary GBM. Denovo or primary GBM can occur in geriatrics; it accounts for > 80% of glioblastoma, characterized by MDM2 augmentation, deletion of CDKN2A, alteration in phosphate, tensin homologue, and overexpression of EGFR. The survey by the American Association of Neuroscience Nurses 2014, revealed that primary gliomas develop from all four lobes of the brain: occipital (3%), parietal (13%), temporal (20%), and frontal (25%) [4-5]. While secondary GBM arises from lower grade oligodendrogliomas or astrocytoma, it occurs mainly in adolescents. It is characterized by mutations in the tumor protein P53. In the primary, secondary, and lower-grade glioma, mutations in isocitrate dehydrogenase-1 and 2 appear [5]. In general, primary and secondary glioblastomas cause mutations in signaling pathways to improve the survival of the cell, enhance cell proliferation and help to run away from the checkpoints of cell cycles such as senesces and apoptosis. These tumors are further sub-classified as mesenchymal, neural, pro-neural, and classical; each has varied disease prognosis and survival rates [4].

2. Etiology

GBM occurs at any age but mainly in geriatrics; it is unusual in pediatrics. The incidences are higher in males than females. Asthma, some nucleotide polymorphisms, eczema, psoriasis, other

allergic conditions, genetic diseases (Turcot syndrome, retinoblastoma, Li-Fraumeni syndrome, tuberous sclerosis, and neurofibromatosis 1 and 2), immune aspects, and prior radiation are risk factors of GBM. Other factors responsible for GBM include pesticides, petroleum refining, vinyl chloride, over usage of drugs, synthetic rubber manufacturing, dietary exposure to NO, obesity, smoking, and alcohol. In untreated patients, the survival is only three months. In GBM GPX8 gene is over-expressed, and various signature genes like SHANK2, MGAT4C, LINC00836, IGFN1, FERMT1, ENHO, CSDC2, and CHST9 are under-expressed; these are involved in different cell proliferation, signal transduction, and biological functions [4-7]. Viruses SV40, and cytomegalovirus, HHV-6 are responsible for GBM in some cases [11-14].

3. Symptoms and Diagnosis:

Symptoms associated with GBM are focal or progressive neurologic deficits, headache, increased intracranial pressure and seizure (seen at later stages of the disease), memory loss, nausea and vomiting, and personality changes. Initial diagnostic imaging may include MRI or CT scan and tissue biopsy [4, 8-9].

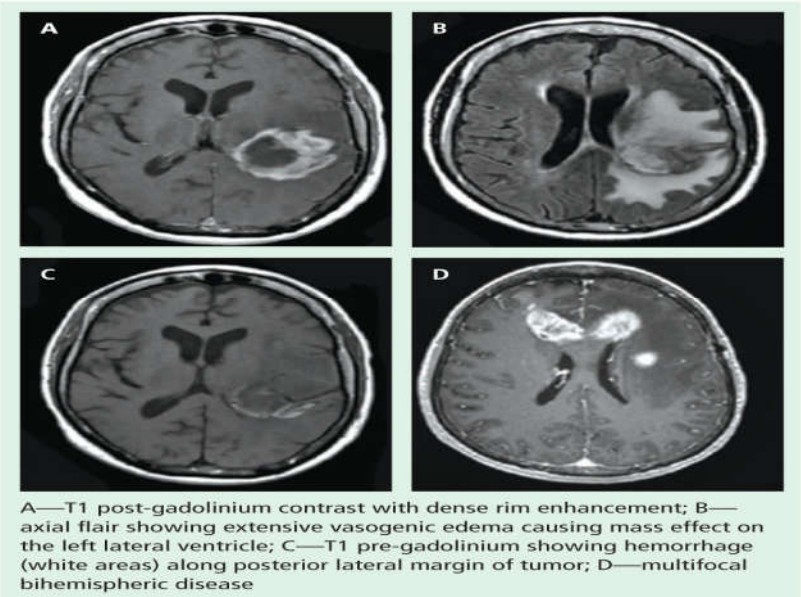


Figure 1. Diagnostic imaging shows ventricular distortion, bleeding, and surrounding vasogenic edema [4]

4. Pathophysiology

GBM microenvironment is a barrier in the treatment of glioblastoma, as this supports tumor growth by providing an encouraging neighborhood. GBM microenvironment contains immune-modulatory cues and immune cells; hypoxia regions, endothelial cells (EC), glioma stem cells (GSC); mesenchymal stem cells (MSC); astrocytes; precursor cells/ neural stem/ (NPC). All of these are involved in the pathology of GBM. NPCs decline with age and secret endovanilloids, which promote the apoptosis of GBMs. GSCs are responsible for proliferation, recurrence, and resistance. MSCs and astrocytes are involved in tumorigenicity, invasion, and resistance. In addition, MSCs induce apoptosis of GBMs. Hypoxia regions and ECs are accountable for

aggressive behavior responsible for resistance and inducing metastasis. Immune cells boost GBM metabolism and cause the infiltrative development of tumors [10].

5. Conventional therapy

Multidisciplinary approaches are necessary for the treatment of GBM. Current therapy consists of surgical resection, simultaneous radiation with temozolomide (TMZ), and adjuvant chemotherapy. It is difficult to obliterate a tumor with surgery because of invasiveness and recurrence. Till 2005, postoperative radiation therapy alone was standard treatment; but later pivotal phase III clinical trial changed the treatment to TMZ with RT combination. This therapy increased the median survival from 12.1 months (RT) to 14.6 months (RT+TMZ) by triggering apoptosis and cytotoxicity and causing DNA damage. Nitrosoureas and TMZ induce apoptosis through mispairing of base pairs. Radiation induces leukoencephalopathy, neurocognitive toxicity, and endocrinopathy in tumor cells and causes apoptosis by DNA cleavage. In managing glioblastoma and to increases the survival rate of patients, surgery is an essential treatment. The use of COX-2 inhibitors has proven protective in glioblastoma. Various techniques like hypofractionation, stereotactic radiosurgery, radioimmunotherapy, and iodine-125 brachytherapy are used to enhance site-specificity and minimize toxicity; however, there is no improvement in survival rate with these methods. Corticosteroids are recommended for vasogenic edema and seizures and anticonvulsants to relieve symptoms [4-6, 15].

6. Disease recurrence

Despite surgery and multimodality treatments, seventy percent of patients experience a disease prognosis within one year of diagnosis. Can treat this recurrence again with radiation, but it increases the risk of necrosis. When treated with corticosteroids and chemotherapy, it enhances the quality of life. Other agents like bevacizumab (Avastin®-monoclonal antibody), irinotecan (Camptosar®), nitrosoureas, etoposide (Toposar®), and carboplatin (Paraplatin®), helps to overcome this challenge. Optune as monotherapy was approved in 2011 by FDA. Minor adverse effects and fewer hematological and gastrointestinal reactions appear with optune use [4].

The excess usage of the temozolomide resulted in resistance [16].To combat resistance, adjuvant therapies and synthetic drugs, phytotherapy, gene therapy, immunotherapy, TTF, and some novel therapies have been employed in recent years.

7. Adjuvant therapy

TMZ, in combination with curcumin, produced cell cycle arrest at the G2/M phase and induced apoptosis. Additionally, curcumin downregulated the PI3K/Akt, NF.κB, STAT-3, and signal transducer. At the same time, TMZ repaired JNK1/2, ATM, MSH6, and p38 and promoted autophagy [19]. TMZ, dinaciclib plus diisothiocyanate-derived mercapturic acids combination restricted cell growth in GBM [17]. Naringenin and TMZ established better cytotoxic effects on LN229 and U87MG cell lines and reduced the migration of tumor cells [18]. Studies revealed that co-administration of TMZ and resveratrol could distinguish a normal cell from the GBM cells. O6-benzylguanine (O6-BG) with TMZ reduces the toxicity like thrombocytopenia, leucopenia, and neutropenia in grade 4 GBM. But this approach is not fit for maintaining the TMZ sensitivity in tumor apoptosis. Valproic acid, radiotherapy, and TMZ enhanced the survival rate from 13.96 to17.35 months. And also, considerable diminution in resistance at MGMT

(methyl guanine methyl transferase) was identified. Further, valproic acid has a vital function as a seizure prophylaxis agent. When combined with TMZ, Levetiracetam enhanced the TMZ action on GBM cells by apoptotic pathways and retarded MGMT. The combination of interferon ß (IF-ß), TMZ, catholic master cells (MSCs), and vitamin D with TMZ significantly improved the survival rate because of the synergistic effect. Patients treated with TMZ, panobinostat, and decitabine prevented the disease prognosis. Ribonucleotide reductase inhibitors (didox and trimidox) combined with TMZ showed synergistic action on GBM. Disulfiram-Copper and dihydroartemisinin in conjugation with TMZ effectively combated the resistance and increased TMZ sensitivity. While, disulfiram-Copper even enhanced sensitivity, especially towards brain tumor-initiating cells. Administration of TMZ plus bevacizumab and radiotherapy managed the disease progression. Quercetin plus edge gamma knife RT with TMZ reduced angiogenesis and enhanced apoptosis of GBM cells. Chloroquine plus sirolimus with TMZ inhibited cholesterol drawing from LDL. And retarded the lysosomal function and prevented LAMP-1 (lysosome-associated membrane protein) clumping. Morphine, along with TMZ, reduced toxicity and improved cell apoptosis. In adjuvant chemotherapy, shikonin induced reactive oxygen species (ROS) in tumor cells and apoptosis by inhibiting caspase-3,8 and 9 pathways. Nitric oxide synthase enzyme caused cell apoptosis and cell damage. Hydroxyl urea in conjugation with TMZ can overcome the resistance. Propyl gallate in adjuvant therapy reduced the migration of cells by inhibiting p- IκB, p-IKK, and p-p65, including the NF- κB pathway. Melatonin co-administration with TMZ can effectively combat multidrug resistance. The alpha-lipoic acid combination with TMZ inhibited the TRPA-1 channel, thereby inducing the antioxidant, anti-inflammatory, and apoptotic activity (hypoxia in DBTRG). Co-loaded therapy with lipid nanoparticles exhibited target-specific delivery and increased quality of life. Combined strategies such as nicotinamide adenine dinucleotide and base excision repair; augment the TMZ effectiveness. Withaferin improves the sensitivity of the TMZ and inhibits MGMT resistance, and shows pro-apoptotic, apoptotic, antiproliferative, and antioxidant properties. TMZ-loaded chlorotoxin nanocarriers prohibited systemic toxicity, degradation and improved target delivery [19]. Moschamine and temozolomide combined mixture promote significant cell cycle arrest [20].

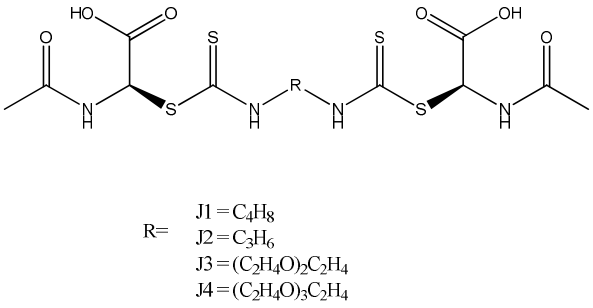


Figure 2. Diisothiocyanate-derived mercapturic acid [17]

8. Immunotherapy

The immunological mechanism of GBM has six stages, starting with the release of antigens from tumor cells and ending with tumor cell death. 1. Release of antigen from tumor cells. 2. Antigen-presenting cells capture antigens to display on major histocompatibility complex (MHC-I and –II) for exposing them to T cells. 3. Antigen exposure on tumor cells activates effector T-cells. 4. These cells pass via BBB and penetrate the tumor site. 5. The immunosuppressive tumor-

associated microglia and macrophage are surmounted to permit activated T cells to identify and attach to GBM cells. 6. After connecting to tumor antigen on MHC-I via the T cell receptor (TCR), activated T cells destroy GBM cells [21-22].

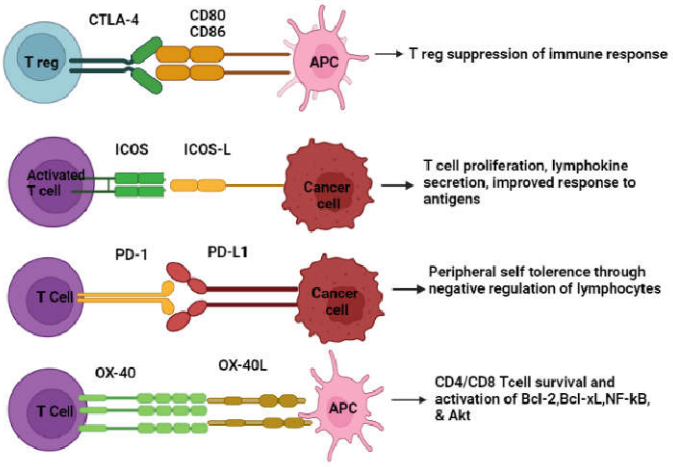


Figure 3. GBM mechanistic immune response

In recurrent glioblastoma, immune checkpoint inhibition is a potential cure. Drugs blocking indoleamine 2,3-dioxygenase(IDO), cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), vascular endothelial growth factor(VEGF), T cell immunoreceptor with Ig and ITIM domains (TIGIT), inducible T-cell co-stimulator, tumor necrotic factor (OX40), myeloid-derived suppressive cell (MDSC), C-X-C chemokine receptor 4 (CXCR4), T cell immunoglobulin programmed cell death protein 1 (PD-1) and its ligand (PD-L1), glucocorticoid-induced tumor necrosis factor-related protein (GITR), and mucin domain containing-3 (TIM-3), lymphocyte activation gene 3 protein (LAG-3) and vaccines are curative in GBM. The effect of immunotherapy with concomitant administration of chemotherapy and radiation on survival is under clinical trials [21, 23].

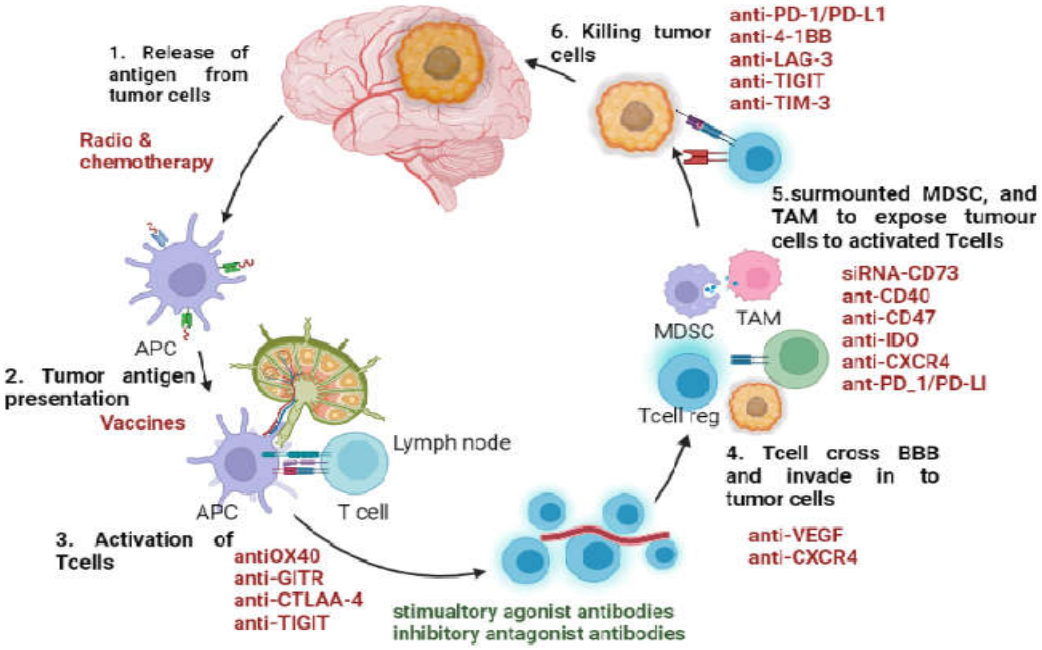


Figure 4. Immunotherapy targeting different checkpoints

9. Other therapy

Tumor-treating field is one of the novel standard care; by this device, 200 kHz electric fields are passed through the shaved scalp. TTF targets microtubules and septin and produces apoptosis via developing abnormal chromosome segregation [7, 15].

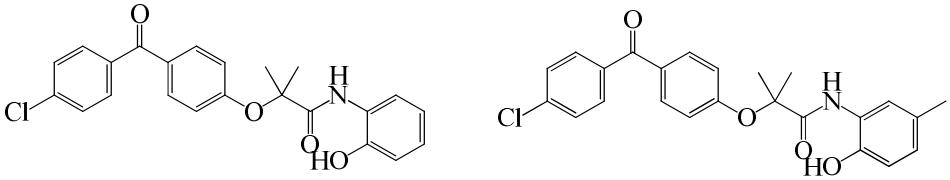
Blood-brain barrier, cellular and molecular heterogeneity of tumor, and infiltrative characters restrict the drug delivery to the GBM. These biological Constraints can be overcome by; focused ultrasound, peptide-based, nanomaterial, controlled release, and convection-enhanced delivery systems [24].

Controlled release drug delivery systems release drugs for a prolonged period. One example is the FDA-approved drug Gliadel® wafer to treat recurrent GBM and manage malignant glioma. The biodegradable wafer polymer utilized in the Gliadel® wafer was BCNU. Other biodegradable polymers and carmustine, temozolomide, and rapamycin are used in implanted controlled drug delivery systems, increasing the survival of rats in malignant glioma models both in the absence and presence of radiotherapy. Convection-enhanced delivery (CED) depends on pressure gradients to transfer drugs to brain tumors; it is a catheter-based drug delivery technique. Subcutaneous immunization conjugation with temozolomide and EGFRVIIIAb with iron oxide nanoparticles showed synergistic action on GBM and increased survival in mouse-GL261 models. With CED, carboplatin is safely delivered to brain tissues. Nanotechnology uses various nanocarriers like a drug, viral, inorganic, polymer-based, lipid-based-conjugated nanoparticles. These carriers help in delivering adjuvants and tumor antigens in immunotherapy. Glycyl-L-histidyl-L-lysine is a natural growth modulating tripeptide successfully delivered to tumor cells by poly E-caprolactone-based nanomaterial system. Iron-platinum nano-particles coated with transferrin and loaded with doxorubicin for intravenous administration developed by a nanobubble-based theranostic system. Mainly three types of peptide-based therapeutics are

present; cell-penetrating peptides, peptides targeting abnormal cellular signaling pathways, and tumor targeting peptides. In combination with the oncolytic virus VSVDM51, Gadolinium could deliver by tumor homing peptides delivery system. Peptide-based therapeutics such as nanocomplex (paclitaxel + PVGLIG + SynB3), zein-curcumin nanoparticles coated with polydopamine and made activated with G23 peptide; WSW fused nanosuspension of paclitaxel, paclitaxel-cholesterol, docetaxel nanoparticles, rabies virus RVG29l, RVG15-liposome, glycoproteins, and self-assembled nanoparticles targeting mitochondria with Cy5.5-SAPD-99mTc peptide probe are potentially delivered drugs to specific sites. Focused ultrasound is a noninvasive and image-guided technique that momentarily opens the blood barrier and effectively transfers drugs to tumor cells. Some of the medications delivered by this method include cisplatin conjugated gold nanoparticles, liposome-encapsulated doxorubicin, liposomal O6-(4-bromothenyl) guanine (O6BTG), BCNU, and temozolomide [24]. Daucus carota L. leaf extract nanoparticles have been cytotoxic against U87MG GBM cells [25].

10. Synthetic therapy

MDM2 inhibitors Nutlin-3 and RG7388 retards cell growth by increasing apoptosis and senescence; it majorly targets MDM2–p53 [15]. Benzimidazoles arrest the G2/M phase of the cell cycle in GBM cells by cyclin B1/ P53/P21pathway. In addition, it stimulates pro-apoptosis of tumor cells via the NF-κB/NLRP3/GSDMD pathway [16]. HR51 and HR59 phenolic variants of benzoyl phenoxy acetamide can cross BBB pericytes, astrocytes, and endothelial cells in the composed model [26]. Flubendazole enhances pro-apoptosis due to decreasing CDKIs, cyclin B1, p53, and CDKIs Rb [27]. Piperidinones up-regulate senescence and apoptosis via blocking MDM2. RITA causes cell cycle arrest due to remodeling of p53 expression. Ribociclib and TG02 induce cell cycle arrest by reconstructing the Rb pathway by targeting CDK4/6 and CDK 9. Thiabendazole targets MCMP2, thus arresting the G2/M phase [28]. 5-aminolevulinic acid targets protoporphyrin IX: and promotes p53 and BAX/BXL2 expression to induce apoptosis [29-30]. Ion channel inhibitors increase Bim, p27, p21, decrease cyclins and BCL2, and arrests G1 and G2 phases [31]. siRNA by downregulating karyopherin-a2 or importin a2 arrests the P53-dependent cell cycle [32]. Selinexor targets XPO1 8; inhibits translocation of subcellular cell cycle regulators [33-34]. JQ1, UM-002, bromodomain, and extra terminal family proteins inhibitor mediates P13k/Akt apoptosis [20, 35-36].



HR49 HR52

Figure 5. Phenolic variants of benzoyl phenoxy acetamide

11. Phytotherapy

Treatments like chemotherapy and radiation produce resistance and various toxic effects. In contrast, plant-based therapy has fewer or no side effects. The development of resistance is also infrequent with plant-based therapy. The following table mentions various phytoconstituents

obtained from plants, category, and their mechanism of action in the GBM therapy [37-43]. Structures of a few essential phytoconstituents are depicted in Figures 6 to 10.

Table1: Plant-based medicine for glioblastoma.

Category	Phytoconstituent	Plant	Mechanism of action
Essential oil	1,8 cineole, alpha-pinene, alpha-terpineol, linalool, citral, nerol	*Lippia multiflora Ocimum basilicum*	Anti-inflammatory/antiproliferative
Essential oil	-	*Hypericum hircinum Ageratum conyzoides Zingiber officinale*	Antiproliferative
Flavonoids	Luteolin	*Aiphanes aculeata*	↓The activation of the PI3K/Akt signaling pathway. Inhibits cellular invasion /migration, ↓ the expression of MMP and FAK.
Flavonoids	Silibinin	*Silybum*	↓VEGF expression via PI3K pathway.
Flavonoids	Hispidulin	*Saussurea involucrata*	↓ mTOR signaling and activation of AMPK.
Flavonoids	Jaceosidin	*Artemisia argyi*	Induces apoptosis and ROS production. Arrest (G2/M) phases of the cell cycle. It reduces cell viability/antiproliferative.
Flavonoids	Quercetin	*Berries, red grapes, tea, apples, parsley, capers, broccoli, red onions,*	↓ Hsp27, ↑ caspase3, 7and 9, and ROS show an apoptotic and pro-apoptotic effect.↑ Sensitivity of TMZ in U87 and U251 GBM cell lines.
Flavonoids	Icariin	*Herba Epimedi*	↓ U87 GBM cells proliferation and ↑ sensitivity of TMZ. ↓ Nf-κB signaling, ↓invasion, ↓migration, and of U87 GBM cells.
Polyphenols	Resveratrol	*Vitis vinifera*	↓The activity of the Wnt. Pathway. Promotes apoptosis ↑ caspase 8, 9, 3 ↓ surviving. Affects the c-MYC expression. Inhibits PI3K /Akt/mTOR, protein kinase C pathways. It increases TTP levels. Arrest cell cycle by decreasing cyclin D, p53, ribonucleotide reductase, and

			STAT3 pathway. Inhibits NF-κB factor and MGMT to suppress tumor growth. Blocks ROS/ERK-mediated autophagy, AMPK, Bcl-2, improves DNA double strands/p53/pATR/pATM, ROS levels, blocks mTOR pathway. ↓ VEGF expression inhibits angiogenesis.
Polyphenols	Curcumin	*Curcuma longa*	↓The expression of VEGF reduces endothelial cell growth. Induces apoptosis by inhibiting caspase-3, 7, 8, 9, BCL-2, Cx43, and anti-apoptotic genes like Bcl-2, NF-κB, and AP-1 JAK/STAT3 pathway. Stimulates cellular arrest and activates the p53, p21 downregulates cyclin D1,↑ expression of DAPK1. Inhibits invasiveness by reducing MMP-2, 9, 14, 15, 24, 25, and HDGF. Induce autophagy by ↓mTOR, BCL-2, BCL-x, and blocks PI3K/Akt/mTOR signaling pathway.
Polyphenols	Demethoxycurcumin	*Curcuma longa*	↑ The levels of pro-apoptotic and apoptotic molecule Smac/Diablo and the cytochrome *c*. ↓ The expression of VEGF, P-Akt1, NF-κB.
Polyphenols	Epigallocatechin gallate	Camellia sinensis	Stimulates cell death, suppresses Bcl2 and Akt phosphorylation and activates BAX caspase. Diminishes MT1-MMP, F-actin, MMP9, IL-6, IL-8, CCL5, and MCP-1 and inhibits invasiveness. Reduces P-gp, telomerase, GRP78, survivin, and PEA15. Blocks PDGF-Rb phosphorylation and inhibits cell proliferation. Decreases inhibition of the 26s subunit of the proteasome.
Monoterpenes	α/β-thujone	*Thuja occidentalis*	↓The expression of angiogenic markers such as CD31 Ang-4 and VEGF in the tumor.

Monoterpenes	Carvacrol	*Origanum* sp.	Inhibits the Ras/MEK/MAPK and PI3K/Akt signaling pathways. ↓The invasive/ migratory U87MG cells. Inhibits TRPM7 and mediates apoptosis by ROS.
Monoterpenes	Perillyl alcohol	*Lavandula* sp.	↓ The secretion and production of VEGF and IL-8 by mTORr signaling. Arrest cell cycle at G1 phase and induces apoptosis. Modulates TGF-beta, M6P/IGF-II, NFKB, Ras/Raf/ERK, and signaling pathways.
Diterpenoids	Pulcherritam A and Pulcherrimin G	*Caesalpinia pulcherrima*	Inhibits U87MG cells viability.
Triterpenoid saponin	Platycodin d	*Platycodon grandiflorus*	↑ Inhibits autophagy and tumor cell death by ↑ LDLR.
Cannabinoid	(9)-tetrahydrocannabinol	*Cannabis sativa*	Displays pro-apoptotic, apoptotic, and antiproliferative activities. Over expresses the transcriptional co-activator p8 and induces ER stress. Stimulates autophagy and apoptosis, activated cannabinoidal receptors.
Cannabinoid	JWH-133	*Cannabis sativa*	In endothelial cells ↓, migration, expression, and cell division of angiopoietin-2. Activates VEGFR-2 and ↓ VEGF production.
Cannabinoid	Cannabidiol	*Cannabis sativa*	↓Transcriptional activity of Id-1 in glioma cells; Erk/Akt signaling pathways and VEGF expression. Pro-apoptotic, apoptotic, and antiproliferative. ↓Growth of GBM tumor through FAAH and 5-lipoxygenase.
Latex	Furanoid, benzaldehyde, benzyl alcohol	Ficus carica	↑Tumor suppressor let- 7miRNA, ↓invasion,↓ of T98G, U138MG, and U87 tumor cell lines proliferation and ↑TMZ sensitivity.

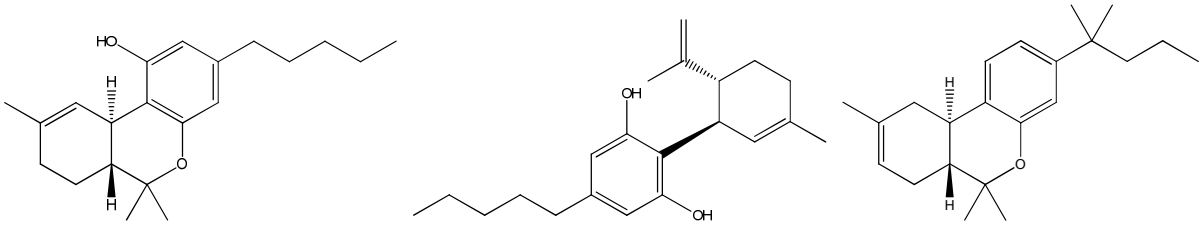
Resin	Propolis is	*Apis mellifera*	↑ Chemosensitivity to TMZ, ↑ TMZ sensitivity of U87 tumor cells, ↓Nf-ĸB signaling, ↓ and cell growth in U251 and U343 cell lines.
Polyphenols	Hydroalcoholic extract	*Zataria multiflora*	↑ Radiosensitivity of A172 GBM cells.
Alkaloid	Tetrandrine	*Stephania Tetrandra S. Moore*	↑U251 and U87 cell lines radiosensitivity,↓ ERK signaling radiation, and growth of genes PCNA and CCND1; ↑G0/G1 cell cycle arrest;
Steroidal lactone	Withaferin A	*Withania somnifera*	↓ Tumor volume, ↓ MGMT, ↑ orthotopic xenograft mouse model median survival rate by 40%, ↓ cell proliferation; the resistance of tumor cell lines U251 TMZ, U87 TMZ, U138, and U251, U87 in a conc. dependent manner.
Phenols	Ferulic acid	Angelica Sinensis	↑ p53 apoptosis, ↓tumor growth.
Triterpenoid saponin	Ardipusilloside 1	Ardisia pusilla	Inhibits tumor growth and retains ADS-1 release for 36 days invitro in Higuchi kinetic model.
Alkaloid	Berberine	*Berberis aristata*	Induces senescence and ↓EGFR-RAF-MEK-ERK signaling. ↓Tumor growth in tumor xenografts exhibits significant cytotoxicity than TMZ in U118, U251, and U87 tumor cell lines.
Saponin	Saponin 1	*Anemone taipaiensis*	↓ Tumor growth in U87 and U251 xenografts in mice. ↓Survivin, XIAP, and Bcl-2/Bax activate caspase-9 &3 and induce apoptosis in U87 and cell lines.
Triterpenoid saponins	Ginsenoside RG3	*Panax ginseng*	↓Angiogenesis,↑ TMZ sensitivity, ↓ BCl-2, HUVEC, VEGF-A, and

			RG3.
Hydroxy isoflavone	Iridin	*Iris versicolor*	↓Intracranial development in G144 and U87 xenografts.
Sesquiterpenoid lactone	Tanacin	*Tanacetum huronense*	Inhibits U87 GBM cell line.
Flavonoid	Procyanidins (F1to F7)	cocoa beans, grape seeds and skin, apples, cinnamon	Inhibits U87 cells proliferation. Cause cell cycle arrest at G2/M. ↓ MMP. Inhibits angiogenesis and U251 cell invasion by ↓ HIF-1α mediated VEGF and MMP-2 expression. Inhibits formyl peptide receptor to prevent tumor angiogenesis and invasion.
Sesquiterpenoid lactone	Tagitinin C	*Tithonia diversifolia*	↓ Survivin
Napthoquinone epoxide	Diosquinone	*Diospyros mespiliformis Diospyros tricolor*	Exhibits cytotoxicity against p53. Inhibits cell proliferation.
Glucoside of tyrosol	Salidroside	*Rhodiola crenulata*	Inhibits Wnt/β-catenin and ↑ expression of the glial fibrillary acidic protein (GFAP). Induces glioma U251 cells cycle arrest at G0/G1 phase.
Xanthone	Cudraxanthone-I	*Milicia excelsa*	Inhibits the resistant U87 and U87 EGFRvIII tumor cell lines cell division.
Lactone	Sesquiterpene lactones	*Vernonia cinerea*	↓viability and inhibits STAT3 in U251 GBM cells.
Flavonoid	Rutin	*Dimorphandra mollis*	↓VEGF and TGF-β1 expression.
Marine Ascidian	Variolin B and Meridianins	*Aplidium meridianum*	Inhibits CDK action and cell division and stimulates apoptosis in GBM cells.
-	Crude extract	*Nardostachys jatamansi*	Inhibits U87 GBM cell proliferation.
Pentacyclic triterpenoid	Betulinic acid	*Betula pubescens Prunella vulgaris*	Induces apoptosis by p53 independent caspase - PARP cascade ↑ BAX, ROS, and DNA fragmentation.
Semi-synthetic derivative	Deoxypodophyllotoxin	*Dysosma versipellis*	Nanomolar concentration induces cell cycle arrest at G2/M in SF126 and U87 GBM cells. ↓ Cdc2, Cdc25C, and cyclin B1 in U87

			GBM cells. Induces apoptosis of U87 and SF126; ↓ MMP, ↓ the Bcl-xL, and Bcl-2 expression.
Red pigment	Brazilin	*Caesalpinia sappan*	↓ caspase -3 and 7, and ↑ PARP expression and proliferation. Induces apoptosis; shown arrest at cell cycle sub-G1 phase.
-	Thymoquinone	*Nigella sativa*	Inhibits proliferation of T98G, U87, and Gli36EGFRvIII.
Xanthone	γ-Mangostin	*Garcinia mangostana*	In conc. dependent manner inhibits proliferation and apoptosis of 8401 and U87 GBM cells. ↑ ROS, hypodiploid cells, and mitochondrial dysfunction.
Ribosome-inactivating proteins	Trichosanthin	*Trichosanthes kirilowii*	Inhibits the cell growth of U251 and U87 cells by decreasing the LGR5 and Wnt/β-catenin. Induces apoptosis in U87 cells.
-	Cactus	*Opuntia humifusa*	Cause G1 phase cell cycle arrest, ↑ROS, ↓ and The proliferation of U87 GBM cells.
-	Crude extract	*Celastrus orbiculatus*	Inhibits PI3K pathway. ↓ Viability of cells, adhesion, migration, and invasion of U251and U87 cells.
Bicyclic diterpenoid lactone	Andrographolide	*Andrographis paniculata*	Inhibits proliferation of U251 and U87 tumor cells. Induces cell cycle arrest (G2/M). ↓ Cdk1, Cdc25C, and PI3K/AKT/mTOR signaling pathway.
Bicyclic naphthoquinone	Plumbagin	*Droseraceae, Plumbaginaceae, and Ebenceae family members*	Induces DNA fragmentation, apoptosis, and cell cycle arrest. Modulates JNK, NF-kB, and Akt/mTOR, signaling pathways. ↓ Bcl2, surviving, E2F1 genes, MDM2, cyclin B1, ↑ caspase-3/7.
	Ethanolic extract	*Tinospora cordifolia*	Inhibits C6 rat glioma cells growth and U87 GBM cells.↓ MMP-9, NCAM and MMP- 2, and PSA-NCAM expression. Arrest cell cycle.↓ Bcl-xL, and cyclin D1.
Diterpenoid	Oridonin	*Rabdosia rubescens*	Inhibits RanGTPase activating protein. InducesU87 GBM cells apoptosis. Affected ncRNA.
Alkaloid	-	*Rhazya stricta*	Chemosensitizing activity
Coumarin	Osthole	*ripe cnidium*	↓ Growth, ↑ apoptosis, and ↑

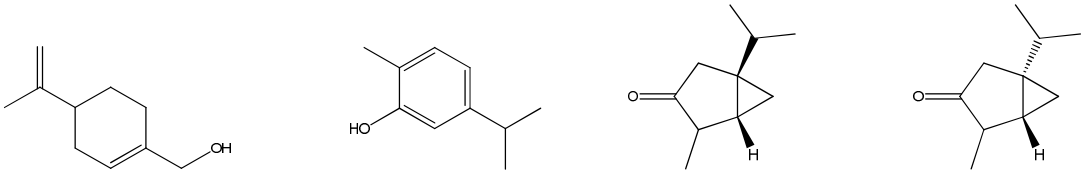
			microRNA-16 miRNA-16. ↓ MMP-9.
Terpene sterols	Cucurbitacins	*Cucurbitaceae family plants*	↑ Apoptosis and cell cycle arrest suppress JAK/STAT3 signaling pathways.
-	Chokeberry extract	*Aronia melanocarpa*	↓ Viability ↑necrosis.↓ mRNA levels, MMP-17, MMP- 16, MMP-14, and MMP-2.
Anthraquinone	Emodin	*Rheum palmatum, Polygonum cuspidatum, Polygonum multiflorum*	Inhibits tumor cell migration by AhR pathway. ↑ Apoptosis. Induced IL24. IL24. Inhibits cell division.
Lichens	Olivetoric psoromic acid	*Cladonia rangiformis Cladonia convolute*	Reduces U87 GBM cell viability by oxidative DNA damage.

Shan et al. summarized phytotherapy for GBM both in in-vitro and invivo studies. The daily consumption of one cup of coffee reduced the risk of GBM. Citrus extract - Nairingin minimized the post craniotomy pyrexia and allied inflammation in patients with GBM. Trigonella foenum graecum reduced metastases of tumor growth and volume and improved survival. The Toosendanin extract reduced the tumor size. Ashwagandha significantly reduced biofluorescent signal in all treated mice. Casearin X exhibited inhibition of growth rate in a dose-dependent manner. 15-alpha-methoxypuupehenol (Hyrtios) momentously decreased tumor volume and showed DNA fragmentation TUNEL scores in all treated mice. Fructus Ligustri Lucidi considerably reduced tumor volume in subjects. Dose-dependent reduction in cell proliferation rate and tumor volume observed with Apigenin extract. Coptis Chinensis reduces the tumor volume and increases patient survival.[44] Canthaxanthin alkaloids 4,5-dimethoxycanthin-6-one obtained from *Picrasma quassiodes* obstruct the chief transcription factor- LSD1-mediated epigenetic alterations, causing pyroptosis and apoptosis.[45] Nordihydroguaiaretic acid (NDGA) phenolic lignan displayed antioxidant activity by reducing the amount of the harmful protein content and ROS-damaged phenylalanine content [46]. Plumeria alba is a member of the Apocynaceae family that induces tumor cell death through early and late apoptosis [47].



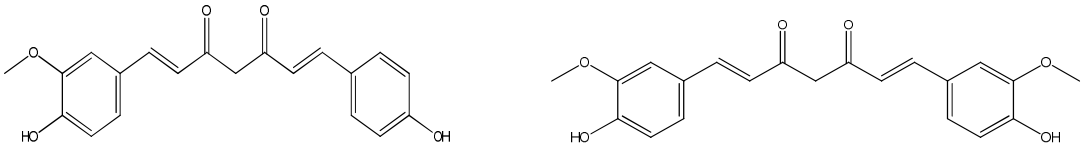
(9)-tetrahydrocannabinol cannabidiol JWH-133

Figure 6. Structures of cannabinoids

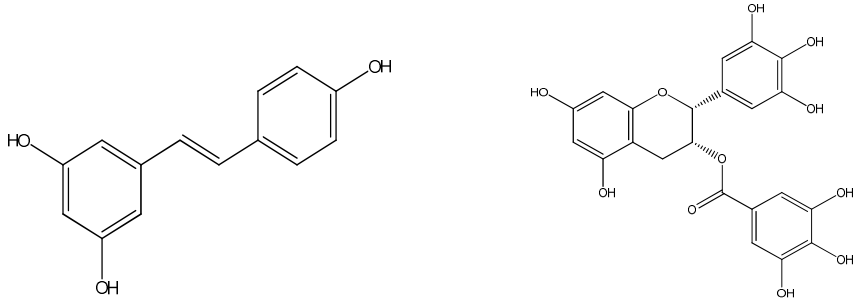


perillyl alcohol carvacrol α-thujone β-thujone

Figure 7. Structures of monoterpenes

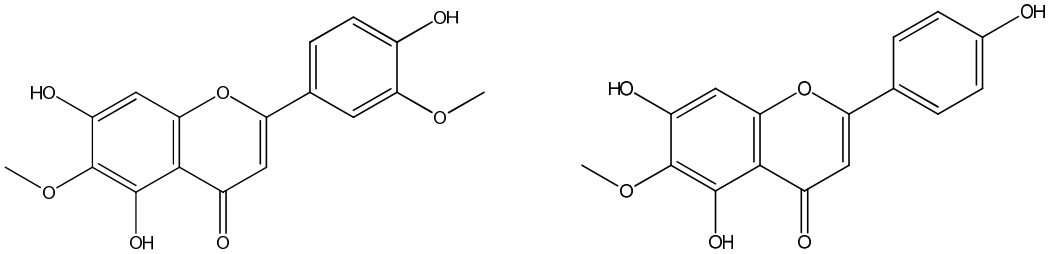


Demethoxycurcumin curcumin

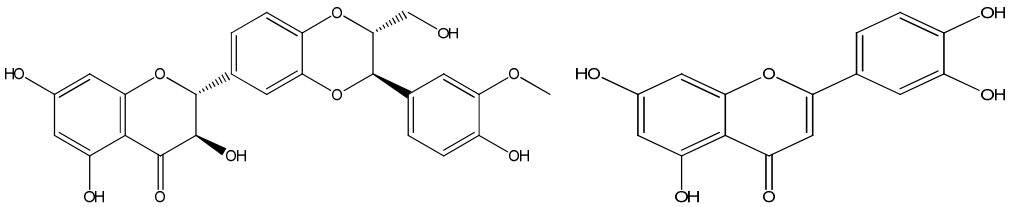


Resveratrol Epigallocatechin gallate

Figure 8. Structures of polyphenols



Jaceosidin Hispidulin



Silibinin Luteolin

Figure 9. Structures of flavonoids

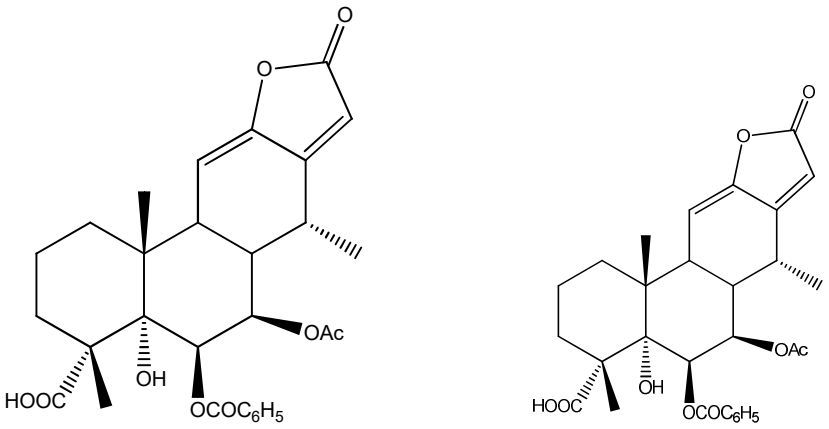


Figure 10. Pulcherritam A and Pulcherrimin G

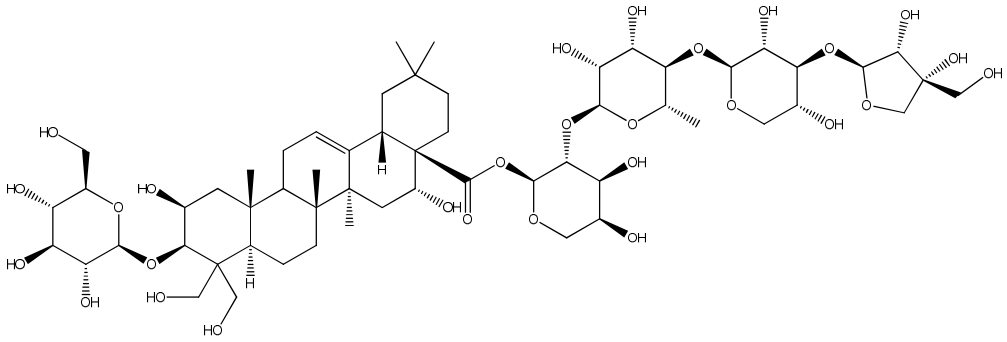


Figure 11. Platycodin D

12. Gene therapy

Researchers have developed LPLNP-PPT core-shell nanostructure for successful gene delivery and tracking, with +ve results. By encoding a TRAIL ligand to induce apoptosis of GBM cells. Though this study is under clinical trials, it has opened gates to clinical applications in stem-cell-based therapy [48].

13. Oncolytic virotherapy

Numerous viruses such as reovirus, poliovirus, adenovirus, and herpes simplex virus are being investigated in phase I and II clinical trials to treat GBM and have improved the quality of patients' lives [49].

14. Intranasal drug delivery

More effective and higher concentrations of drugs in the brain could achieve by intranasal drug delivery [50-51]. Investigated Perillyl alcohol aerosol effect on glioblastoma in Brazil under Phase I and II clinical trials. The outcome was encouraging [3,52].

15. Conclusion

Glioblastoma is a fatal and aggressive disorder of the central nervous system and brain. In recent years, none of the preexisting treatments had proven effective in treating glioblastoma, neither for its unrestrained proliferation, continuous angiogenesis, and ability to infiltrate healthy tissue. Chemotherapy with TMZ and radiation promotes cell cycle arrest and apoptosis of GBM cells. Therefore, therapies targeting the fundamental molecular mechanism may have significant prospective. This review summarized numerous therapeutic approaches that have emerged as novel alternatives to already established treatments; some compounds are investigated invivo, invitro, and targeted GBM microenvironment, whereas others are under clinical trials. Still, there is a need to develop potential drugs or methods targeting molecular mechanisms to combat resistance and minimize side effects by target specificity.

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