Exosomes Molecular Modifications for Drug Delivery: A Gleam of Hope in the Fight against Glioma

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ABSTRACT

Glioma treatment is constrained by two important factors: prompt and effective detection at commencement or recurrence, as well as drug entrance into the brain via the blood-brain barrier (BBB), which influences tumour growth. However, a safe BBB-crossing drug delivery system has given glioma treatment a new lease on life. Exosomes have a high cargo-loading capacity and the ability to pass across the BBB. They can also be given the power to send tailored messages. As a result, exosomes have a lot of promise as a targeted drug delivery vehicle. In this review, we discuss the most recent research on exosome-based drug delivery systems for cancer treatment, with a focus on the different types of exosomes used for delivering drugs. We also cover advancements in drug transport across the blood–brain barrier (BBB) and blood–brain tumour barrier, as well as progress in the development of new targeted drugs for glioblastoma (BBTB), and the limitations of currently available glioblastoma treatment, as well as the mechanism by which tumours become drug resistant. Finally, a model for the likely role of exosomes in delivering drug in glioma treatment is provided, based on knowledge of the most recent scientific research.

KEYWORDS

Glioma treatment; Blood-brain barrier (BBB); Drugs delivery; Brain metastasis; Exosomes

INTRODUCTION

Brain metastases are indeed a serious cancer side effect. Morbidity linked with brain metastasis is another critical problem, since patients with brain tumours have a significantly diminished quality of life [1]. As per research, around 20% of all cancer patients will eventually acquire brain metastasis [2-4]. It's worth noting that the occurrence of brain metastases in adult patients with renal cell carcinoma and colorectal cancer has risen dramatically in recent years, owing to advances in cancer therapy and diagnosis in general [5]. As patient survival improves and our capacity to detect and control metastases in other organs improves, the overall number of persons known to be living with metastatic brain cancer is projected to climb. As a result, studying brain metastases is critical for preventing future cancer-related morbidity and mortality. Gliomas are the most common primary brain and spinal cord tumours. They share histological properties with normal glial cells and are given names based on these similarities [6]. Gliomas are classified as malignancy classes based on histological and genetic characteristics, ranging from confined type I to diffusely infiltrating type II-IV, according to WHO criteria (2016) [7]. Glioblastoma
multiforme (GBM) is the most frequent and fatal kind of grade IV glioma. Surgical resection, chemotherapy, and radiotherapy are currently the standard GBM treatments, and they can improve the prognosis of low-grade gliomas to a degree [8]. High-grade glioma is one of the most destructive cancers that starts in the glial cells of the brain or spinal cord [9,10]. However, despite when many therapies are used, the median 5-year survival rate is just 3%-5% due to resistance mechanisms and low therapeutic penetrance to the tumour site due to hindering attributes of the blood-brain barrier (BBB) and blood-brain tumour barrier (BBTB) [11]. As a result, a novel class of drug delivery methods is urgently needed to efficiently circumvent the BBB and BBTB and deliver chemotherapeutics to glioblastoma [12]. The Blood brain barrier (BBB) is distinguished by its unique qualities of allowing central nervous system (CNS) to maintain homeostasis, which is critical for the CNS to execute precise neuronal action [13-15]. The major purpose of BBB is to provide protection from any infection and toxic agents by separating the brain from any form of connection with the rest of the body [16]. The confining character of BBB has become one of the reasons for drug delivery failure of drug delivery to Brain, as well as BBB contributing to functioning as an impediment by limiting the entrance of therapeutic pharmaceuticals, which provides a home for cancer cells [17-19]. Blood brain barrier system is made up of numerous blood arteries as well as tissue made up of tightly regulated cells that prevent dangerous from accessing the brain system. Several efforts are going on in order to achieve a method by which therapeutic drugs can be passed through BBB without facing any kind of restriction. Despite significant advances in our understanding of the mechanism of metastatic progression over the last few decades, metastasis remains the most perplexing aspect of cancer aetiology. The blood-brain barrier (BBB) and other components of the brain microenvironment shield tumour cells from immune surveillance, chemotherapeutics, and other potentially harmful substances, making the brain a haven for metastatic tumour growth. Three Extracellular vesicle have been reported to have the ability to diffuse through the BBB; however, our understanding of the mechanism that modulate the environment of BBB in order for them to dispersed into brain system is limited, and which types of extracellular vesicle can be used for therapeutics purpose is still being researched. Exosome is the most efficient at propagating into the BBB among three basic forms of extracellular vesicles. Because of their increasingly acknowledged physical and pathological roles, as well as their potential in diagnostic and therapeutic applications, exosomes have drawn great attention from both scientific disciplines and biomedical enterprises [20]. Exosomes have a tendency to move freely through the circulation and can access variety of tissues by avoiding variety of impediments. Because of their origin and propensity to duplicate the molecular contents of parent cells, Exosomes are in high demand [21]. Exosomes have been used to carry medications to the brain for long time, and many breakthroughs have been made. Many genes have been identified which mediate metastasis of cancer cells to the brains such as (ADAM8, cathepsin S, CEMIP, Angiopoietin-2 etc.), however no such genes have been identified that regulate the BBB, which is universal to all types of tumours [22-25]. It is critical to understand the underlying mechanisms involve in biogenesis of Exosome so that Exosomes can be employed to target the blood barrier in the treatment of the brain tumours in the near future. The goal of this study was to look over the literature and summarize what we know about exosome advancements in order to deliver therapeutic medications to patients with glioma, as well as to identify possible targets for preventive and therapeutic techniques and the role of exosomes in brain tumours. Exosome biogenesis in cancer Exosome secretion has emerged as an appealing therapeutic target because to the multiple ways exosomes
contribute to tumour growth, and it has been examined in a variety of circumstances. Exosomes are also thought to play a role in controlling communication between primary tumour cells and distant locations. Exosome secretion is necessary for the formation of invadopodia and invasive activity in breast cancer cells, which could help them exit the main tumour site [20]. Exosome biogenesis can occur via two separate pathways: ESCRT protein-dependent and ESCRT-independent. In early studies of exosome release, ceramide was discovered to be a regulator of exosome secretion. Ceramide is generated by neutral sphingomyelinase and is involved in endosome inward budding to form multivesicular bodies (MVBs) that contain exosomes [26]. Ceramide production has been linked to the secretion of exosomes by cancer cells in a number of different investigations [27-32]. Furthermore, at least one study demonstrated that ceramide is not required for exosome release [33]; as a result, it is unclear whether this pathway is a universal regulator of exosome secretion across all cancer types. The secretion of exosomes has been linked to a wide range of vesicle-trafficking genes. TBC1D10A is a protein that regulates Rab35 in oligodendrocytes to cause exosome extrusion [34]. Rab11 expression in K562 cells is associated with decreased exosome release and MVB interactions with autophagosomes [35]. In K562 cells, Rab11 appears to be necessary for 4 exosome release, although not for exosome secretion in HeLa cells. Rab27A and Rab27B stimulate the release of exosomes in HeLa cells. Rab27A regulates the size of MVBs, while Rab27B regulates their cellular position [36]. Rab27A/ B participation in exosome release has been validated in a variety of cancer cell types [20,37-39]. Rab27A regulates the stability of MVB docking sites in collaboration with cortactin and coronin 1b enabling the secretion of exosomes [39]. Furthermore, the involvement of Rab27A/B in exosome secretion is mostly based on in vitro investigations, and it is uncertain if Rab27A/B work in vivo in the same way. The tumor's microenvironment also influences exosome release. Tumor cells battle for nourishment, oxygen, and growth factors as the tumour grows, and as a result, they create survival mechanisms to deal with the stress. Exosome secretion has been suggested as a way for tumour cells to survive in stressful settings [40,41]. By establishing a secretory lysosome phenotype, a hypoxic microenvironment boosts exosome secretion. Exosomes released in hypoxic conditions have higher levels of STAT3 and FAS, that can be forwarded on to other tumour cells to enable them to grow and spread [42]. Exosomes from hypoxia-cultured glioblastoma cells also induce angiogenesis and tumor progression, possibly by transferring hypoxia-related RNAs and proteins [43]. The expression of PKM2 (Pyruvate Kinase M2) can regulate exosome release, implying a relationship between cellular metabolism and exosome secretion. Through phosphorylation of synaptosome-associated protein 23, PKM2 regulates exosome secretion. (SNAP-23) [44]. Exosomes are also transported from cancer-associated fibroblasts (CAFs) to affect cancer cell metabolism and promote glycolysis, perhaps influencing exosome secretion further [45]. Increased glycolysis and lactate build up in the extracellular environment are frequently associated with hypoxia in tumours, resulting in an acidic microenvironment. Exosome biogenesis is also influenced by intracellular pH, with acidic pH (pH = 6.0) boosting exosome secretion [46]. Exosome secretion, as well as exosomal protein and RNA, are reduced by alkaline pH [47]. In contrast; it has been shown that an acidic extracellular pH influences integrin activation. Integrins are important exosome uptake regulators [48]. As a result, exosome entrance into recipient cells may be influenced by the pH of the microenvironment. According to these findings, hypoxia stimulates the production of tumour cell-derived exosomes, which affect cell activity in the microenvironment. Exosomes in circulation are higher in tumor-bearing patients than in healthy patients, according to studies, implying that carcinogenesis is linked to
increased exosome release [49]. Exosome secretion is increased when oncogenic RAS is expressed in nontumorigenic epithelial cells [50]. Exosome secretion is increased when oncogenic EGFRvIII is overexpressed in glioma cells. These vesicles can be transmitted to additional glioma cells that lack EGFRvIII, resulting in oncogenic activity being transferred [51]. Why exosomes? Exosomes obtained from both healthy and diseased cells could be used as medication delivery vehicles, immunomodulators, and other applications despite their role in tumour progression and metastasis [52-54]. Exosomes is the messengers that allow cells to communicate with one another. Exosomes allow donor cells to transfer foreign molecules including proteins, mRNAs, microRNAs (miRNAs), and lipids to recipient cells. As a result, these naturally equipped nanocarriers have been used to carry drugs [55]. Exosomes derived from a patient's own cells offer superior biocompatibility and lower toxicity than synthetic medication carriers [56]. Exosomes have a variety of benefits over nanoparticles that have been synthesised. Due to membrane proteins like tetraspanin and fibronectin, exosomes have a greater biocompatibility and cellular absorption than ordinary liposomes and artificial nanoparticles and can be easily altered to fit target cells [48,57]. Exosomes, which resembles liposomes in shape and function, are more stable in body fluids. Liposomes, for instance, can be easily eliminated either directly or indirectly by macrophages or reticulo-endothelial cells [58], but exosomes are known to be exceedingly biocompatible due to their endogenous origin. The potential of Exosomes to enter tissues, disperse into the circulation, and even breach the blood-brain barrier is their most promising feature (BBB) [59]. Exosomes have also been demonstrated in multiple studies to elude the immune system and extend circulation time in the body [60-62]. Exosomes can also be genetically modified. Exosomal surface protein engineering confers cell and tissue selectivity. Although, many researchers are interested in using exosomes as drug delivery vehicles.

**Figure 1:** Exosome's influence in glioma advancement.

Exosomes are a valuable addition to the complex mix of metabolites, growth factors, cytokines, and ions produced by tumour cells [63]. Exosomes have been shown to transport histones, oncogenic species (EGFRvIII), non-coding RNA (miRNA), and tumour suppressors (PTEN) in
glioma cells [51,64-66]. Glioma cells produce exosomes, have been linked to a variety of events in the tumour microenvironment, including the transfer of functional RNA transcripts [67]. Exosomes from GBMs may potentially influence the immunological activities of the tumour microenvironment by altering immune cells' phagocytic capacity, as well as changing cell surface protein expression and cytokine production [68,69]. The extraordinarily invasive nature of GBM, as previously mentioned, is a major contributing factor in its likelihood of recurrence following surgical intervention, prompting investigation into the molecular reasons of this potent invasiveness [70]. Over the last 10 years - 15 years, researchers have discovered that various types of tumour cells with high invasive or metastatic potential have the ability to create invadopodia structures [71-74]. Exosomes have recently been demonstrated to mediate multiple phases of the invadopodia lifecycle, including their production, stability, and exocytosis of matrix degrading proteinases [20]. Exosomes can also help modify the microenvironment by switching the phenotype of nearby support cells to one that encourages tumour growth and invasion. Exosomes released by mesenchymal cells can assist tumour growth when cells are incubated with them. Exosomes originating from mesenchymal cells not only impaired normal support cells (astrocytes), but they also caused phenotypic abnormalities in the other molecular subtypes of GBM present. [68]. Angiogenesis is a crucial step in glioma growth, and GBM-derived exosomes contain multiple angiogenic factors that promote angiogenesis [75,76]. Tetraspanins preferentially feed proteins and mRNA to exosomes to mediate information flow between exosomes and vascular endothelial cells, hence boosting angiogenesis [77]. Glioma secrete a range of 6 angiogenic factors, the most common of which is epidermal growth factor receptor variant III [EGFRvIII]. Through a phosphatidylserine-dependent mechanism, the EGFRvIII can be "shared" across glioma cells via the intercellular transfer of exosomes [51]. Exosomes are important in tumour cell adaptation to hypoxia, which is linked to angiogenesis, tumour development, and metastasis. Hypoxia is a feature of the GBM microenvironment, influencing the transcriptome and proteome of tumour cells [76]. Thus, it modifies the protein content of GBM cell-derived exosomes in both a qualitative and quantitative manner by influencing the physiological activity of neighbouring or distant cells. The protein cargo in exosomes has different effects on the expression of different genes. The hypoxic condition of glioma cells is replicated in their cargo [43]. According to King et al., cancer cells respond to hypoxia by increasing the secretion of exosomes into the microenvironment, which increases their survival and invasiveness [78]. Furthermore, tumour growth in normoxic zones is aided by the exosomes produced by hypoxia cancer cells [79]. Exosomal miRNA content and release are regulated by hypoxia [80,81]. Under hypoxic conditions, GBM-derived exosomes have heightened autocrine and pro-migratory activities. Hypoxic exosomes are thus important for tumour vascularization, pericyte vessel coverage, and GBM cell proliferation [43]. Exosomes govern glioma cell proliferation and invasion, which are critical for glioma cell survival and recurrence [82]. Exosomes, which may export medicines from tumour cells, play a crucial role in glioma therapy resistance [83]. Exosomes can cause fibroblastic responses, which operate as a barrier to anticancer medicines by promoting the production of fibroblasts. Exosomes, on the other hand, can use biomolecules like the miRNA to turn drug-sensitive tumour cells into drug-resistant tumour cells [84,85]. In this light, exosome transport intercellular mechanisms can be considered a potential contribution to glioblastoma growth and biogenesis. Understanding the pathways through which exosomes are implicated in the evolution of GBM has established the framework for exploring a variety of potential clinical uses, ranging from prognostic
indications to targeted therapy. Exosome investigation in GBM is advancing in at least four therapeutic directions, with preclinical studies for brain tumour specific applications in: (i) employing exosomes as biological markers and in clinical diagnosis; (ii) hindering various signaling pathways by targeting exosomes; (iii) seeking to exploit exosome targeting and uptake systems that facilitate delivery of molecular or pharmacological therapeutics; and (iv) establishing cancer vaccines.

Figure 2: Structure of GBM derived exosomes.

Despite substantial breakthroughs in drug delivery, delivering anti-cancer drugs to the brain including central nervous system (CNS) illnesses remains a serious issue. The BBB is made up of neurons, astrocytes, pericytes, the endothelial basement membrane, and neighboring microvascular endothelial cells (BMECs). Tight junctions (TJs) and adherent’s junctions (AJs) are found in the brain endothelial cells and serve an important function in regulating paracellular permeability [86]. Most molecules are blocked at these junctions, which illustrate 7 the BBB's changing properties as situations change, with the exception of those needed for homeostasis, such as feeding or bidirectional hormonal communication [87]. The BBB is a key impediment to effective and precise brain medication delivery. It makes drug transport from the bloodstream to the brain parenchyma extremely difficult [88]. To begin with, the BBB's tight connections dramatically decrease ion and other hydrophilic material absorption through the intercellular space, producing a "physical barrier". Second, the "transport barrier" helps to remove metabolic wastes and other foreign chemicals from the brain parenchyma and convey them to the circulation. Furthermore, majority of hazardous chemicals are eliminated by extracellular and intracellular enzymes in the brain parenchyma, forming an "enzymatic barrier" [89]. Exosomes offer substantial benefits in terms of bypassing the BBB due to their small size and endogenous features. Exosomes can penetrate or bypass the BBB with or without surface change in vivo and in vitro, according to new findings. Various forms of natural exosomes can cling to or be picked up by various cells. Exosomes' natural targeting capacity is dependent on the components of
Exosomes as well as the recipient cells' physiologic state. Experiments have indicated that under some conditions, certain types of natural exosomes can cross the BBB, according to a growing body of research. Internalization and functional activity of cancer cell exosomes were mediated by cell surface receptors such as HSPGs [90]. The key mechanism for enabling exosome to cross the BBB was proposed to be the interaction between exosome surface ligands and receptors on brain endothelial cells. Exosomes can also gain access to the brain by crossing the cerebrospinal fluid-brain barrier in the choroid plexus, in addition to the BBB-crossing entrance pathway [91]. These methods could possibly allow exosomes to pass across the BBB. Apart from natural exosome, modified exosome can also cross the BBB, by means of Receptor mediated transcytosis which is a naturally occurring approach that aids in the promotion of exosomes to overcome the BBB.

A scientist combined methotrexate (MTX) with exosomes that were functionalized with therapy by targeting the low-density lipoprotein receptor, which is a BBB receptor, to construct a treatment for glioblastoma multiforme. The peptide LDL facilitated both exosome extravasation across the BBB and drug accumulation in glioma sites, according to the study [92]. Transfecting progenitor cells with a fusion gene that encode a brain focused peptide along with a marker-encoding gene of exosomal protein results in exosomes enriched with the fusion protein and able to cross the BBB [93]. Because the transportation routes of EVs are unclear, the influence of EVs on ECs is also unknown. Five theoretical paths have been highlighted to date to characterize the interaction between EXOs and the receiving cell, with a focus on EXO [94]. The blood–brain barrier, which serves as a highway for EXOs, is potentially a freeway. The following are five routes for EXOs interacting with a receiving cell that have been described. (I) interaction with a cell surface protein G-coupled receptor, resulting in a signaling cascade; (II) EXOs are released into the cytoplasm after attachment and fusing to the cell surface, which can result in a variety of activities, including cell signaling. (III) macropinocytosis is a form of endocytosis that involves the nonspecific uptake of extracellular substances. (IV) It enters the cell through 8 endocytic pathways and is stored in the MVB via receptor-mediated transcytosis (V) nonspecific/lipid raft. No evidence of EXOs crossing the BBB via the paracellular route has been found. Exosome involvement in Brain metastasis Exosomes were once thought to be a way for cells to get rid of extra proteins [95,96]. However, there has been a significant advancement in the study of exosomes in recent decades, and it has now been established that these EVs play a vital role in intercellular communication, which is critical in the context of tumour progression and metastasis [97-99]. According to one recent study, exosomes generated from SK-Mel28 melanoma cells were taken up by a non-random process that relied on transmembrane proteins in human brain capillary endothelial cells (hCMEC/D3) [100]. Recent research has revealed that the successful growth of brain metastases is dependent on a complex intercellular communication mechanism that involves secreted proteins or small vesicles called exosomes that happens between metastatic cancer cells and brain stroma cells [101,102]. The involvement of multiple mechanisms by which exosomes can affect brain colonization by cancer cells in a malicious way demonstrates the significance of an enormous intercellular communication network that can be used as a target for therapeutic strategies perhaps as inspiration for novel drug delivery strategies. While confronting metastasis formation, it is vital to examine the TME's influence, as its dynamic nature allows tumour cells to alter their own habitat. According to emerging research, it is revealed that tumour derived exosome (TDEs) and exosomes generated by TME stromal cells are critical in tumour development, angiogenesis, invasion, survival, and metastasis formation [103,104]. Indeed, when attempting to define the involvement of exosomes in the creation of
brain metastases, the most crucial and exciting phase may be the transmigration of the BBB and subsequent brain parenchyma colonization by cancer cells. However, Tumor cells must first lose their adherence to the surrounding stroma and enter the bloodstream before reaching that stage in the metastatic cascade [105,106]. The TME initiates the metastatic cascade by activating the EMT process in neoplastic epithelial cells [105]. Cells undergoing EMT downregulate epithelial markers like cytokeratin and E-cadherin while upregulating mesenchymal markers like N-cadherin and vimentin [107]. Furthermore, when compared to those produced in a normoxic state, exosomes secreted during hypoxia, which has been linked to EMT and a high risk of metastasis, are richer in EMT inducers [105]. Exosomes produced from cancer-associated fibroblasts (CAFs) delivered miR-92a-3p to colorectal cancer cells, stimulating the Wnt/-catenin signalling pathway and triggering EMT [108].

![Diagram](image)

Figure 3: The following diagram depicts both stages of the metastases formation process with tropism to the brain: establishment of the tumour microenvironment (TME) and the pre-metastatic niche (PMN)/metastasis in the brain. TDEs are responsible for numerous critical TME processes, such as epithelial–mesenchymal transition (EMT) and angiogenesis, which enhance tumor progression, infiltration, survival, as well as metastatic development. During this stage, exosomes can also promote endothelial barrier permeability, enabling cancer cells to more effectively enter the bloodstream. Exosomes from cancer cells trigger a plethora of alterations in the brain that contribute to PMN formation, including BBB permeability, metabolic and immune response modulation, and vascular co-option induction, which helps circulating tumour cells invade the brain parenchyma, generate metastases, and survive. Brain metastasis is aided by crosstalk between cancer cells and BBB cells such as astrocytes. Because of their critical involvement in metastasis formation, exosomes could be a potential target for metastatic cancer therapy using exosome production inhibitors. Extracellular vesicles, on the other hand, have been explored as biomarkers for the diagnosis and prognosis of metastatic cancer, as drug delivery systems (DDS) vehicles, and as cell-free therapeutic tools in anti-tumor vaccination.

Breast cancer cells release exosomes, which activate the Wnt ligand Wnt5a in macrophages. Macrophages are then in charge of transporting Wnt5a to tumour cells, boosting their invasion [109]. Exosomes secreted by mesenchymal stem cells (MSCs)-derived adipocytes, on the other hand, were able to trigger EMT in breast cancer cells via the
Hippo pathway; additional research suggested that activation of the Hippo pathway could be caused by the transfer of exosomal miRNAs or proteins [110-113]. A typical lymphatic system does not exist in the brain. In order to infiltrate this metastatic location, circulating tumour cells (CTCs) must cross the BBB and populate the brain parenchyma [114]. As a result, BBB transmigration is a crucial step in the metastization to the brain process [115]. Once cancer cells have crossed the BBB, they enter the brain parenchyma, where they may benefit from the metastatic niche's extensive intercellular communication network [116]. Several attempts have been made to characterize the role of exosomes in the process of cancer cells transmigrating over the BBB. Tominaga et al. found that EVs, including exosomes, released by brain metastatic derivative (BMD) cell populations chosen from breast cancer cells MDA-MD-231-luc-D3H2LN transmitted miR-181c to brain endothelial cells, resulting in increased BBB permeability (Figure 3).

The disruption of intercellular junctions caused by a shift in the position of tight junction proteins -Claudin-5, Occludin, and ZO-1-N-cadherin, and actin filaments was shown to cause BBB collapse [115]. Kinjo and colleagues recently added to the evidence of exosomes contributing to BBB breaching by showing that precursor B acute lymphoblastic leukemia (BCP-ALL) blasts release exosomes into the blood, and that exosomes derived from BCPALL cells allowed leukemia cells to transmigrate through cultured endothelial monolayers [117]. The capability of CTCs to make contact with and proliferate along brain endothelial cells, known as vascular co-option, has also been linked to the metastization process [24,118]. The function of exosomal cell migration-inducing and hyaluronan-binding protein (CEMIP) in brain metastization by breast cancer cell was found by Rodrigues and colleagues. Brain-tropic breast cancer cells release CEMIP-enriched exosomes, which improve vascular cooption and, as a result, successful invasion and metastatic colonization of the brain. Exosomal CEMIP is also implicated in molecular pathways of brain endothelial cells and microglia that are linked to the formation of brain metastases, according to in vivo investigations [24]. What's wrong with conventional Glioma Treatment? Notwithstanding breakthroughs in diagnostic techniques and comprehensive treatment, all GBM patients eventually have tumour growth and nearly all die. Surgical excision of the majority of the tumour mass is now conventional treatment, followed by radiation therapy and long-term temozolamide (TMZ) therapy [119]. Despite the fact that this combinatorial technique has increased patients' progression-free survival time, overall survival has remained essentially unaltered [120].

Supplemental medicines, such as the novel MGMT inhibitors, have been explored in preclinical studies, however these inhibitors have a high risk of inactivating DNA repair mechanisms in healthy cells [121,122]. This has been attributed to the surviving tumour cells gaining resistance to TMZ by increased production of the O6methylguanine DNA methyltransferase (MGMT) [123-125]. Administering bevacizumab in combination to TMZ, in a different strategy, has indeed resulted in a prolonged disease-free timeframe, suggesting that other resistance mechanisms are quickly engaged [126,127]. The current treatment procedures endure a number of significant obstructions. The difficulty of establishing uniform therapy is exacerbated by genetic variation at both the intertumoral 10 and intratumoral levels [128]. Furthermore, the tumor's aggressive nature precludes surgery as a therapy option. Because tumour tissues have already expanded into surrounding healthy tissues, even high-precision Gamma Knife (radiosurgery) technology will not be able to completely eliminate malignant tissues [129]. The presence of the brain's inherent physiological barrier, the blood–brain barrier (BBB), obstructs the systematic transmission of medications to brain tumour locations, lowering chemotherapy's overall efficacy [130,131].
As a result, glioma treatment has tragically evolved into a question of purchasing more time for the patient to live rather than genuinely healing the patient. It is critical to devise a new strategy that will ultimately lead to the cure of the disease rather than simply acquiring additional time for the patient to survive. To improve a drug's therapeutic efficacy while reducing off-target effects, the drug molecules must concentrate in the affected area(s) in a controlled manner over a lengthy period of time. Despite significant advances in therapeutic technology, the BBB continues to obstruct the flow and accumulation of drugs from the blood to the tumour zone following surgical resection, offering a challenge. As a result, a new drug delivery system that can overcome the barrier and function effectively must be developed. Drugs currently used to treat GBM & underlying mechanism of resistance to them. One of the most significant barriers to successful cancer treatment is drug resistance. Exosomes have been demonstrated to be beneficial in treating cancers that are resistant to drugs. Temozolomide (TMZ) Temozolomide (TMZ), a prodrug that methylates DNA at the O6 position of guanine, is now one of the most effective chemotherapeutic drugs for GBM [132].

TMZ lowered Notch3 levels, which are elevated in gliomas, through activating CHAC1, according to transcriptome microarray and bioinformatic analysis. Because CHAC1 binds to the Notch3 protein and prevents it from activating, CHAC1-inhibited Notch3 signaling can affect TMZ-mediated cytotoxicity [133]. GBM becomes resistant to alkylating medications when phosphoinositide 3-kinase (PI3K) signaling is activated [134]. Small noncoding RNAs, like as miRNAs, have been demonstrated to play a role in TMZ resistance. Because its levels are adversely related with MGMT gene expression, miR-181d could be a possible measure of TMZ resistance in GBM [135]. It was discovered that epithelial-to-mesenchymal transition (EMT) is linked to poor TMZ responses using a gene set enrichment analysis (GSEA). Furthermore, miR-140 suppresses the mesenchymal transition and increases temozolomide cytotoxicity in GBM through targeting cathepsin B (CTSB) signaling [136].

In glioma cell lines, overexpression of FAM289 has recently been discovered to contribute to tumour growth. The association of FAM289 with galectin-1 enhances its entry into the nucleus, where it stimulates the extracellular signal-regulated kinase (ERK) pathway, upregulates DNA methyl transferase 1 (DNMT1) expression, and generates the CSCs 11 phenotype, which leads to TMZ drug resistance in glioma cells [137]. The activation of the transcription factors JUN and CEBPB is linked to cancer, while HDAC3 is linked to cell cycle suppression. The Jun proto-oncogene (JUN), transcriptional factors CCAAT/enhancer binding protein beta (CEBPB), and histone deacetylase 3 (HDAC3) were all shown to be implicated in the drug-resistant phenotype of hypoxia GBM cells in the transcriptome of hypoxic GBM cells [138]. It was discovered that honokiol boosted the effects of TMZ on GBM cell autophagy and apoptosis [139]. As a result, a better knowledge of the mechanisms underlying intrinsic TMZ resistance should aid in the creation of new anticancer medicines or adjuvant therapies to improve treatment outcomes.
Other drugs various therapy techniques can be employed to treat glioblastomas, but each has its own set of limitations (Figure 4). Because of its essential function in GBM metabolism, the fatty acid oxidation (FAO) inhibitor Perhexilene could be a viable treatment medication. Perhexilene caused significant oxidative stress and apoptosis in GMM cells in vitro [140]. In the treatment of GBM, EGFR kinase inhibitors (erlotinib, gefitinib) are employed, however only 10% - 20% of patients respond. EGFR is typically increased, overexpressed, or mutated in glioblastomas, as previously stated [141]. Through the MAPK, phosphoinositide 3-kinase (PI3K)/AKT, and NF-B signalling pathways, the glioma cell line U-87 MG and patient-derived CSCs were made more sensitive to therapy-induced senescence by combining the pan-adenosine triphosphate-binding cassette transporter and L-type voltage-dependent calcium channel inhibitor verapamil with carbustine and irradiation [142]. A number of potential medications have showed promise in in vitro or in vivo research, but their molecular mechanisms of action have yet to be studied, thus any predictions are premature. SP-141 was discovered to be cytotoxic for GBM cells due to decreased MDM2, elevated levels of p53 and p21cip1, arrest of the G2/M cell cycle, and severe apoptosis [143]. Sulforaphane (SFN), a compound found in cruciferous vegetables, was found to cause apoptosis in tumour tissues. Cysteine (SFN-Cys) has been added to this molecule to increase its half-life and consequently plasma enrichment [144]. The long-term activation of ERK1/2- and ERK1/2-mediated signalling pathways, such as the activation of caspase 3 and proteins associated with apoptosis, is required for the induction of cell apoptosis by this SFN-Cys. The curaxin CBL0137 upregulated p53 and downregulated nuclear factor-kappa B (NF-B) and Facilitates Chromatin Transcription by inactivating the chromatin remodelling complex (FACT) [145]. BEV is a VEGF-targeting monoclonal antibody that is used as a monotherapy or in combination with a secondary drug in the treatment of GBM [146]. A meta-analysis conducted by Diaz RJ et al. [147] based on 52 relevant studies of BEV found that while BEV could prolong PFS and OS in recurrent GBM patients either alone or in combination with cytotoxic agents, the survival advantage was limited to 4 months and there was no significant difference in survival.
in the primary setting. BEV would also have a number of serious side effects, as well as the loss of the ability to use other therapeutic options. In vivo and in vitro studies, several other medications are increasingly incorporated into a variety of therapeutic pharmaceuticals or theranostics for glioblastoma. Table 1 listed out all the drugs currently undergoing clinical trials for Glioma treatment.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Target</th>
<th>Mechanism</th>
<th>Clinical Trial Phase</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzastaurin</td>
<td>target both PKC and PI3K/AKT pathways</td>
<td>suppress proliferation and tumor-induced angiogenesis</td>
<td>Phase III</td>
<td>[148,149]</td>
</tr>
<tr>
<td>Cilengitide</td>
<td>αvβ3 and αvβ5 integrin inhibitor</td>
<td>showed a PFS as well as an OS benefit</td>
<td>Phase II</td>
<td>[150]</td>
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<tr>
<td>Cediranib</td>
<td>vascular endothelial growth factor receptor (VEGFR)</td>
<td>tyrosine kinase inhibitor</td>
<td>Phase III</td>
<td>[151]</td>
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<tr>
<td>Everolimus</td>
<td>rapamycin (mTOR) inhibitor</td>
<td>restrict cell growth and proliferation, effective in reducing the volume of subependymal giant cell astrocytoma’s</td>
<td>Phase III</td>
<td>[152]</td>
</tr>
<tr>
<td>Nimotuzumab</td>
<td>Epidermal growth factor receptor (EGFR)</td>
<td>Reduce oncogenesis and progression.</td>
<td>Phase III</td>
<td>[153,154]</td>
</tr>
<tr>
<td>Regorafenib</td>
<td>tyrosine kinase inhibitor</td>
<td>illustrates angiogenesis and other tumor-driven pathways, such as vascular endothelial growth factor receptor (VEGFR) 1-3, PDGFR, fibroblast growth factor receptor (FGFR), the angiopoietin receptor TIE-2, tyrosine kinase receptors, receptor tyrosine kinase genes, leukemia factor 1, the BRAF gene and other protein kinase activities</td>
<td>Phase II</td>
<td>[155,156]</td>
</tr>
<tr>
<td>Borteomib</td>
<td>NF-κB pathway, cell cycle and apoptosis</td>
<td>inhibits cell adhesion, angiogenesis and cytokine-mediated intercellular communication, affects chemotherapy, increasing the sensitivity of tumors to chemotherapy</td>
<td>Phase II</td>
<td>[157]</td>
</tr>
<tr>
<td>Marizomib</td>
<td>proteasome inhibitor</td>
<td>blood-brain barrier permeability and obviously prolonged the survival time of animals with glioma</td>
<td>Phase II</td>
<td>[158]</td>
</tr>
<tr>
<td>Vemurafenib</td>
<td>Inhibitor of the V600E mutation</td>
<td>prevent the occurrence and progression of tumors to a certain extent</td>
<td>Phase II</td>
<td>[159]</td>
</tr>
<tr>
<td>Onartuzumab</td>
<td>anti-MET pathway drug</td>
<td>Inhibit tumor proliferation, survival and metastasis</td>
<td>Phase II</td>
<td>[160]</td>
</tr>
<tr>
<td>APG101</td>
<td>bind to CD95L</td>
<td>blocks CD95L and can inhibit the effects of the binding of CD95 and CD95L</td>
<td>Phase II</td>
<td>[161]</td>
</tr>
</tbody>
</table>

Table 1: List of drug employ for glioma treatment and their clinical trial phase.

Twelve Exosome as an inspiration for drug delivery. Exosomes' nanoscale capabilities have been employed in a rising number of studies to fully leverage the exosome potential in therapeutic applications and to encapsulate and distribute bioactive chemicals such as small molecules (anticancer drugs), proteins, and miRNAs [162]. Membrane decorated Exosome for drug delivery. Exosomes are extracellular vesicles (EVs) that emerge from multivesicular bodies and therefore are not identified by the complement system, consequently they do not elicit unfavorable immunological responses. Exosomes, despite being natural vehicles, can have their surface altered. The objective of surface engineering is to confer cell type targeting specificity. Because the ideal drug delivery system should be able to deliver integrated therapeutics to specific sites while avoiding detection and early
degradation by the body's immune system, as well as regulated cargo molecule release in response to certain stimuli. Nanoscale medication delivery technologies have grown in popularity in recent years. Numerous nano-based medicine formulations have been designed to optimize the therapeutic efficacy of chemical and biomolecular treatments. Exosomes have sparked a lot of research interest since they were identified to serve as intercellular communication systems that deliver cargo to destination cells [163]. Furthermore; they show no long-term accumulation in any organ or tissue, as well as modest systemic toxicity and cellular uptake facilitation [164]. Exosomes can be modified using two approaches: genetic engineering and chemical alterations. Both approaches have their own limits. Chemical modification enables the display of a wide range of natural and synthesized ligands via crosslinking or lipid assembly. On the other hand, the use of genetic engineering to show peptides and proteins on the surface is effective. Crosslinking processes done by via chemical modification can irreversibly as well as firmly modify exosomal surface proteins, although overall efficiency is restricted by the intricacy of the exosome surface, and they typically lack site specificity control and the vehicles normal functioning could also be jeopardized by covalent alteration. Using genetic engineering, we can fuse the gene sequence of a guiding protein or polypeptide with that of a specific exosomal membrane protein. However, it is confined to targeting genetically encodable motifs [165]. Exosome genetic engineering is a convenient way for giving exosomes new features. To begin, ligands or homing peptides are coupled to transmembrane proteins produced on exosome surfaces. Donor cells that have been transfected with plasmids encoding the fusion proteins then produce modified exosomes with targeting ligands on their surfaces. Exosomes can be coupled with a pH-sensitive fusogenic peptide and a cationic lipid for cytosolic distribution [166,167]. Exosomes can also be engineered with PEG and AA for lung metastasis and medication delivery [168,169]. Metal-organic frameworks (MOFs) have gained popularity among academics over the last two decades due to their interesting topologies, excellent crystallinity, outstanding porosity, and diverse modularity that may be used in a variety of sectors [170]. Table 2: update on engineered exosome for drug delivery purpose to treat cancer. 13 Drug delivery using Exosomes The permeability of the BBB is a significant barrier to the administration of chemotherapeutic medicines. Exosomes have features that make them suited for treating CNS tumours, and exosome-based combination medicines can address some of the problems with current GBM treatments [185,186]. Exosome-mediated transfers of lipophilic and hydrophilic medicines, such as curcumin [187] and doxorubicin [171], have been shown in previous investigations to not induce unfavorable immunological responses and are not recognized by the complement system. Temozolomide (TMZ) is a first-line anticancer medication that is commonly used in the treatment of GBM [188,189]. However, the alkylation damage induced by TMZ at the O6 position of DNA guanine can be repaired by O6-alkylguanine-DNA alkyl transferase (AGT), rendering tumour cells resistant to TMZ [190-195]. The combination of TMZ with BG20 reduces the maximum tolerated dose of TMZ, yet BG is not extensively utilized in anti-GBM therapy due to its side effects, which include liver toxicity, myelosuppression, pulmonary fibrosis, and poor BBB penetration [196,197]. To address these issues, a dual-receptor-specific exosome loaded with TMZ and BG (dubbed EXO-An2-AptTMZ and EXO-An2-Apt-BG) has been developed for the first time to maximize systemic TMZ and BG brain delivery for GBM treatment [198]. To conjugate exosomes with drugs, three techniques are used: incubation, which is the simplest method; electroporation, which involves the penetration of exosomes using short, high-voltage pulses; and sonication, which involves the loading of drugs (such as paclitaxel) into exosomes using effective sonication [199-201]. M. Zhuang et al.
administered exosomes containing the STAT3 inhibitor cucurbitacin I to mice with GBM through nasal, resulting in extending their survival from 20 days to 44.5 days without experiencing any negative consequences or behavioral problems [202]. Yang et al. [186] found that when anticancer medications were delivered by brain ECs-derived exosomes, the fluorescence intensity of xenotransplanted zebrafish cancer models and tumour development markers decreased. STAT3 is a protein that is found in a variety of cancers, including GBM. Exosomes have been found to contain hydrophilic and hydrophobic chemotherapeutic drugs such as Dox and PTX. Exosome-mediated chemotherapeutic administration has been established in a growing number of studies to improve anticancer efficacy [203-206]. Dox is a highly effective anticancer medicine that is used to treat leukemia, lymphoma, and a variety of solid tumours. However, due to their poor biocompatibility and substantial adverse effects such as bone marrow suppression and cardiotoxicity, Dox’s clinical application is restricted. Exosomes generated from mesenchymal stem cells have recently been found to improve the cellular absorption rate and anticancer efficacy of Dox in osteosarcoma patients [207]. PTX is another anti-mitotic drug commonly used to treat malignant tumours like glioblastoma multiform and breast cancer [208]. PTX, on the other hand, has a dose dependent toxic effect and limited absorption, making it challenging to use in practice. In 14 numerous trials, PTX was likewise discovered to be unable to cross through the BBB [209-211]. Furthermore, cancer-derived exosomes containing PTX may be able to directly target drug-resistant cancer stem cells, resulting in improved cytotoxicity against autologous cancer cells [212].

<table>
<thead>
<tr>
<th>Therapeutics cargo</th>
<th>Target</th>
<th>Target cells</th>
<th>Function</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRAS siRNA</td>
<td>iRGD peptide</td>
<td>adenocarcinoma, human alveolar basal epithelial cells (A549)</td>
<td>Target oncogenic KRAS</td>
<td>[171]</td>
</tr>
<tr>
<td>DOX</td>
<td>iRGD peptide</td>
<td>breast cancer</td>
<td>Targeted delivery of DOX</td>
<td>[172]</td>
</tr>
<tr>
<td>SOX2 siRNA</td>
<td>Tlyp-1</td>
<td>non-small cell lung cancer, A549 stem cells</td>
<td>Gene delivery for cancer therapy</td>
<td>[173]</td>
</tr>
<tr>
<td>imatinib, BCR-ABL siRNA</td>
<td>IL-3</td>
<td>chronic myelogenous leukemia cells (LAMA84, K562, K562R)</td>
<td>Inhibit cancer cell growth</td>
<td>[174]</td>
</tr>
<tr>
<td>5-fluorouracil antimiRNA-21</td>
<td>zHER affibody</td>
<td>colorectal cancer (HCT-116)</td>
<td>Reverse chemoresistance and improve cancer treatment efficiency</td>
<td>[175]</td>
</tr>
<tr>
<td>Tpd50 siRNA</td>
<td>DARPin</td>
<td>HER2-positive cells (SKBR3)</td>
<td>HER2-positive cells (SKBR3)</td>
<td>[176]</td>
</tr>
<tr>
<td>miRNA-let7a</td>
<td>GE11 peptide</td>
<td>breast cancer (HCC70)</td>
<td>Target EGFR-expressing tumor</td>
<td>[177]</td>
</tr>
<tr>
<td>Smart-exos</td>
<td>αCD3/αEGFR</td>
<td>T-cells (Jurkat), EGFR-positive breast cancer (MDA-MB-468)</td>
<td>Cell-free cancer immunotherapy</td>
<td>[178]</td>
</tr>
<tr>
<td>miRNA-26a</td>
<td>ApoA-1</td>
<td>hepatocellular carcinoma (HepG2)</td>
<td>Suppress tumor cell migration and proliferation</td>
<td>[179]</td>
</tr>
<tr>
<td>curcumin-SPION</td>
<td>neuropilin-1-targeted peptide</td>
<td>glioma (U251)</td>
<td>Simultaneous diagnosis and treatment of glioma</td>
<td>[180]</td>
</tr>
<tr>
<td>PTX</td>
<td>AA</td>
<td>murine lung cancer (3LL-M27), sigma</td>
<td>Improve drug diagnosis and inhibit pulmonary metastases</td>
<td>[170]</td>
</tr>
<tr>
<td>methotrexate, KLA (Lys-Leu-Ala)</td>
<td>ApoA-1 mimic peptide</td>
<td>glioma</td>
<td>Selective brain tumor treatment</td>
<td>[171]</td>
</tr>
<tr>
<td>miRNA-let7, VEGF siRNA</td>
<td>AS1411 aptamer</td>
<td>nucleolin-positive cancer cells (MDA-MA-231)</td>
<td>Tumor-targeted small RNA delivery</td>
<td>[181]</td>
</tr>
<tr>
<td>aSIRPa, aCD47</td>
<td>antibodies</td>
<td>macrophages and tumor cells</td>
<td>s Enhance phagocytosis of cancer cells by blocking SIRPa–CD47 interaction</td>
<td>[182]</td>
</tr>
<tr>
<td>mannosamine</td>
<td>RGD</td>
<td>αβ3 overexpressing cells (HUVEC)</td>
<td>Promote angiogenesis with targeted imaging</td>
<td>[183]</td>
</tr>
<tr>
<td>PTX, tirapazamine</td>
<td>D-CGKRK</td>
<td>B16F10</td>
<td>Hybrid membrane vesicles for targeted therapy</td>
<td>[184]</td>
</tr>
</tbody>
</table>

**Table 2:** Surface engineered exosome for drug delivery for cancer treatment.
<table>
<thead>
<tr>
<th>Cargo</th>
<th>Cancer Type</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>Breast cancer Ovarian cancer, Colon carcinoma</td>
<td>Tumor growth inhibition lowering medication toxicity, Suppression of tumor growth</td>
<td>[213-215]</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Pancreatic adenocarcinoma, Prostate cancer, Pulmonary metastasis, Lung cancer, Glioblastoma-astrocytoma cancer</td>
<td>Improved anticancer effect, Drug resistance was overcome. On cancer cells, increased cytotoxicity, Drug resistance was overcome. On cancer cells, increased cytotoxicity, Suppression of tumor growth Lower systemic toxicity, On cancer cells, increased cytotoxicity. Passed through the BBB,</td>
<td>[215-219]</td>
</tr>
<tr>
<td>TMZ</td>
<td>Glioma</td>
<td>Chemosensitivity has been improved. Anticancer activity has been improved; Tumor development is inhibited. Passed through the BBB, Suppression of tumor growth Improved effect of tumor targeting, Increased the rate of cellular absorption Cancer cell migration and metastases are reduced, Suppression of tumor growth Promoted tumor cell apoptosis, Tumor growth inhibition Drug cytotoxicity is reduced.</td>
<td>[198]</td>
</tr>
<tr>
<td>Nucleic acid</td>
<td>Hepatocellular carcinoma, Brain tumor, Breast adenocarcinoma, Breast cancer Lung metastasis, Hepatocellular cancer, Breast cancer Leukemia</td>
<td>Adenocarcinoma cells undergo induced apoptosis. Drug sensitivity has improved., Immunotherapy accumulation in lymph nodes, Enhanced phagocytosis of tumor cells Suppression of tumor growth, Proliferation and activation of immune cells Suppression of tumor growth</td>
<td>[202,211,215,22,223]</td>
</tr>
<tr>
<td>Protein</td>
<td>Pancreatic adenocarcinoma, Any type of cancer, Colon carcinoma, Colon carcinoma</td>
<td></td>
<td>[224-226]</td>
</tr>
</tbody>
</table>

Table 3: Different cargo encapsulated using exosome.

The different types of exosomes in drug delivery systems (Table 3). Exosome pharmacokinetics are affected by physicochemical qualities that vary based on the type of exosome source [227,228]. As a result, it's crucial to investigate how distinct biochemical properties of exosomes are derived from various sources. Exosomes are a form of nano-sized extracellular vesicle (EV) that can be released by practically any type of cell. Exosomes have been extracted from human embryonic kidney (HEK) cells, cancer cells, immune cells, and stem cells by a number of research groups, and these exosomes have distinct features depending on their origin. Exosomes derived from HEK293T contain membrane resemblances to many organs in human body, according to prior studies [229-232]. Due to its desirable qualities such as ease of growth, low care requirements, and high transfection efficiency, the HEK cell line (HEK293T) is the most often used cell line in the field of biopharmaceutical manufacture [233]. This shows that HEK-derived exosomes can carry drugs to a variety of organs. Exosomes containing therapeutic membrane proteins have also been found to improve tumour penetration and anticancer effectiveness. Native PH20 hyaluronidase expressing exosomes derived from HEK293T cells, according to Hong et al findings, inhibit tumour growth by degrading hyaluronan in the tumour extracellular matrix (ECM), which is a key component of the tumour microenvironment. When PH20 and doxorubicin (Dox) were delivered together in a tumour-bearing mouse model, the anticancer effects were dramatically improved compared to Dox-only administration groups [234]. Cancer cells are also considered good exosome producers because they overexpress two Rab protein subtypes involved in exosome release (Rab27a and Rab27b) [235]. Exosomes generated from cancer cells have shown potential as drug delivery vehicles, but there are fundamental limitations that must be overcome before they can be used to treat cancer [236]. To begin with, the pharmacokinetic profile of naive exosomes produced by cancer cells is less than ideal. Second, multiple studies suggest that cancer exosomes may contribute in tumour dissemination, thus all potential side effects should be considered before employing cancer exosomes as drug carriers [237]. Mesenchymal stem cells (MSCs), which can be extracted from a range of human
tissues and have a great capacity for ex vivo proliferation, are considered an ideal source for preparing exosomes for therapeutic application among the numerous cell types known to secrete exosomes [238,239].

<table>
<thead>
<tr>
<th>Exosome donor</th>
<th>Exosome Acceptor</th>
<th>Exosome loaded</th>
<th>Result</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEK-293T cells</td>
<td>U87-MG, C6 and rat model</td>
<td>miR-21 sponge construct</td>
<td>Tumor volume is reduced by miR-21 down-regulation and overexpression of miR-21 target genes (PDCD4 and RECK)</td>
<td>[240]</td>
</tr>
<tr>
<td>hBMSCs</td>
<td>U251</td>
<td>miR-199a</td>
<td>Down-regulate the expression of AGAP2, in turn inhibits tumour development, invasion, and migration</td>
<td>[241]</td>
</tr>
<tr>
<td>hBMSCs</td>
<td>Glioma cells (SHG44, C6, U87, and U251) and nude mice</td>
<td>miR-375</td>
<td>Encourages apoptosis and inhibits growth, migration, and infiltration via Suppressing SLC31A1</td>
<td>[242]</td>
</tr>
<tr>
<td>DCs carried CRCLs</td>
<td>6-weekold female C57BL/6 mice</td>
<td>CRCLs</td>
<td>Inhibits the expression of EGFR due to which Glioma growth is halted.</td>
<td>[243]</td>
</tr>
<tr>
<td>MSCs</td>
<td>male Fischer rats</td>
<td>miR-146b</td>
<td>Reduces GBM cell chemoresistance to TMZ by decreasing miR9 levels and drug transporter expression in GBM cells. MDR1</td>
<td>[244]</td>
</tr>
<tr>
<td>hBMSCs</td>
<td>U87 cells; T98G cells</td>
<td>Anti-miR-9</td>
<td>Kills autologous glioma cells by inducing the production of glioma-specific CD8+ CTLs.</td>
<td>[245]</td>
</tr>
<tr>
<td>Human GBM cells</td>
<td>CTLs obtained from PBMCs</td>
<td>Tumor antigen</td>
<td>By selectively decreasing the activity of STAT3 and diminishing the expression of IL-1b and IL-6, it promotes tumour cell death and decreases tumour cell proliferation.</td>
<td>[246]</td>
</tr>
<tr>
<td>GL26 cells</td>
<td>Microglial cells</td>
<td>Cucurbitin</td>
<td>Reduces tumorigenesis and prolongs survival by producing immune memory, improving T cell function, and stimulating antibody production.</td>
<td>[247]</td>
</tr>
<tr>
<td>SMA560vIII</td>
<td>VM/Dk mice</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4: Types of different exosome from different source for treating cancer.

Future perspective Exosomes have demonstrated their full capacity for medication delivery in order to overcome any limitations. Because of their unique features, such as endogenous origin and tissue tropism, exosomes hold promise for improving therapeutic delivery. Furthermore, exosomes could be easily modified to improve medication loading and targeting efficiency. Despite the benefits of exosomes, thorough knowledge of exosome biology is still in its infancy, and more study remains to be done in the future. The choice of exosome source for therapeutic applications must be decided with great care. In this sense, strategies for identifying and removing or adding exosomal components are crucial for exosome-based drug delivery for cancer treatment, and they may one day allow us to overcome limitations posed by heterogeneous exosome subpopulations. The loading efficiency necessary for clinical applications is not met by current exosome cargo loading techniques. The basic incubation approach, in particular, is relatively limited in terms of the sort of cargo that may be loaded, and its efficiency is too low to be used in clinical applications, so new approaches are needed to develop. Exosomes offer limitless promise as biomarkers for cancer detection and prognosis, in addition to their potential as medication carriers. Exosomes have been studied extensively in order to better understand their varied profiles and roles, as well as to facilitate their clinical uses. Exosomes have ushered in a new age in drug delivery, owing to their low immunogenicity and high biocompatibility. Due to in vivo degradation of the therapeutic substance and a lack of targeting ability, traditional delivery techniques of anticancer drugs, nucleic acids, and proteins for cancer treatment frequently fail to produce desired effects.
Although there are still a few challenges and roadblocks to overcome in developing a commercial exosome-based drug delivery system, a better understanding of exosomes' detailed biological mechanisms and more clinical research will allow them to emerge as a next-generation therapeutic strategy. In our lab, we're experimenting with exosomes as a drug delivery system to see if we can design a system that is both effective and resistant to degradation. Conclusion Glioblastoma treatment is complicated by resistance to standard medicines and recurrent recurrence. To overcome these obstacles and improve treatment outcomes, new therapeutic strategies must be developed. Internal factors like the blood–brain barrier (BBB), the blood–brain tumour barrier (BBTB), genetic molecular characteristics (heterogeneity, the Warburg effect, oncologically activated alternative splicing pathways), and external factors like a therapeutic agent or the immune system can all contribute to resistance (immune evasion). Because GBM is so heterogeneous, the most promising therapeutic strategy for treating it is to use a combination of methods and treatment regimens. Drugs that penetrate the BBB (upon chemical modification, use of substrates for carrier-mediated and receptor-mediated transcytosis, virus-mediated and exosome-mediated blood-brain barrier delivery) in combination with hyperosmotic agents and focused ultrasound, for example, will be useful with an intact BBB.

REFERENCES


194. Friedman HS, Stephen K, Anthony EP, (2002) "O6-Benzylguanine-mediated Enhancement of Chemotherapy 1 This work was supported by NIH Grants NS30245 (to HSF), NS20023 (to HS F), CA57725 (to AEP, HSF, and MED), and CA81485 (to MED). Drs. Pegg, Moschel, and Dolan have a financial relationship with Access Oncology, the company that is presently licensing O6-benzylguanine. Dr. Friedman is a paid consultant for Access Oncology. 1." Molecular Cancer Therapeutics 1(11): 943-948.


