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# COMPREHENSIVE OVERVIEW ON POTENTIAL ROLE OF EXOSOMES AS A THERAPEUTIC TARGET IN BRAIN TUMORS

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## Abstract

Exosomes are small endosomal derived membrane extracellular vesicles that contain cell specific cargos such as lipid, protein, DNA, RNA, miRNA, long non-coding RNA, and some other cell components that are released into surrounding body fluids upon the fusion of multivesicular bodies (MVB) and the plasma membrane. Exosomes are one of a kind cell-to-cell communication mechanism that might pave the way for target therapy. Brain tumour are a serious concern among both physicians and patients. Therefore, exosomes are a promising therapeutic target for the diagnosis, prognosis, and treatment of brain tumor. On the other way, brain tumor therapy with effective therapeutic components such as siRNAs, mRNAs, proteins, could be developed. This review aims to have a comprehensive appraisal on exosome biogenesis in brain tumors and then highlights the current knowledge of their role by special focusing on the latest ongoing therapeutic strategies on brain tumors. However, further research is needed to fully comprehend the potential involvement of the exosome in brain tumor therapy protocols.

***Keywords: Exosomes, Brain tumor, biomarkers, immunotherapy, solid tumors, predictive biomarkers***

## 1. Introduction

Two decades of research have revealed that many different types of cells shed tiny vesicles that play an important role in intercellular communication. Microvesicles (100 nm to 1 m in diameter), which immediately bud from the plasma membrane, apoptotic blebs (50-500 nm), which are released by apoptotic cells, and exosomes (30-100 nm), which are released via exocytosis from late endosome multivesicular bodies (MVBs)(1,2). Exosomes are small endosomal-derived membrane microvesicles that contain cell-specific cargos such as lipid, protein, DNA, RNA, miRNA, long non-coding RNA, and other cell components and are released into surrounding body fluids following the fusion of multivesicular bodies (MVB) and the plasma membrane (3).

Exosome production begins with cell membrane invagination, which results in the formation of vesicles containing cytoplasmic material known as early endosomes. When the microsomal membrane "sprouts" inward to create intraluminal vesicles,which merge to form the multivesicular endosome, early endosomes mature into late endosomes(4). Following that, the multivesicular endosomes use a variety of pathways to fuse with the cell membrane before being discharged into the extracellular matrix as exosomes [4]. Exosome secretion necessitates the coordinated action of several protein families. Exosome secretion is aided by Rab proteins such as Rab11, Rab27, and Rab35, as well as a soluble N-ethylmaleimide-sensitive-factor (NSF) attachment protein receptor(5). Other variables, including as changes in intracellular pH and potassium concentration, influence exosome production and secretion (6).Exosomes are small vesicles (30 nm to 100 nm in size) that contain lipids, proteins, mRNAs, and miRNAs(7). Cytoskeletal proteins (tubulin and microfilament-binding proteins), membrane fusion proteins (Rab proteins, ALIX, and flotillin), metabolic enzymes, and channel proteins are all frequent exosomal proteins. Exosomes contain proteins that are specific to their biological source(8). Exosomes can contain proteins that are overexpressed in tumour cells, such as Fas ligand proteins, tumour necrosis factor (TNF)-related apoptosis-inducing ligands, tumour antigens, and immunosuppressive proteins (transforming growth factor [TGF]-b)(9). Exosomes include lipids such as lysophosphatidic acid, cholesterol, and ceramide(8).

Exosomes have been shown to contain double-stranded DNA ranging in size from 100 bases to 17 kilobases. Thakur et al. discovered that the majority of tumour cell exosomes contain genomic doublestranded DNA that represents tumour mutation status(10,11). The process by which DNA is carried into exosomes, however, is unknown.

According to several research, a disrupted DNA repair mechanism in tumour cells permits DNA to accumulate in the cytoplasm (in comparison to healthy cells), allowing DNA to enter exosomes (10,12).

A brain tumour is an abnormal and uncontrolled development of brain cells. Because the human skull is a rigid and volume-limited body, any unanticipated development may harm human functions depending on the brain region involved; it may also spread to other bodily organs, harming human functions (13). According to the World Health Organization's (WHO) annual report on cancer, brain cancer accounts for fewer than 2% of all malignancies in people, but it causes tremendous morbidity and effects(14). According to Cancer Research UK, Brain other central nervous system (CNS), and intracranial cancers kill roughly 5,250 people in the United Kingdom each year(15). The brain tumour is classified into two stages: 1) primary and 2) secondary. The tumour can be eliminated in the primary stage, but in the secondary stage, the tumour disease spreads, and as a result, after removal of the tumour, it seldom remains and grows back, which is the major difficulty in the secondary stage of tumour(16).

Exosomes may provide new information about target therapy. The pharmacokinetic features of exosomes may be impacted by their composition, according to some evidence(17).In addition to their therapeutic potential, exosomes may help with the prognosis and diagnosis of diseases like cancer, chronic inflammation, cardiovascular problems, infections, and autoimmune disorders(18).Exosomes are released by a variety of cell types, such as dendritic cells, macrophages, B cells, T cells, epithelial cells, platelets, mast cells, adipocytes, and fibroblasts. This finding suggests that nervous system cells such as Schwann cells, astrocytes, and neurons may also play a role in exosome release(19,20). Additionally, it has been shown that exosomes have a role in the nervous system's operation, including the control of synaptic transmission and neuron regeneration(21). Exosomes in the nervous system are now thought of as a new intercellular communication link that not only contributes to normal neuronal physiology but also plays a significant role in pathogenic events like neurodegenerative disease as a pathogen transmitter or as a potential therapeutic agent. Exosomes have been studied as a potential therapeutic treatment for a variety of malignancies, and this research is ongoing. Exosome therapy for brain tumours has been one of the most significant of them(22,23). Various treatments for brain tumours have been proposed up to this point, including surgery, radiation, and chemotherapy. On the other hand, scientists have expressed significant concerns about the numerous adverse effects and obstacles associated with these types of therapy (23,24). One of the most significant problems is the sensitivity of brain tissue and the requirement for high precision in surgery, as well as the presence of a blood-brain barrier

(BBB) to prevent pharmacological therapies from accessing the brain environment. (25). However, due to the exosome's small size (30-150 nm), it can easily pass this barrier and pursue therapeutic goals (26).

This review will explore the importance of these vesicles in brain tumours as well as their function in therapeutic and therapy techniques.

## 1.1 Biogenesis of exosomes

Exosome biogenesis is a progressive, endosome-dependent cytological process that begins with the budding inward of the plasma membrane to create early endosomes. Intraluminal vesicles (ILV), also known as multivesicular bodies (MVBs) or multivesicular endosomes (MVEs), are generated in the lumen of the late endosomes as a result of the maturation of these early endosomes (27). There are two probable outcomes for MVBs in the cell: either they fuse with the plasma membrane and release their internal content as exosomes into the extracellular environment, or they fuse with lysosomes and are subsequently degraded(28).Exosome biogenesis, release, and uptake are shown in Figure 1.

There are several proteins, RNAs, and lipids in the exosome's cargo. Endosomal sorting complex needed for transport (ESCRT) machinery, ESCRT independent machinery, and other modulatory processes are some examples of the molecular types of equipment that sort exosomal material(29).Exosome biogenesis can be divided into two groups based on how much their transport requires the endosomal-sorting complex response (ESCRT). ESCRT mechanisms were identified in the 2000s and are made up of the proteins ESCRT-0, -I, -II, and -III (30,31). The ESCRT pathway in endosomes is activated by ESCRT-0's affinity for phosphatidylinositol 3-phosphate and ubiquitin. The ESCRT pathway in endosomes is activated by ESCRT-0's affinity for phosphatidylinositol 3-phosphate and ubiquitin. Two ESCRT-0 subunits are Hrs and STAM1/2(32).The ubiquitinated cargos that are intended for degradation are bound by ESCRT-0, which then interacts with ESCRT-I. Like ESCRT-0, ESCRT-I and -II sort ubiquitinated cargos in intraluminal vesicles and have ubiquitin-interaction domains. According to A.J. Jimenez et al. and I.J. McGough , ESCRT-I and ESCRT-II activate ESCRT-III, which results in membranobrane invagination and constriction (33,34). In particular, the development of budding and the sequestering of ubiquitinated proteins are mediated by ESCRT-I and -II, and the dissociation and scission of intraluminal vesicles are mediated by ESCRT-III(35,36).

The number of ESCRT subgroups and activation rate may differ among cell lineages, according to a number of studies(37). In HeLa cells, seven ESCRT proteins have been identified, along with inhibitory effectors from ESCRT-

0 and -I like Hrs, TSG1010, and STAM1 that stop intra luminal vesicle release M. Colombo et al 2013.Alternatively, it has been reported that exosome synthesis and cargo loading also happen independently of the ESCRT (38). It has been demonstrated that the absence of ESCRT machinery in mammalian cells impairs cargo sorting into ILVs and causes changes in ILV size and number but does not prevent the development of MVBs. It implies that the coordinated engagement of both ESCRT-dependent and ESCRT-independent machinery may lead to exosomes biogenesis. Tetraspanin (39), ceramide (40), sphyngosine-1-phosphate (S1P) (41), syndecan-syntenin-ALIX (42), c-Src (43), GTPase Ral, mixed lineage kinas (44). Tetraspanins, ESCRT machinery, and lipid-dependent processes are principally responsible for sorting proteins in exosomes (45).Lipids play a role in how RNA is loaded into exosomes. It is based on the cellular RNA's attraction for the raft-like area of the MVB membrane's outer layer (46).According to reports, sumoylated hnRNPA2B1 is an important factor in how miRNAs are sorted into exosomes. KRAS (Kirsten rat sarcoma viral oncogene homolog) has also been demonstrated to be crucial for miRNA sorting in exosomes (47). Record et al. have reviewed the kinds of lipids that exosomes can carry, as well as their function in determining the destiny and bioactivity of exosomes (48).

Numerous essential components, including as the cytoskeleton, Rab GTPase, and the fusion apparatus SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptors) complex, are necessary for exosome release (49). Additionally, recipient cells can take up exosomes through endocytosis (mediated by clathrin, caveolin, or lipid rafts for various cell types), direct fusion with the plasma membrane, or receptor-ligand contact (50).

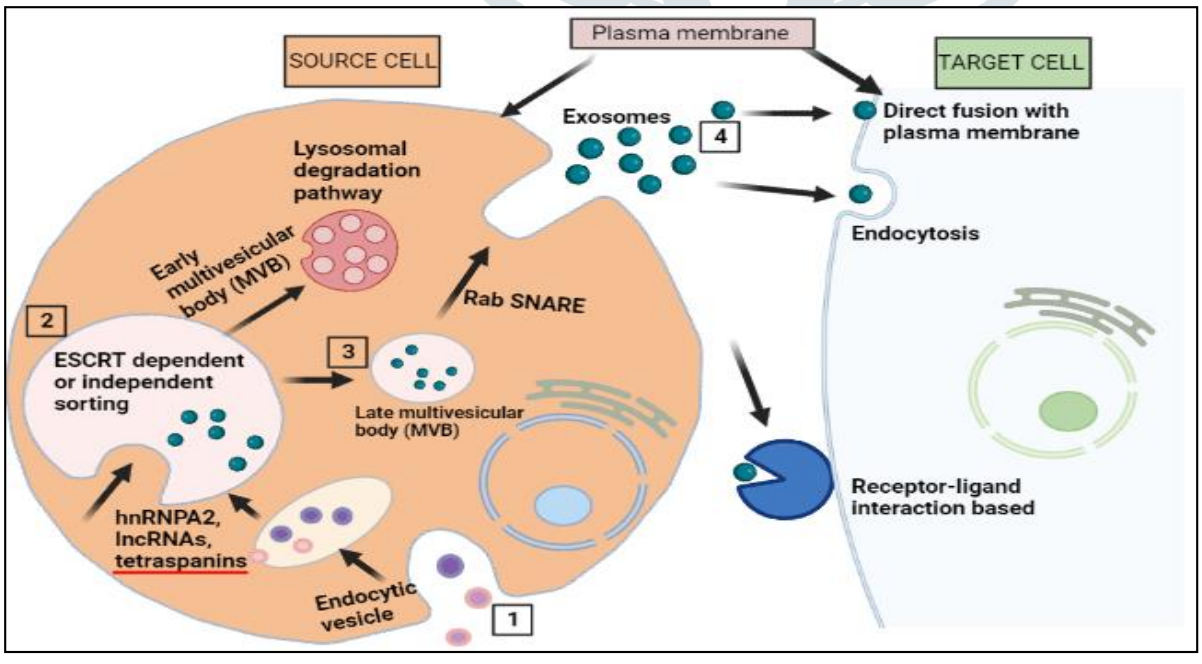


***Figure 1: Exosome biogenesis, release, and uptake***

Exosome biogenesis, release, and uptake begin with the creation of an endosomal vesicle from the plasma membrane in (1). ILV is produced by the endocytic vesicle, and it goes on to create the MVB. (2) Various ESCRT-dependent and independent processes mediate the sorting of exosomal material. The MVB membrane is approached by exosomal payloads (hnRNPA2/B1, lncRNAs, miRNA, tetraspanins, etc.) before being loaded into exosomes. (3) Using the Rab and SNARE complex, the MVBs can either release exosomes outside of the cell or be broken down by lysosomes. (4) The recipient cells can take the released exosomes either directly through fusing to the plasma membrane, through endocytosis, or through ligand-receptor contact. Long noncoding RNA, microRNA, ESCRT (endosomal-sorting complex necessary for transport), multivesicular body, intraluminal vesicle, and soluble N-ethylmaleimide-sensitive fusion attachment protein receptor are all abbreviations for heterogeneous nuclear ribonucleoproteins A2/B1.

## 1.2 Role of Exosomes in brain tumors

It has been discovered that exosomes are essential for the development and progression of brain cancers. Brain tumour cells can release proteins, mRNAs, or other cellular components implicated in cell malignancy by the release of exosomes, which can establish a tiny contact between the malignant cell and the cells around it (51).

However, there has been a significant advancement in exosome research over the past few decades, and it is now known that these EVs are essential for intercellular communication, which is crucial for the formation and metastasis of tumours(52,53). Several investigations have provided evidence of a non-random process that is dependent on transmembrane proteins, even if the methods by which exosomes are taken up by recipient cells are not entirely known(54). For instance, human brain capillary endothelial cells (hCMEC/D3) have recently been found to have potential receptors for the uptake of exosomes generated from SK-Mel28 melanoma cells (54). This research found that hCMEC/D3 cells take up SK-Mel-28-derived exosomes via macropinocytosis and receptor-mediated pathways, with a substantial role for CD46 in hCMEC/D3(54). The particular and crucial role of these vesicles in intercellular communication was briefly defined by the recipient cells' selective absorption and the tightly controlled loading process.Recent studies have revealed that complicated intercellular communication between metastatic cancer cells and brain stroma cells, which involves secreted proteins or small vesicles called exosomes, is essential for the effective growth of brain metastases(55,56).

Exosomes can be used therapeutically to treat a variety of brain tumours, including glioblastoma, neuroblastoma, medulloblastoma, astrocytoma, gliosarcoma, and oligodendroglioma (25,57).It may serve as a target for novel therapeutic strategies or serve as an idea for fresh approaches to drug administration.Although this effect can take on many different forms, some of them include being useful in the early diagnosis of brain cancer, preventing the spread of exosomes containing information from cancer cells to other healthy cells, or using exosomes produced in vitro to deliver treatment-effective factors to the brain's microenvironment (57).

To investigate the effect of exosomes in the treatment of brain cancers, the role of exosomes in the development of various brain cancers and their progression must first be studied in more detail.

### 1.3 Exosome in Primary Brain Tumor

The most common intracranial malignant tumours are brain metastases, and their original foci often include lung cancer (20-56%), breast cancer (5-20%), and melanoma (7-16%), as well as colorectal cancer and renal cell carcinoma(58). Brain metastasis develops as a result of cell multiplication. It could also occur as a result of blood flow from primary tumours to cerebral arteries. If untreated, the median survival duration is only 4-12 months, with a death time of only 1-2 months (22,59)

Gliomas are the most common primary central nervous system (CNS) tumours, and they are notorious for their aggressiveness, relapse, and mortality(60). Gliomas cause 24.7% of all primary brain tumours and 74% of malignant brain tumours(61).Glioblastoma multiforme is responsible for about half of all gliomas (GBM). Patients with glioma frequently get standard treatment, which includes surgical resection, radiation, and temozolomide (TMZ)-based chemotherapy. Despite the fact that the molecular aetiology of gliomas has been established, and advances in glioma detection and therapy have been made, the prognosis of these patients receiving treatment remains dismal (62).Exosomes have also been linked to glioma progression. Tumor-derived exosomes loaded DCs were shown in a study by Bu and colleagues to activate CD8+ CTL response to their tumour cells and kill autologous glioma cells in vitro [Bu, et al 2011]. Exosomal miR-375 increased the proliferation and invasion of glioma cells by activating the CTGF-EGFR oncogenic pathway, according to Xu and colleagues (63).

Glioblastoma (GBM) is one of the most aggressive glial tumours, growing and spreading quickly into neighbouring brain tissue. It develops from astrocytes, which are support cells for nerve cells. The average patient survival time has been found to be between 10 and 15 months (64). Complete remission of GMB is currently not achievable, while

treatments do decrease the disease's course and lessen symptom(65).Exosomes have a significant role in the genesis and progression of GBM. This communication occurs between tumour cells, microglia, parenchymal cells, immune cells, and cancer stem cells (66).Although it sounds like a hypothesis, the exosome traces in the growth of glioma were found by purifying the exosome in culture media containing murine glioma. Furthermore, the researchers discovered that glioma exosomes included a number of proteins implicated in tumour growth as well as surface indicators(67). Heat shock proteins (HSPs) such as HSPB5, HSP 60, 70, and 80 are among the most significant (68). This finding implies that the presence of inflammatory cytokines, such as IL-1, IL-6, and TNF-a, in the presence of HSPs promotes their production, which may contribute to tumour cell immortality and disease progression. Exosomes in solid tumours have been proven to aid tumour growth by inhibiting the immune system(69). Exosomes released by tumour cells also affect the immune system response in GBM by promoting the accumulation of M2 macrophages around the tumour, allowing the tumour to develop and elude the immune system(70). Furthermore, Annexin A2, which is involved in invasion, metastasis, angiogenesis, and proliferation, is one of the major markers detected on the surface of exosomes in GBM(71).Despite Annexin A2, CD44 is found on the surface of exosomes in GBM and acts as a receptor for hyaluronic acid. CD44 has been linked to cell motility, tumour development, angiogenesis, and cancer stem cell survival (72,73).

Neuroblastoma (NB), as the name suggests, is a type of cancer that affects immature nerve cells. NB is a malignant and rapidly progressing cancer that is frequently found in children under the age of five, with higher prevalence in newborns or foetuses (74). It is critical to pay attention to this disease since it is the second most prevalent malignancy in children and one of the most common malignant nervous system malignancies (75). NB typically begins in the adrenal glands but rapidly spreads throughout the body, including the bones, belly, neck, chest, and even under the skin.The International Neuroblastoma Staging System (INSS) has determined that at advanced stages, the NB deviates from the confined form and can spread rapidly to other tissues. This rapid progression, which is analogous to a metastatic process, can be efficiently associated with exosome activity(76).Despite the GBM, few exosome investigations have been conducted in the field of NB, and the significance of exosomes in the advancement of NB remains unknown.Although hsa-miR199a 3p is seen in other tumours and has opposing effects in other cancers, it has a progressive effect and a bad prognosis in NB. The hsa-miR199a-3p function is such that it lowers the expression of an enzyme known as NEDD4. This enzyme inhibits tumour activity by interacting with Myc via ubiquitination

and degradation of Myc protein, as well as facilitating PTEN mono ubiquitination and controlling PTEN nuclear translocation. As a result, inhibiting exosomal hsa-miR199a-3p may be useful in treating NB. Detecting an increase in the level of exosomal hsa-miR199a-3p can also be used as a biomarker to detect NB in its early stages or to predict prognosis (77,78).

## 1.4 Role of exosomes in metastasis

Exosomes play crucial roles in cancer progression, which is a dynamic and multistage process. The most common intracranial malignant tumours are brain metastases, with original foci commonly including lung cancer (20-56%), breast cancer (5-20%), and melanoma (7-16%), as well as colorectal cancer and renal cell carcinoma (79,80).

On the other hand, therapy against anti-metastatic activities could be the missing piece of the therapeutic puzzle. Many research on the involvement of exosomes in tumour metastasis have been undertaken in recent years (81). Metastatic brain tumours are one of the most prevalent types of brain tumours that can develop as a result of other malignancies in the body. As a result, these tumours are often known as secondary tumours (82). In terms of the risk of metastatic brain tumours, it can be stated that most malignancies and systemic tumours have a chance of metastasis to the brain, however cancers of the breast, lung, kidney, and colon are more common (83,84).More than half of persons with metastatic brain tumours had a history of non-small cell lung cancer, according to research (85). Furthermore, this risk is around 30% for patients with a history of breast cancer (83). As previously indicated, exosomal microRNAs play an important role in the genesis of cancer. As a result, additional research into these issues may be valuable (86). High expression of miR-451a and miR-4257, for example, has been linked to non-small cell lung cancer tumour growth and poor prognosis (87). MiR-21 is also linked to lung cancer recurrence and progression (87,88).In fact, patients with non-small cell lung cancer have high levels of exosomal miR-23a, which has angiogenesis activity and can also be effective in brain metastasis (89,90). It has been proven that breast cancer cells release a considerable amount of exosomal miR-122 (91). By influencing normal cells in premetastatic regions, miR-122 inhibits glucose uptake throughout this process, providing the energy required for tumour cell proliferation and metastasis (92). As a result, inhibiting it can be critical in limiting tumour cell spread and progression (92,93). The cells identified as miR-122 receptors were fibroblasts, brain astrocytes, and neurons, showing the involvement of exosomal miR-122 in brain metastasis (94).Furthermore, miR-105 is released by breast cancer cells and has an effect on endothelial cells. This impact can lead to the loss of endothelial walls, which speeds up the metastatic process. It

has also been demonstrated that the breakdown of endothelial barriers leads to the disruption of the BBB, highlighting the importance of exosomal miR-105 in brain metastasis (95).MicroRNAs (miRNAs) govern the complicated gene expression involved with tumour pathogenesis during oncogenesis and development. Only a few studies have been undertaken to identify miRNAs and possible pathways implicated in the aetiology of brain metastases in radiation patients, particularly miRNAs in plasma exosomes. As a result, they planned to use small RNA analysis to discover miRNAs and their potential target genes in plasma exosomes during the onset and progression of brain metastases in radiation patients. High-throughput sequencing technologies are being used (96).

Li Z et al, 2021 (96) discovered 35 differently expressed miRNAs in radiotherapy-treated patients with brain metastases. Gene ontology enrichment study of miRNA targets found that the targets of differentially expressed miRNAs were considerably enriched in the regulation of cellular functions. According to the Kyoto Encyclopedia of Genes and Genomes, the majority of miRNA targets were cancer-related, including genes involved in the mitogen-activated protein kinase signalling pathway, cancer-related pathways, phosphatidylinositol 3-kinase-protein kinase B signalling pathway, microtubule-associated protein kinase signalling pathway, Ras signalling pathway, actin cytoskeleton regulation, and axon guidance. Finally, this study adds to our understanding of the potential role of these miRNAs in the aetiology of brain metastasis (96).

## 1.4 Exosomes based treatment for brain tumors

Exosomes as therapeutic agents, exosome-mediated drug delivery, and exosome-based immunotherapy are currently the three categories under which exosomes are used in clinical settings. Exosomes have a number of benefits as medicines: Good stability (exosomes are bilayered phospholipid membrane vesicles circulating in the blood, their contents are protected by RNase III and prions, and they can be transported to distant target cells); good specificity (exosomes can transport their contents to specific targets via their surface molecules and homing properties); safety (self-derived exosomes are not toxic to the immune system, and they are histocompatible); good safety (self-derived exosomes are not toxic to the immune system(97).Adults with brain cancer most frequently have gliomas, which make up roughly 32% of all CNS and brain tumours and 80% of all malignant brain tumours(98). The primary origins are progenitor cells or neuroglial stem cells, and glioblastomas make up half of all newly diagnosed gliomas. Gliomas are categorised by the World Health Organization as astrocytoma, oligoastrocytoma, oligodendroglioma, and glioblastoma as of 2016. The categories are based on histology, and each class can be further separated based on the

presence or absence of isocitrate dehydrogenase mutations (99) Grades I and II of gliomas advance slowly and less aggressively, grade III is distinguished by a high rate of proliferative activity, and grade IV is distinguished by a higher level of angiogenic activity. The most aggressive form of glioblastoma, grade IV has a median overall survival of nearly 15 months and an incidence rate of 3.19 per 100,000 people(98).

A flawless drug delivery system that can circumvent the brain-blood barrier and increase therapeutic efficacy is urgently required for clinical applications, according to a recent study by Santosh Bashyal and colleagues. Due to their endogenous and inherent characteristics, exosomes offer unmatched advantages as a therapeutic delivery method for treating brain illnesses. Exosomes are well suited for brain-targeted drug delivery due to their special qualities, which include the capacity to cross physical barriers, biocompatibility, intrinsic targeting traits, capacity to use natural intracellular trafficking pathways, preferred tumour homing, and stability.A study of Santosh Bashyal et al,(2022) Even while procedures for immune therapy, gene therapy, radiation, and surgical resection have made significant strides, there is still little hope for a full recovery from glioblastoma(98,100). It is challenging to completely resect GBM tumours due to their aggressive growth among the normal brain tissues and lack of clearly defined limits. The majority of the tumour mass is first surgically removed as part of standard treatment regimens, then radiation therapy is administered with concurrent long-term temozolomide therapy maintenance (101). The development of temozolomide resistance in the surviving tumour cells due to the increased expression of O-6-methylguanine DNA methyltransferase may explain why the combinatorial method boosts the progression-free survival time but has no effect on overall survival (MGMT). Preclinical trials have investigated the use of additional medications to block MGMT; however, these inhibitors run the risk of deactivating DNA repair pathways in healthy cell (101). Bevacizumab and temozolomide have been observed to extend the time without disease in a distinct way, suggesting that alternative resistance mechanisms are quickly triggered.Additionally, the presence of the BBB, which affects the distribution of medications to the tumour sites, and the genetic heterogeneity at the intertumoral and intratumoral levels also hamper the development of standardised therapies (101).It is thought that different formulations, including liposomes, polymeric nanoparticles, and micelles, may enhance drug delivery and increase local availability; however, each formulation has drawbacks. For instance, when administered in vivo, unaltered liposomes have a short circulation duration and low stability(98).Similar to this, micelles can dissociate when diluted and are unstable in biological or aquatic conditions. Targeted nanoparticles made from poly (lactic and glycolic acid) have the potential

to have severe negative effects. Additionally, artificial nanocarriers cannot effectively penetrate the BBB. Consequently, there is an urgent need for safe and efficient methods and substances to enhance the delivery of focused therapeutics with a minimum of off-target consequences. Such strategies ought to be able to deliver medications close to the tumour to lengthen patient longevity and improve their quality of life (102). They should be able to do this via trans-cellular pathways. Exosomes have the ability to address several of these therapeutic difficulties.

Even though it is still in its infancy, research on exosomes in GBM is beginning to yield some exciting results, notably those describing their role in the growth of tumours. Therefore, the next phase is applying this knowledge to develop more customised treatments by concentrating on the biogenesis and uptake of exosomes (103). Due to their advantageous shape, which allows them to pass the blood-brain barrier and carry a range of compounds, lengthy circulation half-lives, and transport selectivity, which allows them to target particular cells, exosomes are incredibly valuable as drug delivery vectors (104).They can diminish chemoresistance and reduce the systemic side effects of therapeutic interventions because they can deliver drugs directly to the tumour (103). There are some intriguing pieces of evidence supporting the use of exosomes in cancer treatment. Due to their endogenous origin, durability, biocompatibility, and other special characteristics, extracellular vesicles (exosomes) appear to be a promising designable platform for conveying particular content, such as medicines, proteins, and regulator RNAs(105).

Radiation therapy can be used as a pre-treatment to boost the uptake of therapeutics-enriched exosomes since it increases the amount of exosomes released by tumour cells and the milieu around them(106). However, increasing invasiveness is a hallmark of post-radiotherapy GBM relapses. According to Arscott et al. (2013), exosomes generated by radiation-exposed cells activate the focal adhesion kinase signalling pathway, one of the pro-migratory molecular pathways(106). Furthermore, Halliday et al. (2014) found that radiation-induced GBMs tended to shift toward the mesenchymal subtype, which is known for having a higher infiltrative capacity due to a process known as the epithelial-mesenchymal transition (EMT)(107). Exosomes are also of importance in the field of immunotherapy due to the aforementioned influence on immune cells, as they can strengthen the immune response to effectively combat cancer cells (108). There are some intriguing pieces of evidence supporting the use of exosomes in cancer treatment. Due to their endogenous origin, durability, biocompatibility, and other special characteristics, extracellular vesicles (exosomes) appear to be a promising designable platform for conveying particular content, such as medicines, proteins, and regulator RNAs (109,110). In their study (O'Brien K et al. 2015), O'Brien and colleagues

demonstrated that exosomes containing miR-134 could inhibit cellular invasion and migration and increase sensitivity to anti-Hsp90 medications. Chemotherapeutic medicines can enhance exosomes, which can then be used to target cancer cells. Imatinib or BCR-ABL siRNA-loaded exosomes may be able to target CML cells and deliver their cargo to desired cells, according to a theory put out by Bellavia D. and colleagues.There are interesting pieces of evidence regarding exosome applicants in cancer therapy. It seems that the extracellular vesicles exosome can be a promising designable platform for transferring specific content such as drugs, proteins, and regulator RNAs due to their endogenous origin, stability, biocompatibility, and other unique features.O'Brien and colleagues showed that exosomes filled by miR-134 could reduce cellular migration and invasion, and enhanced sensitivity to anti-Hsp90 drugs (111).Exosomes also can be enriched by chemotherapeutic drugs and target cancer cells. Bellavia D and colleagues have posited that imatinib or BCR-ABL siRNA-loaded exosomes will be able to target CML cells and unload their cargo to target cells. As IL-3R expression rises on CML cells, they have taken use of this property to target CML cells by creating exosomes that express IL-3-Lamp2b. They claimed that imatinib is effectively administered and that these exosomes successfully target cancer cells. As a result, the multiplication of cancer cells is decreased (112).

New insights into the molecular underpinnings of metastasis and the creation of cutting-edge therapeutic approaches to stop the development of brain metastasis could come from further studies.

## 2. CONCLUSION

Brain tumors are important because, in addition to physical complications, they also have cognitive complications (113). To date, the treatment of brain tumors in medicine has been associated with many challenges. Surgery is still considered the most important step in treating brain tumors, but brain surgery is one of the most difficult types of surgery. In addition, the long recovery period after brain surgery and its complications should not be underestimated (114). Chemotherapy and radiotherapy are also prescribed for malignant tumors in the next step. Although Chemotherapy and radiotherapy have gradually become more effective with advances in medical science, it still does not bring complete remission in the treatment of some malignant and metastatic brain tumors. Furthermore, the risks of chemotherapy are apparent (115). Researchers focus on genetics and epigenetics in molecular investigations of brain tumour pathogenesis, while cellular connections with each other and their surroundings play a critical role in tumour progression.Exosomes, which are generated by membrane extracellular vesicles, play a vital role in the

transfer of biological processes between tumour cells and other cells and tissue(116).As previously stated, exosomes play an important role in the progression of brain tumours. One of the most important roles of exosomes in brain tumours is in tumour metastasis to the brain, for example, by transmitting the contents, or signal for tumour growth and progression, from tumour cells in other tissues to the brain (117). Exosomes bearing useful substances such as mRNAs, proteins, and lipids are used in the therapy of brain cancers. Although not commonly used today, whole-brain radiation therapy, surgery, radiosurgery, chemotherapy, and anticonvulsant medicines are the basic guidelines for treating individuals with brain tumours(118).

Exosome-based therapy has been shown to be effective in a number of early-stage clinical trials. Bioengineered exosomes, in particular, have a lot of potential for developing novel methods for delivering medications and biological cargos to brain cells, such as mRNA, siRNA, proteins, and peptides. Exosomes can be chemically or biologically manipulated to improve their therapeutic potential in neurodegenerative illnesses and brain cancers. Extensive study on modified exosomes or hybrid exosomes, as well as disease pathophysiology, is required to create novel strategies for treating brain diseases(119).

However, more research is needed to fully comprehend the possible involvement of the exosome in therapeutic procedures. Furthermore, the exosome has been proved to be a safe method of increasing the stability of its contents. As a result, in addition to the exosome's ability to cross the BBB, the employment of the exosome as a suitable covering in safeguarding and delivering helpful contents for the treatment of brain tumours can be effective(120).

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