

Review Article

NANOCARRIERS FOR BRAIN TUMOR TREATMENT: RECENT ADVANCES, CHALLENGES AND FUTURE PERSPECTIVES

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ABSTRACT

Brain tumors are considered among the most challenging neurological diseases to treat due to their highly aggressive behavior, fast growth, and poor response to standard treatment methods. Traditional therapies such as surgery, chemotherapy, and radiotherapy are widely used; however, their overall success is often limited because many drugs cannot effectively reach the brain tissue and may also produce serious side effects throughout the body. A major obstacle in brain tumor treatment is the Blood–Brain Barrier (BBB), a protective and highly selective membrane that prevents most therapeutic agents from entering the central nervous system. To overcome these limitations, researchers are focusing on advanced drug delivery systems that can improve targeted delivery of drugs directly to brain tumors while reducing unwanted side effects.

KEY WORDS

Brain tumor, Glioblastoma, Nanocarriers, Blood–Brain Barrier, Targeted drug delivery, Nanomedicine

INTRODUCTION

Brain tumors are one of the most serious diseases affecting the central nervous system. They develop when abnormal cells grow uncontrollably inside the brain or nearby tissues. These tumors can be either benign (non-cancerous) or malignant (cancerous). Even though brain tumors are less common compared to other cancers, they can cause severe health problems because they directly affect important brain functions such as memory, movement, speech, and coordination.[1] In recent years, the number of brain tumor cases has increased worldwide, making it a major challenge for healthcare professionals. Several factors, including genetic changes, exposure to radiation, environmental influences, and hereditary

conditions, are believed to play a role in the development of brain tumors, although the exact cause is still unknown in many patients. [2]

Brain tumors are divided into different types depending on their origin and severity. Glioblastoma is considered one of the most aggressive and dangerous forms of brain cancer found in adults. It grows rapidly, spreads into nearby brain tissues, and responds poorly to treatment, resulting in a low survival rate for patients. Another common type is astrocytoma, which develops from astrocytes, the supportive cells of the brain. Astrocytomas can vary from slow-growing tumors to highly malignant forms. Meningioma is another category that arises from the protective membranes covering the brain and spinal cord. Most meningiomas are benign and

grow slowly, but in some cases, they may become harmful by pressing on surrounding brain structures and causing neurological complications. [3]

The treatment of brain tumors usually includes surgery, chemotherapy, and radiotherapy. Surgery is often the first option because it helps remove as much of the tumor as possible and reduces pressure inside the skull. However, complete removal is difficult in many cases because tumor cells may spread into healthy brain tissues, increasing the risk of damage during surgery. [4] For aggressive tumors such as glioblastoma, surgery alone is generally not enough, and additional therapies are required to control the disease. [5]

Chemotherapy uses anticancer drugs to destroy rapidly dividing tumor cells. Temozolomide is one of the commonly used drugs for treating malignant brain tumors. However, the effectiveness of chemotherapy is limited by the Blood-Brain Barrier (BBB), which prevents many drugs from reaching the brain. As a result, only a small amount of medicine reaches the tumor site, reducing treatment efficiency and increasing side effects in other parts of the body [6]. Radiotherapy is also widely used and works by damaging the DNA of cancer cells using high-energy radiation. Although it can slow tumor growth, radiotherapy may also harm healthy brain tissues and lead to side effects such as fatigue, memory problems, and tissue damage. [7]

Despite progress in medical science, conventional treatments still face many limitations in brain tumor management. Poor drug delivery across the BBB, non-specific action of anticancer drugs, drug resistance, severe side effects, and frequent tumor recurrence remain major concerns.[8] In addition, many drugs have poor solubility and stability, which further

decreases their effectiveness. Because of these challenges, researchers are focusing on advanced drug delivery systems that can improve targeted treatment in brain tumors. [9]

Targeted drug delivery has become a promising approach for improving brain tumor therapy. The main aim of these systems is to deliver medicines directly to tumor tissues while minimizing damage to healthy cells. Nanotechnology-based drug delivery systems have gained significant attention because of their small size, ability to cross biological barriers, and improved drug-carrying capacity.[10] Nanocarriers such as liposomes, polymeric nanoparticles, dendrimers, and solid lipid nanoparticles can increase drug stability, enhance bioavailability, and provide controlled drug release. In addition, modifying the surface of nanocarriers with antibodies, peptides, or ligands can improve their targeting ability and help them cross the BBB more effectively. [11]

The use of nanocarriers in brain tumor treatment is a rapidly growing area of research with strong potential to improve patient outcomes.[12] By enabling targeted drug delivery and reducing unwanted side effects, nanomedicine may provide a safer and more effective alternative to conventional therapies [13]. Therefore, the development of advanced nanocarrier systems has become an important focus in modern pharmaceutical and neuro-oncology research. [14]

Blood-Brain Barrier (BBB) and Drug Delivery Challenges

Structure of Blood-Brain Barrier (BBB)

The Blood-Brain Barrier (BBB) is a protective barrier that separates the brain from harmful substances present in the bloodstream. It plays an important role in maintaining a safe and stable environment inside the central nervous system (CNS). The BBB carefully controls the movement

of different substances between the blood and brain tissues. It is mainly made up of endothelial cells that line the brain capillaries and are tightly joined together by structures called tight junctions. Other components such as astrocytes, pericytes, basement membrane, and microglial cells also support the structure and function of the BBB. Because of its highly selective nature, the BBB prevents many unwanted substances from entering the brain and is considered one of the strongest biological barriers in the human body.[15]

Normally, the BBB allows only essential nutrients like glucose, oxygen, and amino acids to pass into

the brain while blocking toxins, infectious agents, and many foreign chemicals. Although this defense system is necessary for proper brain function, it also creates a major obstacle in the treatment of brain tumors and neurological diseases. Many anticancer drugs are unable to cross the BBB efficiently because they have large molecular size, poor fat solubility, or unsuitable chemical properties. Due to this limitation, only a very small amount of the drug reaches the tumor site, which decreases the effectiveness of treatment and may result in poor therapeutic outcomes.[16]

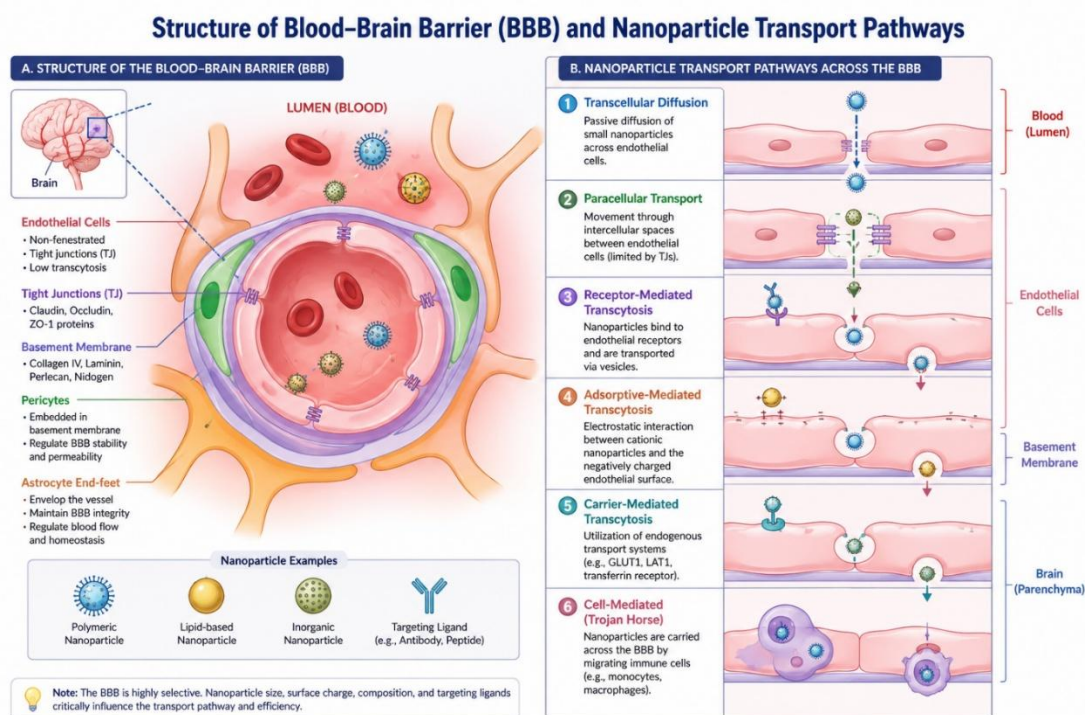


Figure 1. Structure of Blood-Brain Barrier (BBB) and Nanoparticle Transport Pathways [17]

Nanocarriers: Introduction and Characteristics

Nanotechnology has become an important area of research in modern medicine, especially for improving targeted drug delivery systems.[18] In the treatment of brain tumors, nanocarrier-based approaches have attracted significant

attention because they can enhance drug delivery to the brain and improve therapeutic outcomes. Traditional drug delivery methods often show limited success due to problems such as poor drug solubility, rapid breakdown of drugs in the body, unwanted side effects, and difficulty in crossing the Blood-Brain Barrier (BBB).[19]

Nanocarriers help overcome these limitations by providing targeted delivery of medicines directly to the tumor site along with controlled and sustained drug release.[20]

Nanocarriers are extremely small delivery systems that usually range from 1 to 1000 nanometers in size.[21] They are specially designed to carry therapeutic substances such as drugs, proteins, genes, or imaging agents to specific cells or tissues within the body.[22] These carriers can be prepared from different materials including lipids, polymers, metals,

proteins, and inorganic compounds [23]. Because of their tiny size and easily modifiable surface properties, nanocarriers can interact more effectively with biological membranes and successfully pass through complex barriers like the BBB. Several nanocarrier systems such as liposomes, polymeric nanoparticles, dendrimers, solid lipid nanoparticles, metallic nanoparticles, and mesoporous silica nanoparticles are currently being widely explored for targeted brain tumor therapy.[24]

Table: Important Properties of Nanocarriers [25]

Property	Importance
Particle size	Enhances BBB penetration and tumor accumulation
Surface charge	Influences cellular uptake and membrane interaction
Biocompatibility	Ensures safety and reduces toxicity
Drug loading	Improves therapeutic efficiency and drug delivery capacity

TYPES OF NANOCARRIERS USED IN BRAIN TUMOR TREATMENT

These advanced systems help increase the effectiveness of treatment by delivering drugs more efficiently to the tumor site while also minimizing harmful side effects in healthy tissues.[26] In addition, nanocarriers can enhance drug stability, improve bioavailability, and reduce systemic toxicity, making them a promising approach for safer and more effective brain tumor therapy.[27]

Liposomes

Liposomes are spherical vesicles made up of one or multiple phospholipid bilayers enclosing an aqueous central cavity. Because their structure closely resembles natural biological membranes, liposomes possess high biocompatibility and minimal toxic effects, making them highly suitable for drug delivery applications. Liposomes are spherical vesicular structures composed of one or more phospholipid bilayers

surrounding an aqueous core. Due to their structural similarity to biological membranes, liposomes exhibit excellent biocompatibility and low toxicity.[28]

Polymeric Nanoparticles

Polymeric nanoparticles are nanosized carriers formulated from biodegradable and biocompatible polymers for effective drug delivery. They enhance drug stability and enable controlled or sustained release of therapeutic agents. These nanoparticles also improve the transport of drugs across the Blood-Brain Barrier (BBB). Among them, PLGA nanoparticles are widely preferred because of their safe degradation profile and FDA approval.[29]

Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are nanosized drug carriers prepared from solid lipids and stabilized using surfactants. They integrate the beneficial properties of both liposomes and polymeric nanoparticles while minimizing their

drawbacks. SLNs enhance the stability of therapeutic agents and protect them from chemical or enzymatic degradation.[30]

Dendrimers

Dendrimers are nanosized, highly branched structures possessing a central core with numerous functional groups on their surface. Their unique three-dimensional arrangement allows efficient drug loading and easy surface functionalization. These nanocarriers can incorporate therapeutic molecules within internal cavities or bind them through chemical conjugation.[31]

Metallic Nanoparticles

Dendrimers are nanoscale branched carriers with a core structure and multiple active surface groups. Their compact architecture enables efficient drug incorporation and easy chemical modification for targeted delivery. These nanocarriers can either trap drugs inside their structure or attach them onto the surface for therapeutic applications.[32]

Mesoporous Silica Nanoparticles

Mesoporous silica nanoparticles (MSNs) possess a porous framework with a large surface area, enabling high drug loading efficiency. Their nanochannels can effectively carry anticancer agents, proteins, and genetic materials for targeted therapy. MSNs also support controlled and stimulus-responsive release of drugs, improving therapeutic performance and stability.[33]

Biomimetic Nanocarriers

Biomimetic nanocarriers are innovative drug delivery systems developed to mimic natural biological components and functions. A common example includes cell membrane-coated nanoparticles prepared using membranes from red blood cells, immune cells, or tumor cells. These coatings help nanoparticles escape immune detection, extend circulation time, and

enhance tumor-specific targeting with improved biocompatibility.

Targeting Strategies in Brain Tumor Therapy

Targeted drug delivery plays a crucial role in current brain tumor treatment strategies by improving the delivery of anticancer agents directly to tumor sites. Traditional therapies often show limited effectiveness due to inadequate drug accumulation within brain tissues.[34]

Passive Targeting

Passive targeting is primarily based on the Enhanced Permeability and Retention (EPR) effect observed in tumor tissues. Brain tumors such as glioblastomas form abnormal, highly permeable blood vessels during rapid angiogenesis.[35]

Active Targeting

Active targeting uses surface-engineered nanocarriers containing ligands that selectively bind to receptors highly expressed on tumor cells or Blood-Brain Barrier (BBB) endothelial cells. This strategy enhances the precision of drug delivery and promotes greater nanoparticle uptake at the tumor site.

Ligand-Mediated Targeting

Ligand-mediated targeting is one of the most widely investigated strategies in brain tumor therapy. Various ligands such as transferrin, folic acid, lactoferrin, aptamers, and hyaluronic acid are attached to the surface of nanoparticles to facilitate receptor-mediated transport across the BBB. [36]

Antibody-Based Targeting

Monoclonal antibodies are widely explored in nanocarrier-based brain tumor therapy due to their strong specificity for tumor-related antigens. Nanoparticles conjugated with antibodies can selectively identify cancer cells and enhance targeted drug transport.[37]

Peptide-Based Targeting

Peptides are small biomolecules capable of selectively binding to receptors located on tumor cells or Blood-Brain Barrier (BBB) endothelial cells. Their smaller size allows improved tissue penetration and reduced immunogenic reactions compared with antibodies.[38]

Stimuli-Responsive Nanocarriers

Stimuli-responsive nanocarriers are advanced drug delivery systems designed to release therapeutic agents in response to specific internal or external stimuli. These systems improve site-specific drug release and minimize damage to healthy tissues. Stimuli-responsive nanocarriers have attracted significant attention in brain tumor treatment because of their ability to respond to unique tumor microenvironment conditions.[39]

pH-Sensitive Systems

Brain tumors often exhibit an acidic microenvironment due to rapid cell metabolism and inadequate oxygen supply [40]

Temperature-Responsive Systems

Temperature-responsive nanocarriers release drugs in response to elevated temperatures within tumor tissues or externally applied heat

Magnetic Targeting

Magnetic nanoparticles, especially iron oxide nanoparticles, are extensively investigated for magnetic targeting in brain tumor therapy. This approach uses an external magnetic field to direct the nanoparticles specifically toward the tumor region.[41]

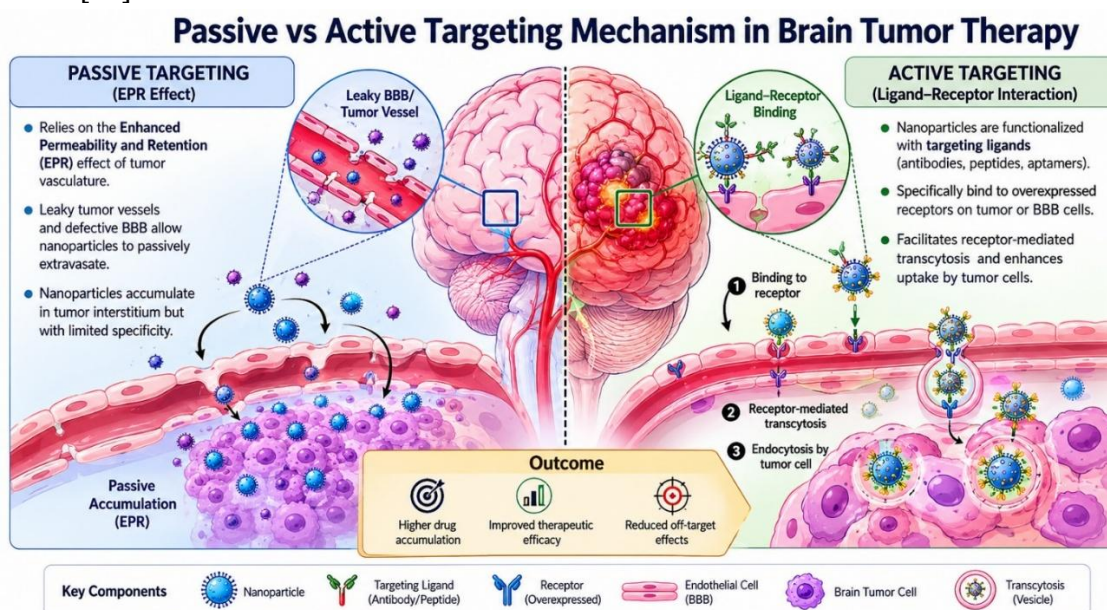


Figure 2. Passive vs Active Targeting Mechanism in Brain Tumor Therapy [42]

Routes of Administration

The success of nanocarrier-based brain tumor therapy greatly depends on the selected route of drug administration.[43] A major obstacle in brain cancer treatment is the Blood-Brain Barrier (BBB), which limits the entry of many therapeutic compounds into the brain.[44]

Choosing an effective delivery route helps improve drug penetration, increase concentration at the tumor site, and minimize systemic side effects. Several approaches such as intravenous administration, intranasal delivery, convection-enhanced delivery, and local implantation are being investigated for targeted

therapy.[45] Among these, intranasal nanosystems have gained significant interest as non-invasive methods for bypassing the BBB and enhancing brain drug delivery. [46]

Intravenous Delivery

Intravenous (IV) administration is one of the most widely used methods for delivering nanocarrier-based anticancer agents in brain tumor treatment. [47] In this approach, nanoparticles are introduced directly into the bloodstream for systemic circulation throughout the body. [48] IV delivery offers rapid drug action, accurate dose control, and convenient repeated administration during therapy.[49]

Intranasal Delivery

Intranasal delivery is considered a promising non-invasive technique for transporting therapeutic agents directly to the brain.[50] This method uses the olfactory and trigeminal nerve pathways in the nasal cavity to bypass the Blood–Brain Barrier (BBB).[51] Intranasal nano systems enable rapid brain targeting while avoiding surgical intervention and reducing systemic drug exposure. [52,53]

AI-Assisted Nanomedicine

Artificial intelligence (AI) has recently emerged as a powerful tool in the development of

advanced Artificial intelligence is playing an important role in the advancement of nanomedicine systems for brain tumor therapy.[54] AI-based technologies help optimize nanoparticle formulation, predict drug–nanocarrier interactions, and improve targeting efficiency. Machine learning algorithms can analyze large datasets related to nanoparticle properties, drug release behavior, toxicity, and tumor response to identify the most effective nanocarrier strategies for personalized treatment. [55,56,57]

Personalized Therapy

Personalized therapy, also called precision medicine, is gaining major importance in brain tumor treatment due to the genetic and molecular diversity of glioblastomas.[58] Traditional therapies often show variable outcomes because patients respond differently to chemotherapy, radiotherapy, and targeted treatments.[59] Nanocarrier-based systems provide a promising approach for customized drug delivery by tailoring therapy according to the specific molecular characteristics of individual tumors.[60,61,62,63,64]

Table: Clinical Applications of Nanocarriers in Brain Tumor Therapy [65,66,67,68]

Study	Nanocarrier	Application	Findings
Liposomal doxorubicin studies	Liposomes	Chemotherapy delivery	Improved circulation time and reduced toxicity
Abraxane clinical studies	Albumin nanoparticles	Paclitaxel delivery	Enhanced tumor targeting and drug solubility
Magnetic nanoparticle trials	Iron oxide nanoparticles	Hyperthermia and imaging	Improved tumor localization and MRI contrast
Gliadel wafer studies	Polymeric implants	Local chemotherapy	Sustained drug release after surgery
siRNA nanoparticle studies	Polymeric nanoparticles	Gene therapy	Suppression of tumor-related genes

Exosome-based studies	Biomimetic nanocarriers	Targeted drug delivery	Enhanced BBB penetration and cellular uptake
AI-assisted nanoparticle design	Multifunctional nanoparticles	Personalized therapy	Improved targeting prediction and treatment optimization

TOXICITY AND SAFETY CONCERNS

Nanocarrier-based drug delivery systems have demonstrated significant potential in brain tumor therapy by improving targeted drug delivery, enhancing Blood–Brain Barrier (BBB) penetration, and minimizing systemic toxicity.[69] However, several safety and toxicity issues still restrict the clinical application of nanomedicine.[70] The biological effects of nanoparticles depend on factors such as particle size, surface characteristics, composition, dosage, and exposure duration, which may lead to adverse reactions.[71] Concerns including neurotoxicity, immune responses, long-term accumulation, and incomplete biodegradation continue to challenge their clinical translation. Therefore, ensuring safety, reproducibility, and effective large-scale application remains essential for successful nanoparticle-based therapies in neuro-oncology.[72]

CONCLUSION

Brain tumors, especially glioblastoma, remain among the most difficult cancers to treat because of their aggressive growth, poor survival rate, and limited response to conventional therapies. The presence of the Blood–Brain Barrier (BBB), tumor heterogeneity, multidrug resistance, and severe side effects of traditional treatments often reduce the effectiveness of chemotherapy and radiotherapy. In recent years, nanocarrier-based drug delivery systems have emerged as a promising strategy to overcome these limitations and improve therapeutic outcomes in brain tumor treatment.

Different nanocarriers such as liposomes, polymeric nanoparticles, solid lipid nanoparticles, dendrimers, mesoporous silica nanoparticles, metallic nanoparticles, and biomimetic systems have shown significant potential in enhancing drug delivery to brain tumors. These nanosystems improve drug stability, prolong circulation time, enable controlled drug release, and increase drug accumulation at the tumor site while minimizing damage to healthy tissues. Surface-modified and ligand-targeted nanoparticles further enhance treatment specificity and reduce systemic toxicity, making nanomedicine an important advancement in neuro-oncology.

Recent progress in gene therapy, immunotherapy based nanocarriers, theragnostic systems, and stimuli-responsive nanoparticles has expanded the applications of nanotechnology in glioblastoma management. In addition, intranasal delivery systems and multifunctional nanoplatforms have demonstrated encouraging results in bypassing the BBB and improving targeted brain delivery. However, challenges such as long-term toxicity, manufacturing difficulties, regulatory barriers, and limited clinical evidence still restrict the large-scale clinical use of nanomedicine.

Further preclinical research and well-designed clinical studies are necessary to establish the long-term safety, reproducibility, and therapeutic effectiveness of nanocarrier systems.

Standardized production methods and clear regulatory guidelines will also be essential for successful clinical translation. Future advancements involving artificial intelligence,

personalized medicine, smart nanoparticles, and CRISPR-based technologies may revolutionize brain tumor therapy by improving treatment precision and reducing adverse effects. Overall, nanocarrier-based drug delivery represents a rapidly developing and highly promising field that may significantly improve the future management of glioblastoma and other malignant brain tumors.

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