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Surface-Functionalized Phytochemical Nanocarriers for Nose-to-Brain Glioblastoma Therapy: Advances and Translational Barriers

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ABSTRACT

Glioblastoma (GBM) remains incurable due to the blood-brain barrier (BBB), tumor heterogeneity, and poor bioavailability of potent phytochemicals such as curcumin. This review analyzes a multi-strategic solution involving the nose-to-brain (N2B) route (bypassing the BBB), advanced nanocarriers (protecting phytochemicals), and surface functionalization (enabling precision targeting). We discuss how active ligands (e.g., lactoferrin), mucoadhesive polymers (e.g., chitosan), cell-penetrating peptides (e.g., TAT), and stealth modifications can transform passive carriers into guided systems. While preclinical data show superior brain targeting and survival benefits, translation is hindered by manufacturing scalability, the lack of standardized N2B protocols, and the high cost of multifunctional systems. This analysis suggests that surface-functionalized N2B nanocarriers offer a viable paradigm, provided that the field prioritizes regulatory-ready, simplified designs over complex, multi-layered platforms.

Keywords: *Glioblastoma; nose-to-brain delivery; surface-functionalized nanocarriers; phytochemicals; active targeting.*

Introduction

Glioblastoma (GBM) is the most challenging primary malignant brain tumor in adults and is classified as grade IV astrocytoma due to its aggressive invasiveness, significant molecular heterogeneity, and consistently poor prognosis. Despite the current standard treatment regimen, which comprises maximal surgical resection followed by radiotherapy and temozolomide chemotherapy, the disease remains incurable, with a median overall survival of only 12–15 months [1]. The therapeutic landscape of GBM is hindered by a combination of biological and pharmacological challenges. Foremost among these is the blood-brain barrier (BBB) is a highly selective physiological barrier that, along with active efflux transporters such as P-glycoprotein (P-gp), prevents most chemotherapeutic agents from reaching the brain parenchyma at therapeutic concentrations. This challenge is further exacerbated by the tumor's intrinsic heterogeneity, which includes clinically distinct subtypes, IDH-wildtype, IDH-mutant, and pediatric-type, each possessing unique molecular drivers that collectively contribute to persistent recurrence and treatment resistance [2].

To overcome these barriers, phytochemicals have attracted considerable interest as potential anticancer agents. Compounds such as curcumin, resveratrol, and thymoquinone exhibit pleiotropic anti-GBM activity, including induction of apoptosis, inhibition of angiogenesis, and selective targeting of therapy-resistant glioma stem cells. However, the clinical translation of these potent agents is significantly hampered by inherent pharmaceutical limitations, such as poor aqueous solubility, chemical instability, and rapid hepatic metabolism, resulting in critically low systemic bioavailability, which impedes their effective delivery to the brain [3].

To address the dual challenges of BBB evasion and systemic bioavailability, the nose-to-brain delivery route has emerged as a transformative alternative to oral administration of drugs. This approach exploits the unique anatomical connection between the nasal cavity and the central nervous system, facilitating direct drug transport via the olfactory and trigeminal nerve pathways. By bypassing the BBB and first-pass hepatic metabolism, this noninva-

sive strategy provides a direct conduit for therapeutics to reach the brain, promising enhanced local drug accumulation with minimal systemic side effects. Nanocarriers have been developed to encapsulate and protect phytochemicals; however, their efficacy is often limited by non-specific biodistribution and rapid clearance from the nasal cavity[4,5]. Figure 1 visually contrasts the N2B pathway (bypassing the BBB) with the systemic route (blocked by BBB).

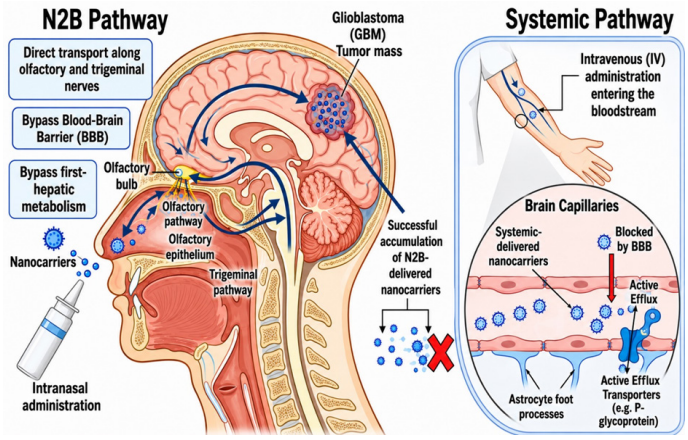

Figure 1. *Schematic comparison of nose-to-brain (N2B) delivery versus systemic intravenous administration for glioblastoma therapy.*

Nanocarrier and Surface Functionalization: A Unified Strategy

The efficacy of N2B delivery relies on two interconnected design aspects: the nanocarrier core and the engineered surface.

Core Nanocarrier Selection

The primary role of the core is to encapsulate phytochemicals and control their release rate. Key options include lipid-based carriers (liposomes, solid lipid nanoparticles, and nanostructured lipid carriers), which offer enhanced stability and controlled release [6]; polymer-based carriers (PLGA, chitosan, and alginate), valued for biodegradability and safety, with chitosan offering innate mucoadhesion [7]; and other systems, such as nanoemulsions and polymeric micelles, which provide high solubilization capacity for lipophilic drugs [8].

The critical formulation parameters for N2B success are particle size (<200 nm for efficient transport), surface charge (cationic is favored for mucoadhesion), high drug loading efficiency, and sustained release kinetics [9–12].

Surface Functionalization: Solving Specific Barriers

The surface of a nanocarrier determines its biological fate. Table 1 summarizes the key functionalization strategies, their mechanisms, and how they specifically address the limitations of phytochemical delivery.

Table 1. Key Surface Functionalization Strategies for N2B Phytochemical Delivery

Strategy	Component Example	Mechanism	Relevance to Phytochemicals	Reference
Active Targeting	Lactoferrin, Angiopep-2	Receptor-mediated transcytosis (BBB) or tumor recognition (CD44, EGFR)	Overcomes poor BBB penetration; directs to GBM cells	[13–17]
Mucoadhesive	Chitosan, Carbopol	Electrostatic/hydrogen bonding with mucin; opens tight junctions	Prevents rapid nasal clearance; allows time for nerve transport	[18,19]
Cell-Penetrating	TAT, Penetratin	Direct translocation/ macropinocytosis across membranes	Facilitates cytosolic delivery, evading P-gp efflux pumps	[20,21]
Stealth	PEGylation	Hydration shell prevents opsonin adsorption	Protects from enzymatic degradation & immune clearance	[22,23]
Stimuli-Responsive	pH/Redox-sensitive bonds	Triggered release in tumor microenvironment (low pH, high GSH)	Reduces systemic toxicity; ensures high intratumoral concentration	[24,25]
Dual-Targeting	Angiopep-2 + cRGD	Sequential: BBB crossing + tumor cell targeting	Delivers to invasive satellite cells missed by surgery	[26]

The integration of active targeting ligands (lactoferrin/Angiopep-2), a stealth PEG layer, cell-penetrating peptides (TAT/Penetratin), and GSH-responsive disulfide bond cleavage mechanism is illustrated in Figure 2 and Figure 3.

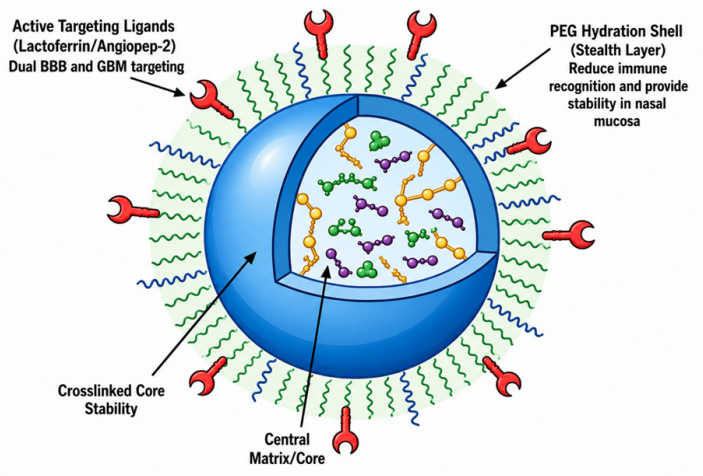

Figure 2. *Schematic representation of the engineered nanoparticle architecture showing the central matrix/core, crosslinked core stability, PEG hydration shell (stealth layer), and active targeting ligands such as lactoferrin/Angiopep-2 for dual blood–brain barrier (BBB) and glioblastoma (GBM) targeting. The PEG shell enhances mucoadhesion, minimizes immune recognition, and improves nanoparticle stability within the nasal mucosa.*

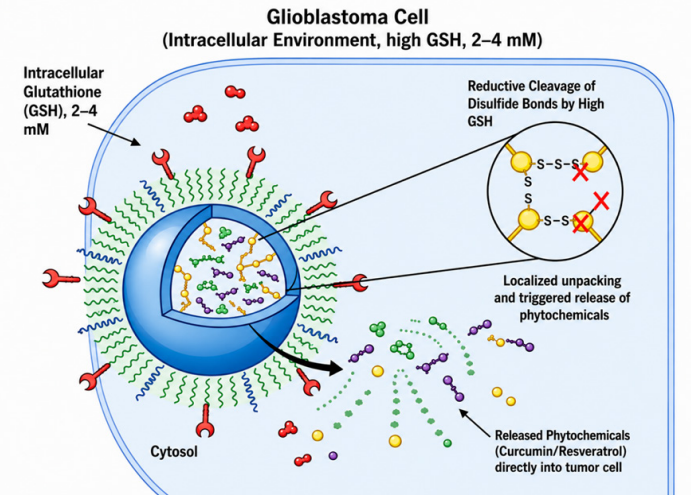

Figure 3. *Illustration of intracellular glutathione (GSH)-responsive nanocarriers within the glioblastoma microenvironment. Elevated intracellular GSH levels induce reductive cleavage of disulfide bonds, resulting in localized nanoparticle unpacking and controlled release of encapsulated phytochemicals such as curcumin and resveratrol directly into tumor cells for enhanced therapeutic efficacy.*

Preclinical Evaluation: From Bench to Animal Models

Preclinical assessments focus on proving that functionalization adds value to non-targeted systems [27,28].

In Vitro Assessment: GBM cell models (U87MG, T98G, and C6) were used to measure cellular uptake via flow cytometry and confocal microscopy, confirming receptor-mediated endocytosis [29]. Cytotoxicity was assessed using MTT assays, with functionalized nanocarriers demonstrating lower IC50 values than free drugs and non-targeted controls [30]. Mechanistic studies have evaluated apoptosis (Annexin V/PI staining), cell cycle arrest, and reduced migration/invasion via scratch and Transwell assays [31–33]. BBB transport is modeled using Transwell co-culture systems, in which human brain microvascular endothelial cells form a monolayer to assess receptor-mediated transcytosis and efflux pump evasion [34–37].

In Vivo Assessment: Orthotopic GBM models in rodents (stereotactic injection of U87MG-luciferase cells) are the gold standard [38,39]. Intranasal instillation (5-10 µL/nostril in mice) under anesthesia delivers the formulation to the olfactory epithelium [40]. Biodistribution using radiolabeled nanocarriers (^{99m}Tc, ^{64}Cu) quantifies brain-targeting efficiency, tumor-to-brain ratio, and off-organ distribution [41,42]. Efficacy studies monitor tumor volume via bioluminescence imaging and survival via Kaplan-Meier analysis, with functionalized carriers showing extended survival compared to controls [43]. Safety assessments include histopathological examination of the nasal mucosa (ciliary integrity) and evaluation of systemic toxicity through body weight, serum biochemistry, and organ histopathology [44].

Major Translational Challenges

Despite the robust preclinical data, clinical translation faces three interconnected hurdles [45].

Manufacturing and Reproducibility

The batch-to-batch consistency of critical quality attributes (particle size, polydispersity index, zeta potential, drug loading, and ligand density) remains difficult to achieve. Ligand density variations affect receptor binding and cellular uptake; insufficient ligands reduce targeting, whereas excess ligands cause steric hindrance [46,47]. Sterilization presents another challenge: autoclaving damages nanocarriers, 0.22 µm filtration fails for particles >200 nm, and gamma irradiation degrades ligands. Aseptic manufacturing is often required [48,49].

Regulatory Hurdles

No standardized protocols exist for the development of N2B nanomedicines. There is no consensus on predictive animal models (rodents have 50% olfactory epithelium vs. 5-10% in humans), and no standardized method to quantify direct N2B transport versus systemic absorption [4,50]. Safety requirements demand proof of no chronic nasal toxicity, ciliary impairment, or neurotoxicity due to direct brain access via the olfactory nerve [50]. Additionally, N2B products are often classified as combination products (drug + device), creating complex regulatory jurisdictions between FDA centers (CDER vs. CDRH) [51,52].

Clinical Translation Barriers

Rodent models poorly predict human responses due to anatomical differences in the nasal cavity, BBB transporter expression, and immune status [53,54]. Most orthotopic models use immunodeficient mice or single cell lines, lacking the genetic heterogeneity of human GBM [55]. Scalability is a major issue: laboratory methods (sonication, solvent evaporation, ultracentrifugation, and dialysis) do not translate to clinical-scale production, requiring complete process redevelopment (e.g., tangential flow filtration)[56,57]. The cost of targeting ligands (especially antibodies and peptides) and the need for cGMP facilities make clinical-scale manufacturing economically challenging, particularly for an orphan disease with only 12,000-15,000 US cases annually [58–61].

Conclusion

The treatment of glioblastoma multiforme (GBM) requires innovative multidisciplinary approaches owing to the limitations of conventional therapy. This review presents a therapeutic paradigm that integrates phytochemicals with nanotechnology and the nose-to-brain (N2B) delivery route to treat neurological disorders. Surface-functionalized nanocarriers have evolved from protective vehicles into sophisticated platforms capable of navigating the biological barriers that characterize GBM's intractability of GBM. The effective delivery of phytochemicals to GBM cells requires a rational design that incorporates active targeting ligands for tumor recognition (via transferrin, EGFR, or CD44 receptors), mucoadhesive polymers for nasal retention, cell-penetrating peptides for intracellular access, and stealth coatings to extend the circulation.

Advanced systems include dual-targeting nanocarriers that traverse the blood-brain barrier (BBB) and target tumors, as well as stimuli-responsive platforms that release therapeutic payloads within the tumor microenvironment. Preclinical evaluations have demonstrated that these systems can achieve superior brain targeting, enhance tumor accumulation, and improve survival rates. However, the clinical translation of these findings faces significant challenges. The complexity of multifunctional systems creates difficulties in manufacturing scalability, reproducibility, and sterilization under current Good Manufacturing Practice (cGMP) guidelines. The regulatory landscape lacks standardized protocols for N2B products and requires rigorous safety measures. The economic feasibility of clinical-scale manufacturing of GBM treatments further complicates their translation. The integration of phytochemicals, surface-functionalized nanocarriers, and N2B delivery offers an innovative framework for treating GBM. While preclinical data are promising, successful clinical translation requires addressing manufacturing, regulatory, and economic challenges through interdisciplinary collaborations. Future success depends on innovation in materials science, scalable manufacturing processes, and clear regulatory pathways to convert poorly bioavailable phytochemicals into effective therapies for this devastating disease.

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AI Disclosure
Artificial intelligence (AI)-assisted tools were utilized during the preparation of this manuscript. AI-based image generation tools were used for creating and refining scientific illustrations and graphical figures, while AI-assisted language editing tools were employed to improve grammar, clarity, and readability of the manuscript. The authors carefully reviewed, validated, and edited all generated content and take full responsibility for the accuracy, originality, and integrity of the final manuscript.

Conflict of Interest and Funding
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