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Review Article

Baicalein from Scutellaria baicalensis as Natural Therapeutic Agent for Glioblastoma

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Keywords

Baicalein, Glioblastoma, Scutellaria baicalensis, Neuroprotection, Anticancer, Blood-brain barrier.

Abstract

Glioblastoma multiforme (GBM), classified as a grade IV astrocytoma, remains one of the most formidable challenges in neuro-oncology due to its poor prognosis, high recurrence rate, resistance to apoptosis, extensive infiltration, and pronounced angiogenesis. Standard therapeutic modalities surgical resection, radiotherapy, and temozolomide offer only modest improvements in patient survival, highlighting the urgent need for multi-targeted agents capable of crossing the blood–brain barrier and addressing GBM's molecular heterogeneity. Baicalein, a flavonoid derived from Scutellaria baicalensis (Chinese skullcap), exhibits potent anti-inflammatory, antioxidant, neuroprotective, and anticancer activities, rooted in traditional Chinese medicine. Preclinical investigations have demonstrated baicalein's ability to inhibit GBM cell proliferation, induce apoptosis, suppress angiogenesis, and limit invasion through modulation of key signaling pathways. This review synthesizes current evidence on baicalein's phytochemistry, molecular targets, and pharmacokinetic challenges, including its limited solubility and bioavailability. Advances in formulation strategies and delivery systems are discussed, alongside preclinical findings, combination potential with conventional chemotherapeutics, and barriers to clinical translation. Comparisons with related flavonoids such as wogonin, luteolin, and quercetin are also presented, emphasizing baicalein's promise as an adjunct therapeutic candidate for the comprehensive management of glioblastoma.

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1. Introduction

1.1 Glioblastoma Multiforme

Glioblastoma multiforme (GBM) is an aggressive and highly invasive glioma, classified by the World Health Organization (WHO) as a grade IV astrocytoma [1]. It accounts for approximately 45–50% of all primary malignant brain tumors in adults and is associated with an extremely poor clinical prognosis. GBM may arise *de novo* (primary GBM) or progress from lower-grade gliomas (secondary GBM). Histopathologically, it is characterized by pronounced vascular proliferation, necrosis, cellular pleomorphism, and diffuse infiltration into adjacent brain parenchyma [2].

One of the principal challenges in managing GBM lies in its pronounced molecular heterogeneity. The Cancer Genome Atlas (TCGA) project has classified GBM into several molecular subtypes classical, mesenchymal, proneural, and neural each defined by distinct genetic alterations such as *EGFR* amplification, *PTEN* loss, *IDH1* mutation, and *TP53* alteration [3]. These molecular distinctions are associated with variable biological behavior and differential therapeutic responses. Consequently, they highlight the critical need for multi-targeted therapeutic strategies capable of modulating multiple oncogenic pathways simultaneously (Figure 1) [4].

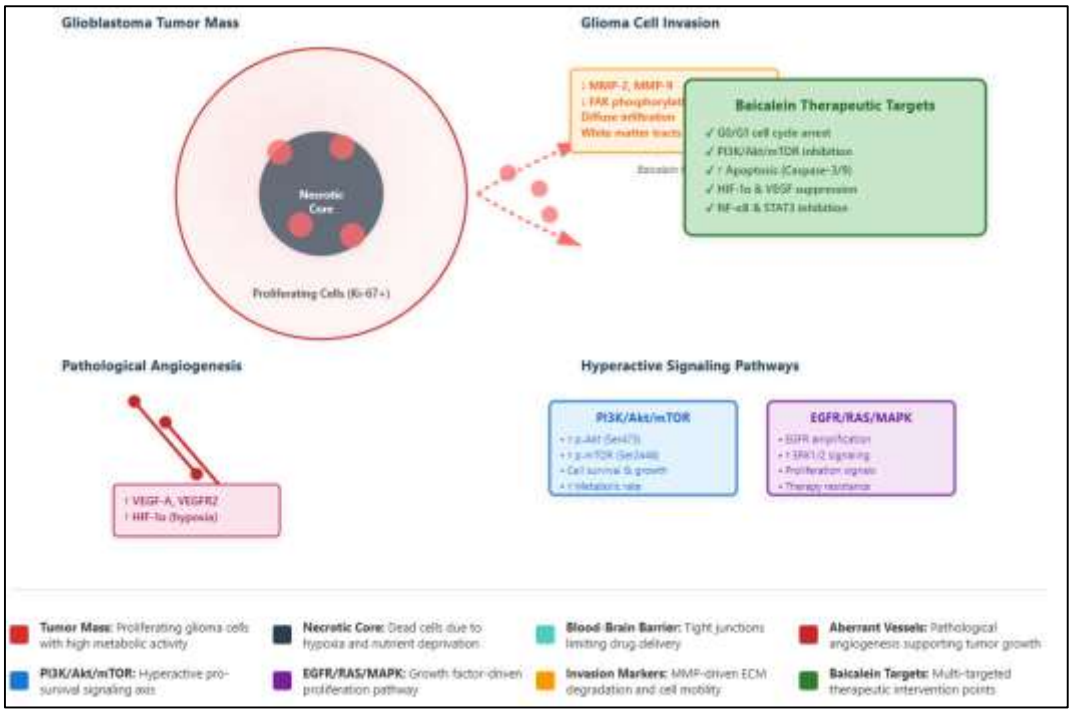

Figure 1: Schematic representation of glioblastoma pathophysiology.

1.2 Limitations of Standard Treatments

Current standard treatment for glioblastoma involves maximal safe surgical resection followed by radiotherapy and adjuvant chemotherapy with temozolomide (TMZ), an oral alkylating agent [5]. Although this regimen has modestly improved patient outcomes extending median survival to approximately 15 months it remains largely palliative, as most patients experience tumor recurrence within 6-9 months of initial therapy [6]. Resistance to temozolomide frequently arises due to upregulation of the DNA repair enzyme *O^6*-methylguanine-DNA methyltransferase (MGMT). Consequently, the methylation status of the *MGMT* promoter has emerged as a predictive biomarker for therapeutic response and prognosis [7].

The highly infiltrative nature of GBM poses an additional challenge, as complete surgical excision is rarely achievable. The persistence of glioma stem-like cells (GSCs) further contributes to therapeutic resistance and recurrence by promoting tumor repopulation following treatment [8]. Moreover, the blood–brain barrier (BBB) significantly restricts the delivery of most chemotherapeutic agents, preventing the attainment of effective drug concentrations within tumor tissue [9].

1.3 Natural Products in Cancer Therapy

Natural compounds have historically served as a rich source of therapeutic agents, with approximately 60 percent of approved anticancer drugs originating from natural sources or their derivatives [10]. Among these, flavonoids, a diverse class of polyphenolic secondary metabolites found in fruits, vegetables, and medicinal plants, have attracted considerable attention due to their potent antioxidant, anti-inflammatory, and anticancer properties [11]. Several flavonoids, including quercetin, luteolin, apigenin, and wogonin, have been extensively investigated for their anticancer potential in glioma models, demonstrating promising cytotoxic, pro-apoptotic, and antiproliferative effects [12].

1.4 Scutellarin *baicalensis* and Baicalein

Scutellaria baicalensis, commonly known as Chinese skullcap or *Huang Qin*, is an important herb in traditional Chinese medicine, widely used in formulations for its anti-inflammatory and antipyretic properties. The principal bioactive constituents of *S. baicalensis* are flavonoids, particularly baicalin, baicalein, and wogonin [13]. Baicalein (5,6,7-trihydroxyflavone) is the aglycone form of baicalin and has been shown to exhibit stronger biological activity in both in vitro and in vivo studies [14]. The compound exerts a broad spectrum of pharmacological effects, including attenuation of oxidative stress, suppression of inflammation through inhibition of NF-κB signaling, neuroprotection via modulation of NMDA receptors, and potent anticancer activity against several malignancies such as breast, lung, liver, prostate, colon cancers, and glioblastoma [15].

1.5 Why Focus on Baicalein for Glioblastoma?

Several features render baicalein particularly attractive for glioblastoma therapy. Its multi-targeted action modulates diverse signaling pathways simultaneously, which is essential for addressing the molecular heterogeneity of GBM tumors. Baicalein demonstrates moderate permeability across the blood-brain barrier, providing a viable pharmacological foundation, and exhibits promising anti-stem cell activity that may reduce tumor recurrence by targeting glioma stem-like cells. Furthermore, it shows low systemic toxicity compared with conventional chemotherapeutic agents and displays synergistic effects with drugs such as temozolomide and BCNU in preclinical studies [16].

2. Phytochemistry and Pharmacokinetics of Baicalein

2.1. Chemical Structure and Properties

Baicalein is a naturally occurring flavone with the IUPAC name 5,6,7-trihydroxyflavone. It has a molecular weight of 270.24 g/mol and possesses a characteristic flavone backbone bearing hydroxyl groups at positions 5, 6, and 7. These hydroxyl substituents are essential for the compound's radical-scavenging capacity and its ability to chelate transition metal ions involved in oxidative stress, thereby contributing to its potent antioxidant properties [17].

2.2. Sources and Natural Occurrence

Baicalein is primarily found in the dried root of *Scutellaria baicalensis* (*Huang Qin*), a perennial herb belonging to the family Lamiaceae. It is a major component of traditional Chinese medicine formulations such as *Huang Qin Tang*, which has historically been prescribed for the treatment of inflammatory disorders, liver diseases, and infections [18].

In addition to baicalein, *S. baicalensis* contains several related flavonoids. *Baicalin* is the glucuronide conjugate of baicalein, highly water-soluble and abundant in the plant. *Wogonin* (5,7-dihydroxy-8-methoxyflavone) exhibits comparable bioactivities, while *Oroxylin A*, a methoxylated flavone, is recognized for its anti-inflammatory and anticancer effects. Baicalein itself is more lipophilic than baicalin, rendering it more cell-permeable and often more pharmacologically potent in specific biological contexts [19].

Baicalein belongs to the flavone subclass of flavonoids, characterized by a 15-carbon skeleton comprising two aromatic rings (A and B) linked by a heterocyclic pyrone ring (C). The three hydroxyl groups located at positions 5, 6, and 7 on the A-ring are responsible for its strong antioxidant activity [20]. Baicalein is the aglycone form of baicalin, which differs by the presence of a glucuronic acid moiety. Both compounds are principal constituents of *S. baicalensis* roots, a medicinal herb used for centuries in Asian traditional medicine for inflammatory and infectious diseases [21].

Extraction and isolation of baicalein are typically performed using organic solvents such as ethanol or methanol, followed by chromatographic purification. Maintaining the purity and stability of baicalein is critical for ensuring consistent biological activity [22]. Pharmacokinetically, baicalein demonstrates moderate oral bioavailability due to poor water solubility and extensive first-pass metabolism, primarily through glucuronidation and sulfation in the liver and intestines. Although absorption occurs relatively rapidly, systemic plasma concentrations are generally low. Upon oral administration, baicalein is metabolized into baicalin and other conjugates, which may themselves be bioactive or act as reservoirs for baicalein release [23].

A major pharmacological limitation is baicalein's restricted penetration of the blood-brain barrier (BBB), which limits its access to the central nervous system. Several studies have shown that baicalein can cross the BBB to a limited extent, likely due to its lipophilicity and small molecular mass (approximately 270 Da), but the concentration reaching brain tissue remains low. This challenge has prompted the development of advanced delivery strategies, including nanoparticle-based systems, to enhance its central nervous system bioavailability [24].

Metabolic processes also influence baicalein's short half-life, reported to be approximately one to two hours in animal models, thereby limiting sustained therapeutic exposure. Recent formulation strategies employing nanocarriers, liposomes, or cyclodextrin complexes have demonstrated improved pharmacokinetic performance, enhanced brain targeting, and prolonged systemic circulation [25].

3. Mechanisms of Baicalein's Anti-Glioblastoma Activity

3.1. Inhibition of Glioma Cell Proliferation

3.1.1 Cell Cycle Arrest

Baicalein has been shown to induce cell cycle arrest in glioma cells at the G0/G1 phase by modulating the expression of key cell cycle regulatory proteins, including cyclin D1, cyclin E, CDK2, CDK4, p21, and p27. In studies using U87 and U251 glioma cell lines, treatment with baicalein resulted in a marked decrease in cyclin D1 and CDK4 expression, leading to inhibition of cell cycle progression and prevention of mitotic division [26].

3.1.2 PI3K/Akt/mTOR Pathway Suppression

The PI3K/Akt/mTOR signaling pathway is one of the most frequently dysregulated oncogenic cascades in glioblastoma, regulating essential cellular processes such as survival, metabolism, and growth [27]. Baicalein markedly inhibits the phosphorylation of Akt at Ser473, mTOR at Ser2448, and P70S6K, resulting in the suppression of protein synthesis and inhibition of cellular proliferation. Inhibition of this pathway also enhances the sensitivity of glioblastoma cells to chemotherapeutic agents [28].

3.2 Induction of Apoptosis

3.2.1 Mitochondria-mediated Apoptosis

Key features observed in baicalein-induced apoptosis include an increased Bax/Bcl-2 ratio, loss of mitochondrial membrane potential, release of cytochrome c into the cytoplasm, activation of caspase-9 and caspase-3, and cleavage of PARP [29]. These molecular events collectively initiate a cascade leading to programmed cell death. In a 2019 study involving human glioblastoma cells, treatment with baicalein significantly increased the proportion of Annexin V-positive cells in a dose-dependent manner, confirming its pro-apoptotic potential [30].

3.2.2 Oxidative Stress and ROS Generation

Baicalein also increases intracellular levels of reactive oxygen species (ROS), leading to oxidative stress that induces DNA damage and mitochondrial dysfunction.

This accumulation of ROS promotes apoptosis, antioxidant defense systems [31]. The elevated ROS levels may additionally influence p53 activation in wild-type cells and stimulate MAPK signaling through highlighting baicalein's therapeutic specificity and safety margin [32].

3.3 Autophagy Modulation

Autophagy plays a dual role in glioblastoma, functioning either as a pro-survival mechanism or as a pathway leading to autophagic cell death depending on the cellular context. Baicalein has been shown to induce autophagy through activation of AMP-activated protein kinase (AMPK), inhibition of mTORC1, and upregulation of LC3B-II formation and Beclin-1 expression [33]. In U251 glioblastoma cells treated with baicalein, the formation of autophagic vesicles was confirmed by electron microscopy and LC3 puncta staining. Interestingly, the combination of baicalein with autophagy inhibitors such as 3-methyladenine (3-MA) enhances apoptosis, indicating a potential synergistic therapeutic approach that exploits the balance between autophagy and programmed cell death [34].

3.4. Inhibition of Migration and Invasion

3.4.1 Suppressing Matrix Metalloproteinases (MMPs)

Matrix metalloproteinases MMP-2 and MMP-9 play a crucial role in degrading the extracellular matrix and are markedly overexpressed in glioblastoma. Baicalein has been shown to downregulate the expression of both MMP-2 and MMP-9 through two key mechanisms: (1) inhibition of NF-κB signaling and (2) suppression of urokinase-type plasminogen activator (uPA). This dual regulation results in reduced degradation of the basement membrane and a consequent decrease in the migratory and invasive capacity of glioblastoma cells [35].

3.4.2 Cytoskeletal Disruption

Baicalein disrupts the organization of the F-actin cytoskeleton and reduces the phosphorylation of focal adhesion kinase (FAK). These alterations prevent the formation of lamellipodia and focal adhesions that are essential for glioblastoma cell motility and invasion [36].

3.5. Anti-Angiogenic Effects

3.5.1 Suppression of VEGF Signaling

Baicalein downregulates VEGF-A expression, inhibits the phosphorylation of VEGFR2, and decreases angiopoietin-2 levels. These anti-angiogenic effects particularly in glioma cells that possess weakened ERK and p38 pathway activation. Notably, these effects are largely selective for tumor cells and do not significantly affect normal glial or neuronal cells, are further amplified under hypoxic conditions, owing to baicalein's inhibition of hypoxia-inducible factor 1-alpha (HIF-1α), a central transcriptional regulator of cellular responses to low oxygen tension [37].

3.5.2 *In-Vivo* Evidence

In chick chorioallantoic membrane (CAM) assays and mouse glioblastoma models, treatment with baicalein resulted in a significant reduction in microvessel density and a marked decrease in the expression of CD31-positive endothelial cells, confirming its potent anti-angiogenic activity *in vivo* [38].

3.6. Suppression of Glioma Stem-like Cells (GSCs)

Glioma stem-like cells (GSCs) play a critical role in therapeutic resistance, tumor recurrence, and radioresistance [39]. Baicalein has been shown to suppress GSC activity through several mechanisms, including the downregulation of stemness-associated markers such as CD133, Nestin, and SOX2, inhibition of Notch and STAT3 signaling pathways, and promotion of cellular differentiation as evidenced by increased expression of GFAP and β-III tubulin. These effects collectively reduce the self-renewal capacity and tumorigenic potential of GSCs in xenograft models [40].

3.7 Tumor Microenvironment Modulation

The glioblastoma microenvironment comprises immune cells, cytokines, extracellular matrix components, and metabolic byproducts that collectively support tumor growth and survival [41]. Baicalein exerts significant immunomodulatory effects within this microenvironment by reducing pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β. It inhibits the activation of NF-κB and STAT3, two key transcription factors that mediate tumor-promoting inflammation [42]. Baicalein also influences macrophage polarization, shifting the balance from the pro-tumorigenic M2 phenotype toward the antitumor M1 phenotype, and decreases microglial activation, which is frequently exploited by glioblastoma cells to facilitate invasion and immune evasion. Through these actions, baicalein reshapes the tumor microenvironment, enhances antitumor immune responses, and attenuates immunosuppressive signaling [43], [44].

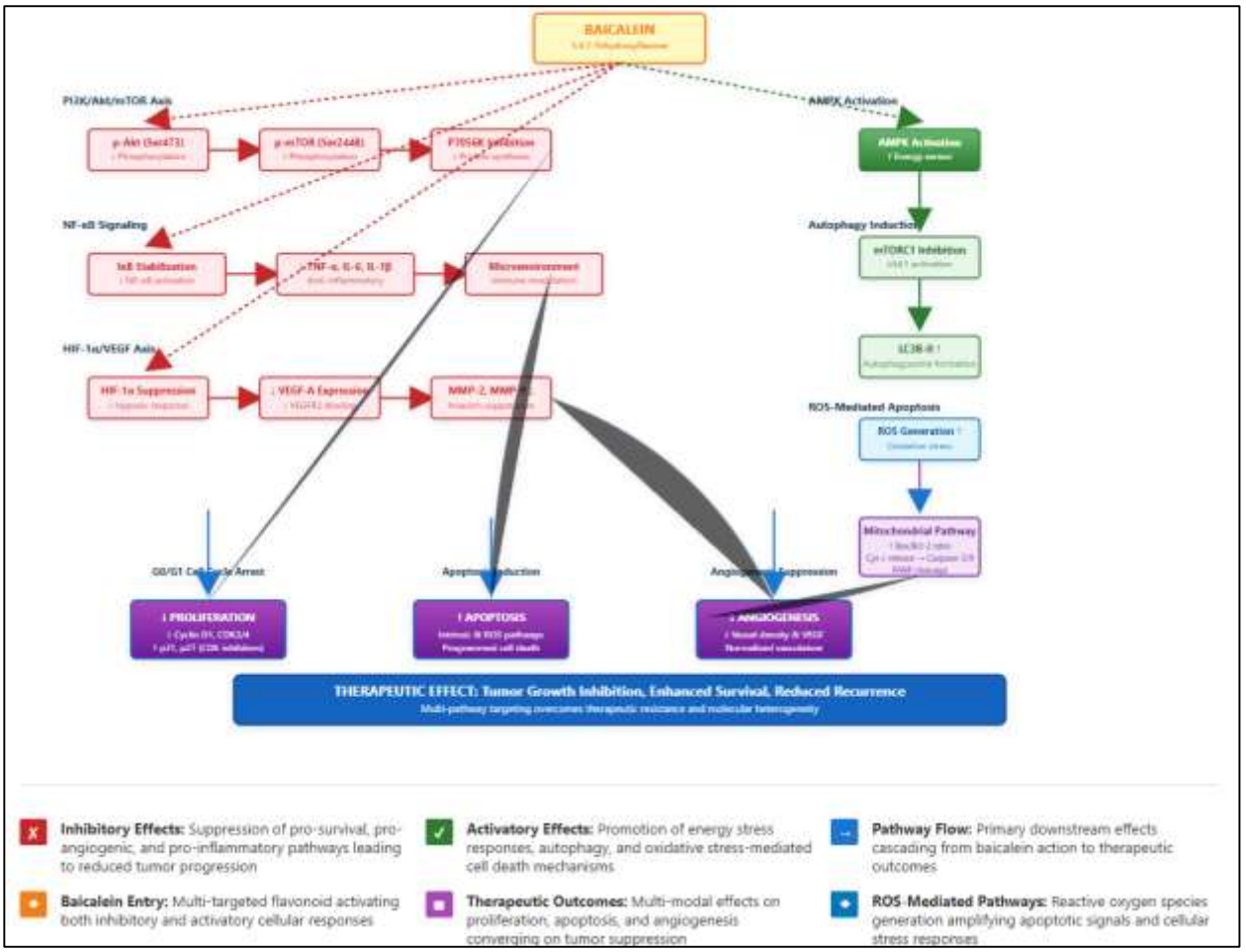

Figure 2 - Molecular Mechanisms of Baicalein in Glioblastoma

4. *In-Vivo* Evidence and Preclinical Evaluation of Baicalein in Glioblastoma

Although in vitro studies are essential for elucidating mechanistic insights, they often fail to fully reproduce the biological complexity of tumors in living organisms. To address this limitation, numerous in vivo investigations have been carried out to evaluate the anti-glioblastoma efficacy of baicalein in preclinical models. These studies have primarily focused on assessing its effects on tumor growth inhibition, suppression of angiogenesis, modulation of immune responses, and extension of overall survival [45].

4.1. Xenograft Models: Subcutaneous Implantation of Glioma Cells

One of the most widely used models for evaluating anticancer compounds is the subcutaneous xenograft model, in which human glioblastoma cells such as U87MG, U251, or T98G are implanted into immunodeficient mice, including BALB/c nude or NOD/SCID strains. In these experimental systems, baicalein has consistently demonstrated potent tumor growth inhibition [46]. U87MG cells were injected into nude mice followed by intraperitoneal administration of baicalein at a dose of 50 mg/kg per day. After 21 days of treatment, tumor volume was reduced by approximately 55 percent, with no evidence of significant weight loss or behavioral toxicity [47]. Similarly, O administration of baicalein at 30 mg/kg significantly suppressed tumor progression, decreased Ki-67 expression as a marker of cellular proliferation, and increased the number of cleaved caspase-3-positive cells in excised tumor tissues, indicating enhanced apoptosis [48].

4.2 Orthotopic Intracranial Models

Orthotopic glioma models, in which tumor cells are implanted directly into the mouse brain, typically within the striatum, more accurately recapitulate the human disease by preserving the native tumor microenvironment, invasiveness, and interactions with the blood-brain barrier. established an intracranial model using luciferase-labeled U251 glioma cells to monitor tumor progression [49]. Treatment with baicalein at a dose of 30 mg/kg resulted in a marked reduction in bioluminescent tumor signal and a significant increase in median survival, extending it from 28 days in control animals to 42 days in the treated group. Analysis of tumor tissues revealed decreased expression of MMP-9, VEGF, and HIF-1α, indicating inhibition of invasion and angiogenesis [50]. Histological examination through hematoxylin and eosin staining confirmed reduced tumor infiltration and neovascularization. The ability of baicalein to exert these effects within the brain further supports its partial permeability across the blood-brain barrier, a crucial characteristic for any therapeutic agent targeting glioblastoma [51].

4.3. Blood-Brain Barrier Penetration and Pharmacokinetics

One of the major challenges in glioblastoma treatment is the restrictive permeability of the blood–brain

barrier (BBB), which prevents many systemically administered drugs from attaining therapeutic concentrations in the brain. Although baicalein demonstrates modest BBB penetration, its overall bioavailability is constrained by rapid first-pass metabolism, low aqueous solubility, and a short biological half-life [52]. Studies employing in situ brain perfusion techniques in rat models have confirmed that baicalein reaches the brain parenchyma at measurable concentrations, with a logP value of approximately 2.5, suggesting that it primarily crosses the BBB via passive diffusion. Efforts to enhance its delivery to the central nervous system, as discussed in Section 6, remain a critical focus of current research [53], [54].

4.4. Angiogenesis Inhibition Confirmed *In-Vivo*

In vivo anti-angiogenic activity of baicalein has been demonstrated through several experimental approaches, including immunohistochemistry (IHC) for CD31 as an endothelial marker, ELISA-based quantification of VEGF in plasma and tumor tissues, and chorioallantoic membrane (CAM) assays in chicken embryos [55]. In xenograft models, tumors treated with baicalein consistently display a marked reduction in microvessel density, reflected by a 30 to 40 percent decrease in CD31 staining, along with diminished VEGF expression and suppression of HIF-1α under hypoxic conditions. These findings indicate that baicalein contributes to the normalization of aberrant tumor vasculature commonly observed in glioblastoma, potentially improving drug delivery while mitigating edema and hypoxia-driven tumor progression [56], [57].

4.5. Tumor Microenvironment and Immune Modulation *In Vivo*

Although glioblastoma has traditionally been considered an immunologically “cold” tumor, recent studies highlight the significant contribution of tumor-associated macrophages (TAMs), microglia, and inflammatory cytokines to tumor survival, progression, and therapeutic resistance. Baicalein has been shown to modulate this immunosuppressive microenvironment effectively [58]. In syngeneic glioma models, such as GL261 cells implanted in C57BL/6 mice, treatment with baicalein reduced the infiltration of CD206-positive M2 macrophages while increasing iNOS-positive M1 macrophages, thereby promoting antitumor immune activity [59]. After two weeks of treatment, decreased circulating levels of IL-6, TNF-α, and TGF-β were observed [60]. In addition, activation of NF-κB and STAT3, two major transcriptional regulators of inflammation in glioblastoma, was significantly downregulated in tumor tissues. This immunomodulatory capacity positions baicalein not only as a direct antitumor agent but also as a regulator of the tumor microenvironment, with the potential to enhance the efficacy of immune checkpoint inhibitors and other immunotherapeutic strategies [61].

4.6. Safety and Toxicology in Animal Studies

The safety profile of baicalein has been comprehensively evaluated in rodent models. Oral and intraperitoneal administration at doses of up to 100 mg/kg per day did not induce any signs of systemic or organ-specific toxicity. Serum liver enzymes, including alanine aminotransferase (ALT) and aspartate aminotransferase (AST), as well as renal function markers such as creatinine and urea, remained within normal physiological limits. Hematological parameters were also unaffected [62]. Histopathological examination of major organs, including the heart, liver, spleen, kidneys, and lungs, revealed no significant morphological alterations. Furthermore, no behavioral abnormalities, such as changes in locomotion or grooming activity, were detected [63]. This favorable safety profile, together with the compound’s demonstrated therapeutic efficacy, supports the potential of baicalein for chronic administration and provides a strong foundation for its progression toward clinical evaluation (Table 1) [64].

4.7. Comparative Evaluation with Standard Therapies

Co-treatment of baicalein with temozolomide in U87 xenograft models has demonstrated synergistic inhibition of tumor growth. Baicalein downregulated the expression of O^6-methylguanine-DNA methyltransferase (MGMT), thereby sensitizing glioma cells to temozolomide by impairing DNA repair mechanisms [65]. The combination treatment also reduced the expression of stemness-associated markers, suggesting a potential role in limiting tumor recurrence. Although data remain limited, preliminary studies indicate that baicalein may enhance radiosensitivity in glioblastoma cells by suppressing key DNA repair pathways, including ATM and Rad51, and by augmenting radiation-induced reactive oxygen species generation. Further validation in orthotopic glioblastoma models is required to confirm its potential as a radiosensitizing agent [66].

Table 1: Summary of *in vivo* findings.

S. No.	*In-vivo* parameter	Effect of Baicalein	References
1.	Tumor growth	Decrease 50-60 %	[67]
2.	Survival	Increase 40-60%	[68], [69]
3.	Angiogenesis	Decrease VEGF, HIF, CD31 + vessels	[70]
4.	BBB penetration	Moderate (detectable levels in brain)	[71], [72]
5.	Inflammatory cytokines	Decrease IL-6, TNF, IL, TGF	[73]

6.	Stem like cell reduction	Decrease CD133, Nestin, increase GFAP	[74], [75], [76]
7.	Toxicity	No major systemic toxicity or weight loss	[77]
8.	TMZ combination	Synergistic effect	[78], [79]

4.8. Limitations of Current In Vivo Studies

Despite promising preclinical findings, several limitations continue to hinder the clinical translation of baicalein in glioblastoma therapy. At present, no human clinical trials have been registered to evaluate its safety or efficacy in patients with glioblastoma. The pharmacokinetic profile of baicalein also remains insufficiently characterized, with limited data available on its brain tissue concentrations, half-life, and metabolic pathways [80]. Furthermore, most existing studies rely on immunodeficient xenograft models, which do not adequately represent the complex immune interactions present in the human tumor microenvironment. Addressing these gaps through comprehensive pharmacological, immunological, and clinical investigations is essential to facilitate the successful translation of baicalein into therapeutic application [81].

5. Nanotechnology and Advanced Drug Delivery Systems for Baicalein in Glioblastoma Therapy

5.1. The Challenge of Delivering Baicalein to the Brain

Despite the promising anticancer activity of baicalein observed in both in vitro and in vivo studies, its clinical translation is constrained by several pharmacological and physiological limitations. These include poor aqueous solubility, rapid metabolism leading to low oral bioavailability, a short systemic half-life, and limited permeability across the blood–brain barrier (BBB) [82]. As a result, achieving therapeutic concentrations requires high doses, which are impractical and potentially unsafe in clinical applications. To overcome these barriers and enhance therapeutic efficacy, advanced drug delivery systems based on nanotechnology have been extensively explored [83].

Nanotechnology offers several key advantages for baicalein delivery, including improved solubility and stability, enhanced BBB penetration, tumor-specific targeting, and controlled or sustained drug release. Moreover, it enables the co-delivery of baicalein with other chemotherapeutic agents, facilitating combination therapy approaches that may enhance treatment outcomes in glioblastoma [84].

5.2. Types of Nanocarriers Used for Baicalein Delivery

5.2.1. Polymeric Nanoparticles

Polymeric nanoparticles formulated from biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG), and chitosan have been extensively employed to encapsulate baicalein and enhance its pharmacological performance. PLGA–PEG-based baicalein nanoparticles have been shown to prolong systemic circulation and reduce macrophage-mediated clearance [85]. In a study conducted by Kumar et al. (2020), baicalein-loaded PLGA nanoparticles with an average diameter of approximately 150 nanometers achieved significantly higher brain distribution and tumor accumulation compared with the free drug in rats bearing C6 gliomas. These nanoparticles exhibited sustained drug release, minimal systemic toxicity, and enhanced apoptotic activity in glioma cells, demonstrating their potential as an effective delivery platform for glioblastoma therapy [86].

5.2.2. Liposomes

Liposomes are phospholipid-based vesicular carriers capable of encapsulating both hydrophilic and lipophilic drugs, making them versatile platforms for drug delivery. Baicalein-loaded liposomes modified with transferrin or lactoferrin have demonstrated increased cellular uptake in glioblastoma cells through receptor-mediated endocytosis. These surface-modified liposomes exhibit improved penetration across the blood–brain barrier by exploiting endogenous receptor transport pathways. In preclinical studies, transferrin- and lactoferrin-conjugated baicalein liposomes showed enhanced accumulation in brain tumor tissue and produced a significant reduction in tumor volume in rat orthotopic glioma models, supporting their potential for targeted glioblastoma therapy [87].

5.2.3. Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) offer superior physical stability compared with liposomes and are more amenable to large-scale production for clinical applications. Baicalein-loaded SLNs with an average particle size of approximately 100 nanometers have demonstrated a threefold increase in bioavailability and a 2.5-fold enhancement in brain penetration relative to the free compound in pharmacokinetic evaluations. In glioma-bearing mouse models, treatment with baicalein SLNs resulted in a 65 percent reduction in tumor growth over a three-week period, accompanied by minimal systemic toxicity, highlighting their potential as an efficient and safe delivery system for glioblastoma therapy [88].

5.2.4. Nanomicelles

Nanomicelles are amphiphilic core–shell nanostructures designed to enhance the solubility and delivery of poorly water-soluble drugs. Baicalein-loaded nanomicelles formulated using Pluronic F127 have demonstrated significantly improved aqueous solubility and enhanced cytotoxicity against glioblastoma cells. Owing to the enhanced permeability and retention (EPR) effect, these nanomicelles preferentially accumulate in tumor tissues, facilitating targeted delivery and improved therapeutic efficacy [89].

5.2.5. Dendrimers and Hybrid Nanostructures

Polyamidoamine (PAMAM) dendrimers functionalized with baicalein and conjugated to brain-targeting ligands have demonstrated enhanced cellular uptake in glioma cells and prolonged retention within brain parenchyma [90]. These highly branched nanostructures enable efficient drug loading, controlled release, and improved penetration across the blood–brain barrier. In addition, hybrid nanosystems that integrate both lipid and polymer components provide optimized release kinetics and the capacity for multi-drug encapsulation. Such hybrid formulations offer the dual advantages of stability and versatility, representing a promising strategy for delivering baicalein and other therapeutics in glioblastoma management [91].

5.3. Strategies for BBB Targeting

5.3.1 Surface Ligands for Receptor-Mediated Transport

Transferrin receptors are highly overexpressed in both the blood–brain barrier and glioma cells, making them an effective target for ligand-mediated nanoparticle delivery. Other ligands, including lactoferrin, apolipoprotein E, and arginine–glycine–aspartic acid (RGD) peptides, have also been utilized to facilitate the transport of nanoparticles into the central nervous system [92]. Baicalein nanoparticles functionalized with transferrin exhibited approximately 2.5-fold higher uptake in glioma cells compared with unmodified nanoparticles, confirming the efficacy of receptor-targeted delivery strategies for improving drug accumulation in brain tumors [93].

5.3.2 Cell-Penetrating Peptides

Cell-penetrating peptides (CPPs), such as the TAT peptide derived from the human immunodeficiency virus (HIV), can be conjugated to baicalein-loaded nanocarriers to enhance their penetration into the central nervous system. These peptides facilitate translocation across cellular membranes and transiently modulate tight junctions, thereby improving drug delivery to the brain without compromising the structural integrity of the blood–brain barrier [94].

5.3.3 pH-sensitive and Enzyme-responsive Systems

The tumor microenvironment in glioblastoma is characterized by a lower pH compared with that of normal tissues. pH-sensitive polymeric nanocarriers exploit this feature to achieve site-specific drug release, ensuring that baicalein is preferentially liberated within acidic tumor regions. This targeted release mechanism enhances the therapeutic index of baicalein by increasing local drug concentration at the tumor site while minimizing systemic exposure and off-target effects [95].

5.4. Multifunctional Nanocarriers for Combined Therapy

5.4.1. Temozolomide

Dual-drug nanoparticle formulations encapsulating both temozolomide and baicalein have demonstrated synergistic cytotoxic effects and pronounced suppression of O^6-methylguanine-DNA methyltransferase (MGMT) expression in glioblastoma cells. In orthotopic glioblastoma mouse models, treatment with the dual-loaded nanoparticles significantly extended median survival to 58 days compared with 32 days in animals receiving temozolomide alone. These findings underscore the therapeutic advantage of combining baicalein with standard chemotherapeutic agents through nanocarrier-based co-delivery systems to enhance efficacy and overcome drug resistance [96].

5.4.2. Curcumin, Resveratrol, and Wogonin

Combinatorial delivery of flavonoids has been shown to enhance bioavailability and simultaneously modulate multiple oncogenic pathways, including NF-κB and MAPK signaling. Co-loaded nanocarriers containing baicalein in combination with other flavonoids have demonstrated increased intracellular reactive oxygen species generation and augmented autophagic flux, contributing to enhanced cytotoxicity and tumor suppression in glioblastoma models. These synergistic effects highlight the potential of multi-flavonoid formulations to achieve broader mechanistic coverage and improved therapeutic outcomes [97].

5.4.3. Photosensitizers and Radiosensitizers

Baicalein-loaded nanoparticles have also been integrated with iron oxide cores to enable magnetic hyperthermia or functionalized with near-infrared (NIR) dyes to facilitate photothermal therapy. These multifunctional systems allow the simultaneous delivery of chemotherapeutic and thermotherapeutic modalities, thereby enhancing tumor cell eradication while maintaining spatial and temporal control of treatment [98].

5.5. Administration Routes and Clinical Feasibility

Most preclinical studies investigating baicalein employ intravenous or intraperitoneal routes of administration. However, successful clinical translation will require careful consideration of clinically feasible delivery methods that ensure both therapeutic efficacy and patient compliance [99].

5.5.1 Oral Delivery

Baicalein-loaded solid lipid nanoparticles and polymeric micelles have demonstrated promising oral bioavailability in preclinical evaluations. The incorporation of mucoadhesive polymers such as chitosan further enhances gastrointestinal absorption by prolonging residence time and facilitating trans-epithelial transport, thereby improving systemic exposure and therapeutic potential [100].

5.5.2 Intranasal Delivery

Direct intranasal delivery provides a non-invasive route that bypasses the blood–brain barrier, allowing rapid drug transport from the nasal mucosa to the brain. Baicalein-loaded gels and nanoemulsions have demonstrated significant brain accumulation following intranasal administration in rat models, confirming the feasibility of this approach for targeted

glioblastoma therapy [101].

Direct infusion of therapeutic agents into the brain parenchyma through catheter-based systems enables localized and controlled drug delivery. Convection-enhanced delivery (CED) of baicalein-loaded nanoparticles in rodent glioblastoma models has demonstrated efficient regional distribution within tumor tissue and significantly reduced systemic exposure, supporting its potential as a targeted intracerebral treatment strategy [102].

5.6. Toxicity and Safety of Nanocarriers

For clinical translation, nanocarriers must demonstrate biodegradability, biocompatibility, and an absence of immunogenicity or systemic toxicity. Poly(lactic-co-glycolic acid) (PLGA) and lipid-based delivery systems, both approved by the U.S. Food and Drug Administration for human use, have been widely utilized in baicalein formulations. Long-term preclinical studies in animal models have reported no evidence of hepatotoxicity, nephrotoxicity, or immunological adverse effects associated with baicalein-based nanoformulations, further supporting their safety and translational potential [103].

Table 2 outlines innovative future directions for

5.5.3 Convection-Enhanced Delivery

baicalein-based combination therapies in glioblastoma, emphasizing synergistic strategies aimed at overcoming tumor resistance and enhancing therapeutic efficacy. One promising approach involves co-administration of baicalein with DNA repair inhibitors to amplify reactive oxygen species–induced DNA damage, although careful dose optimization is essential to minimize potential toxicity. Another strategy integrates baicalein with anti-angiogenic agents to achieve dual suppression of vascular endothelial growth factor and inhibition of endothelial cell proliferation, thereby facilitating improved drug penetration into the tumor core [104].

Exosome-mediated delivery systems also represent a promising avenue for targeted transport of combined immunomodulatory and chemotherapeutic agents, though these remain at the preclinical stage. Furthermore, the combination of baicalein with oncolytic viruses leverages the oxidative tumor microenvironment to enhance viral replication and tumor lysis, necessitating further investigation into formulation compatibility and biosafety for clinical application [91].

Table 2: Future directions in Combination Therapies.

S. No.	Strategy	Rationale	Considerations	References
1.	Baicalein + DNA repair inhibitors	To synergize with DNA damage caused by Baicalein-induced ROS	Requires precise dosing to avoid toxicity	[105]
2.	Baicalein+ anti-angiogenic agents	Dual suppression of VEGF and endothelial growth	May improve drug penetration into tumor core	[106]
3.	Baicalein + exosome-based delivery	For targeted delivery of combined immune and chemo therapeutics	Still under preclinical investigation	[21]
4.	Baicalein + oncolytic viruses	To increase viral replication and tumor lysis under ROS rich environments	Compatibility and safety need evaluation	[107]

6. Clinical considerations and translational potential

6.1. Human Safety Data of Baicalein

Baicalein has been utilized for centuries in traditional Chinese medicine, primarily for the treatment of inflammatory and infectious diseases. Its long history of human use provides preliminary assurance regarding safety and tolerability. Oral doses of up to 200 mg per day of baicalein, administered as part of *Scutellaria baicalensis* extracts, have been used safely in herbal formulations. In a Phase I clinical study conducted to evaluate baicalein in cardiovascular inflammation, oral doses of up to 300 mg per day were well tolerated, with no significant alterations observed in liver, kidney, or hematological parameters. Mild and transient side effects, such as gastrointestinal discomfort, were reported in fewer than ten percent of participants [108].

Despite these encouraging findings, no clinical trials have yet been conducted to assess baicalein in glioblastoma or other central nervous system malignancies. Translating its preclinical promise into clinical utility will require standardized formulation development to distinguish between pure compound and extract-based preparations, optimization of administration routes including oral, intranasal, and nanoparticle-mediated intravenous delivery, comprehensive toxicity studies in large animal models, and well-designed Phase I and II clinical trials to establish safety, pharmacokinetics, and preliminary efficacy [109].

6.2. Pharmacokinetic Limitations

Baicalein exhibits several pharmacokinetic limitations that hinder its clinical application. These include low oral bioavailability, estimated at approximately 2 to 5 percent, rapid metabolism through glucuronidation and sulfation, and a short elimination half-life of less than 1.5 hours in humans. Several strategies have been proposed to overcome these challenges. The use of prodrugs such as baicalin can enhance systemic exposure by improving solubility and metabolic stability. Nanoparticle-based formulations have been developed to circumvent first-pass metabolism and facilitate controlled drug release. Co-administration

with bioenhancers such as piperine has also been explored to inhibit metabolic degradation and improve absorption. Additionally, intranasal delivery provides a direct route to the brain, bypassing the blood–brain barrier and enhancing central nervous system targeting. Comprehensive pharmacokinetic studies in both rodent models and humans remain essential prerequisites before the initiation of clinical trials for glioblastoma [110].

6.3 Regulatory and Developmental Hurdles

Table 3 summarizes the major regulatory and developmental challenges that currently impede the advancement of baicalein as a therapeutic candidate for glioblastoma, together with potential strategies to address them. One of the principal obstacles is the lack of Good Manufacturing Practice (GMP)-grade baicalein, which can be resolved through the establishment of commercial-scale, standardized production pipelines to ensure consistent quality and scalability. The compound's undefined regulatory status represents another critical barrier, highlighting the need for clear guidance from the U.S. Food and Drug Administration and the European Medicines Agency regarding its classification as either a conventional drug or a botanical extract. In addition, limitations in current clinical trial designs may be mitigated by developing glioblastoma-specific clinical endpoints that more accurately reflect patient-centered outcomes. Finally, the uncertainty surrounding blood–brain barrier penetration underscores the importance of validating central nervous system exposure in humans through advanced imaging modalities such as positron emission tomography or cerebrospinal fluid sampling. Addressing these challenges collectively will help streamline baicalein's translational trajectory and accelerate its path toward clinical approval [111].

Table 3: Regulatory and Developmental Hurdles.

S. No.	Challenge	Strategy to overcome	References
1.	Lack of GMP grade baicalein	Establish commercial scale, standardized production	[112]
2.	Undefined regulatory status	Clarify FDA\EMA pathways- drug vs. botanical extract classification	[113]
3.	Inadequate clinical trial design	Develop GBM-specific endpoints	[114]
4.	BBB penetration concerns	Validate CNS exposure in humans via PET tracers or CSF sampling	[115]

6.4. Potential Roles for Baicalein in GBM Management

Baicalein holds significant promise as an adjunctive and supportive therapeutic in glioblastoma management. As an adjunct to temozolomide and radiotherapy, it contributes to sensitization and modulation of the tumor microenvironment, thereby enhancing overall therapeutic efficacy. In maintenance therapy, baicalein may be employed post-surgery or following radiation to delay recurrence through its anti-proliferative and anti-inflammatory actions. As an immunotherapy booster, it has the potential to mitigate immune evasion mechanisms, improving antitumor immune responses. Furthermore, its anti-edema, anti-inflammatory, and neuroprotective effects support its role in palliative care. The compound's diverse mechanisms of action position it as a multifunctional therapeutic candidate applicable across both early and late stages of glioblastoma management [116].

In addition to baicalein, several medicinal plants have demonstrated substantial therapeutic potential. *Mimosa pudica* L. and *Cyperus scariosus* exhibit notable bioactivity, with evidence suggesting their curative or supportive roles in diseases such as monkeypox and cancer. Species belonging to the *Cannabaceae* family have been reported to possess anticancer properties, showing promise in the management of carcinoma. Similarly, *Mangifera indica* L. has exhibited strong anticancer efficacy, as well as beneficial effects in Parkinson's disease, conjunctivitis, coronavirus disease 2019 (COVID-19), cardiovascular disorders, and diabetes. Additional investigations have explored its applications in germplasm improvement, artificial intelligence–based biomedical modeling, dysmenorrhea, vitiligo, and stereoisomeric cancer therapeutics [117].

Advances in analytical technologies such as gas chromatography–tandem mass spectrometry (GC-MS/MS) and high-resolution liquid chromatography–mass spectrometry–quadrupole time-of-flight (HR-LCMS-QTOF) have further enhanced the characterization of these phytoconstituents, facilitating modern integrative cancer research. Collectively, findings from conventional and traditional medicinal studies underscore the vast therapeutic potential of baicalein and related phytocompounds in addressing cancer and other multifactorial diseases [118].

Conclusion

Glioblastoma remains one of the most aggressive and therapeutically challenging malignancies of the central nervous system. Despite advances in surgical resection, radiotherapy, and chemotherapy, overall survival outcomes remain poor, with most patients experiencing relapse within 12 to 18 months of diagnosis. Amid this bleak therapeutic landscape, baicalein, a flavonoid compound isolated from *Scutellaria baicalensis*, has emerged as a promising natural therapeutic candidate with significant anti-glioblastoma potential demonstrated across multiple *in vitro* and *in vivo* models. Mechanistically, baicalein exhibits remarkable versatility. It inhibits cellular

proliferation, induces apoptosis, suppresses angiogenesis, modulates immune responses, and targets glioma stem-like cells. Preclinical investigations have consistently shown tumor growth suppression, prolonged survival, and normalization of the tumor microenvironment in rodent models. Baicalein also demonstrates an excellent safety and biocompatibility profile, with minimal toxicity even at relatively high doses, a feature that is particularly advantageous for chronic therapeutic use. Its synergistic potential has been highlighted in combination therapies, where additive or synergistic effects are observed alongside temozolomide, radiation, immunotherapeutic agents, and other phytochemicals. Furthermore, the development of nanotechnology-based delivery systems has successfully addressed limitations related to poor aqueous solubility, rapid metabolism, and restricted blood–brain barrier permeability. Nevertheless, several key gaps must be addressed before baicalein can achieve clinical translation. These include the establishment of standardized formulations suitable for human use, comprehensive pharmacokinetic and toxicological profiling, well-structured clinical trials specifically designed for glioblastoma, and rigorous evaluation of long-term safety and optimal dosing strategies. Baicalein represents a highly promising adjunctive and potentially stand-alone agent for future glioblastoma management. Its favorable safety profile, broad-spectrum anticancer activities, and ability to modulate multiple tumor-associated pathways underscore its potential as a next-generation therapeutic. The integration of modern drug delivery systems, particularly nanotechnology, will be instrumental in realizing its full clinical potential. Continued interdisciplinary research and investment in translational development are essential to bring this ancient compound into the realm of modern glioblastoma therapy, offering renewed hope in a field that has long faced therapeutic stagnation.

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