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Residual Glioma Stem Cells and the Post-surgical Microenvironment in Glioblastoma Recurrence: Mechanistic Basis and Therapeutic Potential of Chinese Herbal Medicines and Natural Products

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Abstract: ***Standard treatment for glioblastoma (GBM) combines maximal safe resection, radiotherapy, and temozolomide, yet recurrence remains common and is usually detected near the resection cavity. Longitudinal single-cell studies, paired primary-recurrent tumor analyses, and resection models indicate that recurrence reflects more than the persistence of infiltrating tumor cells; it also involves therapy-induced cell-state transitions and post-surgical tissue repair. Residual glioma stem cells (GSCs) may survive treatment through quiescent or slow-cycling states, enhanced DNA damage responses, metabolic reprogramming, and phenotypic plasticity. Reactive astrocytes, immunosuppressive myeloid cells, extracellular matrix remodeling, and changes in vascular barrier function may further support residual-cell survival and regrowth. This narrative review examines the interaction between residual GSCs and the post-surgical microenvironment and evaluates evidence for Chinese herbal formulations and natural products that affect GSC stemness, ferroptosis, proteostasis, inflammatory and immune signaling, or local drug delivery. Current evidence is derived predominantly from in vitro and animal studies, and no clinical study has established that these interventions prevent post-surgical recurrence in patients with GBM. Future work should use immunocompetent models that incorporate resection and standard chemoradiotherapy and should establish quantitative relationships among local exposure, pharmacodynamic biomarkers, formulation quality, and safety in normal brain tissue.***

Keywords: Glioblastoma, Glioma stem cells, Post-surgical microenvironment, Tumor recurrence, Chinese herbal medicine, Natural products, Local delivery.

1. Introduction

1.1 Clinical Context and Patterns of Recurrence

The 2021 World Health Organization classification of central nervous system tumors introduced an integrated molecular framework for adult-type diffuse gliomas; throughout this review, GBM primarily refers to IDH-wildtype glioblastoma [1]. Current management is based on maximal safe resection followed by radiotherapy and temozolomide (TMZ), with treatment adapted to age, performance status, and molecular features [2-4]. Most patients nevertheless experience recurrence, highlighting the clinical importance of tumor cells that persist after initial therapy and of the microenvironment in which they remain.

Recurrence is concentrated within the original surgical cavity and high-dose radiation field, although it is not exclusively local. In a retrospective series of 54 patients treated with TMZ-based chemoradiotherapy, 39 developed recurrence; 80% of these patients had a central recurrence, while in-field noncentral, marginal, and distant failures were also observed [5]. This distribution supports the importance of local minimal residual disease but does not exclude distant infiltration, subventricular dissemination, or therapy-driven clonal and state evolution. A satisfactory model of recurrence must therefore account for both local predominance and spatial heterogeneity.

1.2 Central Question and Rationale

Chinese herbal medicines and natural products encompass substantial chemical diversity, and some constituents can influence GSC survival, redox homeostasis, or microenvironmental signaling. Multitarget activity alone, however, is not a translational advantage. Candidate interventions must achieve relevant exposure, engage verifiable targets, be produced reproducibly, and be evaluated in models that reflect the intended clinical setting. This review therefore focuses on the mechanistic links among residual GSCs, the post-surgical microenvironment, and recurrence, and on intervention strategies that address this axis.

1.3 Scope and Evidence Appraisal

This is a question-driven narrative review rather than a systematic review. Priority was given to international classifications and clinical guidance, studies reporting recurrence location or paired primary-recurrent specimens, functional experiments that track residual cells after treatment, immunocompetent models incorporating surgical resection and longitudinal sampling, and natural-product studies directly examining GSCs, TMZ resistance, glial or immune microenvironments, blood-brain barrier biology, or local delivery. Because the literature search was not preregistered, no pooled effect estimates were calculated and the review does not claim to include every candidate compound.

2. Residual GSCs as Cellular Substrates of Post-surgical Recurrence

2.1 Functional Definition and Cell-state Plasticity of GSCs

GSCs are operationally defined by sustained self-renewal, generation of heterogeneous progeny, and tumor reconstitution in an appropriate model, rather than by expression of CD133, SOX2, or Nestin alone. Transplantation experiments by Singh et al. provided functional evidence for brain tumor-initiating cells [6], and subsequent work showed that stem-like phenotypes vary with patient of origin, anatomical region, and treatment pressure [9]. Recurrence-initiating capacity should therefore be evaluated through cell state, clonal behavior, and tumor-reconstitution assays rather than inferred from a single marker. The cellular- state framework proposed by Neftel et al. and paired primary-recurrent single-cell atlases indicate that GBM cells transition among neural progenitor-like, oligodendrocyte progenitor-like, astrocyte-like, and mesenchymal-like programs; recurrent tumors show an overall shift toward AP-1-associated mesenchymal states [10,11].

2.2 Quiescence, DNA Damage Responses, and Treatment Tolerance

TMZ-induced DNA lesions generally become cytotoxic during replication, potentially giving quiescent or slow-cycling cells a relative survival advantage. In a murine glioma model, Chen et al. traced a relatively quiescent Nestin-positive population that re-entered the cell cycle and contributed to tumor regeneration after TMZ; selective ablation delayed regrowth [8]. Xie et al. subsequently observed enrichment of a quiescent cancer stem-cell state after chemotherapy and at recurrence in transcriptional and patient-derived xenograft models [12]. These findings support the functional relevance of minimal residual states after treatment, but neither Nestin positivity nor a transcriptionally defined quiescent state can be equated with recurrence-initiating cells in every patient.

GSCs may also acquire radioresistance through enhanced DNA damage checkpoint and repair responses. Bao et al. reported a stronger DNA damage response in CD133-enriched GSC-like cells after irradiation, and partial restoration of radiosensitivity after Chk1/Chk2 inhibition [7]. TMZ response is additionally shaped by MGMT, mismatch repair, and base-excision repair pathways [4]. MGMT promoter methylation is therefore an important clinical predictive marker but does not explain all acquired resistance; GSC state and metabolic or repair support from the microenvironment may also modify drug response.

2.3 Metabolic Plasticity and Proteostatic Dependence

Metabolic adaptation in residual GSCs cannot be reduced to increased glycolysis. Nakhle et al. showed that mesenchymal stromal cells transfer mitochondria to GSCs through tunneling nanotubes, increasing glutamine utilization, reductive carboxylation, nucleotide synthesis, and TMZ resistance; the dihydroorotate dehydrogenase inhibitor brequinar restored TMZ sensitivity in this model [13]. Malformin C, in turn, induced proteotoxic stress and blocked autophagic flux in patient-derived GSC models, suggesting that proteostasis may represent a vulnerability of selected GSC states [14]. These dependencies are model- and nutrient-context specific and require validation under hypoxia, standard-treatment exposure, and post-surgical matrix conditions.

3. Interactions Between Residual GSCs and the Post-surgical Microenvironment

3.1 Surgical Injury Responses and Temporal Evolution

Resection markedly reduces tumor burden but simultaneously triggers hemostasis, inflammation, gliosis, vascular repair, and tissue remodeling. In an immunocompetent murine resection-recurrence model, Okolie et al. observed both local and distant recurrence after removal of more than 90% of the tumor; transcriptomic and secretome changes in injury-reactive astrocytes promoted tumor-cell proliferation and migration [15]. These findings implicate post-surgical injury responses in recurrence, although murine models differ from the human resection cavity in anatomical scale, hemostatic materials, corticosteroid exposure, and subsequent chemoradiotherapy.

Longitudinal sampling by Bastiancich et al. defined the temporal evolution of the post-resection microenvironment. Scattered recurrent cells were detectable by day 7 and recognizable tumor masses by day 14 in mice, while local and systemic immune composition changed over time; aspects of these observations were supported by perioperative samples from 10 patients with IDH-wildtype GBM [16]. The data suggest a period before radiographic recurrence in which tumor burden is low but injury and immune remodeling are active. Whether this period is a therapeutically actionable window requires time-resolved intervention studies.

3.2 Glial and Myeloid Cells and Intercellular Material Transfer

Reactive astrocytes release cytokines and matrix components and may also participate in direct material exchange. Liu et al. reported that GSC-derived exosomes induced a tumor-associated phenotype in normal human astrocytes; astrocyte-derived ALKBH7 subsequently increased APNG expression in GBM cells and reduced their sensitivity to TMZ [17]. Mitochondrial transfer from mesenchymal stromal cells to GSCs provides a second mechanism of metabolic support [13]. These coculture and transplantation studies indicate that drug-sensitivity assays in tumor-cell monoculture may underestimate stromal support, but the frequency and quantitative contribution of such transfer in post-surgical human tissue remain unknown.

GBM contains abundant immunosuppressive myeloid cells, and post-surgical inflammatory recruitment and repair programs may further alter their composition. Paired primary-recurrent single-cell analyses linked greater T-cell abundance at recurrence to hypermutated states, but cell number cannot substitute for functional assessment; clonality, exhaustion, spatial localization, and myeloid suppression may all influence antitumor activity [11]. Evaluation of natural-product immunomodulators should therefore prespecify the

cellular subset, timing of administration, and effector function rather than rely on nonspecific claims of immune enhancement.

3.3 Vascular Barriers, Extracellular Matrix, and Bidirectional Coupling

The blood-brain and blood-tumor barriers generate spatially heterogeneous drug exposure, and barrier integrity is often greater at the infiltrative margin than in the tumor core. Jimenez-Macias et al. identified a CDH5-centered blood-tumor barrier transcriptional program; the indirubin derivative 6-bromoindirubin acetoxime suppressed this program in vitro and in mice and increased intratumoral cisplatin delivery [19]. Natural-product-derived scaffolds may therefore serve as delivery modulators, although increased exposure of normal brain and neurotoxicity remain concerns. Drug-resistant GSC cultures also show enrichment of extracellular matrix (ECM)-related transcriptional programs [20], but causal effects of matrix stiffness, adhesion, and migration routes on residual-cell fate at the resection margin remain incompletely defined.

Collectively, the evidence supports a model in which therapeutic selection and tissue repair jointly shape recurrence. The post-surgical residual population comprises cells with different proliferative rates and states, and chemoradiotherapy may select for cells with quiescent, DNA-repair, and metabolic-adaptation programs. In parallel, astrocytic reactivity, myeloid rearrangement, ECM deposition, and vascular change create a dynamic niche. Residual GSCs alter neighboring cells through exosomes, chemotactic factors, and metabolic signals, whereas neighboring cells provide repair proteins, mitochondria, cytokines, and nutrients that promote re-entry into proliferation or transition toward mesenchymal states [11,13,15-18]. This synthesis draws on several experimental systems and should not yet be interpreted as a fully validated causal sequence in post-surgical human tissue.

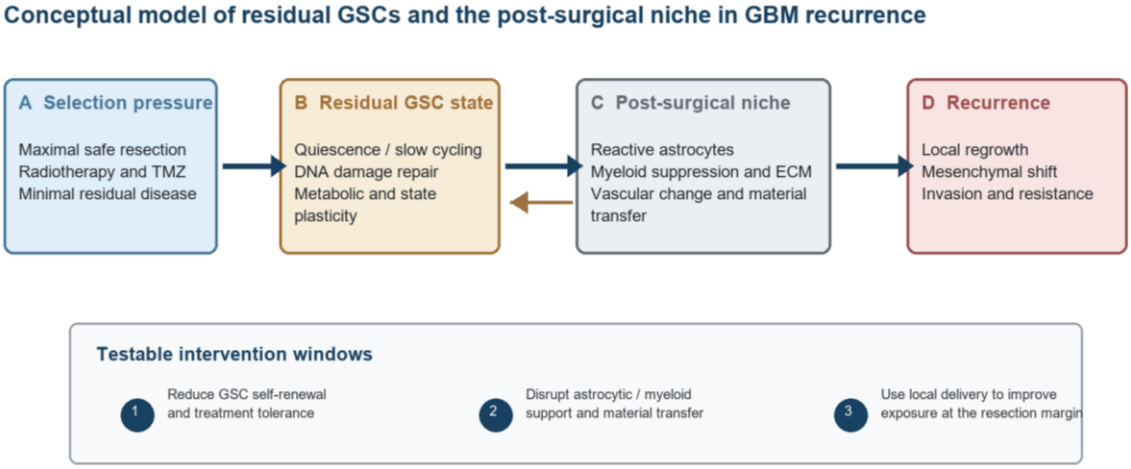

Figure 1: Conceptual model of residual GSCs and the post-surgical microenvironment in GBM recurrence.
Note: Surgery and chemoradiotherapy impose selective pressure, while intrinsic adaptation of residual GSCs interacts with post-surgical tissue repair and may promote local regrowth and treatment resistance. The intervention windows shown are testable hypotheses rather than established clinical effects. The model was synthesized from references [7,11,13,15-18,21].

Table 1: Representative evidence linking residual GSCs, the post-surgical microenvironment, and recurrence

Evidence domain	Study system	Principal finding	Key limitation	Ref.
Clinical recurrence pattern	54 patients treated with chemoradiotherapy; 39 recurrences	Central recurrence in 80% of patients with recurrence; in-field noncentral, marginal, and distant failures also occurred	Retrospective single-center study; recurrence-initiating cells were not identified	[5]
Post-treatment regenerative cells	Genetic-tracing murine glioma	Relatively quiescent Nestin-positive cells contributed to regeneration after TMZ; selective ablation delayed regrowth	Model- and marker-specific; does not encompass all human GSC states	[8]
Radioresistance	Enriched human GSC population	Enhanced DNA damage checkpoint and repair; partial sensitization after Chk1/Chk2 inhibition	CD133 enrichment; requires integration with modern cell-state definitions	[7]
Evolution at recurrence	86 paired primary-recurrent tumors; multi-omics	Overall shift toward AP-1-associated mesenchymal states and tumor-glial-immune signaling networks	Predominantly observational associations; causal validation remains necessary	[11]
Post-surgical injury niche	Immunocompetent murine resection model	Secretome of injury-reactive astrocytes promoted tumor-cell proliferation and migration	Differences from the human cavity and standard adjuvant therapy	[15]
Longitudinal post-surgical TME	Murine time series; perioperative samples from 10 patients	Recurrent-cell emergence and local/systemic immune changes showed temporal staging	Small human cohort; optimal intervention time remains uncertain	[16]
Intercellular resistance support	Coculture, exosomal, and mitochondrial-transfer models	Astrocytes or stromal cells provided repair or metabolic support and increased TMZ resistance	Mechanisms are clear in vitro; quantitative contribution in post-surgical human tissue is unknown	[13,17]
Local combination strategy	GL261 and CT2A resection models	Hydrogel delivery of siNotch1, mitoxantrone, and IL-12 targeted GICs and immunosuppression	Complex combination product; manufacturing, long-term safety, and compatibility with standard therapy remain unresolved	[21]

Note: GSCs, glioma stem cells; GICs, glioma-initiating cells; MSCs, mesenchymal stromal cells; TME, tumor microenvironment. Each entry is limited to the experimental system in which it was generated.

4. Potential Intervention Strategies Using Chinese Herbal Medicines and Natural Products

4.1 Direct Targeting of GSC Stemness and Treatment Tolerance

Among currently investigated candidates, ginsenoside Rg5 and erianin have the most direct links to treatment-resistant GSCs. Rg5 was reported to promote NCOA4-dependent ferritinophagy and ferroptosis through the NR3C1/HSPB1/NCOA4 pathway and to reduce GSC self-renewal, invasion, and tumor-initiating capacity [22]. Erianin acted through the REST/LRSAM1/SLC40A1 axis, induced ferroptosis in TMZ-resistant GSC models, and increased TMZ sensitivity [23]. Both studies included target perturbation and functional validation, but human pharmacokinetic data are lacking. The therapeutic window for inducing lipid peroxidation in post-surgical brain tissue and the consequences for normal neural cells also require evaluation.

Shikonin induced necroptosis, reduced stemness-associated phenotypes, and inhibited (immuno)proteasome activity in GSC-like cells [24]; an earlier in vitro study likewise found that shikonin and topotecan inhibited proliferation and induced apoptosis in U251- and U87-derived GSCs [27]. Malformin C preferentially killed patient-derived GSCs through proteotoxic stress and blockade of autophagic flux [14]. Apigenin induced autophagy and apoptosis in chemoresistant GBM models and altered selected immunomodulatory proteins and glial responses [25]. These studies implicate distinct death and stress pathways, but changes in marker proteins do not establish a reduction in recurrence risk. Long-term self-renewal, limiting-dilution, rechallenge, and post-surgical recurrence assays are needed to confirm functional effects.

4.2 Modulation of the Glial and Immune Microenvironment

Honokiol activity in GSC-like cells and xenograft models has been associated with inhibition of EGFR/JAK-STAT3 signaling [26]. Apigenin studies have examined tumor cells, immunomodulatory proteins, and glial responses [25]. Polymeric or niosomal curcumin formulations affected viability, apoptosis, reactive oxygen species, NF-κB/IL-6 expression, and migration in patient-derived GSCs, although the evidence came from in vitro studies or nonresection animal models [28,29]. Fuzheng Yiliu decoction combined with IL-12-engineered bone marrow mesenchymal stromal cells increased IL-12, IFN-γ, and Bax and suppressed tumor growth in U251 xenografts in nude mice [30]. Because the host was immunodeficient and the model did not incorporate resection, these results cannot establish effects on post-surgical immune remodeling or recurrence.

Microenvironmental studies should define the cellular relationship being tested. Studies seeking to inhibit astrocytic support should evaluate the secretome, exosomal cargo, or material transfer; studies addressing myeloid suppression should distinguish resident microglia from blood-derived macrophages and report spatial localization, phagocytosis, or antigen-presentation functions; and studies targeting ECM should assess adhesion, migration trajectories, and tissue architecture at the recurrence margin. This design logic helps separate direct tumor-cell toxicity from microenvironment-mediated effects.

4.3 Local Delivery, Surgical Synergy, and Human Tumor Exposure

Table 2: Evidence for Chinese herbal medicines and natural products relevant to residual GSCs or the post-surgical microenvironment

Candidate intervention	Evidence system	Principal finding / proposed mechanism	Relevance to post-surgical recurrence and limitations	Ref.
Ginsenoside Rg5	GSCs in vitro; intracranial xenograft	NR3C1/HSPB1/NCOA4; NCOA4-dependent ferritinophagy and ferroptosis	Direct GSC functional evidence; no resection model or human pharmacokinetics	[22]
Erianin	TMZ-sensitive and resistant GSCs; animal models	REST/LRSAM1/SLC40A1; ferroptosis and TMZ sensitization	Strong mechanistic chain in resistant GSCs; clinical exposure and normal-brain safety window unknown	[23]
Shikonin	GSC-like and glioma cells	Necroptosis, reduced stemness-related phenotypes, and (immuno)proteasome inhibition	No central nervous system pharmacokinetics, resection model, or selectivity assessment	[24,27]
Malformin C	Patient-derived GSCs; xenografts	Proteotoxic stress and blockade of autophagic flux	Relative GSC sensitivity; brain exposure and neurotoxicity unknown	[14]
Apigenin	Chemoresistant GBM; glial-response models	Autophagy and apoptosis; altered immunomodulatory proteins and glial responses	Addresses tumor-glial interactions but not post-surgical recurrence	[25]
Honokiol	GSC-like cells; xenografts	Suppression of EGFR/JAK-STAT3-associated stemness and proliferation	Preclinical evidence; bioavailability and target specificity remain uncertain	[26]
Curcumin and nanoformulations	Patient-derived GSCs; animals; small preoperative human PK study	ROS, NF-κB/IL-6, and migration; formulations improve solubility and exposure	Human study supports intratumoral exposure only and did not assess efficacy	[28,29,33]
Berberine plus 5-ALA	GSCs; orthotopic mouse model	Increased ALAS1 and PpIX fluorescence, improving experimental detection of infiltrating cells	No patient-level extent-of-resection or survival endpoint	[32]
Ginsenoside F2 liposomes / FTY720	Cells; orthotopic mice	AMPK/mTOR/GPX4-associated ferroptosis; GLUT1-related targeting	Both ligand and payload are active; attribution and long-term toxicity require clarification	[31]
Fuzheng Yiliu decoction plus IL-12-BMSCs	U251 xenografts in nude mice	Increased IL-12, IFN-γ, and Bax; reduced tumor growth	Immunodeficient, nonresection model; stringent formulation quality control required	[30]

Note: The evidence systems indicate translational stage and do not constitute a formal GRADE assessment. No candidate intervention has confirmatory clinical evidence for preventing post-surgical GBM recurrence in humans.

Local delivery into the resection cavity can increase exposure within areas of residual disease while reducing the effects of blood-brain barrier restriction and systemic clearance. A post-surgical platform developed by Zhu et al. integrated GIC-targeting exosomes, siNotch1, mitoxantrone, and IL-12 in an injectable hydrogel. In GL261 and CT2A resection models, the system reduced GIC stemness, altered immune-cell composition, and delayed recurrence [21]. Although this was not a herbal-medicine study, it provides a relevant experimental framework for local natural-product formulations: release kinetics, cavity coverage, brain-tissue compatibility, compatibility with standard chemoradiotherapy, and immune effects should be assessed concurrently.

Natural products may also serve as surgical or delivery-enhancing modules. Berberine increased ALAS1 expression and 5-aminolevulinic acid-induced protoporphyrin IX fluorescence in GSCs and orthotopic murine glioma, thereby improving experimental visualization of infiltrating cells [32]; no evidence yet shows that it increases the extent of resection or prolongs survival in patients. Ginsenoside F2-modified liposomes delivering FTY720 induced ferroptosis through AMPK/mTOR/GPX4-associated mechanisms and showed GLUT1-related targeting in cellular and orthotopic mouse models [31]. Normal-brain pharmacokinetics, neurotoxicity, and long-term formulation stability remain to be established.

Dützmann et al. administered micellar curcuminoids for 4 days before surgery to 13 patients scheduled for GBM resection; 10 completed the study. Curcumin was detectable in tumor tissue at a mean concentration of 56 pg/mg (range, 9-151 pg/mg), while the mean serum concentration was 253 ng/mL [33]. The study was designed primarily to assess tissue exposure, had a small sample size and short dosing period, and measured total tissue concentration rather than free drug or target occupancy within the GSC niche. It therefore supports limited intratumoral exposure of a micellar formulation but cannot be extrapolated to antitumor efficacy or prevention of recurrence.

5. Translational Barriers and Future Research Directions

5.1 Models and Endpoints Aligned with Clinical Recurrence

Most natural-product studies initiate treatment in unresected tumors and use short-term cell viability or tumor volume as endpoints, limiting their relevance to post-surgical recurrence. Priority models should include molecularly characterized patient-derived GSCs or immunocompetent syngeneic tumors, reproducible microsurgical resection, clinically relevant radiotherapy/TMZ sequencing, spatial sampling of the resection margin, and outcomes such as time to recurrence, tumor-initiating frequency, and long-term survival. Patient-derived organoids and brain slices can support mechanistic screening but should incorporate astrocytes, myeloid cells, vascular elements, or ECM and be cross-validated in vivo [18].

5.2 Pharmacokinetic-Pharmacodynamic Relationships and Quality Control of Formulations

Nominal dose cannot substitute for measured tissue exposure. Barrier heterogeneity and changes in resection-cavity fluid may produce markedly different concentrations in plasma, tumor core, infiltrative margin, and cerebrospinal fluid. Studies should report the spatiotemporal concentrations of parent compounds and active metabolites, protein binding, brain-to-blood ratios, local release, and safety margins in normal brain and should show that these exposures produce the prespecified mechanistic change. Ferroptosis studies should assess lipid peroxidation, iron dependence, rescue experiments, and target perturbation. Stemness studies should measure long-term self-renewal and tumor initiation in vivo rather than rely only on reduced SOX2 or CD133 expression.

Multicomponent formulations may affect both GSCs and the microenvironment, but batch variation, constituent interactions, and exposure uncertainty reduce reproducibility. Quality control should center on quality markers linked to mechanism and in vivo exposure and should combine chemical fingerprints, release criteria, constituent-depletion and add-back experiments, and pharmacokinetic contribution analyses to identify the principal active components. Combination with TMZ, radiotherapy, or corticosteroids also requires systematic assessment of drug-metabolizing enzymes, transporters, myelosuppression, and radiosensitizing or radioprotective effects.

5.3 Clinical Translation and Testable Research Priorities

When human pharmacokinetic and target-engagement data are absent, large survival trials are difficult to interpret if negative. Short preoperative window-of-opportunity studies can obtain paired plasma, cerebrospinal fluid, tumor-core, and infiltrative-margin samples for measurement of drug and metabolites, target occupancy, and single-cell state changes. Local formulations can first be assessed for cavity release, safety, and spatial exposure before randomized studies. Enrollment stratification should consider integrated diagnosis, MGMT promoter methylation, corticosteroid use, and prior therapy, while pharmacokinetic accessibility, target engagement, imaging response, and progression-free survival should be interpreted as distinct tiers of endpoints.

The causal and therapeutic significance of the early post-surgical niche requires time-resolved experiments. Blocking exosomal or mitochondrial transfer, IL-6/STAT3, or related supportive signals within defined windows would allow comparison of early treatment with intervention after tumor establishment. Quiescent or slow-cycling GSCs that persist after therapy should also be compared directly with untreated proliferating cells. Candidates such as Rg5, erianin, and malformin C require rescue experiments, competitive transplantation, and resection-recurrence models to determine whether their effects are state selective.

Local-delivery studies should be grounded in spatial exposure within the residual infiltrative zone and safety in normal brain rather than whole-tumor mean concentration or short-term volume change. Berberine-enhanced 5-ALA fluorescence, modulation of the blood-tumor barrier by indirubin derivatives, and local natural-product formulations can be compared in a common resection model. Longitudinal single-cell and spatial omics can integrate GSC states,

astrocytic responses, myeloid suppression, ECM, and vascular-barrier features; candidate signatures should first be validated against the location and timing of recurrence in independent patient cohorts before use in patient stratification.

6. Conclusion

6.1 Mechanistic Synthesis

Post-surgical GBM recurrence is a dynamic process jointly shaped by therapeutic adaptation of residual GSCs and surgery-induced changes in the microenvironment. Quiescence, DNA damage repair, metabolic reprogramming, and cell-state plasticity allow selected residual cells to survive, while reactive astrocytes, immunosuppressive myeloid cells, ECM, and vascular alterations may further support regrowth.

6.2 Position of the Evidence

Chinese herbal medicines and natural products provide preclinical leads involving ferroptosis, proteostasis, inflammatory signaling, tumor-glial interactions, and drug delivery. Most evidence, however, is derived from in vitro and animal models and does not establish prevention of post-surgical recurrence in humans. Mechanistic activity, brain exposure, and clinical efficacy should therefore be treated as distinct levels of evidence.

6.3 Requirements for Translation

Improving the evidence base will require models aligned with the post-surgical setting, quantitative assessment of local pharmacokinetics and safety in normal brain, falsifiable mechanistic validation, reproducible formulation standards, and biomarker-informed clinical designs. Only by linking residual-cell state, the post-surgical niche, and achievable drug exposure can the true value of Chinese herbal medicines and natural products for preventing recurrence be determined.

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