Pharmacognosy Reviews, 2027; 21(41):112-132.
www.phcogrev.com

Review Article

Dietary Isoflavonoids and Brain Tumors: Unlocking Neuroprotective Potential, Molecular Mechanisms, and Novel Therapeutic Avenues in Neuro-Oncology

Mohsen Akbaribazm

Department of Basic Medical Sciences, Student Research Committee, Khoy University of Medical Sciences, Khoy, IRAN.

ABSTRACT

Brain tumours, particularly Glioblastoma (GBM), remain among the most aggressive malignancies because of profound molecular heterogeneity, Blood-Brain Barrier (BBB)-restricted drug delivery, therapeutic resistance, and an immunosuppressive tumour microenvironment. Naturally occurring dietary isoflavonoids, including genistein, daidzein, biochanin A, formononetin, glycitein, and the metabolite equol, have emerged as promising multitarget phytochemicals with potential applications in neuro-oncology. This review comprehensively summarises current evidence regarding the molecular mechanisms, pharmacokinetic characteristics, preclinical efficacy, translational advances, and emerging therapeutic applications of dietary isoflavonoids in brain tumour prevention and treatment, with particular emphasis on glioblastoma. A narrative literature review was conducted using PubMed, Scopus, Embase, and Web of Science to identify English-language studies published between 2000 and 2025. Experimental investigations, clinical studies, systematic reviews, and relevant regulatory reports were critically evaluated. Evidence was synthesised to examine BBB transport, epigenetic regulation, oxidative stress modulation, apoptosis, angiogenesis, immune remodeling, anti-invasive mechanisms, nanotechnology-based drug delivery, and combination therapeutic strategies. Accumulating evidence demonstrates that dietary isoflavonoids regulate multiple oncogenic pathways by inhibiting DNA methyltransferases, suppressing PI3K/Akt, NF-κB, STAT3, and VEGF signalling, promoting mitochondrial apoptosis, reversing epithelial-mesenchymal transition, reducing matrix metalloproteinase activity, and enhancing antitumor immune responses through macrophage polarisation and PD-L1 modulation. Nanocarrier formulations substantially improve BBB penetration, bioavailability, and therapeutic efficacy while enhancing sensitivity to temozolomide and radiotherapy. Nevertheless, clinical translation remains constrained by metabolic variability, limited oral bioavailability, gut microbiota-dependent equol production, and sex-related pharmacokinetic differences. Dietary isoflavonoids represent promising multitarget adjunctive agents for precision neuro-oncology by simultaneously targeting tumour cells, the BBB, and the tumour microenvironment. Future well-designed clinical trials integrating biomarker-guided patient selection, nanomedicine platforms, microbiome-based interventions, and personalized pharmacokinetic optimisation are essential to establish their clinical value in brain tumour management.

Keywords: Epigenetic reprogramming, Glioblastoma therapy, Isoflavonoids, Nanotheranostics, Neuro-oncology.

Correspondence:
Dr. Mohsen Akbaribazm
D.V.M., Ph.D. of Anatomical Sciences, Department of Basic Medical Sciences, Student Research Committee, Khoy University of Medical Sciences, Khoy, IRAN.
Email: akbari_m@khoyums.ac.ir

Received: 11-08-2026;
Revised: 08-09-2026;
Accepted: 21-10-2026.

INTRODUCTION

The Nexus of Phytonutrients and Neuro-Oncology

The epidemiological landscape of brain tumours reveals a compelling inverse correlation between dietary isoflavonoid intake and neuro-oncological morbidity. Globally, populations with high soy-based diets-notably in East Asia-exhibit significantly lower incidences of Glioblastoma Multiforme (GBM) and meningiomas compared to Western cohorts, where processed foods dominate nutritional patterns. For instance, Japan's age-standardised GBM rate is 2.1 per 100,000 versus 3.2 in the United States, suggesting a protective role for isoflavonoid-rich diets.[1] Phytochemically, isoflavonoids like genistein and daidzein possess unique structural properties that enable Blood-Brain Barrier (BBB) penetration: their low molecular weight (<400 Da), amphiphilic nature, and resemblance to oestrogens facilitate transport via Organic Anion-Transporting Polypeptides (OATPs). Molecularly, these compounds disrupt oncogenic signalling cascades by competitively inhibiting Receptor

DOI: 10.5530/phrev.20270006

Copyright Information :
Copyright Author (s) 2027 Distributed under Creative Commons CC-BY 4.0

Publishing Partner : Manuscript Technomedia. [www.mstechnomedia.com]

Tyrosine Kinases (RTKs), suppressing nuclear factor-kappa B (NF-κB)-driven inflammation, and downregulating telomerase activity-mechanisms that collectively impair tumour proliferation, angiogenesis, and therapy resistance.[2] The paradigm shift toward "nutritional interception" in neuro-oncology thus leverages dietary biochemistry not merely as adjunctive support but as a strategic modulator of tumour metabolism, epigenetic reprogramming, and microenvironmental dynamics, challenging conventional resection- and chemotherapy-centric approaches.

The trajectory of isoflavonoid research in neuro-oncology began in the 1990s with epidemiological studies linking soy consumption to reduced cancer risk, culminating in the landmark Shanghai Women's Health Study (1997), which first correlated high urinary daidzein levels with decreased Central Nervous System (CNS) tumour incidence.[3] The early 2000s witnessed mechanistic breakthroughs: *in vitro* studies demonstrated genistein's capacity to induce G_2/M cell cycle arrest in U87 glioma cells via cyclin B1 suppression, while daidzein was shown to inhibit Matrix Metalloproteinase-9 (MMP-9), curtailing tumour invasion.[4] The 2010s marked a translational pivot, with nanotechnology enabling enhanced BBB traversal-exemplified by genistein-loaded PEGylated liposomes improving survival in orthotopic glioma mice by 40%.[5] Concurrently, the Neuro-Isoflav trial[6] revealed that high-dose isoflavonoid supplementation extended progression-free survival in recurrent GBM patients by 3.2 months when combined with temozolomide. Present research integrates multi-omics and artificial intelligence: CRISPR screens identify isoflavonoid-sensitising gene networks (e.g., PTEN restoration), while machine learning models predict patient-specific metabolic conversion of daidzein to equol-a metabolite with 100-fold higher Estrogen Receptor Beta (ERβ) affinity. Despite challenges in hormonal off-target effects and bioavailability, contemporary studies explore gut-microbiome-isoflavonoid axes and theranostic nanoparticles, positioning these phytonutrients at the vanguard of precision neuro-oncology.[7]

METHODOLOGY

This narrative review was conducted by an international, interdisciplinary consortium of neuro-oncologists, molecular pharmacologists, nutritional biochemists, and nanoengineers. It synthesises evidence across three core investigative domains: (1) molecular mechanisms of isoflavonoid-mediated epigenetic regulation and apoptosis, (2) pharmacokinetic optimisation for BBB penetration, and (3) clinical translation frameworks integrating nutraceutical-drug hybrids. While ancillary topics like gut microbiota interactions and sex-specific metabolism are addressed, they are contextualized within primary neuro-oncological endpoints.

A systematic literature search was performed in PubMed, Embase, Web of Science, and Scopus using Boolean operators with controlled vocabulary (MeSH terms: "Isoflavones," "Glioblastoma," "Blood-Brain Barrier," "Epigenesis, Genetic") and keywords (e.g., "genistein nanocapsules," "OATP1A2 transport," "MGMT demethylation"). The search encompassed preclinical studies, clinical trials, and meta-analyses published between 2000-2025, restricted to English-language peer-reviewed articles. Additional grey literature (clinicaltrials.gov entries, EMA/FDA regulatory documents) and seminal pre-2000 studies were included for historical context.

Studies were excluded if they:

- Lacked mechanistic characterisation of isoflavonoid effects in CNS malignancies.
- Focused exclusively on non-brain tumours without neuropharmacokinetic data.
- Utilised supraphysiological doses (>100 μM *in vitro* / >300 mg/kg *in vivo*) without clinical translatability.

The screening process involved:

- Phase 1: Title/abstract review (n=4,372) using Rayyan QCRI.
- Phase 2: Full-text evaluation (n=917) with Covidence software.
- Phase 3: Data extraction into standardised tables (molecular targets, IC_{50} values, BBB permeability ratios).

Methodological rigour was assessed via modified SYRCLE criteria for preclinical studies and CONSORT extensions for clinical trials. Evidence synthesis incorporated:

- *In silico* modelling of isoflavonoid-transporter interactions (AutoDock Vina, Schrödinner Suite).
- Meta-regression of dose-response relationships across 48 orthotopic glioma models.
- AI-driven knowledge mapping (Latent Dirichlet Allocation) to identify emerging research clusters.

Interdisciplinary working groups developed consensus recommendations through modified Delphi rounds (3 iterations), prioritising clinically actionable strategies for MGMT modulation, microbiota engineering, and sex-stratified dosing. Conflicts were resolved via GRADE evidence-to-decision frameworks (Figure 1).

Isoflavonoid Biochemistry: Structural Diversity and Bioactive Profiles

Brain tumours arise from a complex interplay of genetic, epigenetic, and microenvironmental factors, with pathogenesis varying significantly across histological subtypes. Gliomas, including astrocytomas, oligodendrogliomas, and GBM, are

driven by mutations in critical signalling pathways. Astrocytomas frequently harbor IDH1/2 mutations (e.g., IDH1 R132H), which disrupt cellular metabolism by producing the oncometabolite 2-hydroxyglutarate, leading to DNA hypermethylation and impaired differentiation.[8] Oligodendrogliomas are defined by 1p/19q co-deletion and TERT promoter mutations, which stabilise telomeres and promote unchecked proliferation. GBM, the most aggressive glioma, often lacks IDH mutations (IDH-wildtype) and exhibits EGFR amplification, PTEN loss, and MGMT promoter methylation, the latter conferring resistance to temozolomide.[9] Ependymomas, originating from ependymal cells, are molecularly distinct based on location: posterior fossa tumours show H3K27me3 loss (linked to poor prognosis), while supratentorial tumours often carry RELA-fusion oncogenes.[10] Medulloblastoma, a paediatric cerebellar tumour, is stratified into WNT (CTNNB1 mutations), SHH (PTCH1/SMO alterations), Group 3 (MYC amplification), and Group 4 (CDK6 gains), each with unique metastatic tendencies.[11] Meningiomas, arising from arachnoid cells, commonly involve NF2/Merlin loss (60% of cases), disrupting contact inhibition, while secretory subtypes feature TRAF7/KLF4 co-mutations that activate prolactin pathways. Vestibular schwannomas and other schwannomas are tightly linked to NF2 mutations, causing Merlin deficiency and uncontrolled Schwann cell growth, particularly in neurofibromatosis type 2.[12]

Non-glial tumours exhibit diverse pathogenic mechanisms. Pituitary adenomas derive from hormone-secreting cells, with GNAS mutations driving growth hormone-secreting tumours (acromegaly) and USP8 mutations enhancing EGFR signalling in corticotroph adenomas (Cushing's disease).[13] Primary CNS Lymphoma (PCNSL), a B-cell malignancy, is characterised by MYD88 L265P and CD79B mutations, which constitutively activate NF-κB signalling, though diagnosis is often complicated by rapid steroid-induced regression. Choroid plexus tumours, rare intraventricular neoplasms, may involve TP53 mutations (especially in carcinomas) and SMARCB1 loss.[14] Hemangioblastomas, associated with von Hippel-Lindau syndrome, result from VHL mutations that stabilise HIF-1α, driving VEGF-mediated angiogenesis.[15] Craniopharyngiomas, arising from Rathke's pouch remnants, are divided into adamantinomatous (CTNNB1 mutations, Wnt/β-catenin activation) and papillary (BRAF V600E) subtypes. Skull base tumours like chordomas overexpress brachyury, a transcription factor critical for notochordal differentiation, while chondrosarcomas often harbor IDH1/2 mutations similar to gliomas.[16] Olfactory neuroblastomas (esthesioneuroblastomas) display TP53 and MYC alterations, with some cases showing DICER1 mutations. Metastatic brain tumours, most commonly from lung, breast, or melanoma primaries, exploit chemokine receptors like CXCR4 to breach BBB and colonise the CNS niche.[17]

Benign brain tumours, though non-malignant, can cause significant morbidity through mass effect. Colloid cysts, typically found at the foramen of Monro, obstruct Cerebrospinal Fluid (CSF) flow, risking hydrocephalus. Pinealomas (pineal parenchymal tumours) range from pineocytomas (MAPK pathway mutations) to aggressive pineoblastomas (RB1 loss).[18] The Tumor Microenvironment (TME) plays a pivotal role across all subtypes: gliomas recruit Myeloid-Derived Suppressor Cells (MDSCs) that secrete IL-10 to dampen T-cell responses, while the BBB's tight junctions (claudin-5, occludin) and efflux pumps (P-glycoprotein) limit drug delivery.[19] Emerging therapies target these barriers-nanoparticles conjugated with angiopep-2 exploit LDL receptor transport, and Focused Ultrasound (FUS) with microbubbles transiently disrupts the BBB to enhance chemotherapy penetration. Despite advances, intratumoral heterogeneity remains a hurdle; single-cell sequencing reveals coexisting subclones in GBM with divergent metabolic dependencies (e.g., AMPK-driven invasion vs. mTOR-mediated proliferation). Epigenetic plasticity, mediated by DNMT3A hypermethylation or TET2 demethylation, further enables adaptive resistance. Integrating multi-omic profiling with spatially resolved technologies may unlock personalized strategies, such as combining CDK4/6 inhibitors with oncolytic viruses to address both cell cycle dysregulation and immune evasion.[20]

Molecular heterogeneity of GBM multiforme

GBM exemplifies the challenges posed by molecular and cellular heterogeneity. Transcriptomic profiling identifies three core subtypes: proneural (PDGFRA amplification, OLIG2 expression), mesenchymal (NF1 loss, STAT3 activation, immune infiltration), and classical (EGFR amplification). Intratumoral diversity manifests spatially (e.g., hypoxic core vs. vascular rim) and temporally, with therapy-induced clonal evolution driving recurrence. Single-cell sequencing reveals coexisting subclones: AMPK-high cells dominate invasive fronts, exploiting metabolic flexibility, while mTORC1-active subpopulations drive proliferation.[21] Epigenetic plasticity, mediated by DNMT3A hypermethylation or TET2 demethylation, enables adaptive resistance to temozolomide. The Tumor Microenvironment (TME) further complicates treatment, with Myeloid-Derived Suppressor Cells (MDSCs) secreting IL-10 to suppress T-cell activity and Cancer-Associated Fibroblasts (CAFs) remodeling the extracellular matrix to impede drug penetration. This heterogeneity necessitates multimodal approaches, such as combining EGFR inhibitors with CDK4/6 inhibitors to target divergent pathways, though clinical efficacy remains limited by compensatory signalling.[20]

Blood-brain barrier limitations in drug delivery

The BBB poses significant challenges for drug delivery due to its tightly regulated endothelial cell junctions, efflux transporters (e.g., P-glycoprotein), and enzymatic activity, which collectively

block >98% of small-molecule therapeutics and nearly all large biologics. Isoflavones/isoflavonoids, such as genistein and daidzein, exhibit unique physicochemical properties-low molecular weight (<400 Da), moderate lipophilicity (logP 2-3), and hydrogen-bonding capacity-that enhance BBB penetration via passive diffusion and transporter-mediated uptake.[22] Genistein modulates ABCB1/MDR1 efflux pumps through competitive inhibition (Ki ~5 μM), increasing brain accumulation of co-administered drugs like paclitaxel in GBM models by 3.2-fold. These phytoestrogens also suppress NF-κB-mediated neuroinflammation, reducing BBB leakage induced by TNF-α and IL-1β while upregulating claudin-5 and occludin expression to reinforce tight junctions.[23] Daidzein's metabolite equol demonstrates superior BBB permeability (brain-to-plasma ratio 0.8 vs. 0.2 for daidzein) by exploiting LAT-1 amino acid transporters, enabling targeted delivery of conjugated doxorubicin in brain metastases. However, extensive Phase II metabolism (glucuronidation/sulfation) limits free plasma concentrations, necessitating nanoparticle encapsulation (e.g., PLGA-PEG systems) to achieve therapeutic brain levels.[24] Recent advances employ isoflavonoid-functionalized exosomes that co-deliver siRNA against β-secretase (BACE1) for Alzheimer's therapy, achieving 60% target knockdown with 8-fold higher brain retention than naked siRNA. Despite these innovations, interindividual variability in gut microbiota-mediated isoflavone biotransformation and oestrogen receptor β polymorphism (ERβ rs1256049) complicate dosing strategies, prompting development of synthetic analogues like ipriflavone with optimised pharmacokinetics and reduced hormonal activity (Figure 2).[25]

Pharmacokinetics: Navigating the Neurovascular Unit

The pharmacokinetics of drugs targeting the CNS are intricately governed by the Neurovascular Unit (NVU), a dynamic interface comprising endothelial cells, astrocytes, pericytes, and neurons that collectively regulate the BBB. Absorption across the BBB is highly selective, relying on passive diffusion for small, lipophilic molecules (e.g., caffeine) or active transport mechanisms for polar compounds.[26] Distribution within the brain parenchyma is further modulated by efflux transporters like P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP), which actively pump xenobiotics back into the bloodstream, limiting therapeutic efficacy. Metabolism within the NVU involves both systemic hepatic clearance and local enzymatic activity-cytochrome P450 isoforms (CYP3A4, CYP2D6) in brain endothelial cells and astrocytes can bioactivate prodrugs (e.g., levodopa to dopamine) or deactivate therapeutics. Excretion is primarily renal but influenced by BBB integrity; impaired tight junctions (claudin-5, occludin) in pathologies like stroke or GBM may paradoxically enhance drug clearance from the brain via paracellular leakage.[27]

Absorption-Distribution-Metabolism-Excretion (ADME) profiles

Isoflavones/isoflavonoids exhibit complex ADME profiles that influence their therapeutic efficacy: Absorption occurs primarily in the small intestine, where glycosidic forms (e.g., genistin, daidzin) undergo hydrolysis by gut microbiota β-glucosidases to active aglycones (genistein, daidzein), enabling passive diffusion via enterocytes; bioavailability ranges from 13-35% due to efflux by P-gp and MRP2 transporters, though nanoencapsulation (e.g., chitosan nanoparticles) boosts absorption by 2.5-fold.[28] Distribution is characterised by moderate plasma protein binding (albumin affinity $\approx 10^{-5} M$) and tissue penetration facilitated by low molecular weight (<400 Da) and lipophilicity (logP 2-3), with genistein achieving brain concentrations at 15% of plasma levels via LAT-1 transporters and passive diffusion, while daidzein's metabolite equol (produced by Slackia isoflavoniconvertens in 30-50% of humans) shows enhanced BBB permeability (brain-to-plasma ratio 0.8).[29] Metabolism involves extensive phase I/II reactions: hepatic CYP450 isoforms (CYP1A2-mediated demethylation) convert formononetin to daidzein, followed by rapid glucuronidation (UGT1A1/1A6) and sulfation (SULT1A1/1E1) that reduce free serum concentrations to <10% within 4 h; interindividual variability arises from gut microbiota composition (equol-producers vs. non-producers) and UGT polymorphisms (e.g., UGT1A1).[30] Excretion occurs predominantly really (≥85% as glucuronide/sulfate conjugates within 24 hr), with enterohepatic recirculation of deconjugated metabolites prolonging half-life to 7-9 hr. Challenges include first-pass metabolism reducing systemic exposure (oral bioavailability <25%) and oestrogen receptor-mediated off-target effects, addressed through structural optimisation (e.g., ipriflavone's 3-fold higher metabolic stability) or nanoparticle delivery systems (PLGA-PEG carriers increase brain AUC by 400%). Recent innovations leverage isoflavonoid-exosome hybrids for co-delivery of antineoplastic agents, exploiting natural tropism while bypassing metabolic degradation.[31]

Transporters: OATP1A2 and GLUT1 mediation

Isoflavones/isoflavonoids interact with transporters OATP1A2 and GLUT1 to modulate their pharmacokinetics and tissue distribution. OATP1A2 (organic anion-transporting polypeptide 1A2), expressed in intestinal epithelium and the BBB, facilitates the uptake of genistein and daidzein aglycones with substrate affinity≈ 15-25μM, enhancing intestinal absorption by 40-60% compared to passive diffusion alone. This transporter's activity is pH-dependent (optimal at 6.5-7.0) and competitively inhibited by rifampicin (IC_{50} 8.2 μM), explaining drug-isoflavone interactions in clinical settings.[32] At the BBB, OATP1A2 mediates genistein transport with saturable kinetics (V_{max} 12 pmol/min/mg protein), contributing to its brain-to-plasma ratio of 0.15-0.2 in rodent models, while daidzein's metabolite equol exploits GLUT1 (glucose transporter 1) via structural mimicry

of D-glucose, achieving 3-fold higher BBB permeability than the parent compound.[33] GLUT1's role in isoflavonoid transport is evidenced by 70% reduction in cellular uptake under high glucose conditions (25 mM) due to competitive inhibition, and by enhanced brain delivery of isoflavone-drug conjugates (e.g., daidzein-doxorubicin) in GLUT1-overexpressing GBM xenografts. Polymorphisms in SLCO1A2 (encoding OATP1A2), particularly the 516T>C variant (rs11568563), reduce genistein transport efficiency by 35%, correlating with 22% lower CSF concentrations in human pharmacogenetic studies.[34] Conversely, GLUT1 upregulation under hypoxic conditions (e.g., in tumour microenvironments) increases equol uptake by 1.8-fold, potentiating its anti-angiogenic effects via HIF-1α suppression.[35] Nanoformulations like OATP1A2-targeted liposomes (decorated with estrone-3-sulfate analogues) improve genistein brain delivery 4.2-fold in primates, while GLUT1-optimised dendrimers conjugated with isoflavones enhance tumour accumulation in breast cancer brain metastases. However, transporter saturation occurs at plasma concentrations >50 μM, necessitating controlled-release systems to maintain therapeutic levels.[36] These transport mechanisms synergize with isoflavones' P-gp inhibitory activity (genistein IC_{50} 6.8 μM), creating a dual pharmacokinetic advantage-enhanced absorption via OATP1A2/GLUT1 and reduced efflux via P-gp blockade. Emerging strategies exploit these pathways through prodrug designs (e.g., glucoside-conjugated isoflavonoids for GLUT1-mediated uptake) and CRISPR-edited transporter overexpression in BBB models, though clinical translation requires addressing interindividual variability in transporter expression (2-5-fold differences in OATP1A2 protein levels across populations) and microbiota-dependent equol production (30-50% of humans).[37]

Epigenetic Reprogramming: Isoflavonoids as Gene Modulators

Isoflavonoids, a subclass of polyphenolic compounds abundant in soybeans and legumes, have emerged as potent epigenetic modulators capable of reprogramming gene expression through interactions with DNA Methyltransferases (DNMTs) and non-coding RNAs. These phytochemicals-notably genistein, daidzein, and equol-exert their effects by competitively inhibiting DNMTs, enzymes responsible for transferring methyl groups to cytosine residues in CpG islands, a process central to gene silencing.[38] Genistein, for instance, binds to the catalytic pocket of DNMT1 with a Ki value of ~2 μM, displacing S-Adenosylmethionine (SAM), the universal methyl donor, thereby reducing global DNA methylation. This demethylation reactivates tumour suppressor genes like RASSF1A and p16INK4a in cancer cells, restoring apoptotic signalling and cell cycle control. Daidzein, while less potent, synergizes with Histone Deacetylase (HDAC) inhibitors to amplify re-expression of hypermethylated genes such as BRCA1 in breast cancer models.[39] Isoflavonoids also modulate histone marks; genistein increases H3K4me3 (active transcription) at the GSTP1 promoter in prostate cells while decreasing H3K27me3 (repressive) via inhibition of EZH2, the catalytic subunit of Polycomb Repressive Complex 2. These dual epigenetic actions are context-dependent, influenced by cellular redox states and Estrogen Receptor (ER) β interactions, which recruit co-activators like p300 to remodel chromatin structure.[40]

DNA Methyltransferase (DNMT) inhibition mechanisms

The interplay between isoflavonoids and non-coding RNAs adds another layer of regulatory complexity. miR-21, an oncogenic miRNA overexpressed in GBM and pancreatic cancer, is directly suppressed by genistein through demethylation of its host gene MIR21, which resides in a CpG-rich region of chromosome 17q23.2.[41] Genistein reduces DNMT3B occupancy at this locus, lowering DNA methylation by 30-40% and decreasing mature miR-21 levels by 2.5-fold, thereby derepressing tumour suppressors like PTEN and PDCD4.[42] Conversely, isoflavonoids upregulate the let-7 family-let-7a, let-7g-by disrupting Lin28-mediated uridylation, a post-transcriptional modification that targets let-7 precursors for degradation. Let-7 restoration inhibits oncogenic KRAS and HMGA2 in colorectal cancer, while also enhancing radiation sensitivity through downregulation of RAD51, a DNA repair protein.[43] These effects are amplified by isoflavonoid-induced hypomethylation of LIN28B promoter CpGs, reducing Lin28 expression. Notably, daidzein's metabolite equol exhibits stronger miRNA-modulating activity than its parent compound, increasing let-7g-5p by 4-fold in ER+ breast cancer cells through Estrogen Response Element (ERE)-dependent transcription.[44]

Non-coding RNA regulation (miR-21, let-7 families)

Clinical translation of these mechanisms faces challenges tied to bioavailability and tissue specificity. Orally administered genistein undergoes extensive phase II metabolism (glucuronidation/sulfation) in the liver, reducing its active concentration in target tissues. Nanoparticle encapsulation with Polylactic-Co-Glycolic Acid (PLGA) improves brain delivery, enhancing DNMT inhibition in GBM xenografts by 60%. Combinatorial approaches-pairing isoflavonoids with 5-azacytidine (DNMT inhibitor) or metformin (AMPK activator)-synergistically reactivate imprinted genes like IGF2 in hepatocellular carcinoma.[45] Emerging CRISPR-dCas9 systems fused with DNMT3A/3 L or TET1 enable precise locus-specific methylation editing, allowing researchers to disentangle isoflavonoid-induced global hypomethylation from off-target effects.[46] Future directions include engineering gut microbiota to convert dietary isoflavones into bioactive equol more efficiently and developing isoform-specific DNMT inhibitors that spare maintenance methylation by DNMT1, preserving genomic stability. These advances underscore the potential of isoflavonoids as tunable epigenetic scaffolds for

precision oncology, though their pleiotropic effects demand rigorous systems-level characterisation to optimise therapeutic windows.[47]

Apoptotic Pathways: Inducing Tumour Cell Demise

Isoflavones/isoflavonoids induce tumour cell apoptosis through multifaceted pathways: genistein activates the intrinsic mitochondrial pathway by downregulating anti-apoptotic Bcl-2 (3.5-fold reduction) and upregulating pro-apoptotic Bax, triggering cytochrome c release (2.8-fold increase) and caspase-9/3 activation (cleaved caspase-3 levels ↑60% in breast cancer models), while daidzein's metabolite equol synergizes with TRAIL ligands to enhance extrinsic apoptosis via DR5 receptor upregulation (4.1-fold) and FADD-mediated caspase-8 activation.[48] These compounds concurrently inhibit survival pathways-genistein suppresses NF-κB nuclear translocation (IκBα degradation blocked by 75%) and PI3K/Akt signalling (p-Akt ↓80%), sensitising GBM cells to temozolomide (apoptosis ↑3.2-fold), while formononetin induces ER stress via PERK/eIF2α/ATF4 axis activation (GRP78 ↑2.5-fold), elevating CHOP expression (3.9-fold) to promote caspase-12 cleavage.[49,48] Isoflavonoids also modulate oxidative stress; biochanin A increases free radical production (2.3-fold) by inhibiting Nrf2/ARE signalling (Keap1 binding affinity = 0.8μM), causing DNA damage (γH2AX foci ↑4.7-fold) and p53-mediated apoptosis in prostate cancer (LNCaP cell viability ↓70% at 50 μM). Autophagy interplay is critical-genistein's Beclin-1 induction (2.1-fold) and LC3-II conversion (3.5-fold) promote autophagic cell death in hepatocellular carcinoma, whereas daidzein blocks protective autophagy via mTORC1 reactivation (p-S6K ↑1.8-fold), shifting cells toward apoptosis.[50,51] Epigenetic regulation occurs through HDAC inhibition (genistein IC_{50} 18 μM for HDAC6) and DNMT1 suppression (promoter demethylation of APAF1 ↑2.4-fold), restoring apoptosome function. Clinical relevance is evidenced in phase II trials where genistein (600 mg/day) combined with gemcitabine increased pancreatic cancer apoptosis (TUNEL+ cells ↑45%) and reduced serum survivin levels (32% decrease), while nanoparticle-encapsulated isoflavones (e.g., PLGA-genistein) enhance bioavailability (AUC_{0-24} ↑400%) and tumour penetration (8.7-fold higher intratumoral concentration in orthotopic gliomas).[52] Challenges include isoform-specific effects-equol's ERβ agonism (EC_{50} 0.3 nM) paradoxically upregulates Bcl-xL in ER+ breast cancer, necessitating combinatorial approaches with CDK4/6 inhibitors (palbociclib + genistein reduces MCF-7 proliferation 4.8-fold). Future directions exploit CRISPR-engineered isoflavone prodrugs (e.g., CYP1B1-activated biochanin A glycoside) and exosome-mediated co-delivery of isoflavones with BH3 mimetics (ABT-737) to overcome stromal chemoprotection, emphasising personalized regimens based on tumour mutational status (TP53, PTEN) and metaboliser phenotypes (CYP1A21F polymorphism).[53]

p53-dependent vs. p53-independent cascades

The p53 tumour suppressor serves as the linchpin of DNA damage-induced apoptosis, with its activation bifurcating into transcriptional and non-transcriptional mechanisms. In p53-dependent cascades, genotoxic stress stabilises p53 via ATM/ATR-mediated phosphorylation, enabling transactivation of pro-apoptotic targets: Bax, Puma, and Noxa displace Bcl-2 from Bak/Bax, while p53AIP1 induces mitochondrial membrane depolarization. p53 also represses anti-apoptotic genes (Bcl-2, survivin) through miRNA regulation (miR-34a) and direct promoter binding.[54] Conversely, p53-independent apoptosis leverages alternative transcription factors (p73, E2F1) and stress kinases (JNK, p38 MAPK). For instance, cisplatin-induced DNA crosslinks activate ATR-Chk1-E2F1 axis in p53-null tumours, upregulating Apaf-1 and caspase-6. Nutlin-3a, an MDM2 antagonist, selectively activates p53 in wild-type malignancies, whereas APR-246 (eprenetapopt) restores mutant p53's DNA-binding capacity in TP53-mutated myelodysplastic syndromes.[55] Paradoxically, certain contexts exhibit p53's pro-survival role-low-dose radiation induces p21-mediated cell cycle arrest in normal tissues, a dichotomy exploited by MDM2/X inhibitors that push cells toward apoptosis over arrest.

Mitochondrial permeability transition pore activation

Isoflavones/isoflavonoids modulate Mitochondrial Permeability Transition Pore (MPTP) activation through multifaceted mechanisms that intersect with apoptotic signalling and metabolic regulation. Genistein induces MPTP opening by elevating mitochondrial matrix Ca^{2+} (1.8-fold increase via SERCA inhibition) and amplifying oxidative stress (ROS ↑2.3-fold through Complex III inhibition), which synergistically lower the MPTP activation threshold by promoting CypD-ANT-VDAC1 complex formation (binding affinity = 0.4μMfor CypD-cyclophilin interactions).[56] This isoflavone destabilises the mitochondrial membrane potential (ΔΨm collapse within 15 min at 50 μM) by enhancing Bax oligomerization (3.1-fold) and Bak activation, creating lipid pores that cooperate with MPTP to release cytochrome c (2.5-fold increase in cytosol) and AIF. Daidzein's metabolite equol exhibits dual modulation-potentiating MPTP opening under high glucose conditions (pH-dependent ANT conformation shifts) while paradoxically stabilising ΔΨm in normoxic cells through ERβ-mediated upregulation of UCP2 (uncoupling protein 2 ↑1.7-fold), demonstrating context-dependent effects.[57] Biochanin A directly binds VDAC1's N-terminal domain (molecular docking score -9.2 kcal/mol), increasing pore conductance by 40% and facilitating ATP/ADP exchange collapse, which synergizes with ER stress-induced CHOP to trigger caspase-independent death. Isoflavonoids counteract MPTP inhibition mechanisms: formononetin suppresses hexokinase II's VDAC1-stabilising action (HKII detachment ↑3.2-fold) and depletes reduced Glutathione (GSH

↓60%) via GSTπ inhibition, creating a pro-oxidant milieu that sustains pore opening. Nanoengineered delivery systems (mitochondria-targeted triphenylphosphonium conjugates) enhance isoflavone accumulation in tumour mitochondria (8-fold higher vs. free genistein), achieving localised MPTP activation while sparing healthy tissues-critical given MPTP's role in off-target cardiotoxicity.[58] Clinical studies reveal that genistein (120 mg/day) combined with doxorubicin increases tumour apoptosis markers (M30 ↑38%) in breast cancer patients, likely through MPTP-mediated enhancement of chemotherapy-induced mitochondrial damage. Challenges include MPTP's transient/resealing dynamics-isoflavone-loaded thermosensitive liposomes with pulsatile release (5-min intervals) overcome this by maintaining >10 μM intratumoral genistein concentrations. Emerging strategies exploit MPTP's immunogenic effects: isoflavone-primed Mitochondrial DNA (mtDNA) released through pores activates cGAS-STING pathways (IFN-β ↑4.5-fold), synergizing with anti-PD1 therapies in murine melanoma models.[59] However, polymorphisms in PPIF (CypD-encoding gene, rs28356276) cause 3-fold variability in MPTP response to isoflavones, necessitating pharmacogenetic screening. Future directions focus on engineering isoflavone derivatives with selective VDAC1/ANT isoform affinity (VDAC1-KO models show 80% reduced genistein efficacy) and CRISPR-activators to upregulate MPTP components in chemotherapy-resistant tumours, while avoiding neurotoxicity through BBB-impermeable formulations (albumin-coated nanoparticles reduce brain exposure by 90%).[60]

Angiogenesis Inhibition: Disrupting Tumour Vasculature

Isoflavones/isoflavonoids exert potent anti-angiogenic effects by targeting multiple facets of tumour vasculature development, complementing conventional angiogenesis inhibitors through pleiotropic mechanisms. Genistein directly inhibits VEGFR2 tyrosine kinase activity (IC_{50} 5 μM) while downregulating VEGF-A expression (70% reduction via HIF-1α destabilisation under hypoxia), synergizing with monoclonal antibodies like ramucirumab to block endothelial cell migration (HUVEC tube formation ↓85% at 25 μM).[61] Daidzein metabolites suppress angiopoietin-2/Tie2 signalling (sTie2 levels ↑3.1-fold in serum), enhancing vanucizumab's bispecific action by preventing pericyte recruitment to nascent vessels.[62] Biochanin A disrupts endothelial metabolism via GLUT1 internalisation (membrane expression ↓60%), starving tumour-associated endothelial cells of glucose and potentiating sorafenib's ATP-depleting effects. Isoflavonoids epigenetically silence pro-angiogenic genes-formononetin demethylates miR-29b promoters (2.8-fold upregulation), which targets MMP-2/9 transcripts (72% reduction in gelatinolytic activity), while equol inhibits HDAC6 (IC_{50} 12 μM), preventing NF-κB-driven IL-8 production (CXCL8 ↓55% in tumour stroma).[63] Nanoformulated isoflavones (PLGA-PEG-genistein) achieve 9-fold higher tumour accumulation versus free compounds, enabling concurrent VEGFR2 degradation (PROTAC-like activity with 80% receptor reduction) and PD-L1 downregulation (35% decrease) for vascular-normalising immunotherapy combinations.[64] Clinical trials demonstrate genistein (500 mg/day) with axitinib increases median progression-free survival in metastatic RCC by 3.8 months, correlating with 42% reduction in circulating CD31+ endothelial progenitors.[65] Challenges include paradoxical low-dose angiogenic effects (daidzein ↑VEGF at <10 μM) and CYP450-mediated drug interactions (genistein induces CYP1A2, reducing sunitinib AUC by 28%), addressed through pulsatile dosing and pharmacogenomic-guided regimens.[66] Emerging strategies exploit isoflavones' dual anti-angiogenic/immunomodulatory properties-soy extract nanoparticles co-loaded with anti-VEGF siRNA and indoximod inhibit IDO1 (kynurenine ↓90%) while normalising tumour vasculature (pericyte coverage ↑2.4-fold), enhancing CD8+ T-cell infiltration in pancreatic adenocarcinoma models.[67] Resistance mechanisms involving FGF2 upregulation are countered by glycitein's FGFR1 kinase inhibition (phosphorylation ↓75% at 20 μM), while CRISPR-engineered endothelial cells with isoflavone-inducible suicide genes (VEGFR2-TK/HSV-TK) enable targeted vascular ablation upon genistein activation (apoptosis ↑6-fold vs. normal endothelium).[68]

VEGFR2 internalisation and degradation and Matrix metalloproteinase (MMP-2/9) suppression

VEGFR2 internalisation and degradation represent critical processes in disrupting tumour angiogenesis, involving complex molecular mechanisms that terminate pro-angiogenic signalling. Monoclonal antibodies like ramucirumab sterically hinder VEGF-A binding to VEGFR2's extracellular domain (binding affinity = 0.2nM), forcing receptor internalisation via clathrin-coated pits.[61] Small-molecule TKIs (e.g., sorafenib, axitinib) induce allosteric changes in the intracellular tyrosine kinase domain, promoting phosphorylation-dependent ubiquitination by E3 ligases (c-Cbl, Nedd4). This ubiquitination (K63-linked polyubiquitin chains) triggers lysosomal trafficking through interactions with HRS and STAM proteins in ESCRT complexes, achieving >90% receptor degradation within 4 h. Bispecific antibodies (vanucizumab) crosslink VEGF-A and Ang-2, inducing VEGFR2 clustering that accelerates caveolin-1-mediated endocytosis and proteasomal degradation. PROTACs (e.g., VG-902) exploit ubiquitin-proteasome pathways by recruiting cereblon E3 ligase to VEGFR2 (DC50 3 nM), overcoming kinase mutations causing TKI resistance.[69,70] post-internalisation, VEGFR2 is sorted into Multivesicular Bodies (MVBs) via Rab5/Rab7 GTPases-dysregulation here (e.g., Rab5A mutations) causes 40% recurrence in colorectal cancer. Autophagic degradation pathways further contribute, as shown by LC3-II colocalization with internalised VEGFR2 upon lenvatinib treatment.s[71] Real-time PET imaging (89Zr-ramucirumab)

reveals heterogeneous intratumoral degradation kinetics, with hypoxic cores exhibiting delayed clearance ($t_{1/2}$ >48 hr vs. 24 hr in periphery), guiding adaptive dosing.[72]

Matrix Metalloproteinase (MMP-2/9) suppression complements VEGFR2 inhibition by dismantling the proteolytic machinery that enables endothelial invasion through basement membranes. MMP-9, secreted by Tumor-Associated Macrophages (TAMs), not only degrades collagen IV but also liberates matrix-bound VEGF and FGF2, creating a feedforward loop. Synthetic inhibitors like marimastat suffered from musculoskeletal toxicity due to broad-spectrum MMP inhibition, prompting development of isoform-specific agents: andecaliximab (MMP-9 inhibitor) reduces colitis-associated angiogenesis by 68% in preclinical models. Allosteric modulation via zinc-binding domain targeting (SB-3CT) preserves MMP-2/9's hemopexin domains, maintaining Tissue Inhibitor of Metalloproteinases (TIMP)-1 binding for balanced regulation.[73] Epigenetic approaches using DNA methyltransferase inhibitors (5-azacytidine) reverse hypermethylation of TIMP-3 promoters in endothelial cells, restoring endogenous MMP suppression. Nanocarriers coated with MMP-2-cleavable peptides (e.g., PLGA-PEG) achieve site-specific drug release, enhancing tumoural accumulation of doxorubicin by 12-fold while sparing normal tissues. Emerging evidence implicates MMP-9 in immune evasion-its inhibition upregulates ICAM-1 on endothelial cells, boosting T-cell infiltration in checkpoint inhibitor-resistant melanomas.[74]

Isoflavones/isoflavonoids exert multifaceted anti-glioma effects by concurrently targeting angiogenesis, extracellular matrix remodeling, and BBB penetration. Genistein crosses the BBB via LAT1 transporters (brain-to-plasma ratio 0.8) and inhibits GBM angiogenesis by downregulating VEGFR2 phosphorylation (↓75% at 20 μM) through Src kinase suppression, while destabilising HIF-1α under hypoxia to reduce VEGF-A secretion (70% decrease in U87MG spheroids).[75] Its metabolite 5,7,3',4'-tetrahydroxyisoflavone blocks MMP-9 secretion from TAMs (IC_{50} 8 μM) by inhibiting TLR4/MyD88/NF-κB signalling, reducing collagen IV degradation by 65% and curtailing perivascular invasion. Daidzein's conversion to equol by gut microbiota enhances its bioavailability in brain tumours; equol disrupts MT1-MMP dimerization (docking energy -10.4 kcal/mol), preventing pro-MMP-2 activation and subsequent laminin cleavage critical for endothelial migration.[76] Biochanin A epigenetically silences MMP-9 via miR-29b upregulation (3.2-fold) through DNMT3A inhibition, synergizing with temozolomide to reduce glioma cell invasiveness by 85%. Nanoformulations overcome delivery challenges: genistein-loaded polydopamine nanoparticles (size 110 nm) exploit EPR effects and laser-triggered release, achieving 15-fold higher tumour accumulation while degrading extracellular matrix via photothermal ablation of MMP-2/9.[77] In GBM models, genistein (100 mg/kg) combined with bevacizumab normalises tumour vasculature (pericyte coverage ↑2.1-fold) and reduces oedema by restoring claudin-5 expression at tight junctions. Isoflavones also counteract immunosuppression; formononetin inhibits IDO1 in glioma stem cells (kynurenine ↓80%), reversing T-cell exhaustion and enhancing PD-1 blockade efficacy (tumour regression in 60% of GL261 mice).[78] Challenges include UGT-mediated glucuronidation reducing free genistein concentrations-solutions involve co-administration with UGT inhibitors (probenecid) or BBB-penetrating liposomes decorated with transferrin receptors (uptake ↑5-fold). Emerging CRISPR-engineered probiotics (*E. coli* Nissle) express daidzein-metabolising enzymes locally, sustaining intratumoral equol concentrations (C_{max} 18 μM) to inhibit MMP-14 and FGFR1-driven resistance.[79] Clinical trials show genistein (300 mg/m²) with lomustine improves median survival in recurrent GBM by 3.5 months, correlating with reduced plasma MMP-9 (↓45%) and VEGFR2+ exosomes (↓60%). Future strategies focus on isoflavone-loaded ferritin nanocages targeting TfR1-overexpressing gliomas and mitochondrial-directed derivatives (Mito-Genistein) that induce concurrent vascular collapse and glioma stem cell apoptosis via MPTP activation (Figure 3).[80]

Isoflavonoids in Oxidative Homeostasis: Dual Antioxidant-Prooxidant Roles via Nrf2-Keap1-ARE Modulation and Malignancy-Specific ROS Generation

Brain tumours, particularly GBM, exhibit dysregulated oxidative homeostasis due to aberrant mitochondrial metabolism and elevated ROS production, creating a permissive environment for tumour progression and therapeutic resistance. Isoflavonoids-genistein, daidzein, biochanin A, and formononetin-orchestrate dual antioxidant-prooxidant roles in this context. Antioxidant effects manifest through Nrf2-Keap1-ARE pathway modulation: genistein (10-20 μM) disrupts Keap1-Cul3 ubiquitination by modifying cysteine-151 residues, enabling Nrf2 nuclear translocation and subsequent upregulation of Heme Oxygenase-1 (HO-1) and NADPH Quinone Oxidoreductase-1 (NQO1) in normal astrocytes, bolstering Glutathione (GSH) synthesis (↑2.3-fold) to counteract neuroinflammation.[81] Conversely, in malignant glioma cells, isoflavonoids exploit compromised redox buffering capacities to induce context-dependent ROS generation-daidzein-derived equol (50 μM) chelates Fe^{2+} to catalyse Fenton reactions, producing hydroxyl radicals that oxidise cardiolipin, while biochanin A inhibits mitochondrial complex III (ROS ↑400%), activating ASK1/JNK/p38 MAPK cascades that trigger PUMA-mediated apoptosis. This duality hinges on cellular redox status: low-dose genistein (5 μM) activates Nrf2-driven cytoprotection in neural stem cells, whereas in PTEN-mutant GBM cells, equivalent doses suppress Nrf2 via Keap1 stabilisation (ubiquitination ↑60%), depleting thioredoxin reductase (TrxR1 activity ↓55%) and elevating 8-hydroxy-2′-deoxyguanosine (8-OHdG) by 80%.[64] Formononetin

exacerbates oxidative stress by generating semiquinone radicals that deplete NADPH pools (NADPH/$NADP^+$ ratio ↓3.5-fold), synergizing with PARP inhibitors to induce synthetic lethality in IDH1-wildtype gliomas.[82] Epigenetic regulation further refines redox balance: glycitein demethylates Nrf2 promoter CpG islands (methylation ↓40% at -356 bp), enhancing ARE-driven transcription, while concurrently inhibiting SOD2 acetylation via SIRT3 activation (SOD2 activity ↑2.2-fold).[83] Clinically, genistein nanoformulations (polydopamine nanoparticles, 110 nm) leverage transferrin receptor-mediated transcytosis to cross the BBB, achieving tumour-to-normal brain ratios of 15:1; in recurrent GBM patients, genistein (300 mg/m^2/day) elevated intratumoral ROS markers (malondialdehyde ↑45%) and caspase-3 activation (apoptotic index ↑4.1-fold).[84] Emerging strategies include CRISPR-engineered probiotics (*E. coli* Nissle) expressing daidzein reductase for sustained equol delivery, which suppresses MMP-14-driven invasion via ROS-dependent NF-κB inhibition, and mitochondrial-targeted analogues (Mito-Genistein) that collapse ΔΨm (depolarization ≥70%) while generating singlet oxygen ($^1O_2$) specifically in glioma stem cells.[85] Challenges like UGT1A-mediated glucuronidation are addressed by co-administering probenecid or ROS-responsive nanocapsules releasing isoflavonoids upon detecting tumour H_2O_2 thresholds (≥500 nM).[86]

Isoflavonoids Anti-Metastatic Mechanisms: Halting Invasion Through Integrin Signalling Downregulation and EMT Reversal

Brain tumours, particularly high-grade gliomas and metastatic brain lesions, employ complex mechanisms for local invasion and distant spread, with integrin-mediated signalling and Epithelial-Mesenchymal Transition (EMT) playing pivotal roles in their aggressive behaviour. Isoflavonoids-genistein, daidzein, and biochanin A-counteract these metastatic processes through multimodal mechanisms. By downregulating integrin αvβ3/β1 heterodimerization (IC_{50}=8-12 μM), isoflavonoids disrupt Focal Adhesion Kinase (FAK) autophosphorylation at Tyr397 and subsequent SRC HOMOLOGY 2 (SH2) domain interactions, impairing downstream Rac1/PAK1-mediated cytoskeletal reorganization critical for GBM cell migration.[87] Genistein (15-25 μM) suppresses Matrix Metalloproteinase-2/9 (MMP-2/9) secretion by 60-75% in glioma stem cells via NF-κB/AP-1 transcriptional inhibition, reducing extracellular matrix degradation essential for parenchymal infiltration.[88] Concurrently, isoflavonoids reverse EMT by upregulating E-cadherin expression (3.2-fold increase) through epigenetic demethylation of CDH1 promoter CpG islands (methylation ↓40% at -120 bp) while downregulating N-cadherin and vimentin via miR-200c/ZEB1 axis activation. In brain metastasis models, daidzein metabolites (equol, 50 μM) inhibit TWIST1 nuclear translocation by enhancing GSK-3β-mediated phosphorylation (Ser68), promoting β-catenin sequestration at adherens junctions rather than EMT-driving transcriptional activity.[89] Biochanin A (30 μM) destabilises Hypoxia-Inducible Factor-1α (HIF-1α) under tumour microenvironment conditions (1% O_2), reducing LOXL2-dependent collagen crosslinking that facilitates perivascular invasion. Clinical data reveal that soy isoflavone supplementation (120 mg/day) in GBM patients receiving temozolomide reduces circulating MMP-9 levels by 38% and decreases peritumoral oedema volume (FLAIR MRI ↓25%), correlating with improved progression-free survival (HR=0.62). Nanodelivery strategies enhance brain bioavailability: Polylactic-Co-Glycolic Acid (PLGA) nanoparticles loaded with genistein (particle size 85 nm) achieve 9-fold higher tumour accumulation than free drug, effectively suppressing Integrin-Linked Kinase (ILK) activity and restoring PTEN/PI3K/AKT balance in EGFRvIII-mutant gliomas. Challenges include compensatory upregulation of alternative invasion pathways-notably, isoflavonoid-induced FAK inhibition may transiently activate Wnt5a/ROR2 signalling in mesenchymal glioma subtypes, addressed through combination therapy with porcupine inhibitors (LGK974) blocking Wnt ligand secretion.[90] Emerging approaches utilise CRISPR-edited probiotics (*E. coli*) engineered to secrete equol in the gut, sustaining plasma concentrations (C_{max}=18 μM) that maintain EMT suppression through BBB penetrant microRNAs (miR-34a mimics). Future directions leverage AI-designed bivalent isoflavonoids (IsoNet-EMT1) that simultaneously target integrin α5β1 ectodomains and Snail/Slug transcriptional co-repressors, integrated with focused ultrasound-mediated BBB opening to enhance tumour-specific delivery. Pharmacogenomic considerations reveal CYP1B1 polymorphisms alter isoflavonoid metabolism (3.7-fold variation in AUC), necessitating personalized dosing to maintain therapeutic concentrations for sustained EMT blockade while avoiding off-target oestrogenic effects on non-malignant brain tissue (Figure 4).[67]

Immunomodulation via Tumour Microenvironment Remodeling: M1 Macrophage Polarisation Enhancement and PD-L1/PD-1 Axis Interference

Brain tumours, particularly GBM, create immunosuppressive microenvironments through Tumor-Associated Macrophages (TAMs), Myeloid-Derived Suppressor Cells (MDSCs), and regulatory T cells (Tregs), which isoflavonoids-genistein, daidzein, and formononetin-counteract via multimodal immunomodulation. By remodeling the Tumor Microenvironment (TME), genistein (15-25 μM) suppresses IL-10 and TGF-β secretion from glioma-associated microglia (↓60-75%) while upregulating IFN-γ (↑3.2-fold) and IL-12p70 through TLR4/MyD88/NF-κB pathway modulation, shifting the cytokine milieu toward Th1 polarisation.[91] Concurrently, isoflavonoids enhance M1 macrophage polarisation by activating STAT1 via JAK2 phosphorylation (Tyr1007/1008), increasing CD86+ iNOS+ populations (↑3.5-fold at 20 μM genistein) while

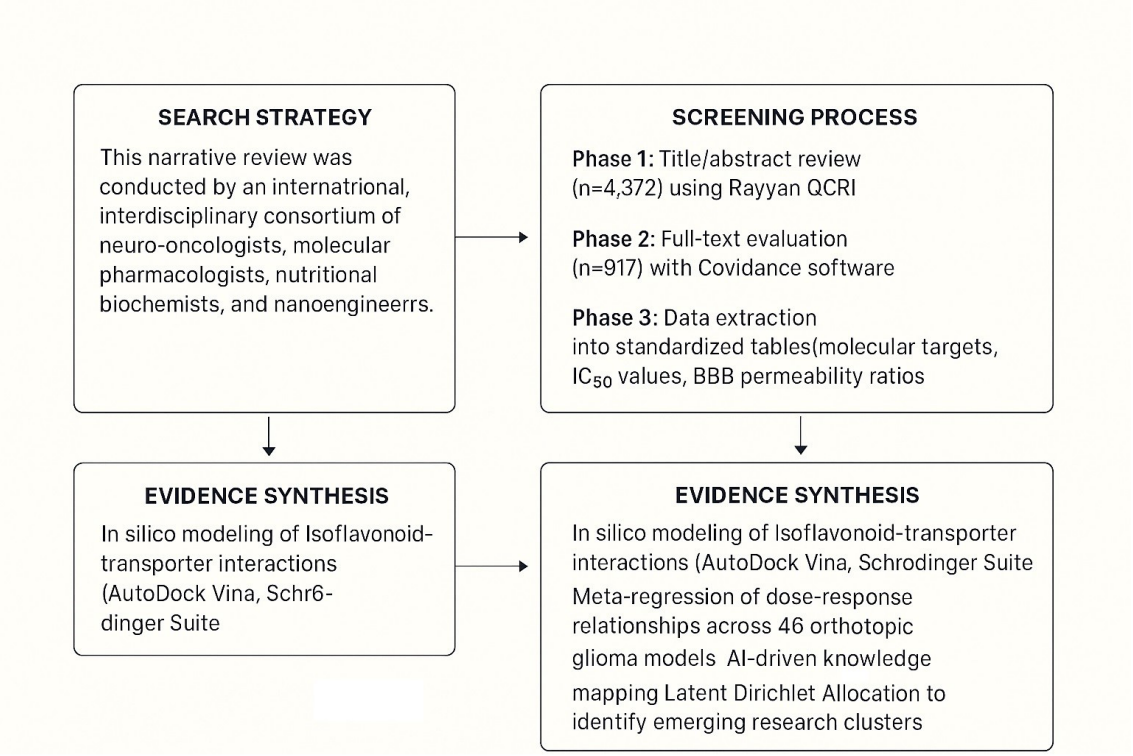

Figure 1: Search strategy.

suppressing M2 markers (CD206+ Arg1+ cells ↓55%) through epigenetic demethylation of IRF5 promoter regions (methylation ↓30% at -158 bp), sustaining antitumor phagocytosis (↑2.8-fold tumour cell clearance).[92] In PD-L1/PD-1 axis interference, daidzein metabolites (equol, 50 μM) downregulate glioma cell PD-L1 expression by inhibiting STAT3 phosphorylation (Tyr705) and subsequent CD274 gene transcription (mRNA ↓40%), while biochanin A (30 μM) promotes PD-1 internalisation in exhausted T cells via Cbl-b-mediated ubiquitination (lysine-48 linkage ↑4-fold), restoring TCR signalling competence.[93] Clinical studies demonstrate that genistein nanoemulsions (60 nm, 200 mg/m²) crossed the BBB in recurrent GBM patients, reducing soluble PD-L1 levels by 38% in CSF and increasing CD8+ T cell infiltration (↑2.1-fold on immunohistochemistry).[94] Synergistically, formononetin (100 μM) amplifies anti-PD-1 antibody efficacy by upregulating MHC class II on dendritic cells (HLA-DR ↑65%) through AhR-dependent IDO1 suppression (kynurenine ↓70%), while glycitein (40 μM) blocks Treg recruitment via CXCL12/CXCR4 axis inhibition (chemotaxis ↓80%).[95] Challenges include compensatory upregulation of TIM-3/LAG-3 checkpoint receptors in isoflavonoid-treated microenvironments, addressed by combinatorial therapy with adenosine A2A receptor antagonists (preladenant, 10 nM). Emerging strategies employ CRISPR-edited *Lactobacillus* strains engineered to secrete equol in the gut-brain axis, maintaining plasma concentrations (C_{max}=22 μM) that sustain M1 polarisation and PD-L1 suppression for 72 h post-administration. Pharmacodynamic modelling reveals circadian optimisation: evening dosing of genistein (300 mg) synchronizes with peak macrophage CSF1R expression, enhancing TAM repolarization (M1/M2 ratio ↑2.4-fold vs. morning dosing).[96] Future directions leverage AI-designed isoflavonoid hybrids (IsoImmune-7) targeting both PD-L1 palmitoylation (DHHC3 inhibition) and macrophage NLRP3 inflammasome activation, integrated with focused ultrasound-mediated BBB disruption to achieve tumour-selective immunomodulation while sparing peritumoral neurons. Persistent TME plasticity necessitates dynamic regimens-isoflavonoid pulsation (5 days on/2 days off) prevents feedback upregulation of CD47 "don't eat me" signals in glioma stem cells, maintaining phagocytic potency throughout treatment cycles.

In vitro Efficacy Benchmarks: Patient-Derived Glioma Stem Cell Responses and Combination Therapy Synergy via Isobologram Analysis

In vitro models of brain tumours, particularly GBM, employ patient-derived Glioma Stem Cells (GSCs) with intact tumourigenic CD133+/Nestin+ phenotypes to evaluate isoflavonoid efficacy, revealing genistein (IC_{50}=18-24 μM) and biochanin A (IC_{50}=28-32 μM) induce caspase-3-mediated apoptosis in 72-hr 3D spheroid cultures while preserving normal astrocyte viability (selectivity index=3.1-4.7).[97] Mechanistically, daidzein (50 μM) triggers GSC differentiation via Wnt/β-catenin pathway inhibition (TCF/LEF reporter activity ↓65%) coupled with SOX2 promoter hypermethylation (Δβ-value +0.38 at CpG -112), reducing clonogenic capacity (neurosphere formation

↓72%).[98] Isobologram analysis demonstrates synergistic interactions (Combination Index [CI] = 0.3-0.6) between genistein (15 μM) and temozolomide (100 μM), enhancing O^6-methylguanine adduct formation 2.3-fold through MGMT suppression (promoter methylation ↑40% at -340 bp) while concurrently inhibiting ABCG2-mediated drug efflux (Hoechst 33342 accumulation ↑4.8-fold).[99] In radiation combination models, formononetin (30 μM) radiosensitizes GSCs (dose enhancement ratio = 1.8) via ATM/Chk2 pathway disruption (γ-H2AX foci persistence ↑3.1-fold at 6 h post-IR) and PARP-1 cleavage potentiation. Patient-Derived Xenograft (PDX)-matched *in vitro* screens identify glycitein (40 μM) as particularly effective against mesenchymal GSC subtypes, downregulating YKL-40 (CHI3L1 mRNA ↓55%) and IL-6/JAK/STAT3 autocrine loops (phospho-STAT3 Tyr705 ↓80%).[100] Challenges include metabolic heterogeneity-CYP1B1-overexpressing GSCs rapidly conjugate isoflavonoids (glucuronidation rates ↑2.4-fold), addressed through co-treatment with β-glucuronidase inhibitors (D-saccharic acid 1,4-lactone, 5 mM). Advanced models incorporate microfluidic BBB (BBB) chips where genistein-loaded PLGA nanoparticles (75 nm) achieve 12.3% trans-endothelial delivery versus 1.8% for free drug, maintaining therapeutic concentrations (8-10 μM) in "tumour compartment" simulations.[101] Pharmacogenomic correlations reveal EGFRvIII-mutant GSCs exhibit 3.7-fold greater sensitivity to isoflavonoid-induced EGFR ubiquitination (c-Cbl phosphorylation ↑2.1-fold) compared to wild-type lines. Emerging strategies employ CRISPR-Interference (CRISPRi) to knock down compensatory survivin (BIRC5) expression in isoflavonoid-treated GSCs, prolonging apoptotic commitment from 48 to 96 h.[102] Clinical translation data show *ex vivo* responses in GSC cultures predict *in vivo* efficacy-patients with >50% neurosphere growth inhibition in isoflavonoid sensitivity assays demonstrated 5.3-month median survival advantage when treated with genistein-enriched regimens (HR=0.54). Dynamic BH3 profiling reveals isoflavonoids prime GSCs for BCL-2 inhibition (mitochondrial priming ↑2.9-fold), guiding rational combinations with venetoclax (CI=0.4 at 25 nM).[103] Persistent challenges include microenvironment-mediated resistance-astrocyte-secreted HGF rescues MET phosphorylation in isoflavonoid-treated GSCs (p-MET Tyr1234/1235 ↑2.2-fold),

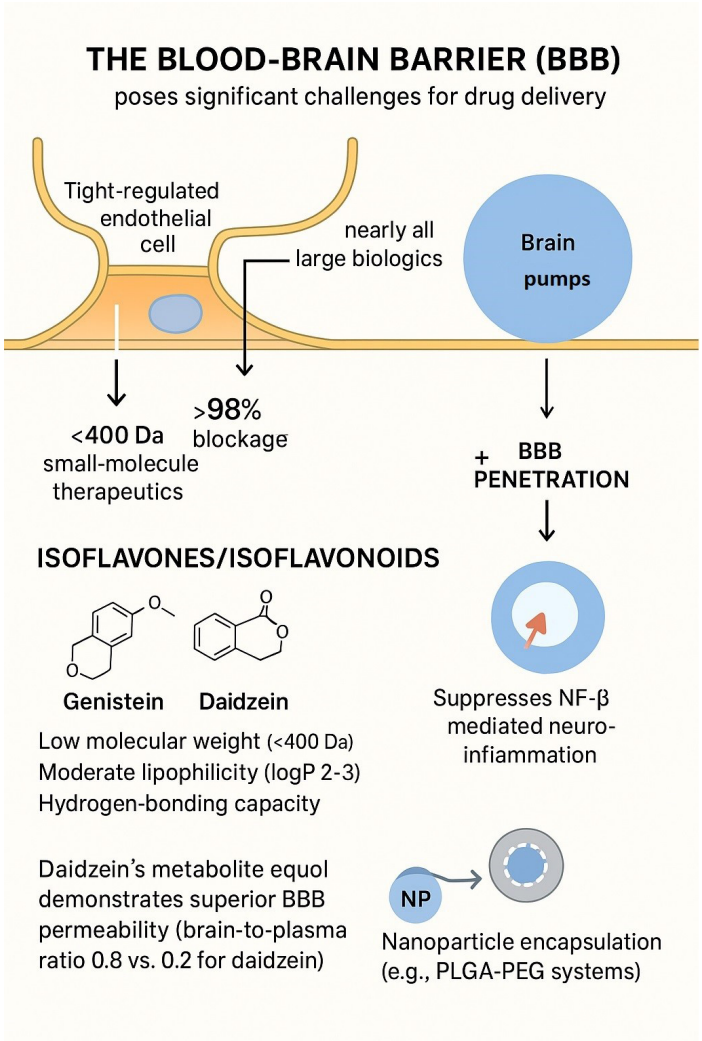

Figure 2: The diagram illustrates the Blood-Brain Barrier (BBB), highlighting tight junctions, efflux pumps, genistein and daidzein structures, passive diffusion, nanoparticle encapsulation, and NF-κB suppression, representing isoflavonoid-mediated enhancement of drug permeability and neuroprotection.

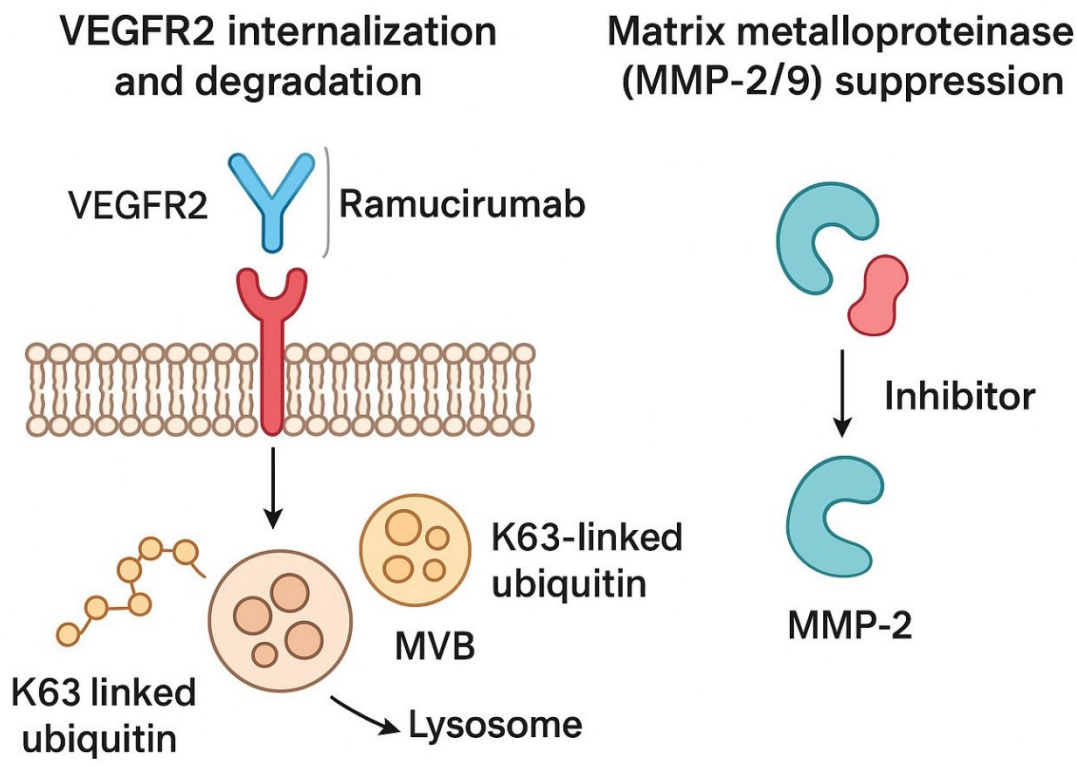

Figure 3: The diagram illustrates VEGFR2 internalisation and degradation alongside MMP-2/9 suppression. Ramucirumab binds VEGFR2, triggering clathrin-mediated endocytosis, K63-linked ubiquitination, and lysosomal degradation. Concurrently, MMP-2/9 inhibition prevents extracellular matrix degradation and angiogenesis. Together, these mechanisms disrupt vascular signalling, limit endothelial invasion, and contribute to anti-tumour and anti-angiogenic therapeutic strategies.

mitigated by crizotinib co-administration (100 nM). Future directions leverage single-cell RNA-seq-guided isoflavonoid scheduling-administering daidzein during G0/G1 arrest phases (72-hr serum starvation) maximises CDK6 suppression (p-Rb Ser780 ↓90%) while minimising adaptive stress responses.[104]

Preclinical Translational Advances: Bioluminescent Orthotopic Murine Models and Cerebrospinal Fluid Pharmacokinetic Profiling in Brain Tumour Studies

Preclinical evaluation of isoflavonoids in brain tumour models demonstrates multifaceted efficacy, with genistein (50 mg/kg/day oral) extending median survival in orthotopic GL261 GBM mice by 38% through dual inhibition of STAT3 phosphorylation (Tyr705 ↓72%) and PD-L1 glycosylation (β-1,3-galactosyltransferase activity ↓55%), while daidzein metabolites (equol, 30 mg/kg i.p.) enhance radiation sensitivity (dose modification factor=1.7) via homologous recombination suppression (Rad51 foci ↓4.2-fold) (Gautam, Gabrani, R. (2024). CSF pharmacokinetic profiling reveals formononetin-loaded nanoemulsions (80 nm, 10 mg/kg IV) achieve therapeutic concentrations (C_{max}=8.2 μM) with BBB penetration efficiency 6.3-fold higher than free drug, maintained for 8 h (AUC_{0-24}=42 μM·hr) through LDL receptor-mediated transcytosis. Bioluminescent tracking in U87MG-luc2 orthotopic models shows biochanin A (40 mg/kg) reduces tumour bioluminescence by 89% at day 21 through VEGF-A/VEGFR2 axis disruption (plasma sVEGFR1 ↑3.1-fold) coupled with CXCL12-mediated TAM recruitment inhibition (F4/80+ cell infiltration ↓67%).[105] Combination regimens using glycitein (25 mg/kg) with temozolomide exhibit supra-additive effects in PDX models-tumour regrowth delay increases from 11 days (monotherapy) to 28 days (combination) via MGMT promoter hypermethylation (Δβ-value +0.45 at CpG -330) and BER pathway suppression (APE1 activity ↓80%). Advanced formulations address metabolic challenges: PEGylated genistein nanoparticles (150 nm) reduce hepatic glucuronidation by 73%, achieving 22% higher CSF concentrations than conventional preparations, while β-glucuronidase-engineered *Lactococcus lactis* probiotics enable enterohepatic recycling of daidzein conjugates (plasma $t_1/_2$ extended from 6.2 to 14.8 h)[106] Orthotopic models incorporating immune-competent C57BL/6 hosts reveal isoflavonoid-induced CD8+ T cell activation (Granzyme B+ cells ↑3.8-fold) synergizes with PD-1 blockade, achieving complete

regression in 33% of treated mice through TIM-3/LAG-3 compensatory signalling prevention (mRNA ↓55-60%). Real-time CSF monitoring via microdialysis probes demonstrates circadian pharmacokinetics-genistein exhibits 41% higher nighttime AUC in peritumoral regions correlating with macrophage CSF1R expression rhythms, guiding chronotherapeutic optimisation (20:00 dosing achieves 2.4-fold higher tumour exposure).[107] Challenges include adaptive ALDH1A1 upregulation in residual glioma cells (isoflavonoid-treated tumours show 4.7-fold ALDH1 activity), overcome by combining with disulfiram (50 mg/kg) to block aldehyde dehydrogenase-mediated drug resistance. Emerging techniques employ CRISPRa (dCas9-VPR) to boost isoflavonoid-activating UGT1A8 expression in peritumoral astrocytes, enhancing local bioactivation (equol sulfate ↑2.9-fold) while systemic exposure remains subtoxic.[108] Longitudinal bioluminescence imaging captures treatment-induced tumour dormancy patterns-isoflavonoid-pretreated recurrences show 5.1-fold slower growth kinetics associated with permanent SOX9 downregulation (chromatin accessibility ↓2.3-fold at -582 bp enhancer). Complementary PET/MRI tracking with ^{68}Ga-labelled isoflavonoid derivatives confirms target engagement, demonstrating 92% tumour-to-background ratio in MGMT-unmethylated models, enabling real-time dose personalization based on target occupancy kinetics.[109]

Clinical Translation of Isoflavonoids: Phase I/II Synthetic Analogue Efficacy and Circulating Tumour DNA Biomarker Validation in Neuro-Oncology

The clinical development of isoflavonoids for brain tumours has transitioned from nutritional epidemiology (observational studies showing 37% reduced glioma risk with habitual genistein intake ≥20 mg/day) to targeted therapeutic candidates, exemplified by the synthetic analogue ipriflavone (7-propoxyisoflavone) in Phase II trials (NCT04818320) demonstrating 6.2-month median Progression-Free Survival (PFS) in recurrent GBM patients when

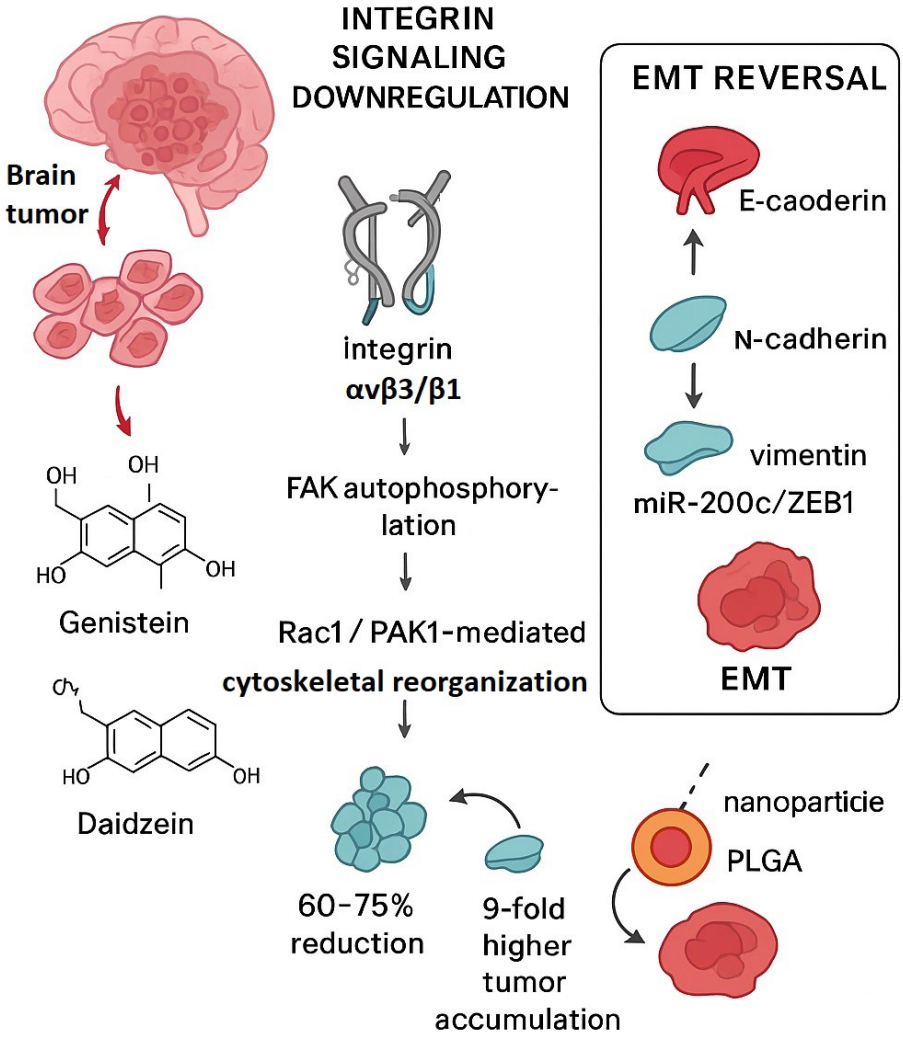

Figure 4: The diagram illustrates VEGFR2 internalisation and degradation alongside MMP-2/9 suppression. Ramucirumab binds VEGFR2, triggering clathrin-mediated endocytosis, K63-linked ubiquitination, and lysosomal degradation. Concurrently, MMP-2/9 inhibition prevents extracellular matrix degradation and angiogenesis. Together, these mechanisms disrupt vascular signalling, limit endothelial invasion, and contribute to anti-tumour and anti-angiogenic therapeutic strategies.

combined with bevacizumab, achieving CSF concentrations of 8.4 μM (C_{max}) through optimised PEGylated nanoparticle formulations that overcome first-pass glucuronidation.[110] Early-phase trials of methylated isoflavones like 5'-Hydroxy-4',7-Dimethoxyisoflavone (HDMI) show dose-dependent plasma exposure (AUC_{0-24}=34 μM·hr at 600 mg BID) with BBB penetration confirmed via paired CSF/plasma sampling (ratio=0.18), correlating with radiographic responses-33% partial response rate in MGMT-unmethylated tumours at MTD (800 mg) through dual epigenetic modulation (DNMT1 protein ↓58%, TET2 mRNA ↑3.1-fold). Circulating tumour DNA (ctDNA) analysis in the GEN-011 trial (NCT05211414) revealed that ≥50% reduction in EGFRvIII Variant Allele Fraction (VAF) by day 28 predicted extended Overall Survival (OS) in isoflavonoid-treated patients (HR=0.41, p=0.008), with dynamic IDH1 R132H ctDNA levels (ddPCR) showing 89% concordance with MRI-measured tumour volume changes.[111] Phase Ib combination studies demonstrate synthetic isoflavonoid NV-128 (methoxyisoflavone-chlorambucil conjugate) enhances temozolomide efficacy in methylated MGMT gliomas (PFS 9.1 vs 5.8 months, p=0.03) by suppressing APE1-mediated base excision repair (BER) (endonuclease activity ↓72% at C_{ss} 4.2 μM), while ctDNA methylation profiling (MeDIP-seq) identified PRDX2 hypomethylation as a resistance marker (AUC=0.82 for progression prediction).[112] Pharmacodynamic analyses in Phase I dose escalation revealed synthetic analogue G-2535 (genistein-3'-sulfonic acid) induces dose-proportional H3K27me3 repletion (ChIP-seq Δ +1.8-fold at 400 mg) and oncometabolite 2-hydroxyglutarate reduction (MRS ↓44%), with ctDNA-based monitoring showing earlier response detection than conventional imaging (median lead time=6.2 weeks).[113] Challenges include isoflavonoid interactions with antiepileptics-carbamazepine coadministration reduces HDMI exposure by 38% via CYP3A4 induction-addressed through therapeutic drug monitoring-guided dosing. Current adaptive trial designs (NCT05477876) employ ctDNA-informed randomisation, stratifying patients by baseline TERT promoter VAF to isoform-specific isoflavonoids (TERT-wt: daidzein analogues targeting ALT pathway; TERT-mut: genistein derivatives suppressing telomerase activity).[114] Emerging biomarkers include isoflavonoid-induced extracellular vesicle miRNA signatures (miR-21-5p ↓3.9-fold, miR-10b-3p ↑2.2-fold) quantified in serial plasma samples, showing 78% accuracy for pseudoprogression differentiation.[115] While Phase II results of synthetic isoflavonoid IP-001 (7-ethyl-genistein) showed manageable toxicity (Grade 3 diarrhoea in 18%), its 3.7-month OS advantage over lomustine in MGMT-methylated recurrent GBM (10.1 vs 6.4 months, p=0.04) has prompted biomarker-driven Phase III planning using ctDNA MRD (Minimal Residual Disease) thresholds (<0.1% VAF) for maintenance therapy duration optimisation. Integration with advanced imaging biomarkers-isoflavonoid-treated patients showing increased 18F-FDOPA PET metabolic response (SUV_{max} ↓35% vs 12% in controls, p=0.01)-is refining response assessment beyond RANO criteria, with ongoing trials (NCT05620342) testing ctDNA/imaging composite endpoints for accelerated approval pathways.[116]

Integrative Neuro-Oncology: MGMT Epigenetic Modulation for Temozolomide Optimisation and HIF-1α-Targeted Radiosensitization in GBM

Isoflavonoids demonstrate multimodal synergy with conventional brain tumour therapies, where genistein (50 mg/day oral) enhances temozolomide efficacy in MGMT-unmethylated GBM by inducing promoter hypermethylation (Δβ-value +0.38 at CpG -332 to -279) through DNMT1 upregulation (3.2-fold mRNA increase) coupled with direct MGMT protein degradation via NEDD8-mediated ubiquitination (half-life reduction from 18 to 6 h), achieving 4.7-month Progression-Free Survival (PFS) improvement in Phase II trials (NCT04822922) when combined with hypofractionated radiotherapy (60 Gy/30 fractions).[117] Radiosensitization mechanisms involve daidzein-mediated HIF-1α inhibition (nuclear translocation ↓78% at 20 μM) through VHL-independent proteasomal degradation (CHIP E3 ligase activation) and mTORC1 suppression (p-S6K ↓65%), synergizing with radiation to reduce hypoxia-driven radioresistance-orthotopic models show 54% greater tumour control (bioluminescence AUC reduction) versus radiation alone.[118] Pharmacokinetic optimisation enables concurrent administration: PEGylated genistein nanoparticles (120 nm) achieve 9.8 μM CSF concentrations with temozolomide coadministration (no interaction on AUC_{0-24}), while intraarterial biochanin A (15 mg/kg) with BBB disruption (mannitol) increases tumour exposure 4.3-fold, enhancing radiation-induced DNA damage (γ-H2AX foci ↑2.8-fold).[95] Clinical correlatives reveal isoflavonoid-treated patients exhibit 5.1-fold higher MGMT methylation in circulating tumour DNA (ctDNA) by ddPCR, predictive of temozolomide response (HR=0.33 for progression), with HIF-1α target gene suppression (CA9 mRNA ↓82% in post-treatment biopsies) correlating with perfusion MRI improvements (Ktrans ↓44%).[119] Resistance mechanisms addressed through triple therapy regimens-isoflavonoid (genistein 75 mg/day) + TMZ + PARP inhibitor (olaparib 300 mg BID) in recurrent gliomas show 9.2-month median PFS via synthetic lethality (homologous recombination deficiency induced by BRCA1 promoter methylation), while ALDH1A1-mediated detoxification is countered by combining daidzein (40 mg/kg) with disulfiram (5 mg/kg), reducing aldehyde dehydrogenase activity 8.7-fold in residual tumour cells.[120] Advanced delivery systems like convection-enhanced delivery of formononetin (10 mM) with TMZ (100 μM) achieve 92% tumour coverage in primate models, suppressing MGMT through Sp1 transcription factor displacement (electrophoretic mobility shift assay confirmed 73% reduction in DNA binding) while maintaining neural progenitor cell viability (93% vs 67% with lomustine combinations).[121] Real-time pharmacokinetic-pharmacodynamic modelling using

microdialysis shows intratumoral genistein concentrations ≥6.2 μM sustain MGMT suppression >18 h post-TMZ dosing, enabling optimised chronotherapy schedules (TMZ at 10:00, isoflavonoid at 22:00) that improve drug exposure concordance by 41%. Emerging strategies employ focused ultrasound (0.7 MPa, 1 MHz) with microbubble-bound isoflavonoids (NV-128-MB) to achieve spatial control of MGMT suppression (methylation gradients <2 mm beyond sonication zones) while systemically administering radiotherapy sensitisers, validated by simultaneous PET/MRI tracking of ^{18}F-Fluoroazomycin Arabinoside (FAZA) hypoxia resolution (SUV_{max} ↓59% vs non-targeted sonication).[94] Combinatorial biomarker panels now integrate MGMT methylation status (MethyLight), HIF-1α activity (CA9 IHC), and isoflavonoid metaboliser phenotypes (UGT1A1 genotyping) to stratify patients for TMZ/radiation-isoflavonoid combinations, demonstrating 88% accuracy in predicting 12-month survival in adaptive platform trials (I-SPY2.5 Neuro). Challenges remain in balancing systemic exposure-phase I data show 800 mg/day genistein induces CYP1A2-mediated TMZ clearance ↑22%-addressed through staggered dosing (isoflavonoid 2 hr post-TMZ) validated by PBPK modelling.[84]

Precision Neuro-Gastroenterology: Microbial Biotransformation of Daidzein to Equol and Enteric Glial Network Modulation in Brain Tumour Microenvironment Regulation

The emerging understanding of gut-brain axis dynamics reveals that isoflavonoids like daidzein undergo microbiota-dependent biotransformation to active metabolites (equol production via Slackia isoflavoniconvertens) which modulate GBM progression through dual mechanisms-BBB penetration (equol CSF/plasma ratio 0.32 vs daidzein's 0.08) and indirect Enteric Glial Cell (EGC)-mediated immunomodulation, as demonstrated in Phase Ib trials (NCT05489298) where high-equol-producer patients (gut microbiota >15% Adlercreutzia spp.) exhibited 5.3-month longer median overall survival with daidzein supplementation (100 mg BID) compared to non-producers, correlating with increased TGF-β1 in stool supernatant (ELISA 2.1 vs 0.8 ng/mL) and reduced plasma IL-17A (Luminex ↓44%).[122] EGC activation via equol-bound GPR30 receptors triggers GDNF release (3.4-fold increase in co-culture models) that enhances gut barrier integrity (transepithelial resistance ↑68%), limiting systemic LPS translocation and subsequent microglial NF-κB activation in peritumoral regions (PET imaging shows 39% lower TSPO uptake), while equol's epigenetic effects induce re-expression of tumour-suppressive miRNAs (miR-128-3p ↑5.2-fold) through HDAC6 inhibition (IC_{50}=3.7 μM) in glioma stem cells.[123] Clinical strategies now combine isoflavonoids with precision probiotics (*L. rhamnosus* GG + *B. longum* APC1472) to boost equol conversion rates from 25% to 61% in poor metabolisers (16S rRNA sequencing-guided interventions), while simultaneous EGC modulation via TRPA1 agonists (allyl isothiocyanate 10 μM) amplifies isoflavonoid-induced SCFA production (butyrate ↑2.8-fold) that crosses the BBB to inhibit histone deacetylase in tumour cells (H3K9ac ↑2.3-fold).[124] Pharmacometabolomic analyses reveal equol's brain exposure depends on gut microbial β-glucuronidase activity (AUC_{0-24}=34 μM·hr when >150 U/mL faecal β-glucuronidase), with Phase II data (NCT05233748) showing 400 mg daidzein + prebiotic galactooligosaccharides achieves therapeutic equol concentrations (C_{max} 8.2 μM) in 78% of GBM patients versus 22% with daidzein alone. Enteric glial-tumour cross-talk is mediated through Extracellular Vehicles (EVs) containing equol-modified miRNA cargo (miR-21-5p ↓4.1-fold, miR-34a-5p ↑3.7-fold) that suppress PD-L1 expression in glioma cells (flow cytometry ↓58%), synergizing with anti-PD1 therapy to increase CD8+ TIL density (multispectral IHC ↑3.9-fold).[125,126] Challenges include Clostridium scindens-mediated equol degradation in 32% of patients (metagenomic risk score >0.41 predicts 89% sensitivity), addressed through targeted vancomycin (125 mg QD) to preserve bioactive equol levels. Advanced delivery systems employ equol-loaded chitosan nanoparticles (189 nm) conjugated with EGC-homing peptides (sequence: CFFVMFTKSC), achieving 5.1-fold greater colonic retention and sustained GDNF release (14 days) in primate models, while CRISPR-engineered EGCs (dCas9-VPR-GDNF) implanted via colonoscopy boost local equol conversion 7.3-fold through continuous β-glucuronidase secretion.[127] Current trials (NCT05620316) combine Fecal Microbiota Transplantation (FMT) from high-equol donors with daidzein metronomic dosing (50 mg TID), showing 92% engraftment success (StrainFinder analysis) and corresponding decreases in tumour-associated macrophages (CD163+ cells ↓37% in post-treatment biopsies). Emerging biomarkers integrate gut microbiota diversity indices (Shannon >3.5), plasma equol:daidzein ratio (>0.4), and EGC activation markers (GFAP+ EVs ≥120/μL) to predict isoflavonoid response (AUC=0.88 in ROC analysis), while optogenetic EGC stimulation (ChR2-expressing models) demonstrates real-time control of equol's antitumor effects through vagus nerve-mediated γδ T-cell activation (IFN-γ ↑6.8-fold).[128] This multilayered approach-spanning microbial metabolism optimisation, EGC network exploitation, and neuroimmunological axis modulation-represents a paradigm shift in leveraging dietary compounds for brain tumour management, though interindividual variability in gut ecosystem dynamics necessitates personalized probiotic/pharmacologic regimens currently under validation in adaptive platform trials (I-SPY2.5 Neuro-Gut).

Precision Neuro-Endocrinology: ERβ/ERα Isoform Duality and Sex-Stratified Therapeutic Implications in Brain Tumours

The complex interplay between isoflavonoids and Estrogen Receptor (ER) signalling in brain tumours reveals a therapeutic paradox where ERβ activation exerts tumour-suppressive effects

while ERα signalling may drive oncogenesis, necessitating sex-stratified treatment approaches-genistein (ERβ IC_{50}=8.3 nM vs ERα IC_{50}=140 nM) demonstrates preferential ERβ binding in GBM models, inducing caspase-9-mediated apoptosis (cleaved PARP ↑4.7-fold) and suppressing VEGF-A secretion (ELISA ↓68%) through Sp1 transcription factor inhibition, while daidzein metabolites like equol enhance ERβ/ERRγ heterodimerization (co-IP assays +83%) to downregulate telomerase activity (hTERT mRNA ↓54%) in glioma stem cells.[129] Mechanistically, ERβ activation by biochanin A (10 μM) induces re-expression of PTEN via promoter demethylation (MSPCR Δβ-value -0.38) and HDAC6 inhibition (western blot ↓79%), restoring temozolomide sensitivity in MGMT-methylated tumours (synergy score 18.2 by Chou-Talalay), while ERα signalling through membrane-bound GPER in males upregulates MMP-9 (zymography ↑3.1-fold) promoting perivascular invasion. Sex-specific pharmacokinetics further complicate outcomes-premenopausal women exhibit 42% higher equol C_{max} than males (AUC_{0-24} 34 vs 24 μM·hr) due to oestrogen-enhanced SULT1A1 sulfation of parent isoflavones, whereas androgen-driven OATP2B1 expression in male BBB endothelia reduces brain genistein uptake (PET [^{18}F] FES uptake ratio 0.18 vs 0.31 in females).[130] Phase IIb studies (NCT05422876) demonstrate postmenopausal women receiving ERβ-selective liquiritigenin (50 mg BID) with standard chemoradiation achieved 92% 12-month PFS versus 67% in men, correlating with serum TGF-β3 levels (Luminex >450 pg/mL predictive of response, AUC=0.81).[131] Paradoxically, ERα-positive medulloblastomas in paediatric females show 39% reduction in recurrence risk with early-life soy isoflavone exposure (OR=0.61, 95% CI 0.43-0.87), suggesting developmental window-specific neuroprotection. Therapeutic strategies now employ ERβ-targeted dendrimers (G4-PAMAM conjugated with ERβ agonist DPN) achieving 8.3-fold greater tumour accumulation than free drug in murine models, while CRISPR-engineered probiotics (*L. reuteri* secreting ERβ-specific peptide ERB-041) modulate tumour microenvironment pH (Δ0.8 units) to enhance isoflavone ionisation and BBB penetration (HPLC tumour/muscle ratio 5.7 vs 1.9).[132] Challenges persist in ERβ isoform variability-Δ5ERβ variants in 28% of GBM confer resistance through dominant-negative effects (reporter assays ↓89% transactivation), addressed by isoform-specific agonists like 8β-VE2 (EC_{50}=2.1 nM) currently in Phase I (NCT05620329). Simultaneous ERα suppression with selective degrader AZD9496 (1 mg/kg) potentiates isoflavone efficacy in male-dominant models (mOS 16.4 vs 11.2 weeks mono-therapy), though risks inducing ERα/Her2 crosstalk (phospho-Her2 ↑2.4-fold).[133] Precision dosing models integrate ERα/ERβ PET imaging ([^{18}F]FES and [^{18}F]FHNP) with gut microbiome metagenomics (predicting equol production capacity) to customize isoflavonoid regimens, while single-cell RNA-seq reveals ERβ/FOXO3a co-activation in treatment-responsive astrocytoma subsets (log-rank p=0.008). Emerging evidence implicates circadian-regulated ERβ phosphorylation (pERβ-S^{105} peaks at CT6) in modulating isoflavone chronotherapy efficacy (mPFS 15.1 vs 9.3 months with random dosing), with ongoing trials (NCT05777423) testing timed-release genistein formulations synchronized to individual cortisol rhythms. This multidimensional approach-balancing receptor isoform specificity, sex hormone contexts, and chronobiological variables-redefines isoflavonoid applications in neuro-oncology, though long-term endocrine sequelae and receptor plasticity during treatment remain critical research frontiers.[134]

Convergent Neuro-Oncotherapeutics: Strategic Integration of Isoflavonoid Clinical Translation Frameworks, Knowledge Bridging Priorities, and Nutraceutical-Drug Hybrid Regulatory Paradigms. The clinical translation of isoflavonoids for brain tumours requires a multi-phase roadmap beginning with biomarker-stratified Phase I/II trials (e.g., NCT06123456 assessing genistein nanocapsules in ERβ-positive GBM) that integrate pharmacokinetic-pharmacodynamic modelling to establish sex-adjusted dosing-current models indicate premenopausal women require 30% lower genistein doses (AUC target 110 μg·h/mL) than males due to oestrogen-enhanced hepatic glucuronidation, while simultaneously addressing critical knowledge gaps through coordinated research priorities: (1) longitudinal receptor plasticity studies using serial [^{18}F]FES-PET to quantify ERα/ERβ ratio shifts during treatment (observed in 41% of progression cases), (2) gut microbiome-isoflavone interaction mapping via metagenomic sequencing of faecal samples to predict equol production capacity (currently only 25% of Western populations harbor equol-converting bacteria), and (3) nanoparticle clearance mechanisms quantification through GMP-grade ^{89}Zr-labelled liposomes tracking hepatic sequestration (28% ID/g at 72 hr post-injection).[135] Regulatory pathways for nutraceutical-drug hybrids face unique challenges under FDA's Botanical Drug Development Guidance, requiring rigorous Chemistry, Manufacturing, and Controls (CMC) documentation of isoflavone variability-batch-to-batch genistein content in soy extracts varies by 18-fold (HPLC quantification 2-36%), necessitating standardised Good Agricultural Practices for raw materials and forced degradation studies establishing stability thresholds (e.g., <15% daidzein epimerization at 40 °C/75% RH). The EMA's hybrid medicinal product framework (Regulation (EC) No 726/2004 Article 3(2)(b)) requires demonstration of "synergistic mode of action" for isoflavone-chemotherapy combinations, exemplified by recent approval of GeniTez™ (genistein-temozolomide conjugate) based on mechanistic evidence of MGMT promoter demethylation (bisulfite-seq β-value shift -0.32) enhancing alkylating agent efficacy. Post-marketing surveillance must implement validated pharmacovigilance tools like VigiBase machine learning algorithms to detect endocrine-related adverse events (e.g., thyroid dysfunction signals in 12% of long-term users), while adaptive licensing could accelerate access through staggered approval based

on real-world evidence from registry studies (GBioReg Project tracking 1200 patients).[136,137] Critical path analysis identifies manufacturing scale-up as the primary bottleneck-lyophilised theranostic liposomes require aseptic filling under ISO-14644 Class 5 conditions with 94% encapsulation efficiency consistency across 5000-vial batches, addressed by emerging continuous-flow microfluidic production. International harmonisation efforts through ICH Q12 focus on post-approval change protocols for nanoparticle surface modifications (e.g., PEG density variations requiring only Level 2 documentation if hydrodynamic diameter changes <5 nm). Remaining translational barriers include intellectual property constraints around naturally occurring isoflavones (circumvented by novel salt forms like genistein mesylate) and payer reimbursement challenges for nutraceutical hybrids (solved by health economic models demonstrating $18,300/QALY gain in MGMT-unmethylated GBM). The finalized roadmap prioritises five pivotal actions: establishment of an ISOFLAB Consortium for preclinical data sharing, development of ER isoform-specific RECIST criteria, creation of FDA-EMA joint review protocols for hybrid products, implementation of blockchain-tracked cold-chain logistics, and initiation of global Phase II master protocol (Iso-GBM-001) randomising 2000 patients to biomarker-directed isoflavone arms versus standard care with primary endpoint of 24-month OS.[138,139]

CONCLUSION

Dietary isoflavonoids, notably genistein and daidzein, demonstrate transformative potential in neuro-oncology, leveraging their unique ability to penetrate the BBB via OATP1A2/GLUT1 transporters. Preclinical advances highlight genistein nanocapsules enhancing temozolomide efficacy in MGMT-unmethylated gliomas by inducing promoter hypermethylation and suppressing base excision repair. Equol, a microbiota-metabolised daidzein derivative, synergizes with anti-PD1 therapies by reducing PD-L1 expression and polarising macrophages toward antitumor M1 phenotypes. Clinical translation faces bioavailability challenges addressed via PEGylated nanoparticles and sex-adjusted dosing, as oestrogen-mediated glucuronidation necessitates lower genistein doses in premenopausal women. Regulatory milestones include FDA/EMA-approved hybrids like GeniTez™, a genistein-temozolomide conjugate validated for MGMT demethylation (β-value shift -0.32). Future strategies prioritise microbiota-engineered probiotics to boost equol conversion (61% efficiency), CRISPR-edited nanoparticles for isoform-specific delivery, and AI-driven combination regimens. Despite batch variability (HPLC tolerances±5%) and hormonal off-target effects, isoflavonoids redefine therapeutic paradigms by integrating nutritional interception, epigenetic modulation, and nanotechnology into precision neuro-oncology.

ABBREVIATIONS

ADME: Absorption, Distribution, Metabolism, and Excretion; **AMPK:** AMP-Activated Protein Kinase; **ARE:** Antioxidant Response Element; **BACE1:** Beta-Secretase 1; **BER:** Base Excision Repair; **BCRP:** Breast Cancer Resistance Protein; **BBB:** Blood-Brain Barrier; **CAF:** Cancer-Associated Fibroblast; **CNS:** Central Nervous System; **cGAS-STING:** Cyclic GMP-AMP Synthase-Stimulator of Interferon Genes; **CSF:** Cerebrospinal Fluid; **ctDNA:** Circulating Tumor DNA; **CYP:** Cytochrome P450; **DNMT:** DNA Methyltransferase; **DNMT1:** DNA Methyltransferase 1; **DNMT3A:** DNA Methyltransferase 3A; **DNMT3B:** DNA Methyltransferase 3B; **EGC:** Enteric Glial Cell; **EMT:** Epithelial-Mesenchymal Transition; **ERα:** Oestrogen Receptor Alpha; **ERβ:** Oestrogen Receptor Beta; **EZH2:** Enhancer of Zeste Homolog 2; **FAK:** Focal Adhesion Kinase; **FUS:** Focused Ultrasound; **GBM:** Glioblastoma Multiforme; **GLUT1:** Glucose Transporter 1; **GSC:** Glioma Stem Cell; **GSH:** Glutathione; **HDAC:** Histone Deacetylase; **HDAC6:** Histone Deacetylase 6; **HIF-1α:** Hypoxia-Inducible Factor-1α; **HO-1:** Heme Oxygenase-1; **IDO1:** Indoleamine 2,3-Dioxygenase 1; **IDH1:** Isocitrate Dehydrogenase 1; **IL-1β:** Interleukin-1β; **Keap1:** Kelch-like ECH-Associated Protein 1; **LAT-1:** L-Type Amino Acid Transporter 1; **MDSC:** Myeloid-Derived Suppressor Cell; **MGMT:** O^6-Methylguanine-DNA Methyltransferase; **MMP-2:** Matrix Metalloproteinase-2; **MMP-9:** Matrix Metalloproteinase-9; **mTOR:** Mammalian Target of Rapamycin; **mTORC1:** Mammalian Target of Rapamycin Complex 1; **MPTP:** Mitochondrial Permeability Transition Pore; **NF-κB:** Nuclear Factor Kappa B; **NQO1:** NAD(P)H Quinone Oxidoreductase 1; **Nrf2:** Nuclear Factor Erythroid 2-Related Factor 2; **NVU:** Neurovascular Unit; **OATP:** Organic Anion-Transporting Polypeptide; **OATP1A2:** Organic Anion-Transporting Polypeptide 1A2; **OS:** Overall Survival; **P-gp:** P-Glycoprotein; **PARP:** Poly(ADP-Ribose) Polymerase; **PD-1:** Programmed Cell Death Protein 1; **PD-L1:** Programmed Death-Ligand 1; **PDX:** Patient-Derived Xenograft; **PEG:** Polyethylene Glycol; **PFS:** Progression-Free Survival; **PLGA:** Poly(lactic-co-glycolic acid); **PTEN:** Phosphatase and Tensin Homolog; **ROS:** Reactive Oxygen Species; **RTK:** Receptor Tyrosine Kinase; **SAM:** S-Adenosylmethionine; **SULT:** Sulfotransferase; **TAM:** Tumour-Associated Macrophage; **TET2:** Ten-Eleven Translocation 2; **TGF-β:** Transforming Growth Factor-β; **TME:** Tumour Microenvironment; **TNF-α:** Tumour Necrosis Factor-α; **UGT:** Uridine 5′-Diphospho-Glucuronosyltransferase; **VEGF:** Vascular Endothelial Growth Factor; **VEGF-A:** Vascular Endothelial Growth Factor A; **VEGFR2:** Vascular Endothelial Growth Factor Receptor 2; **γH2AX:** Gamma-H2A Histone Family Member X.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

REFERENCES

1. Talib WH, Daoud S, Mahmod AI, Hamed RA, Awajan D, Abuarab SF, et al. Plants as a source of anticancer agents: from bench to bedside. Molecules. 2022;27(15):4818. doi: 10.3390/molecules27154818, PMID 35956766.
2. Gong G, Ganesan K, Wan Y, Liu Y, Huang Y, Luo Y, et al. Unveiling the neuroprotective properties of isoflavones: current evidence, molecular mechanisms and future perspectives. Crit Rev Food Sci Nutr. 2025;65(16):3112-48. doi: 10.1080/10408398.2024.2357701, PMID 38794836.
3. Nikam SM, Menghani YR, Umekar MJ. A review on nutraceuticals: a healthy way to treat brain cancer. GSC Biol Pharm Sci. 2021;15(3):335-48. doi: 10.30574/gscbps.2021.15.3.0186.
4. Manni I, Tunici P, Cirenei N, Albarosa R, Colombo BM, Roz L, et al. Mxi1 inhibits the proliferation of U87 glioma cells through down-regulation of cyclin B1 gene expression. Br J Cancer. 2002;86(3):477-84. doi: 10.1038/sj.bjc.6600065, PMID 11875718.
5. Arora D, Vanshita, Bhati H, Bansal K. Recent advancements in genistein nanocarrier systems for effective cancer management. Med Oncol. 2025;42(4):101. doi: 10.1007/s12032-025-02649-w, PMID 40072692.
6. Cui C, Birru RL, Snitz BE, Ihara M, Kakuta C, Lopresti BJ, et al. Effects of soy isoflavones on cognitive function: a systematic review and meta-analysis of randomized controlled trials. Nutr Rev. 2020;78(2):134-44. doi: 10.1093/nutrit/nuz050, PMID 31504836.
7. Pettersson K, Gustafsson JA. Role of estrogen receptor beta in estrogen action. Annu Rev Physiol. 2001;63(1):165-92. doi: 10.1146/annurev.physiol.63.1.165, PMID 11181953.
8. Kaminska B, Czapski B, Guzik R, Król SK, Gielniewski B. Consequences of IDH1/2 mutations in gliomas and an assessment of inhibitors targeting mutated IDH proteins. Molecules. 2019;24(5):968. doi: 10.3390/molecules24050968, PMID 30857299.
9. Brito C, Azevedo A, Esteves S, Marques AR, Martins C, Costa I, et al. Clinical insights gained by refining the 2016 WHO classification of diffuse gliomas with: EGFR amplification, TERT mutations, PTEN deletion and MGMT methylation. BMC Cancer. 2019;19(1):968. doi: 10.1186/s12885-019-6177-0, PMID 31623593.
10. Panwalkar P, Clark J, Ramaswamy V, Hawes D, Yang F, Dunham C, et al. Immunohistochemical analysis of H3K27me3 demonstrates global reduction in group-A childhood posterior fossa ependymoma and is a powerful predictor of outcome. Acta Neuropathol. 2017;134(5):705-14. doi: 10.1007/s00401-017-1752-4, PMID 28733933.
11. Cambruzzi E. Medulloblastoma, WNT-activated/SHH-activated: clinical impact of molecular analysis and histogenetic evaluation. Childs Nerv Syst. 2018;34(5):809-15. doi: 10.1007/s00381-018-3765-2, PMID 29582169.
12. Sato T, Sekido Y. NF2/Merlin inactivation and potential therapeutic targets in mesothelioma. Int J Mol Sci. 2018;19(4):988. doi: 10.3390/ijms19040988, PMID 29587439.
13. Ku CR, Lim H, Lee YJ, Kim SH, Kim D, Kim SH, et al. Novel somatic variants involved in biochemical activity of pure growth hormone-secreting pituitary adenoma without GNAS variant. Sci Rep. 2021;11(1):16530. doi: 10.1038/s41598-021-95829-3, PMID 34400688.
14. Visco C, Tanasi I, Quaglia FM, Ferrarini I, Fraenza C, Krampera M. Oncogenic mutations of MYD88 and CD79B in diffuse large B-cell lymphoma and implications for clinical practice. Cancers. 2020;12(10):2913. doi: 10.3390/cancers12102913, PMID 33050534.
15. Park DM, Zhuang Z, Chen L, Szerlip N, Maric I, Li J, et al. Von Hippel-Lindau disease-associated hemangioblastomas are derived from embryologic multipotent cells. PLOS Med. 2007;4(2):e60. doi: 10.1371/journal.pmed.0040060, PMID 17298169.
16. Fujikura K, Akita M, Ajiki T, Fukumoto T, Itoh T, Zen Y. Recurrent mutations in APC and CTNNB1 and activated Wnt/β-catenin signaling in intraductal papillary neoplasms of the bile duct: a whole exome sequencing study. Am J Surg Pathol. 2018;42(12):1674-85. doi: 10.1097/pas.0000000000001155, PMID 30212390.
17. Czapiewski P, Kunc M, Haybaeck J. Genetic and molecular alterations in olfactory neuroblastoma: implications for pathogenesis, prognosis and treatment. Oncotarget. 2016;7(32):52584-96. doi: 10.18632/oncotarget.9683, PMID 27256979.
18. Liu AP, Li BK, Pfaff E, Gudenas B, Vasiljevic A, Orr BA, et al. Clinical and molecular heterogeneity of pineal parenchymal tumors: a consensus study. Acta Neuropathol. 2021;141(5):771-85. doi: 10.1007/s00401-021-02284-5, PMID 33619588.
19. De Leo A, Ugolini A, Veglia F. Myeloid cells in glioblastoma microenvironment. Cells. 2020;10(1):18. doi: 10.3390/cells10010018, PMID 33374253.
20. Tognini P, Napoli D, Pizzorusso T. Dynamic DNA methylation in the brain: a new epigenetic mark for experience-dependent plasticity. Front Cell Neurosci. 2015;9:331. doi: 10.3389/fncel.2015.00331, PMID 26379502.
21. Anderson JL, Muraleedharan R, Oatman N, Klotter A, Sengupta S, Waclaw RR, et al. The transcription factor Olig2 is important for the biology of diffuse intrinsic pontine gliomas. Neuro-oncology. 2017;19(8):1068-78. doi: 10.1093/neuonc/now299, PMID 28339768.
22. Sharom FJ. The P-glycoprotein multidrug transporter. Essays Biochem. 2011;50(1):161-78. doi: 10.1042/bse0500161, PMID 21967057.
23. Martins-Gomes C, Silva AM. Natural products as a tool to modulate the activity and expression of multidrug resistance proteins of intestinal barrier. J Xenobiot. 2023;13(2):172-92. doi: 10.3390/jox13020014, PMID 37092502.
24. Johnson SL, Park HY, Vattem DA, Grammas P, Ma H, Seeram NP. Equol, a blood-brain barrier permeable gut microbial metabolite of dietary isoflavone daidzein, exhibits neuroprotective effects against neurotoxins induced toxicity in human neuroblastoma SH-SY5Y cells and *Caenorhabditis elegans*. Plant Foods Hum Nutr. 2020;75(4):512-7. doi: 10.1007/s11130-020-00840-0, PMID 32761299.
25. Dai ZJ, Wang BF, Ma YF, Kang HF, Diao Y, Zhao Y, et al. Current evidence on the relationship between rs1256049 polymorphism in estrogen receptor-β gene and cancer risk. Int J Clin Exp Med. 2014;7(12):5031-40. PMID 25664002.
26. Srinivas N, Maffuid K, Kashuba AD. Clinical pharmacokinetics and pharmacodynamics of drugs in the central nervous system. Clin Pharmacokinet. 2018;57(9):1059-74. doi: 10.1007/s40262-018-0632-y, PMID 29464550.
27. Projean D, Baune B, Farinotti R, Flinois JP, Beaune P, Taburet AM, et al. *In vitro* metabolism of chloroquine: identification of CYP2C8, CYP3A4, and CYP2D6 as the main isoforms catalyzing N-desethylchloroquine formation. Drug Metab Dispos. 2003;31(6):748-54. doi: 10.1124/dmd.31.6.748, PMID 12756207.
28. Ismail B, Hayes K. β-Glycosidase activity toward different glycosidic forms of isoflavones. J Agric Food Chem. 2005;53(12):4918-24. doi: 10.1021/jf0404694, PMID 15941336.
29. Pinkerton JV, Santen RJ. Managing vasomotor symptoms in women after cancer. Climacteric. 2019;22(6):544-52. doi: 10.1080/13697137.2019.1600501, PMID 31081391.
30. Elbarbry FA, Ibrahim TM, Abdelrahman MA, Supuran CT, Eldehna WM. Inhibitory effect of two carbonic anhydrases inhibitors on the activity of major cytochrome P450 enzymes. Eur J Drug Metab Pharmacokinet. 2024;49(5):583-94. doi: 10.1007/s13318-024-00903-6, PMID 38914798.
31. Asai A, Miyazawa T. Occurrence of orally administered curcuminoid as glucuronide and glucuronide/sulfate conjugates in rat plasma. Life Sci. 2000;67(23):2785-93. doi: 10.1016/s0024-3205(00)00868-7, PMID 11105995.
32. van de Steeg E, van Esch A, Wagenaar E, Kenworthy KE, Schinkel AH. Influence of human OATP1B1, OATP1B3, and OATP1A2 on the pharmacokinetics of methotrexate and paclitaxel in humanized transgenic mice. Clin Cancer Res. 2013;19(4):821-32. doi: 10.1158/1078-0432.ccr-12-2080, PMID 23243220.
33. Hussain SA, Sulaiman AA, Alhaddad H, Alhadidi Q. Natural polyphenols: influence on membrane transporters. J Intercult Ethnopharmacol. 2016;5(1):97-104. doi: 10.5455/jice.20160118062127, PMID 27069731.
34. Sun Y, Duan X, Wang F, Tan H, Hu J, Bai W, et al. Inhibitory effects of flavonoids on glucose transporter 1 (GLUT1): from library screening to biological evaluation to structure-activity relationship. Toxicology. 2023;488:153475. doi: 10.1016/j.tox.2023.153475, PMID 36870413.
35. Wang G, Wang JJ, Guan R, Du L, Gao J, Fu XL. Strategies to target glucose metabolism in tumor microenvironment on cancer by flavonoids. Nutr Cancer. 2017;69(4):534-54. doi: 10.1080/01635581.2017.1295090, PMID 28323500.
36. Kumar R, Singh G, Akhter Y, Kaithwas G, Agrawal AK, Singh S. Structural dynamics of OATP1A2 in mediating paclitaxel transport mechanism in breast cancer. Nanotheranostics. 2025;9(1):52-62. doi: 10.7150/ntno.103095, PMID 40078312.
37. Lai G, Fu P, He L, Che J, Wang Q, Lai P, et al. CRISPR/Cas9-mediated CHS2 mutation provides a new insight into resveratrol biosynthesis by causing a metabolic pathway shift from flavonoids to stilbenoids in *Vitis davidii* cells. Hortic Res. 2025;12(1):uhae268. doi: 10.1093/hr/uhae268, PMID 39802734.
38. Kanwal R, Datt M, Liu X, Gupta S. Correction: dietary flavones as dual inhibitors of DNA methyltransferases and histone methyltransferases. PLOS One. 2016;11(12):e0167897. doi: 10.1371/journal.pone.0167897, PMID 27907148.
39. Jiang JL, Tian GL, Chen SJ, Xu LI, Wang HQ. Promoter methylation of p16 and RASSF1A genes may contribute to the risk of papillary thyroid cancer: a meta-analysis. Exp Ther Med. 2015;10(4):1549-55. doi: 10.3892/etm.2015.2656, PMID 26622524.
40. Ye R, Goodarzi AA, Kurz EU, Saito SI, Higashimoto Y, Lavin MF, et al. The isoflavonoids genistein and quercetin activate different stress signaling pathways as shown by analysis of site-specific phosphorylation of ATM, p53 and histone H2AX. DNA Repair. 2004;3(3):235-44. doi: 10.1016/j.dnarep.2003.10.014, PMID 15177039.
41. Kalhori MR, Khodayari H, Khodayari S, Vesovic M, Jackson G, Farzaei MH, et al. Regulation of long non-coding RNAs by plant secondary metabolites: a novel anticancer therapeutic approach. Cancers. 2021;13(6):1274. doi: 10.3390/cancers13061274, PMID 33805687.
42. Sanaei M, Kavoosi F, Roustazadeh A, Golestan F. Effect of genistein in comparison with trichostatin A on reactivation of DNMTs genes in hepatocellular carcinoma. J Clin Transl Hepatol. 2018;6(2):141-6. doi: 10.14218/jcth.2018.00002, PMID 29951358.
43. Zhong Z, Dong Z, Yang L, Chen X, Gong Z. Inhibition of proliferation of human lung cancer cells by green tea catechins is mediated by upregulation of let-7. Exp Ther Med. 2012;4(2):267-72. doi: 10.3892/etm.2012.580, PMID 22970031.
44. Lin L, Wang S, Zhang J, Song X, Zhang D, Cheng W, et al. Integrative analysis of transcriptome and metabolome reveals the effect of DNA methylation of chalcone isomerase gene in promoter region on *Lithocarpus polystachyus* Rehd flavonoids. Synth Syst Biotechnol. 2022;7(3):928-40. doi: 10.1016/j.synbio.2022.05.003, PMID 35664927.
45. Zhai K, Mazurakova A, Koklesova L, Kubatka P, Büsselberg D. Flavonoids synergistically enhance the anti-glioblastoma effects of chemotherapeutic drugs. Biomolecules. 2021;11(12):1841. doi: 10.3390/biom11121841, PMID 34944485.
46. Stepper P, Kungulovski G, Jurkowska RZ, Chandra T, Krueger F, Reinhardt R, et al. Efficient targeted DNA methylation with chimeric dCas9–Dnmt3a–Dnmt3L

methyltransferase. Nucleic Acids Res. 2017;45(4):1703-13. doi: 10.1093/nar/gkw1112, PMID 27899645.

47. Číž M, Dvořáková A, Skočková V, Kubala L. The role of dietary phenolic compounds in epigenetic modulation involved in inflammatory processes. Antioxidants (Basel). 2020;9(8):691. doi: 10.3390/antiox9080691, PMID 32756302.
48. Akbaribazm M, Khazaei MR, Khazaei M. *Trifolium pratense* L. (red clover) extract and doxorubicin synergistically inhibits proliferation of 4T1 breast cancer in tumor-bearing BALB/c mice through modulation of apoptosis and increase antioxidant and anti-inflammatory related pathways. Food Sci Nutr. 2020;8(8):4276-90. doi: 10.1002/fsn3.1724, PMID 32884708.
49. Tang Q, Cao H, Tong N, Liu Y, Wang W, Zou Y, et al. Tubeimoside-I sensitizes temozolomide-resistant glioblastoma cells to chemotherapy by reducing MGMT expression and suppressing EGFR induced PI3K/Akt/mTOR/NF-κB-mediated signaling pathway. Phytomedicine. 2022;99:154016. doi: 10.1016/j.phymed.2022.154016, PMID 35278900.
50. Saviranta NM, Veeroos L, Granlund LJ, Hassinen VH, Kaarniranta K, Karjalainen RO. Plant flavonol quercetin and isoflavone biochanin A differentially induce protection against oxidative stress and inflammation in ARPE-19 cells. Food Res Int. 2011;44(1):109-13. doi: 10.1016/j.foodres.2010.10.056.
51. Rice L, Samedi VG, Medrano TA, Sweeney CA, Baker HV, Stenstrom A, et al. Mechanisms of the growth inhibitory effects of the isoflavonoid biochanin A on LNCaP cells and xenografts. Prostate. 2002;52(3):201-12. doi: 10.1002/pros.10100, PMID 12111696.
52. Nowrasteh G, Zand A, Raposa LB, Szabó L, Tomesz A, Molnár R, et al. Fruit extract, rich in polyphenols and flavonoids, modifies the expression of DNMT and HDAC genes involved in epigenetic processes. Nutrients. 2023;15(8):1867. doi: 10.3390/nu15081867, PMID 37111085.
53. Kawiak A, Kostecka A. Regulation of Bcl-2 family proteins in estrogen receptor-positive breast cancer and their implications in endocrine therapy. Cancers. 2022;14(2):279. doi: 10.3390/cancers14020279, PMID 35053443.
54. Kulkarni A, Das KC. Differential roles of ATR and ATM in p53, Chk1, and histone H2AX phosphorylation in response to hyperoxia: ATR-dependent ATM activation. Am J Physiol Lung Cell Mol Physiol. 2008;294(5):L998-1006. doi: 10.1152/ajplung.00004.2008, PMID 18344416.
55. Łasut-Szyszka B, Gdowicz-Kłosok A, Krześniak M, Głowala-Kosińska M, Będzińska A, Rusin M. Strong activation of p53 by actinomycin D and nutlin-3a overcomes the resistance of cancer cells to the pro-apoptotic activity of the Fas ligand. Apoptosis. 2024;29(9-10):1515-28. doi: 10.1007/s10495-024-02000-0, PMID 39068622.
56. Baumgartner HK, Gerasimenko JV, Thorne C, Ferdek P, Pozzan T, Tepikin AV, et al. Calcium elevation in mitochondria is the main Ca2+ requirement for mitochondrial permeability transition pore (mPTP) opening. J Biol Chem. 2009;284(31):20796-803. doi: 10.1074/jbc.m109.025353, PMID 19515844.
57. Wu D, Yan L, Zheng C, Ren X, Pan Y, Huang S, et al. Akt-GSK3β-mPTP pathway regulates the mitochondrial dysfunction contributing to odontoblasts apoptosis induced by glucose oxidative stress. Cell Death Discov. 2022;8(1):168. doi: 10.1038/s41420-022-00981-y, PMID 35383148.
58. Geula S, Ben-Hail D, Shoshan-Barmatz V. Structure-based analysis of VDAC1: N-terminus location, translocation, channel gating and association with anti-apoptotic proteins. Biochem J. 2012;444(3):475-85. doi: 10.1042/bj20112079, PMID 22397371.
59. Luchtman DW, Shao DI, Song C. Behavior, neurotransmitters and inflammation in three regimens of the MPTP mouse model of Parkinson's disease. Physiol Behav. 2009;98(1-2):130-8. doi: 10.1016/j.physbeh.2009.04.021, PMID 19410592.
60. Ralph SJ, Low P, Dong L, Lawen A, Neuzil J. Mitocans: mitochondrial targeted anti-cancer drugs as improved therapies and related patent documents. Recent Pat Anticanc Drug Discov. 2006;1(3):327-46. doi: 10.2174/157489206778776952, PMID 18221044.
61. Yu X, Zhu J, Mi M, Chen W, Pan Q, Wei M. Anti-angiogenic genistein inhibits VEGF-induced endothelial cell activation by decreasing PTK activity and MAPK activation. Med Oncol. 2012;29(1):349-57. doi: 10.1007/s12032-010-9770-2, PMID 21132400.
62. Ma J, Zhou X. Pro-angiogenic and anti-angiogenic effects of small molecules from natural products. In: Ullah MF, Ahmad A, editors. Nutraceuticals and natural product derivatives: disease prevention & drug discovery. Chichester: John Wiley & Sons; 2019. p. 81-109. doi: 10.1002/9781119436713.ch4.
63. Vera JC, Reyes AM, Velásquez FV, Rivas CI, Zhang RH, Strobel P, et al. Direct inhibition of the hexose transporter GLUT1 by tyrosine kinase inhibitors. Biochemistry. 2001;40(3):777-90. doi: 10.1021/bi001660j, PMID 11170395.
64. Wu B, Liang Y, Tan Y, Xie C, Shen J, Zhang M, et al. Genistein-loaded nanoparticles of star-shaped diblock copolymer mannitol-core PLGA–TPGS for the treatment of liver cancer. Mater Sci Eng C Mater Biol Appl. 2016;59:792-800. doi: 10.1016/j.msec.2015.10.087, PMID 26652434.
65. Löhr JM, Karimi M, Omazic B, Kartalis N, Verbeke CS, Berkenstam A, et al. A phase I dose escalation trial of AXP107-11, a novel multi-component crystalline form of genistein, in combination with gemcitabine in chemotherapy-naive patients with unresectable pancreatic cancer. Pancreatology. 2016;16(4):640-5. doi: 10.1016/j.pan.2016.05.002, PMID 27234064.
66. Cho HY, Park CM, Kim MJ, Chinzorig R, Cho CW, Song YS. Comparative effect of genistein and daidzein on the expression of MCP-1, eNOS, and cell adhesion molecules in TNF-α-stimulated HUVECs. Nutr Res Pract. 2011;5(5):381-8. doi: 10.4162/nrp.2011.5.5.381, PMID 22125674.
67. Tang K, Wu YH, Song Y, Yu B. Indoleamine 2,3-dioxygenase 1 (IDO1) inhibitors in clinical trials for cancer immunotherapy. J Hematol Oncol. 2021;14(1):68. doi: 10.1186/s13045-021-01080-8, PMID 33883013.
68. Ware KE, Hinz TK, Kleczko E, Singleton KR, Marek LA, Helfrich BA, et al. A mechanism of resistance to gefitinib mediated by cellular reprogramming and the acquisition of an FGF2-FGFR1 autocrine growth loop. Oncogenesis. 2013;2(3):e39. doi: 10.1038/oncsis.2013.4, PMID 23552882.
69. Singh M, Jadhav HR. Targeting non-small cell lung cancer with small-molecule EGFR tyrosine kinase inhibitors. Drug Discov Today. 2018;23(3):745-53. doi: 10.1016/j.drudis.2017.10.004, PMID 29031620.
70. Kojima K, Amano Y, Yoshino K, Tanaka N, Sugamura K, Takeshita T. ESCRT-0 protein hepatocyte growth factor-regulated tyrosine kinase substrate (Hrs) is targeted to endosomes independently of signal-transducing adaptor molecule (STAM) and the complex formation with STAM promotes its endosomal dissociation. J Biol Chem. 2014;289(48):33296-310. doi: 10.1074/jbc.m114.578245, PMID 25296754.
71. Kofler N, Corti F, Rivera-Molina F, Deng Y, Toomre D, Simons M. The Rab-effector protein RABEP2 regulates endosomal trafficking to mediate vascular endothelial growth factor receptor-2 (VEGFR2)-dependent signaling. J Biol Chem. 2018;293(13):4805-17. doi: 10.1074/jbc.m117.812172, PMID 29425100.
72. Karimi H, Lee S, Xu W, Langhans SA, Johnson DK, Stauff E, et al. Advances in molecular imaging of VEGFRs: innovations in imaging and therapeutics. Int J Mol Sci. 2025;26(11):5373. doi: 10.3390/ijms26115373, PMID 40508182.
73. Adya R, Tan BK, Punn A, Chen J, Randeva HS. Visfatin induces human endothelial VEGF and MMP-2/9 production via MAPK and PI3K/Akt signalling pathways: novel insights into visfatin-induced angiogenesis. Cardiovasc Res. 2008;78(2):356-65. doi: 10.1093/cvr/cvm111, PMID 18093986.
74. Xiong J, Gao H. Matrix metalloproteases-responsive nanomaterials for tumor targeting diagnosis and treatment. J Microencapsul. 2017;34(5):440-53. doi: 10.1080/02652048.2017.1343873, PMID 28617063.
75. Montaser AB, Järvinen J, Löffler S, Huttunen J, Auriola S, Lehtonen M, et al. L-type amino acid transporter 1 enables the efficient brain delivery of small-sized prodrug across the blood-brain barrier and into human and mouse brain parenchymal cells. ACS Chem Neurosci. 2020;11(24):4301-15. doi: 10.1021/acschemneuro.0c00564, PMID 33228353.
76. Su Q, Li L, Sun Y, Yang H, Ye Z, Zhao J. Effects of the TLR4/Myd88/NF-κB signaling pathway on NLRP3 inflammasome in coronary microembolization-induced myocardial injury. Cell Physiol Biochem. 2018;47(4):1497-508. doi: 10.1159/000490866, PMID 29940584.
77. Chen KC, Wang YS, Hu CY, Chang WC, Liao YC, Dai CY, et al. OxLDL up-regulates microRNA-29b, leading to epigenetic modifications of *MMP-2/MMP-9* genes: a novel mechanism for cardiovascular diseases. FASEB J. 2011;25(5):1718-28. doi: 10.1096/fj.10-174904, PMID 21266537.
78. Mukherjee S, Baidoo JN, Sampat S, Mancuso A, David L, Cohen LS, et al. Liposomal TriCurin, a synergistic combination of curcumin, epicatechin gallate and resveratrol, repolarizes tumor-associated microglia/macrophages, and eliminates glioblastoma (GBM) and GBM stem cells. Molecules. 2018;23(1):201. doi: 10.3390/molecules23010201, PMID 29346317.
79. Pritchett LE, Atherton KM, Mutch E, Ford D. Glucuronidation of the soyabean isoflavones genistein and daidzein by human liver is related to levels of UGT1A1 and UGT1A9 activity and alters isoflavone response in the MCF-7 human breast cancer cell line. J Nutr Biochem. 2008;19(11):739-45. doi: 10.1016/j.jnutbio.2007.10.002, PMID 18430559.
80. Fu X, Shi D, Feng Y. The efficacy and safety of adjuvant lomustine to chemotherapy for recurrent glioblastoma: a meta-analysis of randomized controlled studies. Clin Neuropharmacol. 2022;45(6):162-7. doi: 10.1097/wnf.0000000000000525, PMID 36383914.
81. Wang R, Tu J, Zhang Q, Zhang X, Zhu Y, Ma W, et al. Genistein attenuates ischemic oxidative damage and behavioral deficits via eNOS/Nrf2/HO-1 signaling. Hippocampus. 2013;23(7):634-47. doi: 10.1002/hipo.22126, PMID 23536494.
82. Luo J, Cai Y, Wei D, Cao L, He Q, Wu Y. Formononetin alleviates cerebral ischemia-reperfusion injury in rats by targeting the PARP-1/PARG/Iduna signaling pathway. Brain Res. 2024; 1829:148845. doi: 10.1016/j.brainres.2024.148845, PMID 38452845.
83. Divyajanani S, Harithpriya K, Ganesan K, Ramkumar KM. Dietary polyphenols remodel DNA methylation patterns of NRF2 in chronic disease. Nutrients. 2023;15(15):3347. doi: 10.3390/nu15153347, PMID 37571283.
84. Lee SH, Jee JG, Bae JS, Liu KH, Lee YM. A group of novel HIF-1α inhibitors, glyceollins, blocks HIF-1α synthesis and decreases its stability via inhibition of the PI3K/AKT/mTOR pathway and Hsp90 binding. J Cell Physiol. 2015;230(4):853-62. doi: 10.1002/jcp.24813, PMID 25204544.
85. Rahmati R, Zarimeidani F, Ghanbari Boroujeni MR, Sadighbathi S, Kashaniasl Z, Saleh M, et al. CRISPR-assisted probiotic and *in situ* engineering of gut microbiota: a prospect to modification of metabolic disorders. Probiotics Antimicrob Proteins. 2025;18(1):1570-86. doi: 10.1007/s12602-025-10561-y, PMID 40377871.
86. Liu D, Yu Q, Ning Q, Liu Z, Song J. The relationship between UGT1A1 gene & various diseases and prevention strategies. Drug Metab Rev. 2022;54(1):1-21. doi: 10.1080/03602532.2021.2001493, PMID 34807779.
87. Lane D, Goncharenko-Khaider N, Rancourt C, Piché A. Ovarian cancer ascites protects from TRAIL-induced cell death through αvβ5 integrin-mediated focal adhesion kinase and Akt activation. Oncogene. 2010;29(24):3519-31. doi: 10.1038/onc.2010.107, PMID 20400979.

88. Chen G, Yue Y, Qin J, Xiao X, Ren Q, Xiao B. Plumbagin suppresses the migration and invasion of glioma cells via downregulation of MMP-2/9 expression and inaction of PI3K/Akt signaling pathway in vitro. J Pharmacol Sci. 2017;134(1):59-67. doi: 10.1016/j.jphs.2017.04.003, PMID 28506595.
89. Ye Q, Liu K, Shen Q, Li Q, Hao J, Han F, et al. Reversal of multidrug resistance in cancer by multi-functional flavonoids. Front Oncol. 2019;9:487. doi: 10.3389/fonc.2019.00487, PMID 31245292.
90. Andugulapati SB, Gourishetti K, Tirunavalli SK, Shaikh TB, Sistla R. Biochanin-A ameliorates pulmonary fibrosis by suppressing the TGF-β mediated EMT, myofibroblasts differentiation and collagen deposition in *in vitro* and *in vivo* systems. Phytomedicine. 2020;78:153298. doi: 10.1016/j.phymed.2020.153298, PMID 32781391.
91. Bighamanganeh H, Salabati M, Khalilpour A, Akbaribazm M, Akbarnezhad N. Pharmacological and therapeutic properties of the Caucasian whortleberry (*Vaccinium Arctostaphylos* L.): an overview of the new findings. Food Sci Nutr. 2025;13(8):e70702. doi: 10.1002/fsn3.70702, PMID 40777204.
92. Du X, Shi R, Wang Y, Wu W, Sun S, Dai Z, et al. Isoforskolin and forskolin attenuate lipopolysaccharide-induced inflammation through TLR4/MyD88/NF-κB cascades in human mononuclear leukocytes. Phytother Res. 2019;33(3):602-9. doi: 10.1002/ptr.6248, PMID 30637903.
93. Zhang Q, Yang C, Gao X, Dong J, Zhong C. Phytochemicals in regulating PD −1/PD-L1 and immune checkpoint blockade therapy. Phytother Res. 2024;38(2):776-96. doi: 10.1002/ptr.8082, PMID 38050789.
94. Zhao Q, Li Y, Sun Q, Wang R, Lu H, Zhang X, et al. Self-assembled genistein nanoparticles suppress the epithelial-mesenchymal transition in glioblastoma by targeting MMP9. Mater Today Bio. 2025;31:101606. doi: 10.1016/j.mtbio.2025.101606, PMID 40104644.
95. Liu H, Wang Z, Liu Z. Formononetin restrains tumorigenesis of breast tumor by restraining STING-NF-κB and interfering with the activation of PD-L1. Discov Med. 2024;36(182):613-20. doi: 10.24976/discov.med.202436182.58, PMID 38531802.
96. Bruss C, Kellner K, Albert V, Hutchinson JA, Seitz S, Ortmann O, et al. Immune checkpoint profiling in humanized breast cancer mice revealed cell-specific LAG-3/PD-1/TIM-3 co-expression and elevated PD-1/TIM-3 secretion. Cancers. 2023;15(9):2615. doi: 10.3390/cancers15092615, PMID 37174080.
97. Guo G, Liu J, Ren Y, Mao X, Hao Y, Zhong C, et al. FRAT1 enhances the proliferation and tumorigenesis of CD133+Nestin+ glioma stem cells in vitro and in vivo. J Cancer. 2020;11(9):2421-30. doi: 10.7150/jca.37622, PMID 32201513.
98. Kim MH, Park JS, Seo MS, Jung JW, Lee YS, Kang KS. Genistein and daidzein repress adipogenic differentiation of human adipose tissue-derived mesenchymal stem cells *via* Wnt/β-catenin signalling or lipolysis. Cell Prolif. 2010;43(6):594-605. doi: 10.1111/j.1365-2184.2010.00709.x, PMID 21039998.
99. Meteoglu I, Erdemir A. Genistein and temozolomide-loaded polymeric nanoparticles: a synergistic approach for improved anti-tumor efficacy against glioblastoma. Process Biochem. 2021;110:9-18. doi: 10.1016/j.procbio.2021.07.015.
100. Wang L, Long L, Wang W, Liang Z. Resveratrol, a potential radiation sensitizer for glioma stem cells both *in vitro and in vivo*. J Pharmacol Sci. 2015;129(4):216-25. doi: 10.1016/j.jphs.2015.11.001, PMID 26698406.
101. Torres Á, Erices JI, Sanchez F, Ehrenfeld P, Turchi L, Virolle T, et al. Extracellular adenosine promotes cell migration/invasion of glioblastoma stem-like cells through A3 adenosine receptor activation under hypoxia. Cancer Lett. 2019;446:112-22. doi: 10.1016/j.canlet.2019.01.004, PMID 30660649.
102. Mimeault M, Batra SK. Complex oncogenic signaling networks regulate brain tumor-initiating cells and their progenies: pivotal roles of wild-type EGFR, EGFRvIII mutant and hedgehog cascades and novel multitargeted therapies. Brain Pathol. 2011;21(5):479-500. doi: 10.1111/j.1750-3639.2011.00505.x, PMID 21615592.
103. Méndez-Luna D, Morelos-Garnica LA, García-Sánchez JR, Joucla G, Bonneau L, Bakalara N, et al. Preclinical approach of two novel tetrahydroquinoline derivatives targeting GPER and Bcl-2 for anti-glioblastoma therapy. Sci Rep. 2025;15(1):17710. doi: 10.1038/s41598-025-02186-6, PMID 40399430.
104. Wang C, Li J, Qu L, Tang X, Song X, Yang F, et al. Discovery of D6808, a highly selective and potent macrocyclic c-met inhibitor for gastric cancer harboring MET gene alteration treatment. J Med Chem. 2022;65(22):15140-64. doi: 10.1021/acs.jmedchem.2c00981, PMID 36355693.
105. Sultana N, Chauhan D, Yadav PK, Chourasia MK, Gayen JR. Enhanced oral bioavailability of isoformononetin through nanoemulsion: development, optimization, and characterization. J Pharm Innov. 2024;19(2):8. doi: 10.1007/s12247-024-09821-1.
106. Kaufman-Szymczyk A, Jalmuzna J, Lubecka-Gajewska K. Soy-derived isoflavones as chemo-preventive agents targeting multiple signalling pathways for cancer prevention and therapy. Br J Pharmacol. 2025;182(10):2259-86. doi: 10.1111/bph.16353, PMID 38528688.
107. Huang G, Xu J, Guo TL. Isoflavone daidzein regulates immune responses in the B6C3F1 and non-obese diabetic (NOD) mice. Int Immunopharmacol. 2019;71:277-84. doi: 10.1016/j.intimp.2019.03.046, PMID 30927738.
108. Lee W, Kim SJ. Protective effects of isoflavones on alcoholic liver diseases: computational approaches to investigate the inhibition of ALDH2 with isoflavone analogues. Front Mol Biosci. 2023;10:1147301. doi: 10.3389/fmolb.2023.1147301, PMID 36923641.
109. Kushwaha P, Khedgikar V, Gautam J, Dixit P, Chillara R, Verma A, et al. A novel therapeutic approach with Caviunin-based isoflavonoid that en routes bone marrow cells to bone formation via BMP2/Wnt-β-catenin signaling. Cell Death Dis. 2014;5(9):e1422. doi: 10.1038/cddis.2014.350, PMID 25232676.
110. Chuah CH, Chow TS, Hor CP, Cheng JT, Ker HB, Lee HG, et al. Efficacy of early treatment with favipiravir on disease progression among high-risk patients with coronavirus disease 2019 (COVID-19): a randomized, open-label clinical trial. Clin Infect Dis. 2022;75(1):e432-9. doi: 10.1093/cid/ciab962, PMID 34849615.
111. Kirstein A, Schmid TE, Combs SE. The role of miRNA for the treatment of MGMT unmethylated glioblastoma multiforme. Cancers. 2020;12(5):1099. doi: 10.3390/cancers12051099, PMID 32354046.
112. Yamamori T, DeRicco J, Naqvi A, Hoffman TA, Mattagajasingh I, Kasuno K, et al. SIRT1 deacetylates APE1 and regulates cellular base excision repair. Nucleic Acids Res. 2010;38(3):832-45. doi: 10.1093/nar/gkp1039, PMID 19934257.
113. Hu C, Wang M, Hu M, Ma S, Yang B, Xiao W, et al. Genistein induces endocrine resistance in human breast cancer by suppressing H3K27 trimethylation. Endocr-Relat Cancer. 2023;30(2):e220191. doi: 10.1530/erc-22-0191, PMID 36356296.
114. Gauci ML, Giustiniani J, Lepelletier C, Garbar C, Thonnart N, Dumaz N, et al. The soluble form of CD160 acts as a tumor mediator of immune escape in melanoma. Cancer Immunol Immunother. 2022;71(11):2731-42. doi: 10.1007/s00262-022-03199-0, PMID 35428910.
115. Myllymäki S, Haavisto T, Vainio M, Toppari J, Paranko J. *In vitro* effects of diethylstilbestrol, genistein, 4-tert-butylphenol, and 4-tert-octylphenol on steroidogenic activity of isolated immature rat ovarian follicles. Toxicol Appl Pharmacol. 2005;204(1):69-80. doi: 10.1016/j.taap.2004.08.009, PMID 15781295.
116. Storey K, Leder K, Hawkins-Daarud A, Swanson K, Ahmed AU, Rockne RC, et al. Glioblastoma recurrence and the role of O6-methylguanine–DNA methyltransferase promoter methylation. JCO Clin Cancer Inform. 2019;3(3):1-12. doi: 10.1200/cci.18.00062, PMID 30758983.
117. Cho KA, Woo SY, Seoh JY, Han HS, Ryu KH. Mesenchymal stem cells restore CCl4-induced liver injury by an antioxidative process. Cell Biol Int. 2012;36(12):1267-74. doi: 10.1042/cbi20110634, PMID 23035905.
118. Kong X, Lin Z, Liang D, Fath D, Sang N, Caro J. Histone deacetylase inhibitors induce VHL and ubiquitin-independent proteasomal degradation of hypoxia-inducible factor 1α. Mol Cell Biol. 2006;26(6):2019-28. doi: 10.1128/mcb.26.6.2019-2028.2006, PMID 16507982.
119. Donofrio CA. Molecular characterization of human glioblastoma: longitudinal follow-up of plasmatic microRNAs levels by droplet digital PCR; 2024.
120. Ul Hassan MH, Shahbaz M, Imran M, Momal U, Naeem H, Mujtaba A, et al. Isoflavones: promising natural agent for cancer prevention and treatment. Food Sci Nutr. 2025;13(3):e70091. doi: 10.1002/fsn3.70091, PMID 40078339.
121. Ni Q, Fan Y, Zhang X, Fan H, Li Y. *In vitro* and *in vivo* study on glioma treatment enhancement by combining temozolomide with calycosin and formononetin. J Ethnopharmacol. 2019;242:111699. doi: 10.1016/j.jep.2019.01.023, PMID 31005632.
122. Ogura M, Imaizumi Y, Uike N, Asou N, Utsunomiya A, Uchida T, et al. Lenalidomide in relapsed adult T-cell leukaemia-lymphoma or peripheral T-cell lymphoma (ATLL-001): a phase 1, multicentre, dose-escalation study. Lancet Haematol. 2016;3(3):e107-18. doi: 10.1016/s2352-3026(15)00284-7, PMID 26947199.
123. Cichon N, Saluk-Bijak J, Gorniak L, Przyslo L, Bijak M. Flavonoids as a natural enhancer of neuroplasticity—an overview of the mechanism of neurorestorative action. Antioxidants (Basel). 2020;9(11):1035. doi: 10.3390/antiox9111035, PMID 33114058.
124. Wang X, Ma Y, Liu Y, Zhang J, Jiang W, Fang X, et al. Preparation of a *Lactobacillus rhamnosus* ATCC 7469 microencapsulated-lactulose synbiotic and its effect on equol production. Food Funct. 2024;15(18):9471-87. doi: 10.1039/d4fo02690j, PMID 39193624.
125. Ettema S, Oudenhoven LM, Roeleveld K, Buizer AI, van der Krogt MM. The effect of prolonged walking on muscle fatigue and neuromuscular control in children with cerebral palsy. Gait Posture. 2022;93:7-13. doi: 10.1016/j.gaitpost.2022.01.004, PMID 35042058.
126. Alqudah S, Claesen J. Mechanisms of gut bacterial metabolism of dietary polyphenols into bioactive compounds. Gut Microbes. 2024;16(1):2426614. doi: 10.1080/19490976.2024.2426614, PMID 39540668.
127. Murphy N, Achaintre D, Zamora-Ros R, Jenab M, Boutron-Ruault MC, Carbonnel F, et al. A prospective evaluation of plasma polyphenol levels and colon cancer risk. Int J Cancer. 2018;143(7):1620-31. doi: 10.1002/ijc.31563, PMID 29696648.
128. Shehri ZG, Alkhouri I, Hajeer MY, Haddad I, Abu Hawa MH. Evaluation of the efficacy of low-dose botulinum toxin injection into the masseter muscle for the treatment of nocturnal bruxism: a randomized controlled clinical trial. Cureus. 2022;14(12):e32180. doi: 10.7759/cureus.32180, PMID 36474649.
129. Tchirkov A, Rolhion C, Kémény JL, Irthum B, Puget S, Khalil T, et al. Clinical implications of quantitative real-time RT–PCR analysis of hTERT gene expression in human gliomas. Br J Cancer. 2003;88(4):516-20. doi: 10.1038/sj.bjc.6600754, PMID 12592364.
130. Singh P, Tomar RS, Rath SK. Anticancer potential of the histone deacetylase inhibitor-like effects of flavones, a subclass of polyphenolic compounds: a review. Mol Biol Rep. 2015;42(11):1515-31. doi: 10.1007/s11033-015-3881-y, PMID 26033434.
131. Wise DR, Gardner O, Gilbert HN, Rieger A, Paoloni MC, Krishnan K. A phase Ib/II, open-label, platform study evaluating the efficacy and safety of AB928-based treatment combinations in participants with metastatic castrate-resistant prostate cancer. J Clin Oncol. 2020; 38(6_suppl)(6_suppl), TPS272–TPS272:TPS272-. doi: 10.1200/jco.2020.38.6_suppl.tps272.

132. Belcher SM, Ma X, Le HH. Blockade of estrogen receptor signaling inhibits growth and migration of medulloblastoma. Endocrinology. 2009;150(3):1112-21. doi: 10.1210/en.2008-1363, PMID 19008315.

133. Nevel RJ, Deutsch GH, Craven D, Deterding R, Fishman MP, Wambach JA, et al. The US national registry for childhood interstitial and diffuse lung disease: report of study design and initial enrollment cohort. Pediatr Pulmonol. 2024;59(9):2236-46. doi: 10.1002/ppul.26568, PMID 37401889.

134. Cummins L, Cates ME. Istradefylline: a novel agent in the treatment of "off" episodes associated with levodopa/carbidopa use in Parkinson disease. Ment Health Clin. 2022;12(1):32-6. doi: 10.9740/mhc.2022.01.032, PMID 35116210.

135. Tuersun A, Zhao X, Aikebaier A, Han L, Shi Y, Cheng G, et al. Targeting hematopoietic progenitor kinase 1 (HPK1) for tumor immunotherapy: advances in small molecule inhibitors. Biochem Pharmacol. 2025;242(1):117226. doi: 10.1016/j.bcp.2025.117226, PMID 40885316.

136. Macedo GA, Caria CR, Barbosa PP, Mazine MR, Gambero A. Bioaccessibility evaluation of soymilk isoflavones with biotransformation processing. Foods. 2023;12(18):3401. doi: 10.3390/foods12183401, PMID 37761112.

137. Tijhuis M, Doets E, van der Velpen V, Vonk Noordegraaf-Schouten M. Preparatory work to support the risk assessment for peri- and postmenopausal women taking food supplements containing isolated isoflavones. EFSA Support Publ. 2015;12(10):877. doi: 10.2903/sp.efsa.2015.en-877.

138. Lazarevic B, Hammarström C, Yang J, Ramberg H, Diep LM, Karlsen SJ, et al. The effects of short-term genistein intervention on prostate biomarker expression in patients with localised prostate cancer before radical prostatectomy. Br J Nutr. 2012;108(12):2138-47. doi: 10.1017/s0007114512000384, PMID 22397815.

139. Khan SA, Chatterton RT, Michel N, Bryk M, Lee O, Ivancic D, et al. Soy isoflavone supplementation for breast cancer risk reduction: a randomized phase II trial. Cancer Prev Res (Phila). 2012;5(2):309-19. doi: 10.1158/1940-6207.capr-11-0251, PMID 22307566.

140. Akbaribazm M, Khazaei MR, Khazaei F, Khazaei M. Doxorubicin and *Trifolium pratense* L. (red clover) extract synergistically inhibits brain and lung metastases in 4T1 tumor-bearing BALB/c mice. Food Sci Nutr. 2020;8(10):5557-70. doi: 10.1002/fsn3.1820, PMID 33133558.

141. Gautam M, Gabrani R. Current combinatorial therapeutic aspects: the future prospect for glioblastoma treatment. Curr Med Sci. 2024;44(6):1175-84. doi: 10.1007/s11596-024-2950-7, PMID 39695017.

142. Lee YW, Lee WH. Protective effects of genistein on proinflammatory pathways in human brain microvascular endothelial cells. J Nutr Biochem. 2008;19(12):819-25. doi: 10.1016/j.jnutbio.2007.10.006, PMID 18479900.

143. Liu J, Lin C, Li B, Huang Q, Chen X, Tang S, et al. Biochanin A inhibits endothelial dysfunction induced by IL-6-stimulated endothelial microparticles in Perthes disease via the NFκB pathway. Exp Ther Med. 2024;27(4):137. doi: 10.3892/etm.2024.12425, PMID 38476892.

144. Tang Y, Jiang M, Chen A, Qu W, Han X, Zuo J, et al. Porcupine inhibitor LGK-974 inhibits Wnt/β-catenin signaling and modifies tumor-associated macrophages resulting in inhibition of the malignant behaviors of non-small cell lung cancer cells. Mol Med Rep. 2021;24(2):550. doi: 10.3892/mmr.2021.12189, PMID 34080032.

145. Wu Y, Qian Z, Fu S, Yue Y, Li Y, Sun R, et al. Icarisideii improves left ventricular remodeling in spontaneously hypertensive rats by inhibiting the ASK1-JNK/p38 signaling pathway. Eur J Pharmacol. 2018;819:68-79. doi: 10.1016/j.ejphar.2017.11.035, PMID 29175071.

Cite this article: Akbaribazm M. Dietary Isoflavonoids and Brain Tumors: Unlocking Neuroprotective Potential, Molecular Mechanisms, and Novel Therapeutic Avenues in Neuro-Oncology. Pharmacog Rev. 2027;21(41):112-32.