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Review

Progress on the functions and mechanisms of natural products in anti-glioma therapy

Yanting Li[a,Δ], Shuhui Qu[a,Δ], Jiayi Zuo[a,Δ], Haoping Long[a,Δ], Feng Cao[b,*], Feng Jiang[a,*]

[a] Department of Pharmaceutical Engineering, School of Engineering, China Pharmaceutical University, Nanjing, 210009, China
[b] Department of Pharmaceutical, School of Pharmacy, China Pharmaceutical University, Nanjing, 210009, China

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ABSTRACT

Glioma, the most prevalent primary tumor of the central nervous system (CNS), is also the most lethal primary malignant tumor. Currently, there are limited chemotherapeutics available for glioma treatment, necessitating further research to identify and develop new chemotherapeutic agents. A significant approach to discovering anti-glioma drugs involves isolating antitumor active ingredients from natural products (NPs) and optimizing their structures. Additionally, targeted drug delivery systems (TDDSs) are employed to enhance drug solubility and stability and overcome the blood-brain barrier (BBB). TDDSs can penetrate deep into the brain, increase drug concentration and retention time in the CNS, and improve the targeting efficiency of NPs, thereby reducing adverse effects and enhancing anti-glioma efficacy. This paper reviews the research progress of anti-glioma activities of NPs, including alkaloids, polyphenols, flavonoids, terpenoids, saponins, quinones, and their synthetic derivatives over the past decade. The review also summarizes anti-glioma mechanisms, such as suppression of related protein expression, regulation of reactive oxygen species (ROS) levels, control of apoptosis signaling pathways, reduction of matrix metalloproteinases (MMPs) expression, blocking of vascular endothelial growth factor (VEGF), and reversal of immunosuppression. Furthermore, the functions and advantages of NP-based TDDSs in anti-glioma therapy are examined. The key information presented in this review will be valuable for the research and development of NP-based anti-glioma drugs and related TDDSs.

1. Introduction

Glioma, the most common primary tumor of the central nervous system (CNS), accounts for 30% of primary brain tumors and 80% of malignant tumors. The 5-year relative survival rate for glioma is below 5%, making it the leading cause of mortality from primary brain tumors [1]. Current clinical approaches to treating gliomas include surgical resection, radiotherapy, and chemotherapy; however, the disease progresses rapidly despite combining multiple treatment modalities [2]. Temozolomide (TMZ), a United States Food and Drug Administration (FDA)-approved first-line chemotherapeutic agent for glioma treatment, has limitations such as drug resistance [3]. Consequently, the search for novel chemotherapeutic agents has become crucial in glioma treatment.

Natural products (NPs) and their derivatives have been a valuable source of potent therapeutic molecules for centuries. These compounds exhibit strong pharmacological activity, can modulate various signaling pathways, and offer the advantage of multi-targeting [4]. Notable examples include Taxol (isolated from *Taxus brevifolia*), taxotere (DTX, a semisynthetic Taxol analog), and abraxane (an albumin-based Taxol formulation). The FDA approved these drugs for treating advanced ovarian carcinoma in 1984 [5], advanced breast cancer in 1996, and metastatic breast cancer in 2005 [6], respectively. Approximately 60% of FDA-approved cancer medications are derived from natural sources [7]. Consequently, identifying anti-tumor active ingredients from NPs and optimizing their structures represents a promising approach for developing anti-glioma drugs [8].

NPs, characterized by their diverse molecular structures and complex compositions, offer significant advantages in drug discovery, including reduced side effects, cost-effectiveness, and multi-target potential. However, challenges in extraction, isolation, characterization, and biocompatibility hinder their development [9]. The CNS is protected by the blood-brain barrier (BBB), a natural barrier between plasma and brain cells formed by brain capillary walls and glial cells. The BBB impedes the penetration of most drugs into the CNS through mechanisms such as paracellular and transcellular barriers, enzymatic and immunological barriers, and efflux proteins [10, 11]. The BBB's impermeability to most drugs has presented a significant obstacle in developing CNS therapeutic agents. Consequently, overcoming the BBB's blocking effect, enhancing drug accumulation at tumor sites, and minimizing toxic side effects are crucial challenges in glioma treatment. To address these issues, researchers have recently developed various drug delivery systems (DDSs) to improve intracerebral drug delivery [12]. Targeted drug delivery systems

* Corresponding author.
E-mail addresses: cpufengc@cpu.edu.cn (F. Cao); jiangfeng@cpu.edu.cn (F. Jiang)
Δ These authors contributed equally to this work.

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(TDDSs) for NPs can penetrate the deep brain through blood circulation, extending the concentration and residence time of drugs in the CNS, enhancing the targeting efficiency of NPs for glioma, and reducing adverse effects.

This review aims to examine and synthesize the effectiveness and mechanisms of NPs and their synthetic derivatives in glioma treatment, as well as the functions and benefits of NP-based TDDSs against glioma. Anti-glioma mechanisms include inhibiting associated protein expression, reducing the expression of matrix metalloproteinases (MMPs), regulating reactive oxygen species (ROS) levels, modulating apoptotic signaling pathways, inhibiting vascular endothelial growth factor (VEGF), and reversing immunosuppression. TDDSs can penetrate deep brain tissues, increase drug concentration and retention time in the CNS, and enhance the targeting efficiency of NPs, thereby reducing adverse effects and improving anti-glioma efficacy. By comprehensively presenting current research advancements, this review seeks to provide valuable insights for the development of NP-based medications and therapeutic strategies against glioma.

2. NPs against glioma

NPs have historically played a pivotal role in the development of anti-glioma drugs. These NPs encompass alkaloids, terpenoids, polyphenols, flavonoids, saponins, quinones, polysaccharides, and various other anti-tumor compounds characterized by novel structures, distinct activities, and minimal adverse effects. These substances demonstrate efficacy in both cancer prevention and treatment by modulating multiple cellular pathways. This section introduces several glioma-targeted NPs and elucidates their anti-glioma mechanisms (Fig.1). Table 1 presents the names and mechanisms of representative active components of NPs with therapeutic effects on glioma, while their chemical structures are illustrated in the supplementary information.

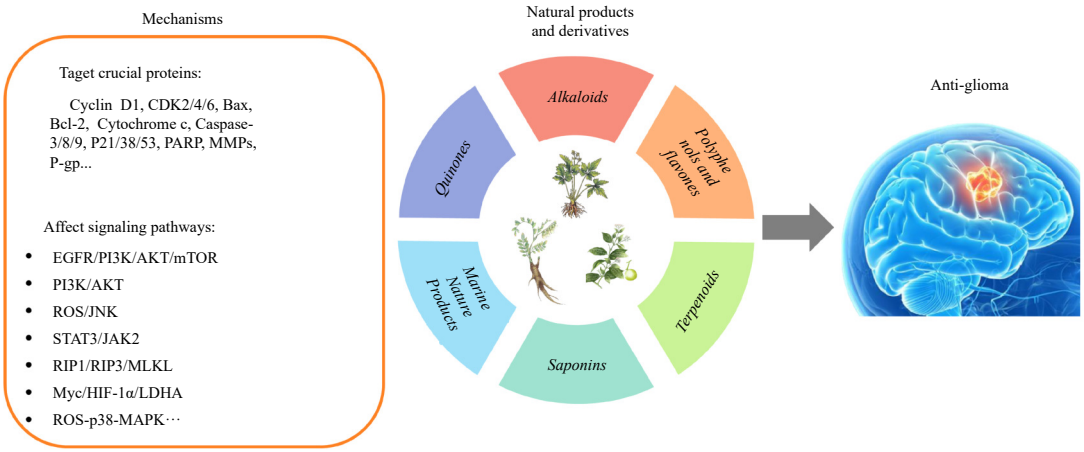

Fig. 1 Schematic diagram of glioma-targeted NPs and their anti-glioma mechanisms.

2.1. Alkaloids

Alkaloids, as a type of nitrogen-containing alkaline organic compounds that exist in plants, fungi and bacteria, have significant biological activities. Alkaloids have attracted much attention in the drug development field due to their physiological ability to target cancer cells [13].

Matrine (**1**), a quinolizidine alkaloid discovered from *Sophora flavescens, Sophora alopecuroides, Sophora* root, etc [14], induced the apoptosis and autophagy of U251 cells *via* inhibition of phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) and Wnt/β-catenin pathways [15] and inhibited the migration and invasion of U251MG cells through the inhibition of epithelial-mesenchymal transition (EMT) [16]. Oxymatrine (OM, **2**), another natural quinolizidine alkaloid extracted from *Sophora flavescens* [17,18], arrested the cell cycle *via* decreasing cyclin D1 and cyclin-dependent kinase (CDK)4/6 and exerted anti-glioma effects through regulating the epidermal growth factor receptor (EGFR)/PI3K/Akt/mammalian target of rapamycin (mTOR) signaling pathway and transducer and activator of transcription-3 (STAT3) [19].

Berberine (**3**), an isoquinoline alkaloid extracted from *Coptis chinensis* [20], inhibited the migration and invasion of glioma cells by depressing the TGF-β1/COL11A1 pathway [21]. Moreover, mounting evidence has suggested that berberine also has pharmacological effects on glioma cell proliferation, angiogenesis, cell cycle arrest, autophagy and apoptosis [22-24]. In addition to berberine, there are some other isoquinoline alkaloids discovered from nature that also have anti-glioma activity. For example, 3,8-diolisoquinoline (**4**) and 1-methoxy-4,5-diolisoquinoline (**5**), extracted from the centipede *Scolopendra subspinipes mutilans L. Koch* [25], induced U87 cells apoptosis by activating caspase-3/9, depressing mitochondrial membrane potential (△Ψm) and the protein ratio of Bcl-2/Bax, and arrested cell cycle progress to inhibit U87 cells proliferation. Jin *et al.* [26] extracted six new aporphine alkaloids from *Thalictrum wangii*, which showed significant anti-human glioma stem cell activity with the half maximal inhibitory concentration (IC_{50}) values of 15−20 μg·mL^{-1}.

Indole alkaloids (IAs), with tryptophan or tryptamine as their precursors, have diverse biological and pharmacological activities [27]. Evodiamine (**6**) is the main indole alkaloid extracted from *Evodia rutaecarpa (E. rutaecarpa)*. Studies have shown that evodiamine increased apoptosis in glioblastoma (GBM) cells *via* downregulating PI3K/AKT signaling and inducing mitogen-activated protein kinase (MAPK) phosphorylation [28] and induced death in U87 cells by sensitizing tumor cells to tumor necrosis factor-α (TNF-α)-related apoptosis-inducing ligand (TRAIL) [29].

Brucine (**7**), a weak alkaline indole alkaloid isolated from *Strychnos nux-vomica*, induced glioma cells death and inhibited xenograft tumor prolification by decreasing the expression of Bcl-2/Bax and cyclooxygenase-2 (COX-2) [30]. Furthermore, Lu *et al.* [31] proved that brucine induces glioma cell death through transferrin receptor (TFR)-regulated ferroptosis.

The indole alkaloid LTr1 (**8**) from cruciferous vegetables can induce cell cycle arrest and apoptosis of SHG-44 and U87 cells through downregulating TrkA/PI3K/AKT pathway [32].

2.2. Polyphenols and flavonoids

Polyphenols and flavonoids are widely distributed in various plants, fruits, and vegetables. Polyphenols are compounds char-

Table 1 Anti-glioma effects of different classes of NPs and their mechanisms

No.	Name	Classification	Source	Mechanism	Function	Refs.
1	Matrine	Alkaloids	*Sophora flavescens, alopecuroides, root*, etc.	↓cyclin D1; ↑p53; ↑c-caspase-3; ↑c-caspase-9; ↓Bcl-2; ↑Bax; ↓P62; ↑Beclin-1; ↑LC3-II/LC3-I; ↓circRNA-104075; ↓ Bcl-9; ↓Wnt-β-catenin; ↓PI3K/AKT; ↓N-cadherin; ↑E-cadherin; ↓EMT; ↓p-p38; ↓p-AKT	Induce cell cycle arrest, apoptosis and autophagy; inhibit migration and invasion	15, 16
2	Oxymatrine	Alkaloids	*Sophora flavescens*	↓cyclin D1; ↓CDK4/6; ↑caspase-3; ↓p-EGFR; ↓p-AKT; ↓p-mTOR; ↓p-STAT3	Induce cell cycle arrest and apoptosis; inhibit proliferation and invasion	19
3	Berberine	Alkaloids	*Coptis chinensis*	↓p-ERK1/2; ↓Ki-67; ↓caspase-1; ↓IL-1β; ↓IL-18; ↓EGFR; ↓RAF-MEK-ERK; ↑AMPK; ↓p-mTOR; ↑p-Beclin-1 Ser93; ↑p-ULK; ↑P27; ↓CDK2; ↓CDK4; ↓cyclin E; ↓cyclin D; ↑ROS; ↑Ca^{2+}; ↑Bax; ↓Bcl-2; ↑pro-caspase-9; ↑caspase-3/8/9; ↑PARP; ↓NAT1; ↓TGF-b1/COL11A1; ↓MMP-2/3/9	Induce cell cycle arrest, autophagy and apoptosis; inhibit angiogenesis, migration and invasion	21-24
4	Isoquinoline alkaloids	Alkaloids	*Scolopendra subspinipes mutilans L. Koch*	↓MMP; ↑caspase-9/3; ↓Bcl-2/Bax	Induce cell cycle arrest and apoptosis; inhibit proliferation	25
5	Isoquinoline alkaloids	Alkaloids				
6	Evodiamine	Alkaloids	*Evodia rutaecarpa (E. rutaecarpa)*	↓PI3K/AKT; ↑MAPK; ↑p-p38; ↑p-JNK; ↑c-caspase-3; ↑c-PARP; ↑Bax/Bcl-2; ↑ROS; ↓MMP; ↑DR4; ↑DR5; ↑caspase-8	Induce apoptosis; inhibit proliferation	28, 29
7	Brucine	Alkaloids	The seeds of *Strychnos nux-vomica*	↓Bcl-2; ↑Bax; ↓COX-2; ↑ATF3; ↑NOX4; ↓xCT; ↑H_2O_2	Induce ferroptosis and apoptosis; inhibit proliferation	30, 31
8	LTr1	Alkaloids	Cruciferous vegetables	↓TrkA; ↓PI3K/AKT; ↑ROS	Induce cell cycle arrest and apoptosis	32
9	Curcumin	Polyphenols	*Curcuma longa*	↑ING4; ↑Par-4; ↑Ceramide; ↓miR-21; ↑miR-146a; ↓PI3; ↓ERK; ↑P38; ↓MAPK; ↓p-JAK1, 2; ↓AKT; ↓Bcl-2; ↑Bax; ↓Bcl-xL; ↑PARP; ↑caspase-3; ↓NF-κB; ↓STAT-3; ↓β-catenin; ↑FOXO1; ↓mTOR; ↓TNF-α; ↓MMP-9; ↓COX-2; ↓IL-8; ↓IL-1β; ↓IL-6; ↑p53; ↑p21; ↓CDK4/6; ↓cyelin D1; ↓VEGF; ↓Ang-2; ↑TSP-1	Induce cell cycle arrest, apoptosis and autophagy; inhibit angiogenesis, proliferation, migration and invasion	36
10	Cannabidiol	Polyphenols	Cannabis	↓MMP-9; ↓TIMP-1, 4; ↓uPA; ↓SerpinE1-PAI-1; ↓VEGF; ↓TGF-b1; ↓Cxcl-16; ↓PDGF-AA; ↓MCP-1; ↓ERK; ↓PI3K/AKT; ↓HIF-1α; ↑TRPV4	Induce autophagy; inhibit angiogenesis, proliferation and invasion	41-43
11	Chlorogenic Acid (CGA)	Polyphenols	Eucommia almoides oliver, Lonicera confuse	↑iNOS; ↑MHC II (I-A/I-E subregions); ↑CD11c; ↓Arg; ↓CD206; ↑STAT1; ↓STAT6; ↓p-c-Myc; ↓miR-20a/93/106b; ↑p21/53; ↑Tuj1; ↑GFAP; ↑Bax/Bcl-2; ↓HIF-1α/AKT; ↓MMP-2/9; ↑E-cadherin; ↓Vimentin; ↓SRC/MAPKs	Induce cell cycle arrest, apoptosis; inhibit angiogenesis, proliferation, migration and invasion	45-47
12	Quercetin	Polyphenolic flavonoids	Diverse fruits and vegetables	↑Bax; ↓Bcl-2; ↓MMP-2/9; ↓GSK3β/β-catenin/ZEB1; ↓Rac1; ↓ROS	Induce cell cycle arrest and apoptosis; inhibit migration and invasion	49, 50
13	Silibinin	Polyphenolic flavonoids	The fruit or seed of *Silymarin*	↓FoxM1; ↓PI3K/AKT; ↑LC3-II/LC3-I; ↓p62; ↓p-mTOR; ↓p-p70S6K; ↓p-4E-BP1; ↓YAP; ↑caspase-3; ↑pro-apoptotic; ↑AMPK/mTOR; ↓xCT; ↑BNIP3; ↑GPX4; ↓HK II; ↓PFKP; ↑p53; ↑ROS; ↓HIF-1α	Induce autophagy, apoptosis, inhibit proliferation	52, 53
14	Resveratrol	Polyphenolic flavonoids	A wide range of fruits, nuts, and red wine	↓cyclin D1/B1; ↑p53; ↑Bax; ↓Bcl-2; ↑caspase-3/8/9; ↓Bcl-xL; ↓PI3K/AKT/mTOR; ↓WNT; ↓MGMT; ↓dynamin1; ↓NF-κB; ↓MMP-2; ↓uPA/uPAR; ↓YKL-40; ↑TTP; ↑LRIG1; ↑miR-34a; ↓miR-19; ↓miR-21; ↓miR-30a-5p; ↑DSBs/pATM/pATR; ↓STAT3; ↑PIAS3; ↓EMT	Induce cell cycle arrest, autophagy and apoptosis; inhibit angiogenesis, proliferation, migration, and invasion	55
15	3-O-acetyl-11-keto-β-boswellic acid (AKBA)	Terpenoids	Frankincense	↓pRB; ↓FOXM1; ↓Aurora A, B; ↓PLK1; ↓CDC25C; ↓p-CDK1; ↓cyclin B1; ↓TOP2A; ↑p21; ↓p-RB; ↑GADD45A; ↑caspase-3/7; ↑PARP; ↓MMP; ↓ATG5; ↓p62; ↓LC3B; ↓p-ERK/ERK; ↑p-mTOR; ↓mTOR; ↓TWIST1; ↓FOXM1	Induce cell cycle arrest and apoptosis; inhibit autophagy and migration	57-60
16	Stellettin B	Terpenoids	Marine sponge	↓AKT/mTOR; ↓p-Girdin; ↓F-actin; ↓VEGF; ↓p-Stat3; ↓HIF-1α; ↓BRCA1/2; ↓RAD51; ↓PI3k	Inhibit angiogenesis, proliferation and migration	61, 62
17	Demethylzeylasteral (T-96)	Terpenoids	*Tripterygium wilfordii*	↑miR-30e-5p/MYBL2	Inhibit proliferation	63
18	Celastrol	Terpenoids	The root of *Tripterygium wilfordii*	↑ROS/JNK; ↓AKT/mTOR; ↑DR5	Induce cell cycle arrest, apoptosis and autophagy	64, 65
19	Triptolide	Terpenoids	*Tripterygium wilfordii Hook. F.*	↑ROS/JNK; ↓AKT/mTOR; ↑IFN-γ; ↓PD-L1; ↓EMT; ↑E-cadherin; ↓N-cadherin; ↓Vimentin; ↓ZEB1; ↓Snail; ↓Slug; ↓Beclin-1; ↓Atg-7; ↑P21; ↑Bax; ↓MMP-2/9; ↓PROX1	Induce cell cycle arrest, apoptosis and autophagy; inhibit proliferation, migration, and invasion	68-71
20	Pseudolaric acid B (PLAB)	Terpenoids	*Pseudolarix kaempferi*	↑p53; ↑Bax; ↓Bcl-2; ↑caspase-3↑p-PARP	Induce apoptosis; inhibit proliferation	72
21	Ginsenoside Rh2 (Gs-Rh2)	Saponins	*Ginseng*	↓AKT; ↓CDK4/cyclin D; ↓EGFA	Induce cell cycle arrest and apoptosis; inhibit proliferation and metastasis	76
22	Ginsenoside Rd (Gs-Rd)	Saponins	*Ginseng*	↓Bcl-2; ↓hTERT; ↑caspase-3	Induce apoptosis; inhibit proliferation	77
23	Ginsenoside 3β-O-Glc-DM (C3DM)	Saponins	*Ginseng*	↓EGFR/PI3K/AKT/mTOR; ↓c-Myc; ↓HIF-1α; ↓LDHA; ↓N-cadherin; ↓snail; ↓VEGF; ↓CD34; ↓Bcl-2	Induce apoptosis; inhibit angiogenesis, proliferation, migration and metabolism	78

Continued

No.	Name	Classification	Source	Mechanism	Function	Refs.
24	Ginsenoside Rg5 (Gs-Rg5)	Saponins	*Ginseng*	↑NR3C1; ↓HSPB1; ↑NCOA4	Induce ferroptosis	79
25	Polyphyllin I (PPI)	Saponins	*Paris*	↑Bax; ↓Bcl-2; ↑cytochrome c; ↑p-JNK	Induce cell cycle arrest and apoptosis; inhibit proliferation	82
26	Polyphyllin D (PPD)	Saponins	*Paris*	↑Bax; ↓ Bcl-2; ↑caspase-3; ↑p-JNK	Induce apoptosis; inhibit proliferation	83
27	Polyphyllin VI (PPVI)	Saponins	*Paris*	↑ROS; ↑JNK; ↑P38; ↑LC3-II; ↑Beclin-1	Induce cell cycle arrest, apoptosis and autophagy	84
28	Polyphyllin VII (PP7)	Saponins	*Paris*	↑ROS; ↓AKT; ↑Bax; ↑cytochrome C; ↓mTORC1	Induce apoptosis and autophagy; inhibit proliferation	85
29	Dioscin	Saponins	*Dioscorea*	↑ROS; ↑Ca; ↑caspase-3/9; ↑PARP; ↓Bcl-2; ↓Bcl-xL; ↑Bak; ↑Bax; ↑Bid; ↓DNA Topo I; ↑p53; ↓CDK2; ↓cyclin A; ↓NF-κB; ↓RBM47	Induce apoptosis; inhibit proliferation	88
30	Shikonin	Quinones	The root of *Lithospermum erythrorhizon*	↑ROS; ↓GSH; ↑p53; ↑c-PARP; ↑SOD-1; ↓Bcl-2; ↑Bax; ↑RIP1/3; ↓CD147; ↑capase-3; ↓Notch2/3; ↓PSMB8/9/10; ↓PSME1/2/3; ↓MMP-2/9	Induce apoptosis, necroptosis; inhibit proliferation, metastasis and invasion	92-97
31	Plumbagin	Quinones	The root of *Plumbago zeylanica L*	↓FOXM1; ↓cyclin D1; ↓Cdc25B; ↓Ki67; ↑p21; ↑p27; ↑c-caspase-3; ↓MMP-2/9; ↓PI3K/AKT; ↓GPX4; ↓xCT; ↑NQO1	Induce ferroptosis and apoptosis; inhibit proliferation, migration and invasion	98-100
32	Juglone	Quinones	*Black walnut*	↑caspase-3; ↓Pin1; ↓TGF-β1/Smad/miR-21 axis; ↑ROS; ↑p-p38; ↑MMP-2; ↓Nrf2; ↓GPX4	Induce ferroptosis and apoptosis; inhibit angiogenesis, proliferation, migration and invasion	101-104
33	Trichobotrysin B	Tetramic acid derivatives	*Trichobotrys effusa* 4729	↓JAK-STAT3; ↑c-caspase-3/9; ↑Bax; ↓Bcl-2	Induce cell cycle arrest and apoptosis; inhibit proliferation	105
34	Bufalin	Steroids	Chan Su	↑AMPK-mTOR; ↑PERK/eIF2α/CHOP; ↑ROS; ↑Bax/Bcl-2; ↑(TNF) -α; ↑TNFR1; ↑RIPK1; ↑cytochrome C; ↑c-caspase-3/4; ↑PARP; ↑LC3-II; ↑ATR-Chk1-CDC25A-CDK2; ↑Chk1; ↑p-Chk1; ↑p53; ↑p-p53; ↑caspase-3; ↑c-Myc	Induce cell cycle arrest, autophagy and apoptosis	108-110
35	Fucoxanthin	Carotenoids	Algae	↑ROS; ↓MAPKs; ↓PI3K-AKT	Induce apoptosis	111
36	Osthole	Coumarin derivatives	*Cnidium monnieri (L.) Cusson*	↑miR-16; ↓MMP-9; ↑ROS	Induce apoptosis and necroptosis; inhibit proliferation	115, 116
37	Radix Hedysari Polysaccharide	Polysaccharides	*Radix hedysari*	↑p53; ↑Bax; ↓Bcl-2; ↓cyclin E/D; ↓TNF-α; ↓caspase-3; ↓NF-κB	Induce cell cycle arrest, autophagy and apoptosis; inhibit proliferation	117
38	Ganoderma lucidum polysaccharides (GL-PS)	Polysaccharides	*Ganoderma lucidum*	↑IL-2; ↑TNF-α; ↑INF-γ	Enhance cellular immunity and improve the immune system	118

acterized by multiple phenolic hydroxyl groups, while flavonoids, which possess a flavone backbone and are often linked to phenolic hydroxyl and other functional groups, are generally considered a subclass of polyphenols. Due to their diverse anti-tumor properties, certain natural flavonoid derivatives have been extensively investigated for their potential in cancer therapy [33].

Curcumin (**9**) is a polyphenol extracted from *Curcuma longa* in 1815 [34]. The lipophilic properties of curcumin allowed it to cross the BBB without obvious toxicity to normal brain cells, making it a potential glioma therapeutic agent [35]. A substantial body of evidence indicates that curcumin exerts anticancer effects against glioma by promoting autophagy and apoptosis while inhibiting the proliferation, angiogenesis, migration, and invasion of glioma cells [36]. For example, curcumin has been proved by Cheng et al. to induce G_2/M cell cycle arrest and apoptosis in U87 cells *via* improving the expression levels of Forkhead box O transcription factor (FoxO1) [37]. Bi et al. [38] showed that curcumin inhibited the heat shock protein 60/toll-like receptor-4/myeloid differentiation primary response protein 88/nuclear factor-κB (HSP60/TLR-4/MYD88/NF-κB) signaling pathway to inhibit the invasion and growth of neuroglioma. Wang et al. [39] found that curcumin effectively decreased the invasion of glioma boosted by psychological stress *via* the inhibition of the MAPK/extracellular signal-regulated kinase (ERK) signaling pathway.

Cannabidiol (CBD, **10**), a cannabinoid compound derived from the plant cannabis [40], can cross the BBB. CBD can effectively inhibit proliferation and invasion in glioma cells by modulating hypoxia-inducible factor-1α (HIF-1α) and the ERK and PI3K/Akt signaling pathways [41]. Volmar et al. [42] demonstrated that CBD induces GBM cell death by modulating the nuclear transcription factor-kappa B (NF-κB) signaling pathway. Huang et al. [43] first showed that CBD induced lethal mitochondrial autophagy to inhibit human glioma by activating the transient receptor potential cation channel subfamily V member 4 (TRPV4). A phase Ib clinical trial (NCT01812603, NCT01812616, Table 3) was completed in 2016, demonstrating that individualized dosing regimens of Sativex (containing 25 mg·mL^{-1} CBD) in combination with TMZ are well-tolerated and may improve survival rates in patients with recurrent GBM. Additionally, Julian et al. [44] completed a four-year clinical trial (NCT03607643, Table 3), reporting a reduction in tumor cell count and volume with no observed side effects.

Chlorogenic acid (CGA, **11**), a polyphenolic compound derived from caffeic acid and L -quinic acid, is widely extracted from various plants, including *Eucommia almoides oliver* and *Lonicera confuse*. Xue et al.[45] demonstrated that CGA inhibited GBM growth by increasing M1-polarized macrophages while reducing M2-phenotypic macrophages. CGA suppressed tumor growth by inducing differentiation [46], triggering cell-cycle arrest and apoptosis, and inhibiting the proliferation, migration, and invasion of glioma cells *via* suppression of the SRC/MAPK signaling pathway [47]. A completed phase I clinical trial (NCT02728349, Table 3) investigating CGA for high-grade glioma (HGG) treatment demonstrated favorable therapeutic effects and high safety. Based on these promising efficacy and safety results, CGA has received ap-

proval from China FDA for a Phase II/III trial (NCT03758014, Table 3).

Quercetin (**12**), a naturally occurring polyphenolic flavonoid, is commonly extracted from various fruits and vegetables [48]. Research has demonstrated that quercetin induces cell apoptosis by enhancing the B-cell lymphoma 2 associated X protein (Bax)/B-cell lymphoma 2 (Bcl-2) protein ratio. Additionally, it inhibits cell migration and invasion through the suppression of glycogen synthase kinase-3β (GSK3β)/β-catenin/Zinc-finger E-box binding protein 1 (ZEB1) signaling [49]. Furthermore, quercetin constrains the production of ROS and tumor growth by inhibiting the activation of Rac1 [50].

Silybin (**13**), a naturally occurring polyphenolic flavonoid, is extracted from the fruit or seed of *Silymarin* [51]. This compound demonstrates the ability to downregulate the expression of Forkhead box M1 (FoxM1) and the phosphatidylinositol 3-kinase (PI3K)/Akt signaling pathway, consequently inhibiting glioma cell proliferation and promoting apoptosis [52]. Furthermore, silybin has been shown to induce autophagy and glioma cell death by facilitating the nuclear translocation of apoptosis-inducing factor (AIF) [53].

Resveratrol (**14**), a natural polyphenolic flavonoid extracted from various fruits, nuts, and red wine [54] has demonstrated significant anti-glioma properties. Mounting evidence indicates that resveratrol exerts its pharmacological effects through multiple mechanisms. It induces cell cycle arrest by downregulating cyclin D1/B1 and c-Myc, promotes apoptosis by activating caspase-3/7/8/9 and p53 while suppressing B-cell lymphoma-extra large (Bcl-xL), enhances autophagy through modulation of the PI3K/AKT/mTOR, P38, and ERK1/2 pathways, and inhibits migration and metastasis by suppressing EMT [55].

2.3. Terpenoids

Terpenoids are olefinic compounds with molecular formulas that are integral multiples of isoprene. These compounds demonstrate significant physiological properties and exhibit remarkable biological activities [56].

The pentacyclic triterpenoid 3-*O*-acetyl-11-keto-β-boswellic acid (AKBA, **15**) is the primary active component of frankincense, demonstrating significant anti-glioma activity [57]. AKBA exerts its anti-glioma effects through multiple mechanisms: (1) It arrests the cell cycle by regulating the p21/FOXM1/cyclin B1 pathway [58]. (2) It promotes apoptosis *via* downregulation of the Aurora B/Topoisomerase II alpha (TOP2A) pathway [58]. (3) It inhibits autophagy, thereby repressing glioblastoma growth, through regulation of the ERK/mTOR and P53/mTOR signaling pathways [59]. (4) It significantly inhibits cell migration by decreasing the expression levels of twist-related protein 1 (TWIST1) and FOXM1 genes [60].

Stellettin B (**16**), a triterpenoid derived from marine sponges, exhibits potential as a therapeutic agent for GBM [61]. Research conducted by Cheng *et al.* [62] demonstrated that Stellettin B inhibits cell proliferation *via* the AKT/mTOR pathway and impedes angiogenesis by blocking Stat3/VEGF signaling.

Several NPs derived from *Tripterygium wilfordii* demonstrate promising anti-glioma activities. For instance, demethylzeylasteral (T-96, **17**), a triterpene compound, potentially modulates the miR-30e-5p/MYBL2 axis to suppress glioma cell growth [63]. Celastrol (**18**), one of the most abundant active molecules extracted from the root of *Tripterygium wilfordii*, induces autophagy and apoptosis in glioma cells by regulating the ROS/c-Jun N-terminal kinase (JNK) and AKT/mTOR signaling pathways [64]. Additionally, celastrol upregulates the expression of death receptor 5 (DR5) and enhances TRAIL-triggered apoptosis [65]. Triptolide (**19**), a phenylethane-type diterpene compound isolated from *Tripterygium wilfordii* Hook. F. *(TwHF)* [66, 67], exhibits multi-modal anti-glioma activities through various mechanisms: (1) It enhances autophagy and apoptosis by inhibiting the ROS/JNK pathway and activating the AKT/mTOR signaling pathway [68]. (2) It exerts immunosuppressive effects by downregulating IFN-γ-induced PD-L1 expression [69]. (3) It increases autophagy in glioma cells, thereby inhibiting EMT and reducing migration and invasion [70]. (4) It inhibits GBM cell viability, proliferation, cell cycle progression, migration, and invasion by targeting PROX1 [71].

Pseudolaric acid B (PLAB, **20**), a diterpenoid compound derived from *Pseudolarix kaempferi*, was found to induce cell cycle arrest and apoptosis in U87 GBM cells [72].

2.4. Saponins

Saponins consist of a lipophilic moiety, which can be either triterpenoid or steroid aglycon, and a hydrophilic moiety composed of sugars. Based on their aglycone structures, saponins are classified into triterpenoid saponins and steroid saponins. These compounds exhibit diverse biological activities and demonstrate significant anticancer potential [73].

Ginsenoside, a triterpenoid saponin, represents the primary active component of ginseng and exhibits diverse pharmacological effects [74, 75]. Ginsenoside Rh2 (Gs-Rh2, **21**), a key bioactive constituent in *American ginseng*, reduces glioma cell viability and induces cell cycle arrest by decreasing cyclin-dependent kinase 4 (CDK4) and cyclin E levels [76]. Ginsenoside Rd (Gs-Rd, **22**) enhances apoptosis and inhibits U251 cell proliferation by suppressing telomerase activity and modulating the expression of Bcl-2, hTERT, and caspase-3 [77]. Tang et al. [78] demonstrated that ginsenoside 3β-*O*-Glc-DM (C3DM, **23**) inhibits glioma tumor growth by suppressing the epidermal growth factor receptor (EGFR)/PI3K/AKT/mTOR signaling pathway. Ginsenoside Rg5 (Gs-Rg5, **24**) impedes GBM progression by activating ferroptosis through nuclear receptor subfamily 3 group C member 1 (NR3C1) [79].

Polyphyllins, the primary bioactive components of *Paris* [80, 81], have demonstrated anti-glioma properties in previous studies. The principal anti-glioma mechanisms involve multiple pathways, including: (1) PPI (**25**) induces G_2/M phase arrest and apoptosis by modulating the expressions of Bax/Bcl-2, cytochrome c and phosphorylated JNK (p-JNK), while also triggering the depolarization of $\triangle\Psi m$ [82]. (2) PPD (**26**) enhances apoptosis by significantly downregulating the expressions of Bax/Bcl-2, caspase-3, and p-JNK in U87 human glioma cells [83]. (3) PPVI (**27**) promotes autophagy and apoptosis through the activation of JNK and p38 pathways [84]. (4) PP7 (**28**) increases autophagy and apoptosis by inhibiting AKT/mTORC1 activity [85].

Dioscin (**29**), a natural steroidal saponin extracted from *Dioscorea* plant roots, possesses the ability to penetrate the BBB [86, 87]. This compound demonstrates substantial anti-GBM efficacy by promoting ROS accumulation, and inducing deoxyribonucleic acid (DNA) damage [88].

2.5. Quinones

Quinones constitute a class of aromatic organic compounds characterized by a six-carbon ring diketone structure with two double bonds. These NPs are widely distributed in nature and exhibit a diverse range of pharmacological properties [89].

Shikonin (**30**), a naphthoquinone compound derived from the root of *Lithospermum erythrorhizon* [90, 91], has demonstrated potential as a therapeutic agent for glioma through various mechanisms: (1) It induces apoptosis by elevating intracellular ROS levels [92]. (2) Apoptosis induction occurs *via* regulation of cluster of differentiation 147 (CD147) expression [93]. (3) Ma *et al.* [94] revealed that shikonin triggers glioma cell apoptosis by interfering with ER stress and mitochondrial outer membrane

permeabilization (MOMP). (4) It inhibits U87 cell proliferation by suppressing Notch2 and Notch3 protein expression and reducing Hes1 and Hey1 levels [95]. (5) Qin et al. [96] observed that shikonin attenuates glioma stemness by downregulating proteasome activity and decreasing PSMB8/9/10 and PSME1/2/3 expression. (6) Shikonin inhibits glioma cell proliferation, metastasis, and invasion by suppressing phosphorylated PI3K and AKT pathways and reducing MMP-2 and MMP-9 levels [97].

Plumbagin (**31**) is a naphthoquinone compound isolated from the roots of *Plumbago zeylanica L*. Compared with shikonin (**30**), plumbagin (**31**) has higher BBB penetration ability [98]. Studies *in vitro* and *in vivo* have shown that plumbagin has anti-glioma activity [99]. It inhibits glioma cell growth by suppressing FOXM1 expression and reduces migration and invasion by downregulating MMP-2/9 expression while suppressing the PI3K/AKT signaling pathway [100]. Additionally, plumbagin inhibits glioma progression by inducing ferroptosis [98].

Juglone (**32**), a naphthoquinone compound extracted from the roots of *Black walnut*, demonstrates anti-tumor properties in human GBM cells [101] and C6 rat glioma cells [102] *in vitro* and *in vivo*, attributed to its lipid-soluble characteristics. Wu et al. [103] discovered that juglone inhibits the growth of tumor stem cell-like cells (TSCs) in gliomas by activating the ROS-p38-MAPK pathway *in vitro*. Furthermore, Guo et al. [104] established that juglone induces ferroptosis in GBM cells through p38MAPK phosphorylation.

2.6. Others

In addition to the aforementioned alkaloids, polyphenols, flavonoids, terpenoids, saponins, and quinone compounds, several other categories of NPs demonstrate significant anti-glioma activity, including steroids and polysaccharides.

Dai et al. [105] recently identified trichobotrysin B (**33**), a marine NP derived from the ascidian-associated fungus *Trichobotrys effusa* 4729. This compound demonstrated inhibitory effects on glioma proliferation and induced apoptosis through modulation of the signal STAT3/JAK2 signaling pathway. Furthermore, several novel compounds extracted from marine-derived fungi exhibited notable anti-glioma activity [106, 107].

Bufalin (**34**), a cardiotonic steroid, was initially discovered in toad venom. Research has shown that bufalin induces apoptosis and autophagy through ER stress [108]. Additionally, it triggers cell death *via* suppression of TNF-α, TNF receptor 1 (TNFR1), and receptor-interacting protein kinase 1 (RIPK1) [109]. Furthermore, bufalin regulates the expression of Annexin A2 and DRP1 to induce apoptosis in U251 cells [110].

Fucoxanthin (**35**), a naturally occurring carotenoid extracted from algae, demonstrates the ability to induce apoptosis in U251 cells. This process is facilitated through the enhancement of ROS-mediated oxidative damage and the modulation of MAPKs and PI3K/AKT signaling pathways [111].

Osthole (**36**), extracted from the *Cnidium monnieri (L.) Cusson* [112-114], exhibits anti-glioma properties through multiple mechanisms. It induces apoptosis and inhibits the proliferation of glioma cells by enhancing miR-16 expression and suppressing MMP-9 [115]. Additionally, it triggers necroptosis in glioma cells through the production of ROS [116].

Additionally, certain natural polysaccharides demonstrate significant anti-glioma activity. These include Radix Hedysari Polysaccharide (**37**) derived from Hedysari Radix [117] and Ganoderma lucidum polysaccharides (GL-PS, **38**) extracted from *Ganoderma lucidum* [118].

3. Synthetic NP derivatives against glioma

Numerous NPs have exhibited significant anticancer properties, yet face considerable challenges in glioma treatment. These obstacles primarily include low bioavailability, difficulty in effectively penetrating the BBB, insufficient antitumor activity to meet clinical needs, and potential increased side effects, which constrain the application of NPs in glioma therapy [119]. A key focus of current research is enhancing the biological activity of NPs through chemical modifications based on their structures. This approach aims to improve the pharmacokinetic properties of NPs, such as increasing their bioavailability and BBB penetration, while also enhancing their antitumor effects and potentially reducing side effects [120]. Consequently, this strategy expands the potential for clinical applications of NPs in glioma treatment. This section examines the effects and mechanisms of synthetic NP derivatives in glioma treatment (their names and anti-glioma action mechanisms are presented in Table 2, with chemical structures shown in supplementary information).

3.1. Alkaloid derivatives

Harmine, a naturally occurring β-carboline alkaloid, demonstrates apoptosis-inducing properties [121]. However, glioma cells exhibit notable resistance to apoptotic induction, necessitating additional strategies to overcome their intrinsic resilience to apoptotic stimuli [122]. Meinguet *et al.* [123] developed a novel harmine derivative, compound **39**, which exhibited significant antiproliferative effects against U373 [half maximal inhibitory concentration (IC_{50} 0.20 μmol·L^{-1}), T98G (IC_{50} 0.70 μmol·L^{-1}), and HS683 (IC_{50} < 0.01 μmol·L^{-1}) cell lines. Compound **39** induced apoptosis through the inhibition of Dual-specificity tyrosine phosphorylation-regulated kinase 1A (DYRK1A) and the activation of caspase-9.

Colchicine, an anti-tubulin and antimitotic agent, demonstrates antitumor properties [124]. However, concerns regarding colchicine's toxicity necessitate the development of derivatives with enhanced efficacy and reduced side effects[125]. In a significant advancement, Fang et al. [126] characterized a novel colchicine derivative, compound **40**, which exhibited potent inhibitory effects on U87-MG and U373-MG cells, with IC_{50} values of 10 nmol·L^{-1} and 50 nmol·L^{-1}, respectively. Compound **40** effectively disrupted glioma cells by inhibiting tubulin polymerization, elevating ROS levels, and inducing autophagy, ultimately leading to cellular apoptosis.

Matrine's adaptable molecular structure and high safety profile render it a promising lead compound with distinctive pharmacological properties [127, 128]. Qiu et al. [129] developed a novel matrine derivative, compound **41**, which demonstrated moderate inhibitory effects on C6 cells *in vitro* (IC_{50} 8.31 μmol·L^{-1}). Compound **41** induces DNA damage by suppressing DNA Topo I expression, resulting in p53 overexpression and subsequent cell apoptosis induction.

Indole, a naturally occurring nitrogen-containing heterocyclic alkaloid, possesses a unique molecular structure that confers exceptional biological activity, particularly demonstrating significant potential in antitumor research. It has emerged as a crucial starting material for the development of novel bioactive molecules [130]. Andrade et al. [131] synthesized a new indole derivative compound **42**, which exhibited potent cytotoxic activity against glioma (C6) with an IC_{50} of 0.4 μg·mL^{-1} while displaying minimal toxicity to non-tumor cells. Compound **42** markedly inhibited glioma cell proliferation and viability, effectively restricting cell migration, potentially through the induction of apoptosis-like morphological changes.

3.2. Flavone derivatives

Chalcone, a naturally occurring flavonoid compound, possesses a flexible chemical structure that facilitates modification

Table 2 Anti-glioma activity of different classes of synthetic derivatives of NPs and their mechanisms

No.	Classification	Mechanism	IC_{50}	Animal study	Advantages	Refs.
39	Alkaloids	↓DYRK1A	0.20 μmol·L^{-1} (U373); 0.70 μmol·L^{-1} (T98G); < 0.01μmol·L^{-1} (HS683)		High solubility; high absorption; higher BBB penetration	122, 123
40	Alkaloids	↓tubulin; ↑ROS; ↑LC3-I/II	10 nmol·L^{-1} (U87-MG); 50 nmol·L^{-1} (U373-MG)	Adult female Sprague Dawley rats (C6)	Low dose efficacy and less side effects	126
41	Alkaloids	↓TopoI; ↑p53; ↓Bcl2; ↑Bax; ↑c-caspase-3; ↑c-PARP	8.31 μmol·L^{-1} (C6)		High safety	129
42	Alkaloids		0.41 μg·mL^{-1} (C6)		Higher cytotoxicity; high safety	131
43	Flavones	↑p21/Cip1; ↓MDM2; ↑Bax; ↑p53;↓ΔΨm; ↑ROS; ↑caspase-9	0.72 μg·mL^{-1} (U87-MG)	Male athymic nude mice (U87-MG)	Increased inhibitory activity; high safety	135
44	Flavones	↑ROS; ↑NO	50.83 μmol·L^{-1} (A172); 90.34 μmol·L^{-1} (GBM1)		Selective cytotoxicity	136
45	Flavones	↓NF-κB; ↑caspase-3	29.49 μmol·L^{-1} (C6)		Selective cytotoxicity	137
46	Flavones	↓GFRs; ↓P-ERK; ↓P-AKT; ↑Bad; ↑Bad/Bcl-xL; ↑cytochrome c; ↑caspase-3/9	< 25 μmol·L^{-1} (U373-MG)		Selective cytotoxicity; BBB permeability	141
47	Terpenoids	↓cAMP	< 8 μmol·L^{-1} (U251); < 8 μmol·L^{-1} (C6)		Better inhibition	143
48	Terpenoids	↓Akt; ↓Erk1/2; ↓p38; ↑c-caspase-3; ↑c-PARP	16.23 μmol·L^{-1} (T98G); 9.11 μmol·L^{-1} (C6)		Better solubility in water and bioavailability	145, 146
49	Terpenoids	↓AKT; ↓Erk1/2; ↓p38; ↑c-caspase-3; ↑c-PARP	19.46 μmol·L^{-1} (T98G); 22.68 μmol·L^{-1} (C6)		Better solubility in water and bioavailability	145, 146
50	Terpenoids	↓EGFR	5.82 μmol·L^{-1} (U251); 8.19 μmol·L^{-1} (T98G); 17.04 μmol·L^{-1} (U87)		Potential high oral bioavailability; BBB permeability	148
51	Terpenoids	↑RIP1/RIP3/MLKL	0.94 μmol·L^{-1} (U251)	Zebrafish (U251)	Better inhibition; acceptable BBB permeability	151
52	Terpenoids	↑ROS; ↓GPX4; ↓COX-2; ↑Nrf2; ↓STX17	5.738 μmol·L^{-1} (U87); 5.119 μmol·L^{-1} (U251)	Female BALB/c nude mice (U87)	Significantly increased anti-GBM activity	152
53	Terpenoids	↓FOXM1	2.014 μmol·L^{-1} (U87); 1.998 μmol·L^{-1} (U251)		Improve water solubility	153
54	Terpenoids	↓CDK-2; ↓MMP-2; ↓MMP-9; ↓EMT	9.532 μmol·L^{-1} (LN18); 30.097 μmol·L^{-1} (T98G); 13.374 μmol·L^{-1} (A172); 19.875 μmol·L^{-1} (LN229)		Good intestinal absorption and BBB penetrability; no developmental toxicity.	155
55	Terpenoids	↑caspase-9; ↑cytochrome c; ↑Bax; ↓Bcl-2; ↑caspase-3; ↑LC3-II; ↓p62	7.41 μmol·L^{-1} (U87)		Increased inhibitory activity and prolonged half-life	160
56	Terpenoids	↓tubulin	6.95 ng·mL^{-1} (U87-MG); 1.95 ng·mL^{-1} (SW1783); 14.5 ng·mL^{-1} (GBM)	Female athymic CD-1 nude mice (U-87-MG)	Increased inhibitory activity and BBB penetrability	161
57	Terpenoids	↓tubulin	9.49 nmol·L^{-1} (U87-MG)		Inhibits proliferation; enhanced radiation response	164
58	Terpenoids	↓tubulin			BBB penetrability	166
59	Terpenoids	↑Tetramerization of PKM2; ↓PKM2 enters nucleus; ↓STAT3	3.03 μmol·L^{-1} (U87); 1.80 μmol·L^{-1} (U118); 7.49 μmol·L^{-1} (SF126); 5.24 μmol·L^{-1} (SHG44); 7.14 μmol·L^{-1} (U251); 1.66 μmol·L^{-1} (C6)	BALB/c nude mice (U118)	BBB penetrability; prolonged half-life（prodrug）	171
60	Terpenoids	↓Bcl-2; ↑Bax	27.18 ± 1.89 μmol·L^{-1}(C6); 20.58 ± 1.61 μmol·L^{-1}(U87MG)	Wistar rats (C6)	BBB penetrability; high safety	173
61	Quinones	↑ROS-p38-MAPK	3.99 μmol·L^{-1} (U87); 7.00 μmol·L^{-1} (U251)		Increased inhibitory activity and antioxidant	176
62	Quinones	↑ROS-p38-MAPK	3.28 μmol·L^{-1} (U87); 5.43 μmol·L^{-1} (U251)	Female BALB/c-nu mice (Human primary GBM cells)	Increased inhibitory activity and antioxidant	176
63	Quinones	↑ROS-p38-MAPK	7.60 μmol·L^{-1} (U87); 8.64 μmol·L^{-1} (U251)	Female BALB/c-nu mice (Human primary GBM cells)	Increased inhibitory activity and antioxidant	176
64	Quinones	↑ROS-p38-MAPK	11.84 μmol·L^{-1} (U87); 18.05 μmol·L^{-1} (U251)		Increased inhibitory activity and antioxidant; BBB penetrability	176
65	Phenolic compounds	↓CDC25C; ↓CCNB1; ↓CDK1; ↓CDK2; ↓CDK6; ↓Nanog	7.43 μmol·L^{-1} (U87-MG); 47.56 μmol·L^{-1} (primary GBM cells)		Increased inhibitory activity	178
66	Phenolic compounds	↑ROS; ↑p-IKKα/β; ↓IκBα; ↑NF-κB	35.12 μmol·L^{-1} (C6); 23.47 μmol·L^{-1} (U87); 40.12 μmol·L^{-1} (U251)	Male Wistar rats(C6)	Higher BBB penetration	182
67	Phenolic compounds	↓TrxR2; ↑ROS; ↓ΔΨm; ↑caspase	0.42 μmol·L^{-1} (U251)	BALB/c nude mice(U251)	Selective cytotoxicity	184

and synthesis, rendering it an ideal precursor for targeted drug development [132-134]. Loch-Neckel et al. [135] developed a novel chalcone-quinoxaline hybrid compound **43**, which exhibited potent inhibitory activity against U87-MG cells (IC_{50} 0.72 μg·mL^{-1}). Compound **43** impeded U87-MG cell proliferation by modulating Bax, p53, p21, and caspase-9 expression, while reducing murine double minute 2 (MDM2) protein levels. In a separate study, Bittencourt et al. [136] synthesized chalcone derivative compound **44**, demonstrating inhibitory effects on A172 (IC_{50} 50.83 μmol·L^{-1}) and GBM1 (IC_{50} 90.34 μmol·L^{-1}) cells. Compound **44** induced apoptosis by elevating ROS and nitric oxide (NO) levels in glioma cells. Additionally, Kiekow *et al.* [137] synthesized chalcone derivative compound **45**, which displayed moderate activity against C6 cells (IC_{50} 29.49 μmol·L^{-1}). Compound **45** triggered cell death in glioma cells by regulating nuclear factor-kappa B (NF-κB) nuclear translocation and activating caspase-3.

Quercetin, a naturally occurring flavonoid compound, demonstrates considerable promise in anti-glioma therapy [138, 139]. It effectively suppresses glioma cell proliferation and promotes apoptosis while exhibiting low toxicity, positioning it as an ideal precursor for further development [140]. In a notable study, Dell' Albani et al. [141] synthesized a quercetin derivative, compound **46**, which exhibited inhibitory effects on U373-MG cells (IC_{50} < 25 μmol·L^{-1}). The mechanism of action for compound **46** involves the induction of apoptosis through the inhibition of ERK and AKT phosphorylation.

3.3. Terpenoid derivatives

Ursolic, a naturally occurring pentacyclic triterpenoid com-

pound, has attracted considerable attention due to its remarkable anticancer properties [142]. In a study by Fan *et al.* [143], an ursolic acid derivative, compound **47**, demonstrated significant inhibitory effects against glioma cell lines U251 and C6, with IC_{50} values below 8 μmol·L^{-1} for both. The research revealed that compound **47** induces apoptosis in glioma cells through the downregulation of cAMP.

Betulin, a naturally occurring pentacyclic triterpene compound, exhibits selective cytotoxicity against cancer cells, rendering it an excellent precursor for novel anticancer derivatives[144]. KrÓL *et al.* [145] reported two newly synthesized betulin derivatives, compounds **48** and **49**. Compound **48** demonstrated IC_{50} values of 16.23 μmol·L^{-1} in T98G cells and 9.11 μmol·L^{-1} in C6 cells, while compound **49** exhibited IC_{50} values of 19.46 μmol·L^{-1} in T98G cells and 22.68 μmol·L^{-1} in C6 cells. These derivatives inhibited Akt and Erk kinase activity, induced apoptosis, and suppressed neuroblastoma cell proliferation[146].

Gypsogenin, an oleanane-type pentacyclic triterpene compound, exhibits diverse pharmacological activities, including anticancer properties, positioning it as a promising precursor compound with substantial pharmacological potential [147]. Ciftci *et al.* [148] synthesized a gypsogenin derivative, compound **50**, which demonstrated moderate activity against glioma cell lines. The compound exhibited IC_{50} values of 5.82, 8.19, and 17.04 μmol·L^{-1} in U251, T98G, and U87 cells, respectively. Compound **50** exerted its anti-glioma effects through the induction of apoptosis and inhibition of EGFR expression.

Celastrol, a quinone-type triterpene compound, exhibits anticancer properties [149, 150]. However, its relatively low efficacy limits its application in glioma treatment. Feng *et al.* [151] addressed this limitation by synthesizing a celastrol derivative, compound **51**, which demonstrated significant antiproliferative activity against U251 cells (IC_{50} 0.94 μmol·L^{-1}). This compound markedly inhibited colony formation and migration in U251 cells. Furthermore, it induced necrotic cell death through activation of the RIP1/RIP3/MLKL signaling pathway.

AKBA, a natural pentacyclic triterpene compound, exhibits significant biological properties [57]. Yang *et al.* [152]synthesized an AKBA derivative, compound **52**, which demonstrated potent antiproliferative activity against glioblastoma cells (U87 and U251), with IC_{50} values of 5.738 μmol·L^{-1} and 5.119 μmol·L^{-1}, respectively. Compound **52** induces ferroptosis in human glioblastoma cells by generating ROS and inhibiting the STX17-mediated fusion of autophagosomes and lysosomes. Sun *et al.* [153] developed another AKBA derivative, compound **53**, which exhibited strong inhibitory effects on U87 and U251 cells, with IC_{50} values of 2.014 μmol·L^{-1} and 1.998 μmol·L^{-1}, respectively. Compound **53** exerts its anti-glioma activity through binding to the transcription factor FOXM1.

Isolongifolanone, a compound derived from the NP *longifolene* through isomerization and oxidation reactions, demonstrates significant antitumor activity [154]. Jiang *et al.* [155] synthesized an isolongifolanone derivative, compound **54**, which exhibited IC_{50} values of 9.532, 30.097, 13.374, and 19.875 μmol·L^{-1} in LN18, T98G, A172, and LN229 cells, respectively. Compound **54** targets CDK-2, thereby inhibiting cell cycle progression and cell proliferation. Furthermore, it suppresses glioma invasion by inhibiting MMP-2/9 and impeding the progression of EMT.

Artemisinin, a naturally occurring sesquiterpene lactone compound [156, 157], has demonstrated significant effects on various tumor types [158]. Isothiocyanates have been shown to enhance the antitumor efficacy of other drugs and function as covalent inhibitors [159]. Nyein et al. [160] synthesized a novel artemisinin-isothiocyanate hybrid compound **55**, which exhibited cytotoxic activity against U87 cells (IC_{50} 7.41 μmol·L^{-1}). This compound induced apoptosis by upregulating the expression of caspase 9/3, cytochrome c, and Bax while downregulating Bcl-2 expression. Furthermore, compound **55** triggered autophagy through the upregulation of LC3-II and downregulation of p62.

Ortataxel (**56**), a taxane analog, demonstrates efficacy against various tumor cells. Compared to paclitaxel (PTX), ortataxel exhibits higher *in vitro* anti-glioma activity against U87-MG (IC_{50} 6.95 ng·mL^{-1}), SW1783 (IC_{50} 1.95 ng·mL^{-1}), and GBM (IC_{50} 14.5 ng·mL^{-1}) cells. In U87-MG xenografts, ortataxel has shown high effectiveness and BBB penetration capability [161]. A Phase II clinical trial (NCT01989884, Table 3) evaluating **56** for recurrent glioblastoma treatment has concluded. The study revealed that **56** did not demonstrate significant activity in patients with recurrent glioblastoma. However, a small subset of patients experienced prolonged benefits [162]. Cabazitaxel (**57**) is a second-generation semisynthetic taxane capable of crossing the BBB [163]. It demonstrates greater efficacy in treating glioblastoma *in vivo* with U87 (IC_{50} 9.49 ng·mL^{-1}) compared to docetaxel (DTX), and its enhanced solubility facilitates improved BBB penetration[164]. Cabazitaxel underwent phase I/II clinical trials (NCT01751308, Table 3) for treating recurrent diffuse intrinsic pontine glioma (DIPG) and HGG in pediatric patients. The study, involving 16 patients, showed manageable side effects but no activity in recurrent/refractory HGG or DIPG[165]. TPI-287 (**58**), a third-generation taxane less affected by P-glycoprotein (P-gp), is lipophilic and capable of BBB penetration[166]. In a phase I/II clinical trial (NCT01933815, Table 3), nine patients with recurrent glioblastoma received TPI-287 combined with bevacizumab. The drug was generally well-tolerated, with 3 out of 7 patients exhibiting partial responses[167]. These taxane analogs function as microtubule inhibitors, inducing apoptosis through microtubule stabilization.

Parthenolide, a natural sesquiterpene lactone, has been identified as a moderate activator of pyruvate kinase M2 (PKM2) [168-170]. Ding et al. [171] synthesized a parthenolide dimer compound **59**, which demonstrated significant anti-GBM activity. The IC_{50} values for the U87, U118, SF126, SHG44, U251, and C6 cell lines were 3.03, 1.80, 7.49, 5.24, 7.14, and 1.66 μmol·L^{-1}, respectively. Compound **59** enhanced the formation of PKM2 tetramers and inhibited PKM2 nuclear translocation in GBM cells, thereby suppressing the STAT3 signaling pathway. This resulted in the inhibition of GBM cell proliferation and the induction of apoptosis. Chen et al. [172] synthesized a parthenolide derivative ACT001 (**60**), which inhibited C6 (IC_{50} 27.18 ± 1.89 μmol·L^{-1}) and U87 (IC_{50} 20.58 ± 1.61 μmol·L^{-1}) cell lines. **60** induces apoptosis in glioma cells through the down-regulation of the anti-apoptotic gene Bcl-2 [173]. A clinical phase I study (ACTRN12616000228482, Table 3) of 60 for the tcreatment of recurrent glioblastoma demonstrated that it was well-tolerated in patients with malignant gliomas, exhibiting satisfactory bioavailability and preliminary evidence of antitumor activity [174]. Based on these favorable efficacy and safety results, compound **60** has progressed to a Phase I/II clinical trial (NCT05053880, Table 3).

3.4. Quinone derivatives

Juglone, a natural quinone compound, has been extensively investigated for its potential antitumor properties. However, the hydroxyl group in juglone is susceptible to oxidation, limiting its application in drug development [175]. Zhang *et al.* [176] addressed this limitation by designing and synthesizing a series of juglone derivatives. In these derivatives, the hydroxyl group was substituted with methyl (**61**), allyl (**62**), butyl (**63**), and benzyl (**64**) groups. The IC_{50} values for U87 cells were 3.99, 3.28, 7.60, and 11.84 μmol·L^{-1}, while for U251 cells, they were 7.00, 5.43, 8.64, and 18.05 μmol·L^{-1}, respectively. These juglone derivatives demonstrated antitumor effects by inducing apoptosis in glioma cells through the activation of the ROS-p38-MAPK signaling pathway.

Table 3 Natural products and their related products treating glioma in clinical trials

No.	Name	Phase	ClinicalTrials.gov ID	Type of glioma	Study Start/ Study Completion	Public Title	Status
10	Cannabidiol	Phase I/ II Phase I/ II Phase I/II	NCT01812603 NCT01812616 NCT03607643	Recurrent Glioblastoma Recurrent Glioblastoma Glioblastoma Multiforme	2013-09/2016-06(Actual) 2014-09/2016-06(Actual) 2019-01-15(Estimated)/2020-12-15(Estimated)	A Safety Study of Sativex in Combination With Dose-intense Temozolomide in Patients With Recurrent Gliob A Safety Study of Sativex Compared With Placebo (Both With Dose-intense Temozolomide) in Recurrent Glioblastoma Patients A Study of the Efficacy of Cannabidiol in Patients With Multiple Myeloma, Glioblastoma Multiforme, and GI Malignancies	Completed Completed Completed
11	Chlorogenic Acid	Phase I Phase II/III	NCT02728349 NCT03758014	Grade IV GBM Grade IV GBM	2016-04-12(Actual)/2017-09-13(Actual) 2018-11-27(Actual)/2021-04-30(Estimated)	Tolerance and Pharmacokinetic Study of Chlorogenic Acid to Advanced Glioblastoma Studies of Chlorogenic Acid for Injection for Safety and Efficacy of Grade IV GBM Patients	Completed Completed
56	Ortataxel	Phase II	NCT01989884	Glioblastoma	2013-11 (Actual)/2016-12(Actual)	Multicenter, Single Arm, Open-Label Phase II Trial On The Efficacy Of Ortataxel In Recurrent Glioblastoma	Completed
57	Cabazitaxel	Phase I/ II	NCT01751308	Malignant Solid Tumor - Malignant Nervous System Neoplasm	2013-02(Actual)/ 2016-02(Actual)	A Phase 1-2 Dose Finding, Safety and Efficacy Study of Cabazitaxel in Pediatric Patients With Refractory Solid Tumors Including Tumors of the Central Nervous System	Completed
58	TPI-287	Phase I/ II	NCT01933815	Glioblastoma Multiforme	2013-02(Actual)/ 2016-02(Actual)	A Phase 1-2 Dose Finding, Safety and Efficacy Study of Cabazitaxel in Pediatric Patients With Refractory Solid Tumors Including Tumors of the Central Nervous System	Completed
60	ACT001	Phase I Phase I/ II	ACTRN12616000228482 NCT05053880	Solid tumors Recurrent Glioblastoma Multiforme	2016-02(Actual)/2022-06(Actual) 2021-09-22(Actual) /2023-11（Estimated）	A phase 1 dose-escalation study to evaluate the safety, tolerability and pharmacokinetics of ACT001 in patients with advanced solid tumors; A Phase 1b/2a Study of ACT001 and Anti-PD-1 in Patients With Surgically Accessible Recurrent Glioblastoma Multiforme	Completed Unknown status
	Liposomal Curcumin Albumin-bound Paclitaxel	Phase I/ II Phase I/ II	NCT05768919 NCT04528680	High-Grade Gliomas Glioblastoma	2023-03-03(Actual)/2027-05(Estimated) 2020-10-29(Actual)/2025-09（Estimated）	Study of Liposomal Curcumin in Combination With RT and TMZ in Patients With Newly Diagnosed High-Grade Gliomas Ultrasound-based Blood-brain Barrier Opening and Albumin-bound Paclitaxel and Carboplatin for Recurrent Glioblastoma SC9/ABX	Ongoing Ongoing

3.5. Phenolic compounds

Nordihydroguaiaretic acid (NDGA), a natural phenolic compound, demonstrates anti-glioma potential and serves as a promising drug precursor [177]. Zhao et al. [178] introduced a novel NDGA derivative, compound **65**, which exhibited moderate inhibition of glioma cell proliferation. The compound achieved IC_{50} values of 7.43 μmol·L^{-1} in U87-MG cells and 47.56 μmol·L^{-1} in primary GBM cells. Compound **65** impeded the tumorigenic capacity of gliomas through multiple mechanisms: blocking the cell cycle of glioma cells, suppressing the expression of the transcription factor Nanog, and inhibiting the self-renewal of glioma stem cells (GSCs).

Apocynin is a naturally occurring polyphenolic compound. Like other polyphenols [179, 180], Apocynin demonstrates multiple pharmacological properties, including antioxidant, anti-inflammatory, and anticancer effects [181]. Yang et al. [182] engineered and produced an Apocynin derivative, compound **66**, which demonstrated effective BBB penetration, enhanced ROS production, and anti-glioma activity (with IC_{50} values of 35.12, 23.47, and 40.12 μmol·L^{-1} in C6, U87, and U251 cells respectively) in both *in vitro* and *in vivo* studies. Compound **66** triggered apoptosis by elevating p-IKKα/β levels, resulting in IκBα degradation, stimulating NF-κB phosphorylation, and nuclear translocation.

Curcumin, a naturally occurring polyphenolic compound, has been extensively investigated and demonstrated to possess significant anti-inflammatory and antitumor properties [183]. In a study by Luo et al. [184], a curcumin derivative, compound **67**, exhibited notable inhibitory effects on U251 glioma cells, with an IC_{50} value of merely 0.42 μmol·L^{-1}. This compound was found to inhibit intracellular TrxR2 and induce mitochondria-dependent apoptosis through caspase activation, ROS production, and a decrease in mitochondrial membrane potential (ΔΨm).

4. Anti-glioma mechanisms of NPs and their synthetic derivatives

NPs operate through a multicomponent-multichannel-multitarget mode of action, with complex and diverse mechanisms. These compounds can effectively target glioma at multiple stages by influencing cyclins and CDKs, modulating ROS, affecting apoptosis signaling pathways, inhibiting MMPs, suppressing P-gp, and reversing the immunosuppressive tumor microenvironment (TME).

4.1. Inhibiting cyclin and CDK

Tumor growth is contingent upon continuous cell proliferation. The cell cycle comprises the M phase and interphase, which adhere strictly to the "G_1-S-G_2-M" pattern and are distributed with distinct checkpoints. Transitions between these phases are driven by specific CDKs, including CDK1, CDK2, CDK4, and CDK6. These CDKs are expressed at significantly elevated levels in glioma and other tumors and are positively regulated by cyclins. Consequently, CDKs and cyclins represent potential novel targets for glioma treatment.

NPs demonstrate potential as CDKs and cyclin inhibitors, inducing tumor cell senescence and halting cell cycle progression, thereby inhibiting glioma growth. Oxymatrine (**2**) and curcumin (**9**) have been shown to downregulate the expression of cyclin D1, CDK4, and CDK6 in glioma cells, leading to cell cycle arrest in the G0/G1 phase [19, 36]. Similarly, Gs-Rh2 (**21**) reduces CDK4/cyclin D levels [76], while plumbagin (**31**) decreases cyclin D1 levels [99], both contributing to glioma growth inhibition. Furthermore, the synthetic derivative **54** targets CDK2, effectively blocking the cell cycle and inhibiting glioma cell proliferation [155].

4.2. Regulating ROS levels

ROS are essential for cellular function, with glioma cells exhibiting higher ROS levels compared to normal cells. In tumor cells and tissues, ROS play a crucial role in various processes, including cell proliferation, by interacting with PI3K/AKT and MAPK-related pathways. Additionally, ROS-activated HIFs, NF-κB, and nuclear factor E2-related factor 2 (Nrf2) regulate the activity of the antioxidant system, maintaining redox balance at elevated levels. MAPK influences multiple signaling pathways, primarily ERK, JNK, and p38, which are involved in the regulation of cellular metabolism, growth, and other physiological activities [185].

NPs can influence glioma proliferation, migration, invasion, and cell death by modulating ROS levels and activating related pathways. LTr1 (**8**) induces ROS production and inhibits the PI3K/AKT pathway [32]. Celastrol (**18**) stimulates JNK activation and ROS generation [64]. PPVI (**27**) enhances ROS accumulation and activates ROS-regulated JNK and p38 pathways [84]. Fucoxanthin (**35**) triggers apoptosis in U251 glioma cells by promoting ROS-mediated oxidative damage and interfering with related pathways, including MAPKs [111]. Furthermore, Zhang *et al.* [176] developed a series of carnosine derivatives, **61**-**64**, which induce apoptosis by activating the ROS-p38-MAPK pathway and generating excessive ROS, ultimately inhibiting glioma cell activity.

4.3. Targeting apoptosis signaling pathways

Apoptosis, the primary mechanism of cancer cell death, is predominantly categorized into mitochondrial apoptosis and DR apoptosis. Targeting intracellular apoptotic pathways and associated targets has the potential to reverse, delay, and halt tumor progression [186].

4.3.1. Targeting Bcl-2

Compounds targeting mitochondrial apoptosis pathways can induce glioma cell death by causing mitochondrial damage and disrupting adenosine triphosphate (ATP) synthesis [187]. The Bcl-2 family regulates mitochondrial apoptosis, with the Bcl-2 subfamily acting as anti-apoptotic genes that inhibit cytochrome c and AIF release, thus preventing apoptosis. Conversely, Bax, a pro-apoptotic gene, promotes cytochrome c release by disrupting the mitochondrial membrane, activating the caspase cascade, and inducing tumor cell apoptosis. NPs can promote glioma cell apoptosis by modulating Bcl-2/Bax levels. Isoquinoline alkaloids (**4**, **5**) from centipede extracts, PLAB (**20**) of terpenoid, and shikonin (**30**) of quinone down-regulate Bcl-2 and upregulate Bax, inducing glioma cell apoptosis [25, 72, 92]. Additionally, a matrine derivative **41** decreases anti-apoptotic Bcl-2 expression while increasing pro-apoptotic Bax [129].

4.3.2. Targeting DRs

Certain mammalian cells possess surface receptors that, when bound to specific ligands, participate in caspase activation and apoptosis pathways. These receptors, termed "DRs", activate caspases through the DR apoptotic pathway. The primary DRs include TNFR1, Fas, DR4, DR5, and others, while the death ligands comprise TNF, Fas-L, and TRAIL [188]. Consequently, enhancing v expression levels could potentially serve as a glioma treatment strategy. Evodiamine (**6**) has been shown to increase DR4/5 expression [29]. Similarly, Celastrol (**18**) upregulates DR5 [65]. Both compounds enhance TNF-triggered apoptosis. Additionally, Bufalin (**34**) induces apoptosis in glioma cells by upregulating TNFR1 [109].

4.4. Inhibiting MMPs

Malignant glioma exhibits a high degree of invasiveness into surrounding normal neural tissue. The tumor invasion process encompasses three primary aspects: (1) neovascularization of tu-

mor vessels, (2) degradation of the extracellular matrix, and (3) adhesion and migration of tumor cells. MMPs play a crucial role in the invasion and metastasis of tumor cells by degrading the extracellular matrix, regulating gene polymorphism, promoting EMT, and inducing adhesion molecule expression. In glioma cells, MMP-2 and MMP-9 levels are elevated compared to normal tissues. These MMPs are significant contributors to invasive metastasis and have emerged as important targets for glioma treatment [189].

NPs can inhibit glioma cell metastasis and invasion by suppressing MMP activity. Specifically, cannabidiol (**10**) and osthole (**36**) have been shown to downregulate MMP-9 expression [41, 115]. Similarly, quercetin (**12**), shikonin (**30**), and the synthetic derivative **54** impair cell migration and invasion *via* downregulation of MMP-2 and MMP-9 expression [49, 97, 155].

4.5. Targeting VEGF

Glioma is characterized by extensive vascularization, with increased neovascularization being a prominent feature. These pathophysiological processes are crucial in tumor development and progression. VEGF, an endothelial cell-specific mitogen, promotes the growth, proliferation, and migration of vascular endothelial cells and is highly expressed in gliomas. Among the various VEGF receptors (VEGFRs), VEGFR2 primarily mediates VEGF's angiogenic functions. Consequently, targeting the VEGF/VEGFR2 pathway can inhibit angiogenesis and impede tumor growth. In clinical practice, tumor anti-vascular therapy is currently implemented through the inhibition of VEGF and VEGFR [190].

NPs demonstrate the ability to target VEGF and inhibit angiogenesis in glioma. Notably, polyphenolic curcumin (**9**) targets VEGF, exerting an anti-vascular therapeutic effect through VEGF inhibition [36]. Furthermore, Stellettin B (**16**) has been shown to block both the expression and secretion of VEGF, a major proangiogenic factor, in glioma cells [62].

4.6. Inhibiting P-gp

The therapeutic effectiveness of current glioma chemotherapeutic agents is frequently constrained by the BBB and drug resistance mechanisms. P-gp, which is abundantly expressed in the BBB, is encoded by the multidrug resistance protein 1 (MDR1) gene and functions as an ATP-dependent membrane transport protein. P-gp facilitates the efflux of intracellular drugs, thereby conferring resistance to cells and diminishing the efficacy of chemotherapeutic agents. Consequently, the development of P-gp inhibitors plays a crucial role in reversing tumor drug resistance.

While synthetic inhibitors may possess more severe toxicities, NPs are characterized by their lower toxicity and higher specificity towards P-gp [191]. Natural borneol (NB) can function as an adjuvant agent, enhancing the cellular uptake of PL by inhibiting P-gp and augmenting neurotransmitter activity [192]. β-Asarone, a primary component of *Acorus*, can reduce the expression of P-gp and MDR1 while increasing BBB permeability. This may facilitate the entry of TMZ into glioma cells, thereby enhancing its antitumor effects [193].

4.7. Reversing immunosuppression

Certain immune cells within the CNS, particularly microglia and macrophages, play a crucial role in the immune response. However, in patients with glioma, the brain's immune system is typically suppressed. Macrophages in gliomas predominantly exhibit an M2-type (pro-tumoral) phenotype, releasing cytokines that promote tumor development. Furthermore, glioma cells secrete factors such as C-C motif chemokine 2 (CCL2), which facilitate the recruitment of tumor-associated macrophages (TAMs) and drive their transformation to the M2-type. This process leads to the formation of an immunosuppressive TME, further promoting glioma cell proliferation. M2-type macrophages secrete cytokines, including interleukin-6 (IL-6) and IL-10, which contribute to the recruitment of regulatory T cells (Tregs) and suppress the activation of effector T cells. Consequently, reversing this immunosuppressive state is particularly critical in the treatment of gliomas.

NPs can modulate the immune system by influencing TAMs, inhibiting myeloid-derived suppressor cells (MDSCs) and Tregs, and reactivating immune effector cells (including T cells and natural killer cells). These actions contribute positively to glioma immunotherapy. Curcumin (**9**), a polyphenol, can induce TAMs to adopt an M1-type (antitumoral) phenotype and reduce the expression of IL-6 and IL-8 [36]. Triptolide (**19**) demonstrates the capacity to counteract the suppressive effects on $CD4^+$ T cells within the immunosuppressive glioma microenvironment [69].

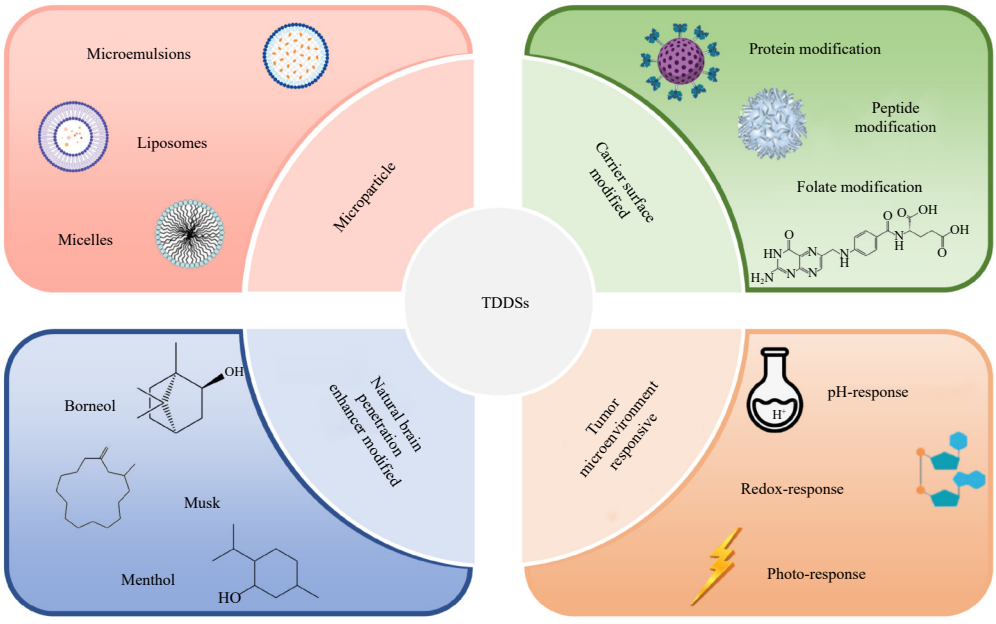

Fig. 2 Schematic diagram of TDDSs of natural products for treatment of glioma.

5. TDDSs of NPs against glioma

While NPs exhibit multi-channel, multi-target, and multi-efficacy characteristics in glioma treatment, the BBB significantly impedes drug penetration to tumor sites, limiting their clinical application [194]. Hydrophobic nanoparticles demonstrate enhanced BBB permeability, enabling efficient drug delivery to tumor locations. Consequently, TDDSs have undergone substantial development [195, 196]. Based on their mechanism of action, TDDSs can be broadly categorized into several types, including microparticle TDDSs, carrier surface modified TDDSs, natural brain penetration enhancer (BPE) modified TDDSs, and TME responsive TDDSs (Fig.2).

5.1. Microparticle TDDSs to deliver NPs

Microparticle TDDSs represent a technology that enables precise drug delivery to tumors, leveraging the enhanced permeability and retention effect of tumor tissue to achieve targeted drug release and action in the body. Delivery carriers such as liposomes, microemulsions, and micelles are extensively utilized in microparticle systems. These carriers possess advantageous characteristics, including small size, excellent biocompatibility, and high drug loading capacity, which effectively enhance drug stability and efficacy *in vivo*.

5.1.1. Liposomes

Liposomes are biofilm-structured DDSs with a unique phospholipid bilayer. They enhance drug bioavailability and stability, reduce peripheral toxicity, modulate various targeting properties, and exhibit high affinities for the BBB. These characteristics enable liposomes to improve drug penetration into the BBB and drug uptake by tumors, making them a promising TDDS for glioma diagnosis and treatment [197]. Ismail et al. [198] developed an ApoE-ApoE-functionalized liposomal nanoplatform based on artesunate-phosphatidylcholine (ARTPC)@TMZ, a liposomal nanomaterial constructed with an ARTPC and TMZ for treating drug-resistant glioma. This liposome achieved deep glioma penetration through low-density lipoprotein receptor-related proteins (LDLRs)-mediated transcytosis, significantly reduced TMZ-associated toxicity, and improved TMZ efficacy. Hong et al. [199] formulated cholesterol-free liposomes co-loaded with Gs-Rh2 and PTX, demonstrating good stability while avoiding cholesterol-induced side effects. AO et al. [200] developed co-loaded liposomes of Annonaceous acetogenins (ACGs) and Gs-Rh2, exhibiting strong antitumor activity and glioma targeting while mitigating ACGs' toxicity. Furthermore, nanoliposomes have progressed to clinical trials for glioma treatment. A phase I/II clinical trial combining curcumin liposomes with TMZ is currently recruiting participants, with expected completion by May 2027 (NCT05768919, Table 3).

5.1.2. Microemulsions

Microemulsion is a specialized type of dispersed colloidal system. Typically, microemulsions comprise a mixture of water and oil, where oil droplets of nanometer size (generally between 10-100 nm) are dispersed in the aqueous phase, resulting in a colloidal liquid state with unique properties. Microemulsions are characterized by their solubilizing properties, high stability, and clarity, making them suitable carriers for stabilizing and delivering active ingredients in pharmaceutical applications. Wang *et al.* [201] developed a magnetic T7 peptide and AS1411 aptamer-modified microemulsion for glioma treatment through triple glioma-targeted delivery of shikonin and DTX (Fe_3O_4@T7/AS1411/DTX & SKN-M). Under an external magnetic field, this microemulsion was selectively distributed around the brain and subsequently entered tumor cells with the assistance of T7 peptide and AS1411 aptamer. The triple targeting strategy significantly enhanced glioma cell uptake and augmented the synergistic antitumor effects of DTX and SKN.

5.1.3. Micelles

Micelles are microscopic colloidal structures formed by the self-assembly of surfactant molecules in solution. They comprise a hydrophobic core and a hydrophilic shell, capable of encapsulating poorly water-soluble drugs for controlled release. As a TDDS, micelles enhance drug solubility, bioavailability, and stability. Additionally, they selectively deliver drugs to tumors, reducing toxicity and side effects on healthy tissues while improving drug targeting and therapeutic efficacy. Lu *et al.* [202] developed a redox-responsive micellar DDS incorporating internalizing arginine-glycine-aspartic acid (iRGD)-modified camptothecin (CPT) and polyethylene glycol (PEG). The results demonstrated that these micelles exhibit good stability and controlled drug release under physiological conditions, effectively crossing the BBB to target gliomas with significant antitumor effects. Wu *et al.* [203] utilized folic acid-modified poly(ethylene glycol)-poly(e-caprolactone) (Fa-PEG-PCL) nanomicelles to encapsulate luteolin, enhancing its bioavailability. These micelles improved the drug's pharmacokinetic properties and sustained its release, resulting in superior anti-glioma efficacy.

5.2. Carrier surface modified TDDSs to deliver NPs

Given that microparticle TDDSs lack selectivity and affinity, the development of carrier surface-modified TDDSs could enable more targeted glioma treatment. These modified TDDSs leverage the high affinity between ligands and receptors, exploiting differences in receptor or antigen expression on tumor cell surfaces compared to normal cells. This approach achieves enhanced BBB permeability or tumor penetration, promoting selective targeting of antitumor drugs to the tumor site. Common targeting carriers include proteins, peptides, and small molecules such as folate.

5.2.1. Protein modification

Transferrin (Tf), an iron carrier protein, is highly expressed in brain capillary endothelial cells and neurons and overexpressed in glioma, with the ability to cross the BBB [204]. Consequently, targeting the Tf receptor (TfR) presents a strategy for delivering drug molecules and nanoparticles. Ramalho *et al.* developed poly(lactic-co-glycolic acid) (PLGA) nanoparticles for Asiatic acid (AA) delivery, modified with Tf for targeted delivery to GBM cells [205]. These nanoparticles preserved AA's anti-glioma activity and enhanced glioma selectivity by increasing uptake through a TfR-mediated endocytosis mechanism. Lactoferrin (Lf), a member of the Tf family, is a double-lobe glycoprotein. The Lf receptor (LfR) is highly expressed in GBM cells. Thus, conjugated Lf can be employed to enhance BBB crossing and glioma penetration *via* receptor-mediated signaling pathways. Zhang *et al.* engineered a nanoparticle loaded with TMZ and Vincristine (VCR), conjugated with Lf and RGD dual-ligand modifications (L/R-T/V-NLCs) for GBM combination therapy [206]. L/R-T/V-NLCs demonstrated sustained-release behavior, high cellular uptake, and synergistic effects. Moreover, the system increased drug accumulation in tumor tissues, improving tumor inhibition while maintaining low systemic toxicity. A phase I clinical trial of albumin-conjugated PTX for non-invasive BBB crossing was completed, with phase II expected to conclude by September 2025 (NCT-04528680, Table 3).

5.2.2. Peptide modification

Peptides utilized for surface modification of nanoparticles in glioma treatment typically comprise short sequences of 2-50 amino acid residues. These peptides offer advantages over proteins in terms of design, synthesis, and modification ease. They

are characterized by high activity, purity, and excellent BBB permeability. Consequently, peptide-modified NP nanoparticles are frequently employed for glioma targeting [207]. The peptides used for modification primarily fall into two categories: (1) Targeting peptides, which bind to specific receptors to achieve cell or tissue specificity. Examples include IL-13 peptide and Pep-1 peptide, which target brain tumor cells *via* the IL-13Rα2 receptor; RGD peptide, which targets brain tumor vessels through the integrin receptor; and Angiopep-2 peptide, which targets brain tumors *via* the LRP-1 receptor. (2) Cell-penetrating peptides, which enable localization to various intracellular components. For instance, the TAT peptide facilitates localization to the nucleus and nucleolus.

tLyp-1 functions as a cell-penetrating peptide. Xiang *et al.* developed tLyp-1-conjugated glutathione-sensitive biodegradable micelles that facilitated enhanced co-delivery of TRAIL and curcumin to glioma. These micelles demonstrated superior tumor-targeting capability and minimal cytotoxicity *in vivo* [208].

Rabies virus glycoprotein (RVG) is a peptide derivative that demonstrates specific affinity for the nicotinic acetylcholine receptor (nAChR), which is overexpressed in glioma cells. Studies have shown that RVG enhances drug permeability across the BBB and improves tumor-specific selectivity. Xin *et al.* developed a brain-targeted liposome (RVG15-Lipo) designed to enhance BBB permeability and facilitate tumor-specific delivery of PTX [209]. The PTX-CHO-RVG15-Lipo formulation significantly increased PTX concentration in the brain, thereby enhancing the antitumor efficacy of PTX in C6 orthotopic glioma.

5.2.3. Folate modification

Folate receptor (FR), a tumor-associated protein, is overexpressed in glioma cells with limited expression in normal cells. Floate (FA), a natural ligand for FR, possesses non-antigenic, low molecular weight, non-immunogenic, cost-effective, highly stable, and FR-binding properties. Consequently, FA-modified nanoparticles can be recognized by FR and enter tumor cells *via* receptor-mediated endocytosis, enhancing drug delivery efficacy [210]. Yang et al. [211] developed a TME-responsive FA derivative and mitochondria-targeting berberine (BBR) derivative co-modified liposome coated with Tween 80 as a delivery system for paclitaxel (PTX-Tween 80-BBR + FA-Lip). The study demonstrated that glioma targeting by FA and mitochondrial targeting by berberine produced effective therapeutic outcomes for gliomas. He *et al.* [212] engineered a poly (ethylene glycol)-poly (lactic acid) nanoparticle modified by FA to encapsulate curcumin (Cur/Fa-PEG-PLA). This formulation enhanced curcumin's pharmacokinetic profile, maintained its controlled release, exhibited good biosafety, and significantly improved anti-GBM efficacy by promoting apoptosis and inhibiting neovascularization in GBM cells.

5.3. Natural BPE modified TDDSs to deliver NPs

Recent studies have demonstrated that aromatic herbal medicine can modulate BBB permeability, potentially facilitating the entry of other drugs into specific brain tissue targets. This mechanism may enhance drug absorption and distribution, thereby improving therapeutic efficacy. Among the natural BPEs, borneol, musk, and menthol are commonly utilized.

5.3.1. Borneol

Borneol, a bicyclic monoterpene extracted from *Dryobalanops aromatica* [213], has demonstrated the ability to traverse the BBB and reduce ZO-1 expression. Lv et al. [214] developed self-assembled redox-responsive nanoparticles of PTX prodrugs modified with borneol and CGKRK (Cys-Gly-Lys-Arg-Lys, a ligand of heparan sulfate overexpressed on glioma cells). The incorporation of borneol and CGKRK significantly enhanced the nanoparticle's BBB penetration and active tumor-targeting efficiency. Zhao et al. [215] engineered a PLGA nanoparticle co-loaded with curcumin and cisplatin, modified with borneol/R8dGR peptide. This modification not only improved BBB penetration but also achieved targeting by binding to integrin αvβ3 receptors. Intranasal administration of these nanoparticles reduced hypoxia in the microenvironment, decreased angiogenesis, and prolonged mouse survival.

5.3.2. Musk

Muscone, the primary chemical component of Musk, is characterized by its low molecular weight and high lipid solubility. This compound enhances drug permeability across the BBB by suppressing the expression of P-gp and MMP-9 [216]. In a study by Qi et al. [217], Lf and muscone dual-modified liposomes were developed to facilitate BBB penetration and targeted delivery of DTX to gliomas (Lf-LP-Mu-DTX). This innovative approach demonstrated improved cellular uptake, enhanced *in vivo* brain-targeting effects, and increased anti-glioma efficacy.

5.3.3. Menthol

Menthol, the primary active component in corn mint, is widely utilized as an aromatic resuscitation agent. It possesses the ability to traverse various physiological barriers, including the BBB, gastrointestinal mucosal barrier, and skin barrier. Menthol enhances the brain penetration of diverse medications by reducing the levels of TJ proteins [218]. Gao et al. [219] developed a menthol-modified casein nanoparticle loaded with 10-hydroxycamptothecin (HCPT) for glioma targeting. These modified nanoparticles demonstrated significantly higher tumor penetration capability compared to their unmodified counterparts. The *in vitro* and *in vivo* studies revealed that these nanoparticles augment drug accumulation in glioma, consequently extending the median survival time of intracranial glioma-bearing mice.

5.4. TME-responsive TDDSs to deliver NPs

TME-responsive TDDSs can achieve targeted drug release by exploiting the unique characteristics of the TME, such as low pH and elevated GSH levels. This approach minimizes damage to healthy tissues, enhances the antitumor efficacy of the drug, and reduces side effects. This system shows promise as a significant research direction in the field of tumor therapy, offering novel strategies and methodologies for targeted tumor treatment.

5.4.1. pH-response

The elevated metabolic rate of tumors generates acidity, a common characteristic of cancer. Glioma tissue typically exhibits a lower pH environment (6.0–7.0) compared to normal tissues (7.2–7.4). pH-responsive systems exploit this pH differential between tumor and normal tissues to facilitate targeted drug release at tumor sites, enabling more precise delivery and enhanced therapeutic efficacy. Shashin et al. [220] developed thymoquinone (TQ)-loaded mesoporous silica nanoparticles (MSNTQ) for TQ release in glioma cells. MSNTQ addressed TQ's limitations of poor water solubility and insufficient targeting. The study demonstrated pH-dependent TQ release, with higher release rates observed in acidic conditions (pH 5.5 and 6.8) compared to pH 7.4. MSNTQ significantly improved glioma cell targeting and enhanced TQ's inhibitory effect on glioma.

5.4.2. Redox-response

Redox-responsive TDDSs exploit elevated intracellular GSH levels to facilitate rapid drug release. Tumor tissues exhibit higher GSH concentrations compared to normal tissues [221]. These systems leverage this characteristic to significantly enhance drug concentration in target cells, thereby improving therapeutic effic-

acy and minimizing systemic toxicity. Liu *et al.* [222] engineered plasma complex component functionalized manganese-doped mesoporous silica nanoparticles (PMMSNs) and loaded them with PTX *via* adsorption for glioma treatment. The doped manganese dioxide (MnO_2) demonstrates potential in reducing oxidative stress and possesses BBB-crossing capabilities. After traversing the BBB, the nanoparticle delivers PTX to the tumor site, exerting an anti-glioma effect. Notably, the redox-responsiveness of the nanoparticle significantly inhibits glioma cell proliferation.

5.4.3. Photo-response

Photo-responsive TDDSs employ light-sensitive materials to regulate drug release. The combination of drugs with these materials enables precise control of drug delivery when exposed to specific light wavelengths, potentially reducing side effects and enhancing therapeutic efficacy. Jing *et al.* [223] developed a novel near-infrared light (NIR)-activated photo-sensitive drug comprising upconversion nanoparticles (UCNPs), Pluronic F127 (F127), and Cur. The resulting UCNPs-F127@Cur demonstrated enhanced deep tissue penetration, significantly improving curcumin's bioavailability and photodynamic therapy efficiency. This hybrid nanodrug notably increased the apoptosis rate of GSCs, elevated intracellular ROS levels, downregulated GSC-associated gene expression, and inhibited GSC tumor growth *in vivo* when exposed to specific excitation light wavelengths.

6. Conclusion and prospects

Glioma, the most common malignant primary brain tumor in adults, is characterized by a low survival rate and poor prognosis. Currently, no treatments have completely eradicated glioma. In addition to the widely used chemotherapeutic agent TMZ, numerous NPs and their synthetic derivatives have demonstrated the ability to inhibit glioma growth. These compounds include matrine (**1**), berberine (**3**), curcumin (**9**), triptolide (**19**), shikonin (**30**), and plumbagin (**31**). Synthetic derivatives, such as harmine derivative compound **39**, colchicine derivative compound **40**, ortataxel (**56**), cabazitaxel (**57**), and curcumin derivative compound **67**, have also shown efficacy. These substances inhibit glioma growth through various mechanisms, including cell cycle arrest, apoptosis induction, and autophagy activation. They also block glioma-related signaling pathways such as AKT/mTOR, PI3K/AKT, and Wnt/β-catenin, while suppressing invasion, migration, and angiogenesis. The therapeutic potential of these NPs and their synthetic derivatives in inhibiting glioma growth renders them promising candidates for glioma treatment.

In the development of anti-glioma drugs, several crucial aspects warrant emphasis: (1) The capacity of drugs to traverse the BBB should be a primary consideration. (2) It is essential to identify and investigate additional NPs with the potential for optimization or significant anti-glioma effects as lead compounds. (3) Researchers should fully leverage the properties of NPs and modify their structures to create highly efficient, low-toxicity therapeutic agents. (4) There is a need to establish more accessible and effective models for evaluating the efficacy of glioma therapeutics. (5) Efforts should focus on enhancing the efficacy of existing chemotherapeutic drugs, minimizing toxicity, and addressing drug resistance.

While NPs and their synthetic derivatives have played a significant role in anti-glioma therapy, substantial challenges remain in their clinical application for glioma treatment. There is an urgent need for medications that can effectively penetrate the BBB and selectively target the lesion site. However, the BBB presents a formidable obstacle for most drugs to effectively reach and accumulate at the glioma site. To address this challenge, researchers have developed an array of novel materials and technologies aimed at enhancing the delivery of brain-targeted pharmaceuticals by modulating the BBB in a controlled and non-invasive manner. Among these approaches, TDDSs have demonstrated significant potential. The advantages of TDDSs are primarily manifested in four aspects: (1) They facilitate efficient BBB crossing for NPs. (2) They enhance the solubility, bioavailability, and stability of NPs *in vivo*. (3) Certain TDDSs, such as those responsive to the TME, can mitigate the side effects of NPs. (4) They promote selective targeting of NPs to the tumor site.

Nevertheless, TDDSs face several challenges, including restricted drug loading capacity, potential toxicity of carrier materials, and high production costs, which have hindered their widespread clinical adoption. Encouragingly, ongoing advancements in preparation processes, novel materials, and modifiers are gradually addressing these issues. It is anticipated that the full potential of TDDSs will be realized in future applications.

The integration of natural medicinal chemistry, pharmacology, pharmacokinetics, and nanotechnology research has facilitated significant advancements in anti-glioma NPs. This interdisciplinary approach shows promise for the future development of highly effective and low-toxicity novel drugs for glioma treatment.

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Supplementary Information

Supplementary data to this article can be obtained by sending E-mail to the corresponding authors.

Declaration of competing interest

These authors have no conflict of interest to declare.

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