

Table 2: Most prominent therapeutic applications and effects using C6 glioma model.

Therapy	In vitro/ vivo	Experimental design	Effects	Reference
Ibuprofen	In vivo	C6/LacZ rat glioma cells into the Wistar rats brain – two treatment groups	Growth inhibition	Dagestan et al. 2012 ⁶⁴
Hyperbaric oxygen (HBO) and temozolomide (TMZ)	In vivo	stereotactic injection of C6/LacZ rat glioma cells into the Wistar rats brain – treatment with HBO, TMZ and a combination of them. Intra-/peri-tumoural vessels, microendothelial proliferations, immunohistochemistry and necrotic area, were evaluated.	Growth inhibition	Dagistan et al. 2012 ⁶⁵
Serine protease urokinase plasminogen activator (uPA), and matrix metalloproteases (MMP-2 / MMP-9)	In vivo/in vitro	Determination of MMP-2, MMP-9, uPAR and uPA in the tumour core and of infiltration zone in vitro C6 glioma cells and in an in vivo orthotopic C6 glioma model in Sprague Dawley rats	Growth and invasion inhibition	Schuler et al. 2012 ⁶⁶
Resveratrol-loaded lipid-core nanocapsules	In vitro/in vivo	RSV-LNC (5 mg/kg/day, i.p.) for 10 days in rats with orthotopic C6 tumours	Growth inhibition	Figueiró et al. 2013 ⁶⁷
Transferrin (Tf)-modified poly ethyleneglycol-poly lactic acid (PEG-PLA) nanoparticles conjugated with resveratrol	In vivo/in vitro	Tf-PEG-PLA-RSV administered in vitro and in vivo in C6 orthotopic glioma model of Wistar rats	Growth inhibition	Guo et al. 2013 ⁶⁸
Diruthenium-Ibuprofen compound	In vivo	The compound was tested in the rat C6 orthotopic glioma model in vivo	Growth inhibition	Benadiba et al. 2014 ⁶⁹
EGFP-EGF1-conjugated nanoparticles (ENPs)	In vitro and in vivo	Balb/c mice –nanoparticles with a fusion protein derived from factor VII facilitate anti-glioma delivery of paclitaxel by targeting both neovascular and glioma cells	cell apoptosis and tumour necrosis	Zhang et al. 2014 ⁷⁰
diruthenium-GLA complex (Ru2GLA)	In vivo/in vitro	Administration of Ru2GLA in an orthotopic C6 glioma model in Wistar rats	C6 cell proliferation in vivo and the changes in tumour morphology	Miyake et al. 2014 ⁷¹
Photodynamic therapy (PDT) and temozolomide	In vivo	The expression of P-glycoprotein (P-gp) in endothelial cells was investigated after treating glioma bearing Wistar rats with temozolomide, PDT or a combination of them	Growth inhibition	Zhang et al. 2014 ⁷²
Resveratrol	In vivo / in vitro	Oral administration of resveratrol in orthotopic glioma model of Wistar rats. The expression of EGFR, GFAP, PCNA, MMP-9, NF-κB, COX-2 and VEGF was investigated	Growth inhibition	Wang et al. 2015 ⁷³
Dopamine	In vivo	reprogramming M2-polarized macrophages	Growth inhibition and vascular normalization	Qin et al. 2015 ⁷⁴
Dimethylaminomicheliodide (DMAMCL)	In vivo/in vitro	Oral administration of DMAMCL in a subcutaneous glioma model in Wistar rats	Growth inhibition	An et al. 2015 ⁷⁵
Lapachol	In vivo / in vitro	Intragastric administration of lapachol in Wistar rats with C6 orthotopic glioma model. Proliferation, apoptosis, DNA damage, topoisomerase I (TOP I) and topoisomerase II (TOP II) activities were detected	Growth inhibition, possibly through inhibiting TOP I and TOP II expression	Xu et al. 2016 ⁷⁶
Anti-vascular endothelial growth factor receptor-1 monoclonal antibody	In vivo	Influence of D16F7 on glioma growth and angiogenesis in vivo using C6 glioma cells transfected with the human VEGFR-1	Growth inhibition and anti-angiogenic effect	Atzori et al. 2017 ⁷⁷
Flavonoid FLA-16	In vivo / in vitro	Intraperitoneal administration of FLA-16 in an intracranial and subcutaneous C6 glioma model in Wistar rats or BALB/c nude	Growth inhibition through CYP4A inhibition by flavonoid FLA-16. Normalization of tumour vasculature through down-regulation of TAMs and EPCs-derived VEGF and TGF-β via PI3K/Akt signaling	Wang et al. 2017 ⁷⁸
Lactoferrin modified daunorubicin plus honokiol liposomes	In vivo / in vitro	Action mechanism studies were performed on BBB model, brain glioma cells and glioma-bearing mice	Growth and invasion inhibition	Liu et al. 2017 ⁷⁹

HBO: Hyperbaric oxygen, TMZ: temozolomide, uPA: urokinase plasminogen activator, MMP: matrix metalloproteases, RSV-LNC: resveratrol-loaded lipid-core nanocapsules, Tf: transferrin, PEG-PLA: modified polyethylene glycol-polylactic acid, ENPs: EGFP-EGF1, Ru2GLA: diruthenium- gamma-linolenic acid complex, PDT: photodynamic therapy, P-gp: P-glycoprotein, GFAP: glial fibrillary acidic protein, PCNA: proliferating cell nuclear antigen, NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells, COX-2: cyclooxygenase-2, VEGF: vascular endothelial growth factor, VEGFR-1: vascular endothelial growth factor receptor-1, DMAMCL: dimethylaminomicheliodide, TOP: topoisomerase, FLA-16: flavonoid-16, CYP4A: cytochromes P450 family, TAMs: tumor-associated macrophages, EPCs: endothelial progenitor cells, TGF-β: transforming growth factor beta, PI3K/Akt signaling: phosphatidylinositol-4,5-bisphosphate 3-kinase/ protein kinase B signaling, BBB: blood-brain barrier.