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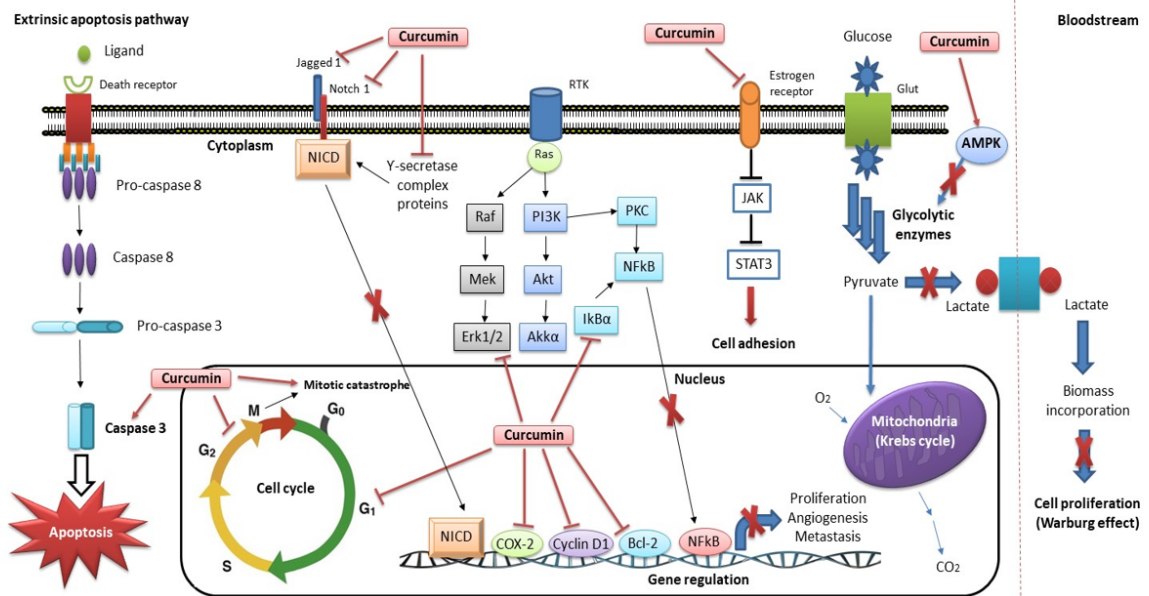
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Journal Pre

## Therapeutic potentials of curcumin in the treatment of glioblastoma

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**Abstract**

Glioblastoma multiforme (GBM), a greatly aggressive malignancy of the brain, is correlated with a poor prognosis and low rate of survival. Up to now, chemotherapy and radiation therapy after surgical approaches have been the treatments increasing the survival rates. The low efficacy of mentioned therapies as well as their side-effects has forced researchers to explore an appropriate alternative or complementary treatment for glioblastoma. In experimental models, it has been shown that curcumin has therapeutic potentials to fight against GBM. Given that curcumin has pharmacological effects against cancer stem cells, as major causes of resistance to therapy in glioblastoma cells. Moreover, it has been showed that curcumin exerts its therapeutic effects on GBM cells via affecting on apoptosis, oxidant system, and inflammatory pathways. Curcumin would possess a synergistic impact with chemotherapeutic agents. Herein, we summarized the current findings on curcumin as therapeutic agent in the treatment of GBM.

**Keywords:** Curcumin, Glioblastoma, Therapy

## 1. Introduction

Gliomas are the most common primary brain tumors in adults, which results from astrocytes or glial precursors transformation. Glioblastoma or glioblastoma multiform (GBM) is the most frequent, aggressive and high-grade (grade IV) form of glioma that occurs in brain or spinal cord. Despite all remarkable progressions in neurosurgery, drug (gene and cell therapy, boron neutron capture therapy, nanotechnology-based therapies) and radiation, various cancer such treatment is still an important concern and the chance of treatment is not promising [1-5]. The usual span of survival following diagnosis is almost fewer than 5 years [6, 7]. The cellular and molecular origin of GBM is not yet fully understood. But, it was shown that dysregulation of cellular signaling pathways and genetic mutations can play a critical role in cancer ignition, invasion and progression. For instance, the hyperactivation of PI3 kinase pathway, mutation in retinoblastoma and *p53* genes, and overexpression of epidermal growth factor receptor (EGFR) were reported in GBM cases [8-10].

From past decades, herbal and natural compounds or their derivatives have attracted much attention as promising therapeutic agents to treat human malignancies, especially cancers. Curcumin is an herbal supplement originating from turmeric (root of the rhizome *Curcuma longa*) and belongs to curcuminoids group, which are plant phenols metabolites causing yellow color in turmeric [11, 12]. Chemically, curcumin is a natural linear diarylheptanoid consisting of two aromatic rings which bind to a heptane with various substitutions. Schematic 1 shows the molecular structure of curcumin [13]. Without any doubt, curcumin plays pivotal roles in various biological processes by its pharmaceutical benefits to remedy diseases. Strong evidences have approved that this polyphenol compound possesses immense biological activities, including anti-oxidant, anti-inflammatory[14], cardioprotective [15], neuroprotective [16], as well as anti-cancer [17]. It is worth notice that lipophilic properties of curcumin and its ability to cross into blood brain barrier (BBB) make it an efficient

therapeutic and protective agents in CNS-related disorders and malignancies, including Alzheimer's [18], Parkinson [19] and GBM [20].

Despite the significant beneficial effects of curcumin, the low bioavailability impedes its wide utilization in medicinal and pharmaceutical applications. To overcome this drawback, many efforts have been focused on developing novel curcumin derivatives, such as demethoxycurcumin (DMC), tetrahydrocurcumin (THC), turmerones and bisdemethoxycurcumin. In comparison to curcumin, altering some substitutions causes an improvement in their bioavailability and biological activities.

Emerging nanotechnological strategies have caused a significant progress in many sciences, including biology and medicine. In order to improve the bioavailability and efficacy of curcumin and its analogues, nanomaterials are used as carriers for their drug delivery. Up to now, many researchers have been interested in curcumin, its analogues and also their related delivery systems to treat many cancers, particularly GBM.

The purpose of this review is to summarize current researches on curcumin in GBM therapy. The curcumin roles and molecular mechanisms involved in GBM treatment have been well introduced. Then, the investigations related to curcumin analogues and curcumin delivery systems for GBM cells have been addressed.

## **2. Curcumin as a therapeutic agent in Glioblastoma**

From the past centuries, products derived from nature have been used for wound healing and disease treatment. Recently, the health application and benefits of these natural compounds have become an attractive research field in modern medicine [21]. Many natural-based components have been identified potentially used in medical applications and disease treatment. Due to intrinsic properties, some of them can penetrate BBB, which is one of the principal consideration for developing drugs for central nervous system (CNS) [22, 23].

Curcumin is an example of natural pharmaceutical compounds which is able to permeate BBB and mainly accumulates in hippocampus. As for abundant amounts of lipids in brain, the lipophilic nature of curcumin causes favorable absorption, availability as well as maintenance in CNS [24]. Numerous studies have investigated the wide range of curcumin pharmaceutical effects, such as anti-microbial, anti-inflammatory, anti-oxidant and especially anti-cancer [25-27]. Regarding this, curcumin has been reported as an effective anti-tumor agent against GBM (**Figure 1**), the most lethal primary CNS tumor [28, 29].

Many evidences have shown the curcumin ability to arrest cell proliferation and induce apoptosis in various cancers, such as colon cancer [30], lung cancer [31], breast cancer [32], melanoma [33] , as well as GBM [34]. The apoptotic function of curcumin is related to induce ROS production, caspases activation and mitochondrial membrane permeability and so on [35, 36]. Ambegaokar and colleagues reported that curcumin could inhibit proliferation and induce apoptosis of GBM cell line. The mechanisms would be either p53 and caspase 3 activation or decreasing anti-apoptotic genes, including AP-1, NF- $\kappa$ B and Bcl2 [37]. Curcumin attenuates cell proliferation and overcomes radioresistant and chemoresistant GBM cells. The molecular mechanisms of this action are related to AP-1 and NF- $\kappa$ B pathways through inhibition of JNK and AKT activation. The decreased expression of bcl-2, and DNA repair enzymes, such as MGMT, ERCC-1, DNA-PK, Ku70 and Ku80 lead to the resistance of glioma cells against radiation and chemotherapeutic agents; however, these cells are sensitive to curcumin. Subsequently, this feature proposes that curcumin is potentially useful as an adjuvant with common chemotherapeutic agents and radiation in GBM treatment [27].

It has been reported that curcumin inhibits migration and invasion in GBM cell line U87. A 6 hours exposure of 10 $\mu$ M curcumin causes a significant decrease in Fascin protein expression by inhibiting STAT3 pathway. A reduction in Fasin expression results in cell shape alternation and filopodia formation reduction in U87 cells [38]. Fascin is an acting binding

protein involved in F actin aggregation, cellular cytoskeleton rearrangement and cell motility. The Fascin expression is associated with invasive behavior of cancer cells, including GBM cells [39]. Of note, the ability of cells for attachment, invasion and migration shows a negative correlation with curcumin concentration and exposure time [40]. Molecular mechanisms and related signaling pathways of anti-tumor properties of curcumin in GBM have been scrutinized. For this purpose, three core pathways investigated in GBM include: 1) the p53 pathway (p53, p21 and cdc2 proteins), 2) PI3kinase pathway (EGFR, Ras, mTOR, PTEN and Akt), and 3) RB pathway (CDKN2A/16 and RB proteins). In a time and dose dependent manner, curcumin either promotes p53 signaling through increasing p53 and p21 and decreasing cdc2 proteins or reduces RB pathway by increasing and decreasing CDKN2A/p16 and phosphorylated RB, respectively. But, it has no significant effect on expression of PI3Kinase of mentioned proteins. Also, it has been shown that increased concentration of curcumin may induce morphological changes in cells, from a flat and columnar shape to small and shrink cells. Furthermore, the cells population arrested in G2/M phase are increased significantly with elevating curcumin concentration and exposure time in DBTRG cell line [41]. Regardless PTEN and p53 mutational status, curcumin inhibits survival pathways, PI3kinase and NF-kB, and bcl-xl, an anti-apoptotic protein. Moreover, curcumin exerts a synergic effects with cis-platin and doxorubicin to reduce GBM tumor size *in vivo* [42].

Perry and colleagues reported anti-carcinogenesis features of curcumin in GBM xenografts. Curcumin administration decreases metalloproteinase-9, gelatinolytic activities, and endothelial cell markers which is an indication of decreased angiogenesis [20]. Furthermore, the restrained effects of curcumin on proliferation, colony formation, migration and tumor size have been evaluated in glioma cell lines and mice model. Curcumin treatment leads to downregulation of SHH/GLI1 signaling (GLI1, Smo and Shh), CyclinD1, Bcl-2 and Foxm1



*in vitro*. It also increases the Bax/Bcl2 ratio, leading to induce apoptosis in tumor cells. Curcumin restrains tumor cells and prolongs the survival period of U87-implanted nude mice compared to control subjects through SHH/GL1 signaling pathway [43].

MicroRNAs (miRNAs) are a class of small non-coding RNAs which play critical roles in post-transcriptional gene regulation. Due to miRNA roles in the regulation of cellular processes and pathways, their aberrant expression can lead to serious malignancies, including cancers [44, 45]. Evaluating the expression of miR-378 revealed that this miRNA is significantly expressed in lower levels in brain tumor tissues. Eventually, miR-378 acts as a tumor suppressor miRNA and inhibits malignant characteristics of glioma [46]. Furthermore, miR-378 enhances the anti-tumor effects of curcumin, and GBM cells response to curcumin treatment through mediating p38 mitogen-activated protein kinase [47]. MiRNA-21 is a well-known oncogene miRNA which is a key regulator in GBM progression [48]. Curcumin reduces pri-miR-21 promoter activity *via* binding to AP1, a transcription factor activating its promoter [49]. Also, curcumin decreases the carcinogenicity of GBM cells through inhibition of miR-21 and anti-apoptotic proteins, and enhances the expression of pro-apoptosis proteins as well as microtubule-associated protein light chain 3-II (LC3-II) expression [50].

Cancer stem cells (CSCs), a small population in tumor environment, are responsible for tumor developing, progression, recurrence and drug resistance in cancers, including GBM [51]. Mounting evidences suggest that curcumin is able to target glioma CSCs through molecular pathways involved in self-renewal. Exposure of glial CSCs to curcumin results in differentiation and self-renewal dysfunction. In glial CSCs, the neurospheres forming ability and neural stem/progenitor markers (CD133 and Nestin) expression are also repressed by treatment of curcumin, even at low concentration (2 $\mu$ M) [52]. Meanwhile, curcumin (2.5 $\mu$ M) makes a remarkable arrest in GBM stem cells *via* MAPK pathway activation, STAT3 and IAP inhibition, and in a ROS-dependent approach. Thus, curcumin potentially prevents GBM

recurrence through anti-proliferative effects on stem cells [53]. **Table 1** illustrated the anti-tumor effects of curcumin in GBM.

### 2.1. Curcumin analogues

Without doubt, curcumin has beneficial effects on inhibition of tumor cell growth. Despite remarkable anticancer features of curcumin, its application in experimental and clinical practices has been restrained due to its poor oral bioavailability and solubility in water. These drawbacks have pushed researchers to develop curcumin derivatives which are as effective as curcumin even at micromolar dosage [78].

There are three sectors in the curcumin structure which have been modified in order to produce an “improved curcumin.” These contain the aromatic rings, the -diketone moiety, and the two flanking double bonds conjugated to the latter. Synthesis of analogues can improve anticancer potential to target different processes or stages in cancer cells. Structure activity relationship (SAR) analysis suggests that a variety of structural types are tolerated for potency [79].

The curcuminoids such as curcumin, demethoxy curcumin and bisdemethoxycurcumin were isolated from the dichloromethane extraction by chromatography. The pyrazole analogues could be prepared by treating the CH<sub>2</sub>Cl<sub>2</sub> extract with hydrazine hydrate in acetic acid and purification by chromatography to give pyrazole derivatives [80]. The isoxazole analogues were prepared by treating the CH<sub>2</sub>Cl<sub>2</sub> extract with hydroxylamine hydrochloride in acetic acid and purification by chromatography. All the compounds demonstrated antioxidant effect; while, among them the pyrazole analogue was showed to be more potent than curcumin but the potential of isoxazole analogue was equipotent to curcumin [81].

## 2.2. Curcumin analogues as powerful tools in glioblastoma therapy

To date, the curcumin analogues have attracted many attentions to be used as anti-cancer agents against a plethora of cancers, including GBM (**Figure 2**). The DMC, THC, turmerones and bisdemethoxycurcumin are considered as curcumin analogues inducing inflammatory and anti-proliferative signals *via* inducing reactive oxygen species (ROS), and potentially can be used as chemoprotective components for cancer treatment [82]. It was investigated that DMC concentration 50µg/ml could induce ROS production, majorly superoxide anion radical ( $O_2^-$ ), and following apoptosis in U87 cells. Based on bioinformatics analysis, DMC could interact with active site residues of mitochondrial superoxide dismutase (mnSOD) and inhibit its activity, resulting in  $O_2^-$  accumulation in cells. In that study, exposure to DMC lead to suppression of PI3kinase/NF-κB signaling and activation of caspase-8 and caspase-9 to release cytochrome *c*, resulting in cell growth arrest and apoptosis in human glioma U87 MG cells [83]. Furthermore, it was revealed that DMC treatment induces G2/M cell arrest and apoptosis through activation of Bcl-2 in those cells [84]. In addition to induction of ROS generation, DMC not only decreased the expression of CDC25C, Cyclin B1 and CDK1 leading to G2/M cell arrest, but also increased ubiquitination and proteasome degradation in U87 cells [85]. Additionally, DMC showed cytotoxic activities against GBM 4801 cells, a human malignant GBM cell line. DMC has been observed to reduce the mitochondrial membrane potential (MMP), and to increase DNA fragmentation and apoptosis *via* activation of caspase-3 and caspase-9 in GBM cell lines. It also inhibits NF-κB signaling pathway, and contributes to arrest cells in SubG0/G1 cell phase [86]. ATP-binding cassette sub-family G member 2 (ABCG2) is a drug transporter overexpressed in glioma stem cells (GSCs), and increases chemotherapy resistance in them [87]. ABCG2 expression showed an inverse correlation with DMC-induced growth inhibition in GSCs, and its suppression resulted in an improvement in DMC efficacy, ROS production and apoptosis induction. This data was also

confirmed in xenograft tumor-bearing mice; the ABCG2 expression was reversely related to anti-tumor effects of DMC on GSCs. These findings suggested ABCG2 expression as a critical mechanism of resistance to DMC and a potential therapeutic target for GBM treatment [88].

Temozolomide (TMZ) is one of the widely used chemotherapeutic agents for GBM treatment, which induces cell apoptosis, cell growth inhibition and autophagy in GBM cells through O<sup>6</sup>-methylguanin formation. Despite impressive antiglioma impacts of TMZ, it cannot effectively inhibit cancer recurrence and CSCs proliferation [89-91]. It was proposed that DMC may be better than TMZ for GSCs therapy, because it could effectively prohibit cell proliferation and activate apoptosis *in vitro* and *in vivo*. The GSCs were negligibly affected by a single dosage of TMZ, however, its combination with DMC synergically increased GSCs apoptosis through modulating ROS generation, caspase-3 signaling activation, and suppression of JAK/STAT3 and PCNA expression [92, 93]. Consistently, Shi et al. showed that DMC more effectively induces cell proliferation arrest and apoptosis activation than TMZ treatment in GBM cell lines and animal model. Similarly, the co-administration of TMZ and DMC synergically results in anti-tumorigenic effects through the same mechanisms presented for GSCs treatment *in vivo* and *in vitro* [94]. Recently, this research group has published contradictory results which refused their previous conclusions. They demonstrated that TMZ is significantly able to induce tumor regression compared to DMC in xenograft GBM mice model. In addition, TMZ has more effective inhibitory effects on expression of Ki67 and proliferating cell nuclear antigen (PCNA). Moreover, only TMZ but not DMC induces a p-AKT decrease and an increase in cleaved caspase-3 and BAX expression [95]. These findings caused a dilemma about DMC and TMZ efficacies in glioblastoma treatment, and it seems that more reliable and accurate researches are needed to clear this ambiguity.

Zhang and colleagues have recently revealed that THC synergically increases radiosensitivity of glioma cells. Therefore, compared to single treatment, a combination therapy of THC and radiation exposure increases apoptosis and G0/G1 cell growth suppression. Also, the S phase cell population and cyclin D1 and PCDNA expression were significantly decreased. Tumor growth was remarkably inhibited in animals treated with combination therapy [96].

Hydrazinobenzoylcurcumin (HBC) is a recently developed derivative of curcumin acting as a  $Ca^{+2}$ /Calmodulin antagonist to inhibit tumor growth in various cancer cells [97, 98]. HBC has a significant role in the suppression of tumorigenic features of GSCs. It not only reduces the self-renewal capacity, migration and invasion, but also promotes caspase-3 and caspase-9 as well as apoptosis process in GSCs. It is worth pointing out that the expression of CD133, Nanog, Sox2 and Oct4, a GSC marker, is considerably decreased due to HBC-induced repression of  $Ca^{+2}$ /Calmodulin-dependent protein kinase II (CaMKII) and c-Met activity [99]. CaMKII modulates many signaling cascades, such as c-Met signaling which is responsible for expression of stemness markers, through activation of ERK1/2, PI3kinase and STAT3 proteins [100, 101]. It was suggested that CaMKII might be a novel therapeutic target to induced apoptosis in GSCs [99]. Table 3 listed various curcumin analogues in GBM therapy.

### 3. Novel therapeutic approaches for curcumin targeting in glioblastoma

Many researches have been clearly approved the chemoprotective and chemotherapeutic effects of curcumin on a wide range of cancers. Although curcumin retards tumor growth, the poor oral bioavailability limits its wide clinical application. It is mainly because of low absorption, rapid metabolisms, as well as rapid elimination from the body [33, 108]. Nanomaterial-mediated targeting system is a promising approach to overcome these problems and raise the possibility of being widely used as a common anticancer therapy [109]. Therefore, developing delivery systems for curcumin has attracted many attentions in recent years. In the following part, recent researches about nanodelivery of curcumin to GBM cells are discussed (**Table 3**).

#### 3.1. Nanoformulation of curcumin

Different types of nanomaterials, such as polymer nanoparticles, polymeric micelles, and liposomes have been used as nanocarriers to deliver curcumin. Bisht et al. developed a polymeric nanoparticle formulation of curcumin (NanoCurc<sup>TM</sup>) that overcomes the major drawback of free curcumin, low bioavailability, and improves treatment efficacy. NanoCurc<sup>TM</sup> is 50nm in size synthesized by encapsulation of curcumin in cross-linked and random copolymers of N-isopropylacrylamide (NIPAAM), N-vinyl-2-pyrrolidone (VP), and poly (ethyleneglycol) monoacrylate (PEG-A). Compared to free curcumin, it showed more solubility in aqueous medium. In addition, its anti-tumorigenic effects on various human cancer cell lines and animal models of human malignancies were remarkable and extremely promising [110, 111]. Also, NanoCurc<sup>TM</sup> showed inhibitory effects on cell proliferation and clonogenicity, and stem-like behavior was examined in GBM and medulloblastoma, as malignant brain tumors. The results showed that this formulation dose-dependently induces a decrease in growth by arresting cells in G2/M cell cycle phase and an apoptotic induction in

various tumor-derived cells, including DAOY, D283Med, GBM neurosphere lines HSR-GBM11 and JHH-GBM14. Furthermore, this polymeric encapsulation of curcumin attenuates clonogenic growth and CD-133-positive stem-like cell population. Downregulation of some immense cellular pathways, including insulin like growth factor, STAT3 as well as Hedgehog signaling pathways can be considered as possible mechanisms for the cellular changes in mentioned cells. Overall, this curcumin nanoparticle is able to inhibit the progression of malignant brain tumors through regulation of cell proliferation, survival and stem cell phenotype [112]. Methoxy polyethylene glycole-poly caprolactone (mPEG-PCL) is an amphiphilic copolymer widely used in medical means and drug delivery systems. Curcumin is loaded in this copolymer to form a core-shell structure. The prepared nanocurcumin is permeated to cells with a significant efficiency through endocytosis mechanism and is localized near the nucleus. In a dose-dependent manner, this nanocurcumin could stimulate pro-apoptosis mechanism in rat model of GBM [113]. Furthermore, curcumin loaded in mPEG-PCL and PCL showed high neuroprotective effects on U251 glioblastoma cells. Treatment of U251 cells and zebrafish embryos with these two nanocurcumins revealed desirable cellular uptake [114].

### **3.1. 1. Solid Lipid Curcumin Particles**

Recently, it was shown that solid lipid curcumin particles (SLCP) more efficiently induce apoptosis and anti-tumorigenesis effects than free curcumin on GBM. Besides, the SLCP causes an enhancement in autophagy markers (Atg5, Atg7, Beclin-1, LC3A/B-I and LC3A/B-II) and cell survival markers. Inversely, PI3kinase pathway (PI3kp85, p-PI3kp85, total AKT, p-AKT, mTOR and P-mTOR) and cell death markers are increased after treatment of cells with SLCP. Subsequently, the authors demonstrated that SCLP could be a non-dangerous and effective carrier for therapeutic application by autophagy regulation in GBM cells [115].

### 3.1.2. Cucurmin-loaded lipid-core nanocapsules

Cucurmin-loaded lipid-core nanocapsules (C-LNCs) has been developed to overcome low bioavailability of curcumin and improve anti-tumor properties of curcumin. Release of curcumin from lipid nanocarrier was efficiently controlled in C6 and U251MG cells. Furthermore, C-LNC shows more cytotoxic effects compared to non-capsulated curcumin *in vitro*. Arresting in G2/M cell cycle phase and autophagy induction were reported in cells treated with C-LNC and free-curcumin. As well, an *in vivo* investigation indicated a significant decrease in brain tumor size and a prolonged survival compared to animals injected with same dose of non-capsulated curcumin [116]. Phytosome, a complex of a natural (usually herbal) compound and a phospholipid, is appropriate to be used as drug delivery system [117]. Curcumin Phytosome Meriva (Meriva®) has been used in more than 25 clinical trials. It yields 29-times better absorption and higher bioavailability than free curcumin [118]. It was reported that GBM -antibody-linked curcumin (CC) and Meriva® could complete remission in approximately 60% of GBM mice models. One possible mechanism can be repolarizing tumor-associated microglia/macrophages (TAM) from the tumor-promoting M2 type to tumoricidal M1-type [119-121]. Also, Meriva® treatment induces 50%-60% of the TAM and activates natural killer cells (NK) to GBM microenvironment. Downregulation of M2-linked tumor-promoting proteins (STAT3, ARG1 and IL10), induction of M1-linked anti-tumor proteins (STAT1 and nitric oxide synthase) in the TAM, clearance of CD133 (+) GBM stem cells and activation of apoptosis through caspase-3 in tumor cells were introduced as potential mechanisms in Meriva®-mediated treatment of mice bearing GBM GL261 cells.

### 3.1.3. Polysaccharide nanoparticles



Two opposite polysaccharides mixing in aqueous solution causes electrostatic interactions and subsequently, polysaccharide nanoparticles (PSNPs) are spontaneously formed [122]. Chitosan (CS) is an amino polysaccharide with linear structure. It is found in nature, and promising future for its utilization in clinical practice can be considered. The positive charge at natural and acidic pH provides PSNPs preparation [123]. Hyaluronic acid (HA) also called hyaluronan, is a negatively charged and non-sulfated glycosaminoglycan having ability to bind CD44 receptor overexpressed in a plethora of cancers [124]. Lactoferrin (Lf) is a positively charged and iron-binding glycoprotein in mammals. BBB and glioma cells express its receptor on their surfaces and facilitate Lf transportation [125]. In a study conducted by Xu et al., in order to provide non-invasive and efficient treatment for GBM, HA and CS hydrochloride (as negatively and positively charged polysaccharides, respectively) were used to form PSNPs as a carrier for curcumin. In addition to PSNPs, further functionalization with Lf caused a dual targeting drug delivery of curcumin to cross BBB and target glioma cells. *In vivo* and *in vitro* studies have reported that Lf-curcumin-PSNPs could cross the BBB efficiently. The results show that Lf-curcumin-PSNPs could target and accumulate in brain tumor after increased BBB crossing, hence it has a vast potential to be used in CNS-related malignancies therapy [126]. Another study carried out by Yang et al., revealed the potential of PSNP-based HA/CS polysaccharides to delivery curcumin against GBM cells. Compared to non-capsulated curcumin, curcumin-PSNP significantly induces cytotoxicity and higher uptake in C6 cell line. Active endocytosis, micropinocytosis, clathrin-, CD44- and caveolae-mediated endocytosis may be involved in curcumin-PSNP uptake in C6 cells [127].

Overall, further investigations are required to prove the effectiveness of mentioned nano-based delivery systems of curcumin in the therapy of GBM.

#### 4. Conclusion

As mentioned earlier, GBM implicates multimodality clinical therapies, such as radiotherapy, chemotherapy and surgery. Malignant gliomas often show radio- and chemo-resistance. Due to the diffuse and aggressive nature of this cancer, and because of poor outcomes of standard therapies, efficient therapeutic methods for GBM treatment are still required. Curcumin has shown beneficial anticancer effects in various malignancies, including GBM. The synergistic impacts of curcumin with radiotherapy and chemotherapy revealed its potential for GBM therapy. Application of this natural compound in combination therapy for affected individuals has a promising future.

#### 5. List of abbreviations

GBM	Glioblastoma or glioblastoma multiform
DMC	Demethoxycurcumin
THC	Tetrahydrocurcumin
CNS	Central nervous system
BBB	Blood brain barrier
miRNAs	MicroRNAs
LC3-II	Light chain 3-II
mnSOD	Mitochondrial superoxide dismutase
MMP	Mitochondrial membrane potential
ABCG2	ATP-binding cassette sub-family G member 2

GSCs	Glioma stem cells
TMZ	Temozolomide
PCNA	Proliferating cell nuclear antigen
HBC	Hydrazinobenzoylcurcumin
CaMKII	Ca <sup>+2</sup> /Calmodulin-dependent protein kinase II
NIPAAM	N-isopropylacrylamide
VP	N-vinyl-2-pyrrolidone
PEG-A	Poly (ethyleneglycol) monoacrylate
mPEG-PCL	Methoxy polyethylene glycol-poly caprolactone
SLCP	Solid lipid curcumin particles
C-LNCs	Curcumin-loaded lipid-core nanocapsules
TAM	Tumor-associated microglia/macrophages
PSNPs	Polysaccharide nanoparticles
CS	Chitosan
HA	Hyaluronic acid
Lf	Lactoferrin

## References

- [1] N. Hashemi Goradel, F. Ghiyami-Hour, S. Jahangiri, B. Negahdari, A. Sahebkar, A. Masoudifar, H. Mirzaei, Nanoparticles as new tools for inhibition of cancer angiogenesis, *233* (2018) 2902-2910.
- [2] Z. Saadatpour, G. Bjorklund, S. Chirumbolo, M. Alimohammadi, H. Ehsani, H. Ebrahiminejad, H. Pourghadamyari, B. Baghaei, H.R. Mirzaei, A. Sahebkar, H. Mirzaei, M. Keshavarzi, Molecular imaging and cancer gene therapy, *Cancer gene therapy*, (2016).
- [3] H. Mirzaei, A. Sahebkar, L.S. Sichani, A. Moridikia, S. Nazari, J. Sadri Nahand, H. Salehi, J. Stenvang, A. Masoudifar, H.R. Mirzaei, M.R. Jaafari, Therapeutic application of multipotent stem cells, *Journal of cellular physiology*, *233* (2018) 2815-2823.
- [4] H.R. Mirzaei, A. Sahebkar, R. Salehi, J.S. Nahand, E. Karimi, M.R. Jaafari, H. Mirzaei, Boron neutron capture therapy: Moving toward targeted cancer therapy, *Journal of cancer research and therapeutics*, *12* (2016) 520-525.
- [5] H.R. Mirzaei, H. Mirzaei, S.Y. Lee, J. Hadjati, B.G. Till, Prospects for chimeric antigen receptor (CAR) gammadelta T cells: A potential game changer for adoptive T cell cancer immunotherapy, *Cancer letters*, *380* (2016) 413-423.
- [6] D. Krex, B. Klink, C. Hartmann, A. von Deimling, T. Pietsch, M. Simon, M. Sabel, J.P. Steinbach, O. Heese, G. Reifenberger, Long-term survival with glioblastoma multiforme, *Brain*, *130* (2007) 2596-2606.
- [7] A. Eramo, L. Ricci-Vitiani, A. Zeuner, R. Pallini, F. Lotti, G. Sette, E. Pilozi, L.M. Larocca, C. Peschle, R. De Maria, Chemotherapy resistance of glioblastoma stem cells, *Cell death and differentiation*, *13* (2006) 1238.
- [8] K. Watanabe, O. Tachibana, K. Sato, Y. Yonekawa, P. Kleihues, H. Ohgaki, Overexpression of the EGF receptor and p53 mutations are mutually exclusive in the evolution of primary and secondary glioblastomas, *Brain pathology*, *6* (1996) 217-223.
- [9] M. Lino, A. Merlo, PI3Kinase signaling in glioblastoma, *Journal of neuro-oncology*, *103* (2011) 417-427.
- [10] E. Poch, R. Miñambres, E. Mocholí, C. Ivorra, A. Pérez-Aragó, C. Guerri, I. Pérez-Roger, R.M. Guasch, RhoE interferes with Rb inactivation and regulates the proliferation and survival of the U87 human glioblastoma cell line, *Experimental cell research*, *313* (2007) 719-731.
- [11] B.B. Aggarwal, C. Sundaram, N. Malani, H. Ichikawa, Curcumin: the Indian solid gold, in: *The molecular targets and therapeutic uses of curcumin in health and disease*, Springer, 2007, pp. 1-75.
- [12] K.M. Nelson, J.L. Dahlin, J. Bisson, J. Graham, G.F. Pauli, M.A. Walters, The essential medicinal chemistry of curcumin: miniperspective, *Journal of medicinal chemistry*, *60* (2017) 1620-1637.
- [13] F. Payton, P. Sandusky, W.L. Alworth, NMR study of the solution structure of curcumin, *Journal of natural products*, *70* (2007) 143-146.
- [14] V.P. Menon, A.R. Sudheer, Antioxidant and anti-inflammatory properties of curcumin, in: *The molecular targets and therapeutic uses of curcumin in health and disease*, Springer, 2007, pp. 105-125.
- [15] G. Srivastava, J.L. Mehta, Currying the heart: curcumin and cardioprotection, *Journal of cardiovascular pharmacology and therapeutics*, *14* (2009) 22-27.
- [16] R. B Mythri, M. M Srinivas Bharath, Curcumin: a potential neuroprotective agent in Parkinson's disease, *Current pharmaceutical design*, *18* (2012) 91-99.
- [17] B.B. Aggarwal, A. Kumar, A.C. Bharti, Anticancer potential of curcumin: preclinical and clinical studies, *Anticancer research*, *23* (2003) 363-398.
- [18] T. Ahmed, A.H. Gilani, Therapeutic potential of turmeric in Alzheimer's disease: curcumin or curcuminoids?, *Phytotherapy Research*, *28* (2014) 517-525.
- [19] J. Pan, H. Li, J.-F. Ma, Y.-Y. Tan, Q. Xiao, J.-Q. Ding, S.-D. Chen, Curcumin inhibition of JNKs prevents dopaminergic neuronal loss in a mouse model of Parkinson's disease through suppressing mitochondria dysfunction, *Translational neurodegeneration*, *1* (2012) 16.

- [20] M.C. Perry, M. Demeule, A. Régina, R. Moumdjian, R. Béliveau, Curcumin inhibits tumor growth and angiogenesis in glioblastoma xenografts, *Molecular nutrition & food research*, 54 (2010) 1192-1201.
- [21] H. Yuan, Q. Ma, L. Ye, G. Piao, The traditional medicine and modern medicine from natural products, *Molecules*, 21 (2016) 559.
- [22] D. Sawmiller, S. Li, M. Shahaduzzaman, A. Smith, D. Obregon, B. Giunta, C. Borlongan, P. Sanberg, J. Tan, Luteolin reduces Alzheimer's disease pathologies induced by traumatic brain injury, *International journal of molecular sciences*, 15 (2014) 895-904.
- [23] A. Ishisaka, S. Ichikawa, H. Sakakibara, M.K. Piskula, T. Nakamura, Y. Kato, M. Ito, K.-i. Miyamoto, A. Tsuji, Y. Kawai, Accumulation of orally administered quercetin in brain tissue and its antioxidative effects in rats, *Free Radical Biology and Medicine*, 51 (2011) 1329-1336.
- [24] Y.-M. Tsai, C.-F. Chien, L.-C. Lin, T.-H. Tsai, Curcumin and its nano-formulation: the kinetics of tissue distribution and blood-brain barrier penetration, *International journal of pharmaceuticals*, 416 (2011) 331-338.
- [25] A. Cianciulli, R. Calvello, C. Porro, T. Trotta, R. Salvatore, M.A. Panaro, PI3k/Akt signalling pathway plays a crucial role in the anti-inflammatory effects of curcumin in LPS-activated microglia, *International immunopharmacology*, 36 (2016) 282-290.
- [26] I. Chattopadhyay, K. Biswas, U. Bandyopadhyay, R.K. Banerjee, Turmeric and curcumin: Biological actions and medicinal applications, *CURRENT SCIENCE-BANGALORE-*, 87 (2004) 44-53.
- [27] K.M. Dhandapani, V.B. Mahesh, D.W. Brann, Curcumin suppresses growth and chemoresistance of human glioblastoma cells via AP-1 and NF $\kappa$ B transcription factors, *Journal of neurochemistry*, 102 (2007) 522-538.
- [28] H. Yin, Y. Zhou, C. Wen, C. Zhou, W. Zhang, X. Hu, L. Wang, C. You, J. Shao, Curcumin sensitizes glioblastoma to temozolomide by simultaneously generating ROS and disrupting AKT/mTOR signaling, *Oncology reports*, 32 (2014) 1610-1616.
- [29] A. Zanotto-Filho, E. Braganhol, K. Klafke, F. Figueiró, S.R. Terra, F.J. Paludo, M. Morrone, I.J. Bristot, A.M. Battastini, C.M. Forcelini, Autophagy inhibition improves the efficacy of curcumin/temozolomide combination therapy in glioblastomas, *Cancer letters*, 358 (2015) 220-231.
- [30] J.J. Johnson, H. Mukhtar, Curcumin for chemoprevention of colon cancer, *Cancer letters*, 255 (2007) 170-181.
- [31] G.R. Pillai, A.S. Srivastava, T.I. Hassanein, D.P. Chauhan, E. Carrier, Induction of apoptosis in human lung cancer cells by curcumin, *Cancer letters*, 208 (2004) 163-170.
- [32] D. Liu, Z. Chen, The effect of curcumin on breast cancer cells, *Journal of breast cancer*, 16 (2013) 133-137.
- [33] H. Mirzaei, G. Naseri, R. Rezaee, M. Mohammadi, Z. Banikazemi, H.R. Mirzaei, H. Salehi, M. Peyvandi, J.M. Pawelek, A. Sahebkar, Curcumin: A new candidate for melanoma therapy?, *International journal of cancer*, 139 (2016) 1683-1695.
- [34] S. Karmakar, N.L. Banik, S.K. Ray, Curcumin suppressed anti-apoptotic signals and activated cysteine proteases for apoptosis in human malignant glioblastoma U87MG cells, *Neurochemical research*, 32 (2007) 2103-2113.
- [35] N.R. Jana, P. Dikshit, A. Goswami, N. Nukina, Inhibition of proteasomal function by curcumin induces apoptosis through mitochondrial pathway, *Journal of Biological Chemistry*, 279 (2004) 11680-11685.
- [36] S. Reuter, S. Eifes, M. Dicato, B.B. Aggarwal, M. Diederich, Modulation of anti-apoptotic and survival pathways by curcumin as a strategy to induce apoptosis in cancer cells, *Biochemical pharmacology*, 76 (2008) 1340-1351.
- [37] S.S. Ambegaokar, L. Wu, K. Alamshahi, J. Lau, L. Jazayeri, S. Chan, P. Khanna, E. Hsieh, P.S. Timiras, Curcumin inhibits dose-dependently and time-dependently neuroglial cell proliferation and growth, *Neuroendocrinology Letters*, 24 (2003) 469-469.

- [38] K.-S. Park, S.-Y. Yoon, S.-H. Park, J.-H. Hwang, Anti-Migration and Anti-Invasion Effects of Curcumin via Suppression of Fascin Expression in Glioblastoma Cells, *Brain tumor research and treatment*, 7 (2019) 16-24.
- [39] A.A. Roma, R.A. Prayson, Fascin expression in 90 patients with glioblastoma multiforme, *Annals of diagnostic pathology*, 9 (2005) 307-311.
- [40] K.S. Park, S.Y. Yoon, S.H. Park, J.H. Hwang, Anti-Migration and Anti-Invasion Effects of Curcumin via Suppression of Fascin Expression in Glioblastoma Cells, *Brain tumor research and treatment*, 7 (2019) 16-24.
- [41] C.-C. Su, M.-J. Wang, T.-L. Chiu, The anti-cancer efficacy of curcumin scrutinized through core signaling pathways in glioblastoma, *International journal of molecular medicine*, 26 (2010) 217-224.
- [42] A. Zanotto-Filho, E. Braganhol, M.I. Edelweiss, G.A. Behr, R. Zanin, R. Schröder, A. Simões-Pires, A.M.O. Battastini, J.C.F. Moreira, The curry spice curcumin selectively inhibits cancer cells growth in vitro and in preclinical model of glioblastoma, *The Journal of nutritional biochemistry*, 23 (2012) 591-601.
- [43] W.Z. Du, Y. Feng, X.F. Wang, X.Y. Piao, Y.Q. Cui, L.C. Chen, X.H. Lei, X. Sun, X. Liu, H.B. Wang, Curcumin Suppresses Malignant Glioma Cells Growth and Induces Apoptosis by Inhibition of SHH/GLI 1 Signaling Pathway in Vitro and Vivo, *CNS neuroscience & therapeutics*, 19 (2013) 926-936.
- [44] A. Movahedpour, N. Ahmadi, Y. Ghasemi, A. Savardashtaki, Z. Shabaninejad, Circulating microRNAs as potential diagnostic biomarkers and therapeutic targets in prostate cancer: Current status and future perspectives, *Journal of cellular biochemistry*, (2019).
- [45] Z. Shabaninejad, F. Yousefi, A. Movahedpour, Y. Ghasemi, S. Dokanehiifard, S. Rezaei, R. Aryan, A. Savardashtaki, H. Mirzaei, Electrochemical-based biosensors for microRNA detection: Nanotechnology comes into view, *Analytical biochemistry*, (2019) 113349.
- [46] B. Li, Y. Wang, S. Li, H. He, F. Sun, C. Wang, Y. Lu, X. Wang, B. Tao, Decreased expression of miR-378 correlates with tumor invasiveness and poor prognosis of patients with glioma, *International journal of clinical and experimental pathology*, 8 (2015) 7016.
- [47] W. Li, W. Yang, Y. Liu, S. Chen, S. Chin, X. Qi, Y. Zhao, H. Liu, J. Wang, X. Mei, MicroRNA-378 enhances inhibitory effect of curcumin on glioblastoma, *Oncotarget*, 8 (2017) 73938.
- [48] M.S. Masoudi, E. Mehrabian, H. Mirzaei, MiR-21: A key player in glioblastoma pathogenesis, *Journal of cellular biochemistry*, 119 (2018) 1285-1290.
- [49] G. Mudduluru, J.N. George-William, S. Muppala, I.A. Asangani, R. Kumarswamy, L.D. Nelson, H. Allgayer, Curcumin regulates miR-21 expression and inhibits invasion and metastasis in colorectal cancer, *Bioscience reports*, 31 (2011) 185-197.
- [50] W.-L. Yeh, H.-Y. Lin, C.-Y. Huang, B.-R. Huang, C. Lin, D.-Y. Lu, K.-C. Wei, Migration-prone glioma cells show curcumin resistance associated with enhanced expression of miR-21 and invasion/apoptosis-related proteins, *Oncotarget*, 6 (2015) 37770.
- [51] J.D. Lathia, S.C. Mack, E.E. Mulkearns-Hubert, C.L. Valentim, J.N. Rich, Cancer stem cells in glioblastoma, *Genes & development*, 29 (2015) 1203-1217.
- [52] W. Zhuang, L. Long, B. Zheng, W. Ji, N. Yang, Q. Zhang, Z. Liang, Curcumin promotes differentiation of glioma-initiating cells by inducing autophagy, *Cancer science*, 103 (2012) 684-690.
- [53] Z.C. Gersey, G.A. Rodriguez, E. Barbarite, A. Sanchez, W.M. Walters, K.C. Ohaeto, R.J. Komotar, R.M. Graham, Curcumin decreases malignant characteristics of glioblastoma stem cells via induction of reactive oxygen species, *BMC cancer*, 17 (2017) 99.
- [54] J.E. Lee, S.S. Yoon, E.Y. Moon, Curcumin-Induced Autophagy Augments Its Antitumor Effect against A172 Human Glioblastoma Cells, *Biomol Ther (Seoul)*, 27 (2019) 484-491.
- [55] B.R. Huang, C.H. Tsai, C.C. Chen, T.D. Way, J.Y. Kao, Y.S. Liu, H.Y. Lin, S.W. Lai, D.Y. Lu, Curcumin Promotes Connexin 43 Degradation and Temozolomide-Induced Apoptosis in Glioblastoma Cells, *The American journal of Chinese medicine*, 47 (2019) 657-674.
- [56] P. Maiti, J. Scott, D. Sengupta, A. Al-Gharaibeh, G.L. Dunbar, Curcumin and Solid Lipid Curcumin Particles Induce Autophagy, but Inhibit Mitophagy and the PI3K-Akt/mTOR Pathway in Cultured Glioblastoma Cells, *International journal of molecular sciences*, 20 (2019).

- [57] M. Garrido-Armas, J.C. Corona, M.L. Escobar, L. Torres, F. Ordonez-Romero, A. Hernandez-Hernandez, F. Arenas-Huertero, Paraptosis in human glioblastoma cell line induced by curcumin, *Toxicology in vitro : an international journal published in association with BIBRA*, 51 (2018) 63-73.
- [58] J. Zhao, J. Zhu, X. Lv, J. Xing, S. Liu, C. Chen, Y. Xu, Curcumin potentiates the potent antitumor activity of ACNU against glioblastoma by suppressing the PI3K/AKT and NF-kappaB/COX-2 signaling pathways, *Oncotargets and therapy*, 10 (2017) 5471-5482.
- [59] Y. Wang, X. Ying, H. Xu, H. Yan, X. Li, H. Tang, The functional curcumin liposomes induce apoptosis in C6 glioblastoma cells and C6 glioblastoma stem cells in vitro and in animals, *Int J Nanomedicine*, 12 (2017) 1369-1384.
- [60] S. Yin, W. Du, F. Wang, B. Han, Y. Cui, D. Yang, H. Chen, D. Liu, X. Liu, X. Zhai, C. Jiang, MicroRNA-326 sensitizes human glioblastoma cells to curcumin via the SHH/GLI1 signaling pathway, *Cancer Biol Ther*, 19 (2018) 260-270.
- [61] S. Mukherjee, J. Baidoo, A. Fried, D. Atwi, S. Dolai, J. Boockvar, M. Symons, R. Ruggieri, K. Raja, P. Banerjee, Curcumin changes the polarity of tumor-associated microglia and eliminates glioblastoma, *International journal of cancer*, 139 (2016) 2838-2849.
- [62] O. Alexandru, A.M. Georgescu, L. Ene, S.O. Purcaru, F. Serban, A. Popescu, C. Brindusa, L.G. Tataranu, V. Ciubotaru, A. Dricu, The effect of curcumin on low-passage glioblastoma cells in vitro, *Journal of cancer research and therapeutics*, 12 (2016) 1025-1032.
- [63] C. Cheng, J.T. Jiao, Y. Qian, X.Y. Guo, J. Huang, M.C. Dai, L. Zhang, X.P. Ding, D. Zong, J.F. Shao, Curcumin induces G2/M arrest and triggers apoptosis via FoxO1 signaling in U87 human glioma cells, *Mol Med Rep*, 13 (2016) 3763-3770.
- [64] H. Wu, Q. Liu, T. Cai, Y.D. Chen, Z.F. Wang, Induction of microRNA-146a is involved in curcumin-mediated enhancement of temozolomide cytotoxicity against human glioblastoma, *Mol Med Rep*, 12 (2015) 5461-5466.
- [65] A. Zanutto-Filho, E. Braganhol, K. Klafke, F. Figueiro, S.R. Terra, F.J. Paludo, M. Morrone, I.J. Bristot, A.M. Battastini, C.M. Forcelini, A.J.R. Bishop, D.P. Gelain, J.C.F. Moreira, Autophagy inhibition improves the efficacy of curcumin/temozolomide combination therapy in glioblastomas, *Cancer letters*, 358 (2015) 220-231.
- [66] H. Yin, Y. Zhou, C. Wen, C. Zhou, W. Zhang, X. Hu, L. Wang, C. You, J. Shao, Curcumin sensitizes glioblastoma to temozolomide by simultaneously generating ROS and disrupting AKT/mTOR signaling, *Oncol Rep*, 32 (2014) 1610-1616.
- [67] P. Langone, P.R. Debata, R. Inigo Jdel, S. Dolai, S. Mukherjee, P. Halat, K. Mastroianni, G.M. Curcio, M.R. Castellanos, K. Raja, P. Banerjee, Coupling to a glioblastoma-directed antibody potentiates antitumor activity of curcumin, *International journal of cancer*, 135 (2014) 710-719.
- [68] B. Wu, X. Yao, X. Nie, R. Xu, Epigenetic reactivation of RANK in glioblastoma cells by curcumin: involvement of STAT3 inhibition, *DNA and cell biology*, 32 (2013) 292-297.
- [69] W. Zhuang, L. Long, B. Zheng, W. Ji, N. Yang, Q. Zhang, Z. Liang, Curcumin promotes differentiation of glioma-initiating cells by inducing autophagy, *Cancer science*, 103 (2012) 684-690.
- [70] A. Zanutto-Filho, E. Braganhol, M.I. Edelweiss, G.A. Behr, R. Zanin, R. Schroder, A. Simoes-Pires, A.M. Battastini, J.C. Moreira, The curry spice curcumin selectively inhibits cancer cells growth in vitro and in preclinical model of glioblastoma, *J Nutr Biochem*, 23 (2012) 591-601.
- [71] C. Senft, M. Polacin, M. Priester, V. Seifert, D. Kogel, J. Weissenberger, The nontoxic natural compound Curcumin exerts anti-proliferative, anti-migratory, and anti-invasive properties against malignant gliomas, *BMC Cancer*, 10 (2010) 491.
- [72] C.C. Su, M.J. Wang, T.L. Chiu, The anti-cancer efficacy of curcumin scrutinized through core signaling pathways in glioblastoma, *Int J Mol Med*, 26 (2010) 217-224.
- [73] M.C. Perry, M. Demeule, A. Regina, R. Moudjian, R. Beliveau, Curcumin inhibits tumor growth and angiogenesis in glioblastoma xenografts, *Mol Nutr Food Res*, 54 (2010) 1192-1201.
- [74] B.H. Choi, C.G. Kim, Y.S. Bae, Y. Lim, Y.H. Lee, S.Y. Shin, p21 Waf1/Cip1 expression by curcumin in U-87MG human glioma cells: role of early growth response-1 expression, *Cancer research*, 68 (2008) 1369-1377.

- [75] K.M. Dhandapani, V.B. Mahesh, D.W. Brann, Curcumin suppresses growth and chemoresistance of human glioblastoma cells via AP-1 and NF $\kappa$ B transcription factors, *Journal of neurochemistry*, 102 (2007) 522-538.
- [76] S. Karmakar, N.L. Banik, S.K. Ray, Curcumin suppressed anti-apoptotic signals and activated cysteine proteases for apoptosis in human malignant glioblastoma U87MG cells, *Neurochemical research*, 32 (2007) 2103-2113.
- [77] S. Karmakar, N.L. Banik, S.J. Patel, S.K. Ray, Curcumin activated both receptor-mediated and mitochondria-mediated proteolytic pathways for apoptosis in human glioblastoma T98G cells, *Neurosci Lett*, 407 (2006) 53-58.
- [78] G. Jayaprakasha, L.J. Rao, K. Sakariah, Antioxidant activities of curcumin, demethoxycurcumin and bisdemethoxycurcumin, *Food chemistry*, 98 (2006) 720-724.
- [79] C.A. Mosley, D.C. Liotta, J.P. Snyder, Highly active anticancer curcumin analogues, in: *The Molecular Targets and Therapeutic Uses of Curcumin in Health and Disease*, Springer, 2007, pp. 77-103.
- [80] S.A. Nouredin, R.M. El-Shishtawy, K.O. Al-Footy, Curcumin analogues and their hybrid molecules as multifunctional drugs, *European journal of medicinal chemistry*, (2019) 111631.
- [81] C. Selvam, S.M. Jachak, R. Thilagavathi, A.K. Chakraborti, Design, synthesis, biological evaluation and molecular docking of curcumin analogues as antioxidant, cyclooxygenase inhibitory and anti-inflammatory agents, *Bioorganic & medicinal chemistry letters*, 15 (2005) 1793-1797.
- [82] S.K. Sandur, M.K. Pandey, B. Sung, K.S. Ahn, A. Murakami, G. Sethi, P. Limtrakul, V. Badmaev, B.B. Aggarwal, Curcumin, demethoxycurcumin, bisdemethoxycurcumin, tetrahydrocurcumin and turmerones differentially regulate anti-inflammatory and anti-proliferative responses through a ROS-independent mechanism, *Carcinogenesis*, 28 (2007) 1765-1773.
- [83] R. Kumar, N. Lal, V. Nemaish, P.M. Luthra, Demethoxycurcumin mediated targeting of MnSOD leading to activation of apoptotic pathway and inhibition of Akt/NF- $\kappa$ B survival signalling in human glioma U87 MG cells, *Toxicology and applied pharmacology*, 345 (2018) 75-93.
- [84] P.M. Luthra, R. Kumar, A. Prakash, Demethoxycurcumin induces Bcl-2 mediated G2/M arrest and apoptosis in human glioma U87 cells, *Biochemical and biophysical research communications*, 384 (2009) 420-425.
- [85] N. Lal, V. Nemaish, P.M. Luthra, Proteasome mediated degradation of CDC25C and Cyclin B1 in Demethoxycurcumin treated human glioma U87 MG cells to trigger G2/M cell cycle arrest, *Toxicology and applied pharmacology*, 356 (2018) 76-89.
- [86] T.-Y. Huang, C.-W. Hsu, W.-C. Chang, M.-Y. Wang, J.-F. Wu, Y.-C. Hsu, Demethoxycurcumin retards cell growth and induces apoptosis in human brain malignant glioma GBM 8401 cells, *Evidence-Based Complementary and Alternative Medicine*, 2012 (2012).
- [87] Q. Jia, X. Zhang, T. Deng, J. Gao, Positive correlation of Oct4 and ABCG2 to chemotherapeutic resistance in CD90+ CD133+ liver cancer stem cells, *Cellular reprogramming*, 15 (2013) 143-150.
- [88] L. Chen, L. Shi, W. Wang, Y. Zhou, ABCG2 downregulation in glioma stem cells enhances the therapeutic efficacy of demethoxycurcumin, *Oncotarget*, 8 (2017) 43237.
- [89] M.J. Clarke, E.A. Mulligan, P.T. Grogan, A.C. Mladek, B.L. Carlson, M.A. Schroeder, N.J. Curtin, Z. Lou, P.A. Decker, W. Wu, Effective sensitization of temozolomide by ABT-888 is lost with development of temozolomide resistance in glioblastoma xenograft lines, *Molecular cancer therapeutics*, 8 (2009) 407-414.
- [90] A.L. Vescovi, R. Galli, B.A. Reynolds, Brain tumour stem cells, *Nature Reviews Cancer*, 6 (2006) 425.
- [91] H. Athanassiou, M. Synodinou, E. Maragoudakis, M. Paraskevaidis, C. Verigos, D. Misailidou, D. Antonadou, G. Saris, K. Beroukas, P. Karageorgis, Randomized phase II study of temozolomide and radiotherapy compared with radiotherapy alone in newly diagnosed glioblastoma multiforme, *Journal of clinical oncology*, 23 (2005) 2372-2377.
- [92] L. Shi, X. Fei, Z. Wang, Demethoxycurcumin was prior to temozolomide on inhibiting proliferation and induced apoptosis of glioblastoma stem cells, *Tumor Biology*, 36 (2015) 7107-7119.



- [93] L. Leng, X. Zhong, G. Sun, W. Qiu, L. Shi, Demethoxycurcumin was superior to temozolomide in the inhibition of the growth of glioblastoma stem cells in vivo, *Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine*, (2016).
- [94] L. Shi, G. Sun, Low-dose DMC significantly enhances the effect of TMZ on glioma cells by targeting multiple signaling pathways both in vivo and in vitro, *Neuromolecular medicine*, 17 (2015) 431-442.
- [95] L. Shi, G. Sun, DMC is not better than TMZ on intracranial anti-glioma effects, *Journal of cellular biochemistry*, 119 (2018) 6057-6064.
- [96] X. Zhang, L. Peng, A. Liu, J. Ji, L. Zhao, G. Zhai, The enhanced effect of tetrahydrocurcumin on radiosensitivity of glioma cells, *Journal of Pharmacy and Pharmacology*, 70 (2018) 749-759.
- [97] J.S. Shim, J. Lee, H.-J. Park, S.-J. Park, H.J. Kwon, A new curcumin derivative, HBC, interferes with the cell cycle progression of colon cancer cells via antagonization of the Ca<sup>2+</sup>/calmodulin function, *Chemistry & biology*, 11 (2004) 1455-1463.
- [98] M. Wu, S.-H. Kim, I. Datta, A. Levin, G. Dyson, J. Li, S. Kaypee, M.M. Swamy, N. Gupta, H.J. Kwon, Hydrazinobenzoylcurcumin inhibits androgen receptor activity and growth of castration-resistant prostate cancer in mice, *Oncotarget*, 6 (2015) 6136.
- [99] H.J. Shin, S. Lee, H.J. Jung, A curcumin derivative hydrazinobenzoylcurcumin suppresses stem-like features of glioblastoma cells by targeting Ca<sup>2+</sup>/calmodulin-dependent protein kinase II, *Journal of cellular biochemistry*, 120 (2019) 6741-6752.
- [100] Y.-y. Wang, R. Zhao, H. Zhe, The emerging role of CaMKII in cancer, *Oncotarget*, 6 (2015) 11725.
- [101] W. Chen, P. An, X.-J. Quan, J. Zhang, Z.-Y. Zhou, L.-P. Zou, H.-S. Luo, Ca<sup>2+</sup>/calmodulin-dependent protein kinase II regulates colon cancer proliferation and migration via ERK1/2 and p38 pathways, *World journal of gastroenterology*, 23 (2017) 6111.
- [102] L. Sansalone, E.A. Veliz, N.G. Myrthil, V. Stathias, W. Walters, Torrens, II, S.C. Schurer, Novel Curcumin Inspired Bis-Chalcone Promotes Endoplasmic Reticulum Stress and Glioblastoma Neurosphere Cell Death, 11 (2019).
- [103] H.J. Shin, S. Lee, H.J. Jung, A curcumin derivative hydrazinobenzoylcurcumin suppresses stem-like features of glioblastoma cells by targeting Ca(2+) /calmodulin-dependent protein kinase II, 120 (2019) 6741-6752.
- [104] J.M. Landeros, F. Belmont-Bernal, A.T. Perez-Gonzalez, M.I. Perez-Padron, P. Guevara-Salazar, I.G. Gonzalez-Herrera, P. Guadarrama, A two-step synthetic strategy to obtain a water-soluble derivative of curcumin with improved antioxidant capacity and in vitro cytotoxicity in C6 glioma cells, *Materials science & engineering. C, Materials for biological applications*, 71 (2017) 351-362.
- [105] L. Shi, G. Sun, Low-Dose DMC Significantly Enhances the Effect of TMZ on Glioma Cells by Targeting Multiple Signaling Pathways Both In Vivo and In Vitro, *Neuromolecular medicine*, 17 (2015) 431-442.
- [106] L. Shi, X. Fei, Z. Wang, Demethoxycurcumin was prior to temozolomide on inhibiting proliferation and induced apoptosis of glioblastoma stem cells, *Tumour biology : the journal of the International Society for Oncodevelopmental Biology and Medicine*, 36 (2015) 7107-7119.
- [107] T.Y. Huang, T.H. Tsai, C.W. Hsu, Y.C. Hsu, Curcuminoids suppress the growth and induce apoptosis through caspase-3-dependent pathways in glioblastoma multiforme (GBM) 8401 cells, *Journal of agricultural and food chemistry*, 58 (2010) 10639-10645.
- [108] P. Anand, A.B. Kunnumakkara, R.A. Newman, B.B. Aggarwal, Bioavailability of curcumin: problems and promises, *Molecular pharmaceuticals*, 4 (2007) 807-818.
- [109] H.R. Rahimi, R. Nedaeinia, A.S. Shamloo, S. Nikdoust, R.K. Oskuee, Novel delivery system for natural products: Nano-curcumin formulations, *Avicenna journal of phytomedicine*, 6 (2016) 383.
- [110] S. Bisht, M.A. Khan, M. Bekhit, H. Bai, T. Cornish, M. Mizuma, M.A. Rudek, M. Zhao, A. Maitra, B. Ray, A polymeric nanoparticle formulation of curcumin (NanoCurc™) ameliorates CCl<sub>4</sub>-induced hepatic injury and fibrosis through reduction of pro-inflammatory cytokines and stellate cell activation, *Laboratory investigation*, 91 (2011) 1383.

- [111] S. Bisht, G. Feldmann, S. Soni, R. Ravi, C. Karikar, A. Maitra, A. Maitra, Polymeric nanoparticle-encapsulated curcumin ("nanocurcumin"): a novel strategy for human cancer therapy, *Journal of nanobiotechnology*, 5 (2007) 3.
- [112] K.J. Lim, S. Bisht, E.E. Bar, A. Maitra, C.G. Eberhart, A polymeric nanoparticle formulation of curcumin inhibits growth, clonogenicity and stem-like fraction in malignant brain tumors, *Cancer biology & therapy*, 11 (2011) 464-473.
- [113] J. Shao, D. Zheng, Z. Jiang, H. Xu, Y. Hu, X. Li, X. Lu, Curcumin delivery by methoxy polyethylene glycol-poly (caprolactone) nanoparticles inhibits the growth of C6 glioma cells, *Acta Biochim Biophys Sin*, 43 (2011) 267-274.
- [114] G. Marslin, B.F.C.C. Sarmiento, G. Franklin, J.A.R. Martins, C.J.R. Silva, A.F.C. Gomes, M.P. Sárria, O.M.F.P. Coutinho, A.C.P. Dias, Curcumin encapsulated into methoxy poly (ethylene glycol) poly ( $\epsilon$ -caprolactone) nanoparticles increases cellular uptake and neuroprotective effect in glioma cells, *Planta medica*, 83 (2017) 434-444.
- [115] P. Maiti, J. Scott, D. Sengupta, A. Al-Gharaibeh, G.L. Dunbar, Curcumin and Solid Lipid Curcumin Particles Induce Autophagy, but Inhibit Mitophagy and the PI3K-Akt/mTOR Pathway in Cultured Glioblastoma Cells, *International journal of molecular sciences*, 20 (2019) 399.
- [116] A. Zanotto-Filho, K. Coradini, E. Braganhol, R. Schröder, C.M. De Oliveira, A. Simões-Pires, A.M.O. Battastini, A.R. Pohlmann, S.S. Guterres, C.M. Forcelini, Curcumin-loaded lipid-core nanocapsules as a strategy to improve pharmacological efficacy of curcumin in glioma treatment, *European Journal of Pharmaceutics and Biopharmaceutics*, 83 (2013) 156-167.
- [117] A. Singh, V.A. Saharan, M. Singh, A. Bhandari, Phytosome: drug delivery system for polyphenolic phytoconstituents, *Iranian Journal of Pharmaceutical Sciences*, 7 (2011) 209-219.
- [118] H. Mirzaei, A. Shakeri, B. Rashidi, A. Jalili, Z. Banikazemi, A. Sahebkar, Phytosomal curcumin: A review of pharmacokinetic, experimental and clinical studies, *Biomedicine & Pharmacotherapy*, 85 (2017) 102-112.
- [119] G. Belcaro, M. Hosoi, L. Pellegrini, G. Appendino, E. Ippolito, A. Ricci, A. Ledda, M. Dugall, M.R. Cesarone, C. Maione, A controlled study of a lecithinized delivery system of curcumin (Meriva<sup>®</sup>) to alleviate the adverse effects of cancer treatment, *Phytotherapy research*, 28 (2014) 444-450.
- [120] T.H. Marczylo, R.D. Verschoyle, D.N. Cooke, P. Morazzoni, W.P. Steward, A.J. Gescher, Comparison of systemic availability of curcumin with that of curcumin formulated with phosphatidylcholine, *Cancer chemotherapy and pharmacology*, 60 (2007) 171-177.
- [121] J. Cuomo, G. Appendino, A.S. Dern, E. Schneider, T.P. McKinnon, M.J. Brown, S. Togni, B.M. Dixon, Comparative absorption of a standardized curcuminoid mixture and its lecithin formulation, *Journal of natural products*, 74 (2011) 664-669.
- [122] M. Li, Z. Tang, D. Zhang, H. Sun, H. Liu, Y. Zhang, Y. Zhang, X. Chen, Doxorubicin-loaded polysaccharide nanoparticles suppress the growth of murine colorectal carcinoma and inhibit the metastasis of murine mammary carcinoma in rodent models, *Biomaterials*, 51 (2015) 161-172.
- [123] D.I. Sánchez-Machado, J. López-Cervantes, M.A. Correa-Murrieta, R.G. Sánchez-Duarte, P. Cruz-Flores, G.S. de la Mora-López, Chitosan, in: *Nonvitamin and Nonmineral Nutritional Supplements*, Elsevier, 2019, pp. 485-493.
- [124] V.M. Platt, F.C. Szoka Jr, Anticancer therapeutics: targeting macromolecules and nanocarriers to hyaluronan or CD44, a hyaluronan receptor, *Molecular pharmaceutics*, 5 (2008) 474-486.
- [125] R.-q. Huang, W.-l. Ke, Y.-h. Qu, J.-h. Zhu, Y.-y. Pei, C. Jiang, Characterization of lactoferrin receptor in brain endothelial capillary cells and mouse brain, *Journal of biomedical science*, 14 (2007) 121-128.
- [126] Y. Xu, S. Asghar, L. Yang, H. Li, Z. Wang, Q. Ping, Y. Xiao, Lactoferrin-coated polysaccharide nanoparticles based on chitosan hydrochloride/hyaluronic acid/PEG for treating brain glioma, *Carbohydrate polymers*, 157 (2017) 419-428.
- [127] L. Yang, S. Gao, S. Asghar, G. Liu, J. Song, X. Wang, Q. Ping, C. Zhang, Y. Xiao, Hyaluronic acid/chitosan nanoparticles for delivery of curcuminoid and its in vitro evaluation in glioma cells, *International journal of biological macromolecules*, 72 (2015) 1391-1401.

- [128] A. Hesari, M. Rezaei, M. Rezaei, M. Dashtianhangar, M. Fathi, J.G. Rad, F. Momeni, A. Avan, Effect of curcumin on glioblastoma cells, 234 (2019) 10281-10288.
- [129] S. Dutzmann, C. Schiborr, A. Kocher, U. Pilatus, E. Hattingen, J. Weissenberger, F. Gessler, J. Quick-Weller, K. Franz, V. Seifert, J. Frank, C. Senft, Intratumoral Concentrations and Effects of Orally Administered Micellar Curcuminoids in Glioblastoma Patients, *Nutrition and cancer*, 68 (2016) 943-948.
- [130] Z. Jamali, M. Khoobi, S.M. Hejazi, N. Eivazi, S. Abdolapour, F. Imanparast, H. Moradi-Sardareh, M. Paknejad, Evaluation of targeted curcumin (CUR) loaded PLGA nanoparticles for in vitro photodynamic therapy on human glioblastoma cell line, *Photodiagnosis and photodynamic therapy*, 23 (2018) 190-201.
- [131] P. Maiti, A. Al-Gharaibeh, N. Kolli, G.L. Dunbar, Solid Lipid Curcumin Particles Induce More DNA Fragmentation and Cell Death in Cultured Human Glioblastoma Cells than Does Natural Curcumin, 2017 (2017) 9656719.
- [132] X. Tan, G. Kim, D. Lee, J. Oh, M. Kim, C. Piao, J. Lee, M.S. Lee, J.H. Jeong, M. Lee, A curcumin-loaded polymeric micelle as a carrier of a microRNA-21 antisense-oligonucleotide for enhanced anti-tumor effects in a glioblastoma animal model, *Biomaterials science*, 6 (2018) 407-417.
- [133] R. Keshavarz, B. Bakhshinejad, S. Babashah, N. Baghi, M. Sadeghizadeh, Dendrosomal nanocurcumin and p53 overexpression synergistically trigger apoptosis in glioblastoma cells, *Iranian journal of basic medical sciences*, 19 (2016) 1353-1362.
- [134] C. Sarisozen, S. Dhokai, E.G. Tsikudo, E. Luther, I.M. Rachman, V.P. Torchilin, Nanomedicine based curcumin and doxorubicin combination treatment of glioblastoma with scFv-targeted micelles: In vitro evaluation on 2D and 3D tumor models, *European journal of pharmaceuticals and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V.*, 108 (2016) 54-67.
- [135] I. Zhang, Y. Cui, A. Amiri, Y. Ding, R.E. Campbell, D. Maysinger, Pharmacological inhibition of lipid droplet formation enhances the effectiveness of curcumin in glioblastoma, *European journal of pharmaceuticals and biopharmaceutics : official journal of Arbeitsgemeinschaft fur Pharmazeutische Verfahrenstechnik e.V.*, 100 (2016) 66-76.
- [136] J.H. Park, J. Han, M. Lee, Thymidine kinase gene delivery using curcumin loaded peptide micelles as a combination therapy for glioblastoma, *Pharmaceutical research*, 32 (2015) 528-537.
- [137] A. Kumar, A. Ahuja, J. Ali, S. Baboota, Curcumin-loaded lipid nanocarrier for improving bioavailability, stability and cytotoxicity against malignant glioma cells, *Drug delivery*, 23 (2016) 214-229.
- [138] M. Tahmasebi Mirgani, B. Isacchi, M. Sadeghizadeh, F. Marra, A.R. Bilia, S.J. Mowla, F. Najafi, E. Babaei, Dendrosomal curcumin nanoformulation downregulates pluripotency genes via miR-145 activation in U87MG glioblastoma cells, *International journal of nanomedicine*, 9 (2014) 403-417.
- [139] S. Mukherjee, A. Fried, R. Hussaini, R. White, J. Baidoo, S. Yalamanchi, P. Banerjee, Phytosomal curcumin causes natural killer cell-dependent repolarization of glioblastoma (GBM) tumor-associated microglia/macrophages and elimination of GBM and GBM stem cells, *Journal of experimental & clinical cancer research : CR*, 37 (2018) 168.

## Figure legends

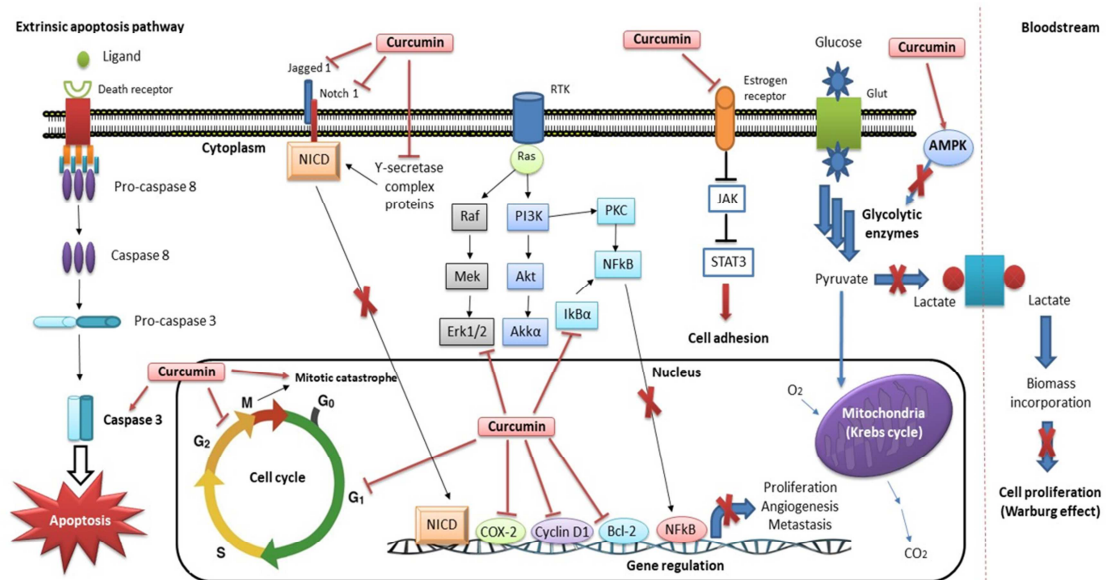
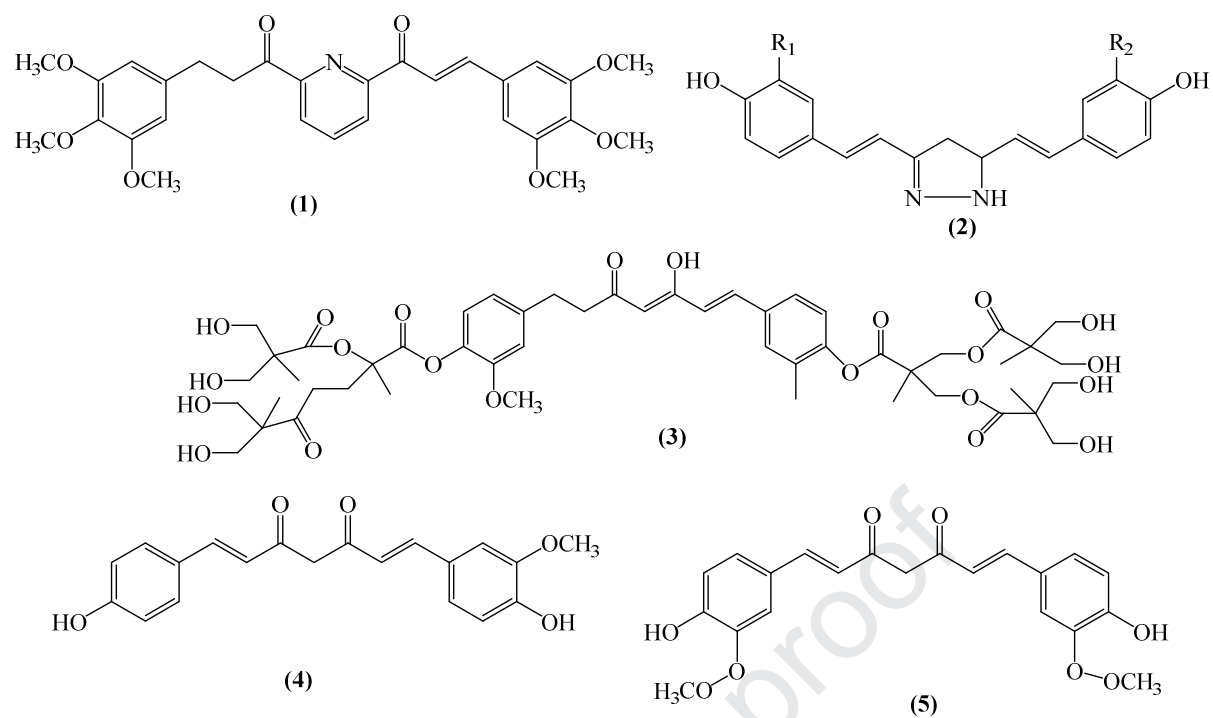


Figure 1. Curcumin and its therapeutic effects on glioblastoma



**Figure 2.** Curcumin analogues. Bis-chalcone 4j (1); Hydrazinobenzoyl curcumin (2); Curumin-[G-2]-OH (3); Demethoxycurcumin (4) ; 1,7-bis(4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3,5-dione (5)

Table 1. Anti-tumor effects of curcumin on glioblastoma

<b>Dose (s)</b>	<b>Main target (s)</b>	<b>Main effect (s)</b>	<b>Model</b>	<b>Cell line (s)</b>	<b>Ref</b>
10 $\mu$ M	Atg5, Beclin-1	Induces autophagy	<i>In vitro</i>	A172	[54]
10 $\mu$ M	Fascin	Anti-migration and anti-invasion effects	<i>In vitro</i>	U87	[40]
10 $\mu$ M	Cx43	Induces apoptosis	<i>In vitro</i>	U251, U87	[55]
25 $\mu$ M	Atg5, Atg7, m PI3K, Akt/mTOR Pathway	Induces autophagy	<i>In vitro</i>	U-87MG, GL261, F98, C6-glioma N2a	[56]
50 $\mu$ M	IRE1, ATF6, miR-27a, -222, -449, AKT-Insulin and p53-Bcl-2 pathways	Induces apoptosis	<i>In vitro</i>	A172	[57]
20 $\mu$ M	CDK1, cyclin A/B, PI3K/AKT, COX-2, NF- $\kappa$ B,	Anti-proliferative and anti-migration effects, induces apoptosis	<i>In vitro</i>	U118MG, U87MG, U251MG SVG, p12	[58]
0.05, 0.1, 0.25, 1, 2.5, 5, 7, 8, 10 $\mu$ M	-	Increases survival Inhibits tumor growth, induces apoptosis	<i>In vitro</i>	C6	[59]
25 & 2.5 $\mu$ M	STAT3, Survivin, MAPK, IAP1, IAP2	Anti-proliferative effects, induction of ROS in tumor cells	<i>In vitro</i>	Glio 3, 4, 9, 11, 14	[53]

10 , 20 and 40 $\mu$ M	miR-326	Cytotoxic effects against tumor cells, induces apoptosis, Anti-proliferation and anti-migration effects	<i>In vitro</i>	U87, U251	[60]
22.5 $\mu$ M	Arginase, iNOS, NF- $\kappa$ B, STAT1	Repolarized tumor-associated microglial cells to the tumoricidal M1 state, increases survival	<i>In vitro, In vivo</i>	GBM994, GBM46, GBM6, GL261 , CD68	[61]
46.4 $\mu$ M, 78,3 $\mu$ M, and 47.7 $\mu$ M	MMPs, glucose-6-phosphate transporter	Induction of cell death	<i>In vitro</i>	GB3B, GB4B, GB5B	[62]
20 and 40 $\mu$ M	cyclin G2, caspase-3, FasL, CDK1, FoxO1	Induces cell cycle arrest and apoptosis , anti-proliferative effects	<i>In vitro</i>	U87	[63]
20 & 100 $\mu$ M	miR-146a, NF- $\kappa$ B	Anti-proliferative effects, induces apoptosis	<i>In vitro</i>	U-87	[64]
50 mg/kg	STAT3, NF $\kappa$ B, PI3K/Akt	Induces autophagy and apoptosis	<i>In vitro, in vivo</i>	U251MG, U87M	[65]
1.25 $\mu$ g/ml	AKT, mTOR	Exerts synergistic effects with chemotherapy drug, induces apoptosis	<i>In vitro, In vivo</i>	U87MG	[66]

8 ,15, 25, 667 $\mu$ M	NF- $\kappa$ B, cyclin D1, VEGF	Reduces tumor load and increases survival of glioblastoma-implanted mice	<i>In vitro</i>	T98G, U87MG, GL261	[67]
30 , 40 $\mu$ M	STAT3	Induces RANK gene reactivation by epigenetic modification	<i>In vitro</i>	U251 U87	[68]
2 $\mu$ M	GFAP, $\beta$ III-tubulin, LC3	Induces autophagy	<i>In vivo, In vitro</i>	SU-2, SU-3	[69]
50 mg/kg/day	PI3K/Akt, NF- $\kappa$ B Caspase-3	Inhibits proliferation and migration, induces cell death	<i>In vivo, In vitro</i>	U138MG, U87 U373 C6	[70]
10, 20, and 50 $\mu$ M	STAT3	Anti-proliferative, anti-migratory, and anti-invasive effects	<i>In vitro</i>	A-172 MZ-18, MZ-54 MZ-256, MZ-304	[71]
10, 20 and 30 $\mu$ g/ml.	EGFR, mTOR, Ras, PTEN, RTK-Ras-PI3K, Bax, caspase-3	induces cell cycle arrest Induces apoptosis	<i>In vitro</i>	DBTRG	[72]
30, 60, 120 mg/kg/day	MMP-9	Anti-angiogenesis effects	<i>In vivo, In vitro</i>	U-87	[73]
5, 10, or 20 $\mu$ M/L	Waf1/Cip1, ERK, JNK, MAPK/Elk-1/Egr-1 pathway	Exerts anti-proliferative effects, induces cell cycle arrest, Regulates differentiation, growth,	<i>In vitro</i>	U-87MG C6	[74]



		and apoptosis			
25–50 $\mu\text{M/L}$	p53- and caspase- , AP-1 and NFkappaB , JNK and Akt , bcl-2 and IAP	Suppresses cell growth and chemotherapy resistance	<i>In vitro</i>	T98G, U87MG, T67, C6	[75]
25 and 50 $\mu\text{M}$	caspase-3, -8, -9 Bax, Bcl-2, NF- $\kappa\text{B}$ , SBDP	Induces apoptosis	<i>In vitro</i>	U87MG	[76]
25 and 50 $\mu\text{M}$	caspase-3, -8, -9 Bax, Bcl-2, NF- $\kappa\text{B}$ , SBDP	Induces apoptosis	<i>In vitro</i>	T98G	[77]

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Table 2. Various curcumin analogues in glioblastoma therapy

Type of curcumin	Dose (s)	Target (s)	Effect (s)	Model	Type of cell line (s)	Ref
(1)	2.7–5.8 $\mu$ M	CHOP, p-jun, caspase-12	Promotes Endoplasmic Reticulum Stress and apoptosis	<i>In vitro</i>	GSCs	[102]
(2)	100 mM	Ca <sup>2+</sup> /calmodulin-dependent protein kinase II, CD133, Sox2	Anti-migration and anti-invasion effects, induces apoptosis	<i>In vitro</i>	U87MG, U373MG	[103]
(3)	100 $\mu$ M	TAC	Antioxidant effects	<i>In vitro</i>	C6	[104]
(4)	10, 30, and 50 mg/kg	JAK, STAT	Inhibits proliferation and induces apoptosis	<i>In vitro, In vivo</i>	GSCs	[93]

(4)	10 & 30 $\mu\text{M}$	ROS, caspase-3- JAK/STAT3	Induces apoptosis , anti-proliferation effects	<i>In vitro, in vivo</i>	U87, U251	[105]
(4)		ROS, caspase-3, JAK/STAT3	Anti-proliferative effects, inhibits of cell growth, induces apoptosis	<i>In vitro</i>	GSCs	[106]
(5)	12.5 to 100 $\mu\text{M}$	Caspase-3, -8, -9, NF- $\kappa\text{B}$	Anti-proliferative effects, induces apoptosis	<i>In vitro</i>	GBM 8401	[107]

Bis-chalcone 4j (1); Hydrazinobenzoyl curcumin (2); Curumin-[G-2]-OH (3); Demethoxycurcumin (4) ; 1,7-bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione (5)

Table 3. Curcumin delivery systems in glioblastoma therapy

<b>Novel curcumin formulation</b>	<b>Dose (s)</b>	<b>Target gene (s)</b>	<b>Effect (s)</b>	<b>Model</b>	<b>Type of cell line (s)</b>	<b>Ref</b>
Nano micelles curcumin	80 mg	cyclin D1, Wnt, NF- $\kappa$ B	Inhibits tumor cell growth, induces apoptosis, anti-invasion effects	<i>In vitro</i>	U-373	[128]
Micellar curcuminoids	70 mg	Intratumoral inorganic phosphate (Pi)	Anti-cancer effects	Human	-	[129]
Curcumin loaded PLGA nanoparticles	10 $\mu$ M	Tyrosine phosphorylation	Anti-cancer effects	<i>In vitro</i>	DKMG	[130]
Solid Lipid Curcumin Particles	25 $\mu$ M	Caspase-3, Bax,, p53, Bcl <sub>2</sub> , c-Myc, Akt	Induces apoptosis	<i>In vitro</i>	U-87MG GL261	[131]
Curcumin-loaded polymeric micelle		miR-21, PDCD4, PTEN	Induces apoptosis, reduces the tumor size	<i>In vitro</i>	C6	[132]

Dendrosomal curcumin		GADD45, NF- $\kappa$ B and c-Myc	Induces apoptosis	<i>In vitro</i>	U87-MG	[133]
Nanoformulation of curcumin and doxorubicin		Caspase-3, -7 GLUT1	Induces apoptosis	<i>In vitro</i>	U87MG	[134]
Micellar curcuminoids	70 mg	Intratumoral inorganic phosphate (Pi)	Anti-tumor effects	<i>Human</i>		[134]
Lipid droplets of curcumin	5–100 $\mu$ M	Caspase-3	Induces apoptosis	<i>In vitro</i>	U251N	[135]
Curcumin loaded R7L10 micelles		pDNA	Induces apoptosis, reduces the tumor size	<i>In vitro, In vivo</i>	C6	[136]
Curcumin-loaded nanocarrier	24.23 $\mu$ M	-	Anti-cancer effects	<i>In vitro, In vivo</i>	U87	[137]

Dendrosomal curcumin	15, 17.5, 20 μM	OCT4A, OCT4B1, SOX-2, miR-145	Inhibits cancer cell growth, Exerts anti-proliferative effects	<i>In vitro</i>	U87MG	[138]
Phytosomal curcumin	2 mg	STAT1, STAT3, ARG1, IL-10, iNO, caspase-3	Anti-cancer effects	<i>In vivo</i>	GL261	[139]

### Highlights

- Glioblastoma multiforme (GBM) is known as a greatly aggressive malignancy of the brain.
- Curcumin has therapeutic potentials to fight against GBM.
- Curcumin exerts its therapeutic effects against GBM cells *via* various activities i.e., antioxidant and anti-inflammatory activities.

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**Declaration of interests**

- ✓  The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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