

Review

## Curcumin for the Treatment of Glioblastoma

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**Abstract.** *Glioblastoma multiforme is a highly aggressive primary cancer of the brain associated with a poor prognosis. Modest increases in survival can sometimes be achieved with the use of temozolomide and radiation therapy after surgery, but second-line therapy after recurrence has a limited efficacy. Curcumin has demonstrated promising results against this form of cancer in experimental models. The reported activity of curcumin against cancer stem cells, a major cause of glioblastoma resistance to therapy, and its ability to augment the apoptotic effects of ceramides, suggest it would have a synergistic effect with cytotoxic chemotherapy agents currently used in second-line therapy, such as lomustine.*

Glioblastoma [glioblastoma multiforme, (GBM)] is a highly malignant (grade IV) tumor arising from astrocytes. Approximately 15% of all primary brain tumors are GBM. GBM may arise *de novo* or, occasionally, from a low-grade astrocytoma. Genetic abnormalities are common (1-4). Median survival with treatment is 15 months, with a two-year survival rate of less than 25%. Survival without treatment is usually only a few months (5-8). Frequent presenting signs include headaches, nausea, seizures, blurred vision, vomiting, and personality changes. Standard treatment is a combination of surgery, radiotherapy, and chemotherapy. The effectiveness of surgery is limited by the difficulty of complete tumor resection and presence of residual tumor cells (9-11). If surgical ablation is not an option due to tumor size, tumor location, or very poor patient performance status, a combination of radiation and chemotherapy is used.

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### Standard Chemotherapy

Temozolomide is an oral alkylating agent which is an imidazotetrazine derivative of dacarbazine. It crosses the blood-brain barrier and is, in combination with radiation, the most frequently used first-line treatment given following surgery for malignant glioma (12-15). The addition of temozolomide to radiation therapy increases patient median survival by 2 to 3 months. In one randomized trial, median survival with this combination was 14.6 months compared to 12.1 months with radiation therapy alone (16-18). Two other agents, bevacizumab, which suppresses angiogenesis, and lomustine, have frequently been used as second-line therapy (19-23). Lomustine is a lipid-soluble, alkylating nitrosourea which also crosses the blood-brain barrier (21-25). However, treatment with these agents results in only minor increases in survival, and overall survival rates remain low, with fewer than 10% of patients alive at 5 years after diagnosis (18, 26). Due to the highly resistant and aggressive nature of GBM, new treatments are required.

### Curcumin

Curcumin (diferuloylmethane) is the principal curcuminoid of turmeric, the Indian spice derived from the plant *Curcuma longa* Linn. Curcumin absorbs light with a wavelength maximum at approximately 420 nm, thus giving turmeric its yellow color. Curcumin has been shown to have antioxidant, anti-infective and anticancer effects, and its use is being investigated in diseases as diverse as diabetes (27), Alzheimer's disease (28), hepatitis (29) and rheumatoid arthritis (30). When orally administered, it is non-toxic and safe (31-35). Curcumin has numerous mechanisms of action, including suppression of pro-inflammatory cytokines such as tumor necrosis factor-alpha, interleukin (IL)1, IL6, IL8, and affects multiple signaling pathways including wingless-related integration site (WNT), NOTCH, mitogen-activated protein kinase, hedgehog and Janus kinase/signal transducer and activator of transcription (JAK/STAT) (36-41). Curcumin is highly lipophilic, and crosses the blood-brain barrier (42, 43).

## Curcumin and GBM

The potential benefits of curcumin as a treatment for GBM have been studied by numerous groups (44-49). Aoki *et al.* showed that curcumin induced autophagy by suppression of the protein kinase B (AKT)/mammalian target of rapamycin (mTOR)/p70S6K and activation of the extracellular-signal-regulated kinase (ERK1/2) pathways in U87-MG and U373-MG human malignant glioma cells harboring a phosphatase and tensin homolog (*PTEN*) mutation. Similar results were seen in KBM-5 human leukemia cells (50). Choi *et al.* reported that curcumin activates p21 in U87-MG human GBM cells *via* ERK and c-JUN N-terminal protein kinase signaling (51). Senft *et al.* studied cell lines from human primary and recurrent GBM, and showed that curcumin reduced cell growth, inhibited migration and decreased invasiveness due to its inhibition of the JAK/STAT3 pathway (52). Similarly, Dhandapani *et al.* showed that curcumin enhanced cell death by reducing the activity of activator protein 1 and nuclear factor of kappa light polypeptide gene enhancer in B-cells 1 binding in human and rat glioma cell lines (53). Zanotto-Filho *et al.* showed that in the C6 implant rat glioma model, curcumin caused reduction in brain tumor volume (54). Perry *et al.* showed that curcumin can suppress growth of human glioma U87 cells xenografted into athymic mice (55).

The effects of curcumin on GBM stem cells may also be important. Beier *et al.* showed that detoxifying enzymes such as O6-methylguanine-DNA-methyltransferase may confer intrinsic resistance of cancer stem cells to alkylating agents (56). Other researchers have also suggested a key role for stem cells in GBM formation and resistance to alkylating agent therapy (57, 58). Fong *et al.* studied rat C6 glioma cells, and showed that curcumin may have the potential to target cancer stem cells (59). Zhuang *et al.* found that curcumin induced differentiation of glioma-initiating cells and inhibited their growth *via* autophagy (60).

### Curcumin: Alternate Delivery Mechanisms

Recently, new mechanisms have emerged, and engendered methods of improving the efficacy of curcumin (61-65). These methods may prove superior because of their ability to deliver greater doses of curcumin to the tumor. Nano-sized capsules of curcumin have been used as a treatment of GBM cells. Lim *et al.* have shown that curcumin nanoparticles can slow-down GBM growth through the inhibition of cell proliferation and a reduction in stem-like tumor cells (66). Langone *et al.* have shown that curcumin coupled to a monoclonal antibody caused a 120-fold increase in the death of human GBM cells in culture compared to curcumin alone. In addition, mice implanted with GBM cells had an extended survival time and a reduction in the size of the brain tumor mass with this treatment (67).

## Rationale for Combination therapy

It is proposed that the optimal method of using curcumin is not as a single agent, but rather in combination with cytotoxic chemotherapy. Ramachandran *et al.* have shown that curcumin could be used to increase the therapeutic potential of temozolomide or of etoposide in brain tumor cell lines (68). Yin *et al.* investigated the use of a combination of curcumin and temozolomide in U87-MG GBM cell lines and in xenograft mouse models, and found that curcumin enhanced the effects of temozolomide by generating reactive oxygen species production, and by suppressing phosphorylated AKT and mTOR, thus causing cell death (69). Zanotto-Filho *et al.* showed that curcumin increased the cytotoxic effects of doxorubicin and cisplatin on GBM cells (70). Wu *et al.* showed that curcumin enhanced temozolomide cytotoxicity against human GBM cells (71). It has been reported that curcumin and paclitaxel act synergistically with much greater activity than seen with each individual agent in increasing the B-cell lymphoma like protein 4/B-cell lymphoma 2 ratio, increasing cytochrome *c*, reducing angiogenesis and causing apoptosis of HBTSC, LN18 and U138-MG cells (72).

These results suggest that the use of curcumin should be investigated in clinical trials of patients with GBM, ideally as a second-line therapy after failure of radiation therapy and temozolomide, and that the optimal method for using curcumin in this setting may be in combination with an established cytotoxic chemotherapy agent with activity against GBM such as carmustine or lomustine. As noted, it appears that a major reason for the very limited efficacy of alkylating agents in established tumors is the resistance of GBM stem cells to therapy. Our previous work and those of others has suggested that curcumin may be effective in reducing or eliminating the population of cancer stem cells, either by causing apoptosis or differentiation (73-76), while conventional chemotherapy alone is ineffective against stem cells, resulting in tumor recurrence even following initial response (77). Furthermore, curcumin may also increase the activity of cytotoxic chemotherapy against mature tumor cells. Curcumin has been shown to enhance ceramide production by increasing the activity of enzyme ceramide synthase (78). It has been suggested that the progression of GBM is caused by a decrease in ceramide levels (79). Increased activity of glucosylceramide synthase, an enzyme that causes a decrease in ceramides, has been associated with GBM progression and resistance to temozolomide (80). In contrast, acid sphingomyelinase, which hydrolyzes sphingomyelin to ceramide and phosphorylcholine, has been shown to sensitize glioma cell lines to chemotherapy or radiation therapy (81, 82). The combination of curcumin and chemotherapy has also been shown to have a synergistic effect on the generation of reactive oxygen species in GBM cell lines and in mouse xenografts (69). This may be an

additional mechanism by which GBM cell destruction might be enhanced, since reactive oxygen species are known to increase acid sphingomyelinase activity and, in consequence, ceramide levels (83-85).

## Conflicts of Interest

Dr. Peter Sordillo is a member of the Scientific Advisory Board of SignPath Pharma, a developmental stage biotechnology company that is studying liposomal curcumin, liposomes and other agents. Dr. Helson is CEO of SignPath Pharma. Laura Sordillo reports no conflicts.

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