Brain tumors are the most common form of solid tumors in children accounting for about 20-25% of all pediatric cancers. Chemotherapy options for brain tumor treatment are very much limited because of the blood brain barrier and emergence of drug resistance in brain tumor cells. The genus Curcuma contains several herbs like mango ginger (Curcuma amada Roxb.), turmeric (C. longa L.) and Javanese turmeric (C. xanthorrhiza Roxb.) that are suggested to have anticancer properties. Previous studies have indicated that curcumin, the major active ingredient in turmeric is cytotoxic to brain tumor cells. In this investigation, we show that the supercritical extract of mango ginger (CA) is superior in terms of cytotoxic effects than turmeric extract (CL), Javanese turmeric extract (CX), curcumin and turmeric force® (a nutraceutical containing supercritical and hydroethanolic extract of turmeric) against human glioblastoma cell lines (U-87MG and U-188MG). The cytotoxicity profile of CA is significantly better than temozolomide and etoposide as it has induced >90% death of tumor cells. The combination index values calculated according to Chou and Talalay’s equations indicated that CA is synergistic (<1) for cytotoxic effects with temozolomide, etoposide and irinotecan in glioma cell lines. Gene expression analysis to explore the mechanism of action indicated that CA downregulates the expression of genes associated with inflammation (NF-kB, COX-2 and STAT3), apoptosis (p21, p53, Bcl-2/Bax ratio), telomerase (hTERT), drug resistance (MRP, DRR, LRP) and oncogenes (N-myc, V-Jun) in the RT-PCR assay. These positive results suggest the need for further evaluation of CA in nude mouse xenograft studies and human clinical trials.