Cytotoxicity and mechanistic divergence of tocotrienol-rich fraction in TMZ-resistant GBM cells

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ABSTRACT

Glioblastoma multiforme (GBM) is a highly aggressive brain malignancy with poor prognosis and resistance to standard chemotherapeutics, particularly temozolomide (TMZ). Despite its limited efficacy, TMZ remains the first-line treatment due to its ability to cross the blood–brain barrier. Vitamin E, a group of lipid-soluble analogues comprising tocopherols (Toc) and tocotrienols (T3), has demonstrated emerging anticancer potential and similarly possesses the ability to penetrate the blood–brain barrier, making it a promising alternative for GBM therapy. To investigate this potential, the TMZ-resistant T98G human glioblastoma cell line was used to assess the effects of vitamin E constituents, including α-tocopherol (α- Toc), α-tocotrienol (α-T3), and tocotrienol-rich fraction (TRF), a mixture of vitamin E analogues. While α-Toc is the most widely studied form of vitamin E, it had no impact on cell viability. Instead, TRF and α-T3 significantly reduced viability with cytotoxic effects surpassing TMZ. These results suggest that the anticancer effects of TRF are driven predominantly by its T3 components. Furthermore, transcriptomic analysis revealed that TRF activates molecular pathways distinct from those of TMZ, indicating a fundamentally different mechanism of action. Together, these findings position TRF as a compelling alternative to TMZ in the treatment of resistant GBM.

Keywords: Glioblastoma multiforme, vitamin e, temozolomide, chemoresistance, anti-cancer