

## **Title: A Comprehensive Analysis of Natural Bioactive Molecules for the Treatment and Control of Glioblastoma Multiforme (GBM) Targeting Underlying Molecular Mechanism**

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**Abstract:** Glioblastoma multiforme (GBM) is a highly aggressive brain tumor characterized by rapid cellular proliferation and invasion, making it difficult to achieve a complete cure. Despite therapies like surgery, radiotherapy, and chemotherapy, GBM results in poor survival rates, with a median survival of just 1 year. This has led to the need for more effective treatment options with fewer side effects. The study aims to explore the mechanisms behind GBM and highlight the potential of natural bioactive compounds, either alone or in combination with conventional therapies, to provide synergistic effects. Several small natural molecules, such as resveratrol, curcumin, rutin, and icariin, have shown promising anticancer and apoptotic properties in drug-resistant and p53-mutant GBM cell lines. These compounds enhance the antitumor effects of temozolomide (TMZ), targeting glioma stem cells, reducing oxidative stress, preventing cell proliferation, triggering apoptosis, and impeding oncogenic processes. Furthermore, combining these bioactive molecules with advanced drug delivery systems offers potential for improved drug targeting, bioavailability, and blood-brain barrier (BBB) penetration, while minimizing off-target effects. This study is clinically significant as it provides alternative therapeutic insights for patients with advanced GBM cancer, particularly in real-world settings or regions where access to EV plus pembrolizumab is limited due to cost, availability, or regulatory constraints. This multimodal therapeutic approach demonstrates promise as a safer and more effective way to treat glioblastoma.

**Keywords:** apoptosis, blood–brain barrier; glioblastoma; natural small molecules; novel drug delivery.

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