

ABSTRACT

Glioma is the most frequent tumor of the central nervous system. Glioblastoma multiforme is a grade IV glioma, the most aggressive malignant glioma with a poor survival rate. The standard glioma therapy includes initial surgical resection followed by radiation therapy and chemotherapy. However, the glioblastoma cell's ability to infiltrate makes removing all of the tumor tissue without hampering the neurological function difficult. Moreover, radiation treatment includes the limitations of radioresistance and tissue necrosis. In the case of chemotherapy, the blood-brain barrier is the major hindrance. The limited availability of chemotherapeutic agents due to highly toxic effects must be overcome.

FLI1, which belongs to the transcription factor family known as the E26 transformation-specific family (ETS), is involved in various physiological processes. This protein is known to be associated with oncogenesis, especially in Ewing sarcoma. Recent studies illustrated the role of FLI1 in therapeutic resistance in glioma. Lumefantrine, an antimalarial drug, has been reported to act as a potential FLI1 inhibitor and found to be effective in resistant gliomas. Our project aims to find a novel and more potent FLI1 inhibitor for glioma therapy.

This research work started with searching for compounds with structural similarities to lumefantrine, followed by screening the compounds based on their ADME properties such as solubility, gastrointestinal absorption, BBB penetration, P-gp substrate, molecular weight, and the presence of H-bond acceptors and H-bond donors. After screening, a library of 57 compounds was prepared for docking with the DNA binding site of the FLI1 protein. The docking result revealed six compounds, Ruboxistaurin, GSK-1521498, PF-00446687, Tolvaptan, Lasofoxifene, and Bisindolylmaleimide, exhibiting more potent interaction with the DNA binding site of FLI1 protein compared to lumefantrine. These substances can potentially be FLI1 inhibitors and can be used to treat gliomas.