ABSTRACT

Glioma is considered one of the incurable cancers due to its high fatality rate. The infiltrative nature, Blood-brain barrier protection, and efflux transporters make glioma therapy more difficult. Clinicians use natural compounds for several diseases, including different cancers. Some natural agents have the benefits of crossing biological barriers like the blood-brain barrier with ease, having little or no impact on the surrounding healthy cells. Therefore, we focused on the natural compounds to find a prospective candidate for glioma therapy.

Magnolol, a natural compound from neolignan group, is well known for its various medicinal activity. Its Blood-brain barrier penetration, brain accumulation, and neuroprotection properties indicate its suitability as an anti-glioma agent. Researchers established its apoptotic effect in glioma. However, we focused on its role in autophagy modulation in glioma. Our study revealed it induced autophagy in glioma by inhibiting PI3K/AKT/mTOR signaling. Autophagy is a complex phenomenon that may cause cytotoxic or cytoprotective effects in cancer, including glioma. Chloroquine, a late-stage autophagy inhibitor, efficiently reversed the Magnolol-induced anti-glioma effect. Hence, we concluded that Magnolol-induced autophagy has a cytotoxic effect on glioma.

Temozolomide is the primarily used drug for glioma, but MGMT enzyme reverses its anti-glioma effect leading to chemoresistance. We explored the role of Magnolol as an MGMT inhibitor. Magnolol inhibited the nuclear translocation of the p65 protein to inhibit the activation of the NF-κB pathway. This effect caused inhibition of MGMT, which is known to be regulated by NF-κB signaling. Thus, Magnolol improved Temozolomide's effect in glioma, and this combination treatment caused a synergistic apoptotic effect. This finding indicated the potential of Magnolol to sensitize glioma tissue to Temozolomide and to treat Temozolomide-resistant gliomas.

We also studied the effect of Magnolol on glioma stem cells as the cancer stem cell population is a well-known cause of chemoresistance in several cancers, including glioma. We observed that it induces a lethal effect on the glioma stem cell population and inhibits their proliferation. To decipher the mechanism associated with it, we performed ligand-protein interaction studies, and the results indicated the inhibition of GP130 protein by MGN. Further studies confirmed the Magnolol-induced GP130 signaling to cause its effect on glioma stem cells.

In conclusion, this research established several novel anti-glioma mechanisms of Magnolol to suggest it as a promising agent for glioma treatment.

Keywords: Glioma, Magnolol, Cytotoxic Autophagy, PI3K/Akt, Temozolomide, Synergistic apoptosis, Nuclear translocation, p65 subunit, MGMT inhibition, Glioma stem cells, GP130 signaling