Oxalis debilis modulates Temozolomide response in glioblastoma cells

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Glioblastoma (GBM) remains the most aggressive primary brain tumor in adults, with poor prognosis largely due to resistance to Temozolomide (TMZ). Overcoming this resistance requires strategies capable of targeting adaptive survival pathways, including oxidative stress responses and hypoxia-driven mechanisms.
Natural compounds derived from biodiversity are emerging as modulators of tumor cell plasticity. Among these, *Oxalis debilis Kunth* has shown promising biological activity. In this study, we investigated its potential as a chemosensitizing agent in TMZ-resistant GBM models, focusing on chaperone-mediated autophagy (CMA) and stress-adaptive pathways.
As expected, TMZ alone exerted limited cytotoxicity in resistant cells. Notably, *Oxalis debilis Kunth* significantly reduced cell viability (~50%) and, when combined with TMZ, sensitized otherwise resistant cells to treatment, resulting in a pronounced reduction in cell survival. This effect was associated with increased oxidative stress, as demonstrated by a ~1.5-fold increase in intracellular ROS levels and enhanced lipid peroxidation. Gene expression analysis revealed modulation of CMA-related genes, with LAMP2A emerging as a key mediator. In particular, LAMP2A expression was altered by ~2-fold following combined treatment. Functional silencing of LAMP2A resulted in a partial rescue of cell viability (~50%), indicating that the cytotoxic effect is, at least in part, CMA-dependent. In parallel, we observed alterations in genes related to oxidative stress response, cell cycle regulation, and epithelial–mesenchymal transition (EMT), indicating a broader reprogramming of tumor cell behavior. Immunofluorescence analyses showed reduced HIF-1α expression and altered subcellular localization, suggesting impairment of hypoxia-driven adaptive mechanisms.
Overall, these findings support a model in which *Oxalis debilis Kunth* enhances TMZ efficacy by modulating CMA-related pathways and redox balance, ultimately sensitizing resistant GBM cells to chemotherapy.