MASTER'S THESIS

Anti-renal Cell Carcinoma Effects and Mechanisms of Action of Deoxyelephantopin

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ABSTRACT

Renal cell carcinoma (RCC) is the most prevalent urological malignancy. Advanced RCC has a 5-year survival rate of 11.7% only and is not responsive to conventional chemotherapies. Although targeted therapies and immune checkpoint inhibitors are available, challenges such as side effects, drug resistance, and limited response rate remain obstacles in RCC management. Hence, there is a need for alternative therapies to treat RCC. Deoxyelephantopin (DEO), a sesquiterpene lactone extracted from *Elephantopus scaber* L., has been shown to have anticancer effects in pharmacological models of diverse cancers. However, no study has explored its effects on RCC. In this study, we aimed to investigate the anti-RCC effects and mechanisms of action of DEO in treating RCC.

Our experiments revealed that DEO dose-dependently inhibited the proliferation and colony formation abilities of human (786-O, Caki-1, A498) and murine (RENCA) RCC cells. Flow cytometry analysis showed that DEO induced apoptosis and G2/M phase cell cycle arrest in 786-O and Caki-1 cells. In RENCA-bearing mice, DEO suppressed RCC growth. To understand the mechanisms of DEO in treating RCC, we employed network pharmacology to predict the pathways it may regulate. Results indicated that the PI3K/AKT signaling and the HIF-1 signaling pathways were the main pathways potentially involved in the anti-RCC effects of DEO. Our studies confirmed that DEO downregulated the protein levels of PI3K P110α and p-Akt (Ser473) in 786-O cells.

Furthermore, DEO downregulated the protein levels of EGFR and p-EGFR (Tyr1068) (PI3K/AKT upstream regulators), as well as mTOR, p-mTOR (Ser2448), p-p70S6K (Thr389), 4E-BP1, p-4E-BP1 (Thr36/46), and HIF-1α (important PI3K/AKT downstream signaling molecules) in 786-O cells.

In conclusion, our results demonstrated that DEO exerts anti-RCC effects in cell and mouse models. Inhibition of the PI3K/AKT/mTOR/HIF-1α pathway is involved in the anti-RCC mechanisms of this compound. This study provides pharmacological data for developing DEO into an anti-RCC agent.

Key words: Deoxyelephantopin; Renal cell carcinoma; PI3K/AKT/mTOR/HIF-1α signaling