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In Silico Targeting of PI3K/Akt Signaling by Polyphenols from *Hypericum alpestre* and *Rumex obtusifolius*: A Molecular Docking Study

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ABSTRACT

The PI3K/Akt signaling pathway is a central regulator of cancer cell survival, proliferation, angiogenesis, and therapeutic resistance. Polyphenolic compounds from medicinal plants have gained attention as potential multi-targeted inhibitors of this pathway. This study explores the binding interactions of major polyphenols from *Hypericum alpestre* (HA) *and Rumex obtusifolius* (RO) with PI3K and Akt using *in silico* approaches. Protein structures of PI3K (PDB ID: 6AUD) and Akt (PDB ID: 2JDO) were retrieved from the RCSB Protein Data Bank. The structures were pre-processed in PyMOL by removing water molecules and co-crystallized ligands. Key phytochemicals from HA (chrysoeriol glucuronide, pseudohypericin) and RO (emodin, endocrocin, luteolin, quercetin) were docked using AutoDock Vina with an exhaustiveness value of 8. Binding affinities, hydrogen bonding, and hydrophobic interactions were analysed. SwissADME was used to evaluate pharmacokinetic properties. Chrysoeriol glucuronide and pseudohypericin showed strong interactions with PI3K and Akt, including hydrogen bonds with Ala805, Ser806, and Glu230. Among RO-derived compounds, emodin, endocrocin, luteolin, and quercetin demonstrated high affinity for both targets. Quercetin formed four hydrogen bonds with Akt and two with PI3K, while emodin interacted with Tyr867, Asp964, and Lys160. These compounds also displayed favourable drug-like properties, meeting Lipinski's Rule of Five criteria and showing potential for oral bioavailability. The molecular docking results indicate that selected polyphenols from HA and RO can stably bind to key residues of PI3K and Akt, supporting their potential as natural inhibitors of this signaling axis. Their pharmacokinetic profiles and interaction patterns suggest suitability for further development in targeted anticancer therapy.

Keywords: PI3K/Akt signaling pathway, *Hypericum alpestre, Rumex obtusifolius*

References:

1. Yang, Y.; Zhou, X.; Xiao, M.; et al. Discovery of chrysoeriol, a PI3K-AKT-mTOR pathway inhibitor with potent antitumor activity against human multiple myeloma cells *in vitro*. *J. Huazhong Univ. Sci. Technol.* **2010,** *30*, 734–740. DOI:10.1007/s11596-010-0649-4
2. Ginovyan, M.; Javrushyan, H.; Hovhannisyan, S.; *et al.* 5-fluorouracil and *Rumex obtusifolius* extract combination trigger A549 cancer cell apoptosis: uncovering PI3K/Akt inhibition by in vitro and in silico approaches. *Sci. Rep*. **2024,** *14*, 14676. DOI:10.1038/s41598-024-65816-5

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