# REPURPOSING 20-HYDROXYECDYSONE FOR CANCER THERAPY: COMPUTATIONAL EVIDENCE FOR AQUAPORIN-5 INHIBITION

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**Relevance:** Aquaporin-5 (AQP5) is a membrane channel protein whose abnormal overexpression has been linked to tumor growth, migration, and metastasis in cancers such as breast, lung, and gastric carcinoma. These oncogenic roles make AQP5 an attractive therapeutic target. Natural compounds like 20-Hydroxyecdysone (ecdysterone), known for diverse biological activities, warrant investigation as potential modulators of AQP5 in cancer.

**Purpose of the study**: In this study, we explored ecdysterone, a naturally occurring phytoecdysteroid, as a potential small-molecule inhibitor of AQP5. While ecdysterone is best known as an insect moulting hormone and a plant-derived defense compound, it also exhibits notable biological activity in mammalian systems, including proposed interactions with estrogen receptor beta. However, its potential role in modulating AQP5 function in cancer has not yet been investigated.

**Materials and Methods:** To assess the inhibitory potential of **(**ecdysterone) against AQP5, we applied a computational workflow combining molecular docking, molecular dynamics (MD) simulations, and MM/GBSA free energy calculations. This in silico strategy enabled the evaluation of structural stability, dynamic behavior, and binding energetics of the ecdysterone–AQP5 complex. Such an approach offers an efficient and cost-effective alternative to early experimental screening, supporting the identification and prioritization of promising lead compounds.

**Results:** Molecular dynamics simulations showed that the AQP5–ecdysterone complex remained stable throughout the 300 ns trajectory, with ligand RMSD stabilizing after ~100 ns, reflecting persistent binding within the channel. RMSF analysis indicated moderate flexibility localized to the hydroxyl-rich side chains, while the steroidal core remained stable. Hydrogen bond analysis revealed that ecdysterone maintained up to two hydrogen bonds with AQP5 during the simulation, supporting a stable interaction profile. MM/GBSA binding free energy calculations yielded a ΔG_bind of −12.8 kcal/mol, with van der Waals (−22.7 kcal/mol) and electrostatic (−10.5 kcal/mol) contributions as major stabilizing forces, partially counterbalanced by polar solvation. These results suggest that ecdysterone binds favorably to AQP5 and may serve as a potential inhibitor of its function.

**Conclusion:** This study provides computational evidence that 20-Hydroxyecdysone (ecdysterone) binds stably to Aquaporin-5 with favorable interaction energies, primarily driven by van der Waals and electrostatic forces. The observed stability and consistent hydrogen bonding suggest that ecdysterone may act as a potential AQP5 inhibitor. These findings highlight its promise as a lead compound for experimental validation in cancer therapy.