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Computational docking and molecular dynamics study of andrographolide binding to aquaporin-4 to explore neurological edema modulation

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Neurological edema is a life-threatening condition characterized by excessive fluid accumulation within neural tissues, commonly associated with traumatic brain injury, stroke, brain tumors and other central nervous system insults. Current therapeutic approaches largely focus on symptomatic management rather than directly targeting molecular regulators of water transport. Aquaporin-4(AQP4), the predominant water channel expressed in astrocytic endfeet, plays a central role in maintaining cerebral water homeostasis and represents a promising therapeutic target. Andrographolide, a bioactive diterpenoid derived from *Andrographis paniculata*, has demonstrated notable neuroprotective properties, suggesting potential relevance in edema modulation. In this study, an in silico approach combining molecular docking and molecular dynamics (MD) simulations was employed to investigate the interactions of andrographolide with human AQP4. Potential ligand-binding regions were identified using a consensus strategy involving PrankWeb, ProteinPlus and COACH-D and further validated against reported functional residues. The receptor was embedded in a lipid bilayer using CHARMM-GUI and subjected to a molecular dynamics simulation with NAMD for 50 ns to obtain a stable conformation representing its relaxed physiological state. Andrographolide was geometry optimized using density functional theory at the RB3LYP/6-31G(d',p') level and parameterized using the CHARMM General Force Field. Molecular docking was subsequently performed using PyRx, focusing on the extracellular pore entrance of AQP4. Docking analysis yielded binding affinities ranging from -6.1 to -5.5 kcal/mol, indicating moderate but favorable ligand-receptor interactions. Key interacting residues included Arg216, Gly209, Asp69, Trp59, Thr56, Ile73, His151, and Ile205, which are associated with channel function. A 100 ns molecular dynamics simulation confirmed the stability of the AQP4-andrographolide complex, with sustained favorable interactions under dynamic physiological conditions. These results establish a computational framework for evaluating andrographolide as a therapeutic agent in neurological edema, warranting further comparative analysis and experimental validation.

Keywords:

Aquaporin-4; andrographolide; cerebral edema; molecular docking; molecular dynamics.

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