

Molecular docking and dynamics of carnosic acid-ALDH1A1 to overcome chemoresistance in ovarian cancer

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Ovarian cancer remains the most lethal gynecological malignancy, primarily due to the development of chemoresistance following platinum-based therapy. Overexpression of aldehyde dehydrogenase 1 A1 (ALDH1A1) is strongly associated with cancer stem cell maintenance, therapeutic resistance, and poor clinical outcomes, making ALDH1A1 an attractive therapeutic target. In this study, an integrated molecular docking and molecular dynamics (MD) simulation approach was employed to investigate the inhibitory potential of carnosic acid (CA) against ALDH1A1. Homology modelling generated a structurally complete three-dimensional model of ALDH1A1, and binding site prediction identified a functionally relevant catalytic cavity. Geometry optimization of CA at the B3LYP/6-311G++(d,p) level yielded a stable minimum-energy conformation suitable for docking analysis. Molecular docking performed using PyRx revealed a binding affinity of -7.3 kcal/mol. CA formed interactions with several key active-site residues, including Phe-466, Gly-475, Asn-474, Gly-468, Gly-473, and Leu-428, indicating favorable ligand–receptor engagement within the catalytic region. To further evaluate the stability of the docked complex under physiological conditions, a 100 ns molecular dynamics simulation was performed. RMSD analysis demonstrated that the ALDH1A1–CA complex achieved conformational stabilization after approximately 30 ns and maintained

stable interactions throughout the remainder of the simulation, supporting the durability and reliability of the binding mode predicted by docking. Toxicological profiling using ADMETLab 2.0 further indicated a favorable ADMET profile for CA. The observed binding interactions with catalytically significant residues, combined with sustained dynamic stability during MD simulation, suggest that CA may interfere with ALDH1A1 enzymatic activity and potentially disrupt mechanisms associated with cancer stem cell preservation and chemoresistance. These findings provide a computational basis for considering carnosic acid as a potential ALDH1A1-targeting lead compound for ovarian cancer therapy. Further in vitro and in vivo experimental validation is warranted to confirm its biological efficacy and therapeutic potential.

Keywords:

ALDH1A1, Carnosic acid, ovarian cancer, molecular docking, molecular dynamics

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