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Empagliflozin Targets NF-κB Signaling Through PTGS2 and TLR4 in Polycystic Ovary Syndrome: A Drug Repurposing Study and Molecular Simulation

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Abstract

Polycystic ovary syndrome (PCOS) is a multifactorial endocrine disorder characterized by chronic inflammation, insulin resistance, and reproductive dysfunction. Although empagliflozin, a sodium-glucose cotransporter-2 inhibitor, has demonstrated anti-inflammatory and metabolic benefits, its molecular mechanisms in PCOS remain poorly understood. This study investigated the anti-inflammatory mechanisms of empagliflozin in PCOS using network pharmacology, molecular docking, and molecular dynamics simulations. Potential drug targets were identified using SwissTargetPrediction and SuperPred, while PCOS- and inflammation-related genes were obtained from GeneCards. Overlapping targets were subjected to Gene Ontology, Kyoto Encyclopedia of Genes and Genomes, protein–protein interaction network, and hub gene analyses. Molecular docking and 50 ns molecular dynamics simulations were performed to evaluate binding affinity and complex stability. Key inflammatory targets identified included TNF, IL6, IL1B, TLR4, STAT3, and PTGS2, with significant enrichment in cytokine-mediated signaling, TNF signaling, and NF-κB pathways. Empagliflozin showed strong binding affinities for PTGS2 (−9.0 kcal/mol) and TLR4 (−8.8 kcal/mol), while molecular dynamics simulations demonstrated stable protein–ligand complexes throughout the simulation. These findings suggest that empagliflozin may alleviate PCOS-associated inflammation by modulating the TLR4/NF-κB/PTGS2 signaling axis, supporting its potential as a repurposed therapeutic agent for PCOS and providing a foundation for future experimental validation.

Keywords:

empagliflozin; polycystic ovary syndrome; network pharmacology; molecular simulation; drug repurposing