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Research Article

Decoding the Therapeutic Potential of Apigenin as a Nonpeptide *PD-1/PD-L1* Immune Checkpoint Inhibitor in Breast Cancer: An Integrated, Multimethod Study Using Network Pharmacology, Bioinformatics, Molecular Docking, and Dynamics Simulations

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There is a notable deficiency in the availability of small-molecule-based therapeutics for cancer immunotherapy, notwithstanding the limited number of compounds advancing through various phases of clinical trials. The current study investigates the inhibitory effectiveness of the dietary flavonoid apigenin on the PD-1/PD-L1 checkpoint in breast cancer, utilizing network pharmacology alongside validation through a comprehensive array of computational chemistry/biology and bioinformatics techniques. The physicochemical properties of apigenin were evaluated using the SwissADME program, while the Superpred and Swiss Target Prediction databases enabled the identification of potential targets for apigenin. Biological targets relevant to breast cancer were sourced from GeneCards, followed by an intersection with apigenin targets facilitated by the Venny 2.0 online tool. The STRING server, in conjunction with Cytoscape software, was utilized for the visualization and analysis of the networks interconnecting these targets. Protein–protein interaction (PPI) analysis elucidated the putative targets associated with apigenin. Molecular docking and dynamic simulation experiments employing AutoDock Vina, CB-Dock2, GROMACS, and iMODS platforms were conducted to investigate binding affinities and the stability of the resulting ligand-protein complexes. A total of 69 potential target genes were identified, representing approximately 5% of all targets from the Gene Cards database (1245 disease-associated targets). Enrichment analysis via the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways revealed various signaling pathways, including critical pathways such as PD-L1 expression and the PD-1 checkpoint pathway, central carbon metabolism in cancer, and the HIF-1 signaling pathway. Molecular docking and 100-ns molecular dynamics simulations showed that apigenin establishes stable, compact, and rigid complexes with PIK3R1, MTOR, and notably with STAT1, which demonstrated the lowest root-mean-square deviation (RMSD) and the highest rigidity, thereby indicating a stable bonding interaction. The findings from GEPIA2 highlighted the prognostic importance of the top five hub genes in breast cancer. The conclusions derived from this computational investigation suggest that apigenin targets essential proteins such as PIK3R1, MTOR, and STAT1, which are in turn associated with PD-L1 expression and the PD-1 checkpoint pathway, indicating its therapeutic potential in cancer immunotherapy.

Keywords: apigenin; gene ontology enrichment analysis; molecular docking; molecular dynamics simulation; network-pharmacology; survival analysis