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Molecular Docking Analysis of Flavonoids Reveal Potential of Eriodictyol for Breast Cancer Treatment

Authors : Nicole C. Valdez, Vincent L. Borromeo, Conrad C. Chong, Ahmad F. Mazahery

Abstract : Breast cancer is the most prevalent cancer worldwide, where the majority of cases are estrogen-receptor positive and involve 2 receptor proteins. The binding of estrogen to estrogen receptor alpha (ERα) promotes breast cancer growth, while it's binding to estrogen-receptor beta (ERβ) inhibits tumor growth. While natural products have been a promising source of chemotherapeutic agents, the challenge remains in finding a bioactive compound that specifically targets cancer cells, minimizing side effects on normal cells. Flavonoids are natural products that act as phytoestrogens and induce the same response as estrogen. They are able to compete with estrogen for binding to ERα; however, it has a higher binding affinity for ERβ. Their abundance in nature and low toxicity make them a potential candidate for breast cancer treatment. This study aimed to determine which particular flavonoids can specifically recognize ERβ and potentially be used for breast cancer treatment through molecular docking. A total of 206 flavonoids comprised of 97 isoflavones and 109 flavanones were collected from ZINC15, while the 3D structures of ERβ and ERα were obtained from Protein Data Bank. These flavonoid subclasses were chosen as they bind more strongly to ERs due to their chemical structure. The structures of the flavonoid ligands were converted using Open Babel, while the estrogen receptor protein structures were prepared using Autodock MGL Tools. The optimal binding site was found using BIOVIA Discovery Studio Visualizer before docking all flavonoids on both ERβ and ERα through Autodock Vina. Genistein is a flavonoid that exhibits anticancer effects by binding to ERβ, so its binding affinity was used as a baseline. Eriodictyol and 4”,6”-Di-O-Galloylprunin both exceeded genistein’s binding affinity for ERβ and was lower than its binding affinity for ERα. Of the two, eriodictyol was pursued due to its antitumor properties on a lung cancer cell line and on glioma cells. It is able to arrest the cell cycle at the G2/M phase by inhibiting the mTOR/PI3k/Akt cascade and is able to induce apoptosis via the PI3K/Akt/NF-kB pathway. Protein pathway and gene analysis were also conducted using ChEMBL and PANTHER and it was shown that eriodictyol might induce anticancer effects through the ROS1, CA7, KMO, and KDM1A genes which are involved in cell proliferation in breast cancer, non-small cell lung cancer, and other diseases. The high binding affinity of eriodictyol to ERβ, as well as its potential affected genes and antitumor effects, therefore, make it a candidate for the development of new breast cancer treatment. Verification through in vitro experiments such as checking the upregulation and downregulation of genes through qPCR and checking cell cycle arrest using a flow cytometry assay is recommended.

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