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Identification of potential inhibitors against prostate cancer metastasis drug target, human fatty acid binding protein-12: An *in silico* study

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Fatty acid-binding proteins (FABPs) play a vital role in fatty acid metabolism, cell growth and proliferation and cancer development in humans. Recent studies have revealed that FABP-12 can promote prostate cancer through activation of peroxisome proliferator-activated receptor gamma (PPAR-γ) which has previously been reported as a driver of metastasis in prostate cancer. Hence targeting the human FABP-12 might be a therapeutic strategy to control prostate cancer metastasis.

Due to the absence of crystal structure of this protein, a 3D homology model of FABP-12 was generated using crystal structure of human myelin protein P2 (PDB ID: 2WUT, Resolution: 1.85 Å) as the template by Modeller 9.23 software. The hypothetical model showed the backbone root mean square deviation (RMSD) value of 0.128 Å after superimposition with the template. Further, the structural quality of the model was validated through QMEAN, VERIFY3D, ERRAT, PROCHECK and PROSA tools.

Structure based drug discovery of the FABP-12 protein was performed using AutoDock4.2 software with a library of ligands consisting experimentally known FABP family inhibitors (BMS309403 and SBFI-26) and anti-prostate cancer phytochemicals that have been reported earlier. Molecular interactions were explored to understand the nature of intermolecular bonds between ligand and the protein binding site residues using BIOVIA Discovery Studio Visualizer. The *in silico* hepatoxicity, mutagenicity and cytotoxicity end points for experimentally known FABP family inhibitors and top docked phytochemicals were examined using ProTox-II web server.

The BMS309403 showed the highest binding affinity of -10.02 kcal/mol closely followed by celastrol, SBFI-26 and glycyrrhetinic acid with binding affinities of -9.39 kcal/mol, - 9.24 kcal/mol and -9.39 kcal/mol respectively. The inhibition constant (Ki) of BMS309403, celastrol, SBFI-26 and glycyrrhetinic acid were 44.94 nM, 131.65 nM, 167.52 nM and 200.62 nM respectively. Moreover, the *in-silico* toxicity results revealed that BMS309403 has a weak hepatotoxic potential. Notably, other three compounds obtained negative results for all toxicity descriptors, implying no severe human side effects. These computational findings indicate that celastrol, SBFI-26, and glycyrrhetinic acid have the ability to suppress FABP-12 activity and hence could be utilized as a starting point for future drug development to treat prostate cancer metastasis.

Keywords: FABP-12, Prostate cancer metastasis, Homology modeling, Molecular docking, Celastrol

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