BINDING INTERACTIONS OF ALDOSE REDUCTASE WITH BIOACTIVE COMPOUNDS EXTRACTED FROM SRI LANKAN PLANTS

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Abstract

Structure-based virtual screening has become an integral part in drug discovery efforts. Aldose Reductase (AR) plays a vital role in the secondary complications of diabetes, and it is an important drug target for the treatment of diabetes. This study was carried out to identify potential inhibitors of AR by screening against a natural product database using AutoDock Vina. The binding energies were compared with that of a known inhibitor of AR, Tolrestat. The active site residues of AR identified from the literature were confirmed based on the sites of Tolrestat binding, using Biovia Discovery Studio. For the ligand preparation, conformational analysis using molecular mechanics and semi-empirical methods was followed by geometry optimisation of the best conformer using HF/6-31G*. The initial analysis was made by examining simulation stability and protein structure. For the selected compound, beta amyrin trans cinnamate, extracted from the plant *Himatanthus articulates*, docking was carried out using AutoDock 4 and iGEMDOCK. The flexibility of the compound was considered in this process, and flexible residues of the receptor were accounted for. Molecular Dynamics was carried out to determine the stability of the receptor-ligand complex in solution medium and for free energy calculations. Furthermore, the optimised structure was used to generate RESP (Restrained Electrostatic Potential) charges for molecular dynamics. The RMSDs of the enzyme-tolrestat complex and the enzyme-beta amyrin cinnamate complex were analyzed using a 100 ns long trajectory to examine the dynamic behaviour of active site residues of AR and their interactions with beta amyrin trans cinnamate. Considering the docking results and the RMSD values from the molecular dynamic simulations we can conclude that beta amyrin trans cinnamate could be a potent non-peptide inhibitor of AR.

Keywords: Aldose Reductase inhibitors, In-silico screening, Sri Lankan plant extracts