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In-silico Reverse Docking Studies for the identification of potential of Betanin on some enzymes involved in diabetes and its complications

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ABSTRACT

Diabetes and its complication results from metabolic disorders arise due to involvement of number of enzymes. The drug discovery and development involve targeting chemical entities to potentially elicit the inhibitory activity on such enzymes. In the present work enzymes were downloaded from protein data bank (PBD) and docked against energy minimized betanin molecule isolated from the beet root using mollegro software. The MolDock result indicated that the molecule is active against enzymes in the decreasing order aldose reductase PID: 4GQQ (-191.486), alpha amylase PID: 4GQQ (-176.7), protein tyrosine phosphate PTP1β PID: 2F70 (-148.693), alpha glucosidase PID: 5NN8 (-144.983), dipeptidyl peptidase DPP-IV PID: 2RIP (-133.45). Betanin is active against all the possible enzymes involve in diabetes and its complication.

Keywords: Ziziphus nummlaria, Antidiabetic potential, Saponin, Alpha amylase activity.

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INTRODUCTION

The computer added drug discovery is potent method which minimizes the unnecessary practical experimental data collection of all the possible ligands for targeted proteins. The *Insilico* docking program predicts the various possible binding modes of the small molecules with the target protein. The reverse docking is recent immerging method which works just opposite to the basic docking process. It works on one ligand and many target protein concept in which virtual screening docking process take place for the identification of best ligand target protein complex for the optimum activity. The best possible proteins involve in diabetes and its complication was subjected to reverse docking studies using ligand betanin, the phytoconstituents isolated from beat roots.[1-3].

MATERIALS AND METHODS

Construction of Protein from database

The potential target proteins with three-dimensional crystal structure presented in research collaborator for structural bioinformatics; protein data bank was taken. Five different protein alpha amylase (PID: 4GQQ), aldose reductase (PID: 1PWM), protein tyrosine phosphate PTP1β PID: 2F70, dipeptidyl peptidase DPP-IV (PID: 2RIP) and alpha glucosidase (PID: 5NN8) were downloaded and were loaded in the Molegro virtual docker (MVD) with the removal of all water molecules. The standard Molegro algorithm was utilized for rendering the missing charges, protonation states, and assigning of polar hydrogen to the receptor.[2]

Selection and Preparation of ligand

Betanin is the main pigment of red beet which is proved to have high free radical scavenging activity have ethno medical importance in diabetes.[4-5] The smile code of structure was generated using marvin sketch and the 3D structures of the betanin was saved in .mol format. Energy minimization was done using MM2 force field. The ligand is imported to the workspace and preparation was done for docking studies.

Docking Scoring Function

The MolDock scoring function (MolDock Score) used by MVD was derived from the PLP (piecewise linear potential) scoring functions which was further improves with a new hydrogen bonding term and new charge schemes. The docking scoring function, Escore, is defined by the energy terms i.e. sum of ligand-protein interaction energy (E inter) and internal energy of the ligand Eintra. The re ranking score function was determine which is computationally more expensive than the scoring function but it is generally better

than the docking score function at determining the best pose among several poses originating from the same ligand. The rerank score in MVD provides an estimate of the strength of the interaction, it is not calibrated in chemical units and it does not take complex contributions (such as entropy) into account. Even though the rerank score might be successful in ranking different poses of the same ligand, it might be less successful in ranking poses of different ligands [3]. The interaction between the ligand and protein in the terms interaction energy, binding energy, hydrophobic interaction, hydrogen bond energy, steric energy and electrostatic energy were calculated.

RESULTS

Reverse docking results

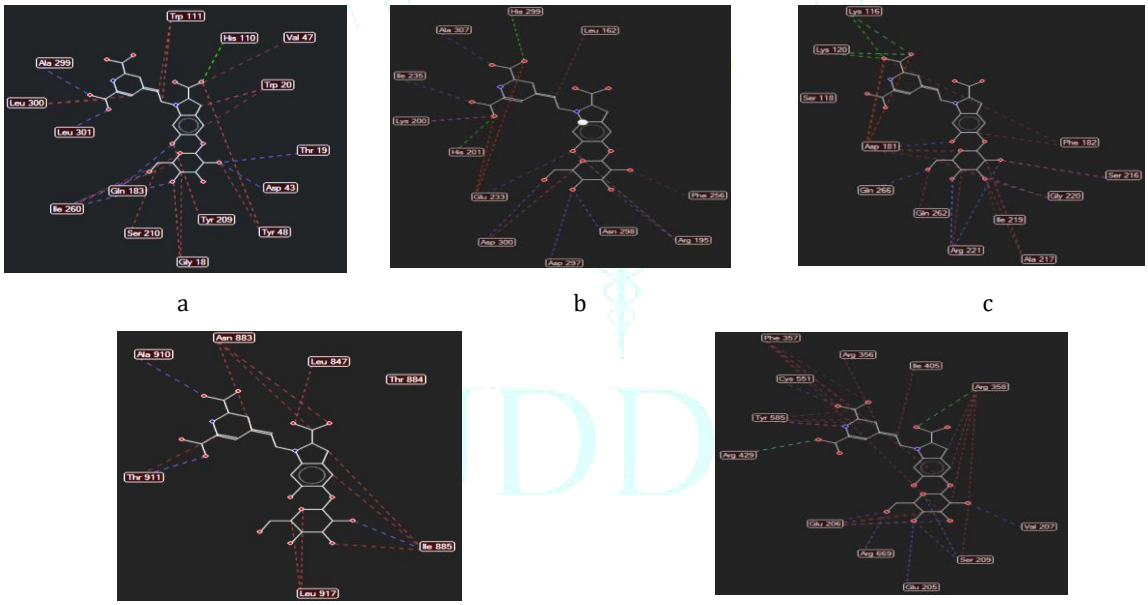
The ability of the betanin to bind with the targets proteins alpha amylase (PID: 4GQQ), aldose reductase (PID: 1PWM), protein tyrosine phosphate PTP1β PID: 2F70, dipeptidyl peptidase DPP-IV (PID: 2RIP) and alpha glucosidase (PID: 5NN8) was given and ranked in terms of MolDock Score. The MolDock Score, rerank score and hydrogen bond interaction, hydrophobic interaction, hydrogen bond energy, steric energy and electrostatic energy was determined as the parameter for analysing the docking results. The pose of the ligand which has least MolDcok score shows a strong affinity towards its enzyme target as shown in Table 1.

Table 1: MolDock Score, Re-rank Score and Hydrogen Bond energy of the docked compounds

Protein	MolDock Score kcal/mol	Re-rank Score	H-Bond
AR- PDB ID-1PWM	-191.486	-151.834	-13.6178
AA - PDB ID-4GQQ	-176.7	-150.195	-14.9588
PTP-1B - PDB ID-2F70	-148.693	-58.368	-17.0357
AG - PDB ID-5NN8	-144.983	-124.123	-6.0386),
DPPIV - PDB ID-2RIP	-133.45	-88.9211	-13.7431

AR-Aldose Reductase, AA - Alpha Amylase, PTP-1B - Protein Tyrosine Phosphate, AG -Alpha Glucosidase, DPPIV- Dipeptidyl Peptidase

Figure 1: The interaction of betanin ligand with enymes



a b c

d e

a=Aldose Reductase, b= Alpha Amylase, c=Protein Tyrosine Phosphate, d=Alpha Glucosidase

e= Dipeptidyl Peptidase

The binding patterns of the poses are captured using ligand energy inspector tool of MVD. The pose is represented in ball and stick model along with the molecular weight and the amino acids in protein are represented in stick frame model with the residue numbers.

The Figure 1 corresponds to the docking pose of betanin evaluated and captured by the ligand energy inspector tool in Molegro virtual docker.

The MolDock, Rerank score and Hydrogen bond interactions result indicated that the molecule is active against enzymes in the decreasing order respectively, aldose reductase PID: 4GQQ (-191.486, -151.834 & - 13.6178), alpha amylase PID: 4GQQ (-176.7, -150.195 & -14.9588), protein tyrosine phosphate PTP1β PID: 2F70 (-148.693, -58.368 & -17.0357), alpha glucosidase PID: 5NN8 (-144.983, -124.123 & -6.0386), dipeptidyl peptidase DPP-IV PID: 2RIP (-133.45, -88.9211 & -13.7431).

CONCLUSION

In silico Reverse docking studies of Betanin on five enzymes was performed. From the result it was concluded that betanin is active towards all the enzymes. In future isolation of betanin from Beta Vulgaris could do and from isolate, formulation will be prepared and used for the treatment of diabetes and its complications which is beneficial for the society.

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