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Molecular Docking of Flindersine with some targets related to β-cells Protection

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ABSTRACT

Diabetes mellitus (DM) is the most widespread metabolic disorder affecting millions worldwide. Molecular docking studies are useful in identifying some useful ligands which could be used to target proteins related to β-cell protection. Flindersine isolated from the plant *Toddalia asiatica* (L.) Lam. (Rutaceae) has been shown by us to possess antidiabetic property. With a view to identify *in silico* the possible mode of docking with different target proteins like PPARγ and GLUT4 which play important roles in protecting β-cells from damage. Chemical characteristics of Flindersine were retrieved from pubchem database http://pubchem.ncbi.nlm.nih.gov. The docking analysis in the active sites of 2PRG and Homology modeled protein structure of GLUT4 were performed by the Auto dock program. The docking results showed good binding interactions of the ligand with both the targets at very low energy level. In our *in silico* analysis, flindersine isolated from *Toddalia asiatica* clearly demonstrated that it could improve diabetic condition by increasing insulin secretion from remnant or regenerated pancreatic beta cells and could promote insulin sensitization and glucose uptake activities. When compared with standard drug Rosiglitazone that is commercially available flindersine can further diminish the degree of shrinkage and necrosis of beta cells of pancreas. Thus flindersine can be considered for developing into a potent antidiabetic drug.

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1. INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia that afflicts severely the world population. DM is classified into two types (type 1 and type 2). Type 2diabetes is sharply increasing globally, including in many parts of the developing world. It is expected that about 366 million people are likely to be diabetic by the year 2030 (Wild et al., 2004). Plants are acknowledged as a good source for medicines. In India, lots of plants are used traditionally for the management and control of diabetes mellitus as alternatives to synthetic antidiabetic drugs. (Singh et al., 2007).One such plant is Toddalia asiatica (L.) Lam. belonging to the family Rutaceae. The fruit is traditionally used to treat malaria and coughs; roots are used to treat indigestion and influenza and the leaves are used to treat diabetes, lung diseases and rheumatism (Muthumani et al., 2010; Rajkumar et al., 2010; Duraipandiyan et al., 2006; Karunai Raj et al., 2012). Compound flindersine was isolated from T. asiatica previously at our institute. (Duraipandiyan et al., 2009). Bioinformatics tools have become very significant to pinpoint the targets for different ligands. We made an attempt in using bioinformatics tools to evaluate whether flindersine is a good ligand to some of the target proteins related to diabetes such as PPARγ and GLUT4. The above mentioned targets were subjected to in Silico docking with a view to identify whether flindersine could be a good molecule to treat diabetes.

2. RESEARCH METHOD

Plant material, method of extraction, isolation and identification of the active compound (flindersine) procedures were published in our previous manuscript (Duraipandiyan *et al*., 2009).

2.1 Ligand preparation

Chemical structure of ligand (flindersine) was taken from Pubchem compound database, (http://www.ncbi.nlm.nih.gov/search). Three dimensional structures for flindersine were generated using ChemDraw Ultra 11.

2.2 Protein selection

Three dimensional structures of PPARγ (PDB ID: 2PRG), were retrieved from the Protein Data Bank (PDB), (http://www.pdb.org). GLUT4 protein structure was taken from our previous published manuscript (G.R. Gandhi *et al*., 2013).

2.3 Docking analysis

The docking analyses of flindersine were carried out by means of the Autodock tools (Sanner, 1999) (ADT) v1.5.4 and Autodock v4.2 program; (Autodock, Autogrid, Autotors, Copyright-1991e2000) from the Scripps Research Institute, http://www.scripps.edu/mb/olson/doc/ Autodock. To run autodock, we used a searching grid extended over the selected target proteins; polar hydrogens were added to the ligand moieties. Kollman charges were assigned and atomic solvation parameters were added. Polar hydrogen charges of the Gasteiger-type were assigned and the non polar hydrogens were merged with the carbons and the internal degrees of freedom and torsions were set. Flindersine was docked to all the target protein complexes with the molecule considered as a rigid body and the ligand being flexible. The search was extended over the whole receptor protein used as blind docking. Affinity maps for the entire atom types were present, as well as an electrostatic map was computed with a grid spacing of 0.375 E. The search was carried out with the Lamarckian Genetic Algorithm (Morris *et al*., 1998). Populations of 150 individuals with a mutation rate of 0.02 have been evolved for 10 generations. Evaluation of the results was done by sorting the different complexes with respect to the predicted binding energy. A cluster analysis based on root mean square deviation values, with reference to the starting geometry, was subsequently performed and the lowest energy conformation of the more populated cluster was considered as the most trustable solution. The hydrophobic effect of ligand was retrieved by ALOGPS 2.1. This Applet provides interactive online prediction of logP, water solubility and pKa(s) of compounds for drug design (ADME/T and HTS) and environmental chemistry studies (Stierand, 2010).

3. RESULTS AND ANALYSIS

3.1. Flindersine and its antidiabetic activity

Flindersine is one of the compounds isolated from the plant *Toddalia asiatica*. It has been traditionally used for the treatment of diabetes mellitus. We had previously carried out to determine the antidiabetic and antioxidant activities of T. asiatica leaves in STZ-induced diabetic rats. (S. Stephen Irudayaraj *et al*., 2012). The antidiabetic effect of flindersine was evaluated using the Streptozotocin (STZ) induced diabetic rat model in vet lab. Diabetic rats treated with 20 mg/kg flindersine significantly reduced fasting blood glucose level and decreased glycosylated haemoglobin (66.96%), glucose-6-phosphatase (40.07%), decreased liver marker enzymes such as AST, ALT, ALP and ACP along with lipid profile and significantly increased plasma insulin (69.05%), liver glycogen (77.15%) and muscle glycogen content (76.86%) and glucose 6 phosphate dehydrogenase (38.52%). Flindersine is a quinolone alkaloid. Reports are available for the antidiabetic activity of quinolones (Marles and Farnsworth, 1995). Hence the activity of T. asiatica leaves may be due to the presence of flindersine.

3.2. Chemical characteristic of Flindersine

Chemical characteristics of Flindersine were retrieved from pubchem database http://pubchem.ncbi.nlm.nih.gov/, Molecular Weight 227.25852 [g/mol], Molecular Formula $C_{14}H_{13}NO_2$, XLogP3-AA: 2, HBond Donor: 1, H-Bond Acceptor: 2, Rotatable Bond Count: 0, Exact Mass: 227.094629, IUPAC Name: 2,2-dimethyl-6H-pyrano[3,2-c]quinolin-5-one.SMILES: CC1(C=CC2=C(O1)C3=CC=CC=C3NC2=O)C. The Chemical properties were also checked in the ALOGPS 2.1. Chemical Formula: C14H13NO2, MW: 227.28, SMILES: CC1(C=CC2=C(O1)C3=CC=CC=C3NC2=O)C, ALOGPs: 2.58, ALOGpS: -3.12, AC_logP: 2.18, AC_logS: -2.84, Average logs: -2.98, ALOGP: 1.52, MLOGP: 2.23, KOWWIN: 2.19, XLOGP2: 2.33, XLOGP3: 1.99, Average logP: 2.14 (Tetko *et al*., 2005).

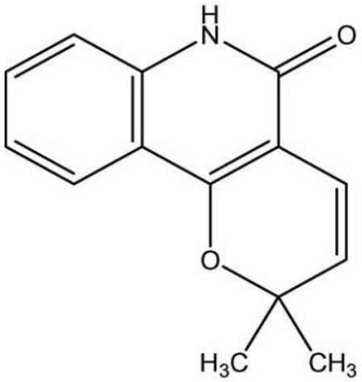

Fig. 1. Flindersine (2,6-dihydro-2,2-dimethyl-5H-pyrano [3,2-c] quinoline-5-one-9cl) isolated from Toddalia asiatica leaves.

3.3. Docking analysis

The docking analysis in the active sites of 2PRG and Homology modeled protein structure of GLUT4 were performed by the Auto dock program. It has been shown effectively and observed experimentally the binding affinities in terms of lowest docking energy. The target protein structure of 2PRG and GLUT4 were docked with flindersine which provided significant results by the least values of the binding energy. The best possible binding affinities of the flindersine at two targeted protein's active sites are displayed and their corresponding energy values are listed in Table 1 by using PYMOL tool v 1.1

Table 1: Docked amino acid residues of target proteins and their interactions with Flindersine and Rosiglitazone.

Ligand	Protein	Amino acid Interaction	Energy Value (kcal/mol)	Inhibition Constant (nM)	RMSD
Flindersine	2PRG (PPAR-Gamma)	ARG`288/HE with 43 atoms, LEU`340/O with 19 atoms	-7.2	5.24	83.35
	GLUT4	GLY`302/O with 7 atoms	-8.27	863.44	63.55
Rosiglitazone	2PRG	ARG`288/HE with 42 atoms, HIS`449/HE2 with 18 atoms	-8.18	1.01	58.31

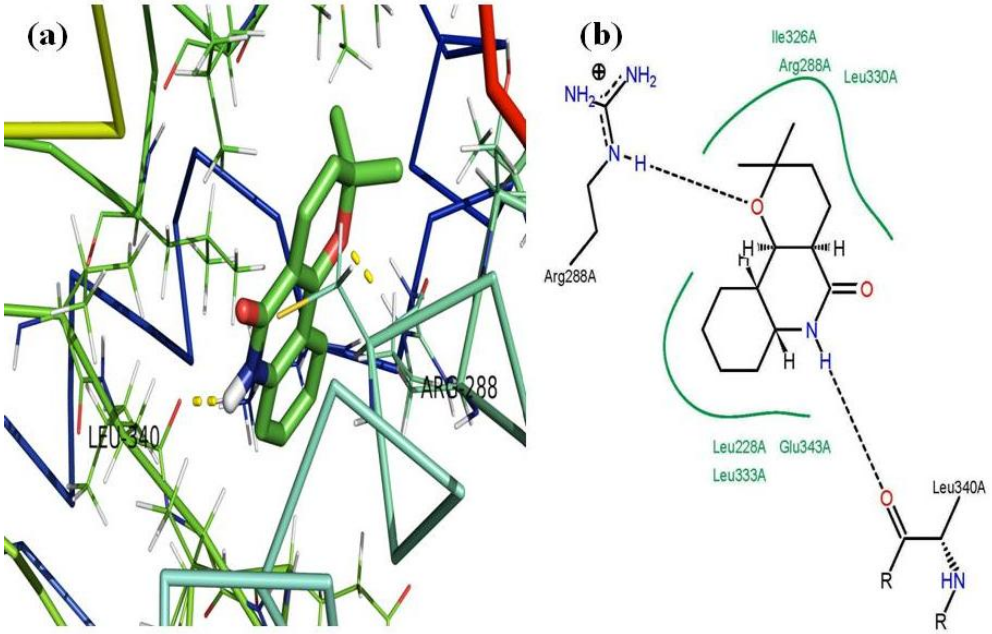

Fig 2 (a)Docked orientation of flindersine with additional depiction of corresponding amino acid residues of PPARγ, Fig 2 (b) hydrophobic interactions between flindersine and PPARγ by Pose View representation

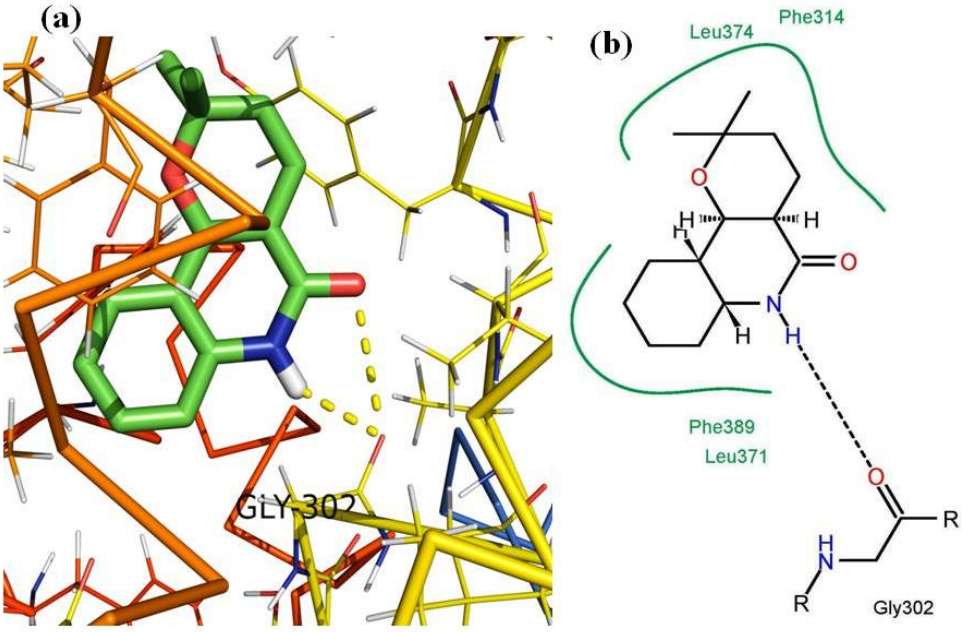

Fig 3 (a)Docked orientation of flindersine with additional depiction of corresponding amino acid residues of GLUT4, Fig 3 (b) hydrophobic interactions between flindersine and GLUT4 by Pose View representation

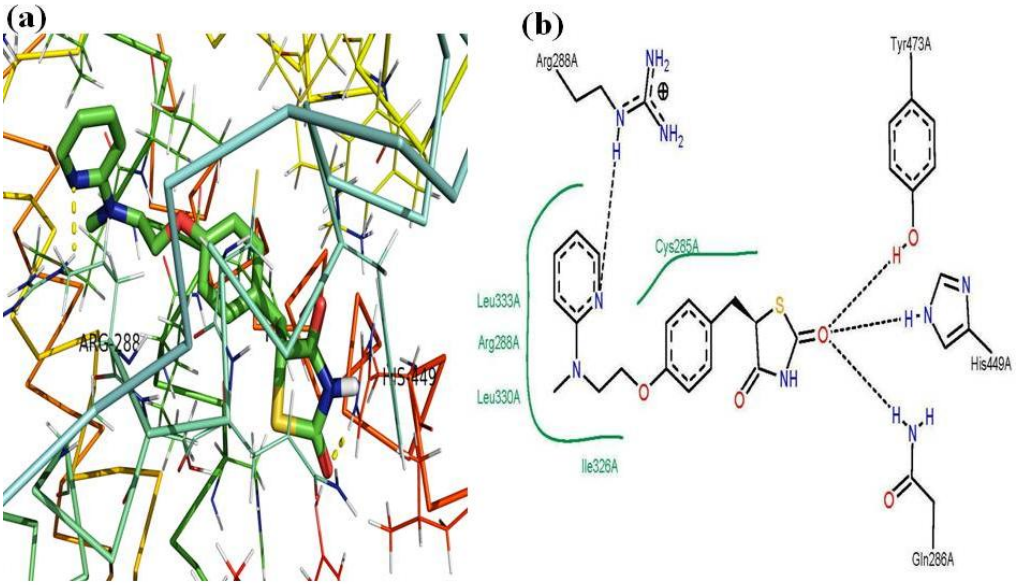

Fig 4 (a)Docked orientation of Rosiglitazone with additional depiction of corresponding amino acid residues of PPARγ, Fig 4 (b) hydrophobic interactions between Rosiglitazone and PPARγ by Pose View representation

Fig. 2 (a) shows the result of docking analysis of PPAR Gamma (2PRG) with flindersine; it showed the binding site of the protein and ligand ARG'288/HE with 43 atoms and LEU'340/O with 19 atoms. Fig. 3 (a) Glucose Transporter 4 (GLUT4) showed binding interaction of protein with ligand GLY-302/O with 7 atoms when docked with lead molecule flindersine. Fig. 4 (a). Our reference drug Rosiglitazone docked with PPAR Gamma (2PRG) showed the binding site of ARG`288/HE with 42 atoms and HIS`449/HE2 with 18 atoms. Hydrophobic interaction of the ligand-protein images are showed in figures 2(b), 3(b), 4(c).

4. CONCLUSION

Docking studies of the ligand flindersine confirmed that this is a good molecule which docks well with target proteins like PPARγ and GLUT4 with least energy values and it can improve glycaemic control mechanism in diabetic condition by increasing insulin secretion from remnant or regenerated pancreatic beta cells. When compared with standard drug Rosiglitazone that is commercially available flindersine can further diminish the degree of shrinkage and necrosis of beta cells of pancreas. In our *in silico* studies, flindersine isolated from *Toddalia asiatica* clearly demonstrated that it could be promoted insulin sensitization and glucose uptake activities by beta cells protective effects. Thus flindersine can be considered for developing into a potent antidiabetic drug.

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