Academic Sciences International Journal of Pharmacy and Pharmaceutical Sciences
ISSN- 0975-1491 Vol 4, Suppl 4, 2012

Research Article

DOCKING STUDIES ON *PEPEROMIA PELLUCIDA* AS ANTIDIABETIC DRUG

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Received: 01 May 2012, Revised and Accepted: 08 Jun 2012

ABSTRACT

Molecular docking, the technique employed for predicting and analyzing the interactions between protein receptors and ligands, is now an integral aspect in drug discovery and development area. In spite of various treatment regimens for diabetes, the third leading cause of death, there exist demand for newer molecules. Hence, the present study was aimed to screen the identified constituents of *Peperomia pellucida*, the traditionally used drug for diabetes, to determine the potent constituent attributing antidiabetic activity using *insilico* approach. Docking studies on the constituents were carried out using Autodock 4.0 software against the receptor aldose reductase. Analysis of the results clearly indicated yohimbine as the potent bioactive constituent attributing antidiabetic activity and it showed significant activity than the standard, Quercetin.

Keywords: Antidiabetic activity, *Peperomia pellucida*, Aldose reductase, Insilico approach, Docking.

INTRODUCTION

Molecular docking is the technique employed for predicting and analyzing the interactions between protein receptors and ligands. It provides most detailed possible view of drug receptor interactions and also has created a new rational approach to drug design[1]. Considering the high incidence of diseases, there is always a demand to find molecules for treatment. Diabetes, the third leading cause of death in the world, has many treatment regimens including insulin injections and oral hypoglycemic drugs[2]. Inspite of these treatment measures, most diabetic patients eventually experience long term diabetic complications, such as retinopathy, neuropathy, cataract and angiopathy. Although there is still no definite pathogenic link between hyperglycemia and diabetic complications, several mechanisms seems to be involved in the toxic effects caused by excess glucose. Among well examined factors, the activation of polyol pathway was first implicated in the etiology of secondary complications of diabetes. Aldose reductase is the first enzyme in the pathway[3]. The schematic representation is depicted in the diagram (Figure: 1).

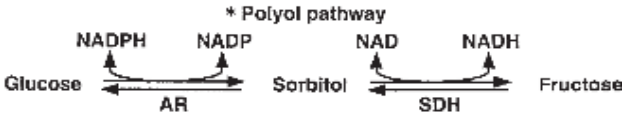

Fig. 1: Polyol pathway

Aldose reductase inhibitors can play a significant role in preventing diabetic complications. The discovery of 3D structure of aldose reductase helped to conduct molecular modeling techniques and thus will be useful for insight into the structure of enzyme bound inhibitor[4]. As traditional knowledge will serve as a powerful search engine and most importantly, will greatly facilitate intentional, focused and safe natural products research. Hence, an effort was made to screen the traditionally used herb, *Peperomia pellucida* for its antidiabetic activity using docking software, autodock 4.0 against the receptor protein aldose reductase.

MATERIALS AND METHODS

Plant material

Peperomia pellucida aerial parts were collected and authenticated. The ethanolic extract of *P.pellucida* was prepared by cold maceration process and subjected for Gas chromatographic mass studies (GCMS) for identifying the constituents present. The identified constituents are tabulated in Table: 1.

Docking studies

The action of identified constituents of *P.pellucida* alcoholic extract against aldose reductase was studied using autodock 4.0 software. The results were compared using the standard, quercetin, a natural ligand with aldose reductase activity.

Table 1: Constituents identified in *P.pellucida* ethanolic extract using GCMS

Constituents
Pentadecane
Hexadecane
1 Naphthalenol dehydrodimethyl deriv
1 Naphthalenol octahydrodimethyl deriv
Bisnorallocholanic acid
Cycloprop [e] azulene
Yohimbine
Heptadecane
Hexadeconoic ethylester
Nonadecane

Protein

The structure of aldose reductase complexed with peptide substrate was obtained from PDB data bank (PDB Code: 1IEI). The resolution factor is 1.45A° and the method of incorporation is X-ray diffraction method (Figure: 2). The minimization of the receptors were done using Swiss PDB viewer and also, the active site residue was identified. Using the control panel of this stand alone software, the ligand molecules attached to the receptor were selected. All the residues surrounding the ligand which comes in 8.0A° were identified and selected[5]. Using argus lab, ligand molecules present were removed and final preparation was done by removing water molecules and adding H-atoms[6].

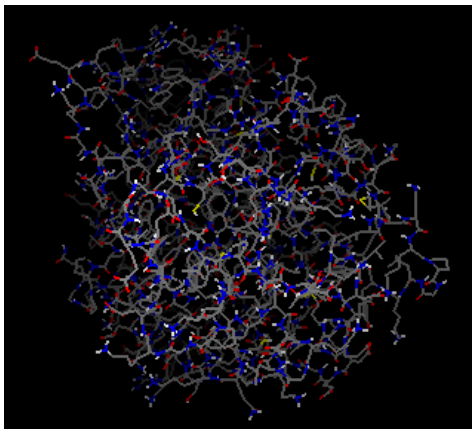

Fig. 2: Structure of 1IEI

Ligand

The compounds identified by GCMS method were then drawn using Chem.Sketch software. The smiles formula obtained from Chem.Sketch was used for the generation of 3D co-ordinate using molecular network software packages by CORINA. The minimization of the ligand was done using Swiss PDB viewer.

Docking software

Autodock 4.0 has the ability to predict the interaction of small molecule with molecular targets with reasonable accuracy and speed. Autodock performs the docking of ligand to a set of grids (pre calculated by autogrid) describing the target protein. The energy grid was built within a cubic box and docking was performed based on Lamarckian genetic algorithm[7].

Table 2: Docking results

Name of constituents	Binding energy K Cal/mol
Pentadecane	-5.94
Hexadecane	-6.38
1 Naphthalenol dehydrodimethyl deriv	-7.51
1 Naphthalenol octahydrodimethyl deriv	-7.97
Bisnorallocholanic acid	-8.01
Cycloprop [e] azulene	-6.67
Yohimbine	**-10.08**
Heptadecane	-6.6
Hexadeconoic ethylester	-7.0
Nonadecane	-6.89
Quercetin	**-9.62**

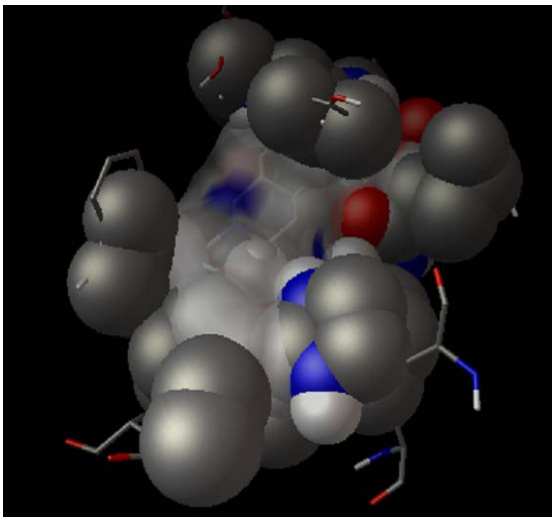

Fig. 3: Interaction of yohimbine with aldose reductase

RESULTS AND DISCUSSIONS

The constituents of ethanolic extract of *P.pellucida* were analyzed by Gas chromatographic mass spectral studies and identified 10 compounds. All the identified compounds were subjected to docking studies against aldose reductase and compared with standard, quercetin. The energy values obtained against the receptor using autodock 4.0 is tabulated in Table: 2. The binding energy between plant constituents and aldose reductase ranged from -5.94 to -10.08 K cal/mol. The binding energy of quercetin against aldose reductase was found to be -9.62K cal/mol.

The results clearly indicated that yohimbine has got maximum activity even greater than the standard compound whereas all other identified constituents also supported its aldose reductase inhibition activity. The interaction of yohimbine with aldose reductase is depicted in Figure 3.

CONCLUSION

The field of molecular docking has emerged during last three decades and now is becoming the integral part in drug discovery and development area. The present study helped to identify the potent bioactive constituent present in the ethanolic extract of *P.pellucida,* attributing aldose reductase inhibitory activity, as yohimbine among all other constituents. This result clearly demonstrates that the approach used in the study is successful in finding novel antidiabetic compounds from plants. Also, the study states and confirms the importance of small molecules from plants, their use in enhancing protein-ligand interaction studies, *insilico* and provide vital clues that can be used to design new molecules with improved activity[8,9].

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