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Molecular docking of compounds elucidated from *Ixora coccinea* Linn. flowers with insulin receptors

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ABSTRACT

The 3D structure of Insulin Receptor tyrosine kinase and the Insulin receptors 5'- adenosine monophosphate (AMP)-Activated Protein Kinase Catalytic Subunit Alpha-1 were obtained from Protein Data Bank (PDB) database. The natural compounds purified from ethanolic flower extract of Ixora coccinea Linn. were docked with Insulin receptor proteins to find out the in silico anti-diabetic activity. The structures of the metformin, quercetin, biochanin A and β – amyrin was drawn using ACD Chem Sketch and copied in to ACD 3D viewer and saved as mol file further mol file was converted to pdb by using Swiss PDB viewer. They were evaluated for the anti-diabetic activity using in silico docking study using Hex 8.0.0. software. All the 3 purified compounds showed good docking profiles with tyrosine and AMP Kinase out of which quercetin showed best when compared with the other compounds and standard drug metformin. Finally the result from the study demonstrates that the ethanolic flower extract of I. coccinea and its compounds quercetin, biochanin A and β – amyrin posses potent anti-diabetic activity against type-2 diabetes mellitus through potential activation of Insulin Receptor tyrosine kinase and AMP kinase cascade system.

Keywords: activation; Adenosine monophosphate kinase; anti-diabetic; *in silico*; tyrosine kinase.

INTRODUCTION

Diabetes mellitus is most common metabolic disease all over the world and number of diabetic patients is still on rise. Reports of 2011 indicate that about 366 million people are diagnosed with diabetes globally, and this may rise to 552 million by the year 2030 [1]. Diabetes mellitus is characterized by abnormally high levels of glucose in the blood. Majority of diabetic people are insulin dependent and depend on insulin injections.

Insulin receptor belongs to the class of tyrosine kinase receptor. The binding of insulin to its receptor causes conformational changes in the receptor leading to the activation of tyrosine kinase beta subunit. Insulin is responsible for phosphorylation of insulin receptor that leads to glucose uptake by the cells. Insulin is secreted by pancreatic islets in response to increase in blood glucose levels. Most cells of the body have insulin receptors which bind the insulin that is present in the blood circulation. When insulin is attached to insulin receptor of the cell, it initiates a cascade of events that mediates the absorption of glucose from the blood into the cell [2]. Cyclic adenosine monophosphate (cAMP) -activated protein kinase, play a key role in the insulin response and regulation. Hence, compounds that augment insulin receptor tyrosine kinase and cAMP kinase activity would be useful in the treatment of diabetes mellitus. To supplement the insulin needs, metabolites that can be administered orally and

mimic insulin action are to be considered. Molecular docking of a small molecule with the receptor is well known computational method used to predict the interactions between two molecules [3].

In the present study, the identified pure compounds quercetin, biochanin A and β – amyrin from the ethanolic flower extract of *Ixora coccinea* Linn. (data were not given) were docked with Insulin receptor proteins to find out the *in silico* anti-diabetic activity. This approach can be further investigated to generate more effective and potential insulin receptor tyrosine kinase activators through ligand based drug designing approaches.

MATERIALS AND METHODS

Preparation of Receptor for docking

The three dimensional structure of Insulin Receptor tyrosine kinase of Homosapiens was obtained from Protein Database (PDB: ID 1IR3) and the Insulin receptors 5'-AMP-Activated Protein Kinase Catalytic Subunit Alpha-1 (PDB: ID 4CFF), were imported from the Protein Data Bank (PDB) database (http://.rcsb.org/pdb/home/home.do)**.** The receptor crystallographic water molecules were removed from the protein and the chemistry of the protein was corrected for missing hydrogen. Crystallographic disorders and unfilled valence atoms were connected using alternate conformations and valence monitor options.

Design of small molecules (Ligands)

The efficacy of the identified three compounds (NMR data not given) from the *I. coccinea* flowers were docked for anti-diabetic activity against the insulin receptors. The identified compounds were drawn using ACD Chem Sketch and copied in to ACD 3D viewer and saved as mol file further mol file was converted to pdb by using Swiss PDB viewer.

Docking of Receptor with ligands

Insulin receptors (PDB: ID 1IR3; 4CFF) were docked with different ligands using Hex 8.0.0. docking software [4, 5]. Hex docking was carried out by setting suitable parameters such as FFT mode-3D fast lite, grid dimension-0.6, receptor range-180, ligand range-180, twist range-360 and distance range-40. The binding energy produced by docking action was tabulated. More negative Etotal value implies that there exists a strong interaction between ligand and receptor and that leads to activation of receptor activity.

RESULTS AND DISCUSSION

The compounds isolated from ethanolic fraction of *I. coccinea* flowers were elucidated by Nuclear magnetic resonance spectroscopy and the structure identified was simulated and presented in the Figure 1.

The HEX docking results of quercetin, biochanin A and β – amyrin with both the human insulin receptors reveal that they have the docking score (Etotal value) as in Table 1 which can be interpreted as interaction energy. More negative Etotal value implies that there exists a strong interaction between ligand and receptor and that leads to activation of receptor activity. Molecular docking of quercetin with both the receptors were shown in Figure 2a and 2b. From the docking score and Etotal value, all the three compounds were found to be more effective than the control drugs metformin.

The protein-ligand interaction plays a significant role in structural based drug designing. The molecules binding to a receptor inhibit its function and thus act as drug [6]. The protein-ligand interaction plays a significant role in structural based drug designing. Similar to our reports, docking of flavonids as insulin receptor tyrosin kinase and AMP kinase- insulin receptor activators, which may cures diabetes mellitus using hex software [5, 7]. It has been demonstrated that flavonoids can act per se as insulin secretagogues or insulin mimetics, by influencing the pleiotropic mechanisms. They may be potential activators of Insulin Receptor tyrosine kinase [4, 8].

Table 1: Docking score of interaction between the compounds with human insulin receptors

Binding parameters with phosphorylated insulin receptor tyrosine kinase Pdb.Id.1IR3	Docking Score / Etotal (Eforce+Eshape)	Eforce (binding energy of ligand)	Eshape (energy content of the protein)
Ligand: metformin	-127.54	0	-127.54
Ligand: quercetin	-226.52	0	-226.52
Ligand: biochanin A	-202.55	0	-202.55
Ligand: β – amyrin	-160.37	0	-160.37
Binding parameters with the receptor: insulin The Insulin receptors 5'-AMP-Activated Protein Kinase Catalytic Subunit Alpha-1 Pdb.Id.4CFF	Docking Score / Etotal (Eforce+Eshape)	Eforce (binding energy of ligand)	Eshape (energy content of the protein)
Ligand:metformin	-77.99	0	-77.99
Ligand: quercetin	-195.60	0	-195.60
Ligand: biochanin A	-141.66	0	-141.66
Ligand: β – amyrin	-112.00	0	-112.00

Figure 1. Structure of quercetin, biochanin A and β-amyrin

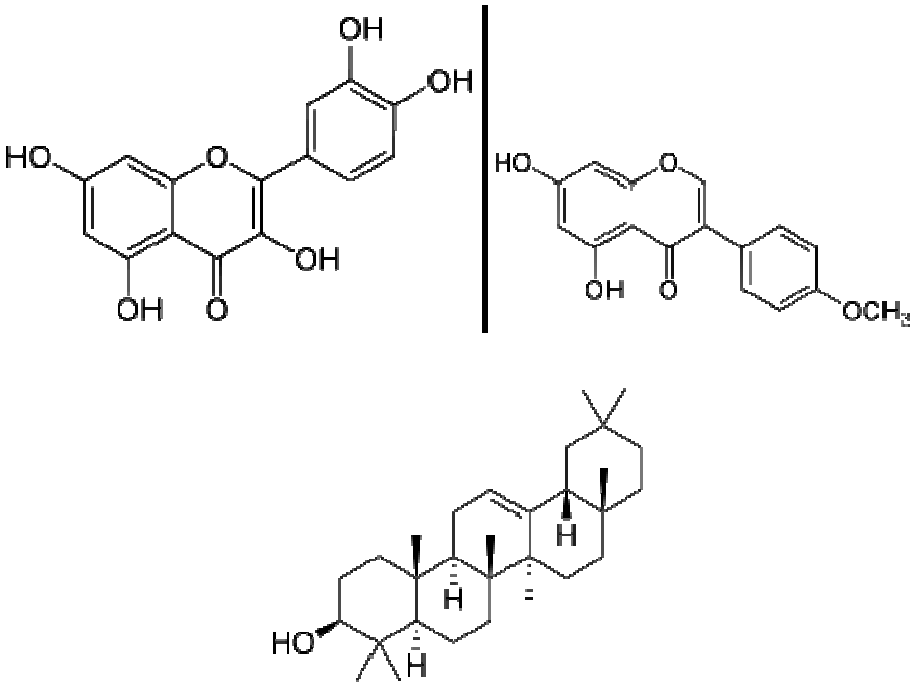


Figure 2a: Molecular docking analysis for quercetin on human insulin receptor (1IR3)

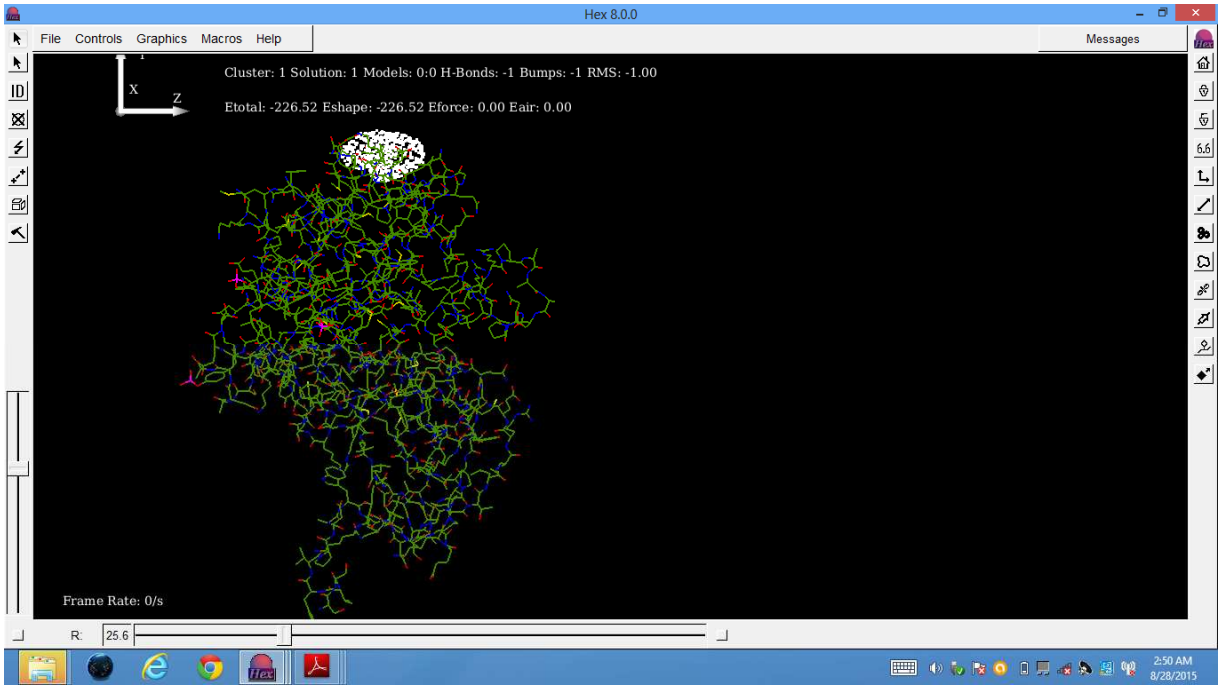
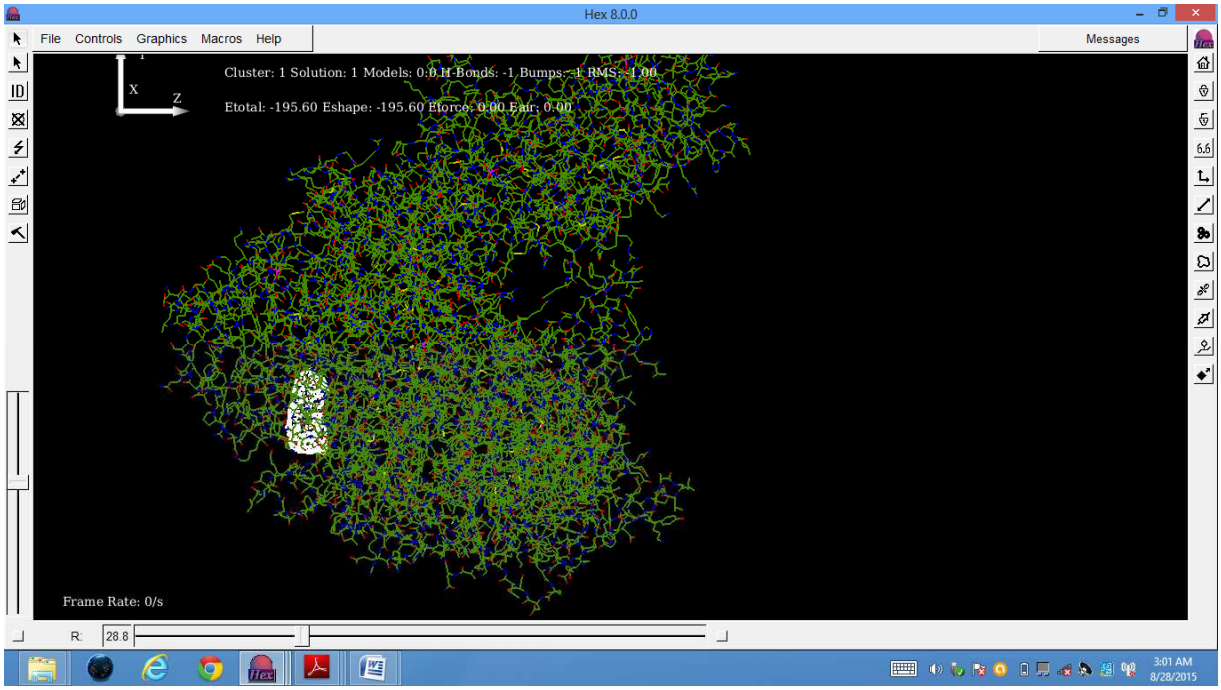


Figure 2b: Molecular docking analysis for quercetin on human insulin receptor (4CFF)



CONCLUSION

The *in silico* docking studies of 3 compounds identified from *I. coccinea* flowers with AMP kinase insulin receptor (Type 2 diabetic targets) demonstrates, all the three compounds were well docked better than standard drug. The Dock score reveals that the active compounds quercetin, biochanin A and β – amyrin may be potential activators of Insulin Receptor tyrosine kinase and have potent anti-diabetic activity. This ultimately confirms that these

compounds induce the secretion of necessary proteins and activates the Insulin receptor substrate proteins in carbohydrate metabolism for maintenance of glucose homeostasis condition during Diabetes mellitus. Therefore this study recommends that the ethanolic extracts of *I. coccinea* flowers and its identified compounds would be taken for the Type 2 Diabetes mellitus and it can be profiled for further clinical studies for the therapeutics of Diabetes mellitus.

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