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DOCKING OF *RHEUM EMODI* COMPOUNDS AGAINST PROTEIN TYROSINE PHOSPHATASE 1B

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ABSTRACT

Protein Tyrosine Phosphatase 1B (PTP1B) has been shown to be a negative regulator of insulin signaling by dephosphorylating key tyrosine residues within the regulatory domain of the β-subunit of the insulin receptor. Also PTP1B is involved in the down regulation of insulin and leptin signaling. Design of small molecule compounds inhibiting the enzymatic function of PTP1B is of great medicinal interest. The aim of the study is to design tyrosine kinase inhibitors from the plant *Rheum emodi* derived compounds namely Emodin and Chrysophanol. These plant derived compounds leads to stronger interaction with PTP1B when compared to the diabetic drug Glibenclamide.

KEYWORDS : Protein tyrosine phosphatase1B (PTP1B), Auto phosphorylation, Docking, Emodin and Chrysophanol.

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INTRODUCTION

Protein tyrosine phosphatase (PTP) 1B is the superfamily of PTPs and a negative regulator of multiple receptor tyrosine kinases (RTKs)[1]. Also PTP1B is involved in the down regulation of insulin and leptin signaling. Thus, inhibitors of PTP1B have potential as therapeutics for treating Type II diabetes and obesity[2]. Tyrosine phosphorylation is controlled by protein tyrosine kinases (PTKs) and phosphatases (PTPs). Protein tyrosine phosphatase 1B (PTP1B) has been implicated as one of the key regulators of insulin and leptin signal transduction pathways. Inhibiting PTP1B action using antisense oligonucletides and small molecule inhibitors represents novel therapeutic approach for the treatment of insulin resistance, type II diabetes, and obesity.Design of small molecule compounds inhibiting the enzymatic function of PTP1B is of great medicinal interest. In particular, PTP1B seems to regulate negatively insulin signaling by dephosphorylating the phosphor-tyrosine residues of the tissue insulin receptor kinase[3].

Insulin plays a key role in the regulation of carbohydrate; lipid and protein metabolism. Insulin exerts anabolic and anti catabolic influences on the body metabolism. Metabolic insulin signal transduction occurs through activation of the insulin receptor, including auto phosphorylaton of tyrosine (Tyr) residues in the insulin-receptor activation loop. This leads to recruitment of insulin receptor substrate (IRs) proteins, followed by activation of phosphatidylinositol-3-kinase (PI3K) and downstream protein kinase B (PKB also known as AKT),and activation and subsequent translocation of the glucose transporterGLUT4.This process is negatively regulated by Protein Tyrosine Phosphatases(PTPs), and is general mechanism for down regulation receptor tyrosine kinase (RTK) activity[4].

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The main objective of this study is to design and to propose potential tyrosine kinase inhibitors from the plant *Rheum emodi* (Polygonaceae).In this study, compounds from the plant namely Chrysophanol and Emodin and diabetic drug Glibenclamide were selected to investigate the inhibitory action of the ligand within their corresponding binding sites.

METHODOLOGY

Crystal structure of PTP1B

The crystal structure of PTP1B (PDB-ID: 1A5Y) was retrieved from protein data bank (http://www.rcsb.org) and its coordinates were selected for docking studies by AutoDock tool 4.2.

Autodock

In this step, all bound waters, ligands and cofactors were removed from the proteins. The macromolecule was checked for polar hydrogens, partial atomic Kollman charges were assigned, and then atomic solvation parameters were allotted. Torsion bonds of the inhibitors were selected and defined. Secondly, the three dimensional grid box was created by Auto Grid algorithm to evaluate the binding energies on the macromolecule coordinates. The grid maps representing the intact ligand in the actual docking target site were calculated with Auto Grid. The results of the Autodock tools were viewed in the Accelerys Discovery Studio Visualiser 2.5.

Active site analysis

The active site was analyzed by using Q site finder.The active sites of Tyrosine-Protein Phosphatase Non-Receptor Type 1 were identified using Q-Site finder are ALA35,LYS36,ASN40,LYS41,ASN42,ARG43,ASN44,ARG45,TYR46,ARG47,VAL49, SER50,PRO51,TYR66,ILE67,ASN68,ALA69,THR84,GLN85,GLY86,PRO87,LEU88,THR91,HIS94,PHE95,MET98,SER216,ALA217,GLY218 .The Protein Tyrosine Phosphatase belongs to Y_ Phosphatase family identified from pfam results.

RESULTS AND DISCUSSION

The docking of *Rheum emodi* compounds namely Emodin and Chrysophanol and the diabetic drug Glibenclamide (Fig 1a,1b and 1c) into active site of PTP1B was carried out using Autodock tool 4.2. The final docking score in Kcal/mol for each docking experiment was calculated and represented in Table no 1.

From docking of Chrysophanol (Fig 2) into active site of PTP1B, we observed three H-bonds with protein amino acid residues that are ASN 42, LYS 41, ASN 44 and Emodin with three H - bond with the protein ARG 45, ASN 44, ASN 42. Glibenclamide formed one H-bond at amino acid ARG 45 with the target protein.

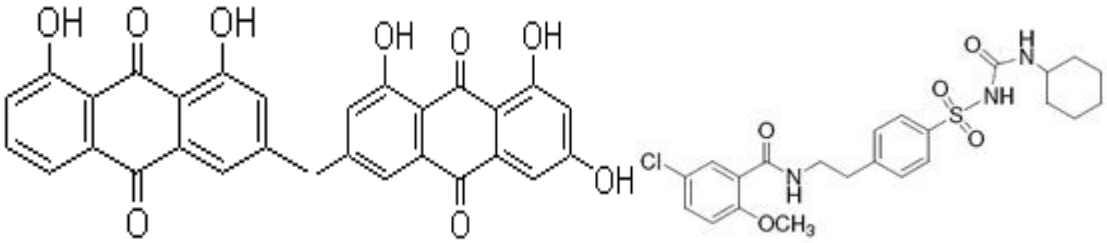

Figure 1a, 1b and 1c
Chrysophanol Emodin and Glibenclamide

Table no 1
Protein Tyrosine Phosphatases Interactions with plant Compounds

Compounds	Docking Score(Kcal/ Mol)	Key atoms	No.of Hydrogen Bonds
Chrysophanol	-5.39	O-ASN42 O-LYS41 O-ASN44	3
Emodin	-5.15	O-ARG45 O-ASN44 O-ASN42	3
Glibenclamide	-5.10	HH-ARG45	1

Hence it has been observed that both Emodin and Chrysophanol have interacted with O atom of Asn 42 and Arg 44. Plant based compounds leads to stronger inhibition with PTP1B when compared to the drug Glibenclamide. According to the report, amentoflavone, naturally occurring bioflavonoids derived from *Selaginella tamariscina*, inhibited activity of PTP1B [5].

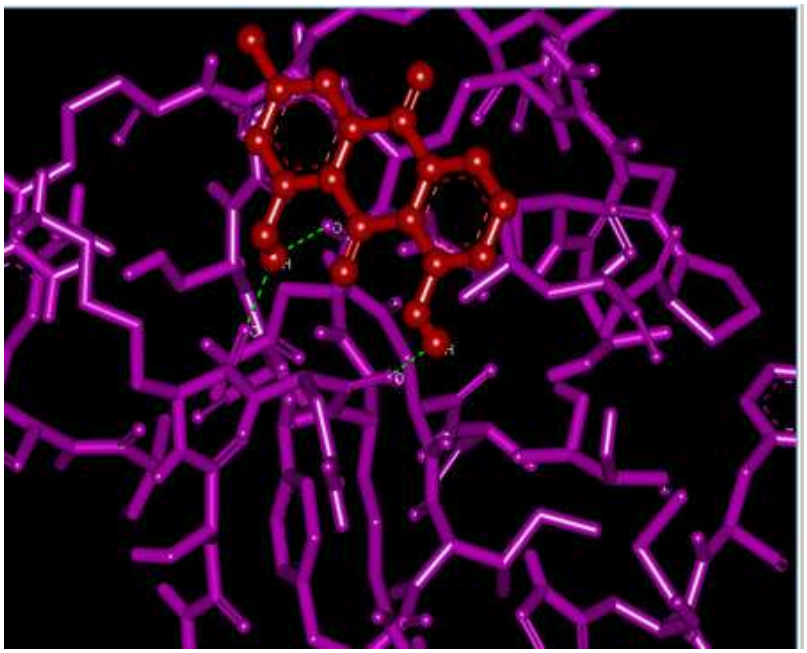

Figure 2
Chrysophanol interaction with PTP1B visualized using Accelrys discovery studio visualizer

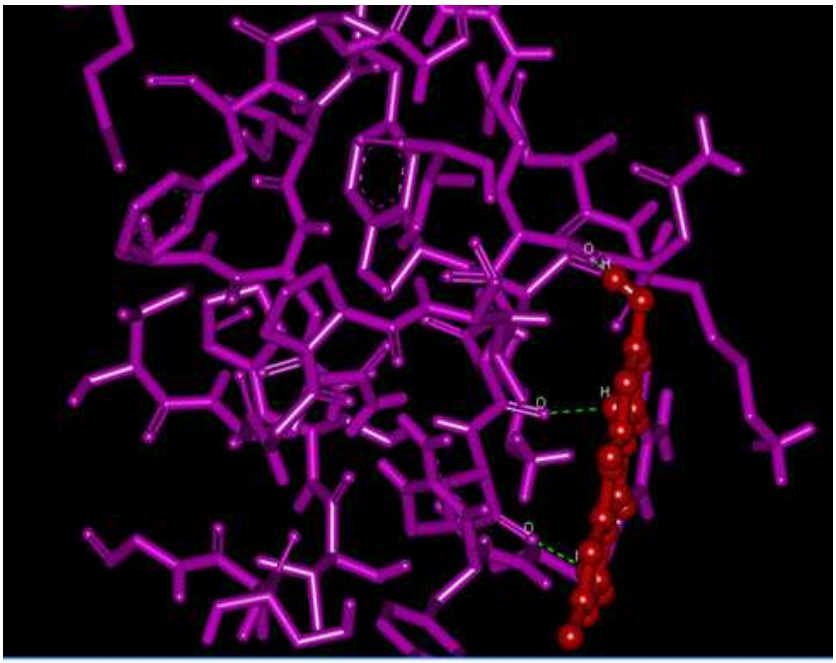

Figure 3
Emodin interaction with PTP1B protein visualized using Accelrys discovery studio visualizer

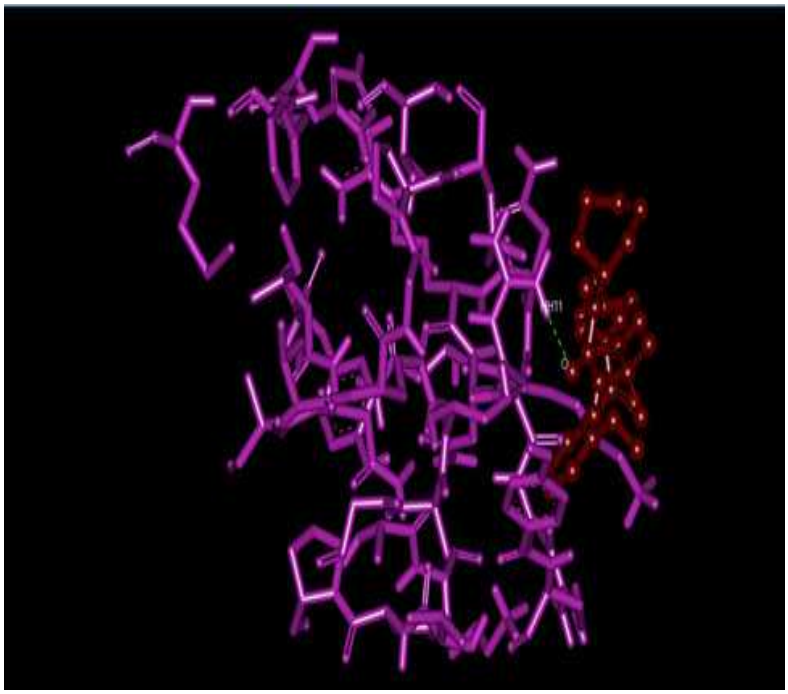

Figure 4
Glibenclamide interaction with PTP1Bprotein visualized using Accelrys discovery studio visualizer

CONCLUSION

A docking analysis of plant derived compounds into active site of PTP1B has been studied in the present work, to identify the inhibitor binding position and affinity to PTP1B using Autodock tool. The drug is mostly an organic small molecule which activates or inhibits the function of biomolecule such as protein PTB1B is a new therapeutic option to in the treatment of type 2 diabetes. Protein Tyrosine Phosphatase 1B (PTB1B) is increasing importance in the pathophysiology of insulin resistance in diabetes mellitus but also a drug target for the management of insulin resistant status such as obesity and type 2 diabetes mellitus. This study may provide a strategy for the development of novel PTP1B inhibitors.

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