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MOLECULAR DOCKING STUDIES OF HYPEROSIDE AND BETA SITOSTEROL WITH HAEMOGLOBIN AS A TARGET FOR TYPE 2 DIABETES

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ABSTRACT

Diabetes mellitus, or simply diabetes, is a group of metabolic diseases having high blood sugar, either because the pancreas does not produce enough insulin, or because the cells do not respond to the insulin. Hyperoside, β-sitosterol was taken as ligand for molecular docking with Type 2 diabetic targets. Human haemoglobin protein whose crystallographic structures are available on the PDB database as 3PI1 was used for the docking analysis using the Schrodinger tool. The docking studies of the protein haemoglobin with two ligand hyperoside and β-sitosterol reveals that these are the good molecules which docks well with targets related to diabetes mellitus. Metformin is used as a standard drug for docking with haemoglobin. Hence hyperoside and β-sitosterol can be considered for developing into a potent antidiabetic drug.

KEYWORDS:Diabetes mellitus, Hyperoside, β-sitosterol and Schrodinger.

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INTRODUCTION

Diabetes mellitus is a group of metabolic diseases that has been classified as a disease of glucose overproduction by tissues without enough insulin production, or a disease resulting from cells not responding to the insulin in human body[1]. The classic symptoms are loss of weight, polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger). Type 2 diabetes makes up about 90% of cases of diabetes with the other 10% due primarily to diabetes mellitus type 1 and gestational diabetes. The development of type 2 diabetes is caused by a combination of lifestyle and genetic factors[2]. Type II diabetes is common in individual over 40 years of age. Some of the risk factors are 1) Having food with high fat content 2) Not doing enough exercise 3) Fatty deposit in Pancreas 4) Set of genes inherited from parents makes islets cells of pancreas to wear out easily 5) Genes responsible for insulin resistance. Some of the medications include: glucocorticoids, thiazides, beta blockers etc. The goal of this paper is to present the docking analysis performed for protein haemoglobin with Hyperoside and β-sitosterol (ligand).

Haemoglobin

Hemoglobin was discovered by Hünefeld in 1840. Hemoglobin (Hb) is a ubiquitous protein found in archaea, bacteria, fungi, plants, animals etc[3]. Hemoglobin (Hb) plays a critical role in human physiological function by transporting oxygen. It can inherently bind gaseous diatomic ligands such as O_2, CO and NO via its heme prosthetic group, which is bound to the protein via the axial histidine ligands. The heme part is synthesized in a series of steps in the mitochondria and the cytosol of immature red blood cells, while the globin protein parts are synthesized by ribosomes in the cytosol. Human HbA is a tetrameric structure comprising of two αβ dimers. In adult humans, the most common hemoglobin type is a tetramer (which contains 4 subunit proteins) called *hemoglobin A*, consisting of two α and two β subunits non-covalently bound. This is denoted as $\alpha_2\beta_2$. Bacterial and yeast flavohaemoglobins, has an additional domain called FAD and NAD(P)H, which has an enzymic function to degrade nitric oxide (NO) and provide protection against nitrosative stress[4]. Hemoglobin is also found outside red blood cells and their progenitor lines. The four polypeptide chains in haemoglobin are bound to each other by salt bridges, hydrogen bonds, and the hydrophobic effect. In the case of type 2 diabetes mellitus, the levels of glycosylated hemoglobin are measured. Poor control of type 2 diabetes mellitus results in high levels of glycosylated hemoglobin in the red blood cells. Several other proteins like Protein Tyrosine Phosphatase has also been shown to be a negative regulator of insulin signalling[5].

Normal levels[6] are:

i) Men: 13.8 to 18.0 g/dL
ii) Women: 12.1 to 15.1 g/dL
iii) Children: 11 to 16 g/dL
iv) Pregnant women: 11 to 14 g/dL

Ligand Molecules

Hyperoside **(**Hyperin) is a flavonol glycoside, which is widely found in many traditional medicines, such as *Semen cuscutae*, *Balbisia calycina*, *Alchornea cordifolia*. Hyperoside has been documented to possess antiviral activity, anti-inflammatory activity, cardioprotective, hepatoprotective, and gastricmucosalprotective effects[7].

β-Sitosterol is one of several phytosterols (plant sterols) with chemical structures similar to that of cholesterol. β-sitosterol is the precursor of anabolic steroid boldenone. Sitosterols are white, waxy powders with a characteristic odor. It is widely distributed in the plant kingdom and found in *Nigella sativa*, pecans *Cucurbita pepo* (pumpkin seed) etc. It is found in fruits, vegetables, nuts, and seeds. β-sitosterol reduces blood levels of cholesterol. High levels of β-sitosterol concentrations in blood have been correlated with increased severity of heart

disease in men having previously suffered from heart attacks[8].

Metformin is the only antidiabetic drug that has been conclusively shown to prevent the cardiovascular complications of diabetes. Metformin is an oral antidiabetic drug in the biguanide class. The main use for metformin is in the treatment of diabetes mellitus type 2, especially in overweight people. The most common adverse effect of metformin is gastrointestinal upset, including diarrhea, cramps, nausea, vomiting etc. Structure of Hyperoside, Beta sitosterol and Metformin is depicted in Fig 1, 2 & 3.

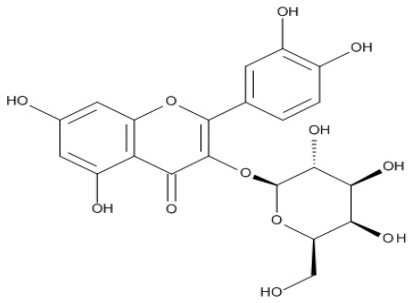

Figure 1
Structure of Hyperoside

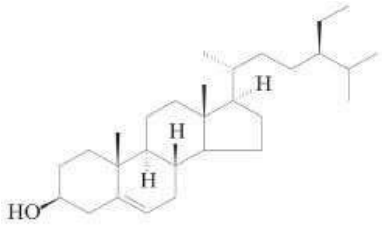

Figure 2
Structure of β-Sitosterol

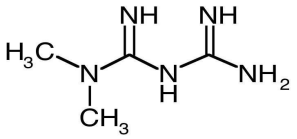

Figure 3
Structure of Metformin

MATERIALS AND METHODS

Protein Data Bank (PDB)

Haemoglobin structure was downloaded from Protein data bank with the specific resolution and the PDB id is 3PI1.

Docking by Glide

The molecular docking tool, Glide (Schrodinger - Maestro v9.3.518) software was used for ligand docking studies in to the Haemoglobin binding pocket. Glide is one of the most

accurate docking tools available for ligand-protein, protein-protein binding studies.

Ligand preparation

The LigPrep process consists of a series of steps that perform conversions, apply corrections to the structures, eliminate unwanted structures, and optimize the structures. Many of the steps are optional and are controlled by selecting options in the LigPrep panel. The process like convert the structure format, select the structures, add hydrogen atoms, remove unwanted molecules, neutralize charged groups, generate ionization states, generate low-energy ring conformations to get the output file.

ADMET predictions by QikProp

QikProp is software used to perform insilico ADMET studies of the ligand molecules. QikFit can calculate all experimental property for molecules in a test file. QikProp helps in analyzing the pharmacokinetics and pharmacodynamics of the ligand by accessing the drug like properties.

RESULTS AND DISCUSSION

Protein-Ligand interaction plays a significant role in structural based drug designing. In the present work we have docked the ligand, hyperoside and β-Sitosterol with haemoglobin (3PI1) that are used as the target for Type 2 diabetes. Docking studies on compounds prepared through LigPrep were carried out in the active site of the protein. The analysis of the docking result allowed us to know the efficiency of the natural bioactive compound to control the diabetes. With the QikProp software, a total of 44 properties of compounds can be predicted, The ADME prediction of hyperoside and β-Sitosterol shows good result as shown in Table 1 (showing the important properties).

Table 1

Showing the Properties of the ligands using QikProp software

Properities	Hyperoside	Beta sitosterol	Metformin
Molecular Weight	464.382	414.713	131.18
Dipole Moment (D)	0	0	0
Total SASA	653.477	750.024	321.506
Hydrophobic SASA	105.792	672.781	128.683
Hydrophilic SASA	342.622	48.365	192.823
Carbon Pi SASA	205.063	28.878	0
Molecular Volume (A^3)	1224.24	1456.413	497.01
Donor - Hydrogen Bonds	7	1	6
Acceptor - Hydrogen Bonds	13.75	1.7	4
QP Polarizability	37.735M	47.913M	11.168M
QP log BB for brain/blood	-3.284	-0.328	-0.324
Max transdermal transport rate	0.002	0	0.02

The docking simulation technique was performed using Glide module (Schrodinger suite[9]) with plant-derived compound hyperoside and β-Sitosterol and it was docked into the protein haemoglobin. Fig 4 shows the result for hyperoside vs haemoglobin, Fig 5 for β-Sitosterol vs haemoglobin and Fig 6 for Metformin vs haemoglobin. RMSD were checked for the reliability of docking method in reproducing the experimentally observed binding mode of the proteins. Table 2 gives the No. of bonds, Bond length and Amino acids involved in the Docking analysis. The bioactive compounds interacted well with the protein with

more number of hydrogen bonds. Active sites for haemoglobin were PHE 29, TYR 30, LEU 33, GLN 39, THR 40, PRO 43, PHE 44, GLN 65, VAL 68, PHE 69,CYS 70, GLY 72, MET 73, PHE 76, MET 93, HIS 97,GLY 101,ILE 102, ARG 103, ASP 106, LEU 107,ALA 110, TYR 111, LEU 114. Amino acid involved in the interaction of haemoglobin with hyperoside were PRO 43, THR 40, ASP 10 and GLN 65 and those involved in the interaction between haemoglobin and β-sitosterol were ASN 71 and TYR 30. Both Hyperoside and β-sitosterol have higher G score than the standard Drug Metformin.

Table 2
Shows the No of bonds, Bond length and Amino acids involved in the Docking analysis

Ligand	No of Bonds	Bond Length	Amino Acid	Protein Atom	Ligand Atom	Gscore
		1.809	PRO 43	O	H	
		2.405	THR 40	O	H	
		1.852	ASP 106	O	H	
Hyperoside	4	2.04	GLN 65	N	O	-10.5
β-sitosterol	1	2.432	ASN 71	H	O	-5.77
		2.217	TYR 30	O	H	
Metformin	2	2.145	HID 97	N	H	-5.14

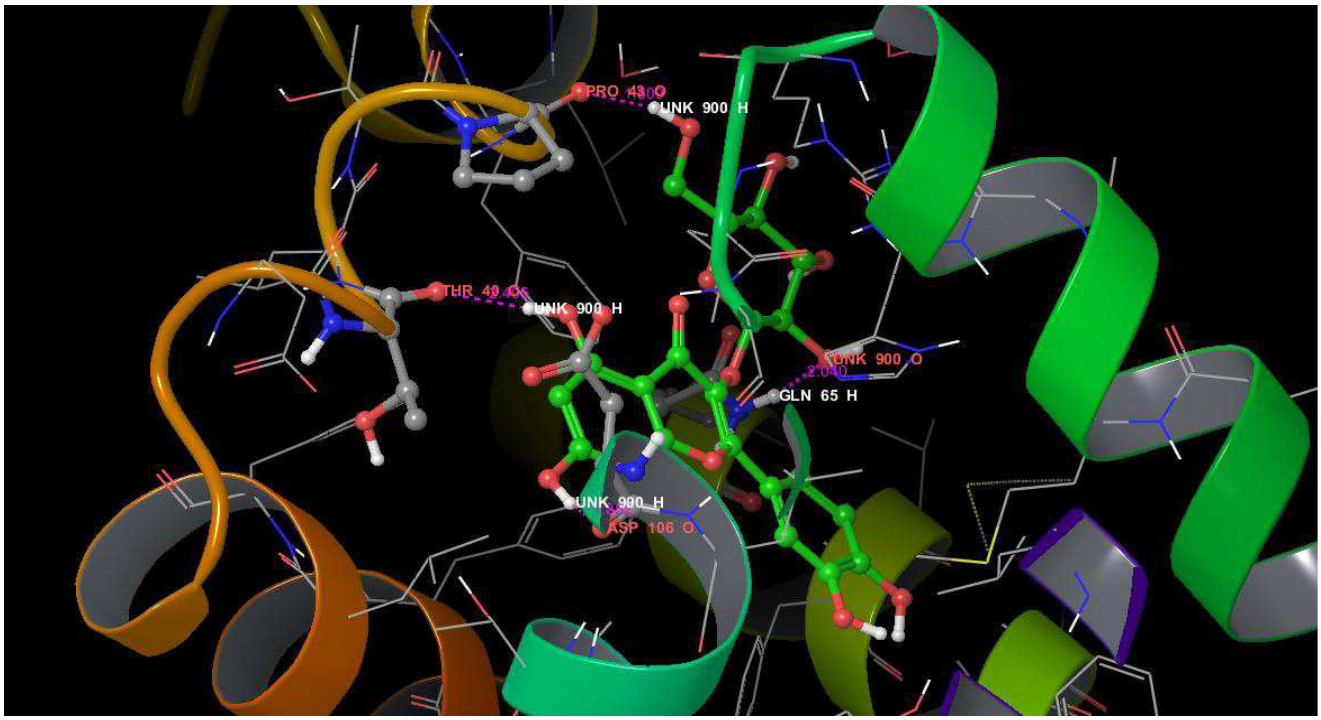

Figure 4
Docking analysis of Haemoglobin (protein) vs Hyperoside(ligand).

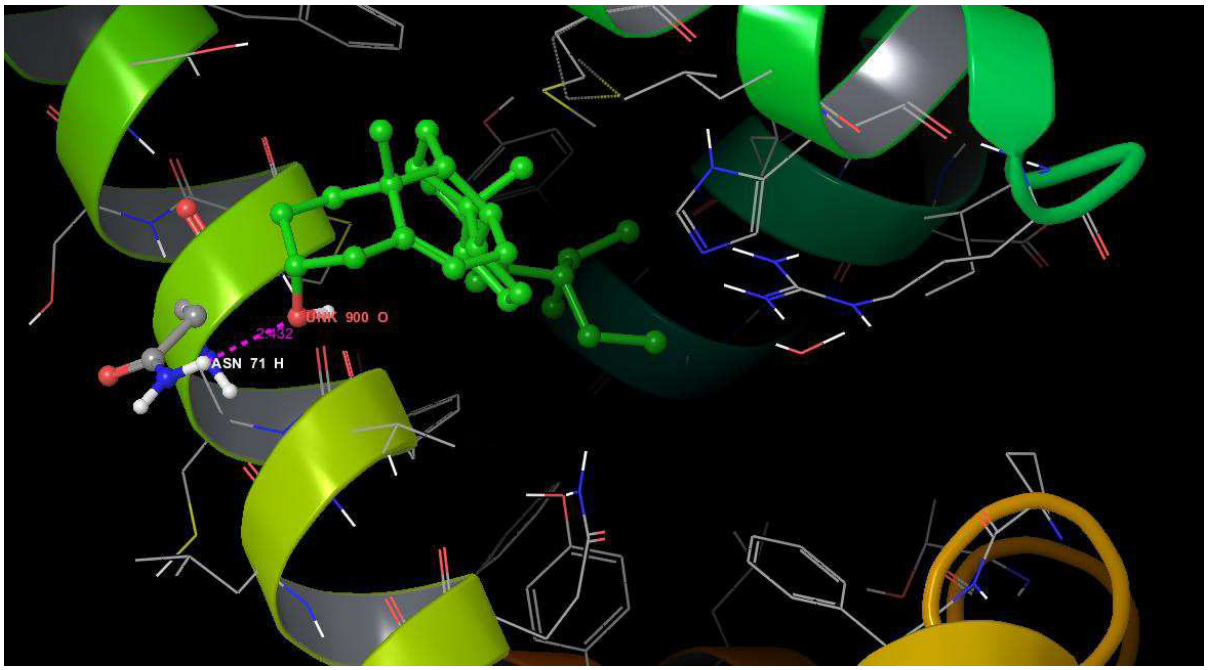

Figure 5
Docking analysis of Haemoglobin (protein) vs β-Sitosterol(ligand).

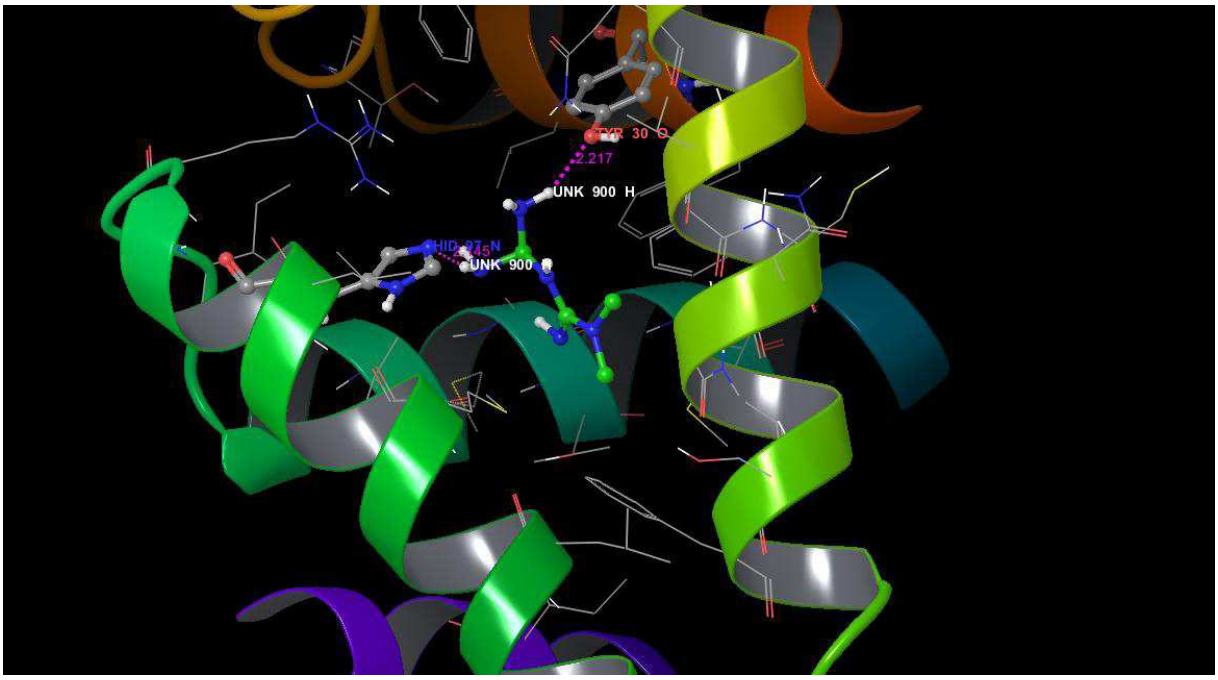

Figure 6
Docking analysis of Haemoglobin (protein) vs Metformin(standard drug).

CONCLUSION

Protein-Ligand interaction plays a significant role in structural based drug designing. In the present work we have docked the ligands hyperoside and β-Sitosterol with haemoglobin (3PI1) that is used as

the target for Type 2 diabetes. Further this may be confirmed by drug trials in animal models. This study can be further use for the synthesis of newer and may be more potent derivatives for developing newer therapy against diabetes.

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