International Journal of Pharmacy and Biological Sciences-IJPBS™ (2020) 10 (3): 271-278
Online ISSN: 2230-7605, Print ISSN: 2321-3272
Research Article | Biological Sciences | OA Journal | MCI Approved | Index Copernicus

Molecular Docking of D-Galactopyranose and Thioredoxin Interacting Protein against Diabetes Mellitus

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Received: 12 Mar 2020 / Accepted: 8 Apr 2020 / Published online: 1 Jul 2020
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Abstract
Background: The main aim of this work was to study the structure based molecular docking analysis of secondary metabolites against TXNIP to treat diabetes mellitus. Methods: Identification and selection of protein molecule Thioredoxin interacting protein (TXNIP) was done followed by identification of ligand molecules by downloading the 3D structure from PubChem and those are D galactopyranose (CID: 439404), Rhamnose (CID: 25310), Palmitic acid (CID: 985) and Tannins (CID: 250395), followed up with optimization of protein molecule by Biovia Discovery studio Visualizer, virtual screening of ligands were performed by PyRx software, performed drug likeliness property analysis of ligands via online web server Swiss ADME, docking of protein target with ligand molecule performed by autodock vina followed up with docking of target protein with best ligand molecule via Biovia Discovery Studio Client 2020 then structure was visualized through PyMol software. Results: The stability of protein TXNIP was analyzed through Rampage and Ramachandran plot was analyzed via VADAR 1.8. D-Galactopyranose (CID: 439404), Rhamnose (CID: 25310), Palmitic acid (CID: 985) and Tannins (CID: 250395) were downloaded. Virtual screening of ligands was done. Ligands selected after PyRx were D-Galactopyranose, Rhamnose and Tannins. Drug likeliness property analysis was done via Swiss ADME. D galactopyranose was the only molecule qualifying all the properties of Drug. The protein target and D-Galactopyranose were docked. It showed 9 poses with different binding affinity, Root mean square deviation Lower Bound (RMSD LB) and Root mean square deviation Upper Bound (RMSD UB). Same molecules docked with Biovia discovery studio client 2020. The drug target showed strong affinity with D-Galactopyranose visualized by PyMol software. Conclusion: The drug target showed best affinity with D-Galactopyranose. D-Galactopyranose was found to be used as an inhibitor for the protein TXNIP for the treatment of Diabetes.

Keywords
Bombax ceiba, diabetes mellitus, D-Galactopyranose, Swiss ADME, TXNIP, virtual screening

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INTRODUCTION
In the present world, diabetes mellitus which is commonly known as Diabetes is one of the most common disorders and effects the world's population. Its common manifestations include increase in hunger, thrust and urination frequency. If it is not treated properly, it can cause many problems.

"It is a chronic, complex, progressive and debilitating disease that at the moment has no cure and is characterized by partial or total deficiency in insulin production" [1]. "Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Besides hyperglycemia, several other factors like hyperlipidemia and enhanced oxidative

stress play a major role in diabetic pathogenesis. The disease is progressive and is associated with high risk of complications. It is a relative or absolute insufficiency in insulin production in the pancreas, which may result in failing and/or inadequate carbohydrate, fat and protein metabolism" [2-4].

"The term "Diabetes mellitus" is derived from the Greek words dia (=through), bainein (=to go) and diabetes exactly means pass through. The disease causes loss of weight as if the body mass is passed through the urine. Although it was known for centuries that the patient's urine with diabetes was sweet, it was not until 1674 that physician named Willis invent the name Diabetes Mellitus (from the Greek word for honey)" [5].

Diabetes insipidus is also a kind of diabetes which is different from Diabetes mellitus. It is a rare form of diabetes which is not linked to blood sugar related D.M (Diabetes mellitus) but share some of its signs and symptoms. It is simply can be defined as excessive urination (Polyuria) and complications is caused by an antidiuretice hormone known as vasopressin.

Classification of Diabetes Mellitus

Diabetes Mellitus has been classified into two types: -

- **Type 1 Diabetes**
- **Type 2 Diabetes**

Type 1 Diabetes

"In this type of Diabetes, pancreas of the patient produces little or no insulin. It develops fast, over the course of several weeks.

Type 1 diabetes (DM 1) is a chronic autoimmune disorder precipitated in genetically susceptible individuals by environmental factors" [6]. "The preclinical period is noticeable by the presence of auto antibodies to beta cell antigens, including insulin, glutamic acid decarboxylase-65 (GAD65) and the insulinoma-associated tyrosine phosphatase, IA-2. The detection of these in the serum is highly predictive of the development of T1D" [7,8]. "In addition to auto antibodies; the preclinical stage of disease is also characterized by the generation of activated, self-reactive lymphocytes that infiltrate the pancreas and selectively destroy the insulin-producing beta cells present in the islets" [9].

Type 2 Diabetes

"People having type 2 Diabetes do not respond to insulin and later in the disease often do not make enough of insulin. They do not have symptoms for many years and do not discover their condition until complications develop. The prevalence of type 2 diabetes is increasing globally" [10-12]. "Epidemiologic evidence indicates that diabetes is a major risk factor for cardiovascular disease (CVD), and recent data suggest that the CVD burden attributable to diabetes is on the rise" [13-16]. "Clinical trials have shown that intensive control of glucose decreases the risk for microvascular complications among patients having type 2 diabetes, but its effect on CVD, including coronary heart disease (CHD), stroke, and peripheral arterial disease, is not certain" [17-19].

Thioredoxin interacting protein is the protein that is the cause for diabetes. Diabetes inhibits thioredoxin function through induction of Txnip (Thioredoxin interacting protein) and causes oxidative stress.

Different allopathic medicines have been used for the treatment of Diabetes mellitus and some common medications include metformin, sulfhonylureas, meglitinides, etc. But these medications cause side effects such as nausea, an upset stomach, weight gain, skin rash and many more, that's why herbal medicines have been used to treat diabetes mellitus.

Nowadays, Herbal medicines are used to cure different kinds of complications caused by diabetes or any other disorders and it has been acknowledged globally. About 80% of the world
population depends upon the traditional medicine which is based on plant material. Many plants were evaluated for the treatment of diabetes and other disorders. *Bombax* is one of the genera which is widely used across the globe for various purpose.

Bombax genus contains different types of species such as *Bombax buonopozense, Bombax costatum, Bombax insigne, Bombax pentandrum L., Bombax albidum, Bombax anceps* and many more. Among these, *Bombax ceiba* is most commonly used because it contains many phytochemicals which can be used as a drug to inhibit the protein that causes diabetes. *Bombax ceiba* is called kings of the trees due to their huge size and flowers. It is a large deciduous tree which has a straight cylindrical stem and horizontally spreading branches. The horizontally branching system in whorls, large size and the buttress at the base are the characteristics to differentiate the species in the forest.

"*Bombax ceiba* is known commonly as silk cotton tree and semal which belongs to family *Bombacaceae*. *Bombax ceiba* is one of the important medicinal plants in tropical and subtropical India and also occurs in Sri Lanka, Pakistan, Bangladesh, Myanmar, Malaysia, Java, Sumatra and Northern Australia. It has number of traditional uses and its medicinal usage has been reported in the Indian traditional systems of medicine such as Ayurveda, Siddha and Unani" [20]. "It is known by several

names such as Red cotton tree, Indian kapok tree (English), shalmali (Sanskrit), semal (Hindi), shimul (Bengali), mullilavu (Malayalam), kondabruga (Telgu), in different languages" [21].

Bombax ceiba contains many phytochemicals which can be described as follows:

Table 1: *Bombax ceiba* with phytochemicals

Species	Phytochemicals
Bombax ceiba	3,4,5,7-tetra hydroxyl-6-methoxy Flavon-3-0- β-D glucopyranosyl-α-D xylopyranoside, tracontanol, β-sitosterol, 1, 6-dihydroxy-3- methyl-5-isopropyl-7- methoxy-8-naphthalene carboxylic acid (81) lactone, L- arabinose, D-xylose, L-rhamnose, uronic acid, 2, 3, 4, 6- tetra – o-methyl glucose, 2, 3, 6-tri-o-methyl glucose, 2- o- methyl glucose, 3-0-methyl glucose, 9 cadinane sesqui terpenoids, D-galactopyranose, tannins, palmitic acid.

Bombax ceiba containing the phytochemical D-galactopyranose is used to inhibit the protein Thioredoxin interaction protein (Txnip) that is responsible for Diabetes mellitus. In this, the phytochemical is the ligand molecule which interacts with the protein molecule i.e. Txnip which can be explained by molecular docking.

"For drug discovery, molecular docking is an important tool. Given a target protein structure molecular docking samples hundreds or thousands of orientations or conformations of a ligand at the putative binding site, evaluates the energy score of each orientation/conformation, and ranks the orientations and conformations according to their scores" [22,23].

"Ligand-induced receptor conformational changes are common in ligand binding, ranging from local rearrangements of side chains to large domain movements. In some cases, even a small change in the receptor conformation would have a remarkable effect on the ligand binding affinity, leading to failure of molecular docking in mode/affinity predictions if this conformational change is not incorporated in docking calculations" [24-26].

"In many popular docking methods, the ligand is treated as flexible, but the conformation of protein is kept rigid. This relies on the Lock-and-Key hypothesis for protein ligand binding. However, it is now widely accepted that ligand binding is not a static event but a dynamic process, in which both the ligand and protein may undergo conformational changes. Incorporating protein flexibility exponentially expands the potential search space and quickly becomes impractical in docking. Therefore, properly accounting for receptor flexibility is much more computationally expensive than doing that for ligands" [27].

METHODOLOGY

Identification and selection of protein molecule

Thioredoxin interacting protein is one of the proteins which causes diabetes mellitus. The protein target was retrieved from Protein Data Bank http://www.rcsb.org/. The thioredoxin interacting protein (PDB ID: 2DIY) was downloaded in 3D structure in .pdb format. The stability of protein was checked through Rampage http://mordred.bioc.cam.ac.uk/~rapper/rampage.php. The downloaded protein molecule was submitted to Rampage. Ramachandran plot analysis was done through VADAR 1.8.

Identification and selection of ligand molecule

The ligand molecules were selected as the secondary metabolites of the plant *Bombax ceiba.* The phytochemical constituent of the plant *Bombax ceiba* were studied through literature. All the 3D structures of the constituents from the plants were retrieved from PubChem https://pubchem.ncbi.nlm.nih.gov/. D galactopyranose (CID: 439404), Rhamnose (CID: 25310), Palmitic acid (CID: 985) and Tannins (CID: 250395) were downloaded in 3D structure from PubChem in .sdf format. Through Online SMILE Translator https://cactus.nci.nih.gov/translate/ all the molecules were converted from .sdf to .pdb format and all the ligands in .pdb format were downloaded.

Preparation and optimization of protein molecule (Biovia Discovery Studio Visualizer)

Biovia Discovery Studio Visualizer is software which is generally used for analyzing the protein molecule in distinct positions. In this software, the structure of docked molecule can also be seen. This software was used to make the protein molecule by deleting the water molecules and extra ligands if they were attached to their active sites. Initially, the protein molecule was loaded in the graphical windows and its hierarchy was analyzed by view option. By selecting the atoms, water molecules and attached ligand molecules were deleted. The protein molecule crystal structure was then saved in .pdb format. This protein molecule was then used for docking.

Virtual Screening by PyRx Software

All the ligands were screened on the basis of the minimum binding energy from the protein target. For screening of ligands PyRx software was used. The protein molecule was loaded in .pdb format and through autodock option it was converted in .pdbqt file. All the ligand molecules were also imported in .sdf format and further the energies from each ligand molecule was minimized to remove errors during interaction. All the ligand molecules were also converted from .sdf to .pdbqt format and docking was performed. The ligand molecules which showed minimum binding energy with the protein target were screened.

Drug Likeliness Property Analysis

Drug likeliness property analysis was done to analyze the ligands for their drug like properties. All the screened molecules were selected for the analysis. Through PubChem their SMILE notations were copied and drug likeliness property analysis was done through online web server Swiss ADME. Swiss ADME provides a platform to check a compound for its properties like molecular weight, Hydrogen bond donor, Lipinski rule of five. The ligands were analyzed for Lipinski rule of five, which are as follows: -

1. Hydrogen bond donors should be less than 5.
2. Hydrogen bond acceptors should be less than 10.
3. The molecular weight should be less than 500 Dalton.
4. Partition coefficient logP should be less than 5.
5. Not more than 1 rule can be violated.

Ligands which were qualifying all the above properties were screened for final docking.

Autodock vina using MGL tools

From Swiss ADME analysis, ligands were screened. Autodock Vina was used as software for docking of the protein target with selected ligand. The protein molecule was loaded in .pdb file and the protein molecule was prepared by adding polar hydrogen atoms, adding up of Kollman charges and by deleting water molecules from the protein. The protein was converted into. pdbqt format for docking. All the ligand molecules were also converted into. pdbqt format. Docking was performed and result was analyzed through PyMol.

Docking through Biovia Discovery studio client 2020

Biovia Discovery Studio Client 2020 was used to make the protein target dock with the best ligand molecule. The protein molecule was prepared for the docking purpose followed by the ligand molecule. Both protein and ligand molecules were loaded on the graphical window followed up with the addition of charges. The best docked molecule displayed the interaction of amino acids between protein and ligand. The absolute energy, clean energy, Confg Number, Mol.Number, Relative energy and Pose Number were then analyzed.

Structure visualization through PyMol software

The structure of protein in. pdbqt was loaded on the graphical window followed by out.pdbqt file and the interactions between the protein and the ligand were analyzed.

RESULTS AND DISCUSSION

The Thioredoxin interacting protein (PDB ID: 2DIY) was downloaded from Protein Data Bank as shown in **Figure 1.** The resolution of the protein was 1.40Å the gene involved was TXNIP. Thioredoxin interacting protein was involved in causing diabetes mellitus. The stability of the protein was analyzed through Rampage as shown in **Figure 2** and result of Ramchandran plot were analyzed through VADAR 1.8 as shown in **Figure 3.** D galactopyranose (CID: 439404), Rhamnose (CID: 25310), Palmitic acid (CID: 985) and Tannins (CID: 250395) were downloaded in .sdf format as shown in **Table 2.**

Fig. 1. Structure of thioredoxin interacting protein (PDB ID: 2DIY)

Residue [A 502: ARG] (65.00, 58.59) in Allowed region

Number of residues in favoured region (~98.0% expected): 88 (98.9%)

Number of residues in allowed region (~2.0% expected): 1 (1.1%)

Number of residues in outlier region : 0 (0.0%)

Fig. 2. Evaluation of protein through Rampage

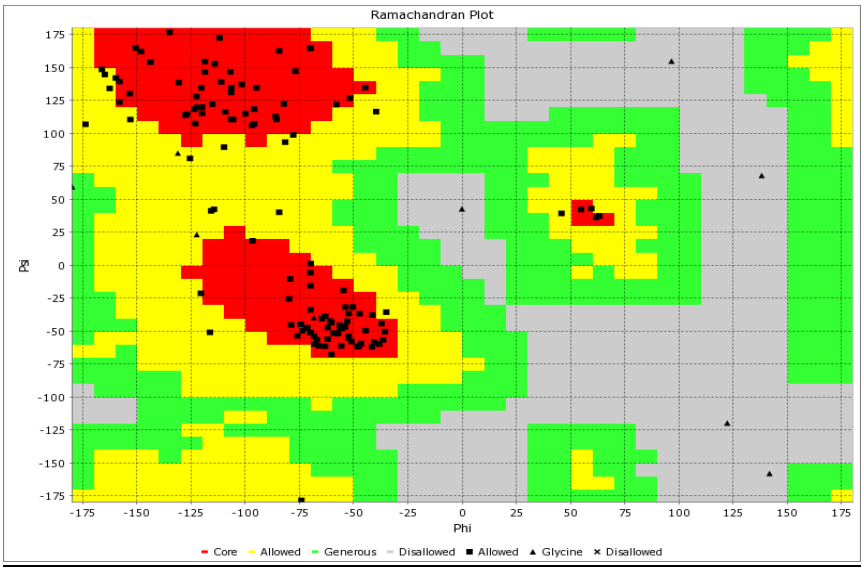
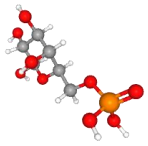
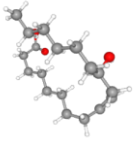
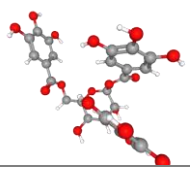


Fig. 3. Ramachandran plot

Table 2: Structure of ligands

Ligand molecule	Pubchem id	3D structure
D-galactopyranose	439404	
Rhamnose	25310	
Palmitic acid	985	
Tannins	250395	

Virtual screening of the ligand molecules from the plant *Bombax ceiba* were screened through PyRx software. According to the minimum binding energy ligands were screened. The binding affinity of D galactopyranose was -6.0 Kcal/mol, Rhamnose was -4.5 Kcal/mol, Palmitic acid was -4.3 Kcal/mol and Tannins was -6.3 Kcal/mol as shown in **Table 3** and the Binding energy of D galactopyranose was -6.0, Rhamnose was -4.5, Palmitic acid was -4.3 and Tannins was -6.4 as shown in **Table 4.** The ligands which were selected after PyRx result were D galactopyranose, Rhamnose and Tannins. These ligands were further analyzed for drug likeliness property analysis.

Table 3: Binding affinity, RMSD lower bound, RMSD upper bound, of different ligands

Ligand molecule	Binding affinity (kcal/mol)	RMSD lower bound	RMSD upper bound
D Galactopyranose	-6.0	1.41	2.686
Rhamnose	-4.5	1.584	2.942
Palmitic acid	-4.3	1.617	3.569
Tannins	-6.3	2.677	6.003

Table 4: Binding energy of different ligands

Ligand molecule	Binding energy (from docking result)
D-Galactopyranose	-6.0
Rhamnose	-4.5
Palmitic acid	-4.3
Tannins	-6.4

Drug likeliness property analysis was done through Swiss ADME and ligands were screened according to Lipinski Rule of Five as shown in **Table 5.** D galactopyranose was the only molecule qualifying all the properties of Drug, while tannins showed two violations in Lipinski's rule of five.

Table 5: Drug likeliness property analysis

Compound name	Molecular weight (g/mol)	Hydrogen donor	Hydrogen acceptor	Partition coefficient	Violations
D-Galactopyranose	260.14	6	9	-3.64	Yes,1violation: NH or OH>5
Tannins	636	11	18	-2.42	No;2violations: N or O>10, NH or OH>5
Rhamnose	164.16	4	5	-1.94	0 violations

The protein target thioredoxin interacting protein (PDB ID: 2DIY) and D galactopyranose (CID: 439404) were docked through Autodock Vina software. The result showed 9 poses with different binding affinity, Root mean square deviation Lower Bound (RMSD LB) and Root mean square deviation Upper Bound (RMSD UB) as shown in **Table 6.**

Table 6: Autodock vina result

Mode	Affinity	RMSD L. B	RMSD U. B
1	-4.9	0.000	0.000
2	-4.9	14.258	15.854
3	-4.8	1.621	2.096
4	-4.6	2.080	3.496
5	-4.5	19.641	22.313
6	-4.4	2.821	4.270
7	-4.5	2.962	6.011
8	-4.4	12.344	14.320
9	-4.4	4.147	6.003

The same molecules were further docked through Biovia Discovery Studio Client 2020 as shown in **Table 7.** The result of Biovia Discovery Studio Client 2020 is in the form of Absolute energy, clean energy, Config number, molecule number, relative energy and the pose number. The interaction was further visualized under PyMol as shown in **Figure 4.**

Table 7: Biovia Discovery Studio Client 2020

D-Galactopyranose	Absolute energy	Clean energy	Conf Number	Mol_Number	Relative energy	Pose_Number
1	-6.0	-6.0	42	1	1.65789	1
2	-5.8	-5.7	66	1	2.31694	2
3	-5.2	-5.3	76	1	1.64089	3

D-Galactopyranose showed a strong binding affinity with the drug target. The interaction of ligand and target protein was visualized through PyMol as shown in figure 4. In this in silico study, D-Galactopyranose may act as an inhibitor and it can be used in the form of drug which may control diabetes. Thus, this drug can prevent diabetes and may form effective drug for the treatment of diabetes.

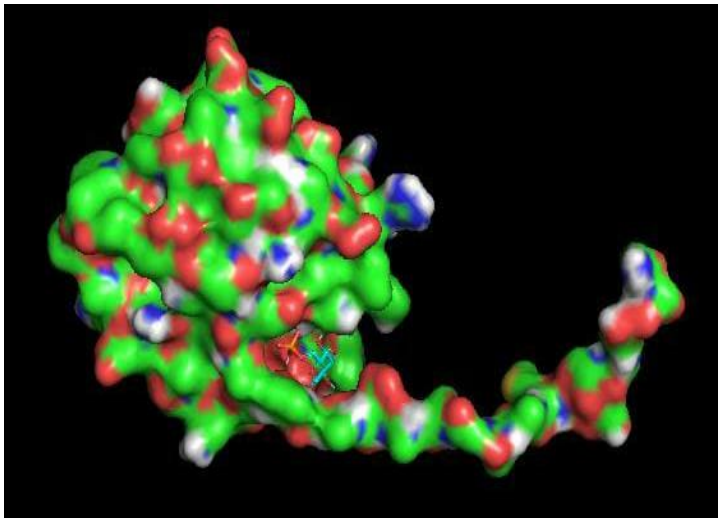


Fig. 4. Interaction of TXNIP with D-Galactopyranose

CONCLUSION

Molecular docking is an interaction of two or more molecules which lead to the stable adduct. In diabetes mellitus, the protein, thioredoxin interacting protein (TXNIP) is responsible for causing diabetes in human beings. This target protein molecule was docked with different ligand molecules i.e. D-Galactopyranose, palmitic acid, tannins, rhamnose and these were the phytochemicals which were taken from the plant *Bombax ceiba.* By performing all the steps of molecular docking, D-Galactopyranose was the only ligand which followed the Lipinski rule of five. The target protein and D-Galactopyranose were docked through autodock vina software which showed 9 poses with different binding affinity, Root mean square deviation Lower Bound (RMSD LB) and Root mean square deviation Upper Bound (RMSD UB). Same molecules were further docked with Biovia discovery studio client 2020 in the form of Absolute energy, clean energy, Config number, molecule number, relative energy and the pose number. D-Galactopyranose showed strong affinity with the target protein and was visualized via PyMol software. Therefore, D-Galactopyranose can be used as an inhibitor and can be further used as a drug for the treatment of Diabetes Mellitus after clinical trials.

ACKKNOWLEDGEMENT

The authors are grateful to Dean,and Head of the Department, Faculty of Life Sciences, and the Institute of Applied Medicines and Research, for constant support and encouragement.

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