Research Article

Molecular Interaction Studies of *Thespesia populnea* Extracts and their Analogs on Therapeutic Targets by Molecular Docking

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ABSTRACT

Most of the world population has faith on herbal medicine because of its safe administration and less side effect property. In general, Phytocompounds are being tested for therapeutic biological activity to know the mechanism of its action. In fact, diabetes mellitus is a group of metabolic diseases. Type 2 diabetes mellitus or non-insulin-dependent diabetes mellitus cases are increasing because of modern lifestyle. Despite several approved drugs are available for type 2 diabetes, there is growing need for novel therapeutic targets and inhibitors to control the disease. Often type 2 diabetes is linked with obesity due to hyper glycaemia. Therefore, in this study, we focused on *Thespesia populnea* bark and leaf extracts and their analogs against type 2 diabetes mellitus and obesity targets namely acetyl-CoA carboxylase 2 (ACC2), intestinal Maltase-Glucoamylase (MGAML), and Dipeptidyl peptidase IV (DPP4). For this analysis, molecular docking approach was used in order to establish the molecular interactions between targets and Phytocompounds.

Keywords: Molecular Docking, Molegro Virtual Docker, Phytochemicals, *Thespesia populnea*, Type 2 diabetes.

INTRODUCTION

Phytochemicals play very important role in novel drug discovery process. They are indispensable components of traditional medicines, often called Ayurveda, in India and other countries. Herbal medicines have been using as indigenous systems of medicine over the years by physicians all over the world.[1,2] Most of the population largely depends on the traditional medicine, particularly Phytocompounds. Because, it is conceived that phyto drugs are relatively safer and have lesser side effects compared to other type of drugs.[3-5] In this view, knowledge of biological effects of Phytocompounds on humans and other organisms is essential. The potency of Phytocompounds are generally tested on various drug targets. In order to establish the bioactive property of the Phytocompounds, the extracted crud mixture of compounds are separated in pure form; they would be screened for either stimulatory or inhibitory properties, such as, antibacterial[6], antifungal[7], anti-cancer[8], diabetes[9], wound healing[10], Alzheimer's[11], cardio vascular[12], respiratory diseases[13] etc.

Thespesia populnea,belongs to Malvaceae family, commonly known as Portia tree, originated from the India. It is generally used for furniture, however, its therapeutic application is not yet been identified. Therefore, in the present study, bark and leaf extracts and their analogs were docked on primarily type 2 diabetes mellitus targets and other diseases. In this study, *T. populnea* extracts and their analogs were checked for potential therapeutic targets of acetyl-CoA carboxylase 2 (ACC2)[14], intestinal Maltase-Glucoamylase (MGAML)[15], and Dipeptidyl peptidase IV (DPP4)[16] by molecular docking approach. ACC2 is therapeutic target for obesity and non-insulin-dependent diabetes mellitus (NIDDM) or type 2 diabetes. Inhibition of ACC2 by Soraphen A, Axokine, and CP-640186 could control the obesity, contrastingly, stimulation by Metformin could control the NIDDM. MGAML is primarily therapeutic target for type 2 diabetes; it can also be used for cardio vascular disorders. Acarbose, Miglitol, and Voglibose are FDA approved inhibitors of MGAML for type 2 diabetes. In addition, Acarbose is in phase III clinical trials for cardio vascular disorders treatment. DPP4 is therapeutic target for type 2 diabetes; Saxagliptin, Sitagliptin, and Vildagliptin are FDA approve inhibitors; Alogliptin and Linagliptin are in phase III clinical trials; Anagliptin and Melogliptin in phas II clinical trials; and Teneligliptin in phse I clinical trials. In the present study, Molecular interaction studies of T. papulnea bark and leaf extracts and their analogs were elucidated by insilico studies.

MATERIALS AND METHODS

Therapeutic Target Selection

In the present study, diabetic and obesity targets were identified from the therapeutic target database (TTD) (http://bidd.nus.edu.sg/group/cjttd/). Several diabetic targets were there in the database, however, we have chosen three potential targets: ACC2, MGAML, and DPP4, based on FDA approved drugs.X-ray crystal structures of the proteins were obtained from the PDB database[17]: one, Crystal structure of the BC domain of ACC2 in complex with soraphen A (PDB ID: 3JRX); two, Crystral Structure of the C-terminal Subunit of Human Maltase-Glucoamylase in Complex with Acarbose (PDB ID: 3TOP); three, Crystal structure of human depiptidyl peptidase IV (DPP-4) in complex with vildagliptin (PDB ID: 3W2T). The protein ACC2 length is 2458 amino acids, but, BC domain of ACC2 (3JRX) 217-775 residues were taken for the study.

Likewise, MGAML residues 960-1853 out of 1857 residues (A chain of 3TOP), and DPP4 residues 33-766 out of 766 residues (A chain of 3W2T) were taken for the study as shown in the table 1.

Table 1: Therapeutic targets used for molecular docking and their associated diseases

Target	TTD ID	Protein Length	Disease	PDB ID	Residues Used in Docking	Approved Drug
ACC2	TTDS00357	2458	Obesity Type 2 diabetes mellitus	3JRX	BC domain (217-775)	Metformin (Activator)
MGAML	TTDS00291	1857	Type 2 diabetes mellitus	3TOP	960-1853	Acarbose (Inhibitor)
DPP4	TTDS00093	766	Autoimmune diseases Type 2 diabetes Mellitus Obesity	3W2T	33-766	Vildagliptin (Inhibitor)

Table 2: IUPAC names, source of extraction of T. populnea compounds 1, 2, and 3; and their respective similarity scores used for analogs finding in Pubchem database. In addition, Molecular weight and predicted LogP values are shown.

IUPAC name	Source	No. of analogs	Similarity score %	Mol. Wt	pLogP
(1R,9S)-1,4,4,6,9-pentamethyl-1H,2H,9H, 10H-naphtho[2,1-c]pyran-7,8-dione	Bark	36	90	286.37	4.16
2S,3R,4R,5R,6S)-2-[(2R,3S,4S,5R)-3,5-dihydroxy-4-methyloxolan-2-yl]methoxy-6-(hydroxymethyl)oxane-3,4,5-triol	Bark	11	95	310.30	-2.80
(2S,3R,4R,5R,6S)-2-[(2E)-but-2-en-1-yloxy]-6-(hydroxymethyl)oxane-3,4,5-triol	Leaf	50	95	234.25	-1.17

Table 3: Molecular dockin scores and RMSD values of initial and final pose of the ligands

Ligand	ACC2		MGAML		DPP4	
	MD score	RMSD	MD score	RMSD	MD score	RMSD
Native	-201.253	0.622	-234.311	0.482	-121.003	0.198
Mol 1	-91.89	0.035	-77.073	0.015	-88.081	0.007
Mol 2	-142.119	0.199	-140.488	0.056	-140.231	0.066
Mol 3	-117.855	1.029	-112.127	1.547	-119.3	0.046
Analog	-150.053	0.456	-171.272	7.488	-155.289	0.402

Active site analysis

For successful docking, active site or binding site information is essential. In fact, the therapeutic targets that had been selected for this study contain protein ligand complexes. Ligand interaction residues were analyzed using PDB ligand explorer tool and visualized in PyMOL.

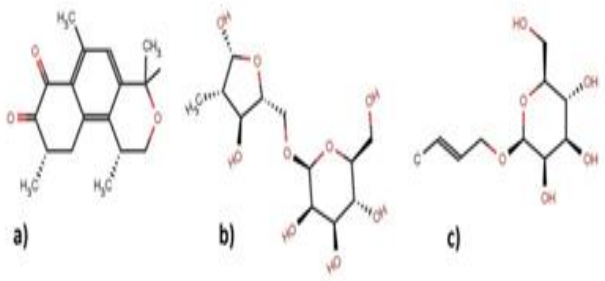

Figure 1: Extracts of *T. populnea*: a) Molecule 1 extracted from bark; b) Molecule 2 extracted from bark; c) Molecule 3 extracted from leaf.

Ligand selection

Three ligands of *T.populnea* and their analogs had been selected for molecular docking. Structures shown in the figure 1. Out of three, two were isolated (figure 1a, 1b) from the bark and one was isolated from the leaf (figure 1c). Analogs of compounds (97 molecules) were obtained from the Pubchem database[18] by more than 90-95% structure identification score as shown in table 2.

Molecular Docking

Molegro Virtual Docker 6.0 (MVD)[19] had been used for the molecular docking of *T. populnea* compounds, which were extracted from bark and leaf; 97 analog compounds which were collected from pubchem database, and type 2 diabetes mellitus targets ACC2, MGAML, and DPP4.

RESULTS AND DISCUSSION

Active site analysis

Active site analysis of three targets was analyzed in PDB ligand explorer. ACC2 active site contains Val273, Lys274,

Arg277, Ser278, Pro590, Glu593, Met594, Val598, Asn599, Trp681, Phe704, and Ser705 residues. MGAML active site contains Asp1157, Asp1279, Trp1355, Met1421, Arg1510, Asp1526, Phe1559, and His1584 residues. DPP4 active site contains Glu205, Glu206, Tyr547, Ser630, Tyr631, Val656, Tyr662, Tyr666, Asn710, and Val711 residues. Further, in MVD same pockets were used for docking. Docking grid of 15Å was used.

Molecular docking

The impact of *T. populnea* extract compounds and their 97 analogs were analyzed by molecular docking in MVD. Native ligands of the protein complexes have been docked for the validation of the docking. They had reported reliable RMSD (root mean squared deviation) values between final pose and native ligand. ACC2, MGAML, and DPP4 had reported RMSD values of 0.662, 0.482, and 0.198 respectively. The MVD moldock scores (MD score), RMSD of extracts, analogs, and native ligands are shown in table 3. It is evidenced from the docking score that native ligands had shown high binding affinity compared to other ligands. After native ligands, analogs had shown high binding affinity followed by extract 3, extract 2, and extract 1 against all the targets as shown in the figure 2.Among all the targets, the binding affinity of molecule 1 and 2 is high for ACC2 protein, while, molecule 3 is for DPP4 (table 3). The binding interactions are shown in figure 3.In molecule 1, H-bond donors or acceptors were absent; in addition, it does not have torsions in the structure, thus poor binding interaction had been reported with ACC2 target compared to other extracts (figure 3a, 3b). In molecule 2, one H-bond interaction (green dashed arrow) was found between amino acid main chain residue Asn679 and O8 (4.5Å); in addition, it has 4 torsions in the structure, thus highest binding affinity had been reported with ACC2 target compared to other extracts (figure 3c, 3d). In molecule 3, six H-bond interactions (blue dashed arrows) were found between amino acid side chain residues: Lys122-O2 (5.3Å), Asp739-O2 (4.2Å), Asp709-O3 (3.6Å), Arg125-O4 (3.2Å), Asn710-O4 (4.4Å), and Arg125-O5 (4.4Å); in addition, it has 4 torsions in the structure, thus, second highest binding affinity had been reported with DPP4 compared to other extracts (figure 3e, 3f).

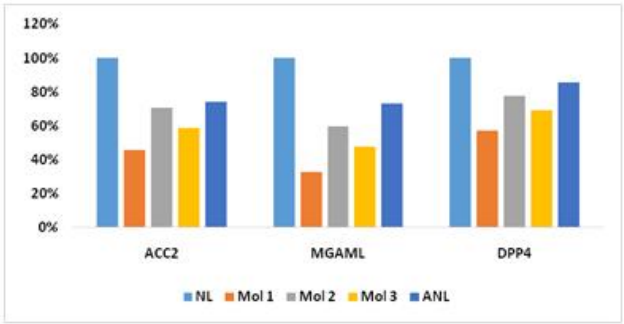

Figure 2: Binding affinity of native ligand (NL), extract 1 (Mol 1), extract 2 (Mol 2), extract 3 (Mol 3), and analog (ANL). The binding affinity is more for native ligand followed by analog, extract 2, 3, and 1.

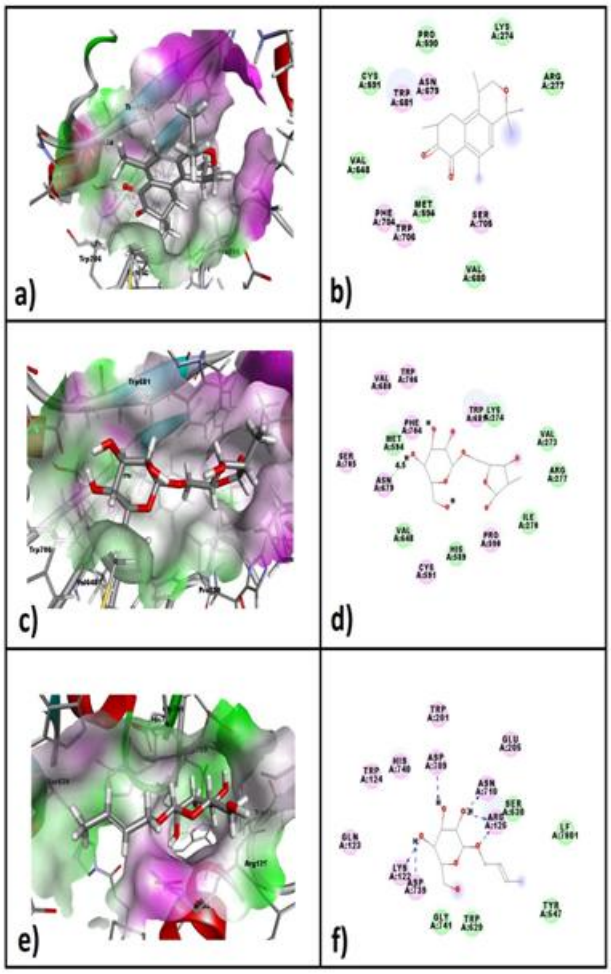

Figure 3: Binding interactions of *T. populnea* extracts in the type 2 diabetes mellitus targets after docking: a) molecule 1 in complex with ACC2; b) Residues of ACC2 around the molecule 1; c) molecule 2 in complex with ACC2; d) Residues of ACC2 around the molecule 2; e) molecule 3 in complex with DPP4; and f) Residues of DPP4 around the molecule 3. H-bond donors are shown in Pink colour, and H-bond acceptors are shown in green colour in a, c, e. Non covalent interactions: Electrostatic (pink), Vander waals (green), H-bond with amino acid main chain (green dashed arrow), and H-bond with amino acid side chain (blue dashed arrow) are shown in b, d, f.

CONCLUSION

Phytocompounds are being used to treat the several diseases like diabetes, cancer, inflammation, allergies, and Alzheimer's etc. for years. There is a notion that Phytocompounds exhibits less side effects; are safe. In the present study, T. populnea bark extract: molecule 1 and molecule 2; leaf extract (molecule 3) were analyzed against type 2 diabetes mellitus targets ACC2, MGAML, and DPP4 by molecular docking approach. However, ACC2 and DPP4 are also therapeutic targets for obesity. Hypoglycemia could be achieved by either stimulation or activation of ACC2, or inhibition of MGAML and DPP4. Therefore these targets were docked with T. populnea extracts and their analogs that were collected from the

pubchem database. The therapeutic targets that were selected for the study contain native inhibitors. In order to compare the binding affinity between ligands native inhibitors of targets also docked. In conclusion, native ligands had shown highest binding affinity followed by analog compounds. In *T. populnea* extracts, molecule 2 of bark extract and molecule 3 of leaf extract had shown highest binding affinity, but, molecule 1 of bark extract had shown poor binding affinity. In fact, this is a preliminary study to evaluate the activity of the *T. populnea* extracts against type 2 diabetes. However, further studies are required to conform the activities. Finally, these studies are useful to design novel derivatives of extracted molecules, which can be evaluated against many diseases.

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