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IN SILICO EVALUATION OF ANTIDIABETIC ACTIVITY USING MOLECULAR DOCKING AND ADMET PREDICTION OF COMPOUNDS FROM *FICUS BENGALENSIS* LINN

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ABSTRACT

Diabetes mellitus is a prevalent metabolic disorder requiring safer and more effective therapeutic alternatives. The present study aimed to investigate the antidiabetic potential of phytochemical derived from *Ficus bengalensis* Linn through in silico molecular docking and ADMET prediction. Phytoconstituents were collected from *F. bengalensis* extract and subjected to molecular docking studies using PyRx with AutoDock Vina. The crystal structures of key diabetes-related protein targets, α-amylase (PDB: 4A5S) and α-glucosidase (PDB: 6FZP), were employed for binding affinity evaluation. The interaction profiles were analyzed to determine binding scores and key amino acid interactions. To assess drug-likeness and pharmacokinetic feasibility, ADMET properties were predicted using Swiss ADME. Compound displayed favorable binding affinities toward both target enzymes, suggesting inhibitory potential. Docking analysis revealed stable interactions with active site residues, indicating possible modulation of carbohydrate metabolism. ADMET predictions demonstrated that the extracted compounds complied with Lipinski's rule of five and showed acceptable pharmacokinetic and safety profiles. The findings suggest that bioactive constituents from *Ficus bengalensis* may serve as promising

antidiabetic lead molecules. Further in vitro and in vivo validation is warranted to substantiate their therapeutic potential.

KEYWORD: α-glucosidase, DPP4, ADMET prediction, diabetes, molecular docking, *Ficus bengalensis.*

INTRODUCTION

Ficus bengalensis Linn. substances were evaluated for their ability to inhibit α-glucosidase. To ascertain the compounds' in silico α-glucosidase inhibitory efficacy against human intestinal α-glucosidase, molecular docking was used. Additionally, ADMET characteristics and drug-likeness prediction of the best binding compounds with a higher or similar binding affinity to the standard acarbose were performed. The molecular docking and pharmacokinetic prediction of chemicals identified in Ficus bengalensis Linn have not yet been the subject of any local or international studies, as far as the researchers aware. Therefore, this study can be used to inform and guide the scientific community regarding the compounds' potential as α-glucosidase inhibitors.

MATERIALS AND METHODS

The literature review has led to the selection of Ficus bengalensis Linn (Moraceae) for dissertation work. This tree is indigenous to India and is found throughout the nation. Summer, monsoon, and winter are the three distinct seasons that make up the study area's tropical climate. The warmest months are April and March through May, when temperatures can reach 35°C to 39°C. The monsoon season, which lasts from June to September, is brought on by the South West monsoon wind and has a mean annual rainfall of 772 mm. between November and February is the winter season. With an average temperature ranging from 10°C to 29°C, the weather is quite pleasant. The month of December is the coldest. The lowest temperature is 10^{o}C.

The Pimpri Chinchwad area has invigorating climate throughout the year, it is high altitude, moderate rainfall and a green covering. In the first week of July, the monsoon season begins and lasts until the middle of September. The average yearly rainfall in Pimpri Chinchwad during this time is 700–800 mm. During the rainy season, the relative humidity can reach 70–80%, while on hot afternoons, it can drop as low as 30%. The plant was gathered from Chinchwad. (India, Pune, M.S.) The specifications of the sample that was gathered were as follows: Spring is the collection season. Collection month April is plant stage. Fruit

Identification: The Botanical Survey of India, Western Regional Center, Pune, verified the authenticity of a fresh and mature Ficus bengalensis Linn plant that was gathered from the roadside area of Pimpri-Chinchwad, Pune, India, during the summer of April 2018. Reference number for the letter (BSI/WRC/100-1 / DEN. CER. 2018/80.) Dated August 8, 2018.

Ficus bengalensis, fresh, ripe aerial portions Linn was gathered in large quantities, washed well with purified water, and then allowed to dry in the shade for 15 days following the necessary verification. A mechanical grinder was used to coarsely powder the materials after they had dried in the shade, and they were then stored in a nylon bag in a deep freezer until they were needed.[1,2,3]

Extraction Method

Material

Petroleum ether, Ethanol, Chloroform.

Method

The pharmaceutical process of extraction uses specific solvents in typical extraction processes to separate the medicinally active parts of plant or animal tissues from the inactive or inert components. Plants were continually extracted using petroleum ether while enclosed in Soxhlet apparatus. After removing petroleum ether, 95% ethanol was used to extract the powdered defatted medication.

The resulting alcoholic extract was then further fractionated using water and chloroform. Each extract and fraction's solvents were extracted using distillation, with the remaining solvent traces being eliminated under low pressure. In order to conduct additional experiments, the extracts were kept in a refrigerator.

Isolation: The Chloroform Fraction of Ficus Bengalensis Linn was studied using column chromatography and thin layer chromatography. To confirm the structure of the stigmasterol compound isolated from the chloroform fraction of Ficus bengalensis, additional structural characterization and elucidation were conducted.

Enzyme Preparation The protein data bank (PDB) file format for the α-glucosidase inhibitor crystal structure, ID 3A4A, was obtained from the RCSB PDB (https://www.rcsb.org/). The α-glucosidase was cleaned of water molecules and heteroatoms using Chimera 1.18. The docking technique used chain A of the α-glucosidase (3A4A) since it is an asymmetric-C1

(Figure 1). Additionally, the same molecule was docked with PDB ID: 6fzp: EDK is the ligand linked to type 2 insulin-resistant diabetes, which is caused by PPARG. At UCSF Chimera, the pre-processed enzyme was subsequently made and hydrogens were added. In pdbqt format, the enzyme file was stored. In the rest of the work, the produced α-glucosidase is just called α-glucosidase.[1][4]

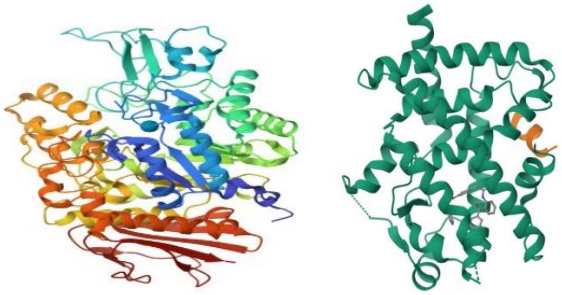

Fig. 1: 3A4S and 6fzp.

Ligand Preparation sdf file, were prepared using the DS Visualizer. Hydrogens were added to the ligands, then the ligands were typed with Merck molecular force field (MMFF) and saved as pdb files. The ligand files were converted to pdbqt file using Open Babel tool in PyRx.[2][5]

Molecular Docking The molecular docking was carried out using Auto Dock Vina in PyRx version and the binding site residues were identified using DS Visualizer. The remainder of the text refers to AutoDock Vina as Vina. From the 6fzp, the basic EDK was taken out. Using DS Visualizer, hydrogens and MMFF charges were added to it. To compare with stigmasterol, the optimal technique that yielded a pose with a low root mean square deviation (RMSD) was found by re-docking the produced EDK to the binding site of the 6fzp using various grid box and exhaustiveness settings. A good position was one with an RMSD value of 0. After the docking approach was validated to EDK, the 10 ligands were docked to the 3A4A and 6fzp.[6]

ADMET and Drug-likeness Prediction: Each compound's simplified molecular input line entry system (SMILES) was imported into the Swiss ADME and pkCSM cheminformatics web tools after being copied from PubChem in order to determine its ADMET characteristics. Swiss ADME also predicted drug-likeness and Lipinski parameters. The outcomes were shown in Table.[7]

Toxicity Study

The web application "Prediction of Toxicity of Chemicals (ProTox-III)" (https://tox-new.charite.de/protox_III/) is designed especially for forecasting the toxicity of compounds before the drug development process begins. Using an advanced method, ProTox-III considers the distance between unknown molecules and the average fatal dose (LD50) of recognized compounds in addition to combining known dangerous components. To assess toxicity, the structural files of potential compounds are converted into SMILES format and uploaded to the ProTox website.

In addition to toxicity levels and predicted LD50 values, the output also includes cytotoxicity, immunotoxicity, mutagenicity, carcinogenicity, and hepatotoxicity. The ProTox-III web server also establishes a chemical's hazard class, from I to VI, based on the LD50 value, in accordance with the standards of the globally standardized system of categorization and labeling of chemicals. ProTox III and other supporting technologies have been created to quickly predict the potentially harmful effects of prospective therapeutic compounds in order to assess the potential harm that specific chemicals may bring to the human body. The LD50 was determined to be 890 mg/kg, and the predicted toxicity class was 4. Table 4 presents the thorough prediction outcomes from this section.

RESULTS AND DISCUSSION

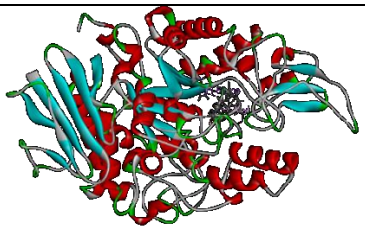

Fig. 2: Interaction with 4A5S

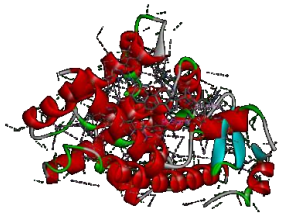

Fig. 3: Interaction with 6fzp.

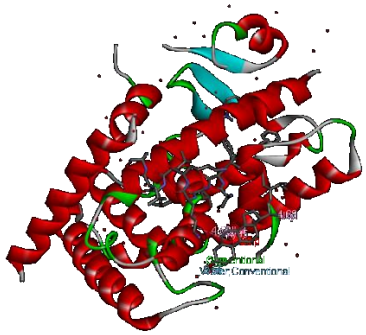

Fig 4: EDK Interaction

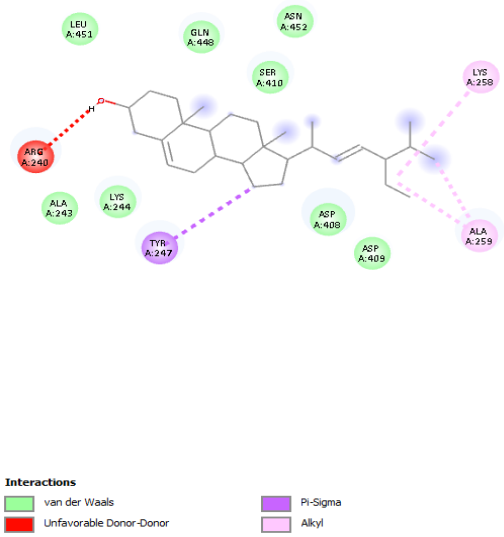

Fig. 5: 6FZP interaction.

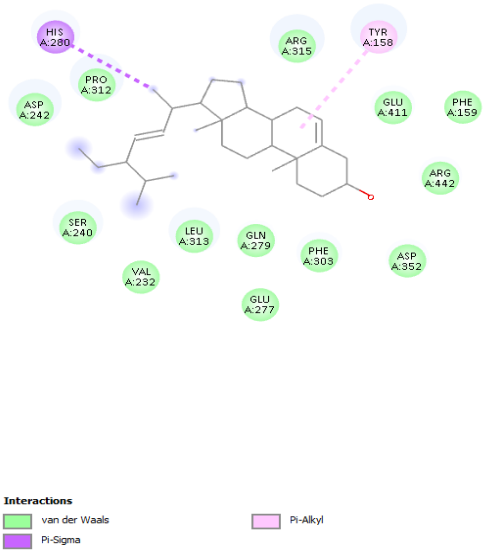

Fig. 6: 3A4S interaction.

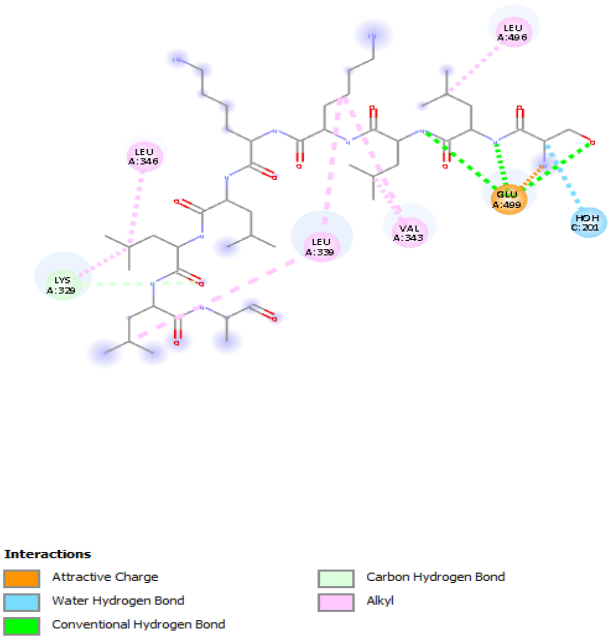

Fig. 7: EDK interaction.

Binding interaction results

Table 1: Docking Results.

Ligand	Receptor	Binding Affinity
Stigmasterol	3a4s	-8.3
Stigmasterol	6fzp	-7.1
EDK	6fzp	-7

Table 2: ADME Study.

Physicochemical Properties		**Water Solubility**	
Formula	C29H48O	ESOL Solubility (mol/l)	3.46E-08
MW	412.69	Class	Poorly soluble
Heavy atoms	30	Log S (Ali)	-8.86
Aromatic heavy atoms	0	Solubility (mg/ml)	5.71E-07
Fraction Csp3	0.86	Solubility (mol/l)	1.38E-09
Rotatable bonds	5	Class	Poorly soluble
H-bond acceptors	1	Log S (Silicos-IT) w	-5.47
H-bond donors	1	Solubility (mg/ml)	0.0014
Molecular Rrfractivity	132.75	Solubility (mol/l)	3.39E-06
TPSA	20.23	class	Moderately soluble
Lipophilicity		Pharmacokinetic	
Log $P_{o/w}$ (ILOGP)	5.08	GI absorption	Low
Log $P_{o/w}$ (XLOGP3)	8.56	BBB permeant	No
Log $P_{o/w}$ (WLOGP)	7.8	Pgp substrate	No
Log $P_{o/w}$ (MLOGP)	6.62	CYP1A2 inhibitor	No
Log $P_{o/w}$ (Silicos-IT Log P)	6.86	CYP2C19 inhibitor	No
Consensus Log $P_{o/w}$	6.98	CYP2C9 inhibitor	Yes
Water Solubility		CYP2D6 inhibitor	No
Log S (ESOL)	-7.46	CYP3A4 inhibitor	No
ESOL Solubility (mg/ml)	1.43E-05	log Kp (cm/s)	-2.74

Table 3: Drug likeliness.

Lipinski violations	Yes	1	Egan violations	No	1
Ghose violations	No	3	Muegge violations	No	2
Veber violations	Yes	0	Bioavailability Score		0.55

Table 4: Toxicity Result.

Classification	**Target**	**Shorthand**	**Prediction**	**Probability**
Organ toxicity	Hepatotoxicity	dili	Inactive	0.87
Organ toxicity	Neurotoxicity	neuro	Active	0.54
Organ toxicity	Nephrotoxicity	nephro	Inactive	0.89
Organ toxicity	Cardiotoxicity	cardio	Inactive	0.85
Toxicity end points	Carcinogenicity	carcino	Inactive	0.6

Predicated LD50:890mg/kg, Predicted Toxicity Class: 4

CONCLUSION

The binding interactions of phytoconstituents derived from *Ficus bengalensis* Linn were investigated through molecular docking studies with the human intestinal α-glucosidase enzyme. Among the examined compounds, stigmasterol exhibited a strong binding affinity toward the receptor, suggesting its potential role as an α-glucosidase inhibitor. Drug-likeness evaluation revealed that stigmasterol satisfactorily met all five major drug-likeness filters, while ADMET predictions indicated favorable absorption, distribution, metabolism,

excretion, and toxicity profiles, further supporting its suitability as a candidate for drug development.

Pharmacological studies performed in acute and sub-acute experimental models demonstrated that the chloroform fraction of *Ficus bengalensis* significantly reduced blood glucose levels in a dose-dependent manner, thereby validating its antidiabetic potential in vivo. The convergence of computational docking results, ADMET predictions, and pharmacological evaluation strengthens the scientific basis for considering stigmasterol and related phytoconstituents as promising lead compounds for the development of novel antidiabetic therapeutics.

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