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Research Communication

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In Silico Pharmacological Investigation of *Bauhinia blakeana* Leaf Against Diabetes Related Diseases

***Abstract*: Diabetes mellitus cures have been extensively investigated in recent decades, but the majority of medications suffer from multidrug resistance. To overcome this barrier, a series of natural compounds from *Bauhinia blakeana* leaves were examined using the molecular docking approach against two protein receptors, 1XU7 and 3C45. Out of the natural ligands, 9-dodecyltetradecahydrophenanthrene revealed to be the most promising in both proteins, with higher binding affinity and lower toxicity than regular metformin. Thus, all of these data point to a potential new medication strategy for diabetes.**

Keywords: Molecular docking, ADME studies, Toxicity prediction, Molecular dynamics

Diabetes mellitus is a chronic metabolic condition characterized by high blood glucose levels. Diabetes mellitus is a prominent cause of mortality and morbidity worldwide. Over 100 million instances of diabetes have been reported in India by 2023, with a significant increase since 2019[1]. All diseases and illnesses involve biological processes such as cell-to-cell communication, brain transmission, and so on, making it difficult to understand the pathway and produce trustworthy results. As a result, treating diabetes safely remains a potential medical effort[2,3].

In last half century many researches regarding control of diabetes have been performed and resulted in multiple successful generations of anti-diabetic drugs which act by either modulating or inhibiting these proteins responsible for diabetes. But most of these drugs have multiple disadvantages like, acute nephro toxicity, multidrug resistance and congestive heart failure[4]. So, an alternative strategy with safety, efficacy and low side effect is the need of the hour. In last few years scientists have grown immense interest in natural product especially plants for obtaining novel molecules. One such very well-known but unexplored plant is *Bauhinia blakeana* of family Fabaceae (Fig. 1), which have been an ornamental plants in many homes can become the hope against diabetes[5]. In this study, some of the compound reported from the leaves of *Bauhinia blakeana*, will be used for the in silico study against diabetes.

Methodologies

Details of Plant: *Bauhinia blakeana*, (family Fabaceae) often known as the Hong Kong orchid tree, is a tiny, multi-trunked, evergreen or semi-evergreen blooming tree with an umbrella-like shape and irregular rounded crown. It normally grows to be 20 feet tall, but in ideal conditions it can reach 40 feet. The plant is distributed Sub-Himalayan tracts, also in dry forests over eastern, central and south India and Myanmar. Although multiple reports of pharmacological properties from other varieties of Bauhinia like diarrhoea, flatulence, fever, piles etc., but very few reports were observed for *Bauhinia blakeana*[6].

In Silico Pharmacological Investigation Bioactive Compound Preparation: According to Geetha and Udhayakumar's findings, the majority of the 3D structures of phytochemicals derived from *Bauhinia blakeana* leaves were generated using Chemdraw Pro 8.0 (Fig 2), while the remainder were downloaded from the National Centre for Biotechnology Information's PubChem Compound section. The three-dimensional structures of the ligands were created in Open Babel and saved in SDF format for future preparation and molecular docking investigations [7].

Receptor Preparation: 3D structures of Human 11beta-hydroxysteroid dehydrogenase type I (PDB: 1XU7), which is implicated in the pathogenesis of type II diabetes and obesity and Human dipeptidyl peptidase IV/CD26 in complex (PDB: 3C45) were downloaded in .pdb format. To prepare the protein for molecular docking, water molecules were removed. Then, using the BIOVIA Discovery Studio 2021 Client programme, hydrogen atoms were introduced to fix the ionisation of the amino acid residues[8].

Molecular Docking Simulation: Molecular docking was carried out utilising the PyRx application and the Auto dock Vina tool once the proteins had been loaded and stored in pdb format. PyRx is a virtual screening method

which is used to dock several tiny chemical compounds, or ligands, with a target protein. It displays the ideal molecule that has a strong orientation to attach to a protein. PyRx provides users with every stage of the virtual screening process, from data preparation to job submission and outcome analysis, and it allows medicinal chemists to conduct virtual screening from any platform. Although it is true that there isn't a magic button for the drug discovery process, PyRx is a useful tool for computer-aided drug design because of its embedded Auto dock vina tool with an intuitive user interface which provides the exact binding energy. Additionally, PyRx has a strong visualisation engine and features akin to chemical spreadsheets, which are crucial for logical drug design. The most stable conformers were determined using the PyPx simulation studies[9]. For the simulation of 1XU7 protein, the grid dimensions of 57.16 Å × 46.13 Å × 54.93 Å and 74.58 Å × 82.31 Å × 74.10 Å were selected, respectively, for 3C45 protein receptors. Using the Discovery Studio 2021 Client programme, the intermolecular interactions between the aromatase inhibitor protein residues and the *Bauhinia blakeana* leaf were identified and visualised [10].

Drug Like Properties of the Ligands: The bioavailability score and Lipinski's rule of five were applied to establish the cutoff values for each ligand's physicochemical qualities. The molecular characteristics MW (molecular weight), HBD (hydrogen bond donor), HBA (hydrogen bond acceptor), log P (lipophilicity log), and log S (aqueous solubility) were used to assess the likelihood of a drug.The parameters were created with the SWISSADME server (www.swissadme.ch/index.php) [11].

Toxicity Prediction: ProTox III software was utilised to forecast the toxicity of the top-scoring ligands in human cells (https://tox-new.charite.de/protox_III/). Using a two-dimensional chemical structure as input, the website provides a potential toxicity profile for each of the 16 models along with confidence scores[12].

Molecular Dynamics: Each and every protein-ligand complex in the docking position has been rebuilt before the Gromacs molecular dynamics simulation. Each ligand was reprepared using the SwissParam programme, and the protein was reprepared using the Gromacs GROMOS96 99SB* force field. After being solvated at least 1.0 Å away from the complex, the protein-ligand complex was minimised using the steepest descent technique, with a maximum of 1,000 steps. For each MD simulation, it employs the particle mesh option with a time step of 2 ms. Several Gromacs techniques were used to analyse the RMSD trajectories[13].

Table 1: Results of compounds docking in diabetic targets

Ligands	Binding Affinity (ΔG in kcal/mol)	
	1XU7	3C45
N-methyl-N-(6-oxo-1-cyclohexen-1-yl) methanesulfonamide	-5.4	-5.0
Methyl 6-hydroxycaproate	-4.7	-5.4
1-(methylenecyclopropyl)-ethanone	-6.9	-4.7
2-(3-Fluoro-Phenylmethanesulfonyl)-3H-imidazo[4,5-B]pyridine	-6.1	-4.7
1H-Indole-3-ethanamine	-6.1	-4.4
2-(2-Ethyl-1-hydroxyhexyl)cyclohexanol	-6.4	-6.9
9-dodecyltetradecahydro Phenanthrene	-8.4	-8.6
1-amino-4-phenyl-1,2,3-Triazole-5-methanol	-6.9	-6.1
1-Tripropylsilyloxytridec-2-yne	-5.9	-5.6
2-(3,4-dihydroxyphenyl)-6,8-di-.beta.-D-glucopyranosyl- 5,7-dihydroxy Benzopyran-4-one	-5.8	-8.8
4-cyclohexylidene-3,3-diethyl-2-Pentanone	-7.1	-6.4
Tetracosanoic acid	-7.0	-7.1
Trilaurin	-5.6	-5.6
Metformin	-7.3	-6.7

Results and Discussion

Free Energy Binding of Bioactive Compounds: Table 1 displayed the ability of each bioactive ligand derived from *Bauhinia blakeana* leaves to bind with proteins associated with type II diabetes in humans. The range of binding affinities for the 16 ligands that were derived from *Bauhinia blakeana* in protein 1XU7 was -8.4 to -4.7 kcal/mol, whereas the range for protein 3C45 was -8.8 to -4.4. The type II diabetes receptor human 11beta-hydroxysteroid dehydrogenase and human dipeptidyl peptidase IV/CD26 in complex along with the most active ligands were visualised using the Discovery Studio 2021 Client programme (Fig. 3, 4 and 5) [14]. These specimens exhibited the anticipated interactions with the amino acids in the protein's active region, suggesting potent antagonistic activity against the protein that binds to the receptor linked to diabetes and suppresses the specific diabetic receptors. 9-dodecyltetradecahydrophenanthrene showed the maximum binding affinity of -8.4 kcal/mol for the protein coding 1XU7 [15] Methyl 6-hydroxycaproate was found to have the ligand with the lowest binding affinity (-4.7 kcal/mol). The binding affinities of only one natural molecule, 9-dodecyltetradecahydrophenanthrene, were found to be higher than those of the commonly used anti-

Fig 1: *Bauhinia blakeana* plant

diabetic medication metformin (-7.3 kcal/mol), suggesting their potential future use in the suppression of diabetes. Conversely, 2-(3,4-dihydroxyphenyl)-6,8-di-. beta for 3C45. The maximum binding affinity was found for -D-glucopyranosyl-5,7-dihydroxybenzopyran-4-one (-8.8 kcal/mol), followed by 9-dodecyltetradecahydrophenanthrene (-8.6 kcal/mol). 2-(2-Ethyl-1-hydroxyhexyl) cyclohexanol has the lowest value (-4.4 kcal/mol). Numerous substances, such as 2-(3,4-dihydroxyphenyl)-6,8-di-. beta and 9-dodecyltetradecahydrophenanthrene, are compared to conventional metformin (-6.7 kcal/mol).Higher values were observed for -D-glucopyranosyl-5,7-dihydroxybenzopyran-4-one[16]. This suggests that the leaf extract from *Bauhinia blakeana* may have promising anti-diabetic properties.

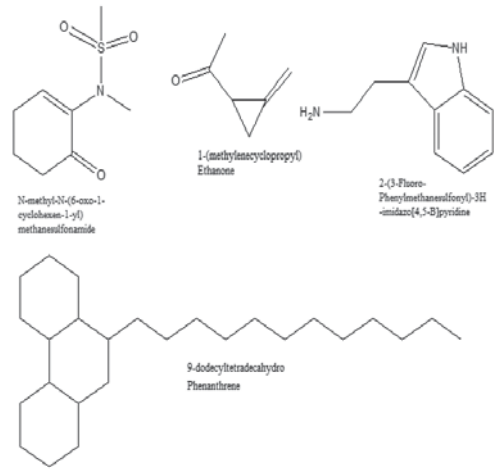

Fig 2: Few ligands from *Bauhinia blakeana*

ADME Studies: The lipophilicity of the ligands from SwissADME was shown by their LogP values, which ranged from 1.29 to 6.51. Their molecular weights ranged from 96.13 to 612.53g. Almost every ligand set's predicted value came inside Lipinski's rule's five cutoff marks. This shows that the ligands higher probability to be quickly be absorbed into the gastrointestinal tract, more or less, and

Table 2 : ADME studies of the natural ligands

Ligands	Mol Wt. (g)	Log P	HBD	HBA	Violation	BB barrier Yes/No	GI Absorption	Bioavailabilty
N-methyl-N-(6-oxo-1-cyclohexen-1-yl) methanesulfonamide	203.26	1.29	0	3	0	Yes	High	0.55
Methyl 6-hydroxycaproate	146.18	2.05	1	3	0	Yes	High	0.55
1-(methylenecyclopropyl)-ethanone	96.13	1.59	0	1	0	Yes	High	0.65
2-(3-Fluoro-Phenylmethanesulfonyl)-3H-imidazo[4,5-B]pyridine	291.3	1.74	1	5	0	No	High	0.55
1H-Indole-3-ethanamine	160.22	1.54	2	1	0	Yes	High	0.55
2-(2-Ethyl-1-hydroxyhexyl)cyclohexanol	228.37	3.07	2	2	0	Yes	High	0.55
9-dodecyltetradecahydro Phenanthrene	360.66	5.73	0	0	1	No	High	0.65
1-amino-4-phenyl-1,2,3-Triazole-5-methanol	370.73	6.51	0	1	1	No	Low	0.55
1-Tripropylsilyloxytridec-2-yne	190.2	1.05	2	3	0	No	High	0.55
2-(3,4-dihydroxyphenyl)-6,8-di-.beta.-D-glucopyranosyl- 5,7-dihydroxy Benzopyran-4-one	352.67	6.02	0	1	1	No	Low	0.55
4-cyclohexylidene-3,3-diethyl-2-Pentanone	612.53	1.33	13	16	3	No	Low	0.17
Tetracosanoic acid	222.37	3.05	0	1	0	Yes	High	0.55
Trilaurin	368.64	5.62	1	2	1	No	Low	0.55

Table 3 Toxicity study of the natural ligands

Ligands	Level of Toxicity (1=highly toxic; 6= safe)	Predicted LD50 (µg/ml)
N-methyl-N-(6-oxo-1-cyclohexen-1-yl) methanesulfonamide	4	825
Methyl 6-hydroxycaproate	5	5000
1-(methylenecyclopropyl)-ethanone	4	620
2-(3-Fluoro-Phenylmethanesulfonyl)-3H-imidazo[4,5-B]pyridine	4	1000
1H-Indole-3-ethanamine	4	940
2-(2-Ethyl-1-hydroxyhexyl) cyclohexanol	5	5000
9-dodecyltetradecahydro Phenanthrene	6	15380
1-amino-4-phenyl-1,2,3-Triazole-5-methanol	6	14000
1-Tripropylsilyloxytridec-2-yne	4	316
2-(3,4-dihydroxyphenyl)-6,8-di-.beta. -D-glucopyranosyl- 5,7-dihydroxy Benzopyran-4-one	45	9605000
4-cyclohexylidene-3,3-diethyl-2-Pentanone	4	1520
Tetracosanoic acid	4	940
Trilaurin	5	5000

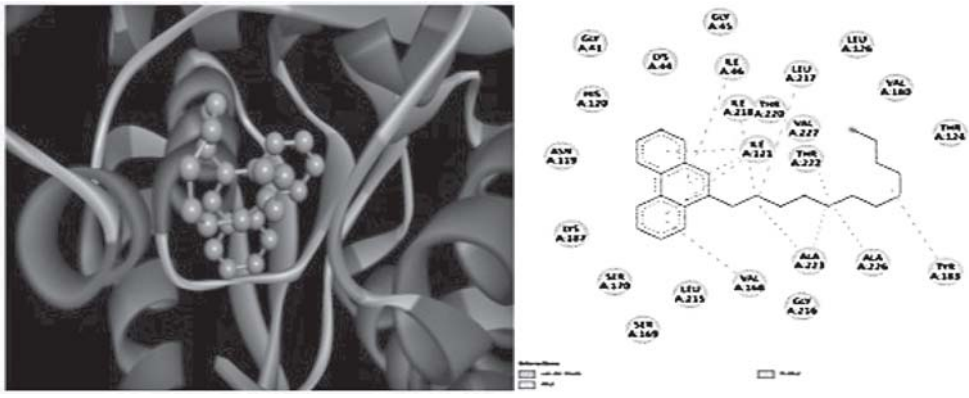

Fig 3: Interaction diagram of 9-dodecyltetradecahydrophenanthrene with 1XU7

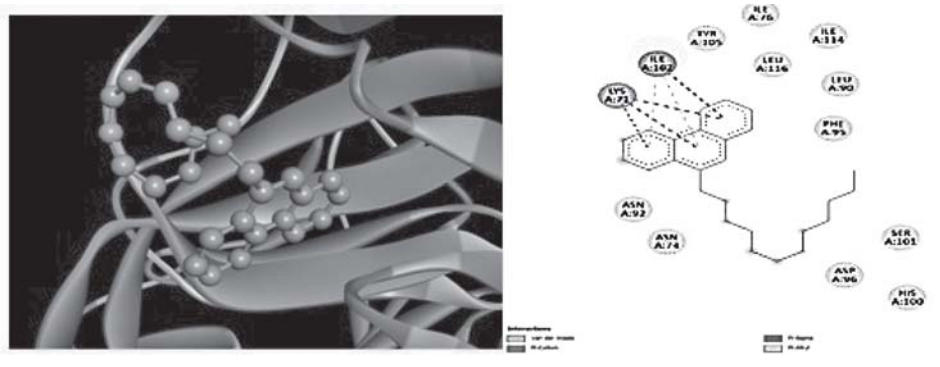

Fig 4: Interaction diagram of 9-dodecyltetradecahydrophenanthrene with 3C45

that the ligands with high bioavailability values indicating easy administration of these ligands as drugs (Table 2). According to recent ADME research and molecular docking score values for ligand detection, compound 9-dodecyltetradecahydrophenanthrene may have very potent anti-diabetic qualities[17].

Toxicity Studies

All the ligands were studied for their oral toxicity using ProTox III software showed all eight ligands had a predicted class 4-6 toxicity with high LD50 values indicating their safe usage in human (Table 3). From the table it can be observable that 9-dodecyltetradecahydrophenanthrene have the lowest level of toxicity (level 6) with LD50 value of 15380 µg/ml, indicating the safety in oral usage [18].

Molecular Dynamics

Following MD simulation, cluster analysis with a 0.1 nm RMSD limit was used to identify the representative structures of each complex. Figure 6 displays the RMSD values as well as two graphical depictions of the dynamics seen for the best bound compounds for both proteins (1XU7 and 3C45) in the clusters during the MD simulation's 0 to 80 ms and 0 to 50 ms, respectively. The RMSD of B (3C45_9-dodecyltetradecahydro phenanthrene) exhibits steadily rising peaks until 18 ns, with a brief stabilisation between 20-30 ns at 0.6-0.7 Å (Fig. 7). In contrast, the RMSD of A (1XU7_9-dodecyltetradecahydro phenanthrene) shows a sudden spike at 27 ns, then stabilises at 0.65 Å and 50 ns. This shows that these ligands remain stable within the protein's active site pocket and do not change their orientation, which is consistent with the

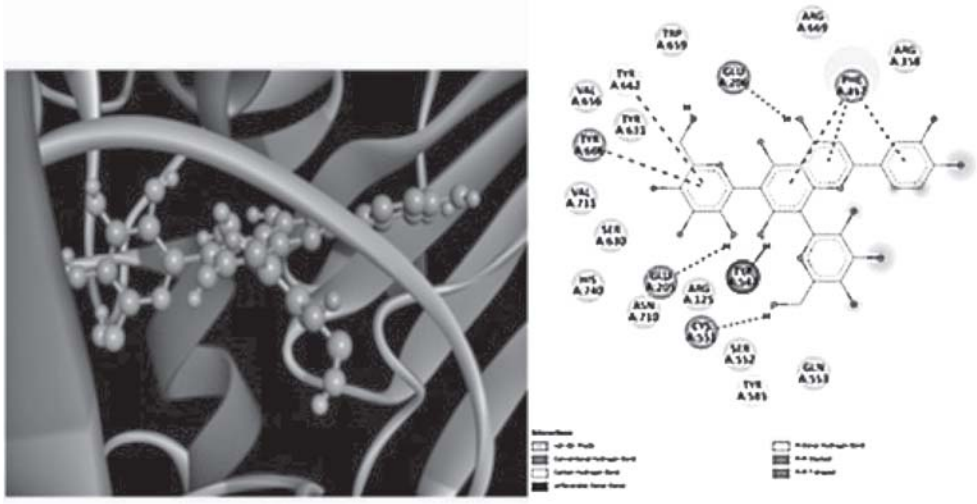

Fig 5: Interaction diagram of 2-(3,4-dihydroxyphenyl)-6,8-di-.beta.-D-glucopyranosyl- 5,7-dihydroxybenzopyran-4-one with 3C45

visualisation produced by molecular docking studies. The 3EQM-ligand complexes showed the best stability, with the largest number of peaks in the 0.6 to 0.8 Å area and the smallest average and total RMSD. The top scoring molecules' molecular dynamics (MD) investigation revealed that the compound stabilises around 20–30 ns for compound contact with 3C45, whereas the first interaction with protein IUX7 demonstrated a stable interaction around 50–80 ns [19].

Conclusion

The prevalence of diabetes mellitus and the detriments of the current batch of available drugs prompted for exploration of new drug for control of diabetes preferably from natural sources. Plants with recorded traditional knowledge or explored plants can provide with some scope in emergence of new therapeutic strategy which will be safe and less toxic, alleviating the situation of diabetes mellitus. The present study provides the anti-diabetic evidence to newly explored plant *Bauhinia blakeana* using molecular docking, and it was found that one compound 9-dodecyltetradecahydrophenanthrene showed better binding activity in both selected anti diabetic receptor protein (1XU7 and 3C45) even better than standard metformin. The ADME study also shows the same compound having high drug likeness with no violations in Lipinski rule and high GI absorption and bioavaility. The predicted toxicity study also suggests 9-dodecyltetradecahydrophenanthrene to be having the least toxicity and highest LD50 value among all ligand. Thus, all these results suggest a potential anti diabetic drug can be obtained from *Bauhinia blakeana* can be further tested clinically for design of a new anti-diabetic strategy.

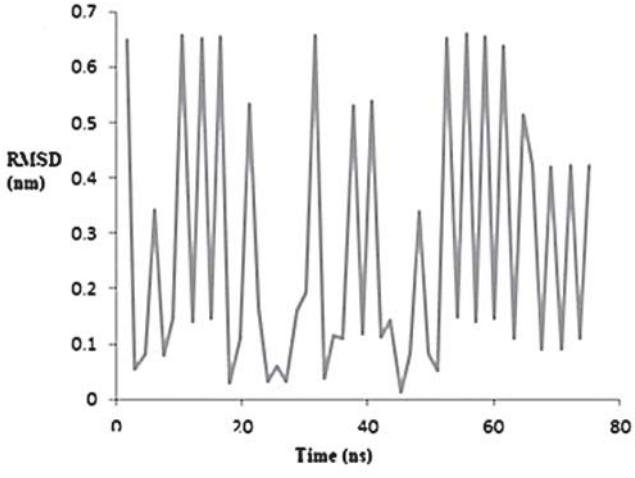

Fig. 6: The root mean square deviation (RMSD) plots for 9-dodecyltetradecahydrophenanthrene with 1XU7 protein.

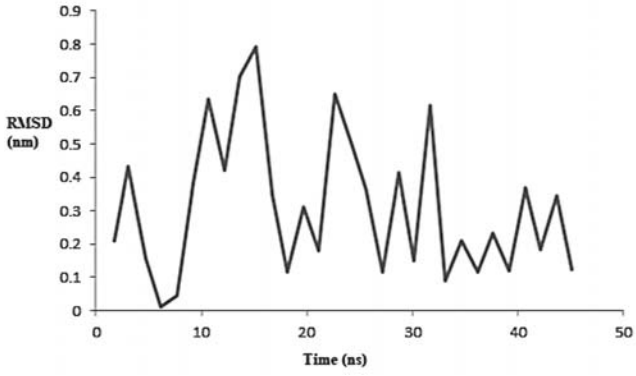

Fig. 7: The root mean square deviation (RMSD) plots for 9-dodecyltetradecahydrophenanthrene with 3C45 protein

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. ❐

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