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In Silico Evaluation of Antidiabetic Properties Obtained from Phytochemical Molecules of *Uraria picta*

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Abstract: Diabetes mellitus is a complex disease condition which can be characterised by chronic high blood glucose levels. Antidiabetic medicines are currently available to treat the related diseases. Their concurrent consequences need the development of an effective and safe medicine designed to lower blood glucose levels with fewer side effects. Several researchers are launching new initiatives to investigate plant sources, which are known to contain a diverse range of active compounds. As a result, the current study sought to investigate the effect of natural compounds derived from *Uraria picta* through *in silico* interaction investigations. Molecular docking studies were carried out for five ligands against 2 (1XU7 and 3C45) target proteins to evaluate its antidiabetic potential. Molecular docking analysis showed that one of the ligand, α – amyrone showed highest binding affinity with both 1XU7 (-12.9 kcal/mol) and 3C45 (-9.3 kcal/mol) proteins. Further, the toxicity studies indicated all ligands including α – amyrone were safe for human with software predicting the ligands to be non-carcinogenic and non-mutagenic along with high IC_{50} value. The drug-likeliness was computed using SwissADME in accordance with Lipinski's rule of five and bioavailability. The chemicals were judged to be compliant with Lipinksi regulations, despite violating two filter criteria. The study suggests that ligands from *Uraria picta*, particularly α-amyrone, could be a viable anti-diabetic drug.

Keywords: Molecular docking, *Uraria picta*, *In silico*, ADME study, Toxicity study

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Introduction

Diabetes type II have been one of the most common chronic disease across the world and the number of affected patients are increasing day by day. Around 200 million people in the world are suffering from diabetes with the number expected to double by 2030 (Safitri *et al.*, 2020). Out of all the patients more than 35% of the patients develop resistance to insulin and has to

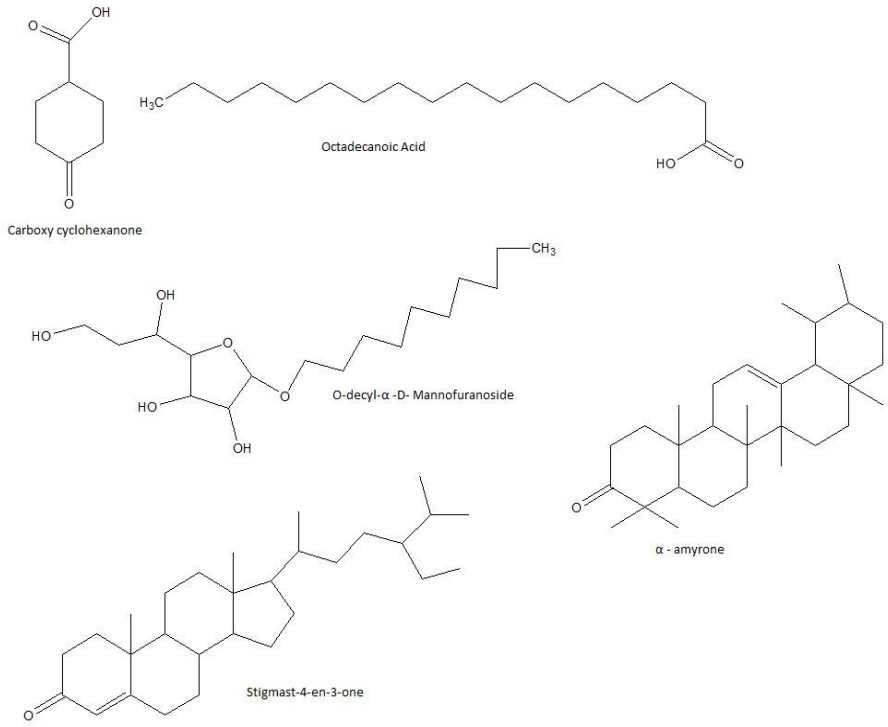

Fig. 1: Ligands from *U. picta.*

be dependent on proper diet, exercises and meditation. With globalization and changes in modern medical scenarios, the cost of synthetic medicine has skyrocketed. Moreover, despite the immense success in last few decades, the treatment has still remained a challenge due to emergence of different side effects and toxicities (Gupta *et al.*, 2017). This has led scientists around the world to investigate traditional treatments derived from natural products. Around 400 plants have been identified around the world as having antidiabetic effects. However, considerably more controlled research is required to develop a potential library of bioactive lead compounds. *In silico* research can provide accurate predictions (Thadhani and Karunaratne, 2017). The study will focus on *Uraria picta*, a lesser-known traditional medicinal plant. *Uraria picta*, a member of the Fabaceae family, is found in the foothills of the Tarai region of the Himalayas and is known as Shankarjata in local language. It has traditionally been used as an anti-microbial, anti-emetics, and anti-inflammatory, but there have been no reports of its anti-diabetic characteristics. So, in this study, the identified phytochemicals from the aerial parts of the plant was explored for its antidiabetic properties in two receptor proteins, human 11beta-hydroxysteroid dehydrogenase type I and Human dipeptidyl peptidase IV/CD26 in complex (Vats *et al.*, 2024).

Materials and Methods

Details of the plants

Uraria picta is a rare species found in tropical India, including the Tarai region of the Himalayas, at heights of up to 300 metres. The plant thrives in tropical and subtropical climes. Loam to clay-loam soil is ideal for farming. It can withstand soil pH levels of up to 8.5. Traditional uses of the plant include antiseptic, anti-inflammatory, anti-bacterial, anti-emetic, aphrodisiac, analgesic, cardiovascular, and expectorant qualities (Kashyap, 2021).

Ligands preparation and optimization

As reported by Mohan *et al*. (2020) 5 ligands from the aerial parts of *U. picta* reported in various literatures, were drawn in Chem Draw Professional 15.0 (Fig. 1). Three-dimensional structures of the ligands were created in Open Babel and saved as SDF format for further preparation and molecular docking analysis

(Mohan *et al.*, 2020).

Preparation of receptor protein

The protein data bank provided the Crystallographic structures of the 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). The water molecules were removed from the protein to get it ready for molecular docking, and then hydrogen atoms were added using the BIOVIA Discovery Studio 2021 Client application to fix the ionization of the amino acid residues (Erdogan and Erdogan, 2023).

Drug like properties of the ligands

The cutoff values for the physicochemical parameters of all ligands were determined using LogS, LogP, Lipinski's rule of five, and the bioavailability score. Drug probability was evaluated using the following molecular parameters: MW (molecular weight), HBD (hydrogen bond donor), HBA (hydrogen bond acceptor), log P (lipophilicity log), and log S (aqueous solubility). The parameters were created with the SWISSADME server (www.swissadme.ch/index.php). (Samajdar, 2023).

Molecular docking analyses and visualization

The PyRx application was used to perform molecular docking using the Auto dock Vina tool once the proteins were saved in pdb format and loaded. The PyPx programme was used to determine which conformer was the most reliable. The grid volume was found to be 58.72 Å x48.39 Å x 53.34 Å for 1XU7 while for 3C45 it was 76.74 Å x 75.98 Å x 74.23 Å. The intermolecular interactions between the *U. picta* leaf ligands and the diabetes related protein were identified and visualized using the Discovery Studio 2021 Client software (Vasanth Kanth *et al.*, 2023).

Toxicity prediction

The top scoring ligands were tested for toxicity in human cells using the ProTox III software (https://tox-new.charite.de/protox_III/). The website accepts a two-dimensional chemical structure as input and presents the likely toxicity profile of the molecule for five models with confidence scores (Ramirreddy *et al.*, 2023).

Results and Discussion

PyRx docking software was used to determine binding affinities and key interactions between human 11beta-hydroxysteroid dehydrogenase type I (PDB: 1XU7), and human dipeptidyl peptidase IV/CD26 in complex (PDB: 3C45) and phytochemical ligands obtained from *U. picta.* The binding affinity of obtained ligands were compared with the binding affinity of standard anti-diabetic drug Metformin. Table 1 shows the binding affinity obtained from the protein bound ligands and the standard drug Metformin (Samajdar, 2022). The binding affinity of *U. picta* for 1XU7 protein ranged from -4.9 to -12.9 kcal/mol, whereas for 3C45, it ranged from -5.1 to -9.3 kcal/mol. The Discovery Studio 2021 Client program was used to visualise the molecular interactions between the most active ligands and the receptor's active site that targets diabetes protein (Figs. 2, 3). These samples showed the expected interactions with amino acids in the protein's active region, implying strong antagonistic characteristics against the diabetic protein, which targets type II diabetes. For 1XU7 and 3C45 α – amyrone had the highest binding affinity of -12.9 kcal/mol -9.3 kcal/mol, respectively. As compared to the widely used anti-diabetic drug Metformin (-5.9 and -5.3 kcal/mol for 1XU7 and 3C45, respectively), the binding affinity of α – amyrone derived from *U. picta* was found to be significantly higher indicating their future usage in inhibition of diabetes type II. These ligands were further studied for their receptor target prediction, and toxicity studies (Samajdar, 2023).

The molecular weights of the ligands from SwissADME ranged from 142.15 to 424.7 g, with LogP values ranging from 0.59 to 7.23, indicating

Table 1: Docking score of *U. picta* ligands

Ligands	Binding Affinity (cΔG in kcal/mol)	
	1XU7	3C45
4- Carboxy cyclohexanone	-6.3	-5.2
Octadecanoic acid	-4.9	-5.6
1- O-decyl -α -D-Mannofuranoside,	-5.5	-5.1
α - amyrone	-12.9	-9.3
Stigmast-4-en-3-one	-10.1	-6.7
Metformin	-5.9	-5.3

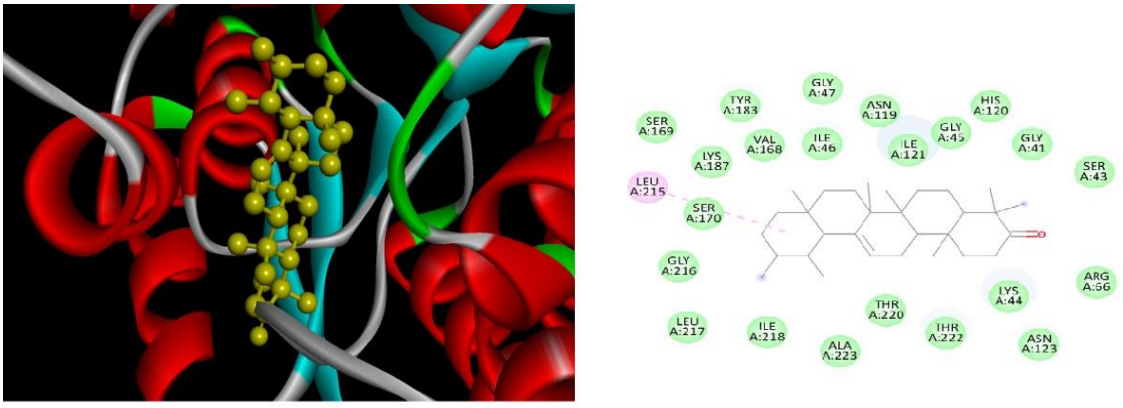

Fig. 2: Interaction diagram between α – amyrone and 1XU7.

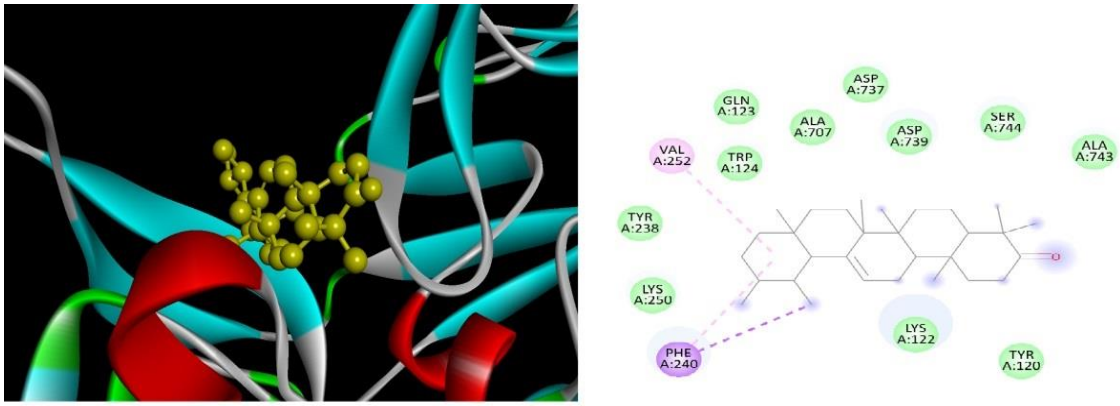

Fig. 3: Interaction diagram between α – amyrone and 3C45.

that molecules with high LogP values are extremely lipophilic. The majority of the ligand set prediction values were within the range of Lipinski's rule of five cutoffs. This is because compounds with high log P values in this range are soluble in fats, oils, lipids, and nonpolar solvents, and all ligands exhibit drug-like characteristics. A few substances, including α-amyrone, demonstrated high GI absorption and bioavailability. This indicates the appropriateness

Table 2: ADME parameters of each ligands in SwissADME

Ligands	Mol Wt. (g)	Log P	HBD	HBA	Violation	BB barrier Yes/No	GI Abs	Bioavl
4- Carboxy cyclohexanone	142.15	0.59	1	3	0	Yes	High	0.85
Octadecanoic acid	284.48	5.93	1	2	1	No	High	0.55
1- O-decyl -α -D-Mannofuranoside,	334.45	2.09	4	6	0	No	High	0.55
α - amyrone	424,7	7.09	0	1	1	No	High	0.85
Stigmast-4-en-3-one	412.69	7.23	0	1	1	No	Low	0.55

Table 3: Toxicity prediction of ligands

Ligands	Level of Toxicity (1=highly toxic; 6= safe)	Predicted LD_{50} (µg/ml)
4- Carboxy cyclohexanone	5	3265
Octadecanoic acid	4	900
1- O-decyl -α -D-Mannofuranoside,	6	23000
α - amyrone	5	5000
Stigmast-4-en-3-one	5	2300

of ligands like α-amyrone in the formulation of oral dosage forms (Neelakandan and Rajanikant, 2024). The same set of ligands were studied for their toxicity using ProTox III software showed that the ligands including α – amyrone had a predicted class 4 to class 6 toxicity with very high LD_{50} values (900-23000 mg/ml) and the software predicted each of the ligand showed no carcinogenic cytotoxicity as well as mutagenic toxicity indicating their safe usage in human (Joshi *et al.*, 2023) (Table 3).

Conclusion

Diabetes, particularly type II, is a rapidly rising disease that will cause significant morbidity and mortality worldwide in the future years. Thus, a strong plan is essential to overcome this circumstance. So, *U. picta,* a little-known and rarely seen plant, may be useful in the treatment of diabetes. A thorough in silico molecular docking study as well as oral ADME and toxicity revealed multiple compounds with antidiabetic properties, but α-amyrone showed a significant binding energy in both the selected receptors with low toxicity and high predicted GI absorption and bioavailability. This confirms that α-amyrone has considerable potential against diabetes. The molecule can be further studied clinically to build a new anti-diabetic strategy.

Ethical Statement

No animal or microbes have been used or sacrificed for this study, hence Ethical Approval not required.

Author Contributions

Sudip Saha: Conceptualization; *Saptarshi Samajdar*: Methodology, Software; *Rumpa Basak*: Validation, Writing; *Abdul Malek*: Data Curation, Validation, *Mahesh Dhibar*: Formal analysis, writing. All authors have read and agreed to the published version of the manuscript.

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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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