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In-silicoevaluation of antidiabetic, toxicity, ADMET, pharmacokinetic study for Ficus Auriculataphy to constituents

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ABSTRACT
The search for a prospective lead chemical is a time-consuming and complicated procedure that necessitates a lot of money, patience, and labour. Because of their wide structural diversity, humans have been using natural products, primarily secondary metabolites, for this purpose since ancient times, and they are still working on them as a potent source for drug discovery. Natural phytoconstituents 95-hydroxy-2-(4-hydroxy-2-methyl-2H-pyran-6-yl)-9-methyl-2H,3H,4H-naphtho[1,2-b] pyran-4-one, Linolenic acid, methyl ester, Methyl palmitate, Methyl Octadeca-9,12-dienoate, Cis-13-Octadecanoic acid, methyl ester, and Methyl stearate are involved in the treatment of numerous biological diseases. The research focuses on molecular docking of 8 phytoconstituents compounds with the PPR-gamma(PDB ID: 2PRG), Aldose reductase (PDB ID: 3V36), DPP4) (PDB ID: 2OQV), and Human pancreatic alpha-amylase (PDB ID: 2QMK) to assess the binding affinity at the binding location with the highest binding affinity. Toxicity studies conformed that less toxic with the minimal dose. ADMET studies confirmed that phytoconstituents are protein binding. These expected results will serve as a starting point for more investigation into the significance of their drug-likeliness properties in the management of diabetes.

Keywords: Diabetes mellitus, In-silico, antidiabetic, toxicity, ADMET, pharmacokinetic, Ficus Auriculata

I. INTRODUCTION

Diabetes mellitus (DM) is a severe endocrine condition marked by increased blood glucose levels that are caused by inadequate pancreatic insulin synthesis at the same time as impairment of insulin function [1, 2].

150 million people worldwide suffer from diabetes, a disease that now affects 10% of the world's population. According to a report by the World Health Organization, there were 171 million cases of diabetes mellitus in 2000, and that figure might rise to 360 million by 2030. 75% of those who have been diagnosed with diabetes should live in developed countries by 2025. Even though the number of people with diabetes is rising globally, the cost of treating the condition is rising both domestically and internationally [3].

Hyperglycemia is a trait shared by a group of linked metabolic illnesses known as diabetes mellitus (DM). Diabetes mellitus is characterized as a chronic hyperglycaemic disease by the WHO Diabetes mellitus Expert Committee. There are many different types of DM, and each one is brought on by a unique interaction between biology, the environment, and lifestyle choices. Depending on the etiology of the diabetes, factors that can cause hyperglycemia include decreased insulin release, decreased glucose uptake, and increased glucose production [4].Diabetes patients and the healthcare system are heavily burdened by secondary pathophysiological alterations caused by DM-associated metabolic abnormalities in several organ systems. End-stage kidney disease (ESRD), non-traumatic lower limb amputations, and adult blindness are all primarily brought on by diabetes mellitus (DM) in the United States. In the upcoming years, DM will be a leading cause of mortality and morbidity due to its widespread incidence [5, 6].

Natural products, especially those with a plant origin, are the main source for the discovery of promising lead compounds. These products are crucial to potential drug development programs. Plant-based medicines are the most popular available remedies, especially in rural areas where they are easily accessible, inexpensive, and have the fewest adverse effects [7, 8]. In fact, certain plants contain many bioactive compounds that have no negative side effects and show potent pharmacological behaviour. Much of the commonly used pharmaceuticals have either been directly or indirectly derived from plants, which have frequently also been effective sources of medicines.The current study investigated the anti-diabetic, toxicity, ADMET, and pharmacokinetic

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properties of Ficus Auriculataselective phytoconstituents by In-silico method.

II. MATERIAL AND METHODS

2.1. Ligands

Compound from LC/MS result was drawn using chem sketch software. 3D structures of five compounds from GC/MS analysis result and standard drugs were downloaded from PubChem database in .sdf format(95-hydroxy-2-(4-hydroxy-2-methyl-2H-pyran-6-yl)-9-methyl-2H,3H,4H-naphtho[1,2-b] pyran-4-one, Linolenic acid, methyl ester, Methyl palmitate, Methyl Octadeca-9,12-dienoate, Cis-13-Octadecanoic acid, methyl ester, and Methyl stearate). These all ligands were prepared to generate all possible conformers and tautomers [9, 10, 11].

2.2. Docking with peroxisome proliferator activated receptor gamma (PPR-gamma) (PDB ID: 2PRG)

The three-dimensional structure of human peroxisome proliferator activated receptor gamma was downloaded from PDB database with PDB ID: 2PRG with crystallographic resolution 2.30 A^0. The protein consists of three polypeptide chain A, B and C. The protein chain consists of 549 amino acids and has a molecular weight of 62724.9 Daltons. In the present study, the active site of protein interacting with the standardized ligand molecules was selected as the binding site. 753 poses of selected ligands in the docked complexes were generated. The interacting molecular complexes among these having high LibDock score and maximum number of hydrogen bonds and active residues were selected. All the 6 compounds were shows good interaction with PPR- gamma comparison with the standard drug, Pioglitazone(PubChem ID: 4829) and Rosiglitazone (PubChem ID:77999). The Table S1 shows the best conformers of the ligands.

2.3. Docking with Aldose reductase (PDB ID: 3V36)

The three-dimensional structure of Aldose reductase complexed with glyceraldehyde was downloaded from PDB database with PDB ID: 3V36 with crystallographic resolution 2.00 A^0. The protein chain consists of 316 amino acids and has a molecular weight of 35733.6 Daltons. The protein consists of one polypeptide chain A. The active site of protein interacting with the standardized ligand molecules was selected as the binding site. 680 poses of selected ligands in the docked complexes were generated. The interacting molecular complexes among these having high LibDock score and maximum number of hydrogen bonds and active residues were selected. All the 6 compounds were shows good interaction with Aldose reductase. Table S3 shows the LibDock score of best conformers of the ligands.

2.4. Docking with Human Dipeptidyl Peptidase IV (DPP4) (PDB ID: 2OQV)

The three-dimensional structure Human Dipeptidyl Peptidase IV (DPP4) with piperidine-constrained phenethylamine wasdownloaded from PDB database with PDB ID: 2OQV with crystallographic resolution 2.80 A^0. The protein chain consists of 1452 amino acids and has a molecular weight of 168280 Daltons. The protein consists of two polypeptide chain A and B. The active site of protein interacting with the standardised ligand molecules was selected as the binding site. 747 poses of selected ligands in the docked complexes were generated. All the 6 compounds were shows good interaction with Human Dipeptidyl Peptidase IV (DPP4). Table S5 shows the LibDock score of best conformers of the ligands. The interacting molecular complexes among these having high LibDock score and maximum number of hydrogen bonds and active residues were selected.

2.5. Docking with Human pancreatic alpha-amylase (PDB ID: 2QMK)

The three-dimensional structure of Human pancreatic alpha-amylase complexed with nitrite was downloaded from PDB database with PDB ID: 2QMK with crystallographic resolution 2.30 A^0 (Fig.4). The protein chain consists of 496 amino acids and has a molecular weight of 55859 Daltons. The protein consists of one polypeptide chain A. The receptor cavity was selected as the binding site. 756 poses of selected ligands in the docked complexes were generated. The interacting molecular complexes among these having high LibDock score and maximum number of hydrogen bonds and active residues were selected. All the 6 compounds were shows good interaction with the receptor Human pancreatic alpha-amylase. Table S7 shows the LibDock score of best conformers of the ligands and standard drug.

2.6. Toxicity Estimations

Toxicity screening results of all the six compounds showed that no risk of carcinogenicity, mutagenicity, and skin irritation, however it possesses high developmental or reproductive

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toxicity potential at high doses or long-term therapeutic use in human. The details of predicted toxicity parameters are summarized in Table 1.

2.7.ADMET Prediction

The drug likeness studies of the ligands were calculated by ADMET descriptors in Discovery studio 2021. The intestinal absorption and blood brain barrier penetration were predicted and is depicted in the plot using descriptors 2D PSA and AlogP98 that at 95% and 99% confidence ellipses.

2.8. Screening through Pharmacokinetic Properties

The drug likeness of the selected 6 compounds were examined by Lipinski and Veber rule filter protocol. The results of pharmacokinetic screening revealed that only one compound (Molecule) followed Lipinski's rule of five.

III. RESULTS AND DISCUSSION

3.1. Docking with peroxisome proliferator activated receptor gamma (PPR-gamma) (PDB ID: 2PRG)

The docking result revealed that all the six compounds possess high affinity to receptor compared with the standard drug Pioglitazoneand Rosiglitazone. Cis-13-Octadecanoic acid, methyl ester (PubChem ID: 12541027) was showed best affinity to receptor PPR-gamma. The docking score 124.249 corresponded to Cis-13-Octadecanoic acid, methyl ester showed high binding affinity with the receptor compared with standard drug molecule. Hydrogen bond residues were also same like to standard drug. The results are summarised in the Table S2. Linolenic acid, methyl ester(PubChem ID: 5319706)and Methyl Octadeca-9,12-dienoate(PubChem ID:8203) displayed second highest affinity with receptor (LibDock Score: 123.62 and 123.36) with 1 hydrogen bonds (TYR473 and ALA292 respectively). Methyl Stearate (PubChem ID:8201), Methyl Palmitate (PubChem ID:8181) and Molecule also shows good affinity with 2, 6 and 5 hydrogen bond interactions respectively. The results revealed that all the six ligands bind the same residues as those which bind with the standard drug. The results show that the 6 compounds in Ficus auriculata Lour. fruit extract has better inhibiting property than the standard drug Rosiglitazone and Pioglitazone.

3.2. Docking with Aldose reductase (PDB ID: 3V36)

The docked complex of Aldose reductase receptor with top scored ligands and standard ligands were analysed to study non-bond interactions between the target and the ligand molecule. The interacting residues, nature of interacting bond and the bond distance are given in Table S4.

3.3. Docking with Human Dipeptidyl Peptidase IV (DPP4) (PDB ID: 2OQV)

The docked complex of Aldose reductase receptor with top scored ligands and standard ligands were analysed to study non-bond interactions between the target and the ligand molecule. The interacting residues, nature of interacting bond and the bond distance are given in Table S6.

3.4. Docking with Human pancreatic alpha-amylase (PDB ID: 2QMK)

The docked complex of Human pancreatic alpha-amylase receptor with top scored ligands and standard ligands were analysed to study non-bond interactions between the target and the ligand molecule. The interacting residues, nature of interacting bond and the bond distance are given in Table S8.

3.5. Toxicity Estimations

Toxicity screening results of all the six compounds showed that no risk of carcinogenicity, mutagenicity and skin irritation, however it possesses high developmental or reproductive toxicity potential at high doses or long-term therapeutic use in human. The details of predicted toxicity parameters are summarized in Table 1.

Table 1: Computational Toxicity Estimation of the Ligands

A: Computer parameters of Toxicity Risk						
Parameters	Molecule	5319706	8181	8203	12541027	8201
Rate oral LD50 (g/kg body weight)	5.26909	5.32905	11.1522	5.47637	11.0253	13.9386

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Rat inhalational LC50 (mg/m3/h)	2568.21	6,471.82	16,594	12,210.80	11,495.30	12,879
Daphnia EC50 (mg/L)	49.4586	0.15916	0.219648	0.151775	0.130897	0.0933472
Rat chronic LOAEL (g/kg body weight)	0.0319364	0.131514	0.594953	0.181494	0.226728	0.590556
Fathead minnow LC50 (g/L)	0.269787	5.10E-06	1.13E-05	2.72E-06	1.44E-06	2.51E-06
Carcinogenic potency TD50 (mg/kg body weight/day)						
Mouse	1.63075	157.959	347.371	241.078	252.96	370.391
Rat	0.0873839	62.7983	26.8207	76.9574	76.5824	27.952
Rat maximum tolerated dose (g/kg body weight)	0.00702588	0.116554	0.169223	0.138806	0.165328	0.196873
B: Computer parameters of USFDA rodent Carcinogenicity, Ames Mutagenicity, Developmental toxicity potential Aerobic biodegradability, Ocular irritancy, and Skin irritancy						
Carcinogenicity						
Mouse female	Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen
Mouse male	Carcinogen	Carcinogen	Non-Carcinogen	Carcinogen	Carcinogen	Carcinogen
Rat female	Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen
Rat male	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen
Ames mutagenicity	Non-Mutagen	Non-Mutagen	Non-Mutagen	Non-Mutagen	Non-Mutagen	Non-Mutagen
Developmental toxicity potential	Toxic	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic
Aerobic biodegradability	Degradable	Degradable	Degradable	Degradable	Degradable	Degradable
Ocular irritancy	Non-Irritant	Non-Irritant	Non-Irritant	Non-Irritant	Non-Irritant	Non-Irritant
Skin irritancy	Mild	Moderate	Moderate	Moderate	Moderate	Moderate

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3.6. ADMET Prediction

Based on the logarithm of the partition coefficient between n-octanol and water (AlogP), polar surface area (PSA), aqueous solubility, plasma protein binding, cytochrome P450 (CYP2D6) binding, penetration of the blood-brain barrier (BBB), hepatotoxicity, and intestinal absorption, ADMET properties of compounds are determined. (Table 2)

Table 2: ADMET prediction of the ligands

Sl. No	PubChem ID	Solubility	BBB	CYP2D6	Hepatotoxic	Absorption	PBB	A Log P	PSA
1	Molecule	3	3	FALSE	FALSE	0	TRUE	1.012	80.306
2	5319706	2	0	FALSE	FALSE	1	TRUE	6.197	26.23
3	8181	2	0	FALSE	FALSE	1	TRUE	6.618	26.23
4	8203	2	0	TRUE	FALSE	1	TRUE	6.641	26.23
5	12541027	2	4	FALSE	FALSE	3	TRUE	7.086	26.23
6	8201	2	4	FALSE	FALSE	3	TRUE	7.53	26.23

3.6. Screening through pharmacokinetic properties

The results of pharmacokinetic screening revealed that only one compound (Molecule) followed Lipinski's rule of five. The results are described in the Table 3.

Table 3: Oral bioavailability of lead molecules screened by Lipinki's rule of five

Ligands	Oral bioavailability: TPSA	MW	ALog P	Number of H Donor	Number of H Acceptor
Molecule	80.306	354.481	1.012	3	5
5319706	26.23	292.456	6.197	0	2
8181	26.23	270.451	6.618	0	2
8203	26.23	294.472	6.641	0	2
12541027	26.23	296.488	7.086	0	2
8201	26.23	298.504	7.53	0	2

IV. CONCLUSION

The measured binding energies from density functional theory studies for 5-hydroxy-2-(4-hydroxy-2-methyl-2H-pyran-6-yl)-9-methyl-2H,3H,4H-naphtho[1,2-b] pyran-4-one, Linolenic acid, methyl ester, Methyl Palmitate, Methyl Octadeca-9,12-dienoate, Cis-13-Octadecanoic acid, methyl ester, and Methyl Stearate were found to be in good accordance with the interaction affinity obtained from docking studies in this analysis. The overall results of our docking study show that the Ficus Auriculata phytoconstituents residues are more effective to treat the diabetic disease.These projected outcomes will serve as a foundation for further research into the importance of their drug likeliness characteristics in the treatment of diabetes.

Conflict of Interests: Nil

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REFERENCE

[1]. Alam S, Sarker MMR, Sultana TN, et al. Antidiabetic Phytochemicals from Medicinal Plants: Prospective Candidates for New Drug Discovery and Development. Front Endocrinol (Lausanne). 2022; 13:800714.

[2]. Gandhi GR, Ignacimuthu S, Paulraj MG. Solanum torvum Swartz. fruit containing phenolic compounds shows antidiabetic and antioxidant effects in streptozotocin induced diabetic rats. Food Chem Toxicol. 2011;49(11):2725-2733.

[3]. https://www.who.int/health-topics/diabetes#tab=tab_1.
[4]. Khan M, Manzoor Z, Rafiq M, Munawar SH, Waqas MY, Majeed H, Ali Shah SZ, Hussain R, Hussain HI, Tahir T, Kotwica-Mojzych K, Mojzych M. Phytochemical Screening, Anti-Inflammatory, and Antidiabetic Activities of Different Extracts from Caralluma edulis Plant. Molecules. 2022 Aug 22;27(16):5346.
[5]. Unnikrishnan R, Anjana RM, Mohan V. Diabetes mellitus and its complications in India. Nat Rev Endocrinol. 2016;12(6):357-370.
[6]. Ghosal S, Batin M. The diabetes epidemic in India: where we stand and future projections. J Indian Med Assoc. 2013;111(11):751-754.
[7]. Shilpa, V. P., K. Muddukrishnaiah, B. Samuel Thavamani, V. Dhanapal, K. N. Arathi, K. R. Vinod, and S. R. Sreeranjini. "In vitro immunomodulatory, antifungal, and antibacterial screening of Phyllanthus niruri against to human pathogenic microorganisms." Environmental Disease 3, 3 (2018): 63.
[8]. Bharti SK, Krishnan S, Kumar A, Kumar A. Antidiabetic phytoconstituents and their mode of action on metabolic pathways. Ther Adv Endocrinol Metab. 2018;9(3):81-100.
[9]. Srinivasadesikan, V., Lu, C.-H., Ramachandran, B., & Lee, S.-L. Effects of microsolvation on the electronic properties of sarcosine: A computational study. ChemistrySelect.2017: 2(28), 8950–8958.
[10]. Ghanta, P., Doble, M., Ramaiah, B. Alkaloids of AdhatodavasicaNees. as potential inhibitors of cyclooxygenases – an in-silico study. J. Biomol. Struct. Dyn. 2021; 1–11.
[11]. Mudi PK, Mahanty AK, Kotakonda M, Prasad S, Bhattacharyya S, Biswas B. A benzimidazole scaffold as a promising inhibitor against SARS-CoV-2 [published online ahead of print, 2022 Jan 8]. J Biomol Struct Dyn. 2022;1-13.