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In silico MOLECULAR DOCKING AND ADME/T ANALYSIS OF SOME SELECTED COMPOUNDS OF *Lepisanthes tetraphylla* (Vahl) Radlk AGAINST TYPE 2 DIABETES MELLITUS

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ABSTRACT

The purpose of this study was to investigate the diabetic effect of phytocompounds of *Lepisanthes tetraphylla* (Vahl) Radlk through *in silico* molecular modelling studies. Molecular docking was carried out against human pancreatic alpha-amylase, human dipeptidyl peptidase IV, human PPAR-gamma and Glucagon receptor using Glide module. ADMET properties were calculated using quikprop module. Phytocompounds showed better binding score against human PPAR-gamma protein. Compound Lucenin was identified as a potent lead molecule in the management of diabetes mellitus.

Keywords: *In silico* docking, Diabetes Mellitus, *Lepisanthes tetraphylla* (Vahl) Radlk, ADMET

INTRODUCTION

Diabetes mellitus (DM) is identified as a metabolic disorder which ends from the blemish in insulin secretion and action **[1]**. An envisioned 422 million adults are dwelling with diabetes mellitus, as per the World Health Organization (WHO 2016)

[2]. At present there are five distinct classes of oral hypoglycemic which includes sulfonylureas, meglitinides, biguanides, thiazolidinediones and alpha glycosidase inhibitors and some under clinical trials. The limitations of the oral hypoglycaemic agents include biguanides are related with lactic acidosis, sulfonylureas with lethal hypoglycemic episodes from treatment failures, thiazolidinediones with obesity. In view of the side effects and exorbitant cost of the therapy, in the recent years, herbal medicines having trust in treating various diseases because of their natural origin and less or no side effects **[3]**.

Many drugs fail to enter market due to poor pharmacokinetic property may turn huge loss to the companies in drug discovery **[4]**. Computer aided tools emerged as advanced method in drug discovery and were applied to screen drugs from among phytochemicals found in the medicinal plant against many **[5]**. The medicinal plants found in world have health benefits. Many countries consume plant-based drug to prevent or eradicate several diseases according to WHO.

Lepisanthes tetraphylla (Vahl) Radlk, commonly called as kurpa, Nekota (Tamil name), is a shrub growing in India which belongs to the family Sapindaceae was used traditionally for the treatment of ephantiasis, skin disease, anti-emetic, contraceptive, fever, anti-microbial and anti-convulsant property. In Ayurvedha, this plant is used in the treatment of eczema, and psoriasis. Isolated constituents and many medicinal plants have demonstrated beneficial therapeutic potentials **[6-8]**.

In continuation to our previous work **[9]**, the aim of the present study is to discover a novel compound present in *Lepisanthes tetraphylla* (Vahl) Radlk against diabetics and to predict ADME/T property studies used to measure the safety of the compounds as drug.

MATERIALS AND METHODS:

Molecular docking and ADME & Toxicity studies

Molecular docking studies of compounds were studies by GLIDE program **[10]**. 18 ligand molecules were selected from the GCMS analysis of *Lepisanthes tetraphylla* (Vahl) Radlk based on their structural and pharmacological profile. The X-ray crystal structures of human pancreatic alpha-amylase (PDB: 1HNY), human dipeptidyl peptidase IV (PDB: 2P8S), human PPAR-gamma (PDB: 2XKW), Glucagon receptor (PDB: 4ERS) retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank was used in this study. “Extra precision” (XP) mode of GLIDE program was implemented in performing docking calculations. GLIDE score (G score) function was used to predict the best docked structure.

ADME/T properties of the test compounds was analysed using Quikprop module of Schrodinger 2016 (https://www.schrodinger.com/qikprop).

RESULTS AND DISCUSSION

G-score is the scoring function of GLIDE docking program. The most forthright method of comparing the accuracy of a docking technique is to determine how carefully the lowermost energy pose (binding conformation) expected with the aid of the object scoring characteristic. In the present study, by removing the inhibitor compound, Extra Precision GLIDE docking procedure was performed and validated. The docking result of these ligands are given in **Table 1**. From the minimized complex interaction energy was calculated. Among the four docked diabetic targets, the selected ligand molecules should potent interaction towards PPAR-gammaprotein and moderate interaction against human pancreatic alpha-amylase, human dipeptidyl peptidase IV and Glucagon receptor. The docking score was found -3.163Kcal/mol to -9.754Kcal/mol for the test compounds against PPAR-gammaprotein. All the test molecules bound to protein by hydrophobic and hydrophilic interaction. Interestingly, compound Lucenin showed a potent binding interaction against all the docked proteins with the binding score of -8.117 Kcal/mol, -10.246 Kcal/mol, -9.754Kcal/mol, -11.832Kcal/mol against human pancreatic alpha-amylase, human dipeptidyl peptidase IV, human PPAR-gamma and Glucagon receptor respectively. Interaction images of Lucenin with the target proteins have shown in **Figure 1-4**. From the *in-silico* results, it shows that the selected test compounds are potent and selective in action towards human PPAR-gammaprotein, which could be the possible mechanism of action. This proves that whole extract of *Lepisanthes tetraphylla* (Vahl) Radlk, especially compound Lucenin could be a potential drug for anti-diabetic drug development.

Ligand based ADME/Toxicity prediction

QuikProp module of Schrodinger was used to predict the drug-like activity of the ligand molecule, shown in **Table 2**. The selected properties are known to influence metabolism, cell permeation, and bioavailability. All the predicted properties of the test compound were in the range for 67 to 100% of known oral drugs and also satisfy the Lipinski's rule of five to be considered as drug like potential.

Table 1: Docking score of selected phytoconstituents of *Lepisanthes tetraphylla* (Vahl) Radlk against diabetic targets

S. No	Compound	Docking score			
		1HNY	2P8S	2XKW	4ERS
1	1,4-Methanoazulen-3-ol, decahydro-1,5,5,8a-tetramethyl	-3.793	-2.202	-3.163	-0.143
2	1,5,5-Trimethyl-6-(3-methyl-2-cyclobuten-1-yl)-7-oxabicyclo[4.1.0]hept-2-yl acetate	-4.348	-3.334	-6.884	-3.895
3	4-(cis-2,3,4, trans-6-Tetramethyl-3-cyclohexenyl) butan-2-one 2,4-dinitrophenylhydrazone	-4.162	-3.552	-4.772	-4.068
4	5-[4-(1,3-Benzodioxol-5-yl) tetrahydro-1H,3H-furo[3,4-c] furan-1-yl]-1,3-benzodioxole	-5.326	-5.487	-8.243	-4.639
5	6,17-Dihydroxy-17-methylandrosta-1,4-dien-3-one	-5.397	-4.748	-4.049	-4.447
6	Acetamide	-4.14	-3.54	-6.219	-3.995
7	Cholan-24-oic acid, 3-(acetyloxy)-7-oxo-, methyl ester	-3.906	-3.987	-6.985	-4.166
8	d-Xylitol, pentaacetate	-4.224	-4.986	-6.105	-4.581
9	Isosesamin	-3.961	-5.012	-6.885	-3.794
10	Lucenin	-8.117	-10.246	-9.754	-11.832
11	Methyl (12e)-12-[(2,4-dinitrophenyl) hydrazono]dodecanoate	-3.282	-3.892	-6.407	-3.328
12	N-(4-Hydroxyphenyl) retinamide	-2.955	-3.598	-6.684	-5.733
13	Pentalene, octahydro-1-(2-octyldecyl)	-3.487	-4.411	-9.047	-3.505
14	Pregnane-3,11,20-trione	-5.338	-3.972	-4.419	-4.048
15	Sesquisabinene hydrate	-3.65	-4.367	-5.978	-3.225
16	Stigmast-5-en-3-ol	-5.161	-4.228	-6.519	-4.346
17	Torreyol	-4.667	-	-4.971	-4.111
18	Vincadifformine	-5.269	-4.505	-3.236	-4.03

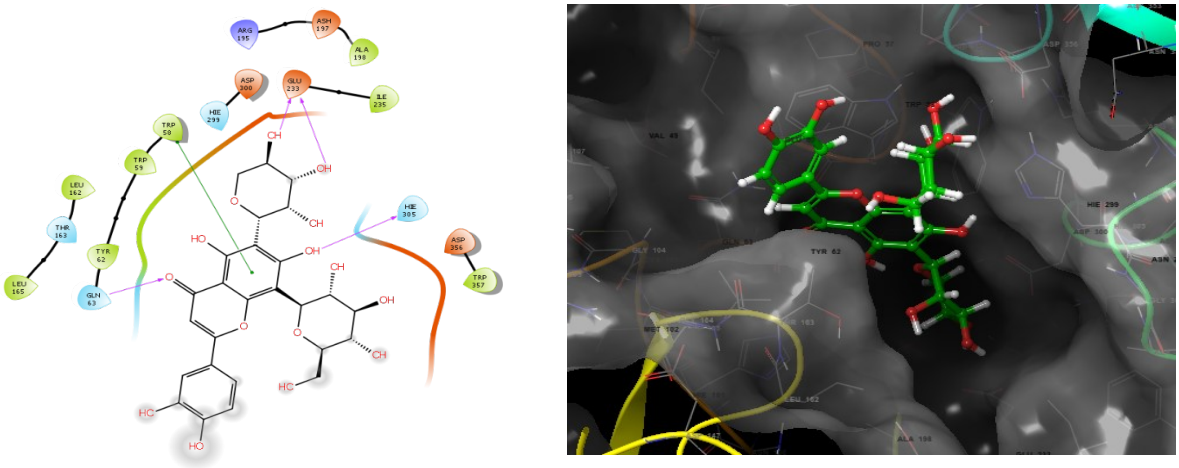

Figure 1: Lucenin against human pancreatic alpha-amylaseprotein

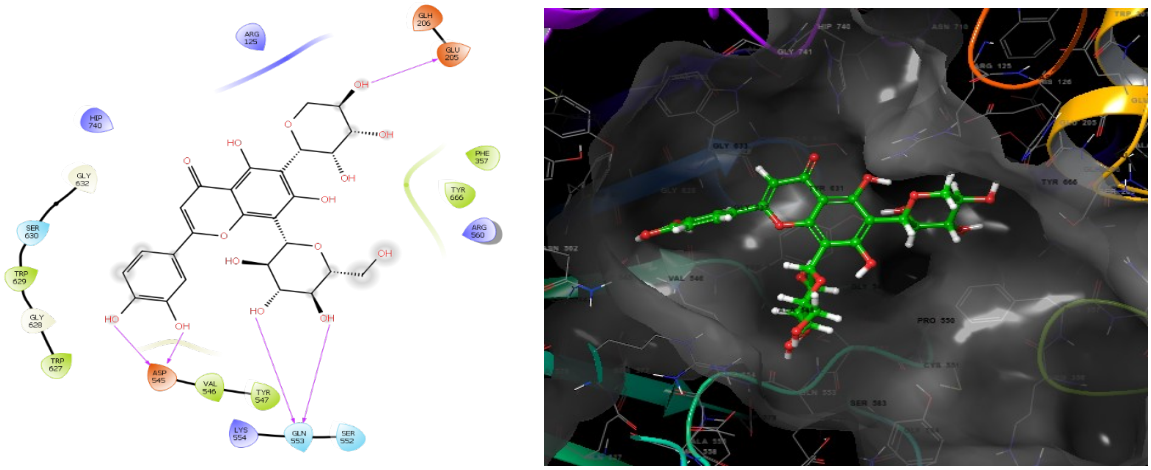

Figure 2: Lucenin against human dipeptidyl peptidase IV protein

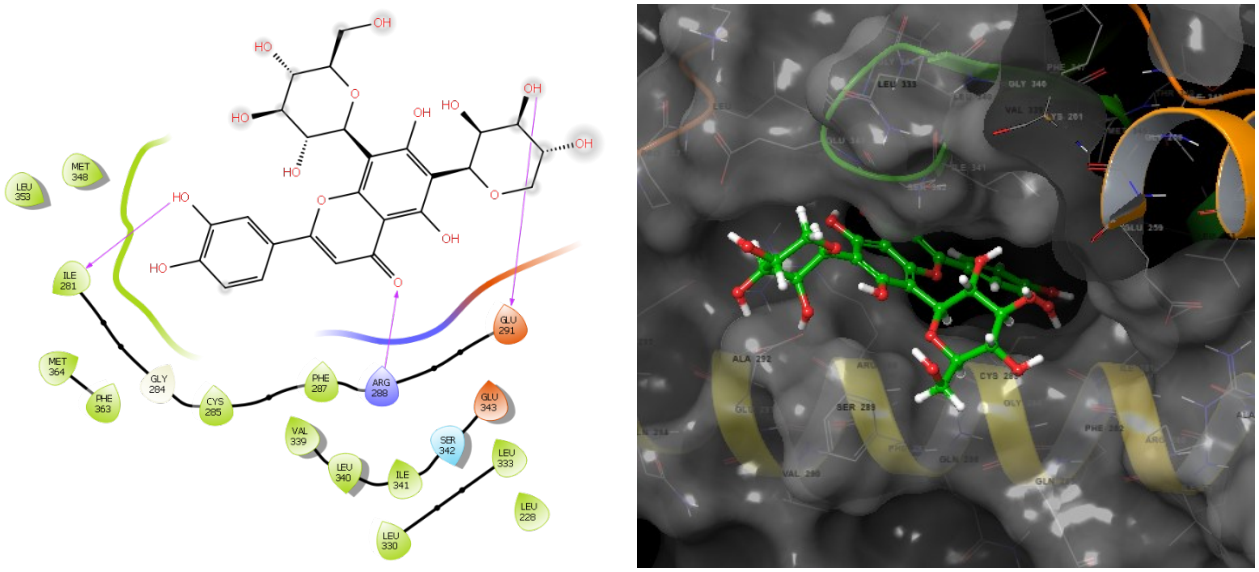

Figure 3: Lucenin against humanPPAR-gamma protein

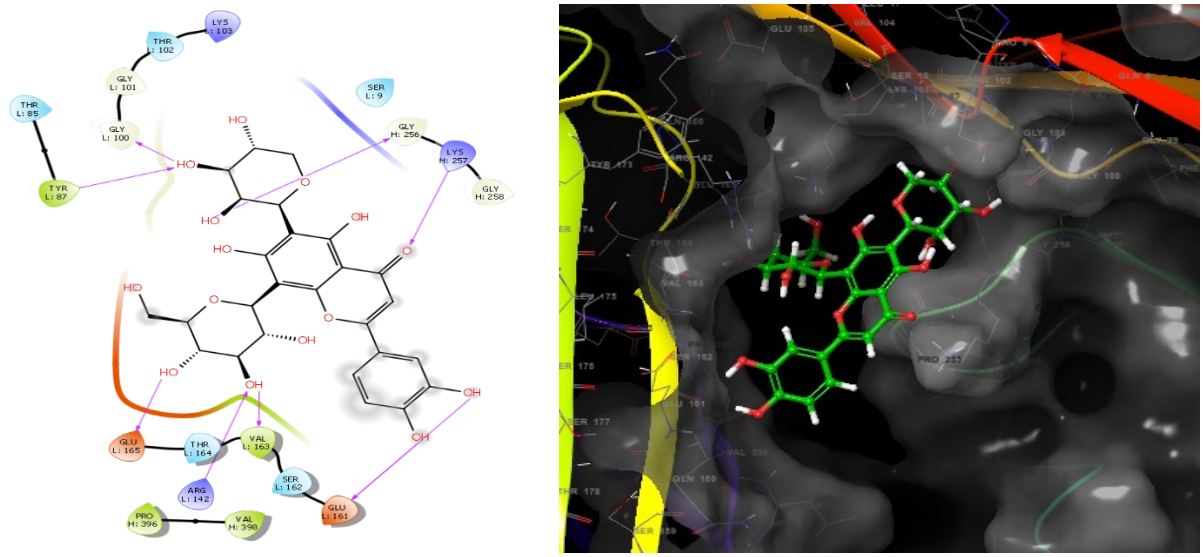

Figure 4: Lucenin against human Glucagon receptor

Table 2: ADMET properties of selected phytoconstituents of *Lepisanthes tetraphylla*

Title	mol MW	donorHB	accptHB	QPlogPo/w	QPlogBB	Percent Human Oral Absorption	Rule ofFive
Acceptable Range	*(130.0 – 725.0)*	*(0-6)*	*(2-20)*	*(–2.0 – 6.5)*	*(–3.0 – 1.2)*	*(>80% is high)*	*(maximum is 4)*
1,5,5-Trimethyl-6-(3-methyl-2-cyclobuten-1-yl)-7-oxabicyclo [4.1.0]hept-2-yl acetate	264.36	0	4	3.195	0.292	100	0
4-(cis-2,3,4, trans-6-Tetramethyl-3-cyclohexenyl) butan-2-one 2,4-dinitrophenylhydrazone	388.46	1	4	4.465	-2.085	90	0
5-[4-(1,3-Benzodioxol-5-yl) tetrahydro-1H,3H-furo[3,4-c] furan-1-yl]-1,3-benzodioxole	354.35	0	6	1.661	-2.178	100	0
6,17-Dihydroxy-17-methylandrosta-1,4-dien-3-one	316.43	2	4	2.771	-0.678	91	0
Acetamide	193.28	1	3	2.046	0.076	100	0
Cholan-24-oic acid, 3-(acetyloxy)-7-oxo-, methyl ester	446.62	0	6	4.975	-1.204	100	0
d-Xylitol, pentaacetate	362.33	0	10	0.721	-2.065	67	0
Isosesamin	354.35	0	6	1.76	-2.175	100	0
Lucenin	580.49	10	19	-3.105	-5.36	0	3
Methyl (12e)-12-[(2,4-dinitrophenyl) hydrazono]dodecanoate	408.45	1	7	3.729	-3.968	72	0
N-(4-Hydroxyphenyl) retinamide	391.55	2	3	6.282	-1.192	100	1
Pentalene, octahydro-1-(2-octyldecyl)	362.6	0	0	3.491	1.922	100	1
Pregnane-3,11,20-trione	330.4	0	6	2.476	-0.442	93	0
Sesquisabinene hydrate	222.3	1	1	4.336	-0.099	100	0
Stigmast-5-en-3-ol	414.7	1	2	7.506	-0.336	100	1
Torreyol	222	1	1	4.046	0.166	100	0
Vincadifformine	338.4	0	3	4.129	0.307	100	0

CONCLUSION

The Protein and ligand play an important role in structural based drug design. In the present work, some selected phytoconstituents of *Lepisanthes tetraphylla* was screened for their in silico anti-diabetic property against human pancreatic alpha-amylase, human dipeptidyl peptidase IV, human PPAR-gamma and Glucagon receptor. From the study it was found that, *Lepisanthes tetraphylla* could be great source of new PPAR-gamma inhibitor. Compound Lucenin was found to be potent molecule in molecular docking analysis. Further, evaluation of *Lepisanthes tetraphylla* and Lucenin by *in vitro* and *in vivo* can prove their efficacy in the diabetic treatment.

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

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