https://doi.org/10.47552/ijam.v16iS2.6278 ISSN No: 0976-5921

Int J. of Ayurvedic Med, "Natural to Synthetic: The Convergence of Traditional Medicine to Modern Medicine" Supplement 2025

In-Silico Prediction of Phytoconstituents from *Manilkara hexandra* for Antidiabetic Activity targeting LRH-1

Research Article

Apeksha P Motghare[1*], Parimal P Katolkar[2], Surbhi Bhope[1], Mohammad Tauqeer Sheikh[1], Pooja Dhenge[1]

1. K. C. Bajaj College of Pharmacy & Research, Jaripatka. Nagpur (MS), India-440014.
2. Department of Pharmaceutical Chemistry, Kamla Nehru College of Pharmacy, Butibori, Nagpur, Maharashtra. India.

Abstract

Objective: A complex metabolic condition known as diabetes mellitus is caused by either inadequate or dysfunctional insulin. Once more, medicinal plants are being researched for the treatment of diabetes. Prototypical compounds found in medicinal plants have been the source of many conventional medications. *In-silico* testing of *Manilkara hexandra* phytoconstituents for antidiabetic efficacy was a part of our investigation. Design: Utilizing Discovery studio, molecular docking is done to assess the pattern of interaction between the phytoconstituents from the *Manilkara hexandra* plant and the crystal structure of the antidiabetic proteins (PDB ID: 4DOS). Later, SwissADME and pkCSM were used to screen for toxicity as well as the pharmacokinetic profile. Results: The docked results suggest that Quercetin (-8.8 kcal/mol),Kaempferol (-8.2 kcal/mol), P-coumaric acid (-6.3 kcal/mol) and cinnamic acid (-6.2 kcal/mol), for 4DOS macromolecule has best binding affinity towards LRH-1 for antidiabetic activity as compared to the standard drug metformin (-4.8 kcal/mol). Furthermore, pharmacokinetics and toxicity parameters were within acceptable limits according to ADMET studies. Conclusion: Results from the binding potential of phytoconstituents aimed at antidiabetic activity were encouraging. It promotes the usage of *Manilkara hexandra* and offers crucial details on pharmaceutical research and clinical care.

Keywords: In-silico, *Manilkara hexandra*, Antidiabetic Activity, 4DOS, Discovery studio.

Introduction

Manilkara hexandra (Roxb.) Dubard, synonym: *Mimusops hexandra* Roxb, which is widely distributed over central India and the Deccan Peninsula. It is grown in all of India's principal regions. It is compared to Khirni as well. One of the most underutilized fruits in the state of Gujarat is the fruit of the plant. It is commonly referred to as Rayan.(1)

It is indigenous to India and is primarily found growing wild in the country's south and north. Our efforts are focused on gathering important data regarding the morphology, microscopy, phytoconstituents, and pharmacological aspects of the plant, which is widely distributed in Gujarat, Rajasthan, Madhya Pradesh, Andhra Pradesh, Kerala, and Maharashtra. Protobassic acid, 16-ahydroxyprotobassic acid, taraxerol, a triterpene ketone, alpha and beta-amyrin, cinnamates, alpha-spinasterol, beta-sitosterol, its beta-D-glucoside, quercetin, and its dihydroderivatives, ursolic acid, are only a few of the important phytoconstituents found The entire plant is traditionally used as an astringent, aphrodisiac, alexipharmic, stomachic, anthelmintic, and to relieve symptoms of fever, flatulence, colic, dyspepsia, helminthiasis, hyperdipsia, and burning sensation. All of these substances asserted to have a range of pharmacological activities, including those of an antioxidant, an antiulcer, an anti-inflammatory, an antidiuretic, and others.(2)

A series of metabolic illnesses known as diabetes mellitus are characterised by chronic hyperglycemia brought on by deficiencies in insulin secretion, insulin action, or both. The significance of insulin as an anabolic hormone leads to metabolic irregularities in carbohydrates, lipids, and proteins. These metabolic abnormalities are brought on by insufficient insulin levels to produce an adequate response and/or insulin resistance of target tissues, primarily skeletal muscles, adipose tissue, and to a lesser extent, liver, at the level of insulin receptors, signal transduction system, and/or effector enzymes or genes. The kind and length of diabetes affect the severity of symptoms. Patients with diabetes can experience polyuria, polydipsia, polyphagia, weight loss, and blurred vision. Some patients with diabetes are asymptomatic, particularly those with type 2 diabetes in the early stages of the disease. However, patients with severe hyperglycemia and, particularly in children, those with absolute insulin deficiency, can experience these symptoms. If untreated, uncontrolled diabetes can cause coma, stupor,

*** Corresponding Author:**
Apeksha Motghare
K. C. Bajaj College of Pharmacy & Research,
Jaripatka.
Nagpur (MS), India-44
Email Id: apekshamotghare6@gmail.com

and, in rare cases, death from nonketotic hyperosmolar syndrome or ketoacidosis.(3-5)

The human nuclear receptor liver receptor homolog-1 (LRH-1) has an important role in controlling lipid and cholesterol homeostasis and is a potential target for the treatment of diabetes and hepatic diseases. LRH-1 is known to bind phospholipids, but the role of phospholipids in controlling LRH-1 activation remains highly debated.

Liver receptor homolog 1 (LRH-1; NR5A2) is a nuclear hormone receptor (NR)3 that controls expression of a diverse set of genes important both in normal physiology and disease. In addition to a vital role during development (6,7) LRH-1 regulates many genes related to metabolism, proliferation, and cell survival. In the liver, LRH-1 regulates bile acid biosynthesis (8) and reverse cholesterol transport (9,10), affecting hepatic and circulating cholesterol levels. Glucose metabolism is also regulated by LRH-1 at several points, including GLUT-4-mediated transport (11) and glucose phosphorylation, the latter of which is essential for proper postprandial glucose sensing, flux through glycolysis and glycogenesis pathways, and *de novo* lipogenesis (12). LRH-1 is a key mediator of the cell stress response through control of genes involved in the hepatic acute phase response(13) and in the cytoprotective resolution of endoplasmic reticulum stress(14). Additionally, LRH-1 can be aberrantly overexpressed in certain cancers and can promote tumor growth through estrogen receptor and β-catenin signaling (15-21).

There are, however, limited investigations on *M. hexandra's* phytoconstituents for the antidiabetic. A molecular docking technique was used in the current work to find possible phytochemicals of *M. hexandra* that are resistant to 4DOS while keeping the aforementioned information in mind.

Materials and Methods

Platform for molecular docking

Using AutoDock Vina software, a computational docking analysis of all the phytoconstituents chosen as ligands with antidiabetic action as the target was carried out. (22)

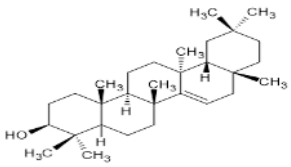
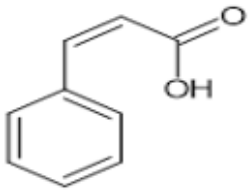
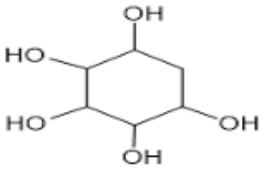
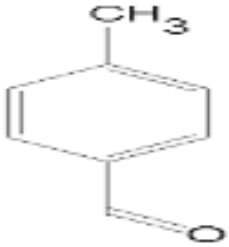
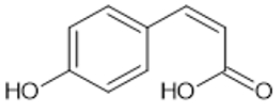
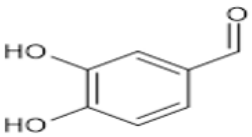
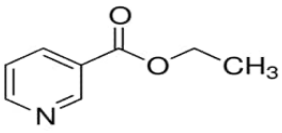
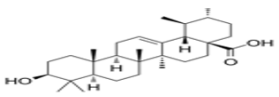
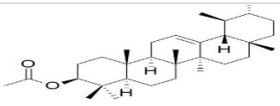
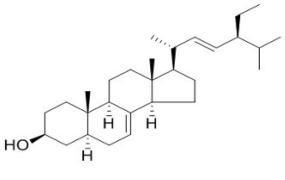
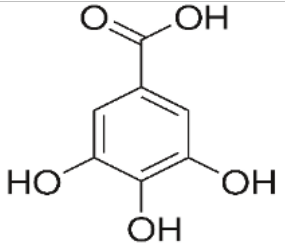
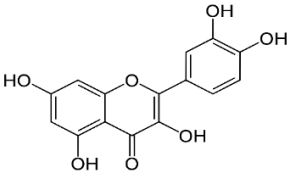
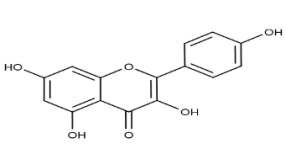
Protein preparation

The 2.00 crystal structure of antidiabetic with inhibitor, (PDB ID:4DOS, having resolution: 2.00, R-Value Free: 0.238, R-Value Work: 0.188, R-Value Observed: 0.191), which was retrieved from the protein data bank (https://www.rcsb.org), was subjected to *in-silico* analysis of a few phytoconstituents. 4DOS is used to treat diabetes. Using Discovery Studio, all additional molecules were eliminated, including undesirable chains, nonstandard residues, and co-crystallized water molecules.(23)

Ligand preparation

Using the Avogadro programme, all constituents' three-dimensional (3D) structures were extracted from the PubChem database on the NCBI website (https://pubchem.ncbi.nlm.nih.gov/). However, the ChemSketch application was used to sketch the geometrical 2D structure. The ligand structures were saved in the PDB format and the two-dimensional (2D) structures were converted into 3D models using the Avogadro software.

Figure 1: Chemical structures of all selected phytoconstituents in the molecular docking studies

1.Taraxerol	2. Hentriacontane
	
3. Cinnamic acid	**4. Quercitol**
	
5. 4-Methyl benzaldehyde	**6. *p*-Coumaric acid**
	
7. 3,4-Dihydroxy benzaldehyde	**8. Ethyl nicotinate**
	
9. Ursolic acid	**10. α-Amyrin acetates**
	
11. A-Spinasterol	**12. Gallic Acid**
	
13. Quercetin	**14. Kaempferol**
	

Molecular docking

In order to determine the scoring function based on geometry and forecast the binding affinity of the ligand molecule,(24,25) molecular docking analyses the interactions between the protein and the ligand. We used molecular docking experiments to examine the interactions between specific phytoconstituents (Fig.1), the conventional medication, and the crystal structure of a macromolecule with antidiabetic activity (PDB ID: 4DOS). PyRx software was used to carry out the molecular docking investigation, and the Vina wizard tool was used to investigate binding affinity. With bound ligands as the benchmark, the final data were analysed and presented using Discovery Studio 2020 Client.(26) The number of contacts and active residues responsible for significant binding at the target enzyme's active site are reflected in the protein-ligand interaction visualisation.

Absorption, distribution, metabolism, and excretion (ADME) and toxicityprediction

The chosen phytoconstituents and the reference medication were then examined for drug-like characteristics in accordance with Lipinski's rule. The tolerability of phytochemicals must be predicted during therapeutic development before they are consumed by people and animal models. SwissADME (http://www.swissadme.ch) and pkCSM (an online server database predicting small-molecule pharmacokinetic features using graph-based signatures, http://biosig.unimelb.edu.au/pkcsm/prediction) were used to determine the pharmacokinetic profile (ADME) and toxicity predictions of ligands. Simplified Molecular Input Line Entry System (SMILES) notations or PDB files were uploaded to examine the toxicological qualities of ligands, and then the necessary models were chosen to generate a wealth of information regarding effects associated to structure.(27,28)

Standard Preparation

The most often given medication for type 2 diabetes mellitus is metformin.(29)

A series of metabolic illnesses known as diabetes mellitus cause blood glucose levels to be higher than usual due to inadequate insulin release or inappropriate cell responses to insulin, which raises blood pressure. Serious difficulties are brought on by the ensuing hyperglycemia. The medicine metformin has been found to reduce the majority of diabetic complications and prevent diabetes in persons who are at high risk. Recent findings on metformin not only show some implications, such as reno protecting characteristics, but some reports also suggest its negative consequences, which are minor when its positive effects are taken into consideration.(30)

The standard is created in a series of phases, such as creating the 2D structure of the standard medicine using the chemsketch tool, then converting the 2D structure into a 3D model using the Avogadro Software, and finally saving it in PDB format. Metformin's molecular docking with 4DOS was carried out utilising PyRx.

Results and Discussion

The objective of the current study was to investigate the phytoconstituents found in *M. hexandra's* antidiabetic activity's inhibitory capacity. Using PyRx, we conducted molecular docking studies of all the phytoconstituents present in *M. hexandra* for this investigation. We next looked at the interactions between the amino acid residues and how they affected the inhibitory potentials of the active components. Using SwissADME and pkCSM servers, selected phytoconstituents with the best fit were further assessed for their absorption, distribution, metabolism, excretion, and toxicity (ADMET) characteristics.

Molecular docking

The docking scores and binding energies of all chemical constituents of *M. hexandra*targeting antidiabetic activity (PDB ID: 4DOS) and binding interactions with amino acid residues are presented in Table 1.

Table 1: Binding interaction of ligands from *M. hexandra* targeting antidiabetic activity (PDB ID: 4DOS)

Sr. No.	Chemical constituent	PubChem ID	Docking Score 4DOS
1	Taraxerol	92097	-9.3
2	Hentriacontane	12410	-4.3
3	Cinnamic acid	444539	-6.2
4	Quercitol	441437	-5.4
5	4-methyl benzaldehyde	7725	-5.5
6	P-coumaric acid	322	-6.3
7	3,4-dihydroxy benzaldehyde	8768	-5.5
8	Ethyl nicotinate	69188	-5.5
9	Ursolic acid	64945	-9.3
10	A-amyrin acetates	92842	-8.9
11	A-spinasterol	5281331	-10.1
12	Gallic acid	370	-6
13	Quercetin	5280343	-8.8
14	Kaempferol	5280863	-8.2
Standard Drug			
15	Metformin	4091	-4.8

The binding affinities of phytoconstituents ranged from -10.1 to -4.3 kcal/mol for 4DOS macromolecule. From the docked results, it is evident that the compounds, A-spinasterol, ursolic acid, *taraxerol*, A-amyrin acetates and quercetin for 4DOS exhibit the most favourable binding affinity (-10.1, -9.3, -9.3, -8.9, -8.8 kcal/mol respectively)in complex with antidiabetic activity, as compared to other docked compounds i.e., kaempferol(-8.2 kcal/mol), p-coumaric acid (-6.3 kcal/mol), cinnamic acid (-6.2 kcal/mol), *gallic acid* (-6 kcal/mol), quercitol(-5.4 kcal/mol), 3,4-dihydroxy benzaldehyde (-5.5 kcal/mol),ethyl nicotinate (-5.5 kcal/mol),4-methyl benzaldehyde (-5.5 kcal/mol) and hentriacontane (-4.3 kcal/mol).

The binding affinity of the standard (metformin) for 4DOS is -4.8 kcal/mol.(31)

In addition, an analysis of the interactions of the 4DOS protein complex and ligand metformin was performed, which showed that the ligand molecule is oriented due to one salt bridge with ASP 389(A) amino acid and ten van der waals interactions with amino acid residues PHE 448(A), LYS 452(A), ILE 356(A), TRP 359(A), PRO 313(A), SER 355(A), VAL 318(A), VAL 406(A), GLU 315(A), ARG 393(A) were also found. (Fig.2)

In addition, an analysis of the interactions of the 4DOS protein complex and ligand quercetin was performed, which showed that the ligand molecule is oriented due to two Pi-Alkyl interaction with ALA 513(A)LEU 517(A), two Pi-Sigma interactions with ALA 349(A), LEU 532(A), one conventional hydrogen bond with ASP 389(A), two unfavourable donor-donor interaction with LEU 386(A), ARG 393(A) and nine van der waals interaction with TYR 516(A), GLU 514(A), SER 383(A), TRP 382 (A), HIS 390(A),MET 345(A), THR 352(A), MET 348(A), VAL 406(A) were also found. (Fig.3.a)

In addition, an analysis of the interactions of the 4DOS protein complex and ligand kaempferol was performed, which showed that the ligand molecule is oriented due to one Pi-sigma interaction with ALA 513(A), two alkyl interaction with LEU 386(A), ALA 349(A), two conventional hydrogen bond with THR 352(A), HIS 390(A), one carbon hydrogen bond with SER 383(A), and eleven van der waals interaction with SER 510(A), GLU 514(A), LEU 532(A), LEU 517(A), ILE 387(A), LEU 427(A), TRP 382(A), LEU 405(A), MET 345(A), VAL 406(A), MET 345(A) were also found. (Fig.3.b)

In addition, an analysis of the interactions of the 4DOS protein complex and ligand p-coumaric acid was performed, which showed that the ligand molecule is oriented due to oneconventional hydrogen bond interaction with TYR 413(A), one attractive charge interaction with HIS 390(A), two Pi-Alkyl interaction with ILE 416(A), MET 428(A), and seven van der waals interaction with ILE 403(A), GLN 432(A), VAL 435(A), ALA 431(A), GLN 394(A), ALA 417(A), ASN 425(A) were also found. (Fig.3.c)

In addition, an analysis of the interactions of the 4DOS protein complex and ligand cinnamic acid was performed, which showed that the ligand molecule is oriented due to onePi-Sigma interaction with ALA 513(A), one carbon hydrogen bond with CYS 346(A), three Pi-Alkyl interaction with LEU 532(A), LEU 386(A), LEU 517(A), and nine van der waals interaction with GLU 514(A), TRP 382(A), SER 383(A), ILE 387(A), ALA 349(A), ASN 530(A), TYR 516(A), PHE 342(A), MET 345(A) were also found. (Fig.3.d)

ADMET study

Pharmacokinetic profile (ADME) and toxicity predictions of the ligands are important attentive parameters during the transformation of a molecule into a potent drug. In the present study, these parameters were assessed using SwissADME and pkCSM. The absorption potential and lipophilicity are characterized by the partition coefficient (Log *P*) and topological polar surface area (TPSA), respectively. For better penetration of a drug molecule into a cell membrane, the TPSA should be less than 140 Å. However, the value of Log *P* differs based on the drug target. The ideal Log *P* value for various drugs are as follows: oral and intestinal absorption, 1.35 − 1.80; sublingual absorption, > 5; and central nervous system (CNS). The aqueous solubility of ligands ideally ranges from –6.5 to 0.5 , while the blood brain barrier (BBB) value ranges between –3.0 and 1.2 (32). In addition, non-substrate P-glycoprotein causes drug resistance (33).

In our study, all the selected ligands followed the TPSA parameter, P-glycoprotein non-inhibition, thereby showing good intestinal absorption and an acceptable range of BBB values. All the compounds showed aqueous solubility values within the range. Further, it was predicted that the selected ligands do not show AMES toxicity, hepatotoxicity, and skin sensitivity. In addition, it did not inhibit hERG-I (low risk of cardiac toxicity). Lipinski's rule violations, *T. pyriformis* toxicity, minnow toxicity, maximum tolerated dose, rat acute oral toxicity, and chronic toxicity are depicted in table 2.(34)

Standard Drug

Figure 2: Docking scores and binding interaction of metformin (PDB ID: 4DOS).The ligand is shown in line and stick representation along with its 2D diagram and hydrogen bond interaction.

1. Metformin, 4DOS

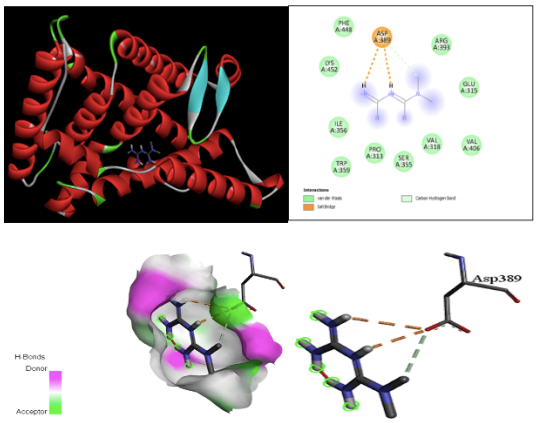


Table 2: ADME and toxicity predicted profile of ligands with superior docking scores

ADMET Properties	Formula	MW (g/mol)	Log P	TPSA (Å²)	HB donor	Hb acceptor	Aqueous solubility (Log mol/L)	Human intestinal absorption (%)	Blood-brain barrier
Taraxerol	C30H50O	426.72	8.17	20.23	1	1	-6.87	97.652	0.715
Hentriacontane	C31H64	436.84	12.34	0.00	0	0	-6.09	85.891	1.222
Cinnamic Acid	$C_9H_8O_2$	148.16	1.68	37.30	1	2	0.65	94.35	-0.312

https://doi.org/10.47552/ijam.v16iS2.6278 ISSN No: 0976-5921

Quercitol	$C_6H_{12}O_5$	164.16	-2.81	101.15	5	5	0.10	38.499	-1.082
4-Methyl Benzaldehyde	C_8H_8O	120.15	1.81	17.07	0	1	-1.71	97.33	0.394
P-Coumaric Acid	$C_9H_8O_3$	164.16	1.38	57.53	2	3	-2.01	93.512	-0.184
3,4-Dihydroxy Benzaldehyde	$C_7H_6O_3$	138.12	0.91	57.53	2	3	-0.75	77.745	-0.306
Ethyl Nicotinate	$C_8H_9NO_2$	151.16	1.26	39.19	0	3	-0.75	98.458	-0.236
Ursolic Acid	$C_{30}H_{48}O_3$	456.70	7.09	57.53	2	3	-4.65	97.503	-0.379
A-Amyrin Acetates	$C_{32}H_{52}O_2$	468.75	8.60	26.30	0	2	-7.04	100	0.662
A-Spinasterol	$C_{29}H_{48}O$	412.69	7.80	20.23	1	1	-7.10	95.981	0.805
Gallic Acid	$C_7H_6O_5$	170.12	0.50	97.99	4	5	-2.17	42.498	-0.958
Quercetin	$C_{15}H_{10}O_7$	302.24	1.99	131.36	5	7	-3.13	69.235	-1.372
Kaempferol	$C_{15}H_{10}O_6$	286.24	2.28	111.13	4	6	-3.30	74.567	-1.218
Metformin	$C_4H_{11}N_5$	129.16	-1.03	88.99	4	2	-2.67	57.273	-1.117

Table 2 Continued

ADMET Properties	P-glycoprotein substrate	Total clearance (Log ml/(min.kg))	Bio availability score	AMES toxicity	Max tolerated dose (Log mg/(kg.d))	hERG I inhibitor	hERG II inhibitor
Taraxerol	NO	-0.081	0.55	NO	-0.066	NO	YES
Hentriacontane	NO	2.188	0.55	NO	-0.254	NO	YES
Cinnamic Acid	NO	0.869	0.85	NO	1.17	NO	NO
Quercitol	NO	0.595	0.55	NO	2.461	NO	NO
4-Methyl Benzaldehyde	NO	0.265	0.55	NO	1.121	NO	NO
P-Coumaric Acid	NO	0.682	0.85	NO	1.089	NO	NO
3,4-Dihydroxy Benzaldehyde	NO	0.552	0.55	NO	0.739	NO	NO
Ethyl Nicotinate	NO	0.782	0.55	NO	1.122	NO	NO
Ursolic Acid	YES	0.079	0.85	NO	-0.65	NO	NO
A-Amyrin Acetates	NO	0.029	0.55	NO	0.423	NO	YES
A-Spinasterol	NO	0.611	0.55	NO	-0.318	NO	YES
Gallic Acid	YES	0.527	0.56	NO	1.414	NO	NO
Quercetin	YES	0.502	0.55	NO	0.779	NO	NO
Kaempferol	YES	0.538	0.55	NO	0.935	NO	NO
Metformin	YES	0.332	0.55	YES	0.364	NO	NO

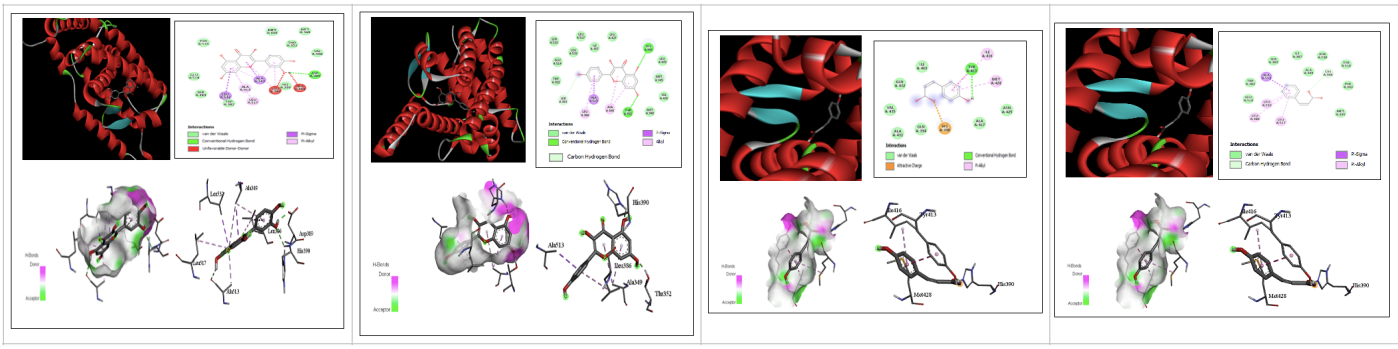
Table 2 Continued

ADMET Properties	Acute oral rat toxicity, LD50 (mol/kg)	Oral rat chronic toxicity (Log mg/kg bw/day)	Hepato-toxicity	Skin sensitisation	*T. Pyriformis* toxicity (Log µg/L)	Minnow toxicity (Log mmol/L)	Lipinski's rule violations
Taraxerol	2.828	1.288	NO	NO	0.41	-1.741	YES (1)
Hentriacontane	1.86	0.848	NO	YES	0.287	-5.021	YES (1)
Cinnamic Acid	2.05	2.549	NO	NO	-0.944	2.705	YES (0)
Quercitol	1.385	3.506	NO	NO	0.283	3.837	YES (0)
4-Methyl Benzaldehyde	1.731	1.959	NO	YES	-0.059	1.453	YES (0)
P-Coumaric Acid	1.912	2.953	NO	NO	0.223	1.79	YES (0)
3,4-Dihydroxy Benzaldehyde	1.865	2.149	NO	NO	-0.17	2.336	YES (0)
Ethyl Nicotinate	2.093	2.534	NO	YES	-0.39	2.187	YES (0)
Ursolic Acid	4.086	2.043	YES	NO	0.315	-0.596	YES (1)
A-Amyrin Acetates	2.261	2.187	NO	NO	0.37	-4.263	YES (1)
A-Spinasterol	2.454	1.125	NO	NO	0.56	-2.141	YES (1)
Gallic Acid	1.987	2.773	NO	NO	0.285	2.64	YES (0)
Quercetin	2.513	2.636	NO	NO	0.374	1.776	YES (0)
Kaempferol	2.329	2.616	NO	NO	0.448	1.034	YES (0)
Metformin	2.322	2.162	NO	YES	0.205	4.157	YES (0)

Drugs considered for 4DOS macromolecule

Figure 3: Docking scores and binding interaction for antidiabetic activity (PDB ID: 4DOS). The ligand is shown in line and stick representation along with its 2D diagram and hydrogen bond interaction.

a. Quercetin	b. Kaempferol	c. P-Coumaric Acid	d. Cinnamic Acid



Combine Boiled Egg Diagram

BOILED means **B**rain **O**r **I**ntestina**LE**stimate**D** permeation predictive model.

The boiled egg diagram shows two regions white and yellow.

The white region is the physicochemical space of molecules with highest probability ofbeing absorbed by the gastrointestinal tract, and the yellow region (yolk) is the physicochemical space of molecules with highest probability to permeate to the brain.

In addition, the points are coloured in blue if predicted as actively effluxed by P-gp(PGP^+) and in red if predicted as non-substrate of P-gp(PGP^-).

Conclusion

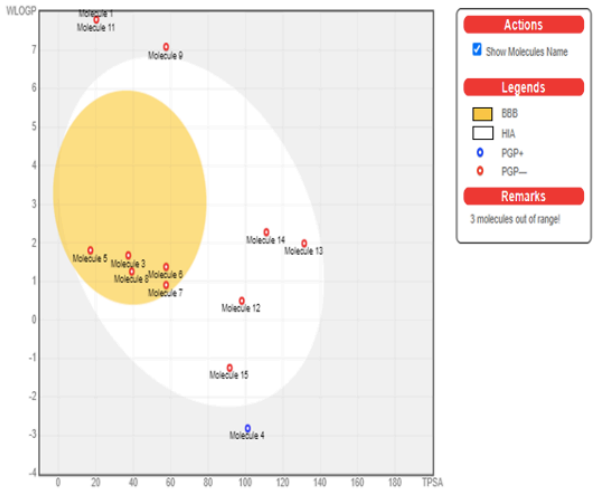
Glucose metabolism is also regulated by LRH-1 at several points, including GLUT-4-mediated transport and glucose phosphorylation, the latter of which is essential for proper postprandial glucose sensing, flux through glycolysis and glycogenesis pathways, and *de novo* lipogenesis and played important role in diabetes management. In this study, we have carried out an *in-silico* screening of the phytoconstituents of *Manilkara Hexandra*. This study demonstrate that thirteen compounds from selected phytoconstituents showed docking results from -10.1 to -5.4 kcal/mol. Among all, quercetin gave the lowest binding energy (-8.8 kcal/ mol) with 4DOS macromolecule, whereas the reference compound, metformin showing a docking score with a binding energy -4.8 kcal/mol.

To summarize, phytoconstituents present in *Manilkara Hexandra* possess strong inhibitory effects against 4DOS and could be further evaluated for their antidiabetic activity.

Table 3: Molecule names in boiled egg diagram

Molecule No.	Drug Name
1	Taraxerol
2	Hentriacontane
3	Cinnamic acid
4	Quercitol
5	4-methyl benzaldehyde
6	P-coumaric acid
7	3,4-dihydroxy benzaldehyde
8	Ethyl nicotinate
9	Ursolic acid
10	A-amyrin acetates
11	A-spinasterol
12	Gallic acid
13	Quercetin
14	Kaempferol
15	Metformin

Figure 4: Combined boiled egg diagram of all phytoconstituents with standard.



References

1. Bhutya RK. Ayurvedic Medicinal Plants of India (Vol. 1). Scientific Publishers; 2011 Mar 1.
2. 2.https://ijpsr.com/bft-article/a-comprehensive-pharmacognostic-review-manilkara-hexandra-roxb-dubard/
3. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2014;37 Suppl 1: S81–S90.
4. Craig ME, Hattersley A, Donaghue KC. Definition, epidemiology and classification of diabetes in children and adolescents. Pediatric diabetes. 2009 Sep;10:3-12.
5. Galtier F. Definition, epidemiology, risk factors. Diabetes & metabolism. 2010 Dec 1;36(6 Pt 2):628-51.
6. Gu P, Goodwin B, Chung AC, Xu X, Wheeler DA, Price RR, Galardi C, Peng L, Latour AM, Koller BH, Gossen J. Orphan nuclear receptor LRH-1 is

required to maintain Oct4 expression at the epiblast stage of embryonic development. Molecular and cellular biology. 2005 May 1;25(9):3492-505.
7. Wagner RT, Xu X, Yi F, Merrill BJ, Cooney AJ. Canonical Wnt/β-catenin regulation of liver receptor homolog-1 mediates pluripotency gene expression. Stem cells. 2010 Oct;28(10):1794-804.
8. Lu TT, Makishima M, Repa JJ, Schoonjans K, Kerr TA, Auwerx J, Mangelsdorf DJ. Molecular basis for feedback regulation of bile acid synthesis by nuclear receptors. Molecular cell. 2000 Sep 1;6(3):507-15.
9. Stein S, Oosterveer MH, Mataki C, Xu P, Lemos V, Havinga R, Dittner C, Ryu D, Menzies KJ, Wang X, Perino A. SUMOylation-dependent LRH-1/PROX1 interaction promotes atherosclerosis by decreasing hepatic reverse cholesterol transport. Cell metabolism. 2014 Oct 7;20(4):603-13.
10. Schoonjans K, Annicotte JS, Huby T, Botrugno OA, Fayard E, Ueda Y, Chapman J, Auwerx J. Liver receptor homolog 1 controls the expression of the scavenger receptor class B type I. EMBO reports. 2002 Dec 1;3(12):1181-7.
11. Bolado-Carrancio A, Riancho JA, Sainz J, Rodríguez-Rey JC. Activation of nuclear receptor NR5A2 increases Glut4 expression and glucose metabolism in muscle cells. Biochemical and biophysical research communications. 2014 Apr 4;446(2):614-9.
12. Oosterveer MH, Mataki C, Yamamoto H, Harach T, Moullan N, Van Dijk TH, Ayuso E, Bosch F, Postic C, Groen AK, Auwerx J. LRH-1–dependent glucose sensing determines intermediary metabolism in liver. The Journal of clinical investigation. 2012 Aug 1;122(8):2817-26.
13. Venteclef N, Smith JC, Goodwin B, Delerive P. Liver receptor homolog 1 is a negative regulator of the hepatic acute-phase response. Molecular and cellular biology. 2006 Sep 15;26(18):6799-807.
14. Mamrosh JL, Lee JM, Wagner M, Stambrook PJ, Whitby RJ, Sifers RN, Wu SP, Tsai MJ, DeMayo FJ, Moore DD. Nuclear receptor LRH-1/NR5A2 is required and targetable for liver endoplasmic reticulum stress resolution. Elife. 2014 Apr 15;3:e01694.
15. Bayrer JR, Mukkamala S, Sablin EP, Webb P, Fletterick RJ. Silencing LRH-1 in colon cancer cell lines impairs proliferation and alters gene expression programs. Proceedings of the National Academy of Sciences. 2015 Feb 24;112(8):2467-72.
16. Bianco S, Brunelle M, Jangal M, Magnani L, Gévry N. LRH-1 Governs Vital Transcriptional Programs in Endocrine-Sensitive and-Resistant Breast Cancer CellsLRH-1 and Endocrine-Resistant Breast Cancer. Cancer research. 2014 Apr 1;74(7):2015-25.
17. Chand AL, Herridge KA, Thompson EW, Clyne CD. The orphan nuclear receptor LRH-1 promotes breast cancer motility and invasion. Endocrine-related cancer. 2010 Oct 29;17(4):965.
18. Clyne CD, Kovacic A, Speed CJ, Zhou J, Pezzi V, Simpson ER. Regulation of aromatase expression by the nuclear receptor LRH-1 in adipose tissue. Molecular and cellular endocrinology. 2004 Feb 27;215(1-2):39-44.
19. Lai CF, Flach KD, Alexi X, Fox SP, Ottaviani S, Thiruchelvam PT, Kyle FJ, Thomas RS, Launchbury R, Hua H, Callaghan HB. Co-regulated gene expression by oestrogen receptor α and liver receptor homolog-1 is a feature of the oestrogen response in breast cancer cells. Nucleic acids research. 2013 Dec 1;41(22):10228-40.
20. Thiruchelvam PT, Lai CF, Hua H, Thomas RS, Hurtado A, Hudson W, Bayly AR, Kyle FJ, Periyasamy M, Photiou A, Spivey AC. The liver receptor homolog-1 regulates estrogen receptor expression in breast cancer cells. Breast cancer research and treatment. 2011 Jun;127(2):385-96.
21. Lin Q, Aihara A, Chung W, Li Y, Huang Z, Chen X, Weng S, Carlson RI, Wands JR, Dong X. LRH1 as a driving factor in pancreatic cancer growth. Cancer letters. 2014 Apr 1;345(1):85-90.
22. Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS, Olson AJ. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. Journal of computational chemistry. 2009 Dec;30(16):2785-91.
23. Pettersen EF, Goddard TD, Huang CC, Couch GS, Greenblatt DM, Meng EC, Ferrin TE. UCSF Chimera—a visualization system for exploratory research and analysis. Journal of computational chemistry. 2004 Oct;25(13):1605-12.
24. Verdonk ML, Cole JC, Hartshorn MJ, Murray CW, Taylor RD. Improved protein–ligand docking using GOLD. Proteins: Structure, Function, and Bioinformatics. 2003 Sep;52(4):609-23.
25. Leach AR, Shoichet BK, Peishoff CE. Prediction of protein− ligand interactions. Docking and scoring: successes and gaps. Journal of medicinal chemistry. 2006 Oct 5;49(20):5851-5.
26. BIOVIA DS. Discovery studio modeling environment, release 2017, San Diego: DassaultSystèmes, 2016. Available from:(Accessed 1 September 2016). 2016 Sep.
27. Arora S, Lohiya G, Moharir K, Shah S, Yende S. Identification of potential flavonoid inhibitors of the SARS-CoV-2 main protease 6YNQ: a molecular docking study. Digital Chinese Medicine. 2020 Dec 1;3(4):239-48.
28. Shah S, Chaple D, Arora S, Yende S, Moharir K, Lohiya G. Exploring the active constituents of Oroxylum indicum in intervention of novel coronavirus (COVID-19) based on molecular docking method. Network Modeling Analysis in Health Informatics and Bioinformatics. 2021 Dec;10(1):1-2.
29. Wang YW, He SJ, Feng X, Cheng J, Luo YT, Tian L, Huang Q. Metformin: a review of its potential indications. Drug design, development and therapy. 2017;11:2421.
30. Nasri H, Rafieian-Kopaei M. Metformin: current knowledge. Journal of research in medical sciences:

the official journal of Isfahan University of Medical Sciences. 2014 Jul;19(7):658.

31. Yende SR, Shah SK, Arora SK, Moharir KS, Lohiya GK. In silico prediction of phytoconstituents from Ehretia laevis targeting TNF-α in arthritis. Digital Chinese Medicine. 2021 Oct 1;4(3):180-90.
32. Kaloni D, Chakraborty D, Tiwari A, Biswas S. In silico studies on the phytochemical components of Murraya koenigii targeting TNF-α in rheumatoid arthritis. Journal of Herbal Medicine. 2020 Dec 1;24:100396.
33. Joshi T, Sharma P, Joshi T, Chandra S. In silico screening of anti-inflammatory compounds from Lichen by targeting cyclooxygenase-2. Journal of Biomolecular Structure and Dynamics. 2020 Aug 12;38(12):3544-62.
34. Nisha CM, Kumar A, Vimal A, Bai BM, Pal D, Kumar A. Docking and ADMET prediction of few GSK-3 inhibitors divulges 6-bromoindirubin-3-oxime as a potential inhibitor. Journal of Molecular Graphics and modelling. 2016 Apr 1;65:100-7.

*****