Ilaro Journal of Science and Technology (IJST) 2024
Published Online October 2024 (https://sciencetechjournal.federalpolyilaro.edu.ng)
Volume 4, 2024 Edition
ISSN: 2437-1505

Insilico Assessment Of Antidiabetic Activity Of *Rhus Longipes* Leaf Phytocompounds Against Alpha-Glucosidase And Aldose-Reductase Proteinsassociated With Diabetes

ADEDOYIN A. OLASUNKANMI
THE FEDERAL POLYTECHNIC ILARO/SLT, ILARO, NIGERIA
E-mail: adedoyin.olasunkanmi@federalpolyilaro.edu.ng

OYEWALE O. AFUYE
THE FEDERAL POLYTECHNIC ILARO/SLT, ILARO, NIGERIA
E-mail: oyewale.afuye@federalpolyilaro.edu.ng

Abstract: *Diabetes is a dangerous metabolic condition that is treated with a variety of medicinal herbs in conventional medicine. Plant extracts are widely used in Nigeria as important sources of antidiabetic agents, despite the use of synthetic drugs by the vast majority of the populace. Rhuslongipesis well-known for its conventional therapeutic usage. With the use of insilico approach, the current study aims at investigating the molecular docking and ADME/drug screening of bioactive components found in the Rhuslongipes leaf ethanol extract. Using Pyrx software, molecules were molecularly docked to two target proteins: aldose reductase and α-glucosidase. SwissADME, an online application, was used to calculate the physicochemical, ADMET, and drug similarity characteristics. Because of the strong binding affinities between the chemicals octadecanamide, 2-[3-(cyclohexylamino) propyl]-guanidine, elaidic acid, and caffeic acid and at least one of two target proteins, the results validated the plant's antidiabetic properties. Eight compounds (four of each): estriol, cholest-2-Eno[2,3-B], (+)-catechin, Apigenin; octadecanamide, 2-[3(cyclohexylamino)propyl] -guanidine, elaidic acid, and caffeic acid; and estriol, cholest-2-eno [2, 3B], gave the best binding score for target proteins, for which relatively optimal drug-like and pharmaceutical chemistry properties were identified. The plant's ethanol extract was shown to have antidiabetic properties in our most recent investigation, and we also found a number of potentially useful chemicals. Consequently, the current study came to the conclusion that these compounds might have had a role in the plant's reported antidiabetic qualities and might further be studied as prospective medications.*

Keywords: Insilico, Diabetes, ADMET, *Rhus longipes*, Antioxidant

Introduction

Diabetes can be described as metabolic disorder linked to blood sugar evels. Hyperglycemia is a sign of diabetes that is brought on by a decrease in insulin function (Rosa, Elya, Hanafi & Khatib, 2022). Because it can harm other organs, including the heart, blood vessels, kidneys, and eyes, this condition escalates to a very critical level (Piero, Nzaro, & Njagi, 2014). It was reported by IDF(International Diabetes Federation) that 537 million people has diabetesand it is anticipated that it will increase to 783 million in 2045 (Sakulkeo, Wattanapiromsakul, Pitakbut, Dej-Adisai, 2022). Type 1diabetes, which is as a result of lack of insulin because of beta cell malfunction, and type 2 diabetes, which is caused by an inability of body cells to produce insulin, are the two main forms of the disease. Individuals with uncontrolled blood glucose levels fall into both categories. For individuals with type 1 diabetes, exogenous insulin is a possibility, whereas other glucose-lowering medication classes are employed for individuals with type 2 diabetes (American Diabetes Association). According to Chaudhury *et al.* (2017), medicinal approach harnessed for diabetes mellitus are complex, despite the availability of several therapeutic molecules. According to Daub *et al.* (2020), it has the abilityof alpha-glucosidase in the small intestine mucosa to breakdown glycosidic bonds of different glucose compounds that results in the production of oligosaccharide, monosaccharides or glycosaminoglycans leading to the increase in glucose levels in the blood after meals. The primary risk factor for type 2 diabetes development and progression is postprandial hyperglycemia. By delaying the breakdown of carbohydrates, inhibition of α-glucosidase activity reduces glucose level in the blood and decreases the amount of glucose absorbed into the circulation. According to Syabana *et al.* (2021), this kind of inhibition is regarded as a crucial medicalauthenticationgoal for the management of type 2 diabetics. Aldose reductase is a member of the superfamily ofaldo-ketoreductase. This

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first rate-limiting enzyme of the polyolpathway uses NADPH as a cofactor and converts glucose to sorbitol. The transformation of sorbitol into fructose is catalyzed by the enzyme sorbitol dehydrogenase (Kasthuri *et al.*, 2022). Less than 3% of glucose is used via the polyol route, which is a comparatively small mechanism of glucose consumption. But this route is more active when blood glucose levels rise, and it can make up as much as 30% of the total amount of glucose consumed (Yingying, Haijuan, Haoyu, & Penghang, 2022). Osmotically active sorbitol increases during diabetes due to aberrant activation of the polyol pathway. This leads to osmotic and oxidative stress, which damages tissue. Beta-glucosidase and aldose reductase inhibition is a basic strategy for treating and avoiding diabetes problems and may be a target for medication development (Syabana *et al.*, 2021).

Rhus longipes, often known as *Searsia longipes*, is a naturally occurring plant that is not widely used at the moment. In Yoruba, it's called Ewe Orijin (Olorunnisola *et al.*, 2017), this plant, which is a member of the *Anacardiaceae* family, is believed to have a variety of traditional uses. The antibacterial and antioxidant qualities of the ingredients of Rhuslongpes were reported by Olaolunkanmi *et al.* in 2021. R. longipes is commonly used by traditional practitioners as an antimalarial, wound-healing, and early abortion remedy, according to Oladeleet al. (2011). The roots are hanessed as a laxative and, when mixed with the leaf juice, might cause miscarriage (Maroyi, 2011). Many unexplored therapy options for various ailments are provided by the traditional therapeutic approach. Amazing outcomes can be achieved if contemporary computational chemistry techniques are applied to examine the efficacy of the traditional therapeutic approach. Many researchers have previously carried out comparable studies in which bioactive substances were docked on a particular receptor to ascertain their affinity. *Rhuslongipes*leaves contain certain antidiabetic compounds that can be a good source of diabetes treatment. Hence, this study aims to find safe, efficient, and therapeutically useful lead drug compounds from R. longipes leaf extract that can inhibit aldose reductase and alpha-glucosidase.

Materials and Methods

Preparationof plant sample

Rhuslongpes leaves were gotten from Oja-Odan in Ogun State. The *R. longpes leaf* sampleswere washed and air-dried under the shade. The dried *R. longpesleaves* were ground to powdery form by means of an electric blender. The powdery plant l was soaked in 80% ethanol at a ratio of 1:5 *R. longpes*toethanolfor 72 hours. The mixture was then filtered through Whatman No. 1, and the filtrate was condensedin a rotary evaporator at (45^{o}C). The condensed extract was placedin a water bath at 60^{o}C to evaporate the ethanol residue, yielding a crude extract.

GC-MS ANALYSIS OF *R. LONGIPES*

The Agilent Technologies 789OA mass spectrometer, equipped with an automatic injector (10 L syringe) and a three-axis detector (VL5675C), was utilized for the GC-MS experiment. On a 30 m^2 capillary column, helium (he) was handled as the gas carrier at a steady flow rate of 1.5 ml/min for 250 lm and 0. 25 lm. One liter of sample was injected, and the split ratio (split mode) was one to three. The temperature of the column was raised from 35°C to 150°C for five minutes, and then it was raised to 2500°C for five minutes at a rate of 200°C per minute. By comparing each component's spectrum with the reference spectrum (National Library of Standards and Technology), the chemicals were identified.

MOLECULAR DOCKING

Preparation of Protein

Structures of the enzymes; aldose reductase and alpha-glucosidase linked with peptide substrate were retrived from PDB data bank (Alpha Glucosidase (PDB ID: 8EMR) and Aldose Reductase (PDB ID: 2ACQ). 1.45Å was the resolution factor and X-ray diffraction method was used as the method of incorporation. Receptors were reduced by Swiss PDB viewer and active sites of residues wererecognized using online server Castp. Ligandslinked with targets wereselectedby means of the control panel of stand-alone program. The ligands were isolated using Pymol software and the finishing preparation was done by extracting water molecules and attaching H –atoms.

Selection and preparation of ligands

Arannilewa *et al.* (2018) reported that the structures of 35 ligands of Rhuslongipes, Miglitol, and Sorbinil were retrieved from the PubChem compound database (https://pubchem.ncbi.nlm.nih.gov) and employed with PyRx and Open Babel prior to docking to create universal nominal structures. These ligands' MOL SDF design was

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converted to a PDBQT file using PyRx to create atomic coordinates, and energy was decreased by utilizing the optimization algorithm at the force field set at mmff94 (a necessary parameter) on PyRx (Elekofehintia *et al.*, 2018).

Molecular docking using PyRx

Following the production of receptors and ligands, PyRx was used to perform molecular docking analysis with the AutoDockVina option, which is based on scoring functions (Trott & Olson, 2010). With default settings for other parameters, this program was operated with a probing grid extensive to the ligands with a box spacing of 25×25×25 with coordinates for x, y, and z of -8.6805, -7.4304, and 26.9770, respectively. Using the same grid box dimension, the compounds containing standard pharmaceuticals were docked into the binding sites of aldose reductase and alpha glucosidase. The resultantinterface was then likened to the conventional medications into analogous active sites. The mainlysteady conformation of every one molecule for binding to the alpha glucosidase and aldose reductase protein-active site is predicted to be the best possible docking posture (Arannilewa *et al.*, 2018)

Confirmation of Docking Results

The collated compounds were cleaved and transformed to 2D (in sdf format) by Data Warrior software (version 5.5.0) and transformed to pdbqt pattern by PyRx tool (Trott & Olson, 2010). The docking scores of the 35 generated compounds was plotted against their corresponding binding affinity values in a correlation coefficient graph (Ambrose *et al.*, 2018).

Subsequently, protein-ligand complex was generated for four compounds having the best binding affinity tagged the "hit compounds" and also the standard drug (Miglitol and Sorbinil). 2D interactions to show the distance, type of bond and amino acid residues each ligand is interacting with in the protein was generated using Discovery Studio. Pocket view for each protein-ligand complex was also generated using Pymol (Olasunkanmi & Phillip, 2023).

The prediction of ADME/T

The SwissADME and ADMETsar web servers were utilized to assess the toxicity and drug-likeness of the target compounds. The factors that are utilized to filter the compounds include the Lipinski rule of five (RO5), gastrointestinal (GI) absorption, inhibition of CYP450 isoenzymes, hepatotoxicity, ocular irritation and corrosion, biodegradation, among others. (Ajiboye et al., 2022).

Results

Table 1: GC-MS profile of *Rhuslongipes*ethanol leaf extract

Retention Time	Identified Compound	Percentage (%)
3.441	Cholest-2-eno[2,3-b]quinoxaline,3',8'-dichloro-	0.12
5.791	1-(3-Cyclohexylaminopropyl)guanidine	0.12
5.893	Aziridine, 1-(2-buten-2-yl)-	0.40
6.428	.pi.-Cyclopentadienyl-dicarbonylethylisonitril-trichlorgenyl-tungsten	0.35
7.135	1,5-Methano-1H,7H,11H-furo[3,4-g]pyrano[3,2-b]xanthene-7,15-dione, 3 ,3a,4,5-tetrahydro-8-hydroxy-1-(4 -hydroxy-3-methyl-2-butenyl)-3,3,11,11-tetramethyl-13-(3-methyl-2-butenyl)-, [1R-[1.alpha.,1(Z),3a.beta.,5.alpha.,14as*]]-	0.20
4.868	N-Hydroxybenzenecarboximidoyl bromide	0.23
7.895	3-Pyridinecarboxylic acid, 1,4,5,6-tetrahydro-1,2-dimethyl-6-oxo-, ethyl ester	0.16
8.771	2,2-Dibromocholestanone	0.22
9.800	Oleanan-29-oic acid, 3-(acetyloxy)-12,13-epoxy-11-oxo-, methyl ester, (3.beta.,12.beta.,20.beta.)-	0.27
11.185	9,19-Cyclolanost-6-ene-3,7-diol, diacetate	0.09
11.735	4a,7a-Epoxy-5H-cyclopenta[a]cyclopropa[f]cyclotridecen-4(1H)-one, 2,7,10,11-tetrakis(acetyloxy)-1a,2,3,6,7,10,11,11a-octahydro-1,1,3,6,9-pentamethyl-, [1ar-(1ar*,2R*,3S*,4as*,6S*,7S*,7as*,8E,10R*,11R*,11as*)]-	0.09
11.839	Cholestan-6-en-3-ol, O-acetyl-24-methyl-5,8-[tetrahydrofuran-2,5-diono-3,4-diyl]-	0.08
14.224	Acetic acid, 17-(4-chloro-5-methoxy-1,5-dimethylhexyl)-4,4,10,13,14- pentamethyl-2,3,4,5,6,7,10,11,12,13,14,15,16,17-tetradecahydro-1- phenanthryl	0.11
14.486	Tricyclo[5.4.0.0(2,8)]undec-9-ene,2,6,6,9-tetramethyl-, (1R,2S,7R,8R)-	0.42
16.666	3-Methyl-6-(6-methylhept-5-en-2-yl)cyclohex-2-enone	1.48
16.992	Neophytadiene	0.72
17.206	Silane, [[(3.beta.,5.beta.)-cholest-4-ene-3,6-diyl]bis(oxy)]bis[trimethyl-	0.43
18.118	3.beta.,4.beta.-Bis(trimethylsiloxy)cholest-5-ene	0.18
18.617	.psi.,.psi.-Carotene, 7,7',8,8,11,12,15,19,20,540-04-5 10,11',12,12'- tetrahydro-	0.46
19.608	3-Diethoxyphosphonyl-demethylthiocolchicine	0.22
19.661	9-Octadecenoic acid, (E)-, TMS derivative	0.16
20.508	Z-28-Heptatriacontien-2-one	0.44
25.508	cis-4-Trimethylsilyloxy-cyclohexyl (trimethylsilyl)carboxylate	0.11
26.253	Fasiol, 3 TMS derivative	0.13
26.347	1',1'-Dicarboethoxy-1.beta.,2.beta.-dihydro-3'Hcyclopropa[1.,2]cholesta-1,4,6-trien-3-o	0.12

Table 2: Molecular docking result of Alpha glucosidase protein

S/N	Ligands	Binding Affinity
1	Miglitol (standard drug)	-2.1
2	Octadecanamide	-4.1
3	2-[3-(Cyclohexylamino)Propyl]Guanidine	-4.1
4	Elaidic acid	-4.2
5	Caffeic acid	-4.3

Table 3: Molecular docking result of Aldo reductase protein

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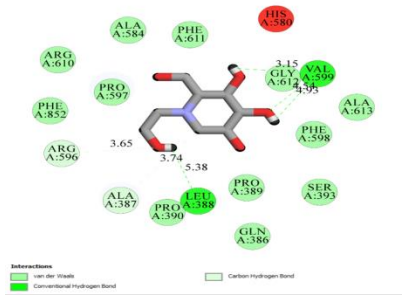
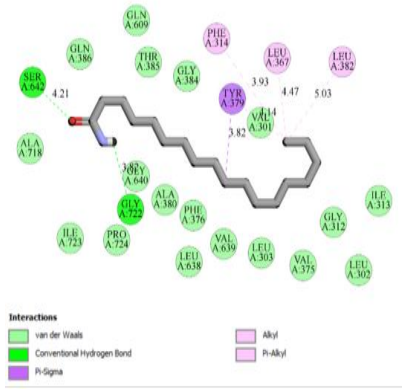
S/N	Ligands	Binding Affinity
1.	Sorbinil (standard drug)	-8.3
2.	Estriol	-8.8
3.	Cholest-2-Eno[2,3-B]	-8.9
4.	(+)-catechin	-9.9
5.	Apigenin	-10.2

Table 4: Basic ADMET properties and computational descriptors of the screened compounds

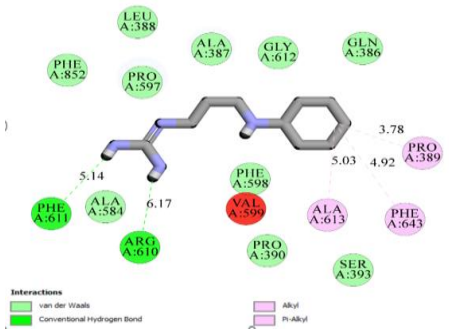
Compound Name	Mw	TPSA	GI Abs.	Lipinski Violation	CypP1A2 Inhibitor	CypC19 Inhibitor	Cyp2C9 Inhibitor	Cyp2D6 Inhibito
Sorbinil	236.2	67.43	High	0	No	No	No	No
Estriol	274.35	60.69	High	0	No	No	No	Yes
Cholest-2-Eno[2,3-B]	517.75	71.6	Low	2	No	Yes	No	No
(+)-catechin	290.27	110.38	High	0	No	No	No	No
Apigenin	270.24	90.9	High	0	Yes	No	No	Yes



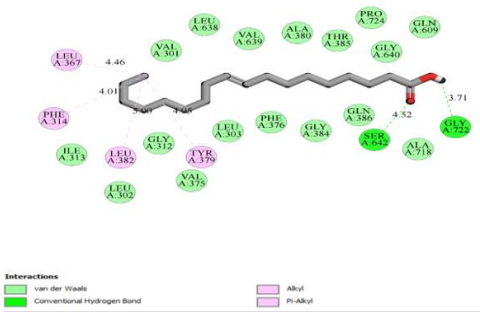
2D view of miglitol and alpha glucosidase



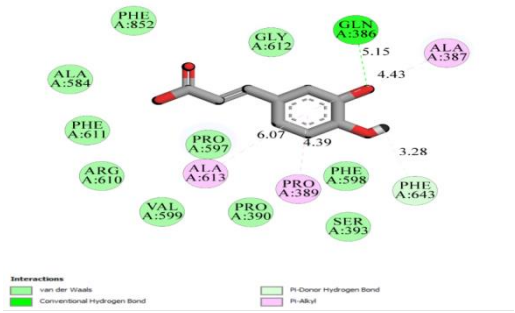
2D view of octadecanamide and alpha glucosidase



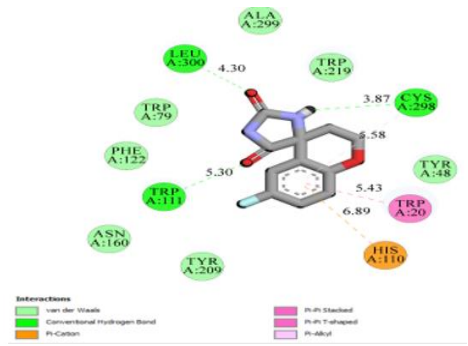
2D view of 2-[3-(Cyclohexylamino)Propyl]Guanidine and alpha glucosidase



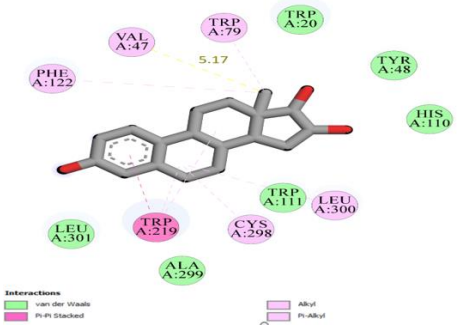
2D view of elaidic acid and alpha glucosidase



2D view of caffeic acid and alpha glucosidase



2D view of sorbinil and aldose reductase



2D view of estriol and aldose reductase

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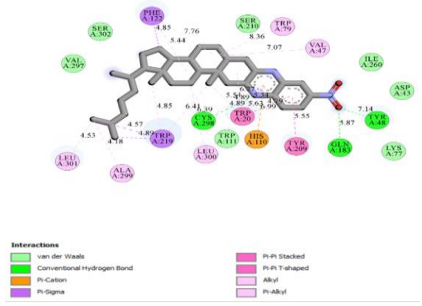
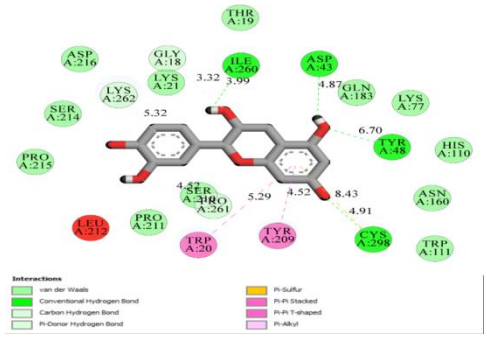
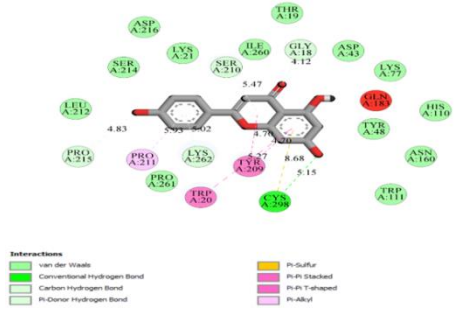


2D view of cholest-2-Eno[2,3-B] and aldose reductase



2D view of (+)-catechin and aldose reductase



2D view of apigenin and aldose reductase

Discussion

The regular medical method gives opportunities for the treatment of many sickness yet to be explored. An astounding results can be obtained if recent computational chemistry methods are harnessed to examine the capability of the regular medicinal method. The docking presented in this study were rated according to their docking ratings and numerous scientists has performed an alike experiments in the previously in which bioactive compounds were docked on a specific receptor to determine their affinity. Four drug-like compounds in all have higher binding affinities than the benchmark medication, miglitol (-2.1 kcal/mol), according to the docking results. The highest binding affinities are found for caffeine (-4.3 kcal/mol), followed by octadecanamide (-4.1 kcal/mol) and 2-[3-(cyclohexylamino)propyl]. Elaidic acid (-4.2 kcal/mol) and guanidine (-4.1 kcal/mol). The four substances with the highest binding affinities compared to the reference medication were chosen, and they were all attached to the receptors to create a complex at the proper active site. Utilizing BIOVA Discovery software, the receptor-ligand complex's two-dimensional structure was created. This structure displays the distance between protein-receptor complexes, hydrophobic interactions, hydrogen bond interactions, amino acid proximity between compounds, binding affinities, and unfavorable bonds.

Miglitol (Standard drug) has a total of 17 amino acids at the active sites and it forms a conventional hydrogen bond with VAL A:599 and LEU A:388, unfavorable hydrogen bond with HIS A:580, it forms a carbon hydrogen bond with ALA A:387 and ARG A:596 and van der waals interaction with ALA A:584, PHE A:611, ARG A:610, GLY A:612, ALA A:613, PRO A:597, PHE A:852, PRO A:390, PRO A:389, SER A:393, GLN A:386 and PHE A:598

Octadecanamide has a total of 24 amino acids at the active sites and it forms Pi-sigma interaction with TYR A:739 and also an alkyl interaction with PHE A:314, LEU A:367, LEU A:382, convectional hydrogen bond with SER A:642, GLY A:722, van der waals interaction with GLN A:386, GLN A:609, THR A:385, GLY A:384, VAL A:301, ALA A:718, GLY A:640, ALA A:380, PRO A:724, ILE A:723, PHE A:376, VAL A:639, LEU A:303, GLY A:312, ILE A:313 VAL A:375, LEU A:638, LEU A:302.

2-[3-(Cyclohexylamino) Propyl] Guanidine has a total of 16 amino acids at the active site, and it forms a conventional hydrogen bond with VAL A:599, it also forms a pi-alkyl interaction with PRO A:389, PHE A:643, ALA A:613, convectional hydrogen bond with PHE A:611, ARG A:610, van der waals interaction with LEU A:388, ALA A:387, GLY A:612, GLN A:386, PHE A:852, PRO A:597, PHE A:598, ALA A:584 PRO A:390, SER A:393

Elaidic acid has a total of 23 amino acids at the active site and it forms convectional hydrogen bond interaction with SER A:642 and GLY A:722, it also forms some pi-alkyl interactions with TYR A:379, LEU A:382, LEU A:367, PHE A:314, van der waals interaction with VAL A:301, LEU A:638, VAL A:639, ALA A:380, THR A:385, PRO A:724, GLY A:640, GLN A:609, ILE A:313, LEU A:302, GLY A:312, VAL A:375, LEU A:303, PHE A:376, GLY A:384, GLN A:386, ALA A:718.

Caffeic acid has a total of 15 amino acids at the active site, it forms a conventional hydrogen bond with GLN A:386, it also forms some pi-alkyl interactions with ALA A:387, ALA A:613, PRO A:389, it forms some pi-donor hydrogen bond interactions with PHE A:643, van der waals interaction with PHE A:852, GLY A:612, ALA A:584, PHE A:611, ARG A:610, VAL A:599, PRO A:390, PHE A:598, SER A:393, PRO A:597.

For aldose reductase, a molecular docking process was carried out between the receptor ROR gamma protein with a pubchem ID of 2ACQ and a total of 35 compounds obtained from the GCMS analysis of *Rhuslongipes*leaves and a standard drug (sorbinil). The protein was first obtained from the PDB (Protein Data Bank), and some criteria like low resolution, the E. coli expression system, and homo sapiens were considered. The protein was prepared using pymol and water constituents, and other unwanted constituents were removed. The 35 bioactive compounds, including the standard drug (sorbinil), were retrieved using PUBCHEM, and the PUBCHEM ID was noted. The compounds were prepared using Babel software and concatenated into the desired format. Criteria for protein and ligand binding, such as size and shape of the active sites, binding or functional group, position of the active site, and the enzyme substrate and ligand binding, were considered and met, and a docking process using Pyrex software was done. Four compounds in all have higher binding affinities than the benchmark medication, sorbinil, according to the docking data, which are -8.3. The binding affinities are -10.2 for apegenin, -8.8 for estriol, -8.9 for cholest-2-eno [2,3-B], and -9.9 for (+)-catechin. The four substances with the highest binding affinities compared to the reference medication were chosen, and they were all attached to the receptors to create a complex at the proper active site. Utilizing BIOVA Discovery software, the receptor-ligand complex's two-dimensional structure was created. This structure displays the distance between protein-receptor complexes, hydrophobic interactions, hydrogen bond interactions, amino acid proximity between compounds, binding affinities, and unfavorable bonds.

The standard drug sorbinil contains 12 amino acids at the active site. It forms a pi-cation interaction with HIS A:110, a van der Waals interaction with ALA A:299, TRP A:219, TRP A:79, PHE A:122, ASN A:160, TYR A:48, and TYR A:209. It also forms a convectional hydrogen bond with LEU A:300, CYS A:298 and TRP A:111.Estriol has a total of 12 amino acids at the active site and it forms a pi-pi stacked interaction with TRP A:219, it also forms an alkyl interaction with PHE A:122, VAL A:47, TRP A:79, LEU A:300, CYS A:298, it forms a van der waals interaction with TRP A:20, TYR A:48, HIS A:110, TRP A:111, LEU A:301, ALA A:299. Cholest-2-Eno[2,3-B] has a total of 20 amino acids at the active site, it forms a conventional hydrogen bond with CSY A:298, GLN A:183 and TYR A:48, it forms a pi-sigma bond with PHE A:122, TRP A:219, it forms a pi-cation bond with HIS A:110, it also forms a alkyl interaction with TRP A:79, VAL A:47, LEU A:300, LEU A:301, ALA A:299, it forms a pi-pi stacked interaction with TRP A:20, TYR A:209, it also forms a van der waals interaction with SER A:302, SER A:210, VAL A:297, ILE A:260, ASP A:43, TRP A:111, LYS A:77.(+)-Catechin has a total of 22 amino acids at the active site, it forms a conventional hydrogen bond with ILE A:260, ASP A:43, TYR A:48, CYS A:298, it forms a carbon hydrogen bond with PRO A:261, LYS A:262, GLY A:18, it forms an unfavourable hydrogen interaction with LEU A:212, it forms a van der waals interaction with THR A:19, ASP A:216, LYS A:21, GLN A:183, LYS A:77, SER A:214, PRO A:215, SER A:210, PRO A:211, HIS A:110, ASN A:160, TRP A:111, it forms a pi-pi stacked interaction with TRP A:20, TYR A:209.Apigenin has a total of 22 amino acid at the active site, it forms a conventional hydrogen bond with CYS A:298, it also forms a pi-pi stacked interaction with TYR A:209, TRP A:20, it forms a pi-alkyl interaction with PRO A:211,it forms an unfavourable hydrogen bond with GLN A:183, it forms a carbon-hydrogen bond with SER A:210, GLY A:18, PRO A:215, LYS A:262, it forms a van der waals interaction with ASP A:216, LYS A:21, ILE A:260, THR A:19, SER A:214, ASP A:43, LYS A:77, LEU A:212, TYR A:48, HIS A:110,ASN A:160, PRO A:261, TRP A:111.

Datawarrior software was used to plot a graph showing the binding affinities of the standard drug (Docetaxel) and the ligands, which usually use different colors to indicate their different binding affinities. The pocket view of the receptor-ligand complex was done using the Pyrex software; this shows the binding and conformation of the ligand at the binding site of the active site of the protein, indicating the amino acid sequences and bonds. A reasonably high potential efficiency of binding and contact was demonstrated by compounds (octadecanamide, 2-[3-(cyclohexylamino) propyl] guanidine, elaidic acid, caffeic acid), estriol, cholest-2-eno [2,3-B], (+)-catechin, and apigenin) with at least one of the three selected target proteins. The binding energy and binding scores that were observed were similar to those of the reference medications, sorbinil and miglitol. Overall, the docking interaction results demonstrate that the majority of compounds exhibiting numerous

interactions with the target protein's active site residues are also those with high binding affinity (according to the binding site). These substances—octadecanamide, 2-[3-(cyclohexylamino) propyl] guanidine, elaidic acid, caffeic acid, and estriol, cholest-2-Eno 2,3-B], (+)-catechin, and apigenin—interacted by forming hydrogen bonds with the catalytic active site residues of aldose reductase and alpha glucosidase, as well as miglitol and sorbinil (Hubbard, 1997). It is anticipated that this will have a substantial impact on target protein activity and modify their inhibitory action. As noted by William *et al.* (2012) in their investigation of myricetin and ethyl caffeate, such an interaction may also affect the target protein's activity by rupturing the polypeptides that make up the active site. Thus, our result supports the potential of plant extracts to treat hypoglycemia after a meal by corroborating the inhibition of α-glucosidase and aldose reductase enzymes previously described by Ibrahim *et al.* (2017). This is a strong indication that these chemicals may have had a significant role in the plant extract's observed hypoglycemic activity; they may work in concert to create large effects near one another. This could be because chemicals derived from plants and frequent substrates or ligands of the target protein share structural similarities.

A prospective molecule must have the intended biological action as well as appropriate or ideal pharmacokinetics and safety features so that it can be considered as appropriate drug for future usage (Hu *et al.*, 2018). Therefore, Swiss ADMEm is used in silico suite to evaluate the chosen compounds from the docking simulation in order to ascertain their pharmacokinetics, drug-likeness, and ideal medicinal chemistry properties. The lipophilic characteristic of the medication considerably affects the drug's total ADMET property.

It is crucial for the passage of medications through cell membranes (Arnott and Planey, 2012). A lipophilicity range of 0 to 5 is typically thought to be ideal for drug design, according to the majority of filters (rule of 5) for drug-likeness (Waring et al., 2010; Lipinski et al., 2001). Compounds such as octadecanamide, 2-[3-(Cyclohexylamino) Propyl] Guanidine, Elaidic Acid, and Caffeic Acid, as well as estriol, cholest-2-Eno[2,3-B], (+)-catechin, and apigenin, as well as conventional medications like sorbinil and miglitol, have shown optimal lipophilicity in the current investigation. This suggests that in order to achieve high bioavailability, these substances will penetrate effectively through the membranes into the circulatory system. Conversely, solubility is a physicochemical characteristic of pharmaceuticals that influences formulation, distribution, and absorption (Daina et al., 2017). Drugs are anticipated to be present at the site of absorption as aqueous substances to aid in their absorption (Savjani *et al.*, 2012).

All of the compounds that were chosen for the current investigation exhibited comparatively moderate solubility, indicating that these compounds—which have optimal lipophilicity and moderate solubility—can attain bioavailability. Excellent oral absorption. On the other hand, sorbinil and miglitol have very high lipophilicity and are very soluble which cause inadequate absorption from the GIT into the circulation. Since the GIT is the site of action of medications, the consequences may not be severe, as it is anticipated that these drugs will combine and block glucosidase and amylase enzymes (Rosak & Mertes, 2014). Apart from the GIT, other drugs with different target sites (like insulin, metformin, or glibenclamide) will need to have relatively better lipophilicity and solubility in order to improve drug absorption outside of the GIT and reach the target sites at effective concentrations. Drugs' ultimate fate in humans is determined by their ADME attributes (Shin et al., 2016).For the best pharmacokinetics, medications taken orally must be adequately absorbed in the GIT. According to Abbott (2002), the BBB plays a critical role in preventing medicines from entering the central nervous system (CNS). All chemicals were shown to be well absorbed into the GIT circulation and to have entered the BBB in the current investigation. Nevertheless, when it has a noticeable harmful impact on the central nervous system, the amount of penetration is probably negligible because the computation method does not measure it. Given that these interactions are essential for the conversion and elimination of medications from the body system, understanding how chemicals interact with the cytochrome P450 (CYP) system is crucial to characterizing the pharmacokinetics of potential drugs (Daina *et al.*, 2017).

Drug-induced toxicity may arise from the inhibition of isoforms of this enzyme system by medications, which may lead to inadequate elimination. Because of this, it's critical that a potential medication exhibit little inhibitory effect against certain enzyme isoforms. This researchshows that not any of the five P450 isoforms could be inhibited by the substances octadecanamide, 2-[3-(Cyclohexylamino) Propyl] Guanidine, Elaidic Acid, and Caffeic Acid, as well as the medications miglitol and sorbinil, and the compounds estriol, cholest-2-Eno [2,3-B], (+)-catechin, and apigenin. This impiles that these

substances would be quickly excreted from the body and properly metabolised in the liver. The overall drug-like attributes measure how closely a compound's physicochemical and structural characteristics resemble those of the most popular medications. In order to establish consensus in the prediction, this was forecasted using the five "rule of 5" computational filters: Lipinski (Pfizer), Ghose (Amgen), Verber (GSK), Egan (Pharmacia), and Muegge (Bayer) (Daina *et al.*, 2017). The first "rule of 5" for drug-likeness was Lipinski's rule, and the study's findings demonstrated that all eight of the substances examined complied with it. The chemicals (2-[3-(Cyclohexylamino) Propyl] Guanidine, caffeic acid) and estriol, (+)-catechin, and apigenin) revealed no violations when multiple filters were used (to boost prediction accuracy). It was found that both Ghose and the compounds had a Muegge violation. Each of the remaining chemicals breached multiple screens. This discovery demonstrates the superior therapeutic qualities of estriol, (+)-catechin, apigenin, and 2-[3-(cyclohexylamino) propyl] guanidine and caffeic acid over other substances.

Conclusion

Using insilico approaches, the current study examined possible antidiabetic chemicals found in *Rhuslongipes*extracts. The extract's ability to prevent diabetes was confirmed by the results, which also showed that some of the discovered chemicals had a stronger affinity for binding target proteins than the reference medications (sorbinil and miglitol). Additionally, four drug-like and lead-like candidates were discovered (prioritized) by the drug-likeness screening of the intriguing compounds: elaidic acid, 2-[3-(cyclohexylamino) Propyl]Guanidine, Octadecanamide, and Caffeic acid from the set. With more research, each of these molecules can now be assessed separately for potential antidiabetic effects, a clear mechanism of action, and optimization.

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