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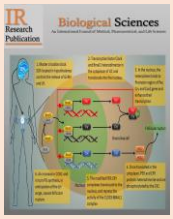

α-Amylase Inhibitory Potential of Antidiabetes Ligands in *Spondias Mombin* Plant Extract: Molecular Docking and ADMET Profiling

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ABSTRACT

Diabetes mellitus is majorly characterised by hyperglycemia, resulting from the disturbance of glucose homeostasis in the body due to excess calories of dietary sugar. α-amylase enzyme, involved in the digestion of carbohydrate, when inhibited causes a significant reduction in the post-prandial increase of blood glucose, which makes it an important strategy in the management of type 2 diabetes. Literatures have revealed series of compounds from *Spondias mombin* that exhibited antidiabetes activity. Therefore, this study sought to evaluate the antidiabetic potential of some *Spondias mombin* compounds using moleculardocking and ADMET profiling. Molecular docking analysis was carried out to study the binding interaction of some phytocompounds; Chlorogenic acid, Zeinoxanthin, Lutein, Isoquercetin, Quercetin, Rutin, Rhamnetin and Rutinose from *Spondias mombin* against α-amylase via Maestro 2017. Following the selection of the top five molecules, their bioavailability, drug-likeness, pharmacokinetic properties and toxicity were evaluated using the swissadme and protox iii webserver. Rhamnetin (-8.0 kcal/mol), quercetin (-7.8 kcal/mol), rutin (-7.9 kcal/mol), isoquercetin (-8.4 kcal/mol) and chlorogenic acid (-7.8 kcal/mol) gave higher docking score against α-amylase than the standard drug, acarbose (-7.2 kcal/mol). Quercetin and Rhamnetin also demonstrated high bioavailability, drug-likeness, pharmacokinetic properties and less toxicity. This study therefore uncovers potential α-amylase inhibitors in *Spondias mombin* with better binding affinities than acarbose and good ADMET properties, which may then serve as potential drug candidates for the management of diabetes. However, pharmacophore modelling is proposed in furtherance of this findings to identify possible variations of binding affinities with modification in their properties.

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Introduction

Diabetes mellitus (DM) is a group of metabolic disorders characterized by hyperglycemia, emanating from the consequence of absolute deficiency of insulin secretion, resistance to insulin or both [7]. In 2021, it was estimated that 537 million people have diabetes and 541 people have impaired glucose tolerance [8]. Dietary sugar

remains the major source of glucose in the body; this sugar is converted to monosaccharides in the body before absorption and transportation by the blood to the cells and tissues for metabolism. Excess calories of dietary sugar, the major source of glucose in the body disturbs glucose homeostasis in the body causing obesity which can leads to other metabolic disorders such as fatty liver, hypertension and eventually the onset of type-2 diabetes mellitus [4].α-amylase, a key pancreatic enzyme, involved in

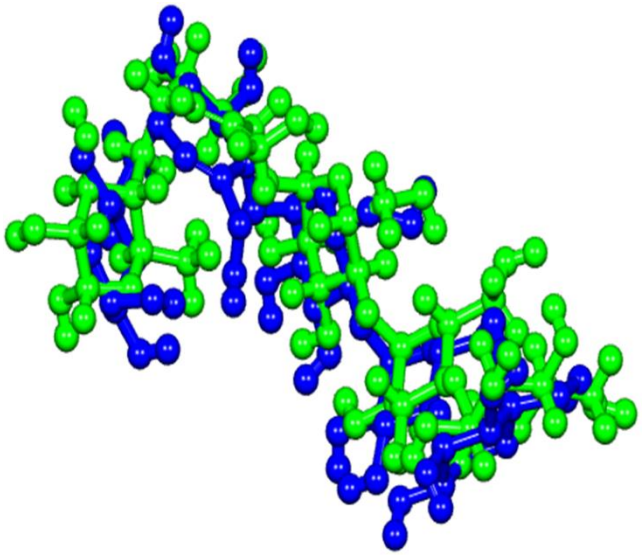

Figure 1. The binding mode of the re-docked (blue) and the co-crystallized (green) ligands within the active site of α-amylase (2QV4).

digestion of carbohydrate through the breakdown of complex carbohydrates into simple sugar such as glucose, when inhibited causes a significant reduction in the post-prandial increase of blood glucose, which makes it an important strategy in the management of type 2 diabetes [10]. *Spondias mombin* (Linn) belongs to the family of Anacardiacae, commonly known as Hog plum, and is readily common around us in South West of Nigeria (Yoruba) and is called "Iyeye" or "Akikan" in the local dialect [6].The anti-diabetes potential of the leaves of S. mombin has been reported in

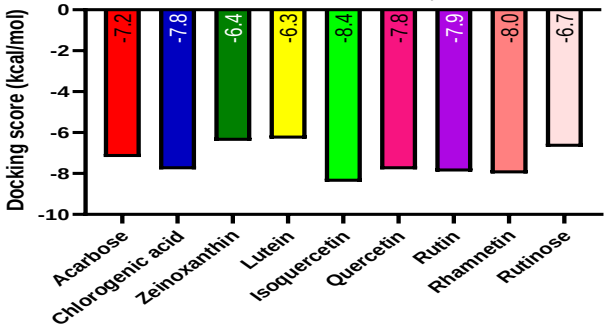

Figure 2. Docking scores from the binding interactions of bioactive compounds

alloxan induced rats [1] and streptozotocin-induced diabetes rats [3]. The hypoglycemic effect of S. mombin stem bark has been reported in healthy rats [2]. Geraniin and 2-O-Caffeoyl-(+)-allohydroxycitric acid from ethanolic leaf extracts of *Spondias mombin* were identified as potential SARS-CoV-2 inhibitor [15]. Dual inhibition of aldose reductase and glycogen synthase kinase 3β from *Spondias mombin* against diabetes mellitus were discovered [14]. Olarewaju et al. (2024) also reported the optimal binding affinities of *Spondias mombin* compounds against Parkinson's disease related protein targets. Molecular docking is an important tool in drug design and discovery. It predicts the effective interaction mode of small molecules for a defined binding site of the targeted receptor [5]. In drug discovery, a large number of compounds may exhibit pharmacological effects, but only a few of them possess required pharmacokinetics properties. For a successful drug development, there is need for the assessment of the compounds' bioavailability, absorption, distribution, metabolism, excretion (ADME properties) and toxicity. In silico ADME and toxicological profiling offers a means of predicting the in vivo performance of the compounds[13].Series of compounds from *Spondias mombin* stem bark extract that exhibited antidiabetes activity have been revealed [9].Therefore, this study sought to validate the antidiabetic potential of *Spondias mombin* stem bark compounds via their binding interaction with α-amylase using molecular docking and ADMET profiling.

Materials and Methods

Protein retrieval

The crystal structure of the target protein, α-amylase bound to the ligand Acarbose, was sourced from the protein databank (http://rcsb. org), under the accession code 2QV4, boasting a resolution of 1.97 Å.

Ligand retrieval

2D structures of Acarbose (reference drug) and series of bioactive compounds (Rhamnetin, Chlorogenic acid, Isoquercetin, Quercetin, Rutin, Rutinose, Zeinoxanthin and Lutein) that have been derived fromS. mombinby HPLC analysis were sourced from the PubChem (https:// pubchem.ncbi. nlm.nih.gov) repository.

Molecular docking

Eight compounds from S. mombin and reference drug were screen against the catalytic sites of the protein using the binding pocket of the co-

Table 1. Interaction of the docked complexes.

S/N	Compound Name	Docking score (kcal/mol)	No of Hydrogen interaction	Other interactions	Amino acids at protein active site
1.	Acarbose	-7.2	6	6	THR 163, ASP 300,GLU 240, ASP 197,GLU 233, ARG 195, HIS 201, ALA 307& LYS 200.
2.	Isoquercetin	-8.4	6	3	THR 161, TYR 151, LEU 162, ILE 235, HIS 299, ASP 300, HIS 201, ASP 197 & LYS 200
3.	Quercetin	-7.8	4	6	GLU 233, ASP 197, ASP 300, TYR 62, HIS 305, THR 163, HIS 101 & LEU 165
4.	Chlorogenic acid	-7.8	6	2	HIS 201, LEU 162,ASP 300, TRP 59, HIS 299& GLN 63
5.	Zeinoxanthin	-6.4	-	2	TYR 174 & LYS 63
6.	Lutein	-6.3	1	5	TYR 174, PRO 130, LYS 63 & ASP 77
7.	Rhamnetin	-8.0	-	7	ILE 235, LYS 200, LEU 165, LEU 162, ALA 198, HIS 201
8.	Rutinose	-6.7	6	2	GLU 233, THR 163, LEU 165, ARG 195, LEU 162, ASP 300
9.	Rutin	-7.9	2	1	GLU 240, ALA 198& ILE 235

crystallized ligand with grid coordinate of x= 39.01, y= 31.15, z = 25.00. Screening and docking of compounds against the protein was performed using Autodock 4.0 via PyRx [11]. The protein and ligands were prepared prior to docking. The co-crystallized ligand was re-docked into the catalytic site of the proteins to confirm the accuracy of the screening and docking scores [12]. The protein-ligand interactions were converted to 2D format using discovery studio 2020.

ADMET analysis

The smiles of those bioactive compounds were also retrieved from the PubChem (https:// pubchem.ncbi. nlm.nih.gov) repository. An evaluation of the absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties; drug-likeness, bioavailability score, p-glycoprotein substrate specificity, GI absorption, BBB permeability, hepatotoxicity, nephrotoxicity and neurotoxicity was carried out using the SwissADME and the ProTox iii webserver.

Results and Discussion

The docking procedure was validated by superimposition of extracted co-crystalized ligands from the crystallographic structure of the protein. The Root means square deviation (RMSD) of the re-docked ligands (blue) from its original geometry with 0.868 Å (less than 2.0 Å). Fig. 1 shows the binding conformation of the re-docked (blue) and the co-crystallized (green) ligands within the binding pocket of α-amylase.

The 2D interaction diagrams for all docked compounds are presented in Fig. 3. The compounds interacted with the amino acid residues of the protein binding pockets with various interactions such as hydrogen bond, van der waal interactions, pi-pi stacked etc). The interaction of small molecules with the amino acid residues at the binding site of target has been reported to be vital for the inhibition of such protein [17]. The binding poses and interactions of the compounds with the active site amino acid residues of the target, α-amylase were comprehensively examined. The specific amino acid residues involved in this evaluation of the docking scores among the top five compounds and reference drug, Acarbose. Notably, five compounds (Isoquercetin, Rhamnetin, Rutin, Quercetin and Chlorogenic acid) exhibited higher binding affinities (-8.4, -8.0, -7.9, -7.8 and-interactions are listed in Table 1, with a comparative 7.8kcal/mol respectively) than that of the standard drug, Acarbose (-7.2kcal/mol). Isoquercetin, being

Table 2. Drug-likeness of lead molecules and Acarbose using the Lipinski's rule.

Molecule	Mol. Weight (g/mol)	H-bond acceptors	H-bond donors	Lipophilicity (iLOGP)	Lipinski violations
Isoquercetin	464.38	12	8	0.94	2
Quercetin	302.24	7	5	1.63	0
Rhamnetin	316.26	7	4	2.23	0
Rutin	610.52	16	10	0.46	3
Chlorogenic acid	354.31	9	6	0.87	1
Acarbose	645.60	19	14	1.43	3

Table 3. Pharmacokinetic profile of lead molecules and Acarbose.

Compound Name	Drug-likeness	Bioavailability score (%)	P-g substrate specificity	GI absorption rate	BBB permeability
Isoquercetin	No	17	No	Low	No
Quercetin	Yes	55	No	High	No
Rhamnetin	Yes	55	No	High	No
Rutin	No	17	Yes	Low	No
Chlorogenic acid	Yes	11	No	Low	No
Acarbose	No	17	Yes	Low	No

Table 4. Pharmacokinetics of lead molecules using Cytochrome P450 inhibition.

Compounds	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4
Isoquercetin	No	No	No	No	No
Quercetin	Yes	No	No	Yes	Yes
Rhamnetin	Yes	No	No	Yes	Yes
Rutin	No	No	No	No	No
Chlorogenic acid	No	No	No	No	No
Acarbose	No	No	No	No	No

the lead compound, exhibited a binding energy of –8.4 kcal/mol. It had hydrogen bond interactions with active site amino acids residues including THR 161, HIS 299, ASP 300, HIS 201, ASP 197 & LYS 200 and engaged with hydrophobic residues such as TYR 151, LEU 162& ILE 235 amino acids.

197, TYR 62, HIS 305 and THR 163, and other interactions with ASP 197, TYR 62, HIS 101 & LEU 165. Similarly, Chlorogenic acid, displaying a docking score of –7.8 kcal/mol, engaged in 6 H-bonds with HIS 201, ASP 300, TRP 59, HIS 299 & GLN 63 (2). Its hydrophobic interactions involved LEU 162 and TYP 59. The standard drug, Acarbose, exhibited a docking score of – 7.2 kcal/mol. Similar

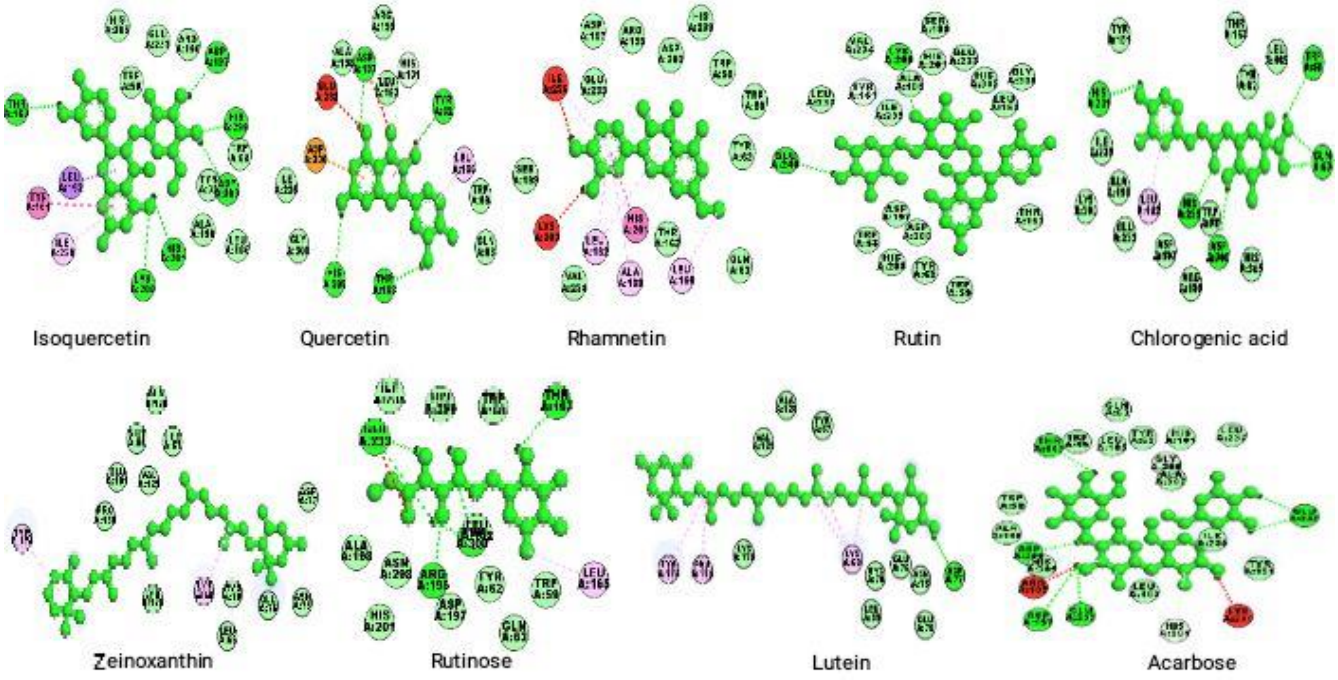

Figure 3. 2D molecular interaction of Bioactive compounds with binding pocket of α-amylase (2QV4).

In contrast, Rhamnetin, with a docking score of – 8.0 kcal/mol, formed no hydrogen bond interaction. Hydrophobic contacts were observed with ILE 235, LYS 200, LEU 165, LEU 162, ALA 198, HIS 201. Rutin, with a docking score of – 7.9 kcal/mol, established two H-bond with GLU 240 and ALA 198 and hydrophobic association with ILE 235.Furthermore, Quercetin exhibited 4 H-bond interactions with ASP

to chlorogenic acid, it formed 6 H-bonds with THR 163, ASP 300, GLU 240 (2), ASP 197 and GLU 233, other interactions with ARG 195, HIS 201, ALA 307 & LYS 200 amino acid residues. Having subjected the lead molecules in comparison with the reference drug to scrutiny for drug-likeness and bioactivity using the SWISSADME and ProTox iii online webserver, the drug-likeness was assessed via the

Lipinski's rule. Lipinski's rule of five (ROV), a widely recognized guideline, stipulates that orally active drugs should adhere to specific criteria: fewer than 5 hydrogen bond donors (HBD <5), fewer than 10 hydrogen bond acceptors (HBA <10), molecular weight below 500 Da (MW < 500 Da), and a partition coefficient (LogP) lower than 5[18]. Compliance with no more than one of these criteria defines a drug-like molecule. The results in Table 2 indicate that Quercetin and Rhamnetin, two of the top-ranked compounds met all of Lipinski's rule of five, and chlorogenic as well only violated one of the Lipinski rule, which consequently render the three molecules drug-like and hold potential as promising therapeutic candidates as against Isoquercetin, Rutin and the reference drug, Acarbose which violated the Lipinski rule.

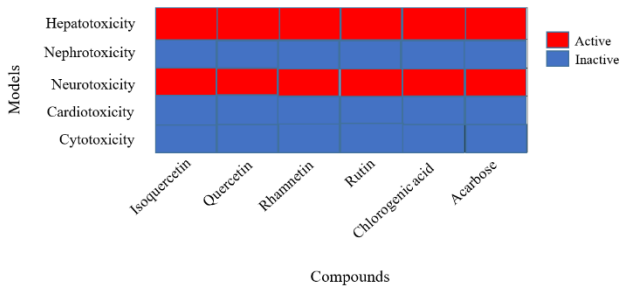

Figure 4. Toxicity profile of the lead compounds and Acarbose. LD50 of the above top-ranked compounds are 1190 mg/kg.

Absorption analysis revealed high GI absorption rates, with bioavailability of 55% for quercetin and rhamnetin compounds as against all other compounds, including the standard drug (Table 3). Additionally, all compounds are non-inhibitors of P-glycoprotein, a transporter that eliminates drugs from cells, except Rutin and the standard drug, Acarbose, which were predicted to be substrates [19].

In distribution analysis, all compounds exhibited blood-brain barrier non-permeability, indicating their inability to cross into the brain. Metabolism analysis indicated non-inhibition of CYP2C9 and 2C19 by all compounds. However, Quercetin and Rhamnetin compounds were predicted as CYP1A2, CYP2D6 (an essential liver enzyme system) and CYP3A4 substrates contrasting that of other compounds, including the standard, which were non-inhibitors (Table 4). Lastly, toxicity assessment demonstrated that all compounds, including the standard, were non-cytotoxic, non-nephrotoxic, and non-cardiotoxic (Fig. 4). All compounds including the standard showed hepatotoxicity and neurotoxicity. However, their non-BBB (blood-brain-barrier) permeability and high LD50 of 1190 mg/kg serve as strategies against their neurotoxicity and hepatotoxicity.

Conclusion

Overall, Quercetin and Rhamnetin which demonstrated higher binding affinity than acarbose and high bioavailability, drug-likeness, pharmacokinetic properties and less toxicity, potentiate better α-amylase inhibitors, which may therefore serve as potential drug candidates for the management of diabetes. However, pharmacophore modelling is proposed in furtherance of this findings to identify possible variations of binding affinities with modification in their properties.

Contribution of authors

MDA conducted the research and drafted the manuscript. SAO corrected the manuscript.

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Conflict of Interest

We confirm that there are no conflicts of interest associated with this publication, and there have been no significant financial support for this work that could have influenced its outcome.

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Data Availability Statements

The original data presented in this study are included in the article. Further inquiries can be directed to the corresponding author(s).

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