



In Silico Molecular Docking Studies of *Azadirachta indica* Stem Bark Phytochemicals against α -Amylase for Type 2 Diabetes Management

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Diabetes mellitus and drug resistance pose significant challenges in treatment. Crude extracts from plants, such as *Azadirachta indica*, which is known for its medicinal properties, could offer alternative agents for diabetes management. However, the specific bioactive compounds responsible for its antidiabetic activity remain poorly understood. In this study, phytochemicals from the stem bark of *Azadirachta indica* were extracted using chloroform and identified by gas chromatography-mass spectrometry (GC-MS). The antidiabetic potential of these compounds was assessed through *in silico* molecular docking against the enzyme α -amylase. The results showed that the binding free energy of Indazol-4-one, 3,6,6-trimethyl-1-phthalazin-1-yl-1,5,6,7-tetrahydro- (-

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9.4 kcal/mol) had a better binding affinity than the control drug Acarbose (-8.5 kcal/mol), while Resveratrol (-8.0 kcal/mol) showed a similar affinity to Acarbose. Both compounds adhered to Lipinski's rule, demonstrating drug-likeness and highlighting their potential as drug candidates for type 2 diabetes mellitus treatment

Keywords: *Azadiracta indica*; phytochemicals; α -amylase; diabetes; docking.

1. INTRODUCTION

"The concern about diabetes mellitus (DM) which is among the most prevalent non-communicable illnesses, and its influence on morbidity and death rates is increasing globally" (Ma et al., 2003; Florencia & Alex, 2014). The most commonly diagnosed diabetes mellitus are Type 1 and Type 2 in which Type 1 is tissue resistance to the pancreas-produced insulin (Richard, 2018) while Type 2 is characterised by insulin resistance and reduction of insulin production (Chatterjee et al., 2017), both leading to the uncontrollability of blood-sugar levels in man (EISayed et al., 2023). Recent reports showed that the type 2 diabetes mellitus is common and accounts for 90–95% of all cases resulting in glucotoxicity (Bensellam et al., 2012), lipotoxicity (Yazici & Sezer, 2017), oxidative stress (Rochette et al., 2014), inflammation (Hameed et al., 2015; Wang et al., 2012), obesity (Eckel et al., 2012) and many other effects. Owing to the development of drug resistance, increasing cost of drug and higher adverse effects of synthetic drugs, plant secondary metabolites are significantly being used for preventing and curing a wide range of illnesses like diabetic mellitus and oxidative stress.

Different plant species have been found useful in the treatment of diabetes which include; *Zingiber zerumbet* (Boyle et al., 2012), *Cinnamon* (Zarezadeh et al., 2023), *Allium sativum* (Jiang et al., 2022), *Aloe vera* (Prakash et al., 2023), *Uvariachamea* (Emordi et al., 2016) among others. *Azadiracta indica* has been used in Indian (Subapriya & Nagini, 2005), Nigeria (Lawal et al., 2010), South Africa (Afolayan & Sunmonu, 2010), and several other countries (Iwu, 2014) for herbal treatment of various diseases and ailments, including diabetes. However, detailed studies on the chemical composition and antidiabetic potentials of the compounds of *Azadiracta indica* stem bark have not been investigated. The aim of this study is to use *In silico* molecular analysis of the phytochemicals of *A. indica* stem bark against the alpha-amylase enzyme to examine the anti-diabetic potentials of the plants stem bark.

2. MATERIALS AND METHODS

2.1 Identification of Plant Material and Extraction

Fresh *A. indica* stem bark was collected in August 2024 from the premise of Imo State University Owerri, Imo State, Nigeria (behind the University main library). The identification of the plant samples was done by a professional taxonomist Prof. F.N. Mbagwu of the Department of Plant Science and Biotechnology, Imo State University, Owerri, Nigeria. The voucher specimen was deposited at the Imo State University Herbarium, with herbarium. Thoroughly washed sample stem bark (250 g) were grinded using new corona grinder and immersed in 250 mL chloroform in a corked amber bottle. The mixture was allowed to stand at room temperature for a period of 3 days and then filtered. "The solvent was then evaporated to get the crude sample extract" (Ikpa & Tochukwu, 2012).

2.2 GC-MS Analysis

The GC-MS analysis was done at Zaria, Kaduna State Nigeria. The compounds in the sample were identified using GC-MS (Agilent 19091-433HP, USA) coupled to a mass spectrophotometer. The initial column temperature was 35 °C with a hold time of 3 minutes. The temperature was programmed to rise by 8 °C/min with a final temperature of 280°C. In the process, 1µl of the sample was injected into the port and immediately vaporized and moved down the column with helium as the carrier gas with flow rate of 1 ml/min. The MS Spectrum was taken at 70 eV. "The identification of the compounds was done by comparing the spectrum of unknown compounds with the spectrum of known compounds in NIST14 structural library" (Ikezu & Ikpa, 2024).

2.3 Identification and Preparation of Ligands

The 3D structure-data files (SDF) of the compounds in the crude extract sample and anti-

diarrhea drug were identified and downloaded from the PubChem database. They were minimized in PyRx virtual screening tool, using Universal Force Field at 200 steps and converted to AutoDock ligands (pdbqt) and then used for the docking analysis. Identification and preparation of molecular targets crystal structure of porcine alpha amylase with PDB ID :1OSE with resolution 2.30 Å was identified and downloaded from the Protein Data Bank (PDB). "The interfering crystallographic water molecules and co-crystallized ligands were removed, and minimization of the energy of the protein was then done using Biovia Discovery studies" (Ikezu & Ikpa, 2024).

Docking and post-docking studies Multiple docking of the ligands on a specified porcine α -amylase protein binding pocket was done with AutodockVina in PyRx software 20 (version 0.8). The center grid box sizes were center_x = 33.3989753023; center_y = 29.4163125264; center_z = 8.82035253863. The binding free energies of the compounds on the protein target were obtained after the docking process. BIOVIA Discovery studio 4.5 model (BioviaDS, 2015) was used to visualize the interactions between the protein-ligand complexes after the docking process.

2.4 Drug Likeness

"The compounds with higher inhibition potency (lowest binding energies) and the control drug were chosen and sent to the SwissADME (<http://swissadme.ch/>) server to examine its drug-likeness properties" (Daina et al., 2017). The simplified molecular input line entry system (smiles) of the identified compounds with higher inhibition potency were obtained from pubchem online data base and submitted to SwissADME.

3. RESULTS AND DISCUSSION

3.1 Phytochemical Screening

The GC–MS analysis of chloroform extract of *Azadirachta indica* stem bark was recorded in the Table 1. Results presented in Table 1 revealed the presence of 20 phytochemical compounds along with their retention time, percentage abundance, chemical name, Pubchem ID, molecular weight, molecular structure and binding energy. Some of the compounds identified in this present study have previously reported to possess medicinal potentials for instance; Indazol-4-one, 3,6,6-trimethyl-1-phthalazin-1-yl-1,5,6,7-tetrahydro- is used as an opiod pain killer (Chao et al., 2017), resvaretol

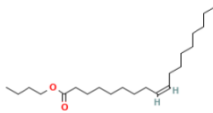

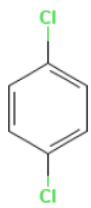
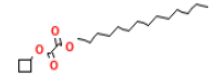

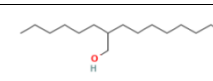
which has the highest percentage abundance (7.74%) has anticancer (Lin et al., 2014), antioxidant (Chong et al., 2015), anti-inflammatory (Gaballah et al., 2016) and antidiabetic (Wu et al., 2016) properties while stilbenes and many others has anticancer properties (Sirerol et al., 2016). These compound may be responsible for the medicinal potentials of the *A. indica* stem bark.

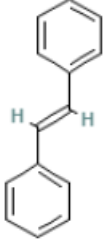
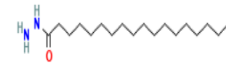
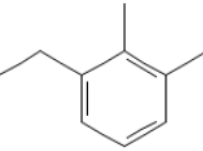
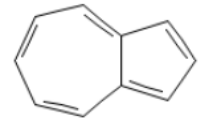
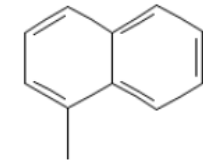
3.2 Molecular Docking

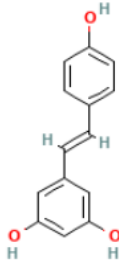

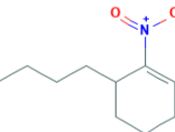
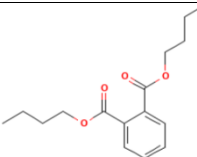
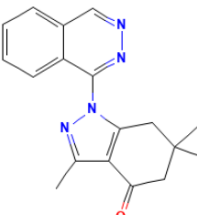
"The α -amylase (Fig. 1) was chosen because is a prominent enzyme found in saliva and pancreatic juice which helps to break down large insoluble starch molecules into glucose that is absorbable by the digestive system" (Afifi et al., 2011). "The inhibitors of α -amylase help to delay the breakdown of starch into glucose molecules" (Kwon et al., 2007). "In patients with hyperglycemia, an effective treatment option could be the inhibition of pancreatic α -amylase that controls carbohydrate absorption" (Thilagam et al., 2013). "The result from this study showed that most of the docked compounds with relative binding scores bind either at the active site or very close to the site of the clinically available inhibitor Acarbose, though it has been reported to have several side effects" (Yu et al., 2011).

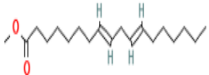
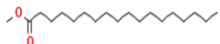
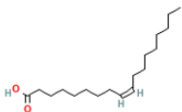

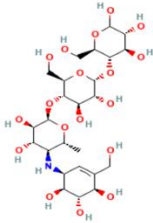
The binding energy value in Kcal/mol was used to score the binding affinity. Compounds with higher negative energy values were ranked as having higher binding affinity. In this study, the binding score of Indazol-4-one, 3,6,6-trimethyl-1-phthalazin-1-yl-1,5,6,7-tetrahydro- (-9.7 Kcal/mol) is higher than that of acarbroso (8.5 Kcal/mol) the co-crystallize ligand/control drug while the binding score of resveratrol (8.0 Kcal/mol) is relative to that of the control drug. The enzyme ligand interaction visualization with Biovia discovery indicated that the compound with the highest binding score Indazol-4-one, 3,6,6-trimethyl-1-phthalazin-1-yl-1,5,6,7-tetrahydro- showed strong hydrogen bonding with GLU:233 and ASP:300 (Fig. 2b), while the next resveratrol showed hydrogen bonding at ASP:197 and ASP 300 (Fig. 2c) and these are similar to the hydrogen bonding interaction of the co-crystallized/control (acarbroso) at ASP:197, GLU:233, HIS:229, ASP:300 (Fig. 2a) etc. Other strong bonds like carbon hydrogen bonds and pi bonds observed in both the control and the two highly potent compounds Indazol-4-one, 3,6,6-trimethyl-1-phthalazin-1-yl-1,5,6,7-tetrahydro- and Resveratrol contributes to strong binding affinity of the compounds with the alpha amylase enzyme.

Table 1. The result of the GC-MS and binding energy of chloroform extract of *Azadirachta indica* stem bark

S/N	RT	% ABD	Compound name	PUB CHEM ID	MW g/mol	Structure	Binding energy (Kcal/mol)
1	5.253	0.99	Butyl 9-octadecenoate	5354342	338.6		-6.3
2	6.884	1.04	Trifluoroacetoxy hexadecane	522035	338.4		-5.3
3	7.425	1.22	Benzene, 1,4-dichloro-	4685	147		-4.8
4	8.669	1.13	Oxalic acid, cyclobutyl tetradecyl ester	6420628	340.5		-5.6
5	9.619	2.96	Hydroxylamine, O-decyl-	34704	173.3		-5.3
6	10.158	5.09	1-Decanol, 2-hexyl-	95337	242.44		-5.1

S/N	RT	% ABD	Compound name	PUB CHEM ID	MW g/mol	Structure	Binding energy (Kcal/mol)
7	10.638	2.67	Stilbenes	638088	180.24		-7.7
8	11.329	0.36	Stearic acid hydrazide	20088	298.5		-5.8
9	11.571	0.33	Benzene, 1-ethyl-2,3-dimethyl-	13621	134.22		-6.2
10	12.595	1.21	Azulene	9231	128.169		-6.3
11	15.872	0.77	Naphthalene, 1-methyl-	7002	142.20		-6.6

S/N	RT	% ABD	Compound name	PUB CHEM ID	MW g/mol	Structure	Binding energy (Kcal/mol)
12	22.133	7.74	Resveratrol	445154	228.24		-8.0
13	23.597	0.32	Carbonic acid, eicosyl vinyl ester	91693137	368.6		-5.5
14	26.072	4.36	Cyclohexene, 6-butyl-1-nitro-	535089	183.25		-6.1
15	30.527	0.88	Dibutyl phthalate	3026	278.34		-6.1
16	30.887	0.62	Indazol-4-one, 3,6,6-trimethyl-1-phthalazin-1-yl-1,5,6,7-tetrahydro-	5293334	306.4		-9.4

S/N	RT	% ABD	Compound name	PUB CHEM ID	MW g/mol	Structure	Binding energy (Kcal/mol)
17	31.550	1.57	8,11-Octadecadienoic acid, methyl ester	5319737	294.5		-5.7
18	31.764	0.72	Methyl stearate	8201	298.5		-5.3
19	32.601	0.86	Oleic Acid	445639	282.5		-5.9
20	33.375	1.25	2- Chloropropionic acid, hexadecylester	522865	332.9		-5.4
cnt			Acarbose	41774	645.6		-8.5

RT= Retention time; % ABD=Percentage abundance; M/W= Molecular weight

Table 2. Result of the physicochemical analysis of the compounds with good α -amylase inhibition potency

S/N	CID	Parameters								
		MW(g/mol)	NA	AA	RB	HBa	HBd	LogS	DL	LV
cnt	41774	645.60 (>500)	44	0	9	19(>10)	14 (>5)	-2.3	NO	3
1	5293334	306.36	23	15	1	4	0	-3.90	YES	0
2	445154	228.24	17	12	2	3	3	-3.62	YES	0

MW= Molecular Weight; NA= Number of Atoms; AA=Aromatic Atoms; RB= Rotable Bonds; HBa: Hydrogen Bond Acceptors; HBd: Hydrogen Bond Donors; Log S: Water Solubility; DL: Drug Likeness; LV: Lipinski Violation

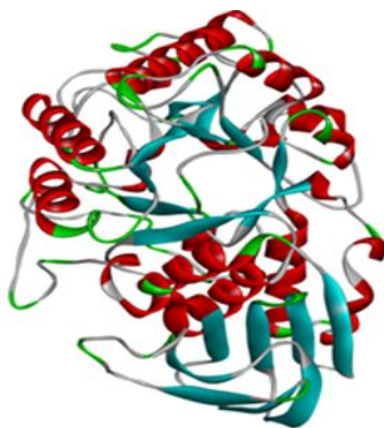
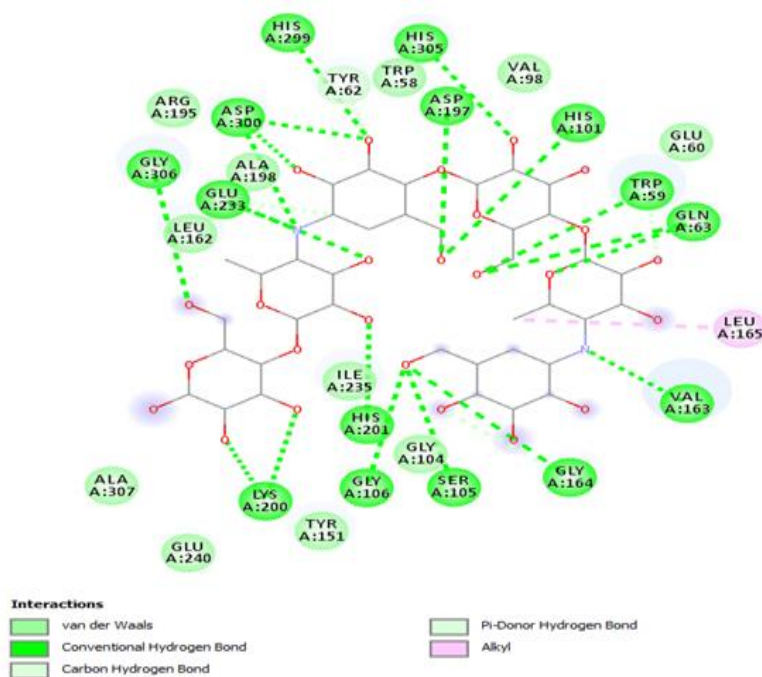


Fig. 1. 3D view of protein



Fig, 2a: CD:41774 (cnt)

BA: 8.5

Fig. 2a. Visualization of the control drug

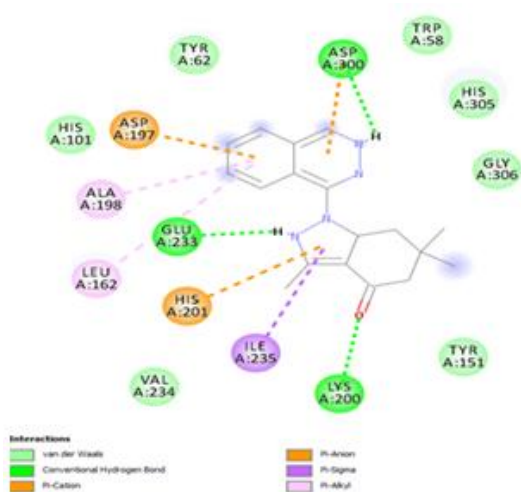


Fig. 2b: CD: 5293334 BA: 9.4

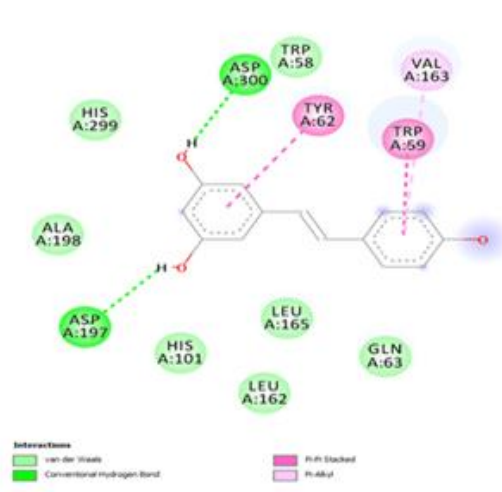


Fig. 2c: CD: 445154 BA: 8.0

Fig. 2(b-c). Visualization of the compounds with good binding affinity

3.3 Physicochemical Results

The drug likeness of the extract compounds with good binding scores as well as the control drug was revealed by their physicochemical properties using SwissADME (Table 2). The drug likeliness of all these compounds was assessed from Lipinski's rule of five. "Good drug candidates should not violate more than one of the rules" (Lipinski, 2016). Interestingly, all of the analyzed compounds were found to meet the Lipinski's rule of five, with most of them attaining a good score of bioavailability by having molecular weight less than 500 g/mol, The hydrogen bond donor (not more than five hydrogen) and hydrogen bond acceptor (not more than ten hydrogen) of the compounds agreed with the rule of five. One more important attribute is two these compounds, Indazol-4-one, 3,6,6-trimethyl-1-phthalazin-1-yl-1,5,6,7-tetrahydro-and Resveratrol were moderately soluble in water which is acceptable for a drug.

4. CONCLUSION

This study demonstrated promising antidiabetic potentials of *Azadirachta indica* stem bark. The results of this study suggest that extracts of the stem bark of *A. indica* represent a dependable source of novel bioactive compounds for pharmaceutical applications for management of type 2 diabetes. Therefore, further research is encouraged which may include; the analysis of other chemical extracts of the plant, isolation of pure compounds from the plant and *In vivo* *In*

vitro evaluation study to further validate the computational findings.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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