



Arid Zone Journal of Basic and Applied Research

Faculty of Science, Borno State University
Maiduguri, Nigeria

Journal homepage: <https://www.azjournalbar.com>



Research Article

In silico Evaluation of Phytocompounds from *Bougainvillea spectabilis* leaves as Potential Inhibitors of α -Amylase, α -Glucosidase, and GSK-3 β for Management of Diabetes Mellitus

Maryam Ado Mahmud^{1*}, Ali Abdullahi Damasak², Hamsatu Mohammed Malut³, Mustafa Alhaji Isa⁴ and Yagana Shettima Abba⁵

¹Department of Biochemistry, Yobe State University, Nigeria

²Department of Nutrition and Dietetics, University of Maiduguri, Nigeria

³Department of Biological Sciences, Borno State University, Nigeria

⁴Department Microbiology, University of Maiduguri, Nigeria

⁵Department of Biochemistry, University of Maiduguri, Nigeria

*Corresponding author's Email: maryamadamahmud101@gmail.com, doi.org/10.55639/607.02010051

ARTICLE INFO:

Keywords:

Diabetes mellitus,
Bougainvillea spectabilis,
 α -amylase,
glucosidase

ABSTRACT

Diabetes mellitus is a metabolic condition characterized by abnormal blood sugar levels. Targeting starch hydrolyzing enzymes and glycogen synthase kinase-3 β is one of the key strategies to lower the risk of type 2 Diabetes mellitus. - *Bougainvillea spectabilis* Willd leaves extract have been reported to have antidiabetic properties. In this study, GC-MS analysis was carried out and antidiabetic activity of the identified phytocompounds was checked by molecular docking method against α -amylase, α -glucosidase and glycogen synthase kinase-3 β using AutoDock 4.0 program, Swiss ADME was used to analyze the physicochemical and pharmacokinetic properties of the compounds. GC-MS analysis showed the presence of seventeen phytocompounds, compounds with desirable physicochemical and pharmacokinetic properties were docked into the active site of the target proteins. Docking results revealed that among all 1-hexyl-2-Nitrocyclohexane (-6.44 Kcal/mol), 2-Isopropyl-5-methylcyclohexyl-3-(-1-(4-Chlorophenyl)-3-Oxobutyl)-Coumarin-4-y Carbonate (-7.21 Kcal/mol) and Decahydro-1-naphthalenol (-4.91 Kcal/mol) have the highest binding affinity for α -amylase, α -glucosidase and glycogen synthase kinase-3 β respectively. Overall, using the *in silico* approaches it was predicted that *Bougainvillea spectabilis* Willd leave extract contain potential phytocompounds with diverse antidiabetic properties.

Corresponding author: Maryam Ado Mahmud, **Email:** maryamadamahmud101@gmail.com
Department of Biochemistry, Yobe State University, Nigeria

INTRODUCTION

Diabetes mellitus is a long-term health condition that affects how the body manages blood sugar. It happens either when the body doesn't produce enough insulin or cannot effectively use the insulin it makes. Over the years, diabetes has become one of the leading causes of illness and early death worldwide, with low- and middle-income countries like Nigeria facing the greatest impact (International Diabetes Federation, 2021). According to the World Health Organization (2023), the number of people living with diabetes has surged in recent decades, and this trend is expected to continue, especially in sub-Saharan Africa, due to changing lifestyles, poor diet, and limited access to healthcare. In Nigeria, the number of people living with diabetes is steadily rising, with millions of adults currently affected. Sadly, many people cannot afford conventional drugs or do not have access to proper treatment, particularly in rural areas. This has led researchers and healthcare practitioners to explore natural, plant-based alternatives that are more affordable and easier to access (Ajiboye *et al.*, 2022).

One such plant gaining attention is *Bougainvillea spectabilis*, commonly known as the paper flower and widely grown across Nigeria as an ornamental plant. While it's admired for its colorful appearance, it's also used in traditional medicine to treat various ailments. Recent scientific studies have shown that this plant may help manage diabetes by targeting the enzymes that control how the body breaks down and stores sugar. Specifically, compounds found in its leaves have been shown to block the activity of enzymes like α -amylase, α -glucosidase, and glycogen synthase kinase-3 β (GSK-3 β), which play major roles in blood sugar regulation (Mahmud *et al.*, 2023; Ojo *et al.*, 2022; Sharma & Gupta, 2019). Given its traditional use, wide availability in Nigeria, and the encouraging findings from recent studies, *Bougainvillea spectabilis* holds real promise as a natural and affordable option for diabetes management. This study explores the bioactive compounds in the plant's ethanolic leaf extract using GC-MS and computer-based (*in silico*) methods to evaluate their potential to inhibit key enzymes involved in diabetes.

MATERIALS AND METHODS

All chemicals and reagents used in the study are of analytical grade and were purchased from BDH Chemicals Ltd. Poole, England.

Plant Collection and Identification

B. Willd (also known as Paper flower) fresh leaves were gathered from the natural surroundings of Faculty of Science at University of Maiduguri located in Borno state Nigeria in September 2021. The sample was identified and authenticated by botanist of the Department of Biological Sciences, University of Maiduguri, Nigeria.

Preparation of Plant Material

The fresh leaves of *Bougainvillea spectabilis* Willd was washed to remove any unwanted adhering materials and shade-dried at room temperature. It was pulverized using pestle and mortar to fine powder. The fine powder was sieved with a 0.01mm sieve size and stored in a container for further analysis.

Plant Extraction

Five hundred grams (500 g) powder of *Bougainvillea spectabilis* Willd leaves was extracted with 70 % ethanol using cold maceration method, the product was evaporated to dryness and then stored in a refrigerator until used.

Gas chromatography-Mass spectrometry (GC-MS) Technique

GC-MS analysis was carried out in a combined 7890A gas chromatogram system (Agilent 19091-433HP, USA) and mass spectrometer, fitted with a HP-5MSF used silica gel column, interfaced with 5675C inert MSD with triple axis detector. Helium gas was used as carrier gas and was adjusted to column velocity flow of 1.0 ml/min. 1 μ l sample injection volume was utilized. The inlet temperature was maintained at 250 $^{\circ}$ C. The oven temperature was programmed initially at 110 $^{\circ}$ C for 4 min, then an increase to 240 $^{\circ}$ C, and then increased to 280 $^{\circ}$ C at a rate of 20 $^{\circ}$ C ending with 5 min. The source temperature was maintained at 180 $^{\circ}$ C. GC-MS was analyzed using electron impact ionization at 70 eV and data was evaluated using total ion count (TIC) for compound identification and quantification. The spectrum of the components were compared with the database of spectrum of known components stored in GC-MS library (Elizabeth *et al.*, 2013).

To identify the compounds, the generated spectra were compared with known reference spectra from the NIST (National Institute of Standards and Technology) and Wiley libraries. Only compounds with a match score of 80% or higher were selected to ensure accuracy and reliability. These identified compounds were then further analyzed for their potential health benefits, particularly in managing diabetes.

***In silico* Molecular Docking Analysis**

Physicochemical Analysis of the Phytocompounds of Ethanolic Leaves Extract of *Bougainvillea spectabilis* Willd (Paper flower)

The phytocompounds obtained from the GC-MS analysis of the ethanolic leaf extract of *Bougainvillea spectabilis* Willd were evaluated for their drug-likeness based on established physicochemical thresholds guided by Lipinski's Rule of Five (The molecular weight, number of hydrogen bond donors (HBDs ≤ 5), number of hydrogen acceptors (HBAs ≤ 10), Log P ≤ 5 and Drug likeness). Specifically, each compound was assessed to ensure its molecular weight did not exceed 500 Daltons, the number of hydrogen bond donors (HBDs) was not more than 5, and the number of hydrogen bond acceptors (HBAs) did not exceed 10. Additionally, the log P (partition coefficient) value, which indicates lipophilicity, was expected to be less than or equal to 5, ensuring optimal balance between solubility and permeability. Only compounds that met these criteria were considered likely to possess good oral bioavailability. Furthermore, compounds were screened for positive drug-likeness scores using the DataWarrior tool, which integrates these physicochemical parameters to predict the overall drug-like behavior of a molecule (Lipsinski, 2012).

Preparation of Crystal Structures of Glycogen Synthase Kinase-3 β (GSK-3 β), pancreatic α -amylase and Intestinal α -glucosidase

The crystal structure of the target proteins Glycogen Synthase Kinase-3b (PDB Code 2OW3), α -amylase (PDB Code 1hny) and α -glucosidase (PDB Code 7jty) were obtained from Protein Data Bank (PDB) (Berman *et al.*, 2000). The structures of the proteins were set, the attached ligands and metallic cofactors were removed. The missing atoms and residues were

inserted. All missing hydrogens and loops were identified and added, and alternate conformation were checked and removed. All non-protein residues were separated via energy minimization and structure optimization using programs implemented in Chimera (Pettersen *et al.*, 2004), Swiss PDB Viewer (Johansson *et al.*, 2012) and Chiron energy minimization and refinement tool (Ramachandran *et al.*, 2011).

Absorption, Distribution, Metabolism, Excretion, (ADME) and Toxicity Analysis of the Phytocompounds of Ethanolic Leaves Extract of *Bougainvillea spectabilis* Willd (Paper flower)

The ADME and toxicity properties of a compound is an essential component of drug design and development since many compound fail to reach clinical trial because of poor absorption, distribution, metabolism, excretion and toxicity properties. In this study, all the phytoconstituents with drug-likeness properties were selected and their ADME and toxicity properties were determined using the data warrior and swiss ADME tools. The properties include Gastro Intestinal Absorption (GIA), Cytochrome P2D6 (CYP 2D6) Inhibitor, Blood-Brain Barrier (BBB) penetration, Mutagenicity, Irritation, Tumorigenicity and Reproduction. These features were evaluated to determine the effect of the phytoconstituents on the human body, which affects its pharmacological activity (Yulan *et al.*, 2015).

Docking Analysis of the Phytocompounds of Ethanolic Leaves of Extract of *Bougainvillea spectabilis* Willd (Paper flower) with the Target protein Glycogen Synthase Kinase 3 β (GSK-3 β), α -amylase and α -glucosidase

All compounds with desired physicochemical properties were selected for the docking studies using the Auto Dock 4.0 program, which is an extension of the python molecular viewer that is used to prepare both the protein and ligand for molecular docking. A Lamarckian GA was used to perform the automated docking of the protein with each ligand. Torsion bonds and side chains of the ligands was allowed to rotate freely. Polar hydrogen atoms was also added, while Gasteiger charges were computed. A total of 10 run with population size of 150, a maximum of 250,000 generations were performed (Morris *et al.*, 1998).

RESULTS**Table 1:** Properties of Phytocompounds of Ethanolic Leaf Extract of *Bougainvillea spectabilis* Willd (Paper flower)

S/No	Compound Name	Chemical Formular	Molecular Weight	Retention Time	Peak
1.	1-Hexyl-2-Nitrocyclohexane	C ₁₂ H ₂₃ NO ₂	213.32	2.656	1
2.	Decahydro-1-naphthalenol	C ₁₀ H ₁₈ O	154.20	4.367	2
3.	Ethanol,2-methoxy-,acetate	C ₅ H ₁₀ O ₃	118.13	4.367	2
4.	Etilefrine	C ₁₀ H ₁₅ NO ₂	181.23	4.367	2
5.	D-fructose,3-o-methyl	C ₇ H ₁₄ O ₆	194.18	6.953	3
6.	3-o-methyl-D-Glucose	C ₇ H ₁₄ O ₆	194.18	6.953	3
7.	Glucal	C ₆ H ₁₀ O ₄	146.14	6.953	3
8.	Meso-2,5-Dimethyl-3,4-hexanediol	C ₈ H ₁₈ O ₂	146.23	6.953	3
9.	4-methyl-2,3-pentanediol	C ₆ H ₁₄ O ₂	118.17	6.953	3
10.	Hexadecanoic acid, methyl ester	C ₁₇ H ₃₄ O ₂	270.50	8.904	4
11.	Tetradecanoic acid,12-methyl-,methyl ester(s)-	C ₁₆ H ₃₂ O ₆	256.42	8.904	4
12.	1-cyclohexylnonene	C ₁₅ H ₂₈	208.38	10.575	5
13.	Phytol	C ₂₀ H ₄₀ O	296.50	10.695	6
14.	2-isopropyl-5-methylcyclohexyl3-(1-(4-chlorophenyl)-3-oxobutyl)-coumarin-4-yl carbonate	C ₃₀ H ₃₃ ClO ₆	525.00	15.49	10
15.	Cyclooctane, (methoxymethoxy)	C ₁₀ H ₂₀ O ₂	172.26	30.831	13
16.	4-flouro-1-methyl-5-carboxylic acid (ethyl ester)	C ₇ H ₉ FN ₂ O ₂	172.00	31.311	14
17.	4-propionyl-oxypiperidine	C ₈ H ₁₅ NO ₂	157.21	31.311	14

Table 2: Physicochemical Properties of the Phytocompounds of Ethanolic Leaves Extract of *Bougainvillea spectabilis* Willd (Paper flower)

S/No.	PubChem ID	Molecular weight (≤500)	Number of HBA (≤10)	Number of HBD (≤5)	MolLogP (≤5)	Druglikeness
1.	CID_544017	213.320	3	0	3.1361	-21.133
2.	CID_102425	154.252	1	1	2.1293	-5.2681
3.	CID_8054	118.131	3	0	0.0363	-6.082
4.	CID_3306	181.234	3	3	0.4366	2.4132
5.	CID_118290	194.182	6	4	-2.7491	1.1901
6.	CID_8974	194.182	6	4	-2.9302	-2.4899
7.	CID_89465	146.141	4	3	-1.6857	-0.78815
8.	CID_552199	146.229	2	2	1.1878	-1.6676
9.	CID_552109	118.175	2	2	0.5151	-2.8266
10.	CID_8181	270.455	2	0	6.4904	-35.364
11.	CID_21206	256.428	2	0	5.7999	-21.356
12.	CID_5364533	208.387	0	0	5.7043	-22.811
13.	CID_5280435	296.537	1	1	7.4212	-3.7661
14.	CID_537118	525.039	6	0	7.3414	-22.803
15.	CID_542175	172.267	2	0	2.9682	-5.9291
16.	CID_534521	172.158	4	0	0.7781	-1.9363
17.	CID_12410235	157.212	3	1	0.8314	2.0675

Key:

HBD-Hydrogen bond donors

HBA- Hydrogen bond acceptors

Table 3: Pharmacokinetic Properties of Phytocompounds of Ethanolic Leaves extract of *Bougainvillea spectabilis* Willd.

S/No	Compound name	BBB	CYP2D6 inhibitor	GIA	Mutagens	Tumorigens	Reproducibility	Irritant
1.	1-Hexyl-2-Nitrocyclohexane	Yes	Non inhibitor	High	None	None	None	None
2.	Decahydro-1-naphthalenol	Yes	Non inhibitor	High	None	None	None	None
3.	Ethanol,2-methoxy-,acetate	No	Non inhibitor	High	None	None	None	High
4.	Etilefrine	Yes	Non inhibitor	High	None	None	Low	None
5.	D-fructose,3-o-methyl	No	Non inhibitor	Low	None	None	None	None
6.	3-o-methyl-D-Glucose	No	Non inhibitor	Low	None	None	None	None
7.	Glucal	No	Non inhibitor	High	None	None	None	None
8.	Meso-2,5-Dimethyl-3,4-hexanediol	Yes	Non inhibitor	High	None	None	None	None
9.	4-methyl-2,3-pentanediol	No	Non inhibitor	High	None	None	None	None
10.	Hexadecanoic acid, methyl ester	Yes	Non inhibitor	High	None	None	None	None
11.	Tetradecanoic acid,12-methyl-,methyl ester(s)-	Yes	Non inhibitor	High	None	None	None	None
12.	1-cyclohexylnonene	No	Non inhibitor	Low	None	None	None	None
13.	Phytol	No	Non inhibitor	Low	None	None	None	None
14.	2-isopropyl-5-methylcyclohexyl3-(1-(4-chlorophenyl)-3-oxobutyl)-coumarin-4-yl carbonate	No	Non inhibitor	Low	None	None	High	High
15.	Cyclooctane, (methoxymethoxy)	Yes	Non inhibitor	High	None	None	None	None
16.	4-flouro-1-methyl-5-carboxylic acid (ethyl ester)	Yes	Non inhibitor	High	None	None	None	None
17.	4-propionyl-oxypiperidine	Yes	Non inhibitor	High	None	None	None	None

Key;

BBB-Blood brain barrier

Cyp2D6-Cytochrome P2D6

GIA-Gastro intestinal absorption

Table 4: Docking Scores and Residues Involved in H-bond formation between Glycogen Synthase Kinase-3 β and the Phytocompounds of Ethanolic Leaves Extract of *Bougainvillea spectabilis* Willd (Paper flower)

S/No.	Compound ID	Docking score (kcal/mol)	Residues involved in H-bonds	Distance (Å)
1.	CID_102425	-4.91	Tyr117	3.05
			Tyr117	3.18
			Val41	3.07
2.	CID_3306	-4.69	Asp77	2.59
			Asp77	2.63
			Ser55	2.95
3.	CID_542175	-4.47	Tyr117	3.04
			Tyr117	3.15
4.	CID_534521	-4.33	Val41	3.01

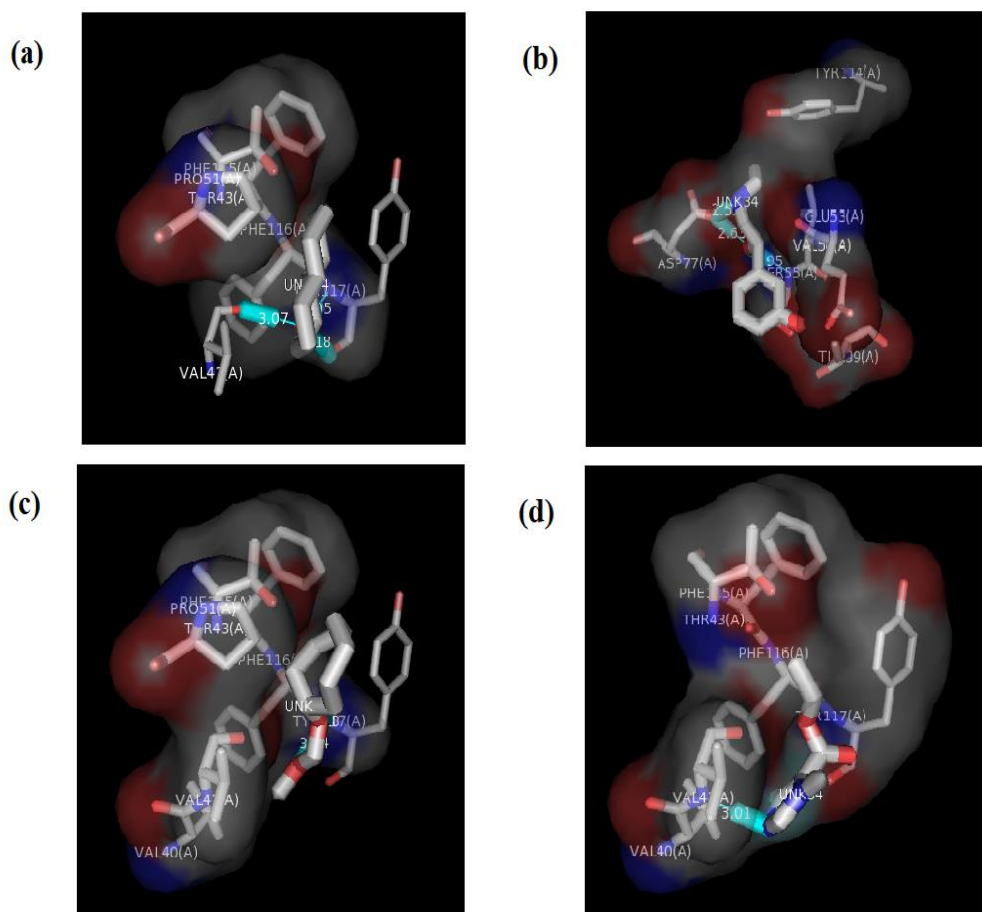
**Figure 1:** Ligand Interaction of Glycogen Synthase Kinase 3 β Enzyme with: (a) Decahydro-1-naphthalenol, (b) Etilefrine, (c) Cyclooctane, (methoxymethoxy) and (d) 4-flouro-1-methyl-5-carboxylic acid (ethyl ester)

Table 5: Docking Scores and Residues Involved in H-bond formation between α -amylase and the Phytocompounds of Ethanolic Leaves Extract of *Bougainvillea spectabilis* Willd (Paper flower)

S/No	Compound ID	Docking scores (kcal/mol)	Residues involved in H-bonds	Distance (Å)
1.	CID_544017	-6.44	Lys227 Leu211	2.70 3.16
2.	CID_102425	-6.32	Leu211 Lys227	2.45 2.91
3.	CID_3306	-5.65	Lys227 Leu211 Asp212	3.07 2.76 2.65
4.	CID_552199	-5.01	Lys227 Leu211 Leu211	2.86 2.80 2.76
5.	CID_537118	-7.21	Lys227	2.56
6.	CID_12410235	-5.05	Asp212 Lys227	2.68 2.66

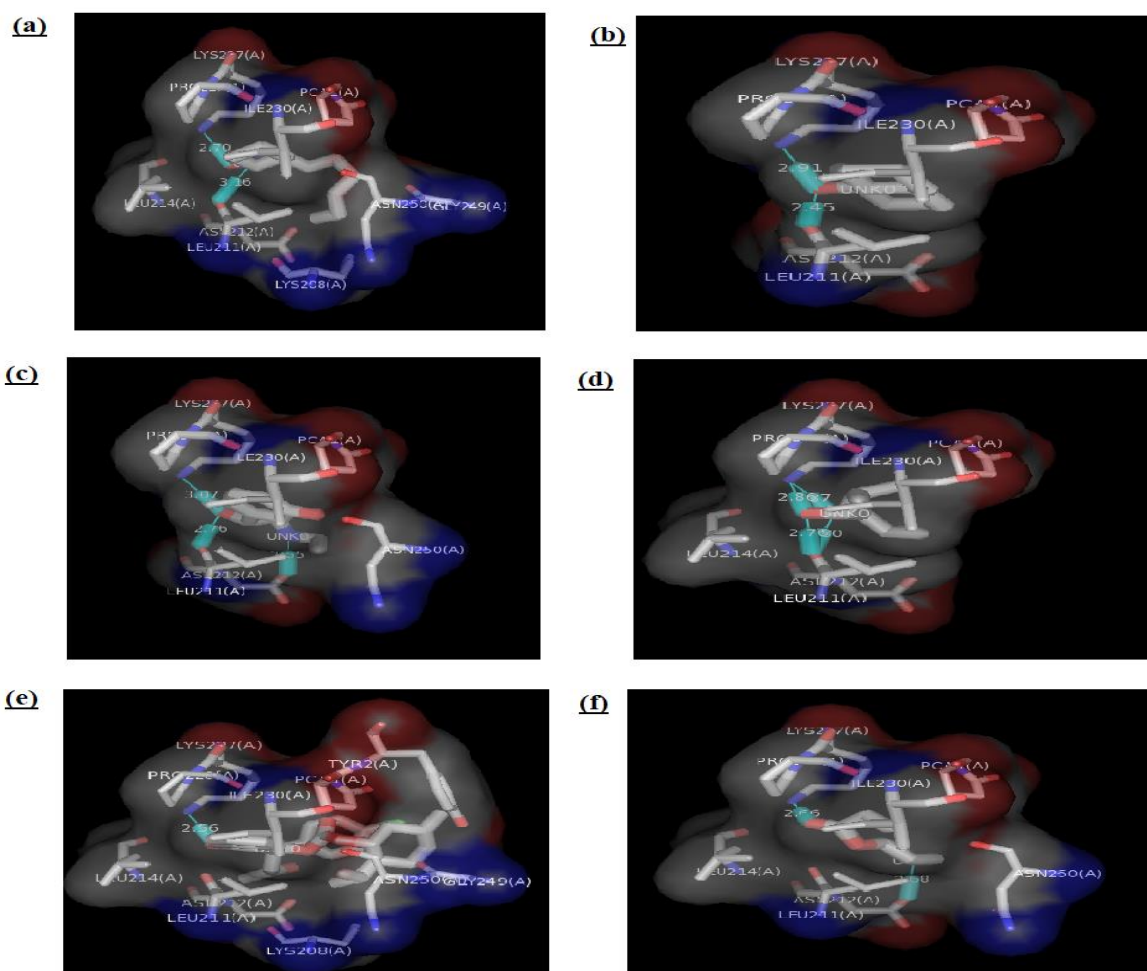
**Figure 2:** Ligand Interaction of α -amylase Enzyme with: (a) 1-Hexyl-2-Nitrocyclohexane, (b) Decahydro-1-naphthalenol, (c) Etilefrine, (d) meso-2,5 Dimethyl-3,4-hexanediol, (e) 2-isopropyl-5-methylcyclohexyl-3-(-1-(4-chlorophenyl)-3-oxobutyl)-coumarin-4-yl carbonate and (f) 4-propionyl-oxypiperidine

Table 6: Docking Scores and Residues Involved in H-bond formation between α -glucosidase and the Phytocompounds of Ethanolic Leaves Extract of *Bougainvillea spectabilis* Willd (Paper flower)

S/No	Compound ID	Docking scores (kcal/mol)	Residues involved in H-bond	Distance (Å)
1.	CID_544017	-6.31	Arg173	3.19
			Arg54	3.04
			Ser348	2.92
2.	CID_102425	-5.56	Asp346	2.51
			Asp374	2.79
3.	CID_537118	-7.21	Arg54	3.02
4.	CID_542175	-5.52	Thr293	2.95

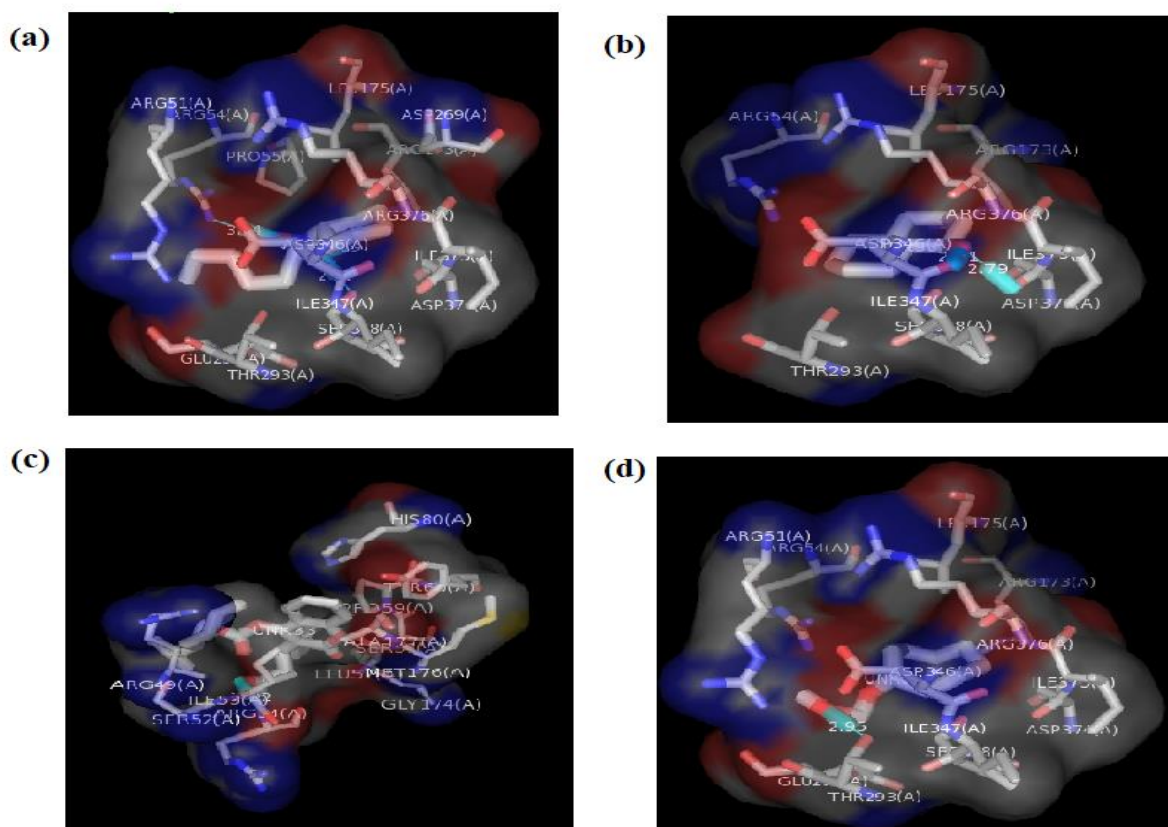


Figure 3: Ligand Interaction of α -glucosidase Enzyme with: (a) 1-Hexyl-2-Nitrocyclohexane, (b) Decahydro-1-naphthalenol, (c) 2-isopropyl-5-methylcyclohexyl-3-(-1-(4-chlorophenyl)-3-oxobutyl)-coumarin-4-yl carbonate and (d) Cyclooctane (methoxymethoxy)

DISCUSSION

Glucose homeostasis depends on proper uptake and storage mechanisms primarily through glycogen synthesis in the liver and muscles. Disruptions in these pathways contribute to insulin resistance and the development of diabetes mellitus (Ullah *et al.*, 2021). GSK-3 β negatively regulates glycogen synthase, making it a valuable target: its inhibition promotes glycogen storage and improves insulin sensitivity. Similarly, α -amylase and α -glucosidase

catalyze carbohydrate breakdown, elevating postprandial glucose levels. Thus, their inhibition offers an effective strategy to manage postprandial hyperglycemia (Kajaria *et al.*, 2013; Augustine *et al.*, 2019).

The GC-MS analysis of *Bougainvillea spectabilis* ethanolic leaf extract identified several bioactive compounds. These were subjected to molecular docking to predict their affinity and interaction with key diabetes-related enzymes: GSK-3 β , α -

amylase, and α -glucosidase. The NIST/Whiley spectral library was employed with a set threshold for peak matching to ensure compound identity. Drug-likeness was evaluated using Lipinski's Rule of Five, considering molecular weight, hydrogen bonding capacity, lipophilicity (LogP), and overall bioavailability (Lipinski, 2012). Most compounds met these criteria, with good gastrointestinal absorption and low likelihood of CYP2D6 inhibition, suggesting favorable pharmacokinetic profiles (Pires *et al.*, 2018; Yulan *et al.*, 2015).

Nine phytochemicals docked into the active site of GSK-3 β (PDB ID, resolution 2.8 Å), four of which Decahydro-1-naphthalenol, Etilefrine, Cyclooctane, and 4-fluoro-1-methyl-5-carboxylic acid exhibited notable binding affinities (ranging from -4.33 to -4.91 kcal/mol). Interactions with Tyr117, Val41, Asp77, and Ser55 were observed. While not catalytic residues, these are involved in substrate recognition and ligand anchoring.

Six compounds interacted strongly with α -amylase. Notably, 2-isopropyl-5-methylcyclohexyl-3-(4-chlorophenyl)-3-oxobutyl-coumarin-4-yl carbonate displayed the best affinity (-7.21 kcal/mol), binding to Lys227, a known catalytic residue critical for enzymatic cleavage confirming its potential as a strong inhibitor. Other compounds, including 1-Hexyl-2-Nitrocyclohexane and Etilefrine, interacted with Lys227, Leu211, and Asp212, supporting their role in competitive inhibition.

Four compounds exhibited promising binding to α -glucosidase. The highest docking score (-7.21 kcal/mol) was again recorded for the coumarin-based compound, interacting with Arg54, a residue involved in substrate positioning. Other key interactions occurred with Asp346, Asp374, and Ser348, which contribute to the enzyme's substrate binding pocket. The docking scores of the top compounds, especially those targeting Lys227 in α -amylase and Arg54 in α -glucosidase, are comparable to or exceed those of standard inhibitors reported in earlier studies (e.g., acarbose or miglitrol),

indicating strong potential for therapeutic application.

CONCLUSION

In conclusion, the docking scores suggest potential inhibitory activity of the phytochemicals identified from ethanolic leaves extract of *Bougainvillea spectabilis* Willd., but further validation via *in vitro* or *in vivo* assays is required.

CONFLICT OF INTEREST

The authors do hereby declare that there are no conflicts of interest on this work.

ACKNOWLEDGEMENTS

The authors are thankful to the Head of Research Laboratory, Mal. Idris, Department of Chemistry, Yobe State University for providing the necessary assistance needed to complete the research.

REFERENCES

- Ajiboye, B. O., Yakubu, M. T., Oladiji, A. T., & Akanji, M. A. (2022). Therapeutic potentials of medicinal plants in diabetes management: A review. *Journal of Ethnopharmacology*, 294, 115336. <https://doi.org/10.1016/j.jep.2022.115336>
- Augustine, A., Chukwuma, C. I., Odonwodo, I., & Azuka, O. (2019). Inhibitory effects of plant-based natural products on α -amylase and α -glucosidase: Potential mechanisms and implications for diabetes management. *Pharmacognosy Reviews*, 13(26), 60–70. https://doi.org/10.4103/phrev.phrev_16_19
- Berman, H. M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T. N., Weissig, H., ... & Bourne, P. E. (2000). The Protein Data Bank. *Nucleic Acids Research*, 28(1), 235–242. <https://doi.org/10.1093/nar/28.1.235>
- Elizabeth, O. O., Olayemi, A. M., & Samuel, O. A. (2013). GC-MS analysis of phytochemicals in the leaves of selected medicinal plants. *International Journal of Pharmaceutical Sciences and Research*, 4(12), 4532–4537.

- International Diabetes Federation. (2021). IDF Diabetes Atlas (10th ed.). <https://diabetesatlas.org>
- Johansson, M. U., Zoete, V., Michielin, O., & Guex, N. (2012). Defining and searching for structural motifs using DeepView/Swiss-PdbViewer. *BMC Bioinformatics*, 13, 173. <https://doi.org/10.1186/1471-2105-13-173>
- Kajaria, D., Tripathi, J. S., Tiwari, S. K., & Rana, V. (2013). Study on mechanism of anti-diabetic activity of polyherbal formulation in experimental animals. *International Journal of Ayurvedic Medicine*, 4(1), 24–33.
- Lipinski, C. A. (2012). Lead- and drug-like compounds: the rule-of-five revolution. *Drug Discovery Today: Technologies*, 1(4), 337–341. <https://doi.org/10.1016/j.ddtec.2004.11.007>
- Mahmud, M. A., Damasak, A. A., Malut, H. M., Isa, M. A., & Abba, Y. S. (2023). Preliminary phytochemical screening and antidiabetic properties of *Bougainvillea spectabilis* leaf extract. *African Journal of Biomedical Research*, 26(2), 121–130.
- Morris, G. M., Goodsell, D. S., Halliday, R. S., Huey, R., Hart, W. E., Belew, R. K., & Olson, A. J. (1998). Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. *Journal of Computational Chemistry*, 19(14), 1639–1662. [https://doi.org/10.1002/\(SICI\)1096-987X\(19981115\)19:14<1639::AID-JCC10>3.0.CO;2-B](https://doi.org/10.1002/(SICI)1096-987X(19981115)19:14<1639::AID-JCC10>3.0.CO;2-B)
- Ojo, O., Adegboye, A. R. A., & Wang, X. H. (2022). The role of plant-based compounds in managing diabetes mellitus: A review. *Nutrients*, 14(7), 1426. <https://doi.org/10.3390/nu14071426>
- Pettersen, E. F., Goddard, T. D., Huang, C. C., Couch, G. S., Greenblatt, D. M., Meng, E. C., & Ferrin, T. E. (2004). UCSF Chimera—A visualization system for exploratory research and analysis. *Journal of Computational Chemistry*, 25(13), 1605–1612. <https://doi.org/10.1002/jcc.20084>
- Pires, D. E. V., Blundell, T. L., & Ascher, D. B. (2018). pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. *Journal of Medicinal Chemistry*, 58(9), 4066–4072. <https://doi.org/10.1021/acs.jmedchem.5b00104>
- Ramachandran, S., Kota, P., Ding, F., & Dokholyan, N. V. (2011). Automated minimization of steric clashes in protein structures. *Proteins: Structure, Function, and Bioinformatics*, 79(1), 261–270. <https://doi.org/10.1002/prot.22879>
- Sharma, R., & Gupta, R. (2019). Ethnopharmacological potential of *Bougainvillea spectabilis* in metabolic disorders: A review. *Journal of Medicinal Plants Studies*, 7(2), 50–55.
- Ullah, H., Khan, A., Saeed, M., & Rehman, N. U. (2021). Role of GSK-3 β in insulin resistance and diabetes mellitus: Update on therapeutic intervention. *Current Pharmaceutical Design*, 27(6), 835–843. <https://doi.org/10.2174/1381612826666201102122101>
- World Health Organization. (2023). Diabetes. <https://www.who.int/news-room/fact-sheets/detail/diabetes>
- Yulan, L., Liyuan, D., & Qiong, Z. (2015). In silico evaluation of ADME and toxicity of phytochemicals in drug discovery. *Pharmacognosy Magazine*, 11(41), 150–154. <https://doi.org/10.4103/0973-1296.149721>