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MOLECULAR DOCKING STUDIES AND ADMET PROFILING OF BIOACTIVE COMPOUNDS FROM *Acalypha wilkesiana* MUELL. ARG ETHANOL LEAF EXTRACT AS POTENTIAL ALPHA GLUCOSIDASE INHIBITOR

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ABSTRACT

Type 2 diabetes, which affects the majority of diabetic patients, is a serious health issue in both developed and developing nations. One of the biggest challenges in managing this condition is controlling hyperglycemia. An effective therapeutic approach for controlling hyperglycemia associated with type 2 diabetes is to target alpha-glucosidase, an enzyme that functions by hydrolysing carbohydrates into their glucose subunits. One of the main goals in the search for possible medications to treat type 2 diabetes is the inhibition of this enzyme, which lowers the absorption of glucose in the small intestine. Phytochemicals from Acalypha wilkesiana have demonstrated its antidiabetic properties. This study aimed to predict the binding interactions between phytoconstituents of Acalypha wilkesiana as alpha-glucosidase Inhibitors. The GC-MS analysis revealed a total of 38 compounds, of which 16 had desirable physicochemical properties. All desirable compounds were tested for docking activities and five (5) have shown a binding affinity towards the target enzyme with different binding energies .i.e CID 542175 (Cyclooctane) -5.60 kcal/mol, CID 591597 (4-Acetoxy-3-methoxystyrene),-5.58kcal/mol, CID 537288 (4-Acetoxy-3-methoxystyrene) -5.28 kcal/mol, CID 19490 (2H-pyran-2-one,tetrahydro-3,6-dimethyl) -5.24 kcal/mol, and CID 545772 (3-methyl-2-(2-oxopropyl)furan) with -5.01 kcal/mol arranged in descending order of binding affinity. All five compounds were further tested for pharmacokinetics activities such as BBB, GIA, CYP2D6 Inhibitor, etc and all had desirable pharmacokinetics properties. Following successful validation, the compounds exhibiting favorable pharmacokinetic characteristics were identified and deemed appropriate candidates for alpha-glucosidase inhibitory activity.

Keywords: Diabetes; *Acalypha wilkesiana*; Gas Chromatography-Mass Spectrometry; Molecular Docking

INTRODUCTION

Controlling hyperglycemia, or a condition where there is a high concentration of glucose in the blood, is one of the main challenges in managing diabetes mellitus, a harmful metabolic disorder with a high rate of prevalence and complications [1,2,3]. Hyperglycemia has become a serious health concern in both industrialized and developing countries [4]. Diabetes is clinically classified into three types: type 1, type 2, and gestational diabetes. Each has distinct characteristics and onset patterns. Type 1 diabetes is an autoimmune illness that is frequently identified in infancy, but type 2 diabetes, the most prevalent kind, usually arises in adulthood and is strongly linked to lifestyle factors such as obesity and sedentary behavior. Pregnancy-related gestational diabetes expands the range of disorders [1].

Diabetes is a chronic metabolic disease that is far more common in middle-class and lower-class nations than in wealthy ones. It affects every nation on the planet [5]. Africa has the most cases, with Nigeria, the continent's most populous country, having the highest prevalence and incidence. Diabetes mellitus is prevalent in some rural parts of Nigeria, with rates ranging from 0.8 to 4.4% [6]. While its incidence in cities is between 4.6 and 7% [6]. Most recently, a systematic review and meta-analysis published various research analyzing the incidence of diabetes mellitus in Nigeria, which found an increase to 5.77% [7] as the overall pooled prevalence. According to World Health Organization (WHO) estimates for 2021, the number of cases of diabetes mellitus (DM) increased significantly from 108 million in 1980 to 422 million in 2014. The death rates from diabetes, broken down by age, increased by 3% between 2000 and 2019. Over 2 million deaths were attributed to DM in 2019 [8]. There is a need to create cheaper antidiabetic medications, such as alpha-glucosidase inhibitors, with few or no adverse effects, that can be used to manage type 2 diabetes and as a hypoglycemic agent.

Alpha-glucosidase with an enzyme commission (E.C 3.2.1.20) is a hydrolase enzyme located in the brush edges of the small intestinal mucosa that breaks down glycosidic linkages in diverse sugar molecules. It is associated with conversion of starch and disaccharide into glucose for simple absorption into cells [9]. Inhibition of this enzyme is an important target in the process of creating new medicines to manage type 2 diabetes by lowering small intestine glucose absorption [10].

The plant "Java white," *Acalypha wilkesiana*, belongs to the Euphorbiaceae spurge family. Its essential oils, which are extracted from the plant's leaf, have been shown to possess antibacterial and phytochemical qualities against *Staphylococcus aureus* and *Klebsiella aerogenes* [11]. It is a tropical and subtropical evergreen shrub with mottled green leaves that range from greenish yellow to white and have erratic green spots. It grows in several parts of Africa but is endemic to the South Pacific Islands. Although it is native to the South Pacific Islands, it is found throughout Africa. *Acalypha wilkesiana* leaf decoction prepared by boiling is utilized in western Nigeria and is employed to treat fungal infections in infants, as well as hypertension and diabetes in adults [12].

Drug development often involves screenings to discover lead compounds and thoughtful designs to enhance these molecules. The current paradigm for drug discovery is from discovery to design, which necessitates understanding the disease's biochemistry, pathways, and disease-causing proteins before creating compounds that can affect their functions. This is a standard procedure in the biopharmaceutical sector. Drug development and discovery deal with the application of both computational and experimental techniques, and they typically complement one another. To tackle the problems of imperfect medications, an effective drug development process is required. The process of designing, developing, and commercializing drugs is time-consuming and costly [13]. To meet these obstacles, many interdisciplinary approaches to drug development are required; combined, these approaches would serve as the foundation for the In-Silico strategy in drug design [14]. By employing in-silico techniques, researchers can identify phytoconstituents that are promising from *Acalypha wilkesiana* and also assess their potential as alpha-glucosidase inhibitors before proceeding to in vivo and in vitro studies. Several studies have reported the antibacterial, anti-inflammatory and antidiabetic properties of *Acalypha wilkesiana* [11, 12], however the interaction between alpha-glucosidase and phytocompounds of this plant using computational approach remains largely unexplored. This study

aims to investigate the phytoconstituents from *Acalipha wilkesiana* leaf extract as alpha-glucosidase inhibitors utilizing *in silico* approaches. The finding of this study could pave the way for the development of novel, plant-based therapeutic agents for managing diabetes.

MATERIALS AND METHODS

Plant Sample Collection and Solvent Extraction

Pesticide-free leaves of *Acalypha wilkesiana* were collected from the University of Maiduguri's garden. To avoid losing phytochemicals from the leaves, they were carefully cleaned with distilled water and shade-dried for a week. The dried samples were then processed into a powder form in a stainless-steel blender and stored for testing. A sample of approximately 500g of powdered *Acalypha wilkesiana* leaves was extracted exhaustively with 70% ethanol and 30% water in a Soxhlet extraction apparatus. The extract was concentrated to dryness until it reached a pourable consistency after being poured into an ore weight beaker and dried in a 40°C oven.

Gas Chromatography-Mass Spectrometric (GC-MS) Analysis

The ethanol leaf extract of *Acalypha wilkesiana* was subjected to GC-MS analysis. The following experimental conditions are applied in the gas chromatograph interfaced to the mass spectrometer instrument. The extract (2g) was dissolved in a test tube using ethanol by adding 5mL of any solvent to the extract. The analysis was conducted in a GC (Agilent Technologies 7890B model) and MS (Silent Technologies 5977A MSD model). Centrifuge (model TDL-50B) for five minutes to achieve resolution. After completing centrifugation, the supernatant was injected into three tubes of the GC machine, two of which were used for washing and one as trash. Acetone was used as a solvent to wash the GC model.

Physicochemical Analysis

Using the Data Warrior programme, the physicochemical characteristics of each component from the GC-MS study were checked, including lipophilicity, molecular weight, and the quantity of hydrogen-bond donors (HBDs) and acceptors (HBAs). A programme built into Swiss PD Viewer was used to optimize and calculate the energy.

Protein Preparation and Molecular Docking

The alpha-glucosidase structure (PDB ID: 7JTY) was retrieved from protein data bank. The structure was optimized by removing water molecules, adding hydrogen atoms and performing energy minimization using PyMOL and Autodock tool 4.2. According to Kitchen *et al*., [15], docking is essential to the logical design of pharmaceuticals. The AutoDock tool 4.2, an addition to the Python Molecular Viewer that readies the protein and ligand for molecular docking, was used to select all compounds with the proper physicochemical properties for docking investigations. Each computed ligand was automatically docked with the protein using a Lamarckian genetic approach. Ten runs totaling 150 population individuals, up to 2,500,000 evaluations, and up to 27,000 generations were finished. With 60 Å × 60 Å × 60 Å as its size, the grid had a spacing of 0.375 Å.

Pharmacokinetic Analysis

Using the AdmetSAR tool 2.0 and the ADME/TOX program, the compounds with high binding energies from the docking studies were further assessed for pharmacokinetic properties (absorption, distribution, metabolism, and excretion). Furthermore, the toxicity of each compound was assessed using the ADME/TOX program, the AdmetSAR tool, and the DataWarrior tool.

RESULTS AND DISCUSSION

Studying natural product compounds through molecular informatics helps us better comprehend their potential pharmaceutical uses. Studies on chemicals derived from *Acalypha wilkesiana* plants for possible use as antidiabetics have not, however, been conducted in cheminformatics very often. *Acalypha wilkesiana* has been demonstrated to have antidiabetic efficacy in many components, which is what prompted us to do this investigation.

The GC-MS analysis revealed a total number of 38 compounds that are present in the ethanol leaf *Acalypha wilkesiana* (Table 1) and These compounds underwent additional screening according to Lipinski's rule of five (molecular weight

< 500 Da, number of hydrogen bond donors ≤ 5, logP ≤ 5, and logs ≤ 5) in terms of their physicochemical characteristics. Sixteen compounds were ultimately chosen with the desired results of the physicochemical properties, and five compounds were selected with the most desired result of docking score activities (Table 2). Alpha-glucosidase's active site is docked with organic compounds to score and compute its affinity for binding in the repository. Based on the docking test analysis, the docking data showed that only five of the screened compounds have shown binding interactions towards the target enzyme with their binding residues. With Autodock 4.0, the binding free energy of each protein-ligand complex was calculated. According to the docking data, CID 542175 established two hydrogen bonds with Thr293 (Distance=3.12) and Arg54 (Distance=3.25) giving it the best binding energy with -5.60 kcal/mol. Comparatively, CID 591597 demonstrated a minimum binding energy of -5.28 kcal/mol and established three hydrogen bonds with Thr293 (distance=3.06), Arg51 (distance=3.13), and Arg54 (distance=2.66). CID 537288 also possessed a binding affinity of -5.58 kcal/mol. CID 19490 established two hydrogen bonds with Arg54 (distance=2.84) and Arg293 (distance=2.93), with a binding energy of -5.24 kcal/mol. and CID 545772 established two hydrogen bonds with Thr293 (Distance=2.74) and Arg51 (Distance=2.93), with a minimal binding energy of 5.01 kcal/mol. (Table 3).

Jhong *et al*. [16] reported that Curcumin docked with alpha-glucosidase revealed three interactions of ligand molecules, they are: Arg197, Arg407, and Phe282. Phytochemical screening revealed that *Acalypha wilkesiana* Muell. Arg contains numerous bioactive components, including phenols, tannins, and flavonoids. Some of these phytochemicals are thought to be responsible for the plant's blood-glucose-lowering benefits. Martin *et al* [17] found a high correlation between tropical plants' antioxidant activity and polyphenol content. This means that plants high in phenolic compounds are excellent providers of antioxidants. Certain alpha-glucosidase inhibitors that reduce postprandial hyperglycemia may carry cardiovascular disease-related concerns. Otherwise, long-term usage of certain medications reduces triglycerides and blood total cholesterol in diabetic patients and improves insulin resistance. The molecular docking results are significant and could be used as a pharmacophore model in the management of chronic diabetes mellitus. The docking results provide better insights into the development of more effective α-glucosidase inhibitors from Ashitaba (Angelica keiskei Koidzumi) isolates to treat diabetes-related secondary issues [18]. In the present research, we assessed alpha-glucosidase's inhibitory effectiveness, the inhibition of the enzyme performed has an efficacy towards the target enzyme because all the compounds had the docking score binding energies within the normal range of (-3 to -9.5kcal/mol). The binding energies of all the compounds were CID 542175 (Cyclooctane) -5.60kcal/mol, CID 591597 (4-Acetoxy-3-methoxystyrene) -5.58kcal/mol, CID 537288 (4-Acetoxy-3-methoxystyrene) -5.28kcalmol, CID 19490 (2H-pyran-2-one,tetrahydro-3,6-dimethyl) -5.24kcal/mol, and CID 545772 (3-methyl-2-(2-oxopropyl)furan) -5.01kcal/mol, and this demonstrated the rank of inhibiting the enzyme by the natural compounds in descending order of their affinity. All the compounds were further tested based on their Pharmacokinetics studies under the attributes of absorption, distribution, metabolism, excretion, and toxicity (ADMETOX), all the compounds were good and exhibit most of the pharmacokinetics properties such as BBB, mutagens, gastrointestinal absorption, tumorigens, reproducibility e.t.c (Table 4). Each compound possesses at least seven of the Pharmacokinetics properties and has shown a desirable characteristic to the enzyme. The phytoconstituent of this plant with the desired properties can be considered alpha-glucosidase inhibitors after successful validation.
This study not only identifies promising lead compounds for diabetes treatment but also it findings might have practical implications for developing cost-effective therapies and also contribute to the understanding of natural product-based interventions in managing type 2 diabetes. However, there is need for further in vitro and in vivo studies to confirm the efficacy and safety of the identified compounds. Therefore, further research should focus on conducting in vitro and in vivo experiments to validate efficacy of the identified compounds and also there is need to investigate the structure activity relationships of the compounds identified so as to optimize their potency and selectivity.

Table 1: Gas Chromatography-Mass Spectrophotometric Analysis

S/N	Compound Name	Peak	Molecular formular	PubChem ID
1	Beta-D-Glucopyranose -1,6-anhydro	1	C6H10O5	CID 2724705
2	1-methylethyliene	1	C9H14O5	CID 249904187

3	2H-pyran-2-one, tetrahydro-3,6-dimethyl	2	C7H12O2	CID 19490
4	4-Acetoxy-3-methoxystyrene	3	C11H12O3	CID 591597
5	2-methoxy-4-vinylphenol	3	C9H10O2	CID 332
6	Ethanone-1-(2-hydroxy-5-methyl phenyl)	3	C9H10O2	CID 15068
7	Isoxazolidine-5–2,4-dimethyltrans	5	C7H15NO	CID 22212546
8	Beta-D-glucopyranose-1,6-anhydro	5	C6H10O5	CID 2724705
9	4-Acetoxy-3-methoxystyrene	6	C11H16O4	CID 537288
10	2-Methyl-5-phenylpent-4-enoic acid	6	C27H38O6S3	CID 162785511
11	Cyclooctane	15	C10H20O2	CID 542175
12	(1S,1SS)-Bicycle (13.1.0) hexadecan-2-one	15	C16H28O	CID 13760785
13	Cyclohexane	15	C20H40	CID 41687
14	Phytol	16	C20H40O	CID 5280435
15	2-Heptadecenal	18	C17H32O	CID 5363335
16	2-Heptadecenal	19	C17H32O	CID 5363335
17	2-Heptadecenal	20	C17H32O	CID 5363335
18	2-Heptadecenal	21	C17H32O	CID 5363335
19	Undecanoic acid	22	C11H22O2	CID 8180
20	1-decanol,2-hexyl	23	C16H34O	CID 95337
21	2-Heptadecanol	24	C17H32O	CID 5363335
22	2-Heptadecanol	25	C17H32O	CID 5363335
23	2-Heptadecanol	26	C17H32O	CID 5363335
24	3,7,11,15-tetramethyl-2-hexadecan-1-ol	27	C20H40O	CID 5366244
25	3,7,11,15-tetramethyl-2-hexadecan-1-ol	28	C20H40O	CID 5366244
26	3,7,11,15-tetramethyl-2-hexadecan-1-ol	29	C20H40O	CID 5366244
27	3,7,11,15-tetramethyl-2-hexadecan-1-ol	30	C20H40O	CID 5366244
28	3,7,11,15-tetramethyl_2-hexadecan-1-ol	31	C20H40O	CID 5366244
29	3,7,11,15-tetramethyl-2-hexadecan-1-ol	32	C20H40O	CID 5366244
30	3,7,11,15-tetramethyl-2-hexadecan-1-ol	33	C20H40O	CID 5366244
31	3-methyl-2-(2-oxopropyl)furan	34	C8H10O2	CID 545772
32	3-methyl-2-(2-oxopropyl)furan	35	C8H10O2	CID 545772
33	3-methyl-2-(2-oxopropyl)furan	36	C8H10O2	CID 545772
34	Diisooctylphthalate	37	C24H38O4	CID 33934
35	Diisooctylphthalate	38	C24H38O4	CID 33934
36	2,4-Dimethyl -7-oxo-4,7-dihydro-triiazolo(3,2-c)triazine	39	C6H7N5O	CID 596585

37	Diisooctylphthalate	40	C24H38O4	CID 33934
38	Supraene	42	C30H50	CID 638072

Table 2: Physiochemical Properties of the selected compounds.

S/N	PubChem ID	Molecular Weight (≤500)	Number of HBA(≤10)	Number of HBD(≤5)	MolLogP (≤5)	Druglikeness
1	CID 19490	128.170	2	0	-1.9745	-0.45711
2	CID 591597	192.213	3	0	2.2792	-4.4307
3	CID537288	212.244	4	0	0.8154	-16.496
4	CID542175	172.267	2	0	2.9682	-5.9291
5	CID545772	138.165	2	0	1.3531	-1.9776

Table 3: Docking Results and Residues in the Formation of H-Bond

S/N	Compound Identification	Docking Score (kcal/mol)	H-bonding residues	Distance (A)
1	CID 19490	-5.24	Arg 54	2.84
			Arg 376	2.93
2	CID 591597	-5.58	Arg 54	2.65
3	CID 537288	-5.28	Thr 293	3.06
			Arg 51	3.13
			Arg 54	2.76
4	CID 542175	-5.60	Thr 293	3.12
			Arg 54	3.25
5	CID 545772	-5.01	Thr 293	2.74
			Arg 51	2.93

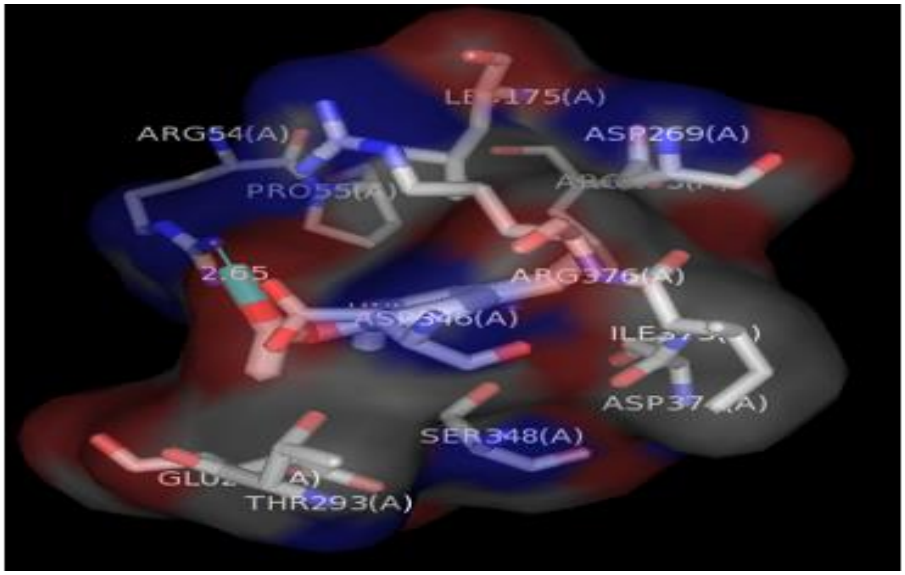


Figure 1: Hydrogen bonding and electrostatic interaction of CID 591597. with Alpha glucosidase

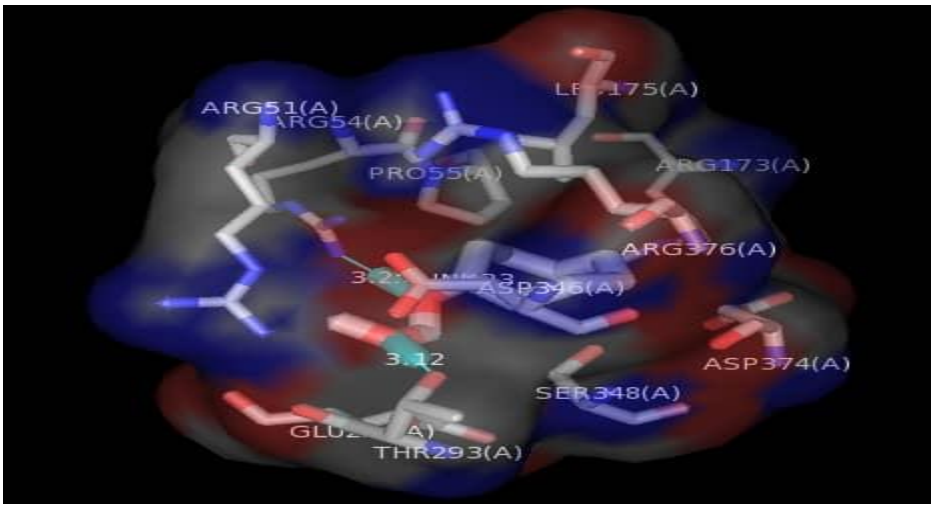


Figure 2: Hydrogen bonding and electrostatic interaction of CID 542175 with Alpha glucosidase

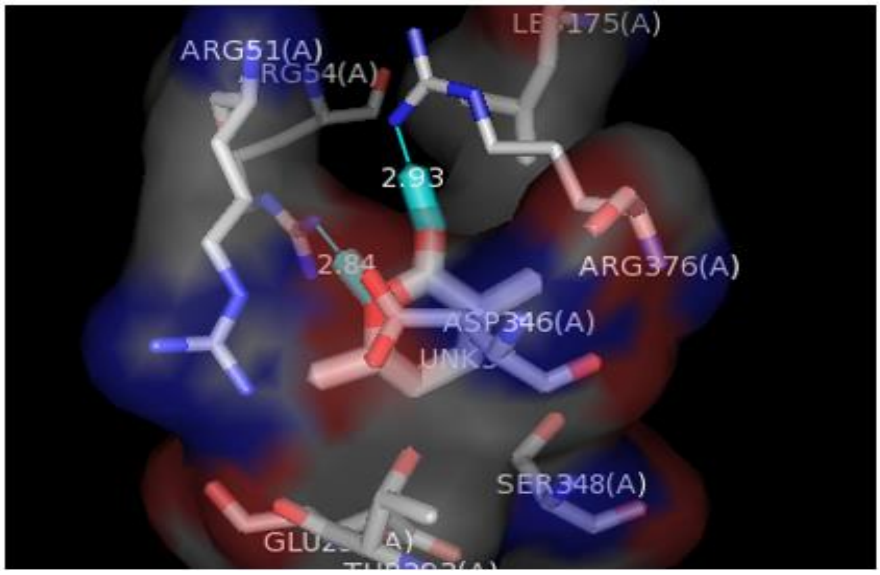


Figure 3: Hydrogen bonding and electrostatic interaction of CID 19490 with Alpha glucosidase.

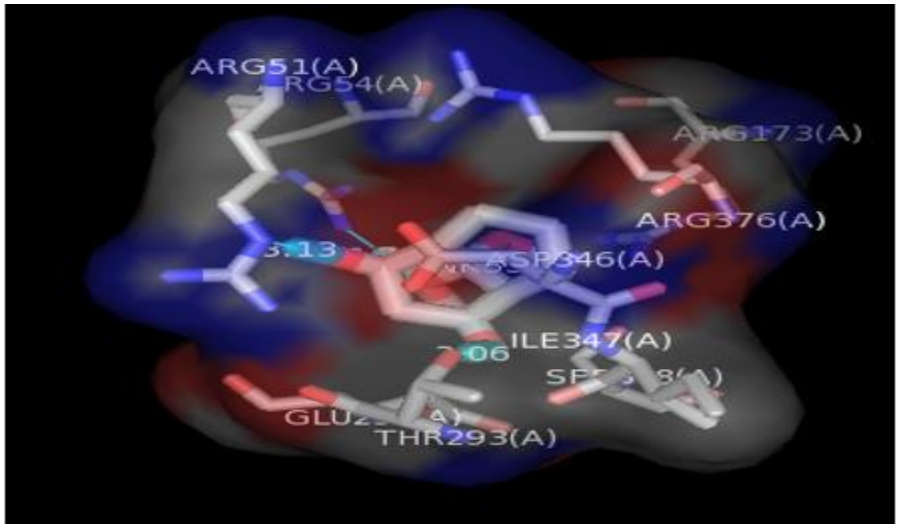


Figure 4: Hydrogen bonding and electrostatic interaction of CID 537288 with Alpha glucosidase.

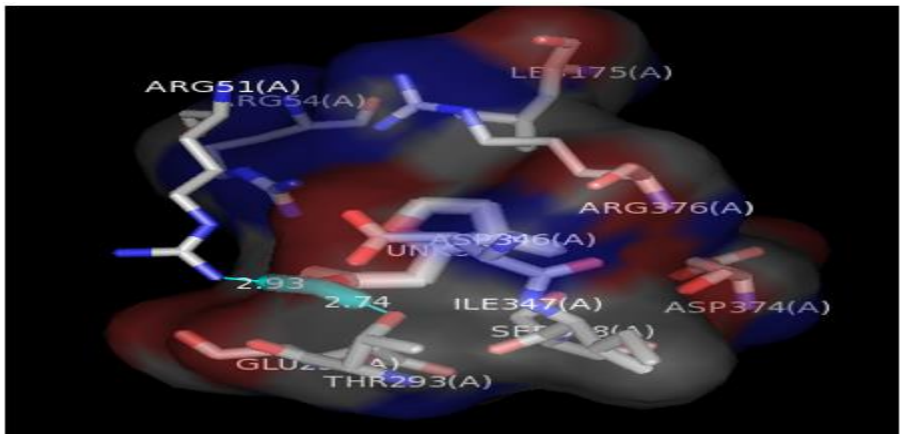


Figure 5: Hydrogen bonding and electrostatic interaction of CID 545772 with Alpha glucosidase

Table 4 : Pharmacokinetic Properties

S/N	Compound ID	BBB	CYP 2D6 Inhibitor	GIA	Mutagens	Tumorigens	Reproducibility	Irritant
1	CID 19490	+	Non Inhibitor	+	None	None	Low	None
2	CID 591597	+	Non Inhibitor	+	None	None	None	High
3	CID 537288	+	Non Inhibitor	+	None	None	None	+
4	CID 542175	+	Non Inhibitor	+	None	None	None	None
5	CID 545772	+	**Non Inhibitor**	+	None	None	None	High

CONCLUSION

A total of 16 compounds were identified by GC-MS and screened in silico for physicochemical properties, with only five (5) (CID (19490, 591597, 537288, 542175, and 545772) having the desired binding affinities against alpha-glucosidase were screened for pharmacokinetic properties. Following a successful validation process, the compounds with favorable pharmacokinetic properties were chosen and considered promising potential inhibitors of alpha-glucosidase.

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