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Blockage of Endothelin 1 Activity to Ameliorate Erectile Dysfunction by Phyto-Compounds of Tefairia Occidentalis From UPLC Using Computational Analysis

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Abstract

Erectile dysfunction (ED) is male sexual disorder that affects millions of people globally. Telfairia occidentalis (TO) is a medicinal plant reported to possess therapeutic ability but there is a paucity of information on mechanisms involved. Endothelin is a vasoconstrictor that limits blood flows. This study investigated the inhibitory potentials of TO leaf phytocompounds on endothelin 1 using a computational approach. Schrodinger suites was used to evaluate 352 TO natural compound gotten from UPLC-MS analysis and sildenafil (standard ED drug) with endothelin 1 protein. The molecular and induced-fit docking, MMGBSA and ADMET properties where evaluated. The molecular docking results (kcal/mol) of the 6 TO hit compounds that passed pharmacotoxicity are: Isochlorogenic acid (-10.158), 1-Caffeoylquinic acid (-9.538), 2-((6-O-(beta-D-Apiofuranosyl) beta-D-glucopyranosyl)oxy)propane (-9.281), 3-Feruloylquinic acid (-9.246) and (5S)-5-Methoxy-7-(4-hydroxyphenyl)-1-phenyl-3-heptanoneare (-8.447) are better compared to the standard drug sildenafil (-5.997 kcal/mol) with endothelin. The induced-fit scores of the hit compounds (-748 to -741.35 kcal/mol) are also better than sildenafil (-738.69 kcal/mol). The pharmacotoxicity study of these hit compounds showed they adhere to Lipinski's rule of five with good MMGBSA results. The study suggests that these compounds are potential vasodilating drugs that could be helpful in combating ED. Further in vivo studies could be done on them.

Keywords: Telfairia Occidentalis, Erectile Dysfunction, Endothelin, Molecular and Induced-Fit Docking, Mmgbsa, Admet

Statement of Significance

Erectile dysfunction (ED) has been a major problem in Nigeria, Africa and the world. This has led to many cases of depression, broken homes and threaten the institution of a family which is the unit of society. Conventional drugs have offered little temporary help with several reported side effects. Medicinal plants such as Telfairia occidentalis contain phytochemicals and are known to be very effective with no side effects. Some phytocompounds were gotten from the plant and analyzed by computation. The study suggests that these compounds from Telfairia occidentalis are drug

candidate for the blockage of Endothelin 1 (a vasoconstrictor that causes erectile dysfunction) as potential vasodilating drugs that could be helpful in combating ED.

Introduction

Sexual health is said to be a vital determinant of quality of life. Disorders such as erectile dysfunction (ED) are getting increasingly more prevalent as a result of the aging population. The successful treatment of these disorders has been proven to improve coital satisfaction, and as well as the overall quality of life and relieve manifestations of depression. ED is typically defined as inability to reach or maintain erection sufficient for satisfactory sexual performance. This definition is now widely accepted and recommended by a consensus panel of the National Institutes of Health (NIH), which further classifies it as organic, psychogenic, or mixed. ED is also a rather common pathology worldwide, affecting over 332 million men. For every 1000 men between 40 and 69 years of age in the United States, 26 new cases of ED are diagnosed every year. Also, a demographic study done in Nigeria by among about 92 men, 23 of them cannot sustain erection enough to have satisfactory sexual intercourse. Although ED is common in men older than 65, it can occur at any age. Male sexual arousal or erection is an intricate process that involves the brain, hormones, emotions, nerves, muscles and blood vessels. Erectile dysfunction can stem from a problem with any of these. The etiology of organic ED is associated to dysfunction of the endothelium. Endothelial cells can become damaged through a variety of techniques, most of which cause oxidative stress on the tissues. Oxidative stress induced ED are related to lifestyle issues from high blood pressure, hyperglycemia and dyslipidaemia. ED is a consistent or recurrent inability to either attain or keep a penile erection hard enough for sexual activity ED becomes more common in older men because it is associated with the same underlying risk factors as hypertension, diabetes mellitus, smoking, and obesity which are common during aging Same was a stress, fear and mental health problems can lead to or worsen erectile dysfunction. It could also be due to depression or to the use of antidepressant drugs like paroxetine which serve as agonist for receptors for selective serotonin reuptake inhibitors (SSRI) or block dopamine pathway [1,2]. Treatments of ED include non-pharmacological procedures like vacuum pump, surgery, psychotherapy, penile implants and pharmacological ones like use of sildenafil, yohimbine, papaverine and intracarvenous injection of vacoactive drugs which have been associated with several side effects like priapism with some resulting in addictions [3]. Several enzymes/protein receptors mediate the pathway of penile Erection, such as Endothelin 1 (ET1), Nitric Oxide synthase, (NOS), Guanylyl Cyclase, Acetylcholinesterase, Adenosine deaminase, Arginase, phosphodiesterase -5 (PDE-5) and others. PDE-5 is a key enzyme that breaks down cyclic guanosine monophosphate (cGMP) inducing flaccidity of the penis, Inhibition of this enzyme is a key therapeutic target against ED this has long being established but the knowledge of its link with ET1 has not being well documented. Endothelin 1 is a vasoactive peptide that acts by binding to two G-protein-coupled receptors, ETA and ETB, to exert its effects on vascular tone and cell proliferation. This study established the reduction of ET1 sensitivity, as phytocompounds from Telfairia occidentalis act on ET1 as antagonist of its activity to suppress its constriction ability. Hence causing the smooth muscles of the penile tissue to dilate naturally. Synthetic PDE-5 inhibitor such as Sildenafil, tadalafil and other conventional approach have been used over the years in the management of ED, these are packed with several side effects such as hearing loss, breathing problems, swelling of the face or lips, dizziness, priaprism [3]. Medicinal plants are diverse and they contain phytochemicals including flavonoids, alkaloids, tannins, saponins and terpenoids, which have been exploited over the years in the treatment of various ailments. This is an important alternative because of side effects and rising cost of conventional drugs [4].

Fluted pumpkin also called as Telferia occidentalis is a medicinal plant of a species from cucurbitaceae family in the tropics and largely consumed in Nigeria, Ghana and Sierra Leone. Telfairia occidentalis, christened after an Irish botanist, Charles Telfair (1778 – 1833), which consists mostly of herbs or rarely under shrub with water juice. It is a tropical vine grown in West Africa and hugely reputed in traditional medicine [5]. The plant is commonly called Fluted pumpkin. Locally, it is known as Ubong in Efik and Ibibio, Ugwu in Igbo, Ewe Aworoko in Yoruba [6]. The leaves of Telfairia occidentalis have been known to have different biological characteristics and are used in traditional medicine in Africa and Asia to manage many ailments. The plant is particularly noted traditionally for its healing properties and is usually taken in the form of herbal decoctions/concoctions as a hematinics, to treat unexpected attacks of convulsions, pain, malaria and anaemia. Report from studies has also shown various phytochemical and pharmacological research done on the methanolic extract of the seeds of Telfairia occidentalis that evaluated its antioxidant and antinociceptive properties to substantiate its traditional use [7]. Telfairias Occidentalis (TO) is a plant used for the enhancement of male sexual performance in Nigeria [8]. Saponins are lavishly present in Telfairias Occidentalis as documented from phytochemical screening done by. Saponins are plant chemicals and antioxidants implicated in the treatment of diabetes, hypertension, obesity and dyslipidemia.

Androgens like testosterone and dihydrotestosterone are steroid male sex hormones needed for development of male reproductive system and functions. Saponins are structural analogs of androgens and due to this similarity in structure, it could be hypothesized that saponins from Telfairias Occidentalis may be responsible for its aphrodisiac or increased sexual activity effect. Telfairias Occidentalis is also believed to modulate fertility as earlier stated in both genders, though the mechanisms are not elucidated [9]. Few works have been reported on its sexual enhancing property while none has been reported on the molecular basis for this property. Molecular docking serves as an in-silico strategy for predicting the singled-out inclination of small molecules within the active site of a receptor or target protein. This procedure anticipates the optimal binding mode and binding affinities between ligands and their receptors, making it broadly applied in virtual screening for lead compound optimization. The basic components of the molecular docking approach

encompass search algorithms and scoring functions employed to create and assess various ligand conformations. To this end, compounds from TO were evaluated against the Phosphodieterase 5 (PDE-5) protein using molecular and induced-fit docking protocols, prime Molecular Mechanics Generalized Born Surface Area post-docking protocol, and ADMET profiling among many others. Hence, this study aims to explore the potential of the phytochemicals present in Telfairias Occidentalis leaves to serve as inhibitors of the PDE-5 using a computational approach.

Materials and Methods

Computational Tools

The analytical tools employed here were Schrodinger suites software (ver. 2018-4) for Windows [10].

Ligand Preparation

Three hundred fifty-two compounds (352) of Tefairia occidentalis leaf phytocompounds, obtained from ultra-performance liquid chromatography-mass spectrometry (UPLC-MS), were engaged for this in silico study (Figure S1, Table S1). The structures were downloaded from PubChem compounds. At pH 7.4, the ligand was prepared with the ligprep panel on Maestro with an OPLS4 force field.

Protein Preparation

The RCSB repository (http://www.rcsb.org/pdb) provided endothelin, whose protein data bank ID is 6K1Q. It was then imported into the Maestro workspaces. The Schrodinger suite's protein creation wizard was used to create the downloaded protein. Het states were set to pH 7.0 +/- 2.0, metal ions and water were eliminated from the 5.0 A het group, and bond orders were assigned during the protein preprocessing. The retrained minimization was carried out using an OPLS4 force field and an RMSD of 0.30 A after water molecules were eliminated.

Receptor Grid Generation, Molecular and Induced-Fit Docking

The receptor grid creation panel was used to create the receptor grid file, which shows the receptor's active regions for glide ligand docking operations. By selecting the protein structures of interest in the workspace, the ligand-binding site was located [11]. The receptor grid box's coordinates are x = 37.97, y = 37.92, and z = 24.25. The induced-fit Docking (IFD) was then carried out using the glide and refinement module as described by Akinjiyan et al. (2025)

Admet Prediction

The physicochemical properties and absorption, distribution, metabolism, and excretion (ADMET) of leading compounds were predicted using Qikprop [12].

Binding Energy Prediction

The stability of the complex produced was assessed using the binding free energy of MM-GBSA as described by [13].

Results and Discussion

The receptor grid creation panel was used to create the receptor grid file, which shows the receptor's active regions for glide ligand docking operations. By selecting the protein structures of interest in the workspace, the ligand-binding site was located [11]. The receptor grid box's coordinates are x = 37.97, y = 37.92, and z = 24.25. The induced-fit Docking (IFD) was then carried out using the glide and refinement module as described by Akinjiyan et al. (2025). The interactions were estimated using discovery studio of the Maetro workflow. The table above shows the binding affinities of molecular docking and induced-fit docking (kcal/mol) of the hit phytochemicals from TO with endothelin, also revealing the amino acids involved.

S/N	Phytocompound	H-Bond and Interacting Amino acids	Docking Score (kcal/mol)	IFD Score (kcal/mol)	Hydrophobic Interaction
1	(2~{S})-2-[[(2~{R})-2-[(3,5-dimethylphenyl) carbonyl-methyl-amino]-3-(4-phenylphenyl) propanoyl] amino]-3-(1~{H}-indol-3-yl) propanoic acid (D2U)	4(LYS 161, ARG 243, LYS 182, LYS 182)	-16.075	-748	12(PHE 240, TRP 167, CYS 174, VAL 177, ALA 375, ILE 372, LEU 339, TRP 336, VAL 185, TRY 281, LEU 277, PRO 178)
2	Isochlorogenic acid	4(LYS 182, ARG 343, GLN 181, GLN 181)	-10.158	-746.28	8(ALA 375, ILE 372, VAL 185, TRY 281, LEU 277, TRP 336, LEU 339, VAL 177)
3	1-Caffeoylquinic acid.1	2(SER 184, ALA 375)	-9.538	-743.19	4(VAL 185, TRP 336, ALA 375, ILE 372)
4	2-((6-O-(beta-D-Apiofuranosyl)beta-D-glucopyranosyl)oxy)propane	4(ASN 158, ASN 104, SER 108, GLN 181)	-9.281	-741.91	6(VAL 185, TRP 336, ALA 375, ILE 372, LEU 162, VAL 159)
5	3-Feruloylquinic acid	2(ARG 343, SER 184)	-9.246	-747.27	4(ILE 372, TRP 336, ALA 375, VAL 185)

6	8-Gingediol		-9.025	-741.35	6(TYR 281, LEU 277, LEU 339, TRP 336, ALA 375, VAL 185)
7	(5S)-5-Methoxy-7-(4-hydroxyphenyl)-1-phenyl-3-heptanone	2(ARG 343, SER 184)	-8.447	-742.91	7(VAL 185, TRP 336, LEU 339, LEU 277, TYR 281, ILE 372, ALA 375)
8	Sildenafil		-5.997	-738.69	8(PHE 240, VAL 177, PRO 178, VAL 185, ALA 375, TRP 336, ILE 372, LEU 162)

Table 1: Molecular docking scores, induced fit docking, H-bond, amino acid and hydrophobic interaction of leading Tefairia occidentali phytocompounds, D2U and Sildenafil with phosphodiesterase 5 The structure of Human endothelin and Molecular Interaction (3D) of Tefairia Occidentalis Phytocompounds, D2U (co-ligand) and Sildenafil (standard drug) with Endothelin anr shown in the diagrams below as observed in the study.

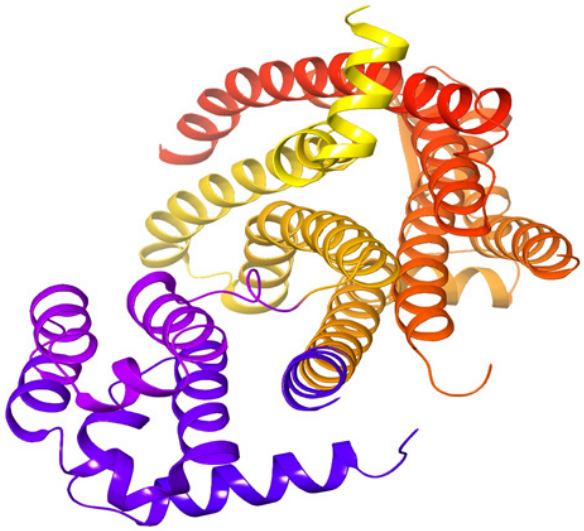

Figure. 1: Human Endothelin 1 Receptor (3D)

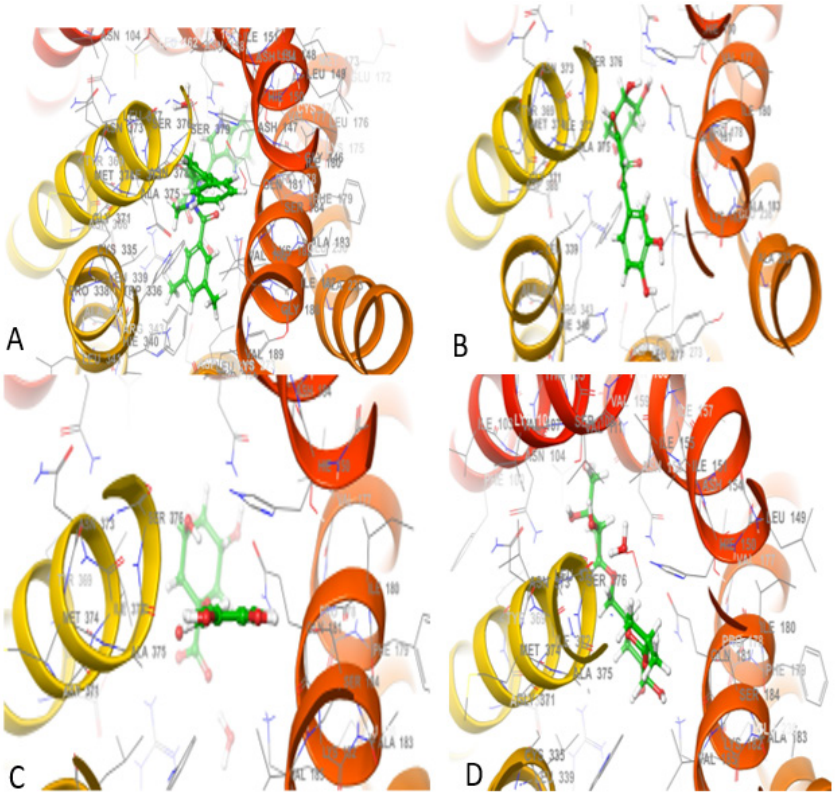

Figure 2: 3D molecular interaction of 2~{S})-2-[[(2~{R})-2-[(3,5-dimethylphenyl) carbonyl-methyl-amino]-3-(4-phenylphenyl) propanoyl] amino]-3-(1~{H}-indol-3-yl) propanoic acid (D2U, Co-ligand) (A), Isochlorogenic acid (B), 1-Caffeoylquinic acid (C), 2-((6-O-(beta-D-Apiofuranosyl)beta-D-glucopyranosyl)oxy)propane (D) with the endothelin protein.

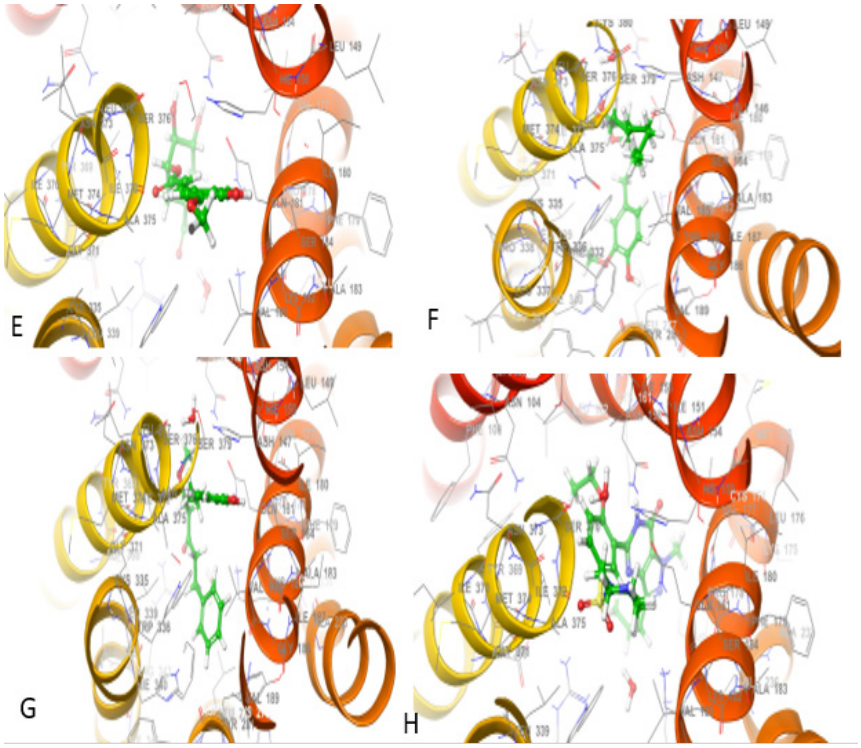

Figure. 3: 3D molecular interaction of 3-Feruloylquinic (E), 8-Gingediol (F), (5S)-5-Methoxy-7-(4-hydroxyphenyl)-1-phenyl-3-heptanone (G) and Sildenafil (H) with endothelin. Molecular interaction (2D) of Tefairia occidentalis phytocompounds, D2U (co-ligand) and Sildenafil (standard drug) with Endothelin

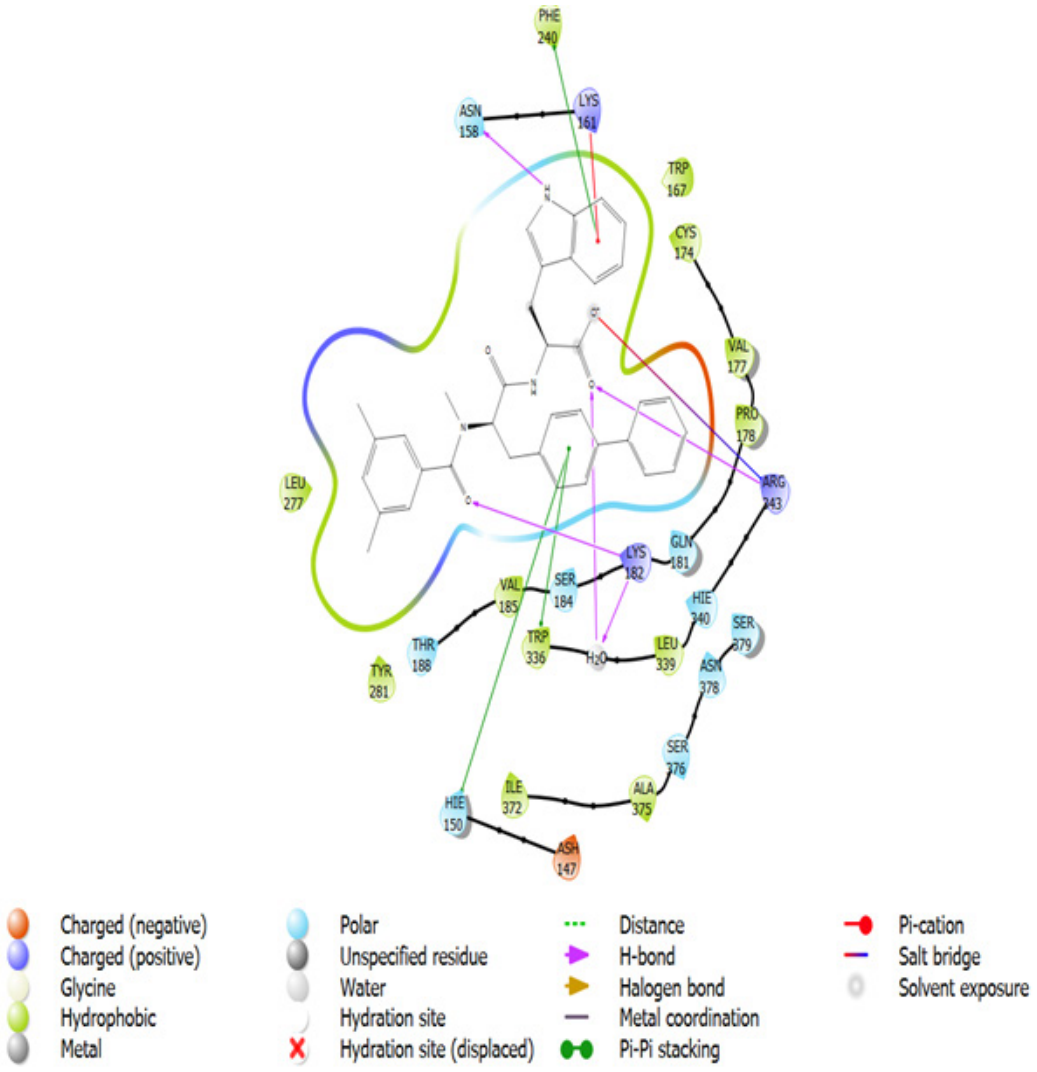

Figure 4: Molecular Interaction (2D) of (2~{S})-2-[[(2~{R})-2-[(3,5-dimethylphenyl) Carbonyl-Methyl-Amino]-3-(4-Phenylphenyl) Propanoyl] Amino]-3-(1~{H}-Indol-3-yl) Propanoic acid (D2U) with Endothelin

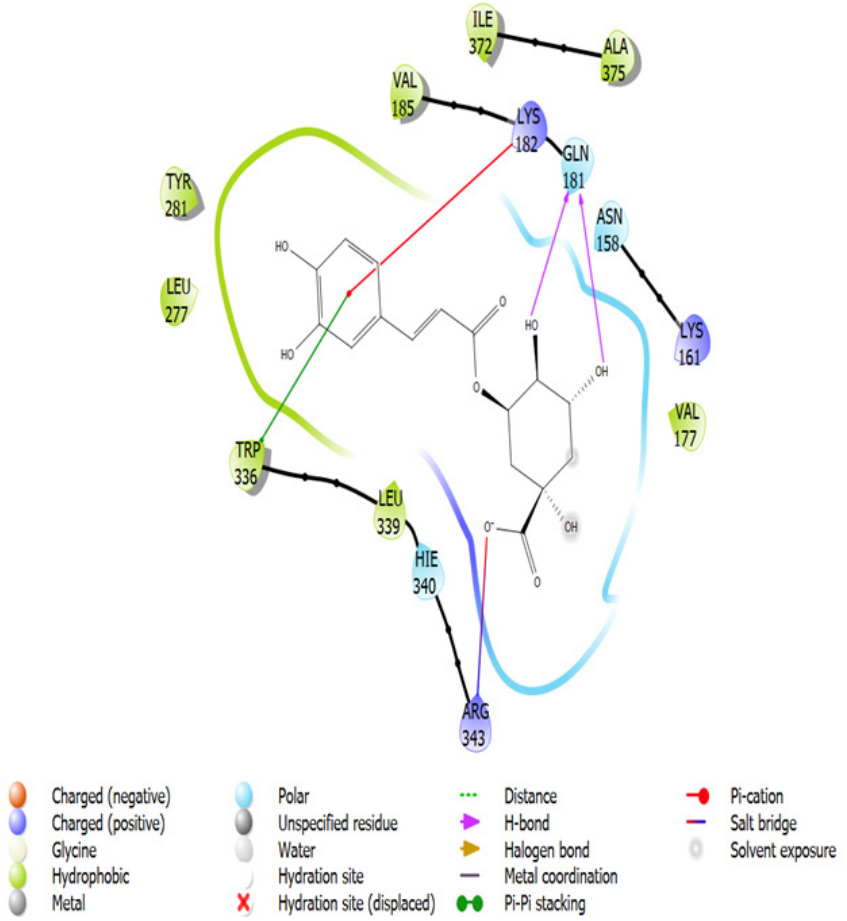

Figure 5: Molecular Interaction (2D) of Isochlorogenic acid with Endothelin

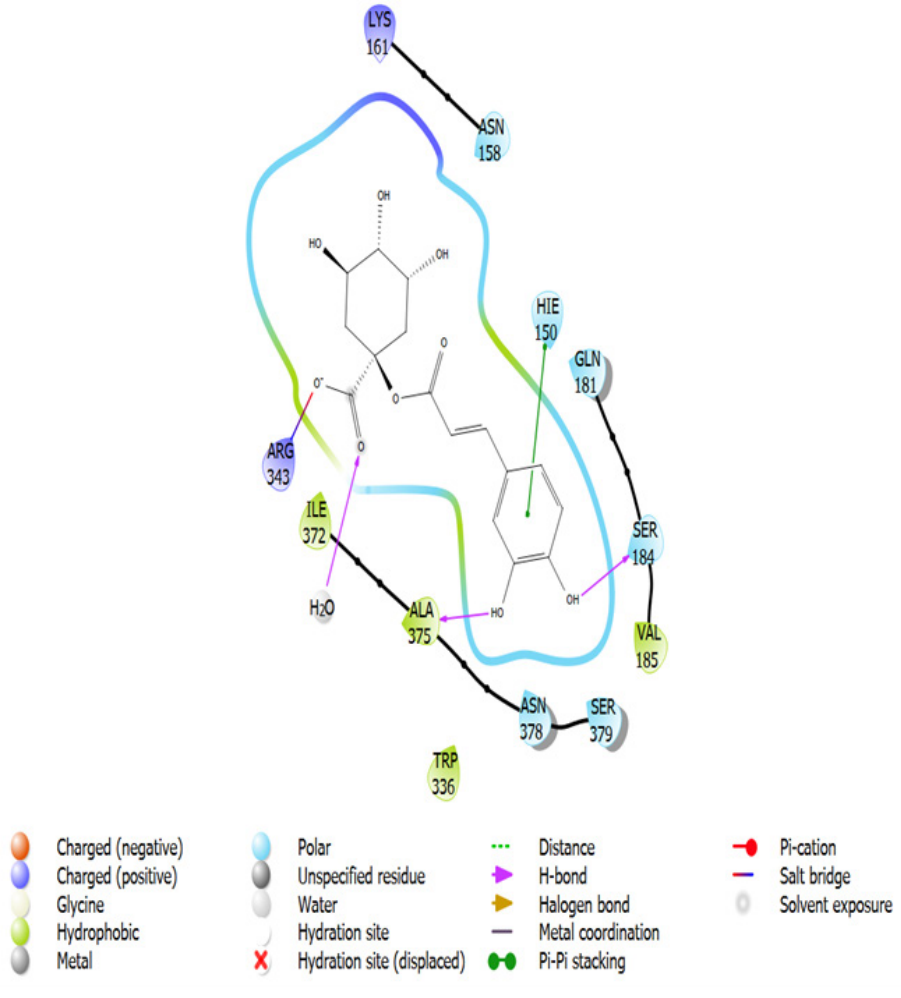

Figure 6: Molecular Interaction (2D) of 1-Caffeoylquinic acid with Endothelin

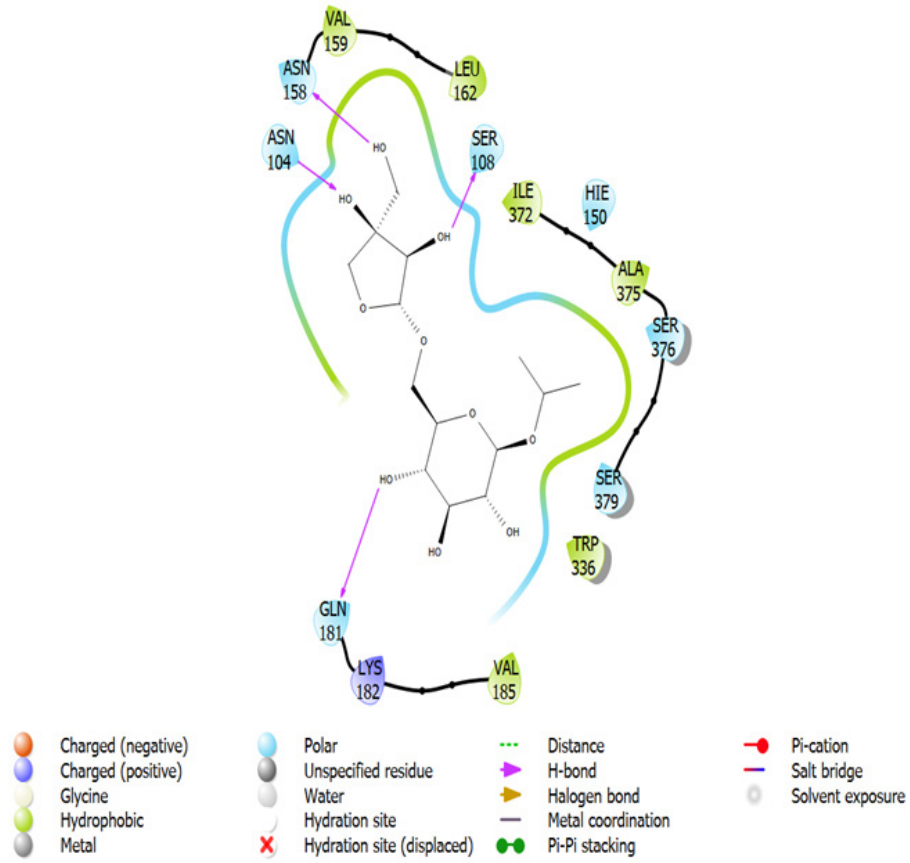

Figure 7: Molecular Interaction (2D) of 2-((6-O-(beta-D-Apiofuranosyl) beta-D-glucopyranosyl) oxy) Propane with Endothelin

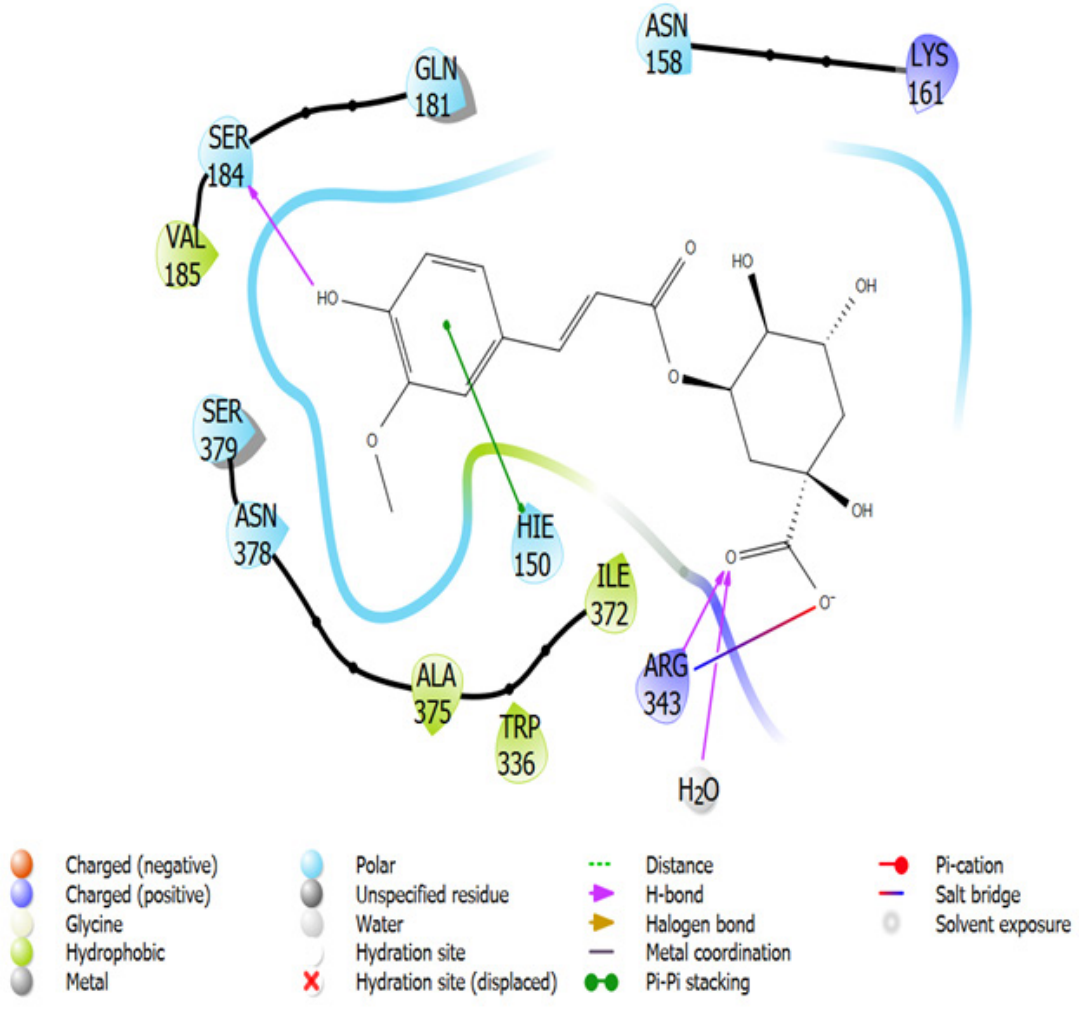

Figure 8: Molecular Interaction (2D) of 3-Feruloylquinic acid with Endothelin

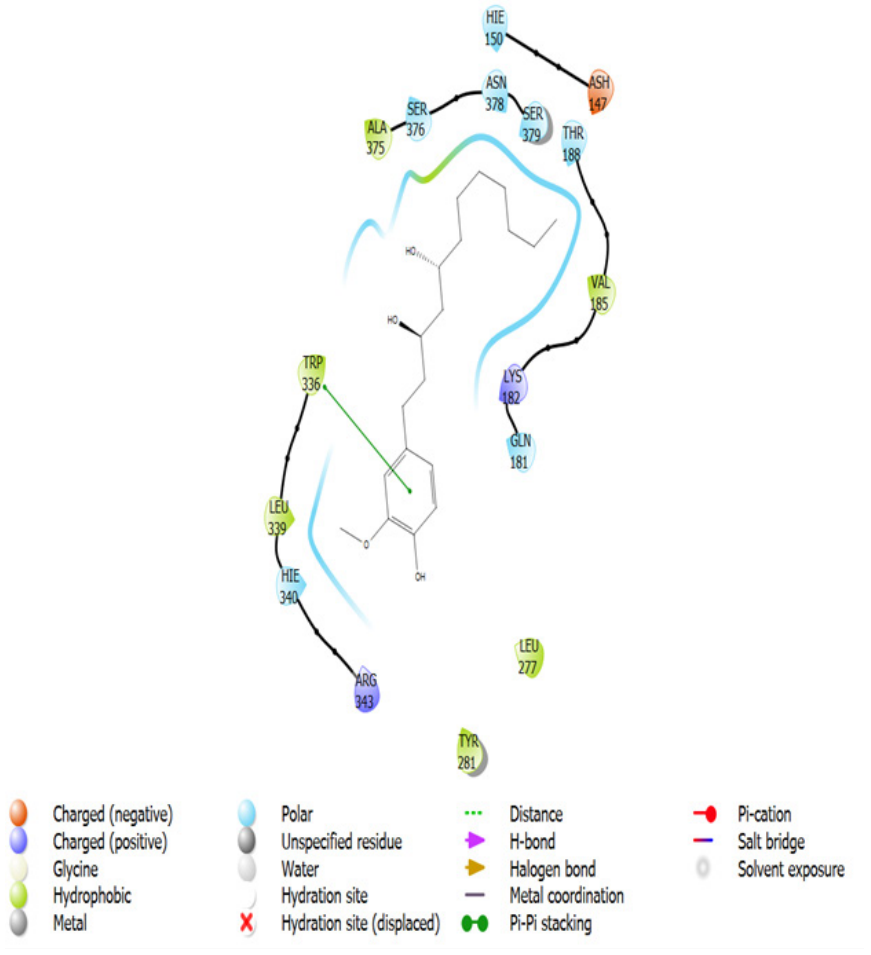

Figure 9: Molecular Interaction (2D) of 8-Gingediol with Endothelin

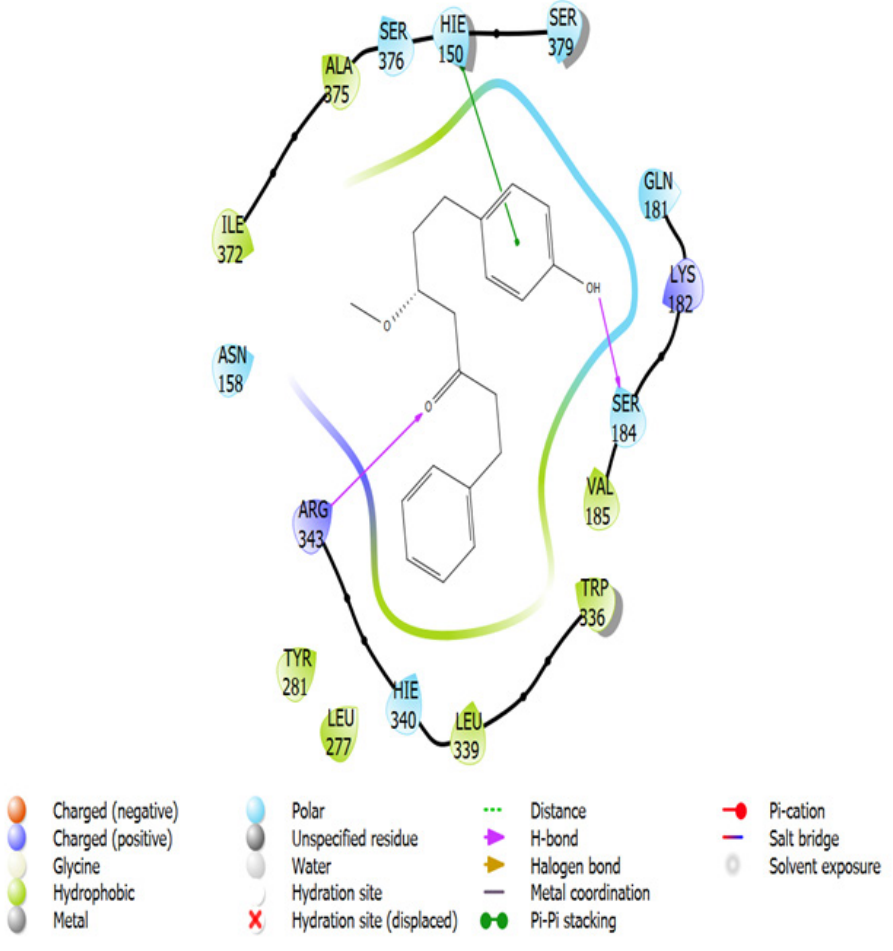

Figure 9: Molecular Interaction (2D) of (5S)-5-Methoxy-7-(4-hydroxyphenyl)-1-Phenyl-3-Heptanone with Endothelin

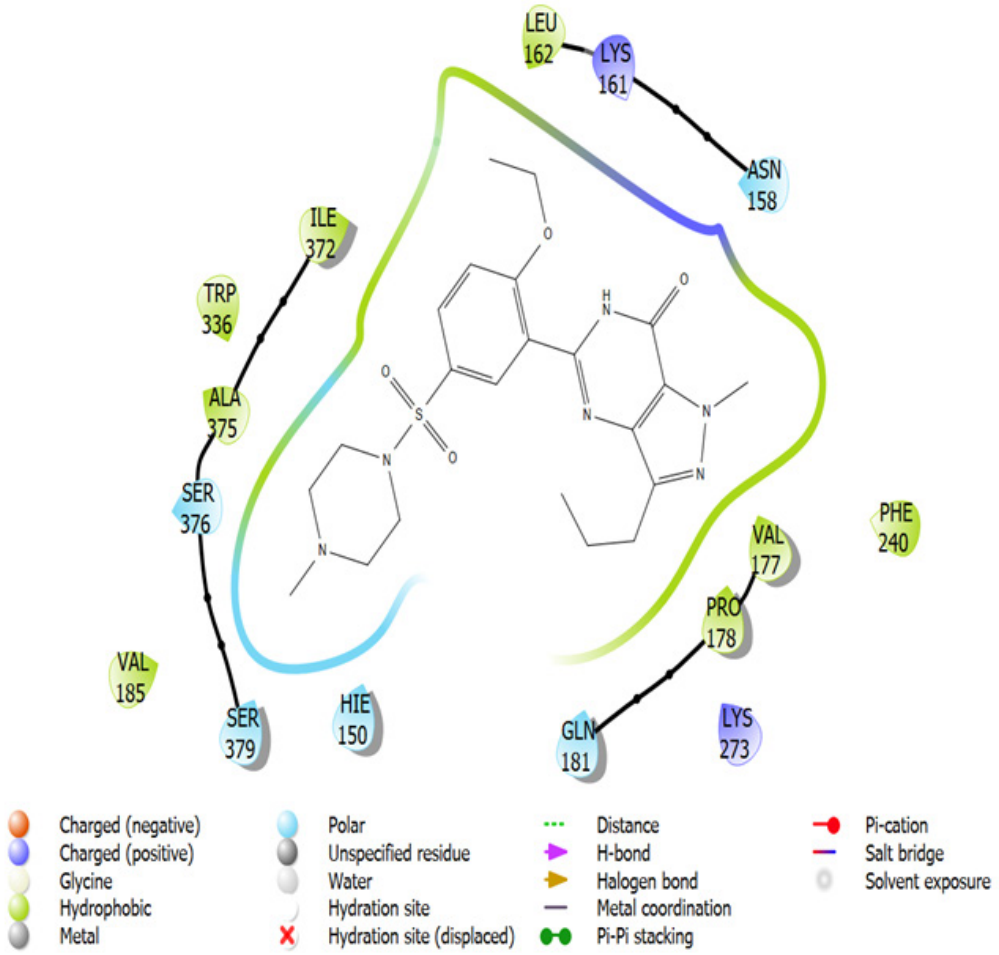

Figure 10: Molecular Interaction (2D) of Sildenafil with Endothelin

Admet Analysis

The physicochemical descriptors and pharmaceutically pertinent qualities were evaluated for ADMET analysis when examining druggable features. The following parameters were considered for this study: molecular weight, H-bond donors, H-bond acceptors, predicted polar surface, QPlogPo/w, and Lipinski's Rule of Five (RO5). Lipinski's RO5 aids in assessing drug-likeness and determining the likelihood of not binding compounds to a human orally active medication. The ADMET results for the lead compounds were retrieved from the workflow and are presented in Table 4 below.

Entry Name	accptHB	donorHB	mol MW	PSA	QPlogPo/w	Rule of Five
D2U (co-ligand Endothelin)	6.750	2.250	573.690	118.357	6.721	2
(5S)-5-Methoxy-7-(4-hydroxyphenyl)-1-phenyl-3-heptanone.1	4.450	1.000	312.408	55.417	4.310	0
1-Caffeoylquinic acid.1	10.600	6.000	354.313	181.694	-0.504	1
2-((6-O-(beta-D-Apiofuranosyl) beta-D-glucopyranosyl) oxy) propane.1	16.050	6.000	354.353	159.191	-2.123	1
3-Feruloylquinic acid.1	9.650	5.000	368.340	173.599	0.530	0
8-Gingediol.1	4.900	3.000	324.459	70.489	3.865	0
Isochlorogenic acid.1	9.650	6.000	354.313	186.138	-0.266	1
sildenafil.1	11.750	1.000	474.577	118.598	1.935	0

Table 2: ADMET results of leading Tefairia occidentalis phytocompounds, D2U (co-ligand) and Sildenafil (standard drug) with Endothelin

Binding Energy Evaluation

The free energy of binding, which predicts binding free energies for compounds/ligands by combining solvation models and molecular mechanics calculations, was used to validate the docking scores. Studies have indicated that the post-docking technique MMGBSA is the most appropriate for determining the ligand's affinity upon binding to its protein target. Numerous investigations have shown that the post-docking approach of MMGBSA accurately determines how effectively a ligand binds to its protein target. The findings from the postdocking analysis of the MMGBSA are shown in Table 3.

Entry Name	MMGBSA dG Bind	MMGBSA dG Bind Coulomb	MMGBSA dG Bind Hbond	MMGBSA dG Bind Packing	MMGBSA dG Bind Solv GB	MMGBSA dG Bind vdW
D2U (co-ligand)	-127.21	-64.56	-3.56	-8.35	77.68	-83.39
Isochlorogenic acid.1	-65.51	-51.78	-4.22	-1.05	65.78	-41.58
1-Caffeoylquinic acid.1	-48.95	-55.29	-3.30	-2.87	64.49	-40.83
2-((6-O-(beta-D-Apiofuranosyl) beta-D-glucopyranosyl) oxy) propane	-48.67	-36.90	-3.14	0.00	32.25	-27.86
3-Feruloylquinic acid	-55.18	-61.11	-4.20	-2.39	62.53	-38.63
8-Gingediol	-57.79	-9.44	-0.93	-0.90	24.01	-52.57
(5S)-5-Methoxy-7-(4-hydroxyphenyl)-1-phenyl-3-heptanone	-38.88	-19.17	-2.00	-4.68	24.31	-31.41
Sildenafil	-61.41	12.22	-1.34	-6.15	3.09	-35.36

Table 3: Postdocking analysis of the MMGBSA (3D) of Tefairia occidentalis phytocompounds, D2U (co-ligand) and Sildenafil (standard drug) with Endothelin

Discussion

The ligand of the plant compound used in this study (Telfairia occidentalis) were docked into the binding site of Endothelin 1 to aggregate the docking scores and glide docking was used in this respect. Research have shown that the inhibitory property of compounds can be estimated by the docking score of the ligand-receptor interaction between a compound and the active site of the protein [14]. The docking result of six leading compound of Telfairia occidntalis (TO) gotten through UPLC from this study against Endothelin 1 possessed a better docking score than the standard drug pyrozolo (4,3) pyrimidine-7-one (Sildenafil) used clinicall to manage Erectile dysfunction.

The molecular docking results (kcal/mol) of the 6 TO hit compounds that passed pharmacotoxicity are: Isochlorogenic acid (-10.158), 1-Caffeoylquinic acid (-9.538), 2-((6-O-(beta-D-Apiofuranosyl) beta-D-glucopyranosyl)oxy)propane (-9.281), 3-Feruloylquinic acid (-9.246) and (5S)-5-Methoxy-7-(4-hydroxyphenyl)-1-phenyl-3-heptanoneare (-8.447) are better compared to the standard drug sildenafil (-5.997 kcal/mol) with endothelin. The induced-fit scores of the hit compounds (-748 to -741.35 kcal/mol) are also better than sildenafil (-738.69 kcal/mol). The comparison of the binding free energies of the hit compound also showed that isochlorogenic acid has the most preferred reaction with Endothelin 1, having a free binding energy of -65.51 kcal/mol, as a good binding free energy is indicated by its negative value [16]. Revealing that the leading compound in this study has a better therapeutic property than Sidenafil. The study also showe that the amino acid interaction at the active site of Endothelin 1 and sildenafil 8(PHE 240, VAL 177, PRO 178, VAL 185, ALA 375, TRP 336, ILE 372, LEU 162) are quite related to that of the hit compounds and the peptide Endothelin 1, indicating the series of important amino acid at the reactive site of endothelin 1 which play a vital role for its inhibition in curbing ED. The pharmacotoxicity and kinetics (ADMET) study of these hit compounds showed they adhere to Lipinski's rule of five which states that:

- The compound should not have more than 5 hydrogen bond donors
- There should not be more than 10 Hydrogen bond acceptors
- The molecular weight of the compound must be less than 500 dalton
- The octanol-water partition coefficient (log p) ≤ 5.

The ADME result in Table 3 showed that the hit compounds obey the Lipinski's rule of five as none of them violated more than one of the rules. The study suggests that these compounds from Telfairia occidentalis are drug candidate for the blockage of Endothelin 1 (a vaso- constrictor that causes erectile dysfunction) as potential vasodilating drugs that could be helpful in combating ED

Conclusion

In this paper, computational tools were exploited to investigate and select natural compounds From Telfairia Occidentalis leaves from UPLC that have inhibitory and pharmacological properties against the Endothelin 1 peptide. Druggable compounds of Tefairia occidentalis leaves demonstrated an excellent binding affinity to block Endothelin 1 vasoconstriction pipetide and pleasing ADMET profiles compared to standard drugs (Sidenafil) using MMGBSA models. The study suggests that ADMET prediction, IDF and molecular docking are reliable methods for discovering new drugs to combat onslaught of Erectile Dysfunction. This accentuate the need for novel inhibitors due to the development of unpleasant side effects and hike in price of Drugs and orthodox treatments. These promising compounds should undergo further validation, including atomistic simulation, in-vitro, quantitative Structural Analysis relationship (QSAR) model and in-vivo experiments, to proof their potentials as effective erectile dysfunction drugs [17-24].

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Availability of Data and Materials

The dataset generated and/or analyzed in this study is available from the corresponding author upon reasonable request.

Competing Interests
The authors hereby declare no conflicts of interest.

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