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Involvement of *Cissus populnea* Derived Compounds in Phosphodiesterase Pathway in Erectile Dysfunction: *In Silico* Study

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Abstract

Erectile Dysfunction (ED) has been a threat among couples and is one of the challenging disorders in Nigeria and the world. Various drugs targeting Phosphodiesterase 5 (PDE5) inhibition like Pyrazinopyridoindole (Tadalafil), have been used for the treatment of ED but, they are associated with side effects such as headache, diarrhea, back pain, and stomach upset among others. Medicinal plants are now being explored for the treatment of various diseases and disorders including ED because they are affordable with little or no side effects. *Cissus populnea* (CP) is a popular plant in Nigeria used in the management of ED but there is a paucity of information on the mechanisms involved. In this study, Schrodinger suites were employed for docking of thirty-eight CP phytocompounds gotten from HPLC analysis and works of literature against Phosphodiesterase PDE5, a key enzyme in the erection pathway. Seven leading compounds were found to have higher docking scores and binding affinity compared to Pyrazinopyridoindole (Tadalafil), with 9-octadecenoic acid, having the highest docking score of -13.078 Kcal/mol. The hit compounds were further subjected to ADME prediction. The findings suggested that *C. populnea* compounds are potential drug candidates with better hit than Tadalafil in managing ED and merit additional investigation.

Keywords: Erectile dysfunction • Molecular docking • Phosphodiesterase 5 • *Cissus populnea*

Introduction

Erectile Dysfunction (ED) is a threat to relationships, and a major health challenge in Nigeria, Africa and the world. It is projected to affect about 300 million people globally by 2025 [1]. ED is a medical condition when men cannot consistently achieve or maintain an erection for satisfactory sexual performance [2]. ED can result from lifestyle, physical causes like diabetes, and low testosterone; physiological causes like depression, stress, and fatigue among others [3]. Penile erection is achieved by blood flow into it as a result of the stimulation of the cavernous nerve with the aid of neurotransmitters like dopamine, and enzymes like guanylate cyclase which aid in vasodilation [4]. Phosphodiesterase 5 is a vasoconstrictor that plays a critical role in the erection pathway; it's up regulation has been associated with erectile dysfunction [5].

Phosphodiesterase 5 (PDE5) is a well-studied PDE that particularly targets cyclic Guanosine Monophosphate (cGMP), which is generally produced by Nitric Oxide (NO) mediated activation of the soluble guanylate cyclase [6]. Given the importance of cGMP produced by activating this cellular signaling pathway in a range of physiological processes, pharmacological inhibition of PDE5 has been shown to have numerous therapeutic potentials in combating erectile dysfunction [7]. PDE5 catalyzes the conversion of cGMP to Guanosine Triphosphate (GTP), this process leads to flaccidity of the penis by restricting blood flow into it, a vasoconstriction process [8]. It works allosterically with guanylate cyclase which catalyzes and initiates the process of vasodilation leading to an erection.

Many drugs have been designed at inhibiting PDE5 but they all have short-term effects, and side effects; some are also known to cause addiction [9]. Some therapies, injections, vacuum pumps, surgeries and other methods employed to solve this problem are also

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expensive and oftentimes require expertise and knowledge Medicinal plants also known as traditional plants are now being explored to manage several ailments including ED because they are relatively safe and cheap with little or no side effects [10]. These plants are known to contain phytocompounds with great therapeutic potential [11].

Cissus populnea (Guill. and Perr.) belongs to the family Amplidaceae. Local names in Nigeria include "Okoho" (Ibos, Igala and Idoma tribes), "Dafara" or "Latutuwa" (Hausas), "Afato, Orogbolo or Ajara" (Yoruba) folks in Nigeria [12]. It is a climbing tropical shrubs plant that contains many phytochemicals and has been reported to be able to survive in all seasons [13]. It is edible and has been associated with several medicinal uses in Nigeria, Africa and many parts of the world [14]. *Cissus populnea* (CP) is a plant used for enhancement of male sexual performance in Nigeria but its mechanisms remain unclear [15]. The plant has also been reported to possess antioxidant, antibacterial, anti-trypanosomal and aphrodisiac properties [16]. Some of the phytochemicals that are present and active in CP include, such as tannins, glycosides, flavonoids, carotenoids, anthraquinones, and vitamin C [17]. *Cissus populnea* is also believed to among the local communities to promote fertility as earlier stated in both genders, though the mechanisms are not elucidated [18]. This work uses computational tools to investigate the mechanisms of action by which phytocompounds in CP interact with phosphodiesterase 5, a key enzyme in ED pathway.

Materials and Methods

The computational tools used in this study were created using the Schrodinger suites software (version 2018-4). The computer programs used in this study are Schrodinger suites software for Windows (version 2018-4) and Ubuntu version.

Ligand preparation

A library of around 38 phytocompounds of *Cissus populnea* with low molecular weights was used for this *in silico* study. These compounds were gotten from HPLC analysis of the aqueous and n-butanol extract of the plant, works of literature and PubChem. At pH 7.0, the ligand preparation was accomplished using the ligprep panel on Maestro 11.5 with an OPLS3 force field ± 2.0. Desalt and generate tautomers were selected as options, and the stereoisomer computation was done. The result was left at the maestro's discretion.

Protein preparation

The protein phosphodiesterase 5 of two forms with PDB ID: 1 UDU and PDB ID: 1 UDT were obtained from the RCSB directory and uploaded to the maestro 11.8 workspaces. The downloaded protein was made using the protein creation wizard in the Schrodinger suite. During the protein preprocessing, bond orders were assigned, waters were removed from the 5.0 A het group, and het states were set to pH 7.0 ± 2.0 [19]. Water molecules were removed and the retrained minimization was performed with an OPLS3 force field and an RMSD of 0.30 A [20].

Receptor grid generation

The receptor grid file, which depicts the receptor's active areas for glide ligand docking operations, was prepared using the receptor grid creation panel. The ligand-binding site was found by choosing the protein structures of interest on the workspace [21]. Previously isolated *Cissus populnea* compounds from pieces of literature and ones gotten from Pubchem were docked into the active region of phosphodiesterase 5 to anticipate binding affinity and molecular interaction.

ADME predictions

Qikprop was used to predict the Absorption, Distribution, Metabolism, and Excretion (ADME) of the lead compounds, as well as their physicochemical characteristics [22].

Results

Result of HPLC analysis of *Cissus populnea* aqueous extract using UV detector (Figure 1 and Table 1).

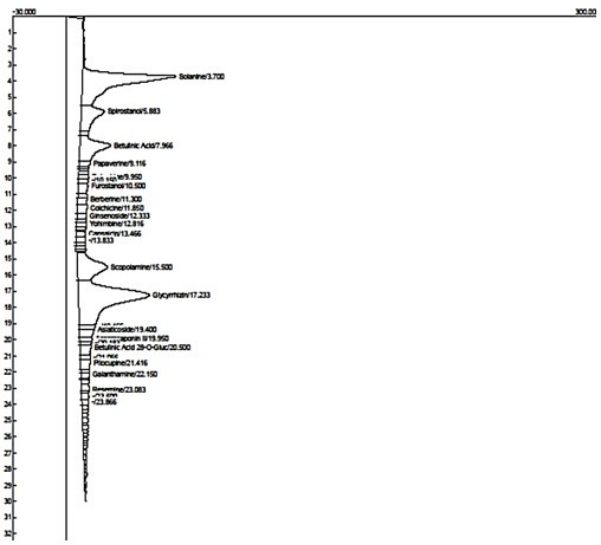

Figure 1. *Cissus populnea* aqueous extract HPLC analysis.

Component	Retention	Area	Height	External units
Solanine	3.700	2621.3140	52.516	0.000%
Spirostanol	5.883	767.6190	13.163	83.4524 ppm
Betulinic Acid	7.966	927.8450	17.463	103.4806 ppm
Papaverine	9.116	117.1350	6.217	0.0000

Ephedrine	9.950	98.4310	5.792	0.0000
Furostanol	10.500	201.4200	5.531	0.0000
Berberine	11.300	122.8860	5.370	0.0000
Colchicine	11.850	180.4900	5.643	0.0000
Ginsenoside	12.333	103.7040	5.315	0.0000
Yohimbine	12.816	101.3145	5.559	0.0000
Capsaicin	13.466	109.3930	5.279	0.0000
Scopolamine	15.500	1077.9995	16.944	0.0000
Glycyrrhizin	17.233	3212.62	40.018	0.0000
Asiaticoside	19.400	234.2665	8.369	0.0000
Asparasaponin II	19.95	101.3825	7.007	0.0000
Betulinic Acid 28-O-Glu2 c	0.500	197.3760	6.236	0.0000
Pilocupine	21.416	191.0525	5.608	0.0000
Galanthamine	22.150	77.0945	4.718	0.0000
Reserpine	23.083	105.4955	4.361	0.0000

Table 1. Phytocompounds obtained from HPLC analysis of Cissus populnea aqueous extract.

Result of HPLC analysis of *Cissus populnea* n-butanol extract using UV detector (Figure 2 and Table 2).

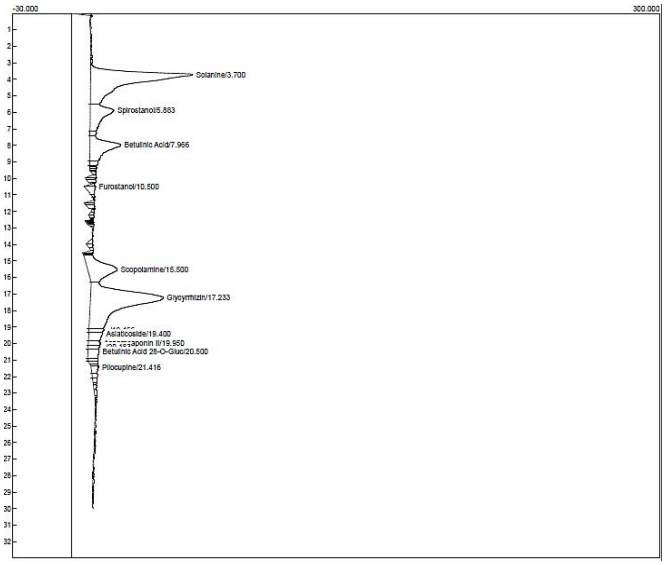

Figure 2. *Cissus populnea* n-butanol extracts HPLC analysis.

Component	Retention	Area	Height	External	Units
Solanine	3.700	2535.3200	52.098	0.0000	%
Spirostanol	5.883	655.8750	12.122	69.4844	ppm
Betulinic Acid	7.966	768.4680	15.829	83.5585	ppm
Furostanol	10.500	109.0060	5.854	0.0000	
Scopolamine	15.500	906.6530	15.164	0.0000	

Glycyrrhizin	17.233	2808.8970	37.280	0.0000
Asiaticoside	19.400	200.6005	7.149	0.0000
Asparasaponin II	19.95	89.1275	6.173	0.0000
Betulinic Acid 28-O-Glu2 c	0.500	185.2890	5.788	0.0000
Pilocupine	21.416	92.5485	3.839	0.0000

Table 2. Phytocompounds obtained from HPLC analysis of *Cissus populnea* n-butanol extract.

Docking results *of Cissus populnea* phytocompounds against phosphodiesterase 5

The virtual screening workflow in Maestro was used to dock and score the compounds originating from *Cissus populnea* and Tadalafil (a standard drug of erectile dysfunction) against Phosphodiesterase 5. The 2D and 3D structures inclusive, binding affinity, protein interactions and ADME results were retrieved from the workflow and presented below Tables 3-5.

No	Phytochemical	H-bond	Docking score	Hydrophobic interaction
1	9-Octadecenoic acid	0	-13.078	LEU725, LEU765, TYR812, ALA767, ILE768, ALA779, VAL782, ALA783, PHE786, PHE787, ILE813, LEU804, MET816, PHE820
2	6-octadecenoic acid.	0	-12.296	PHE787, ILE813, PHE786, MET816, LEU804, ALA783, VAL782, PHE820, ALA779, ILE778, ILE768, ALA767, LEU765, TYR612, LEU725
3	Daucosterol	0	-11.776	LEU725, ILE824, PHE820, MET816, LEU804, PHE787, PHE786, ILE813, ALA783, VAL 782, ALA 779
4	Asparasaponin11	2 (GLN917, GLN 725)	-11.084	TYR612, LEU765, ALA767, ILE768, ILE778, ALA779, VAL782, LEU804, TYR664, LEU725
5	Betulinic acid	2 (GLN917, GLN775)	-10.286	TYR612, LEU765, VAL782, ALA767, ILE768, ALA729, ILE778, LEU729, TYR664, LEU804, PHE820, PHE786
6	Stigmasterol	1 (GLN775)	-9.945	ILE768, ALA767, LEU765, ILE778, ALA779, VAL782, TYR612, TYR664, LEU725, ALA726, ILE729, ILE 824, LEU804, PHE 789, PHE820
7	Furostanol	1 (HIS 613)	-8.43	PHE786, VAL782, TYR612, LEU725, LEU765, TYR 664, ILE 824, ALA823, PHE820, MET816, LEU804
8	Pyrazinopyridoindole (Tadalafil)	1 (GLN 817)	-6.558	PHE820, MET816, LEU804, ILE778, ALA779, VAL782, ILE768, ALA767, LEU 765, TYR612, PHE786, ILE 824, LEU725

H-bond: Hydrogen bonding

Table 3. Molecular docking results of the seven leading compounds from *Cissus populnea* and pyrazinopyridoindole (Tadalafil) against phosphodiesterase 5.

Compound name	MMGBSA DG bind	MMGBSA DG bind coloumb	MMGBSA DG bind H-bond	MMGBSA DG bind lipo	MMGBSA DG bind solv GB
9-Octadecenoic acid	7.14	-94.64	0	-28.37	166
6-octadecenoic acid	2.43	-89.68	0	-25.82	148.51
Daucosterol	12.82	-44.43	-1.79	-32.69	112.89
Asparasaponin 11	96.56	-72.79	-0.96	-34.45	190.33
Betulinic acid	96.5	-72.79	-0.96	-34.45	190.27
Stigmasterol	-35.39	-5.71	-0.42	-40.5	41.34
Furostanol	41.15	-27.96	-0.53	-34.17	109.63
Pyrazinopyridoindole	-15.54	2.05	-0.49	-21.41	50.49

Table 4. Binding free energy results.

Compound name	Glide rotatable bonds	Mol MW	Donor HB	AccptHB	Qplog Po/w	PSA	Rule of Five
9-Octadecenoic acid	15	282.465	1	2	5.619	50.437	1
6-octadecenoic acid	15	282.465	1	2	5.665	49.682	1
Asparasaponin 11	3	456.707	2	3.7	6.293	61.291	1
Betulinic acid	3	456.707	2	3.7	6.297	60.266	1
Furostanol	5	402.659	1	3.4	5.995	29.553	1

Table 5. ADME results of *Cissus populnea* phytocompounds with phosphodiesterase.

The *in silico* molecular interactions of Cissus populnea phytocompounds and tadalafil with phosphodiesterase 5 (Figures 3-10).

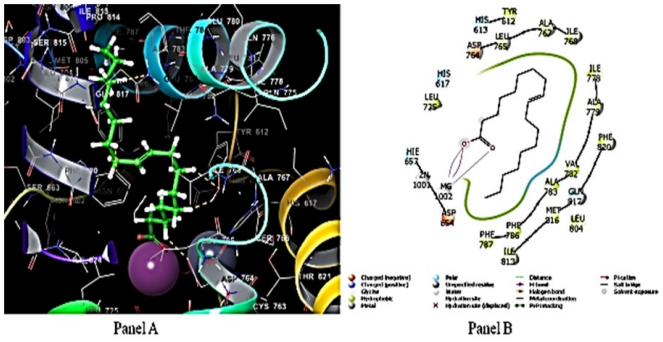

Figure 3. Binding pose and site of 9-Octadecenoic acid with phosphodiesterase 5 (Panel A), molecular interaction of 9-Octadecenoic acid with amino acid residues within the binding pocket of the protein structure (Panel B).

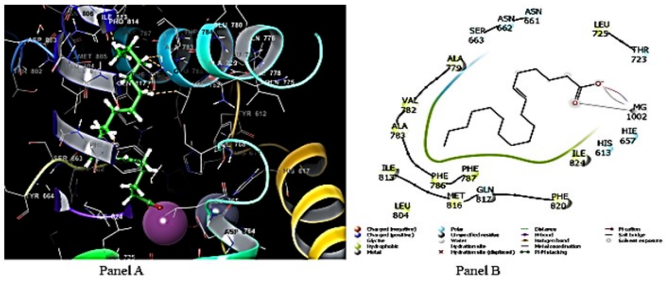

Figure 4. Binding pose and site of 6-octadecenoic acid with phosphodiesterase 5 (Panel A), molecular interaction of 6-octadecenoic acid with amino acid residues within the binding pocket of the protein structure (Panel B).

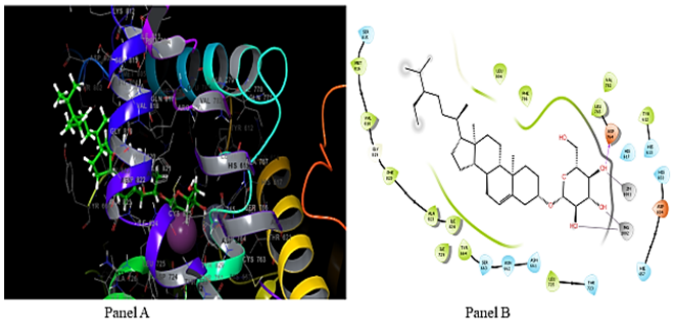

Figure 5. Binding pose and site of Daucosterol with phosphodiesterase 5 (Panel A), molecular interaction of Daucosterol with amino acid residues within the binding pocket of the protein structure (Panel B).

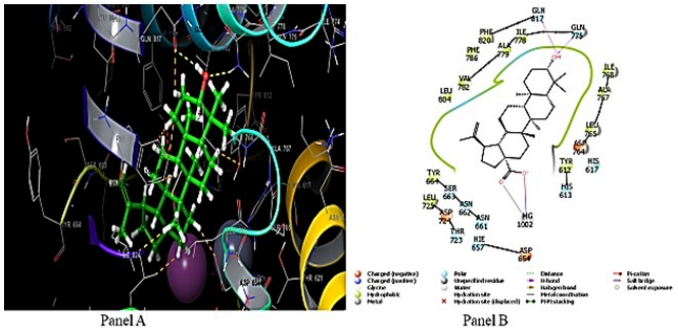

Figure 6. Binding pose and site of Asparasaponin 11 with phosphodiesterase 5 (Panel A), molecular interaction of Asparasaponin 11 with amino amino acid residues within the binding pocket of the protein structure (Panel B).

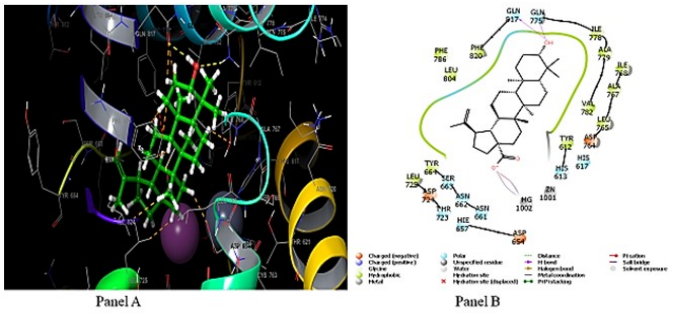

Figure 7. Binding pose and site of Betulinic acid with phosphodiesterase 5 (Panel A), molecular interaction of Betulinic acid with amino acid residues within the binding pocket of the protein structure (Panel B).

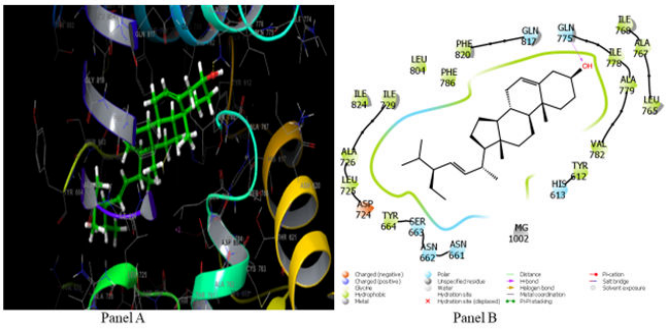

Figure 8. Binding pose and site of Stigmasterol with phosphodiesterase 5 (Panel A), molecular interaction of Stigmasterol with amino acid residues within the binding pocket of the protein structure (Panel B).

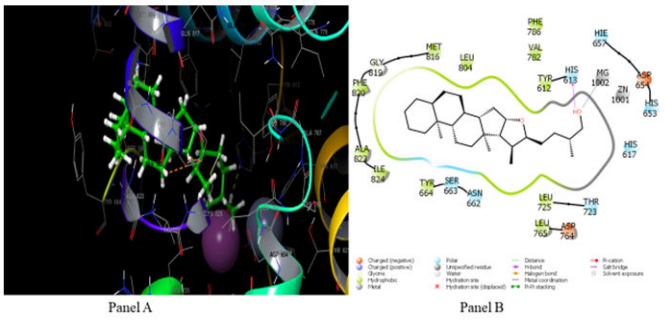

Figure 9. Binding pose and site of Furostanol with phosphodiesterase 5 (Panel A), molecular interaction of Furostanol with amino acid residues within the binding pocket of the protein structure (Panel B).

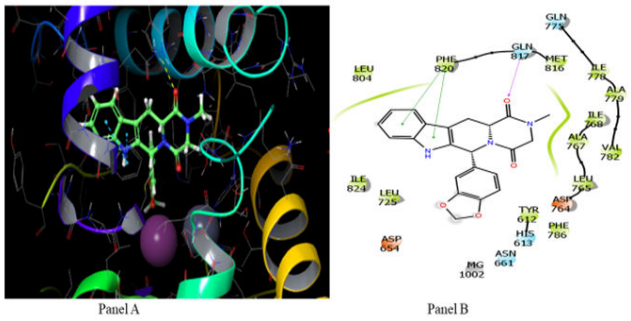

Figure 10. Binding pose and site of Pyrazinopyridoindole (Tadalafil) with phosphodiesterase 5 (Panel A), molecular interaction of Pyrazinopyridoindole (Tadalafil) with amino acid residues within the binding pocket of the protein structure (Panel B).

Discussion

The ligands of the plant compounds used in this study were docked into the binding sites of PDE 5 to collate the docking scores and glide docking was employed in this regard [23]. Studies have shown that the inhibitory properties of compounds can be measured by the docking score of the ligand receptor interaction between a compound and the active site of the protein [24]. The docking results of seven leading compounds which were selected from CP in this study, against Phosphodiesterase 5, portrayed a better docking score than Pyrazinopyridoindole (Tadalafil), which is a standard clinical drug used for the management and treatment of erectile dysfunction [25]. The first leading compound in this study is 9-octadecenoic acid, having a docking score of -13.078 Kcal/mol, followed sequentially by 6-octadecenoic acid (-12.296 Kcal/mol), Daucosterol (-11.776 Kcal/mol), asparasaponin 11 (-11.084 Kcal/mol), betulinic acid (-10.286 Kcal/mol), stigmasterol (-9.945 Kcal/mol), Furostanol (-8.43 Kcal/mol); while Tiladafil has a docking score of (-6.558 Kcal/mol). The comparison of the binding free energies of the various compounds also depicted that 9-Octadecenoic acid has the most favorable reaction with PDE 5, having a binding free energy of -94.64 kcal/mol, as a good binding free energy of a compound is indicated by its negative value [26,27]. This shows that the leading compound from this study is a better cure than Tadalafil for erectile dysfunction, as it has a better docking score. It appeared from the molecular docking study that there exists a hydrophobic interaction between the amino acid residues (PHE820, MET816, LEU804, ILE778, ALA779, VAL782, ILE768, ALA767, LEU 765, TYR612, PHE786, ILE 824, LEU725) at the binding site of PDE 5 and Tadalafil. This type of interaction was also found to exist between the compounds of *Cissus polpunea* and Tadalafil, sharing similar ligand protein interactions by binding to similar amino acid residues. This showed that some peculiar amino acid residues at the binding sites of phosphodiesterase 5 play pivotal roles in the inhibition of PDE 5, as was earlier stated by Iwaloye et al. in one of their studies [28,29].

Pharmacokinetics and toxicity prediction study of the compounds contained in the CP was also carried out to ensure that their absorption, distribution, metabolism and elimination are such that are organ-friendly and safe for use, and this study was carried out by subjecting the virtual screening of the plant compounds to ADME

Lipinski rule of 5 which states that for any compound to be considered as a potential orally active drug candidate, it must not violate more than one of the following Lipinski's rule:

- The compound should not have more than 5 hydrogen bond donors.
- There should be no 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 [30].

The ADME result in Table 3 showed the compounds which obey the Lipinski rule of 5, as none of the compounds violated more than one of the Lipinski rules.

It is evident from the parameters used in this study that the selected *Cissus populnea* compounds demonstrated a higher inhibitory potential on PDE5 than the common drug being sold. Thus, making *Cissus populnea* a potential drug candidate for erectile dysfunction, as its inhibitory effect on PDE 5 can cause vasodilation, thereby causing an erection. This study can be further confirmed through *in vivo* and *in vitro* research [31].

Conclusion

From the outcome of this investigation, considering the docking score, favorable binding affinity, and adherence to the ADMET profile, all compounds with a major focus on 9-octadecenoic acid with the highest docking score in *Cissus polpunea* are concluded to have more effective and efficient potential. Thus, this investigation deduces that these compounds have shown better efficacy than the standard drug, Tadalafil, and can be considered for the experimental design and development of new therapeutics for the treatment of ED. Also, it is further suggested that biological investigations like *in vivo* and *in vitro* studies are to be considered for more clarity.

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Competing interests

The authors declare no conflict of interest.

Ethical Protocol

Not applicable

Availability of Data and Materials

Nil

Authors' Contributions

This work was carried out in collaboration with all authors. Authors OOE and MOA designed the work. Authors MOA, EBA, FC, IAO, and OOE did the laboratory work. Author MOA performed the statistical analysis and drafted the manuscript. Authors OO and OOE edited the manuscript.

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