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Spectroscopic Analysis, Aphrodisiac Potential of *Carapa Procera* Stem Bark Extract in Male Wistar Rats and *In Silico* Studies of Hexadecanoic and Oleic Acids on Phosphodiesterase-5 and Adenylcyclase Enzymes

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ABSTRACT

Background: *Carapa procera D.C Meliaecae* is a medicinal plant used by the Ijaw in the management of erectile dysfunction in men. The aim was to assess the aphrodisiac effect of *Carapa procera* in male Wistar rats.

Materials and Method: The crude stem bark was assessed for elemental content and aphrodisiac effect using the physical behavioral mating method. The extracts were administered mg/kg/day for 7 days. On the 8th day male Wistar rats were sacrificed, liver, kidney, testis, seminal vesicle, epididymis, and vas deferens were harvested, weighed, and testes were subjected to histological appraisal. Purification of the dichloromethane fraction of the stem bark using chromatographic techniques yielded Sample A_1.

Results: The aphrodisiac assay in male Wistar rats showed that the extracts reduced mount latency at $p<0.05$-0.001. It also affects intromission latency at $p<0.001$. The DCMb, HDcb, and STD significantly reduced PEI at $p<0.05$-0.01, this proved the aphrodisiac potential of the extracts. It displayed 16 carbon atoms as revealed by ^{13}C NMR spectroscopy. Fourteen methylene, methyl (Sp^3), and quaternary carbon (Sp^2) signals. The ^1H-NMR further confirmed the assignment of these signals; 2.73 (J = 8.0) showed triplet assigned to C-2, multiplet at 1.65 ppm assigned to C-3 position, and due to 2H and intense peak appearing as multiplet at 1.27 ppm integrated for 20 protons assigned (C-4 to C-13) position and triplet at 0.90 ppm assigned to C-16. The spectrum showed a carbonyl group of carboxylic acid appearing at δ 179.9 ppm affording the most deshielded carbon. The IR spectra also revealed a diagnostic peak at 1781 cm^{-1} due to the carbonyl group of carboxylic acid and a signal at 2914.8 and 2847.7 cm^{-1} due to the C-H stretch. The GC-MS analysis showed a molecular ion peak of 256 due to $C_{16}H_{32}O_2$.

Conclusion: The extract of *Carapa procera* enhanced sexual indices in male albino Wistar rats. This corroborates the use of *Carapa procera* stem bark in ethnomedicine as an aphrodisiac agent Sample A1 (-4.4) and had a binding affinity lower than the standard drug sildenafil (-6.5) against the Phosphodiesterase enzyme while in adenyl-cyclase enzyme model; Alprostadil, Oleic acid and hexadecanoic acid had a binding affinity (-6.35, -2.61 and -1.48) respectively.

Keywords: *Carapa Procera*; Aphrodisiac; Phosphodiesterase; Adenyl Cyclase; Hexadecanoic Acid; Spectroscopic Analysis

Abbreviations: BM: Basal Membrane; cAMP: Cyclic Adenosine Monophosphate; CDCl3 Deutrated Chloroform; DCMb: Dichloromethane Fraction; DEPT: Distortionless Enhanced Polarisation Transfer; EF: Erection Frequency; EL: Ejaculatory Latency; HDcb: High Dose Crude Extract; HMBC: Heteronuclear Multiple Bond Correlation; HMQC: Heteronuclear Multiple Quantum Coherence; IL: Intromission Latency; IF: Intromission Frequency; ISS: Interstitial Spaces; MDcb: Median Dose Crude Extract; MF: Mount Frequency; ML: Mount Latency; NIST: National Institute of Standard and Technology; PE: Penile Erection; PEI: Post Ejaculation Interval; VLC: Vacuum Liquid Chromatography

Introduction

Carapa procera D.C Meliaecae is a species of forest tree of about 17 m high in swampy forest. These species are widely distributed from Senegal to Angola and East Africa, as well as in tropical America in the Amazon [1]. The stem bark is used in folkloric medicine to treat paralysis, epilepsy, skeletal spasms, and eye problems and as a genital stimulant [1,2]. All parts of the plants are bitter which is due to terpene called meliacins [3]. Male impotence also called sexual dysfunction is a common medical condition that affects the sexual life of millions of men worldwide and is a serious medical and social problem that occurs in 10-52% of men. This could be a result of social or biological issues such as; loss of libido, problems with ejaculation, and failure of the testicles to produce the normal quantity of male sex hormones. This could be a very distressing condition for men socially, and biologically and may lead to a loss of self-esteem [4]. The use of *Carapa procera* for the management of impotence in folkloric medicine could lead to the isolation of novel or existing compounds with a new mechanism of action [5].

Materials and Methods

Materials

Chemicals/Reagents: All chemicals and reagents used are of analytical grade: sigma and JHD products and reputable Pharmaceutical companies. Methanol (Sigma-Aldrich U.K), Dichloromethane (JHD) n-Hexane (Sigma-Aldrich U.K) Ethylacetate (Sigma-Aldrich U.K), Dimethylsulphoxide (Sigma-Aldrich U.K), Sephadex LH-20 (Sigma-Aldrich U.K), Silica gel 200-400 (Sigma-Aldrich U.K), Tween 80 (JHD), Testosterone (Testost™, Embassy Pharmaceutical, Nigeria), Oestradiol benzoate 10 mg/ml (Naman Pharma Drugs, India), Progesterone 25 mg (Pauco Pharmaceutical, Nigeria), Corn oil (Atara edible oil Ltd).

Methods

Collection and Identification of Plant Materials: The fresh stem bark was collected from the wild at Otabi Community in Ogbia Local Government Area of Bayelsa State. It was identified and authenticated at the Forestry Research Institute of Nigeria, Ibadan, and Herbarium number FHI 112975 was assigned.

Extraction: About 3271 g of the powder stem bark was extracted successively using n-hexane, dichloromethane, and 70% methanol (4x2.5L) respectively, for The extracts were concentrated at 50oC in vacuo and were subjected to phytochemical screening using standard procedures (Figure 1).

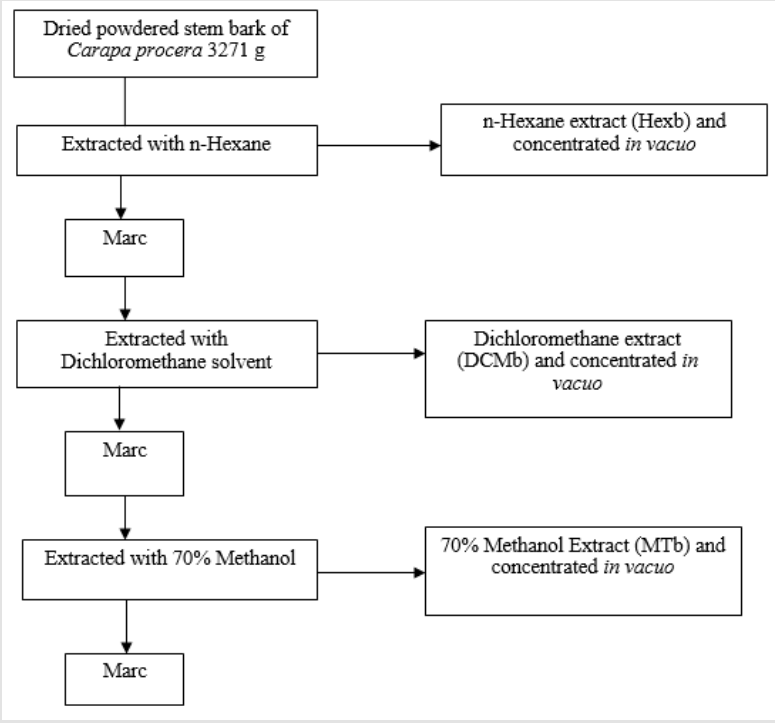

Figure 1: Extraction scheme of stem bark of Carapa procera.

Experimental Animals: Forty-eight matured male albino rats of about twelve weeks old weighing between 130-281 g were used for the experiment. They were kept in a well-ventilated conventional cage 28-31°C, photoperiod of darkness for 12 hours and 12 hours of natural light. The animals were allowed to acclimatize for two weeks were fed on a standard diet and had free access to water. The experiment was carried out according to the standard laboratory conditions as approved by the animal's ethical committee of the University [5-7]. The animals were divided into eight groups of six animals per group.

Aphrodisiac Assay: Based on the LD50, the crude extract was administered at a dose of 44.72, 89.44, and 134.16 mg/ kg, and the fractions given a median dose (89.44 mg/kg) of the fractions were administered. Group I and II were given 10 mL and 1 mg/kg of distilled water and testosterone administered subcutaneously respectively. Groups III to V were administered crude extract at 44.72, 89.44, and 134.16 mg/kg respectively. Groups VI to VIII were given 89.44 mg/kg of n-hexane, dichloromethane, and 70% methanol fractions daily for 7 days respectively. The female rats were brought to oestrus by the sequential administration of 17β-oestradiol (8 ug/kg, and progesterone 500 µg/kg) were given through subcutaneous injections, 48hrs and 4 hrs respectively before pairing [7,8]. Sexual behavior assessment was conducted using male rats on receptive females and the male exhibiting low sexual activity was excluded from the experiment. The following parameters were determined, Mount Latency (ML), Intromission Latency (IL), Ejaculatory Latency (EL), Mount Frequency (MF), Intromission Frequency (IF), Penile Erection (PE), Post Ejaculation Interval (PEI), Erection Frequency (EF), by adopting standard procedures [7,9]. The organs and tissues were collected, weighed, and tested preserved in 10% (v/v) formalin were subjected to histological analysis [10].

Isolation of Dichloromethane Fraction: About 20 g of dichloromethane fraction was subjected to Vacuum Liquid Chromatography and the following solvent system was gradiently eluted from n-hexane (100%) to methanol 100%. Fractions 4-5 gave a similar spot on TLC in a solvent system n-hexane: ethylacetate (7:3) and were pooled together and weighed 3.327g. This was subjected to gel filtration using a column (72.5 cm x 1.3 cm) and Sephadex LH-20 (25 g) as the stationary phase. Elution commences isocratically, using dichloromethane, 20 mL of the eluent was collected and 21 fractions were obtained based on the TLC in a solvent system n-hexane; ethylacetate (5:1), fraction 8-14 were pooled together weighed 0.563 g. This was further purified using silica gel (120 g, 200-400 mesh) in column chromatography and elution commences gradiently using n-Hexane; Ethylacetate (95:5) to Ethyl acetate (100%), 20 mL of the eluent was collected. Fractions 8-11 were pooled together and weighed about 0.191 g. It was further subjected to purification using a silica gel (20 g, 200-400 mesh) in a column (72.5 x 1.3 cm) and elution commenced gradiently from n-hexane (100%) to ethylacetate (100%). Fraction 19 gave a single spot in a solvent system n-Hexane: Ethylacetate (9:4), and weighed 26.1 mg. It was subjected to spectroscopic studies to elucidate the structure.

GC-MS and IR Analyses of the Samples: n- Hexane fraction, Fractions A_2, A_3, and A_4 dichloromethane extract of the Stem bark obtained from VLC, were subjected to Gas Chromatography Mass Spectrometry for determination of chemical constituents as shown in Table 1-3.

Table 1: GC-MS analysis of fraction A_2 obtained from dichloromethane (DCMb) extract.

S/N	Chemical Formula	Name	RT	Area (%)
1.	$C_{12}H_{24}$	1-Dodecene	9.444	0.40
2.	$C_{14}H_{30}$	Tridecane	9.603	0.34
3.	$C_{19}H_{38}$	1-Nonadecene	12.225	0.14
4.	$C_{15}H_{30}O_2$	Ethyltridecanoate	12.346	0.35
5.	$C_{16}H_{32}$	1-Hexadecene	12.560	2.08
6.	$C_{16}H_{34}$	2-methy lPentadecane	12.692	0.70
7.	$C_{16}H_{32}$	1-Decylcyclohexane	13.539	0.54
8.	$C_{10}H_{23}NO$	O-Decylhydroxylamine	14.142	0.30
9.	$C_{28}H_{56}O_2$	Heptacosanoic acid methyl ester	14.285	0.31
10.	$C_{14}H_{28}$	1,5-diisopropyl-2,3-dimethylcyclohexane	14.432	0.25
11.	$C_{16}H_{32}O_2$	n-Butyl Laureate	15.151	0.67
12.	$C_{16}H_{32}O_2$	Myristic acid ethylester	15.266	0.51
13.	$C_{18}H_{36}$	1-Octadecene	15.493	2.85
14.	$C_{20}H_{40}$	2-Methyloctadecane	15.595	0.80
15.	$C_{13}H_{26}O$	6,10-dimethyl undecan-2-one	16.021	0.34
16.	$C_{17}H_{34}O$	9-Heptadecanone	16.456	3.26
17.	$C_{16}H_{34}$	Decylcyclohexane	16.525	0.30
18.	$C_{15}H_{30}O_2$	Ethyltridecanoate	16.650	0.34

19.	$C_{17}H_{34}O_2$	Methylhexanoate	17.110	2.45
20.	$C_{16}H_{22}O_4$	DibutylPhathalate	17.280	0.14
21.	$C_{14}H_{24}O_3$	Oxacyclotetradecane	17.401	2.41
22.	$C_{18}H_{36}O_2$	n-Butylmyristate	17.835	0.26
23.	$C_{18}H_{36}O_2$	Ethylhexanoate	18.105	7.90
24.	$C_{17}H_{32}O$	E-15-Heptadecenal	18.210	2.65
25.	$C_{18}H_{38}$	n-Octadecane	18.285	1.98
26.	$C_{19}H_{38}O_2$	Isopropylpalmitate	18.388	0.19
27.	$C_{19}H_{38}O_2$	Propylhexanoate	19.271	3.68
28.	$C_{19}H_{36}O_2$	Methyloctadec-10-enoic acid	19.381	1.25
29.	$C_{19}H_{38}O$	Methylstereate	19.716	0.77
30.	$C_{18}H_{34}O$	3,13-Octadien-1-ol	20.195	14.8
31.	$C_{20}H_{40}O_2$	2-methylpropylhexadecanoic acid	20.512	13.0
32.	$C_{20}H_{40}$	1-Eicosene	20.685	1.90
33.	$C_{19}H_{40}$	2-Methyloctadecane	20.752	0.53
34.	$C_{12}H_{24}O_2$	3-Methylbutylheptanoate	21.104	0.80
35.	$C_{20}H_{36}O_2$	Ethyloctadecan-9,12-dienoate	21.215	0.33
36.	$C_{28}H_{54}O_2$	Decyloleate	21.305	0.56
37.	$C_{20}H_{40}O_2$	Tertbutylpalmitate	21.600	1.10
38.	$C_{19}H_{38}$	n-Tridecylcyclohexane	21.753	0.30
39.	$C_{19}H_{34}O_2$	Methylocta-9,11-dienoate	21.928	0.28
40.	$C_{26}H_{52}O_2$	Decyloleate	22.023	0.40
41.	$C_{21}H_{38}O_4$	2,3-dihydroxypropyl-9,12-Octadienoate	22.515	4.89
42.	$C_{28}H_{54}O_2$	Oleic acid	22.662	4.80
43.	$C_{22}H_{44}O_2$	2-Methylpropyl Octadecanoate	22.985	4.33
44.	$C_{21}H_{44}O$	1-Heneicosanol	23.205	0.66
45.	$C_{24}H_{50}$	Tricosane	23.285	0.28
46.	$C_{14}H_{26}O$	2-Cyclododecylethanone	23.345	0.15
47.	$C_{14}H_{22}O_3$	4-Decenyl furan 2,5-dione	24.172	0.86
48.	$C_{20}H_{38}$	1,11-Eicosadiene	24.295	0.28
49.	$C_{26}H_{52}$	Eicosylcyclohexane	24.394	0.13
50.	$C_{24}H_{38}O_4$	Di-OctylPhathalate	24.805	4.63
51.	$C_{19}H_{36}O$	2-Methyloctadeca-3,13-dienol	25.068	1.41
52.	$C_{30}H_{58}O_2$	Tetradecyl-9-hexadecenoate	25.391	3.32
53.	$C_{24}H_{48}O_2$	Ethyl docosanoate	25.515	0.39
54.	$C_{27}H_{56}O$	Heptacosanol	25.664	0.37
55.	$C_{24}H_{34}O_2$	Methyl eicosatetraenoate	27.071	0.62
56.	$C_{20}H_{36}O_2$	6,7-Octadecadienylacetate	27.283	0.78
57.	$C_{18}H_{36}O_2$	Butylmyristate	27.732	0.35
58.	$C_{26}H_{52}O_2$	Ethyltetracosanate	27.805	0.28

Table 2: GC-MS analysis of fraction A_3 of dichloromethane extract of stem bark of *C. procera*.

S/N	Chemical Formula	Name	RT	Area (%)
1.	$C_{14}H_{22}O$	3,5-bis(1,1-dimethylethyl)-Phenol	11.725	0.56
2.	$C_{15}H_{26}O$	2-Napthalene methanol	13.315	0.46
3.	$C_{23}H_{38}O_3$	3-acetoxy-20-Hydroxypregnane	14.430	3.87
4.	$C_{12}H_{24}$	Dodecene	14.540	0.96
5.	$C_{20}H_{30}O_4$	Butyloctyl-3-ylPhthalate	15.945	0.83
6.	$C_{11}H_{20}O_2$	Hydroxyundecanoic acid	16.050	1.14
7.	$C_{18}H_{48}O_2$	Ethylhexadecanoate	16.395	2.32
8.	$C_{15}H_{32}O_2$	2-dodecyl-1,3-propanediol	16.516	1.27
9.	$C_{10}H_{20}$	IsobutylCyclohexane	17.360	0.77
10.	$C_{18}H_{32}O_2$	9-Octadecynoic acid	17.990	2.04
11.	$C_{18}H_{30}O_2$	Linolenic acid	18.08	9.36
12.	$C_{20}H_{40}O_2$	Hexadecanoic acid 1,1-dimethylethylester	18.235	4.09
13.	$C_{18}H_{46}O_2$	Ethylhexadecanoate	18.305	0.73
14.	$C_{15}H_{32}O_2$	Dodecyl 1,3-Propanediol	18.420	1.07
15.	$C_{25}H_{42}O_2$	10,12-Pentacosadiynoic acid	18.950	3.14
16.	$C_{28}H_{46}O$	Cholestan-8,24-dien-3-ol	19.140	0.97
17.	$C_{10}H_{18}O_2$	2-Decenoic acid	19.455	0.87
18.	$C_{14}H_{22}O_3$	3-dec-2-enyl Furan 2,5-dione	19.725	2.28
19.	$C_{18}H_{34}O$	9-Octadecenal	19.780	2.74
20.	$C_{24}H_{46}O_2$	Oleic acid hexylester	20.010	9.04
21.	$C_{23}H_{42}O_2$	1-Heptadec-1-ynlcyclohexanol	20.185	0.73
22.	$C_8H_{12}O_2$	7-Oxabicyclo [4.1.0] heptane-3-oxirane	20.935	4.31
23.	$C_{24}H_{38}O_4$	DioctylPhthalate	21.245	24.09
24.	$C_{20}H_{36}O_2$	5,7-Octadecadienylacetate	21.290	5.73
25.	$C_{20}H_{36}O_2$	6,13-Octadecadienylacetate	21.440	4.60
26.	$C_{20}H_{30}O_5$	Andrographolide	21.530	1.34
27.	$C_{24}H_{46}O_2$	Oleic acid hexylester	21.650	6.52
28.	$C_{16}H_{32}Cl_2$	1,6-dichlorohexadecane	21.705	3.10
29.	$C_8H_{10}N_6S$	Thiazole-4-Carboximidamide	22.995	1.08

Table 3: GC-MS Analysis of A_4 (16-19) obtained from dichloromethane.

S/N	Chemical Formula	Name	RT	Area (%)
1.	$C_{16}H_{30}O_2$	11-Cylopentylundecanoic acid	9.155	10.29
2.	$C_{10}H_{20}O_2$	n-Decanoic acid	10.259	7.46
3.	$C_{19}H_{38}O_2$	Nonadecanoic acid	12.360	7.59
4.	$C_{16}H_{34}$	2-Methylpentadecane	13.780	2.41
5.	$C_{18}H_{38}$	2-methylheptadecane	14.617	2.57
6.	$C_{12}H_{14}O_4$	2-(isobutoxycarbonyl)benzoic acid	15.00	9.99
7.	$C_{17}H_{24}O_3$	7,9-diisobutyloxaspiro (4,5)-deca-6,9-diendione	15.556	8.82
8.	$C_{20}H_{42}$	2-methylnonane	16.599	3.58
9.	$C_{14}H_{30}$	2-Methyltridecane	17.563	5.21
10.	$C_{12}H_{26}O$	5,9-Dimethyldecanol	19.721	30.55
11.	$C_{25}H_{52}$	2-Methyltetracosane	19.802	11.5

Molecular Docking of the Isolated Compounds: The isolated compounds were subjected to molecular docking against the phosphodiesterase enzyme. Hexadecanoic acid, Oleic acid, and Sildenafil Citrate were designed with ChemDraw Pro 12.0 (Cambridge Soft Corporation, USA) and saved in SDF format. The Phosphodiesterase V enzyme was downloaded in PDB format from the Protein data bank (http://www.rcsb.org/pdb/home/home.do). Ligands and targets were converted to pdbqt format using PyRx (https://pyrx.sourceforge.io/). Molecular docking of the ligands with each of the target proteins was done using Autodock Vina (http://vina.scripps.edu/), to obtain their respective binding affinity. Discovery Studio (Dassault Systèmes), and Ligplot (https://www.ebi.ac.uk/thorntonsrv/software/LIGPLOT/) were used to analyze ligand-protein binding interactions. Calculated molecular properties were obtained from the molinspiration website (https://www.molinspiration.com/cgi-bin/properties), while pharmacokinetic inetic properties from pKCM website (http://biosig.unimelb.edu.au/pkcsm/prediction); [11]. The ligand alprostadil, oleic, and hexadecanoic acids against Enzyme/protein ID: 8C0T and docking score recorded respectively as shown in Table 4 [12].

Table 4: GC-MS analysis of n-hexane extracts of stem bark.

S/N	Chemical Formula	Name	RT	Area (%)
1.	$C_{10}H_{16}O$	Carveol	3.753	0.95
2.	$C_{10}H_{14}$	4-ethyl-1,2-dimethylbenzene	4.128	1.04
3.	$C_{10}H_{12}$	Methanoindene	4.251	1.23
4.	$C_{11}H_{10}O$	Cycloprop[a]inden-6-ol	4.319	2.22
5.	$C_{17}H_{24}O$	Falcarinol	4.521	4.97
6.	$C_{15}H_{32}$	Pentadecane	4.750	1.01
7.	$C_{17}H_{36}O$	n-Heptadecanol	5.848	0.79
8.	$C_{19}H_{40}$	6-methyloctadecane	6.219	1.73
9.	$C_{17}H_{32}O$	E-15-Heptadecenal	6.246	0.79
10.	$C_{17}H_{34}O$	9-Heptadecanone	6.965	2.87
11.	$C_{16}H_{32}O$	Hexadecanoic acid	7.284	1.19
12.	$C_{18}H_{36}O_2$	Ethylhexadecanoate	7.636	4.86
13.	$C_{15}H_{30}O_2$	Pentadecanoic acid	7.726	8.60
14.	$C_{18}H_{32}O_2$	Octadecadienoic acid	8.116	0.77
15.	$C_{20}H_{40}O_2$	Butylhexadecanoate	8.409	8.51
16.	$C_{18}H_{30}O_2$	9,12,15-Octadecatrienoic acid	8.487	8.12
17.	$C_{20}H_{40}$	1-ethenyloxy-Octadecane	8.566	9.19
18.	$C_{21}H_{40}O_4$	9-Octadecenoic acid, 2-hydroxymethyl) ethylester	8.663	5.07
19.	$C_{22}H_{44}O_2$	Propyloctadecanoate	9.132	0.94
20.	$C_{20}H_{38}O_4$	E-9-Octadecenoic acid ethyl ester	9.529	3.83
21.	$C_{24}H_{38}O_4$	Octylphathalate	9.672	1.03
22.	$C_{19}H_{36}O$	14-methyloctadec-5,16-dien-1-ol	9.773	2.04
23.	$C_{32}H_{62}O_2$	9-Hexadecanoic hexadecylester	10.440	1.29
24.	$C_{26}H_{54}$	3-ethyl-5-(2-ethylbutyl)-octadecane	10.965	10.9
25.	$C_{20}H_{34}O_2$	8,11,14-Eicosatrienoic acid	11.096	1.01
26.	$C_{23}H_{38}O_3$	20-hydroxylPregnane-3-acetate	11.272	4.39

Statistical Analysis

The results obtained were expressed as multiple comparisons of Mean ± S.E.M. Significance was determined using one-way ANOVA followed by Tukey Kramer multiple comparison post-test with a $p < 0.05$ was considered significant [5,7,13].

Discussion

Extraction and Phytochemical Analysis

The yield obtained from stem bark extracts were 0.5%, 0.83%, and 1.0% for n-hexane, dichloromethane, and 70% methanol fractions respectively, while the stem bark crude extract yielded 4%.

Phytochemical screening of the stem bark revealed the presence of coumarin, cardiac glycoside; terpenes, tannins, and saponins however, alkaloids, carbohydrates, and flavonoids were absent in stem bark extracts [14,15].

Aphrodisiac Assessment

Aphrodisiac evaluation of the stem bark extracts revealed an increase in sexual indices of vigor, libido, and potency. The standard drug (testosterone); LDcb, HDcb, and MTb fraction significantly reduced the mount latency at p<0.01 and 0.001 when compared to control as shown in Table 5. The STD and MDcb significantly reduced the mount frequency at p< 0.05. The intromission latency; STD, LDcb, MDcb, and HDcb significantly decreased the IL at p< 0.001 compared to the control. This showed that *Carapa procera* stem bark extracts significantly enhanced sexual function [8]. STD, LDcb, MDcb and dichloromethane fraction significantly reduced the ejaculation latency at p<0.05-0.001 when compared to control respectively. These are in line with results obtained from the literature [7,9,16,17]. The post-ejaculatory interval is the time taken for the male animal to recover from the depressive effect of ejaculation and subsequent intromission with the female rats. The STD, LDcb, MDcb, HDcb, and DCMb significantly reduced the post-ejaculation interval at p < 0.05 and 0.001 when compared to control as shown in Table 5 [7,16,18]. This ratify that the extracts could reduce the depressive effect of ejaculation and would make the animals have erections for intromission and increase pleasure and satisfaction by both partners [19]. The increase in sexual activity could be due to an increase in the concentration of several anterior pituitary hormones, and dilation of the blood vessel to supply the penile organ which could be due to the inhibition of phosphodiesterase enzyme and potentiates serum testosterone which could stimulate dopamine receptor and sexual behavior [20-21]. Penile erection, the time required for the experimental rats to have an erection after ejaculation characterized by licking of the penile organ is significantly decreased at p<0.05-0.001 for LDcb, MDcb, HDcb, n-Hexane, dichloromethane, and 70% Methanol fractions when compared to control as shown in Table 5.

Table 5: Aphrodisiac assay of stem bark extracts of *Carapa procera*.

Sample	ML(Sec)	MF	IL(Sec)	IF	EL(Sec)	PEI(Sec)	EF	PE(Sec)
VEH	86.0±20.01	17.17±1.91	215.83±62.49	11.83±0.87	761.83±69.89	1037±42.35	1.67±0.33	973.0±51.46
STD	14.83±2.02^{c}	9.67±2.45^{a}	19.17±2.18^{c}	7.00±1.92	345.17±103.61^{a}	683.50±42.24^{a}	1.50±0.34	651.67±47.84
LDcb	24.00±7.75^{b}	11.33±1.41	35.67±12.91^{c}	9.83±1.66	216.67±37.55^{c}	433.50±50.39^{c}	2.00±0.26	419.33±50.44^{c}
MDcb	36.50±11.29	10.00±0.77^{a}	42.17±12.58^{c}	8.83±1.10	323.83±44.88^{b}	700.67±51.27^{a}	1.83±0.31	626.83±49.49^{a}
HDcb	19.50±5.05^{c}	14.00±1.37	24.00±4.81^{c}	10.33±1.76	399.33±102.63	630.50±110.68^{b}	3.31±0.31^{c}	614.17±110.12^{a}
n-Hexb	70.67±7.91	14.83±1.78	126.33±26.71	10.67±1.75	925.33±134.95	1323.0±123.75	1.17±0.17	1306.8±122.93^{a}
DCMb	109.17±9.66	13.50±0.62	116.17±8.96	10.17±0.31	319.0±21.67^{b}	648.50±26.62^{a}	2.17±0.31	613.33±30.98^{a}
MTb	26.83±2.44^{b}	14.83±0.70	32.33±2.87	11.83±0.60	500.17±63.95	721.33±67.29	1.67±0.33	623.0±57.88^{a}

Note: Values represent Mean ± SEM, Significance relative to control; ap<0.05, bp<0.01, cp<0.001, (n = 6)

Keys; VEH= Distilled water (10ml /kg), STD = Standard drug (Testosterone 1 mg/kg), LDcb = Low Dose Crude Extract (44.72 mg/kg), MDcb = Median Dose Crude Extract (89.44 mg/kg), HDcb = High Dose Crude Extract (134.16 mg/kg), n-Hex = n-Hexane fraction (89.44 mg/kg), DCMb = Dichloromethane fraction (89.44 mg/kg) and MTb = 70% Methanol fraction (89.44mg/kg).

The High dose of the crude extract significantly increased the erection frequency at p<0.01 these are following standard literature [7,22,23]. The presence of 3-acetoxy-20-hydroxypregnane, linolenic acid, Furan, 2,5-dione, oleic acid hexylester, andrographolide and 3-Hydroxycholestan-8,24-diene, 4-decenylfuran-2,5-dione, 7,9-di-isobutyloxaspiro(4,5)-deca-6,9-diendione and 20-hydroxylpregnane-3-acetate could enhance the sexual effect of DCMb as revealed by the GC-MS analysis of n-hexane extract (Table 4) and A_2 (Table 3), A_3 (Table 1), A_4 (Table 2) fractions obtained from chromatographic fractionation of DCMb extracts. The median dose of the crude extracts significantly increased the weight of the animals at p<0.05 compared to the control, which could be due to the anabolic effect of the extracts (Table 6). The standard drug (Testosterone), Low-dose crude extract and dichloromethane fraction significantly increased the weight of the liver at p<0.05, 0.001, and 0.01 respectively which could be a sign of toxicity. The stem bark extract did not have any significant effect on the weight of the testes, epididymis, kidneys, and vas deferens. The extracts showed an insignificant effect on the weight of the seminal vesicle, however, dichloromethane increased significantly the weight of the seminal vesicle at p<0.05. This could be due to enhanced sperm production due to the effect of steroids and triterpenes presence [7,19].

Table 6: Effect of stem bark extract of Carapa procera on organs and tissues.

Sample	IW	WAT	LV	Testes	EPID	KID	VD	SV(g)
VEH	168.17±7.30	158.0±4.89	4.96±0.21	2.36±0.15	1.77±0.16	1.10±0.04	0.12±0.01	0.48±0.08
STD	170.17±9.14	162.50±8.80	5.50±0.16[b]	2.46±0.14	1.61±0.16	1.09±0.03	0.13±0.01	0.96±0.11
LDcb	198.0±6.33	183.83±7.36	6.52±0.39[c]	2.60±0.06	2.67±0.23	1.25±0.05	0.11±0.01	0.52±0.06
MDcb	197.67±5.75	200.67±6.77[a]	6.94±0.39	2.59±0.11	2.76±0.33[a]	1.29±0.03	0.12±0.01	0.48±0.08
HDcb	212.0±9.41	184.0±7.25	5.65±0.19	2.52±0.12	2.48±0.27	1.23±0.04	0.15±0.01	0.72±0.12
n-Hexb	165.50±6.38	164.0±6.39	6.54±0.19	2.38±0.08	1.71±0.16	1.51±0.42	0.12±0.01	0.63±0.02
DCMb	187.0±4.75	196.83±4.95[a]	6.52±0.31[b]	2.53±0.09	2.16±0.06	1.29±0.07	0.16±0.01	1.03±0.07[a]
MTb	204.50±14.0	192.17±14.23	5.36±0.35	2.53±0.08	2.72±0.23	1.22±0.07	0.16±0.01	0.98±0.11

Note: Values represent Mean ± SEM, Significance relative to control; ap<0.05, bp<0.01, cp<0.001, (n = 6).

Histological Assessment of Stem Bark

The histological assessment of the testis showed the presence of spermatogonia, spermatozoa in seminiferous tubules, and Leydig cells, but interstitial space is normal compared to control (distilled water), and the standard drug (testosterone) administered daily for 7 days (Figure 2).

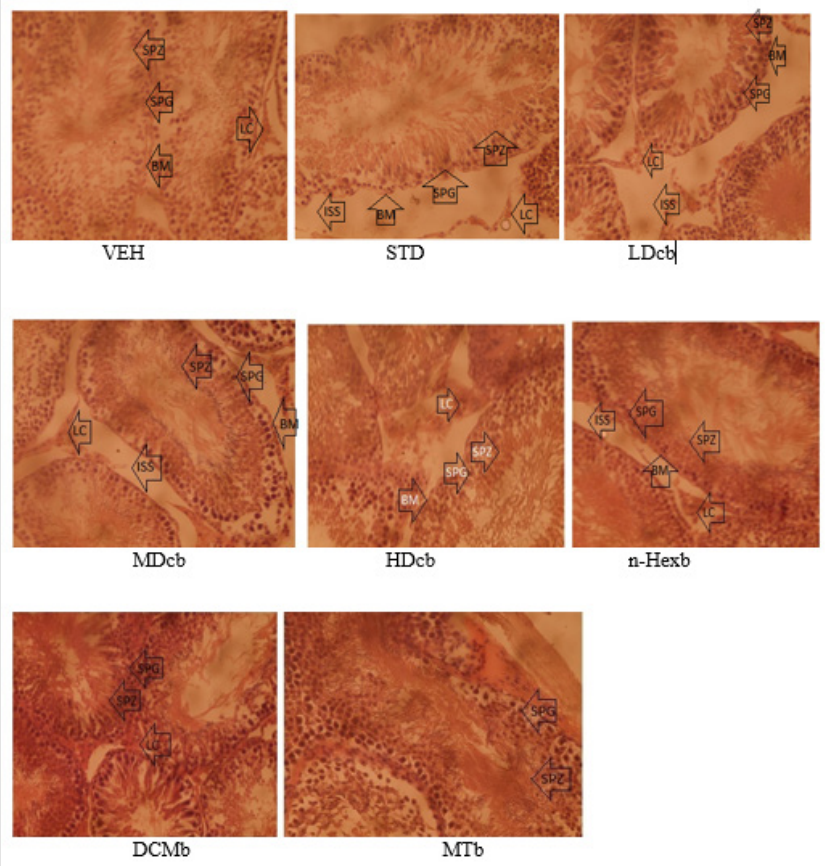

Figure 2: Histological effect of stem bark extracts and fractions of Carapa procera on the testis (H&Ex400).
Keys: BM = Basal Membrane, SPG =Spermatogonia, SPZ = Spermatozoa, ISS = Insterstitial Spaces, LC = Leydig cells.

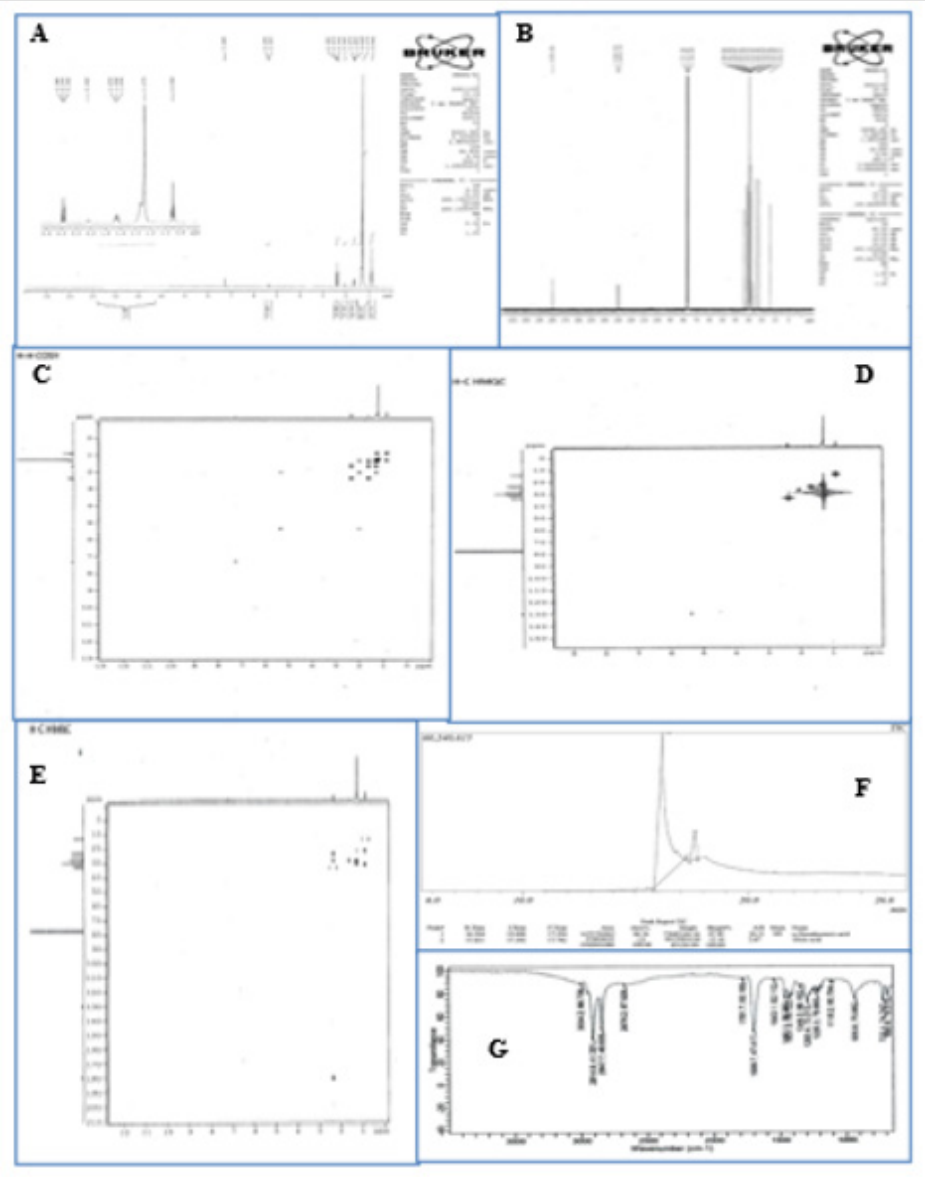

Figure 3: Spectroscopic features of the plant extracts: A: 1H-NMR, B: 13C-NMR, C: H-H COSY, D: H-C HMQC, E: H-C HMBC, F: GC Chromatogram, G: IR of Sample A1.

Spectroscopic Analysis

The proton NMR spectrum of the compound (Sample A_1) exhibited four prominent peaks. A signal at 2.37(J = 8.0 H3) integrating for 2H showed as a triplet and assigned to CH_2- attached to the C-2 position. This downfield chemical shift value is due to the deshielding effect by the neighboring carboxylic acid group. A multiplet at 1.65 was assigned to the CH_2 of carbon (C-3) position and integrated for 2H. An intense peak appearing as a multiplet at δ 1.27 integrated for 20 protons, representing long chain $(CH_2)n$ and assigned to position (C-4 to C-13) protons. A triplet at δ 0.90 integrating for 3H representing Sp^3 hybridized proton was assigned to position C-16. This confirmed the presence of the alkyl chain in fatty acid molecules. The ^{13}C NMR spectrum displayed 16 carbon atoms; Ten methylene (CH_2), Methyl, and a quarternary carbon signals. The spectrum showed a carbonyl group appearing at 179.9 ppm the most downfield carbon (C-1), this also showed an important correlation in H-C HMBC spectra, that the carbonyl carbon correlates with proton signal at 2.37 ppm assigned and attached to carbon at position C-2 Signal at δ 34.0 was assigned to carbon (C-2), signal δ 31.9, was assigned to C-3, signal δ 29.1-29.7 assigned to C-4 to C-13, a signal at δ 24.68 and 22.69 assigned to car-

bon (C14-15) respectively. The signal at δ 14.1 was assigned to C-16, terminating the alkyl fatty acid. This is also supported by the result of IR analysis showed prominent peaks at 1781 cm^{-1} due to the carbonyl group of carboxylic acid, 3004.2 cm^{-1} due to $=CH_2$ stretch, 2914.8 and 2847.7 cm^{-1} due to CH_2 and CH_3 stretch.

Sample A1 was subjected to GC-MS analysis revealed the presence of two peaks with a retention time (16.204 and 17.631) and percentage area (98.20 and 1.80) percent. This further revealed that sample A_1 contained hexadecanoic acid as the major constituent (98.20) and oleic acid (1.80) as a contaminant. This was ratified by the ^1H and ^{13}C-NMR spectra using $CDCl_3$ as a solvent which also served as an internal reference (^1H NMR shift value of residual proton at δ 7.29 ppm) as shown in Table 7 [24]. DEPT-45 displayed methine (CH), methylene (CH_2), Methyl (CH_3), and the absence of carbonyl or quarternary carbon. The ^1H NMR further revealed the presence of olefinic protons resonates at a narrow chemical shift δ 5.369 and δ 5.367 ppm [25]. This is also reflected on the ^{13}C-NMR spectra at δ 130.03 and δ 129.73 ppm due to the unsaturated ethylene group (CH=CH) due to the unsaturated oleic acid group. This was also reflected in the H-C HMQC corresponding to δ 5.369 and δ 5.367 ppm respectively. H-C HMQC further, revealed the absence of H-C correlation at δ 7.29 ppm as stated by Knothe and Kenar, 2004 [24]. The HMQC also revealed that carbon 34.02 and 31.93 ppm is attached to the H_2 proton at 2.37 ppm, and multiplet at δ 1.6 ppm to carbon δ 31.93 ppm. The intense peak at 1.27 ppm of ^1H-NMR is due to long-chain fatty acid corresponding to δ 29.6-29.06 ppm of the ^{13}C NMR. The carbon peak at δ 14.1 ppm is attached by (H_3) to 0.90 ppm of the proton which is triplet [26].

Table 7: ^1H and ^{13}C-NMR of Sample A_1 [26, 28, 30, 31, 32, 33, 34].

Position of Carbon	Sample A_1		Standard sample	
	^1H	^{13}C	^1H	^{13}C
	Ppm	ppm	Ppm	ppm
1		179.91		174
2	2.37 J =8.0, t	34.02	2.28 J = 8.0, t	34
3	1.6 5, m	31.93		24.4
4	1.27, m	29.69		C_{4-13} 29.0-29.8
5		29.67		
6		29.64		
7		29.59		
8		29.43		
9		29.36		
10		29.24		
11		29.06		
12		29.06		
13		29.06		
14		24.68		31.91
15		22.69		22.71
16	0.9	14.11	0.84	14.13

These are in line with H-H COSY. The oleic acid is a minor contaminant because it is colorless liquid oil at room temperature with a melting point (13-14°C) while hexadecanoic acid (60-62°C) melting point determined using gallenkamp melting point apparatus while the reference standard (62.9°C). The GC-MS analysis of sample A_1 (Table 4), gives a molecular ion peak of 256 due to $C_{16}H_{32}O_2$ and the elimination of C_2H_5 gives m/z = 29, and gives 227, and the elimination of methylene ion (CH_2^+ = 14); yield; 213; 199; 185; 171; 157; 143; 129; 115 and elimination of (OH^+ = 17) to give m/z = 98 [27-29]. This was compared with the NIST library. Based on the foregoing, sample (A_1) was proposed as hexadecanoic acid, and it was compared to previous literature (Figure 3) [26,28,30-34].

Molecular Docking

Molecular docking is used to predict the affinity of ligands against target proteins [35]. The binding affinity (kcal/mol) and interaction of sildenafil, hexadecanoic, and oleic acids are; -6.5, -4.4, and -4.5 respectively. The calculated molecular properties and interaction of the ligand with amino acid residues of phosphodiesterase enzyme as shown in Table 8, and Figure 4. This implies that sildenafil had a higher binding affinity when compared to hexadecanoic and oleic acid in inhibiting phosphodiesterase 5 enzyme [11,36,37] However, the Adenyl cyclase model, alprostadil may directly stimulate this enzyme by binding as an agonist on the EP2 receptor, which in turn activates adenylate cyclase leading to accumulation of 3'5'-cAMP which is responsible for therapeutic effect which include, smooth muscle relaxation and increasing peripheral blood flow. Alprostadil had a binding affinity of -6.35 when compared to oleic and hexadecanoic acid with a docking score of -2.61 and -1.46 respectively. This implies that alprostadil had a higher binding affinity compared to oleic and hexadecanoic acid in stimulating adenyl cyclase enzyme which is implicated in male erection as shown in Figure 5 [38]. The pharmacokinetics and calculated molecular properties (Table 9) [39], of the samples obeyed the Lipinski rule of five and implied the potential drug-like molecule of the samples [38].

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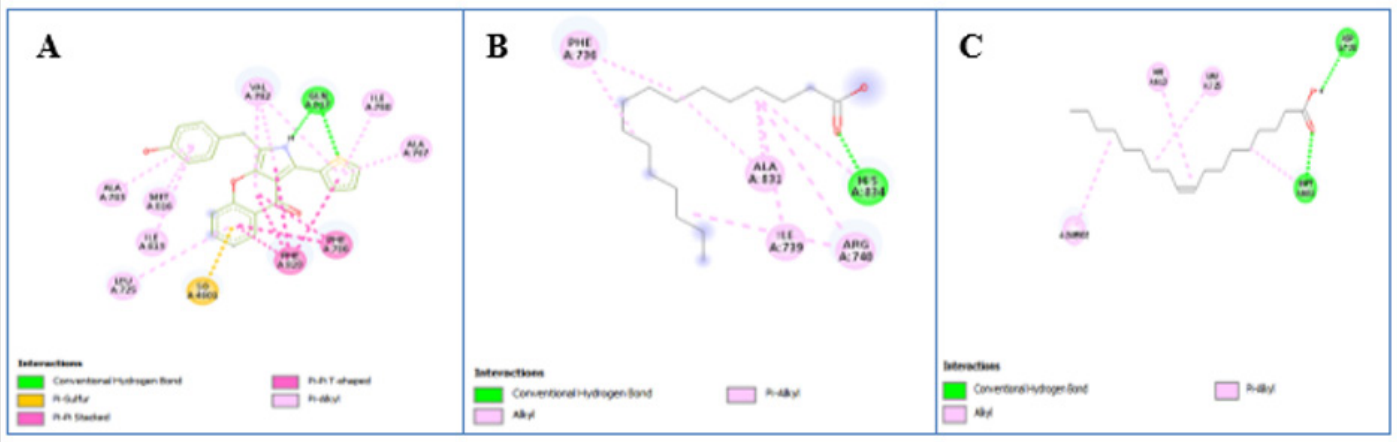

Figure 4: Interaction of ligand (2D) with amino acid residues of phosphodiesterase 5 enzyme. A: Sildenafil, B: Hexadecanoic acid, C: Oleic acid.

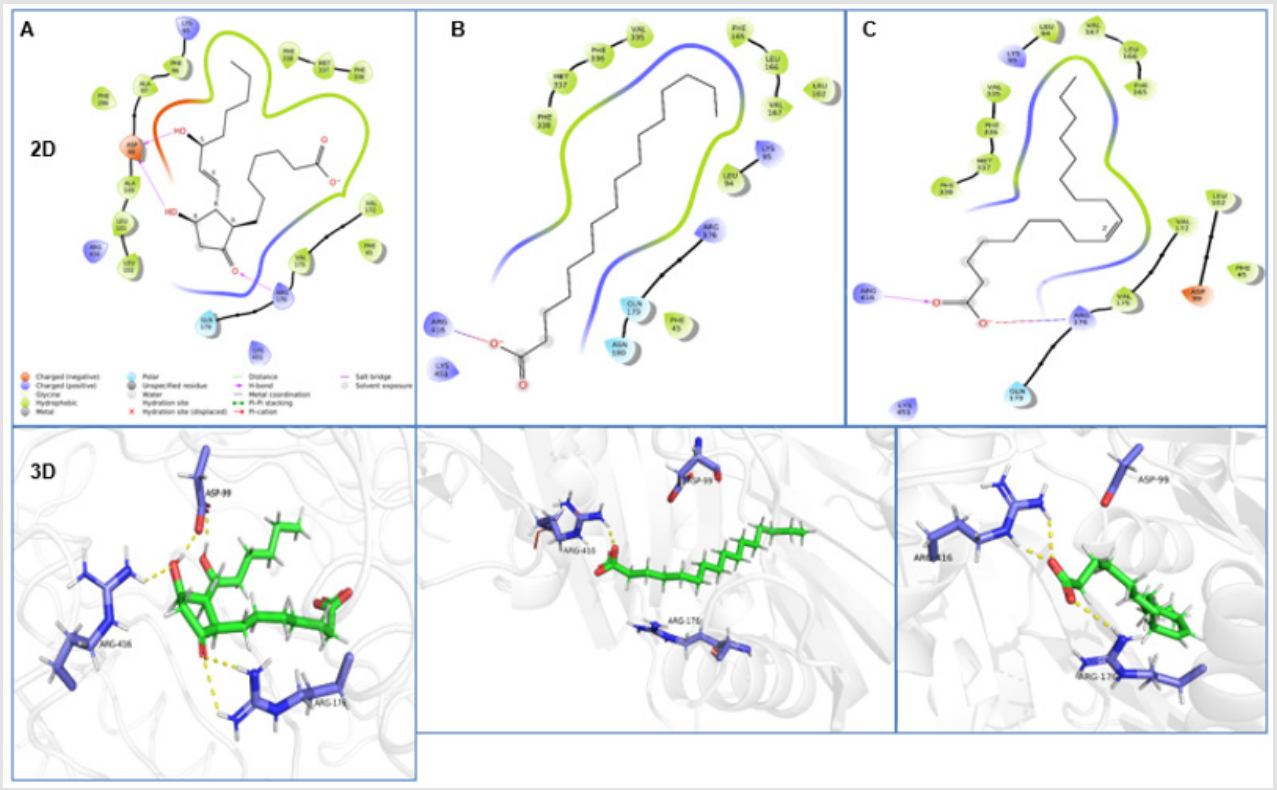

Figure 5: Molecular interactions of the test sample with protein residues, Adenyl cyclase enzyme; PDB ID: 8COT. Molecular docking was performed at pH: 7.0 ±2.0, with docking affinity scores of -6.35, -2.61, and -1.48 kcal/mol^{-1}, for Alprostadil (A), Hexadecanoic acid (B), and Oleic acid (C) respectively. The green cartoon in the 3D interactions represents the compounds, while the deep blue represents the protein ligands.

Table 8: Calculated molecular properties and binding affinity.

Ligand	Log P (< 5)	No. of Atom (C, N, O, S)	Molecular weight (< 500 g)	n ON Acceptor (< 10)	nOH NH donor (< 5)	N violators	Binding Affinity (kcal/mol)
Hexadecanoic acid	7.06	18	256.43	2	1	1	-4.4
Oleic Acid	7.58	20	282.47	2	1	1	-4.5
Sildenafil	-0.24	33	474.59	10	1	0	-6.5

Table 9: Pharmacokinetic Properties.

Ligand	Intestinal Absorption (Human) in %	Fraction Unbound (Human) (Fu)	CYP3A4 inhibitor	Total Clearance (log ml/min/kg)	AMES Toxicity	Max. Tolerated Dose (Human) (Log mg/ kg/ day)	LD_{50} (mol/kg)	Oral Rat Chronic Toxicity (Log mg/ kgbw/ day	Hepatotoxicity	Water Solubility (Log mol/L)
Palmitic acid (A)	-5.324	0.094	Yes	1.763	No	-0.818	1.595	3.173	No	-5.324
Oleic acid (B)	91.776	0.046	No	1.884	No	-0.943	1.604	3.251	Yes	-5.686
Sildenafil (C)	74.903	0.205	Yes	0.261	No	0.147	2.459	2.021	Yes	-3.045

Conclusion

The extract of *Carapa procera* enhanced sexual indices in male albino Wistar rats. This corroborates the use of *Carapa procera* stem bark in ethnomedicine as an aphrodisiac agent. It also ratifies that the best solvent for extraction to obtain an optimum aphrodisiac effect is 70% methanol.

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ADCO, ECJ, and EIM designed the research, the experiments were carried out by ADCO and AF while ECJ, and EIM supervised the studies. Molecular docking was performed by SJB. AF and ROR reviewed the manuscript. ADCO wrote the manuscript and performed data analysis. Vetted by ECJ and EIM, and proof read by all the authors.

Author Contribution

ADCO, ECJ, and EIM designed the research, the experiments were carried out by ADCO and AF while ECJ, and EIM supervised the studies. Molecular docking was performed by SJB and PAC, Data analysis and the manuscript were written by ADCO, Vetted by ECJ and EIM, and proofread by all the authors.

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Availability of Data and Material

Further data that support the findings of this study are available with the corresponding author, upon reasonable request.

Declaration

Ethics approval and consent to participate: Ethical approval was obtained from the animal ethical committee of the Department of Pharmacology and Toxicology, Faculty of Pharmacy, Niger Delta University on the Use of Laboratory, Animals and in line with international standard guidelines.

Consent for Publication

All Authors agreed to publish this article.

Conflict of Interest

No conflict of interest.

Guideline and Legislation on the Use of Medicinal Plants

Not applicable.

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