Analysis of the Chemical Constituents of Xylopia Aethiopica targeting the Progesterone Receptors for inhibiting the growth of Uterine Leiomyoma in-Silico approach

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ABSTRACT

Background: *Uterine leiomyoma also known as uterine fibroid is a disease that is characterized by a growth in the uterus of a woman especially during the child bearing age.*

Objectives: *The present work involves the extraction of the active chemical constituents of Xylopia aethiopica and the investigation of their anti-fibroid activities through molecular docking.*

Method: Fourier transform infrared spectroscopy (FTIR) and gas-chromatography mas spectrophotometry (GC-MS) experiments were used to identify the chemical constituents of ethanol extract of Xylopia aethiopica fruits, Computational molecular docking method was used to estimate the fibroid growth inhibiting property of the chemical constituents, density functional theory was used to calculate the molecular structures of the three constituents with the highest binding affinities and their drug-like properties, Pharmacokinetics, and pharmacodynamics properties were estimated using Absorption, Distribution, Metabolism, Elimination and Toxicity (ADMET) Screening methods.

Results: *The GC-MS experiments revealed some constituents which are associated with medicinal properties. The molecular docking result showed that Spathulenol showed a good binding score (-8.4 k cal mol^{-1}) which is very close to the control (Norethindrone: -8.5 kcal mol^{-1}). The density functional theory calculations and ADMET behaviors revealed that the extract constituents showed good drug activities, none was carcinogenic.*

Conclusion: *The results obtained showed that compounds contained in Xylopia aethiopica could be good candidates for fibroid growth inhibition.*

Keywords: *Uterine leiomyoma, Xylopia aethiopica. Molecular docking, density functional theory, Norethindrone*

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INTRODUCTION

Uterine leiomyomas (fibroids) are swellings in the women uterus that develop during the child bearing age (1-4). They are often benign gynecological lumps that grow from the proliferation of smooth muscle cells within the uterus (5-7). Research has shown that about 60-70% of every woman would develop fibroid at some point during their life time and majority of these cases would show no symptoms (8). Some risk factors include obesity, family history of the disease and early puberty in girls (9). There are no known specific symptoms of the disease but some clinical indications of fibroid include: abnormal bleeding, menorrhagia, infertility, pelvic discomfort, miscarriages and other obstetric difficulties experienced by women (10-11). It has been reported that leiomyomas interfere with female reproduction leading to infertility in women, early spontaneous abortion of pregnancies and advanced pregnancy complications and women between the ages of 25-50 are the ones affected mostly by this menace (12-13).

The therapeutic properties of medicinal plants are attributed to the presence of bioactive secondary metabolites in the crude extract of the plant (14).

One of such plants known to possess enormous medicinal potentials is *Xylopia aethiopica*. Itis a tropical plant found in most West African countries especially Zambia, Ghana, Mozambique Angola and Nigeria and abounds in most lowland rainforest and fringe forest in the savanna zones (15-16). The plant is known to possess many medicinal and nutritional properties, some of which include treatment of boils, cuts, sores, cough and wounds (17-18). Nyebuagu and co-workers have reported the antifertility effect of *Xylopia aethiopica* (19-20). Muanya (21) reported that fruits of the *Xylopia aethiopica* could be used by herbalists for enhancing menstrual flow and for inducing non-spontaneous abortion (21).

Molecular docking is a computational tool used to predict the binding potentials of chemical compounds (ligands) to a target (protein) (22). It is an essential facet of in-silico drug preparations (23).it helps researchers to study the bahaviours of small compounds within the binding site of a protein target as well as understand the elementary biochemical processes underlying the interaction. It is a structural based method involving a high-resolution 3D structure of the protein target acquired through Nuclear Magnetic Resonance Spectroscopy (NMR), X-ray crystallography or Cryo-Electron Microscopy (24-25).

Admetsar helps medicinal chemist in the prediction of absorption, distribution, metabolism, elimination and toxicity (ADMET) properties of a drug, it is an important computational tool that helps chemist to optimize lead compounds with better ADMET properties (26). The webserver uses canonical simplified molecular input line entry system(SMILES) as input structure data for the compounds to be predicted. The canonical smiles is a specification in the form of a line notation that is used in the description of a chemical structure.

In the present work, GC-MS and FTIR analysis were used to investigate the chemical constituents of *Xylopia aethiopica,* their uterine leiomyoma growth inhibiting potentials were investigated using molecular docking approach and their chemical activities were investigated using density functional theory.

MATERIALS AND METHODS

Preparation of plant extracts

Fresh seeds of *Xylopia aethiopica* were obtained from a local village in Imo State, Nigeria and identified by Dr. J. Akalazu of the Plant Science and Biotechnology Department of the Imo State University Owerri. The seeds were harvested, dried at 25°C and ground to powdered form using mortar and pestle and immersed in 98 % ethanol and left for 48 hours. The mixture was filtered using whatman grade 1 cellulose filter paper of size 580 x 680 mm and the filtrate concentrated by evaporation under the sun and used for the experiments

Fourier Transform Infrared Spectroscopy (FTIR) Examination

FTIR examination was performed on the filtrate to identify the functional groups it contained. The analysis was performed at a frequency range of 4000-400 cm^{-1}. The leave extracts were encapsulated in 200 mg of KBr salt pellet, by using a mortar and pestle, pressed into a thin pellet, the sample scans were left at 30 for proper calibration. Resolution was left at 8.2 and the Background Scans was set at 16 [27].

Gas Chromatography- mass spectrometry (GC-MS) examination

To identify the chemical constituents of the leave extract of *Xylopia aethiopica,* GC-MS analysis was performed. An Agilent technology GC-MS instrument (model: 19091S-433UI) USA was used for the GC-MS study. The parameters for the analysis were as follows: the initial temperature was 50°C held for 2 minutes at a rate of 5 °C/min, increased to 180 °C held for1 min at the rate of 20 °C/min, further increased to 270 °C at a heldtime of 0 min. the maximum temperature was 325 °C. Helium was used as the carrier gas, the initial pressure was 7.3614 psi and final pressure of 0 psi. The obtained result was compared with the spectra standard imbibed in the National Institute of Standards and Technology (NIST) mass spectral library (28).

Absorption, Distribution, Metabolism, Elimination and Toxicity (ADMET) Screening

pubchem database was used to obtain the canonical simplified molecular input line entry system (smiles) of the compounds which were further used for ADMET prediction using ADMETsar 2 server. The compounds were screened for drug-like properties, pharmacokinetics, and pharmacodynamics properties (29).Properties like human Intestine Absorption, Acute Oral Toxicity, Blood Brain Barrier, Water Solubility, carcinogenicity status were determined

Ligand preparation

The pubchemconformers of the compounds identified in the GC-MS experiment were downloaded from pubchem database, minimized in PYRX visual screening and molecular docking tool at a universal force field of 200 steps, converted to

Authodock ligand and used for the molecular docking processes.

Preparation of Molecular Target

The molecular target progesterone Receptor ligand binding domain (PDB -1SQN) was identified and downloaded from protein data bank (pdb) online database. The molecular target was opened in Biovia discovery studio software where the inferring co-crystallized ligands and crystallographic water particles were removed and the energy minimized with UCSF Chimera (1.14) (30). The protein was then minimized at 300 steepest steps at 0.02 Å and saved as pdb document. Figure 1 shows the 3D image of the protein target with the amino acid residues around the active site. The amino acids at the active site are LEU715, LEU 718, ASN 719, GLN 725, ARG 766, MET 759, MET 801, CYS 891,

Molecular docking

The Autodock Vina in PYXR software was used for the screening of the compounds from the plant by docking them on the binding pockets of the fibroid protein using Norethindrone as drug control (31). PYRX is an online tool for molecular docking and simulation. The docking was performed in a grid box of size centerx: 4.79, center y: -1.73 and center z: 31.97. The molecular docking rr results (docking scores in (kcal/mol) were listed on an excel spread

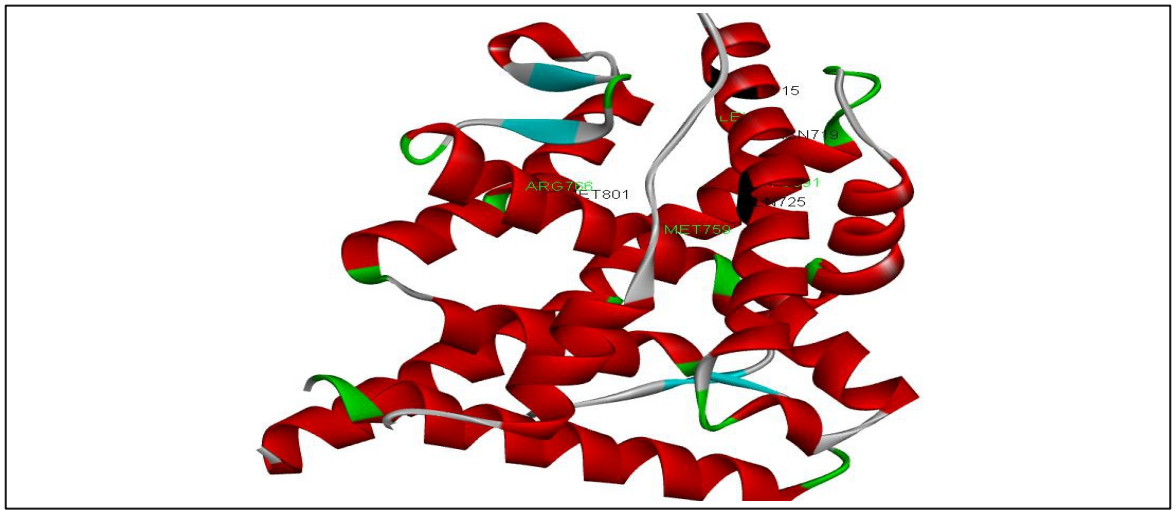


Figure 1. the progesterone Receptor molecular target.

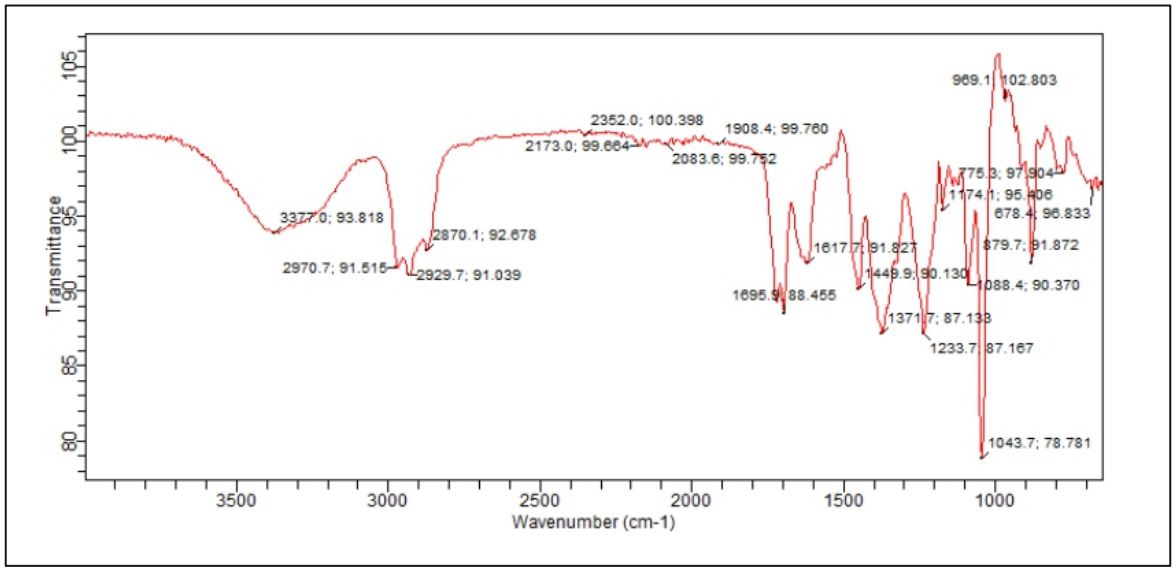


Figure 2. FTIR spectraum of *Xylopia aethiopica*

sheet. Post docking visualizing of the protein-ligand interactions were performed in BioviaDiscovery studio 4.5 (32).

Density functional theory (DFT) calculations

Electronic structures of the identified molecules were calculated using density functional theory (DFT) electronic structure workstation with DMol^3 found in the Materials Studio 7.0 simulation software (Accelrys, Inc.). In this method, the properties of the-electron system were determined by using functionals. Geometric optimization was performed on the compounds after which frontier molecular orbitals energies were calculated.

RESULTS

FTIR Results

The functional groups present in the plant material were identified using FTIR analysis. The spectrum is presented in Figure 2. The results are in agreement with functional groups reported elsewhere to be beneficial in drug activity (33). The peaks found in the FTIR result include1617.7 cm^{-1}, 1695.9 cm^{-1}, which correspond to C=C, 2870.1cm^{-1}, 2829.7 cm^{-1}, 2970.7cm^{-1}, belonging to C-H stretch and 3377.0 cm^{-1}, corresponding to O-H stretch of alcohol.

GC-MS Result

Lately, gas chromatography-mass spectrophotometry GC-MS analysis has been used for the identification of various bioactive therapeutic compounds that are found in medicinal plants (34). The GC-MS result showed 35 compounds listed in Table 1, the chromatogram is shown in Figure 3. The identified compounds are likely to be responsible for the medicinal properties of Xylopia aethiopica seeds.

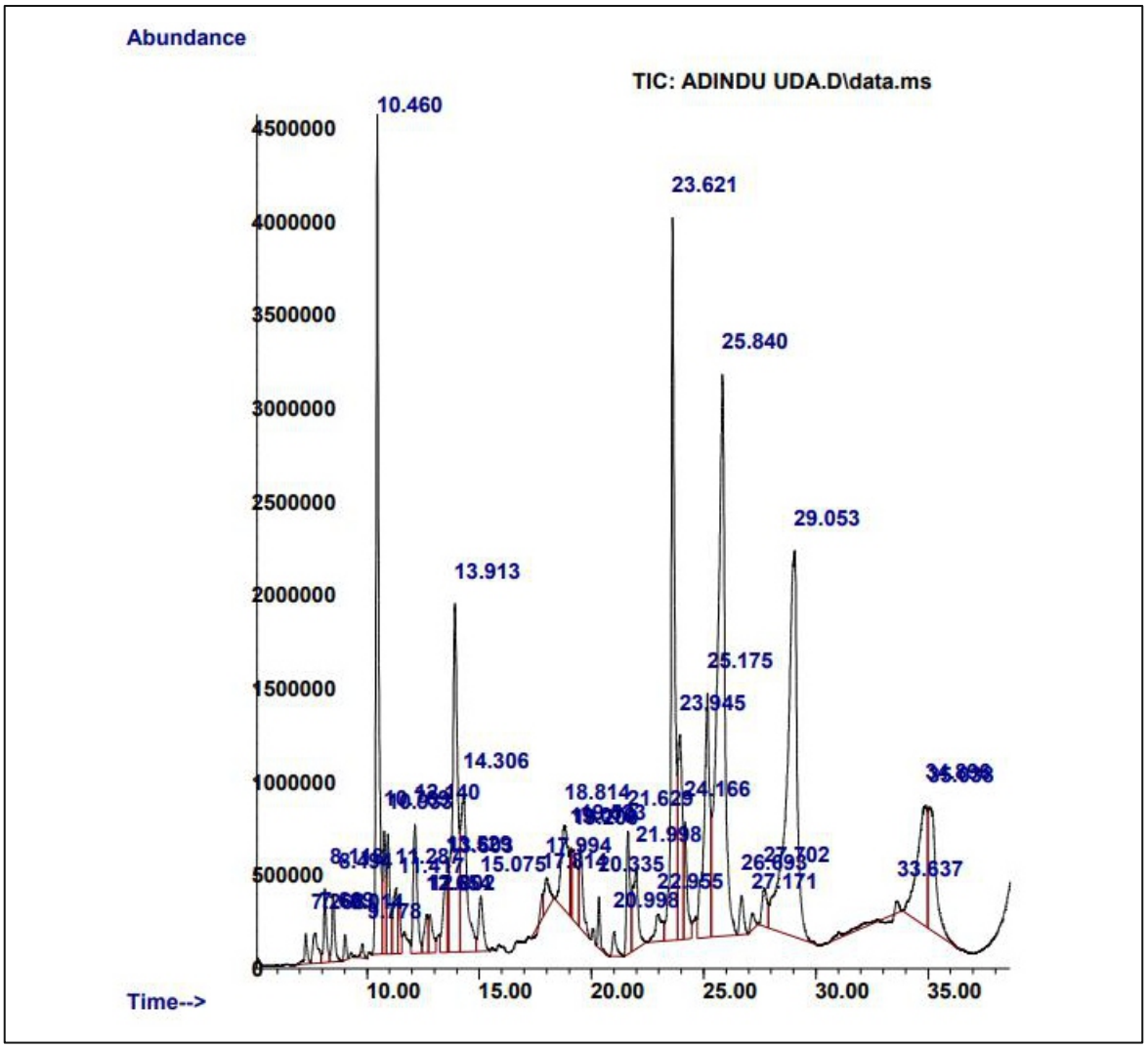
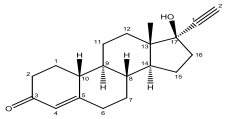
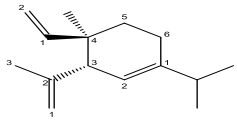
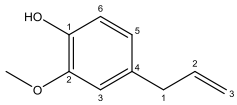
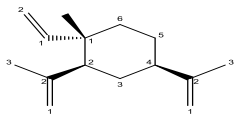
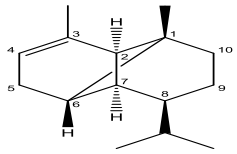
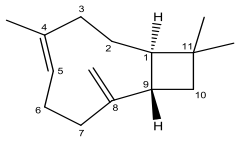
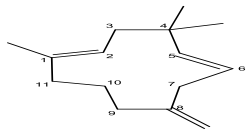
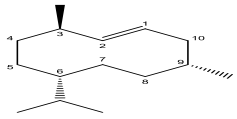
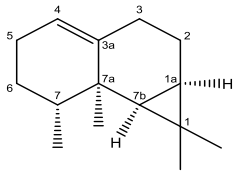
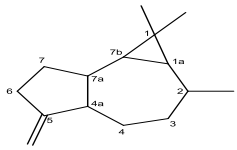
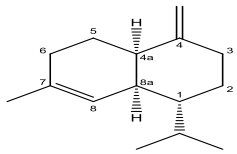
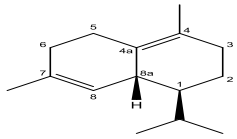
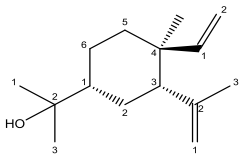
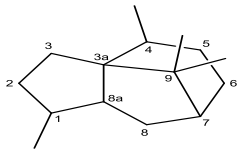
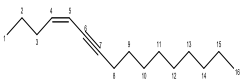
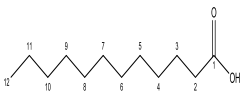
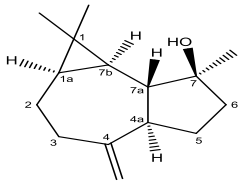
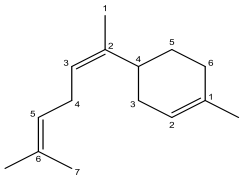
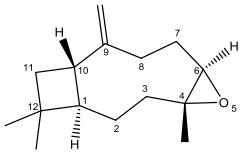
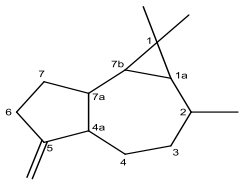
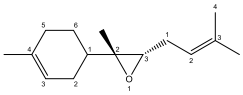
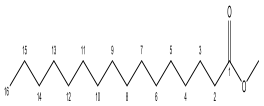
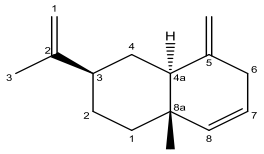
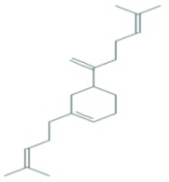
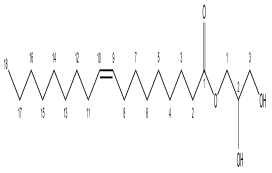
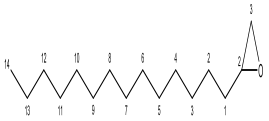
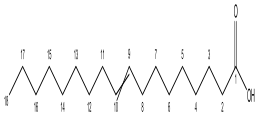
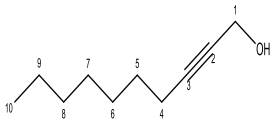
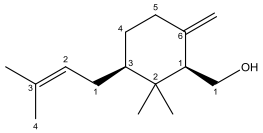


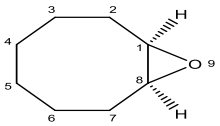
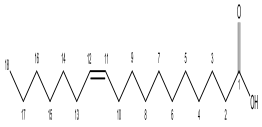
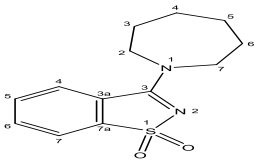
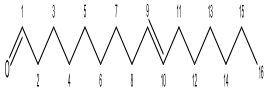
Figure 3. GC-MS Chromatogram of Xylopia aethiopica powder.

Table 1Compounds identified from the ethanol extract of *Xylopia aethiopica*

S/No.	Compound	Area (%)	Pubchem Id	Molecular Structure	Molecular Formula	Molecular Weght (g)
1.	Norethindrone	Standard ligand	6230		$C_{20}H_{26}O_2$	298.4
2.	δ-Elemene	0.307	89316		$C_{15}H_{24}$	204.35
3.	Eugenol	0.5477	3314		$C_{10}H_{12}O_2$	164.20
4.	(-)-cis-.beta.-Elemene	0.7063	6431151		$C_{15}H_{24}$	204.35
5.	Copaene	0.7624	12303902		$C_{15}H_{24}$	204.35
6.	Caryophyllene	0.222	5281515		$C_{15}H_{24}$	204.35
7.	Humulene	0.1434	5281520		$C_{15}H_{24}$	204.35
8.	Germacrene D	7.896	5317570		$C_{15}H_{24}$	204.35
9.	beta.-Gurjunene	1.2941	6432176		$C_{15}H_{24}$	204.35
10.	Alloaromadendrene	1.3406	10899740		$C_{15}H_{24}$	204.35
11.	gamma.-Muurolene	0.9757	12313020		$C_{15}H_{24}$	204.35
12.	Cadina-1(10),4-diene	0.5173	10223		$C_{15}H_{24}$	204.35

13.	Cyclohexanemethanol, ethenyl-4- .alpha., .alpha. ,4-trimethyl-3- (1- methylethenyl)- , [1R- (1.alpha.,3.alp ha.,4.beta.)]-	1.863	547972		$C_{15}H_{26}O$	222.37
14.	1H-3a,7- Methanoazule ne, octahydro- 1,4,9,9- tetramethyl-	0.5607	29408		$C_{15}H_{26}$	206.37
15.	4-Hexadecen- 6-yne, (Z)-	0.5823	5367377		$C_{16}H_{28}$	220.39
16.	Dodecanoic acid	1.3666	3893		$C_{12}H_{24}O_2$	200.32
17.	Spathulenol	6.7605	6432640		$C_{15}H_{24}O$	220.35
18.	cis-.alpha.- Bisabolene	3.7325	5352653		$C_{15}H_{24}$	204.35
19.	Caryophyllene oxide	0.6085	1742210		$C_{15}H_{24}O$	220.35
20.	Aromandendre ne	2.2151	91354		$C_{15}H_{24}$	204.35
21.	cis-Z-.alpha.- Bisabolene epoxide	2.804	91753574		$C_{15}H_{24}O$	220.35

22.	Hexadecanoic acid, methyl ester	0.3998	8181		$C_{17}H_{34}O_2$	270.5
23.	(-)-Eudesma-1,4(15),11-triene	0.3462	91699613		$C_{15}H_{22}$	202.33
24.	m-Camphorene	1.6707	5315649		$C_{20}H_{32}$	272.5
25.	9-Octadecenoic acid (Z)-, 2,3-dihydroxypropyl ester	0.6882	5283468		$C_{21}H_{40}O_4$	356.5
26.	9-Octadecenoic acid, methyl ester, (E)-	9.443	5280590		$C_{19}H_{36}O_2$	296.5
27.	Oxirane, tetradecyl-	3.2732	23741		$C_{16}H_{32}O$	240.42
28.	Heneicosanoic acid, methyl ester	1.3751	22434		$C_{22}H_{44}O_2$	340.6
29.	9-Octadecenoic acid (Oleic acid)	5.2655	637517		$C_{18}H_{34}O_2$	282.5
30.	2-Decyn-1-ol	15.1693	77763		$C_{10}H_{18}O$	154.25
31.	1-Methylene-2b-hydroxymethyl-3,3-dimethyl-4b-(3-methylbut-2-	0.5753	550196		$C_{15}H_{26}O$	222.37

	enyl)-cyclohexane					
32.	9-Oxabicyclo[6.1.0]nonane, cis-	0.9546	642975		$C_8H_{14}O$	126.20
33.	cis-Vaccenic acid	14.4669	5282761		$C_{18}H_{34}O_2$	282.5
34.	9-Octadecenoic acid (Z)-, 2-hydroxy-1-(hydroxymethyl)ethyl ester	0.4064	5319879		$C_{21}H_{40}O_4$	356.5
35.	1,2-Benzisothiazole, 3-(hexahydro-1H-azepin-1-yl)-, 1,1-dioxide	4.4513	535203		$C_{13}H_{16}N_2O_2S$	264.35
36.	E-9-Hexadecenal	3.5309	5283375		$C_{16}H_{30}O$	238.41

Admet properties

The absorption, distribution, metabolism elimination and toxicity properties of the compounds which show their pharmacokinetics and pharmacodynamics behaviours are summarized in Table 2. Properties listed include: Human Intestine Absorption (HIA), Acute Oral Toxicity (AOT), Carcinogenicity, Blood Brain Barrier (BBB), Water Solubility (WS), number of hydrogen bond acceptor, number of hydrogen bond donor and number of rotatable bonds, Human intestine absorption (HIA) is a vital parameter for predicting the movement of the drugs to their targets, compounds with positive HIA are easily absorbed through gastrointestinal tract when administered orally, all the compound studied have positive HIA, acute oral toxicity is a tool that is used to determine the adverse effects occurring following oral administration of a single dose of a drug within 24 hours. Carcinogenicity is a property that determines if the compound will promote cancer formation, none of the compounds studied showed positive carcinogenicity. The BBB regulates the drug permeability into the brain, two of the compounds showed negative BBB while 33 were positive. The Lipinski's rule of five is a rule of thumb used to test the druglikeness of a chemical compound with various pharmacological activities to evaluate if it has the required chemical or biological properties that would make it a likely orally consumable drug in humans. According to the rule, A chemical compound which must serve as an orally active drug should have no more than 5 hydrogen bond donors, have a molecular mass of less than 500 daltons, no more than 10 hydrogen bond acceptors, its calculated octan-water partition coefficient (Clog *P*) should not exceed 5 as seen, all the numbers are multiples of 5 which is the origin of the name of the rule (35-36). Interestingly, none of the identified compounds violated more than one of the rules.

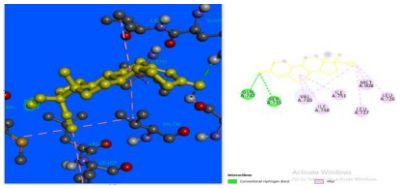
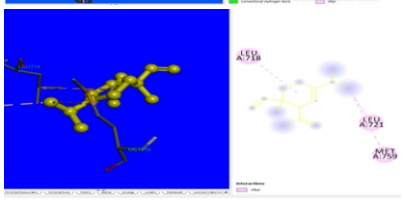
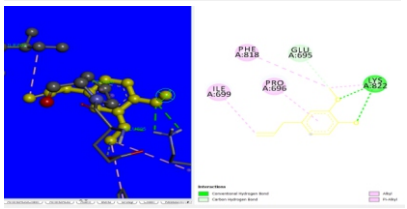
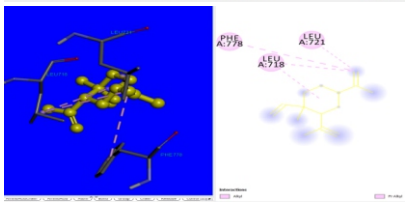
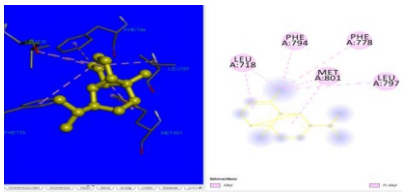
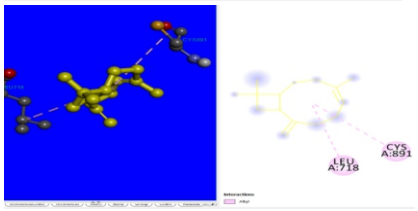
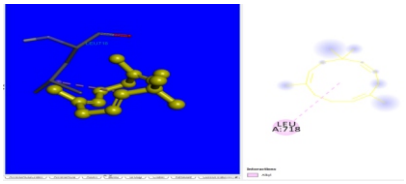
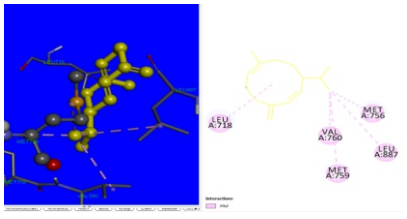
Table 2: Admetbehaviour of the compounds

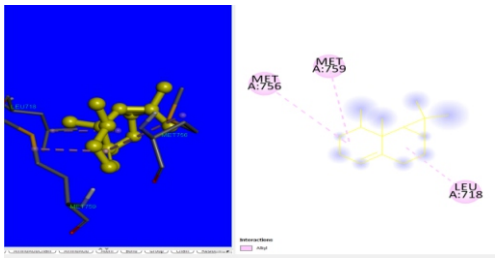
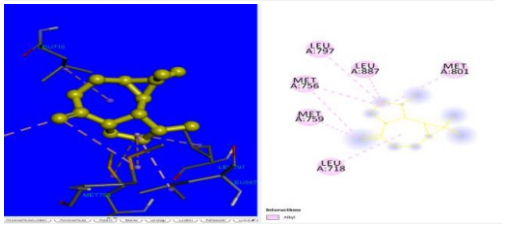
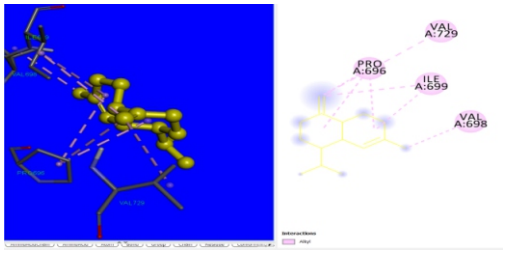
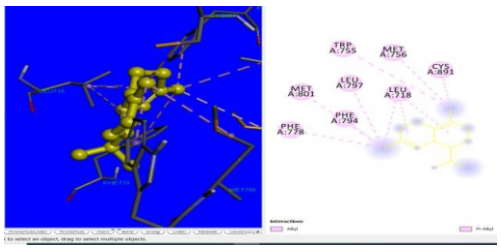
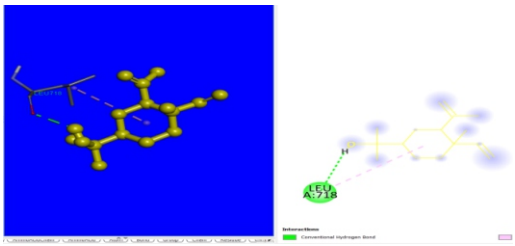
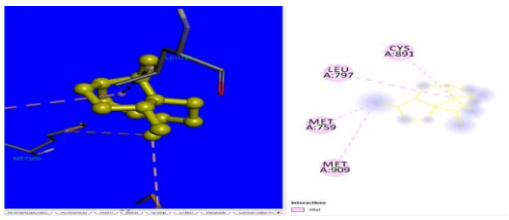
S/ No	Compound	HIA	AOT	Carcinogenicity	BBB	WS	H-bond acceptor	H-bond donor	Rotatable bonds
1.	Norethindrone	+	0.774	-	+	-4.632	2	1	0
2.	δ-Elemene	+	0.818	-	+	-3.726	0	0	3
3.	Eugenol	+	2.020	-	-	-1.918	2	1	3
4.	(-)-cis-.beta.-Elemene	+	0.883	-	+	-4.309	0	0	3
5.	Copaene	+	0.934	-	+	-5.054	0	0	1
6.	Caryophyllene	+	1.896	-	+	-4.687	0	0	0
7.	Humulene	+	1.214	-	+	-5.046	0	0	0
8.	Germacrene D	+	1.704	-	+	-5.023	0	0	1
9.	beta.-Gurjunene	+	1.985	-	+	-5.366	0	0	0
10.	Alloaromadendrene	+	2.345	-	+	-5.127	0	0	0
11.	gamma.-Muurolene	+	2.007	-	+	-5.37	0	0	1
12.	Cadina-1(10),4-diene	+	1.649	-	+	-5.248	0	0	1
13.	Cyclohexanemethanol, 4-ethenyl-.alpha.,.alpha.,4-trimethyl-3-(1-methylethenyl)-,[1R-(1.alpha.,3.alpha.,4.beta.)]-	+	1.092	-	+	-2.631	1	1	3
14.	1H-3a,7-Methanoazulene, octahydro-1,4,9,9-tetramethyl-	+	1.015	-	+	-5.403	0	0	0
15.	4-Hexadecen-6-yne, (Z)-	+	1.955	-	+	-4.544	0	0	9
16.	Dodecanoic acid	+	1.233	-	+	-3.502	1	1	10
17.	Spathulenol	+	1.570	-	+	-3.648	1	1	0

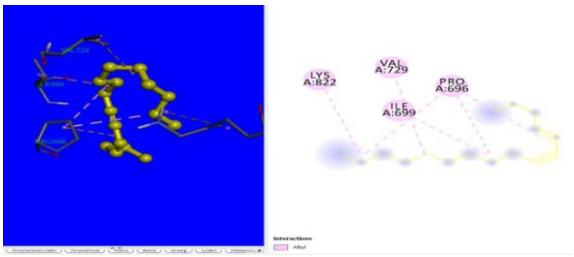
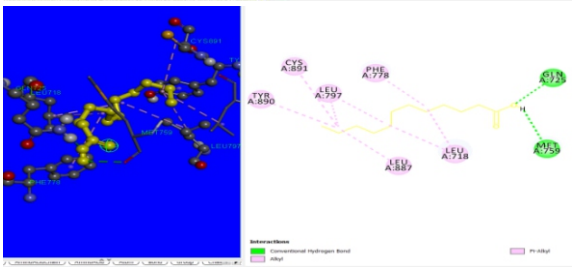
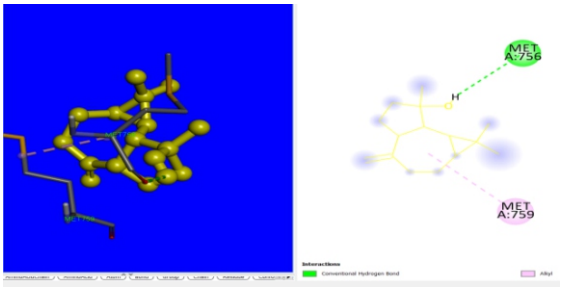
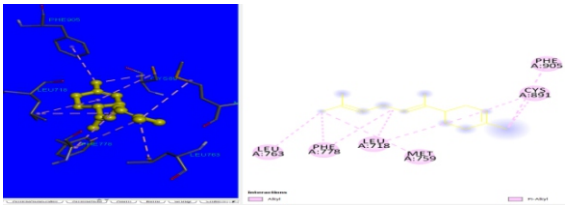
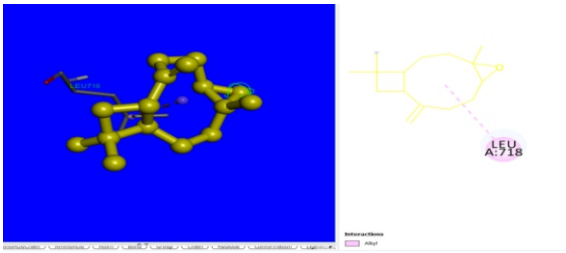
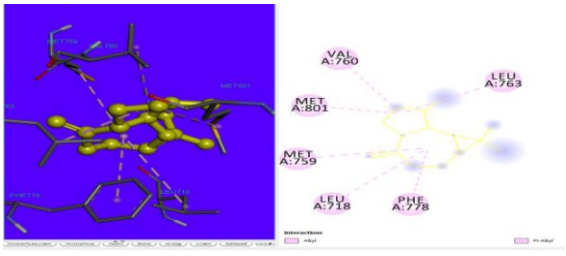
18.	cis-.alpha.-Bisabolene	+	1.136	-	+	-4.937	0	0	3
19.	Caryophyllene oxide	+	1.469	-	+	-3.236	1	0	0
20.	Aromandendrene	+	2.345	-	+	-5.127	0	0	0
21.	cis-Z-.alpha.-Bisabolene epoxide	+	0.574	-	+	-3.52	1	0	3
22.	Hexadecanoic acid, methyl ester	+	1.180	-	+	-3.399	2	0	14
23.	(-)-Eudesma-1,4(15),11-triene	+	1.419	-	+	-5.204	0	0	1
24.	m-Camphorene	+	1.35	-	+	-4.651	0	0	7
25.	9-Octadecenoic acid (Z)-, 2,3-dihydroxypropyl ester	+	1.451	-	-	-2.401	4	2	18
26.	9-Octadecenoic acid, methyl ester, (E)-	+	1.553	-	+	-3.898	2	0	15
27.	Oxirane, tetradecyl-	+	1.494	-	+	-2.277	1	0	13
28.	Heneicosanoic acid, methyl ester	+	1.118	-	+	-3.399	2	0	19
29.	9-Octadecenoic acid (Oleic acid)	+	1.246	-	+	-4.04	1	1	15
30.	2-Decyn-1-ol	+	2.324	-	+	-1.724	1	1	5
31.	1-Methylene-2b-hydroxymethyl-3,3-dimethyl-4b-(3-methylbut-2-enyl)-cyclohexane	+	1.171	-	+	-2.96	1	1	3
32.	9-Oxabicyclo[6.1.0]nonane, cis-	+	1.87	-	+	-1.825	1	0	0
33.	cis-Vaccenic acid	+	1.238	-	+	-4.04	1	1	15
34.	9-Octadecenoic acid (Z)-, 2-hydroxy-1-(hydroxymethyl)ethyl ester	+	1.776	-	+	-2.089	4	2	18
35.	1,2-Benzisothiazole, 3-(hexahydro-1H-azepin-1-yl)-, 1,1-dioxide	+	1.969	-	+	-3.348	3	0	0
36.	E-9-Hexadecenal	+	1.516	-	+	-3.062	1	0	13

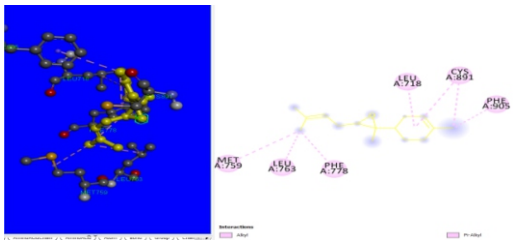
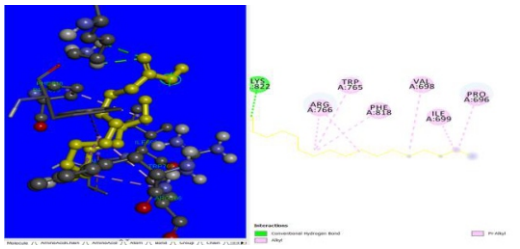
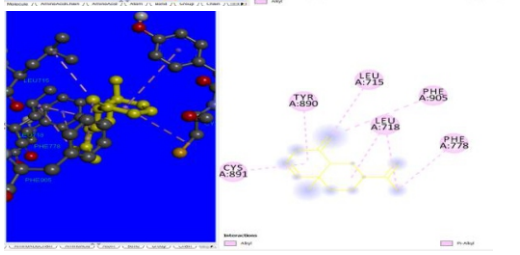
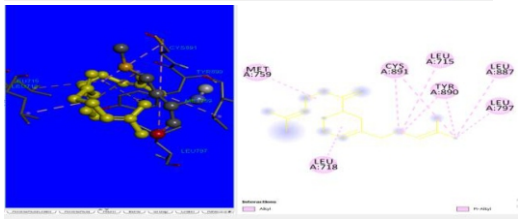
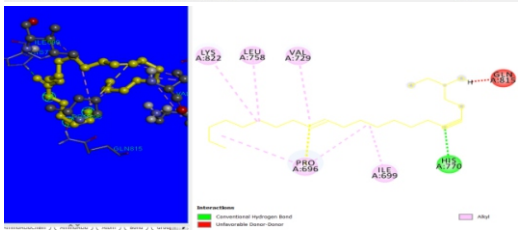
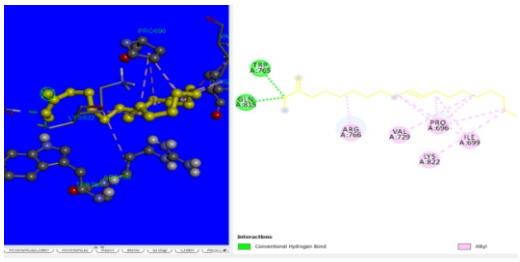
HIA=Human Intestine Absorption, AOT=Acute Oral Toxicity, BBB=Blood Brain Barrier, WS=Water Solubility

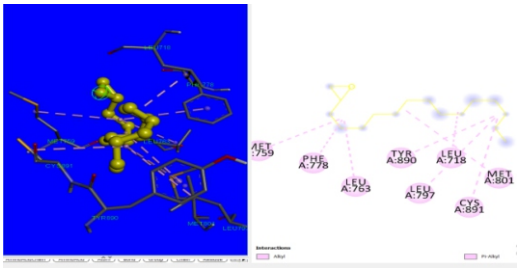
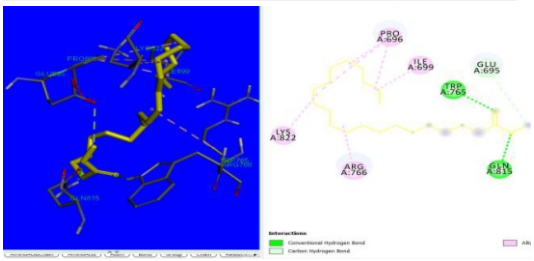
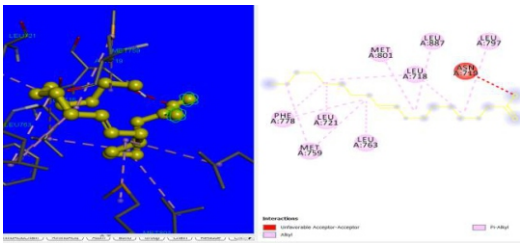
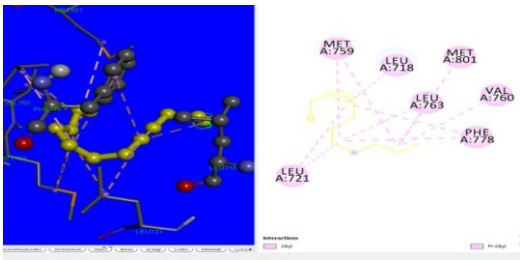
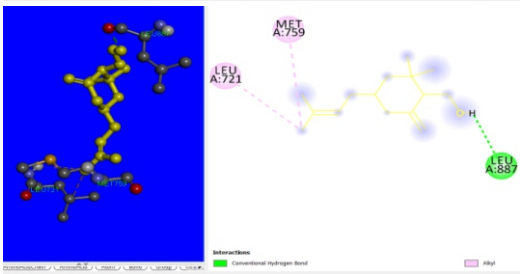
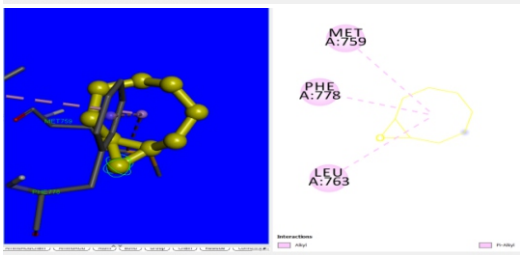
Table 3. Interactions of the identified compounds with the progesterone Receptor target

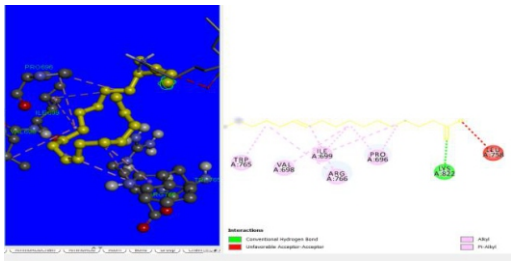
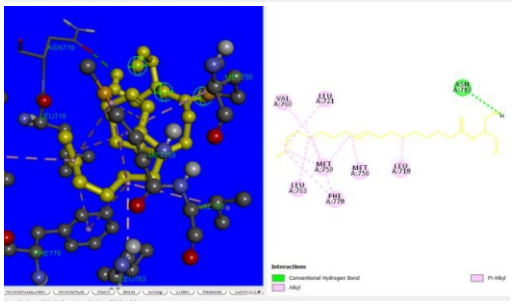
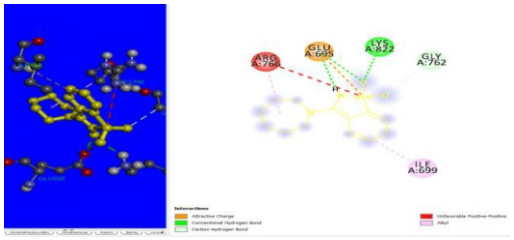
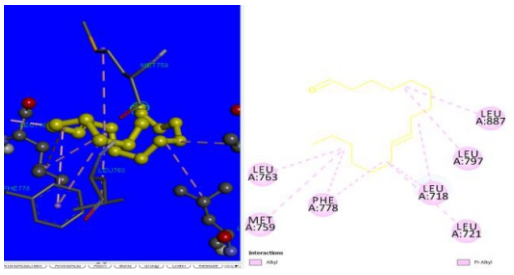
S/ No.1	Pubchemid	Name of compound	3D and 2D interactions
	6230	Norethindrone	
2	89316	δ-Elemene	
3	3314	Eugenol	
4	6431151	-)-cis-.beta.-Elemene	
5	1230390	Copaene	
6	5281515	Caryophyllene	
7	5281520	Humulene	
8	5317570	Germacrene D	

9	6432176	beta.-Gurjunene	
10	10899740	Alloaromadendrene	
11	12313020	gamma.-Muurolene	
12	10223	Cadina-1(10),4-diene	
13	547972	Cyclohexanemethanol, 4-ethenyl-.alpha.,.alpha.,4-trimethyl-3-(1-methylethenyl)-, [1R-(1.alpha.,3.alpha.,4.beta.)]-	
14	29408	1H-3a,7-Methanoazulene, octahydro-1,4,9,9-tetramethyl-	

15	5367377	4-Hexadecen-6-yne, (Z)-	
16	3893	Dodecanoic acid	
17	6432640	Spathulenol	
18	5352653	cis-alphs,-Bisabolene	
19	1742210	Caryophyllene oxide	
20	91354	Aromandendrene	

21	91753574	cis-Z-.alpha.-Bisabolene epoxide	
22	8181	Hexadecanoic acid, methyl ester	
23	91699613	(-)-Eudesma-1,4(15),11-triene	
24	5315649	m-Camphorene	
25	5283468	9-Octadecenoic acid (Z)-, 2,3-dihydroxypropyl ester	
26	5280590	9-Octadecenoic acid, methyl ester, (E)-	

27	23741	Oxirane, tetradecyl-	
28	22434	Heneicosanoic acid, methyl ester	
29	637517	9-Octadecenoic acid (Oleic acid)	
30	77763	2-Decyn-1-ol	
31	550196	1-Methylene-2b-hydroxymethyl-3,3-dimethyl-4b-(3-methylbut-2-enyl)-cyclohexane	
32	642975	9-Oxabicyclo[6.1.0]nonane, cis-	

33	5282761	cis-Vaccenic acid	
34	5319879	9-Octadecenoic acid (Z)-, 2-hydroxy-1-(hydroxymethyl)ethyl ester	
35	535203	1,2-Benzisothiazole, 3-(hexahydro-1H-azepin-1-yl)-, 1,1-dioxide	
36	5283375	E-9-Hexadecenal	

Quantum chemical calculations

Density functional theory calculations were performed on the thre emolecules with the highest binding energies. Calculations were achieved using the electronic structure program DMol[3] in the frame work of Mulliken population analysis, the DND basis set and the Perdew-Wang (PW) local correlation density functional (37). The highest occupied molecular orbital(HOMO) represents the willingness of a molecule to donate electronwhereas the lowest unoccupied molecular orbital (LUMO) represents it ability to accept electron and a low energy gap shows the ease of electron transfer. The low values of HOMO and LUMO energy gap observed for the compounds describe their stability as well as biological activities.The optimized structures of the selected compounds as well as their HOMO and LUMO orbitals are presented in Figure 3, while the global descriptors for the chemical activities of the compounds including the absolute electronegativity (χ), absolute hardness (η) and softness (δ) are presented in Table 5.The global descriptors were estimated as below (38):

$$\chi = \frac{I + A}{2} \qquad (1)$$

$$\eta = \frac{I - A}{2} \qquad (2)$$

$$\delta = \frac{1}{\eta} \qquad (3)$$

Table 4 Binding affinity, interactions and amino acid residues involved in the molecular docking studies

S/no.	Compound	Binding affinity (kcal/mol)	Type of interaction	Amino acid involved
1.	Norethindrone	-8.5	Conventional hydrogen bond, alkyl	LEU 726, LEU 727, VAL 730, SER 733, GLN 747 ILE 748, ILE 751, MET 908.
2.	Cyclohexene,4-ethenyl-4-methyl-3-(1-methylethenyl)-1-(1-methylethyl)-,(3R-trans)-	-7.3	Alkyl	LEU 718, LEU 721, MET 759,
3.	Eugenol	-6.1	Conventional hydrogen bond, carbon hydrogen bond, alkyl and pi-alkyl	GLU 695, PRO 696, ILE 699, PHE 818, LYS 822,
4.	Cyclohexane,1-ethenyl-1-methyl-2,4-bis(1-methylethenyl)-,[1S-(1.alpha.,2.beta.,4.beta.)]-	-7.3	Alky and pi-alkyl	LEU 718, LEU 721, PHE 778
5	Copaene	-8	Alkyl and pi-alkyl	LEU 718, PHE 778, PHE 794 LEU 797, MET 801
6.	Caryophyllene	-7.6	Alkyl	LEU 718, CYS 891
	Humulene	-7.7	Alkyl	LEU 718
	Germacrene D	-7.8	Alkyl	LEU 718, MET 756, MET 759, VAL 760, LEU 887
9.	1H-Cyclopropa[a]naphthalene, 1a,2,3,5,6,7,7a,7b-octahydro-1,1,7,7a-tetramethyl-,[1aR-(1a.alpha.,7.alpha.,7a.alpha.,7b.alpha.)]-	-7.6	Alkyl	LEU 718, MET 756, MET 759
10	Alloaromadendrene	-7.7	Alkyl	LEU 718, MET 756, MET 759, LEU 797, MET 810, LEU 887,
11	gamma.-Muurolene	-7.5	Alkyl	VAL 729, PRO 696, VAL 698, ILE 699,
12	Cadina-1(10),4-diene	-7.5	Alkyl, pi-alkyl	LEU 718, TRP 755, MET 756, PHE 794, PHE 778, LEU 797, MET 801, CYS 891,
13	Cyclohexanemethanol,4-ethenyl-.alpha.,.alpha.,4-trimethyl-3-(1-methylethenyl)-,[1R-(1.alpha.,3.alpha.,4.beta.)]-	-7.2	Conventional hydrogen bond, alkyl	LEU 718,
14	1H-3a,7-Methanoazulene,octahydro-1,4,9,9-tetramethyl-	-7.8	Alkyl	MET 759, LEU 797, CYS 891, MET 909,
15	4-Hexadecen-6-yne, (Z)-	6.1	Alkyl	PRO 696, ILE 699, VAL 729, LYS 822,
16	Dodecanoic acid	-5	Conventional hydrogen bond, alkyl, pi-alkyl	LEU 718, GLN 725, MET 759, PHE 778, LEU 797, LEU 887,

17	Spathulenol	-8.4	Conventional hydrogen bond, alkyl	TYR 890, CYS 891, MET 756, MET 759,
18	cis-.alpha.-Bisabolene	-7.6	Alkyl, pi-alkyl	LEU 718, MET 759, LEU 763, PHE 778, CYS 891, PHE 905,
19	Caryophyllene oxide	-7.7	Alkyl	LEU 718,
20	Aromandendrene	-7.6	Alkyl, pi-alkyl	LEU 718, MET 759, VAL 760, LEU 763, PHE 778, MET 801,
21	cis-Z-.alpha.-Bisabolene epoxide	-7.5	Alkyl, pi-alkyl	LEU 718, MET 759, LEU 763, PHE 778, CYS 891, PHE 905,
22	Hexadecanoic acid, methyl ester	-6.1	Conventional hydrogen bond, alkyl, pi-alkyl	VAL 698, PRO 696, ILE 699, TRP 765, ARG 766, PHE 818, LYS 822,
23	(3R,4aS,8aS)-8a-Methyl-5-methylene-3-(prop-1-en-2-yl)-1,2,3,4,4a,5,6,8a-octahydronaphthalene	-7.9	Alkyl, pi-alkyl	LEU 715, LEU 718, PHE 778, TYR 890, CYS891,PHE 905,
24	m-Camphorene	-7.7	Alkyl, pi-alkyl	LEU 715, LEU718,MET 759, LEU 797, TYR, 887 LEU890, CYS 891,
25	9-Octadecenoic acid (Z)-, 2,3-dihydroxypropyl ester	-5.4	Conventional hydrogen bond, unfavorable donor-donor, alkyl	PRO 696, ILE 699, VAL 729, LEU 758, HIS 770, GLN 815, LYS 822,
26	9-Octadecenoic acid, methyl ester, (E)-	-5.7	Conventional hydrogen bond, alkyl	PRO 696, ILE 699, VAL 729, ARG 766, TRP 765, GLN 815, LYS 822,
27	Oxirane, tetradecyl-	-5.9	Alkyl, pi-alkyl	LEU 718, MET 759, LEU 763, PHE 778, LEU 797, MET 801, TYR 890, CYS 891
28	Heneicosanoic acid, methyl ester	-5.3	Conventional hydrogen bond, carbon hydrogen bond, alkyl	PRO 696, GLU 695, ILE699, TRP 765, ARG 766, GLN 815, LYS 822,
29	9-Octadecenoic acid (Oleic acid)	-6.2	Unvavorable acceptor-acceptor, alkyl, pi-alkyl	LEU 718, ASN 719, LEU 721, MET 759, LEU 763, PHE 778, LEU 797,MET 801, LEU 887
30	2-Decyn-1-ol	-4.9	Alkyl pi-alkyl	LEU 718, LEU 721 MET 759, VAL 760, LEU 763, PHE 778 MET 801
31	1-Methylene-2b-hydroxymethyl-3,3-dimethyl-4b-(3-methylbut-2-enyl)-cyclohexane	-7.4	conventional hydrogen bond, alkyl	MET 721, MET 759, LEU 887
32	9-Oxabicyclo[6.1.0]nonane, cis-	-5.5	Alkyl, pi-alkyl	LEU 759, LEU 763, PHE 778
33	cis-Vaccenic acid	-5.5	Conventional hydrogen bond,	PRO 696, VAL 698,

			unfavorable acceptor-acceptor, alkyl, pi-alkyl	ILE 699, TRP 765, ARG 766, LEU 758, LYS 822
34	9-Octadecenoic acid (Z)-,2-hydroxy-1-(hydroxymethyl)ethyl ester	-5.1	Conventinal hydrogen bond, alkyl, pi-alkyl	LEU 718, ASN 719, LEU 721, MET 756, MET 759, VAL 760, LEU 763, PHE 778
35	1,2-Benzisothiazole, 3-(hexahydro-1H-azepin-1-yl)-, 1,1-dioxide	-8.3	Attractive charge, conventional hydrogen bond, unfavorable acceptor-acceptor, alkyl	GLU 695, ILE 699, GLY 762, ARG 766, LYS 822
36	E-9-Hexadecenal	-5.8	Alkyl, pi-alkyl	LEU 718, LEU 721, MET 759, LEU 763, PHE 788, LEU 797, LEU 887

The absolute electronegativity is a property of the compound which describes its tendency to attract electron to itself. The absolute hardness shows the compound's resistance to charge transfer and it reflects a good indicator to chemical reactivity while the softness relates the ability of the compound to accept electron (39).

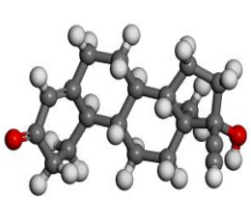
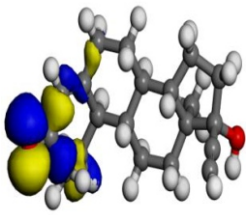
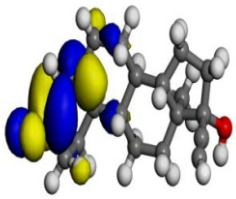
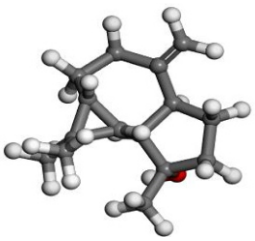
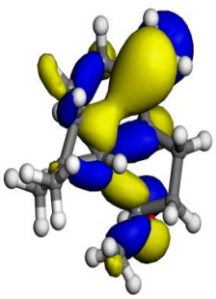
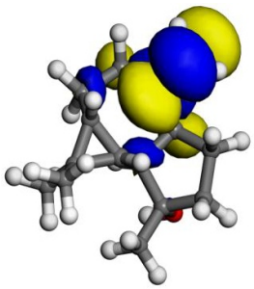
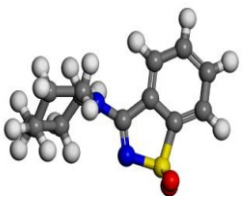
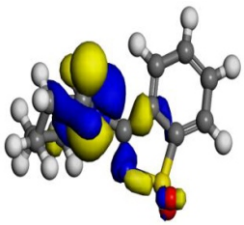
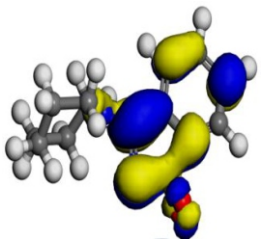
Compound	Optimized structure	HOMO orbital	LUMO orbital
Norethindrone			
Spathulenol			
1,2-Benzisothiazole, 3-(hexahydro-1H-azepin-1-yl)-,1,1-dioxide			

Figure 4. The optimized structures, HOMO and LUMO orbitals of norethindrone, Spathulenol and 1,2-Benzisothiazole, 3-(hexahydro-1H-azepin-1-yl)-, 1,1-dioxide

Table 5 Quantum chemical parameters of the selected compounds

Compound	E_{HOMO}(Ha)	E_{LUMO}(Ha)	I= - E_{HOMO}(Ha)	A= - E_{LUMO}(Ha)	Energy gap (Ha)	χ	η	δ
Norethindrone	-0.189	-0.081	0.189	0.081	0.108	0.135	0.108	9.259
Spathulenol	-0.204	-0.008	0.204	0.008	0.196	0.106	0.098	10.204
1,2-Benzisothiazole, 3-(hexahydro-1H-azepin-1-yl)-,1,1-dioxide	-0.193	-0.124	0.193	0.124	0.0069	0.159	0.035	28.571

CONCLUSION

The chemical constituents of *Xylopia aethiopica* were extracted in ethanol and analyzed for their uterine fibroid inhibiting properties using molecular docking method,Density functional theory calculations were performed to investigate the reactivity of the three compounds with the highest binding scores. The FTIR result showed that the plant contained some functional groups which have been previously reported for their pharmacological activities. The GC-MS result revealed that*Xylopia aethiopica* containedcompounds with known therapeutic and biological properties. The molecular docking results showed that most of the compounds contained in the plants gave very good binding scores indicating that *Xylopia aethiopica* would be a good candidate for inhibiting the growth of uterine fibroid in humans. The DFT results revealed low energy gaps for the compounds which is a good indicator for their reactivity. The ADMET studies further showed that they presented favorable pharmacodynamics and pharmacological properties in humans.

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