Identification of compounds from *Aframomum melengueta* (alligator pepper) as potential inhibitors of the Sex Hormone Binding Globulin (SHBG) in male infertility

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ABSTRACT

Human sex hormone binding globulin (SHBG) is a glycoprotein produced and secreted by the liver and is capable of binding androgens and estrogens in males. Both androgens and estrogens are important hormones that help in the development of sexual and reproductive tissues. The present work investigates the active chemical components of Aframomum melegueta (Alligator pepper) as well as study their involvement as potential drug lead to inhibiting Sex hormone binding globulin (SHBG) receptor protein that is involved in the various cases of male infertility. Phytochemical identification of the constituents was achieved by Fourier transform infrared spectroscopy (FTIR) and gas chromatography-mass spectrophotometry GC-MS experiments, while the ligand-target interaction to discover the drug lead candidates was achieved by molecular docking. Adsorption, distribution, metabolism, excretion, and toxicity (ADMET) screening was performed to ascertain the suitability of the compounds as drug lead candidates. The GC-MS result revealed a total of 30 compounds, the molecular docking results showed that 5-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)decan-3-one which was found to be present in 43.2511%, *gave a binding energy of -7.0 Kcal mol^{-} which is an indication that it might form a good drug lead candidate for the inhibition of the Sex hormone binding globulin. The ADMET study showed that all the compounds above 1% from the GC-MS study proved leading drug candidates with great efficacy, no toxicity, no cardiotoxicity and no carcinogenicity was observed.*

Keywords: *Aframomum melegueta*, Sex hormone binding globulin, male infertility, Androgen, estrogen

INTRODUCTION

Infertility is a reproductive disorder that affects many families especially in Africa [1-3]. Male infertility affects at least one in every six couples and interferes with the process of

spermatogenesis [4]. It also reduces sperm quality as well as quantity. Male infertility occurs concurrently with diabetes mellitus, cardiovascular disorder, high blood pressure, chronic liver disease and vitamins deficiency [5-8]. Drug misuse, excessive stress, environmental hazards are also reported in many cases of male infertility [9-10].

Androgen is a sex steroid hormone that regulates the development and maintenance of male sex characteristics [11-12].it plays a significant role in maintaining normal spermatogenesis (the process of sperm cells production) in man. If the amount of androgen reduces in man it could result in male infertility. A special form of estrogen hormone called estradiol is very crucial in sperm production and male sexuality [13-14]. High estrogen level can cause slow sperm production and makes it difficult for the individual to create healthy sperm. Human Sex hormone binding globulin (SHBG) is the high molecular weight plasma protein produced by the liver and controls the quantity of testosterone that the body tissue can use [15-16], it binds androgens and estrogens and plays an important role in maintaining the balance between unbound and bound sex steroids. little SHBG in the body can cause problem to the individual. Obesity, liver problem, hyperthyroidism and age can affect the level of SHBG in the body. The genetic mutations in the genes of the SHBG, specifically mutated rs6259 and rs727428 loci, can lead to infertility in men [17].

Many phytochemicals with medicinal applications have been discovered in medicinal plants. Interestingly, traditional medicines have proven to show fewer side effects as well as attacking several targets [18-20].

Aframomum melegueta (Alligator pepper) is a spice that belongs to *the* Zingiberaceae family [21-22]. Seeds of *Aframomum melegueta* are used as spice in African dishes due to its sweet-smelling aroma [23]. Is also serves as a material of ethnomedical preparations used for the treatment of stomach ache, diarrhea, and in some cases snack bite [24-25]. The present work investigates the active components of *Aframomum melegueta* as well as their Sex Hormone Binding Globulin (SHBG) inhibiting potential in male infertility.

MATERIALS AND METHODS

Preparation of plant material

The *Aframomum melegueta* (Alligator pepper) used for this study was obtained from a local market in Owerri Imo State Nigeria and ground into powdered form. It was then

dipped in chloroform and left for 72 hours [26-27] and filtered. The filtrate was evaporated and sent for FTIR and GC-MS studies.

Preparation of Ligands

GC-MS analysis was used to identify 30 compounds from the *Aframomum melengueta* powder. The 3-Dimensional (3D) conformers (SDF files) of the active ingredients were downloaded from the pubchem online data base [28] and used as the ligand for the molecular docking analysis,

Preparation of protein target

The three-dimensional structure of the sex hormone-binding globulin (SHBG) receptor with PDB ID: 1KDM was identified from literature [29] and downloaded from Protein Data Bank (PDB) and formed the target for the docking process. Target preparation was done in discovery studio online software where the interfering crystallographic water particles and the co-crystalized ligand were removed. The amino acids found in the active site of the target are Asp 50, Lys 134, Ala 160, Glu 52, Asp 85, Asn 82, Leu 171, Thr 40, Ser 41, Asp 65

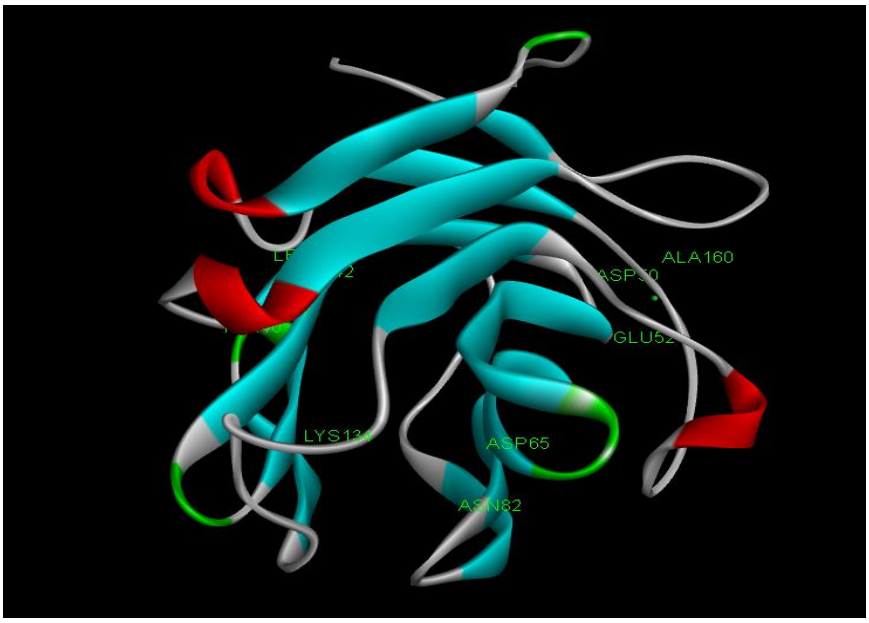


Figure 1 The sex hormone-binding globulin protein target with the active site amino acids

Drug Screening

The suitability of the identified compounds as drug candidates was performed using admetsar online software. Their canonical smiles were retrieved from pubchem software and submitted to admesar for ADMET (absorption, distribution, metabolism, excretion, and toxicity) predictive results. The reason for this screening is to identify the drug like candidate suitable to be recommended as acceptable drug candidate which do not violate more than one of Lipinski's rule of five (Ro5) [30-31], which states that a compound which is to be accepted as drug should have a molecular mass of < 500 Dalton, the hydrogen bond acceptor should be not be more than 10, the hydrogen bond donor should not exceed 5, molar refractive index should be between 40–130, and that the partition coefficient (LogP) should be less than 5.

Molecular docking study

Molecular docking simulation was done between the 30 plant-derived phytochemical and the previously prepared sex hormone-binding globulin protein target using PYRX software. The protein target was used as the macromolecule and the ligands were minimized in PYRX and set as Autodock ligand pdbqt. The docked conformations with the lowest docking energies were ascribed as the best ones [32-33]. The post post-docking visualization of the interaction between the protein target and the ligands was performed in discovery studio.

RESULTS

Phytochemical Results

Fourier transform infrared spectroscopy (FTIR) and gas chromatography-mass spectroscopy experiments were performed on the *Aframomum melegueta* powder to identify the phytochemicals therein. The FTIR result showed the functional groups in Table 1 while the GC-MS analysis revealed 30 compounds with medicinal and therapeutic properties [34]. Figure 2 shows the FTIR spectrum while Figure 3 shows the GC-MS chromatogram. The phytochemical compounds are presented in Table 2.

Table 1 Functional groups from the FTIR spectrum

S/No.	Peak (cm^{-1})	Functional group
1.	3405.1	(O-H) Hydrogen bonded alcohols, phenols
	3004.2	$C-H$ (aromatic ring)
2.	2926.0, 2855.1	C-H (alkyl)

3	1736, 1517.0	1707,	C=O, C=C
4	1267,3		C-C

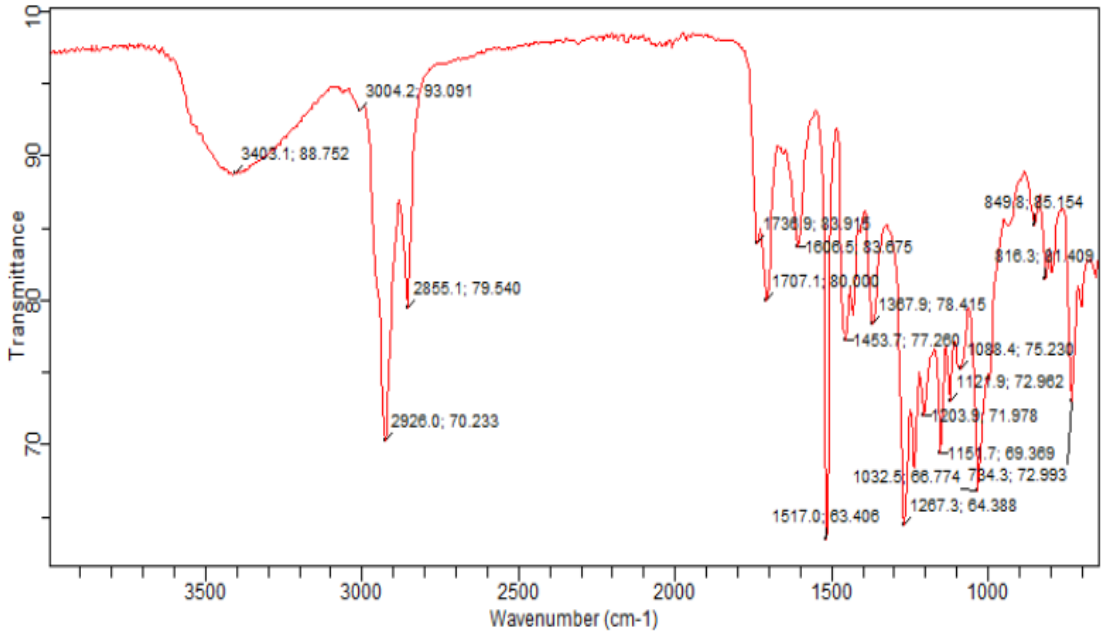


Figure 2 the FTIR spectrum of *Aframomum melegueta*

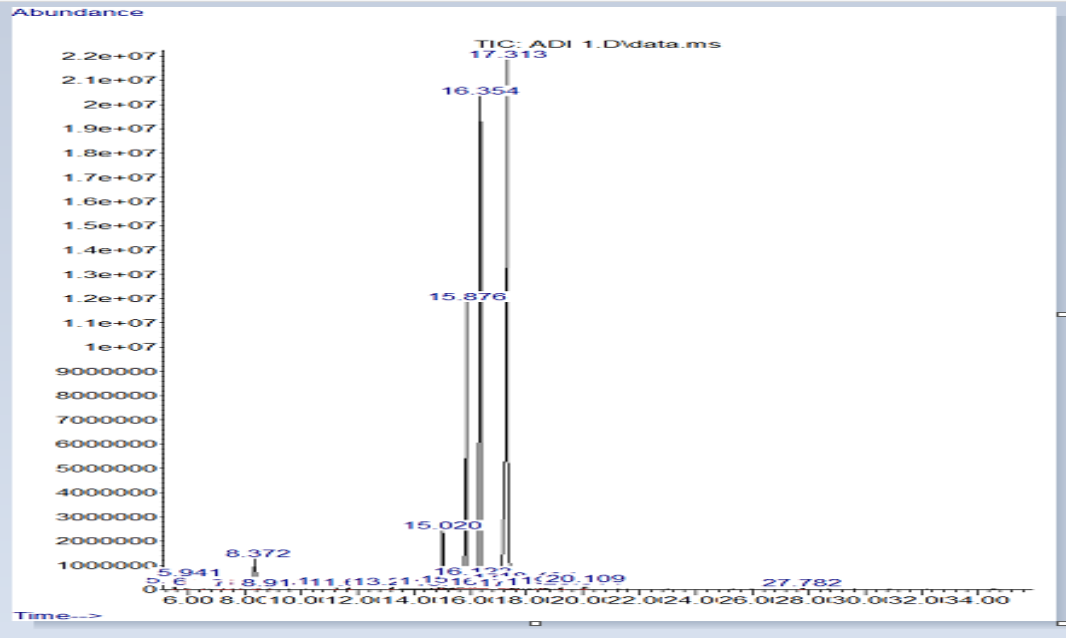
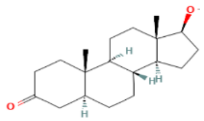
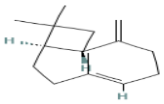
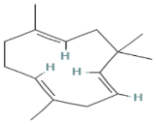
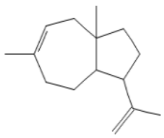
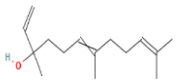
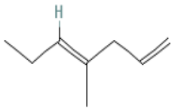
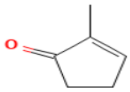
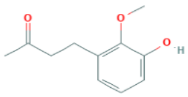
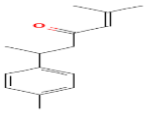
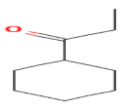
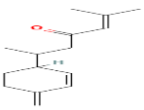
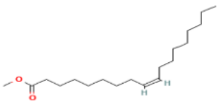
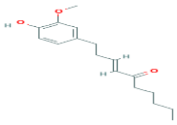
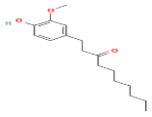


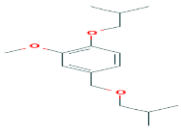
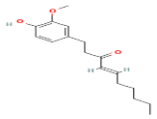
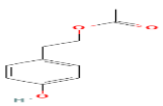
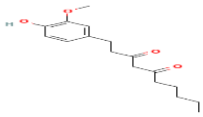
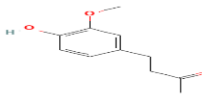
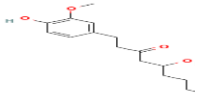
Figure 3. The GC-MS microgram of *Aframomum melegueta*

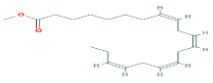
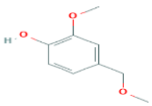
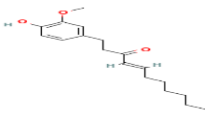
Table 2 Compounds identified from the GC-MS analysis and their docking scores

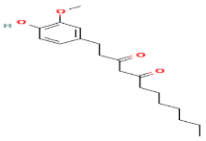
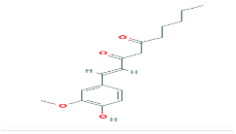
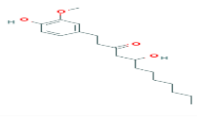
S.no	**Compound**	**Area peak**	**Pubchem id**	**Structure**	**Molecular formula**	**Molecular weight**	**Docking score (k cal mol $^{-1}$)**
1	Androstanolone	Control	10635		$C_{19}H_{30}O_2$	290.4	-11.1
2	Caryophyllene	0.1674	5281515		$C_{15}H_{24}$	204.35	-8.5
3	Humulene	0.4481	5281520		$C_{15}H_{24}$	204.35	-8.5
4	(3S,3aS,8aR)-6,8a-Dimethyl-3-(prop-1-en-2-yl)-1,2,3,3a,4,5,8,8a-octahydroazulene	0.0910	73809332		$C_{15}H_{24}$	204.35	-7.7

5	1,6,10-Dodecatrien-3-ol, 3,7,11-trimethyl-	0.0469	8888		$C_{15}H_{26}O$	222.37	-7.2
6	4-Methyl-1,4-heptadiene	0.0543	5362810		C_8H_{14}	110.20	-5.1
7	2-Cyclopenten-1-one, 2-methyl-	0.0471	14266		C_6H_8O	96.13	-4.9
8.	Butan-2-one, 4-(3-hydroxy-2-methoxyphenyl)-	2.2364	586455		$C_{11}H_{14}O_3$	194.23	-6.8
9.	Ar-tumerone	0.0454	558221		$C_{15}H_{20}O$	216.32	-8.4
10	1-Propanone, 1-cyclohexyl-	0.0466	70748		$C_9H_{16}O$	140.22	-5.9
11	Curlone	0.0334	196216		$C_{15}H_{22}O$	218.33	-8.4

12	Pentadecanoic acid, 14-methyl-, methyl ester	0.0851	21205		$C_{17}H_{34}O_2$	270.5	-4.5
13	n-Hexadecanoic acid	0.0905	985		$C_{16}H_{32}O_2$	256.42	-6.6
14	9-Octadecenoic acid (Z)-, methyl ester	0.1835	5364509		$C_{19}H_{36}O_2$	296.5	
15	(E)-1-(4-Hydroxy-3-methoxyphenyl)dec-3-en-5-one	0.1242	11694761		$C_{17}H_{24}O_3$	276.4	-7.9
16	3-Decanone, 1-(4-hydroxy-3-methoxyphenyl)-	2.7131	94378		$C_{17}H_{26}O_3$	278.4	-4.5
17	1-(3,4-Dimethoxyphenyl)decan-3-one	0.0325	85807832		$C_{18}H_{28}O_3$	292.4	-4.4

18	4-Hydroxy-3-methoxybenzyl alcohol, di(2-methylpropyl) ether	0.3196	91715787		$C_{16}H_{26}O_3$	266.38	-6.8
19	1-(4-Hydroxy-3-methoxyphenyl)dec-4-en-3-one	14.2235	5281794		$C_{17}H_{24}O_3$	276.4	-5.1
20	Tyrosol, acetate	1.1612	637753		$C_{10}H_{12}O_3$	180.20	-6.8
21	1-(4-Hydroxy-3-methoxyphenyl)decane-3,5-dione	32.5600	162952		$C_{17}H_{24}O_4$	292.4	-5.0
22	2-Butanone, 4-(4-hydroxy-3-methoxyphenyl)-	0.0934	31211		$C_{11}H_{14}O_3$	194.23	-7.0
23	5-Hydroxy-1-(4-hydroxy-3-	43.2511	3473		$C_{17}H_{26}O_4$	294.4	-7.0

	methoxyphenyl)decan-3-one						
24	1-(3,4-Dimethoxyphenyl)-5-hydroxydecan-3-one	0.2926	71391212		$C_{18}H_{28}O_4$	308.4	-7.1
25	Methyl 8,11,14,17-eicosatetraenoate	0.0386	14122970		$C_{21}H_{34}O_2$	318.5	-7.0
26	Phenol, 2-methoxy-4-(methoxymethyl)-	0.7151	79662		$C_9H_{12}O_3$	168.19	-5.9
27	1-(4-Hydroxy-3-methoxyphenyl)dodec-4-en-3-one	0.1080	6442560		$C_{19}H_{28}O_3$	304.4	-8.0

28	1-(4-Hydroxy-3-methoxyphenyl)dodecane-3,5-dione	0.2384	14440537		$C_{19}H_{28}O_4$	320.4	-7.7
29	(E)-1-(4-hydroxy-3-methoxyphenyl)dec-1-ene-3,5-dione	0.2171	9796015		$C_{17}H_{22}O_4$	290.4	-8.0
30	5-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)dodecan-3-one	0.2823	5275725		$C_{19}H_{30}O_4$	322.4	-4.3
31	1,7-bis(4-Hydroxy-3-methoxyphenyl)heptane-3,5-dione	0.0536	124072		$C_{21}H_{24}O_6$	372.4	-5.0

Absorption, distribution, metabolism, excretion, and toxicity (ADMET) Results

ADMET properties were predicted using admetsar software; the results are presented

in Table 3. The results showed that none of compounds violated more than one of Lipinski's rule of five [30]. Based on the observed results all the studied compounds can be regarded as good drug lead candidates for the Sex hormone binding globulin.

Table 3 ADMET properties of some of the identified compounds with % > 1

No.	Compound	MW	HIA	AOT	C	BBB	WS	AlogP	HBA	HBD	NRB
1.	Androstanolone	290.45	+	1.996	-	+	-4.098	3.96	2	1	0
2.	Butan-2-one, 4-(3-hydroxy-2-methoxyphenyl)-	194.23	+	2.052	-	-	0.676	1.92	3	1	4
3.	3-Decanone, 1-(4-hydroxy-3-methoxyphenyl)-	278.39	+	1.961	-	+	-3.872	4.26	3	1	10

4.	1-(4-Hydroxy-3-methoxyphenyl)dec-4-en-3-one	276.38	+	2.26	-	+	-4.158	4.04	3	1	9
5.	Tyrosol, acetate	180.20	+	1.711	-	+	-2.475	1.50	3	1	3
6.	1-(4-Hydroxy-3-methoxyphenyl)decane-3,5-dione	292.38	+	2.355	-	+	-3.715	3.44	4	1	10
7.	5-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)decan-3-one	294.4	+	1.864	-	-	-3.234	3.23	2	4	10

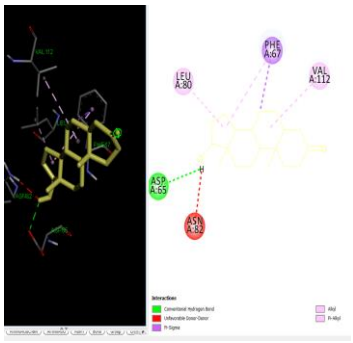
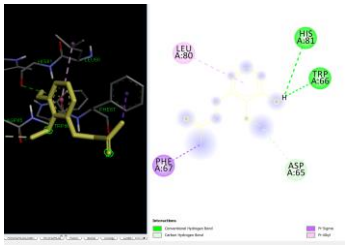
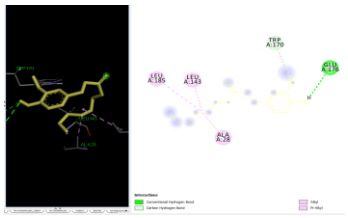
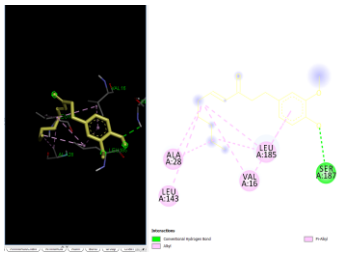
MW-Molecular weight, HBA-Number of hydrogen bond acceptor, HBD-Number of hydrogen bond donor, NRB-Number of rotatable bonds, C- Carcinogenicity,

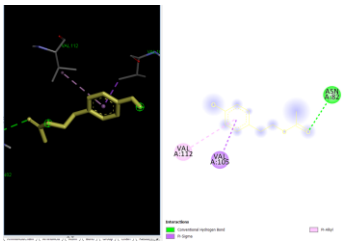
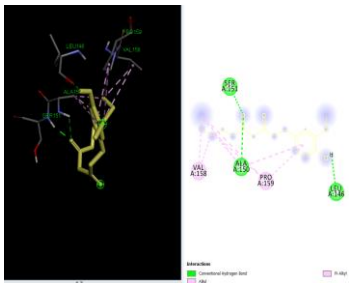
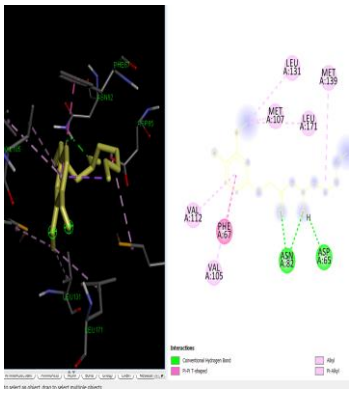
Molecular docking Result

A total of 30 compounds obtained from the GC-MS analysis were docked with the sex hormone-binding globulin protein target using androstanolon as control for the molecular docking interaction to identify the compounds with good binding energies for the studied sex hormone-binding globulin (SHBG) receptor. Table 2 shows the binding scores for the 30 phytochemical compounds and the control while Table 4 show the binding scores, 3D and 2D interactions, forces of interaction and the amino acids involved in the molecular docking of compounds with greater or equal to 2 % in the GC-MS experiment. Low binding energy is an indication that a compound has good interaction with the protein target [35]. Of all the phytochemicals studied, 5-Hydroxy-1-(4-hydroxy-3-methoxyphenyl)decan-3-one which was found to be present in 43.2511% of the sample, gave a binding energy of -7.0 Kcal mol^{-1}. It showed good interaction with the amino acids of the active site (asp 65 & Asn 82). It was found that the compound fitted perfectly into the binding pocket of the sex hormone-binding globulin. All the compounds studied had binding energies lower than -4.0 which is an indication of good interaction between the ligand and protein target.

Table 4: 3D and 2D protein-ligand interaction, amino acid of interaction and forces involved in the molecular docking reactions

S/no.	**Compound**	**Area peak**	**Docking score**	**3D and 2D interactions**	**Amino acids**	**Interaction forces**

1	Androstanolone		-11.1		Asp, 65, Asn 82, Phe 67, Leu 80, Val 112	Conventional hydrogen bond, unfavorable donor-donor, alkyl, pi-sigma, pi-alkyl
2	Butan-2-one, 4-(3-hydroxy-2-methoxyphenyl)-	2.2364	-6.8		Asp 65,Phe 67, Leu 80, His 81, Trp 66	Conventional hydrogen bond , carbon hydrogen bond, pi-sigma, pi-alkyl
3	3-Decanone, 1-(4-hydroxy-3-methoxyphenyl)-	2.7131	-4.5		Ala 28, Trp 170, Glu 176, Leu 143, Leu 185	Conventional hydrogen bond , carbon hydrogen bond, alkyl, pi-alkyl
4	1-(4-Hydroxy-3-methoxyphenyl) dec-4-en-3-one	14.2235	-5.0		Val 16, Ala 28, Leu 143, Leu, 185, Ser 187	Conventional hydrogen bond. Alkyl, pi-alkyl

5	Tyrosol, acetate	1.1612	-6.8		Asn 82, Val 105, Val 112	Conventional hydrogen bond, pi-alkyl, pi-sigma
6	1-(4-Hydroxy-3-methoxyphenyl) decane-3,5-dione	32.56	-5.0		Ala 150, Leu 146, Val 158, Ser 151, Pro 159	Conventional hydrogen bond. Alkyl, pi-alkyl
7	5-Hydroxy-1-(4-hydroxy-3-methoxyphenyl) decan-3-one	43.2511	-7.0		Asp 65, Phe 67, Val 105, Val 112, Met 139, Asn 82, LEU 131, Met 107	Conventional hydrogen bond. Alkyl, pi-alkyl, pi-pi, T-shaped

CONCLUSION

Infertility is a problem that has affected many families today. In African, it is one of the main reasons for divorce. The present work investigates the role of *Aframomum melegueta* (Alligator pepper) in the inhibition of sex hormone-binding globulin (SHBG) in relation to male infertility. FTIR and GC-MS examinations were performed on *Aframomum melegueta* powder to identify the functional groups and active components

therein, Admet examination was used to screen the compounds for drug likeliness while molecular docking was performed to identify the ligand-target interactions between the compound and the sex hormone-binding target. The phytochemical screening revealed 30 compounds. The molecular docking result revealed good interactions between the ligands and target while ADMET study showed that the compounds above 1 % in the GC-MS study represents good drug-lead candidates for the sex hormone-binding globulin studied.

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