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Bioactive effect of Globulixanthone B from symphonia globulifera on spermatogenesis and male infertility (the insilico approach)

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Abstract

Infertility has been one of the most common issue in the medical field, male infertility is more common and can be expressed in several forms, moreover a decrease in male reproductive hormones has been proven to affects spermatogenesis and due to this reason, pharmacognosy has been explored by researchers to provide alternatives for this problem. Symphonia globulifera, a plant widely distributed across the neotropic region and equatorial Africa has been used in traditional medicine due to its potency caused by the presence of potent metabolites.

Objectives: This study is carried out to evaluate the bioactive effect of globulixanthone B on spermatogenesis and male infertility

Method: This study was carried out using molecular docking to analyze the binding energy of the phytocompounds in symphonia globulifera on CYP11A, 3B-HSD, LHR and FSH-R which were furtherly visualized to calculate the chemical properties between the ligands and the receptors then the lead compound was register for druglikeness screening.

Results: This study has shown that Globulixanthone B is a lead compound with a significant binding energy with good binding affinity due to it hydrophobic interactions with the receptors. It has fufilled the five rules of druglikeness properties.

Conclusion: This present work shows that Globulixanthone B is not only an highly efficacious compound but also a therapeutic alternative for boosting spermatogenesis and reducing oligospermia

Keywords: CYP11A • 3B-HSD • Globulixanthone B • HEM • NAG • LHR • FSH-R

Introduction

Infertility is a scenario identified by the inability to conceive after sexual intercourse for about 12 months, it has been shown by the world health organization that males are responsible for about 50% of the cases, male infertility manifests in forms like low sperm count (oligospermia), no sperm count (azoospermia), low sperm motility (asthenozoospermia), low sperm count with low motility (oligoasthenozoospermia) and low sperm count with abnormal sperm morphology (oligoasthenoterazoospermia) which has been confirmed using standard protocols like semen analysis to determine sperm motility, vitality, morphology and concentration and advanced protocols like chemiluminescence assay for quantifying reactive oxygen species (ROS) and antioxidants in the semen, Male Infertility Oxidative System for determination of the oxidation–reduction potential in semen and terminal deoxynucleotidyl transferase mediated dUTP nick-end labelling (TUNEL) assay for determination of sperm DNA fragmentation, The form of infertility targeted in this study is oligospermia [1,2].

However, most forms of infertility are linked to spermatogenesis, a complex process made of events that involves the transformation and differentiation of spermatogonia to matured spermatozoa, this process is takes about 74 days to be completed, it is induced and completed by the participation of some vital hormones in the hypothalamic-pituitary-gonadal axis like GnRH (gonadotropin releasing hormone),LH (luteinizing hormone), FSH (follicle stimulating hormone) and testosterone coupled with some of their receptors, this process is also regulated by LH production by the pituitary gland which is induced by GnRH pulse caused by the hypothalamic GnRH neurons, the LH secreted from the hypothalamus initiates formation of steroids by binding to the Leydig cell LH receptor (LHR) which, through coupling to G protein, stimulates Leydig cell cyclic adenosine 3',5'-monophosphate (cAMP) production which now stimulates cholesterol translocation from intracellular cavities to the mitochondria [3,4]. This is followed by formation of pregnenolone from cholesterol with the the aid of a rate limiting enzyme cholesterol desmolase (CYP11A1) in the mitochondria and then converted to testosterone by 3β-HSD (3β-hydroxysteroid dehydrogenase) in the smooth endoplasmic reticulum, the testosterone converted is a prerequisite for spermatogenesis [5].

Also, FSH, a pituitary gonadotropin binds to it cognate receptor (FSH-R) on the Sertoli cells to stimulates testicular fluid production and synthesis of intracellular androgen receptor proteins to support spermatid maturation.

Proteomics, using the in silico approach has helped to identify and study alteration in the proteins involved in fertility and the proteins necessary for spermatogenesis, this proteins has been shown in previous studies and some were selected in this review as drug targets against the phytocompounds in symphonia globulifera. Symphonia globulifera is a plant known in Africa, south America and other neotropic regions for it potent biological metabolites used in treating several illness like Scabies, Coughs, intestinal worms, prehepatic jaundice, fever, Antiparasitic, Skin disease, malaria, diabetes, Body pain, pulled muscles, fractures, Vaginal discharge and Cutaneous leishmaniasis,

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due to this reason it popularity has grown over the years in traditional medicine and pharmacognosy and has made some of it phytocompounds druggable targets for the treatment of several illness [6,7].

Methodology

Selection and preparation of ligand

The structures of about twenty-eight phytocompounds present in symphonia globulifera according to the GC-MS by Fromentin were obtained from both pubchem compound database (https://pubchem.ncbi.nlm.nih.gov) and chemspider compound database [8].

These compounds where gotten in standard document format (MOL SDF) and were converted to PDBQT format with the use pyRx which also minimizes the energy of the compounds using optimization algorithm at a force field in order to conformation of the atoms, It was set at uff which is a force field for all atoms which is required on pyRx [9,10].

Preparation of target protein

The proteins targeted in this study are CYP11A (cholesterol desmolase or p450scc) (PDB:3n9y), LHR (luteinizing hormone receptor) (PDB:1lut), FSH-R (follicle stimulating hormone receptor) (PDB: 1xwd) and 3β-HSD (3β-hydroxysteroid dehydrogenase) whose FASTA sequence was obtained from uniprot webserver (https://www.uniprot.org/) and converted to protein databank (pdb) format using the open babel tool .The proteins obtained from the protein databank webserver were retrieved alongside with their co-crystallized ligands which are (PDB:HEM) for CYP11A and (PDB:NAG) for FSH-R except the LHR which was a theoretical model also from the protein databank webserver, RCSB PDB.[11] he appropriate co-crystallized ligand was identified and extracted around the active binding pocket by set measures, water and other co-crystallized molecules were removed during the course of preparing the targeted protein using the Pymol tool [12,13].

Accession and preparation of standard

The standards used in the present study are the co-crystalized ligand of the targeted proteins with the ID (PDB:HEM) with the structural formula of (3-[(5Z,10Z,14Z,19Z)-18-(2-carboxyethyl)-8,13-bis(ethenyl)-3,7,12,17-tetramethyl-21,23-dihydroporphyrin-2-yl]propanoic acid), a molecular formula of C34 H32 Fe N4 O4 and a molecular weight of 616.49, (PDB:NAG) with the structural formula of (n-acetyl-d-glucosamine) and a molecular weight of 616.49 then enclomiphene citrate, with a structural formula of C8 H15 N O6. The ligands (HEM and NAG) were extracted from their targeted proteins while enclomiphene citrate was obtained from the pubchem compound database (https://pubchem.ncbi.nlm.nih.gov), the ligands were all prepared using the Pymol tool and converted to PDBQT format after energy minimization which was done using the pyRx tool at the set force field (uff) [14].

Molecular docking using PyRx

After the preparation of the protein and ligand, molecular docking analysis was done using the PyRx tool whose Autodock vina analyses docking results as scores. After the energy minimization and conversion to PDBQT, the ligands and the targets were selected for docking protocol and the resolution of the grid box was taken along the x, y and z axes respectively at a dimension of 25 x 25 x 25 Å to define the binding site of the protein [15,16].

The standards were docked against the receptors CYP11A, 3β-HSD, LHR, and FSH-R and were compared to the phytocompounds of symphonia globulifera also in the same binding site [17].

Validation of docking protocol

The docking pose obtained were validated by redocking of the standard ligands into the catalytic domain or binding site of the proteins used for the study by using the PyRx tool.

Results and Discussion

Cholesterol side-chain cleavage enzyme (cyp11a) is a steroidogenic enzyme that belongs to the cytochrome p450 superfamily of enzymes whose function is to convert cholesterol to pregnenolone in the mitochondria, therefore it is logical to say cyp11a plays an agonizing function towards the formation of testosterone and thereby inducing spermatogenesis and the inhibition of it function will cause spermatogenic defects (Figures 1-6).

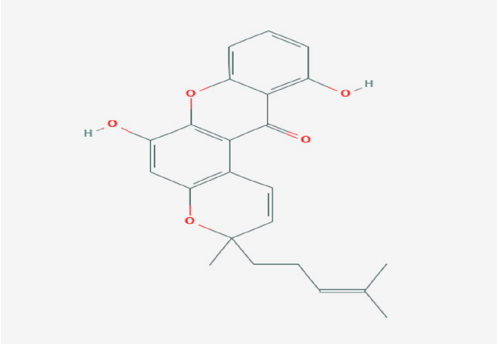

Figure 1: Structure of Globulixanthone B.

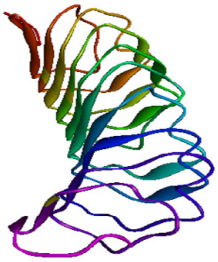

Figure 2: 3D structure of prepared LH receptor.

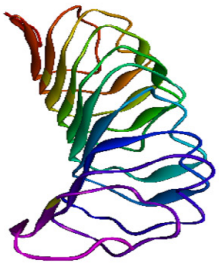

Figure 3: 3D structure of prepared FSH receptor.

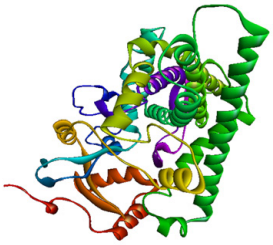

Figure 4: Diagram showing a prepared 3D cholesterol side cleavage enzyme.

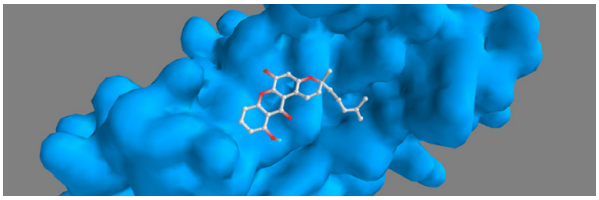

Figure 5: A molecular view of globulixanthone B in it binding site in LH-receptor (LHR).

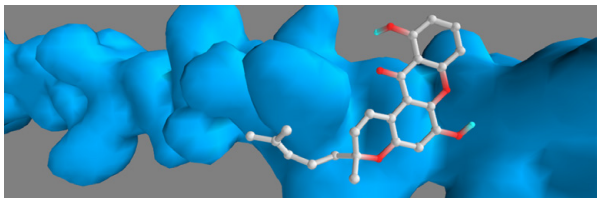

Figure 6: Globulixanthone B in it binding site in 3β-Hydroxysteroid dehydrogenase (3β-HSD).

3β-Hydroxysteroid dehydrogenase (3β-HSD) is also a steroidogenic enzyme that belongs to the family of oxidoreductases that act on the CH-OH group with acceptors like NAD+ or NADP+, they are also involved in estrogen and androgen metabolism and they have two isoforms HSD3B1 and HSD3B2. 3β-HSD converts pregnenolone to testosterone in the endoplasmic reticulum of the Leydig cell, therefore, inhibition of this enzyme will cause some forms of male infertility (Figures 7-13).

Luteinizing hormone receptor (LHR) is a transmembrane receptor that is found in the Leydig cell with about 674 amino acids and a molecular mass

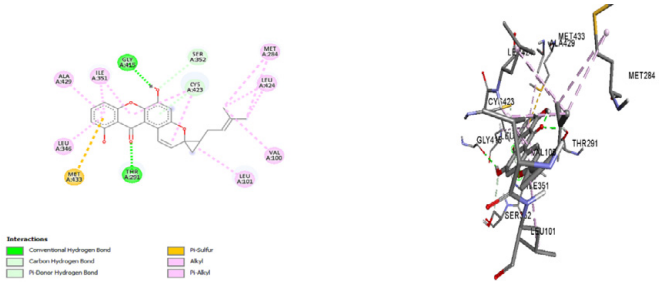

Figure 7: Globulixanthone B interacts with CYP11A.

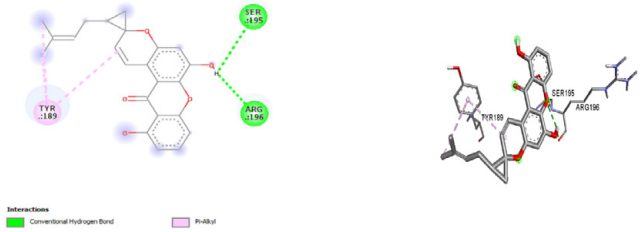

Figure 8: Globulixanthone B interacts with 3B-HSD.

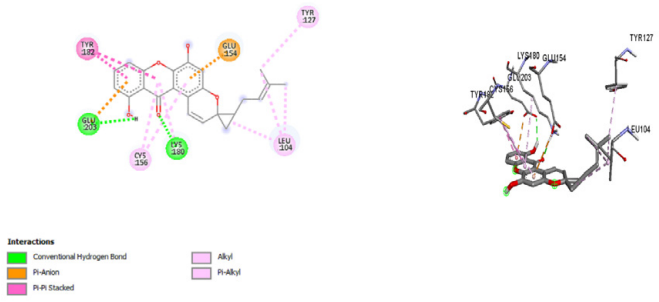

Figure 9: Globulixanthone B interacts with CYP11A, 3B-HSD, LHR.

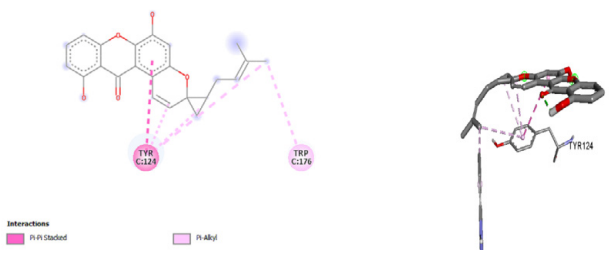

Figure 10: Gobulixanthone B interacts with FSHR.

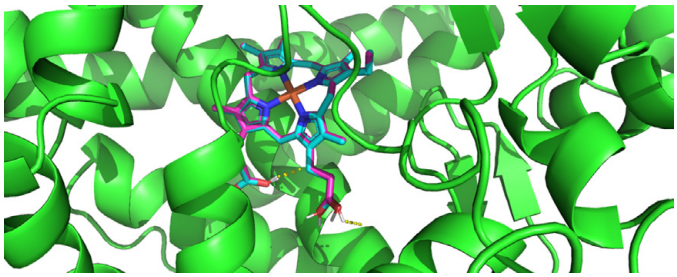

Figure 11: the overlapping pose of HEM in CYP11A, the presence of two colors on the ligands indicates the presence of two identical compounds with the same docking pose.

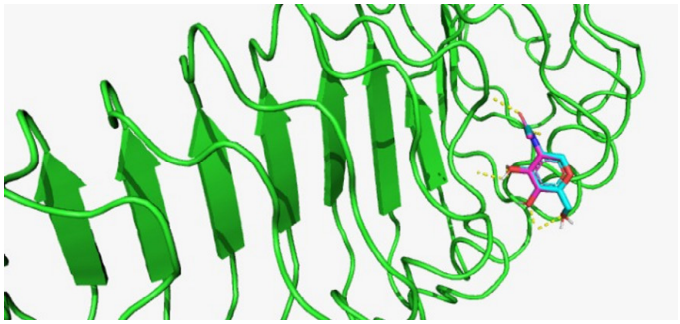

Figure 12: A superimposed pose of NAG in FSHR indicated by the presence of two colors.

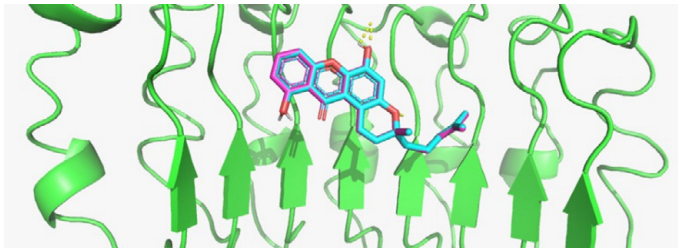

Figure 13: A totally overlapped pose of globulixanthone in LHR indicated by double colors on the ligand.

of about 85–95 kDA, this receptor stimulates the production of Leydig cell cyclic adenosine 3',5'-monophosphate (cAMP) with the aid of G protein coupling receptor (GPCR). There by the inhibition of this receptor will prevent the translocation of cholesterol into the mitochondria and also prevent cholesterol conversion (Tables 1-8).

Follicle-stimulating hormone receptor (FSHR) is also a transmembrane receptor found on the sertoli cells that interacts with fsh to enhance the functionality of the hormone which is of nutritional benefit to developing spermatozoa which makes the receptor a critical one for spermatogenesis.

These receptors are necessary and equally important for spermatogenesis, inhibition of any of these receptors will lead to several forms of male infertility, this reason makes them pharmacological targets to either improve spermatogenesis or cure some forms of male infertility.

Therefore, twenty-eight phytocomponds gotten from the plant were docked into the druggable pocket for their agonistic property and it was discovered that morelloflavone with the chemspider id 4576660 and globulixanthone B with the pubchem id 10452251 had repetitive high binding energy in all the receptors in comparison to the standard enclomiphene citrate with the pubchem id 6420009 andsome co-crystallized ligand like NAG (from FSHR) and HEM (from CYP11A) as shown in table 2-5. Though morelloflavone had the highest binding energy it failed the ADME evaluation test and the drug-likeness test by expressing 25%, 50%, 66.67%, 33.33% and 40% after subjection to Lipinski's, Ghose's, Oprea's, Verber's and Varma's rules respectively therefore globulixanthone B was selected and it expressed 75%, 100%, 66.67%, 100% and 100% after subjection to the same set of drug-likeness rules.

Table 1: A table showing the Lipinski's, Ghose's, Opera's, Varma's and Verber's drug-like properties of Globulixanthone B, 'a set of rules describing pharmacokinetic properties (absorption, distribution, metabolism, and excretion ("ADME")) of drug in the human body using an online webserver (http://admet.scbdd.com). MW= Molecular weight, Hacc=Hydrogen acceptor, Hdon=Hydrogen donor, natoms=number of atoms, nRotbound=Number of ratable bound, TPSA=Topological surface area, N=Number and MR=Molar Refractivity'(oche et al., 2018).

Lipinski's Rule	Ghose' s Rule	Opera's Rule	Varma' s Rule	Verber's Rule
(MV<=500) globulixanthone B = 378.424	(-5.6 <McLog P< -0.4 Mean = 2.52) globulixanthone B = 5.268	(nrings≥3) globulixanthone B = 4	(MW<=500) globulixanthone B = 378.424	(nRotbond=12) globulixanthone B = 3
(LogP <= 5) globulixanthone B =5.268	(160<MW<480 Mean = 357) globulixanthone B =378.424	(nrigidbond≥18) globulixanthone B = 28	(TPSA <=125) globulixanthone B = 79.9	(TPSA<=140) globulixanthone B = 79.9
(Hacc<= 10) globulixanthone B =5	(40<MR<130 Mean = 97) globulixanthone B = 110.052	(nRotbond≥6) globulixanthone B = 3	(-5<LogD<-2) globulixanthone B = 1.667	(Hacc + Hdon=12) globulixanthone B = 7
(Hdon<= 5) globulixanthone B = 2	(20<natoms<70 Mean = 48) globulixanthone B = 50		(Hacc + Hdon=9) globulixanthone B = 7	
75%	100%	66.67%	100%	100%

Table 2: Docking scores and RMSD values of the phytocompounds of symphonia globulifera against FSH receptor

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
Xanthone vi	-1.9	0	0
Symphoxanthone	-5.8	0	0
Symphonone H	-6.7	0	0
Symphonone I	-4.9	0	0
Symphonone G	-4.8	0	0
Symphonone F	-5.7	0	0
Symphonone E	-4.9	0	0
Symphonone D	-5.6	0	0
Symphonone C	-2.3	0	0
Symphonone B	-7.3	0	0
Symphonone A	-5.8	0	0
symphonin	-6.4	0	0
Globuxanthone	-6.2	0	0
Globulixanthone C	-6.1	0	0
Globulixanthone B	-7.3	0	0
Globulixanthone A	-5.8	0	0
globuliferin	-6.4	0	0
7-epi isogarcinol	-5.3	0	0
7-epi garcinol	-4.8	0	0
14-Deoxy-7-epi-isogarcinol	-3.6	0	0
1356_tetrahdroxyxanthone	-6	0	0
morelloflavone	-7.9	0	0
ugaxanthone	-5.6	0	0
noratriol	-5.8	0	0
156_trihdroxyxanthone	-5.7	0	0
gentisein	-5.7	0	0
17_dihdroxyxanthone	-5.9	0	0
NAG	-5.8	0	0
Clomiphene citrate	-4.3	0	0

Table 3: Docking scores and RMSD values of the phytocompounds of symphonia globulifera against 3B-HSD receptor

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
globuliferin	-6.1	0	0
Globulixanthone B	-6.9	0	0
symphonin	-6.4	0	0
symphoxanthone	-6	0	0
7-epi-isogarcinol	-6.5	0	0
Symphonone A	-6.8	0	0
Symphonone B	-6.2	0	0
Symphonone C	-6.2	0	0
Symphonone D	-6.9	0	0
Symphonone E	-7	0	0
Symphonone F	-6.7	0	0
Symphonone G	-6.8	0	0
Symphonone H	-6.4	0	0
Symphonone I	-6.5	0	0
7-epi garcinol	-5.5	0	0
14-Deoxy-7-epi-isogarcinol	-6.9	0	0
Xanthone vi	-1.5	0	0
17_dihdroxyxanthone	-5.2	0	0
gentisein	-5.2	0	0
156_trihdroxyxanthone	-5.5	0	0
noratriol	-5.1	0	0
ugaxanthone	-6	0	0
morelloflavone	-7.4	0	0
1356_tetrahdroxyxanthone	-5.3	0	0
Globulixanthone C	-6.6	0	0
Globulixanthone A	-5.9	0	0
globuxanthone	-6	0	0
Clomiphene citrate	-3.7	0	0

The high binding affinity of globulixanthone B is thought to be as a result of it large number of hydrophobic interactions (twelve in CYP11A in comparison to none in clomiphene, nine in LHR in comparison to none in clomiphene, three in 3B-HSD in comparison to none in clomiphene and five in FSHR in comparison to none in both clomiphene and NAG) that encloses hydrogen bond binding it to it receptor.

The accuracy of the docking protocol was attained by redocking of the co-crystalized ligand HEM and NAG then also globulixanthone into the binding site of CYP11A, FSHR and LHR respectively and the redock pose showed that the ligands were superimposed perfectly with a total overlap with the experimental pose and this proves the accuracy of autodock vina of PyRx docking protocol and also validates the methodology behind the docking scores (Tables 9-15).

Table 4: Docking scores and RMSD values of the phytocompounds of symphonia globulifera against CYP11A receptor.

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
globuliferin	-8.7	0	0
Globulixanthone B	-10.5	0	0
Symphorin	-9.9	0	0
symphoxanthone	-8.8	0	0
7-epi-isogarcinol	-11.3	0	0
Symphonone A	-11.3	0	0
Symphonone B	-10.7	0	0
Symphonone C	-10.3	0	0
Symphonone D	-10.1	0	0
Symphonone E	-10.8	0	0
Symphonone F	-10.9	0	0
Symphonone G	-10.8	0	0
Symphonone H	-11	0	0
Symphonone I	-8.6	0	0
7-epi garcinol	-9.4	0	0
14-Deoxy-7-epi-isogarcinol	-10.2	0	0
Xanthone vi	-2.1	0	0
17_dihdroxyxanthone	-8	0	0
gentisein	-7.9	0	0
156_trihdroxyxanthone	-7.8	0	0
noratriol	-7.7	0	0
ugaxanthone	-8.6	0	0
morelloflavone	-12.3	0	0
1356_tetrahdroxyxanthone	-7.7	0	0
Globulixanthone C	-9.4	0	0
Globulixanthone A	-8.9	0	0
Globuxanthone	-8.6	0	0
HEM	-11.9	0	0
Clomiphene citrate	-5.6	0	0

Table 5: Docking scores and RMSD values of the phytocompounds of symphonia globulifera against LH receptor.

Ligand	Binding Affinity	rmsd/ub	rmsd/lb
globuliferin	-6.1	0	0
Globulixanthone B	-7.8	0	0
symphonin	-6.9	0	0
symphoxanthone	-7.2	0	0
7-epi-isogarcinol	-6.4	0	0
Symphonone A	-5.8	0	0
Symphonone B	-7	0	0
Symphonone C	-5.7	0	0
Symphonone D	-5.4	0	0
Symphonone E	-5.4	0	0
Symphonone F	-5.7	0	0
Symphonone G	-5.6	0	0
Symphonone H	-6.4	0	0
Symphonone I	-5.2	0	0
7-epi garcinol	-5.2	0	0
14-Deoxy-7-epi-isogarcinol	-5.7	0	0
Xanthone vi	-1.9	0	0
17_dihdroxyxanthone	-6.6	0	0
gentisein	-6.8	0	0
156_trihdroxyxanthone	-7	0	0
noratriol	-6.6	0	0
ugaxanthone	-6.9	0	0
morelloflavone	-6.9	0	0
1356_tetrahdroxyxanthone	-7	0	0
Globulixanthone C	-7.3	0	0
Globulixanthone A	-6	0	0
globuxanthone	-7	0	0
Clomiphene citrate	-4.4	0	0
Clomiphene citrate	-5.6	0	0

Table 6: Interaction table showing several chemical interactions of globulixanthone B within the binding pocket of LHR.

Names	`Category	Types
1. .:LYS180:HZ2 - N:UNK1:O	Hydrogen Bond	Conventional Hydrogen Bond
2. N:UNK1:H - .:GLU203:OE2	Hydrogen Bond	Conventional Hydrogen Bond
3. .:GLU154:OE1 - N:UNK1	Electrostatic	Pi-Anion
4. .:GLU203:OE1 - N:UNK1	Electrostatic	Pi-Anion
5. .:TYR182 - N:UNK1	Hydrophobic	Pi-Pi Stacked
6. .:TYR182 - N:UNK1	Hydrophobic	Pi-Pi Stacked
7. N:UNK1 - .:LEU104	Hydrophobic	Alkyl
8. N:UNK1:C - .:LEU104	Hydrophobic	Alkyl
9. N:UNK1:C - .:LEU104	Hydrophobic	Alkyl
10. .:TYR127 - N:UNK1:C	Hydrophobic	Pi-Alkyl
11. N:UNK1 - .:CYS156	Hydrophobic	Pi-Alkyl
12. N:UNK1 - .:LYS180	Hydrophobic	Pi-Alkyl

Table 7: Interaction table showing several chemical interactions of clomiphene citrate (standard) within the binding pocket of LHR.

Names	Category	Types
1. .:LYS180:HZ1 - N:UNK1:O	Hydrogen Bond	Conventional Hydrogen Bond
2. .:LYS180:HZ3 - N:UNK1:O	Hydrogen Bond	Conventional Hydrogen Bond

Table 8: Interaction table showing several chemical interactions of globulixanthone B within the binding pocket of 3B-HSD.

Names	Category	Types
1. N:UNK1:H - .:SER195:O	Hydrogen Bond	Conventional Hydrogen Bond
2. N:UNK1:H - .:ARG196:O	Hydrogen Bond	Conventional Hydrogen Bond
3. .:TYR189 - N:UNK1	Hydrophobic	Pi-Alkyl
4. .:TYR189 - N:UNK1:C	Hydrophobic	Pi-Alkyl
5. .:TYR189 - N:UNK1:C	Hydrophobic	Pi-Alkyl

Table 9: Interaction table showing several chemical interactions of clomiphene citrate (standard) within the binding pocket of 3B-HSD.

Name	Category	Types
1. .:ARG196:HN - N:UNK1:O	Hydrogen Bond	Conventional Hydrogen Bond
2. N:UNK1 3. :H - .:GLU193:O	Hydrogen Bond	Conventional Hydrogen Bond
3. N:UNK1:H - .:SER195:O	Hydrogen Bond	Conventional Hydrogen Bond
4. N:UNK1:H - .:ARG196:O	Hydrogen Bond	Conventional Hydrogen Bond

Table 10: Interaction table showing several chemical interactions of globulixanthone B within the binding pocket of FSH-R.

Names	Category	Types
1. N:UNK1:H - N:UNK1:O	Hydrogen Bond	Conventional Hydrogen Bond
2. C:TYR124 - N:UNK1	Hydrophobic	Pi-Pi Stacked
3. C:TYR124 - N:UNK1	Hydrophobic	Pi-Alkyl
4. C:TYR124 - N:UNK1	Hydrophobic	Pi-Alkyl
5. C:TYR124 - N:UNK1:C	Hydrophobic	Pi-Alkyl
6. C:TRP176 - N:UNK1:C	Hydrophobic	Pi-Alkyl

Table 11: Interaction table showing several chemical interactions of clomiphene citrate (standard) within the binding pocket of FSH-R.

Name	Category	Types
1. C:ARG101:HH21 - N:UNK1:O	Hydrogen Bond	Conventional Hydrogen Bond
2. C:TYR124:HH - N:UNK1:O	Hydrogen Bond	Conventional Hydrogen Bond
3. C:SER128:HG - N:UNK1:O	Hydrogen Bond	Conventional Hydrogen Bond
4. C:SER128:HG - N:UNK1:O	Hydrogen Bond	Conventional Hydrogen Bond
5. C:GLN152:HE21 - N:UNK1:O	Hydrogen Bond	Conventional Hydrogen Bond
6. N:UNK1:H - C:GLU103:OE1	Hydrogen Bond	Conventional Hydrogen Bond
7. N:UNK1:H - C:ASP153:OD2	Hydrogen Bond	Conventional Hydrogen Bond
8. N:UNK1:H - C:ASP150:OD2	Hydrogen Bond	Conventional Hydrogen Bond
9. N:UNK1:H - C:GLN152:OE1	Hydrogen Bond	Conventional Hydrogen Bond

Table 12: Interaction table showing several chemical interactions of NAG (co-crystalized standard) within the binding pocket of FSH-R.

Names	Category	Types
1. C:HIS139:HD1 - N:UNK1:O	Hydrogen Bond	Conventional Hydrogen Bond
2. C:GLU161:HN - N:UNK1:O	Hydrogen Bond	Conventional Hydrogen Bond
3. N:UNK1:H - C:LEU135:O	Hydrogen Bond	Conventional Hydrogen Bond
4. N:UNK1:H - C:PRO136:O	Hydrogen Bond	Conventional Hydrogen Bond
5. N:UNK1:C - C:SER164:OG	Hydrogen Bond	Carbon Hydrogen Bond
6. N:UNK1:C - C:ASN163:O	Hydrogen Bond	Carbon Hydrogen Bond
7. N:UNK1:H - C:ASP153:OD2	Hydrogen Bond	Conventional Hydrogen Bond
8. N:UNK1:H - C:ASP150:OD2	Hydrogen Bond	Conventional Hydrogen Bond
9. N:UNK1:H - C:GLN152:OE1	Hydrogen Bond	Conventional Hydrogen Bond

Table 13: Interaction table showing several chemical interactions of globulixanthone B within the binding pocket of CYP11A.

1. A:THR291:HG1 - N:UNK1:O	Hydrogen Bond	Conventional Hydrogen Bond
2. N:UNK1:H - A:GLY415:O	Hydrogen Bond	Conventional Hydrogen Bond
3. N:UNK1:H - N:UNK1:O	Hydrogen Bond	Conventional Hydrogen Bond
4. A:SER352:CB - N:UNK1:O	Hydrogen Bond	Carbon Hydrogen Bond
5. A:CYS423:SG - N:UNK1	Hydrogen Bond	Pi-Donor Hydrogen Bond
6. A:MET433:SD - N:UNK1	Other	Pi-Sulfur
7. 7. A:CYS423 - N:UNK1	Hydrophobic	Alkyl
8. N:UNK1 - A:LEU101	Hydrophobic	Alkyl
. N:UNK1:C - A:VAL100	Hydrophobic	Alkyl
10. N:UNK1:C - A:MET284	Hydrophobic	Alkyl
11. N:UNK1:C - A:LEU424	Hydrophobic	Alkyl
12. N:UNK1:C - A:MET284	Hydrophobic	Alkyl
13. N:UNK1:C - A:LEU424	Hydrophobic	Alkyl
14. N:UNK1 - A:ILE351	Hydrophobic	Pi-Alkyl
15. N:UNK1 - A:CYS423	Hydrophobic	Pi-Alkyl
16. N:UNK1 - A:LEU346	Hydrophobic	Pi-Alkyl
17. N:UNK1 - A:ILE351	Hydrophobic	Pi-Alkyl
18. N:UNK1 - A:ALA429	Hydrophobic	Pi-Alkyl

Table 14: Interaction table showing several chemical interactions of clomiphene citrate (standard) within the binding pocket of CYP11A.

Name	Category	Types
1. A:SER452:HG - N:UNK1:O	Hydrogen Bond	Conventional Hydrogen Bond
2. A:LYS466:HZ3 - N:UNK1:O	Hydrogen Bond	Conventional Hydrogen Bond
3. N:UNK1:H - A:SER452:O	Hydrogen Bond	Conventional Hydrogen Bond
4. N:UNK1:H - A:SER452:OG	Hydrogen Bond	Conventional Hydrogen Bond
5. N:UNK1:H - A:HIS450:O	Hydrogen Bond	Conventional Hydrogen Bond
6. N:UNK1:H - N:UNK1:O	Hydrogen Bond	Conventional Hydrogen Bond

Table 15: Interaction table showing several chemical interactions of HEM (co-crystalized standard) within the binding pocket of CYP11A.

1. A:ARG81:HH11 - N:UNK1:O	**Hydrogen Bond**	**Conventional Hydrogen Bond**
2. A:ARG81:HH21 - N:UNK1:O	Hydrogen Bond	Conventional Hydrogen Bond
3. A:SER352:HG - N:UNK1:O	Hydrogen Bond	Conventional Hydrogen Bond
4. A:CYS423:SG - N:UNK1:N	Hydrogen Bond	Conventional Hydrogen Bond
5. A:CYS423:SG - N:UNK1:N	Hydrogen Bond	Conventional Hydrogen Bond
6. A:LEU424:HN - N:UNK1:O	Hydrogen Bond	Conventional Hydrogen Bond
7. N:UNK1:H - A:ARG421:O	Hydrogen Bond	Conventional Hydrogen Bond
8. N:UNK1:H - A:GLN422:O	Hydrogen Bond	Conventional Hydrogen Bond
9. N:UNK1:Fe - A:CYS423:SG	Other	Metal-Acceptor
10. N:UNK1:Fe - N:UNK1:N	Other	Metal-Acceptor
11. N:UNK1:Fe - N:UNK1:N	Other	Metal-Acceptor
12. A:LEU424:HN - N:UNK1	Hydrogen Bond	Pi-Donor Hydrogen Bond
13. N:UNK1:C - A:PHE416	Hydrophobic	Pi-Sigma
14. A:GLY287:C,O;GLY288:N - N:UNK1	Hydrophobic	Amide-Pi Stacked
15. A:ALA429 - N:UNK1:C	Hydrophobic	Alkyl
16. A:ALA429 - N:UNK1:C	Hydrophobic	Alkyl
17. N:UNK1:C - A:LEU424	Hydrophobic	Alkyl
18. N:UNK1:C - A:ILE171	Hydrophobic	Alkyl
19. N:UNK1:C - A:ILE351	Hydrophobic	Alkyl
20. N:UNK1:C - A:LEU355	Hydrophobic	Alkyl
21.N:UNK1:C - A:ILE428	Hydrophobic	Alkyl
22. N:UNK1:C - A:LEU346	Hydrophobic	Alkyl
23. A:PHE416 - N:UNK1:C	Hydrophobic	Pi-Alkyl
24. N:UNK1 - A:CYS423	Hydrophobic	Pi-Alkyl
25. N:UNK1 - A:CYS423	Hydrophobic	Pi-Alkyl
26. N:UNK1 - A:ALA429	Hydrophobic	Pi-Alkyl
27. N:UNK1 - A:CYS423	Hydrophobic	Pi-Alkyl
28. N:UNK1 - A:ILE351	Hydrophobic	Pi-Alkyl
29. N:UNK1 - A:CYS423	Hydrophobic	Pi-Alkyl
30. N:UNK1 - A:ALA429	Hydrophobic	Pi-Alkyl

Conclusion

In conclusion, this in silico review and ADMET evaluation has shown that globulixanthone B, a drug-able compound derived from symphonia globulifera plays an active role in boosting the process of spermatogenesis by agonizing CYP11A, 3B-HSD, LHR and FSHR and this makes it an inhibitor of male infertility.

References

1. Ambrose GO. Selection of Luteolin as a potential antagonist from molecular docking analysis of EGFR mutant. Bioinformation 14(2008): 241-247.
2. Arannilewa AJ. Molecular docking analysis of Cianidanol from Ginkgo biloba with HER2+ breast cancer target. Bioinformation 14(2018): 482-487.
3. Fromentin. Symphonia Globulifera, a widespread source of complex metabolites with potent biological activities. Planta Med 81(2015): 95–107.
4. Lazar Z. K, Lian H, Po-Ki L, Hao F et al. The Hypothalamic GnRH Pulse Generator: Multiple Regulatory Mechanisms. Trends Endocrinol Metab. 20(2009): 402–408.
5. Barry R. Z, Vassilios P. Leydig cells: formation, function, and regulation. Biology of Reproduction 99(2018): 101–111
6. Olayiwola O. O, Hellevi P and Ilpo T. H. Role of Follicle-Stimulating Hormone in Spermatogenesis. Frontiers in Endocrinology 736(2018): 1-11
7. Qing R. F and Wayne A. H. Structure of human follicle-stimulating hormone in complex with its receptor. Nature 433(2005):269-277.
8. Ascoli M, Fanelli F and Segaloff DL. The lutropin/choriogonadotropin receptor, a 2002 perspective. Endocrine Reviews 23 (2002): 141–74.
9. Dufau ML. The luteinizing hormone receptor. Annual Review of Physiology 60(1998): 461–96.
10. Hanukoglu I. Steroidogenic enzymes: structure, function, and role in regulation of steroid hormone biosynthesis. The JSter BiochemMol Bio 43 (1992): 779–804.
11. Lavoie HA and King SR. Transcriptional regulation of steroidogenic genes: STARD1, CYP11A1 and HSD3B. Experimental Biology and Medicine. 234 (2009): 880–907.
12. Simard J et al (2005). Molecular biology of the 3beta-hydroxysteroid dehydrogenase/delta5-delta4 isomerase gene family. Endocr. Rev. 26 (4): 525–82.
13. Lachance Y. Characterization of human 3 beta-hydroxysteroid dehydrogenase/delta 5-delta 4-isomerase gene and its expression in mammalian cells. J.Biol. Chem. 267 (1992): 3551.
14. Andrzej T. SNovel activities of CYP11A1 and their potential physiological significance. Steroid Biochem. Mol. Biol.(2015).
15. Maria PP and Claudio S. Role of RNA-binding proteins in mammalian spermatogenesis. Int J Andrology 33(2010): 2–12.
16. Manesh KPS and Ashok A. Update on the proteomics of male infertility: A systematic review. Arab Journal of Urology 16(2018): 103–112.
17. Holly A.L and Steven R.K. Transcriptional Regulation of Steroidogenic

Genes: STARD1, CYP11A1 and HSD3B. Exp Biol Med (Maywood) 234(2009): 880.

18. Elaheh O. The Effect of Compound Herbal Remedy Used in Male Infertility on Spermatogenesis and Pregnancy Rate. International Journal of Women's Health and Reproduction Sciences Vol. 4(2016): 185–188.

19. Ambrose GO. QSAR Model Generation of Phthalazinones as Poly (ADP-Ribose) Polymerase Inhibitors by the Genetic Algorithm and Multiple Linear Regression (GA-MLR) Method: A Ligand-Based Approach for Cancer Drug Design. J Proteomics Bioinform 11(2018): 183-191.

20. http://www.rcsb.org/pdb/home/home.do

21. Ashok A, Manesh K S and Saradha B. Proteomic Analyses of Human Sperm Cells: Understanding the Role of Proteins and Molecular Pathways Affecting Male Reproductive Health. Int. J. Mol. Sci. 21(2020): 1621.

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