Journal of Science and Practice of Pharmacy
December 2023; 10 (1): 522-532
Available at http://www.jsppharm.org; https://doi.org/10.47227/jsppharm.v10i1.5
ISSN: 2449-0458 (print); 2449-0466 (electronic)

Original Research Article

Molecular docking assessment of the tocolytic potential of phytoconstituents of five medicinal plants used against preterm labour

Uyi M Ogbeide*, Eunice Oriotor and Henry A Okeri
Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Benin, PMB 1154, Benin City, 300001, Nigeria.

* For correspondence: *Email: uyi.ogbeide@uniben.edu. Tel: 07038058676*

Abstract

Introduction: Preterm labour is currently being treated with a number of medications with untoward side effects, but many medicinal plants have also been found useful. This study aims to assess the tocolytic potentials of the phytoconstituents of *Barteria fistulosa*, *Ficus capensis*, *Ficus exasperate*, *Newbouldia laevis* and *Zingiber officinale*.
Methods: Phytoconstituents present in these plants were obtained from literature sources, their 3D SDF structures were obtained from PubChem; the protein Beta-2 adrenergic receptor (7DHI) was processed using Chimera and molecular docking was done using PyRx software. Post-docking analysis was done using Bio-discovery Studio 2.0 and ADMET profiling was done using the Swiss ADME web server and ProTox-II virtual lab.
Results: A binding affinity value of less than -7 kcal/mol was found for nine (9) phytoconstituents in *Zingiber officinale*, fourteen (14) phytoconstituents in *Ficus capensis*, three (3) phytoconstituents in *Ficus exasperata*, one (1) phytoconstituent in *Barteria fistulosa* and forty-four (44) phytoconstituents in *Newbouldia laevis*. Following post-docking analysis and ADMET profiling of specific ligands from the plants, Kaempferol, Chrysoeriol and Lapachol - all present in *Newbouldia laevis* - were identified as putative drug molecules based on their higher binding affinity and hydrogen bond interaction with the target proteins' active site amino acid residues.
Conclusion: The tocolytic potential of *Zingiber officinale*, *Ficus capensis*, *Barteria fistulosa* and *Newbouldia laevis* as a medicinal plant for the treatment of preterm labour is validated. Kaempferol, Chrysoeriol and Lapachol, phytoconstituents in *Newbouldia laevis* possess the potential as a source of new drugs for the treatment of preterm labour.

Keywords: Preterm labour, tocolysis, molecular docking, drug design

Introduction

Preterm labour is the leading cause of perinatal morbidity and mortality as preterm babies account for 40-60 % of all perinatal deaths in Nigeria [1]. Preterm birth is associated with 5-18 % of pregnancies and is a leading cause of infant morbidity and mortality with spontaneous preterm labour causing up to 70 % of preterm birth [2].

The exact mechanism by which preterm labour occurs has remained unclear, it could however be associated with premature activation of the physiological contraction process or due to a pathological condition responsible for uterine contractions thus leading to preterm delivery [3].

Different pathways have however been identified through which preterm labour may occur and they include over-distension of the uterus due to multiple pregnancies or polyhydramnios, inflammatory processes, cervical disease, immunological and allergic processes, placenta ischaemia, prematurity of the foetus due to maternal or foetal conditions,

decidual or retroplacental haemorrhage, foetal endocrine activation and intrauterine infections [3].

Tocolytics are medications used to suppress premature or preterm labour; the rationale for the use of these agents in preterm labour is to inhibit uterine contractions and thus delay delivery by at least 48 hours, so that the mother can be safely transferred to a tertiary facility. It also allows administration of other medications such as corticosteroids to induce fetal lung surfactant production and prevent neonatal risks associated with prematurity. Tocolytics, however, do not lengthen significantly, the age of gestation beyond 7 days [3,4].

Contraction of the myometrium is a complex process which involves the presence of various hormonal receptors, regulator proteins such as angiotensin, oxytocin, tachykinin and endothelin, ion channels and intercell gap functions; it is also based on myocytes function. Uterine smooth muscle contraction is largely based on the increased concentration of intracellular calcium [3].

Uterine relaxation may therefore be obtained by the interference of an intracellular messenger responsible for contractile protein effects such as nitric oxide donors, beta-adrenergic receptor agonists, magnesium sulphate and calcium channel blockers; it may also be obtained by inhibiting the synthesis or effect of the contracting factors such as oxytocin receptor antagonists and prostaglandin synthase inhibitors [3].

Presently, various tocolytic agents have been made available for the treatment of preterm labour but the usage of most of these agents has been met with various challenges. For example, atosiban, an oxytocin receptor antagonist which is known to have the best fatal and maternal safety profile does not significantly reduce neonatal complications [4]; nifedipine, a calcium channel blocker which is known to delay delivery significantly thereby reducing adverse neonatal outcomes may however cause transient hypotension as a complication [4,5]; salbutamol, ritodrine and terbutaline, beta-mimetics which have been known to reduce the number of women who deliver with preterm labour may cause complications such as hypokalemia, hyperglycemia, hypotension, pulmonary edema, arrhythmia, cardiac insufficiency, myocardial ischemia, maternal death [4,5].

These shortcomings then pose a gap in the management of preterm labour and necessitate the need for the discovery of new agents in the management of preterm labour. Many medicinal plants including *Zingiber officinale* rhizome [6], *Ficus capensis* leaves [7], *Ficus exasperata* leaves [8], *Barteria fistulosa* leaves [9] and *Newbouldia laevis* stembark [10] have been found useful in the treatment of various birth and pregnancy-related problems including premature uterine contraction. Scientific studies are however necessary to examine whether physiological and pharmacological evidence is supportive of these traditional uses, which can thus create a way for future drug development [6].

Methods

The study made use of the following software: PyRx, Pymol, Biovia Discovery Studio 2020, and Chimera. Swiss ADME and ProTox-II online servers; the databases used were Protein Data Bank and PubChem [13-17].

Preparation of protein target

The target protein, the beta-2 adrenergic receptor was downloaded from the protein data bank (https://rcsb.org) [18]. Editing of the target protein was done on UCSF Chimera to remove all non-standard residues, water molecules and other chains not useful for molecular docking. The protein was hereafter minimized at 200 steepest descent and then hydrogen ions and charges were added. The prepared protein was thereafter saved in the PDB format.

Identification and preparation of ligands

Compounds which have been isolated from *Ficus capensis*, *Ficus exasperata*, *Newbouldia laevis*, *Barteria fistulosa* and *Zingiber officinale* and identified using GC-MS were downloaded from PubChem as SDF files and imported into PyRx software using the Open Babel plug-in. The compounds were then minimized and converted to pdbqt format to be used as ligands for molecular docking.

Identification of binding site

The active/binding amino acids were identified using PyMOL, this was possible because the protein is co-crystallized with salbutamol which is a known ligand.

Molecular docking and post-docking analysis

The protein target which was previously prepared and saved in the PDB format, was loaded into PyRx and made a macromolecule; all the ligands were also imported into PyRx. The binding amino acids on the macromolecule were then labelled and the Autodock Vina plug-in was used for docking while the grid box was placed on the binding amino acids, this was carried out at an exhaustiveness of 8. Upon completion of docking, the binding affinities were obtained for all ligands and those with a binding affinity ≤ -7 kcal/mol were selected for analysis of receptor-ligand interaction. The various binding conformation of each ligand against the protein was saved from PyRx in the PDB format. The binding site and ligand interaction between the identified binding amino acid residues and the ligands were then analyzed using Biovia Discovery Studio Visualizer 2020. 3-dimensional and 2-dimensional analyses were done to visualize the various binding models of each ligand and determine the ligands with higher potential of tocolytic activity.

ADMET profiling

Some ligands were selected for ADMET profiling based on higher hydrogen bond interaction and the highest binding affinity. The ADME properties of these ligands were then obtained using the Swiss ADME web server and the ligands which failed to violate any of the Lipinski rule of five were then selected and their toxicity checked using the ProTox-II virtual lab.

Results

Binding site amino acids

The binding site amino acids identified with the aid of PyMOL are: TRP 109, THR 110, ASP 113, VAL 114, VAL 117, THR 118, PHE 193, TYR 199, SER 203, SER 204, SER 207, TRP 286, PHE 289, PHE 290, ASN 293, TYR 308, ASN 312, TYR 316

Molecular docking analysis

Compounds from *Zingiber officinale, Ficus capensis, Ficus exasperata, Barteria fistulosa and Newbouldia laevis* all showed varying degrees of binding affinities for the protein target (7DHI).

Zingiber officinale

Nine (9) compounds and salbutamol (control ligand) bound with different affinities to the target protein as can be seen in Table 1. 2D and 3D views of the molecular interaction of the amino acid residues of selected ligands with the receptor can be seen in Figure 1.

Ficus capensis

Fourteen (14) compounds and salbutamol (control ligand) bound with different affinities to the target protein as can be seen in Table 2. 2D and 3D views of the molecular interaction of the amino acid residues of a selected ligand with the receptor can be seen in Figure 2.

Ficus exasperata

Three (3) compounds and salbutamol (control ligand) bound with different affinities to the target protein as can be seen in Table 3. 2D and 3D views of the molecular interaction of the amino acid residues of a selected ligand with the receptor can be seen in Figure 3.

Barteria fistulosa

One (1) compound and salbutamol (control ligand) bound with different affinities to the target protein as can be seen in Table 4. 2D and 3D views of the molecular interaction of the amino acid residues of the ligand with the receptor can be seen in Figure 4.

Newbouldia laevis

Fourty-four (44) compounds and salbutamol (control ligand) bound with different affinities to the target protein as can be seen in Table 5. 2D and 3D views of the molecular interaction of the amino acid residues of a selected ligand with the receptor can be seen in Figure 5.

ADME Profiling

Five (5) ligands selected based on binding affinity and hydrogen bond interaction passed as druglike as can be seen in Table 6.

Toxicity Prediction

Toxicity prediction results of the ligands which passed as druglike can be seen in Table 7.

Table 1: Binding affinities of *Z. officinale* compounds with 7DHI

S/N	Compounds	PubChem CID	ΔG Energy (kcal/mol)
1	Salbutamol*	2083	-7.5
2	Folic acid	135398658	-7.3
3	Alloaromadendrene	12305247	-7.2
4	8-isopropenyl-1,5-Dimethyl-Cyclodeca-1,5-diene	5365775	-7.3
5	Fenretinide	5288209	-7.6
6	Secalciferol	5283748	-7.6
7	Piperine	638024	-9.5
8	Bicyclo [4.4.0] Dec-2-ene-4-ol, 2-methyl-9-(Prop-1-en-ol-2-yl)-	535256	-7.1
9	Gingerdione	162952	-7.3
10	Alpha-curcumene	92139	-7.7

*Standard ligand

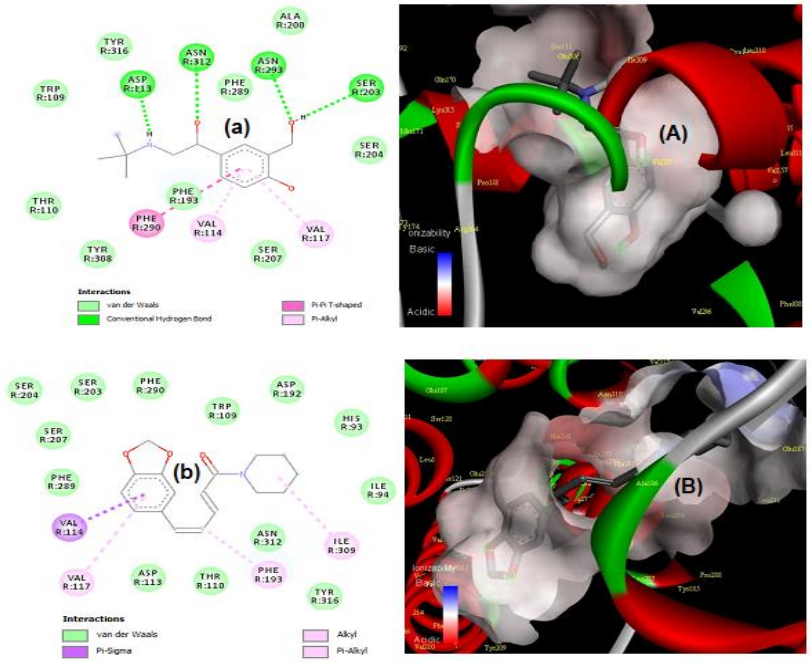

Figure 1: Molecular interactions of amino-acid residues of beta-2 adrenergic receptor with salbutamol in 2D (a) and 3D (A) views and piperine with 2D (b) and 3D (B) views in *Zingiber officinale*

Table 2: Binding affinities of *F. capensis* compounds with 7DHI

S/N	Compounds	PubChem CID	ΔG Energy (kcal/mol)
1	Salbutamol*	2083	-7.5
2	Beta-amyrin	73145	-9.6
3	Alpha-amyrin	73170	-8.5
4	Lupeol acetate	92157	-8.0
5	6,10,14-Trimethylpentadecan-2-one	10408	-7.1
6	Geranyl acetone	1549778	-7.5
7	Scytalone	162567	-7.5
8	Campesterol	173183	-9.8
9	Caryophyllene oxide	1742210	-7.2
10	Beta-sitosterol	222284	-9.6
11	Alpha-caryophyllene	23204	-7.1
12	Xanthotoxin	4114	-7.5
13	Quercetin	5280343	-9.0
14	Stigmasterol	5280794	-10.4
15	4-(2,6,6-Trimethylcyclohexa-1,3-Dienyl)But-3-en-2-one	5352711	-7.9

*Standard ligand

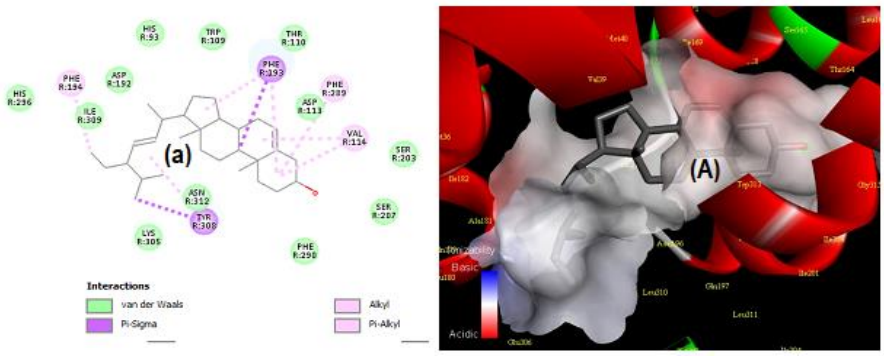

Figure 2: 2D (a) and 3D (A) views of the molecular interactions of amino-acid residues of beta-2 adrenergic receptor with stigmasterol in *Ficus capensis*.

Table 3: Binding affinities of compounds from *F. exasperata* with 7DHI

S/N	Compounds	PubChem CID	ΔG Energy (kcal/mol)
1	Salbutamol*	2083	-7.5
2	Cis-9,12,15-octadecatrienoic acid	445640	-7.3
3	2-methyl-Z,Z-3,13-octadecadienol	5364412	-7.1
4	Trans-11-octadecenoic acid	5281127	-7.1

*Standard ligand

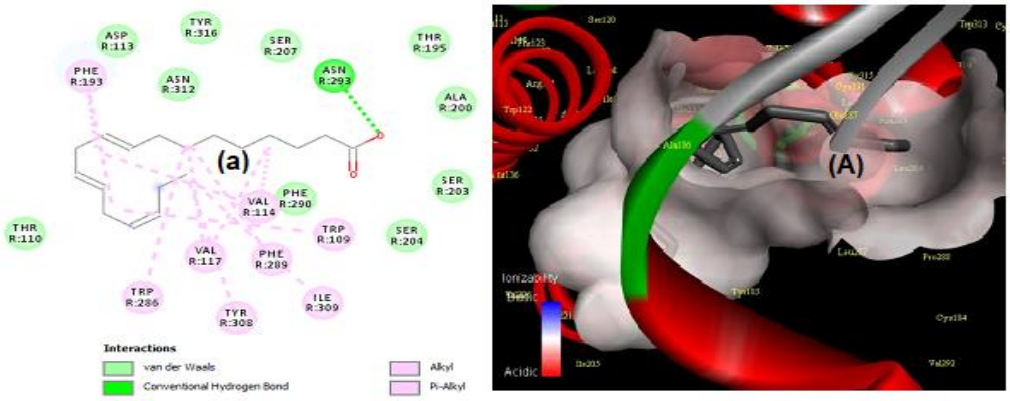

Figure 3: 2D (a) and 3D (A) views of the molecular interactions of amino-acid residues of beta-2 adrenergic receptor with cis-9,12,15-octadecatrienoic acid in *Ficus exasperata.*

Table 4: Binding affinities of compounds from *B. fistulosa* with 7DHI

S/N	Compounds	PubChem CID	ΔG Energy (kcal/mol)
1	Salbutamol*	2083	-7.5
2	Shanzhiside methyl ester	13892722	-8.1

*Standard ligand

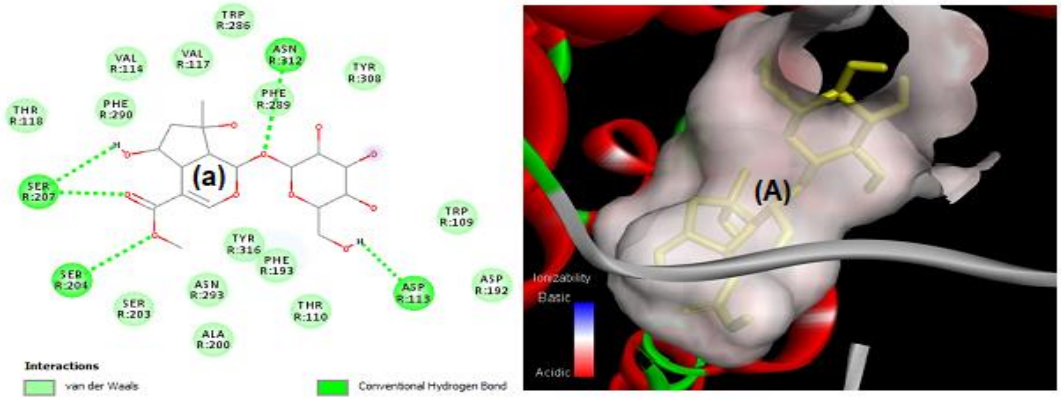

Figure 4: 2D (a) and 3D (A) views of the molecular interactions of amino-acid residues of beta-2 adrenergic receptor with shanzhiside methyl ester in *Barteria fistulosa*

Table 5: Binding affinities of compounds from *N. laevis* with 7DHI

S/N	Compounds	PubChem CID	ΔG Energy (kcal/mol)
1	Salbutamol*	2083	-7.5
2	Harmalol	3565	-7.1
3	Lapachol	3884	-8.4
4	Beta-lapachone	3885	-8.8
5	2-methyl anthraquinone	6773	-8.9
6	Oleanolic acid	10494	-7.7
7	6-phenyl undecane	20660	-7.3
8	Ursolic acid	64945	-7.9
9	Chrysophanol-9-anthrone	68111	-8.7
10	(-)-Epicatechin	72276	-8.7
11	Beta-sitosterol	222284	-9.6
12	5-hydroxydehydroiso- alpha- lapachone	392175	-9.2
13	Withasomnine	442877	-8.0
14	Arachidonic acid	444899	-7.9
15	3,8-dihydroxydehydroiso- alpha- lapachone	467769	-9.0
16	3-hydroxydehydroiso- alpha- lapachone	467770	-9.0
17	2-adamantanone semicarbazone	541478	-7.2
18	1,3-Bis-T-Butylperoxy- Phthalan	552032	-8.3
19	Squalene	638072	-8.8
20	Caffeic acid	689043	-7.3
21	Chlorogenic acid	1794427	-9.0
22	Quercetin	5280343	-9.1
23	Trans-phytol	5280435	-7.4
24	Linoleic acid	5280450	-7.2
25	Quercetin-3-Rhamnoside	5280459	-7.6
26	Chrysoeriol	5280666	-9.6
27	Stigmasterol	5280794	-10.4
28	Isoquercetin	5280804	-7.5
29	Kaempferol	5280863	-9.1
30	Verbascoside	5281800	-9.5
31	Evocarpine	5317303	-8.6
32	Martynoside	5319292	-9.0
33	1,3-Bis-(2-cyclopropyl, 2-methyl cyclopropyl)-But-2-en-1-one	5362887	-8.2
34	Beta-sitosterol glucoside	5742590	-7.7
35	Stigmasterol glucoside	6602508	-8.2
36	Napabucasin	10331844	-8.8
37	5,7- Dihydroxydehydroiso-alpha-lapachone	10802099	-9.1
38	Newbouldiaquinone	11474887	-9.8
39	Tithoniaquinone A	11550926	-8.4
40	Newbouldine	46914545	-8.1
41	N-demethyl tapentadol	71159880	-7.2
42	4'- hydroxywithasomnine	71607972	-8.0
43	4'- methoxywithasomnine	86191194	-7.8
44	4'- hydroxynewbouldine	101937080	-8.0
45	4'- methoxynewbouldine	101937081	-8.2

*Standard ligand

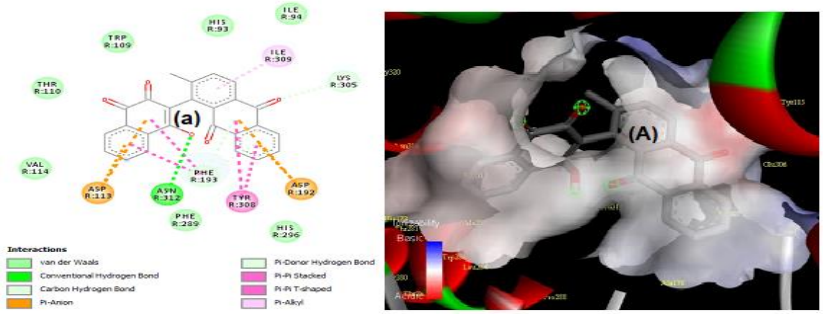

Figure 5: 2D (a) and 3D (A) views of the molecular interactions of amino-acid residues of beta-2 adrenergic receptor with newbouldiaquinone in *Newbouldia laevis.*

ADME profiling

Table 6: ADME profiling of selected ligands

Property	Kampferol	Newbouldiaquinine	Chrysoeriol	Lapachol	Quercetin
Formula	$C_{15}H_{10}$	$C_{25}H_{14}O_5$	$C_{16}H_{12}O_6$	$C_{15}H_{14}O_3$	$C_{15}H_{10}O_7$
Molecular weight	286.24 Da	394.38 Da	300.26 Da	242.27 Da	302.24 Da
Number of Hydrogen bond acceptors	6	5	6	3	7
Number of Hydrogen bond donors	4	1	3	1	5
Consensus Log $P_{O/W}$	1.58	3.35	2.18	2.54	1.23
Bioavailabity score	0.55	0.56	0.55	0.85	0.55
Druglikeness (Lipinski)	Yes	Yes	Yes	Yes	Yes

Toxicity prediction

Table 7: Toxicity prediction of selected ligands

Property	Kampferol	Newbouldiaquinine	Chrysoeriol	Lapachol	Quercetin
Predicted LD_{50}	3919 mg/kg	1600 mg/kg	4000 mg/kg	680 mg/kg	159 mg/kg
Predicted toxicity class	5	4	5	4	3
Hepatotoxicity	Inactive	Inactive	Inactive	Inactive	Inactive
Carcinogenicity	Inactive	Inactive	Inactive	Inactive	Active
Immunogenicity	Inactive	Active	Inactive	Inactive	Inactive
Mutagenicity	Inactive	Inactive	Inactive	Inactive	Active
Cytotoxicity	Inactive	Inactive	Inactive	Inactive	Inactive

DISCUSSION

Molecular docking analysis of compounds (ligands) against a known target produces a score known as the docking score which can be used to predict the binding affinity and thereafter activity of the ligand with the protein target [19-21]. Salbutamol was used in this study as the standard ligand for comparative analysis having a binding affinity of -7.5 kcal/mol; compounds/ ligands with binding affinities greater than or equal to -7.0 kcal/mol are considered as probable drug molecules in this study.

Identification of active site/binding amino acids in the target protein (7DHI) enabled the performance of site-specific docking, thus also allowing the prediction of ligand activity by the number of active amino acids that is bound by each ligand in the target protein.

Zingiber officinale

Ten (10) compounds including the standard ligand bound to the target protein with varying binding affinities as can be seen in Table 1; binding affinities ranged from -7.1 to -9.5 kcal/mol while salbutamol had a binding affinity of -7.5 kcal/mol. Piperine had the highest binding affinity of -9.5 kcal/mol while gingerdione with a binding affinity of -7.3 kcal/mol was the only ligand that interacted with the active sites amino acid with a strong hydrogen bond (^{312}ASN). The 2D and 3D views of the molecular interactions of amino-acid residues of beta-2 adrenergic receptor with salbutamol and piperine can be seen in Figure 1. Other compounds interacted with some of the active site amino acids van der Waal's forces and pi bonds.

Ficus capensis

Fifteen (15) compounds including the standard ligand bound to the target protein with varying binding affinities as can be seen in Table 2; binding affinities ranged from 7.1 to 10.4 kcal/mol with salbutamol having a binding affinity of 7.5 kcal/mol. Stigmasterol had the highest binding affinity of -10.4 kcal/mol while alpha-caryophyllene and 6,10,14-trimethyl pentadecane-2-one had the least binding affinity of 7.1 kcal/mol.

However, quercetin and geranyl acetone bound the most with the strong conventional hydrogen bond to active/ binding site amino acids despite having a binding affinity of -9.0 and -7.5 kcal/mol, respectively, while stigmasterol despite having the highest binding affinity, did not bind to any of the active/binding site amino acids with the strong hydrogen bond. The 2D and 3D views of the molecular interactions of amino-acid residues of beta-2 adrenergic

receptor with stigmasterol can be seen in Figure 2. Ligands bound to the active site amino acids in the order: ^{312}ASN > ^{293}ASN > ^{204}SER > ^{193}PHE, ^{113}ASP > ^{110}THR, ^{114}VAL > ^{203}SER, ^{308}TYR, ^{316}TYR.

Ficus exasperata

Four (4) compounds including the standard ligand bound to the target protein with varying binding affinities as can be seen in Table 3; binding affinities ranged from -7.1 to -7.5 kcal/mol of the standard ligand. Trans-11-octadecenoic acid had the highest interaction with 2 of the active/binding site amino acids through hydrogen bonding while cis-9,12,15-octadecatrienoic acid had the highest binding affinity of -7.3 kcal/mol. The 2D and 3D views of the molecular interactions of amino-acid residues of Beta-2 adrenergic receptor with cis-9,12,15-octadecatrienoic acid can be seen in Figure 3.

Barteria fistulosa

One (1) compound and the standard ligand were docked with the target protein, the binding affinity was thereafter obtained as seen in Table 4. The standard ligand (salbutamol) had a binding affinity of -7.5 kcal/mol while the other ligand (shanzhiside methyl ester) had a higher binding affinity of -8.1 kcal/mol. Shanzhiside methyl ester interacted strongly (hydrogen bond) with 4 of the active site amino acids namely: ^{113}ASP, ^{204}SER, ^{207}SER and ^{312}ASN while the standard ligand also interacted with 4 of the binding site amino acids namely: ^{113}ASP, ^{312}ASN, ^{203}SER and ^{293}ASN. The 2D and 3D views of the molecular interactions of amino-acid residues of Beta-2 adrenergic receptor with shanzhiside methyl ester can be seen in Figure 4.

Newbouldia laevis

Forty-five (45) compounds alongside the standard ligand were docked with the target protein and the binding affinities were obtained as seen in Table 5. The standard ligand (salbutamol) had a binding affinity of -7.5 kcal/mol; Stigmasterol had the highest binding affinity of -10.4 kcal/mol while harmalol had the least binding affinity of -7.1 kcal/mol. However, lapachol, arachidonic acid, chlorogenic acid, verbascoside and kaempferol all interacted the most using the strong hydrogen bond to two (2) each of the active/ binding site amino acids while stigmasterol with the highest binding affinity did not interact using the strong hydrogen bond with any of the active/binding site amino acids.

The 2D and 3D views of the molecular interactions of amino-acid residues of Beta-2 adrenergic receptor with newbouldiaquinone having a high binding affinity of -9.8 kcal/mol can be seen in Figure 5. Ligands bound to the active site amino acids in the order: ^{312}ASN > ^{193}PHE > ^{293}ASN, ^{110}THR, ^{113}ASP > ^{316}TYR, ^{207}SER > ^{203}SER, ^{308}TYR > ^{114}VAL > ^{204}SER > ^{118}THR.

It is worthy of note that some ligands were found repetitively in more than one plant, these ligands are beta-sitosterol and stigmasterol found in *Ficus capensis* and *Newbouldia laevis* having a binding affinity of -9.6 and -10.4 kcal/mol, respectively in both plants. However, both compounds did not bind favorably to the active site amino acids.

Salbutamol, a beta-sympathomimetic is used clinically as a tocolytic agent in the management of preterm labour; it does this by enhancing the production of intracellular cyclic adenosine monophosphate (cAMP), which in turn facilitates the binding of intracellular calcium to the cell membrane thus decreasing calcium concentration within cells and facilitating smooth muscle relaxation.

However, these plants studied in this research have been used traditionally in the management of preterm labour and the molecular docking studies of compounds present in these plants can aid in the discovery of new drugs for the management of preterm labour; this is necessary as the beta-sympathomimetics present with certain side effects such as palpitations, tremor, nausea, vomiting, headache, breathlessness, pulmonary oedema which necessitates close monitoring and measurement of maternal pulse, blood pressure and fetal heart rate for up to 24 hours [22].

ADMET profiling

Absorption Distribution Metabolism and Excretion (ADME) studies help in the estimation of drug-likeness of compounds before synthesis as this helps to decrease the occurrences of pharmacokinetic-related failure in drug development. Different rules are available which help in the prediction of drug-likeness but for this project, the Lipinski Rule of 5 was used. The Lipinski Rule of 5 states that an orally active

drug must not break more than one of the following criteria: hydrogen bond donor ≤ 5; hydrogen bond acceptor ≤ 10; molecular weight ≤ 500 Daltons; octanol-water partition coefficient ≤ 5.
For each plant, ligands were selected for ADMET study based on higher binding affinity and highest hydrogen bond interaction.
Eight (8) compounds were selected from *Newbouldia laevis* namely- verbascoside, kaempferol, chlorogenic acid, newbouldiaquinone, chrysoeriol, martynoside, lapachol and arachidonic acid; ADME study was done and only 4 of the compounds passed as drug-like namely- kaempferol, newbouldiaquinone, chrysoeriol and lapachol.

Kaempferol has 4 hydrogen bond donors, 6 hydrogen bond acceptors, octanol-water partition coefficient of 1.58 and molecular weight of 286.24 Da; newbouldiaquinone has 1 hydrogen bond donor, 5 hydrogen bond acceptors, molecular weight of 394.38 Da and octanol-water partition coefficient of 3.35; chrysoeriol has 3 hydrogen bond donors, 6 hydrogen bond acceptors, molecular weight of 300.26 Da and octanol-water partition coefficient of 2.18 and lapachol has 1 hydrogen bond donor, 3 hydrogen bond acceptors, molecular weight of 242.27 Da and octanol-water partition coefficient of 2.54.

These 4 compounds were then put through the toxicity test and kaempferol, chrysoeriol, and lapachol not having any toxicity on any major organ qualified as potential drug molecules while newbouldiaquinone was found to be immunotoxic thus failing to qualify as a potential drug molecule. For *Ficus capensis*, quercetin was the only compound selected and after ADME profiling, the compound passed as drug-like but failed the toxicity testing as the compound was found to possess possible carcinogenicity and mutagenicity thus disqualifying it as a potential drug molecule. Table 6-7 shows the ADME profiling and toxicity prediction of kaempferol, newbouldia-quinone, chrysoeriol, lapachol and quercetin.

For *Barteria fistulosa*, shanzhiside methyl ester failed the drug-likeness test as it violated 2 rules of the Lipinski rule of 5 with 11 hydrogen bond acceptors (rule: hydrogen bond acceptor ≤ 10) and 6 hydrogen bond donors (rule: hydrogen bond donor ≤ 5), thus not qualifying as a potential drug molecule.

Zingiber officinale had just one of its compounds- gingerdione which bound to the active site amino acid residue with the strong conventional hydrogen bond but this compound had a binding affinity of -7.3 kcal/mol which is less than that of the standard- salbutamol (-7.5 kcal/mol); thus the compound was not considered for ADMET profiling.

Ficus exasperata had 3 compounds which bound to the active site amino acid by interaction with the strong conventional hydrogen bond, however, all 3 compounds had a binding affinity less than that of the standard (-7.5 kcal/mol) and were therefore not considered for ADMET profiling. These compounds are cis-9,12,15-octadecatrienoic acid, trans-11-octadecenoic acid and 2-methyl-Z, Z-3,13-octadecadienol.

Conclusion

The binding affinities and interaction with active site residues possessed by phytoconstituents present in *Zingiber officinale*, *Ficus capensis*, *Barteria fistulosa* and *Newbouldia laevis* validates their use traditionally for the treatment of preterm labour; however, the use of *Ficus exasperata* leaves traditionally for the treatment of preterm labour could not be validated as the binding affinities of its phytoconstituents were less than that of the standard molecule-salbutamol.

Newbouldia laevis stem bark also poses great potential as a plant for the discovery of new drug molecules for the management of preterm labour. However, more molecular dynamic simulation studies should be done as this will contribute immensely to the discovery of new and better drugs for the management of preterm labour.

Abbreviations

3D: Three-dimensional, **ADME:** Absorption, Distribution, Metabolism and Excretion, **ADMET:** Absorption, Distribution, Metabolism, Excretion and Toxicity, **ASN:** Asparagine, **ASP:** Aspartic acid, **cAMP:** Cyclic Adenosine Monophosphate, **DNA:** Deoxyribonucleic Acid, **GC-MS:** Gas Chromatography- Mass Spectrometry, **LD_{50}:** Lethal Dose, 50%, **PDB:** Protein Data Bank, **PHE:** Phenylalanine, **QSAR:** Quantitative Structure Activity Relationship, **RCSB:** Research Collaboratory for Structural Bioinformatics, **RNA:** Ribonucleic

Acid, **SDF:** Structure Data File, **SER:** Serine, **THR:** Threonine, **TYR:** Tyrosine, **UCSF:** University of California, San Francisco, **VAL**: Valine

Conflict of Interest

No conflict of interest is associated with this work.

Contribution of Authors

We affirm that the authors listed in this article completed this work, and they will be responsible for any liabilities arising from claims pertaining to its content. UMO was the study's designer, while EO handled the data management, *in silico* work, and writing of the manuscript. UMO and HAO critically reviewed the manuscript. The final draft of the manuscript was read and approved by all the authors.

References

1. Zini, M.E. and Omo-Aghoja, L.O. Clinical and sociodemographic correlates of preterm deliveries in two tertiary hospitals in southern Nigeria. Ghana Medical Journal. 2019;53(1): 20-28.
2. Roberto, R., Sudhansu, K.D. and Susan, J.F. Preterm labor: one syndrome, many causes. Science. 2014;345(6198):760–765.
3. Hubinont, C. and Debieve, F. Prevention of preterm labour: 2011 update on tocolysis. Journal of Pregnancy. 2011;1-6.
4. Haram, K., Mortensen, J.H.S. and Morrison, J.C. Tocolysis for acute preterm labor: Does anything work. The Journal of Maternal-Fetal & Neonatal Medicine. 2015;28(4):371–378.
5. Weismiller, D.G. Preterm labor. American Family Physician. 1999;59(3):593–602.
6. Kupittayanant, S., Munglue, P., Lijuan, W., Promprom, W., Budhaklala, N. and Wray, S. Finding new agents in medicinal plants to act on the myometrium. Experimental Physiology. 2014;99(3):530-537.
7. Owolabi, O.J., Nworgu, Z.A., Falodun, A., Ayinde, B.A. and Nwako, C.N. Evaluation of tocolytic activity of ethanol extract of the stem bark of *Ficus capensis* Thunb. (Moraceae). Acta Poloniae Pharmaceutica - Drug Research. 2009;66(3):293–296.
8. Bafor, E.E., Omogbai, E.K. and Ozolua, R.I. Oxytocin inhibing effect of the aqueous leaf extract of *Ficus exasperata* (Moraceae) on the isolated rat uterus. Acta Poloniae Pharmaceutica-Drug Research. 2011;68(4):541-547.
9. Ndjateu, F.S.T., Tsafack, R.B.N., Nganou, B.K., Awouafack, M.D., Wabo, H.K., Tene, M., Tane, P. and Eloff, J.N. Antimicrobial and antioxidant activities of extracts and ten compounds from three cameroonian medicinal plants: *Dissotis perkinsiae* (Melastomaceae), *Adenocarpus mannii* (Fabaceae) and *Barteria fistulosa* (Passifloraceae). South African Journal of Botany. 2014;91:37–42.
10. Ayinde, B.A., Owolabi, O.J. and Okolo, C.I. Effect of methanol extract of *Newbouldia Laevis* stem bark on the uterus of non-pregnant rats. Nigerian Journal of Science and Environment. 2013;12(2):90-94.
11. Burley, S.K., Bhikadiya, C., Bi, C., Bittrich, S., Chen, L., Crichlow, G.V., Christie, C.H., Dalenberg, K., Di Costanzo, L., Duarte, J.M. et al. RCSB protein data bank: powerful new tools for exploring 3D structures of biological macromolecules for basic and applied research and education in fundamental biology, biomedicine, biotechnology, bioengineering and energy sciences. Nucleic Acids Research. 2021;49(D1):D437–D451.
12. Yang, F., Ling, S., Zhou, Y., Zhang, Y., Lv, P., Liu, S., Fang, W., Sun, W., Hu, L.A., Zhang, L. et al. Different conformational responses of the β2-adrenergic receptor-gs complex upon binding of the partial agonist salbutamol or the full agonist isoprenaline. National Science Review. 2021;8(9):284.
13. Pettersen, E.F., Goddard, T.D., Huang, C.C., Couch, G.S., Greenblatt, D.M., Meng, E.C. and Ferrin, T.E. UCSF Chimera--A visualization system for exploratory research and analysis. Journal of Computational Chemistry. 2004;25(13):1605–1612.
14. Couch, G.S., Hendrix, D.K. and Ferrin, T.E. Nucleic acid visualization with UCSF chimera. Nucleic Acids Research. 2006;34(4):e29–e29.
15. Yuan, S., Chan, H.C.S. and Hu, Z. Using PyMOL as a platform for computational drug design. WIREs Computational Molecular Science. 2017;7(2):1298.
16. Daina, A., Michielin, O. and Zoete, V. SwissADME : A free web tool to evaluate pharmacokinetics, drug- likeness and medicinal chemistry friendliness of small molecules. Nature Publishing Group. 2017;(January):1–13.
17. Banerjee, P., Eckert, A.O., Schrey, A.K. and Preissner, R. ProTox-II : A webserver for the prediction of toxicity of chemicals. Nucleic Acids Research. 2018;46(April):257–263.
18. Berman, H.M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T.N., Weissig, H., Shindyalov, I.N., and Bourne, P.E. The protein data bank. Nucleic Acids Research. 2000;28(1):235–242.
19. Prakash, N. Molecular docking studies of antimalarial drugs for malaria. Journal of

Computer Science & Systems Biology. 2010;03(03):70-73.

20. Wang, G. and Zhu, W. Molecular docking for drug discovery and development: A widely used approach but far from perfect. Future Medicinal Chemistry. 2016.
21. Dar, A.M. and Mir, S. Molecular docking: approaches, types, applications and basic challenges. Journal of Analytical & Bioanalytical Techniques. 2017;08(02):8–10.

22. .

Junejo, N., Mumtaz, F. and Unar, B.A. (2008) 'Comparison of salbutamol and nifedipine as a tocolytic agent in the treatment of preterm labour. JLUMHS. 115–119