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***In Silico* Absorption, Distribution, Metabolism, Excretion, and Toxicity Profiling and Post-Docking Analysis of Phytoconstituents of *Aframomum Sceptrum* and *Ricinodendron Heudelotii* against Plasmepsin II as Potential Antimalarial Admixture**

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ABSTRACT: Chemical Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET), plays key role in drug discovery. Food spices have been identified to help manage malaria and various diseases through *in vitro* and *in vivo* studies. Consequently, the objective of this paper was to investigate the *in silico* ADMET profiling and post-docking analysis of the phytoconstituents of *Aframomum sceptrum* and *Ricinodendron heudelotii* against plasmepsin II as potential antimalarial admixture. Phytoconstituents in these food spices were obtained from the literature (GC-MS analysis), and their 2D and 3D SDF structures were obtained from PubChem. The protein target Plasmepsin II (ILF3) was obtained from Protein Data Bank and prepared using Biovia Discovery Studio 2020. Molecular docking and Post-docking analysis were done using PyRx and Biovia Discovery Studio 2020, respectively, and ADMET profiling using the Swiss ADME webserver and ProTox-3.0 virtual lab. Twenty phytoconstituents in *Aframomum sceptrum* and *Ricinodendron heudelotii* had ≤ -6.5 kcal/mol binding free energy values against the target protein (Plasmepsin II). Compounds 18 and 19 from *Aframomum sceptrum* showed good binding free energy values of - 8.6 kcal/mol, while 10, 11, 12, and 18 had binding energy values comparable to Artesunate (standard antimalarial agent) used in this study. *In silico* ADMET profiling and post-docking analysis of *Aframomum sceptrum* and *Ricinodendron heudelotii* phytoconstituents showed antimalarial activity when compared with a standard drug (Artesunate), which validated their traditional use for the treatment of malaria. Some of the phytoconstituents showed organ toxicities; hence, further research may be needed to improve their safety profile and efficacy. This study validates the ethnomedicinal uses of these plant extracts in treating malarial and related diseases. Further *in vivo* and isolation studies are required to identify the phytoconstituents with potent antimalarial activity.

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Keywords: Plasmepsin II; Antimalarial activity; ADMET profiling; *Aframomum sceptrum*; *Ricinodendron heudelotii*;

Malaria is a fatal disease caused by five major plasmodium parasites (*P. ovale*, *P. falciparum*, *P. vivax*, *P. malariae*, and *P. knowlesi*). The most lethal is *Plasmodium falciparum*. The parasite is transmitted through the bite of an infected female Anopheles mosquito. It is endemic in most tropical countries, Africa, Asia, and South America (WHO, 2023). It has been known to be responsible for over 608,000 deaths annually, with over 80% of these among children under five years and pregnant women (WHO, 2023). The emergence of resistance strains of *P. falciparum* against first-line medications, including sulfadoxine, amodiaquine, artemisinin, and chloroquine, posed a significant threat in treating malaria disease. Specifically, it has been observed that four Asian countries have lately developed malaria resistance to artemisinins (the newest first-line drug against malaria). So, addressing this distressing state of affairs is imperative by stepping up efforts to identify novel natural product leads through concerted efforts in drug discovery (Johnson, 2015). Numerous data indicate that natural compounds are the best and most potent antimalarials (Newman, 2008; Paul *et al.*, 2013; Shanker *et al.*, 2012; Wright, 2005; Ginsburg, 2011). Natural products have also played a significant role in creating effective medications against malaria. Nevertheless, many natural compounds are not easily turned into antimalarial medicines; yet, the lead compound(s) found provide numerous critical

bioactive scaffolds that could be changed to create effective antimalarials using semi-synthetic techniques (Ginsburg, 2011). The ability to screen many compounds quickly is made possible by developing *in silico* drug design tools. These methods are now widely used in developing novel medications or lead identification with improved binding modes, reduced adverse effects, simplicity, reduced time, and prompt identification of key pharmacophores (Singla, 2015; Zothantluangam and Chetia, 2022). In *Plasmodium falciparum*, haemoglobin breakdown is caused by three distinct groups of proteases, including aspartic proteases (plasmepsin I, II, IV, and HAP), cysteine proteases (falcipain-1, -2, and -3), and metalloproteases (falcilysin) (Gulati *et al.*, 2015). The precursor of plasmepsin, membrane-bound pro plasmepsin, is generated and then processed into mature plasmepsin and falcipain, both classified as cysteine proteases (Soh *et al.*, 2013). For many years, antimalarial drug development has focused on plasmepsin and falcipain because they are involved in the haemoglobin breakdown process, which is essential for the growth of parasites in the body (Gulati *et al.*, 2015; Soh *et al.*, 2013). Plasmepsin is regarded as the best target for antimalarial medications among these two proteins (Cheuka *et al.*, 2020). Targeting this protein can impede the parasite's life cycle (Favuzza *et al.*, 2020) by inhibiting its metabolic functions. Furthermore, Plasmepsin II is the most thoroughly researched of

these aspartyl proteases and catalyses the first stage of the parasite's haemoglobin degradation. *Aframomum sceptrum*, family Zingiberaceae, has been used in ethnomedicine to treat different diseases, including malaria, inflammations, cancers, and antidiabetes, etc., and is known to express labdane diterpenoids known for various pharmacological activities (Amadi *et al.*, 2016; Tomla *et al.*, 2002). *Ricinodendron heudelotii* (Baill.) Pierre, family, Euphorbiaceae, has been shown to find uses as a spice in many delicacies in Southern Nigeria and has been reported to possess unique pharmacological activities, anticancer, antioxidant, antimalarial, anti-inflammations, etc. (Zingué *et al.*, 2024; Sut *et al.*, 2020). Studies have reported the isolation of some potent anticancer agents from the seed of this plant (Yakubu *et al.*, 2019). Other bioactive compounds, including heudelotenol 1, taraxerone, friedelin, aleuritolic acid, etc., have also been reported in this plant (Momeni *et al.*, 2006). Consequently, the objective of this paper was to investigate the *in silico* ADMET profiling and post-docking analysis of the phytoconstituents of *Aframomum sceptrum* and *Ricinodendron heudelotii* against plasmepsin II as potential antimalarial admixture

MATERIALS AND METHODS

Materials: A computer system: A Dell Inspiron laptop – 15 N5050, 500GB HDD, Operating system: Windows 10 Pro, Processor: Core i5, 1.99 GHz, 4 GB RAM, System type: 64-bit, and a Mouse. Databases, Webservers: PubChem, RCSB Protein databank, SwissADME, and Prottox II; Software: PyRx, Pymol 3.0, and Biovia Discovery Studio

Preparation of Protein Target: The target protein, plasmepsin II, was downloaded from RCSB PDB (<https://rcsb.org>) (Berman *et al.*, 2000). To prepare the target protein for molecular docking, all non-standard residues, water molecules, and other chains

were eliminated using Biovia Discovery Studio. After that, the protein was reduced to 200 steepest declines, and charges and hydrogen ions were added and saved in PDB format.

Identification and Preparation of Ligands: The 3D structure data files (SDF) of the bioactive compounds of *Aframomum sceptrum* and *Ricinodendron heudelotii*, identified using GC-MS (Imieje *et al.*, 2023, unpublished work), were downloaded from the PubChem (<https://pubchem.ncbi.nlm.nih.gov/>) database and imported into PyRx 0.9x (<https://pyrx.sourceforge.io/>) software using the Open Babel plug-in. The compounds were minimised and converted to Autodock ligands (pdbqt) format for molecular docking.

Identification of Binding Site: The protein co-crystallizes with the known ligand EH58, making identifying the active/binding amino acids easy using PyMOL 3.1 (<https://www.pymol.org/>).

Molecular Docking: The previously prepared protein target (plasmepsin II) was made a macromolecule using PyRx and saved in the PDB format. All of the ligands were also imported into PyRx. After labelling the binding site amino acids on the macromolecule, the grid box was positioned on the binding amino acids, and docking was done using the Autodock Vina plug-in at an exhaustiveness of 8.

Post-Docking Analysis: Each ligand's distinct binding conformation against the protein was preserved in PDB format via PyRx. Afterwards, the Biovia Discovery Studio Visualizer 2020 was used to examine the binding site interactions between the ligands and the discovered binding site amino acid residues. The different binding models of each ligand were visualised using 3-dimensional and 2-dimensional analysis, which also helped identify the

ligands with the highest potential for antimalarial efficacy.

ADMET Profiling: All ligands had their binding affinities determined when docking was complete, and those with a binding affinity < -7.0 were chosen for ADMET profiling. After obtaining the ligands' ADME properties from the Swiss ADME (<https://swissadme.ch>) web server, the ligands that met the Lipinski rules of five (R05) were chosen, and their toxicity was assessed using the ProTox-3.0 (<https://comptox-charite.de/protox3>) virtual lab.

RESULTS AND DISCUSSION

Molecular docking (MD) is a powerful tool for fast-tracking drug discovery due to its simplicity, reduced time, and cost implications. It has helped pharmaceutical companies reduce drug failure rates during clinical trials, especially with early detection of physicochemical properties, toxicity issues, pharmacokinetic parameters, and drugability. The binding site amino acids in plasmepsin II identified using PyMOL were ASP 34, VAL 78, SER 79, ASP 214, GLY 216, and SER 218. Compounds from *Aframomum sceptrum* and *Ricinodendron heudelotii* showed varying degrees of binding affinities for the protein target (1LF3). Twenty (20) compounds from *Aframomum sceptrum*, the native ligand (EH58), and the standard control (Artesunate) ligand bound to the target protein with varying binding affinities (Table 1). The 2D and 3D views of the molecular interaction of the amino acid residues of selected ligands with the receptor are presented in Figure 1. Similarly, twenty phytoconstituents from *Ricinodendron heudelotii* and the controls bound to the target protein with varying binding affinities (Table 2), and their 2D and 3D views of the molecular interaction of the amino acid residues of selected ligands with the receptor are presented in Figure 2. Similarly, post-docking analysis revealed the amino acids that the ligands from both plants interacted with via

conventional H-Bonds or other bonds on the Plasmepsin II receptor (Tables 3 and 4). The phytochemicals from both plants were subjected to ADME profiling using the SwissADME web server, and the results are presented in Tables 5 – 10, as well as their *in silico* toxicity profiles (Tables 3 and 4).

Table 1: Binding affinities of *Aframomum sceptrum* compounds with 1LF3

S/N	Compounds	PubChem CID	ΔG Energy (Kcal/mol)
1	Terpinyl acetate	111037	-6.5
2	Copaene	19725	-6.7
3	alpha-Guaiene	107152	-7
4	(-)-Isoaromadendrene-(V)	556206	-6.7
5	Valencene	288227	-6.8
6	beta-Selinene	519361	-6.9
7	gamma-Gurjunene	90805	-6.8
8	Guaial	227829	-7.1
9	alpha-Caryophyllene	5281520	-6.9
10	1,5,5,8-Tetramethyl-12-oxabicyclo[9.1.0]dodeca-3,7-diene	23274265	-6.5
11	gamma-Gurjunenepoxide-(1)	5362873	-6.6
12	beta-Eudesmol	91457	-6.9
13	alpha-Bisabolol	442343	-6.6
14	Glaucyl alcohol	604966	-6.5
15	4,8,13-Duvatriene-1,3-Diol	5367548	-7.5
16	Costunlide	5281437	-6.9
17	(-)-Isolongifolol, acetate	14634627	-6.5
18	21.xi-methyl-17-isocholestan-5-en-3,16-dione	566071	-8.6
19	9-Fluorenebenzenesulfonyl	596827	-8.6
20	Manool	3034394	-7.2
21	*N-(3-((2-benzo[1,3]dioxol-5-yl-ethyl)[3-(1-methyl-3-oxo-1,3-dihydro-isindol-2-yl)propionyl]-amino)-1-benzyl-2-(hydroxyl-propyl)-4-benzyloxy-3,5dimethoxy-benzamide (EH58)	446918	-9.2
22	**Artesunate	6917864	-7.6

*The native ligand (EH58) **the positive control ligand (Artesunate)

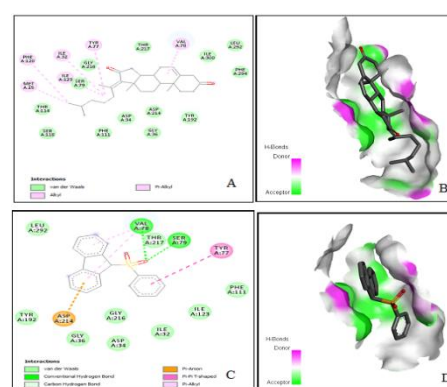


Fig 1: The 2 D (A & C) and 3D (B & D) molecular interactions of compounds 18 and 19 from *Aframomum sceptrum* (Table 1) with the amino-acid residues of Plasmepsin II receptor.

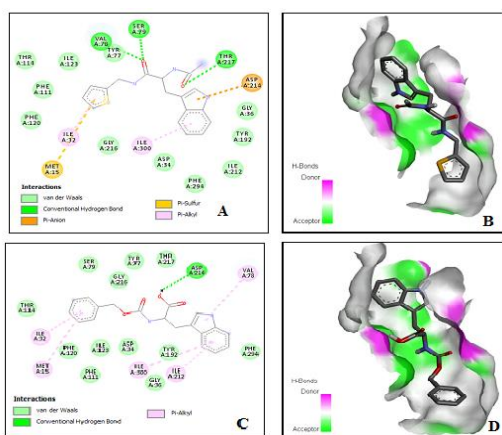


Fig. 2: The 2 D (A & C) and 3D (B & D) molecular interactions of compounds **9** and **10** from *Ricinodendron heudelotii* (Table 2) with the amino-acid residues of Plasmepsin II receptor.

In underdeveloped nations, malaria is a public health issue that can be fatal, particularly for high-risk populations. Searching for viable medicinal plants is essential to discover new and potent antimalarial agents. Medicinal plants are a potential source of novel antimalarial substances, such as *Aframomum sceptrum* and *Ricinodendron heudelotii*. This study used the phytoconstituents of *Aframomum sceptrum* and *Ricinodendron heudelotii* to identify anti-malarial phytochemicals. GC-MS analysis of *A. sceptrum* and *R. heudelotii* yielded 53 and 116 probable compounds, respectively, of which the compounds with a binding affinity of less than or equal to -6.5 kcal/mol were further subjected to *in silico* antimalarial investigation against *Plasmodium falciparum* aspartyl protease Plasmepsin II as shown in Tables 1 and 2, respectively. All probable compounds detected by GC-MS from previous studies (were used as ligands in molecular docking to establish their potential antimalarial properties.

Artesunate is an artemisinin derivative indicated as a first-line drug for treating severe malaria. It was used in this study as a positive control standard. N-(3-{(2-benzo[1,3]dioxol-5-yl-ethyl)[3-(1-methyl-3-oxo-1,3-dihydro-isindol-2-yl)propionyl]-amino}-1-benzyl-2-

(hydroxyl-propyl)-4-benzyloxy-3,5-dimethoxy-benzamide (EH58) which was co-crystallise with the target protein (Plasmepsin II) made it possible for the identification of the active amino acids at the binding site. Plasmepsin II is an aspartyl protease from the human intraerythrocytic parasite *Plasmodium falciparum*. It is involved in the degradation of the host cell haemoglobin within the acidic food vacuole of the parasite, it is a potential target for the development of antimalarial drugs. Molecular docking analysis of the ligands against a known target produces docking scores to predict the binding affinity of the ligand with the protein target (Prakash, 2010; Wang and Zhu, 2016; Dar and Mir, 2017)

Artesunate was used in this study as the standard ligand for comparative analysis, having a binding energy of -7.6 kcal/mol; compounds/ligands with binding affinities less than or equal to -7.0 kcal/mol were considered probable drug candidates in this study. The identification of active site/binding amino acids in the target protein (1LF3) enabled the performance of site-specific docking, thus also allowing the prediction of ligand activity by the number of active amino acids bound to each ligand in the target protein.

The docking study revealed that the ligands exhibited binding affinities ranging from -6.5 to -8.6 kcal/mol, while Artesunate had a binding affinity of -7.6 kcal/mol. Compounds 18 and 19, 21.xi-methyl-17-isocholestan-5-en-3,16-dione and 9-Fluorenebenzenesulfonyl, respectively, from *A. sceptrum* had the highest binding affinity of -8.6 kcal/mol (Table 1). Artesunate and 9-Fluorenebenzenesulfonyl interacted with the active sites amino acid with strong hydrogen bonds (SER 79 & VAL 78) Table 2. Hydrogen bonds promote ligand binding affinity by displacing protein-bound water molecules; hence, hydrogen bonds play a crucial role in determining ligand binding specificity.

Table 2: Binding affinities of *Ricinodendron heudelotii* compounds with 1LF3

S/N	Compounds	PubChem CID	ΔG Energy (Kcal/mol)
1	5-Hydroxy-1-isopropyl-6,6-dimethyl-5-phenyl-piperidin-2-one	547495	-7.6
2	2,6-Dimethyl-8-(tetrahydropyran-2-yloxy)-octa-2,6-dien-1-ol	5367918	-6.5
3	2(1H)-Naphthalenone, octahydro-4a-methyl-7-(1-methylethyl)-, (4a.alpha.,7beta,8beta)-	41133	-6.9
4	Nordextromethorphan	6603912	-7.3
5	1-Methylene-2b-hydroxymethyl-3,3-dimethyl-4b-(3-methylbut-2-enyl)-cyclohexane	550196	-6.5
6	(1S,4aS,4bS,7S,8aS,10aS)-7-Isopropyl-1,4a-dimethyltetradecahydrophenanthrene	6451376	-7.6
7	1H-Indole-2-carboxylic acid, 6-(4-ethoxyphenyl)-3-methyl-4-oxo-4,5,6,7-tetrahydro-, isopropyl ester	4916205	-7.7
8	N-Methyl-1-adamantanecetamide	610088	-6.6
9	Propionamide, 2-acetyl-amino-3-(1H-indol-3-yl)-N-thiophen-2-ylmethyl-	2965173	-7.7
10	L-Tryptophan, N-[(phenylmethoxy)carbonyl]-	101176	-8.5
11	2,2,3,3,3-Pentafluoro-N-(3-(methylthio)phenyl)propanamide	91740953	-6.5
12	2-(n-Propyl)oxybenzylidene acetophenone	91733926	-6.7
13	2-(Ethyl)oxybenzylidene acetophenone	21433393	-6.7
14	1H-Indole, 5-methyl-2-phenyl-	83247	-7.5
15	2-Methyl-7-phenylindole	610181	-7.4
16	1H-Indole, 1-methyl-2-phenyl-	77095	-6.7
17	5-Methyl-2-phenylindolizine	610180	-7
18	gamma-Tocopherol	92729	-7.6
19	beta-Tocopherol	6857447	-6.6
20	(R)-6-Methoxy-2,8-dimethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman	67475966	-7.1
21	*N-(3-{(2-benzo[1,3]dioxol-5-yl-ethyl)[3-(1-methyl-3-oxo-1,3-dihydro-isoindol-2-yl) propionyl]-amino}-1-benzyl-2-(hydroxyl-propyl)-4-benzoyloxy-3,5dimethoxy-benzamide (EH58)	446918	-9.2
22	**Artesunate	6917864	-7.6

*The native ligand (EH58) **the positive control compound (Artesunate)

Table 3: The various interaction types between the ligands (*Aframomum sceptrum* compounds) and amino acids on the target protein (Plasmepepsin II)

S/N	Compound	Hydrogen bond	Vanderwaals	Others
1	Terpinyl acetate	ARG 307, ASN 13	GLU 271, HIS 161, LYS 163, LYS 308	Alkyl, Pi-Alkyl
2	Copaene		ASP 34, GLY 216, ILE 123, PHE 111, PHE 120, SER 79, THR 77, THR 114	Alkyl
3	alpha-Guaiene		ASP 34, GLY 216, SER 79, THR 114	Alkyl, Pi-Alkyl
4	(-)-Isoaromadendrene-(V)		GLU 271, HIS 164, LYS 163, LYS 308	Alkyl, Pi-Alkyl
5	Valencene		ASP 34, GLY 216, ILE 123, PHE 111, SER 79, THR 114, VAL 78	Alkyl, Pi-Alkyl
6	beta-Selinene		GLU 271, LYS 163, LYS 308, LYS 327	Alkyl, Pi-Alkyl
7	gamma-Gurjunene		ASP 34, GLY 36, GLY 216, ILE 32, ILE 123, PHE 111, SER 37, SER 79, THR 217, TYR 192	Alkyl, Pi-Alkyl, Pi-Sigma
8	Guaiol	SER 79	ASP 34, GLY 216, PHE 111, THR114, THR 217, VAL 78	Alkyl, Pi-Alkyl
9	alpha-Caryophyllene		ARG 307, ASN 13, GLU 271, LYS 163, LYS 327	Alkyl, Pi-Alkyl
10	1,5,5,8-Tetramethyl-12-oxabicyclo[9.1.0]dodeca-3,7-diene		ASP 34, ASP 214, GLY 36, GLY 216, SER 37, SER 79, THR 192, THR 217	Alkyl, Pi-Alkyl
11	gamma-Gurjunenepoxide-(1)		ASP 34, GLY 216, ILE 32, PHE 111, PHE 120, SER 79, THR 114	Alkyl, Pi-Alkyl
12	beta-Eudesmol	ASP 214	ASP 34, GLY 36, GLY 216, ILE 123, PHE 111, PHE 120, SER 79, THR 114, THR 217, VAL 78	Alkyl, Pi-Alkyl
13	alpha-Bisabolol		ASP 34, ASP 214, GLY 36, GLY 216, PHE 111, SER 79, THR 217	Alkyl, Pi-Alkyl
14	Glaucyl alcohol	HIS 164, LYS 327	ASN 13, LYS 308, TYR 272	Alkyl, Carbon Hydrogen Bond
15	4,8,13-Duvatriene-1,3-Diol	ASP 34	ASP 214, GLY 36, GLY 216, ILE 123, PHE 111, SER 37, SER 79, THR 114, THR 217, TYR 77, VAL 78	Alkyl, Pi-Alkyl
16	Costunlide		GLY 216, ILE 32, ILE 123, MET 15, PHE 111, PHE 120, SER 79, THR 114, THR 217, TYR 77, VAL 78	
17	(-)-Isolongifolol, acetate		ASN 210, GLN 194 HIS 189, ILE 212, LEU 191, THR 298, TYR 192	Alkyl, Pi-Alkyl
18	21.xi-methyl-17-isocholestan-5-en-3,16-		ASP 34, ASP 214, GLY 36, GLY	Alkyl, Pi-Alkyl

	dione		216, ILE 300, LEU 292, PHE 111, PHE 294, SER 79, SER 118, THR 114, THR 217, TYR 192	
19	9-Fluorenebenzenesulfonyl	SER 79, VAL 78	LEU 292	Carbon Hydrogen Bond, Pi-Anion, Pi-Alkyl, Pi-Pi T-shaped Alkyl
20	Manool		ASP 34, ASP 214, GLY 36, GLY216, ILE 32, ILE 123, ILE 212, LEU 292, PHE 294, SER 37, SER 79, THR 217, TYR 77, TYR 192	
21	*N-(3-((2-benzo[1, 3]dioxol-5-yl-ethyl)[3-(1-methyl-3-oxo-1,3-dihydro-isoindol-2-yl)propionyl]-amino)-1-benzyl-2-(hydroxyl-propyl)-4-benzoyloxy-3,5dimethoxy-benzamide (EH58)	ASP 214, THR 217, TYR 192	ASN76, GLY 36, ILE 123, ILE 290, MET 75, PHE 111, PHE 294, SER 37, SER 79, SER 218, THR 114, TYR 77	Carbon Hydrogen Bond, Alkyl, Pi-Alkyl, Pi-Sulfur
22	**Artesunate	SER 79, VAL 78	ASP 34, ASP 214, GLY 216, ILE 32, ILE 123, ILE 300, LEU 292, PHE 294, THR 217, THR 221	Pi-Alkyl

Table 4: The various types of interaction between the ligands (*Riciodendron heudelotii* compounds) and amino acids on the target protein

(Plasmepepsin II)				
S/N	Compound	Hydrogen bond	Vanderwaals	Others
1	5-Hydroxy-1-isopropyl-6,6-dimethyl-5-phenyl-piperidin-2-one	VAL 78	ASP 34, GLY 216, ILE 32, ILE 123, PHE 111, PHE 120, SER 79, THR 217, TYR 77, TYR 192	Pi-Alkyl, Pi-Anion
2	2,6-Dimethyl-8-(tetrahydropyran-2-yloxy)-octa-2,6-dien-1-ol		ASP 214, GLY 216, ILE 14, ILE 32, ILE 123, MET 15, PHE 120, SER 35, SER 79, SER 218, THR 114, THR217, TYR 192	Alkyl, Pi-Alkyl, Carbon Hydrogen Bond
3	2(1H)-Naphthalenone, octahydro-4a-methyl-7-(1-methylethyl)-, (4a.alpha,7beta,8beta)-		GLU 271, LYS 163 LYS 308, LYS 327	Alkyl, Pi-Alkyl
4	Nordextromethorphan		LYS 308, TYR 157, TYR 272	Alkyl, Pi-Alkyl
5	1-Methylene-2b-hydroxymethyl-3,3-dimethyl-4b-(3-methylbut-2-enyl)-cyclohexane	TYR272	ARG 307, ASN 13, GLU 271, HIS 161, LEU 274, PRO 304, TYR 273	Alkyl, Pi-Alkyl
6	(1S,4aS,4bS,7S,8aS,10aS)-7-Isopropyl-1,4a-dimethyltetradecahydrophenanthrene		ASN 13, GLU 271, HIS 164, LEU 274, LYS 327	Alkyl, Pi-Alkyl
7	1H-Indole-2-carboxylic acid, 6-(4-ethoxyphenyl)-3-methyl-4-oxo-4,5,6,7-tetrahydro-, isopropyl ester		ASP 34, GLY 216, ILE 14, ILE 32, ILE 123, MET 15, PHE 111, PHE 120, SER 79, SER 218 THR 77, THR 114, THR 217	Alkyl, Pi-Alkyl, Pi-Anion
8	N-Methyl-1-adamantaneacetamide	SER 79, VAL 78	ASP 34, ASP 214, GLY 216, MET 15, PHE 111, PHE 120, THR114, THR 217, TYR 77	Alkyl
9	Propionamide, 2-acetyl-amino-3-(1H-indol-3-yl)-N-thiophen-2-ylmethyl-	SER 79, THR 217, VAL 78	ASP 34, GLY 36, GLY 216, ILE 123, ILE 212, PHE 111, PHE 120, PHE 294, THR 114, TYR 77, TYR 192	Pi-Alkyl, Pi-Anion, Pi-Sulfur
10	L-Tryptophan, N-[(phenylmethoxy)carbonyl]-	ASP 214	ASP 34, GLY 36, GLY 216, ILE 123, PHE 111, PHE 120 PHE 294, SER 79, THR 217, TYR 77, TYR 114, TYR 192	Pi-Alkyl
11	2,2,3,3,3-Pentafluoro-N-(3-(methylthio)phenyl)propanamide	ASP 34	ASP 214, ASN 74, GLY 36, ILE 32, MET 75, PHE 111, SER 37, SER 79, TYR 192, VAL 78	Alkyl, Carbon Hydrogen Bond, Halogen (Flourine) Pi-Alkyl
12	2-(n-Propyl)oxybenzylidene acetophenone		ASP 34, GLY 36, GLY 216, ILE 123, MET 15, PHE 111, SER 37, SER 39 THR 114, THR 217, TYR 79, TYR 192	Alkyl, Pi-Alkyl, Pi-Anion, Pi-Pi T-Shaped
13	2-(Ethyl)oxybenzylidene acetophenone	VAL 78	ASP 34, GLY 36, GLY 216, ILE 123, MET 15, PHE 111, SER 79, THR 114, TYR 77, TYR 192	Pi-Alkyl, Pi-Anion, Pi-Pi T-Shaped
14	1H-Indole, 5-methyl-2-phenyl-	ASP 34	ASP 214, GLY 36, GLY 216, SER 79 THR 114, TYR 77, TYR 192	Alkyl, Pi-Alkyl
15	2-Methyl-7-phenylindole		ASN 13, HIS 164, LYS 163, LYS 308	Pi-Alkyl, Pi-Pi T-Shaped
16	1H-Indole, 1-methyl-2-phenyl-		ASN 13, HIS 161, LYS 163, LYS 308, LYS 327	Pi-Alkyl, Pi-Pi T-Shaped
17	5-Methyl-2-phenylindolizine		ASN 13, GLU 271, LEU 274, LYS 163, LYS 308, TYR 272	Pi-Alkyl
18	gamma-Tocopherol		ASP 34, ASP 214, GLY 36, GLY 216, LEU 292, PHE 111,	Alkyl, Pi-Alkyl, Pi-Sigma

19	beta-Tocopherol	PHE 120, SER 79, SER 118, THR 114, THR 217, THR 221	Alkyl, Pi-Anion, Pi-Alkyl, Pi-Sigma, Unfavourable Acceptor
20	(R)-6-Methoxy-2,8-dimethyl-2-((4R,8R)-4,8,12-trimethyltridecyl)chroman	ASP 34, GLY 36, GLY 216, ILE 212, ILE 300, PHE 111, PHE 120, PHE 294, SER 79, SER 218, THR 114, THR 217	Alkyl, Pi-Alkyl, Pi-Sigma
		ASP 34, ASP 214, GLY 36, GLY 216, ILE 14, LEU 292, PHE 111, PHE 120, PHE 294, SER 79, SER 118, THR 114, TYR 217	

Table 5: Physicochemical Properties of the Phytoconstituents of *Aframomum sceptrum*

S/N	Ligands PubChem CID	Formula	Molecular Weight (g/mol)	Num. Heavy Atoms	Num. Arom. Heavy Atoms	Fraction CSP3	Num. Rotatable bonds	Num. H- bond acceptors	Num. H- bond donors	Molar Refractivity	TPSA (Å²)
1	111037	C ₁₂ H ₂₀ O ₂	196.29	14	0	0.75	3	2	0	58.53	26.3
2	19725	C ₁₅ H ₂₄	204.35	15	0	0.87	1	0	0	67.14	0
3	107152	C ₁₅ H ₂₄	204.35	15	0	0.73	1	0	0	69.04	0
4	556206	C ₁₅ H ₂₄	204.35	15	0	0.73	1	0	0	69.04	0
5	288227	C ₁₅ H ₂₄	204.35	15	0	0.73	1	0	0	68.78	0
6	519361	C ₁₅ H ₂₄	204.35	15	0	0.73	1	0	0	68.78	0
7	90805	C ₁₅ H ₂₄	204.35	15	0	0.73	1	0	0	69.04	0
8	227829	C ₁₅ H ₂₆ O	222.37	16	0	0.87	1	1	1	70.72	20.23
9	5281520	C ₁₅ H ₂₄	204.35	15	0	0.6	0	0	0	70.42	0
10	23274265	C ₁₅ H ₂₄ O	220.35	16	0	0.73	0	1	0	69.91	12.53
11	5362873	C ₁₅ H ₂₄ O	220.35	16	0	1	0	1	0	66.66	12.53
12	91457	C ₁₅ H ₂₆ O	222.37	16	0	0.87	1	1	1	70.46	20.23
13	442343	C ₁₅ H ₂₆ O	222.37	16	0	0.73	4	1	1	72.36	20.23
14	604966	C ₁₅ H ₂₄ O	220.35	16	0	0.73	2	1	1	70.2	20.23
15	5367548	C ₂₀ H ₃₄ O ₂	306.48	22	0	0.7	1	2	2	97.08	40.46
16	5281437	C ₁₅ H ₂₀ O ₂	232.32	17	0	0.53	0	2	0	69.85	26.3
17	14634627	C ₁₇ H ₂₈ O ₂	264.4	19	0	0.94	3	2	0	78.26	26.3
18	566071	C ₂₇ H ₄₂ O ₂	398.62	29	0	0.85	5	2	0	122.85	34.14
19	596827	C ₁₉ H ₁₄ O ₂ S	306.38	22	18	0.05	2	2	0	87.5	42.52
20	3034394	C ₂₀ H ₃₄ O	290.48	21	0	0.8	4	1	1	93.76	20.23

Table 6: Pharmacokinetics Parameters of the Phytoconstituents of *Aframomum sceptrum*

S/N	Ligands PubChem CID	GI Absorption	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log K _p (skin permeation) (cm/s)
1	111037	High	Yes	No	No	No	Yes	No	No	-4.69
2	19725	Low	Yes	No	Yes	Yes	Yes	No	No	-4.37
3	107152	Low	No	No	No	Yes	Yes	No	No	-4.29
4	556206	Low	No	No	No	Yes	Yes	No	No	-3.71
5	288227	Low	No	No	No	Yes	Yes	No	No	-3.83
6	519361	Low	No	No	No	Yes	Yes	No	No	-3.68
7	90805	Low	No	No	No	Yes	Yes	No	No	-3.8
8	227829	High	Yes	No	No	No	No	No	No	-5.48
9	5281520	Low	No	No	No	No	Yes	No	No	-4.32
10	23274265	High	Yes	No	No	No	Yes	No	No	-4.91
11	5362873	High	Yes	No	Yes	Yes	Yes	No	No	-4.9
12	91457	High	Yes	No	No	No	Yes	No	No	-5
13	442343	High	Yes	No	No	No	Yes	No	No	-4.97
14	604966	High	Yes	No	No	Yes	Yes	No	No	-5.28
15	5367548	High	Yes	No	No	Yes	No	No	Yes	-5.36
16	5281437	High	Yes	No	No	Yes	Yes	No	No	-6.23
17	14634627	High	Yes	No	No	Yes	Yes	No	No	-4.35
18	566071	Low	No	No	No	No	Yes	No	No	-4.07
19	596827	High	Yes	No	Yes	Yes	No	No	No	-5.29
20	3034394	High	Yes	No	No	Yes	Yes	Yes	No	-4.01

Table 7: Lipophilicity Characteristics and Druglikeness of *Aframomum sceptrum* compounds

S/N	Ligands PubChem CID	Lipophilicity (Log P _{o/w} (iL OGP))	Lipophilicity (Log P _{o/w} (XLOGP3))	Lipophilicity (Log P _{o/w} (MLOGP))	Lipophilicity (Log P _{o/w} (SILICOS- IT))	Lipophilicity (Consensus Log P _{o/w})	Druglikeness (Lipinski)
1	111037	2.93	3.96	2.65	2.6	3.04	Yes, 0 violation
2	19725	3.4	4.47	5.65	3.73	4.3	Yes; 1 violation:
3	107152	3.35	4.58	4.63	4.14	4.29	Yes; 1 violation:
4	556206	3.3	5.4	4.63	3.35	4.22	Yes; 1 violation:
5	288227	3.32	5.24	4.63	4.14	4.41	Yes; 1 violation:
6	519361	3.28	5.44	4.63	4.43	4.5	Yes; 1 violation:
7	90805	3.42	5.27	4.63	3.75	4.33	Yes; 1 violation:
8	227829	3.29	3.07	3.67	3.35	3.46	Yes; 0 violation

9	5281520	3.27	4.55	4.53	3.91	4.26	Yes; 1 violation:
10	23274265	3.11	3.85	3.56	3.78	3.71	Yes; 0 violation
11	5362873	3.19	3.86	3.81	3.78	3.65	Yes; 0 violation
12	91457	3.06	3.74	3.67	3.64	3.61	Yes; 0 violation
13	442343	3.46	3.79	3.56	3.74	3.76	Yes; 0 violation
14	604966	2.98	3.33	3.56	3.51	3.42	Yes; 0 violation
15	5367548	3.75	3.96	3.73	3.44	3.93	Yes; 0 violation
16	5281437	2.72	2.09	3.26	3.25	2.97	Yes; 0 violation
17	14634627	3.14	5.02	4.04	3.72	3.99	Yes; 0 violation
18	566071	4.25	6.56	5.21	6.68	5.9	Yes; 1 violation:
19	596827	2.49	4.05	3.94	3.89	3.87	Yes; 0 violation
20	3034394	3.93	5.72	4.75	5.4	5.06	Yes; 1 violation:

Table 8: Physiochemical Properties of the Phytoconstituents of *Ricinodendron heudelotii*

S/N	Ligands PubChem CID	Formula	Molecular Weight (g/mol)	Num. Heavy Atoms	Num. Arom. Heavy Atoms	Fraction CSP3	Num. Rotatable bonds	Num. H- bond acceptors	Num. H- bond donors	Molar Refractivity	TPSA (Å²)
1	547495	C ₁₆ H ₂₃ NO ₂	261.36	19	6	0.56	2	2	1	80.65	40.54
2	5367918	C ₁₅ H ₂₆ O ₃	254.37	18	0	0.73	7	3	1	74.49	38.69
3	41133	C ₁₄ H ₂₄ O	208.34	15	0	0.93	1	1	0	65.12	17.07
4	6603912	C ₁₇ H ₂₃ NO	257.37	19	6	0.65	1	2	1	81.58	21.26
5	550196	C ₁₅ H ₂₆ O	222.37	16	0	0.73	3	1	1	72.06	20.23
6	6451376	C ₁₉ H ₃₄	262.47	19	0	1	1	0	0	86.84	0
7	4916205	C ₂₁ H ₂₅ NO ₄	355.43	26	11	0.43	6	4	1	100.29	68.39
8	610088	C ₁₃ H ₂₁ NO	207.31	15	0	0.92	3	1	1	61	29.1
9	2965173	C ₁₈ H ₁₉ N ₃ O ₂ S	341.43	24	14	0.22	8	2	3	95.67	102.23
10	101176	C ₁₉ H ₁₈ N ₂ O ₄	338.36	25	15	0.16	8	4	3	93.23	91.42
11	91740953	C ₁₀ H ₈ F ₃ NOS	285.23	18	6	0.3	5	6	1	57.61	54.4
12	91733926	C ₁₈ H ₁₈ O ₂	266.33	20	12	0.17	6	2	0	82.35	26.3
13	21433393	C ₁₇ H ₁₆ O ₂	252.31	19	12	0.12	5	2	0	77.55	26.3
14	83247	C ₁₅ H ₁₃ N	207.27	16	15	0.07	1	0	1	68.7	15.79
15	610181	C ₁₅ H ₁₃ N	207.27	16	15	0.07	1	0	1	68.7	15.79
16	77095	C ₁₅ H ₁₃ N	207.27	16	15	0.07	1	0	0	68.64	4.93
17	610180	C ₁₅ H ₁₃ N	207.27	16	15	0.07	1	0	0	67.8	4.41
18	92729	C ₂₈ H ₄₈ O ₂	416.68	30	6	0.79	12	2	1	134.31	29.46
19	6857447	C ₂₈ H ₄₈ O ₂	416.68	30	6	0.79	12	2	1	134.31	29.46
20	67475966	C ₂₈ H ₄₈ O ₂	416.68	30	6	0.79	13	2	0	133.81	18.46

Table 9: Pharmacokinetics Parameters of the Phytoconstituents of *Ricinodendron heudelotii*

S/N	Ligands PubChem CID	GI Absorption	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor	Log K _p (skin permeation) (cm/s)
1	547495	High	Yes	No	No	No	No	Yes	No	-6.57
2	5367918	High	Yes	No	No	No	No	No	No	-5.69
3	41133	High	Yes	No	No	No	Yes	No	No	-4.78
4	6603912	High	Yes	Yes	No	No	No	Yes	No	-5.76
5	550196	High	Yes	No	No	No	Yes	No	No	-4.78
6	6451376	Low	No	No	Yes	Yes	Yes	No	No	-2.44
7	4916205	High	Yes	No	No	Yes	Yes	Yes	Yes	-5.68
8	610088	High	Yes	No	No	No	No	No	No	-5.48
9	2965173	High	No	Yes	No	Yes	Yes	Yes	Yes	-6.94
10	101176	High	No	Yes	No	Yes	Yes	No	No	-6.72
11	91740953	High	Yes	No	Yes	Yes	No	No	No	-5.25
12	91733926	High	Yes	No	Yes	Yes	Yes	Yes	No	-4.4
13	21433393	High	Yes	No	Yes	Yes	Yes	Yes	No	-4.68
14	83247	High	Yes	Yes	Yes	Yes	No	Yes	No	-4.67
15	610181	High	Yes	Yes	Yes	Yes	No	Yes	No	-4.67
16	77095	High	Yes	No	Yes	Yes	No	Yes	No	-4.67
17	610180	High	Yes	No	Yes	Yes	No	Yes	No	-4.23
18	92729	Low	No	Yes	No	No	No	No	No	-1.51
19	6857447	Low	No	Yes	No	No	No	No	No	-1.51
20	67475966	Low	No	Yes	No	No	No	No	No	-1.53

This implies that ligands such as 9-Fluorenebenzenesulfonyl, which have higher binding affinity than the standard drug (Artesunate) and interact with some targets using conventional hydrogen bonds, will have a high ligand-receptor specificity. In contrast, compound 18, despite having a high binding affinity as compound 19, did not bind

to any of the active/binding site amino acids with hydrogen bonds, possibly interacting with the allosteric sites of the protein through non-covalent interactions (Bhagavan and Ha, 2011). Compounds 8, 12, and 15, with a binding affinity of -7.1, -6.9, and -7.5 kcal/mol, respectively, bound with only one conventional hydrogen bond to the active/binding site

amino acids. Other compounds interacted with some of the active site amino acids through van der Waal's forces and other interactions such as Alkyl, Pi-Alkyl, Pi-Sigma, Pi-Anion, Unfavourable Aceptor-Aceptor, Halogen (Flourine), Pi-Pi T-Shaped, Sulfur and Carbon Hydrogen bond.

Furthermore, ADMET studies were conducted on these ligands to assess their druggability and possible organ toxicity because excellent ligand-receptor binding does not translate to druggability (Buchwald, 2019). Similarly, phytoconstituents of RH bound to the target protein with varying binding affinities, as shown in Table 2. Their binding affinities ranged from -6.5 to -8.5 kcal/mol, compared to Artesunate (-7.6 kcal/mol), the standard antimalarial agent. Compound 10 had the highest binding affinity of -8.5 kcal/mol, and compounds 1, 8, 9, 13, and 14 had binding affinities of -7.6, -6.6, -7.7, -6.7 and -7.5 kcal/mol, respectively. Compounds 8 and 9 are bound with two conventional hydrogen bonds to the active site amino acids, while compounds 1, 10, 13, and 14 are bound with only one conventional hydrogen bond to the active site amino acids. Other compounds interacted with some of the active site amino acids through van der Waal's forces, and others, such as Alkyl, Pi-Alkyl, Pi-Sigma, etc. Absorption Distribution Metabolism Excretion and Toxicity (ADME-TOX) studies help estimate the drug-likeness of compounds before synthesis, as this helps decrease the occurrences of pharmacokinetic-related failure in drug development. Modern drug discovery involves the assessment of the competence of the dynamic molecules and their strength to reach the target site in bioactive form, which involves cellular, animal, and human clinical trials that are highly priced and encumbered with risks (Ndombera *et al.*, 2019; Ranjith and Viswanath, 2019). Presently, computer-aided drug development encourages the estimation of absorption, distribution, metabolism, and excretion of drugs (ADME). They postulate anticipatory and dependable data quickly and complement experimental approaches (Sliwoski *et al.*, 2014; Ndombera *et al.*, 2019). It has been determined that the initial appraisal of ADME properties in the discovery period diminishes

remarkably the fraction of pharmacokinetics-related failures in the clinical phase (Ndombera *et al.*, 2019; Hay *et al.*, 2014). In this study, the ADME properties of the potent phytochemicals of *Aframomum sceptrum* and *Ricinodendron heudelotii* were evaluated using the SwissADME web tool, available at <http://www.swissadme.ch>, known for its simplicity and results reproducibility, especially for non-expert in CADD (Daina *et al.*, 2017). The test ligands (40) from *Aframomum sceptrum* and *Ricinodendron heudelotii* were analysed using the SwissADME web tool to study the physicochemical properties (Tables 5 and 8, respectively), pharmacokinetic parameters (Tables 6 and 9, respectively), lipophilicity characteristics and drug-likeness rule (Tables 7 and 10, respectively), and the toxicity profile (Tables 11 and 12, respectively). Physiochemical properties of the phytoconstituents of *Aframomum sceptrum* and *Ricinodendron heudelotii* revealed that all the compounds have a molecular weight of less than 500 Da, which is a prime property of drug-likeness. The pharmacokinetics parameters determination performed using SwissADME showed a high level of gastrointestinal tract (GI) absorption by all the phytoconstituents in Table 6 except for compounds 2, 3, 4, 5, 6, 7, 9, and 18 and high BBB permeability except compounds 3, 4, 5, 6, 7, and 18 for *Aframomum sceptrum*. The ligands in *Aframomum sceptrum* are not the substrates for P-glycoproteins (P-gp). The Swiss ADME model returns "Yes" or "No" if the compound under examination has a greater probability of being a substrate or non-substrate of P-gp or inhibitor or non-inhibitor of Cytochrome P 450 isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4). All the ligands returned "No" for the P-gp substrate (Table 6). Almost all ligands were returned as non-inhibitors for the inactivation of CYP isoenzymes, except for a few (Table 6). The skin permeability coefficient (Log Kp) is a multiple linear regression; the more negative the log Kp (with Kp in cm/s), the less skin permeates the molecule. Among the phytoconstituents of the *Aframomum sceptrum*, compound 16 with CID: 5281437 (-6.23 cm/s) has the most negligible skin permeability, and compound 4 (-3.71 cm/s) exhibited the highest skin permeability.

Table 10: Lipophilicity Characteristics and Drug Likeness Rule of *Ricinodendron heudelotii*

S/N	Ligands PubChem CID	Lipophilicity (Log Po/w (iLOGP))	Lipophilicity (Log Po/w (XLOGP3))	Lipophilicity (Log Po/w (WLOGP))	Lipophilicity (Log Po/w (SILICOS- IT))	Lipophilicity (Consensus Log P_{ow})	Drug likeness (Lipinski)
1	547495	2.91	1.87	2.19	2.87	2.41	Yes; 0 violation
2	5367918	3.58	3.05	3.19	3.36	3.07	Yes; 0 violation
3	41133	2.8	3.93	3.82	3.74	3.54	Yes; 0 violation
4	6603912	2.97	2.97	2.66	3.65	3.11	Yes; 0 violation
5	550196	3.21	4.05	3.94	3.89	3.73	Yes; 0 violation
6	6451376	3.97	7.69	5.91	4.77	5.82	Yes; 1 violation:
7	4916205	3.63	3.93	4.2	5.16	3.85	Yes; 0 violation
8	610088	2.42	2.93	2.34	2.48	2.56	Yes; 0 violation
9	2965173	2.72	2.03	2.44	4.26	2.54	Yes; 0 violation
10	101176	1.79	2.31	2.94	2.97	2.37	Yes; 0 violation
11	9174095	2.02	3.93	5.45	3.24	3.55	Yes; 0 violation
12	9173392	3.31	4.97	4.26	4.73	4.16	Yes; 0 violation
13	2143339	3.08	4.45	3.87	4.35	3.8	Yes; 0 violation
14	83247	2.43	4.08	4.14	4.62	3.72	Yes; 0 violation
15	610181	2.6	4.08	4.14	4.62	3.75	Yes; 0 violation
16	77095	2.61	4.08	3.85	3.58	3.49	Yes; 0 violation
17	610180	2.88	4.69	3.91	3.54	3.67	Yes; 0 violation
18	92729	5.76	10.33	8.53	9.2	7.95	Yes; 1 violation:
19	6857447	4.94	10.33	8.53	9.2	7.79	Yes; 1 violation:
20	6747596	5.54	10.3	8.53	9.22	7.91	Yes; 1 violation:

Table 11: Toxicity Profile of the Phytoconstituents of *Aframomum sceptrum*

S/N	Ligands PubChem CID	Hepa- totoxicity	Neuro- toxicity	Nephro- toxicity	Respiratory toxicity	Cardio- toxicity	Carcino- genicity	Immuno- toxicity	Muta- genicity	Cyto- toxicity
1	111037	+	-	-	-	-	-	-	-	-
2	19725	-	-	-	-	-	-	-	-	-
3	107152	-	+	-	-	-	-	-	-	-
4	556206	-	+	-	-	-	-	-	-	-
5	288227	-	+	-	-	-	-	-	-	-
6	519361	-	+	-	-	-	-	-	-	-
7	90805	-	+	-	-	-	-	-	-	-
8	227829	-	-	-	+	-	-	-	-	-
9	5281520	-	-	-	-	-	-	-	-	-
10	23274265	-	-	-	-	-	-	-	-	-
11	5362873	-	-	-	-	-	-	+	-	-
12	91457	-	+	-	+	-	-	-	-	-
13	442343	-	-	-	-	-	-	-	-	-
14	604966	-	-	-	-	-	-	-	-	-
15	5367548	-	-	-	+	-	-	+	-	-
16	5281437	-	-	-	+	-	-	+	-	-
17	14634627	-	-	-	-	-	+	-	-	-
18	566071	-	+	-	+	-	-	+	-	-
19	596827	-	-	-	-	-	-	-	+	-
20	3034394	-	-	-	+	-	-	-	-	-

Where + = Toxic, - = Not toxic

Table 12: Toxicity Profile of the Phytoconstituents of *Ricinodendron heudelotii*

S/N	Ligands PubChem CID	Hepa- totoxicity	Neuro- toxicity	Nephro- toxicity	Respiratory toxicity	Cardio- toxicity	Carcino- genicity	Immuno- toxicity	Muta- genicity	Cyto- toxicity
1	547495	-	+	-	+	-	-	-	-	-
2	5367918	-	-	+	-	-	-	-	-	-
3	41133	-	+	-	-	-	-	-	-	-
4	6603912	-	+	-	+	-	-	+	-	-
5	550196	-	-	-	-	-	-	-	-	-
6	6451376	-	-	-	-	-	-	-	-	-
7	4916205	-	-	+	+	-	-	-	-	-
8	610088	-	+	-	+	-	-	-	-	-
9	2965173	-	+	-	+	-	-	-	-	-
10	101176	-	+	+	+	+	-	-	-	+
11	91740953	+	+	-	+	-	-	-	-	-

12	91733926	-	+	-	-	-	-	+	-	-
13	21433393	-	+	-	-	-	-	+	-	-
14	83247	+	+	-	-	-	-	-	+	-
15	610181	+	+	-	-	-	-	-	+	-
16	77095	-	+	-	+	-	+	-	+	-
17	610180	-	+	-	-	-	-	-	+	-
18	92729	-	-	-	+	-	-	-	-	-
19	6857447	-	-	-	+	-	-	-	-	-
20	67475966	-	-	-	-	-	-	-	-	-

Where + = Toxic, - = Not toxic

The pharmacokinetics parameters analysis of RH ligands showed a high level of GI absorption for all the phytoconstituents except compounds 6, 18, and 20 and high BBB permeability except compounds 5, 9, 10, 18, 19, and 20 (Table 9). Most of the ligands of RH are not substrates for P-gp. Compounds 4, 9, 10, 14, 15, 18, 19, and 20 returned "Yes" for the P-gp substrate and all remaining ligands as "No" for the P-gp substrate (Table 9). Almost all ligands were returned as non-inhibitors for the inactivation of CYP isoenzymes, except for a few. Among the phytoconstituents of the RH compound, 9 (-6.94 cm/s) showed the least skin permeability, while 18 and 19 (-1.51 cm/s) were the highest.

The compounds' lipophilicity qualities influence the solubility and permeability through cellular membranes (Kadela-Tomanek *et al.*, 2021). The partition coefficient LogP of a particular molecule between the n-octanol and water system is a quantitative indicator of lipophilicity (Daina *et al.*, 2014). N-octanol is thought to be a suitable mimic of the properties of phospholipid membranes due to its amphiphilic nature (Liu *et al.*, 2010). Log Po/w can be computed using a variety of algorithms that are based on factual methods. Molecular structures are divided into molecular fragments by the first division of the classic log P predictors, which includes the fragmental approach (Klopman *et al.*, 1994) and KLOGP. ALOGP (Ghose & Crippen, 1986; Ghose *et al.*, 1998), XLOGP (Wang *et al.*, 1997, Cheng *et al.*, 2007), and KOWWIN (Meylan and Howard, 2000) are examples of analogous approaches. Counts or flags for particular atoms, groups, or structural features, such as MLOGP, are among the topological methods in the second section. This allows for the description of molecules about their topology. The forecast was obtained by manifold linear regression,

which was trained on extensive molecular data sets. Utilising a hybrid approach that integrates topological parameters and molecular fragments, SILICOS-IT was trained on 23,455 molecules with experimental n-octanol/water partition values. It is based on 27 fragments and 7 topological descriptors (Daina *et al.*, 2014). Based on a system of 87 fragments and two correcting factors, the XLOGP atomic model version three was developed. When an input structure resembles a reference compound, the fragments that distinguish them are handled differently, and their respective log P contributions are added to the log P value of the reference structure (Cheng *et al.*, 2007). Lipophilicity estimated as consensus Log P, which is the average value of all Log P evaluated with various lipophilicity criteria, determined compound 18 as most lipophilic whereas compound 1 as least lipophilic and water solubility of the ligands ranged from highly water soluble (CID: 111037, Terpinyl acetate) to least water-soluble or insoluble (CID: 566071, 21.xi-methyl-17-ischolestan-5-en-3,16-dione), respectively for *Aframomum sceptrum*. Compounds 18 and 10 of *Ricinodendron heudelotii* are the most and least lipophilic, respectively.

Different rules are available to help predict drug likeness, but the Lipinski Rule of 5 (RO5) was used for this study. The RO5 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 . A total of 40 potent phytoconstituents of *Aframomum sceptrum* and *Ricinodendron heudelotii* were analysed using the Lipinski Rule. They showed that none of the ligands failed more than one of the criteria, thus qualifying as potential drug molecules. Furthermore, the test ligands were subjected to an *in silico* toxicity study using the ProTox II web server. The results

showed that compounds 2, 9, 10, 13, 14, 5, 6 and 20 did not have any toxicity on any major organ and hence qualified as potential drug molecules.

Conclusion: Molecular docking analysis reveals that the binding affinities and interaction by some of the phytoconstituents present in *Aframomum sceptrum* and *Ricinodendron heudelotii* with the active site amino acid residues of the target protein (Plasmepsin II) validate their use traditionally for the treatment of malaria when compared with the standard drug (Artesunate). A few phytoconstituents in *Aframomum sceptrum* and *Ricinodendron heudelotii* showed toxicity concerns from ADMET analysis. This study validates the ethnomedicinal uses of these plant extracts in treating malarial and other diseases. Further in vivo and isolation studies are required to identify the phytoconstituents with antimalarial activity.

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Declaration of Data Availability Statement: The data can be obtained upon request from the corresponding author

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