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Exploring the Therapeutic Potential of *Antiaris africana*: Targeting Cyclin-Dependent Kinases 8 and 13 for Cancer Treatment through Molecular Docking Studies

Mutiu A. Alabi[a], Elizabeth O. Oladoye[a], Taofeeq A. Adedokun[b], Adelowo A. Adebiyi[c], Raphael S. Olatoye[a], Beloved K. Ajani[a], Damasuno S. Ibrahim[a], Halimah Olayiwola[a], Racheal I. Enobiomanor[a], and Emmanuel O. Ajani[a]

[a] *Biochemistry Department, Faculty of Pure and Applied Sciences, Kwara State University, Malete, Ilorin, Nigeria*
[b] *Pharmacognosy department, Faculty of Pharmacy, Olabisi Onabanjo University, Ago-Iwoye, Nigeria*
[c] *Biochemistry Department, Faculty of Basic Medical Sciences, Olabisi Onabanjo University, Ago Iwoye, Nigeria*

CORRESPONDANCE
Mutiu A. Alabi
mutiu.alabi@kwasu.edu.ng

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ABSTRACT: ***Background:*** *Cancer remains a major global health burden that significantly affects human populations. The ongoing need for innovative therapeutic strategies to both manage and prevent this life-threatening disease is paramount. The quest for creative and less toxic cancer therapies has led to a vast exploration of plant-derived compounds.* ***Objective:*** *This study investigated the anticancer potential of phytochemicals extracted from Antiaris africana (A. africana), a traditional medicinal plant used in ethnomedicine in West Africa, through molecular docking studies.* ***Methods:*** *The stem bark extract, prepared via maceration with methanol, was analyzed by gas chromatography mass spectrometry (GC-MS), revealing 36 bioactive compounds. In silico evaluations, including molecular docking, ADME prediction, and toxicity assessments, were carried out to identify inhibitory effects on cyclin-dependent kinases 8 (CDK8) and 13 (CDK13), key regulators of cancer progression.* ***Results:*** *GC-MS analysis of the methanolic extract of A. africana revealed 36 phytochemicals with possible anticancer potential. Notable phytochemicals, such as bis(2-ethylhexyl) phthalate and campesterol, exhibited significant binding affinities to CDK8 and CDK13, with high Glide scores and favorable pharmacokinetic profiles, adhering to Lipinski's five rule. ADME analyzes highlighted the druglikness and minimal toxicity of the compound, supporting its potential as an orally bioavailable therapeutic. In silico studies revealed bis(2-ethylhexyl) phthalate, 2,6,10,15,19,23-hexamethyltetracosa-2,10,14,18,22-pentaene-6,7-diol and 3-12-formyl-digoxigenin as lead compounds, which offered promising insights into the anticancer potential of the compounds.* ***Conclusions:*** *This study underscores A. africana as a promising source of lead compounds for targeted cancer therapies. Further in vitro and in vivo studies are recommended to validate these findings and explore the therapeutic landscape of these bioactive molecules.*

KEYWORDS: *Antiaris africana; Cyclin-dependent kinases; Phytochemicals; Molecular docking; Anticancer drug discovery*

INTRODUCTION

Cancer is a leading global cause of death, with significant morbidity and mortality projected to rise by 2030 [1], [2]. It involves uncontrolled cell growth leading to tumors and systemic impairments [3]–[5]. Research focuses on discovering less toxic, targeted therapies [6], [7], including plant-derived compounds [8]–[10], identified through bioactivity assessment, compound isolation, and rational drug design [9], [11], [12]. Therapeutic resistance, including drug-tolerant persisters (DTPs), remains a challenge [13]–[19]. *Antiaris africana (syn. A. toxicaria subsp., A. africana)*, a medicinal

plant native to tropical Africa/Madagascar [2], [20]–[22], is used ethnomedicinally for various ailments, including cancer [23], [24]. It exhibits morphological variation linked to environment and occurs in diverse habitats [25], [26]. Its latex contains toxic cardiac glycosides [27], [28], causing skin/respiratory issues [29].

Cyclin-dependent kinases (CDKs) like CDK13 and CDK8 are serine/threonine kinases regulating cell proliferation, transcription, and other processes via cyclin binding [30]–[34]. CDK13, with undetermined exact function but large terminus, is ubiquitously expressed [18], [35], [36]. CDK8, with cyclin C, is part of the Mediator complex regulating transcription via RNA Pol II phosphorylation and interacts with TFIIH [37]–[42]. CDKs also link to differentiation, apoptosis, and neurocytoskeleton dynamics [43]–[45].

FDA-approved CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib) combined with endocrine therapy represent a major advance in treating HR+/HER2- metastatic breast cancer, improving progression-free and overall survival to establish a new standard of care [46]. Their mechanism involves targeting the CDK4/6-cyclin D complex, inducing G1 arrest and suppressing proliferation in pathway-dependent cancers [47]. However, significant challenges remain, including inevitable primary and acquired resistance limiting long-term efficacy, manageable but impactful toxicities (e.g., neutropenia, fatigue, GI disturbances) requiring dose adjustments [48], and high costs creating access barriers. Consequently, discovering novel CDK inhibitors, particularly from natural sources offering potentially improved safety, distinct mechanisms, or lower costs, is a critical research focus.

Computational approaches have significantly contributed to the discovery of inhibitors targeting CDK8 and CDK13, both of which are key regulators in cancer. Studies using molecular docking and virtual screening have identified compounds such as Senexin B [49], kaempferol, and ruxolitinib as potential CDK8 inhibitors [50]. Ponatinib has been reported as a dual CDK8/19 inhibitor through repurposing strategies [51].

For CDK13, structure-based methods have identified selective inhibitors like THZ531 derivatives [2], [52]. Pharmacophore modeling have been used to discover novel CDK13-binding scaffolds [53]. These studies affirm the value of *in silico* methods in kinase-targeted drug discovery and support their application in identifying promising anticancer leads.

This study aims to perform *in silico* screening of *A. africana* compounds against CDK13 and CDK8 as potential anticancer agents using molecular docking, Swiss ADME, and PASS online.

MATERIALS AND METHODS

A. africana Sample Collection and Preparation of Extract

Fresh *A. africana* stem bark was collected from a local farm in Offa, Kwara State, Nigeria. The bark was air-dried at an ambient temperature for two weeks and then ground into a fine powder. Methanol extraction was performed by macerating 5 kg of powdered bark with 15 L of methanol at room temperature for 72 hours. The solvent was subsequently removed under reduced pressure using a rotary evaporator (65 °C, 130 rpm), yielding a dark brown crude methanolic extract.

Gas Chromatography-Mass Spectrophotometry (GC-MS) Analysis

Chemical characterization was performed by gas chromatography-mass spectrometry (GC- MS) utilizing a Shimadzu QP 2010SE system (Tokyo, Japan). For analysis, 3 mg of the extracted powder was solubilized in aqueous solvent. The analytical conditions comprised an initial column oven temperature of 60 °C and an injector temperature maintained at 250 °C. The chromatographic separation employed a linear velocity flow control mode with 1:1 split injection. Helium carrier gas (99.99 % purity) was maintained at a constant column flow rate of 3.22 mL/min. The temperature program was initiated at 60 °C (1 min hold), ramped at 15 °C/min to 120 °C (2 min hold), followed by a second ramp at 15 °C/min to 300 °C (3 min hold). Separation was performed using a 30 m × 0.25 mm ID column with 0.25 μm stationary phase thickness. Mass spectrometric detection parameters included an ion source temperature of 200 °C and interface temperature of 240 °C, with mass spectra acquired over the m/z range 1 45-700.

In silico Analysis

Molecular docking simulations were performed using the Maestro 12.8 Glide software suite to evaluate the theoretical binding interactions of pre-screened phytochemical compounds, including positive controls, with active site residues localized within defined grid boxes of the target protein

receptors [54], [55]. Computational docking algorithms were employed to assess the molecular interactions between phytochemical compounds and active-site residues of the target receptor. These simulations evaluated binding affinity (ΔG), docking scores, Glide SP (Standard Precision) scoring metrics, and ligand-receptor spatial conformations. Phytochemical-receptor complexes demonstrating superior binding parameters relative to both co-crystallized ligands and positive controls were prioritized for subsequent investigation.

The crystallographic structures of selected human (Homo sapiens) receptors (detailed in Table 1) were obtained from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein D ata Bank and subjected to molecular preprocessing using the Protein Preparation Wizard module in Schrödinger Maestro v12.5.139. The co-crystallized ligand (KVB) was excised, and the protein structure was optimized under OPLS2005 force field parameters at pH 7.0±2.0. Structural refinements included elimination of steric clashes, restoration of hydrogen bond networks, and reconstruction of missing residues (side chains/loops) via Prime. Heterogenous groups [34] underwent curation through removal of water molecules exceeding 5.00 molecular weight or lacking ≥ 3 hydrogen bonds to non-aqueous atoms, followed by bond order assignment. Final energy minimization was conducted with a polar hydrogen charge at 0.25.

Table 1. Representation of studied receptors with their corresponding PDB ID and active modulators, along with plant compounds denotation

Receptor	RCSB PDB ID	Standard / Type	Plant Compounds Representation
Cyclin K–Cyclin-dependent Kinase 13	7NXJ	THZ531R	*A. africana*
Cyclin C–Cyclin-dependent Kinase 8	4CRL	Cortistatin A	*A. africana*

The two-dimensional (2D) chemical structures of the investigated compounds were acquired from the PubChem chemical repository and subsequently processed through the LigPrep module within the Schrödinger Maestro computational suite (v12.5). Ligand preparation included desalination, generation of potential ionization states (Epik) and tautomeric forms at physiological pH 7.0±0.2, followed by structural optimization via energy minimization employing the OPLS_2005 force field parameters in the MacroModel molecular mechanics package.

The co-crystallized ligand was excised from the active site of each receptor chain, with non-bonded interaction parameters standardized to a Van der Waals radius of 1.0 Å and partial atomic charge threshold of 0.25. A three-dimensional bounding box, centered on the workspace centroid of residues proximally to the original ligand, delineated the active site. Employing default parameters within the Glide algorithm (Schrödinger Suite), a receptor grid was programmatically generated. All ligand docking simulations were subsequently performed within this pre-defined grid framework as part of the computational workflow.

ADME Pharmacokinetics, Drug-likeness, Bioactivity, and Toxicity Prediction

The SwissADME tool was employed to assess the oral bioavailability of selected compounds [56]. Additionally, the drug-likeness profiles of each phytochemical were predicted using Admetsar 3.0 as part of the screening protocol. Key pharmacokinetic parameters, including blood-brain barrier (BBB) permeability, gastrointestinal (GI) absorption efficiency, P-glycoprotein (P-gp) substrate specificity, and cytochrome inhibition profiles, were systematically assessed through computational predictive frameworks such as the Biopharmaceutics Drug Disposition Classification System (BDDCS), Lipinski's Rule of Five, and established druggability criteria [57].

To elucidate potential polypharmacological anticancer mechanisms, computational bioactivity profiling of the phytochemical candidates was conducted via PASS Online (Prediction of Activity Spect ra for Substances). Structural inputs in SMILES notation generated probabilistic outputs quantified as Pa/Pi (Probability of Activity/Inactivity) scores, predicting mechanistic engagement in antineoplastic activity, apoptotic agonism, CYP2J2 substrate interactions, testosterone 17β-dehydrogenase ($NADP^+$) inhibition, and anti-inflammatory pathways. Benchmark compounds included the established anticancer agents N-[4-[(3R)-3-[[5-chloro-4-(1H-indol-3-yl)pyrimidin-2-yl]amino]piperidin-1-yl]carbonylphenyl]-4-(dimethylamino)butanamide and Cortistatin A, which served as pharmacological reference standards.

Additionally, computational toxicological profiling of the prioritized compounds was conducted via

web-based predictive platforms, including ProTox-3 [58] and StopTox [59]. ProTox-II facilitated a quantitative assessment of lethal dose (LD50, mg/kg) and toxicological classification, while StopTox evaluated acute toxicological endpoints for the candidate molecules.

RESULTS AND DISCUSSION

GC-MS Analysis

The methanolic stem bark extract of *A. africana* was analyzed using gas chromatography–mass spectrometry (GC–MS), resulting in the identification of 36 distinct phytochemical constituents. These compounds are listed in Table 2 and their retention times are illustrated in the chromatographic profile, as shown in Figure 1. The identified phytochemicals span a wide range of molecular weights and structural classes, contributing to the extract's pharmacological complexity and supporting its ethnomedicinal applications.

Among the major constituents detected, N-[4-[(3R)-3-[[5-chloranyl-4-(1H-indol-3-yl)pyrimidin-2-yl]amino]piperidin-1-yl]carbonylphenyl]-4-(dimethylamino)butanamide and Cortistatin A are of particular interest due to their known or predicted bioactivity. These compounds provide mechanistic insights into the potential therapeutic effects of *A. africana*, aligning with its traditional use in managing cancer, inflammatory conditions, and infectious diseases.

Several compounds demonstrated high relative abundance, as indicated by their area percentages. Notable examples include 5-hydroxymethylfurfural ($C_6H_6O_3$) and dibutyl phthalate ($C_{16}H_{22}O_4$), both of which exhibited significant peaks and are recognized for their pharmacological relevance. Additionally, Hexanoic acid 6-bromo- ($C_6H_{11}BrO_2$) and 2-furanmethanol ($C_5H_6O_2$) were identified, further underscoring the chemical diversity of the extract [60]–[63].

The presence of N, N-dimethyltryptamine ($C_{12}H_{16}N_2$) and 9-octadecenoic acid (Z)-methyl ester ($C_{19}H_{36}O_2$) suggests potential for neuroactive, anti-inflammatory, or anticancer activity. These findings are consistent with ongoing research into plant-derived compounds for drug development, particularly in the context of targeting cyclin-dependent kinases (CDK-8 and CDK-13), which play pivotal roles in cell cycle regulation and transcriptional control [23], [64].

Overall, the comprehensive GC–MS profiling provides a robust biochemical basis for the traditional medicinal use of *A. africana*, and identifies several bioactive candidates for further *in silico*, in vitro, and in vivo investigation. These compounds may serve as promising scaffolds in the development of novel CDK-targeting anticancer agents [65], [66].

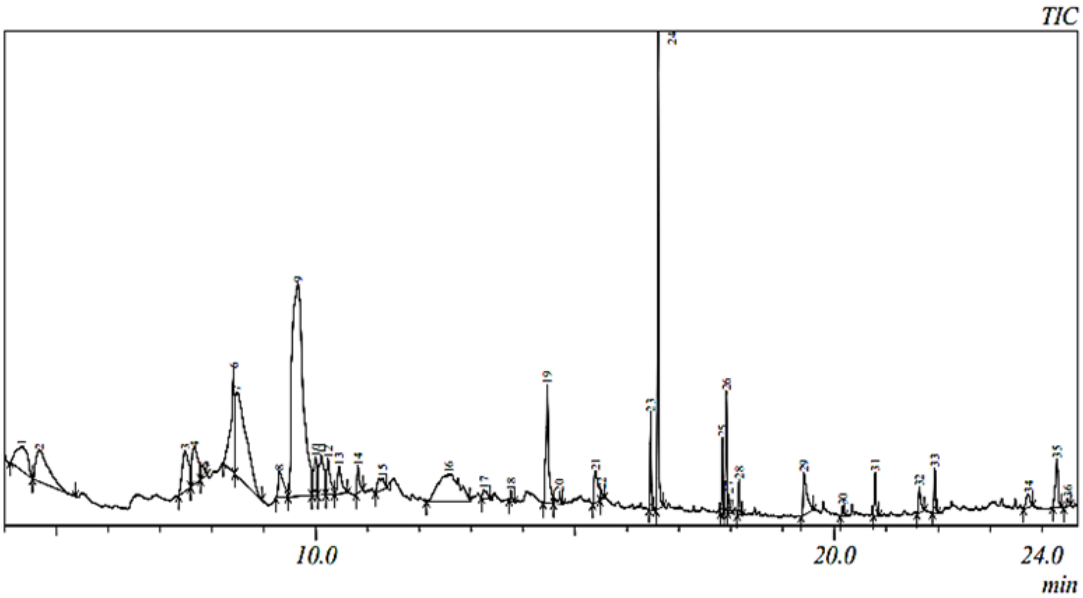

Figure 1. GC-MS chromatogram of the extract

Table 2. Bioactive compounds identified in the extract of *A. africana* using GC-MS

S/No	Real-Time	Area (%)	Height (%)	Compound name	Mol. weight	Mol. formula
1	4.325	3.35	1.21	Hexanoic acid, 6-bromo-	195	$C_6H_{11}BrO_2$
2	4.663	4.87	1.56	2-Furanmethanol	98	$C_5H_6O_2$
3	7.476	3.12	2.00	2,5-Dimethyl-4-hydroxy-3(2H)-furanone	128	$C_6H_8O_3$
4	7.650	2.74	1.86	Phenol, 2-methoxy-	124	$C_7H_8O_2$
5	7.858	0.57	0.40	Ethanone, 1-(1-cyclohexen-1-yl)-	124	$C_8H_{12}O$
6	8.414	4.54	5.11	Cyclohexane carboxylic acid	128	$C_7H_{12}O_2$
7	8.470	11.06	4.08	4H-Pyran-4-one, 2, 3-dihydro-3,5-dihydroxy-6	144	$C_6H_8O_4$
8	9.293	1.68	1.34	Hexahydrobenzo [1,3]dioxin-4-one	156	$C_8H_{12}O_3$
9	9.651	27.28	10.48	5-Hydroxymethylfurfural	126	$C_6H_6O_3$
10	9.992	1.68	1.87	1,2-Benzenediol, 3-methoxy-	140	$C_7H_8O_3$
11	10.102	2.55	1.96	Ethanone, 1-(2,5-dihydroxy phenyl)-	152	$C_8H_8O_3$
12	10.235	1.53	1.76	5-Acetoxymethyl-2-furaldehyde	168	$C_8H_8O_4$
13	10.446	1.34	1.36	2-Methoxy-4-vinyl phenol	150	$C_9H_{10}O_2$
14	10.808	0.72	1.36	Phenol, 2,6-dimethoxy-	154	$C_8H_{10}O_3$
15	11.283	0.93	0.58	2-Undecenoicacid	184	$C_{11}H_{20}O_2$
16	12.563	6.96	1.33	1,3-Propanediol, 2-(hydroxymethyl)-2-nitro-	134	$C_6H_{14}O_3$
17	13.246	0.42	0.43	Dodecanoic acid	200	$C_{12}H_{24}O_2$
18	13.762	0.21	0.52	Megastigmatrienone	190	$C_{13}H_{18}O$
19	14.462	3.64	5.85	1,2-Benzene dicarboxylic acid, butylmethyles	236	$C_{13}H_{16}O_4$
20	14.700	0.35	0.58	Methyl tetradecanoate	242	$C_{15}H_{30}O_2$
21	15.393	1.49	1.57	N, N-Dimethyltryptamine	188	$C_{12}H_{16}N_2$
22	15.508	0.23	0.48	Dimethylmalonic acid, ethyl 2-ethyl hexyl ester	272	$C_{15}H_{28}O_4$
23	16.459	1.29	4.81	Hexadecanoic acid, methyl ester	270	$C_{17}H_{34}O_2$
24	16.599	6.72	23.49	Dibutyl phthalate	278	$C_{16}H_{22}O_4$
25	17.840	1.13	3.68	9,12-Octadecadienoic acid, methyl ester, (E, E)	294	$C_{19}H_{34}O_2$
26	17.914	2.03	6.00	9-Octadecenoic acid, methyl ester, (E)-	296	$C_{19}H_{36}O_2$
27	17.964	0.31	0.94	9-Octadecenoic acid (Z)-, methyl ester	296	$C_{19}H_{36}O_2$
28	18.164	0.57	1.76	Methyl stearate	298	$C_{19}H_{38}O_2$

Table 2. *Continued*

29	19.412	1.90	2.09	1(2H)-Isoquinolinone, 3,4-dihydro-7-hydroxy	207	$C_{11}H_{13}NO_3$
30	20.163	0.21	0.51	Methyl 18-methyl nonadecanoate	326	$C_{21}H_{42}O_2$
31	20.789	0.78	2.13	N-(4-Aminobutyl)-2-ethyl piperidine	184	$C_{11}H_{24}N_2$
32	21.640	0.67	1.25	n-Nonadecanol-1	284	$C_{19}H_{40}O$
33	21.936	0.79	2.21	Bis(2-ethylhexyl) phthalate	390	$C_{24}H_{38}O_4$
34	23.749	0.59	0.66	Campesterol	400	$C_{28}H_{48}O$
35	24.294	1.50	2.39	2,6,10,15,19,23-Hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol	412	$C_{30}H_{52}O_2$
36	24.505	0.22	0.41	1-Pyrrolidinebutanoic acid, 2-[(1,1-dimethyl ethoxy) carbonyl]-. alpha.-nitro-, 2,6-bis(1,1-dimethylethyl)-4-methoxyphenyl ester	520	$C_{28}H_{44}N_2O_7$

Glide Standard Precision Docking and Molecular Mechanics-Generalized Born Surface Area Calculations against CDK13

The Glide Standard Precision [46] docking protocol, employed for ligand-receptor interaction analysis, identified nine compounds demonstrating binding affinity to the CDK13 receptor. Among these, THZ2531R, a covalent CDK13 inhibitor, exhibited significant mechanistic relevance by potently downregulating transcriptional expressions of DNA damage response (DDR) genes and critical super-enhancer-associated transcription factors [67]. The glide scores of most ligands were significantly higher than that of the co-crystallized ligand, with only two ligands bis(2-ethylhexyl) phthalate and 2,6,10,15,19,23-hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol showing Glide SP MMGBSA values that are close to the standard used, making them the only compounds that are high tight binders to the receptor CDK13, as shown in Table 3.

Table 3. Standard precision molecular docking and MMGBSA screening of hit compounds against the protein receptor CDK13

S/No	Name of Compound	Glide Score (kcal/mol)	Glide SP MMGBSA (kcal/mol)
1	3-Methoxycatechol	-0.181	-40.13
2	Methyllinolelaidate	-0.73	-39.75
3	Methyl oleate	-0.735	-40.12
4	3-12-Formyl-digoxigenin	-1.493	-39.79
5	Dimethylmalonicacid,ethyl2-ethyl hexyl ester	-2.63	-36.67
6	Dibutyl phthalate	-2.668	-38.67
7	Bis(2-ethylhexyl)phthalate	-3.506	-53.16
8	2,6,10,15,19,23-Hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol	-5.218	-42.73
9	Dimethyltryptamine	-7.053	-35.01
10	N-[4-[(3r)-3-[[5-Chloranyl-4-(1h-Indol-3-Yl) pyrimidin-2-Yl]amino]piperidin-1-Yl] carbonylphenyl]-4-(Dimethylamino) butanamide (THZ531R)	-10.002	-75.46

Glide Standard Precision Docking and Molecular Mechanics-Generalized Born Surface Area Calculations against CDK8

The Glide Standard Precision docking used to dock the ligands into the target receptor grid showed that only nine compounds were able to bind to the receptor CDK8. The Glide scores of the ligands were higher than that of the co-crystallized ligand, with only three ligands – dibutyl phthalate, bis(2-ethylhexyl) phthalate, and 2,6,10,15,19,23-hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol showing Glide SP MMGPSA values closest to the standard used. These three ligands are the only compounds that are high-affinity binders to the receptor CDK8, as shown in Table 4.

Table 4. Standard precision molecular docking screening of hit compounds against the protein receptor CDK8

S/No	Name of Compound	Glide SP Score (kcal/mol)	Glide SP MMGPSA (kcal/mol)
1	Methyl tetradecanoate	-0.748	-34.65
2	3-12-Formyl-digoxigenin	-1.301	-34.43
3	Methyl stearate	-1.399	-34.37
4	Dibutyl phthalate	-2.419	-43.24
5	Bis(2-ethylhexyl) phthalate	-4.696	-41.73
6	2,6,10,15,19,23-Hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol	-4.946	-48.07
7	Campesterol	-5.746	-34.05
8	N-(4-Aminobutyl)-2-ethyl piperidine	-6.074	-34.44
9	3,4-Dihydro-7-hydroxy-6-methoxy-1(2H)-isoquinoline	-7.444	-32.84
10	Cortistatin A	-8.635	-62.05

Glide Quantum Polarized Ligand Docking and MMGBSA against CDK13

The glide quantum polarized ligand docking used to dock the ligands into the target receptor grid also showed only nine compounds including THZ2531R that were able to bind to the receptor CDK13. The glide scores of the ligands were higher than that of the co-crystallized ligand with only two ligands, 3-12-formyl-digoxigenin and 2,6,10,15,19,23-hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol but latter has the closest Glide QPLD MMGPSA value to the standard, the values of these two ligands makes them the only compounds that are high tight binders to the receptor CDK13 after docking, as shown in Table 5.

Table 5. QPLD molecular docking screening of hit compounds against the protein receptor CDK13

S/N	Name of Compound	XP GScore (kcal/mol)	MMGPSA dG Bind (kcal/mol)
1	Methyl oleate	-3.416	-43.67
2	Dibutyl phthalate	-6.033	-43.61
3	Bis(2-ethylhexyl) phthalate	-5.754	-42.78
4	3-12-Formyl-digoxigenin	-3.768	-49.91
5	3-Methoxycatechol	-3.006	-42.36
6	Methyllinolelaidate	-3.006	-43.01
7	2,6,10,15,19,23-Hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol	-6.927	-60.14
8	Dimethylmalonic acid, ethyl2-ethyl hexyl ester	-3.566	-23.79
9	N-[4-[(3r)-3-[[5-Chloranyl-4-(1h-Indol-3-Yl)] pyrimidin-2-Yl]amino] piperidin-1-Yl]carbonylphenyl]-4-(Dimethylamino) butanamide (THZ531R)	-12.216	-75.696

Glide Quantum Polarized Ligand Docking and MMGBSA against CDK8

The glide quantum polarized ligand docking used to dock the ligands into the target receptor grid also showed only eight compounds that were able to bind to the CDK8 receptor. The glide scores of the ligands were higher than those of the co-crystallized ligand with only two ligands Campesterol and Bis(2-ethylhexyl)phthalate showing the closest Glide QPLD MMGPSA value to the standard, the values of these two ligands make them the only compounds that are high tight binders to the receptor CDK8 after docking, as shown in Table 6.

Table 6. QPLD and MMGBSA screening of hit compounds against the protein receptor CDK8

S/N	Name of Compound	XP GScore (kcal/mol)	MMGPSA dG Bind (kcal/mol)
1	N-(4-Aminobutyl)-2-ethyl piperidine	-3.055	-36.4
2	Methyltetradecanoate	-3.926	-36.38
3	Dibutyl phthalate	-4.523	-23.61
4	Methyl stearate	-4.688	-31.86
5	Bis(2-ethylhexyl) phthalate	-5.31	-42.76
6	3-12-Formyl-digoxigenin	-5.456	-39.3
7	Campesterol	-6.232	-42.37
8	2,6,10,15,19,23-Hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol	-6.807	-30.12
9	3,4-Dihydro-7-hydroxy-6-methoxy-1(2H)-isoquinoline	-7.579	-34.74
10	Cortistatin A	-10.615	-66.44

Panels A to C of Figure 2 depict the binding pocket interactions between CDK13 and three ligands. Compound (A), 3-12-Formyl-digoxigenin, exhibits defined hydrogen bonding and likely hydrophobic interactions with critical residues in the CDK13 active site, suggesting a stable and specific binding mode. Compound (B), 2,6,10,15,19,23-Hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol, interacts through a more intricate network of contacts, where its hydroxyl groups may facilitate hydrogen bonding while the hydrocarbon backbone promotes hydrophobic engagement. In contrast, compound (C), THZ531R, a known CDK inhibitor, is employed as a reference molecule. Its consistent interaction pattern serves to validate the docking approach and offers a benchmark against which the binding efficacy of novel ligands can be assessed.

Panels D to F of Figure 2 illustrate interactions within the CDK8 binding pocket. Compound (D), Bis(2-ethylhexyl) phthalate, engages primarily through hydrophobic interactions, aligning well with the nonpolar nature of the pocket. Compound (E), Campesterol, a plant sterol, appears to form van der Waals interactions with surrounding residues, suggesting moderate binding affinity influenced by its rigid, lipophilic structure. Meanwhile, compound (F), Cortistatin A, displays a rich interaction profile, including potential $\pi - \pi$ stacking, hydrogen bonding, and hydrophobic contacts. This multifaceted engagement reflects the structural complexity and pharmacophoric features of Cortistatin A, highlighting its promise as a strong binder within the CDK8 active site.

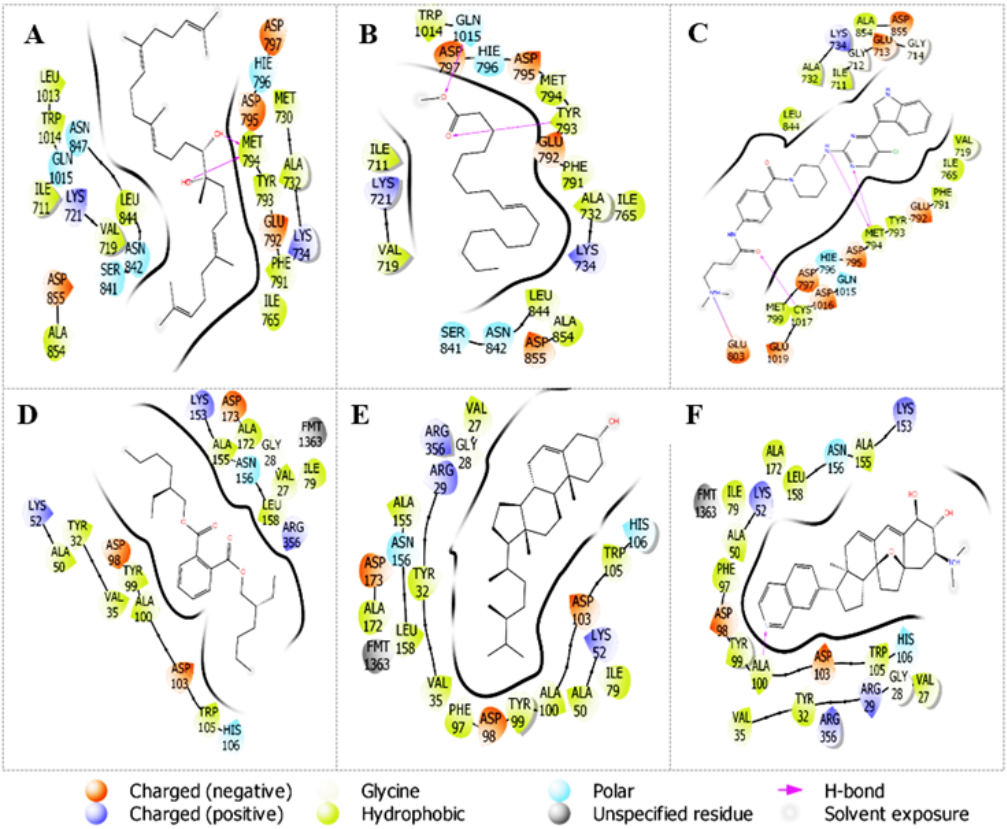

Figure 2. Binding pocket and two-dimensional interactions between the receptors and the hit compounds. This figure presents a detailed view of the binding pocket interactions between CDK13 with 3-12-Formyl-digoxigenin (A), 2,6,10,15,19,23-Hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol (B) and THZ531R (C); and CDK8 with Bis(2-ethylhexyl) phthalate (D), Campesterol (E) and Cortistatin A (F). These interactions are elucidated following Glide Quantum Polarized Ligand Docking, offering insights into the molecular dialogue between these phytochemicals and the active site amino acids of CDK13 and CDK8

ADME Pharmacokinetics and Drug-Likeness Prediction

The *in silico* ADME analysis, incorporating physicochemical properties, water solubility, lipophilicity, pharmacokinetics, drug-likeness, and medicinal chemistry, of the five hit compounds was performed using Admetsar 3.0, as shown in Table 7. The compounds analyzed include bis(2-ethylhexyl) phthalate, 2,6,10,15,19,23-hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol, 3-12-formyl-digoxigenin, and campesterol.

All the compounds were found to comply with Lipinski's rule of five, indicating their potential as orally active drugs with no violations. Each compound exhibited a bioavailability score of 0.55, further supporting their drug-like properties. Among the compounds, bis(2-ethylhexyl) phthalate, and 3-12-formyl-digoxigenin demonstrated high gastrointestinal absorption. However, only dibutyl phthalate was able to permeate the blood-brain barrier. The topological polar surface area (TPSA) ranged from 20.23 to 99.13 Å^2, with the consensus log Po/w, an indicator of lipophilicity, ranging from 2.86 to 7.96. Bis(2-ethylhexyl) phthalate and 3-12-formyl-digoxigenin showed no permeability glycoprotein substrate (P-gp), indicating better absorption and bioavailability. 2,6,10,15,19,23-Hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol was the only compound found to interact with the CYP1A2 isoenzyme of the cytochrome P450 family, suggesting minimal toxicity and potential for drug-drug interactions.

Among the four compounds, 3-12-formyl-digoxigenin stands out as the best candidate due to its favorable ADME properties. It shows high gastrointestinal absorption, acceptable lipophilicity (consensus log Po/w of 2.86), no violation of drug-likeness rules, and minimal interaction with CYP450 enzymes, indicating lower toxicity risk.

Table 7. *In silico* ADME analysis of the five hit compounds

S/No	Descriptors	A	B	C	D
Physicochemical properties					
1.	Formula	$C_{24}H_{38}O_4$	$C_{30}H_{52}O_2$	$C_{25}H_{34}O_7$	$C_{28}H_{48}O$
2.	Molecular weight (g/mol)	390.56	444.73	446.53	400.68
3.	Number of heavy atoms	28	32	32	29
4.	Number of aromatic heavy atoms	6	0	0	0
5.	Fraction Csp3	0.67	0.67	0.8	0.93
6.	Number of rotatable bonds	16	16	5	5
7.	Number of H-bond acceptors	4	2	7	1
8.	Number of H-bond donors	0	2	1	1
9.	Molar refractivity	116.30	146.32	116.56	128.42
10.	Topological polar surface area (Å²)	52.60	40.46	99.13	20.23
Lipophilicity					
11.	Log Po/w (iLOGP)	4.77	6.54	3.06	4.92
12.	Log Po/w (XLOGP3)	7.45	9.38	2.28	8.80
13.	Log Po/w (WLOGP)	6.43	8.77	2.94	7.63
14.	Log Po/w (MLOGP)	5.24	6.01	2.97	6.54
15.	Log Po/w (SILICOS-IT)	6.98	9.10	3.03	6.63
16.	Consensus log Po/w	6.17	7.96	2.86	6.90
Water solubility					
17.	Log S (ESOL)	-6.06	-7.45	-3.71	-7.54
18.	Solubility (mg/ml)	$3.42\text{x}10^{-4}$	$1.58\text{x}10^{-5}$	$8.61\text{x}10^{-2}$	$1.16\text{x}10^{-5}$
19.	Class	Poorly soluble	Poorly soluble	Soluble	Poorly soluble
20.	Log S (Ali)	-8.39	-10.13	-4.00	-9.11
21.	Solubility (mg/ml)	$1.60\text{x}10^{-6}$	$3.26\text{x}10^{-8}$	$4.48\text{x}10^{-2}$	$3.13\text{x}10^{-7}$
22.	Class	Poorly soluble	Insoluble	Soluble	Poorly soluble
23.	Log S (SILICOS-IT)	-7.40	-6.30	-3.12	-5.79
24.	Solubility (mg/ml)	$1.56\text{x}10^{-5}$	$2.21\text{x}10^{-4}$	$3.36\text{x}10^{-1}$	$6.42\text{x}10^{-4}$

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Table 7. *Continued*

25.	Class	Poorly soluble	Poorly soluble	Soluble	Moderately soluble
Pharmacokinetics					
26.	GI absorption	High	Low	High	Low
27.	BBB permeant	No	No	No	No
28.	P-gp substrate	Yes	No	Yes	No
29.	CYP1A2 inhibitor	No	Yes	No	No
30.	CYP2C19 inhibitor	No	No	No	No
31.	CYP2C9 inhibitor	Yes	Yes	No	No
32.	CYP2D6 inhibitor	No	No	No	No
33.	CYP3A4 inhibitor	Yes	No	No	No
34.	Log Kp (skin permeation) (cm/s)	-3.39	-2.35	-7.41	-2.50
Drug-likeness					
35.	Lipinski	Yes; 1 violation: MLOGP>4.15	Yes; 1 violation: MLOGP>4.15	Yes; 0 violation	Yes; 1 violation: MLOGP>4.15
36.	Ghose	No; 1 violation: WLOGP>5.6	No; 3 violations: WLOGP>5.6, MR130, #atoms>70	Yes	No; 2 violations: WLOGP>5.6, #atoms>70
37.	Veber	No; 1 violation: Rotors10	No; 1 violation: Rotors10	Yes	Yes
38.	Egan	No; 1 violation: WLOGP>5.88	No; 1 violation: WLOGP>5.88	Yes	No; 1 violation: WLOGP>5.88
39.	Muegge	No; 2 violations: XLOGP>35, Rotors>15	No; 2 violations: XLOGP>35, Rotors>15	Yes	No; 2 violations: XLOGP>35, Heteroatoms2
40.	Bioavailability score	0.55	0.55	0.55	0.55
Medicinal chemistry					
41.	PAINS	0 alert	0 alert	0 alert	0 alert
42.	Brenk	1 alert: more_than_2_esters	1 alert: isolated_alkene	2 alerts: aldehyde, more_than_2_esters	1 alert: isolated_alkene
43.	Lead likeness	No; 3 violations: MW>350, Rotors>7, XLOGP>33.5	No; 3 violations: MW>350, Rotors>7, XLOGP>33.5	No; 1 violation: MW>350	No; 2 violations: MW>350, XLOGP>33.5
44.	Synthetic accessibility	4.12	5.51	5.72	6.17

A– Bis(2-ethylhexyl) phthalate, **B**– 2,6,10,15,19,23-Hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol, **C**– 3-12-Formyl- digoxigenin, and **D**– Campesterol

PASS Bioactivity Prediction

Table 8 presents the predicted biological activity of the hit compounds using PASS (Prediction of Activity Spectra for Substances) software. The table listed six types of biological activities: anti-neoplastic, anti-carcinogenic, CYP2J substrate, apoptosis agonist, cancer-associated disorder treatments, and anti-inflammation. For each phytochemical, the table provided the probability of activity (Pa) and probability of inactivity (Pi) for these biological activities.

For anti-neoplastic activity, 2,6,10,15,19,23-hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol had a notable Pa of 0.058, although this was relatively low, indicating a minor probability of being active. 3-12-Formyl-digoxigenin showed a Pa of 0.013, also suggesting low activity. Campesterol presented a slightly higher Pa of 0.104, indicating a better but still limited likelihood of activity.

For anti-carcinogenic activity, 3-12-formyl-digoxigenin showed the highest Pa of 0.157, suggesting some potential anti-carcinogenic activity. Other compounds exhibited lower Pa values, with campesterol showing a Pa of 0.021 and 2,6,10,15,19,23-hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol a Pa of 0.021, indicating lesser probabilities of activity.

For CYP2J substrate activity, campesterol demonstrated the highest Pa of 0.832, suggesting a strong likelihood of being a CYP2J substrate. Dibutyl phthalate followed with a Pa of 0.817, indicating a significant probability of activity. 2,6,10,15,19,23-Hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol also showed notable activity with a Pa of 0.779.

For apoptosis agonist activity, campesterol showed the highest Pa of 0.668, indicating a considerable probability of acting as an apoptosis agonist. 3-12-Formyl-digoxigenin also displayed potential with a Pa of 0.650.

For cancer-associated disorder treatments, only bis(2-ethylhexyl) phthalate had a reported Pa value of 0.286, suggesting some potential in treating cancer-associated disorders.

For anti-inflammatory activity, 2,6,10,15,19,23-hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol had the highest Pa of 0.687, suggesting a significant probability of anti-inflammatory activity. Bis(2-ethylhexyl) phthalate showed a Pa of 0.537, also indicating potential anti-inflammatory effects.

The predicted activities using PASS software provided insights into the potential pharmacological properties of these phytochemicals. Notably, campesterol and 2,6,10,15,19,23-hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol showed the most promising results across multiple activities, particularly in anti-inflammatory and apoptosis agonist categories. The high Pa values for CYP2J substrate for campesterol and dibutyl phthalate suggested a significant interaction with the CYP2J enzyme, which could have implications for drug metabolism and pharmacokinetics [8]. For anti-inflammatory activity, the substantial Pa values for bis(2-ethylhexyl) phthalate and 2,6,10,15,19,23-hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol supported further investigation into their potential as therapeutic agents for inflammatory conditions [68]. The anti-carcinogenic potential of 3-12-formyl-digoxigenin, albeit moderate, warranted additional research, especially considering its other predicted activities that could synergistically contribute to cancer therapy [69].

Table 8. Predicted Biological activity of selected phytochemicals using PASS

	Anti-neoplastic		**Anti-carcinogenic**		**CYP2J substrate**		**Apoptosis agonist**		**Cancer associate disorder treatments**		**Anti-inflammation**	
	Pi	Pa	Pi	Pa	Pi	Pa	Pi	Pa	Pa	Pi	Pa	Pi
A	-	-	-	-	0,769	0,029	0,191	0,137	0,286	0,118	0,537	0,046
B	0,546	0,058	0,485	0,021	0,779	0,026	0,637	0,022	-	-	0,687	0,017
C	0,793	0,013	0,171	0,157	0,455	0,147	0,650	0,021	-	-	-	-
D	0,400	0,104	0,482	0,021	0,832	0,014	0,668	0,018	-	-	0,502	0,052

A– Bis(2-ethylhexyl) phthalate; **B**– 2,6,10,15,19,23-Hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol; **C**– 3-12-Formyl-digoxigenin; and **D**– Campesterol

Mutagenicity

Table 9 provides a toxicological analysis of selected phytochemicals, detailing their oral toxicity as predicted by Protox-3 and their acute toxicity as predicted by StopTox. The table included the predicted LD_{50} values (the lethal dose for 50% of the population) in mg/kg, predicted toxicity classes,

and assessments for acute dermal toxicity, acute inhalation toxicity, acute oral toxicity, eye irritation and corrosion, skin sensitization, and skin irritation and corrosion.

Bis(2-ethylhexyl) phthalate had a predicted LD_{50} of 1340 mg/kg, placing it in toxicity class 4. This indicated moderate toxicity [38]. Experimental data pertaining to acute dermal toxicological endpoints, inhalation toxicological parameters, oral toxicological profiles, ocular irritancy potential, and cutaneous effects were unavailable.

2,6,10,15,19,23-Hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol had a predicted LD_{50} of 4300 mg/kg, which corresponded to toxicity class 5, indicating low toxicity [38]. It was predicted to cause skin sensitization and skin irritation, but no data was provided for other toxicological endpoints.

3-12-Formyl-digoxigenin was predicted to have an LD_{50} of 34 mg/kg, classifying it as toxicity class 2, which indicated high toxicity [38]. This compound was predicted to cause acute inhalation toxicity and skin sensitization but was not predicted to cause acute oral toxicity, eye irritation, or skin irritation.

Campesterol had a predicted LD_{50} of 890 mg/kg, placing it in toxicity class 4 [38]. It was not predicted to cause acute dermal, inhalation, or oral toxicity or eye irritation but might have caused skin irritation.

The toxicological analysis highlighted the varying levels of toxicity among the phytochemicals. 3-12-Formyl-digoxigenin, with the lowest LD_{50} of 34 mg/kg, exhibited the highest toxicity among the compounds analyzed, falling into toxicity class 2 [38]. This high level of toxicity, combined with its potential for acute inhalation toxicity and skin sensitization, indicated the need for careful handling and consideration in therapeutic applications.

In contrast, 2,6,10,15,19,23-hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol, with higher LD_{50} values and lower toxicity classes, suggested that this compound had lower toxicity risks. However, it was predicted to cause skin sensitization and irritation, which could have limited its application in products applied to the skin.

Campesterol and Bis(2-ethylhexyl) phthalate showed moderate toxicity, falling into toxicity class 4 [38]. Campesterol's potential for skin irritation and the lack of additional toxicological data for Bis(2-ethylhexyl) phthalate indicated areas for further research [70].

Overall, these findings underscored the importance of comprehensive toxicological assessments in evaluating the safety and potential therapeutic use of phytochemicals. Compounds with lower toxicity, such as those in classes 4 and 5, might have been more suitable for development, provided that their efficacy in desired biological activities was also confirmed.

Table 9. Toxicological analysis of the hit compounds

Phytochemicals	Oral toxicity of phytochemicals (PROTOX 3)		Acute Toxicity of Phytochemicals (StopTox)					
	Predicted LD50 (mg/kg)	Predicted toxicity class	Acute Dermal Toxicity	Acute Inhalation Toxicity	Acute Oral Toxicity	Eye irritation & Corrosion	Skin sensitization	Skin irritation & Corrosion
Bis(2-ethylhexyl) phthalate	1340	4	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic
2,6,10,15,19,23-Hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol	4300	5	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	Toxic	Toxic
3-12-Formyl-digoxigenin	34	2	Non-Toxic	Toxic	Non-Toxic	Non-Toxic	Toxic	Non-Toxic
Campesterol	890	4	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	Non-Toxic	Toxic

CONCLUSION

The methanolic extract of *A. africana* contains 36 phytochemicals from different organic families by GC-MS analysis and these substances have demonstrated anticancer activity in the past. To ac-

curately evaluate the potential of the phytochemicals as effective therapeutic agents, more advanced computational methods are required. *In silico* analysis on bis(2-ethylhexyl) phthalate; 2,6,10,15,19,23-hexamethyl-tetracosa-2,10,14,18,22-pentaene-6,7-diol and 3-12-formyl-digoxigenin provided valuable insights into their potential anticancer efficacy. The results of this study suggest that these phytochemicals from *A. africana* have the potential to inhibit CDK13 and CDK8, which are important in cancer progression. However, this work offers a potential framework for future therapeutic approaches addressing accessibility, safety, and resistance issues associated with current anticancer drugs, while outlining future directions for experimental validation, including in vitro cytotoxicity assays and kinase inhibition studies. While this study is computational in scope, we emphasize it as a hypothesis-generating foundation for subsequent laboratory validation.

SUPPLEMENTARY MATERIAL

The following supporting information can be downloaded at: https://mjs.uomustansiriyah.edu.iq/index.php/MJS/article/view/1679/821.

AUTHOR CONTRIBUTIONS

Mutiu A. Alabi: Conceptualization, Data curation, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. Elizabeth O. Oladoye: Data curation, Investigation, Methodology, Resources. Samson O. Idris: Formal analysis, Investigation, Methodology, Resources. Taofeeq A. Adedokun: Formal analysis, Investigation, Methodology, Resources. Adelowo A. Adebiyi: Data curation, Formal analysis, Investigation, Validation. Beloved K. Ajani: Investigation, Methodology, Resources, Writing – original draft. Quadris P. Brimmo: Data curation, Investigation, Methodology, Resources. Damasuno S. Ibrahim: Data curation, Formal analysis, Investigation, Methodology, Resources. Halimah Olayiwola: Data curation, Investigation, Methodology, Resources. Racheal I. Enobiomanor: Data curation, Formal analysis, Investigation, Methodology. Emmanuel O. Ajani: Conceptualization, Data curation, Supervision, Writing – review & editing.

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DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article (and its supplementary material file).

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICAL APPROVAL

This research does not involve any studies with human participants or animals conducted by the authors.

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