MOLECULAR DOCKING STUDIES OF POTENTIAL HUMAN TOPOISOMERASE IB INHIBITORS FROM SELECTED NIGERIAN ANTI-TUMOR PLANTS

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Abstract

The purpose of this study was to use a molecular docking approach to identify potential topoisomerase IB from selected Nigerian plants. Plant isolates from selected Nigerian plants were clustered with known topoisomerase IB inhibitors. The compounds that showed similarity with the known drugs were docked with topoisomerase IB enzyme complexed with DNA. The physicochemical property analysis and ADMET prediction were also done for these plants. Most of the compounds that clustered with topoisomerase IB were from *Cadaba farinosa*. All the compounds that clustered with irinotecan docked on the topoisomerase IB enzyme with different binding energies with cadabacine diaceate having the lowest binding energy and 3(4-formylphenoxy)-4-methoxybenzaldehyde with the highest binding energy of in their best-docked conformations Apigenin-7-O-glucoside and suspensaside had the lowest binding energy which is lower than that of etoposide showing higher affinity for the enzyme than etoposide. Rutin also had a higher affinity than etoposide. Secologanoside had the highest binding energy on the topoisomerase IB enzyme. This study has revealed potential topoisomerase inhibitors from Nigerian plant origin but more studies on the structure-activity relationship (SAR) of these compounds are required to determine their usefulness in anti-cancer therapy.

Keywords: Docking, topoisomerase IB, plant isolates.

Introduction

A large population of Africa relies on traditional systems of medicine for the treatment of various illnesses including cancer which is a leading cause of death in the world today (WHO, 1993). These medicines are often inexpensive, most affordable and are easily accessible means of health care in African rural communities (Busia, 2005), and the reports of their efficacy make ethnomedicine an important area of interest in drug discovery. Research on medicinal plants is geared towards verifying and validating such ethnomedicinal claims with the ultimate aim of isolating the active metabolites in the plants and standardization for subsequent drug development (Mohammed *et al*., 2014). Various interesting compounds used in the treatment of cancer today have been isolated by phytochemical evaluation of plants used in folkloric medicine as anticancer agents (Dhanamani, 2011). Examples include the vinca alkaloids from the Madagascan periwinkle *Catharanthus roseus*, taxanes from the bark of the yew tree *Taxus brevifolia* and campothecins from *Campotheca acuminata* (Sofowora, 2008). Most of these plant derivatives approved for the treatment of cancer act as anti-mitotic or bind to topoisomerase enzymes, making them fascinating targets in drug discovery.

Although; there are many plants with anti-tumour activity,the lack of knowledge on their mechanism of action has limited their clinical use. With the advent of bioinformatics, it is possible to determine their possible mechanism of action using molecular docking if the chemical composition of these plants is known (Glushchenko *et al*., 2015). Molecular docking approach models the interaction between a small molecule and a protein at the atomic level, which allows for the characterization of the behaviour of small molecules in the binding site of target proteins as well as elucidating the fundamental biochemical processes (McConkey *et al*., 2002). The docking process which involves the prediction of the ligand conformation as well as its position and orientation within these sites (usually referred to as pose) and the assessment of the binding affinity (Meng *et al*., 2011); helps to reduce the expenses and time associated with carrying out similar procedures using a high-performance biological screening (Sarfaraz and Feroz, 2014). Nigerian plants used in this study have been used by traditional healers in the treatment of cancer. This study is aimed at the *in-silico* search for topoisomerase 1B binding compounds from indigenous plants in Nigeria with reported anti-cancer properties.

METHODS AND COMPUTATIONAL DETAILS

Structure download and cleaning: The medicinal plants and their active compounds were identified from an extensive literature search.

The structures of the isolated compounds were imported from PubChem using their chemical identifications (CIDs) to the ChemMine tools workbench. Compounds which were not available on PubChem were drawn using ChemDraw 8.0 Pro software (PerkinElmer Informatics, Waltham, MA, USA) and imported to ChemMine tools using their SMILES entry (Vaniya *et al*., 2016).

Screening based on clustering and physicochemical property analysis: The compounds from each plant were clustered with reference topoisomerase inhibitors using the Tanimoto coefficient. Physicochemical properties of their chemical structures were screened with open babel descriptors in ChemMine R. The chemical structures were further screened for good oral bioavailability using Lipinski's rule of five filters (Beg & Athar, 2020).

Conversion and optimization: The compounds that passed the screening were converted from their SMILES format to Protein Data Bank (PDB) format using open babel GUI and optimized using PyMol software (Beg & Athar, 2020).

Preparation, analysis and validation of target protein structure: The protein structure of topoisomerase I 70kDa complexed with other ligands was downloaded from rcsb.org (ID: 1TL8) (Ianoviciu et *al*., 2005). The protein was then separated from the complex using discovery studio

4.5 visualizer and ActiveX control.

Protein-ligand docking: The protein structure and all the ligands were converted to PDBQT format using autodock tools. Molecular docking studies to determine the active binding poses of inhibitors in the active sites of the enzyme were performed using autodock vina.

ADMET prediction: The compound's ability to be absorbed into the systemic circulation (absorption), reach the appropriate target efficiently (distribution), be stable enough to survive the journey (metabolism), its elimination from the body in a rescannable period of time (elimination) and also its LD50 in rats, fish and protozoa (toxicity) were measured using admetSAR, an online tool predicting ADMET endpoint.

RESULTS AND DISCUSSION

In this study, the inhibitory potential of natural compounds from African medicinal plants on the topoisomerase enzyme IB in the management of cancer was explored with various *in silico* applications. Topoisomerase enzyme was targeted in this study as a sizeable number of compounds from plant origin that target cancer acts via inhibition of the enzyme. Topoisomerase enzyme inhibition has been shown to induce apoptosis by interfering with mammalian-type eukaryotic topoisomerases in cancer cells (Kolaric *et al*., 2020). Using a computer-aided drug design, cancer was identified as the target disease and isolated compounds from plants localized in Nigeria with validated anti-tumour activity were sought out. A total of six (6) plants were identified following an extensive literature search and screened for anticancer properties. A brief summary of their activity is shown in table 1.

Clustering

The plant isolates were clustered with the standard topoisomerase inhibitors (irinotecan and etoposide) based on tanimoto coefficients which are used to generate networks capable of clustering drugs that bind to multiple targets with an aim to predict novel off-target effects (Sliwoski *et al*., 2014). Simply put, the Tanimoto coefficient uses the ratio of the intersecting set to the union set as the measure of similarity. In this study, lead compounds from *Cadaba farinosa* Forssk and *Olea europea* which formed a cluster with Topoisomerase IB include cadabacine, cadabacine methylether, cadabacine diacetate, thiazolidine compound, methyl cinnamate methyl ferulate ether, ether of p-cinnamic acid-m-ferulic acid, and 3,4-formylphenoxy-4-methoxybenzaldehyde (Fig. 1).

Physicochemical property analysis

The drug-likeness properties of all isolated compounds were assessed (Table 4). In this study, twelve compounds had molecular weight in the range 256-450 which is within Lipinski's limits range (≤500). All the compounds except secologanoside had more than 10 bonds. Lipophilicity (log P) values ranged from -1.9792 to 6.09 with only the thiazolidine compound in *Cadaba farinosa* having a value above 5. All isolated compounds from *Annona reticulate* except isoorientin and isoquercetin had an H-bond donor within Lipinski's limits range of 0-5 (H-bond donor). All compounds from *Olea europea* had topological polar surface area (TSPA) values higher than 140Å All compounds from Annona reticulate and *Cadaba farinosa* had TSPA values less than 140Å except isoorientin and isoquercetin

Protein-ligand docking

Known topoisomerase inhibitors irinotecan and etoposide were docked on the topoisomerase enzyme to define the ligand binding site and as a standard of comparison for the plant isolates. Ten conformational models were generated for each compound and the binding energy determined their affinity (i.e. the lower the binding energy the higher the affinity. The RSMD (Root Mean Square Deviation) which is the measure of the distance between the atoms of superimposed protein or the measure of the difference between a crystal conformation of the ligand conformation and a docking prediction was also taken into consideration (Sliwosky *et al*., 2014). The table below shows the best-docked conformation of the topoisomerase enzyme with compound. The topoisomerase enzyme is shown in white; the DNA is in yellow, blue, orange and red while the compound is in purple. Irinotecan docked to topoisomerase I enzyme with a binding energy of -11.2kcal/mol. All the compounds that clustered with irinotecan docked on the topoisomerase I enzyme with different binding energies with cadabacine diaceate having the lowest binding energy of -10.7kcal/mol, and 3(4-formylphenoxy)-4-methoxybenzaldehyde with the highest binding energy of -7.6kcal/mol in their best-docked conformations.

ADMET prediction

The compound with the best binding interaction is not necessarily the best choice of drug to use in medicine thus drug design is aimed at ensuring that the drug can be absorbed into the systemic circulation (absorption), reach the appropriate target efficiently (distribution), be stable enough to survive the journey (metabolism) and will be eliminated in a rescannable period of time (elimination). For this reason, the physicochemical property of the drug was analysed and the ADMET profile was predicted. Using the Lipinski rule which states that for good bioavailability a compound should not have more than ten hydrogen bond acceptors, more than five hydrogen bond donors, logP (n-octanol water partition coefficient), not more than five and a molecular weight not more than 500 daltons (Lipinski *et al*., 1997), only a few compounds such as reticuline, norushinsunine and 3(4-formylphenoxy)-4-methoxy benzaldehyde fit the qualification specified. However, optimum pharmacokinetics can be achieved by different strategies such as masking polar functional groups to increase absorption, introducing metabolic susceptible groups to aid metabolism, and reducing toxicity by varying harmless substituents such as the addition of a halogen. **Recommended values: QPlogS: predicted aqueous solubility should be between -6.5 and 0.5 mol dm-3; Caco-2 cell permeability: <25 nm/s poor and >500 nm/s great;*

Table 1: Plants with possible anticancer activities, identified by literature search

S/N	Name	Parts used	Activity	References
1	*Annona reticulate* (Annonaceae)	Leaves, stem-bark, seed.	Anti-proliferative , cytotoxic, anti-inflammatory, Nitric oxide inhibition, antimicrobial and antioxidant	Chang *et al*., 1998; Brunken *et al*., 2008; Suresh *et al*., 2011; Thang *et al*., 2013; Prasad *et al*., 2014.
2	*Annona senegalensis* Pers. (Annonaceae)	Stem, leaves	Anti-diarrhoeal trypanocidal, cytotoxic, anti-malarial	Mohammed *et al*., 2014; Ajaiyeoba et al., 2006; Ogbadoyi *et al*., 2007; Brunken *et al*., 2008; Suleiman *et al*., 2008; Ameen *et al*., 2011
3	*Cadaba farinosa* Forssk (Capparaceae)	Leaves	Analgesic, anti-proliferative and anti-inflammatory	Otimenyan *et al*., 2007; Brunken *et al*., 2008
4	***Crinum*** *ornatum* (Amaryllidaceae)	Bulb	Moderate anti- breast tumour activity, *in vitro* anti-HIV1 & 2, anti- bacterial, *in vitro* anti-viral	Mahmood *et al*., 1993; Abreu *et al*., 1999; Kudi and Myint, 1999; Brunken *et al*., 2008; Oloyede *et al*., 2010; Mohammed *et al*., 2014
5	*Kigelia* ***africana*** (Lam.) Benth (Bignoniaceae)	Leaves and stem bark	Anti-proliferative and anti-inflammatory	Burkill, 1985: Brunken *et al*., 2008; Olatunji and Atolani, 2009; Atolani *et al*., 2010; Atolani *et al*., 2012; Mohammed *et al*., 2014
6	*Olea* ***europaea*** L. (Oleaceae)	Seed oil and leaves	Anti-proliferative, anti-inflammatory, anti-rheumatic	Neuwinger, 1996; Brunken *et al*., 2008; Lawal *et al*., 2012; Mohammed *et al*., 2014; Ali Hashmi *et al*., 2015

Binding to human serum albumin: QPlogKhsa should be between -1.5 and 1.5; Human oral absorption: <25% poor and >80% great; Rat oral LD50: <50mg/kg is fatal if swallowed; Blockage of hERG K+ channels: concern if predicted QPlogHERG is < -5.

Since, the object of this research is geared towards discovering antitumor compounds that act through topoisomerase inhibition, parameters such as logP are very important for they determine the ability of the compound to cross certain barriers such as the BBB (Blood Brain Barrier) and the testicular barrier (Kujawski et al., 2012). In this case, the polarity of the compound can be reduced, restricting it to the Peripheral Nervous System or the tumour cells can be targeted by designing the drug to make use of specific molecular transport (Kujawski et al., 2012); the idea is to attach the active drug to an important building block molecule that is needed in large amounts by the rapidly divided tumour cells, it could be an amino acid or nucleic base such as Uracil mustard.

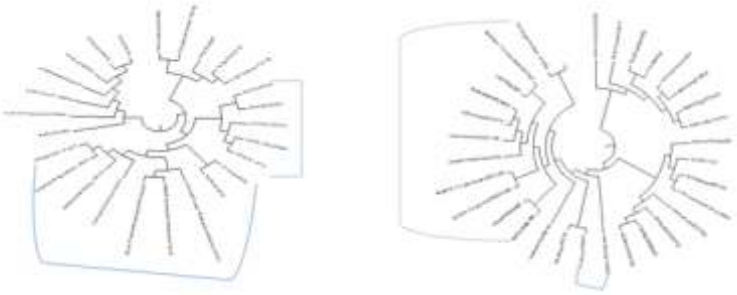


Fig.1: Clustered compounds from Cadaba farinosa Forssk and Olea europea
Most of the compounds that were clustered with topoisomerase IB were isolated from Cadaba farinose.

TABLE 4: Physicochemical properties of the clustered compound using open babel descriptors in ChemMine.

COMPOUND	MW	abonds	Atoms	bonds	HBA1	HBA2	HBD	LogP	MR	TPSA
Known standard drugs										
Irinotecan	586.678	17	81	87	47	10	1	3.9669	169.6328	114.2
Topotecan	421.4458	17	54	58	30	8	2	1.8468	114.8138	104.89
Etoposide	588.5566	12	74	80	45	13	3	1.3386	139.1076	160.83
Teniposide	656.6537	17	78	85	45	14	3	2.7529	156.6646	189.07
Annona reticulate										
Liriodenine	275.2583	17	30	34	13	4	0	3.1749	76.6745	48.42
Norushinsunine	282.3138	12	37	41	19	3	2	2.8591	82.2592	55.3
Reticuline	329.3902	12	47	49	28	5	2	2.8246	97.006	62.16
Cadaba farinose										
3(4-formylphenoxy)4-methoxybenzaldehyde	256.2534	12	31	32	16	4	0	3.1125	70.225	52.6
Cadabacine	435.5155	12	61	63	36	7	4	4.2032	136.8621	99.69
cadabacine diacetate	519.5888	12	71	73	42	9	2	4.2909	156.2464	114.04
cadabacine methylether	449.542	12	64	66	38	7	3	4.5062	141.3311	88.69
Isoorientin	448.3769	17	52	55	30	11	8	-0.2027	108.6312	201.28
Isoquercetin	464.3763	17	53	56	31	12	8	-0.5389	110.1572	210.51
Methyl cinnamate,	368.423	12	51	52	29	5	0	4.7664	105.245	53.99

methyl ferulate ether										
Quercetin	302.2357	17	32	34	16	7	5	1.988	78.035	131.36
Thiazolidine compound	540.7404	12	59	62	33	9	0	6.0974	162.779	156.79
Olea europea										
Apigenin-7-O-glucoside	432.3775	17	51	54	29	10	6	0.0499	106.1112	170.05
Apigenin-7-O-rutinoside	578.5187	17	71	75	43	14	8	-1.0983	137.3328	228.97
Rutin	610.5175	17	73	77	45	16	10	-1.6871	141.3788	269.43
Suspensaside	640.5865	12	81	84	52	16	10	-i.525	149.5848	265.52
Secologanoside	390.3393	0	49	50	33	11	6	-1.9792	85.2958	183.21

abonds = Number of aromatic bonds; atoms = Number of atoms; bonds = Total number of bonds; HBA = Hydrogen bond acceptor; HBD = Hydrogen bond donor; LogP = n-octanol water coefficient; MR = Molar refractivity; MW = Molecular weight; TSPA = Total polar surface area

Topoisomerase IB

S/N	Compound	Best docked conformation to topoisomerase IB and DNA	Binding energy (kcal/mol)
1	Irinotecan		-11.2
2	Cadabacine		-10.1
3	Cadabacine		-10.80
4	Cadabacine methylether		-9.70
5	Liriodenine		-9.70
6	3(4-formylphenoxy)-4-methoxybenzaldehyde		-7.60

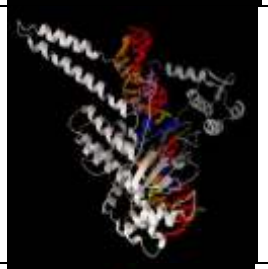
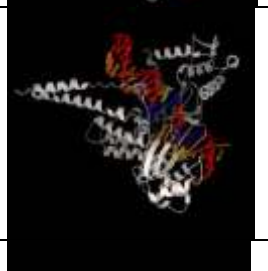
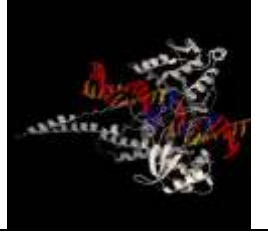
7	Methyl cinnamate, methyl ferulate ether		-8.00
8	Norushinsunine		-9.50
	Irinotecan		-11.20
	Reticuline		-8.80
	Thiazolidine		-9.90

Table 5: Summary of the Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) parameters predicted in silico for predicted active compounds for Topoisomerase I binders

S/N	**Compound**	**Absorption**							
		BBB	Water solubility (LogS)	CaCO$_2$ permeability (Log Papp, cm/s)	Intestinal absorption (human)	P-glycoprotein substrate	P-glycoprotein I inhibitor	P-glycoprotein II inhibitor	Renal Organic Cation transporter
1	Cadabacine	+	-2.378	0.499	HIA+ (0.958)	S (0.812)	NI (0.897)	NI (0.963)	NI (0.766)
2	Cadabacine diacetate	+	-2.999	0.562	HIA+ (0.964)	S (0.875)	I (0.537)	NI (0.948)	NI (0.729)

3	Cadabacine methylether	+ (0.749)	-2.335	0.749	HIA+ (0.982)	S (0.879)	NI (0.595)	NI (0.933)	NI (0.713)
4	Linodenine	+ (0.973)	-3.110	1.431	HIA+ (1.000)	NS (0.528)	NI (0.912)	NI (0.916)	NI (0.789)
5	3(4-formylphenoxy)-4-methoxybenzaldehyde	+ (0.887)	-3.290	1.041	HIA+ (0.993)	NS (0.605)	I (0.548)	NI (0.614)	NI (0.844)
6	Norushinsunine	+ (0.682)	-2.239	0.311	HIA+ (0.568)	S (0.659)	NI (0.995)	NI (0.994)	NI (0.699)
7	Reticuline	+ (0.954)	-2.937	0.940	HIA+ (0.918)	S (0.873)	I (0.580)	I (0.583)	I (0.602)
8	Thiazolidine	+ (0.927)	-3.541	1.555	HIA+ (0.954)	S (0.565)	I (0.659)	NI (0.870)	I (0.575)

S/N	Compound	Toxicity									
		HERG Inhibition	AMES Toxicity	Carcinogens	Fish Toxicity (pLC_{50}, mg/L)	Rat Acute Toxicity (LD_{50}, mg/L)	*Tetrahymena Pyriformis* Toxicity ($pIGC_{50}$, ug/L)	Honey Bee Toxicity	Biodegradation	Acute Oral Toxicity	Carcinogenicity (Three-class)
	Cadabacine	Weak inhibitor (0.972)	Non-toxic (0.538)	Non-carcinogens (0.943)	1.827 Low (0.628)	2.179	0.304 High (0.851)	Low (0.776)	Readily biodegradable (0.533)	III (0.625)	Non-required (0.674)
	Cadabacine acetate	Weak inhibitor (0.981)	Non-toxic (0.709)	Non-carcinogen (0.895)	1.387 High (0.881)	2.375	0.414 High (0.904)	Low (0.764)	Readily biodegradable (0.544)	III (0.637)	Non-required (0.625)
	Cadabacine methylether	Weak inhibitor (0.962)	Non-toxic (0.604)	Non-carcinogen (0.947)	1.753 Low (0.602)	2.237	0.412 High (0.957)	Low (0.731)	Not readily biodegradable (0.544)	III (0.651)	Non-required (0.639)
	Linodenine	Weak inhibitor (0.985)	Toxic (0.911)	Non-carcinogen (0.970)	1.233 High (0.571)	2.235	0.491 High (0.776)	High (0.569)	Readily biodegradable (0.647)	III (0.651)	Non-required (0.608)
	3(4-formylphenoxy)-4-methoxybenzaldehyde	Weak inhibitor (0.957)	Non-Toxic (0.908)	Non-carcinogen (0.876)	0.102 High (0.965)	1.789	0.456 High (0.970)	High (0.691)	Readily biodegradable (0.646)	III (0.658)	Non-required (488)

Norushinsunine	Weak inhibitor (0.928)	Non-Toxic (0.598)	Non-carcinogen (0.955)	2.002 Low (0.811)	2.685	0.265 Low (0.535)	Low (0.631)	Readily biodegradable (0.601)	III (0.467)	Non-required (0.624)
Reticuline	Weak inhibitor (0.713)	Non-Toxic (0.722)	Non-carcinogen (0.959)	1.167 High (0.836)	2.691	0.748 High (0.883)	Low (0.597)	Not Readily biodegradable (0.974)	III (0.735)	Non-required (0.717)
Thiazolidine	Weak inhibitor (0.960)	Non-Toxic (0.658)	Non-carcinogen (0.921)	1.083 High (0.955)	2.656	0.656 High (0.976)	Low (0.547)	Not Readily biodegradable (0.928)	III (0.557)	Non-required (0.717)

S/N	Compound	CYP 450 2C9 Substrate	CYP 450 2D6 Substrate	CYP450 3A4 Substrate	CYP 450 1A2 Inhibitor	CYP 450 2C9 Inhibitor	CYP 450 2D6 Inhibitor	CYP 450 2C19 Inhibitor	CYP 450 3A4 Inhibitor	CYP Inhibitory Promiscuity
1	Cadabacine	NS (0.799)	NS (0.778)	NS (0.531)	NI (0.853)	NI (0.883)	NI (0.872)	NI (0.873)	NI (0.881)	Low (0.974)
2	Cadabacine acetate	NS (0.809)	NS (0.784)	S (0.643)	NI (0.895)	NI (0.829)	NI (0.851)	NI (0.793)	NI (0.728)	Low (0.936)
3	Cadabacine methylether	NS (0.785)	NS (0.764)	S (0.609)	NI (0.848)	NI (0.773)	NI (0.835)	NI (0.808)	NI (0.754)	Low (0.944)
4	Linodenine	NS (0.857)	NS (0.771)	NS (0.620)	I (0.959)	NI (0.699)	NI (0.606)	I (0.595)	I (0.633)	High (0.725)
5	3(4-formylphenoxy)-4-methoxybenzaldehyde	NS (0.747)	NS (0.865)	NS (0.580)	I (0.953)	I (0.508)	NI (0.926)	I (0.827)	I (0.780)	High (0.566)
6	Norushinsunine	NS (0.891)	NS (0.653)	NS (0.658)	NI (0.582)	NI (0.880)	NI (0.583)	NI (0.766)	NI (0.978)	Low (0.887)
7	Reticuline	NS (0.778)	S (0.514)	S (0.773)	I (0.813)	NI (0.903)	I (0.884)	NI (0.880)	NI (0.895)	Low (0.875)
8	Thiazoline	NS (0.750)	NS (0.760)	S (0.613)	I (0.772)	I (0.840)	NI (0.790)	I (0.820)	I (0.821)	High (0.978)

CONCLUSION AND RECOMMENDATION

This study has revealed potential topoisomerase inhibitors from plant origin, especially from *Cadaba farinosa* and Olea europea. However, for these compounds to be useful as an anti-cancer therapy, there is a need to understand the structure-activity relationship of these compounds. Furthermore, validation studies using molecular dynamics simulation, and *in vitro* and *in vivo* methods should be done.

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Supplementary

Table 1: Selected plants and their predicted bioactive compounds.

S/N	Name	Active compounds present	References
1	*Annona reticulate*	Annonaretin A, Kaurenoic acid, Taraxerol, β-sitosterol, 16α-hydro-19-al-ent-kauran-17-oic acid, 6β-hydroxystigmast-4-en- 3-one, 16α-hydro-ent-kauran-17, 19-dioic acid, 2S)-di-O-methylquiritigenin, Annoreticuin, Annoreticuin-9-one, Cis bullatacinone, Trans-bullatacinone, Bullatacin, Squamosine, Rolliniastatin, Molvizarin, Kaurane, Liriodenine, Reticuline, Norushinsunine.	Chang *et al*., 1998; Thang *et al*., 2013

2	*Annona senegalensis* Pers.	α–thujene, α–pinene, β–pinene, Myrcene, Cymene, Benzyl alcohol, 1, 8–cineole, Cis–ocimene, γ–terpinene, Iso–Artemisia, Linalool, Pinine–2–ol, Allo ocimene, Citronellal, Borneol, Terpine–4–ol, α–terpineol, Citronellol, Neral, Linalyl acetate, Geranial, Borneol acetate, Thymol, Carvacrol, β–elemen, α–copaene, β–caryophyllene, Ethyl cinnamate, Germacrene D, Bicyclogermacrene, β–bisabolene, Acetyleugenol, Elemicin, Viridiflorol, Torreyol, Benzyl benzoate.	Ameen *et al*., 2011
3	*Cadaba farinosa* Forssk	Lupeol, β-sitosterol, Ursolic acid, 12-aminododecanoic, Stachydrine, Cadabacine, Cadabacine methylester, Cadacine di acetate, Cadabicilone, Vanillic acid, Isoorientin, Thiazolidine compound, Syringic acid, L-strychidine, 3-hydroxy stachydrine, Methyl cinnamate, methyl ferulate ester, 3(4-formyl phenoxy) 4-methoxy benzaldehyde, Isoquercetin, Quercetin, 3-hydroxybenzoic acid, 'A,β-dihydroferulic acid, 2-hydroxy-4-methoxy benzoic acid, Ether of p-cinnamic acid-m-ferulic acid.	Nawal et al., 2013; Umesh et al., 2013.
4	*Crinum ornatum*	2,4-dimethylhexane, Methyl benzene, Nonacosane, Cis-1,3-dimethylcyclohexane, Cis-decahydronaphthalene, Undecanoic acid, ethylester, Caryophyllene, Dodecanoic acid, 1 4-Methylpentanedecanoic acid methylester,	Mahmood *et al*., 1993; Abreu *et al*., 1999; Kudi and Myint, 1999; Oloyede *et al*., 2010; Mohammed *et al*.,
		2,6,10,15-Tetramethylheptanedecane, n-hexanedecanoic acid, Eicosane, Heneicosane, 9,12-Octadecadienoic acid, Eicosanoic acid, ethylester, Tetratriancontane, Tetratetracontane, Trans-decahydronaphthalene	2014
5	*Kigelia africana* (Lam.) Benth	Hentriaoontane, 3,4 dihydro-8-phytene, Trans-phytol, (9Z,12Z)methyloctadeca-9,12-dienoate, 1,3,3,5,6,6-hexmethylcyclohexa-1,4-diene, Beta-tocopherol	Burkill, 1985: Olatunji and Atolani, 2009; Atolani *et al*., 2010; Atolani *et al*., 2012; Mohammed *et al*., 2014
6	*Olea europaea* L.	Oleuropein, Secologanoside, Hydroxytyrosol-elenolate, Elenolic acid methyl ester, Ligstroside, *β* -amyrin, *β* -sitosterol, Oleanolic acid, Erythrodiol, Betulinic acid, Uvaol, Ursolic acid, Maslinic acid, Rutin, Diosmetin, Apigenin-7-O-rutinoside, Luteolin-7-O-glucoside, Apigenin-7-O-glucoside, Hydroxyl tyrosol, Suspensaside, Hellicoside, Orobanchoside, Acetoside, Wedelosine, Oleuropein aglycone, Ligstroside aglycone, Elenolic acid, P-coumaric acid, Vanillin, Homovanillyl alchohol, Apigenin, Luteolin, Isochromans	Neuwinger, 1996; Lawal *et al*., 2012; Mohammed *et al*., 2014; Ali Hashmi *et al*., 2015