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The uniqueness and therapeutic value of natural products from West African medicinal plants, part II: Terpenoids, geographical distribution, drug discovery

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Covering: 1971 to 2014

In this review series, an attempt has been made to give indepth coverage of natural products derived from West African medicinal plants with diverse biological activities. In part II of this series, emphasis has been laid on terpenoids from West African flora having remarkable biological activities, as well as a correlation between biological activities of the derived compounds and the uses of the plants in African traditional medicine. The impact of geographical distribution on the chemical contents of selected plant genera and their chemotaxonomic classifications have also been included in the discussion. Suggestions for drug discovery projects beginning with natural products from West Africa have also been provided.

1 Introduction

The African flora contains an enormous wealth in terms of biodiversity and phytochemical composition of plant species.[1] Natural products are a rich source of bioactive compounds with a wide range of potential applications (including food science, fragrance industries, agriculture and medicine). Natural products have been used for centuries as popular medicines in different human communities. In recent decades they have been a focus of the scientific community due to increasing evidence that associates them with health benefits and the prevention of several diseases. Progress made during the past decade on natural products is substantial and informative, and it is clear that metabolites isolated from plants coupled with drug discovery and development programs have been particularly fruitful for their medicinal potential, in the form of drugs, food supplements, nutraceuticals, complementary and alternative medicine. In particular, African traditional medicine (ATM) has exploited the riches of plant materials for several centuries and the phytochemical constituents of these plants have been investigated by several research teams on the continent, often in collaboration with partners from abroad, with the view of drug discovery.[2-3] Even though several thousands of pure compounds have been isolated from medicinal plants growing in Africa, the local populations continue to depend on herbs for the treatment of several remedies, as no approved drug has been derived from the African flora until now.[2-4] The dependence on local remedies is also noted in other developing economies of Asia and Latin America, due to the limited availability of pharmaceutical medicines and the low purchasing power of these populations.[5-6] An overview of the plant isolates from plants employed in ATM has revealed that these which might have implications in drug discovery programs, either directly as

drug molecules or as lead compounds for the synthesis of more potent and/or less toxic analogues with improved pharmacokinetic profiles.[2,5,6]

Reports focused on plant-derived active principles from Africa can be sourced from university libraies in MSc and PhD theses (often not available online), journal publications (local and international) and a few textbooks. Moreover, attempts to develop databases of metabolites isolated from plants used in ATM are only recent.[7-12] Thus, the wider community of investigators on the components of ATM only have access to information available in "internationally recognized" journal papers. Additionally, very little has been done to bridge the gap that exists between academic research conducted in African research/academic institutions and the industrial sector, so as to transform the research outputs into concrete drug discovery/development endeavours, with the view of manufacturing drugs for the sick populations.[2] To the best of our knowledge, drug discovery efforts from within the African continent have been limited to the random screening of crude extracts, essential oils and isolated metabolites, mostly against the neglected tropical diseases that affect a vast majority of the African population (malaria being the most conspicuous).[13-18] Other review articles have discussed the results of crude extracts and compounds isolated from African flora with the potential for the treatment of trypanosomiasis,[19-20] diabetes,[21] tuberculosis,[22] bacterial infections,[23] leishmaniasis,[24] asthma,[25] psychosis,[26] hepatitis[27] and cancer.[28] Some review articles rather focus on particular plant families, genera or species,[29-32] as well as bioactive metabolites which have been isolated from particular countries[23,33-36] and regions,[16,18] with none covering the entire ethnobotanically rich region of West African until now. It therefore becomes imperative to put together the most important results from the dispersed data, so as to assist research groups interested in drug discovery from African medicinal plants and make suggestions to pave the way forward.

The West Africa sub region includes the following sixteen (16) countries, covering a total of surface area of over 6,140,000 km^2 (Fig. 1), according to the United Nations Organization.[37] The natural environment of West Africa consists of subtropical and tropical regions with semi-arid and humid climates.[38] In the first part of this review series,[39] emphasis was laid on unique compound classes from West African flora having remarkable biological activities, stressing on establishing a correlation between biological activities of the derived compounds (alkaloids and flavonoids) and the uses of the plants in African traditional medicine and their chemotaxonomic classifications. In the present review, a correlation between the biological activities of the derived terpenoids and the uses of the plants in ATM is established. The impact of the geographical distribution of plant species on the phytochemical contents and the chemotaxonomic classifications of selected genera are also covered, while a cheminformatics approach is used to assess the 'drug-likeness' of the derived compounds and insight on how the available data could be exploited in drug discovery is provided.

2 Ethnobotany *versus* bioactivity survey of terpenoids

Terpenoids are a large and diverse class of naturally occurring compounds, mostly with multicyclic structures, known to exert a wide range of biological activities.[40] Terpenoids are "secondary metabolites", with important physiological function in the interaction between plants and the ecosystem. They have a variety of roles in attracting or deterring/defending the host organisms and the environment, in opposition with "primary metabolites" which are essential for plant growth and development. Terpenoids constitute important components of many plant extractives, and are often the major constituents in plant hormones, essential oils, latexes, resinous exudates and rubber. They are omnipresent in prokaryotic and eukaryotic organism and represent an abundant class of chemical compounds derived from the terpenoid pathways. In nature, terpenoids are found to occur both in free and combined states. They are a big chemical family of natural products found and comprise more than 40,000 different structures with considerable complexity. Their origin is from five-carbon isoprene units, and according to the number of isoprene molecules incorporated, and can be classified into hemiterpenoids (5 carbon atoms), monoterpenoids (10 carbon atoms), sesquiterpenoids (15 carbon atoms), diterpenoids (20 carbon atoms), sesterterpenoids (25 carbon atoms), triterpenoids (30 carbon atoms), tetraterpenoids (40 carbon atoms), and polyterpenoids (more than 40 carbon atoms).

A summary of the most important findings for bioactive terpenoids derived from West African flora has been given in Table 1. The text of this table has been highlighted in bold, wherever there is correlation between ethnobotanical uses of the plants studied and the biological activities of the isolated compounds.

The leaf decoction of *Croton zambesicus* (Euphorbiaceae) is used in Benin for anti-hypertensive, anti-microbial (urinary) infections and to treat fever associated with malaria.[41-43] Block *et al*. have isolated the diterpenes ent-18-hydroxy-trachyloban-3-one (**1**), isopimara-7,15-dien-3-ol (**2**), ent-trachyloban-3-one (**3**), *trans*phytol (**4**), ent-18-hydroxytrachyloban-3β-ol (**5**) and ent-18-hydroxyisopimara-7,15-diene-3β-ol (**6**) from the dichloromethane extract of the leaves of the plant harvested in Benin,[44] whereas Aderogba *et al*. isolated flavonoids exhibiting antioxidant properties from the aqueous methanol extract of the leaves of the species growing in Nigeria.[145] The presence of these antioxidant compounds in the leaf extract of *C. zambesicus* could provide a rationale for the ethnomedicinal use of the plant in the management of oxidative-stress-related diseases in folk medicine.[45] Among the isolated compounds from the Beninese species ent-trachyloban-3β-ol showed cytotoxic activities on HeLa cells (IC_{50} on HeLa cells = 7.3 μg mL^{-1}). The cytotoxicities of ent-18-hydroxy-trachyloban-3-one

and ent-trachyloban-3-one were a little lower but no clear specificity between cell lines could be observed, even though trachyloban-3-one is 2.5 times more active on HeLa cells (cancer cell line) than on WI-38 (non-cancer cell line). *Trans*phytol (**46**) showed a similar range of activity as the trachylobanes.[148] The cytotoxic activity of phytol could be attributed to the induction of apoptosis.[46]

Ganfon *et al*. have investigated the antiparasitic activities of two sesquiterpenic lactones isolated from *Acanthospermum hispidum* (Asteraceae), a plant used traditionally to treat various diseases, especially for malaria in Benin.[47] 15-Acetoxy-8-[(2-methylbutyryloxy)]-14-oxo-4,5-*cis*-acanthospermolide (**7**) and 9-acetoxy-15-hydroxy-8-(2-methylbutyryloxy)-14-oxo-4,5-*trans*-acanthospermolide (**8**) were isolated from the aerial parts of the plant. The antiplasmodial activity was evaluated *in vitro* against a chloroquine-sensitive strain of *P. falciparum* (3D7) using the measurement of the plasmodial lactate dehydrogenase activity and *in vivo* against *P. berghei berghei* by the 4-day suppressive test. Selectivity of the extract and purified compounds on *Plasmodium* parasites were evaluated by using the MTT test on J774 macrophage like murine cells and WI38 human normal fibroblasts and also against two other parasites: *Trypanosoma brucei brucei* and *Leishmania mexicana mexicana*. Acute and sub-acute toxicities of a crude extract were evaluated on mice. Compounds **7** and **8** showed *in vitro* antiplasmodial activity against the chloroquine-sensitive strain (3D7) with IC_{50} of 2.9 ± 0.5 and 2.23 ± 0.09 µM respectively. Only compound **8** showed a high selectivity index (SI: 18.4) on *Plasmodium* compared to cytotoxicity against human fibroblasts cell line (WI38). Compounds **7** and **8** also showed interesting antiparasitic activities *in vitro* against *Trypanosoma brucei brucei* (IC_{50} of 2.45 ± 0.49 and 6.36 ± 1.42 µM respectively) and *Leishmania mexicana mexicana* (IC_{50} of 0.94 ± 0.05 and 2.54 ± 0.19 µM respectively). Furthermore, the crude acidic water extract and fractions containing one of the two isolated compounds displayed weak *in vivo* antimalarial activity against *Plasmodium berghei berghei* with a long half-life, causing a delayed effect. *In vivo* acute (2000 mg/kg) and sub-acute (1000 mg kg^{-1}) toxicity tests on the crude acidic water extract did not show toxicity.

Lupeol (**9**) has demonstrated diverse biological activities, including antiplasmodial,[48] cytotoxicity[44] and antitrypanosomal activities.[49] These activities justify the the use of *Cassia siamea* in the treatment of malaria and *Strychnos spinosa* in the management of African trypanosomiasis. The leaves of *Tithonia diversifola* (Compositae) have also been extensively used in Nigerian traditional medicine to treat malaria and fevers.[35] Oral decoction of the leaves of *Tithonia diversifolia* are used for the treatment of hepatitis, diabetes, malaria, pain, chemoprevention and anti-*Helicobacter pylori*,[50-52] external application of dried leaves on wounds and infusion of leaves for the treatment of measles.[53] Goffin *et al*. isolated the sesquiterpene tagitinin C (**10**) from the leaves of this plant.[53] The anti-plasmodial compound **10** has been proven to be the active principle responsible for the use of the plant leaves in malaria treatment.[53] Tagitinin C also demonstrated therapeutic abilities against gastric ulcer.[54] *Pteleopsis suberosa* (Combretaceae) from West Africa has been used in the treatment of meningitis, convulsive fever, and headache, while the bark is reported to be able to increase cereal productivity and to treat jaundice, asthenia, and dysentery.[55] De Leo *et al*. isolated thirteen (13) oleanane saponins (**11** - **12**), from the stem bark of the plant and tested them against *Helicobacter pylori* standard and *vacA*, and *cagA* clinical virulence genotypes. Results showed that compound **16** has an anti-*H. pylori* activity against three metronidazole-resistant strains (Ci 1 *cagA*, Ci 2 *vacA*, and Ci 3).[56]

The leaves of *Alchornea cordifolia* are also used as a remedy for arthritis, muscle pain and other inflammatory disorders. Okoye *et al*. carried out an analysis of the volatile oil extracted from the fresh leaves of *A. cordifolia* and revealed the presence of high concentrations of eugenol (**24**: 41.7%), cadinol (**25**: 2.46%), caryophylene (**26**: 1.04%), linalool (**27**: 30.59%) and (*E*)-α-bergamotene (**28**: 4.54%). These compounds could be contributing to the topical anti-inflammatory effects of *A. floribunda* and *A. cordifolia* leaf extracts.[57] *Hyptis suaveolens* (Lamiaceae), used in the treatment of respiratory tract infections, colds, pain, fever, cramps and skin diseases has been investigated by Chukwujekwu *et al*.[58] A bioactivity-guided fractionation of the petroleum ether extract of the leaves of this plant led to the isolation of the abietane-type diterpenoid endoperoxide, 13α-*epi*-dioxiabiet-8(14)-en-18-ol (**29**), a molecule with high antiplasmodial activity (IC_{50} = 0.1 µg mL^{-1}). This might explain the usefulness of the plant for treating fever, which might be due to malaria.

Laggera pterodonta, is often used against insect attack, athlete's foot, skin infections, pediatric malaria and wounds.[59] The plant is also used in the treatment of hepatitis, arthritis, bronchitis and nephritis. Five sesquiterpenes (**30** - **34**), exhibiting antimicrobial activities, have been identified from the species growing in China.[60] The essential oil of *Keetia leucantha* (Rubiaceae) from Benin, along with seven of its constituents and the three triterpenic acids were evaluated for their antitrypanosomal activity on *Trypanosoma brucei brucei* bloodstream forms (*Tbb* BSF) and procyclic forms (*Tbb* PF) to identify an activity on the glycolytic process of trypanosomes. The oil showed an IC_{50} of 20.9 µg mL^{-1} on *Tbb* BSF and no activity was observed on *Tbb* PF. The best antitrypanosomal activity was observed for ursolic acid with IC_{50} of 2.5 and 6.5 µg mL^{-1} respectively on *Tbb* BSF and *Tbb* PF. Several of its constituents and three triterpenic acids present in the dichloromethane leaves extract showed a higher antitrypanosomal activity on bloodstream forms of *Tbb* when compared to procyclic forms, namely geranyl acetone, betulinic acid (**35**), phytol (**36**), α-ionone, β-ionone, oleanolic acid (**37**) and ursolic acid (**38**). Compounds **35**, **37**, **38** and β-ionone were proven to be inhibitors of trypanosomal GAPDH, which may in part explain these antitrypanosomal activities.[61] The

antitrypanosomial activity of ent-trachyloban-3β-ol (**39**) may also justify the use of this plant to treat parasitic diseases, including African trypanosomiasis.[61] In the quest to identify the chemical components of the poisonous wild pea, *Justicia anselliana* (Acanthaceae) from Benin, lupeol (**9**) was isolated from the allelopathic ethanol extract of the aerial parts of the plant, along with the steroids stigmasterol (**40**) and β-sitosterol (**41**).[62] The cytotoxicity assay however showed that all three compounds were not cytotoxic. Lupeol and stigmasterol however showed anti-parasitic activity against *Trypanosoma brucei brucei* with IC_{50} values of 19.3 ± 1.6 and 55.5 ± 4.19, respectively, along with α-amyrin (**42**: IC_{50} = 48.9 ± 3.1) and β-amyrin (**43**: IC_{50} = 54.2 ± 0.7),[49] thus demonstrating the antitrypanosomal potential of *Strychnos spinosa*. Oleanolic acid (**37**) and ursolic acid (**38**) have been identified as the active antibacterial ingredients (exhibiting antimicrobial activity on *Dermatophilus congolensis*) responsible for the use of *Mitracarpus scaber* in the treatment of various human skin diseases including eczema and ringworm.[63]

Janson *et al*. identified urospermal A-15-*O*-acetate (**44**) as the main active compound responsible for the anti-plasmodial activity of *Dicoma tomentosa* (Asteraceae) from Burkina Faso.[64] Based on the results of these authors, the IC_{50} value of the compound was < 1 μg mL^{-1} against both 3D7 and W2 strains. Compound **44** was also found to be the main cytotoxic compound (SI = 3.3). The Eastern Nigeria mistletoe, *Loranthus micranthus* (Loranthaceae), is used in the treatment of several diseases including immune-modulating diseases,[65] as well as exhibiting antioxidant activity, especially in several debilitating diseases, including cancer, flu and other viral infections.[66] Ogechukwu *et al*. have isolated 2,3-dimethoxy-benzo [*a*,*b*] cyclopentenyl-3',3',5'-trimethyl pyran-4-carboxylic acid or loaranthoic acid (**45**), along with the alkaloid lupinine (**46**). The isolates were screened for immunostimulatory activities on isolated C57BL/6 mice splenocytes and early activation marker, CD69 at concentrations of 10, 25, and 100 μg mL^{-1} using flow cytometry techniques and compared to lipopolysaccharide (10 μg mL^{-1}) and concanavalin A (2 μg mL^{-1}) as standards. The compounds (at concentrations of 25 μg mL^{-1}) showed statistically significantly ($p < 0.05$) stimulatory activity on the splenocytes with values of 56.34 ± 0.26% and 69.84 ± 0.19%, respectively, compared to 7.58 ± 0.42% recorded for the unstimulated control. Similarly, the CD69 expression assay showed immunostimulation with statistically significant values ($p < 0.05$) of 2.31 ± 0.07% and 2.71 ± 0.03%, respectively, compared to 1.69 ± 0.05% recorded for the nonstimulated control. It could be concluded that these compounds may be responsible in part, for the immunostimulatory activities already established for the Eastern Nigeria mistletoes.

The whole plant or parts of *Platostoma africanum* are commonly used in Nigeria in the treatment of rheumatic symptoms, dysmenorrhoea, headache, hematuria and as a local hemostatic, alongside other uses.[67] Both the hexane and dichloromethane extracts showed significant antioxidant activity with the dichloromethane extract exhibiting an IC_{50} comparable to that of the synthetic antioxidant BHT. This study confirms the ethnomedicinal use of the plant in the treatment of rheumatic symptoms.[68] Aladedunye *et al*. further carried out a phytochemical investigation of the extracts and afforded eight acidic pentacyclic triterpenes, namely, ursolic acid (**38**), oleanolic acid (**37**), epimaslinic acid, maslinic acid, corosolic acid, hyptadienic, euscaphic acid and tomentic acid, and a mixture of β-sitosterol and stigmasterol.[68] Vernodalin (**47**) is among the antibacterial isolates from *Struchium sparganophora* (Asteraceae) identified by Kasim *et al*.[69] This plant is used traditionally to treat malaria, measles and other ailments, including tumour-related problems.[69] The isolated compounds; vernodalin, luteolin (**47'**) and 3-methyl-2,6-hexacosedienol demonstrated antimicrobial activities against the bacteria *Staphylococcus aureus* (NCTC 6571), *Klebsiella aerogenes* (Welcome Res. Lab.CN 345), *Escherichia coli* (NCTC 9001) and *Proteus vulgaris* (NCTC 8313), as well as against the fungal strains *Candida albicans* (ATCC10231) and *Aspergillus niger* (NCPF3149). Compound **219** has also been isolated from *Vernonia amygdalina*, along with vernomygdin, and demonstrated antitumour activities.[70]

Hypoestoxide (**48**) is a natural diterpene isolated from the shrub *Hypoestes rosea* (Acanthaceae), a plant indigenous to the rain forest regions of Nigeria.[71-73] The natives have long used the *H. rosea* leaf extracts in folk medicine to treat skin rashes and fungal infections.[74] The compound also inhibits the growth of a variety of human and murine tumor cell lines *in vitro* at concentrations ranging from 0.3 to 10 μM and was inactive as a mutagen in the Ames test. It exhibited highly potent (0.3–10 mg kg^{-1} dose ranges) activities against B16 melanoma growth in C57BL/6 mice and P388D1 leukemia in C57BL/6 x DBA/2 F1 mice, respectively. At a low maximal effective dose of 5 mg kg^{-1}, the compound induced significant *in vivo* antitumor activities that were better than or comparable with most of the standard chemotherapeutic antiangiogenic agents tested.[75] *Entada africana* (Leguminosae) is used in Malian traditional medicine for various types of illnesses, because of the anti-inflammatory, hepatoprotective, and wound-healing effects of the plant.[76] Decoctions of the root or the bark are used to treat hepatitis and to wash wounds. The juice of the fresh root or the bark is also used for its hemostatic properties.[77-79] Cioffi *et al*. have isolated nine (9) ester saponins (**49 - 57**) from the roots of the plant, all showing moderate to high cytotoxic potency.[76] *Combretum nigricans* (Combretaceae) is a small African tree widespread in the Sahelian savanna. It is used in folk medicine for the treatment of various diseases such as cataract, conjunctivitis, icterus and rheumatism.[80] Simon *et al*. isolated 11α-acetoxy-20,24-epoxy-25-hydroxy-dammar-3-one (**58**) and 20,24-epoxy-11α-25-dihydroxy-dammar-3-one (**59**), which are supposed to be responsible, at least in part, for the cytotoxic activity of the methanolic extract of the plant.[81]

The seeds of *Abrus precatorius* (Fabaceae) are used widely in Africa, the USA and Asia for a wide range of pharmacological

possibilities. In many parts of world and in Nigeria, they are used for the treatment of inflammatory conditions such as arthritis.[82] Anam has identified two saponins; 3-*O*-1{[β-D-glucopyranosyl-(1→4)-β-D-glucopyranosyl-(1→3)]-[β-D-glucopyranosyl-(1→2)]-β-D-fucopyranosyl}-olean-12-ene-3β, 23, 28-triol (**60**) and 3-*O*-1{[β-D-glucopyranosyl-(1→4)-β-D-glucopyranosyl-(1→3)]-[β-D-glucopyranosyl-(1→2)]-β-D-fucopyranosyl}-olean-12-ene-3β,16β, 23, 28-triol (**61**) from the aerial parts of the plant, both exhibiting significant anti-inflammatory activity.[83] Dichapetalin M (**62**) has been been isolated from the root extract of *Dichapetalum madagascariensis* (Dichapetalaceae), harvested in Ghana,[84] a shrub used for the treatment of viral hepatitis while the stem bark is used alone in treating jaundice, sores and urethritis.[85-86] The compound has exhibited greater toxicity towards brine shrimp larvae than the analogue dichapetalin A, which has demonstrated cell inhibition against various cancer cell lines.[84]

Among the plants indicated by traditional healers in Ivory Coast for the handling of parasitic diseases, *Afrormosia laxiflora* and *Aframomum sceptrum* (Zingiberaceae) have shown significant anti-malarial activity.[87] Additionally, the rhizomes of *A. sceptrum* are traditionally used in Ivory Coast for infectious diseases, including human African trypanosomiasis (sleeping sickness).[88] Cheikh-Ali *et al*. have conducted a bioguided fractionation of the methanol extract of the rhizomes of the plant, leading to the isolation of sceptrumlabdalactones A (**63**) and B (**64**), along with stigmast-4-en-6β-ol-3-one and caryophylene oxide.[89-90] The evaluation of the *in vitro* trypanocidal and leishmanicidal activities of the labdanes **63** and **64** showed that compound **64** exhibited activity similar to that of reference drugs against *Leishmania donovani* (Pentamidine and Miltefosine). Ogechukwu *et al*. have also identified steroids and triterpenoids from the Eastern Nigerian mistletoe, *Loranthus micranthus* (Loranthaceae) which are parasitic on *Kola acuminata* and having immunomodulatory potentials.[66] Among the isolated compounds, the lupeol-based triterpenoid esters; 7β,15α-dihydroxyl- lup-20(29)-ene-3β-palmitate (**65**), 7β,15α-dihydroxyl-lup-20(29)-ene-3β-stearate (**66**) and 7β,15α-dihydroxyl-lup-20(29)-ene-3β-eicosanoate (**67**) exhibited lower stimulatory activity on the C57B1/6 splenocytes, when compared with the stigmastane steroids; stigmast-7,20 (21)-diene-3β-hydroxy-6-one and 3β-hydroxystigmast-23-ene.

Khaya senegalensis is a large tree native to the sub-Saharan savannah from Senegal to Uganda, being used as a source of popular traditional medicine in Africa, whereby the decoction of the stem bark is extensively used as a febrifuge, which could be associated with its use in the handling of malaria, cancer, among many ailments.[91-92] The plant is also known from indigenous knowledge systems in Nigeria for the treatment of African trypanosomiasis.[93] Zhang isolated eleven (11) limonoids (**68 - 79**) from the methanolic extract of stem bark of the plant, harvested from Guinea Republic.[94] In the anti-proliferative bioassay, 3α,7α-dideacetylkhivorin (**68**) and 1α,3α,7α-trideacetylkhivorin (**69**) showed significant growth inhibitory activities against MCF-7, SiHa, and Caco-2 tumor cells with IC_{50} values in the range of 35 to 69 μg mL^{-1}, while other compounds did not show anticancer activity even at high concentration 200 μg mL^{-1}.[94] Different parts of *Azadirachta indica* and *Khaya grandifoliola* (Meliaceae) are also used in West Africa for traditional preparations to treat malaria.[95-97] The limonoid gedunin (**80**), isolated from the leaves of *A. indica*, inhibits *P. falciparum* at IC_{50} of 1.25 μg mL^{-1}.[95,98] Gedunin was also isolated from *K. grandifoliola*, along with the other limonoids 2,6-dihydroxyfissinolide (**81**), methylangolensate (**82**), 7-deacetylkhivorin (**83**), 1-deacetylkhivorin (**84**) and 6-acetylswietenolide (**85**), exhibiting significant antiplasmodial activities.[98] Additionally, gedunin has displayed anticancer activities[99] and Hsp90 inhibition.[100]

Three (3) colossolactones; colossolactone E (**86**), colossolactone B (**87**) and 23-hydroxycolossolactone E (**88**), have been isolated and from an *n*-hexane: dichloromethane (2:7) extract of the mushroon *Ganoderma colossum*, harvested from Nigeria.[101] The antimicrobial screening of these compounds revealed that colossolactone E and 23-hydroxycolossolactone E were active against *Bacillus subtilis* and *Pseudomonas syringae*. Potency of the compounds against the tested bacteria supports the use of this mushroom in therapeutic medicine, since this genus of mushrooms is known to possess anti-tumor, anti-cancer, immunomodulatory and immunotherapeutic qualities.[102] Colossolactone B was not active against the bacteria. Other colossolactones (V, VI, VII, VIII and G) and schisanlactone A have also been isolated from the mushroom, harvested from Vietnam, together with colossolactone E (**86**). The isolated compounds were evaluated for inhibition of HIV-1 protease, with IC_{50} values for the most potent compounds ranging from 5 to 13 μg mL^{-1}.[103] Colossolactone G showed the most promising anti-viral activity, thereby justifying the immunomodulatory and immunotherapeutic qualities of this mushroom.

The sesquiterpene lactones 15-Acetoxy-8-[(2-methylbutyryloxy)]-14-oxo-4,5-*cis*-acanthospermolide (**89**) and 9-Acetoxy-15-hydroxy-8-(2-methylbutyryloxy)-14-oxo-4,5-*trans*-acanthospermolide (**90**), isolated from *Acanthospermum hispidum* (Asteraceae), a plant used locally in the treatment of malaria in Benin, have also shown antiplasmodial activity.[47]

3 Impact of geographical distribution of plant species on their phytochemical content

The focus of this paragraph is to discuss the intervariability of the terpenoid content of the genus *Croton* and the phytochemical content of the alkaloid-producing species of the genera *Fagara* or *Zanthozylum* and *Strychnos* from West Africa. In addition to the aforementioned variations seen in the Ancistrocladacea and Dioncophylae naphthylisoquinolines and those from the *Araliopsis*, *Oricia* and *Teclea* genera discussed in our previous review,[18] a

comparison of these three genera is currently made with those from other regions in Africa and from the rest of the world.

3.1 *Croton species*

The genus *Croton* is particularly rich in secondary metabolites like alkaloids, terpenoids, and flavonoids, the most common subclass of compounds being represented by diterpenoids. Among the *Croton* species from America, Asia and Australia, *C. draco*, *C. kongensis*, *C. sublyratus* and *C. tonkinensis* are characterised by kaurane diterpenes meanwhile labdane diterpenoids are more common in *C. joufra*, *C. oblogifolius* and *C. zambesicus* and trachylobanes are abundant in *C. insularis*, *C. macrostachys*, *C. rubustus* and *C. zabesicus*.[104] Apparently, clerodane is the widest spread class of diterpenoids in *Croton*, which has been found in species from America (e.g. *C. cajucara*), Africa (e.g. *C. macrostachyus*) and Asia (e.g. *C. tiglium*). The genus is also rich in constituents with biological activities, chiefly diterpenoids such as labdane (**91**), clerodane (**92**), kaurane (**93**), trachylobane (**94**) and pimarane (**95**). Among the *Croton* sp. studied from West Africa, the alkaloid, julocrotine or 2-[*N*-(2-methylbutanoyl)]-*N*-phenylethyl-glutarimide (**96**) was isolated from the roots of *C. membranaceus* harvested in Ghana,[105] while the Beninese *C. zambesicus* gave trachylobane- and isopimarane-type diterpenoids exhibiting vascular activity[106] as well as anticancer properties.[44,107-109] *C. zambesicus* from Nigeria gave *p*-coumaroyl flavonoid glycosides exhibiting antioxidant activity,[45] while the root extract exhibited antiulcer and anticonvulsant activities[110] and the leaf extract of the species harvested from Benin exhibited hemolytic or antiplatelet activity.[111] Clerodane and trachylobane diterpenoids were isolated from the stem bark of the same species from Central Africa,[112-113] while the methanol extract of the dried fruits of this plant, harvested from North Africa, gave a kaurane-type diterpene, along with the flavonoid vitexin (**97**) and the triterpenoids lupeol, betulinic acid and betulin.[114] Phytochemical investigation of the dichloromethane extract of the stem bark of *C. macrostachyus* from East Africa led to the isolation of two triterpenoids,[115] while the combined hexane and methylene chloride leaf extracts of *C. gratissimus* from South Africa afforded ten (10) cembranolides.[116] The clerodane diterpene, crotomacrine (**98**) was isolated from fruits of *C. macrostachyus* growing in Central Africa,[117] meanwhile 8,9-secokaurane diterpenes, exhibiting antimycobacterial and anti-malarial activities were obtained from the methylene chloride extract of the dried leaves of *C. kongensis* from South East Asia.[118] This was the first time the occurrence of 8,9-secokauranes was mentioned in this genus.

3.2 *Strychnos species*

Strychnos species (Loganiaceae) are known to be an important source of anti-malarial alkaloids from Central Africa, the dominant species being *S. icaja*.[119-122] *Strychnos spinosa* from West Africa is rather known for its triterpenoids and sterols exhibiting antitrypanosomial activities,[49] while phenolic and bis-iridoid glycosides have been derived from the East African species, *S. cocculoides*.[123] a full discussion of the pharmacology and phytochemistry of the *Strychnos* genus has been provided elsewhere.[124]

3.3 *Fagara species*

Within the Rutaceae family, *Fagara* and *Zanthoxylum* have long been regarded as one genus.[125] The phytochemistry of this genus is dominated by alkaloids, mainly isoquinoline alkaloids (benzylisoquinolines, berberine and protoberberine alkaloids), along with quinoline alkaloids, lignans, coumarines, amides, flavonoids and terpenoids. The isolated phytochemicals have exhibited a wide range of biological activities, including allelopathic, analgesic, anticonvulsant and antimicrobial activities.[126] Previously investigated *Fagara* species from West Africa include *Fagara zanthoxyloides* from Burkina Faso,[127-128] *Zanthoxylum leprieurii*, *Z. bouetense* and *Z. dinklagei* from Nigeria[214] and *F. macrophylla* from Guinea Republic.[46] The species from Burkina Faso gave the three previously described isomeric divanilloylquinic acids (**99 - 101**) with antisickling properties,[45] while Guinean species gave the aporphine alkaloids oblongine (**102**), tembetarine (**103**) and magnoflorine (**104**), along with the lignan sesamin (**105**), the acridones 1-hydroxy-3-methoxy-*N*-methyl-acridone (**106**), arborinine (**107**), xanthoxoline (**108**) and 1-hydroxy-3-methoxyacridone (**109**) and the flavonoid hesperidin (**110**), all exhibiting antifeedant activities against larvae of both *Spodoptera frugiperda* and *S. littoralis*.[130] Meanwhile, investigated species from Central Africa include *F. heitzii*,[131-132] *F. tessmannii*,[133-134] *Z. leprieurii*,[135-136] *Z. buesgenii*[137] and *F. macrophylla*.[138] *F. heitzii* from Central Africa was characterised by oxidative burst inhibitory and cytotoxic amides and lignans,[131-132] while *Z. leprieurii* was characterised by cytotoxic, antiplasmodial and antioxidant acridones.[135-136] *F. macrophylla* was characterised by moderate to weakly cytotoxic amides[138] and *F. tessmannii* was noted to contain pentacyclic triterpenes with α-glucosidase inhibitory activity.[133-134] The dichloromethane extracts of the roots and the bark of the East African *Z. usambarense* gave the fungicide canthin-6-one (**111**) and the insecticide pellitorine (**112**), along with other alkaloids and lignans.[139] A full discussion of the pharmacology and phytochemistry of this genus can be consulted elsewhere.[212]

The intervariability of species observed in the various geographical regions could be explained globally by adaption of the various plant species to environmental conditions like temperature, soil pH, humidity, soil types, altitude, etc. This is because the above factors, which are specific for each niche, may greatly influence the biosynthetic processes leading to the plant metabolites indentified. Another factor that is often ignored is the experimental conditions during the extraction and purification processes. Very often, the natural product chemist does not initially set out to completely explore the phytochemistry of a given plant species. In most cases, the expedition is bioactivity-oriented, which seems to be quite biased. The inactive fractions are often ignored. However, be they active against the diseases for which the plant is used locally, the "inactive" factions may also contain potentially bioactive compounds or compounds which are of importance for the chemotaxonomic classification of the plant species and

genera. The account presented in this review is just a base line from which further investigations can be carried out.

4 Cheminformatics analysis of medicinal potential of natural products from West Africa

A number of cheminformatics parameters (computed molecular descriptors) are often utilized to assess the "drug-likeness" of a natural product compound library collected on the basis of phytochemicals from West African flora. Lipinski's "Rule of Five" (ro5)[140-141] uses simple molecular parameters like molecular weight (MW), lipophilicity parameters, e.g., the logarithm of *n*-octanol/water partition coefficient (log P), the number of hydrogen bond acceptors (HBA) and the number of hydrogen bond donors (HBD) to roughly determine the proportion of compounds within a library which can be developed into drugs.[7,10-12,142] This "rule", which defines the parameters of a "drug-like" compound as; MW ≤ 500 Daltons (Da), log P ≤ 5, HBA ≤ 10 and HBD ≤ 5, initially omitted natural products, since Lipinski had initially postulated that NPs do not comply with the ro5. However, NP libraries have been previously analysed comparatively using this "rule" in order to have a rough idea of the extent of their "drug-likeness" , with the view of drug discovery.[7,10-12,142] A summary of the percentage of the NPs from West Africa complying with the ro5, along with the maximum, minimum and mean values for each parameter have been shown in Table 2. Our analysis showed that 56.70% of the compounds respected the ro5 and up to 89.39% had ≤ 2 violations for the recommended range of values for the aforementioned parameters. Additionally, up to 37.74% of the compounds could be described as "lead-like", complying with Oprea's "Rule of 3.5" (150 ≤ MW ≤ 350; log P ≤ 4; HBD ≤ 3; HBA ≤ 6),[143-145]

Following the publication of Lipinski's ro5, several thumb attempts have been made to develop simple rules based on calculated compound characteristics for the selection of compounds to be used in drug discovery programs.[146] A full cheminformatics analysis of the NP library from the West African flora will be reported separately.

5 Enhancing drug discovery programs from West Africa, starting with natural products from medicinal plants

The reasons why drug discovery programs often begin with NP lead compounds of plant origin cannot be overemphasized. This is because plants are known to be a rich source of diverse and potent drugs and/or drug leads. A study by Newman and Cragg showed that about half of pharmaceuticals and pesticides were either NPs or their derivatives.[147-148] Although NPs of plant origin often fail the ro5,[142-143] they are known to be rich in stereogenic centres and cover segments of chemical space which are typically not occupied by a majority of synthetic molecules and drugs.[149-150] Generally, pure NPs contain more oxygen atoms and chiral centres, and have less aromatic atoms on average, when compared with most drugs.[151]

Some major limiting factors along the way of drug discovery programs from plant sources include the often small quantities of isolated phytochemicals for screening purposes, the labour-intensive and time consuming protocol of extraction and bioassay-guided fractionation of plant materials, compounded by the fact that forests, especially in Africa, are slowly disappearing and hence plant species are being threatened by extinction. Additionally, the plant-derived NPs are sometimes faced by unacceptable levels of toxicity due to poor pharmacokinetic profiles. The anti-malarial naphthoisoquinolines, for example, have not yet been exploited as starting points for the development of real drugs in the market. In order to rationally exploit NPs for drug discovery, techniques for enhancement of quantities of plant products must be employed, as well as the modification or fine-tuning of structural and hence physicochemical properties by chemical synthesis, leading to "drug-like" molecules with desirable DMPK profiles. These are often referred to as nature-inspired drugs.[152] Thus, modern drug discovery programs often resort to natural sources to guide the careful design of "drug-like" leads from suitable scaffolds, often by synthetic modifications of the latter.[153-155]

Available data show that Africa as a whole accounted for only 0.9% share of world gross expenditure on research and development (GERD) in 2007 while Asia had 32.2%, Oceania 1.6%, Latin America and the Caribbean 3%, Europe 27.4% and North America 38.0%.[156-158] Research and development (R&D) of drugs is an expensive endeavour.[159] However, the government budgets of West African states (as is the case with most of the continent) do not emphasize on research and development of drugs from the Western point of view. With the almost total absence of the basic required instrumentation for modern drug design and discovery (chemical synthesis, compound characterisation, 3D X-ray crystallography and biological screening) in a majority of laboratories in West African countries, current efforts involving NPs in drug discovery are geared towards improved traditional medicines (crude extracts, essential oils, etc. from plants of known remarkable activities) based on ethnobotanical knowledge. From our survey, more than half of the identified published papers were based on bioactivities of crude extracts and essential oils, only the minority leading up to the identification and characterisation of the active metabolites. The trend is for the researchers to go for active total extracts within acceptable levels of toxicity, not having access to the required instrumentation for the isolation and characterisation of the pure compounds. Academically oriented research programs in some West African laboratories (as is the case with most of the continent) is in this direction and much of the results have been published in journals like *Phytomedicine*, *Phytotherapy Research*, *BMC Complementary and Alternative Medicine*, *African Journal of Complementary and Alternative Medicine*, *Journal of Ethnopharmacology*, *Natural Product Research/Letters*, *South African Journal of Botany* and *Fitoterapia*, just to mention a few, along with a host of Asian, African and national journals.

What do the West African forests and savannas promise to humanity? Taking into consideration the amount of published data on anti-malarial compounds alone, it can be noticed that Asia has

offered artemisinin to humanity while Latin America has offered quinine. It is the opinion of many researchers that the time has come for the continent of Africa to produce a new marketable anti-malarial drug to humanity. This claim is supported by the fact that tropical rainforest plants are known to have higher concentrations of natural chemical defences and a greater diversity than plants from any other biome, thus they are potential sources of new medicines.[160] A recent literature review showed that > 500 compounds with anti-malarial properties from "weakly active" to "highly active" have been identified from the African flora, about one fifth coming from West Africa.[14,15] How this information can be translated into a marketable drug remains the main challenge for African scientists and policy makers.

The small quantities of NP samples available for testing in bioassays have often suggested the incorporation of computer-aided drug discovery (CADD) approaches like docking, pharmacophore-based virtual screening and neural networking in drug/lead identification projects on the continent. Such methods have proven successful elsewhere[161-163] and could be successful in Africa if random screening of samples is replaced by the screening of selected virtual hits with promising binding affinities or modulatory properties at the receptor site of known drug targets. This approach could be largely exploited by the research groups on the continent since computer-based methods have proven to be cost-effective.[159] This will however require investment in terms of training and development of critically masses of skilled researchers in the discipline of molecular modelling and medicinal chemistry in general.[2]

The African Network for Drugs and Diagnostics Innovation (ANDI)[164] is a WHO/TDR led initiative set up in 2008 with the mandate to promote and sustain African-led product R&D innovation through the discovery, development and delivery of affordable new tools, including those based on traditional medicines. ANDI is a well coordinated and results-driven effort that builds on existing activities in Africa, with strong elements of public-private partnerships.[165] With the West African hub based in Nigeria, ANDI generates and manages intellectual property and explores innovative mechanisms to encourage and reward local innovation. Nigeria alone is known to be the habitat of about 7,895 plant species[166] and the practice of traditional medicine as well as the development of improved traditional remedies is quite common.[35] A recent ethnobotanical versus bioactivity survey of medicinal plants in this country revealed that the biological activities of ~100 metabolites have been correlated with the ethnobotanical uses of the plant species from which they were isolated.[36] Nigeria alone hosts 16 institutions, referred to as *Centres of Excellence* (CoEs) for carrying out research on medicinal plants with the view of discovery of drugs and/or the development of improved phytomedicines.[167] This is only second to South Africa (the continents giant in pharmaceutical R&D), Nigeria having more CoEs than all the other West African nations put together, as well as more than all Central African nations put together.[167] Unfortunately it has been demonstrated that most African researchers in biomedically-related disciplines collaborate more with European and North American partners and have little or no local or intra-continental collaborations.[165] Pan-African collaborations like that which is currently going on, aimed at the formation of a pan-African network for the development of a continental repository (the p-ANAPL library)[11] for collecting physical samples of compounds derived from African medicinal plants could prove to be fruitful. Nigerian actors are also involved in the p-ANAPL project and such efforts could be encouraged nationally and across the West African region as a whole.

6 Conclusions

This review series is based on a cross examination of natural products from West African flora with a focus on drug discovery. We have carried out an assessment of over 700 NPs from 97 plant species and 41 families, which have exhibited diverse biological activities. It was generally noted that there was a gross absence of synergy between academia and industry, hence research towards drug discovery from West African flora was mostly in the hands of academic groups with little funding, while some of the research is also funded *via* travel grants for intermittent visits of senior staff and graduate students to research laboratories in the North and in countries with transition economies in Asia, latin America and Eastern Europe, due to the absence of basic instrumentation in a majority of the laboratories. The absence of adequate sample storage facilities for reagents, extracts and purified compounds calls for the intervention of pan-African organizations in charge of research, like WHO/TDR's ANDI,[164,165] which could play a key role in buiding bridges between African reasercher inter-alia. This second part review emphasises the utter stupidity of large parts of the Pharmaceutical sector during the 1990s in rejecting nature as a source of lead compounds. Beyond the scope of this article, other collections and encyclopedia listing the physicochemical properties and biochemistry with literature background of pure natural products in general[168-170] and terpenoids[171-172] in particular do exist. It is also observed that much all the research up to now in West Africa is on higher plants, with very little work done with bacteria, fungi and other microorganisms. This pushes us to think beyond what happens with the disappearance of a large part of the African forests though deforestation.

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8 Notes and references

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Table 1: Bioactivity of selected derived terpenoids *versus* ethnobotanical uses of plant species from West Africa

Compound	Plant species (Country)	Family	Ethnobotanical use	Measured Activity	References
1-6	*Croton zambesicus* (Benin)	Euphorbiaceae	The leaf decoction is used in Benin as anti-hypertensive, anti-microbial (urinary infections) and to treat fever associated with malaria.	Cytotoxicity.	Block *et al.*[44]
7, **8**	*Acanthospermum hispidum* (Benin)	Asteraceae	Aerial parts of acanthospermum hispidum d.c. Are often used by traditional healers in benin for various diseases and especially for **malaria**.	**Antiplasmodial**, Antitrypanosomial and Antileischmanial activities.	Ganfon *et al.*[47]
9	*Cassia siamea* (Nigeria)	Fabaceae	Treatment of **malaria.**	**Antiplasmodial** activity.	Ajaiyeoba *et al.*[48]
	Croton zambesicus (Benin)	Euphorbiaceae	Anti-hypertensive, anti-microbial and to treat fever associated with malaria.	Cytotoxicity.	Block *et al.*[44]
	Strychnos spinosa (Benin)	Loganiaceae	Is used traditionally to treat **African trypanosomiasis**.	**Antitrypanosomal** activity.	Hoet *et al.*[49]
10	*Tithonia diversifola* (Nigeria)	Compositae	Treatment of **malaria**, hepatitis, diabetes, malaria, pain, measles, chemoprevention and anti-*Helicobacter pylori*.	**Antiplasmodial** and anti-ulcer activities.	Kuroda *et al*.,[50] Castillo-Juárez *et al*.,[51] Adebayo *et al*.,[52] Goffin *et al.*[53] Sánchez-Mendoza *et al*.[54]
25-28	*Alchornea cordifolia* (Nigeria)	Euphorbiaceae	Remedy for arthritis, muscle pain and other **inflammatory** disorders.	**Anti-inflammatory** activity.	Okoye *et al.*[104,105]
29	*Hyptis suaveolens* (Nigeria)	Lamiaceae	Treatment of respiratory tract infections, colds, pain, **fever**, cramps and skin diseases.	**Antiplasmodial** activity.	Chukwujekwu *et al.*[58]

30 - **34**	*Laggera pterodonta* (Nigeria)	Compositae	Against insect attack, **athlete's foot, skin infections**, pediatric malaria and wounds. Also used in treatment of **hepatitis**, arthritis, bronchitis and nephritis.	**Antimicrobial** activity.	Egharevba *et al.*[59]
35	*Keetia leucantha* (Benin)	Rubiaceae	To treat **parasitic diseases**.	**Antitrypanosomal** activity.	Bero *et al.*[61]
37, **38**	*Mitracarpus scaber* (Benin)	Rubiaceae	Used to treat various human **skin diseases** including **eczema and ringworm.**	**Antimicrobial tests**	Gbaguidi *et al.*[63]
	Keetia leucantha (Benin)	Rubiaceae	To treat parasitic diseases.	**Antitrypanosomal activity.**	Bero *et al.*[61]
39	*Croton zambesicus* (Benin)	Euphorbiaceae	Leaves use to treat hypertension, anti-microbial and to treat fever associated with malaria.	Cytotoxicity assay.	Block *et al.*[44]
	Keetia leucantha (Benin)	Rubiaceae	To treat parasitic diseases.	**Antitrypanosomal activity.**	Bero *et al.*[61]
40	*Justicia anselliana* (Benin)	Acanthaceae	Poisonous wild pea.	Not active in the cytotoxicity assay.	Kpoviessi *et al.*[62]
	Strychnos spinosa (Benin)	Loganiaceae	Used traditionally to treat **African trypanosomiasis.**	**Antitrypanosomal activity.**	Hoet *et al.*[49]
42, **43**	*Strychnos spinosa* (Benin)	Loganiaceae	Is used traditionally to treat **African trypanosomiasis**.	**Antitrypanosomal activity.**	Hoet *et al.*[49]
44	*Dicoma tomentosa* (Burkina Faso)	Asteraceae	Traditionally used in Burkina Faso to treat malaria in adults and children, particularly malaria with spleen and liver "inflammation". The plant is also known for its benefits against cough and in postnatal care to "wash the belly", but it is not recommended for pregnant women because it is known to cause abortion.	Antiplasmodial activity.	Jansen *et al.*[64]

45	*Loranthus micranthus* (Nigeria)	Loranthaceae	Treatment of several diseases including **immune-modulating diseases**.	**Immunostimulatory activity**	Ogechukwu *et al.*[66]
45'	*Platostoma africanum* (Nigeria)	Lamiaceae	Treatment of rheumatic symptoms. The leaf sap is instilled into the eyes for fever in Ghana, and in the Ivory Coast the juice obtained by rubbing the leaves is applied to prevent infection and mouth sores. It is also used as an anti-diabetic plant in the Southern part of Nigeria.	Anti-inflammatory; antioxidant.	Aladedunye *et al.*[68]
47	*Struchium sparganophora* (Nigeria)	Asteraceae	Treatment of malaria and **measles,** cutaneous, subcutaneous **parasitic infection**, rheumatic pains, **diarrhea, dysentery** as well as **venereal diseases**, as an abortifacient, and in the treatment of inflammatory and **tumor-related** ailments. Also used in the preparation of soup in the South Western part of Nigeria.	**Antimicrobial** and **antitumour** activities.	Kasim *et al.*,[69] Kupchan *et al.*[70]
48	*Hypoestes rosea* (Nigeria)	Acanthaceae	To treat skin rashes and fungal infections.	Anti-inflammatory and antitumour activities.	Ojo-Amaize *et al.*[75]
49 - 57	*Entada africana* (Mali)	Leguminosae	Decotions of the root or the bark are used to treat hepatitis and to wash wounds. The juice of the fresh root or the bark is also used for its hemostatic properties.	Antiproliferative activity.	Cioffi *et al.*[76]
58 – 59''	*Combretum nigricans* (Burkina Faso)	Combretaceae	Treatment of various diseases such as cataract, conjunctivitis, icterus and rheumatism.	Cytotoxic activity.	Simon *et al.*[81]
60, **61**	*Abrus precatorius* (Nigeria)	Fabaceae	Treatment of **inflammatory** conditions such as arthritis.	**Anti-inflammatory** activity.	Anam.[83]
62	*Dichapetalum madagascariensis* (Ghana)	Dichapetalaceae	The whole plant is used for the treatment of viral hepatitis while the stem bark is used alone in treating jaundice, sores and urethritis.	Cytotoxicity.	Osei-Safo *et al.*[84]
63, **64**	*Aframomum sceptrum* (Ivory Coast)	Zingiberaceae	Traditionally used in ivory coast for infectious diseases including human **African trypanosomiasis** (sleeping sickness).	**Antiparasitic** activity.	Cheikh-Ali *et al.*[89-90]

65 - 67	*Loranthus micranthus* (Nigeria)	Loranthaceae	As an immunostimulant and antioxidant especially in several debilitating diseases including cancer, flu and other viral infections but not limited to these.	Proliferative activity.	Ogechukwu *et al.*[66]
68 - 79	*Khaya senegalensis* (Guinea)	Meliaceae	The decoction of its stem bark is commonly used as a bitter tonic in folk and popular medicines for malaria, fever, trypanosomiasis, mucous diarrhea, **cancer** and venereal diseases as well as for an anthelmintic and a taeniacide remedy.	**Anti-proliferative** activity.	Zhang[94]
80 - 85	*Khaya grandifoliola* (Nigeria)	Meliaceae	Treatment of **malaria**, as remedy against rheumatoid arthritis. Extracts also show anti-inflammatory and toxic effects.	**Antiplasmodial activity** and anticancer activities and Hsp90 inhibition.	Agbenanusi *et al.*,[96,97] Bickii *et al.*,[98] Kamath *et al.*,[99] Brandt *et al.*[100]
86 - 88	*Ganoderma colossum* (Nigeria)	Ganodermataceae (Fungus)	Mushrooms of this genus are known to possess anti-tumour, anti-cancer, **immunomodulatory and immunotherapeutic qualities.**	Antimicrobial activity, **activity against HIV-1 protease.**	Ofodile *et al.*,[101] Paterson,[102] El Din *et al.*[103]
87	*Pteleopsis suberosa* (Mali)	Combretaceae	Treatment of meningitis, convulsive fever, and headache, while the bark is reported able to increase cereal productivity and to treat jaundice, asthenia, and **dysentery**.	**Antibacterial** activity.	De Leo *et al.*[56]
89, **90**	*Acanthospermum hispidum* (Benin)	Asteraceae	Treatment of **malaria.**	**Antiplasmodial** activity.	Ganfon *et al.*[47]

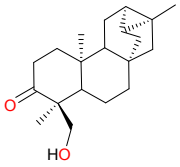
Table 2: Percentage compliances, minimum values, mean values, maximum values and recommended ranges for Lipinski parameters

Parameter	% Compliance	Minimum	Mean	Maximum	Recommended range
MW	81.57	122.12	406.66	1999.16	<500
log P	75.65	-8.09	3.29	18.21	<5
HBA	83.30	0	6.35	44	<10
HBD	82.96	0	2.94	22	<5
ro5	56.70	0	0.75	4	0

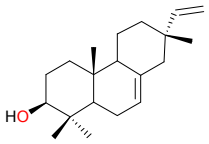
The map of Africa, with West African Nations highlighted.
203x211mm (100 x 100 DPI)

RSC Author Templates - ChemDraw (CDX) - Double Column Artwork

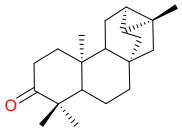
All text and images must be placed within the frame.



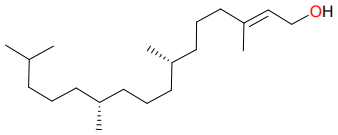
Ent-18-Hydroxy-trachyloban-3-one (**1**)



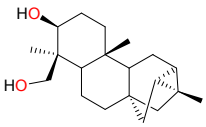
Isopimara-7,15-dien-3β-ol (**2**)



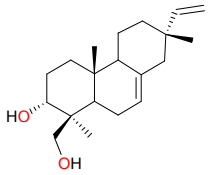
Ent-Trachyloban-3-one (**3**)



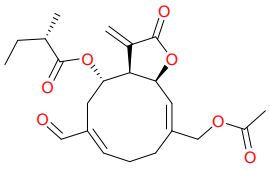
Trans-phytol (**4**)



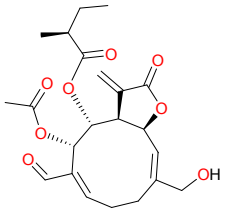
Ent-18-Hydroxytrachyloban-3β-ol (**5**)



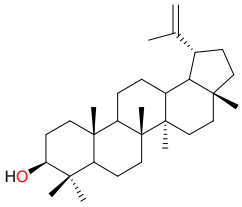
Ent-18-Hydroxyisopimara-7,15-diene-3β-ol (**6**)



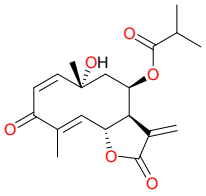
15-Acetoxy-8β-[(2-methylbutyryloxy)]-14-oxo-4.5-*cis*-acanthospermolide (**7**)



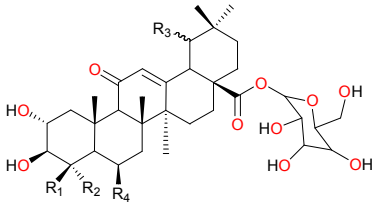
9β-acetoxy-15-hydroxy-8β-(2-methylbutyryloxy)-14-oxo-4.5-*trans*-acanthospermolide (**8**)



Lupeol (**9**)



Tagitinin C (**10**)

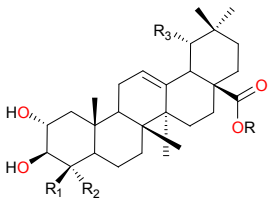


2α,3β,19α,23,24-pentahydroxy-11-oxo-olean-12-en-28-oic acid 28-O-β-D-glucopyranosyl ester (**11**)
R_1=R_2=CH_2OH, R_3=αOH, R_4=H

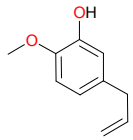
2α,3β,19β,23,24-Pentahydroxy-11-oxo-olean-12-en-28-oic acid 28-O-β-D-glucopyranosyl ester (**12**)
R_1=R_2=CH_2OH, R_3=βOH, R_4=H

2α,3β,19α,23-tetrahydroxy-11-oxo- olean-12-en-28-oic acid 28-O-β-D-glucopyranosyl ester (**13**)
R_1=CH_3, R_2=CH_2OH, R_3=αOH, R_4=H

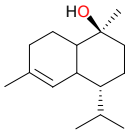
2α,3β,6β,19α,24-Pentahydroxy-11-oxo-olean-12-en-28-oic acid 28-O-β-D-glucopyranosyl ester (**14**)
R_1=CH_2OH, R_2=CH_3, R_3=αOH, R_4=OH



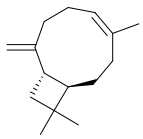
Trachelosperidoside E-1 (**15**)	Glc	$-CH_2OH$	$-CH_2OH$	-OH
Arjunglucoside I (**16**)	Glc	$-CH_3$	$-CH_2OH$	-OH
Sericoside (**17**)	Glc	$-CH_2OH$	$-CH_3$	-OH
Arjunetin (**18**)	Glc	$-CH_3$	$-CH_3$	-OH
Arjunglucoside II (**19**)	Glc	$-CH_3$	$-CH_2OH$	-H
Bellericoside (**20**)	Glc	$-CH_2OH$	$-CH_2OH$	-H
Sericic acid (**21**)	-H	$-CH_2OH$	$-CH_3$	-OH
Arjungenin (**22**)	-H	$-CH_3$	$-CH_2OH$	-OH
Trachelosperogenin (**23**)	-H	$-CH_2OH$	$-CH_2OH$	-OH



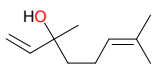
3-Allyl-6-methoxyphenol OR Eugenol (**24**)



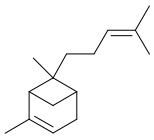
2-Isopropyl-5-metyl-9-methylene-5-hydroxy-Bicyclo[4.4.0]dec-1-ene OR Cadinol (**25**)



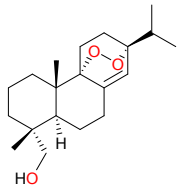
Caryophylene (**26**)



Linalool (**27**)



(*E*)-α-Bergamotene (**28**)



13α-*Epi*-dioxiabiet-8(14)-en-18-ol (**29**)

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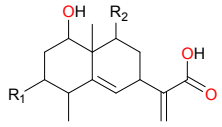
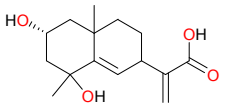
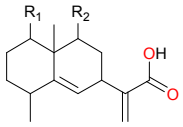
All text and images must be placed within the frame.



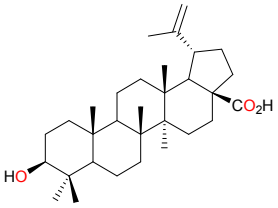
1β,9β–Dihydroxy-5,11(13)-dien-eudesman-13-oic acid (**30**): R_1 = H, R_2 = OH
1β,3α-Dihydroxy-5,11(13)-dien-eudesman-13-oic acid (**31**): R_1 = OH, R_2 = H



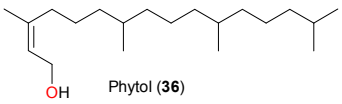
2β-Dihydroxy-ilicic acid (**32**)



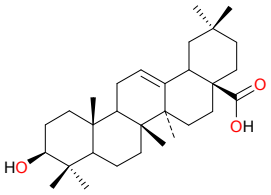
1β-hydroxy-pterodontic acid- 1-*O*-β-D-glucopyranoside (**33**): R_1 =*O*-β-D-Glc; R_2 = H
9β-hydroxy-pterodontic acid-9-*O*-β-D-glucopyranoside (**34**): R_1 = H, R_2 = *O*-β-D-Glc



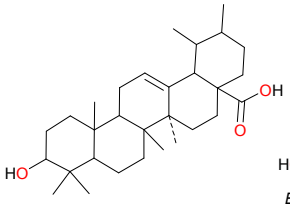
Betulinic acid (**35**)



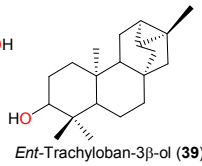
Phytol (**36**)



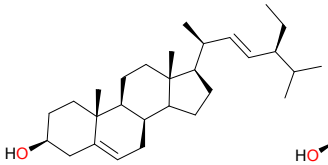
Oleanolic acid (**37**)



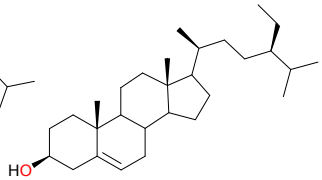
Ursolic acid (**38**)



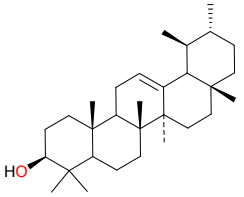
Ent-Trachyloban-3β-ol (**39**)



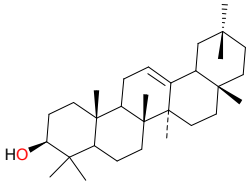
Stigmasterol (**40**)



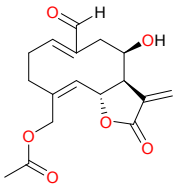
β-Sitosterol (**41**)



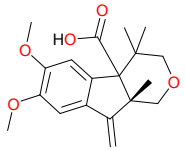
α-Amyrin (**42**)



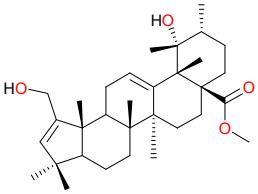
β-Amyrin (**43**)



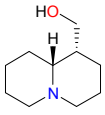
Urospermal A-15-*O*-acetate (**44**)



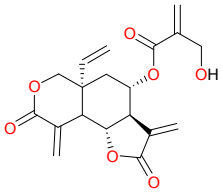
2,3-Dimethoxy-benzo [*a*, *b*] cyclopentenyl-3',3',5'-trimethyl pyran-4-carboxylic acid OR Loaranthoic acid (**45**)



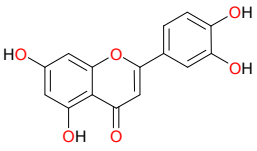
Methyl A(1)-1,19α-dihydroxy-urs-2(3),12-dien-28-oate (**45'**)



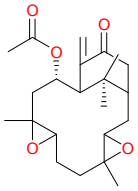
Lupinine (**46**)



Vernodalin (**47**)



Luteolin (**47'**)



Hypoestoxide (**48**)

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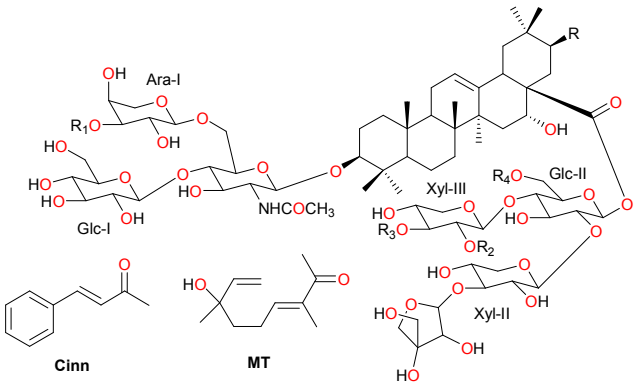


	R	R_1	R_2	R_3	R_4
49	H	Xyl-I	Cinn	MT	Ac
50	H	Xyl-I	H	MT	Ac
51	OH	Xyl-I	H	MT	Ac
52	H	Xyl-I	Cinn	H	Ac
53	H	Xyl-I	H	H	Ac
54	H	Xyl-I	H	H	H
55	OH	Xyl-I	H	H	Ac
56	H	Ara-II	Cinn	H	Ac
57	H	Ara-II	H	H	Ac

3β-O-{β-D-xylopyranosyl-(1→3)-α-L-arabino-pyranosyl-(1→6)-[β-D-glucopyranosyl-(14)]-2-(acetamido)-2-deoxy-β-D-glucopyranosyl}echinocystic acid 28-O-{β-D-apiofuranosyl-(1→3)-β-D-xylopyranosyl-(1→2)-[(2-O-cynnamoyl), (3-O-(2E,6R)-2,6-dimethyl-6-hydroxy-2,7-octadienoyl)-β-D-xylopyranosyl-(1→4)]- (6-O-acetyl)-β-D-glucopyranosyl ester (**49**)

3β-O- {β-D-xylopyranosyl-(1→3)-α-L-arabinopyranosyl-(1→6)-[β-D- glucopyranosyl-(1→4)]-2-(acetamido)-2-deoxy-β-D-glucopyranosyl}- echinocystic acid 28-O-{β-D-apiofuranosyl-(1→3)-β-D-xylopyrano- syl-(1→2)-[(3-O-(2E,6R)-2,6-dimethyl-6-hydroxy-2,7-octadienoyl)- β-D-xylopyranosyl-(1→4)]-(6-O-acetyl)-β-D-glucopyranosyl ester (**50**)

3β-O-{β-D-xylopyranosyl-(1→3)-α-L-arabinopyranosyl- (1→6)-[β-D-glucopyranosyl-(1→4)]-2-(acetamido)-2-deoxy-β-D-glucopyranosyl}acacic acid 28-O-{β-D-apiofuranosyl-(1→3)-β-D-xylo- pyranosyl-(1→2)-[(3-O-(2E,6R)-2,6-dimethyl-6-hydroxy-2,7- octadienoyl)-β-D-xylopyranosyl-(1→4)]-(6-O-acetyl)-β-D-glucopyranosyl ester (**51**)

3β-O- {β-D-xylopyranosyl-(1→3)-α-L-arabinopyranosyl-(1→6)-[β-D- glucopyranosyl-(1→4)]-2-(acetamido)-2-deoxy-β-D-glucopyranosyl}- echinocystic acid 28-O-β-D-apiofuranosyl-(1→3)-β-D-xylopyrano- syl-(1→2)-[(2-O-cinnamoyl)-β-D-xylopyranosyl-(1→4)]-(6-O-acetyl)- β-D-glucopyranosyl ester (**52**)

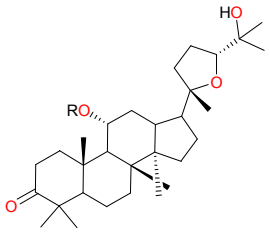
3β-O-{β-D-xylopyranosyl-(1→3)-α-L-arabinopyrano- syl-(1→6)-[β-D-glucopyranosyl-(1→4)]-2-(acetamido)-2-deoxy-β- D-glucopyranosyl}echinocystic acid 28-O-β-D-apiofuranosyl-(1→3)-β-D-xylopyranosyl-(1→2)-[(-β-D-xylopyranosyl-(1→4)]-(6-O-acetyl)-β-D-glucopyranosyl ester (**53**)

3β-O-{β-D-xylopyranosyl-(1→3)-α-L-arabino- pyranosyl-(1→6)-[β-D-glucopyranosyl-(1→4)]-2-(acetamido)-2- deoxy-β-D-glucopyranosyl}echinocystic acid 28-O-β-D-apiofuranosyl- (1→3)-β-D-xylopyranosyl-(1→2)-[(β-D-xylopyranosyl-(1→4)]-β-D- glucopyranosyl ester (**54**)

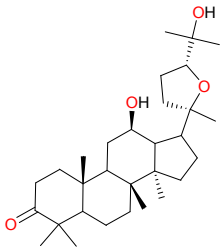
3β-O-{β-D-xylopyranosyl-(1→3)-α-L-arabinopyranosyl-(1→6)-[β- D-glucopyranosyl-(1→4)]-2-(acetamido)-2-deoxy-β-D-glucopyr- anosyl}acacic acid 28-O-β-D-apiofuranosyl-(1→3)-β-D-xylopyrano- syl-(1→2)-[(-β-D-xylopyranosyl-(1→4)]-(6-O-acetyl)-β-D-glucopyrano- syl ester (**55**)

3β-O-{α-L-arabinopyranosyl- (1→3)-α-L-arabinopyranosyl-(1→6)-[β-D-glucopyranosyl-(1→4)]-2-(acetamido)-2-deoxy-β-D-glucopyranosyl}echinocystic acid 28- O-{β-D-apiofuranosyl-(1→3)-β-D-xylopyranosyl-(1→2)-[(2-O-cinnamoyl)-β-D-xylopyranosyl-(1→4)]-(6-O-acetyl)-β-D-glucopy- ranosyl ester (**56**)

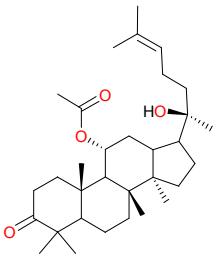
3β-O-{α-L-arabinopyranosyl-(1→3)-α-L-arabinopyrano-syl-(1→6)-[β-D-glucopyranosyl-(14)]-2-(acetamido)-2-deoxy-β-D- glucopyranosyl}echinocystic acid 28-O-{β-d-apiofuranosyl-(1→3)-β-D-xylopyranosyl-(1→2)-[(β-D-xylopyranosyl-(1→4)]-(6-O-acetyl)-β-D-glucopyranosyl ester(**57**)



11α-Acetoxy-20,24-epoxy-25-hydroxy-dammar-3-one (**58**) R=Ac
20,24-Epoxy-11α–25-dihydroxy-dammar-3-one (**59**) R=H



20,24-epoxy-11β–25-dihydroxy-dammar-3-one (**59'**)



Arcapitin (**59''**)

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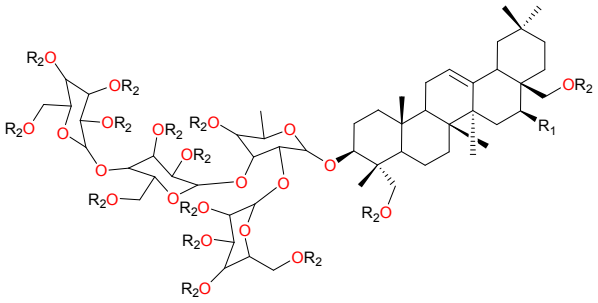
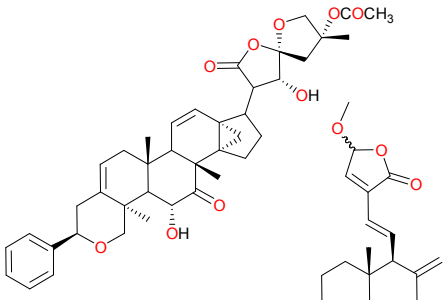
All text and images must be placed within the frame.



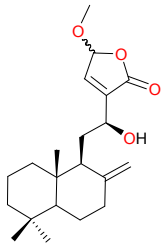
3-O-1{[β-D-glucopyranosyl-(1→4)-β-D-glucopyranosyl-(1→3)]-[β-D-glucopyranosyl-(1→2)]-β-D-fucopyranosyl}-Olean-12-ene-3β, 23, 28-triol (**60**) R_1=H, R_2=H

3-O-1{[β-D-glucopyranosyl-(1→4)-β-D-glucopyranosyl-(1→3)]-[β-D-glucopyranosyl-(1→2)]-β-D-fucopyranosyl}-Olean-12-ene-3β,16β, 23, 28-triol (**61**) R_1=OH, R_2=H

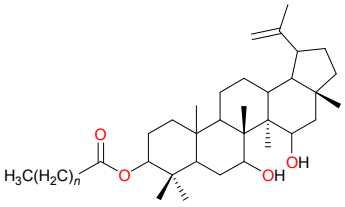


Dichapetalin M (**62**)

Sceptrumlabdalactone A (**63**)



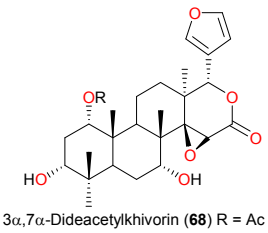
Sceptrumlabdalactone B (**64**)



7β, 15α-dihydroxy-lup-20-(29)-en-3β-*O*-palmitate (**65**): *n* = 12

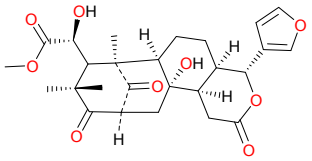
7β, 15α-dihydroxy-lup-20-(29)-en-3β-*O*-stearate (**66**): *n* = 14

7β, 15α-dihydroxy-lup-20-(29)-en-3β-*O*-eicosanoate (**67**): *n* = 16

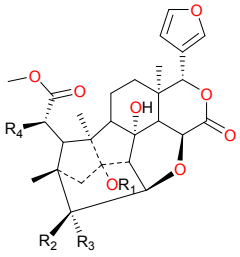


3α,7α-Dideacetylkhivorin (**68**) R = Ac

1α,3α,7α-trideacetylkhivorin (**69**) R = H



Mexicanoloid limonoid khayanone(**70**)



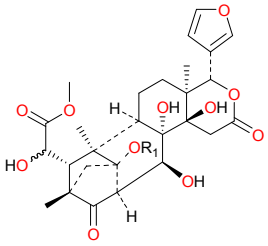
1-*O*-Deacetylkhayanolide B (**71**) R_1 = Ac R_2 = OH R_3 = H R_4 = OH

Khayanolide B (**72**) R_1 = H R_2 = OH R_3 = H R_4 = OH

Khayanolide E (**73**) R_1 = Ac R_2 = R_3 = O R_4 = OH

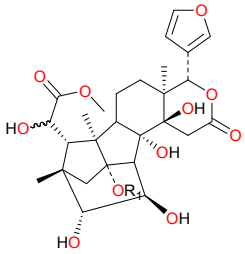
1-*O*-Deacetylkhayanolide E (**74**) R_1 = H R_2 = R_3 = O R_4 = OH

6-Dehydroxykhayanolide E (**75**) R_1 = H R_2 = R_3 = O R_4 = H



Methyl 1α-Acetoxy-6,8α,14β,30β-tetrahydroxy-3-oxo-[3.3.1^{10,2}.1^{1,4}]-tricyclomeliac-7-oate (**76**) R_1 = Ac

Methyl 1α,6,8α,14β,30β-pentahydroxy-3-oxo-[3.3.1^{10,2}.1^{1,4}]-tricyclomeliac-7-oate (**77**) R_1 = H



1α-Acetoxy-2β,3α,6,8α,14β-pentahydroxy-[4.2.1^{10,30}.1^{1,4}]-tricyclomeliac-7-oate (**78**) R_1 = Ac

1α,2β,3α,6,8α,14β-Hexahydroxy-[4.2.1^{10,30}.1^{1,4}]-tricyclomeliac-7-oate (**79**) R_1 = H

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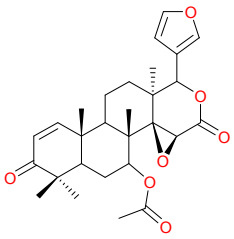
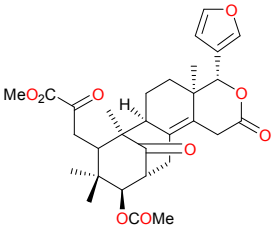
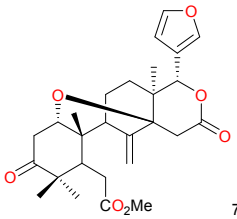


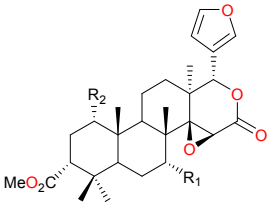
Gedunin (**80**)



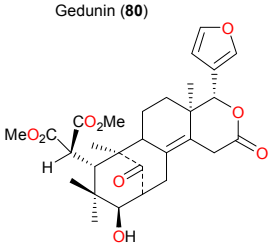
Fissinolide (**81**)



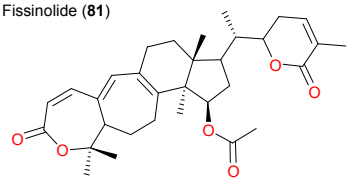
Methylangolensate (**82**)



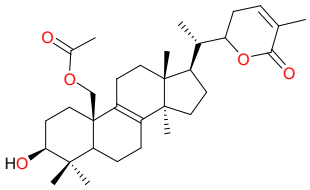
7-Deacetylkhivorin (**83**): R_1 = OH, R_2 = CO_2Me
1-Deacetylkhivorin (**84**): R_1 = CO_2Me, R_2 = OH



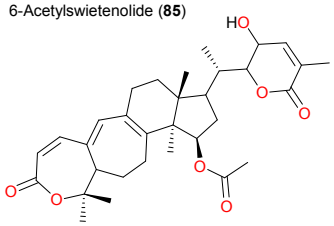
6-Acetylswietenolide (**85**)



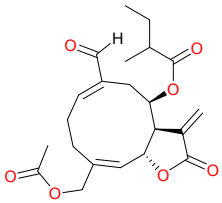
Colossolactone E (**86**)



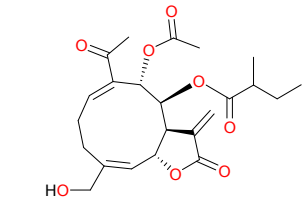
Colossolactone B (**87**)



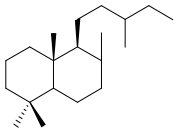
23-Hydroxycolossolactone E (**88**)



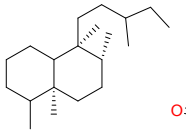
15-Acetoxy-8-[(2-methylbutyryloxy)]-
14-oxo-4,5-cis-acanthospermolide (**89**)



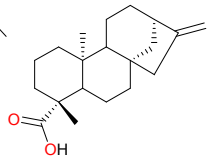
9-Acetoxy-15-hydroxy-8-(2- methylbutyryloxy)-
14-oxo-4,5-trans-acanthospermolide (**90**)



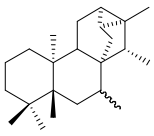
Labdane (**91**)



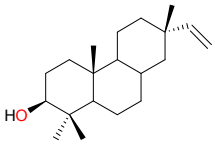
Clerodane (**92**)



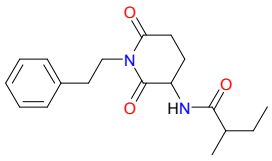
Kaurane (**93**)



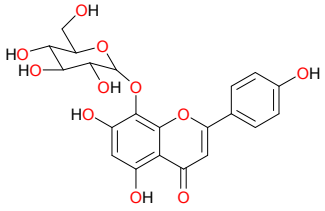
Trachylobane (**94**)



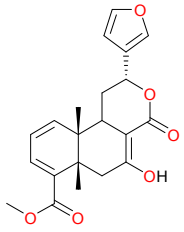
Pimarane (**95**)



Julocrotine (**96**)



Vitexin (**97**)



Crotomacrine (**98**)

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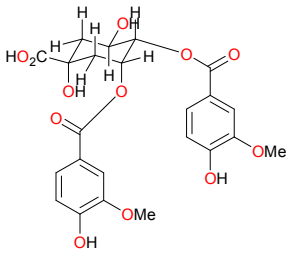
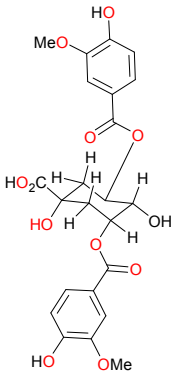
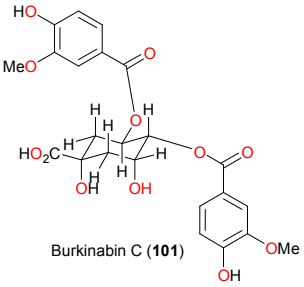


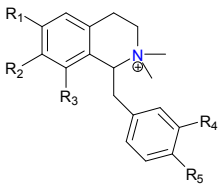
Burkinabin A (**99**)



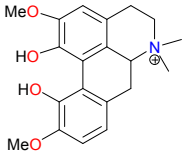
Burkinabin B (**100**)



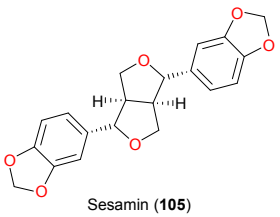
Burkinabin C (**101**)



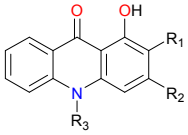
Oblongine (**102**): $R_1 = R_4 = H$, $R_2 = OMe$, $R_3 = R_5 = OH$
Tembetarine (**103**): $R_1 = R_5 = OH$, $R_2 = R_4 = OH$, $R_3 = H$



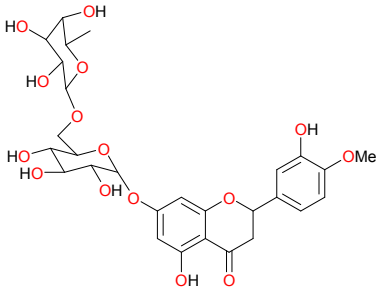
Magnoflorine (**104**)



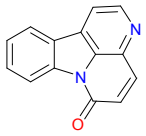
Sesamin (**105**)



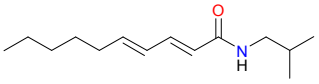
1-Hydroxy-3-methoxy-*N*-methyl-acridone (**106**):
$R_1 = H$, $R_2 = OMe$, $R_3 = Me$
Arborinine (**107**): $R_1 = OMe$, $R_2 = OMe$, $R_3 = Me$
Xanthoxoline (**108**): $R_1 = OMe$, $R_2 = OMe$, $R_3 = H$
1-Hydroxy-3-methoxyacridone (**109**): $R_1 = H$,
$R_2 = OMe$, $R_3 = H$



Hesperidin (**110**)



Canthin-6-one (**111**)



Pellitorine (**112**)