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The uniqueness and therapeutic value of natural products from West African medicinal plants, part I: Uniqueness, Chemotaxonomy

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Covering: 1971 to 2013

This review gives in depth coverage of natural products derived from West African medicinal plants with diverse biological activities. Unique compound classes from West African flora having remarkable biological activities have been highlighted, as well as a correlation between biological activities of the derived compounds and the uses of the plants in African traditional medicine and their chemotaxonomic classifications have also been included in the discussion. In the first part of the review, the focus is on alkaloids and flavonoids.

1 Introduction

Traditional medicine is known to cater for the health care needs of a significant proportion of the world's population, particularly in the developing economies of Africa, Asia and Latin America because of the limited availability of pharmaceutical medicines and the low purchasing power of these populations.[1] The use of plants in the treatment of several diseases is common practice in Africa[2] and it is believed that the derived natural products (NPs) hold enormous potential for drug discovery.[3] This has also been encouraged by the diverse uses of a plethora of these plants in traditional medicinal practices. Hence, research groups in Africa have embarked on the extraction, bioassay-guided fractionation, isolation and characterisation of bioactive metabolites from the plants commonly used in African traditional medicine (ATM), with the view of identifying the active ingredients, which might have implications in drug discovery program. This could be either directly as drug molecules or as hits/leads for synthetic modifications that should lead to more potent or less toxic analogues with improved drug metabolism and pharmacokinetic (DMPK) profiles.[1,2b]

However, some of the important data on bioactive metabolites derived from African medicinal plants with implications in ATM are dispersed in journal articles, as well as in MSc and PhD theses in university libraries (which, most often than not, are without online internet access). This renders such information inaccessible to the wider scientific community. Moreover, the efforts of African researchers have been limited to the random screening of crude extracts, essential oils and isolated metabolites from plants used in ATM in diverse bioassays in the search for hits and leads with promising activities, particularly against the neglected tropical diseases that affect a vast majority of the African population. Unfortunately, such efforts have not been complemented with similar efforts from the industrial sector towards transforming the research results into drug discovery/development programs aimed at manufacturing drugs for the sick populations. It therefore becomes imperative to summarise the most important findings for drug discovery from the dispersed data on African

medicinal plants, critically analyse such data and hence make suggestions to pave the way forward.

Recent review papers on the potential of NPs, and in particular those isolated from African medicinal plants have been focused on particular plant families, genera or species,[4] particular diseases,[2a,5] particular countries[6] and particular sub-regions.[7] Our recent review series has been focused on bioactive metabolites derived from medicinal plants growing in Central Africa,[6b,7b] including the development of NP databases[7] and the pharmacokinetics profiling of NPs derived from plants materials.[9] This has received significant attention from readership and consequently motivated similar efforts for the other regions on the continent, knowing that the West African region has not been investigated thoroughly, inspite of its rich floral biodiversity and phytochemistry.

According to the United Nations, the West Africa sub region includes the following sixteen (16) countries: Benin, Burkina Faso, Cape Verde, Ivory Coast, the Gambia, Ghana, Guinea, Guinea-Bissau, Liberia, Mali, Mauritania, Niger, Nigeria, Senegal, Sierra Leone and Togo. These countries occupy an area of over 6,140,000 km^2 and the natural environment in this area consists of subtropical and tropical regions with semi-arid and humid climates.[10] In these communities, traditional herbalists operate closer to the people, taking advantage of the biodiversity of plant species to cure various diseases and ailments. Numerous varieties of medicinal plants growing in West Africa are widely used against many diseases ranging from endemic tropical diseases like malaria,[5d,5m,6c,11] trypanosomiasis[5i] and leishmaniasis[12] to complex illnesses such as asthma,[13] psychosis,[14] hepatitis[15] and even cancer.[16] In the first part of the present review, unique compound classes from West African flora will be highlighted, along with a correlation between the biological activities of the derived alkaloids and flavonoids and the uses of the plants in ATM. The second part will be focused on the huge class of terpenoids along with the remaining classes, the impact of the geographical distribution of plants on the chemical contents and a study of selected genera will also be covered and insight on how the available data could be exploited in drug discovery.

2 Unique natural products from West Africa

Among the promising compounds derived from West African medicinal plants for the very first time are the aporphine alkaloids (**1** to **7**) from *Cassytha filiformis* (Lauraceae).[17] These compounds have been shown to be cytotoxic agents, in addition to the *in vitro* antitrypanosomal properties on *Trypanosoma brucei brucei*, exhibited by actinodaphnine (**1**), cassythine (**2**), and dicentrine (**3**). The *in vitro* anticancer test on HeLa cells showed that glaucine (**7**) was the most cytotoxic compound (IC_{50} = 8.2 μM) in the series. Mechanistic studies using optical measurements indicated that all seven aporphines effectively bind to DNA and behave as typical intercalating agents. Biochemical experiments also showed that actinodaphnine, cassythine and dicentrine interfere with the catalytic activity of topoisomerases in contrast to the four other aporphines. These interactions with DNA may explain, at least in part, the effects observed on cancer cells and on trypanosomes. Even though aporphinoids are also known to have been isolated from several species,[18] including *Siparuna* sp. from French Guyana,[19] *Spirospermum penduliflorum* from Madagascar,[20] *Glaucium* sp. from diverse regions,[21] *Corydalis yanhusuo*[22] and *Croton lechleri* from China,[23] *Papaver aculeatum* from South Africa,[24] *Enantia chlorantha* from Cameroon,[25] and *Artabotrys brachypetalus* from Zimbabwe,[26] those from the West African *Cassytha filiformis* are remarkable for their cytotoxic/antitrypanosomal activities.[27] The aporphines (+)-anolobine (**8**), (-)-litseferine (**9**), (-)-anolobine (**10**), (-)-roemeroline (**11**), (-)-norlirioferine (**12**) and (-)-corydine (**13**) have also been unusually found recently in *Monodora* sp. from Ivory Coast (*M. crispata* and *M. brevipes*, Annonaceae).[28] Aporphines **9**-**12** are new to the *Monodora* genus, while **8** and **13** had been observed in only one Monodoreae (*M. tenuifolia*)[29] and analogues have been identified in *M. angolensis*,[30] *M. junodii*[31] and *M. tenuifolia*[29] harvested in other parts of the world.

Another remarkable and unique subclass of alkaloids from West Africa is the indoloquinoline alkaloids exhibiting anti-malarial, antitrypanosomial and cytotoxic properties. Cryptolepine (**15**) was isolated from *Sida acuta* (Malvaceae) harvested in Ivory Coast[32] and from *Cryptolepis sanguinolenta* (Periplocaceae) growing in diverse regions in West Africa.[33] Cryptolepine derivatives (**16** to **26**), isolated from the stems, roots and root bark of *Cryptolepis sanguinolenta* have also exhibited potent anti-malarial properties.[34] Cryptolepine is one of those rare highly potent anti-malarial agents unique for structure and biological activty. It is currently used as an anticancer drug because of its ability to intercalate into DNA at the cytosine-cytosine sites.[35]

Nauleamide E (**27**) is a unique monoterpene indole alkaloid possessing a pentacyclic ring system with an amino acetal bridge has been isolated from *Nauclea latifolia* (Rubiaceae) harvested in Calabar, Nigeria.[36] Even though this type of monoterpene indole alkaloid is rare, vallesiachotamine (**27'**) has been obtained from the Peruvian plant *Vallesia dichotoma*.[37]

Naphthylisoquinoline alkaloids represent another set of potent naturally occurring antimalarial/antileishmanial agents from the West African flora. Habropetaline A (**28**),[38] dioncophylline A (**29**) and its 5'-*O*-demethylated analogue (**30**),[39] 8-*O*-methyldioncophyllinol B (**31**),[40] dioncophylline B (**32**) and dioncopeltine A (**33**)[39,41] from *Triphyophyllum peltatum* (Dioncophyllaceae) are in this category. Korupensamines A (**34**) and B (**35**) have been isolated from both *Ancistrocladus guineensis* (Nigeria)[42] and the sister species *A. korupensis* (Cameroon),[43] while ancistroguineines A (**36**) and B (**37**), ancistrotectorine (**38**) and ancistrobrevine B (**39**) were unique to the Nigerian species.[44] The chemistry and biological activities of the other naphthylisoquinolines from Central and East Africa have been discussed in recently published reviews.[5d,7]

Other rare compound types identified from the West African flora are unusual furanone-substituted flavones[44] and divanilloylquinic acids.[45] The former has been isolated from the leaves of *Hoslundia opposita* (Lamiaceae) while the latter was derived from *Fagara zanthoxyloides* (Rutaceae), a plant species used in folk medicine for its antisickling properties in Burkina-Faso and other West African countries. The isolated NPs from *Fagara zanthoxyloides*; burkinabins A (**40**), B (**41**) and C (**42**) showed promising activities against sickle cell anaemia.[45] The unusual 6-furanoflavones, hoslunfuranine (**43**) and 5-*O*-methylhoslunfuranine (**44**), isolated from *H. opposita*, are characterised by a furanone moiety being branched in position C-4''. Compound **44** exhibited leishmanicidal potential in the micromolar range.[44] Another aporphine alkaloid, magnoflorine (**14**), isolated from a sister *Fagara* species (*F. macrophylla*) from the Republic of Guinea, exhibited antifeedant properties against *S. frugiperda*.[46]

3 Analysis of plant families, compound types and attempted chemotaxonomic classification

In the current survey a literature search on the major natural product journal websites was carried out, based on country names in the search engines of each journals. The article hits were filtered based on the geographical location of the harvested plant materials and only articles describing NPs isolated from plants harvested in West Africa were retained. The data from each article was extracted on an excel sheet with several fields, including plant species names, family names, ethnobotanical uses, compound types identified (e.g. alkaloids, flavonoids, terpenoids, etc.), biological activities of isolated metabolites, collection dates of plant samples, authors, references, etc. Our collection was composed of about 700 input compounds, previously isolated/derived from 97 plant species belonging to 41 families. Data was collected from 5 MSc theses 9 PhD theses and 445 articles from 134 peer reviewed journals. We have carried out an analysis on the collected data, based on numbers of compounds isolated per plant species and per family. A majority of the metabolites are shown to have been previously isolated from plants harvested in Nigeria.

In this analysis, emphasis was laid on those plant families from which at least ~2% of the secondary metabolites have been isolated. The majority of the compounds were isolated from the Euphorbiaceae family, constituting 13.67%. This was followed by the Annonaceae (10.83%), the Leguminosae (9.67%), the Guttiferae (8.67%), the Rubiaceae (4.50%), the Loganiaceae and the Meliaceae (both 4.17%), the Compositae (3.61%), the Combretaceae and the Loranthaceae (both 3.50%), the Rutaceae (2.83%), the Lamiaceae (2.50%), and finally the Apocynaceae and the Asteraceae (both 2.00%), Fig. 1.

An overall distribution by compound type (based solely on unique compounds, not compound concentrations in the plants) is shown in Fig. 2. Our results showed that terpenoids were most abundant among the isolated compounds, constituting 29.91% of the isolated compounds, a similar picture to our previously analysed data from Central Africa.[7b] This was followed by alkaloids (23.83%), flavonoids (22.09%), xanthones (4.70%), steroids (4.00%), phenolics (3.83%), and glycosides (3.48%). The remaining compounds classes constituted < 2.00% each of the isolated compounds in terms of numbers.

Table 1 shows a summary of dominant compound types isolated *versus* recorded biological activities for the most outstanding plant families. The Euphorbiaceae family is dominated by terpenoids (39.51%) and flavonoids (24.70%). Alkaloids dominated the Annonaceae family, constituting 49.21%, while the Leguminosae were dominated by flavonoids as usual (23.68%).[6b,7b] The other alkaloid-rich families were the usual Apocynaceae (75.00%), Rutaceae (40.00%) and Rubiaceae (43.75%). The Asteraceae, Combretaceae, Euphorbiaceae, Loganiaceae, Loranthaceae and Meliaceae families were seen to contain large numbers of terpenoids, when compared with the other compound classes, constituting respectively 63.64%, 85.00%, 39.51%, 56.00%, 33.33% and 100%. The Compositae family was equally rich in terpenoids and flavonoids, while xanthones and flavonoids were dominantly present among the Guttiferae. Even though the above percentages could be seriously affected by the limited number of NPs in this study, compared with our previous Central African study, even though the overall classification is similar.[7b]

Previous attempts towards the taxonomic classification of West African medicinal plants have been carried out.[47] However, a vivid discussion of the classification of plant families by compound type has not been presently presented. In addition to the above mentioned main compound classes, we provide a summary of the compound subclasses that characterise selected genera and species. Within the Annonaceae family, for example, the isolation of the the acyclic diterpene alcohol *trans*-phytol (**45**) from *Piptostigma fasciculate*, harvested from Ghana, is of taxonomic interest (unique to the genus),[48] since diterpenes encountered so far in the family are clerodane, trachylobane, kolavane and predominantly kaurane derivatives.[49] This compound is rather most commonly found in species of marine algae,[50] as well as in a number of higher plants, including *Fatsia japonica* (Araliaceae),[51] *Tetragonia tetragonoides* (Aizoaceae)[52] and *Artemisia annua* (Compositae)[53] Moreover, the morphinandienones (-)-mocrispatine (**46**) and pallidine (**47**) obtained from *Monodora crispata*, harvested from the South of Ivory Coast are unusual in the Annonaceae,[28] pallidine having been encountered as the major aporphine in several tribes within the Annonoideae.[54] Keblan *et al*. also studied another species within the *Monodora* genus from Ivory Coast.[28] It was observed that compounds **46** and **47** were rather absent in the batch of *M. brevipes*, confirming that morphinandienones are rare compounds within *Monodora* sp., with no chemotaxonomical value at the

supraspecific level. It is noteworthy that morphinandienones from Annonaceae bear the *S* configuration at *C*-9, as observed in other Magnoliids (*Magnoliale*s, *Laurales*), contrary to their counterparts isolated from Papaveraceae (*Ranunculales*, *Eudicots*).[55] Within the Asteraceae family, for example, the presence of a number of acetyl chromenes in *Ageratum conyzoides* is believed to be of chemotaxonomic significance. It indicates that the genus is chemically closer to the Ageritanae subtribe, as opposed to the Piqueriiae group to which it was previously assigned.[56] Among plants of the *Vernonia* genus so far studied for biological activity, a good number of the biological activity claims have been associated with the presence of terpenoids in the plants. Despite the fact that the literature reports the isolation of several terpenoids from the *Vernonia* genus, only a limited number have been tested for bioactivity.[4c]

Paulo and Houghton have extensively discussed the chemotaxonomy of the *Cryptolepis* genus,[57] which is mostly represented in West Africa by *C. sanguinolenta*, noted for the presence of a special class of indole alkaloids (cryptolepines), exhibiting antiplasmodial activities, named after this genus.[32,33] According to these authors, the genus *Cryptolepis* could be carefully placed under the subfamily Periplocoideae and related families Asclepiadaceae and Apocynaceae. This is because the chemistry of the genus *Cryptolepis* is in agreement with its taxonomic position within the taxon Periplocaceae/Periplocoideae. Additionally, chemical evidence obtained so far is consistent with the idea that the taxon Periplocaceae/Periplocoideae is an evolutionary link between the families Apocynaceae and Asclepiadaceae. The authors further advance strong arguments that the taxon Periplocaceae/Periplocoideae could be considered an independent family.[57] The taxonomy of the genus *Echium* (Boraginaceae) is known to be quite complex.[58] The exploration of two endemic specis, *E. Stenosiphon* and *E. hypertropicum*, from Cape Verde has led to the identification of the hepatotoxic diesters echimidine (**48**) and 7-(2-methylbutyryl)-9-echimidinylretronecine (**49**) in both species. Echimidine was the major component in the diethyl ether fraction from leaves of *E. hypertropicum*, whereas 7-(2-methylbutyryl)-9-echimidinylretronecine was the major component in the dichloromethane fraction from leaves of *E. stenosiphon*.[59] According to the study by Carvalho *et al*., *E. stenosiphon* subsp. *stenosiphon* and *E. hypertropicum* were found to be rich in pyrrolizidine alkaloids (PAs), having the common structural features i.e. 1,2 unsaturation, an esterified allylic hydroxyl group at *C*9 and an esterified alcoholic hydroxyl group at *C*7, which generally make PAs potentially toxic.[60] The authors cautioned that these two species be regard as potentially hepatotoxic, thus discouraging their use in traditional medicine. However, PAs could be used as chemotaxonomic markers for the genus *Echium*.[59]

The investigations of Niassy *et al*. on the aerial parts of two species of the genus *Tephrosia* (*T. deflexa* and *T. albifoliolis*, Leguminosae), harvested from the Nature Reserve of Niokolo-Koba in the South-East of Senegal, made a significant contribution towards the understanding of the chemistry of this genus.[61] Although the presence of *C*-prenylflavonoids appears to be widespread in this genus,[62] these authors could only demonstrate the presence of rotenone (**50**) in *T. deflexa*, along with other common flavonoids. No prenylated flavonoids, considered as intermediates in the synthesis of rotenoids, were detected in either of the two species. The investigations of Niassy *et al*. thus led to the first report of the occurrence of flavonols in the genus *Tephrosia*. Moreover, until the time of the publication of their results, the four quercetagetin derivatives, namely jacein, eupatolin, quercetagetin-3,3'-dimethylether-7-*O*-glucoside and quercetagetin 3'-methylether-7-*O*-glucoside had been encountered in the Compositae, but not in the Leguminosae.[63] Within the Loganiaceae family, lichexanthone (**51**), previously known as a fungal metabolite,[64] has been isolated from *Anthocleista djalonensis*, collected in Ibadan, Nigera.[65] This compound co-occurs with alternariol methyl ether within this plant. The above observations have led to conclusions that alternariol (**52**), and thus its mono methyl ether, are biosynthesized *via* nor-lichexanthone. The co-occurrence of 3,4'-dihydroxy-5-methoxy-6'-methyl dibenzo-α-pyrone (mono methyl ether alternariol) with lichexanthone in *A. djalonensis* could be of chemotaxonomic importance as supportive evidence in favour of nor-lichexanthone as a precursor of alternariol methyl ether.[66] In the Loranthaceae family, the presence of the unusual dihydroxylated lupeol-based fatty acid esters (**53 - 55**) in mistletoes (*Loranthus micranthus*), harvested in Eastern Nigeria,[67] as well as from mistletoes growing in Japan[68] is an indication that they may be mistletoe-specific. This however warrants further investigation.

As a family, the Meliaceae are known for the abundance of limonoids.[69] In this family, attempts to classify the genus *Trichilia* have often led to conflicting conclusions.[70] As an example, it is believed that the antischistosomal and antiplasmodial properties and a thorough biosystematic study of *T. emetica*, possibly including *T. dregeana*, should provide valuable insights on the chemotypic variation and the intraspecific taxonomy of these two ethnobotanically important species.[71] Bero *et al*. carried out a study of the leaf extracts of *T. emetica* subsp. *suberosa* collected from Benin and these showed no activity on *Plasmodium falciparum*, except for the dichloromethane extract which had a very moderate effect (IC_{50} = 59.2 µg mL^{-1}). These results confirmed the results obtained by Traore *et al*.[72] In Mali, another study on this subspecies showed antiplasmodial activity for the dichloromethane extract, with an IC_{50} of 11.9 µg mL^{-1}.[73] This activity could be due to variations in the chemical content of samples from different localities. The other subspecies, *Trichilia emetica* subsp. *emetica* was active in various studies.[74] However, the taxonomic differentiation is the proof of different biological properties linked to different chemical compositions.[75]

Sonibare *et al*. have identified the chemotaxonomic significance of leaf alkanes in species of *Ficus* (Moraceae) from Nigeria.[76] The alkane pattern of leaf waxes from twenty four tropical *Ficus* species in Nigeria was determined by gas chromatography and gas chromatography–mass spectrometry. Of the twelve alkanes identified, hentriacontane and tritriacontane were the major components in all the species studied. This indicates that alkane occurrence in *Ficus* could provide useful information to the understanding of species variability. Le *et al*. have identified bioactive polyphenols in *Ximenia americana* (Olacaceae) used traditionally among Malian healers against throat infections, amenorrhea, as tonic, for wound healing and against pain.[77] Sambunigrin (**56**) was the main compound in the EtOAc soluble fraction of the alcoholic extract of *Ximenia americana* leaves. Nine other compounds, including gallic acid (**57**), two gallotannins and six flavonoids were identified for the first time in the genus *Ximenia*. While Sambunigrin was previously known from *Ximenia americana* leaves,[78] the other nine compounds had not been reported in the genus *Ximenia* before. While some of these compounds are nearly ubiquitous, others (such as the galloylated flavonol glycosides) have a limited distribution in nature. Their presence in this plant species may therefore be of chemotaxonomical interest.

Flavonoids from *Vetiveria zizanioides* and *Vetiveria nigritana* (Poaceae), harvested in Koulikoro, near Bamako (Mali), also have a significance for chemotaxonomy of West African medicinal plants.[79] Apart from isoorientin (**58**), which is only present in *V. zizanioides*, the same flavonoids were identified in both species. The aerial parts of both species contained mainly 6,8-di-*C*-heterosides of luteolin. These flavonoids share a common structural part, probably indicating the existence of a *C*-glycoside step in the flavone biosynthesis system. Some authors considered *C*-glycosyl flavones to be the basic flavonoids in many Poaceae,[80] including species of the genus *Vetiveria*. However, flavone-*C*-glycosides cannot be considered specific to Poaceae, since they are also found in many other families such as Passifloraceae, Orchidaceae, and Caryophyllaceae. Moreover, the report of Gluchoff-Fiasson *et al*. was the first time 6,8-di-*C*-arabinopyranosylluteolin was isolated in the Poaceae family. The compound tricin-5-*O*-glucoside, has been already reported in other species of Poaceae: *Triticum* spp.[80b] and *Oryza sativa*.[81] Its presence in the roots of the two *Vetiveria* species could be significant from a chemotaxonomic point of view.

Within the Rubiaceae family, naucleamides are monoterpene indole alkaloids isolated for the very first time from *Nauclea latifolia* (Rubiaceae), from Calabar, Nigeria.[36] This type of monoterpene indole alkaloid is rare, and Nauleamide E (**27**) is a unique monoterpene indole alkaloid possessing a pentacyclic ring system with an amino acetal bridge, used to identify the species. Biosynthetically, naucleamides A-E (**27**, **59** - **62**) may be derived from strictosamide (**63**) through reductive and/or oxidative cleavage of ring E.

4 Ethnobotany *versus* bioactivity survey

The biological activities of the selected compounds, along with the ethnobotanical uses of the plants from which they were derived have been summarised in Tables 2 to 4. Whenever there is a correlation between bioactivity and ethnobotany, these have been highlighted in bold in the table. The discussion that follows is arranged according to the various compound classes identified, with a focus on the most abundant classes; alkaloids, flavonoids, and terpenoids.

4.1 Alkaloids

Bioactive alkaloids from West African flora have been isolated from across a broad range of plant species and families (Table 2). The measured biological activities are mostly antiparasitic, the dominant activity being anti-malarial.

Yohimbine (**64**) is another unique alkaloid derived from a plant growing in West Africa (*Pausinystalia johimbe*). This plant commonly used to treat erectile dysfunction in ATM in West and Central Africa.[82] Both yohimbine[83] and its hydrochloride[84] have proven to be potent in the treatment of erectile dysfunction by preferential blockade of presynaptic α-adrenoceptors in rabbits.[85a] Yohimbine (**64**) had received great attention from chemists, and the total synthesis of this alkaloid has been achieved.[85b-d]

Cassytha filiformis (Lauraceae) is a widely distributed antiparasitic plant containing several aporphine alkaloids. This plant has been used in African folk medicine to treat cancer, African trypanosomiasis and other diseases.[17] Six (6) aporphines have been isolated by Hoet *et al*. from samples of *C. filiformis* harvested in Benin. The compounds have been tested for the *in vitro* cytotoxic properties on different cancer and non-cancer cell lines. The major alkaloids; actinodaphnine (**1**), cassythine (**2**), and dicentrine (**3**) were also shown to possess *in vitro* antitrypanosomal properties on *Trypanosoma brucei brucei*, thus showing that the use of this plant in traditional medicine is coherent with its phytochemical content. The cytotoxicity of compound **7** demonstrates that it is the active ingredient in this plant, justifying the use of the plant in cancer treatment in ATM.

Another set of aporphine alkaloids (**8** to **13**) have been isolated from *Monodora* sp. from Ivory Coast. These include *M. crispata* and *M. brevipes*.[28] The plant species are not reported to be used in ATM and the isolated compounds have not been tested yet, although they may serve in the chemotaxonomic classification of the plant species of the genus *Monodora*. In contrast to the other genera of the Monodoreae tribe (*Isolona*, *Hexalobus*, *Monocyclanthus* and *Uvariopsis*), *Monodora* sp. show a strong tendency towards the production of quaternary ammonium derivatives, which could be proposed as a distinctive generic trait.[28] *Fagara macrophylla*, harvested from the Republic of Guinea, is known to be used to cure of toothache, rheumatism and urogenital affections as well as to prepare poisonous arrows, among other uses. The poisonous substances in the plant may explain why insects do not feed on it. As

an example, Tringali *et al*. have isolated the aporphine magnoflorine (**14**), along with the acridones 1-hydroxy-3-methoxy-*N*-methyl-acridone (**97**) and arborinine (**98**), along with the aporphine tembetarine (**102**), which have all demonstrated antifeedant properties against *Spodoptera frugiperda*.[48]

The indoloquinoline alkaloid cryptolepine (**15**) has been isolated from *Sida acuta* (Malvaceae) from Ivory Coast and Burkina Faso,[32,33] while other derivatives (**16** to **26**) have been isolated from *Cryptolepis sanguinolenta* (Periplocaceae) from Ghana, Cape Verde, Guinea Bissau, and other countries in the West African region.[33] Banzouzi *et al*. carried out an anti-malarial assay on the extracts from *Sida acuta*. The IC_{50} values obtained ranged from 3.9 to 5.4 μg mL^{-1}. Cryptolepine was identified as the active anti-plasmodial constituent of the plant after purification of the active fraction. This compound showed IC_{50} values against the chloroquine-sensitive strain (respectively 0.13 and 0.17 μg mL^{-1} after 24 and 72 hours) from Nigeria and the Fcm29 chloroquine-resistant strain (respectively 0.17 and 0.17 μg mL^{-1} after 24 and 72 hours) from Cameroon. Cryptolepine derivatives (**16** to **26**), which were isolated from the stems, roots and root bark of *Cryptolepis sanguinolenta*,[33] showed antiplasmodial activities as well. Cimanga and his coworkers also observed that cryptolepine and its hydrochloride salt, 11-hydroxycryptolepine (**18**), and neocryptolepine (**23**) showed strong *in vitro* antiplasmodial activities against *P. falciparum* chloroquine-resistant strains (D-6), while quindoline (**16**) was less active. The highest activity was obtained with cryptolepine. *In vivo* tests on infected mice showed that cryptolepine exhibited a significant chemosuppressive effect against *Plasmodium yoelii* and *Plasmodium berghei*, while cryptolepine had the same effect against *P. yoelii* only. Compounds **16** and **18** did not show activity in the *in vivo* test system.[33c] Another study by Paulo *et al.* on the roots of *Cryptolepis sanguinolenta* harvested from Guinea-Bissau led to the isolation of cryptolepinoic acid (**24**) and methyl cryptolepinoate (**25**) in addition to **15**, **16** and **17** from the ethanol and chloroform extracts of the leaves.[33e] The isolated compounds and extracts were tested *in vitro* against *P. falciparum* K1 (multidrug-resistant strain) and T996 (chloroquine-sensitive clone). All extracts had 90% inhibition of *P. falciparum* K1 growth at concentrations of < 23 μg mL^{-1}. Cryptolepine was the most active alkaloid tested with IC_{50} values (0.23 μM to K1; 0.059 μM to T996), compared to chloroquine (0.26 μM to K1; 0.019 μM to T996). The indolobenzazepine alkaloid cryptoheptine (**19**) was the second most active with IC_{50} values of 0.8 μM (K1) and 1.2 μM (T996). Cryptolepinoic acid (**24**) showed no significant activity while its ethyl ester derivative (**26**) was active against *P. falciparum* K1 (IC_{50} = 3.7 μM). All the indoloquinoline alkaloids showed cross-resistance with chloroquine but not the indolobenzazepine cryptoheptine (**19**). It was noticed that alkaloids with weakly basic characteristics were active whereas other structurally related alkaloids with different acid–base profiles were inactive. These observations are in agreement with the anti-malarial mechanism of action for quinolines. According to Hadden *et al*., the unusual incorporation of the isopropyl group at the 11-position of the indolo [3,2-*b*] quinoline nucleus in 11-isopropylcryptolepine is suggestive of a mixed biosynthetic origin for the alkaloid.[33f]

The Dioncophyllaceae and Ancistrocladaceae (the only genus is *Ancistrocladus*) families are closely related and represent rich sources of naphthylisoquinoline alkaloids. In West Africa, the Ancistrocladaceae are present in Nigeria (*A. uncinatus* and *A. guineensis*), Ghana (*A. abbreviatus*) and the Republic of Guinea (*A. barteri*), while the carnivorous *Triphyophyllum peltatum* (Dioncophyllaceae) is a native of Ivory Coast. From *T. peltatum* several naphthylisoquinolines (**28** – **33**, **84**, **86** - **91**) have been isolated. These compounds have demonstrated activities against *P. falciparum* and other parasites, supporting the use of the plant in the treatment of malaria, leishmaniasis, dysentery and elephantiasis, among other uses.[40-43] Jozipeltine A (**85**) was later isolated from a mixture of *T. peltatum*, *Dioncophyllum tholloni* and *Habropetalum dawei*, harvested from Ivory Coast and Sierra Leone. The anti-malarial property of this compound supports the use of these plants, in combination, for the treatment of malaria. Although this compound showed some *in vitro* anti-plasmodial activity against *P. falciparum* (K1 = 875 ng mL^{-1}, NF54= 2530 ng mL^{-1}), it is significantly less active than its monomeric precursor, dioncopeltine A (**33**) (K1= 4.8 ng mL^{-1}, NF54=3.3 ng mL^{-1}). This observation could lead to the conclusion that only naphthylisoquinolines containing one phenolic OH group each, such as dioncophylline A (**29**) and ancistrocladine (**95**), could easily undergo the required dimerization reaction, implying that doubling of the number of free OH groups would increase the antiplasmodial activity.[86] Additionally, the 5,8'-coupled naphthylisoquinolines, ancistroguineines A (**36**) and B (**37**), were isolated from the Nigerian species (*A. guineensis*), along with the 7,3'-coupled ancitrotectorine (**38**),[44] which is dominantly present in the South-East Asian species (*A. tectorius*).[87] Korupensamines A (**34**) and B (**35**) are rather known to contain the anti-malarial "halves" of the anti-HIV michellamines, derived from the Cameroonian species (*A. korupensis*).[88] Both species (*A. guineensis* and *A. korupensis*) grow in Cameroon,[89] the former being more dominant in Nigeria, even though its traditional use is not reported and the biological activities of the isolated ancistriguineines have not been assessed. The Ghanaian species (*A. abbreviatus*) has been used traditionally as treatment against measles and fever, the active ingredient being ancistrobrevine D (**94**).[90] A full discussion of the naphthylisoquinolines has been presented in a separate review.[91]

The root bark of *Fagara zanthoxyloides* or *Zanthoxylum zanthoxyloides* (Rutaceae) is widely used in folk medicine for its antisickling properties in Burkina Faso and other West African countries.[45,47,92] Ouattara *et al*. have isolated three (3) isomeric divanilloylquinic acids, **40** to **42** (3,4-*O*-divanilloylquinic acid or burkinabin A; 3,5-*O*-divanilloylquinic acid or burkinabin B and 4,5-*O*-divanilloylquinic acid or burkinabin C respectively), with antisickling properties.[45] The investigations of Ouattara *et al*. also demonstrated that burkinabin C, the most abundant burkinabin in the plant, had the same range of activity as the reference drug, cromoglycate. These results could further validate the hypothesis of Elujoba

and Sofowora,[93] which stipulated that antisickling compounds in *Fagara* sp. require a single benzene ring, a carboxylic acid and an electron rich group in the benzoic acid series. However, Ouattara *et al*. could further show that compounds with two aromatic rings are also active. Even though other phenolics contained in the plant could also participate in the antisickling activity,[94] such compounds were only present in minute quantities in the plant material investigated.[45] The report of Ouattara *et al*. was the first report of the antisickling properties of these divanilloylquinic acid derivatives. The conclusions drawn could further support the traditional use of *F. zanthoxyloides* and would encourage the development of "improved traditional medicines" containing this plant in sickle cell disease management.

Alkaloids (**65** to **70**) derived from *Crinum* sp. (*C. glaucum* and *C. jagus*), from the Amaryllidaceae family, have demonstrated acetylcholinesterase inhibition.[95-97] This may be a justifiable reason why the plants are being used for the treatment of convulsions among other ailments. Specifically, *C. glaucum* is used in the treatment of cough, asthma, and convulsions in Nigeria,[95,96] while *C. jagus* is used either singly or in a combination with *Chromoleana odorata* and *Emilia prateramisa* (both of Asteraceae family) in the treatment of all forms of convulsion.[97] The most active isolated alkaloid is hamayne (**69**, IC_{50} = 250 µM) and lycorine (**67**, IC_{50} = 450 µM), while the other alkaloids were comparatively inactive, with haemanthamane (**68**) giving 3% inhibition and crinamine (**70**) giving 4.4% inhibition at 50 mg mL^{-1} (174 µM). These results contrast with the positive control physostigmine which gave IC_{50} of 0.25 µM. Thus, cholinesterase activity appears to be associated with the presence of two free hydroxy groups in this structural type of Amaryllidaceae alkaloids. Crinamine has also been isolated from the aerial parts of the Asian subspecies *C. asiaticum* var. *japonicum*, together with lycorine, norgalanthamine and epinorgalanthamine.[98] The compound showed potent dose dependent inhibition (IC_{50} = 2.7 µM) of hypoxia-inducible factor (HIF-1α) in a cell-based reporter gene assay.[98] The other components of the Asian subspecies (from Korea) showed no significant inhibition of HIF-1α induced transcriptional activity.

As part of the investigations of the medicinal value of plants from the Loranthaceae family in Nigeria, the results of Omeje *et al*. showed that the immunostimulatory activities of lupinine (**71**) and the sesquiterpene 2,3-dimethoxy-benzo[*a,b*]cyclopentenyl-3',3',5'-trimethylpyran-4-carboxylic acid (**158**) from *Loranthus micranthus* could justify the use of the plant leaves in the treatment of several diseases including immune-modifying diseases.[99]

Enantia chlorantha is an ornamental tree of the Annonaceae family, whose stem bark is used against fever/malaria by traditional medicine practitioners in the forest regions,[6c] in addition to its use in the treatment of jaundice, dysentery, hypertension, inflammation, and liver-related diseases.[100] The isolated compounds palmatine (**72**) and jatrorrhizine (**73**) are known to exhibit anti-malarial activity,[101] while palmatine (**72**) also has weak *in vitro* activity against flavivirus.[102] From the stem bark and seeds of *Picralima nitida* (Apocynaceae), a plant used in the treatment of malaria and in the management of pains and other ailments,[103,104] seven (7) compounds with anti-malarial properties, including; akuammicine (**74**), akuammine (**75**), alstonine (**76**), picratidine (**77**) picranitidine (**78**) and ψ-akuammigine (**79**) have been isolated. The extract showed potent and dose-dependent anti-inflammatory, anti-pyretic and anti-malarial activities. Given intraperitoneally, this extract inhibited carrageenan-induced rat paw oedema with IC_{50} of 102 mg kg^{-1}, and with the highest dose tested (300 mg kg^{-1}) producing 72.2% inhibition. On the LPS-induced pyrexia in rabbits, 50 mg kg^{-1} of the extract produced a mean percentage antipyrexia of (38.7%) compared with (29.0%) by 200 mg kg^{-1} of aspirin. In a 4-day *in vivo* schizontocidal test in mice infected with *P. berghei berghei*, up to 300 mg kg^{-1} daily for 4 days was ineffective in preventing the development of parasitaemia or the consequent mortality. However, marked inhibitory activity was obtained on multi-drug resistant human *P. falciparium* parasites cultured *in vitro*. The dose causing 50% inhibition of parasite growth was 1.75 µg mL^{-1}, compared with 0.14 µg mL^{-1} for Chloroquine. The results justify the use of this plant by natives of West Africa in the treatment of malaria. Akuammidine (**78'**) and ψ-akuammigine (**79**), are known to be potent µ-opioid agonists, although not particularly selective.[105] An enterprising Ghanaian hospital has started manufacturing standardised 250 mg capsules of the powdered *P. nitida* seed, and they are being commercialised around the country where they have become widely accepted as a safe and effective pain relief products.

Guiera senegalensis (Combretaceae) is often used in Nigeria for the treatment of malaria. The leaf extract of the plant harvested in Nigeria showed positive anti-malarial activity *in vitro* in *Plasmodium yoelii nigeriensis*.[106] The alkaloids harman (**80**) and tetrahydroharman (**81**) and the methoxylated naphthalene derivative guieranone A (**159**) were shown to be the active principles from this species harvested in Mali and São Tomé[107,108] in addition to the antifungal activity of compound **159**.[109] The presence and anti-plasmodial property of the alkaloid fagaronine (**82**), with an IC_{50} of 0.018 µM against the 3D7 strain of *P. falciparum*, in *Fagara zanthoxyloides* (Rutaceae), could explain why the roots of this plant are used in preparations against malaria, among other applications in ATM.[110]

Ajaiyeoba *et al*. also reported the use of the leaves and stem bark of *Cassia siamea* in the treatment of malaria.[111] Investigation of the leaves of this plant led to the isolation of the active ingredient cassiarin A (**83**), along with emodin (**168**) and lupeol (**161**). The IC_{50} values of the isolated compounds were respectively 5.0 µg mL^{-1} against the K1 strain for both emodin and lupeol, while an IC_{50} value of 0.02 µM was recorded for cassiarin A.[112,113] In Asian traditional folk medicine, the stem bark of *Cassia siamea* is used as a mild,

pleasant, safe purgative; a decoction of the bark is given to treat diabetes; a paste is used as a dressing for ringworm and chilblains; the roots are used as an antipyretic; and the leaves are used for the treatment of constipation, hypertension, and insomnia.[112] The vasodilator effect of cassiarin A (**83**), could explain the use of this plant in the treatment of hypertension, amongst other ailments.[113,114] Mayumbine (**103**), an isomer of ajmalicine (**104**), is a naturally occurring heteroyohimbine, which was isolated from *Rauwolfia vomitoria* extracts, a plant used in Ghana to treat sexual weakness. This compound was shown to have potency (IC_{50} = 76 ± 3.5 nM) against the *in vitro* binding of ^{3}H-diazepam to the benzodiazepine sites within the rat gamma-amino-butyric acid ($GABA_A$) receptor complex.[115] From the study of Ai *et al.*,[115] it is obvious that the substitutions at the E-ring of the heteroyohimbine structure determine the binding activity towards the $GABA_A$/Benzodiazepine (BZD) receptor, since structurally related compounds such as yohimbine **(64)** and reserpine are inactive at the BZD receptor.[116] The potency of mayumbine (**103**) to displace ^{3}H-Diaz binding in cortex, cerebellum and hippocampus suggests that mayumbine does not distinguish between different BZD receptor subtypes expressed in these brain areas. This could offer some explanation why the plant is used in the treatment of sexual weakness in ATM.[115]

4.2 Flavonoids

The summary of the most important findings on bioactive flavonoids from West African flora are given in Table 3. *Hoslundia opposita* (Lamiacea) is a widely distributed shrub in West Africa.[46,117] This plant has also been found in Southern Africa[118] and Central Africa.[119] Various parts of the plant are popular remedies for, inter alia, snake bites, herpes, conjunctivitis, epilepsy, chest pain, yellow fever, stomach troubles, and mental disorders. Infusions of its leaves have found wide use in traditional medicine as a purgative, diuretic, febrifuge, antibiotic and antiseptic. From the leaves of the plant harvested from West Africa, pyrone and unusual furanone substituted flavones (**43** and **44**) have been isolated by Salame *et al.*, along with the known methylpyranoflavonic analogues hosloppin (**129**), hoslundin (**130**), 5-*O*-methylhoslundin (**131**) and oppositin (**132**).[46] The Southern African species gave three known compounds; 5,7-dimethoxy-6-methylflavone, hoslunddiol and euscaphic acid[118] while the Central African species originally gave hoslundin (**130**), hoslundal and hoslunddiol.[119] It was observed that 5,7-dimethoxy-6-methylflavone inhibits the HIV-1 reverse transcriptase enzyme by 52% at 100 µg mL^{-1} while euscaphic acid was found to exhibit a minimum inhibitory concentration (MIC) of 50 µg mL^{-1} against a drug-sensitive, H37Rv, reference strain (27294) of *Mycobacterium tuberculosis*. Of the compounds isolated from the plant harvested from West Africa, oppositin and 5-*O*-methylhoslunfuranine (**44**) exhibited leishmanicidal potential in the micromolar range.[48] Both compounds also demonstrated significant activity against *Trypanosoma brucei brucei*.[48]

Ixora coccinea (Rubiaceae) is used to treat a variety of infections, including hypertension, menstrual irregularities, sprains, chronic ulcers and skin diseases.[120] Idowu *et al.* identified a doubly linked, A-type proanthocyanidin trimer (ixoratannin A2, **96**), along with other constituents from the leaves of the plant.[120] The antioxidant and antibacterial properties of the identified compounds (**96**, **105**, **142-146)** were also investigated. All tested compounds inhibited the growth of *B. subtilis*, while only epicatechin (**142**) and quercetin-3-*O*-α-L-rhamnopyranoside (**105**) inhibited the growth of *E. coli*. Antioxidant evaluation of isolated compounds revealed that ixoratannin A-2 (**96**) and cinnamtannin B-1 (**160**) were the most active compounds in DPPH, inhibition of lipid peroxidation and nitric oxide radical scavenging assays. This could explain why the plant is effective in the treatment of chronic ulcers. *Pavetta crassipes* (Rubiaceae) has been used in handling respiratory infections and abdominal disorders,[121] A bioactive flavonoid (quercetin-3-*O*-rutinoside, **105**) has been isolated from the aqueous extract of *P. crassipes* leaves, which showed activity against some pathogenic microorganisms, including *Streptococcus pyogenes*, *Corynebacterium ulcerans*, *Klebsiella pneumoniae*, *Neisseria gonorrhoeae*, *Pseudomonas aeruginosa*, and *Escherichia coli* at a concentration < 50 µg mL^{-1}.[121] Compound **105** had MIC values ranging from 6.25 to 12.5 µg mL^{-1} and minimum bactericidal concentrations (MBC) ranging from 12.5 to 25 µg mL^{-1}. This supports the ethnomedicinal use of the plant in the treatment of respiratory infections and abdominal disorders.[121]

Ximenia americana is a medicinal bushy, spiny shrub or small tree used in Mali and other West African countries for the treatment of various diseases, the most common being infectious and inflammatory ailments.[77] Fractionation of the ethanol extract led to the isolation and identification of the cyanogenic glycoside sambunigrin (**58**), along with gallic acid (**57**) and the gallotannins; β-glucogalline and 1,6-digalloyl-β-glucopyranose. The flavonoids quercetin (**114**), quercitrin or quercetin-3-O-α-rhamnopyranoside (**107**), avicularin or quercetin-3-O-α-arabinofuranoside (**108**), quercetin-3-O-β-xylopyranoside (**109**), quercetin-3-*O*-(6''-galloyl)-β-glucopyranoside (**110**) and kaempferol-3-*O*-(6''-galloyl)-β-glucopyranoside (**111**) were also isolated. The flavonoids were active both as enzyme inhibitors and DPPH radical scavengers. Sambunigrin (**58**) was the main compound in the EtOAc soluble fraction of the alcoholic extract of *X. americana* leaves and the identified compounds may give a rationale for the traditional use of *X. americana* in Mali, since traditional healers interviewed reported the use against throat infections, amenorrhea, as tonic, for wound healing and against pain.[77]

Bryophyllum pinnatum (Crassulaceae) has diverse uses in ATM. The flavonoid luteolin (**141**), epigallocatechin 3-*O*-syringate (**112**) and gallic acid (**57**) have been identified as the active principles responsible for the antibacterial activity of this plant, which explains why it is used in many West African

traditional medicinal recipes for the treatment of ulcers.[122] The main antibacterial constituent was found to be free gallic acid (**57**), which accounted for about 0.014 % w/w of the fresh aerial part. However, luteolin (**141**) and a new acylated flavan-3-ol, epigallocatechin-3-*O*-syringate, were isolated as minor constituents in the active fraction. Luteolin exhibits a wide range of biological activities, including antioxidant activity promotion of carbohydrate metabolism, and immune system modulation. Other *in vitro* studies suggest that luteolin has anti-inflammatory activity,[123,124] and that it acts as a monoamine transporter activator,[125] a phosphodiesterase inhibitor[126] and an interleukin 6 inhibitor.[123] *In vivo* studies show that luteolin affects xylazine/ketamine-induced anesthesia in mice.[126] *In vitro* and *in vivo* experiments also suggest that the compound may inhibit the development of skin cancer.[127]

The plant *Byrsocarpus coccineus* (Connaraceae) is indigenous to Africa, especially Togo, Ghana and Nigeria.[128] This plant has diverse uses in ATM, including the treatment of venereal diseases, as an antidote to arrow poisoning and as a remedy for diarrhoea.[129] Ahmadu *et al*. have investigated the bioactive ethyl acetate and *n*-butanol soluble parts of an ethanolic extract of leaves of this plant and led to the isolation of three flavonoid glycosides identified as quercetin 3-O-α-arabinoside (**113**), quercetin (**114**) and quercetin 3-β-*D*-glucoside (**115**).[130] It may be interesting to test these compounds against a wide range of bacteria responsible for the aforementioned ailments. Vassallo *et al*. also investigated antioxidant flavonoid glycosides from *Chrozophora senegalensis*, also known as *Croton senegalensis* (Euphorbiaceae) harvested in Mali.[131] It is a small tree widely distributed in Mali where it grows wild and is used in folk medicine for the treatment of diarrhea, rheumatism, teniasis, stomach ache, rachitis, and venereal diseases. The leaf and root decoctions are also drunk for hairloss.[132] In order to justify the ethnobotanical use of *C. senegalensis*, the leaf extracts were assayed for *in vitro* antioxidant activity. Bioassay-guided fractionation revealed the methanol extract to be active. Separation of this extract led to the isolation of three new flavonoids (**116** - **118**), along with known flavonoids (**119** - **122** and **124**), a phenolic derivative and three megastigmane glycosides. All isolated compounds were tested for their antioxidant activity on DPPH stable radical, superoxide anion, metal chelating activity, and DNA cleavage induced by the photolysis of H_2O_2. Compound **116**, quercetin 3'-methyl ether-3-*O*-α-*L*-rhamnopyranoside (**119**), and 4'''-methyl ether amenthoflavone (**124**) exhibited the highest antioxidant capacity being also able to modulate hydroxyl radical formation more efficiently than other compounds acting as direct hydroxyl radical scavengers and chelating iron.[131]

Cajanus cajan or pigeon pea is a perennial member of the family Fabaceae. The leaves are used as a weak decoction for the treatment of measles, malaria, catarrh, hepatitis and cancer.[133] An aqueous infusion of the seeds sometimes mixed with the leaves is dispensed for the management of sickle-cell anaemia.[134] The seed extract has been shown to possess hypoglycaemic and antimicrobial activities,[135] as well as demonstrated activity against the chloroquine-sensitive *P. falciparum* strain (3D7).[136] Shode *et al*. demonstrated that phenylalanine is the predominant antisickling agent in the seed extract of *C. cajan*.[137] In the course of examining the rationale behind the use of this plant in the treatment of cancer, Ashidi *et al*. isolated six compounds from the dichloromethane fraction; hexadecanoic acid methyl ester, α-amyrin, β-sitosterol, the flavonoid pinostrobin (**125**), as well as the stilbenoids longistylin A (**162**) and longistylin C (**163**).[133] Pinostrobin and longistylins A and C were tested for cytotoxicity on the cancer cell lines. In addition, an adriamycin-sensitive acute T-lymphoblastic leukaemia cell line (CCRF-CEM) and its multidrug-resistant sub-line (CEM/ADR5000) were used in an XTT assay to evaluate the activity of the pure compounds obtained. It was observed that the dichloromethane fraction of *C. cajan* had IC_{50} value 5–10 µg mL^{-1}, with the two constituent stilbenes, longistylins A and C, being primarily responsible, with IC_{50} values of 0.7–14.7 µM against the range of cancer cell lines. Ajaiyeoba *et al*. recently examined the antiplasmodial components of the plant and their study led to the isolation of cajachalcone or 2',6'-dihydroxy-4-methoxy chalcone (**126**), as the biologically active constituent from the ethyl acetate fraction. Cajachalcone had an IC_{50} value of 2.0 µg mL^{-1} (7.4 µM) and could be a lead for anti-malarial drug discovery.[138]

The leaves of *Chromolaena odorata* (Asteraceae) are exploited extensively in West and Central African ethnopharmacy for the treatment of a wide range of conditions, including the treatment of malaria, abdominal, cervical pain, and of wounds as a local antiseptic and antiinflammatory agent.[139] Kouamé *et al*. isolated 5-hydroxy-7,4'-dimethoxyflavanone (**127**) and 2'-hydroxy-4,4',5',6'-tetramethoxychalcone (**128**), along with 1,6-dimethyl-4-(1-methylethyl)naphthalene (cadalene) from the hexane-soluble fraction of the leaf extract of the plant and tested their impact on the viability and clonogenicity of cancer cell lines.[140] All three compounds were tested for their cytotoxicity and anticancer properties. Compound **128** was found to be both cytotoxic and anticlonogenic at 20 µM in Cal51, MCF7 and MDAMB-468 cell lines, and to act synergistically with the Bcl2 inhibitor ABT737 to enhance apoptosis in Cal51 breast cancer cells.[140]

The flowers, fruits, leaves and stem bark of *Spathodea campanulata* (Bignoniaceae), popularly known as African tulip tree, are used in the treatment of several diseases (ulcers, dysentery, oedemas, skin eruptions, scabies, wound healing and urethral discharge), in addition to veterinary applications.[6c] Kaempferol 3-*O*-β-*D*-(2-*O*-β-*D*-glucopyranosyl) glucopyranoside (**133**) has been isolated from this plant, along with ursolic acid (**164**), verminoside (**159**), specioside (**165**) and caffeic acid (**166**).[141] The antioxidant activities of these compounds, isolated from the flowers, fruits, leaf and stem bark of the same plant have been investigated by Elusiyan *et al*.[141] The results show that the antioxidant principles isolated from the various parts of the plant are verminoside, from the leaves, stem bark

and flowers (EC_{50} = 2.04 μg mL^{-1}), specioside, from the flowers (EC_{50} = 17.44 μg mL^{-1}), kaempferol diglucoside (**133**), from the leaves (EC_{50} = 8.87 μg mL^{-1}) and caffeic acid (**166**), from the leaves and fruits.[141] Flavonoid glycosides exhibiting antioxidant activities have also been isolated from *Securinega virosa* (Euphorbiaceae) harvested in Mali.[142] This plant has been used traditionally in the treatment of many diseases, including diarrhea, rheumatism, malaria, liver disease, inflammation and pain. Extracts of the plant are used for the expulsion of worms and in the treatment of bilharziasis, and for other urinary and genital tract disorders.[143] Kaempferol 3-*O*-(4-galloyl)-β-*D*-glucopyranoside (**134**), quercetin-3-*O*-β-*D*-glucopyranoside (**135**), corilagin (**136**), 11-*O*-caffeoylbergenin (**137**), glucogallin (**138**), geraniin (**139**) were isolated. *In vitro* biological analysis of the isolated compounds showed that they were able to quench DPPH radicals and had a direct scavenging activity on superoxide anion. Kaempferol 3-*O*-(4-galloyl)-β-*D*-glucopyranoside, 11-*O*-caffeoylbergenin, and glucogallin exhibited the highest antioxidant capacity, being also able to modulate hydroxyl radical formation more efficiently than the other compounds, acting as direct hydroxyl radical scavengers and chelating iron.[142] The flavonoid glycoside AFF1 or 3,5,7,3'-tetrahydroxyflavone-3-*O*-α-*L*-rhamnoside (**140**) was isolated from *Alchornea floribunda* (Euphorbiaceae) from Nigeria. The leaves of this plant are traditionally used as a remedy for arthritis, muscle pain and other inflammatory disorders. Okoye *et al*. demonstrated that the anti-inflammatory activity of this compound could justify the aforementioned uses of this plant in ATM.[144,145] The anti-inflammatory activity (50 mg kg^{-1}) of this compound was higher than that of the standard anti-inflammatory drug, aspirin (100 mg kg^{-1}). The compound also significantly ($p < 0.001$) inhibited heat-induced haemolysis of human erythrocytes *in vitro*.[109] These results demonstrated that the anti-inflammatory activity of *A. floribunda* leaves may be, in part, a result of the flavonol glycoside, compound **140**. The antifeedant activity of hesperidin (**147**), isolated from *Fagara macrophylla* from Guinea, gives further arguements towards the justification of the use of the plant in arrow poisoning among other uses.[46]

Chaabi *et al*. have also isolated some acylated flavonol pentaglycosides from the leaves of *Baphia nitida* (Fabaceae), a plant whose leaves are used traditionally in many African countries, particularly for gastro-intestinal complaints.[146] Two new acylated flavonol pentaglycosides were isolated from the butanolic extract of *B. nitida* leaves and identified to be kaempferol 3-O-β-*D*-xylopyranosyl(1→3)-(4-*O*-*E*-*p*-coumaroyl-α-L-rhamnopyranosyl(1→2))[β-*D*-glucopyranosyl(1→6)]- β-*D*-galactopyranoside-7-*O*-α-*L*-rhamnopyranoside (**148**) and kaempferol 3-O-β-*D*-xylopyranosyl(1→3)- (4-O-Z-*p*-coumaroyl-α-L-rhamnopyranosyl(1→2))[β-*D*-glucopyranosyl(1→6)]-β-*D*-galactopyranoside- 7-O-α-*L*-rhamnopyranoside (**149**) The antioxidant activity of the two compounds was assessed in the peroxynitrite assay. Compounds **148** and **149** displayed mild antioxidant activities in the *in vitro* peroxynitrite assay with EC_{50} values of 62 ± 9.3 μM and 19 ± 2.9 μM, respectively. These values were higher than those of the reference compound, gallic acid (4.9 ± 0.4 μM). The isomeric difference of activity might be explained by the higher reactivity of *cis*, compared to *trans* bonds.[146]

Piliostigma thonningii (Caesalpiniaceae) is a tropical African plant used to treat a variety of infections, fever and inflammatory conditions.[89] Ibewuike *et al*. investigated the anti-inflammatory and antibacterial activities of *C*-methylflavonols (**150 - 157**) from the leaves of the plant and tested the isolated compounds for their ability to inhibit prostaglandin synthesis *in vitro* and antibacterial activity against *Staphylococcus aureus*.[147] From their results, it was observed that the influence of the B ring 3',4' diol group on the activity of *C*-methylflavonols in the inhibition of prostaglandin synthesis differ from that observed for a series of flavonoids without *C*-methyl groups. The antibacterial activity in the series mirrors those of methylated antimicrobial flavonoids. The traditional uses of the plant in the treatment of infections and inflammatory conditions were rationalized on the basis of the activities of the isolated compounds.[147]

Garcinia kola (Clusiaceae) is an African medicinal plant known for its use as chewing sticks in maintaining oral health.[148] The use of the trunk and roots as chewing stick is reported to lower the rate of dental caries and provide better general oral health to its users than non-users. It is believed that the positive effects of chewing stick could be partly attributed to the antimicrobial substances present in the stick. The biflavonoid 3'',4',4''',5,5'',7,7''-heptahydroxy-3,8''-biflavanone, otherwise known as GB1 (**167**) has been isolated from this plant, as the major constituent of the antibacterial fraction of the stem bark.[148a] This biflavonoid has shown antibacterial activities against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) with MIC of 32 and 128 μg mL^{-1}, respectively,[148b] as well as activity against *Streptococcus mutans* and other oral bacteria with minimum inhibitory concentration (MIC) values from 32 to 64 μg mL^{-1}.[148c] GB1 also exhibited α-glucosidase and aromatase inhibitory activities, as well as antiplasmodial activity, but was not toxic against cell lines tested.[148a] It could therefore be inferred that GB1 may be a potential dietary supplement or phytomedicine for the prevention of breast cancer and type 2 diabetes mellitus.

5 Conclusions

This review focused on NPs derived from medicinal plants from West Africa. The entire study showed that about 700 NPs from 97 plant species grouped into 41 families, exhibiting diverse biological activities. The claim that medicinal plants from West Africa hold a huge potential for drug discovery cannot be disputed. How this potential could be released remains the driving theme of current synergistic efforts for drug discovery by Africans for Africans, both on the continent and in the Diaspora. The exploitation of data from medicinal plants for

drugs will require a synergy between academia and industry, since this is currently almost inexistent in this part of the World. Our observations are that almost all of the research is inadequately funded. Existing funding sources include university grants to research staff, funding schemes targeting laboratories in the South like the Third World Academy of Sciences (TWAS), the International Foundation for Science (IFS), the International Society for Infectious Diseases (ISID), just to mention these ones. Such funding programs are usually geared towards providing basic supplies like the procurement of plant samples, solvents, reagents, basic tools and national travel costs. The acquisition and/or repair of heavy instrumentation are not often considered. 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, mainly for sample analysis, since modern analytical instrumentation like IR, Mass, NMR, etc., spectrometers are grossly absent in African laboratories.

Much of the research efforts, whose results have been discussed in this review paper, were also funded *via* collaborative programs tailored such that the African researchers play the role of plant sample collectors. This is because the most equipped laboratories in Africa barely host enough instrumentation to be able to perform extractions and purifications. A bulk of the published work from West Africa has followed the last mentioned scheme. The authors of this review do not envisage this approach as research towards the development of African researchers and African institutions, since the analysis and almost all the screening results are determined in the laboratories of developed countries (Europe and North America) and some countries with transition economies like Brazil, India and China *via* the TWAS funding scheme. The African often travels abroad with samples from an entire research team for analysis and/or screening (samples are often barely enough for both purposes) and returns home with a scientific publication, most often without samples for further analysis/testing. This may partly explain why so much data has been made available, but very little exploitation and implementation has followed. A detailed analysis of the African scene in terms of biomedical and NP research is beyond the scope of this review. However, the empowerment of African researchers and research institutions *via* synergistic networks like the ANDI[149,150] may be the promising way forward. This entails the strengthening of intra-continental efforts and adopting governmental funding schemes that target research towards the validation and implementation of results aimed at making African-driven research products available to the local populations at affordable costs. One laudible effort from the African continent has been to collect physical sample of NPs at a site, which could be directly available for bioassays.[151] Such an agenda will greatly enhance drug discovery efforts from the continent.

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7 Notes and references

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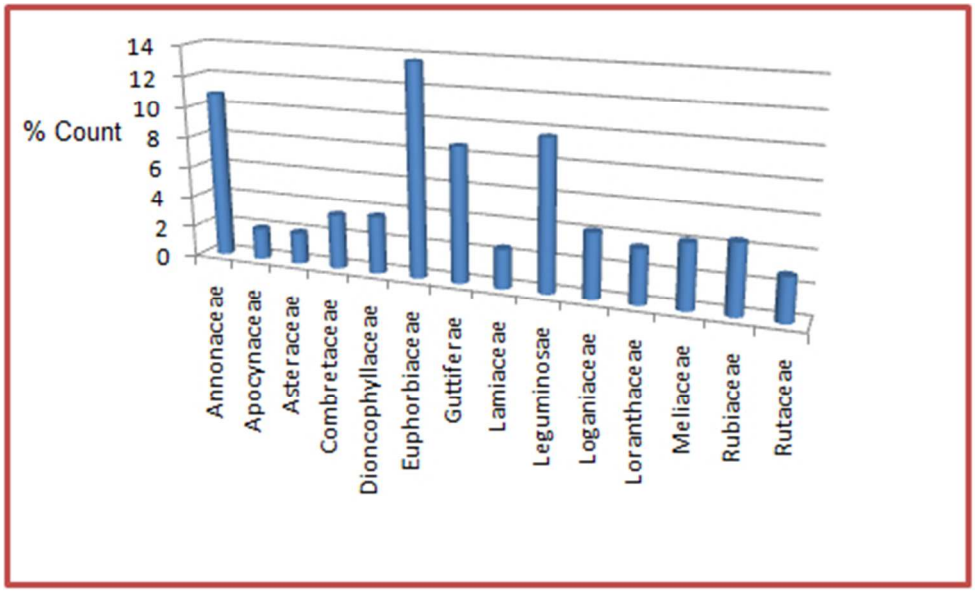
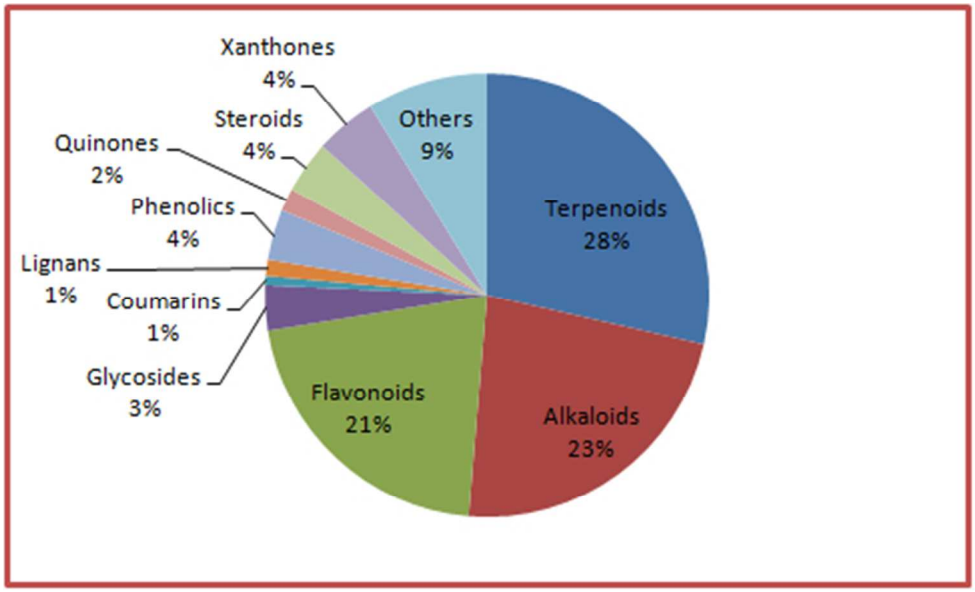
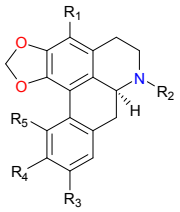


Bar chart showing the distribution of percentage number of compounds isolated per plant family.

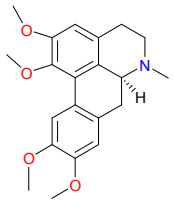


Pie chart showing the distribution of number of compounds isolated per class

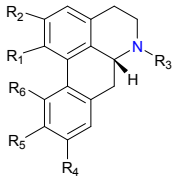


	R_1	R_2	R_3	R_4	R_5
Actinodaphnine (**1**)	H	H	OH	OCH_3	H
Cassythine (**2**)	OCH_3	H	OH	OCH_3	H
Dicentrine (**3**)	H	CH_3	OCH_3	OCH_3	H
Norneolitsine (**4**)	H	H	-O-CH_2-O-		H
Neolitsine (**5**)	H	CH_3	-O-CH_2-O-		H
Cassythidine (**6**)	OCH_3	H	-O-CH_2-O-		H
(+)-anolobine (**8**)	H	H	OH	H	H

Aporphine alkaloids (**1** to **6** and **8**)

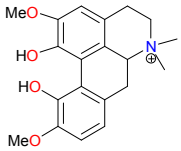


Glaucine (**7**)

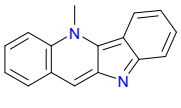


	R_1	R_2	R_3	R_4	R_5	R_6
(-)-Litseferine (**9**)	-O-CH_2-O-		H	OCH_3	OH	H
(-)-Anolobine (**10**)	-O-CH_2-O-		H	OH	H	H
(-)-Roemeroline (**11**)	-O-CH_2-O-		CH_3	OH	H	H
(-)-Norlirioferine (**12**)	OCH_3	OCH_3	H	OCH_3	OH	H
(-)-Corydine (**13**)	OH	OCH_3	CH_3	H	OCH_3	OCH_3

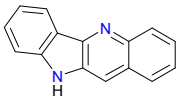
Aporphine alkaloids (**9** to **13**)



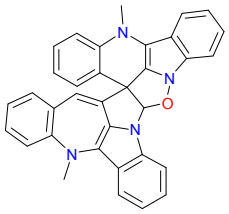
Magnoflorine (**14**)



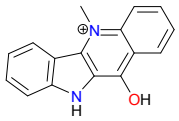
Cryptolepine (**15**)



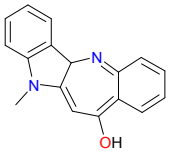
Quindoline (**16**)



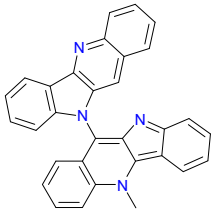
Cryptospirolepine (**17**)



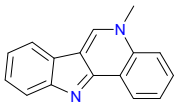
Hydroxycryptolepine (**18**)



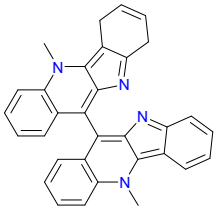
Cryptoheptine (**19**)



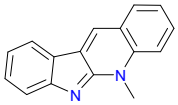
Cryptoquindoline (**20**)



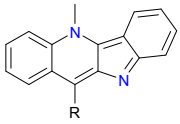
Isocryptolepine (**21**)



Biscryptolepine (**22**)



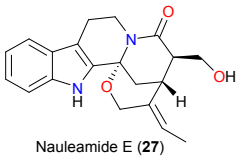
Neocryptolepine (**23**)



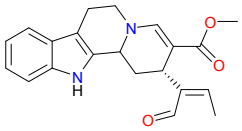
Cryptolepinoic acid (**24**): R = COOH

Methyl cryptolepinoate (**25**): R = $COOCH_3$

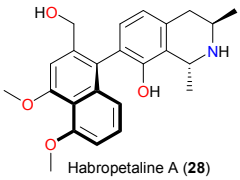
Ethyl cryptolepinoate (**26**): R = $COOCH_2CH_3$



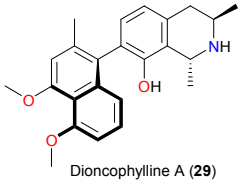
Nauleamide E (**27**)



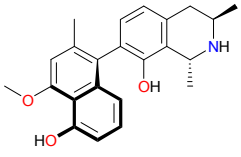
Vallesiachotamine (**27'**)



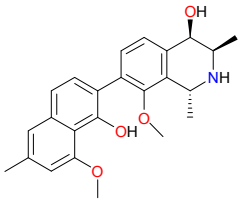
Habropetaline A (**28**)



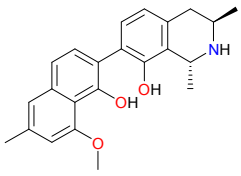
Dioncophylline A (**29**)



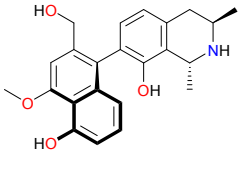
5'-*O*-Demethyl-dioncophylline A (**30**)



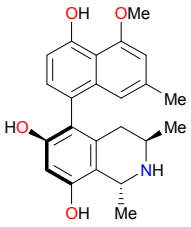
8-*O*-Methyldioncophyllinol B (**31**)



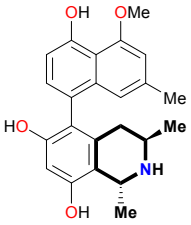
Dioncophylline B (**32**)



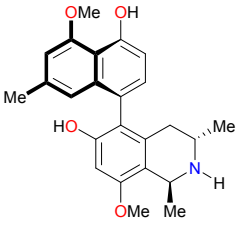
Dioncopeltine A (**33**)



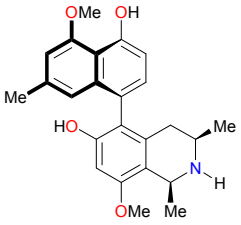
Korupensamine A (**34**)



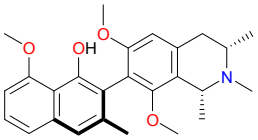
Korupensamine B (**35**)



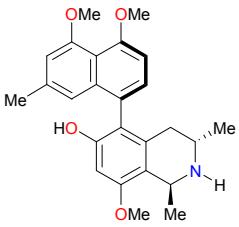
Ancistroguineine A (**36**)



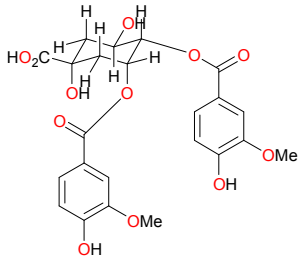
Ancistroguineine B (**37**)



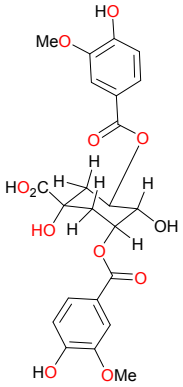
Ancistrotectorine (**38**)



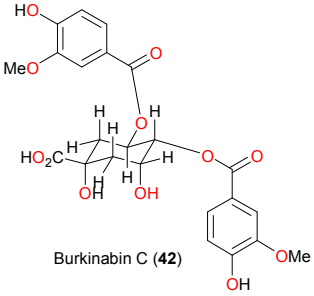
Ancistrobrevine B (**39**)



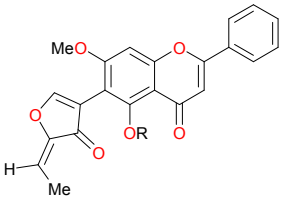
Burkinabin A (**40**)



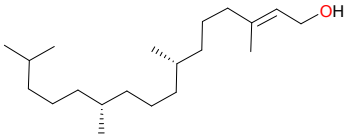
Burkinabin B (**41**)



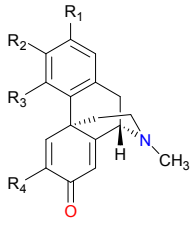
Burkinabin C (**42**)



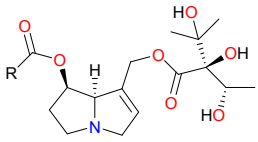
Hoslunfuranine (**43**): R = H
5-*O*-Methylhoslunfuranine (**44**): R = Me



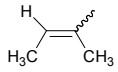
Trans-phytol (**45**)



(-)-Mocrispatine (**46**): R_1 = H, R_2 = Me, R_3 = OH, R_4 = OH
Pallidine (**47**) : R_1 = OH, R_2 = OMe, R_3 = H, R_4 = OMe

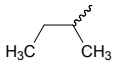


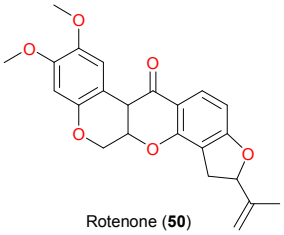
Echimidine (**48**): R =



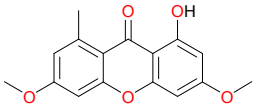
7-(2-Methylbutyryl)-9-echimidinylretronecine (**49**):

R =

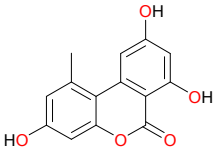




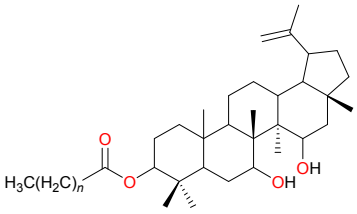
Rotenone (**50**)



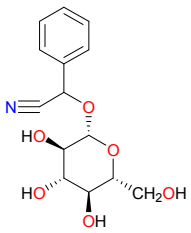
Lichexanthone (**51**)



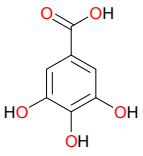
Alternariol (**52**)



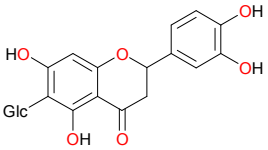
7β, 15α-dihydroxy-lup-20-(29)-en-3β-*O*-palmitate (**53**): *n* = 12
7β, 15α-dihydroxy-lup-20-(29)-en-3β-*O*-stearate (**54**): *n* = 14
7β, 15α-dihydroxy-lup-20-(29)-en-3β-*O*-eicosanoate (**55**): *n* = 16



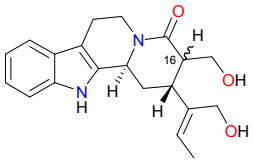
Sambunigrin (**56**)



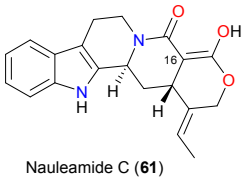
Gallic acid (**57**)



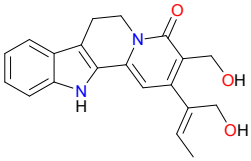
Isoorientin (**58**)



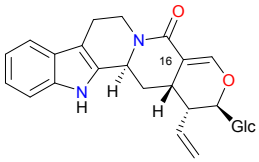
Nauleamide A (**59**): H-16α
Nauleamide B (**60**): H-16β



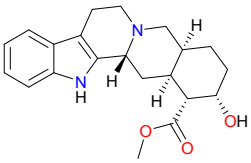
Nauleamide C (**61**)



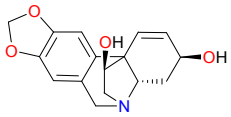
Nauleamide D (**62**)



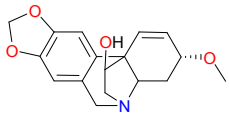
Strictosamide (**63**)



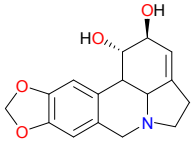
Yohimbine (**64**)



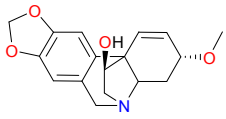
(*S*) Hamayne (**65**)



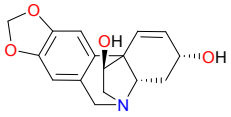
(*R*) Crinamine (**66**)



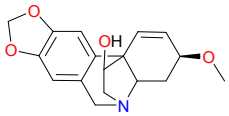
Lycorine (**67**)



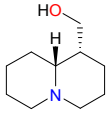
Haemanthamane (**68**)



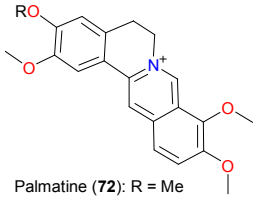
(*R*) Hamayne (**69**)



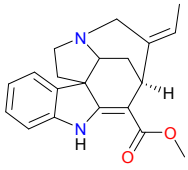
(*S*) Crinamine (**70**)



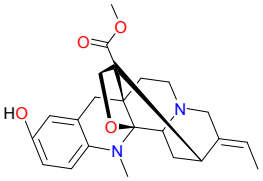
Lupinine (**71**)



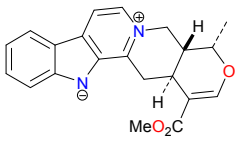
Palmatine (**72**): R = Me
Jatrorrhizine (**73**): R = H



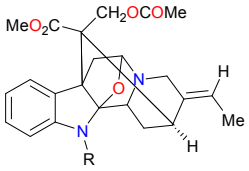
Akuammicine (**74**)



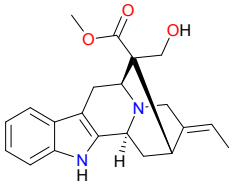
Akuammine (**75**)



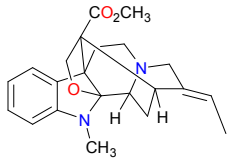
Alstonine (**76**)



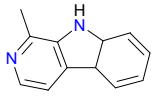
Picratidine (**77**): R = Me
Picranitidine (**78**): R = H



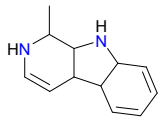
Akuammidine (**78'**)



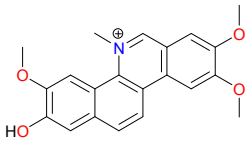
ψ-Akuammigine (**79**)



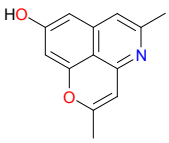
Harman (**80**)



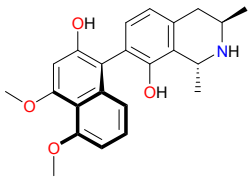
Tetrahydroharman (**81**)



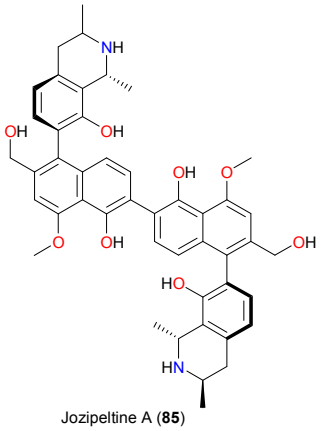
Fagaronine (**82**)



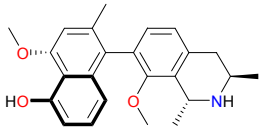
Cassiarin A (**83**)



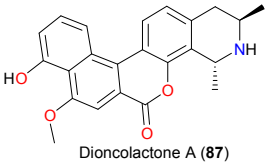
Habropetaline A (**84**)



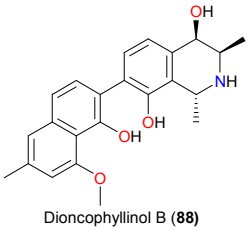
Jozipeltine A (**85**)



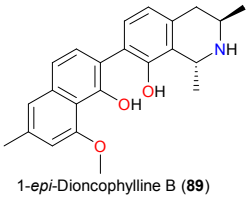
5'-O-Demethyl-8-O-methyl-dioncophylline A (**86**)



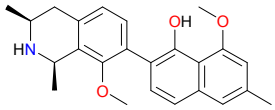
Dioncolactone A (**87**)



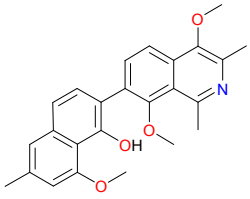
Dioncophyllinol B (**88**)



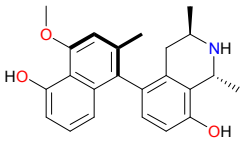
1-*epi*-Dioncophylline B (**89**)



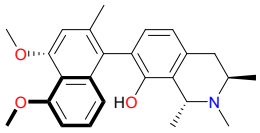
8-*O*-Methyl-1-*epi*-dioncophylline B (**90**)



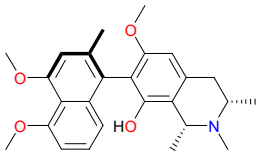
Dioncophyllacine B (**91**)



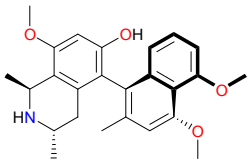
Dioncophylline C (**92**)



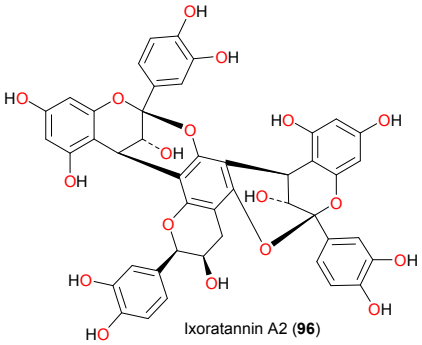
N-Methyldioncophylline A (**93**)



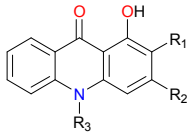
Ancistrobrevine D (**94**)



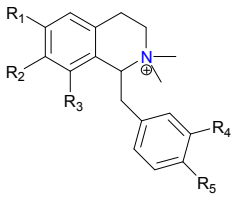
Ancistrocladine (**95**)



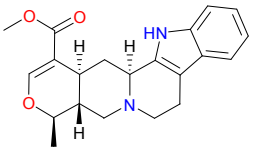
Ixoratannin A2 (**96**)



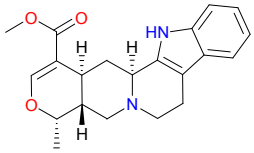
1-Hydroxy-3-methoxy-*N*-methyl-acridone (**97**): R_1 = H, R_2 = OMe, R_3 = Me
Arborinine (**98**): R_1 = OMe, R_2 = OMe, R_3 = Me
Xanthoxoline (**99**): R_1 = OMe, R_2 = OMe, R_3 = H
1-Hydroxy-3-methoxyacridone (**100**): R_1 = H, R_2 = OMe, R_3 = H



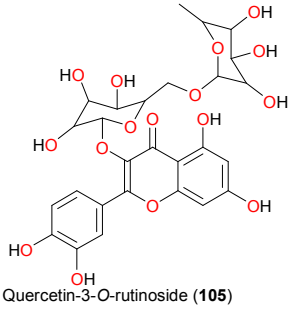
Oblongine (**101**): $R_1 = R_4 = H$, $R_2 = OMe$, $R_3 = R_5 = OH$
Tembetarine (**102**): $R_1 = R_5 = OH$, $R_2 = R_4 = OH$, $R_3 = H$



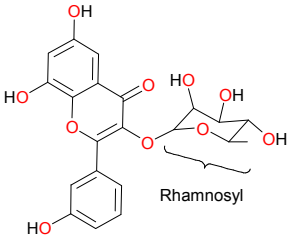
Mayumbine (**103**)



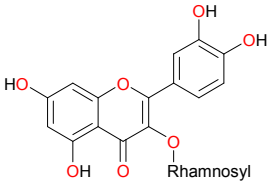
Ajmalicine (**104**)



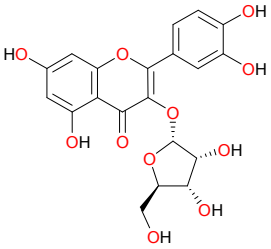
Quercetin-3-*O*-rutinoside (**105**)



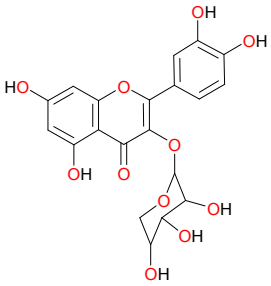
3,5,7,3'-Tetrahydroxyflavone-
3-O-α-L-rhamnoside (**106**)



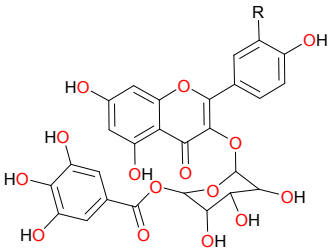
Quercitrin (**107**)



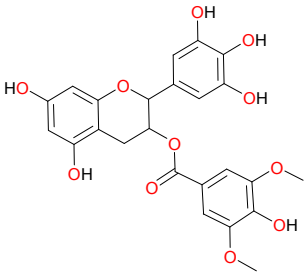
Avicularin (**108**)



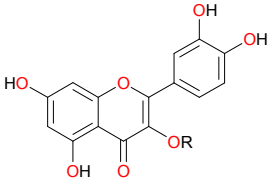
Quercetin-3-O-β-xylopyranoside (**109**)



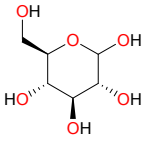
Quercetin-3-O-(6" -galloyl)-β-glucopyranoside (**110**)
R = OH
Kaempferol-3-*O*-(6" -galloyl)-β-glucopyranoside (**111**)
R = H



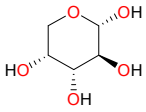
Epigallocatechin 3-*O*-syringate (**112**)



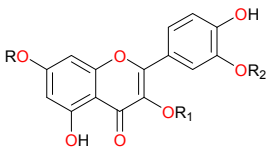
Quercetin-3-*O*-α-arabinoside (**113**): R = α - arabinose
Quercetin (**114**): R = H
Quercetin-3-β-*D*-glucoside (**115**): R = β-D-glucose



D-glucoside



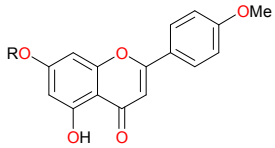
α-arabinoside



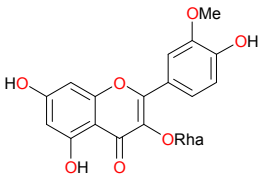
3-*O*-(6''-Caffeoyl)-β-D-glucopyranoside-3'-*O*-β-D-glucopyranoside (**116**): R = H, R_1 = (6''-caffeoyl)Glc, R_2 = Glc

Quercetin 3-methyl ether-7-O-α-L-rhamnopyranosyl-(1→6)-(2''-*p*-coumaroyl)-β-D-glucopyranoside (**117**) :

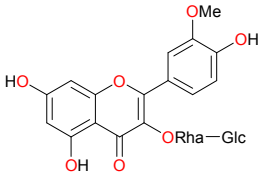
R = (2''-*p*-coumaroyl)-Glc-(6→1)-Rha, R_1 = Me, R_2 = H



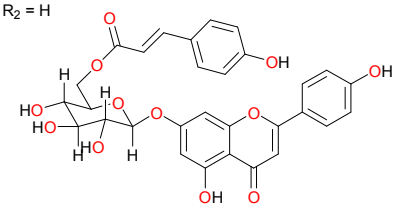
Acacetin 7-O-(6''-*p*-coumaroyl)-β-D-glucopyranoside (**118**): R= (6''-*p*-coumaroyl)Glc



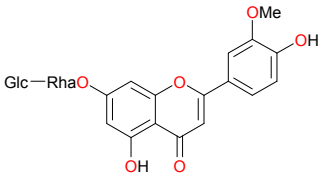
Quercetin 3'-Methyl ether-3-O-α-L-rhamnopyranoside (**119**)



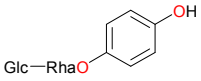
Quercetin 3'-methyl ether-3-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside (**120**)



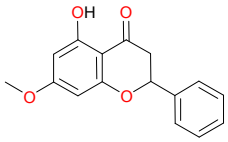
Apigenin 7-*O*-(6''-*p*-coumaroyl)-β-D-glucopyranoside (**121**)



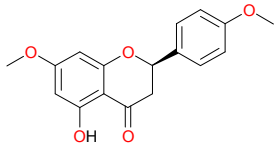
Quercetin 3-methyl ether-7-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside(**122**)



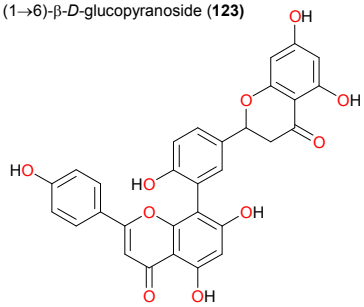
4-Hydroxyphenyl-O-α-L-rhamnopyranosyl-(1→6)-β-*D*-glucopyranoside (**123**)



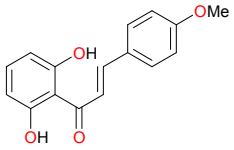
Pinostrobin (**125**)



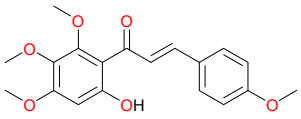
5-Hydroxy-7,4'-dimethoxyflavanone (**127**)



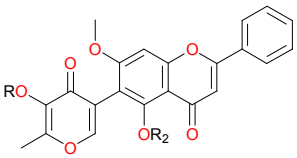
4'''-Methyl ether amenthoflavone (**124**)



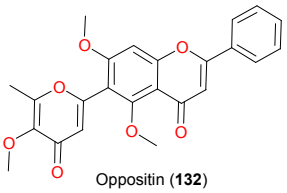
Cajachalcone (**126**)



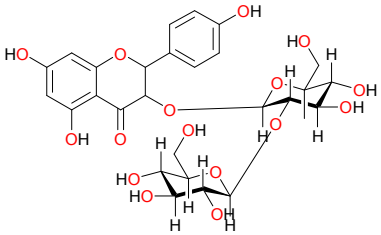
2'-Hydroxy-4,4',5',6'-tetramethoxychalcone (**128**)



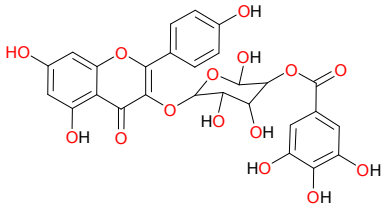
Hosloppin (**129**) R_1=Me, R_2=H
Hoslundin (**130**) R_1=R_2=H
5-*O*-Methylhoslundin (**131**) R_1=H, R_2=Me



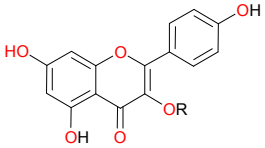
Oppositin (**132**)



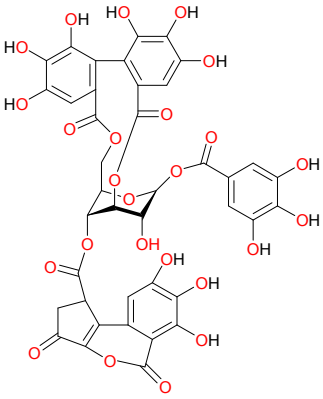
Kaempferol 3-*O*-β–*D*-(2-O-β–D-glucopyranosyl) glucopyranoside (**133**)



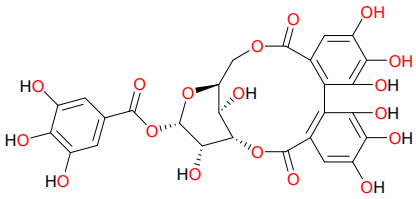
Kaempferol 3-O-(4-galloyl)-β-D-glucopyranoside (**134**)



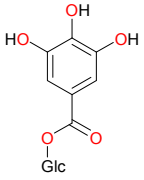
Quercetin-3-O-β-D-glucopyranoside (**135**) R=β-D-Glu



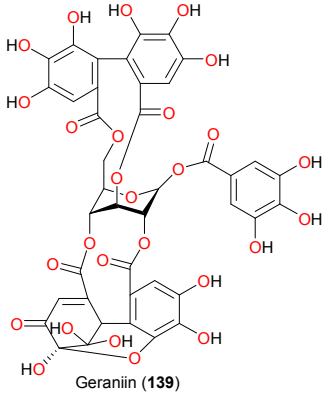
Acalyphidin M (**137**)



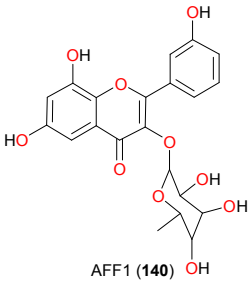
Corilagin (**136**)



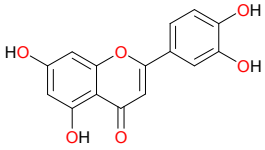
Glucogallin (**138**)



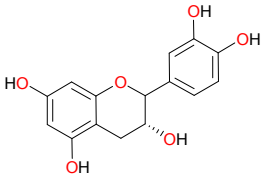
Geraniin (**139**)



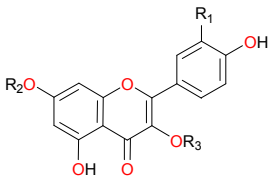
AFF1 (**140**)



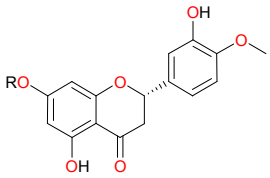
Luteolin (**141**)



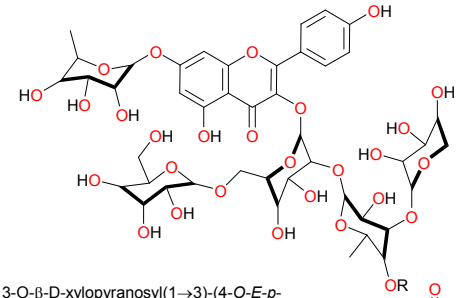
Epicatechin (**142**)



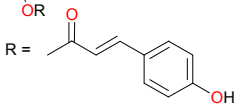
Quercetin-3-O-α-L-rhamnopyranoside (**143**): R_1=OH, R_2=H, R_3=Rha
Kaempferol-3-O-α-L-rhamnoside (**144**): R_1=R_2=H, R_3=Rha
Kaempferol-3,7-O-α-L-dirhamnnoside (**145**): R_1=H, R_2=R_3=Rha
Kaempferol-7-O-α-L-rhamnoside (**146**): R_1=R_3=H, R_2=Rha



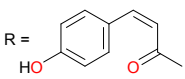
Hesperidin (**147**) R = Glc[6→1]Rham

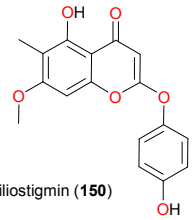


kaempferol 3-O-β-D-xylopyranosyl(1→3)-(4-*O*-*E*-*p*-coumaroyl-α-L-rhamnopyranosyl(1→2))[β-D-glucopyranosyl(1→6)]-β-D-galactopyranoside-7-O-α-L-rhamnopyranoside (**148**)

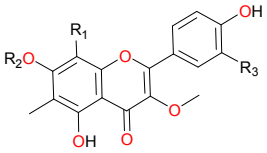


kaempferol 3-O-β-D-xylopyranosyl(1→3)-(4-*O*-*Z*-*p*-coumaroyl-α-L-rhamnopyranosyl(1→2))[β-D-glucopyranosyl(1→6)]-β-D-galactopyranoside-7-O-α-L-rhamnopyranoside (**149**)

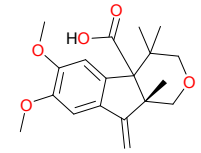




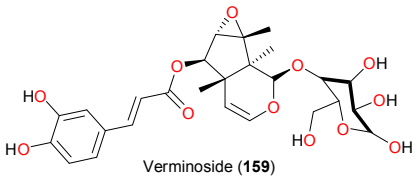
Piliostigmin (**150**)



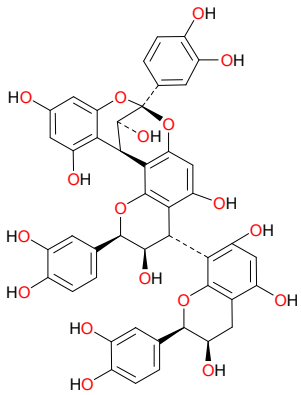
6,8-di-*C*-Methylkaempferol-3,7-dimethyl ether (**151**) R_1=R_2=CH_3, R_3=H
6-*C*-Methylquercetin-3,7,3'-trimethyl ether (**152**) R_1=H, R_2=CH_3, R_3=OCH_3
6-*C*-Methylquercetin-3-methyl ether (**153**) R_1=R_2=H, R_3=OH
6,8-di-*C*-Methylquercetin-3-methyl ether (**154**) R_1=CH_3, R_2=H, R_3=OH
6-*C*-Methylquercetin-3,7-dimethyl ether (**155**) R_1=H, R_2=CH_3, R_3=OH
6,8-di-*C*-Methylquercetin-3,7-dimethyl ether (**156**) R_1=R_2=CH_3, R_3=OH
6,8-di-*C*-Methylkaempferol-3-methyl ether (**157**) R_1=CH_3, R_2=R_3=H



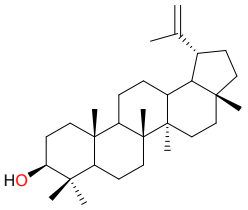
2,3-Dimethoxy-benzo [*a*, *b*] cyclopentenyl-3',3',5'-trimethyl pyran-4-carboxylic acid OR Loaranthoic acid (**158**)



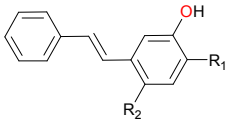
Verminoside (**159**)



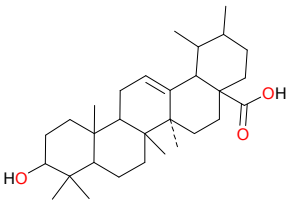
Cinnamtannin B-1 (**160**)



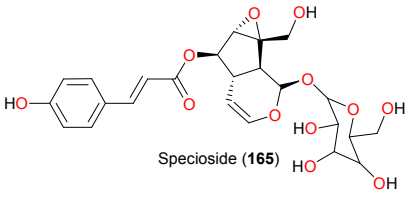
Lupeol (**161**)



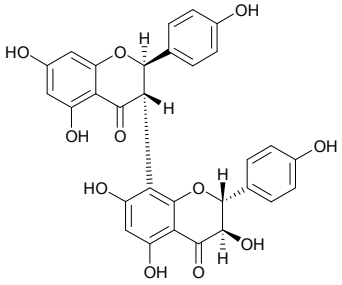
Longistylin A (**162**): R_1 = Prenyl, R_2 = OMe
Longistylin C (**163**): R_1 = OMe, R_2 = Prenyl



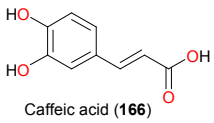
Ursolic acid (**164**)



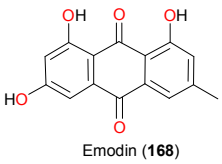
Specioside (**165**)



GB1 (**167**)



Caffeic acid (**166**)



Emodin (**168**)

Table 1 Summary of the chemical composition and recorded biological activities of the remarkable plant families with abundant phytochemicals isolated.

Plant family	% of isolated compounds	Remarkable compound classes (% composition)	Genera studied	Recorded biological activities of isolated compounds
Annonaceae	10.83	Alkaloids (49.21%)	*Enantia*, *Dennettia*, *Monodora*, *Uvaria*, *Freisodielsia*, *Piptostigma* and *Annona*	Antiplasmodial
Apocynaceae	2.00	Alkaloids (75.00%)	*Picralima*, *Rauwolfia* and *Strophanthus*	Antiplasmodial and inhibition of binding of ^{1}H-diazepam to the benzodiazepine sites within the rat GABA receptor complex.
Asteraceae	2.00	Terpenoids (63.64%)	*Acanthospermum*, *Chromolaena*, *Dicoma* and *Struchium*	Antiplasmodial, antileischmanial, antitrypanosomial, antimicrobial, cytotoxicity and anticancer properties
Combretaceae	3.50	Terpenoids (85.00%)	*Guiera*, *Pteleopsis* and *Combretum*	Antiplasmodial, antibacterial and cytotoxic
Compositae	2.00	Terpenoids (50.00%) Flavonoids (50.00%)	*Tithonia*, *Centaurea* and *Laggera*	Antiplasmodial and antimicrobial
Dioncophyllaceae	3.67	Alkaloids (100.00%)	*Triphyophyllum*	Antiplasmodial and antiparasitic
Euphorbiaceae	13.67	Terpenoids (39.51%) Flavonoids (24.70 %)	*Securinega*, *Alchornea*, *Jatropha*, *Croton* and *Elaeophorbia*	Cytotoxic, anti-inflammatory, antioxidant and antimicrobial
Guttiferae	8.67	Xanthones (52.00%) Flavonoids (32.70%)	*Garcinia*, *Tithonia*, *Centaurea* and *Laggera*	Antimicrobial
Lamiaceae	2.50	Flavonoids (85.71%) Terpenoids (14.30%)	*Hyptis*, *Hoslundia* and *Platostoma*	Antiplasmodial, antiparasitic, cytotoxicity, anti-inflammatory and antioxidant
Leguminosae	9.67	Flavonoids (23.68%) Terpenoids (15.79%) Alkaloids (8.00%)	*Abrus*, *Cassia*, *Erythrina*, *Millettia*, *Cajanus*, *Abrus*, *Russelia*, *Baphia* and *Leptoderris*	Antiplasmodial, cytotoxicity, antibacterial, anti-inflammatory, anti-inflammatory, antinociceptive, antinociceptive, antioxidant and antioxidant
Loganiaceae	4.17	Terpenoids (56.00%)	*Strychnos* and *Anthocleista*	Antitrypanosomal
Loranthaceae	3.50	Terpenoids (33.33%)	*Loranthus*	Antioxidant, immunostimulatory and proliferative
Meliaceae	4.17	Terpenoids (100%)	*Azadirachta* and *Khaya*	Antitrypanosomal
Rubiaceae	4.50	Flavonoids (43.33%) Alkaloids (40.00%)	*Nauclea*, *Mitracarpus* and *Ixora*	Aantimicrobial and antioxidant activities
Rutaceae	2.83	Alkaloids (43.75%)	*Murraya* and *Fagara*	Antisickling and antifeedant activities

Table 2: Bioactivity of derived alkaloids *versus* ethnobotanical uses of plant species

Compound	Plant species (Country)	Family	Ethnobotanical use	Measured Activity	References
1 - 7	*Cassytha filiformis* (Benin)	Lauraceae	Used in African folk medicine to treat **cancer**, **African trypanosomiasis** and other diseases.	**Antitrypanosomal activity**, **cytotoxicity**, and Interaction with DNA and Topoisomerases.	Hoet *et al.*[17]
8 – 13	*Monodora* sp. (Ivory Coast)	Annonaceae	Not reported	Not tested	Kablan *et al.*[28] Spiff *et al.*[29]
14, 97 - 102	*Fagara macrophylla* (Guinea)	Rutaceae	Used as a remedy for several afflictions, in particular for the cure of toothache, rheumatism and urogenital affections as well as to prepare **poisonous arrows**.	**Antifeedant** against *S. frugiperda.*	Tringali *et al.*[46]
15, 16	*Sida acuta* (Burkina Faso, Ivory Coast)	Malvaceae	Treatment of **malaria**, diarrhea and many other diseases.	**Antiplasmodial** and anticancer activities.	Banzouzi *et al.*,[32] Karou *et al.*[33g]
16 - 26	*Cryptolepis sanguinolenta* (Ghana, Cape Verde, Guinea Bissau, etc)	Periplocaceae	Treatment of various fevers, including **malaria** and hepatitis.	**Antiplasmodial** activity.	Barku *et al.*, Cimanga *et al.*, Ablordeppey *et al.*, Paulo *et al.*, Hadden *et al.*, Karou *et al.*[33]
64	*Pausinystalia johimbe*	Rubiaceae	Treatment of **erectile dysfunction**.	Blockade of presynaptic **α-adrenoceptors** in rabbits.	Vasisht and Kumar,[36] Morales *et al.*,[37] Susset *et al.*,[38] Starke *et al.*[39]
28 – 33, 84, 86 - 91	*Triphyophyllum peltatum* (Ivory Coast)	Dioncophyllaceae	Treatment of **malaria**, leishmaniasis, dysentery and elephantiasis.	Activity against ***P. falciparum*** and other parasites.	Bringmann *et al.*[40-43]

85	Mixture of *Triphyophyllum peltatum*, *Dioncophyllum tholloni* and *Habropetalum dawei* (Ivory Coast, Sierra Leone)	Dioncophyllaceae	Treatment of **malaria.**	**Anti-malarial activity.**	Bringmann *et al.*[86]
34 - 39	*Ancistrocladus guineensis* (Nigeria)	Ancistrocladaceae	Not reported.	Not tested	Bringmann *et al.*[42]
93 - 95	*Ancistrocladus spp* (Ivory Coast)	Ancistrocladaceae	Treatment of malaria, dysentery and elephantiasis.	Antiparasitic activity.	François *et al.*[41]
40 - 42	*Fagara zanthoxyloides* **(** Burkina Faso)	Rutaceae	used in folk medicine for its **antisickling properties** in Burkina-Faso and other West African countries.	**Antisickling activity.**	Ouattara[45]
65 - 67	*Crinum glaucum* (Nigeria)	Amaryllidaceae	Used in the treatment of cough, asthma, and **convulsions**.	**Acetylcholinesterase** inhibition.	Okpo and Adeyemi,[95] Houghton *et al.*[97]
68 - 70	*Crinum jagus* (Nigeria)	Amaryllidaceae	Treatment of all forms of **convulsions**.	**Acetylcholinesterase** inhibition	Houghton *et al.*,[97] Azikiwe *et al*.[96]
71	*Loranthus micranthus* (Nigeria)	Loranthaceae	Treatment of several diseases including **immune-modulating diseases.**	**Immunostimulatory activity.**	Omeje *et al*.[99]
72, **73**	*Enantia chlorantha* (Nigeria)	Annonaceae	Treatment of **malaria,** jaundice, dysentery, hypertension, skin, gastric and duodenal ulcers, inflammation, and liver-related diseases.	**antiplasmodial** and antiviral activities.	Adebayo *et al*.,[6c] Bhadra and Kumar,[100] Bidla *et al.*,[101] Jia *et al*.[102]
74 -79	*Picralima nitida* (Nigeria)	Apocynaceae	Treatment of **malaria,** diarrhea and as a **painkiller**.	**Antiplasmodial activity**, antipsychotic and anxiolytic properties and known **potent μ-opioid agonists**.	Adebayo *et al*.,[6c] Ezeamuzie *et a*l.,[103] Okokon *et al*.[104] Elisabetsky and Costa-Campos[105]

80, **81**	*Guiera senegalensis* (Nigeria)	Combretaceae	Treatment of **malaria**, diarrhea, dysentery, venereal diseases and **microbial infections.**	**Antiplasmodial** and **antifungal** activities.	Iwalewa *et al.*,[106] Ancolio *et al.*,[107] Combier *et al.*[108] Silva and Gomes[109]
82	*Fagara Zanthoxyloides* (Nigeria)	Rutaceae	Treatment of **malaria.** The stem and the root of the plant are both used as chewing stick in Nigeria particularly among the Yoruba ethnic group in South-Western Nigeria.	**Antiplasmodial activity**	Odebiyi and Sofowora[110]
83	*Cassia siamea* (Nigeria)	Leguminosae	Treatment of **malaria.** In Asia, stem bark is used as a mild, pleasant, safe purgative; to treat diabetes; a paste is used as a dressing for ringworm and chilblains; the roots are used as an antipyretic; and the leaves are used for the treatment of constipation, **hypertension**, and insomnia	**Antiplasmodial activity, vasodialator effect.**	Ajaiyeoba *et al.*,[111] Morita *et al.*,[112] Oshimi *et al.*,[113] Matsumoto *et al.*[114]
103	*Rauwolfia vomitoria* (Ghana)	Apocynaceae	Treatment of **sexual weakness**.	Inhibition of the ***in vitro*** **binding of ^{3}H-diazepam to the benzodiazepine sites within the rat GABA$_A$ receptor complex**.	Ai *et al.*[115]

Table 3: Bioactivity of derived flavonoids *versus* ethnobotanical uses of plant species

Compound	Plant species (Country)	Family	Ethnobotanical use	Measured Activity	References
43, 44	*Hoslundia opposita* (Ivory Coast)	Lamiaceae	Various parts of the plant are used against snake bites, herpes, conjunctivitis, epilepsy, chest pain, yellow fever, stomach troubles, and mental disorders. Infusions of the leaves are used as a purgative, diuretic, febrifuge, antibiotic and antiseptic.	Leishmanicidal potential in the micromolar range,· cytotoxicity.	Salame *et al*.,[44] Tringali *et al.*[46]
96, 142 - 146	*Ixora coccinea* (Nigeria)	Rubiaceae	Treatment of a variety of infections; hypertension, menstrual irregularities, sprains, **chronic ulcers** and skin diseases.	**Antioxidant activity.**	Idowu *et al.*[120]
105	*Pavetta crassipes* (Nigeria)	Rubiaceae	Management of **respiratory infections** and abdominal disorders.	**Antimicrobial activity.**	Bello *et al*.[121]
107 - 111, **114**	*Ximenia americana* (Mali)	Olacaceae	Treatment throat infection, malaria, dysmenorrhea, malaria, leprotic, **ulcers**, skin diseases and for wound healing.	**Antioxidant activity.**	Le *et al*.[77]
112	*Bryophyllum pinnatum* (Nigeria)	Crassulaceac	Treatment of **ulcers**, allergic inflammation and epilepsy.	**Antibacterial activity.**	Ogungbamila *et al*.[122]
113 - 115, **141**	*Byrsocarpus coccineus* (Nigeria)	Connaraceae	Leaf decoction for venereal diseases and as antidote to arrow poisoning also as remedy for pile, while the decoction of the whole plant is applied to swelling and tumours and also to arrest bleeding, the plant has also been reported as a remedy for diarrhea.	Not tested	Ahmadu *et al*.[130]
116 - 124	*Chrozophora senegalensis* (Mali)	Euphorbiaceae	Treatment of diarrhea, rheumatism, teniasis, stomach ache, rachitis, and venereal diseases. The leaf and root decoctions are also drunk for **hairloss**.	**Antioxidant activity**	Vassallo *et al*.[131]
125, **126**	*Cajanus cajan* (Nigeria)	Fabaceae	The leaves are used as a weak decoction for the treatment of measles, **malaria**, catarrh and hepatitis and **cancer**. An aqueous infusion of the seeds sometimes mixed with the leaves is dispensed for the management of sickle-cell	**Cytotoxicity** and **antiplasmodial activity.**	Ashidi *et al*.,[133] Ajaiyeoba *et al*.[138]

			anaemia.		
127, **128**	*Chromolaena odorata* (Ivory Coast)	Asteraceae	Aqueous extracts used for the treatment of malaria, abdominal, **cervical pain**, and of wounds as a local antiseptic and antiinflammatory agent.	Cytotoxicity and **Anticancer properties.**	Kouamé *et al*.[140]
129 - 132	*Hoslundia opposita* (Ivory Coast)	Lamiaceae	The leaves are infused to treat a wide range of ailments, from wounds, fractures, skin and eye infections, to psychiatric and convulsive illnesses, jaundice, and snake bite.	Antiparasitic and cytotoxicity activity.	Salame *et al*.[44]
133	*Spathodea campanulata* (Nigeria)	Bignoniaceae	Treatment of diseases (**ulcers**, dysentery, oedemas, skin eruptions, scabies, wound healing and urethral discharge) and veterinary application have been attributed to the plant in different cultures.	**Antioxidant** activity.	Elusiyan *et al*.[141]
134 - 139	*Securinega virosa* (Mali)	Euphorbiaceae	It is used in traditional medicine for many diseases, including diarrhea, rheumatism, malaria, liver disease, inflammation and pain. Extracts of the plant are used for the expulsion of worms and in the treatment of bilharziasis, and for other urinary and genital tract disorders.	Antioxidant Activity.	Sanogo *et al*.[142]
140	*Alchornea floribunda* (Nigeria)	Euphorbiaceae	Leaves are traditionally used as a remedy for arthritis, muscle pain and other **inflammatory disorders**.	**Anti-inflammatory** activity.	Okoye *et al*.,[144] Okoye and Osadebe.[145]
147	*Fagara macrophylla* (Guinea)	Rutaceae	Cure of toothache, rheumatism and urogenital affections as well as to prepare **poisonous arrows**.	**Antifeedant** activity.	Tringali *et al*.[46]
148, **149**	*Baphia nitida* (Ivory Coast)	Fabaceae	For gastro-intestinal complaints among other uses.	Antioxidant activity.	Chaabi *et al*.[146]
150 - 157	*Piliostigma thonningii* (Nigeria)	Caesalpiniaceae	To treat a variety of infections, fever and **inflammatory conditions.**	**Anti-inflammatory** and Antibacterial activities.	Ibewuike *et al*.[147]
167	*Garcinia kola*	Clusiaceae	The roots and stems are used as **chewing stick**, while the seeds are also chewed	**Antibacterial,** α-glucosidase inhibitory, aromatase inhibitory, and antimalarial activities	Antia *et al*., Lee *et al*., Xe *et al*. [148]