Bioactive natural products derived from the East African flora

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This review describes bioactive natural products isolated from East African medicinal plants. It includes 211 bioactive compounds from 41 plant species, and cites 116 references.

1 Introduction

The East African region is highly endowed with plant biodiversity, and it is estimated that there are over 21 000 higher plant species in the region. This provides ethnopharmacologists with a wide range of plant species for phytochemical and pharmacological studies. In addition, the region is home to one of the ecological hotspots of plant species, the Eastern Arc Mountains, along the eastern coast of Tanzania.

Much of the ethnopharmacological work conducted using plant samples from East Africa has involved higher plants, most of which are endemic. As a result, novel natural products with intriguing chemical structures and pharmacological properties have been elucidated. This review presents the anticancer, antimalarial, antimicrobial, anti-HIV and antileishmanial natural products isolated from medicinal plants growing in East Africa (Table 1). It aims to coherently document the valuable but scattered reports on the ethnopharmacology of medicinal plants collected from three East African countries, namely Kenya, Tanzania and Uganda (Fig. 1).

Fig. 1 Map of East Africa.

2 Natural products with anticancer activity

Cancer is one of the leading causes of mortality, accounting for about 8 million deaths worldwide. Currently there are about 20 million people with cancer worldwide, and the number is projected to increase to 30 million by the year 2020.[1] In East Africa the most prevalent types of cancer include lung, liver, colon, cervical, prostate and breast cancer. Since many people in Africa live in rural areas, treatment of cancer-related illnesses has mostly involved plant extracts. Although several anticancer drugs such as taxol derivatives are already in the clinic, they are expensive and thus not affordable by these communities. Therefore, there remains a great need for affordable and reliable anticancer drugs, and much effort has been put into the search for anticancer natural products from medicinal plants. As a result, in the last two decades, several anticancer natural products from East African medicinal plants have been characterized and their activities against different types of human cancer cell-lines established. These anticancer compounds include sesquiterpenes, flavonoids, diterpenes, benzofurans, steroidal saponins and triterpene saponins.

Sesquiterpenoids are an important class of compounds due to their diverse biological activities. From the East African flora, various sesquiterpenes have been reported to possess anticancer

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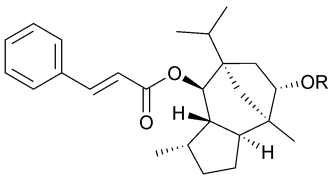
properties. One of the most interesting results has been the elucidation of two novel guaiane sesquiterpenes, namely englerin A (**1**) and englerin B (**2**), from the stem bark of *Phyllanthus engleri* (Euphorbiaceae). The isolation of these sesquiterpenoids was a result of ethnomedical reports of the root and stem bark of this species being poisonous.[2] Englerin A, which was identified as the major compound, exhibited 1000-fold selectivity relative to taxol against six renal cancer cell lines, with GI_{50} values ranging from 1–87 nM, while englerin B and its acetate (**3**) analogue were inactive.[3]

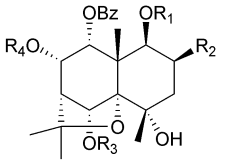
In this assay, englerin A (**1**) performed better than taxol in most of the renal cancer cells except for CAKI-1, SN12C and TK-10 (Table 2).



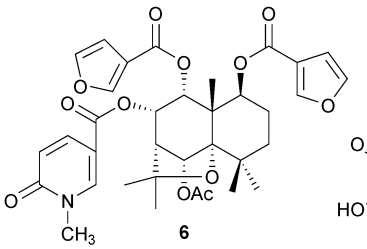
1: R = $COCH_2OH$
2: R = H
3: R = Ac

A preliminary anticancer screening of the methanol extract of *Reissantia buchananii* (Celastraceae) showed growth inhibition of several tumor cells. Phytochemical analysis on this species yielded five new agarofuran sesquiterpenes, namely reissantins A–E (**4–8**),[4] as well as two known triterpenoids, celastrol (**9**)[5] and its methyl ester (**10**).[6] In an anticancer screen, **9** and **10** were revealed to be the most active compounds against nine cancer cell lines (A549, MCF-7, HCT-8, KB, KB-VIN, U-87-MG, PC-3, 1A9 and PTX10), with ED_{50} values ranging from 0.076 to 0.34 μg mL^{-1}. Although **8** and **10** exhibited relatively high anticancer activity, they were less active than taxol (Table 3).[4]

Anticancer diterpenes have also been reported from the stem wood of *Euphorbia quinquecostata* (Euphorbiaceae). The compounds include two new diterpenes, (3*R*,12*R*)-dihydroxy-*ent*-8(14),15-isopimaradien-18-al (**11**), and (−)-*trans*-9-acetyl-4,9′-di-*O*-methyl-3′-de-*O*-methyldehydrodiconiferyl alcohol (**12**),[7] together with, 7,7-dihydroxy-6,8′-bicoumarin (bicoumol)



4: R_1 = Ac, R_2 = H, R_3 = CNMP, R_4 = Ac
5: R_1 = Ac, R_2 = OBz, R_3 = CNMP, R_4 = Ac
7: R_1 = Ac, R_2 = H, R_3 = H, R_4 = H
8: R_1 = Ac, R_2 = H, R_3 = H, R_4 = Ac
CNMP = 5-carboxy-*N*-methyl-2-pyridone



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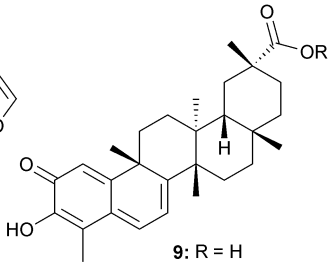

9: R = H
10: R = CH_3

(**13**) and 3,4-dimethoxycinnamaldehyde (**14**).[8,9] These compounds were evaluated for cancer chemopreventive properties using an *in vitro* assay, which determines quinone reductase induction in murine Hepa1c1c7 hepatoma cells[10] and the inhibition of the transformation of murine epidermal JB6 cells.[11] Out of them, only 3,4-dimethoxycinnamaldehyde (**14**) showed significant activity, with a CD (concentration to double induction) value of 9.5 μg mL^{-1} (52.8 μM) (QR assay) and an IC_{50} value of 2.3 μg mL^{-1} (12.8 μM) (JB6 assay), respectively.

The stem bark of *Albizia grandibracteata* (Fabaceae) is used in Uganda for the treatment of meteorism. The leaves, which are known to be rich in saponins, are normally consumed by Red Colobus monkeys (*Procolobus badius*), purportedly for nutritional purposes, while chimpanzees in the Kibale National Park, Uganda, ingest leaves for self-medication.[12,13] These observations prompted a phytochemical investigation of the methanolic extract of the leaves of *A. grandibracteata*, which yielded three novel oleanane-type triterpene saponins, namely grandibracteosides A–C (**15–17**).[14] The crude extract, together with these compounds, exhibited significant inhibitory activity two tumor

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Joseph Magadula was born in Mwanza, Tanzania, in 1965, and received his BSc in Physics and Chemistry in 1997 at the University of Dar es Salaam, Tanzania. He then enrolled for an MSc in Chemistry at the University of Dar es Salaam, graduating in 2000. In 2001 he joined the Institute of Traditional Medicine at Muhimbili University, Tanzania, as a research fellow before joining the University of KwaZulu-Natal, South Africa, receiving his PhD in Chemistry in May 2006. His research interests focus on the discovery of novel HIV-1 protease and reverse transcriptase inhibitors from Tanzanian medicinal plants.

Paul Erasto

Paul Erasto received his BSc (Physics and Chemistry) in 2000 at the University of Dar es Salaam, Tanzania, and his MPhil (Chemistry) in 2003 at the University of Botswana. He received his PhD in Botany (Phytomedicine) in May 2007 from the University of Fort Hare, South Africa, and subsequently worked as a post-doctoral fellow under Prof. A. M. Viljoen in the School of Pharmacy at TUT, South Africa. Currently he is a research fellow at the Institute of Traditional Medicine of Muhimbili University, Tanzania. His research focuses on antidiabetic, antituberculosis and antifungal natural products derived from terrestrial and marine plants.

Table 1 Medicinal plants from the East African flora investigated for bioactive natural products

Species	Family	Ethnomedical use	Place of collection	Reference
Plants with anticancer natural products				
Phyllanthus engleri	Euphorbiaceae	Poison	Iringa, Tanzania	3
Reissantia buchananii	Celastraceae	—	Iringa, Tanzania	4
Euphorbia quinquecostata	Euphorbiaceae	—	Tanzania	7
Albizia grandibracteata	Fabaceae	Meteorism	Uganda	14
Sansevieria ehrenbergii	Agavaceae	—	Kenya	20
Plants with antimalarial natural products				
Ajuga remota	Lamiaceae	Malaria	Nairobi, Kenya	35
Ancistrocladus robertsoniorum	Ancistrocladaceae	Malaria	Coast, Kenya	38
Ancistrocladus tanzaniensis	Ancistrocladaceae	Malaria	Mt Udzungwa, Tanzania	41
Teclea trichocarpa	Rutaceae	Malaria, fever, helminths	Nairobi, Kenya	46
Strychnos usambarensis	Loganiaceae	Malaria, fever	Akagera River, Tanzania/Rwanda	48
Ekebergia capensis	Meliaceae	Heart burn, boils and pimples, respiratory infections, fever	Nanyuki, Kenya	56
Vernonia amygdalina[a]	Asteraceae	Malaise, helminths, fever	Kigoma, Tanzania	57,112
Vernonia brachycalyx	Asteraceae	Parasitic infections, stomach-ache, purgative	Machakosi, Kenya	74
Cussonia zimmermanii	Araliaceae	Malaria, fever, epilepsy	Pugu, Chalinze, Tanzania	76
Toddalia asiatica	Rutaceae	Malaria, fever, stomach-ache, cough, toothache	Kenya	54,75
Vepris uguenensis	Rutaceae	Malaria, kidney disorder, headache, lung disease, colds and influenza	Rachuonyo, Kenya	60
Salacia madagascariensis	Celastraceae	Malaria, fever and menorrhagia	Tanzania	63
Erythrina abyssinica[a]	Leguminosae	Malaria, microbial infections	Thika Town, Kenya	65,66,94
Millettia usaramensis	Leguminosae	Snake-bite	Jadini Forest, Kenya	68
Milletia dura	Leguminosae	—	Nairobi, Kenya	80
Derris trifoliata	Leguminosae	—	Coast Province, Kenya	81
Friesodielsia obovata	Annonaceae	Snake-bite, fever, stomach-ache	Tabora, Tanzania	71
Hugonia busseana	Linaceae	—	Rufiji, Tanzania	78
Hugonia castenifolia[a]	Linaceae	—	Pugu, Tanzania	79,104
Monodora angolensis	Annonaceae	—	Namikwe Island, Tanzania	52
Isolona cauliflora[a]	Annonaceae	—	Namikwe Island, Tanzania	52
Uvaria sp.	Annonaceae	—	Tanzania	70
Cyperus rotundus	Cyperaceae	—	Tanzania	55
Zanthoxylum gilletii	Rutaceae	—	Tanzania	55
Hoslundia opposita	Lamiaceae	Malaria	Pugu, Tanzania	77
Neorautanenia mitis[b]	Fabaceae	Insects, syphilis, bilharzia	Iringa, Tanzania	23,82
Plants with antimicrobial natural products				
Schizozygia coffaeoides	Apocynaceae	Skin infections	Kenya	87
Embelia schimperi	Myrsinaceae	Worms, bacterial infections	Ngong Hills, Kenya	90
Erythrina burtii	Leguminoseae	Microbial infections	Emali, Kenya	93
Leucas volkensii	Lamiaceae	—	Kenya	98
Myrsine africana	Myrsinaceae	—	Machakos, Kenya	99
Melia volkensii	Meliaceae	Analgesic	Voi, Kenya	100,101
Warburgia ugandensis	Canellaceae	Spices, infection	Uganda	105,106
Aspilia mossambicensis	Asteraceae	Infection	Mahale, Tanzania	113,114
Garcinia livingstonei	Clusiaceae	Infection	Tanzania	115
Maprounea africana	Euphorbiaceae	—	Tanzania	116

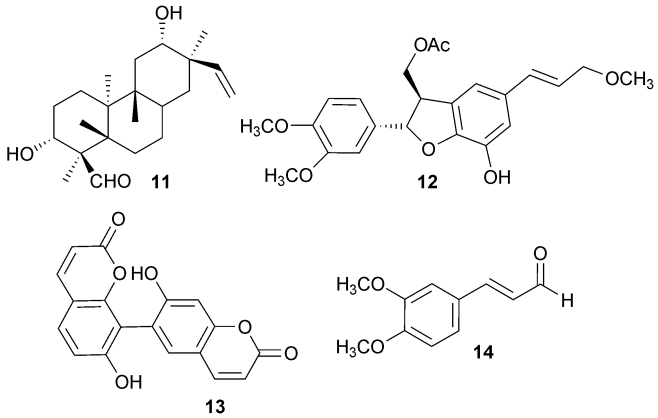
[a] Medicinal plants investigated for both antimicrobial and antimalarial activity. [b] Medicinal plants investigated for both antimalarial and anticancer activity.

Table 2 Anticancer activity of englerin A (**1**) isolated from *Phyllanthus engleri*

	GI_{50}/μM	
Renal cell line	Englerin A (**1**)	Taxol
786-0	<0.01	0.034
A498	<0.01	0.10
ACHN	<0.01	0.65
CAKI-1	15.5	0.35
RXF-393	0.011	0.041
SN12C	0.087	0.018
TK-10	15.5	0.11
UO-31	<0.01	0.45

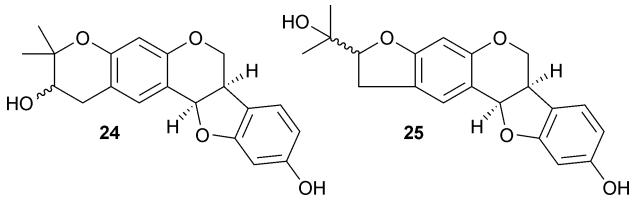
cell lines, with IC_{50} values for **15–17** of 0.04, 0.06 and 3.3 μM (KB cell line) and 0.008, 0.01 and 1.8 μM (MCF-7 cell line), respectively.[14] The standard anticancer compound adriblastine had an IC_{50} value of 0.1 μM against all cell lines. Elucidation of cytotoxic triterpenes from this species confirms a chemo-systematic relationship with most species in the genus *Albizia*, as they are known to be rich in triterpenoid saponins. An example of this is the cytotoxic triteterpene saponins julibrosides J1, J2 and J9, which have been reported from *A. julibrissin*.[15,16]

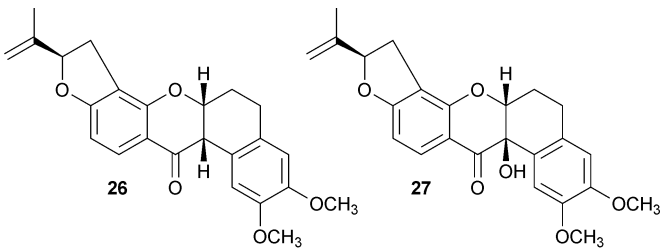
Steroidal saponins are a group of compounds known to have cytotoxic effects. The variability in cytotoxicity and general activities of steroidal saponins is of interest because it is highly influenced by the complexity of the sugar moiety. For instance,

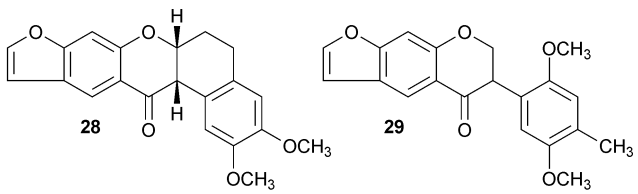


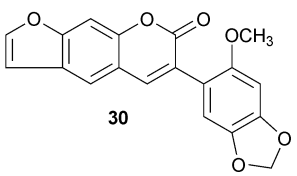
cytotoxic activities of steroidal saponins have been found to be sensitive to the monosaccharides constituting the sugar moieties, their sequence and also the structures of the aglycons.[17] A few anticancer steroidal saponins have been documented from the aerial parts of *Sansevieria ehrenbergii* (Agavaceae). The species in this genus are known to be rich in bioactive pregnane glycosides and steroidal saponins.[18,19] Three new spirostanol saponins, namely sansevierin A (**18**), sansevistatin 1 (**19**) and sansevistatin 2 (**20**), together with three known steroidal saponins (**21–23**) have been documented.[20–22] On screening these compounds against the P388 lymphocytic leukemia cell line and a panel of human cancer cell lines, all compounds except **18** were found to inhibit the growth of cancer cells (Table 4).

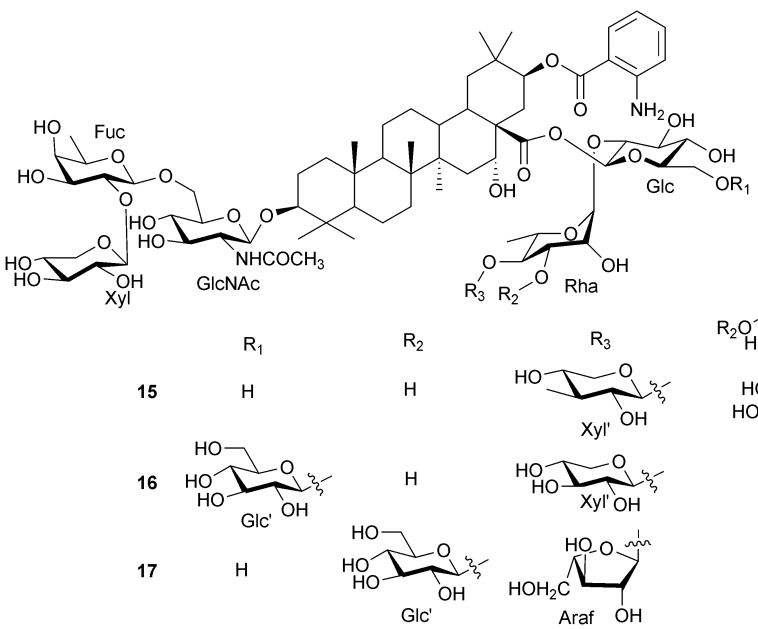
Flavonoids possess various pharmacological properties such as anti-oxidant, anti-inflammatory and also anticancer. Some anticancer flavonoids have been reported from the root bark of *Neorautanenia mitis* (Fabaceae) collected from Rukwa, Tanzania.[23] They include two new pterocarpans, rautandiol A (**24**) and rautandiol B (**25**), three known rotenoids, rotenone (**26**), 12-hydroxyrotenone (**27**) and 12-hydroxyerosone (**28**), isoelliptol (**29**), as well as a coumarin, pachyrrizine (**30**).[24–28] Out of ten isolated compunds, only rotenone (**26**) and 12-hydroxyrotenone (**27**) showed significant cytotoxic activity against MCF-7 and A-549 cells, with IC_{50} values of 0.008–0.01 μg mL^{-1} (MCF-7 cells) and 0.04–0.06 μg mL^{-1} (A-549 cells), respectively.[29] The observed cytotoxicity of the two compounds agrees with the ethnomedical use of the root bark of this species – indigenous people in Rukwa use it for fish poisoning and as an insecticide.[30]











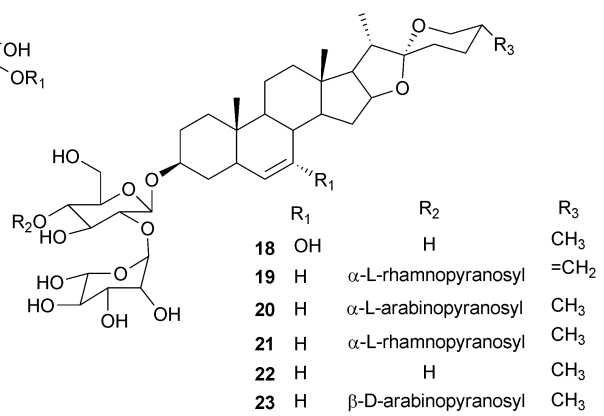


Table 3 *In vitro* cytotoxicity activity of compounds isolated from *Reissantia buchananii*

	ED_{50}/μg mL^{-1} [a]								
Cpd	A549	MCF-7	HCT-8	KB	KB-VIN	U-87-MG	PC-3	1A9	PTX10
4	>20	>20	>20	>20	NA	NA	>20	>20	>20
5	15.3	>20	>20	17.1	17.1	>20	>20	17.1	>20
6	>20	16.2	NA	>20	NA	NA	>20	>20	>20
7	>20	>20	>20	14.4	16.5	NA	>20	>20	>20
8	0.25	0.21	0.23	0.20	0.34	0.22	0.27	0.09	0.10
10	0.31	0.14	0.15	0.10	0.29	0.17	0.23	0.10	0.11
Taxol	0.005	ND	0.011	0.001	ND	ND	ND	0.002	ND

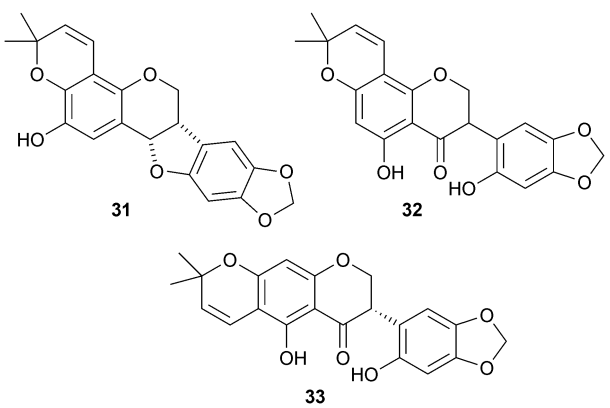
[a] A549 (lung cancer); MCF-7 (breast cancer); HCT-8 (ileocecal cancer); KB (epidermoid nasopharyngeal carcinoma); KB-VIN (vincristine-resistant KB); U-87-MG (glioblastoma); PC-3 (prostate cancer); 1A9 (ovarian cancer); PTX10 (ovarian cancer cell line with a β-tubulin mutation). NA = not active at 20 μg mL^{-1}.

Table 4 *In vitro* cytotoxicity activity of compounds isolated from *Sansevieria ehrenbergii*

		GI_{50}/μg mL^{-1} [b]					
Cpd	ED_{50}/μg mL^{-1} [a] P388	BXPC-3	MCF-7	SF-268	NCI-H460	KM20L2	DU-145
18	>10	>10	>10	>10	>10	>10	>10
19	1.6	1.1	1.1	1.3	0.43	0.47	1.0
20	1.7	0.93	0.62	0.68	0.26	0.22	0.42
21	1.5	1.1	1.6	1.2	1.6	1.6	1.6
22	1.5	1.8	2.0	1.8	1.8	1.7	1.6
23	2.6	1.7	1.4	1.3	1.2	0.5	1.1

[a] P388 (murine lymphocytic leukemia). [b] BXPC-3 (pancreas adenocarcinoma); MCF-7 (breast adenocarcinoma); SF268 (CNS glioblastoma); NCI-H460 (lung large cell); KM20L2 (colon adenocarcinoma); DU-145 (prostate carcinoma).

Anticancer flavonoids have also been reported from the root bark of *Berchemia discolor* (Rhamnaceae), a medicinal plant used in the treatment of various diseases. In Urambo, Tanzania, the boiled stem bark of *B. discolor* and whole roots of *Cordia crenata* and *Tamarindus indica* are used for the treatment of malaria, among several other diseases.[31] Bioactivity-guided fractionation of the root bark of this plant species yielded five new prenylated flavonoids, (6a*S*,11a*S*)-2-hydroxyleiocarpin (**31**), discoloranone A (**32**), (3*S*)-isodiscoloranone A (**33**), (3*S*)-discoloranone B (**34**) and (3*S*)-isodiscoloranone B (**35**).[32] All isolated compounds were evaluated for cytotoxicity against three human cancer cells, the new flavonoid **34** and the known flavonoids nitidulin (**36**), amorphigenin (**37**) and dabinol (**38**) exhibiting cytotoxic activity, with ED_{50} values of 9.6, 4.2, 4.8 and 3.1 μg mL^{-1} (Lu1 cell line), 6.4, 4.1, 7.9 and 5.4 μg mL^{-1} (LNCaP cell line) and 3.6, 3.5, >20 and 13.1 μg mL^{-1} (MCF-7 cell line), respectively.[32–34] Furthermore, nitidulin (**36**) was screened *in vivo* in a hollow fiber assay and found to be active against LNCaP (human hormone-dependent prostate cancer) cells implanted intraperitoneally, at doses of 10, 20 and 40 mg kg^{-1}.[32]



3 Natural products with antimalarial activity

Malaria is one of the major tropical diseases, affecting over 2 billion human beings worldwide. Currently malaria causes an estimated 1.5 to 2.7 million deaths each year, 90% of these being from sub-Saharan Africa.[35] For the past two decades treatment of malaria in Africa has been a big challenge due to evolution of *Plasmodium falciparum* strains that are resistant to chloroquine and other synthetic antimalarial drugs. Consequently, this has raised the need to urgently evaluate antimalarial properties of medicinal plants and their chemical constituents. In East Africa, the effort has targeted *P. falciparum* and the larvae of the mosquitoes that act as the vector.

Over 20 different medicinal plants from East African flora have been investigated for antimalarial properties (see Table 1). This has revealed a wide range of antimalarial natural products, which include phenolics, terpenoids, quinones, polyacetylenes and alkaloids. An account of plant species and their antiplasmodial and larvicidal compounds is given below.

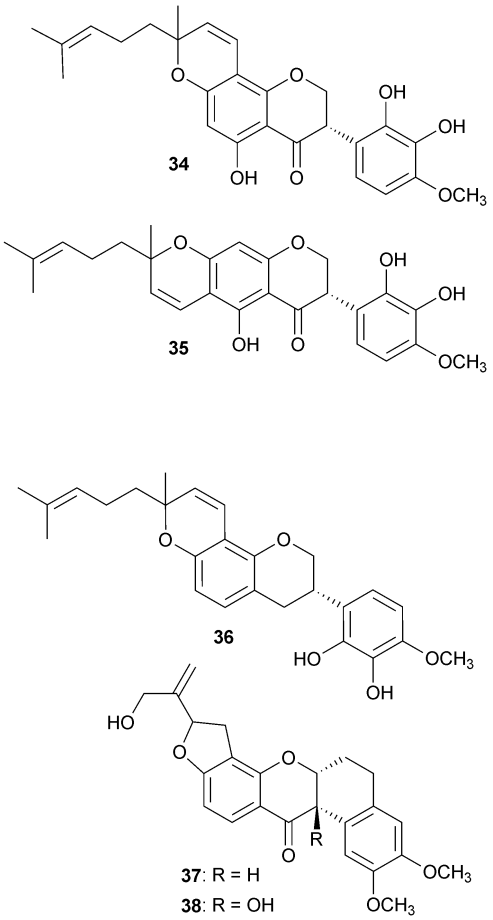


Table 5 *In vitro* antiplasmodial activity of alkaloids from *Ancistrocladus robertsoniorum*, *A. tanzaniensis* and *Teclea trichocarpa* against four strains of *Plasmodium falciparum*

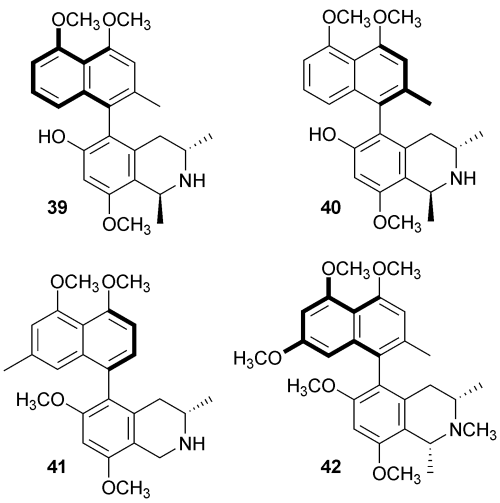
Alkaloid	K-1	NF54	3D7	HB3
Alkaloids from *Ancistrocladus robertsoniorum* (IC_{50}/μM)				
Ancistrobrevin B (**41**)	2.0	4.7	—	—
Ancistrobertsonine A (**42**)	15.9	>23.7	—	—
Ancistrobertsonine B (**43**)	9.0	>23.0	—	—
Ancistrobertsonine C (**44**)	4.5	10.1	—	—
Ancistrobertsonine D (**45**)	—	4.8	—	—
Alkaloids from *Ancistrocladus tanzaniensis* (IC_{50}/μg mL^{-1})				
Ancistrotanzanine C (**47**)	0.1	—	4.2	—
O-Dimethylancistrocladinine (**48**)	2.2	—	5.4	—
O,*N*-Dimethylancistrocladine (**49**)	3.6	—	34.1	—
Ancistrocladidine (**50**)	0.3	—	1.9	—
Ancistrotectorine (**51**)	0.7	—	9.1	—
Chloroquine	0.044	—	0.01	—
Alkaloids from *Teclea trichocarpa* (IC_{50}/μM)				
Normelicopicine (**56**)	14.7	—	—	8.25
Arborinine (**57**)	9.34	—	—	3.85
Skimmianine (**58**)	59.0	—	—	47.5
Melicopicine (**60**)	>100	—	—	>100
Tecleanthine (**61**)	53	—	—	23.2
6-Methoxytecleanthine (**62**)	56.9	—	—	32.3
Chloroquine diphosphate	0.63	—	—	0.028

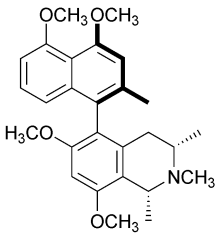
3.1 Antiplasmodials

Alkaloids are important natural products known for their medicinal potential since ancient times. Because of their chemical nature, they are useful lead compounds for the discovery and development of drugs. A number of plant species have yielded antimalarial alkaloids, and these include plant species of the genera *Ancistrocladus*, *Teclea*, *Strychnos*, *Monodora*, *Isolona*, *Vepris*, *Toddalia* and *Zanthoxylum*.

Ancistrocladus robertsoniorum is an important medicinal plant endemic to Kenya. It has been found to be rich in naphthylisoquinoline alkaloids, a class of alkaloids that has high anti-infective properties, particularly against protozoan pathogens.[36–40] The chemical significance of naphthylisoquinoline alkaloids rests on their unique structure and their biological activities. From the stem and leaves of *A. robertsoniorum*, eight antiplasmodial alkaloids have been documented.[38] The major alkaloids are the 5,1′-coupled alkaloids ancistrocladine (**39**) and hamatine (**40**) as well as two 5,8′-linked naphthylisoquinolines, ancistrobrevine (**41**) and ancistrobertsonine A (**42**). The minor alkaloids are all naphthylisoquinolines, namely ancistrobertsonines B (**43**), C (**44**) and D (**45**), and 1,2-didehydroancistrobertsonine D (**46**). These compounds exhibited moderate antimalarial activity against the chloroquine-resistant K-1 strain and the chloroquine-susceptible NF54 strain of *Plasmodium falciparum* (Table 5).[38] Further investigation inton the newly identified *Ancistrocladus tanzaniensis* by Bringmann and co-workers[41] reported three new and five known naphthylisoquinoline alkaloids. These include the 7,3′-coupled ancistrotanzanine C (**47**), the 5,1′-coupled *O*-methylancistrocladinine (**48**) and 5,1′-*O*,*N*-dimethylancistrocladine (**49**). The known naphthylisoquinolines were ancistrocladidine (**50**), ancistrotectorine (**51**), ancistrotanzanine A (**52**), ancistrotanzanine B (**53**) and ancistrotectoriline A (**54**). Compunds **52**–**54** have previously been reported from South Asian *Ancistrocladus tectorius*.[41] As for the other naphthylisoquinolines, these alkaloids also exhibited moderate antimalarial activity against the chloroquine-resistant K-1 strain and the chloroquine-susceptible 3D7 strain of *P. falciparum* (Table 5).

Antiplasmodial naphthylisoquinoline alkaloids have also been reported from various *Ancistrocladus* species growing

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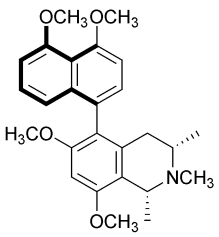
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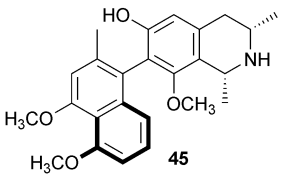
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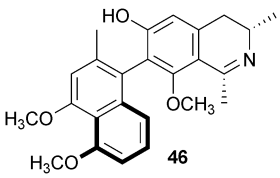
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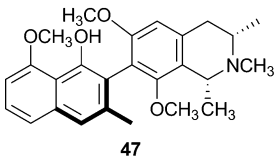
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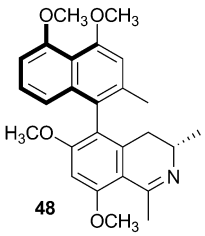
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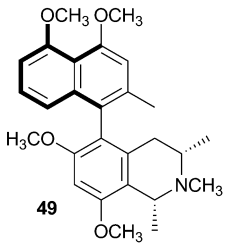
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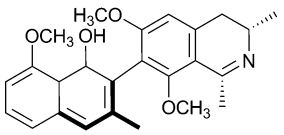
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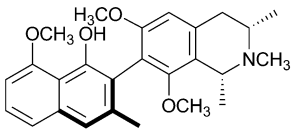
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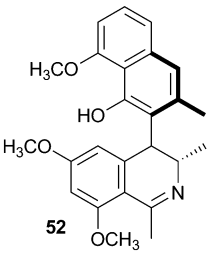
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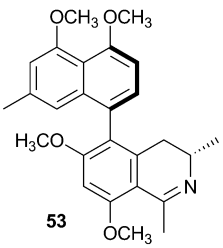
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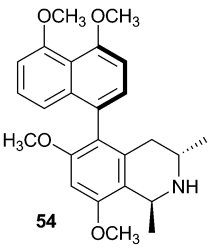
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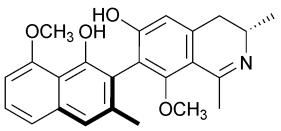
elsewhere in sub-Saharan Africa and Asia. For instance, *Ancistrocladus heyneanus* growing in India has been found to have several 7,3′-coupled naphthylisoquinoline alkaloids, among which are the known ancistrotanzanine C (**47**) and ancistrocladidine (**50**), as well as the new ancistroheynine B (**55**).[42] While the known alkaloids had similar activity to those isolated from East African *Ancistrocladus* species, **55** had an IC_{50} value of 0.5 μg mL^{-1}.[41,42]

Naphthylisoquinoline alkaloids have been reported from *Ancistrocladus likoko* and *A. congolensis* found in the Democratic Republic of Congo. Again the alkaloids had moderate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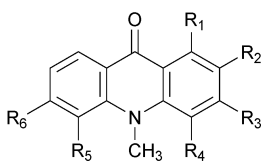
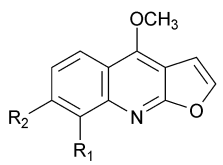
antimalarial activity of the same order to those obtained from *A. tanzaniensis* and *A. robertsoniorum*.[43,44] More alkaloids have recently been reported from a newly discovered *Ancistrocladus* taxon closely related to *A. congolensis*. Unfortunately the alkaloids had weak antimalarial activity compared to compounds from other *Ancistrocladus* species.[45]

The leaves of *Teclea trichocarpa* have been found to contain antiplasmodial acridone alkaloids.[46] Four new alkaloids, namely normelicopicine (**56**), arborinine (**57**), skimmianine (**58**) and dictamnine (**59**), as well as three known acridones, melicopicine (**60**), tecleanthine (**61**) and 6-methoxytecleanthine (**62**), have been reported from the leaves of *T. trichocarpa*. The alkaloids exhibited moderate activity against the chloroquine-sensitive HB3 and the chloroquine-resistant K-1 strains of *P. falciparum* (Table 5).[46] Generally, it has been observed that plants of the genus *Teclea* have wide medicinal uses both in tropical and warm-temperate climatic areas. For instance, the bark of *Teclea nobilis* is used in South Africa as a remedy for gonorrhea, while in Ethiopia the bark and leaves of the same species are used as analgesics.[10] In North Cameroon *T. ouabanguiensis* is used as a remedy for coughs and asthma, while *T. trichocarpa* is widely used in Kenya for the treatment of malaria, fever and helminths.[46]



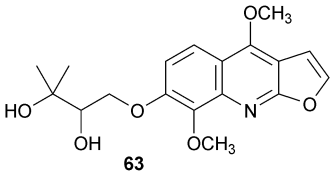


56: R_1 = OH; R_2 = R_3 = R_4 = OCH_3; R_5 = R_6 = H
57: R_1 = OH; R_2 = R_3 = OCH_3; R_4 = R_5 = R_6 = H
58: R_1,R_2 = OCH_3
59: R_1,R_2 = H
60: R_1 = R_2 = R_3 = R_4 = OCH_3; R_5 = R_6 = H
61: R_1 = OCH_3; R_2,R_3 = -OCH_2O-; R_4,R_6 = H; R_5 = OCH_3
62: R_1 = OCH_3; R_2,R_3 = -OCH_2O-; R_4 = H, R_5 = R_6 = OCH_3

The other *Teclea* species commonly used for medicinal purposes in sub-Saharan Africa include *T. natalensis* and *T. gerrardii*.[47] From the latter, several acridone alkaloids have been elucidated, but only arborinine (**57**) and evoxine (**63**) have moderate antimalarial activity against CQS D10 strain of *P. falciparum*, with IC_{50} values of 12.3 and 24.5 μM respectively.[47]

Indole alkaloids are known to be active against various pathogens. In East Africa, a limited number of indole alkaloids have been isolated and screened for antimalarial activity. One of the plants found to have indole alkaloids is *Strychnos usambarensis*,[48] from which Frédérich and co-workers reported a tertiary phenolic bisindole alkaloid, 10′-hydroxyusambarensine (**64**). This alkaloid had high antimalarial activity against the chloroquine-resistant FCA20 Ghana and W2 Indochina strains of *P. falciparum*, with IC_{50} values of 0.48 and 0.16 μg mL^{-1} respectively. This activity was comparable to bisindole alkaloids reported from *Strychnos icaja* found in Central Africa.[49–51]

Indole alkaloids have been reported from the stem and root bark of *Monodora angolensis* and *Isolona cauliflora*.[52] These include 6-(3-methylbut-2-enyl)-1,3-dihydroindol-2-one (**65**),



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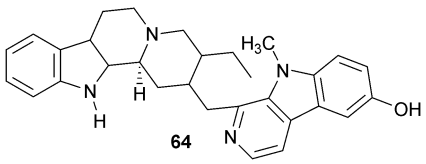

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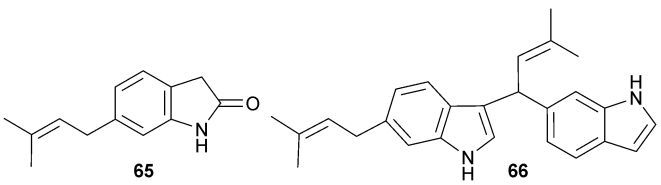
annonidine F (**66**), 1*H*-indole-5-carbaldehyde (**67**), 6-(3-methyl-2-butenyl)-1*H*-indole (**68**), 6-(3-methylbuta-1,3-dienyl)-1*H*-indole (**69**), 6-(4-oxobut-2-enyl)-1*H*-indole (**70**) and 3-geranylindole (**71**) obtained from *Monodora angolensis*, while 3-(1,1-dimethylbut-2-enyl)-5-(3-methylbut-2-enyl)-1*H*-indole (caulidine A) (**72**) and 4-[3-(1,1-dimethyl-but-2-enyl)-1*H*-indol-5-yl]-but-3-en-2-one (caulidine B) (**73**) were isolated from *Isolona cauliflora*. Out of these compounds, only indoles **68** and **69** exhibited moderate antimalarial activity against the multidrug-resistant K-1 strain of *P. falciparum*, with IC_{50} values of 0.21 mg mL^{-1} for both compounds.[52]



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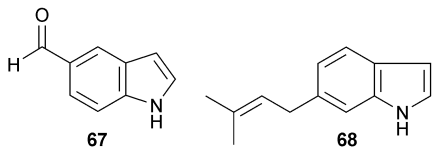

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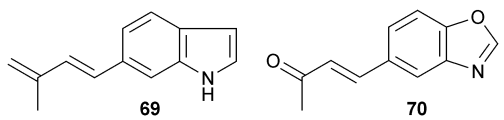

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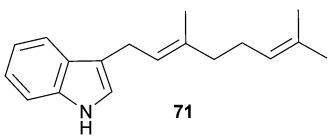

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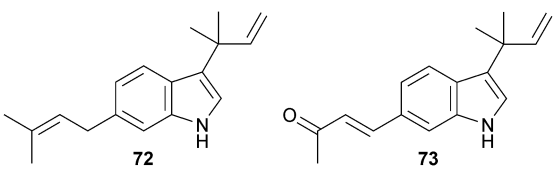
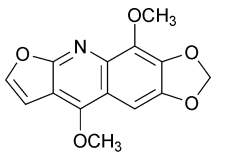


72 73

Vepris is another genus of interest whose species are known to contain furoquinoline alkaloids.[53] Several species of this genus are present in East Africa, the most-used species for medicinal purposes being *V. uguenensis*. Cheplogoi and co-workers have investigated the roots of this plant for antiprozoal natural products, from which three furoquinoline alkaloids were reported, namely flindersiamine (**74**), maculosidine (**75**) and syringaldehyde (**76**).[53] With the exception of flindersiamine (**74**), which lacked antimalarial efficacy against all strains, alkaloids **75** and **76** exhibited moderate antimalarial activity against two strains of *P. falciparum*, with IC_{50} values of 29.2 and 13.0 μg mL^{-1} (chloroquine-susceptible 3D7 strain) and 40.4 and 21.4 μg mL^{-1} (chloroquine-resistant FCM29 strain), respectively.[53]



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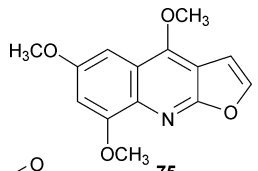

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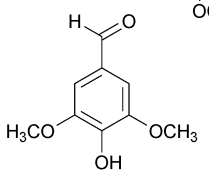

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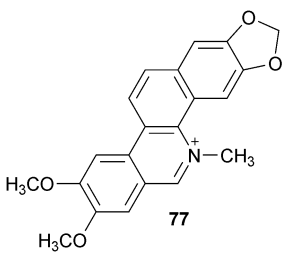
Nitidine (**77**) is a well-known cytotoxic agent which has received considerable attention as a potential anticancer agent. Investigating the antiplasmodial activity of the alkaloidal extract of the roots of *Toddalia asiatica*, Gakunju *et al.*[54] reported high activity against the chloroquine-resistant K39 strain of *P. falciparum*, with an IC_{50} value of 0.04 μg mL^{-1}. Further phytochemical analysis on the extract yielded nitidine as a major compound. When screened against the K39 strain of *P. falciparum*, nitidine exhibited high antiplasmodial activity, with an IC_{50} of 0.045 μg mL^{-1}. However due to toxicity, a derivative of nitidine was sought through structural modification to see if the toxicity could be reduced while maintaining a high antiplasmodial activity. The resulting derivative, an alkaloid 5,6-dihydronitidine (**78**) had an IC_{50} of 1.03 μg mL^{-1} (23 times weaker than nitidine).[54]



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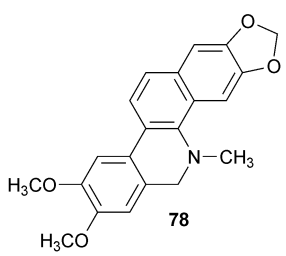

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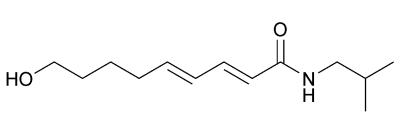
Zanthoxylum gilletii is a widely used plant species in the treatment of fever and malaria-related ailments. From this species two alkaloids, *N*-isobutyldeca-2,4-dienamide (**79**) and securinine (**80**), have been documented.[55] Both had moderate antiplasmodial activity against the K-1 strain of *P. falciparum*, with IC_{50} values of 5.4 and 5.4 μg mL^{-1}, respectively.[55]

Another class of antimalarial natural products reported from East Africa are the triterpenes. Murata *et al.* reported four



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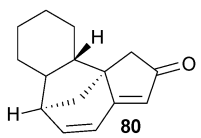

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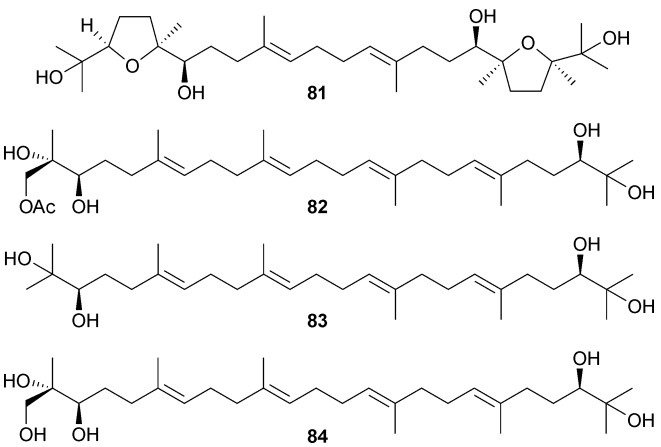
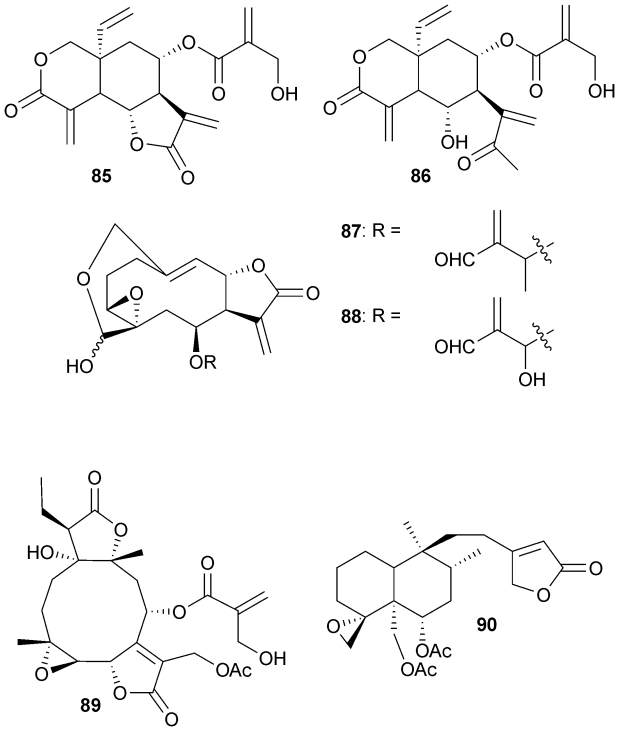
antimalarial triterpenes from the stem bark of *Ekebergia capensis*,[56] comprising two new and two known acyclic triterpenoids, namely ekeberin D4 (**81**) and D5 (**82**), (3*R*,22*R*)-2,3,22,23-tetrahydroxy-2,6,10,15,19,23-hexamethyl-6,10,14,18-tetracosatetraene (**83**) and (2*R*,3*R*,22*R*)-2-hydroxymethyl-2,3,22,23-tetrahydroxy-2,6,10,15,19,23-hexamethyl-6,10,14,18-tetracosatetraene (**84**) respectively. The triterpenoids **83** and **84** exhibited moderate antimalarial activity against the FCR-3 strain of *P. falciparum*, with IC_{50} values of 55 and 18 μM respectively. Furthermore, compounds **83** and **84** were screened against the chloroquine-resistant K-1 strain, against which they had IC_{50} values of 7 and 59 μM. The triterpene **81** lacked efficacy, while **82** had an IC_{50} of 137 μM against the same parasite. [56]



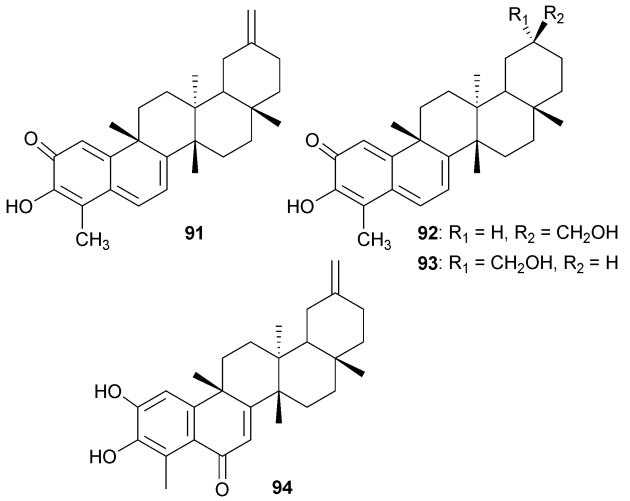
The genus *Vernonia* is one of the major natural sources of bioactive sesquiterpenoids. In East Africa various antiplasmodial sesquiterpenes have been reported from *V. amygdalina* and *V. brachycalyx*. From the leaves of *V. amygdalina*, Ohigashi *et al.*[57] reported four sesquiterpene lactone (STLs), namely vernodalin (**85**), vernodalol (**86**), vernolide (**87**) and hydroxyvernolide (**88**). These exhibited moderate antiplasmodial activity against the multidrug-resistant K-1 strain of *P. falciparum*, vernodalin being the most active compound with an IC_{50} value of 4 μg mL^{-1}, while **86**, **87** and **88** had IC_{50} values of 4.2, 8.4 and 11.4 μg mL^{-1} respectively.[57] These observations agree with the known ethnomedical uses of the leaves of *V. amygdalina* in the treatment of various diseases, including malaria.[58] Quantitative analysis showed that young leaves of this species have a higher concentration of vernodalin than the other STLs, suggesting that the antimalarial efficacy of the leaf extracts of this species may partly be due to the high content of this natural product.[57] Similar STLs have been reported from *V. colorata* from Zimbabwe. The isolated compounds had similar antiplasmodial activities to those of *V. amygdalina*, with the exception of a lactone, 11β,13-dihydrovernolide, which was more active, with an IC_{50} of 1.1 μg mL^{-1}.[59] Oketch-Rabah *et al.*[60] reported a germacrane dilactone, 16,17-dihydrobrachycalyxolide (**89**), from the leaves of *V. brachycalyx* as a major antiplasmodial compound. The dilactone exhibited moderate to high antiplasmodial activity against the K39, 3D7, V1/S and Dd2 *P. falciparum* strains, with IC_{50} values of 4.2, 13.7, 3.0 and 16 μg mL^{-1} respectively. Although this compound exhibited high antiplasmodial activity, it also had higher toxicity against human lymphocytes. This therefore indicates that the antiplasmodial activity may have been due to the general toxicity the compound has on cells.[60] It has also been reported that dry leaves of *V. brachycalyx* contain 0.2–0.4% of this sesquiterpene dilactone. Despite these observations, the leaves of this species are still used in the treatment of malaria and parasitic infections in East Africa.[60] Another sesquiterpene, ajugarin-1 (**90**), has been reported from aerial parts of *Ajuga remota*. It has moderate antimalarial properties against the chloroquine-sensitive FCA 20/GHA strain of *P. falciparum*, with an IC_{50} of 23 μM.[35]



Weenen and co-workers reported five sesquiterpenes from the tubers of *Cyperus rotundus*, namely α-cyperone, humelene, α-selinene, β-selinene and cyperene. Only α-cyperone exhibited high antiplasmodial activity against the multidrug-resistant K-1 strain, with an IC_{50} of 5.5 μg mL^{-1}, the other sesquiterpenes lacking efficacy against the test organism.[55]

Salacia madagascariensis (Celastraceae) is a shrub found in East Africa whose roots are used in the treatment of malaria, fever, and menorrhagia in Tanzania.[61,62] It is rich in bisnortriterpenes with potent antiprotozoal activity. From the roots of this species four bisnortriterpenes, isoiguesterin (**91**), 20-*epi*-isoiguesterinol (**92**), isoiguesterinol (**93**) and 6-oxoisoiguesterin (**94**), have been reported.[63] Only **91** and **92** showed high activity, with IC_{50} values of 200 and 68 ng mL^{-1} (against the D6 strain of *P. falciparum*), and 170 and 68 ng mL^{-1} (against the W2 strain of *P. falciparum*), respectively.[63]

A steroid, ergosterol-5,8-endoperoxide (**95**), isolated from the aerial parts of *Ajuga remota*, is another antiplasmodial compound exhibiting high activity against the chloroquine-sensitive FCA 20/GHA strain of *P. falciparum*, with an IC_{50} value of 8.2 μM.[35] Other documented antimalarial steroids have been steroidal saponins from the leaves of *Vernonia amygdalina*, Ohigashi and co-workers reporting vernonioside A1 (**96**), A2 (**97**), A3 (**98**), A4 (**99**) and B1 (**100**). These saponins had weak antiplasmodial activity against the multidrug-resistant K-1 strain



of *P. falciparum*, with IC_{50} values of 139.7, 94.1, 245.1, 81.8 and 46.1 μg mL^{-1} respectively.[57] Apart from having antiplasmodial activity; these saponins are the bitter compounds in the leaves of *V. amygdalina*.

Several bioactive flavonoids have been isolated from the East African flora, most of them having shown mild to high antimalarial activity. The mechanism of action of flavonoids is still uncertain, but some have been shown to inhibit the influx of L-glutamine and myoinositol into infected erythrocytes.[64] Yenesew and co-workers have reported several antimalarial flavonoids from the stem bark of *Erythrina abyssinica*. These include chalcones, prenylated and non-prenylated isoflavones and flavones, pterocarpenes and flavenes.[65,66] All compounds exhibited moderate antimalarial activity against the D6 and W2 strains of *P. falciparum* (Table 6). The discovery of flavonoids from this species was chemosystematically consistent with a general observation that *Erythrina* species are rich in bioactive flavonoids, and that they are widely used for medicinal purposes.[67]

Milletia usaramensis ssp. *usaramensis* has also been reported to contain antimalarial flavonoids, particularly rotenoids.[68] Seven rotenoids have been reported from this species, including usararotenoid C (**109**), usararotenoid A (**110**), (+)-usararotenoid B (**111**), (+)-12a-*epi*-millettosin (**112**), barbigerone (**113**) and 4′-*O*-geranylisoquiritigenin (**114**), which exhibited moderate to weak antiplasmodial activity against the D6 and W2 strains of *P. falciparum*

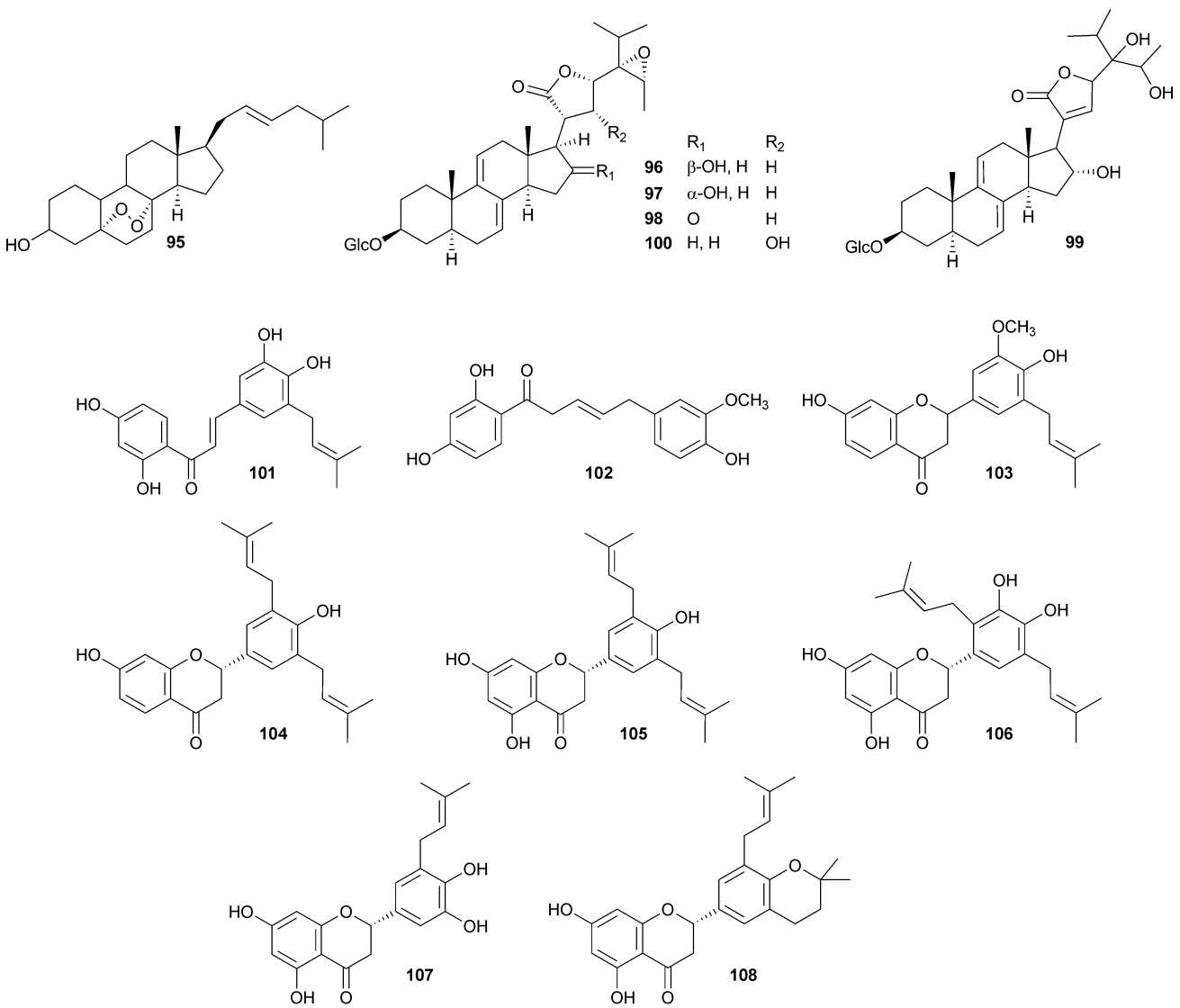


Table 6 *In vitro* antiplasmodial activity of flavonoids isolated from *Erythrina abyssinica* and *Milletia usaramensis* ssp. *usaramensis* against the W2 and D6 strains of *P. falciparum*

Flavanoid	IC_{50}/μM	
	D6	W2
Flavonoids from *E. abyssinica*		
5-Prenylbutein (**101**)	10.3	11.2
Homobutein (**102**)	15	16.1
Licoagrochalcone A	12.7	12
5-Deoxyabyssinin II (**103**)	13.6	13.3
Abyssinin III	5.8	5.2
Abyssinone IV (**104**)	5.4	5.9
Abyssinone V (**105**)	4.9	6.1
Abyssinone V-4′-methyl ether	11.3	11.1
Sigmoidin A (**106**)	5.8	5.9
Sigmoidin B (**107**)	8.1	9.3
Sigmoidin B-4′-methyl ether	13	12.7
Sigmoidin C	17.8	15.8
Sigmoidin E (**108**)	9.1	11.8
Erythrabssin ferulate	8.1	6.5
Octacosyl ferulate	>50	>50
3-Hydroxy-9-methoxy-10-prenylpterocarpene	18.2	20.3
7,4′-Dihydroxy-2′,5′-dimethoxyisoflav-3-ene	22.0	24.9
Flavonoids from *M. usaramensis* ssp. *usaramensis*		
Usararotenoid C (**80**)	70.1	25.8
Usararotenoid A (**81**)	60.7	66.6
Usararotenoid B (**82**)	>100	>100
12a-*epi*-Millettosin (**83**)	19.4	22.2
6a,12a-Dehydromillettone (**84**)	39.1	33.3
Barbigerone (**85**)	27.3	27.0
4-*O*-Geranylisoquiritigenin (**86**)	10.6	8.7
Reference drugs		
Chloroquine	0.009	0.094
Quinine	0.044	0.209

(Table 6). While studying the activities of *Milletia* rotenoids, Yenesew and co-workers established some structure–activity relationships. It was observed that rotenoids containing a prenyl unit or a 2,2-dimethylpyrano substituent were more potent than the non-prenylated rotenoid, *e.g.* usararotenoid A (**110**). It was further reported that there is no significant activity for usararotenoid B (**111**), suggesting the importance of the carbonyl function at C-12 in usararotenoid A (**110**) for the weak antiplasmodial activity observed. Since rotenoids have been reported to be less toxic to mammals than to insects,[69] it would be of interest to establish more precisely the structural requirement for antiplasmodial activity.

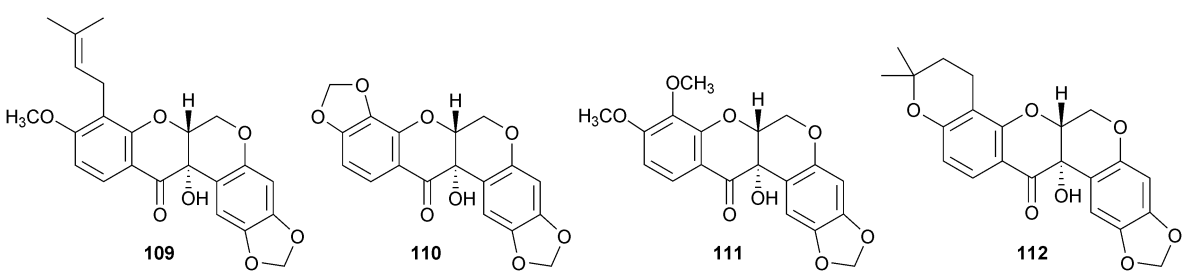
An investigation into various *Uvaria* species growing in Tanzania yielded five important chalcones, uvaretin (**115**), diuvaretin (**116**), triuvaretin, isotriuvaretin and chamuvaretin (**117**).[70] The chalcones exhibited moderate to high antiplasmodial activity against the multidrug-resistant K-1 strain of *P. falciparum*, with IC_{50} values of 3.49, 4.2, 46.02, 20.85 and 5.32 μg mL^{-1} respectively. Two more bioactive chalcones, 3′,5′-diformyl-2′,4′,6′-trihydroxychalcone **118** and 3′,5′-dimethyl-2′,4′,6′-trihydroxychalcone **119**, have been reported from the root bark of *Friesodielsia obovata*. These too exhibited moderate antiplasmodial activity against the K-1 strain of *P. falciparum*, with IC_{50} values of 23 and 9.7 μg mL^{-1}. The same trend of activity was observed against the NF54 strain, against which the compounds had IC_{50} values of 29 and 8.5 μg mL^{-1} respectively.[71]

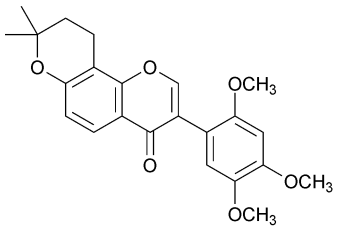
Coumarins have been studied extensively for their biological properties; however, there are a limited number of reports on the antiplasmodial activity of coumarins from East Africa.[72,73] Two isomeric 5-methylcoumarins have been reported from the roots of *V. brachycalyx* – these include 2′-*epi*-cycloisobrachycoumarinone epoxide (**120**) and cycloisobrachycoumarinone epoxide (**121**). Screening against the chloroquine-susceptible 3D7 and chloroquine-resistant Dd2 strains of *P. falciparum*, coumarin **120** exhibited weak activity, with IC_{50} values of 160 μM and 54 μM, while coumarin **121** had IC_{50} values of 111 μM and 54 μM respectively. Oketch-Rabah and co-workers have reported a new antimalarial coumarin, 5,7-dimethoxy-8-(3′-hydroxy-3′-methyl-1′-butene)coumarin (**122**), from the roots of *Toddalia asiatica*.[75] This had moderate activity against the chloroquine-sensitive K39 and chloroquine-resistant V1/S strains of *P. falciparum* strains, with IC_{50} values of 16.2 μg mL^{-1} and 8.8 μg mL^{-1} respectively.

Polyacetylenes are rare and often unstable compounds, and because of their unique chemical structure, are highly reactive and thus have wide variety of biochemical and pharmacological uses. From the root bark extract of *Cussonia zimmermanii* (Araliaceae), a widely used plant species in the treatment of malaria, fever and epilepsy, four polyacetylenes, namely 8-hydroxyheptadeca-4,6-diyn-3-yl acetate (**123**), 8-hydroxyheptadeca-1-ene-4,6-diyn-3-yl acetate (**124**), 16-acetoxy-11-hydroxyoctadeca-17-ene-12,14-diynyl acetate (**125**) and 11,16-diacetoxyoctadeca-17-ene-12,14-diynyl acetate (**126**), have been reported.[76] The first three exhibited high antimalarial activity against *P. falciparum*, with IC_{50} values of 5.9, 0.44 and 0.84 μM respectively.[76]

Four limonoids, namely 7-deacetoxy-7-oxogedunin (**127**), ekeberin C1 (**128**), C2 (**129**) and C3 (**130**), have been reported from the stem bark of *Ekebergia capensis*.[56] Only 7-deacetoxy-7-oxogedunin (**127**) exhibited significant activity against the chloroquine-susceptible FCR-3 strain of *P. falciparum*, with an IC_{50} of 6 μM, but it lacked efficacy against the chloroquine-resistant K-1 strain. The other limonoids were inactive against both strains.

Quinones are another important class of natural compounds with diverse pharmacological properties. Achenbach and co-workers reported some quinone derivatives from the root bark of *Hoslundia opposita*.[77] The compounds include 3-*O*-benzoylhosloppone





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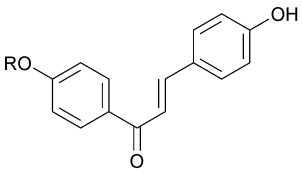
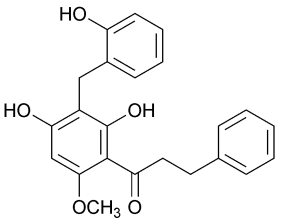


114 R = geranyl



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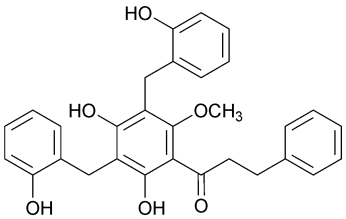

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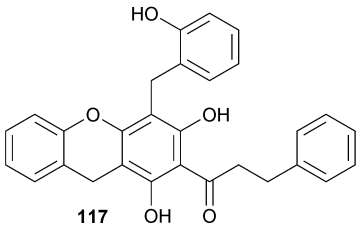

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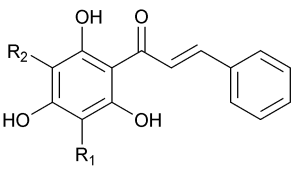
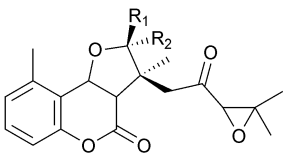
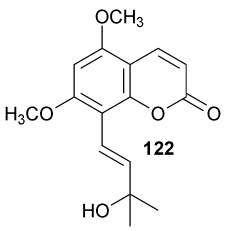


118: R_1 = CHO, R_2 = CHO
119: R_1 = CH_3, R_2 = CH_3



120: R_1 = CH_3, R_2 = H
121: R_1 = H, R_2 = CH_3



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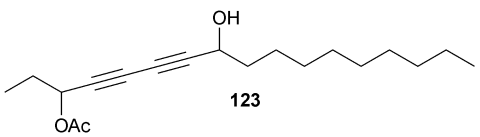

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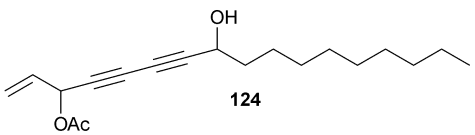

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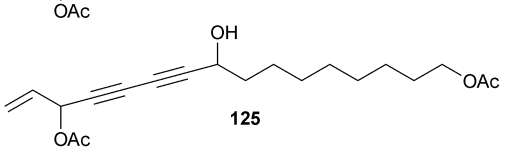

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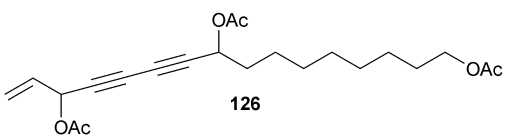

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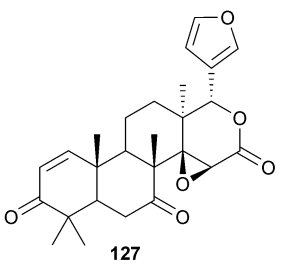

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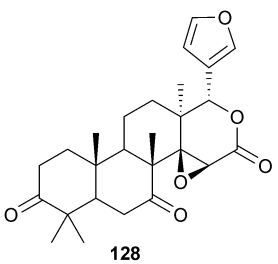

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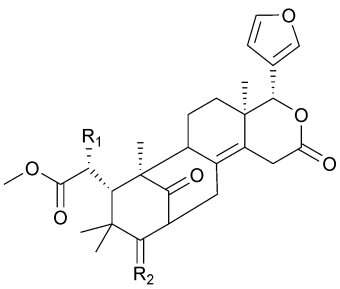
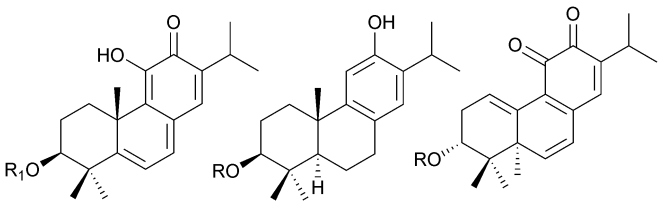


129: R_1 = H, R_2 = *O*-angelate, αH
130: R_1 = $OCOCH_3$, R_2 = O

(**131**), 3-*O*-cinnamoylhosloppone (**132**), 3-*O*-benzoylhinokiol (**133**) and 3-*O*-benzoylhosloquinone (**134**). The isolation of these compounds was carried out as a result of an ethnomedical use of *H. opposita* in the treatment of malaria; a preliminary antimalarial screening of the *n*-hexane extract of the root bark gave an IC_{50} of 5.6 μg mL^{-1}. The extract also exhibited a 26% inhibition of growth of *Plasmodium berghei* in mice, at a daily dose of 190 mg kg^{-1} body weight, for four days.[77] A quinone, 3-*O*-benzoylhosloppone (**131**), showed significant *in vitro* activity against the multidrug-resistant K-1 strain and the chloroquine-sensitive NF54 strain of *P. falciparum*, with IC_{50} values of 0.4 and 0.22 μg mL^{-1} respectively. Unfortunately the other metabolites were not screened due to the limited amount available.[77]



131: R = benzoyl
132: R = cinnamoyl

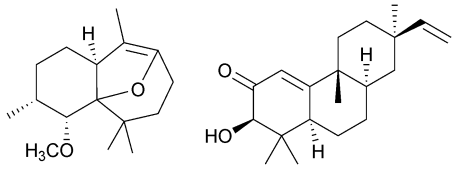
133 R = benzoyl

134 R = benzoyl

3.2 Larvicidals and mosquitocidals

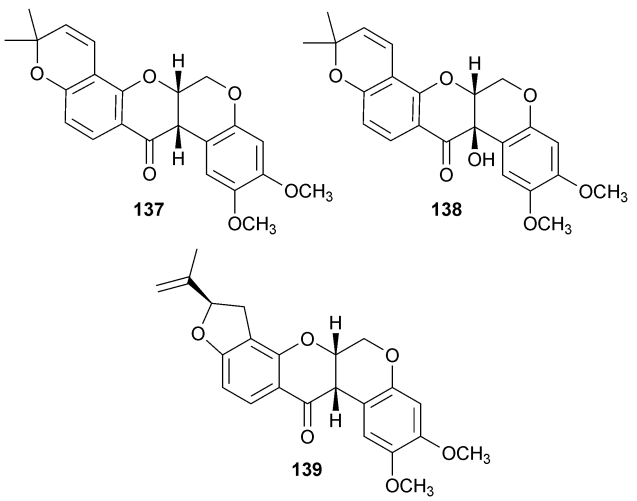
The attempts to control malaria have not only focused on the *P. falciparum* parasite, but also the larvae and adults of various other mosquito species. Contributing to this effort, Baraza and co-workers investigated the larvicidal properties of compounds

isolated from the root bark of *Hugonia busseana*.[78] In this account, a new himachalene sesquiterpenoid, hugonianene A (**135**), was identified as the major compound responsible for the larvicidal effect of the extract. It exhibited high activity against *Anopheles gambiae* mosquito larvae after 24 h at a concentration of 0.237 mg mL^{-1}, and after 48 h and 72 h of contact, the compound caused complete larval mortality, even on exposure to a concentration of as low as 0.01369 mg mL^{-1}. Further studies on the genus *Hugonia* yielded a larvicidal rosane diterpenoid, hugorosenone (**136**), from the root bark of *H. castaneifolia*. The diterpenoid exhibited appreciable activity, with LC_{50} values of 0.3028, 0.0674 and 0.0582 mg mL^{-1} after 24, 48 and 72 h of exposure to the compound, respectively.[79]

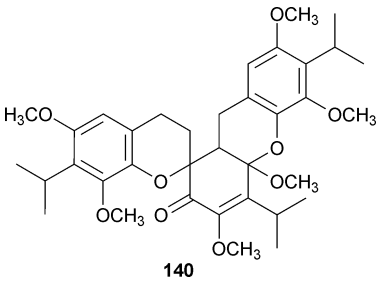


135 **136**

Two rotenoids, deguelin (**137**) and tephrosin (**138**), isolated from the seeds of *Milletia dura* have shown high larvicidal properties against the larvae of the mosquito *Aedes aegypti*. The compounds had LC_{50} values of 1.6 and 1.4 μg mL^{-1} after 24 h, respectively.[80] By comparing the larvicidal activity of these two rotenoids and the antiplasmodial activity of the rotenoids isolated from *Milletia usaramensis* ssp. *usaramensis*, it is clear that rotenoids can be good lead compounds for the development of larvicidal agents, rather than as antiplasmodial drugs. This, however, depends much on the chemical structures of the compounds, and hence the active sites for larvicidal and antiplasmodial activity. More larvicidal rotenoids have been reported from the roots of *Derris trifoliata*.[81] However, only the known rotenoids, rotenone (**139**) and deguelin (**137**), exhibited high larvicidal activity against the second instar larvae of the mosquito *Culex quinquefasciatus*, with LC_{50} values of 0.45 μg mL^{-1} and 1.8 μg mL^{-1} after 24 h respectively.



A trimeric monoterpene, (±)-schefflone (**140**), isolated from the root bark of *Uvaria scheffleri* has been found to have moderate larvicidal activity against *Anopheles gambiae* mosquito larvae, with LC_{50} values of 0.93, 0.018 and 0.0005 mg mL^{-1} after 48, 72 and 96 h of exposure respectively. (±)-Schefflone is a derivative of the known antiparasitic aromatic monoterpene espintanol.[52]



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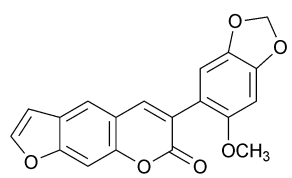
The plant species in the genus *Neorautanenia* are widely known for their insecticidal properties, various species of this genus growing in Tanzania being used for the control of insects. Following the long history of insecticidal use, Joseph and co-workers investigated the larvicidal and mosquitocidal activity of the extracts and pure compounds from the tubers of *Neorautanenia mitis*.[82] The petroleum ether extract was found to have high activity against *Anopheles gambiae* and *Curex quinquefaciatus* larvae, with LC_{50} values of 0.068 and 0.16 mg L^{-1}, respectively. Phytochemical investigation of this extract yielded six flavonoids, namely pachyrrhizine (**141**), neotenone (**142**), neorautanone (**143**), neoduline (**144**), 4-methoxyneodulin (**145**) and nepseudin (**146**). These flavonoids exhibited high mosquitocidal activity against *A. gambiae*, with LC_{50} values of 0.007, 0.008, 0.009, 0.005, 0.011 and 0.003 mg mL^{-1} respectively,[82] compared to that of the standard mosquitocidal compound permethrin, with an LC_{50} of 0.00004 mg mL^{-1}. The level of activity of these compounds indicates that they are potential lead compounds for the development of natural mosquitocidal agents.



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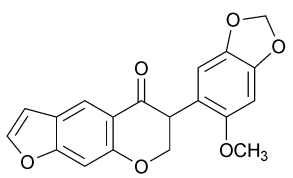

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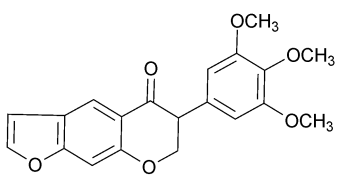

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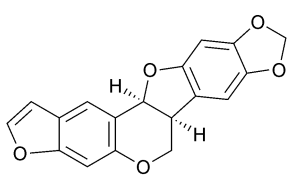

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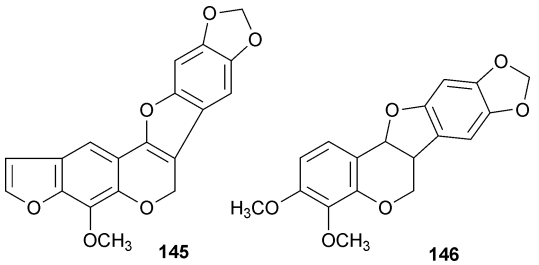
4 Natural products with antileishmanial activity

Leishmaniasis is a complex of neglected diseases caused by the trypanosomatid parasites *Leishmania* spp. The disease is endemic in certain densely populated regions of the world.[83] Drugs available for the treatments of this disease are expensive and thus not affordable for populations in developing countries.



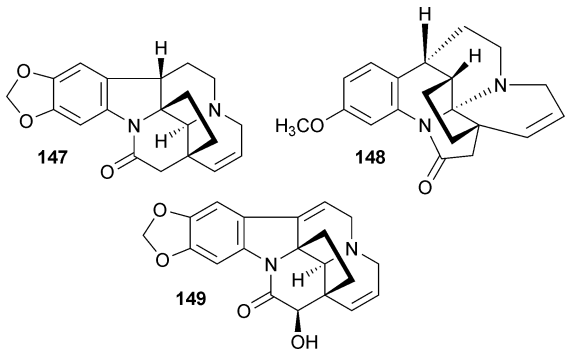
Consequently, most African populations, particularly those in rural areas, use medicinal plants instead. From East Africa, several medicinal plants have been investigated for anti-leishmanial activity, but only a few had compounds with appreciable activities. From the root bark of *Cussonia zimmermanii* three antileishmanial compounds have been reported.[76] These include 8-hydroxyheptadeca-4,6-diyn-3-yl acetate (**123**), 8-hydroxyheptadeca-1-ene-4,6-diyn-3-yl acetate (**124**) and 16-acetoxy-11-hydroxyoctadeca-17-ene-12,14-diynyl acetate (**125**). The polyacetylenes **123**, **124** and **125** exhibited high antileishmanial activity against an axenic culture of *Leishmania donovanii*, with IC_{50} values of 7.8, 0.13 and 0.14 μM respectively, while Miltefosine, a standard antileishmanial drug, had an IC_{50} of 0.44 μM. Furthermore, the polyacetylenes were active against *L. donovanii* in infected macrophages, with LC_{50} values of >10, 0.32 and 2.3 μM respectively, while Miltefosine had an IC_{50} of 0.71 μM.[77]

Antileishmanial natural products have also been reported from the roots of *Salacia madagascariensis*, and include isoiguesterin (**91**) and 20-*epi*-isoiguesterinol (**92**).[63] These two bis-nortriterpenoids exhibited high antileishmanial activity against *L. donovanii*, with IC_{50} values of 0.032 and 0.027 μg mL^{-1} respectively, while the standard drug amphotericin had an IC_{50} of 0.11 μg mL^{-1}. Further analysis showed that these two natural products had IC_{90} values of 0.055 and 0.057 μg mL^{-1} respectively, against the same parasite, whereas amphotericin had an IC_{90} of 0.23 μg mL^{-1}.[63]

5 Natural products with antimicrobial activity

The practice of using plant extracts in the treatment of infectious diseases has existed for many years.[84] As a result, a large number of reports of antimicrobial natural products have been documented from various parts of the world. An interesting observation is that plant species collected based on ethnomedical information had a higher probability of having antimicrobial compounds than plants collected randomly. This has also been the case in East Africa, where various medicinal plants investigated for antimicrobial natural products have yielded several bioactive compounds.

One of the reports from East Africa has been the characterization of antimicrobial compounds from the leaves and roots of *Schizozygia coffaeoides* (Apocynaceae). This species is used in Kenya in the treatment of skin diseases, and its extract has shown high antimicrobial activity against various fungal and bacterial species.[85,86] Bioassay-guided fractionation of the extracts gave two known alkaloids, schizozygine (**147**) and isoschizogaline (**148**), and a new indoline alkaloid, 6,7-dehydro-19β-hydroxy-schizozygine (**149**). These alkaloids exhibited high antimicrobial activity (Table 7), indicating that they are responsible for the observed antifungal and antibacterial properties of the crude extracts of *S. coffaeoides*.[87]



The steroidal saponins **18–22** isolated from *Sansevieria ehrenbergii* exhibited strong antimicrobial activity against the pathogenic yeasts *Cryptococcus neoformans* and *Candida albicans*, with minimum inhibitory concentrations (MICs) in the range of 1–2 μg mL^{-1}.[27] Furthermore, in addition to antifungal activity, saponins **19–21** possess antibacterial activity.[27]

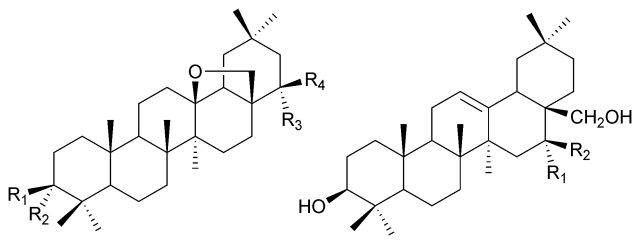
The extracts of the fruits of *Embelia schimperi* (Myrsinaceae) are used by the Kenyan Maasai people as an antibacterial and

Table 7 Antimicrobial activities of compounds from *Schizozygia coffaeoides*[a]

	MIC/μg mL^{-1}				
Organism	**147**	**148**	**149**	Ketoconazole	Ampicillin
Bacillus subtilis	>500	62.5	>500	NT	12.5
Candida albicans	>500	>500	7.8	25	NT
Cladosporium cladosporioides	>500	>500	7.8	25	NT
Cladosporium harbarum	>500	>500	15.6	50	NT
Epidermophyton floccossum	>500	>500	>1.95	25	NT
Escherichia coli	>500	>500	>250	NT	20
Microsporum gypseum	>500	>500	1.95	6.25	NT
Pseudomonas aeruginosa	>500	>500	>500	NT	25
Staphyloccoccus aureus	>500	125	>500	NT	12.5
Trichophyton interdigitale	>500	>500	<3.9	25	NT
Trichophyton mentagrophytes	>500	>500	<1.95	6.25	NT
Trichophyton tonsurans	>500	>500	3.9	50	NT

[a] NT = Not tested.

antihelminthic medicine.[88,89] Phytochemical analysis on the chloroform extract of the stem bark of *Embelia schimperi* gave five oleanane-type pentacyclic triterpenes. These include triterpenoids **150–152**, which have a methyleneoxy bridge, and **153** and **154**, which have unsaturation.[90] It has been reported that compounds **151** and **153**, which have with four or five sugar moieties at position 3, exhibited strong molluscicidal and antifungal properties.[91,92] Three bridged triterpenoids, embelinone (**150**), aegicerin (**151**) and protoprimulagenin (**152**), have been found to be moderately active against a Gram-positive strain of *Rhodococcus* sp., with an average growth inhibition of 1.0, 1.1 and 1.8 cm at a concentration of 50 mg mL^{-1} respectively, while the antibiotic ampicillin, a standard antibacterial agent, had an average growth inhibition of 3.0 cm. Schimperinone (**153**) and primulagenin A (**154**) lacked efficacy.

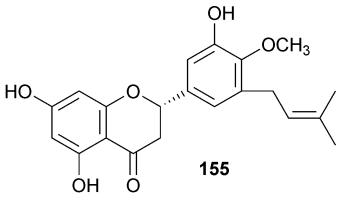


150: R_1,R_2 = O; R_3,R_4 = O
151: R_1 = OH; R_2 = H; R_3,R_4 = O
152: R_1 = R_3 = OH; R_2 = R_4 = H
153: R_1,R_2 = O
154: R_1 = OH; R_2 = H

Like many other *Erythrina* species, the extracts of *E. burttii* (Leguminosae) are used in the treatment of microbial infections.[89] The chloroform extract of the stem bark of *E. burttii*, together with several flavonoids also isolated from it, has shown moderate antifungal and antibacterial activities.[93] The flavonoids isolated from this species include sigmoidin B 4′-methylether (**155**), abyssinone V (**105**), calopocarpin (**156**), neorautenol (**157**) and bidwillon A (**158**).[93] Although these compounds were active against fungi and Gram-positive bacteria, they generally had weak activity against Gram-negative bacteria (Table 8).

Flavonoids have been reported from the root bark of *Erythrina abyssinica*,[94] and include erythrabyssins I (**159**) and II (**160**), abyssinones I (**162**), II (**161**), III (**163**), IV (**104**), V (**105**) and VI (**164**),[94] and two known flavonoids, phaseollin (**165**) and phaseollidin (**166**).[95] All exhibited moderate antimicrobial activity against various microbes (Table 9).[94]

Antifungal prenylindoles have been reported from the stem and root bark of *Isolona cauliflora* (Annonaceae). This species is



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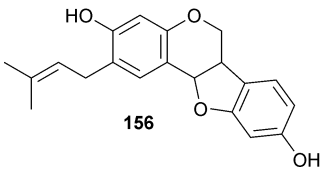

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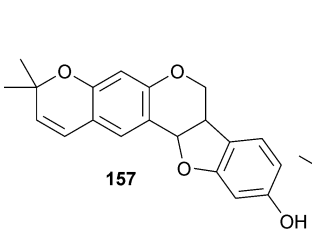

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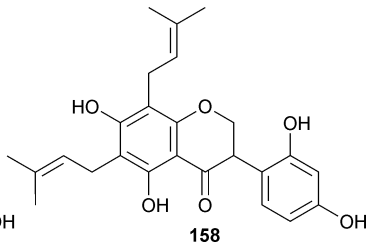


158

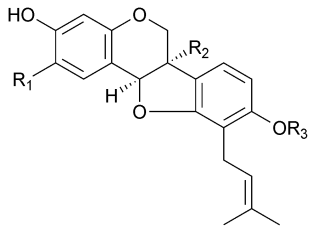
currently endangered due to overharvesting and grows in the East Usambara Mountains, Tanzania.[96] Four compounds have been reported from this species, namely caulindoles A (**167**), B (**168**), C and D.[97] At a concentration of 2.73 mmol mL^{-1}, caulindole A (**167**) exhibited mild growth inhibitory activity against the plant-pathogenic fungi *Botryodiplodia theobromae*, *Aspergillus niger* and *A. flavus* by 20.5, 18.0 and 18.3% respectively, while at 1.99 mmol mL^{-1} caulindole D inhibited fungal growth by 15.1, 12.5 and 16.0% respectively.[97] The other compounds lacked efficacy.

The methanol extract of *Leucas volkensii* (Lamiaceae) has been found to have high antimycobacterial activity against *Mycobacterium tuberculosis*.[98] A monoterpenoid (*E*)-phytol (**169**) was identified as the major compound in the extract, and had high antimicrobial activity against *M. tuberculosis*, with an MIC value of 2 μg mL^{-1}. Other compounds, namely (*Z*)-phytol (**170**), (3*R*,5*R*,7*R*,11*R*)-phytanol (**171**), (*E*)-phytol acetate (**172**), a mixture of the (2*S*,3*S*)- and (2*R*,3*R*)-isomers of (*E*)-phytyl epoxide (**173**) and (3*R*,5*S*,7*R*,11*R*)-phytanic acid (**174**), had significant antimicrobial activities activity against the test organisms.[98] The monoterpenes geraniol (**175**) and farnesol (**176**)

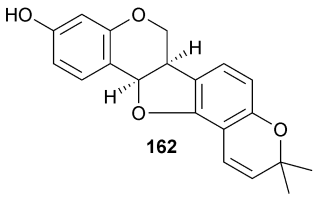
Table 8 Antimicrobial activities of compounds isolated from *Erythrina burttii*[a]

	Inhibition zone/mm						
Organism	**105** (100)	**155** (100)	**156** (100)	**157** (100)	**158** (100)	Nystatin (5)	Oxacillin (1)
Candida albicans (ATCC 90028)	NA	20	26	6	9	12	NA
Escherichia coli (ATCC 25922)	NA	NA	NA	NA	NA	NA	6
Microsporum gypsum (clinical isolate)	NA	30	34	12	15	30	NA
Saccharomyces cerevisiae (ATCC 9763)	NA	14	20	15	18	32	NA
Staphylococcus aureus (ATCC 25923)	12	15	23	12	15	NA	18
Trychophyton mentagrophyte (clinical isolate)	NA	26	40	26	25	14	NA

[a] NA = Not active. The loading per disc in μg is given in parentheses for each compound.



159: R_1 = H, R_2 = OH, R_3 = CH_3
160: R_1 = $CH_2CH{=}C(CH_3)_2$, R_2 = R_3 = H
161: R_1 = R_2 = R_3 = H



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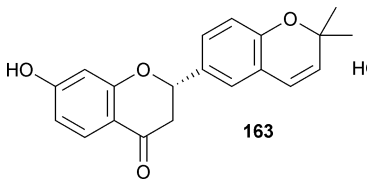

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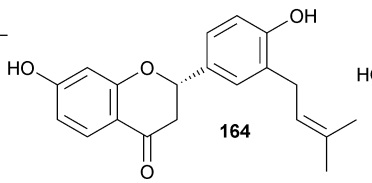

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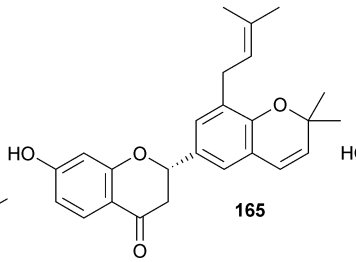

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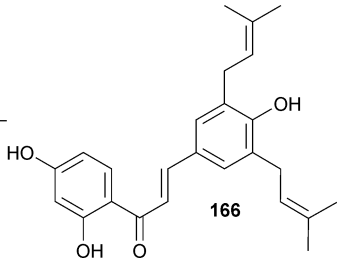

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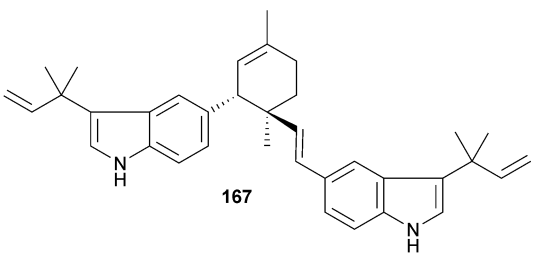
Table 9 Antimicrobial activities of compounds from *Erythrina abyssinica*

	MIC/μg mL^{-1}							
Organism	**159**	**160**	**161**	**162**	**163**	**164**	**165**	**166**
Bacillus subtilis	6.25	3.13	50	25	>100	>100	6.25	25
Candida utilis	50	>100	100	100	>100	>100	50	>100
Escherichia coli	>100	>100	>100	>100	>100	>100	>100	>100
Mucor mucedo	25	>100	50	50	>100	>100	12.5	100
Penicillium crustosum	>100	>100	>100	>100	>100	>100	>100	>100
Pseudomonas aeruginosa	>100	>100	>100	>100	>100	>100	>100	>100
Saccharomyces cerevisiae	50	>100	100	100	>100	>100	25	>100
Staphylococcus aureus	12.5	3.13	50	25	>100	>100	12.5	50



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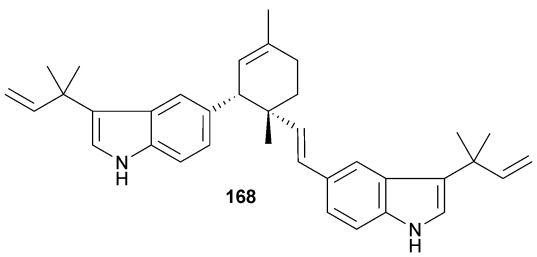

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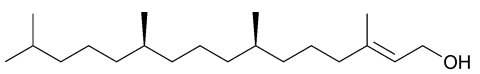

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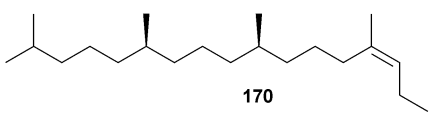

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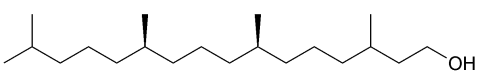

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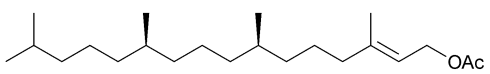

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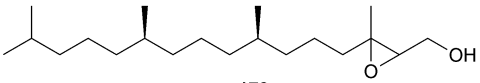

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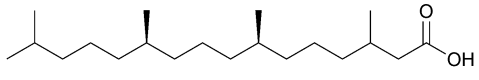

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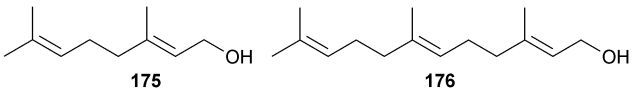
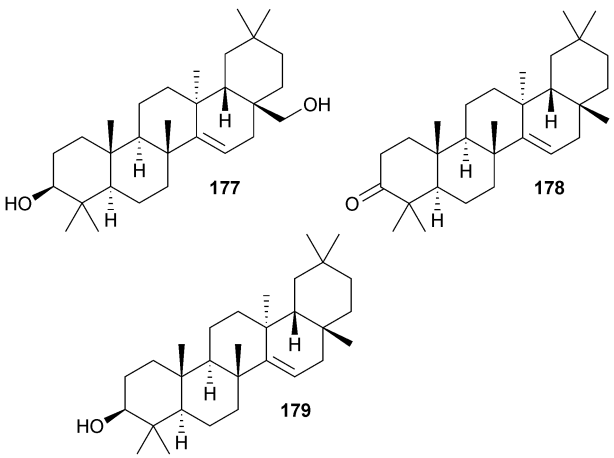
(which resembles (*E*)-phytol) had MIC values of 64 and 8 μg mL^{-1}, respectively.[98]

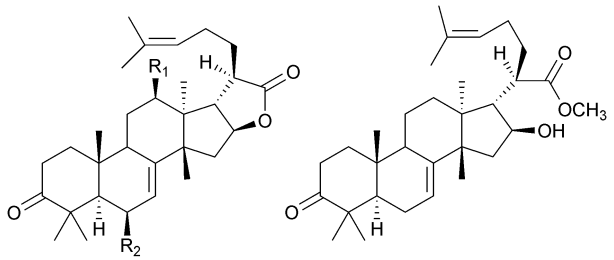


175 **176**

Three pentacyclic triterpenes, namely myricadiol (**177**), taraxerone (**178**) and taraxerol (**179**), have been reported from the leaves of *Myrsine africana* (Myrsinaceae) collected from Machakos, Kenya. All compounds exhibited moderate growth inhibition of the fungus *Cladosporium cucumerinum*. [99] Triterpenoids have also been reported from the methanolic extracts of the seeds of *Melia volkensii* (Meliaceae), a medicinal plant widely used in Kenya for alleviation of pain.[100] These include two new (20*R*)-euphane-type triterpenoids, 12β-hydroxykulactone (**180**) and 6β-hydroxykulactone (**181**),[100] together with a known compound, kulonate (**182**).[101,102] These three compounds exhibited high activity against *M. tuberculosis*,with MIC values of 16, 4, and 16 μg mL^{-1} respectively.[101]



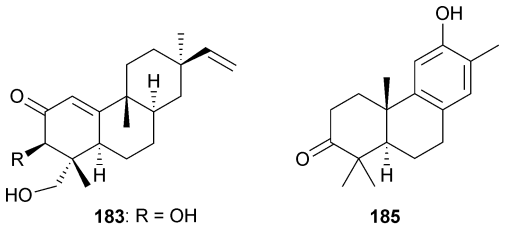
177 **178** **179**



180: R_1 = OH, R_2 = H
181: R_1 = H, R_2 = OH

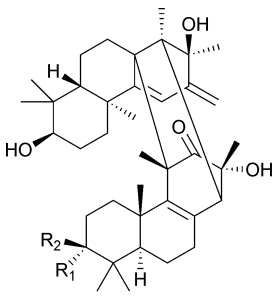
182

Hugonia castaneifolia (Linaceae) an important medicinal plant in Tanzanian folk medicine, has been reported to be rich in rosane diterpenes.[103] Four diterpenoids, namely hugorosenone (**136**), 18-hydroxyhugorosenone (**183**), 18-hydroxy-3-deoxyhugorosenone (**184**) and 12-hydroxy-13-methylpodocarpa-8,11,13-trien-3-one (**185**), have been isolated from the root bark of this species. The compounds exhibited high antifungal activity against *Cladosporium cucumericum*, while five dipodocarpanoids also from *H. castaneifolia*, hugonones A (**186**) and B (**187**), hugorosenol (**188**), hugonianene B (**135**) and 2-hydroxyhenpentacont-2-enal (**189**), had weak activity. [79,104]

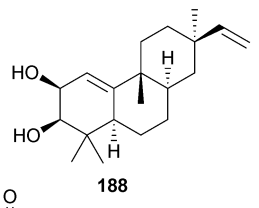


183: R = OH
184: R = H

185



186: R_1 = H, R_2 = OH
187: R_1,R_2 = O



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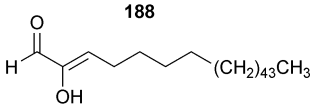
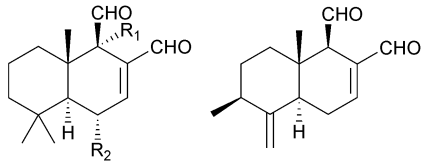


189

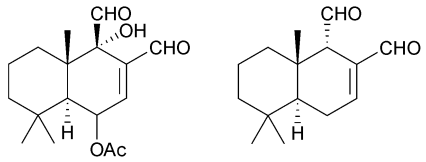
Warburgia ugandensis (Canellaceae) is a well known and widely used plant in folk medicine and food spices in East Africa.[89] Bioassay-directed fractionation of the hexane extract of its bark yielded two new active sesquiterpene dialdehydes, warburganal (**190**) and muzigadial (**191**), in addition to a known congener, polygodial (**192**).[105,106] Furthermore, three sesquiterpene dialdehydes, mukaadial (**193**), ugandensidial (**194**) and epipolygodial (**195**), have also been characterized from the active fraction.[107–109] All sesquiterpenes exhibited moderate antimicrobial activity, with the exception of **192**, which had higher activity against the test organisms (the MIC values were 0.78, 6.25, 1.56, 1.56 and 1.56 μg mL^{-1} against *Saccharomyces cerevisiae*, *Schizosaccharomyces pombe*, *Hensenula anomala*, *Candida utilis* and *Sclerotinia libertiana*, respectively). The level of activity was comparable to that of amphotericin B, a standard antibiotic drug, suggesting that polygodial may be potent enough to be considered for practical application.[105,106] Similar antimicrobial sesquiterpene dialdehydes have also been reported from the bark of *Warburgia stubfmunnii*.[110]

Antimicrobial sesquiterpenes have also been isolated from the leaves of *Vernonia amygdalina* (Asteraceae). Apart from being used by humans for medicinal purposes, this plant species has been found to be consumed by wild chimpanzees, purportedly for self-medication purposes.[111] Several sesquiterpene lactones (STLs), namely vernodalin (**85**), vernodalol (**86**), vernolide (**87**), hydroxyvernolide (**88**), vernolepin (**196**), vernomenin (**197**), 4,15-dihydrovernodalin (**198**), 1,2,2′,3′-tetrahydrovernodalin (**199**), 1,2,11,13,2′,3′-hexaahydrovernodalin (**200**) and 1,2,4,11,13,15,2′,3′-octahydrovernodalin (**201**), have been reported. These STLs were screened against two Gram-positive (*Bacillus subtilis* and *Micrococcus lutea*) and two Gram-negative (*Escherichia coli* and *Agrocterium tumefaciens*) bacteria species. Compounds **85**,



190: R_1 = OH, R_2 = H
192: R_1 = H, R_2 = H
193: R_1 = OH, R_2 = OH

191



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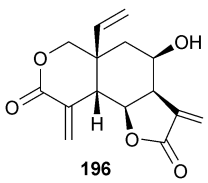
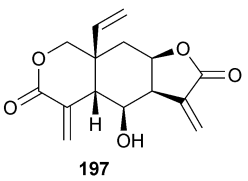
195

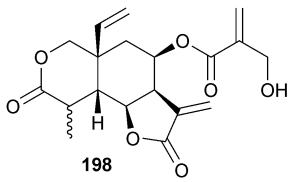
87, **88**, **200** and **201** strongly inhibited the growth of *B. subtilis* and *M. lutea* at 5 μg per disc,[112] but all the STLs lacked efficacy against the Gram-negative bacteria.



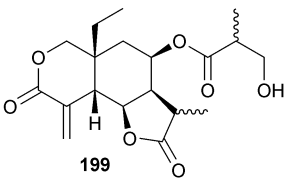
196



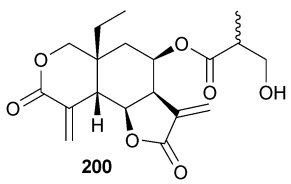
197



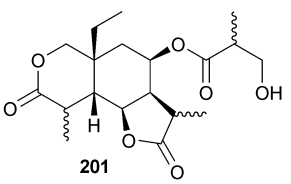
198



199



200

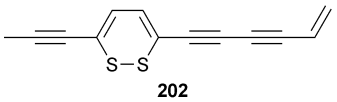


201

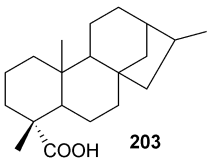
Aspilia mossambicensis (Asteraceae) is another plant species used by both humans and chimpanzees for medicinal purposes. The leaves contains a potent antibiotic compound, thiarubrine A (**202**), which has been found to be the major compound in the extract of this plant species.[113] The abundance of thiarubrine A in the leaves supports a hypothesis that wild chimpanzees consume leaves of *Aspilia* species for self-medication purposes. Furthermore, two more antibacterial diterpenes, kaurenoic (**203**) and grandiflorenic acid (**204**), have been reported from the leaves of this species.[114]

6 Anti-HIV natural products

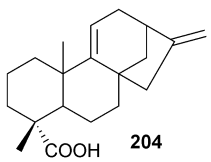
The search for anti-HIV natural products from the East African flora has been limited due to the sensitivity of the infection itself and also due lack of facilities to conduct antiviral assays. Although there are numerous claims of efficacious herbal



202



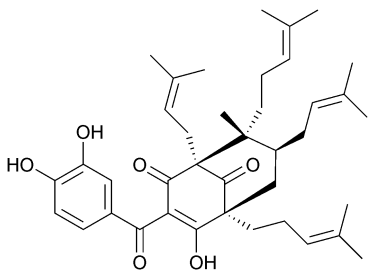
203



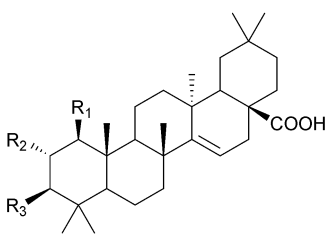
204

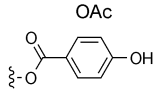
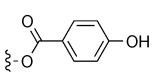
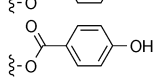
formulations used as natural anti-retroviral agents, most of these claims remain unvalidated. Consequently, this has raised the interest of screening crude plant extracts for anti-HIV activity, while little research has been done on pure compounds.

East African *Garcinia* species have been found to possess antiviral benzophenones.[115] An example of this is a polyisoprenylated benzophenone commonly known as guttiferone A (**205**), isolated from the roots of *Garcinia livingstonei* (Clusiaceae). Guttiferone A was found to inhibit the cytopathic effects in human lymphoblastoid CEM-SS cells *in vitro*, with EC_{50} values of $\leq$10 μg mL^{-1}.[115] Antiviral natural products have also been reported from the root bark of *Maprounea africana* (Euphorbiaceae), which includes four pentacyclic triterpenes, namely maprounic acid (**206**), maprounic acid acetate (**207**), 1β-hydroxymaprounic acid 3-*p*-hydroxybenzoate (**208**) and hydroxymaprounic acid 2,3-bis-*p*-hydroxybenzoate (**209**).[116] The four triterpenoids, together with hydrolysis products of **208** and **209** (**210** and **211**) were tested for their HIV-1 reverse trancriptase



205



	R_1	R_2	R_3
206	H	H	OH
207	H	H	OAc
208	OH	H	
209	H		
210	OH	H	OH
211	H	OH	OH

inhibition. Only **208**–**211** were found to inhibit HIV-1 RT, with IC_{50} values ranging from 3 to 5 μM.[116]

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