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Phytochemical and Pharmacological Studies of some Medicinal Plants from Tanzania

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A B S T R A C T

In the past 6 years of our phytochemical and pharmacological studies of important medicinal plants growing in Tanzania, we investigated 11 plant genera namely *Allanblackia*, *Annona*, *Antidesma*, *Baphia*, *Croton*, *Dalbergia*, *Garcinia*, *Harrisonia*, *Mammea*, *Milletia* and *Teclea*. In different species of these genera, we isolated and reported over 50 secondary metabolites, among them 15 compounds were new to the chemical literature. Furthermore, we explored the biological activities of extracts and pure compounds isolated from these plants. Our focus was on anti-HIV, anticancer, antimicrobial, antimalarial and antioxidant activities. Interesting biological activities were noted and paved ways for further studies that might lead to potential drug discovery.

Introduction

Tanzania represents a potential treasure trove of natural products being the 13th most biodiverse country on the planet. East African flora has over 21,000 higher plant species out of which 10,600 are found in Tanzania. The country has over 2,600 species that are reported to be used for medicinal purposes while about 1200 are endemic to Tanzania.

It is estimated that over 70% of the Tanzanian population live in the rural areas, making up 120 distinct tribes. These tribes all have knowledge of traditional medicines which they generate from plant materials. Although some of the plant species are used as herbal remedies and for other applications, not many studies have been carried out to untie the chemical constituents and biological properties of some of the Tanzania plant species, particularly those considered to be restricted to this country. Hence, the active components of the vast majority of these medicines remain unknown. As many of the species in these genera are endemic to Tanzania there is considerable scope to identify new natural products with important pharmacological properties to fight disease causing pathogens. Microorganisms are frequently a cause of prevailing diseases, presenting a serious public health issue in a significant segment of the population as showed by both private and official health care systems in Tanzania and around the global. On the other hand, chronic diseases like HIV/AIDS and cancer have raised the world's health crisis due to both their emergent and long-term development. Cancer cases distribution shows no differences in its epidemiology in all regions of the world whereas, HIV/AIDS have affected the world excessively and the greatest burden being in sub-Saharan Africa (WHO, 2008). Currently, about 80% of the populations in developing countries use traditional medicine for their healthcare (Bannerman et al., 1983) with at least 25% of drugs been derived from plants. This necessitates the demand for the development of new drugs particularly of plant origin.

Our efforts to investigate into the phytochemistry of the Tanzanian medicinal plants have led to the isolation of many secondary metabolites of intriguing chemical structures as well as noticeable biological activities. This paper reviews our investigations for natural products from some Tanzanian medicinal plant species during the past 7 years, some of the compounds having unusual chemical structures and important biological properties

Plants Investigated

Our focus was mainly to investigate plants that are not studied but have reported for use in traditional medicine as well as those which are endemic to Tanzania. Furthermore our choice was also guided by the ethnomedical information obtained from the plant locality as well as the chemotaxonomical and/or ethnobotanical information. Table 1 indicates the status of the investigated plants whereby seven (7) plants were indigenous, two (2) were exotic and seven (7) were endemic to Tanzania.

Phytochemistry

Different chromatographic techniques were employed during the phytochemical work of the plants under this study. These include column chromatography, preparative column chromatography, size exclusion technique and high performance liquid chromatography. Structure elucidation and identification of the isolated compounds were made possible by using spectroscopic facilities obtained from our collaborators in Germany and France. Our results revealed the presence of different classes of natural products that are classified in the following broad structural categories namely alkaloids, benzophenones, coumarins, flavonoids, limonoids, terpenoids, xanthones and other classes (Table 2).

Alkaloids

Alkaloid is a class of naturally occurring organic nitrogen-containing bases. They are known to have diverse and important physiological effects on humans and other animals. Although the chemical structures of alkaloids are extremely variable, they contain at least one nitrogen atom in an amine-type structure. The well-known alkaloids that have high application in modern medicine include vincristine, vinblastine, morphine, strychnine, quinine, ephedrine and nicotine (Wink, 1998).

Our investigations on three Tanzanian medicinal plants (*Annona senegalensis*, *Annona squamosa* and *Teclea amaniensis*) resulted into isolation of nine (9) alkaloids.

Table.1 List of Plants investigated under study

S/N	Plant*	Family	Place of collection/Region	Part collected	Voucher specimen
1	*Annona senegalensis* I	Annonaceae	Changanyikeni/DSM	Leaves	OT 00352
2	*Annona squamosa* X	Annonaceae	Bunju/DSM	Leaves	OT 00353
3	*Baphia kirki* E**	Fabaceae	Pugu/DSM	Stem	EBM601
4	*Baphia puguensis* E**	Fabaceae	Pugu/DSM	Root	EBM 560
5	*Antidesma venosum* I	Euphorbiaceae	Handeni/Tanga	Root & Stem	HOS 974
6	*Croton jatrophoides* I	Euphorbiaceae	Pande/DSM	Root	ZHM 12576
7	*Dalbergia vacciniifolia* I	Fabaceae	Changanyikeni/DSM	Stem	FM 1682
8	*Allanblackia ulugurensis* E	Clusiaceae	Morningsite/Moro	Stem	BM 6401
9	*Garcinia edulis* X	Clusiaceae	Amani/Tanga	Root	HOS 3426
10	*Garcinia semseii* E	Clusiaceae	Kihansi/Iringa	Stem	FM 1629
11	*Garcinia volkensii* I	Clusiaceae	Amani/Tanga	Stem	HOS 3409
12	*Mammea usambarensis* E	Clusiaceae	Shagayu/Tanga	Stem & Fruits	SM 732
13	*Harrisonia abyssinica* I	Simaroubaceae	Mza/DSM	Root & Stem	HSO 5627
14	*Milletia puguensis* E	Leguminosae	Pugu/DSM	Root	EBM 561
15	*Teclea amanuensis* E	Rutaceae	Amani/Tanga	Stem	FM1321

*** E = Endemic, I = Indigenous, X = Exotic**
**** =** threatened by habitat loss

Table.2 List of compounds isolated

Class	Name	Source	Part
Alkaloids	(-)-Roemerine (**1**)	*Annona senegalensis*	Leaves
	Annonaine (**2**)	*A. squamosa*	Leaves
	Tecleamaniensine A (**3**)	*Teclea amaniensis*	Stem
	Tecleamaniensine B (**4**)	*T amaniensis*	Stem
	Amaniensine (**5**)	*T amaniensis*	Stem
	Dictamnine (**6**)	*T amaniensis*	Stem
	Kokusaginine (**7**)	*T amaniensis*	Stem
	Evoxanthine (**8**)	*T amaniensis*	Stem
Benzophenone	Semsinones A (**9**)	*Garcinia semseii*	Stem
	Semsinones B (**10**)	*G. semseii*	Stem
	Semsinones C (**11**)	*G. semseii*	Stem
	Guttiferone A (**12**)	*G. semseii*	Fruit hulls
	Guttiferone K (**13**)	*G. semseii*	Fruit hulls
	Guttiferone F (**14**)	*Allanblackia ulugurensis*	Root
	30-*epi*-cambogin (**15**)	*A. ulugurensis*	Root
Coumarins	Mammea B/BB (**16**)	*Mammea usambarensis*	Stem
	Mammea B/BD (**17**)	*M. usambarensis*	Stem
	Mammea B/AB (**18**)	*M. usambarensis*	Fruit
	Mammea B/AB cyclo D (**19**)	*M. usambarensis*	Fruit
Flavonoids	Puguflavanone A (**20**)	*Baphia puguensis*	Root
	Puguflavanone B (**21**)	*B. puguensis*	Root
	Erythrisenegalone (**22**)	*B. puguensis*	Root
	6,2'-dimethoxy-7,4'-dihydroxyisoflavone (**23**)	*Dalbergia vacciniifolia*	Stem
	6,2',4'-trimethoxy-7-hydroxyisoflavone (**24**)	*D. vacciniifolia*	Stem
	6,2',4',5'-tetramethoxy-7-*O*-[β−D-apiofuranosyl-(1→6)-β−D-glucopyranoside] isoflavone (**25**)	*D. vacciniifolia*	Stem
	6,2',4',5'-tetramethoxy-7-hydroxyisoflavone (**26**)	*D. vacciniifolia*	Stem
	Morelloflavone (**27**)	*Garcinia volkensis*	Stem
Limonoids	Harrisonin (**28**)	*Harrisonia abyssinica*	Root
	Pedonin (**29**)	*H. abyssinica*	Root
Terpenoids	Achilleol A (**30**)	*Garcinia semseii*	Stem

	Isoteucvin (**31**)	*Croton jatrophoides*	Root
	Jatrophoidin (**32**)	*C. jatrophoides*	Root
	Penduliflaworosin (**33**)	*C. jatrophoides*	Root
	Teucvin (**34**)	*C. jatrophoides*	Root
	Lupeol (**35**)	*Garcinia edulis*	Root
	Lupeol acetate (**36**)	*Garcinia edulis*	Root
	Betulinic acid (**37**)	*A. venosum*	Root
	Friedelin (**38**)	*Garcinia edulis*	Root
	*Epi*friedelanol (**39**)	*A. venosum*	Root
Xanthones	Baphikixanthones A (**40**)	*Baphia kirkii*	Stem
	Baphikixanthones B (**41**)	*B. kirkii*	Stem
	Baphikixanthones C (**42**)	*B. kirkii*	Stem
	Garceduxanthone (**43**)	*Garcinia edulis*	Root
	Forbexanthone (**44**)	*G. edulis*	Root
	Isorheediaxanthone B (**45**)	*Garcinia volkensis*	Stem
	12-hydroxy-des-D-garcigerrin A (**46**)	*G. volkensis*	Stem
	Rheediaxanthone B (**47**)	*G. volkensis*	Stem
Other compounds	3-hydroxy-5-methoxybiphenyl (**48**)	*Allanblackia ulugurensis*	Stem
	3-Methoxy-8,9-methylenedioxypterocarpene (**49**	*Baphia puguensis*	Root
	4-hydroxy-3-methoxycinnamate (**50**)	*B. puguensis*	Root
	Baphikinone (**51**)	*Baphia kirkii*	Stem
	(3*R*,4*R*,5*S*)-4-hydroxy-5-methyl-3-tetradecanyl γ-lactone (**52**)	*A. venosum*	Stem

From the ethyl acetate of the leaves of *A. senegalensis* and *A. squamosa* we isolated (-)-roemerine (1) (You et al., 1995) and annonaine (2) (Miski et al., 1995) respectively, while from the stem bark of an East African medicinal plant, *Teclea amaniensis* we isolated two novel furanoquinoline alkaloids named tecleamaniensine A (3) and tecleamaniensine B (4) as well as an acridone alkaloid, amaniensine (5), in addition to dictamnine (6), kokusaginine (7) and evoxanthine (8). Compounds 6, 7 and 8 were previously reported from *Teclea natalensis* (Tarus et al., 2005), *Comptonella sessifoliola* (Pusset et al., 1991) and *Vepris sclerophylla* (Rasoanaivo et al., 1999) respectively. The chemical structures of compounds 1-8 are presented in Fig. 1.

Benzophenones

Our phytochemical investigation on some Tanzanian *Garcinia* species revealed the presence of benzophenones. This class gives a series of oxidized and isoprenylated compounds that are believed to originate from the mixed shikimate and acetate biosynthetic pathways (Beerhues and Liu, 2009). Many benzophenone compounds from the genus *Garcinia* contains the cyclohexatrione moiety, which is generated by incorporation of several isoprenyl groups into C-2 and C-4 of a 1,3,5-trihydroxybenzophenone to form a bicyclo[3.3.1]nonane (Oliveira et al., 1999). This type of bridged polycyclic skeletons is widely distributed in the genus *Garcinia* and they are associated with a wide range of biological and pharmacological activities (Wu et al., 2008).

This type of compounds has been isolated from Tanzanian plant species of the family Clusiaceae. Investigation from the ethanol extract of the stem bark of *Garcinia semseii* gave four isoprenylated benzophenones, named semsinones A-C (**9-11**), while study on the fruit hulls of *G. semseii* yielded guttiferones A (**12**) and K (**13**). We also investigated the stem bark of *Allanblackia ulugurensis* that afforded guttiferone F (**14**) and 30-*epi*-cambogin (**15**). Their structures were established using spectral data and by comparison with the closely related compounds reported in the literature (Fig. 2).

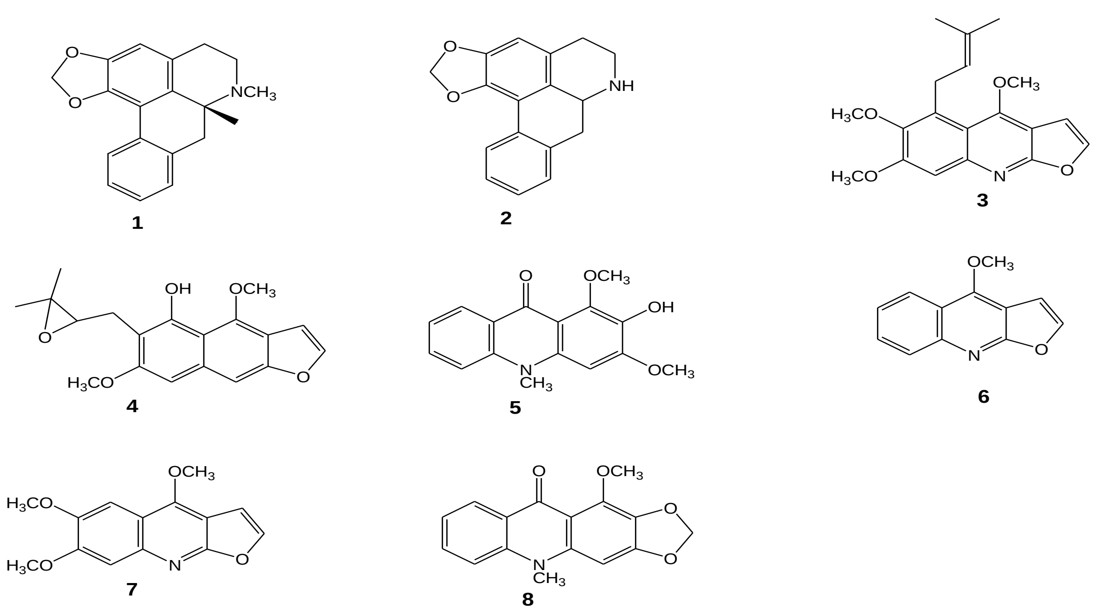

Fig.1 Structures of alkaloids isolated from some Tanzanian plants

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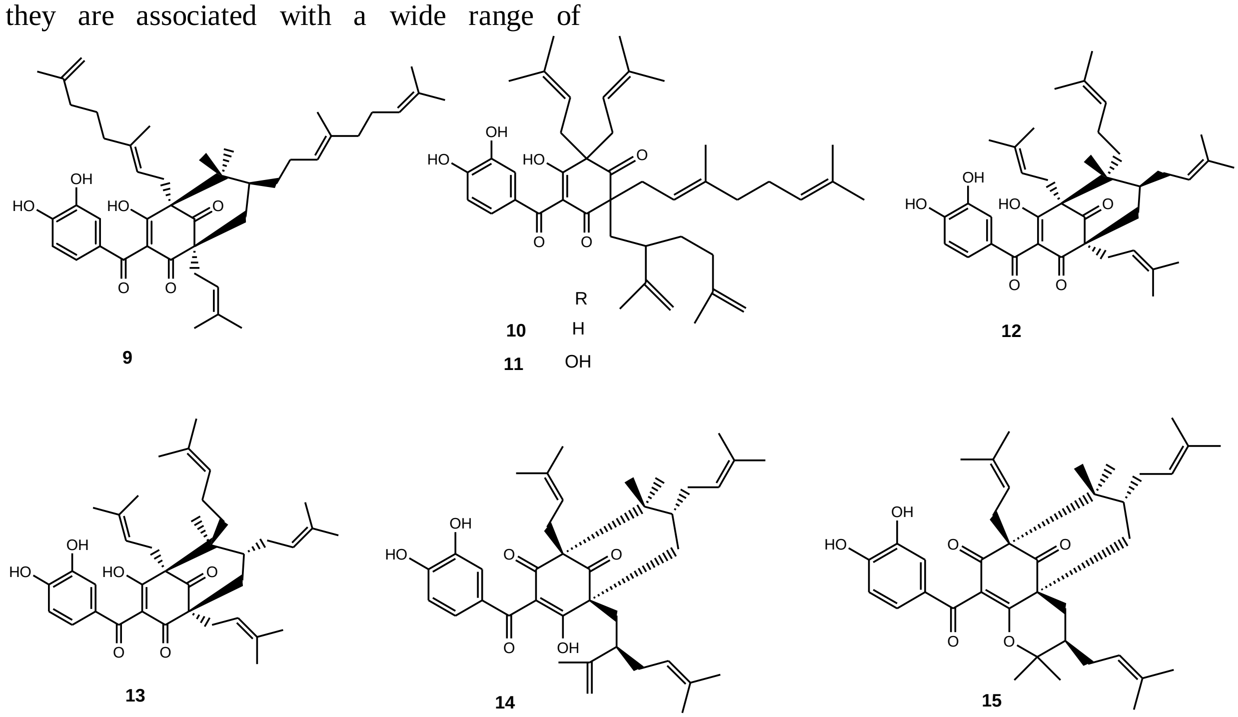


Fig. 2 Structures of benzophenones isolated from some Tanzanian plants

Coumarins

This is a group of plant-derived polyphenolic compounds that belong to the benzopyrones family. Several natural and synthetic coumarins and derivatives possess potent biological activities including antiviral, anticancer, anti-inflammatory, anticoagulant, antifungal, antioxidant, and cytotoxic agents. Furthermore, these compounds have some industrial uses whereby a coumarin like 7-hydroxycoumarin is widely used in polymer science research.

Our research on Tanzanian medicinal plants, revealed the presence of an interesting group of coumarins known as mammea-type coumarins (**16-19**) as per Table 2. These compounds were isolated from *Mammea usambarensis*, the plant that is endemic to Tanzania with its fruits being edible to both wild animals and human beings. Figure 3 indicates the chemical structures of mammea-type coumarions.

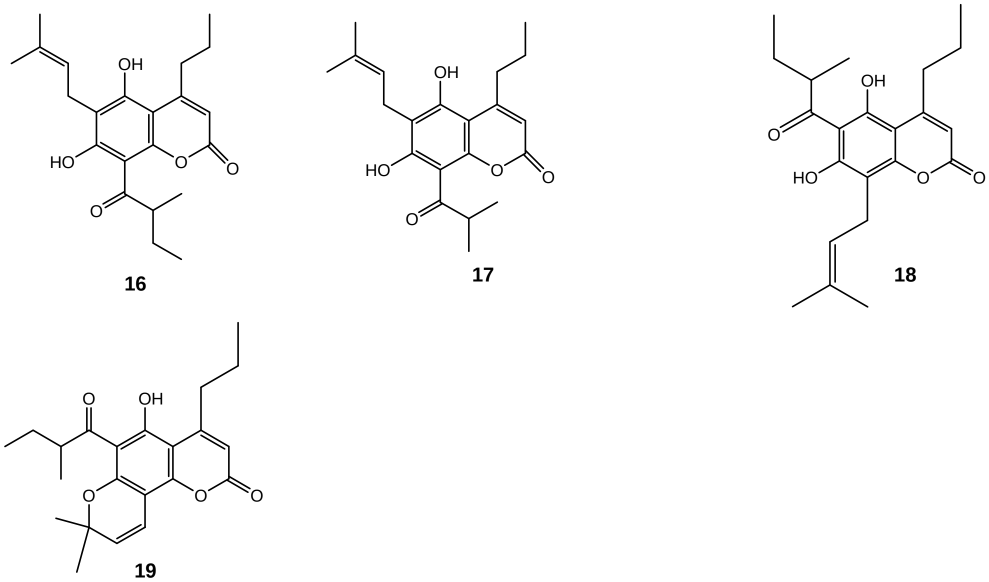


Fig.3 Structures of mammea-type coumarins isolated from some Tanzanian plants

Flavonoids

This is a class of secondary metabolites which is characterized by compounds having yellow colour in nature. Chemically, they have the general structure of a 15-carbon skeleton, which consists of two phenyl rings and heterocyclic ring, abbreviated as C6-C3-C6 skeleton. The three cycle or heterocycles in the flavonoid backbone are generally called ring A, B and C with ring A usually shows a phloroglucinol substitution pattern.

In this investigations, three plants namely *Dalbergia vacciniifolia*, *Garcinia volkensis* and *Baphia puguensis* were investigated phytochemically leading to the isolation of eight flavonoids (**20-27**) as indicated in Table 2. Their structures (Fig. 4) were determined by using available spectroscopic techniques.

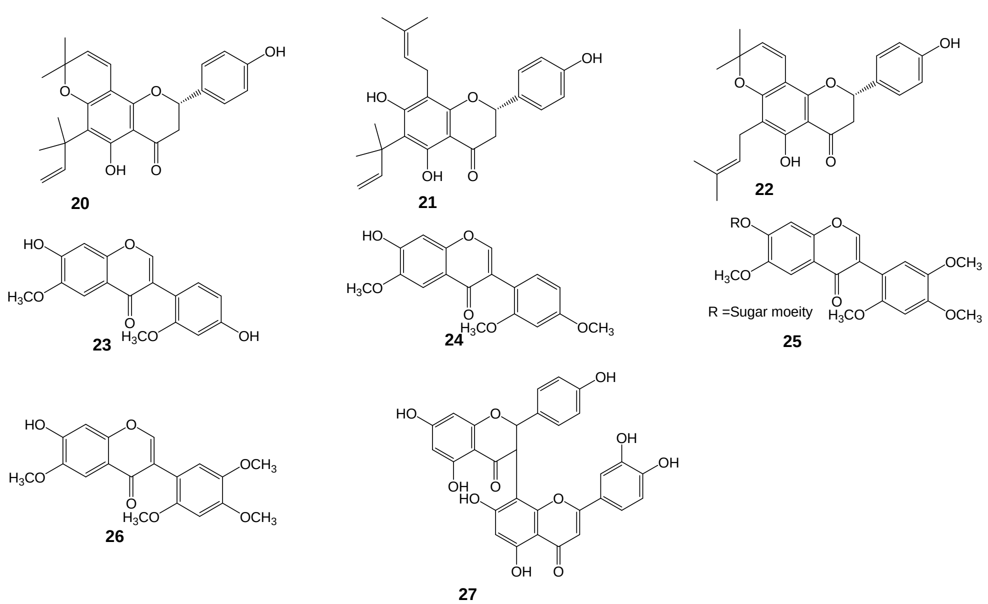
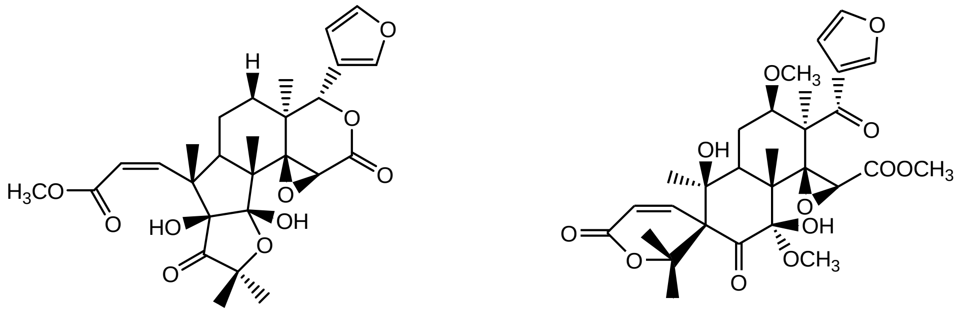


Fig.4 Structures of flavonoids isolated from some Tanzanian plants

Limonoids

These are the natural products that are reported to be abundant in citrus fruit and other plants of the families Rutaceae and Meliaceae. The chemical structures of limonoids consist of a furanolactone as a core structure together with four six-membered rings and a furan ring. Sometimes they are classified as tetranortriterpenes.

In our research done from a Tanzanian plant *Harrisonia abysinica*, two limonoids (28-29) were isolated and their structures (Fig 5) were determined by extensive use of different spectroscopic techniques



28 **29**

Fig.5 Structures of limonoids isolated from some Tanzanian plants

Terpenoids

Terpenoids belong to a large and structurally diverse class of naturally occurring organic compounds which are distributed throughout the plant kingdom. They are commonly found in higher plants, lower animals (anthropods, coelenterates and molluscs), fungi, lichens and algae (Leistner, 2000). This class of compounds comprises natural products which are derived from a common biosynthetic pathway based on mevalonate as parent. Terpenoids are generally grouped into four common groups depending on the number of carbon atoms in the basic skeleton. These groups are monoterpenoids (C_{10} skeleton), sesquiterpenoids (C_{15} skeleton), diterpenoids (C_{20} skeleton) and triterpenoids (C_{30} skeleton).

In our phytochemical study from some Tanzanian medicinal plants, we investigated four plant species namely *Garcinia edulis*, *Garcinia semseii*, *Croton jatrophoides* and *Antidesma venosum* (Table 2). Ten compounds (**30-39**) were isolated having different chemical structures as indicated in Fig. 6.

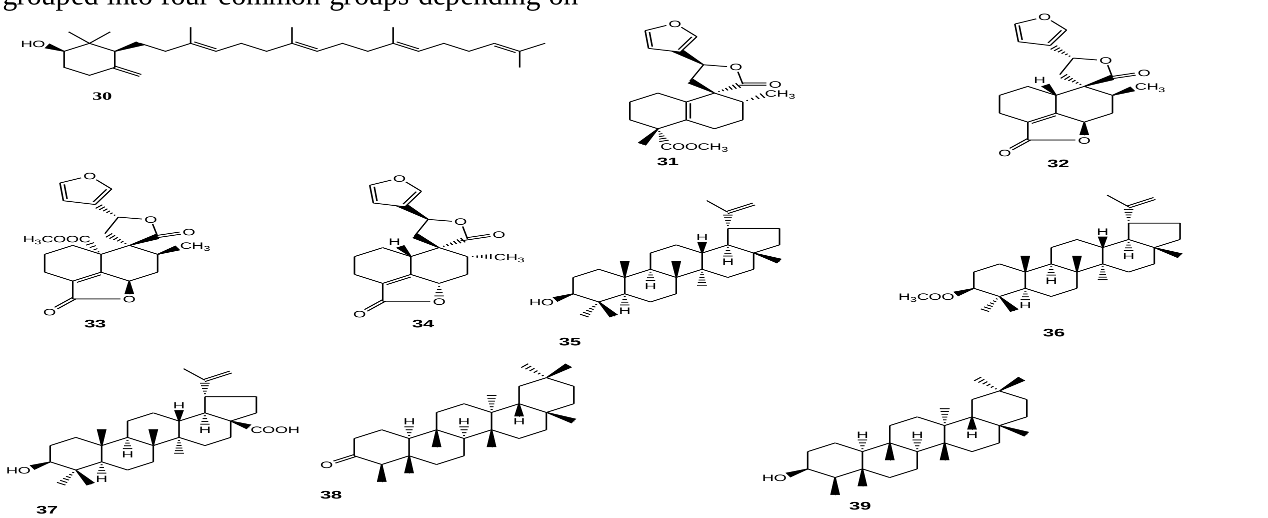
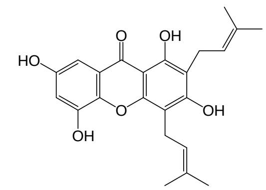


Fig.6 Structures of terpenoids isolated from some Tanzanian plants

Xanthones

This is a unique group of plant polyphenols with structures characterized by the presence of more than one phenolic group. The chemical structure of xanthones forms the central core of a variety of naturally occurring organic compounds with their planar-six carbon molecules in a conjugated ring system consisting of a backbone molecule and various chemical groups attached to it. Currently, there is over 200 xanthones have been identified different plant families, notably from Clusiaceae, Bonnetiaceae and many others. Phytochemical investigations recently done in our research group revealed eight xanthones (40-47) isolated from *Baphia kirkii*, *Garcinia edulis* and *Garcinia volkensis* (Table 2). Their structures (Fig. 7) were established by using a combination of spectroscopic techniques.



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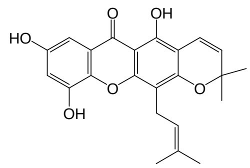

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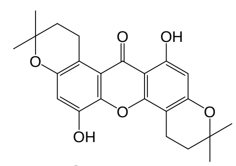

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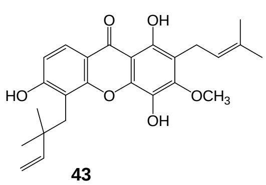

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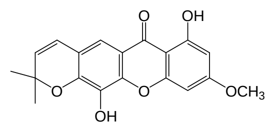

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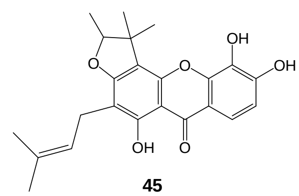

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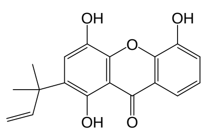

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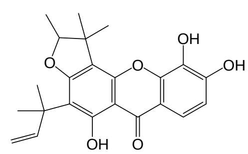

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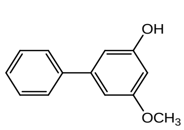
Fig.7 Structures of xanthones isolated from some Tanzanian plants

Other compounds

In this category, we obtained five compounds (Fig. 8) namely 3-hydroxy-5-methoxybiphenyl (48) isolated from *Allanblackia ulugurensis*, 3-Methoxy-8,9-methylenedioxypterocarpene (49) from *Baphia puguensis*, 4-hydroxy-3-methoxycinnamate (50) from *Baphia puguensis*, Baphikinone (51) from *Baphia kirkii* and (3*R*,4*R*,5*S*)-4-hydroxy-5-methyl-3-tetradecanyl γ-lactone (52) from *Antidesma venosum*.



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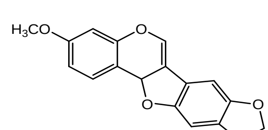

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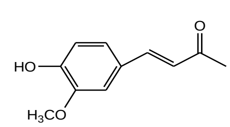

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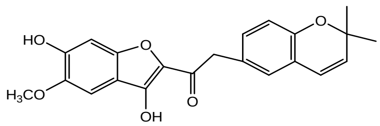

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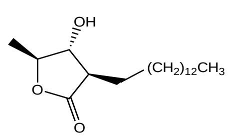

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Fig.8 Structures of other classes of compounds isolated from some Tanzanian plants

Table.3 Biological activities of extracts and pure compounds

	Plant	Part used	Tested organism/condition	Remarks
Extracts				
	Annona senegalensis, & *A. squamosa*	Leaves	*Culex quinquefascintus* larva	The LC_{50} value for crude extracts of *A. senegalensis* and *A. squamosa* were 0.67 and 0.64 µg/mL respectively for shrimp and 23.42 and 11.01 µg/mL respectively for *Culex quinquefascintus*
	Garcinia semseii	Fruit hulls	anti-HIV-1 protease activities	A series of isolated benzophenones indicated remarkable activity in human cell lines with CC_{50} values ranging from 1.97-16.1 µg/ml. The fruit hulls of *Garcinia semseii* showed the most potent inhibitory activity against HIV-1 PR with an IC_{50} value of 5.7 µg/ml
	Garcinia edulis	Stem bark	Anti-HIV-1 protease	The crude ethanol extract of the root bark of *G. edulis* exhibited a mild anti-HIV-1 PR activity with IC_{50} value of 51.7 µg/mL
	Garcinia kingaensis	Stem bark	Anti-HIV-1 protease	The stem bark extracts of *Garcinia kingaensis* with IC_{50} values of 15.2 µg/ml.
	Mammea usambarensis	Stem bark	Antioxidant	The stem bark extract of *M. usambarensis* showed the highest DPPH activity value of 6,165 ± 152 µmol TE/g,
	Allanblackia ulugurensis	Root & stem	Anti-HIV-1 protease	The root bark and stem bark of *A. ulugurensis* showed strong inhibitory activities against HIV-1 protease with IC_{50} values of 4.1 and 5.6 µg/ml
	Antidesma venosum	Root & Stem	Antimicrobial (a wide range of bacteria and fungus)	The root and stem bark showed significant activity against a wide range of gram +ve bacteria ranging from 0.00195-0.7812 mg/ml

	Garcinia livingstoneii	Fruits	Anticancer	Fruit extracts of *G. livingstonei* showed significant anti-HIV-1 activity with EC_{50} value of 2.25 ± 0.51 µg/ml
	Garcinia semseii	Fruits	Anticancer	Fruit extracts showed moderate to mild cytotoxic activities against A549, DU145, KB and Kbivin human cell lines with 50 % cytotoxic (CC50) values ranging from 5.7-20.0 µg/ml
Compounds				
	Guttiferone F	From *Allanblackia ulugurensis*	Anti-HIV-1 protease	Indicated activity at IC_{50} value of 11.3 µg/ml
	30-epi-cambogin	*Allanblackia ulugurensis*	Anti-HIV-1 protease	Indicated activity at IC_{50} value of 22.7 µg/ml
	Morelloflavone	From *Garcinia volkensis*	Antimicrobial, Antioxidant	The compound exhibited higher antibacterial activity having the MIC values in the range of 0.049->2.50 mg/ml.
	Semseinones A-C	From *Garcinia semseii*	Anticancer, antioxidant	Benzophenones indicated remarkable activity in human cell lines with CC_{50} values ranging from 1.97-16.1 µg/ml.
	Guttiferones A & K	From Fruit hulls of *G. semseii*	Anti-HIV-1, cytotoxicty, antioxidant	Benzophenones indicated remarkable activity in human cell lines with CC_{50} values ranging from 1.97-16.1 µg/ml.
	Garceduxanthone	From *Garcinia edulis*	Anti-HIV-1 and cytotoxicty	The compound showed anti-HIV-1 protease activity with IC_{50} value of 11.3 µg/mL. Furthermore, it showed potent cytotoxic activity with LC_{50} value of 2.36 µg/mL against brine shrimp larva *in vitro*.
	Mammea B/BB	*M. usambarensis*	Antioxidant activity in DPPH assay	Antioxidant activity in DPPH assay with a DPPH assay of 4,012±117 µmolTE/g
	Mammea B/BD	*M. usambarensis*	Antioxidant activity in DPPH assay	Antioxidant activity in DPPH assay with a DPPH assay 2,176±102 µmolTE/g

Biological activities

In these studies we tested crude extracts, semi-purified fractions and pure compounds from the plants under investigations for different biological assays. The assays include antimicrobial, anticancer, antioxidant, antimalarial, anti-HIV and larvicidal activities. Our results indicated significant activities against a wide range of microoganisms tested in this study. Table 3 summarizes the activities noted from different assays.

Conclusion

This article summarizes reported findings on investigations for natural products from Tanzanian indigenous plant species as carried out at the Institute of Traditional Medicine of the Muhimbili University of health and Allied Sciences for the past 7 years. Indeed, a number of compounds with unusual chemical structures were isolated and characterized as indicated in this article. From plant species investigated, over 50 natural products were isolated, among them 15 compounds were reported for the first time. Similarly, several endemic plant species have been a subject of our investigations, whereby they indicated to be the source of interesting secondary metabolites having quite unusual chemical structures. However, it is a fact that, there are still quite a number of plant species awaiting scientific identification in our virgin Tanzanian forests. Therefore, further and continued investigations of Tanzanian plants are recommended.

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