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Ximenia americana: Chemistry, Pharmacology and Biological Properties, a Review

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1. Introduction

The use of plants as medicinal agents to the treat of many diseases has been investigated for a long time since the antique civilizations. Several plants are used in traditional medicine against inflammatory diseases as well as various types of tumors on the base the potential of their chemical constituents. Although many compounds are extremely toxic, when we have the relation between the toxicity of a compound and its chemical pattern of substitution that can result in a more in-depth understanding of these compounds (Atta-ur-Rahman, 2005). Today, even after more than 200 years, the chemistry of natural products remains a challenge and an important field of research in several science areas (chemistry, biology, medicine, agronomy, botany and pharmacy). The reasons for it's large use are the considerable pharmacological potential observed in natural products, in the great development in the process of detection, isolation, purification and, especially, the advances in spectrometric techniques [infrared (IR), mass spectrometry (MS) and nuclear magnetic resonance (NMR ^{1}H and ^{13}C) for structural elucidation of new and complex compounds. These advances were outstanding in both NMR and MS spectrometry. The NMR allows the complete ^{1}H and ^{13}C NMR spectral assignments (chemical shifts and coupling constants) which serve to build a data base to support computer assisted structure elucidation. These data are also useful in the fuller understanding of the correlations between molecular conformation and biological activity of natural substances with biological importance (Loganathan *et al.*, 1990). Mass spectrometry has a huge application in chemistry, biochemistry, medicine, pharmacology, agriculture and food science. Although the mass spectrometric ionization techniques EI (electron impact) and CI (chemical ionization) required the analyte molecules to be present in the gas phase and were thus suitable only for volatile compounds, the development of several desorption ionization methods [FD (field desorption), FABMS (fast atom bombardment), ESIMS (electrospray), MALDI-MS (matrix assisted laser desorption ionization)] allowed the hight-precision mass spectrometric analysis of different classes of biomolecules.

The genus Ximenia belongs to the Olacaceae and comprises about 8 species (Brasileiro et al., 2008): Ximenia roiigi, Ximenia aegyptiaca, Ximenia parviflora, Ximenia coriaceae, Ximenia aculeata, Ximenia caffra, Ximenia americana and Ximenia aegyptica. X. caffra stands out for

being used in Tanzania for the treatment of irregular menstruation, rheumatism and cancer (Chhabra & Viso, 1990) and, in Limpopo Province, South Africa, for treatment diarrhea (Mathabe, 2006). However, X. americana Linn. is the most common, being native to Australia and Asia where is commonly known as Yellow Plum or Sea Lemon. It is found mainly in tropical regions (Africa, India, New Zealand, Central America and south America), specially Africa and Brazil. The plant is characterized as a small tree spinose 3-4 feet tall, gray or reddish bark, with leaves small, simple, alternate, of bright green color and with a strong smell of almonds. The flowers are yellowish-white, curved and aromatic. Fruit are yellow-orange, aromatic, measuring 1.5 to 2.0 cm in diameter, surrounding a single seed and have a pleasant plum-like flavor (Matos, 2007). In Asia, the young leaves are consumed as a vegetable, however, the leaves also contain cyanide and need to be thoroughly cooked, and should not be eaten in large amounts.

X. americana, commonly called "ameixa do mato", "ameixa de espinho" and "ameixa da Bahia", is widely distributed in northeast Brazil. A tea obtained from its barks has been used in popular medicine as cicatrizing, adstringent and as an agent against excessive menstruation. As a powder, it treats stomach ulcers and the seeds are purgative (Braga, 1976; Pio-Correia, 1984). This specimen has been recently examined (Araújo *et al*., 2008,2009) and the stem ethanolic extract afforded steroids (stigmasterol and sitosterol), triterpenoids (betulinic acid, oleanolic acid, 28-O-(-D-glucopyranosyl) oleanolic acid, 3-oxo-oleanolic acid, 3β–hydroxycicloart-24(*E*)-ene-26-oic acid and sesquiterpenoids (furanoic and widdrane type). A large number of sesquiterpenes are constituents of essential oils of higher plants and seem to intervene in the pharmacological properties attributed to these volatile fractions (Bruneton, 1999). It has been clarified that the biological activities of the liverworths are due to terpenoids and lipophilic aromatic compounds (Atta-ur-Rahman, 1988). Steroids and triterpenes with therapeutic interest and manufacturing employment, are a group of secondary metabolites of outstanding importance (Bruneton, 1999). Considerable recent work strongly indicates the great potential of the triterpenoids as source of use medicinal (Mahato *et al*., 1992).

Investigations in the past 10 years showed that the constituents of *X. americana* have shown several biological activities such as, antimicrobial, antifungal, anticancer, antineoplastic, antitrypanosomal, antirheumatic, antioxidant, analgesic, moluscicide, pesticidal, also having hepatic and heamatological effects.

In general, the compounds found in *X. americana* were saponins, glicosydes, flavonoids, tannins, phenolics, alkaloids, quinones and terpenoids types. In addition, the plant is potentially rich in fatty acids and glycerides and the seeds contain derivatives cyanide. The identified compounds did not demonstrate a representative pattern of each class. For example, the sesquiterpene were furanoic and widdrane while, triterpenes exhibited oleanane and cycloartane skeletal type. Concerning the fatty acids, in addition to common C16, C18 and C22, a distinctive feature is the presence of acetylenic, as well as, very long chain fatty acids.

We can see, from all the information summarized above, that work on plants of the genus Ximenia is justified, particularly *Ximenia americana* species, where systematic study is still not satisfactory, specially, relative to specific biological activity of their chemical constituents.

The present review compiles the published chemical and pharmacological information on the species *X. americana* and update important data reported in the last ten years in the scientific literature.

2. Biological activity

2.1 Antimicrobial and antifungal activities

To evaluate the scientific basis for the use of numerous plants species used to treat diseases of infectious origin, crude extracts of these plants were investigated. The antimicrobial activity of the extracts of the various parts of the investigated plants such as roots, leaves, seeds, stem barks and fruits, appears to be due to the presence of secondary metabolites such polyphenols, triterpenes, sterols, saponins, tannins, alkaloids, glycosides and polysaccharides (Geyid *et al.*, 2005; James *et al.*, 2007; Maikai *et al.*,2009; Ogunleye *et al.*, 2003).

X. americana is a plant used in traditional medicine for the treatment of malaria, leproutic ulcers and infectious diseases of mixed origin by natives in Ethiopia, Guinea, Sudan and in the Northern part of Nigeria (Geyid *et al.*, 2005; James *et al.*, 2007; Magassouba *et al.*, 2007; Maikai *et al.*, 2009; Ogunleye *et al.*, 2003; Omer & Elnima, 2003).

The crude extracts of *X. americana* show antimicrobial and antifungal activities. The crude aqueous, methanolic, ethanolic, butanolic and chloroform extracts from different parts (leaves, root, stem and stem bark) of the plant were subjected to phytochemical screening and from the test carried out, it was observed that the secondary metabolites contained were saponins, flavonoids, tannins, terpenoids, sterols, quinones, alkaloids, cyanogenetic glycosides, cardiac glycosides and carbohydrates in the form of sugars and soluble starch. The results of phytochemical screening of various parts solvent extracts of *X. americana* are presented in Table 1.

The MeOH extract from leaves of *X. americana* inhibited or retarded growth of *Neisseria gonorrhea* organism at dilution as low as 250 µg/ml. This same extract showed antifungal effect against *Candida albicans* and *Cryptococus neoformans* in concentration of 4000 µg/ml. Chemical screening conducted on the extract showed the presence of several secondary metabolites as tannins, sterols, terpenoids, flavonoids and saponins (Geyid *et al.*, 2005). The antimicrobial activities of ethanol extract of the leaves were evaluated against six common bacterial isolates (*Pseudomonas aeruginosa*, *Proteus vulgaris*, *Bacillus subtilis*, *Escherichia coli*, *Staphylococus aureus* and *Candida albicans*) and was active against all of them. The highest degree of activity was for *P. aeruginosa* (inhi bition zone: 20 mm), followed by *B. subtilis* and *C. albicans* (inhibition zone: 10 mm). Activity of the organic extract of the plant was comparable to that of commercially available penicillin disc (2 µg) which was more active against *P. aeruginosa* but less effective against *S. aureus.* The results of phytochemical analysis indicated the presence of saponins, flavonoids, tannins and cyanogenetic glycosides. Alkaloids and anthraquinones were not present (Ogunleye *et al.*, 2003). The root, stem bark and leaves aqueous and methanolic extracts of *X. americana* were tested against five bacteria and they inhibited the growth of *Staphylococus aureus* and *Klebsiella pneumoniae* while *Shigella flexineri* was inhibited by only methanolic leaves, aqueous bark and aqueous leaves extracts. *Salmonella typhi* and *Escherichia coli* were not affected by these extracts. The

Plant part	Solvent	Class of Compounds									Ref.
		Tannins	Steroids	Terpenes	Saponins	Flavonoids	Alcaloids	Cardiac	Glycosids	Quinones	
Leaves	MeOH	+		+	-	+	-	-		-	Geyid *et al.*, 2005
Leaves	H_2O	+	-	-	+	+	-	+		-	Ogunleye *et al.*, 2003
	EtOH	+	-	-	+	+	-	+		-	
Leaves	H_2O	+	-	-	+	+	-	+		+	James *et al.*, 2007
	MeOH	+	-	-	+	+	-	+		-	
Stem bark	H_2O	+	-	-	+	+	-	+		+	
	MeOH	+	-	-	+	+	-	+		+	
Root	H_2O	+	-	-	+	+	-	+		+	
	MeOH										
Stem bark	BuOH	+	-	+	+	+	+	+		-	Maikai *et al.*, 2009
	MeOH	+	-	+	+	+	+	+		+	
	H_2O	+	-	+	+	+	-	-		+	
Root	$CHCl_3$										Omer & Elnima, 2003)
	MeOH				+	+					
Stem	EtOH		+	+							Araújo *et al.*, 2008,2009

+: present; -: absent; Ref.: references

Some extracts showed the presence of carbohydrates in the form of sugars and soluble starch (James *et al.*, 2007 & Ogunleye *et al.*, 2003); few extracts showed also the presence of cyanogenetic glycosides (Ogunleye *et al.*, 2003). Quinones are of the anthraquinone type; terpenes are sesquiterpenes and triterpenes type (Araújo *et al.*, 2008, 2009).

Table 1. Phytochemical screening of stem bark, leaves, root and stem extracts of *X. Americana.* (Placed on the table 1)

Minimum Inhibitory Concentration (MIC) was only evident for the methanolic extracts at $1.25x10^4$ μgmL^{-1} (1:4) against *Staphylococus aureus* while the Minimum Bactericidal Concentration (MBC) of the extracts was obtained at $2.50x10^{-4}\mu g\ mL^{-1}$ (1:2) (James *et al.*, 2007). From the results, inhibitory activity of extracts (methanolic root) was more pronounced on *Klebsiella pneumonia* whereas it shows no activity against *Escherichia coli*, *Salmonella typhi* and *Shigella flexineri*. The methanolic root extract showed highly significant ($p<0.05$) activity on *Klebsiella pneumonia* when compared with leaf extracts and methanolic bark extract. The phytochemical constituents present in the extracts were carbohydrates in the form of sugars and soluble starch (except for aqueous and leaves extracts), cardiac

glycosides, saponins, tannins and flavonoids while alkaloids were absent in all the extracts. It was concluded that the extracts of methanolic roots, stem bark and leaves have bacteridal activities over the concentration of $2{,}5x10^4$ - $1{,}25x10^4$ μgmL^{-1} and that the presence of carbohydrates, glycosides, flavonoids and tannins in the diferent extracts are responsible for their antibacterial activity. The antimicrobial properties of the bark, leave, root and stem extracts of *Ximenia americana* were screened against *Bacillus subtilis*, *Staphyllococus aureus*, *Escherishia coli* and *Pseudomonas aeruginosa* (Table 2) using the cup-plate agar diffusion method and the minimum inhibitory concentration by agar dilution method (Omer *et al*., 2003).

Part used	Solvent system	% Yield	Inhibition zone (mm)				MIC (mg/ml)			
			B.s	S.a	E.c	Ps.a	B.s	S.a	E.c	Ps.a
Bark	$CHCl_3$	1.1	13	12	11	15	N.D	N.D	N.D	N.D
	MeOH	21.1	23	30	19	22	0.31	0.62	19.79	19.79
	H_2O	8.9	18	18	16	14	0.40	1.62	3.24	1.62
Leaves	$CHCl_3$	10.7	13	14	-	12	N.D	N.D	N.D	N.D
	MeOH	26.6	23	22	-	25	1.55	0.77	9997	12.45
	H_2O	5.0	17	19	16	22	0.59	1.19	>25.5	19.11
Root	$CHCl_3$	2.2	15	13	12	13	N.D	N.D	N.D	N.D
	MeOH	3.7	15	21	19	15	3.27	6.54	>34.88	>34.48
	H_2O	5.7	13	13	-	-	2.68	10.74	28.65	28.65
Stem	$CHCl_3$	2.7	-	11	11	-	N.D	N.D	N.D	N.D
	MeOH	11.8	20	25	-	24	>72.75	3.41	>72.75	>72.75
	H_2O	2.7	17	17	13	13	5.12	5.12	>13.65	>13.65

B.s, *Bacillus subtilis;* S.a, *Staphyllococus aureus*; E.c, *Escherichia coli*; Ps.a, *Pseudomonas aeruginosa;* concentration of extracts 100 mg/ml, 0.1 ml/cup; inhibition zones are the mean of three replicates. MIC, minimum inhibitory concentration; N.D, not detected.

Table 2. Antibacterial activity of *Ximenia americana* extracts against standard organisms. (Placed on the table 2)

The methanolic extract was the most active one. The aqueous extract also exhibited high activity which justifies its traditional use. *Staphyllococus aureus* was the most susceptible bacterium among the tested organisms. The table 3 show the antibacterial activity of *Ximenia Americana* against the pharmaceuticals patterns.

Several other studies to determine the presence of antimicrobial activity in crude extracts of *Ximenia americana* were performed (Magassouba *et al*., 2007; Maikai *et al*., 2009). In all, the various extracts were found to have broad spectrum effect against standard organisms (*Escherichia coli*, *Pseudomonas aeruginosa, Staphylococus aureus, Proteus vulgaris, Candida albicans, Bacillus subtilis, Salmonella typhi* and *Shigella flexineri*) and supports the traditional usage of this plant as remedy in treatement of microbial infections.

In general, the antimicrobial activity of extracts of the various parts of the plants appears to be due to presence of secondary metabolites. In some experiments, was remarked that the

Reference drugs	Concentration µ/ml	MDIZ			
		B.s	S.a	E.c	Ps.a
Ampicillin	40	14	25	-	-
	20	13	22	-	-
	10	-	19	-	-
	5	-	18	-	-
Benzyl penicillin	40	-	37	-	-
	20	-	33	-	-
	10	-	28	-	-
	5	-	24	-	-
Cloxacillin	40	-	29	-	-
	20	-	27	-	-
	10	-	22	-	-
	5	-	18	-	-
Gentamicin	40	24	18	25	22
	20	22	16	17	15
	10	17	14	16	12
	5	15	13	11	-

Interpretation of sensitivity test results: Gram(+) bacteria*; Gram(-) bacteria **;
>18 mm (M.DIZ)= sensitive; >16 mm (M.DIZ)=sensitive;
14-18 mm (M.DIZ)= intermediate; 13-16 mm (M.DIZ)= intermediate;
<14 mm (M.DIZ)= resistant; and < 13mm (M.DIZ)= resistant.

Table 3. The activity of *Ximenia Americana* against the clinical isolates. (Placed on the table 3)

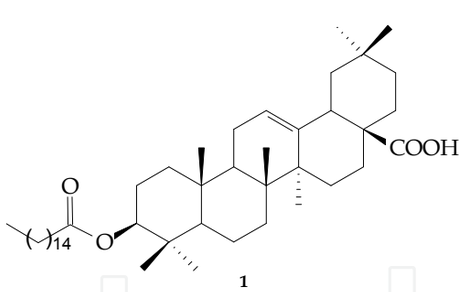
plants which accumulate polyphenols, tannins and unsaturated sterols/terpenes showed to inhibit or significantly retard growth of eight of the ten test organisms; the species, which constitute polyphenols and unsaturated sterols/terpenes; and polyphenols, tannins, unsaturated sterols/terpenes, saponins and glycosides inhibited six organisms each while, those with polyphenols, tannins, unsaturated sterols/terpenes, saponins; and alkaloids and unsaturated sterols/terpenes inhibited growth of five bacterial strains each (Geyid *et al.*, 2005). Cyanogenetic glycosides are reported to possess antimicrobial activity (Finnermore *et al.*, 1988). Tannins have been traditionally used for protection of inflamed surfaces of the mouth and treatment of catarrh, wounds, haemorrhoids and diarrhea and as antidote in heavy metal poisoning. They have the ability to inactivate microbial adhesions, enzymes, cell envelope transport proteins and also complex with polysaccharide (Maikai *et al.*, 2009; Scalbert, 1991; Ya *et al.*, 1988). Flavonoids are naturally occurring phenols, which posses numerous biological activities including anti-inflamatory, antiallegic, antibacterial, antifungal and vasoprotective effects and, also have been reported to complex with extracellular and soluble proteins and to complex with bacterial cell walls (Dixon *et al.*, 1983; Geyid *et al.*, 2005; Hostettman *et al.*, 1995; James *et al.*, 2007; Maikai *et al.*, 2009; Ogunleye *et al.*, 2003). Terpenoids have also been reported to be active against bacteria, the mechanism of action involve membrane disruption by the lipophilic compounds (Geyid *et al.*, 2005; James

et al., 2007; Maikai *et al*., 2009; Ogunleye *et al*., 2003). Although it is difficult to speculate on the mechanism of action of the constituents of the extracts on the basis of studies conducted to date, the antimicrobial activity of these extracts is due, no doubt, the presence of these secondary metabolites. In the case of extracts of *Ximenia americana,* probably, due the presence of tannins, flavonoids, triterpenes/steroids, saponins or cyanogenetic glycosides.

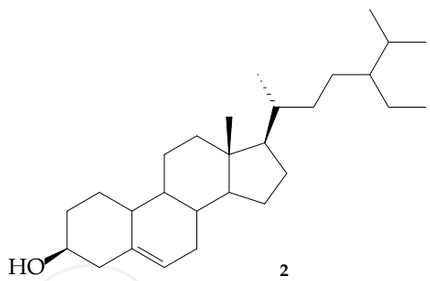
In summary, the results justified the use of *X. americana* as having antibacterial properties and support its use as agent in new drugs for therapy of infectious diseases caused by pathogens.

2.2 Pesticidal activity

Olecaceous seed oils are a rich source of acetylenic lipids and unsaturated fatty acids (Badami & Patil, 1981 & Sptizer *et al*., 1997). Acetylenic metabolites show some biological activities including, insecticidal activity (Jacbson, 1971). *X. americana* was recorded to contain octadec-11-en-9-ynoic acid, named xymeninic acid as well as icosenoic-triacontenoic acids, all of which belong to the ω-9 series (Rezanka, & Sigler, 2007). Bioactivity-driven fractionation of the $CHCl_3$ extract of the root of *X. americana* using the Brine Shrimp Lethality Test (BST) and hatchability test with *Clavigralla tomentosicollis* eggs yielded two fractions (F006, soluble in petroleum ether and F005, soluble in 10% H_2O in MeOH) as the most actives (F005, BST LC_{50} 78 (129-48) µg/mL and F006, BST $LC\%_{50}$ 76(121-49) µg/mL) (Fatope *et al*., 2000). A combination of F005 and F006 was submitted to hatchability test (inhibition of hatching = 68 % of control) and successive BST-dircted fractionation on silica gel column and preparative TLC yielded oleanene palmitates (**1**), β-sitosterol (**2**) and C_{18} acetylenic fatty acids (**3** and **4**) as yellow oils.



1



2

The substance **4** suppressed the hatchability of *C. tomentosicollis* eggs at 92 % of control when tested at 4 x 10^4 µg/mL (correcting for unhatched eggs in the control using Abbott's formula):

% control = [(% unhatched of treated group - % unhatched of untreated group)/ (100 - % unhatched of untreated group)] x 100

These acetylenic fatty acids show characteristic spectrometric data. The ^{13}C NMR spectrum of **3** displayed absorptions diagnostic of acetylenic carbons at δ_C 80.4 (C) and 80.1 (C) and of carboxylic carbon at δ_C 189.1 (C), in agreement with its IR spectrum which exhibited bands at 2200 and at 1713 cm^{-1}, characteristic of acetylenic and acid groups, respectively. Compound **3** had molecular formula$C_{18}H_{32}O_2$, as established by HREI-MS (*m/z* 280.2378 for $[M^+]$) in combination with its ^1H and ^{13}C NMR spectra. From analysis spectral data compound **3** was thus established as octadeca-5-ynoic acid (tariric acid). Compound **4** had a

mol wt 6 mass units less than that of **3** with molecular formula $C_{18}H_{26}O_2$ as revealed by HREI-MS (*m/z* 274.2021 for [M+]) in combination with its ^{1}H and ^{13}CNMR spectra. The ^{13}C NMR spectrum of **4** displayed absorptions diagnostic of acetylenic carbons at δ_C 83.4 (C) and 74.1 (C) and of carboxylic carbon at 179.3 (C), in agreement with its IR spectrum which exhibited bands at 2232 and 1702 cm^{-1}, characteristic of acetylenic and acid groups, respectively. The ^{13}C RMN spectrum also exhibited six resonance at δ_C 148.2 (CH), 140.9 (CH), 136.9 (CH), 129.8 (CH), 109.3 3(CH) and 108.6 (CH), revealing the presence of three double bonds. From a detailed spectral analysis considering, especially, the multiplicity of signals and coupling constants in the ^{1}H NMR spectrum, as well as the presence of diagnostic peaks in the mass spectrum, compound **4** was thus established as 10*Z*,14*E*,16*E*-octadeca - 10,14,16-triene-12-ynoic acid, a ene-ene-yneene acetylenic fatty acid (Fatope *et al.*, 2000).

$CH_3—(CH_2)_{11}C{\equiv}C—(CH_2)_3CO_2H$ **3**

$CH_3CH{=}C_{16}HCH{=}C_{14}HC{\equiv}C_{12}CH{=}C_{10}H(CH_2)_8CO_2H$ **4**

In addition, *Ximenia* seed oil have been found to contain fatty acids with more than 22 carbon atoms (very long fatty acids) which are found only rarely in nature. Using liquid chromatography in combination with mass spectrometry was founded that *Ximenia* oil to contain fatty acids with chain length C_{34} and C_{36} (Rezanka & Sigler, 2007). Effectively, two very long chain unsaturated fatty acids C_{40} and C_{35} (**5** and **6**) were isolated (Saeed & Bashier, 2010) from *X. americana* seeds and fruits, respectively. The mass spectrum of the major component (**5**) showed a molecular ion at m/z 604 corresponding to the molecular formula $C_{40}H_{76}O_3$. The IR spectrum of **5** showed a broad absorption band at 3600-3200 cm^{-1} (OH) and the presence of strong absorption at 1742 cm^{-1} attributed to ester group. The base peak appeared at m/z 55 (C_4H_7+) due to allylic bond cleavage and peaks at m/z 479 and 151 furnished from fragmentation in C_{28}-C_{29} and C_{26}-C_{27}, respectively. In addition, the peaks at m/z 31, 59, 73 and 74 (McLafferty rearrangement) were compatible with unit $CH_3OCO(CH_2)_3$-. The compound **5** was identified as methyl-14,14-dimethyl-18-hydroxyheptatracont-27,35-dienoate. The mass spectrum of **6** showed a molecular ion at 578, corresponding to the molecular formula $C_{35}H_{62}O_6$. The IR spectrum showed bands at 3500, 1731 and 1645 cm^{-1} corresponding to OH, C=O and C=C groups, respectively. The base peak appeared at m/z 73 ($C_3H_5O_2$+) which is characteristic for the methyl ester, reinforced by additional peaks at m/z 31, 59 and 74 (McLafferty rearrangement). An peak at m/z 479 was due to M-$C_5H_7O_2$ and one at m/z 339 is due to the cleavage C_{13}-C_{14} while, those at m/z 126 and 265 were due to $C_7H_{10}O_2$ and M-$C_{17}H_{28}O_2$, respectively. The compound **6** was identified as dimethyl-5-Methyl-28,29-dihydroxydotriacont-3,14,26-triendioate.

$[CH_3OCO(CH_2)_{12}C(CH_3)_2(CH_2)_3CHOH(CH_2)_8CH{=}CH(CH_2)_6CH{=}CHCH_3]$

5

$[CH_3OCOCH_2)CH{=}CHCH_3(CH_2)_8CH{=}CH(CH_2)_{10}CH{=}CH(CHOH)_2(CH_2)_2COOCH_3]$

6

2.3 Analgesic activity

The aqueous extract of stem bark of *X. american* has analgesic properties that justify its use popular in countries such as Tanzania, Senegal, Zimbawe and Nigeria. The extract of *X.*

americana in doses containing 10 to 100 mg/kg P.C, inhibits contractions of the abdomen with analgesic effects comparable to those of phenylbutazone. In fact, at doses of 100 mg / kg P.C, phenylbutazone causes an inhibition of pain in 45.2±2%. The percentage of inhibition by extract of *X. ameriacana* is 61.1±% in the same concentration. These properties are probably due to the presence of flavonoids and saponins, detected in the extract (Soro *et al.*, 2009). The analgesic activity of the methanol extract of *X. americana* leaf was investigated in chemical models of nociception in mice. The extract at doses of 200, 400 and 600 mg/kg i.p. produced an inhibition of 54.13, 63.74, and 66.4% respectively, of the abdominal writhes induced by acetic acid in mice. In the formalin test, the administration of 200, 400 and 600 mg/kg i.p. had no effects in the first phase (0 to 5 min) but produced a dose dependent analgesic effect on the second phase (15 to 40 min) with inhibitions of the licking time of 29.3, 47.8 and 59.8%, respectively. These observations suggested that methanol extract of *X. americana* leaf possesses analgesic activity (Siddaiah *et al.*, 2009).

2.4 Antipyretic activity

The bark of stem of *X. americana* has been used in West Africa for the treatment of pain and fever. To verify this second property, the treatment of rats in hyperthermia with *Ximenia americana* stem bark aqueous and with beer yeast was compared to those obtained with lysine acetylsalicylate (Aspegic). The study showed an antipyretic action of the extract. Moreover, the toxicological study of the stem extract indicated a LD_{50} of 237.5 mg/kg P.C according to the classification of Diezi this plant is relatively toxic. The experiments show that the properties of *X. americana* could due to the presence of saponosides, as show by screening tests performed in this study. These results justified the use of *X. americana* in traditional cure of fever treatment (Soro *et al.*, 2009).

2.5 Antitrypanosomal activity

The in vitro antitrypanosomal activity of methanolic and aqueous extracts of stem bark of *Ximenia americana* was evaluated on Trypanosoma congolense. Blood obtained from a high infected mice with *T. congolense* (10(7) was incubated with methanolic and aqueous extracts at 20, 10 and 5 mg/ml and Diminal(R) (diminazene aceturate) at 200, 100 and 50 µg/ml in a 96 micro plate. The results revealed that methanol and aqueous extracts had activity at 20 and 40 mg/ml however, the methanolic extracts were more active than aqueous extracts at 10 and 5 mg/ml. Phytochemical screening of the methanolic and aqueous extracts of the bark showed that they both had flavonoids, anthraquinones, saponins, terpenes and tannins. The aqueous and methanolic extracts appears to show some potential activity against *T. congolense* (Maikai *et al.*, 2008).

2.6 Anticancer activity

Plants have been show to provide a useful source of natural products that are effective in the treatment of human neoplastic diseases. Information recorded from ancient civilizations has demonstrated the use of plants in search of treatment for various types of cancer (Hartwell, 1967-1971). An analysis of plant materials that had been studied at the National Cancer Institute (NCI), USA for discovering new anticancer drugs showed that if ethnopharmacological information had been used, the yield of plants harboring antineoplastic activity would have been significantly increased (Spjut & Perdue, 1976). The

list of natural products stored for study as more effective drugs for the treatment of human cancers (NCI) were generated by searching for specific structural types (Steven & Russel, 1993). However, the presence of some large class cannot be ruled out. Examples of anticancer agents developed from higher plants are the antileukemic bis-indole alkaloids vinblastine and vincristine from the *Catharantus roseus* (Apocynaceae); diterpene taxol, used to treat breast cancer, lung cancer, and ovarian cancer and also used to treat AIDS-related (Kaposi's sarcoma) from *Taxus breviflora* (Taxaceae); pyrrolo[3,4,b]-quinoline alkaloid camptothecin (antileukemic) from *Camptotheca acuminate* (Nyssaceae) and pyridocarbazole alkaloid elipticine (antitumor) contained in *Ochrosia elliptica* (Apocynaceae). A large number of other active natural products with toxicity to cells in culture (Walker carcinosarcoma 256, mouse L-1210 leukemia, Ehrlich ascite tumor, sarcoma 180 and mouse P-388 leukemia cell lines) have been detected (Geran *et al.*, 1972 & Lee *et al.*, 1988).

Cell line				
Tumor cell lines	IC_{10}[a](ug/ml medium)	IC_{50}[b] (ug/ml medium)	IC_{90}[c] (ug/ml medium)	IC_{90}/IC_{10}[d] medium)
MCF7	0.6	1.7	10	16.7
BV173	0.4	1.8	7.0	17.5
CC531	0.8	3.3	12	15.0
U87-MG	1.0	9.0	100	100
K562	5.0	11	180	36
SKW-3	3.1	20	700	226
HEp2	5.0	21	100	20
NC1-H460	4.0	21	150	38
PC3	3.5	26	>1000	>300
MDA-MB231	5.0	33	100	20
HT29	8.0	40	350	44
U333	7.0	65	300	43
SAOS2	20	66	1000	50
LAMA84	10	90	600	60
HL60	30	90	1000	33
CML-T1	2.5	160	1000	400
AR230	17	170	700	41
Non tumor cell lines				
MCF10	35	>100	>100	>2.0
MDCK	12	27	60	5.0
N1H/3T3	2	33	>100	>50
PNT-2	2	20	>100	>50

[a]Inhibitory concentration 10 (concentration inhibiting the cell growth by 10%), as accessed by MTT assay;
[b]Inhibitory concentration 50 (concentration inhibiting the cell growth by 50%), as accessed by MTT assay.
[c]Inhibitory concentration 90 (concentration inhibiting the cell growth by 90%), as accessed by MTT assay.
[d]Ratio of IC_{90} and IC_{10} values.

Table 4. Antiproliferative activity of an aqueous extract from *X. americana* in 16 human and one rodent tumor cell lines and in 4 immortalized non-tumor cell lines.

The antineoplastic activity in vitro of various extracts from *Ximenia americana*, plant used in African traditional medicine for the treating cancer, was investigated (Voss *et al*., 2006, 2006). The most active, aqueous extract was subjected to a detailed investigation in a panel of 17 tumor cell lines (Table 4) originating from human (16 lines) and rat (1 line), showing a averageI C_{50} of 49 mg raw powder/ml medium. The majority of cell lines (11 out of 17) were classified as sensitive (the sensitivity varied from 1.7 mg/ml in MCF7 breast cancer cells to 170 mg/ml in AR230 chronic-myeloid leukemia cells) and three of these (MCF7 breast cancer, BV173 CML and CC531 rat colon carcinoma) showed a particularly high sensitivity, with ratios lower than 0.1 of the average IC_{50}. The *in vivo* antitumor activity was determined in the CC531 coloretal rat model and significant anticancer activity was found following peroral administration, indicating a 95% reduced activity.

A comparison of the antineoplastic activity of the extract with three clinically used agents is given in Table 5. The cytotoxicity profiles of four cell lines are illustrated by the respective IC_{10}, IC_{50} and IC_{90} values, as well as by the corresponding IC_{90} to IC_{10} ratio, describing the slop of the concentration-effect curve. Most prominently, the ranking in sensitivity differed between the extract and the positive controls. In variance to the extract, which resulted in the lowest IC_{50} and IC_{90}/IC_{10} ratio in MCF7 cells, miltefosine and cisplatinum caused the lowest IC_{50} and IC_{90}/IC_{10} ratio in HEp2 cells. Similar to the extract, the lowest IC_{50} following gemcitabine exposure was seen in NCF7 cellls. However, this agent differed from all the others by its lack in effecting 90% growth inhibition, were the HEp2 cells; notably, the cells were most resistant to the agent. In contrast, SAOS2 cells were found to best most resistant to the extract as well as to miltefosine and cisplatinum.

Cell line	Treatment	IC_{50}	IC_{50}	IC_{90}	IC_{90}/IC_{10}
MCF7	Extract (µg/ml)	0.6	1.8	10	16.7
	Miltefosine (µM)	6.5	40	80	12.3
	Cisplatinum (µg/ml)	0.22	2.2	10	45
	Gemcitabine (µM)	0.001	0.012	>100	$>10^5$
U87-MG	Extract (µg/ml)	1.0	9.0	100	100
	Miltefosine (µM)	4.7	27	70	14.9
	Cisplatinum (µg/ml)	0.12	1.6	18	150
	Gemcitabine (µM)	0.002	0.014	>100	$>5x10^4$
HEp2	Extract (µg/ml)	5.0	21	100	20
	Miltefosine (µM)	1.2	2,8	8.0	6.7
	Cisplatinum (µg/ml)	0.09	0.4	1.4	15.6
	Gemcitabine (µM)	0.2	0.47	17	85
SAOS2	Extract (µg/ml)	20	66	1000	50
	Miltefosine (µM)	5.0	40	120	24
	Cisplatinum (µg/ml)	0.11	3.1	10	91
	Gemcitabine (µM)	0.007	0.034	>100	$>10^4$

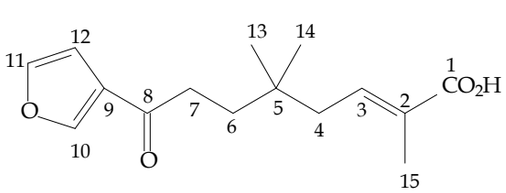
Table 5. Cytotoxicity profiles of the extract and three standard antineoplastic agents in a subpanel of the cell lines

In order to define the substance class of the active component(s) (Voss *et al*., 2006) experiments were carried out on physicochemical properties. In the process, lipids and lipophilic plant secondary metabolites could be excluded, since the biological activity was only extracted by strongly polar solvents. Large amounts of tannins were identified in the aqueous extract. However, extracts prepared in methanol or 70% acetone, both solvents known to efficiently extract tannins from plant materials, had only a low (methanol) or no (70% acetone) cytotoxic activity. Molecules smaller than 10 kDa were excluded by ultrafiltration. Out of the known class of plant cell macromolecules, DNA and RNA were not found in the aqueous extract and digestion experiments with DNase or RNase had not effect biological activity. However, proteins and polysaccharides were shown to be present in the aqueous extracts and could not be further separated by physicochemical methods. Digestion experiments with trypsin and proteinase K hinted at a protein being responsible for the cytotoxic activity.

A well-defined family of cytotoxic plant proteins is that of the type II ribosome-inactiving proteins (RIPs). These proteins with molecular weight of about 60 kDa, consist of two polypeptide chain, termed A- and B- chain, with an MW of about 30 kDa each, being held together by disulphide bridge. Cumulative evidences (cytotoxic effects, MW, two-chain structure of the proteins in the affinity-purified fraction and one mass-spectrometrically sequenced tryptic peptides) strongly suggests that the active components of the plant material are so far unknown proteins belonging to the type II RIP family.

By a combination of preextraction, extraction, ion exchange and affinity chromatography, a mixture of two cytotoxic proteins was isolated. The eluted peptides were analyzed by electro-spray ionization mass spectrometry (MS/MS). The MS/MS mass spectrum is a method in which a first analyzer isolates a precursor ion which then undergoes a fragmentation yielding a product ions and neutral fragments. A second spectrometer analyzes the product ions. MS/MS applications are plentiful in the study of fragmentation mechanisms, observation of ion-molecule reactions, applications to high-selectivity and high-sensitivity analysis and determination of elementary compositions. Thus, it is a rapid selective analysis method for the components of a complex mixture and macromolecules in biological fluids. The homology of the translated protein sequence from isolated peptides to known type II RIP precursor protein sequence demonstrates that the new protein termed "riproximin" is a so far unknown member of this class. In conclusion, from biological activity of each of the two proteins as well as from MS/MS sequence analysis, showing the presence of two B-chain and two A-chain in the mixture, the *X. americana* extract analyzed contains a mixture of two new proteins, riproximin, belongs to the family of type II ribosome-inactivating proteins.

Two sesquiterpenes (**7** and **8**) isolated from the EtOH extract of the stems of *X. americana* did not inhibit the growth of HL-60 (human leukemia), HTC-8 (human colon) and MDA-MB-435 (human breast cancer) cell lines.



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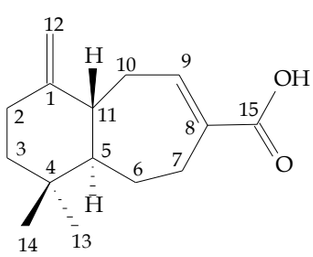

8

The compounds **7** and **8** were recently isolated and their structures were elucidated on the basis of spectral analysis (IV, MS and NMR) and the complete assignment of the ^{1}H and ^{13}C NMR signals were achieved by 1D(^{1}H, ^{13}C and DEPT) and 2D (^{1}H - ^{1}H COSY, ^{1}H - ^{13}C HMQC, ^{1}H-^{13}C HMBC and ^{1}H - ^{1}H NOESY) NMR experiments. The sesquiterpene **7**, isolated as a white powder, has molecular formula$C_{15}H_{20}O_4$ deduced from its EIMS ($M^{+\cdot}$ 264) in combination with its ^{1}H and ^{13}C NMR spectra. The ^{1}H and ^{13}C NMR spectra combined with distortionless enhancement by polarization transfer (DEPT) technique exhibited signals that allowed characterize the three isoprene units (C-1, C-2, C-3, C-4 and C-13; C-8, C-9, C-10, C-11 and C-12; C-5, C-6, C-7, C-14 and C-15) of **7**. Thus, the ^{13}C NMR spectra exhibited signals for six sp^2 carbons [olefinic bond: C-2 (δ_C 128.9), C-3 (δ_C 141.7) and furan ring: C-9 (δ_C 127.9), C-10 (δ_C 147.1), C-11 (δ_C 144.4), C-12 (δ_C 108.9)], two carbonyl [conjugated ketone, C-8 (δ_C 195.3) and conjugated carboxylic acid, C-1 (δ_C 173.1)]), three methylene [C-4 (δ_C 41.2), C-6 (δ_C 36.5) and C-7 (δ_C 35.9), three methyl [C-13 (δ_C 12.4), C-14 (δ_C 25.9) C-15 (δ_C 25.9) and one quaternary carbon [C-5 (δ_C 34.3)]. One conjugated ketone (δ_C 195.3) was also evident from the absorption at 1682 cm^{-1} in the IR spectrum. In the HMBC spectrum, obvious long-range connectivities between the methylene group 2H-7 (δ_H 2.71, dd, 7.9, 6.0 Hz) and C-8 (δ_C 195.57) and between the methylene group 2H-4 (δ_H 2.20, d, 7.7 Hz) and C-5 (δ_C 34.56) allowed the assembly of the molecule and show it to consist of a furanoid sesquiterpene. Others diagnostic ^{1}H-^{1}H COSY, ^{1}H-^{13}C HMQC and ^{1}H-^{13}C HMBC correlations permitted to assign all the hydrogen and carbon atoms. The sesquiterpene, **8** isolated as a white solid, has molecular formula$C_{15}H_{22}O_2$ deduced from its EIMS ($M^{+\cdot}$ 234) in combination with its ^{1}H and ^{13}C NMR spectra. The ^{1}H and ^{13}C NMR spectra combined with distortionless enhancement by polarization transfer (DEPT) technique exhibited signals that allowed characterize the three isoprene units (C-1, C-2, C-3, C-11 and C-12; C-4, C-5, C-6, C-13 and C-14; C-7, C-8, C-9, C-10 and C-15) of **8**. The ^{13}C NMR spectra exhibited signals for four sp^2 carbons [three substituted, C-8 (δ_C 132.34) and C-9 (δ_C 145.01) and disubstituted, C-1 (δ_C 154.71) and C-12 (δ_C 111.63) bonds; one conjugated carboxylic acid, C-15 (δ_C 173.71), besides signals to five methylene, two methyne, one quaternary and two methyl carbons. The possibility of himachalano type structure was eliminated based on the interpretation of spin-spin interactions revealed by ^{1}H-^{1}H COSY spectrum, which clearly showed the presence of cross peaks corresponding to the couplings of two atoms of hydrogen 2H-6 [δ_H 1.68 (m) and 1.50 (m)] with H-5 hydrogen [δ_H 1.81 (m)] and with the two hydrogen atoms 2H-7 (δ_H 2.45 and 2.35) besides interaction of H-5 (δ_H 1.81) with H-11 (δ_H 2.50, q). This sequence does not appear in the skeleton type himachalano. The *trans* configuration fusion ring was supported by correlations observed in NOESY NMR spectrum, that exhibited the presence of nOes indicating that the hydrogens 3H-13 (δ_H 1.01, s), H-5 (δ_H 1.81) and H-3ax (δ_H 1.58, t, 10.8 Hz) are oriented on the same side (á) of the molecule, while the hydrogens 3H-14 has the same orientation (â) that the hydrogens H-11 (δ_H 2.50, q), H-6ax (δ_H 1.50) and H-3eq (δ_H 1.74, dd, 10.8 , 8.9). Others diagnostic ^{1}H-^{1}H COSY, ^{1}H ^{13}C C HMQC and ^{1}H ^{13}C ^{13}C HMBC correlations permitted to assign all the hydrogen and carbon atoms.

2.7 Others activities

2.7.1 Antiviral effect

The stem bark MeOH extract of *X. americana* as well as several others plant species used by the Maasai pastoralis of East Africa showed antiviral effect against measles virus *in vitro* by

plaque reduction neutralization assay. Potentially active constituents from extracts of all the plants include polyphenols, alkaloids, tannins, sterols, terpenes, saponins and glycosides, between others (Parker *et al.*, 2007).

2.7.2 Hepatic and heamatological effects

A study (James *et al.*, 2008) was conducted from the leaves, stem bark and root aqueous extract of *X. americana* with albino rats. The results of this work shows that the extracts significantly ($P<0.05$) increasing the level of serum alanine transaminase (ALT) and aspartate transaminase (AST), results indicative of hepatocellular damage. The result also shows that the root has the ability to impair albumin synthesis as observed by the decrease of level of serum albumin. The weight of the animal showed a significant ($P<0.05$) reduction on administering the leaves extract as compared to the control and the others extracts. This reduction might be due to poor intake and utilization of food by the animals in the leaves extract group. The significantly ($P<0.05$) higher content of hydrogen cyanide, saponins, and oxalates in the root extracts indicates that the root extracts may be more toxic. Hydrogen cyanide is known to cause gastrointestinal inflammation and inhibition of cellular respiration. Saponins are known to have haemolytic properties and the ability to reduce body cholesterol by preventing its reabsorption. The high saponin content in the root may lead to gastroenteritis manifested by diarrhea. Oxalates have been known to cause irreversible oxalate nefrosis when ingested in large doses. Thus, there is need to isolate the specific component(s) responsible for the toxicity in the root extract in order to standardized the preparation for maximum therapeutic benefit.

2.7.3 Toxicity

The stem bark of *X. americana* was evaluated for its phytochemical constituents and acute toxicity effect on the Swiss albino mice (Maikai *et al.*, 2008). The results from the extracts administered intraperitoneally/orally at doses of 10, 100 and 1000 mg/kg body weight revealed no death with doses up 5000 mg/kg body weight. Post mortem, hematological and histopathological examination did not show any significant ($P<0.05$) weight changes. Phytochemical screening of the aqueous extract stem bark revealed the presence of cardiac glycosides, flavonoids, saponins and tannins. The results suggested that the aqueous extract is not acutely toxic to the mice.

2.7.4 Food composition and cosmetic use

Glyceride blends containing ximenynic acid (**9**) (found in *X. americana*) are useful for the preparation of food compositions or food supplements, including margarine, chocolate, ice cream, mayonnaises, cheese, dry soups, drinks, cereal bars and sauces and snack bars. The blend provides a composition providing health benefits consisting of insulin resistance, or related disorders such as diabetes, delaying the onset of symptoms related to development of Alzheimer's disease, improving memory function, lowering blood lipid levels, anticancer effects or skin antiageing effects (Koenen *et al.*, 2004). Food *X. americana* flowers are a replacement for orange blossoms with similar fragrance and soothing cosmetic properties (Paolo, 1979).

$$CH_3(CH_2)_5CH\overset{E}{=}C\equiv C(CH_2)_7CO_2H$$

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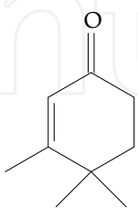
3. Others constituents isolated from *X. americana*

Besides the substances mentioned in the text of this chapter, several other originated from *Ximenia americana* were isolated.

Isoprenoids



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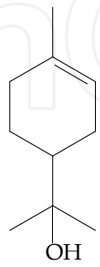

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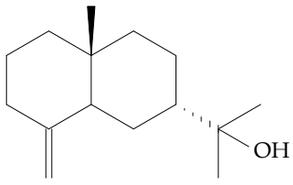

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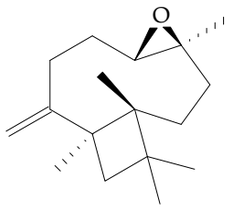

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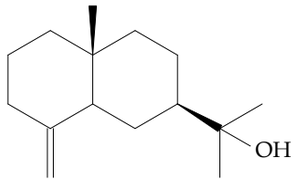

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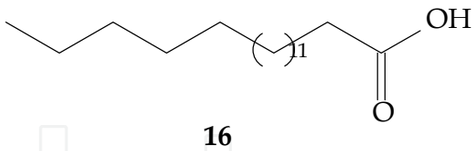
Fatty acids



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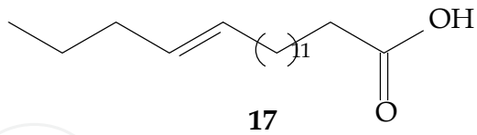

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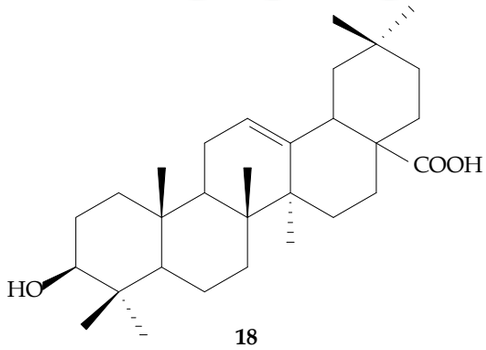
Triterpenes



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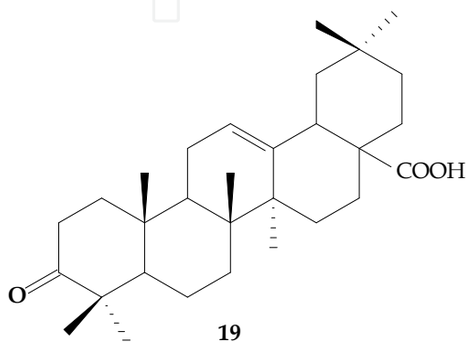

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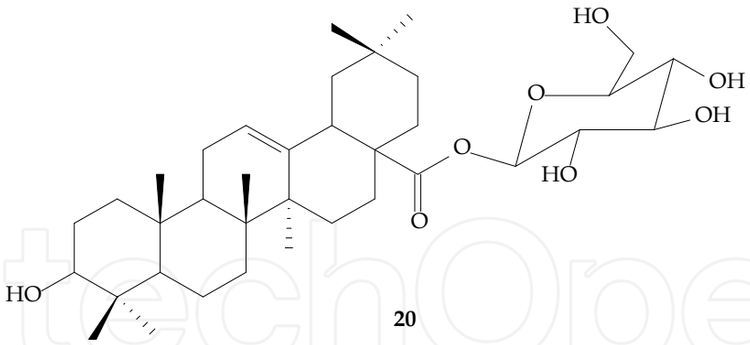
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OH
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HO
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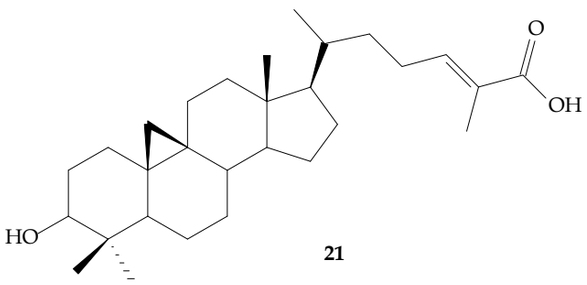
HO

20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OH
HO

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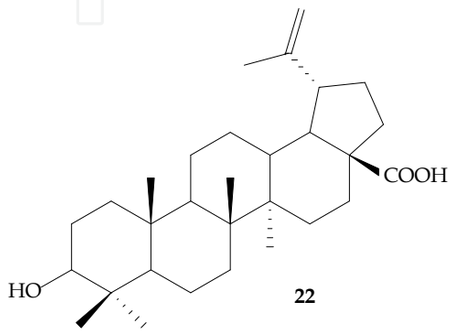
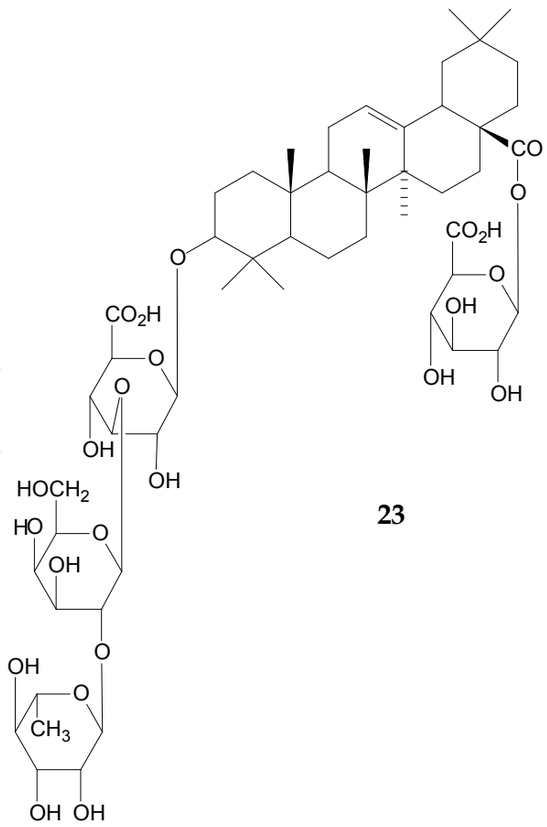

COOH
HO

22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CO2H
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OH
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OH
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CO2H
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HOCH2
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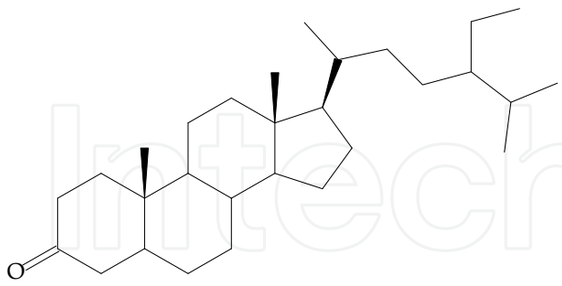
CH3
OH OH

23

Steroids



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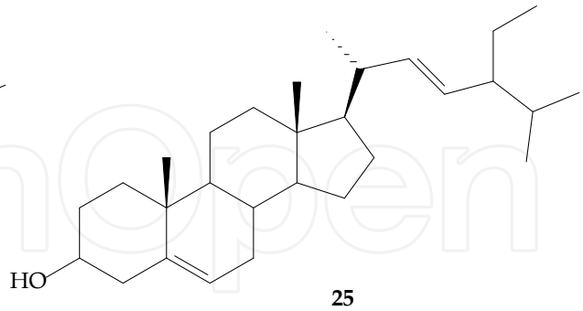

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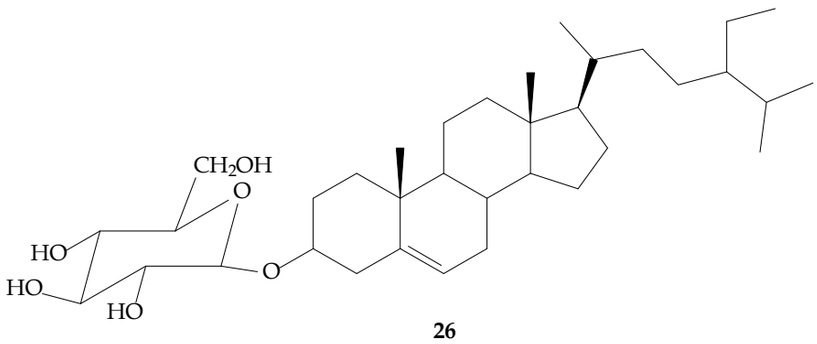

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4. Summary/conclusion/future directions

From an extensive literature review was observed that the *Ximenia americana* is widely used as a popular alternative remedy in certain regions of some countries of the Africa (Guinea, Ethiopia, Nigeria, Sudan) and in the Brazil. The plant, used by their crude extracts, especially, aqueous and methanolic, showed several biological activities such as antimicrobial, antifungal, anticancer, antitrypanosomal, antirheumatic, antioxidant, analgesic, moluscicide, pesticidal, antipyretic, antifugal, among others. There are several papers in the literature confirming these activities. The crude extracts consist of complex mixture of compounds called secondary metabolites produced by plants, which include, mainly, flavonoids, saponins, alkaloids, quinones, terpenoids, phenols, glycosides and sterols.

Many plants have a prolonged and uneventful use that may serve as indirect evidence to their efficacy. However, in the absence of objective proof of efficacy and without the knowledge of the constituents responsible for the physiological actions, the validity of the remedies is questionable and its use restricted. It generally was observed that the more the constituents in a given species, the more diverse the micro-organisms it acts upon. The difference of activity appears to be directly related to the qualitative and/or quantitative diversity of the compounds that are being accumulated by the plants investigated.

However, detailed studies on the toxicity of extracts revealed through phytochemical screening showed that many constituents chemicals can affect the animal positively or negatively as a result of prolong usage. Thus, was founded that tannins and anthraquinones are thought to have both proxidant and antioxidant effects on the body. While the antioxidant protects, the proxidant damage the tissues and organs. Also, was observed that the presence of tannins and other compounds interferes with absorption of nutrients such proteins and minerals resulting in weight loss. The extracts contained the presence of saponins has been reported to produce free radicals and hydrogen peroxide during its oxidation to semiquinone in the body, is thought to damage the cells of the body. The results of several studies conducted so far have produced a scientific basis that can justify the use of *Ximenia americana* in medicine. As we see the many works on *X. americana* show its effectiveness in treating various diseases. In all studies, were highlighted the participation and importance of secondary metabolites produced by them. However, there are still many details to be clarified. As mentioned above, in general, it was observed that the more the constituents in a given species, the more diverse the micro-organisms it acts upon. Moreover, the activity of plant extracts seems to be related to quality and quantity of metabolites present, possibly due to the possibility of synergism while, different types of metabolites appear to be related to specific biologic actions. In this context it is important to point out that the norisoprenoid isophorane (**10**), shown to be carcinogenic agent (Mevy *et al.*, 2006), was identified in the leaves of *X. americana*, which would conflict with its use in treating cancer. The last report about compounds isolated from *X. americana* up to date were the sesquiternes **7** and **8**, triterpenoids **18**-**22** and steroids **24**-**26,** all from ethanol extract of stems (Araújo *et al.*, 2008, 2009). Some of them have not yet been exhaustively investigated from the point of view of biological activity.

Future studies should be performed using chromatographic methods such as HPLC (high performance liquid chromatography) and LC-MS (Liquid chromatography coupled to mass spectroscopy) to obtain the chromatographic profile of the chemical composition of the extracts. Then carry out guided study (biological activity) in order to isolate and identify the pure constituents. Finally, as reported, many compounds may exhibit both carcinogenic and anticarcinogenic effects but it is not excluded that the occurrence of compounds other than volatile constituents may act in the anticarcinogenic process. Consequently, these results encourage further investigations to extracts and identify the active chemical compounds responsible for the specific biological activity in order to standardized the plant preparation for maximum therapeutic benefit.

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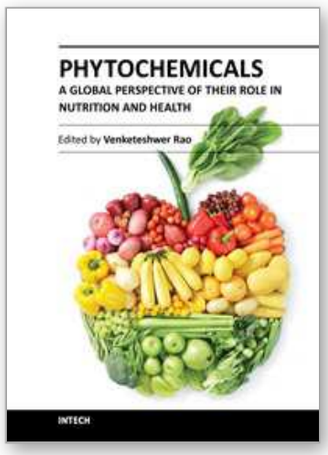

Phytochemicals - A Global Perspective of Their Role in Nutrition and Health

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