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THE NIGERIAN *ZANTHOXYLUM*; CHEMICAL AND BIOLOGICAL VALUES

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Abstract

The Nigerian *Zanthoxylum* is a common component of the rain forest vegetation of Southern Nigeria, and is represented by eleven species. A few of these species occur more abundantly in the savannah and dry forest vegetation of South-western Nigeria. The eleven *Zanthoxylum* species demonstrate very close similarities and relationships among themselves, and are identified as trees, erect shrubs or small trees, straggling or scandent shrubs or as a forest liane. Traditional healers throughout Nigeria have used species of the *Zanthoxylum* for the treatment of a wide range of disorders, including toothache, urinary and venereal diseases, rheumatism and lumbago. Metabolites isolated from *Zanthoxylum* species so far include alkaloids, aliphatic and aromatic amides, lignans, coumarins, sterols, carbohydrate residues etc. Some of the metabolites have shown cytotoxic, molluscicidal, anticonvulsant, anti-sickling, anaesthetic, antibacterial, anti-hypertensive and anti-inflammatory properties. A common feature of most, if not all, the species studied is the wonderful capacity to produce gums and volatile oils. These vary in composition and so show different properties. In this presentation, the author has discussed the chemistry of the various species examined to date. The focus has been on the local uses and commercial importance of the species, the values of the various metabolites in medicine and their general potential in drug development.

Key words: Nigerian *Zanthoxylum*, Medicinal plants, Medicinal values, Drug development

Introduction

Many developing countries of the world are endowed with vast resources of natural products. This priceless heritage which includes medicinal plants, have been used by indigenes for centuries as drug substances for relief from illnesses, as health-care products, fragrances, flavours, sweeteners and as materials for pest-control. And today, plants appear to be the almost exclusive source of drugs for the majority of the world's population, with

substances derived from higher plants constituting about a quarter of all prescribed medicines (Principe, 1989). Such drugs derived from natural products include: (1) purgative drugs, usually a mixture of anthraquinone derivatives from *Cassia* or related species. (2) anti-ulcer drugs, carbenoxolone from *Glycyrrhiza glabra* roots; also *Pulvia Bismuth Compositus* BP which is a mixture of bismuth carbonate, magnesium carbonate and sodium carbonate and (3) the antihepatotoxic drug, *Legalon* which contains in part, the flavononol lignans, silymarin from *Silybum marianum* L. Gaertn. Others include (4) the antimalarial drug, quinine from *Cinchona bark*, and (5) emetine from the root of *Ipecacuanha* to mention but a few.

Of great concern, however, is the fact that many of these natural products are exported (Pousset, 1988) to developed countries as raw materials for their industries overseas. The refined products, that is, the valued-added products are then imported back and these usually cost many times more than the original benefits derived from exporting the raw materials. African countries export so much of their natural products to pharmaceutical industries overseas annually maybe for want of a quick monetary reward or for lack of know-how or trained man-power to develop them locally. The implications are that the actual values of these natural products are not retained in the countries of origin.



Figure 1: *Zanthoxylum rubescens* growing in the wild

The genus *Zanthoxylum* Linn (Rutaceae) is represented (Olatunji, 1983) in Nigeria by eleven distinct species (Table 1).

Table 1: *Zanthoxylum* species identified in Nigeria

No	Names
1.	<i>Zanthoxylum bouetense</i> (Pierre ex. Letouzey) Waterm.
2.	<i>Zanthoxylum buesgenii</i> (Engl.) Waterm.
3.	<i>Zanthoxylum dinklagei</i> (Engl.) Waterm.
4.	<i>Zanthoxylum gillettii</i> (De Wild) Waterm.
5.	<i>Zanthoxylum lemairie</i> (De Wild) Waterm.
6.	<i>Zanthoxylum leprieurii</i> (Guill et Perr) Engl. Ex Waterm.
7.	<i>Zanthoxylum rubescens</i> (Planch ex. Hook. F.) Engl. Ex Waterm.
8.	<i>Zanthoxylum tessmannii</i> (Engl.) Ayafor Comb. nov.
9.	<i>Zanthoxylum thomense</i> (Engl.) A. Chev. Mss ex Waterm.
10.	<i>Zanthoxylum viride</i> (A. Chev.) Waterm.
11.	<i>Zanthoxylum zanthoxyloides</i> (Lam.) Waterm.

These species were formerly known under the generic name *Fagara* Linn and it was recent chemosystematic considerations that led to the 'sinking' of *Fagara*. These eleven species of *Zanthoxylum* all belong to the sub-Family Rutoideae; tribe, Zanthoxyleae in the family Rutaceae and demonstrate (Olatunji, 1983) close similarities and relationships among themselves. The species, like other African *Zanthoxylum* species, are distinguishable by taxonomic characteristics-anatomical and morphological features of the root, leaf, fruit etc. They are all primarily plants of the forest vegetation and are found frequently in the Southern parts of Nigeria. *Z. gillettii*, *Z. tessmannii* and *Z. leprieurii* are trees and are common in the wet and dry forest vegetation of Southern Nigeria, with *Z. gillettii*, occurring more commonly in wetter locations along rivers, streams and wet valleys. *Z. zanthoxyloides* occurs more abundantly in the savannah and dry forest vegetations and is found in the drier parts of South Western Nigeria extending to Niger States. *Z. rubescens* occurs as a small tree, it is rather sparsely distributed throughout the Southern forest regions extending also into the northern parts of the country. *Z. viridis* has been recorded only in the drier parts of Oyo and Kwara States, *Z. thomense* in Ondo and Edo States and *Z. lemairiei* in Edo and Benue States. *Z. dinklagei* occurs in Edo and the South Eastern State while *Z. bouetense* and *Z. buesgenii* are found only from the Oban forest in the South Eastern States, close to the Republic of Cameroon.

A major characteristic is that the trunks, branches, branchlets, leaf stalks and inflorescence axes of all these species are covered by prickles or what others describe (Waterman, 1986) as spines. This makes the *Zanthoxylum* species a big nuisance to farmers who always mark them for destruction when cited on farms and vegetations. Of value, however, is the characteristic that like a true Rutaceae, the leaflets and inflorescences of these species contain volatile oils which bring forth sweet smells/odours and fragrances.

Economic and Medicinal Uses of the *Zanthoxylum* Species:

Economically, the timber of *Z. gillettii*, *Z. tessmannii*, *Z. lemairiei* and *Z. leprieurii* are used (Dalziel, 1937; Oliver-Bever, 1982) in house and boat-building, decorative paneling,

joinery, construction of talking drums and in the paper and pulp industry. The roots, bark and leaves of many species are used in various medicinal preparations for curing (Olatunji, 1983; Oliver-Bever, 1982) stomachache, tooth-ache, coughs, urinary and venereal diseases, leprosy ulcerations, rheumatism, lumbago etc. They are used as components of antiseptic, antiparasitic and analgesic preparations for managing small pox, syphilis and related disease conditions. Since the root and stem bark of many species are poisonous to some species of water fleas, mice, fish and paramecia, these roots are used as vermifuge, febrifuge and piscicide.

Perhaps the most popular domestic use to which the roots are put is as chewing stick to clean the mouth. The roots usually give a warm, pungent and benumbing effect on the palate when chewed, and this aromatic warm taste with attendant profuse salivation is believed to be beneficial to the elderly and those with sore gums and other oral disease conditions.

The Chemistry and Biological Values of the Nigerian *Zanthoxylum*

The large pan-tropical genus *Zanthoxylum* Linn is very well known (Mester, 1983; Simanek, 1985) for its diverse chemistry, particularly of alkaloids, aromatic and aliphatic amides, sterols and phenylpropanoids-lignans and coumarins. These secondary metabolites are well distributed in the *Zanthoxylum* species investigated to date. It is equally interesting to note that scientific studies including selected biological leads, based on ethnomedical information have helped to discover new bio-active extracts and compounds some of which have good potentials for pharmaceutical development.

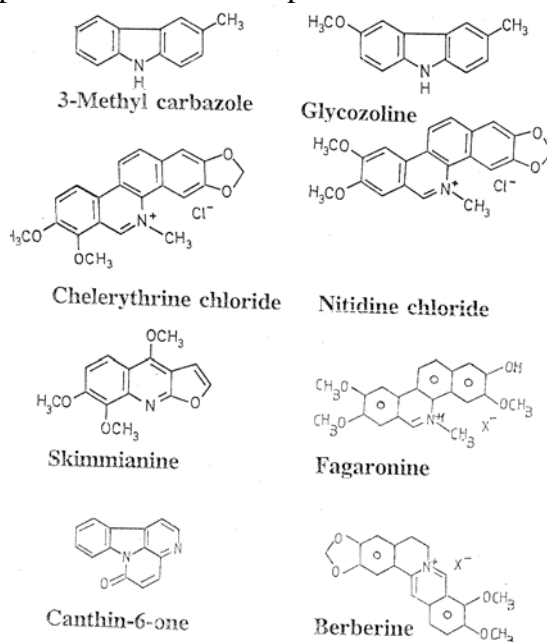


Figure 2: Structure of some alkaloids

Alkaloids in the Nigeria *Zanthoxylum*

The Nigerian species of the sub-family, Rutoideae (Rutaceae) have proved to be a good source of the benzophenanthridine (Krane et al., 1984) and the aporphine alkaloids that typify the family (see Table 2.)

Table 2: Alkaloid distribution in the Nigeria *Zanthoxylum*

Compound	rubescens RT.SB.FR	zanthoxyloides RT.SB.FR.	leprieurii RT.SB.FR	tessmannii RT.SB.FR.	gillettii RT.SB.FR	thomense RT.SB.FR	lemairie RT.SB.FR
BENZO-PHENANTHRIDINES							
1.Nitidine	□		□ □	□	□ □		
2.Dihydronitidine				□			
3.Oxynitidine					□		
4.Fagaronine	□	□ □	□		□		□ □
.Dihydroavicine	□ □	□	□				□ □
6.Chelerythrine	□ □	□ □	□ □	□ □	□		
7.Dihydrochelerythine	□ □			□	□	□	□ □
8.Methoxychelerythine	□			□	□	□	
9.Norchelerythrine	□		□	□ □	□		
10.Oxychelerythrine		□					
11.Decarine							
12.Fagaridine				□			
FUROQUINOLINES							
13.Dictamine				□ □	□	□	
14. 8-Methoxydictamine		□		□	□ □	□ □	
15.Skimmianine	□	□	□		□ □	□ □ □	□ □
16.3-Dimethylallyl-4-methoxy-2-quinolone		□					
CARBAZOLES							
17. 3-Methylcarbazole					□		
18.Glycozoline							□ □
APORPHINES							
19.Berberine		□					
20.Tembetarine	□	□			□		
21.Magnoflorine	□	□	□ □				
22.N-methyl-corydine	□	□	□		□		
CANTHINONES							
23. 6-Canthinone		□					
ACRIDONES							
24.1-Hydroxy-3-Methoxy-10-Methylacridon-9-one			□ □ □				
25.1-Hydroxy-10-Methylacridon-9-one			□ □ □				
26.Zanthozolin.			□ □				

KEY: □, compounds reported in literature, RT = root, SB = stem bark, FR = Fruit

Carbazoles, canthinones and acridone alkaloids have also been found restricted to some species. Other alkaloids based on anthranilic acid or tryptophan are furoquinolines such as skimmianine which appear common to all the species investigated. Three acridone alkaloids have been isolated (Reisch et al., 1985) from the root, stem and pericarps of *Zanthoxylum leprieurii*. The benzophenanthridines, nitidine and chelerythrine, the furoquinoline, skimmianine and the aporphines, berberine, magnoflorine etc. have all been isolated (Vaquette et al., 1978) from *Zanthoxylum bouetense* and *Zanthoxylum dinklagei* roots and stem bark.

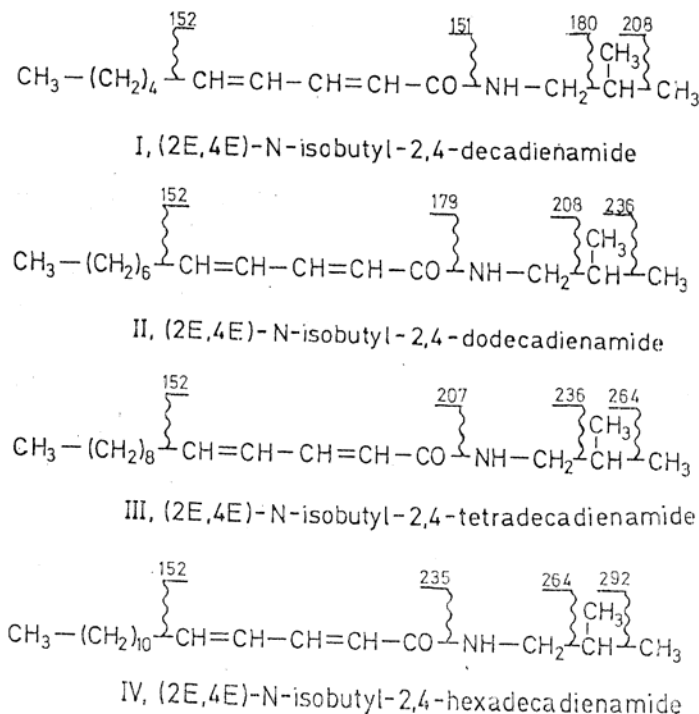


Figure 3: Some aliphatic amides

Despite the fact that there are no known folkloric reports of their use in the management or cure of tumours and cancerous conditions, scientists have been attracted because of the anti-leukemic properties and other values of the isolates from these plants. Nitidine isolated (Arthur et al., 1958) from *Zanthoxylum nitidum* in 1958 and later from (Fish and Waterman, 1971) *Fagara macrophylla* (*Zanthoxylum macrophylla*) in 1971 demonstrated strong antileukemic activities (Wall et al., 1987) against L1210 and P388 and showed growth inhibition of *Lewis lung carcinoma*. It was also found to be marginally active against *B 16 melanoma*. A phenolic benzo[C] phenanthridine, fagaronine, was isolated (Messmer et al., 1972) from *Zanthoxylum zanthoxyloides* as the active principle demonstrating strong antileukemic activity against both L 1210 and P-388 leukemia in 1972. It gave prolongations of life of the order of 265, 210 and 190% T/C at doses of 100, 50 and 25 mg/kg respectively. The benzophenanthridine alkaloids of the *Zanthoxylum* generally show some anti-neoplastic activities but their toxicities have been found to be a serious problem; this has also prevented them from clinical use.

The acridone class of alkaloids has been surveyed with special emphasis on experimental cancer chemotherapy studies of acronycine. Studies on acronycine's broad antitumour spectrum and its toxicity have been carried out (Gerzon and Svoboda, 1983) as a prelude to an introduction to its clinical evaluation in patients. The mode of action of acronycine reportedly involves its incorporation into cellular and subcellular membranes resulting in the inhibition of nucleoside. Further studies need to be carried out on these group of compounds which have been found to lack activity against the four primary tumour models rightly held to be of high predictive merit for clinical efficacy. Acridone alkaloids isolated from *Z. leprieurii* have shown antibacterial effect.

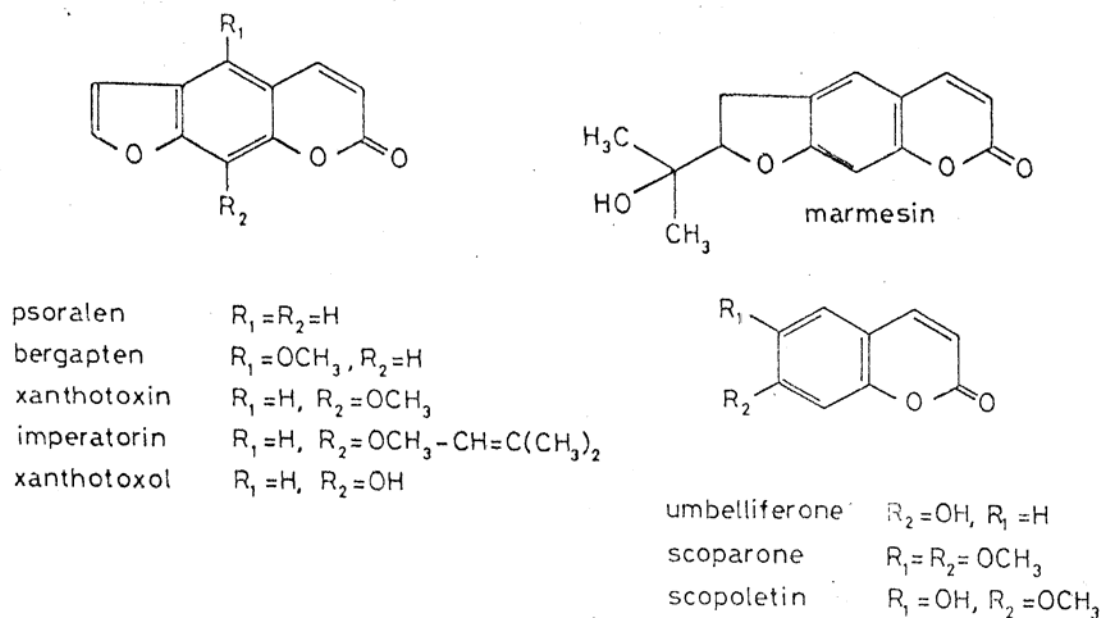


Figure 4: Coumarins in the Nigerian *Zanthoxylum*

Paris and his co-workers observed that a crude extract of *F. macrophylla* root (0.1g/kg) caused bradycardia and hypotension in dogs (Paris and Moyse-Mignon, 1951). The isolated pure alkaloid was found to lower both the systolic and diastolic blood pressures. This finding was confirmed by Addae-Mensah and his co-workers (Addae-Mensah et al., 1986). A single dose of nitidine chloride (1-2mg/kg) lowered the blood pressure by about 20% within 90 minutes and this was maintained for up to six hours. Doses of 500, 600, 700, 800 and 900 mg/kg, administered at 80 minutes intervals, cumulatively lowered the blood pressure by about 25%. The drug also antagonized the effects of angiotension-induced hypertension. Its delayed introduction into clinical medicine may have been informed by its reported toxicity.

The benzophenanthridine, chelerythrine and aporphine, berberine, and the phenolic canthine-6-one isolated from the powdered root of *Fagara zanthoxyloides* have also been identified (Odebiyi and Sofowora, 1973) with antimicrobial activity. These show that the

alkaloids of the *Zanthoxylum* have shown anti-tumour, anti-hypertensive and anti-microbial effects.

Amides in the *Zanthoxylum*:

The hot, peppery taste of the *Zanthoxylum* roots is a common feature of all the roots known. The benumbing effect on the palate when chewed is characteristic and has been used to advantage in the treatment of mouth infections particularly in the elderly.

The genus *Zanthoxylum* is characterized (Mester, 1983; Fish and Waterman, 1973) chemically by the frequent accumulation of olefinic alkamides (unsaturated aliphatic acid amides), a biogenetic capacity derived from the condensation of fatty acids such as linolenic and linoleic acids with isobutyl amines. By 1963, Bowden and Ross identified the hot peppery component of the root of *Zanthoxylum zanthoxyloides* as pellitorine (Bowden and Ross, 1963), "the local anaesthetic component" of the roots. This property had earlier on been noted by Paris and Mignon in 1947. Pellitorine and many other structurally-related components, for example, N-isobutyl-*trans*-2-*trans*-4-octadienamide, N-isobutyl-*trans*-2-*trans*-4-tetradecadienamide, N-isobutyl-*trans*-2-*trans*-4-eicosadienamide, gamma-sanshool (N-isobutyl-2,4,8,10,12-tetradecapentaenamide) which are pungent, have been isolated (Mizutani et al., 1988; Gregor, 1984; Adesina et al., 1997) from *Zanthoxylum lemairie* and many other *Zanthoxylum* species and have been implicated for the organoleptic properties of the roots. Seven of such amides have been described in the Nigerian *Zanthoxylum* (see Table 3.) The structural type and concentration of each amide appear very relevant in considering how pungent the roots are.

Table 3: **Distribution of aliphatic amides in the Nigerian *Zanthoxylum***

Compounds	rubescens RT.SB.FR	zanthoxyloides RT.SB.FR.	leprieurii RT.SB.FR.	tessmanni RT.SB.FR.	gillettii RT.SB.FR.	thomense RT.SB.FR.	lemairie RT.SB.FR.
ALIPHATIC AMIDES							
1.N-isobutylocta2,4-dienamide		□ □ □					
2.N-Isobutyldeca,2,4-dienamide		□ □ □		□ □	□ □		□ □
3.N-Isobutyldodeca2,4-dienamide	□			□ □	□ □		
4.N-Isoutyltetradeca 2,4-dienamide	□ □ □	□		□ □	□ □	□ □	□ □
5.N-Isobutylhexadeca-2,4-dienamide		□		□ □	□ □ □		
6.N-Isobutyleicosa-deca-2,4-dienamide			□				□ □
7.N-Isobutyl-2,4,8,10,12-tetradecapentaenamide.	□ □	□	□	□ □	□	□	□ □

KEY: □, compounds reported in literature.

Biologically, the isobutyl amides have been shown to have strong insecticidal properties. The main component of pellitorine, N-isobutyldeca-*trans*-2-*trans*-4-dienamide is very potent causing (Gregor, 1984; Yasuda et al., 1981) marked paralysis of mucous membranes and was about half as toxic as the pyrethrins to the house fly, *Musca domestica* L. It has also been found to show antibacterial and antimalarial properties (Weenen et. al., 1990). On the other hand N-isobutyldodeca-2,4-dienamide obtained from four *Zanthoxylum* species is only weakly pungent and is inactive to house flies (Yasuda et. al., 1981; Jacobson, 1954). Kubo and his co-workers have confirmed that pellitorine isolated from *Fagara macrophylla* was a potent insecticide.

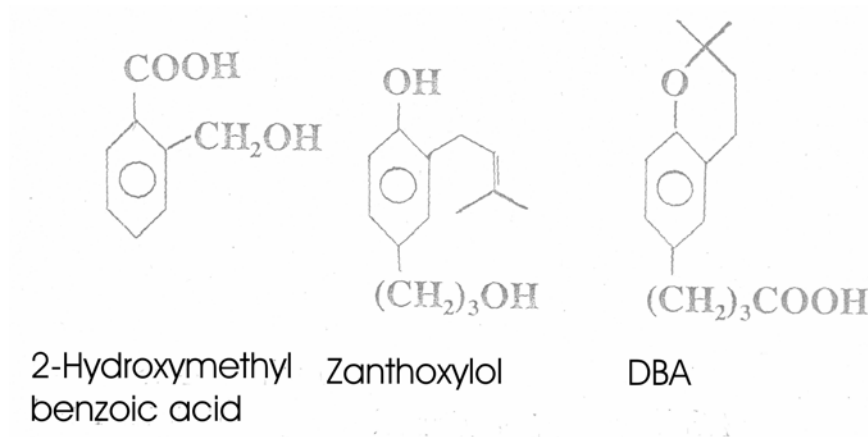


Figure 5: Compounds with anti-sickling properties

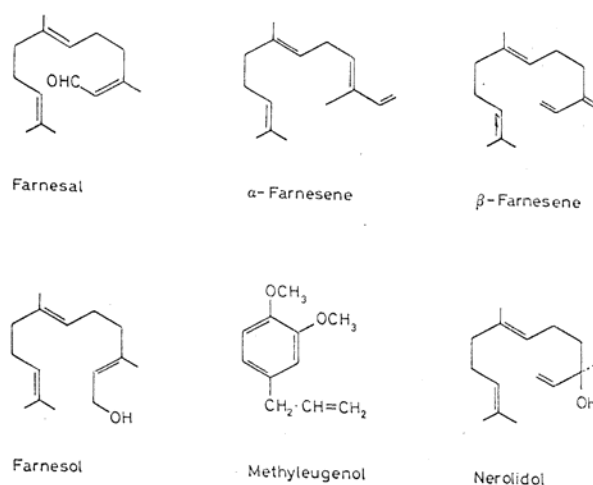


Figure 6: Volatile oil constituents of the Nigerian *Zanthoxylum*

Some olefinic isobutylamides have also been shown (Yasuda et. al., 1981; Kubo et. al., 1984) to be effective as molluscides and cercaricides and are thus of potential use against bilharzia. Alkamides have been used medicinally since ancient times as sialogogues, antitussive and analgesic and their presence in the *Zanthoxylum* may be of immense benefit to medicine.

The other type of amides encountered in the *Zanthoxylum* are the aromatic amides described occasionally also as alkaloids or *trans*-cinnamoylamides. The roots, stem-barks and pericarps of all the seven *Zanthoxylum* species examined have been found to contain amides, but the structural types and concentrations of these amides vary from one species to the other. In all, over twenty aromatic amides have been identified in the Nigerian *Zanthoxylum* (see Table 4.)

Table 4: **Distribution of aromatic amides in the Nigerian *Zanthoxylum***

Compounds	rubescens RT.SB.FR.	zanthoxyloides RT.SB.FR.	leprieurii RT.SB.FR.	tessmannii RT.SB.FR.	gillettii RT.SB.FR.	thomense RT.SB.FR.	lemairie RT.SB.FR.
1.arnottianamide	□ □	□	□		□		□
2. Cyclopropane -carboxamide	□ □						
3.Dioxamin	□ □ □						
4.Dioxamide	□ □ □				□ □ □	□ □	□ □
5.Fagaramide	□	□ □		□ □	□		
6.Dihydrofagaramide				□ □		□	□ □
7.Herclavine	□ □ □						□
8.Lemairamin	□ □				□ □	□	□
9.Lemairamide	□ □						
10.N-Isoutyl-cinnamamide					□		
11.Isoarnottianamide	□						
12.Piperlonguminine		□			□		□ □
13.N-isopentyl- cinnamamide	□ □	□	□				
14.Rubemamin	□	□ □		□ □	□ □		
15.Rubemamide	□					□	
16.Rubescenamin	□ □						
17.Rubescenamide	□						
18.Zanthomamin	□ □						
19.Zanthomamide	□						
20.Zanthosinamide	□ □ □				□ □ □	□ □ □	□ □
21.Zanthosin.	□ □ □				□	□	□ □
	□						

KEY: □, compounds reported in literature

While *Z. rubescens* and *Z. gillettii* appear to be very rich in aromatic amides, only a few have been identified in *Z. leprieurii*. This peculiarity is interesting, when one notes that it is only *Z. leprieurii* that accumulates acridone alkaloids in its organs.

Some of the identified amides have the 6C-3C- or 6C-2C-N unit in their molecules and this indicates that, in part, they have originated from the tyrosine/p-coumaric acid pathway.

Fagaramide which was detected in all but one of the species investigated has a cinnamic acid moiety combined with isobutylamine which itself may have originated from the amino acid, valine. Many of the amides share this structural type or their derivatives. Herclavine identified in *Z. rubescens*, *Z. lemairie* and *Z. thomense* appears to be a direct product of tyrosine, p-coumaric acid condensation. Unlike arnottianamide and its isomer which are oxidation products of chelerythrine and nitidine respectively (Ishii et al., 1976), all these amides are condensation products of cinnamic acid derivatives and those of amino acids. Very recently, fagaramide was identified alongside with piperlonguminine, herclavine, zanthomamide, zanthosinamide, lemairamin and lemairamide from *Zanthoxylum lemairie* Adesina et al., 1997a; Adesina et al., 1997b). Fagaramide had earlier on been found to demonstrate weak anti-inflammatory effects (Oriowo, 1982) in laboratory animals, suggesting that structurally-related compounds may also show this effect. Of value also is the report that fagaramide is a more active molluscicide against *Biomphalaria glabratus* than piperlonguminine (Kubo et. al., 1984).

Zanthoxylum rubescens appears to occupy a unique position as many aromatic amides have been isolated (Adesina and Reisch, 1989) from the root and stem bark. These include N-(3,4-dimethoxyphenylethyl)-3,4-dimethoxy-cinnamamide (rubemamin), N-methyl, N-3,4-dimethoxyphenylethyl-3,4-dimethoxycinnamamide (rubemamide), N-methyl, N-(3,4-methylenedioxyphenylethyl)-3,4-methylenedioxycinnamamide (dioxamide) and N-(3,4-methylenedioxyphenylethyl)-3,4-methylenedioxycinnamamide (dioxamin) isolated from the roots in 1989. Three other unsaturated aromatic amides, N-methyl, N-(3,4-methylenedioxyphenylethyl), 3,4-(dimethoxycinnamoyl)amide (rubescenamide), N-(3,4-dimethoxyphenylethyl, 3', 4-methylenedioxycinnamoyl)amide (zanthosin) were isolated also from the stem bark. When tested for anticonvulsive effects in mice, dioxamin and rubemamin separately showed strong anticonvulsive effects in laboratory animals. This probably explains the strong anticonvulsive effects of *Z. rubescens* stem and root bark extracts.

Phenylpropanoids in the Nigerian *Zanthoxylum*:

Phenylpropanoids are perhaps the most widespread types of natural products occurring in nature. Chemical investigations on the whole root, stem and aerial parts of all the *Zanthoxylum* species collected revealed simple coumarins only. Aesculetin dimethylether (scoparone) and 6,7,8-trimethoxy coumarin were present in all these species (Table 5). Furocoumarins were detected in two species only, in *Z. zanthoxyloides* and *Z. lemairiei*. Surprisingly, however, there has not been a known report of any coumarin in *Zanthoxylum rubescens*.

Biologically, coumarins are very useful and many of them have exhibited (Mabry and Ulubelen, 1980) antibacterial, anti-tumour, vasodilatory (in coronary vessels) and anticoagulant activities. It was long noted that most coumarins are free from toxic side effects and may be given for years without side effects; overdose, however, causes haemorrhages (Lau-Cam and Chu-Fong, 1972).

Table 5: **Distribution of coumarins in the *Zanthoxylum***

Compounds	rubescens RT.SB.FR.	zanthoxyloides RT.SB.FR.	leprieurii RT.SB.FR.	tessmannii RT.SB.FR.	gillettii RT.SB.FR.	thomense RT.SB.FR.	lemairie RT.SB.FR.
1.Umbelliferone		□					
2.Scopoletin		□				□	
3.Scoparone		□ □ □	□ □	□ □	□ □		□ □
4.6,7,8-trimethoxy- coumarin							
5.Xanthotoxin		□ □	□ □	□ □	□ □	□ □	□ □
6.Imperatorin		□					
7.Bergapten		□					
8.Marmesin		□					
9.Pimpinellin		□					
10.Xanthyletin							□ □ □

KEY: □, compounds reported in literature

Some coumarins such as umbelliferone, scopoletin, scoparone and the furocoumarins-xanthotoxin, imperatorin, bergapten, marmesin etc, isolated from the *Zanthoxylum* (Adesina, 1986), have shown antibacterial and antifungal activities (Mabry and Ulubelen, 1980). The coumarins inhibit the growth of the yeast *Saccharomyces cerevisiae* and at higher concentrations retard the germination of the spores of *Aspergillus niger* and *Penicillin glaucum*. Furocoumarins also have the potential of snail control by exerting a molluscicidal activity (Mabry and Ulubelen, 1980; Adesina and Adewunmi, 1985), comparable to some of the most powerful synthetic agents and these probably contribute in part to the molluscicidal activities of *Zanthoxylum zanthoxyloides* root-bark extracts. Furocoumarins have also been used (Mabry and Ulubelen, 1980) to treat vitiligo and psoriasis. Both scoparone and scopoletin have demonstrated (Ojewole and Adesina, 1983; Jamwal et al., 1972) marked anticonvulsive effects in experimental animals and have been found to be the major active compound of some plants implicated in the management of convulsions.

The phenylpropanoids described as lignans are also widely distributed in higher plants and more than 200 compounds have been identified. They are biogenetically derived (Mabry and Ulubelen, 1980; Massnaet et al., 1989) by the oxidative dimerisation of two C₆-C₃ units, that is, two characteristic phenylpropanoid units. The degree of oxidation and types of substituents determine the emerging lignan structure. There are also naturally occurring dimers that exhibit peculiar-type linkages. Only two structural types of lignans have been encountered in the Nigeria *Zanthoxylum* and these are (1) those lignans containing the 2,3-bis (substituted benzyl) - γ -butyrolactone unit, for example, arctigenin methylether, hinokinin, savinin, 2,3-Di (3',4'-methylenedioxybenzyl)-2-buten-4-olide isolated from *Z. lemairei*

(Adesina et al. 1997a) and (2), those containing 2, 6-diaryl-3, 7-dioxabicyclo (3-3-0) octane ring structure typified by sesamin. Apart from the nine lignans previously reported in the Nigerian *Zanthoxylum* (Table 6), five other lignans -2 α and 2 β -vertrylmethyl-3 α -piperonylmethyl- γ -butyrolactones, kubosin, guayadequine and methyl trachelogenin were recently described from *Z. lemairei* (Adesina et al. 1997a).

Table 6: **Distribution of lignans in the *Zanthoxylum***

Compounds	rubescens RT.SB.FR	zanthoxyloides RT.SB.FR.	leprieurii RT.SB.FR	tessmannii RT.SB.FR.	gillettii RT.SB.FR	thomense RT.SB.FR	lemaire RT.SB.FR.
1.Sesamin		□ □ □	□	□ □	□ □ □	□ □	□□□
2.Asarinin		□	□	□ □ □	□ □	□ □	
3.Savinin				□	□ □		□□□
4.Hinokinin				□ □	□ □ □		□□□
5.Arctigenin-methylether				□	□ □ □	□ □	□□□
6.Arctigenin					□		
7.Matairesinol				□	□		
8.2,3-Di(3'4' methylenedioxy-benzyl)-2-buten-4-olide					□		□□□
9.Lirioesinol-dimethylether			□				

KEY:

□, compounds reported in literature .

The range of lignan structures and biological activities (Massnaet et al., 1989; MacRae and Towers, 1984) is broad. Various lignans are known to have anti-tumor, anti-mitotic and antiviral activity and to specifically inhibit certain enzymes. At the ecological level, there is the evidence that lignans play a role in plant-fungus, plant-plant and plant-insect interactions. Some lignans are toxic to fungi and insects. Other physiological properties of lignans have also been observed. Sesamin, for example, has been used (Vickery et. al., 1950) as an anti-oxidant. Sesamin and asarinin are effective in enhancing the toxicity of a wide variety of insecticides and have themselves been used as insecticides. These lignans have been used (Hallen et. al., 1942) as synergists, like known synthetic insecticide synergists, with other insecticides such as pyrethrins. Of particular interest is the fact that savinin, hinokinin, matairesinol and its dimethylether are all insecticide synergists. Trachelogenin and arctigenin were found to demonstrate potent and long-lasting antihypertensive effects on spontaneously hypertensive rats (Ichikawa et al., 1986). It is not known whether methyl trachelogenin and arctigenin dimethyl ether also isolated (Adesina et al., 1997a) from the Nigerian *Zanthoxylum* will show this effect. These bisepoxy lignans kobusin and sesamin were shown to inhibit the growth of silkworm (*Bombyx mori*) larvae; thus demonstrating antifungal effects.

Other Extractives from the Nigerian *Zanthoxylum*

Chemical studies (Eshielt and Taylor, 1966; Eshielt and Taylor, 1968) of some *Zanthoxylum* species led to the isolation and characterization of zanthoxylol identified as 3-dimethylallyl-4-hydroxyphenyl propanol from *Fagara zanthoxyloides* among other compounds. This plant has also furnished diosmin, fagarol and hesperidin (Okogun, et al., 1978).

Sterols are common components of many plants and have been isolated from virtually all plants. Whereas β -sitosterol appears ubiquitous in nature, the triterpene lupeol appears restricted to the *Zanthoxylum*. Lupeol, β -sitosterol, usually associated with stigmasterol and campesterol and β -amyirin have been isolated from the various morphological parts of all the *Zanthoxylum* species investigated.

The results of biological work on β -sitosterol has been very interesting indeed. This compound was found to possess potent anti-inflammatory activity (Gupta et al., 1980) similar to hydrocortisone and oxyphenbutazone when administered intraperitoneally. This compound was also orally effective against carrageenin-induced oedema. The anti-inflammatory activity of this compound was independent of pituitary adrenal axis. β -sitosterol also exhibited anti-pyretic activity similar to acetylsalicylic acid. β -sitosterol was found to show a wide margin of safety since the approximate LD₅₀ was more than 3g/kg i.p. in mice and minimum ulcerogenic dose was 600mg/kg i.p. in rats. Because of these properties and the wide margin of safety, β -sitosterol may be of therapeutic value.

Of great interest too is the isolation and identification of antifungal and antioxidant compounds from the root bark of *Fagara zanthoxyloides* (Chaaib et al., 2003).

The *Zanthoxylum* Species in the Management of Sickle-cell Disease (SCD)

The interesting story of *Fagara zanthoxyloides* (syn. *Zanthoxylum zanthoxyloides*) probably started in this environment with the observation or chance discovery by El-Said (El-Said et al., 1971) and his team in 1971 that the *Fagara* root extract possessed activity on the red cell membrane. El-Said and his collaborators reported that the extract of this plant, apart from being antibacterial preserved the colour of the blood within its zones of inhibitions when examined on blood agar plates. Sofowora and Isaacs (1971) later reported on the reversal of sickling and crenation in erythrocytes by the root extract of *Fagara zanthoxyloides*. Both authors and their associates have separately reported these effects at different scientific meetings (Isaac-Sodeye, 1973; Sofowora, 1974; Isaac-Sodeye et al., 1975). In 1975, Sofowora and his team reported the isolation and characterization of 2-hydroxymethyl benzoic acid as one of the anti-sickling agents of the plant (Sofowora et al., 1975).

Though Honig et al, adopting a different methodology of evaluation and working on plant specimens purportedly collected in Ghana could not confirm these effects (Honig et al., 1975), Sophia Abu and his collaborators confirmed the antisickling effects of *Fagara zanthoxyloides* root extract (Abu et al., 1981). Since then, biological and chemical assays have been developed for the estimation of antisickling agents in the roots of many Nigerian *Zanthoxylum* species (Elujoba and Sofowora, 1977; Adeoye, 1978; Adesanya, 1980). Very

recently, in 1989, Osoba and his team studied the effect of the root extract of *Zanthoxylum zanthoxyloides* and some selected substituted benzoic acids on glucose-6-phosphate and 6-phosphogluconate dehydrogenases in HBSS red blood cells and found out that the antisickling fraction of the root of *Z. zanthoxyloides*, vanillic acid, p-hydroxy benzoic acid and p-fluoro benzoic acid possessed antisickling inhibitory activity at low concentrations Osoba et al., 1989). The authors found out that p-fluorobenzoic acid was the most active. It was also noted that the agent did not affect the activities of glucose-6-phosphate and 6-phosphogluconate dehydrogenases while exhibiting antisickling activity nor disrupt the cell membrane to the extent of causing leakage to the media.

The quest for ant-sickling agents continued in other laboratories with time. In preliminary assays carried out at the University of Ibadan, Isaacs Sodeye noted that it seemed that zanthoxylol isolated from *Zanthoxylum zanthoxyloides* in 1966 possessed antisickling activity. Zanthoxylol was modified chemically to 3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-6-butyric acid (DBA). This compound was found to efficiently prevent and reverse sickling (Ekong et al., 1975). It also had no acute toxicity in male mice. Zanthoxylol has since been isolated and estimated from the root of *Zanthoxylum zanthoxyloides* (Elujoba and Nagels, 1985) the only Nigerian *Zanthoxylum* in which it was detected.

In very recent times, Fadulu, (a former associate of El-Said, Kuye and Sofowora) and his American collaborators reported a potent anti-sickling compound code-named NX-06999 (The World Sickle Cell Foundation Inc., 1990). It was reported to be free from any toxic side effects and was already being subjected to preliminary clinical trials in Nigeria, Gabon and Panama. There is, therefore, no doubt that *Zanthoxylum* extracts and the "unknown antisickling candidate" coded NX-06999 had some promise as possible additions to the regime of managing Sickle Cell Disease. A most recent report by Ouattara et al. (2004) of the analysis of isomeric divanilloylquinic acids from the root bark of *Fagara zanthoxyloides* Lam. is of great scientific interest. The new isomeric divanilloylquinic acids- 3,4-O-divanilloylquinic acid, 3,5-O-divanilloylquinic acid and 4,5-O-divanilloylquinic acids were obtained from the roots of *Fagara zanthoxyloides* Lam. collected in Burkina Faso. The authors concluded that these new compounds named burkinabins A-C could play a useful role in sickle cell disease as the active agents of the root of *Fagara zanthoxyloides* previously referred to as unidentified aromatic compounds by Adesanya and Sofowora.

***Zanthoxylum* gum (Rutaceae)**

The dried gummy exudates from the stem of many trees or plants are used by pharmaceutical industries as binder, emulsifying agent or even as a diluent. The composition of the exudates vary very much in the contents of ash or carbohydrate moieties etc and these usually influence the properties of these gums. Gum arabic, (from *Acacia* species), for instance, is principally Calcium, Magnesium and Potassium salts of the polysaccharide acid, arabic acid and is used extensively as a suspending agent for insoluble substances in water, in the preparation of emulsions and for making pills and troches. It has also been used for its demulcent action in inflammations of the throat or stomach. Similarly, the dried gummy exudation, gum tragacanth or Hog Gum from *Astragalus gummifer* (Leguminosae), contains 60-70% of *bassorin* and 30-40% soluble gum *tragacanthin*. *Bassorin* consists of complex

methoxylated acids resembling pectin in *tragacanthin* which yields carbohydrate moieties, mainly glucuronic acid and arabinose on acid hydrolysis. The pharmaceutical industries have found gum tracaganth a useful suspending agent in lotions, mixtures and extemporaneous preparations and prescriptions; as a pill excipient and in various confectionary products.

Some investigations were carried out on the gum collected as dried tears from the slashed bark of *Zanthoxylum tessmannii*. The gum was analysed for ash, carbohydrate residues and a peroxidase enzyme. The studies (Orafidiya et al., 1992a) were limited to some physico-chemical properties of the gum, the rheological properties (Orafidiya, 1989) of aqueous solution of the gum and some factors affecting (Orafidiya et al., 1992b) the stability of emulsions prepared for it. There is still the need for more investigations regarding its binding and gliding capabilities and the properties of gums from other *Zanthoxylum* species.

Natural Volatile Concentrates

Many plants are able to accumulate volatile odoriferous substances in order to attract insects or other animals for pollination and seed dispersal, to repel others which may be harmful or to protect themselves from pathogenic micro-organisms.

In recent times, these odoriferous substances, mainly volatile oils have been put into good use by man. These include (1), direct culinary use as fresh or dried herbs, spices and condiments; (2), in perfumery, cosmetic and house-hold and personal hygiene products; (3), as flavors in food, drink and confectionery; (4), as components of pharmaceutical preparations in human and veterinary medicine; (5), as pesticides as insect repellents in agriculture particularly crop protection and (6), as anti-infective agents, particularly as anti-bacterial and anti-fungi agents. The rich volatile oils have also found ample use in many industrial institutions.

Like Citrus species (Rutaceae) which accumulate volatile oils with strong antiseptic and disinfectant properties in the fresh fruit, peel, leaves and dried fruit, the *Zanthoxylum* species also accumulate volatile oils in the leaves, fruit and inflorescences. For example the volatile constituents (Reisch et al., 1986) of *Z. macrophylla* pericarp include α -pinene, limonene, linalool, methyl eugenol, guaiene and other components while nerolidol and farnesol derivatives have been found in high quantities in the pericarp of *Zanthoxylum tessmannii*. There is no doubt that the volatile oils of the leaves, fresh flowers and fruits of these *Zanthoxylum* species will give good yields of volatile oils if exploited.

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