UNIVERSITY OF ABUJA
ABUJA – NIGERIA

BIOACTIVE ORGANIC SUBSTANCES FROM PLANTS FOR USE IN AGRICULTURE AND MEDICINE: NATURAL PRODUCTS CHEMISTRY

INAUGURAL LECTURE SERIES 5

Delivered By

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on

THURSDAY 25th May, 2006

PROTOCOL

The Vice-Chancellor and Chairman of Occasion,

The Deputy Vice-Chancellors,

Principal Officers of the University,

Deans and Directors,

Heads of Department and Support Units,

Distinguished Invited Guests and Friends of the University,

Colleagues from other Universities and other Higher Institutions,

Members of the University Community,

Members of the Press,

Ladies and Gentlemen

INTRODUCTION

I wish to express my gratitude to God Almighty and the Vice-Chancellor for providing this forum to present my inaugural lecture, the fifth in the series, which has been due since 1993 when I became a Professor of this University. This lecture is the second in Science, and the first in Chemistry, coming after that by Professor A.A. Olatunde of Biological Sciences department which was titled "Fish: their life–our life". Following in the footsteps of Prof. Olatunde is not new as I was his immediate successor as the dean of the Faculty of Science then known as the College of Science and Agriculture. Prof. Olatunde gloriously retired in December 2005. I wish to use this occasion to congratulate him for a very successful academic career. As the foundation dean of the Faculty, it is the structure he laid that has been the strength of the faculty.

In selecting the topic of this lecture, "**Bioactive organic substances from plants for use in Agriculture and Medicine: Natural Products Chemistry**," I aim at justifying some of our traditional practices such as herbal medicine, use of botanic pesticides and local vegetable tanning materials through biological and chemical studies on Nigerian plants. The effort is to obtain lead compounds of industrial significance from local plants, which have some physiological and other biological properties and make them accessible through synthesis. Since 1973, when I had my B.Sc. degree in Chemistry at the University of Ibadan, Nigeria, till today, that has been my area of research and some significant results have been achieved. Some of these contributions and experiences covering biological screening of plant species and identification of their chemical constituents in various laboratories within and outside Nigeria including the University of Ibadan (1972-1978), Ahmadu Bello University Zaria (1978-1985), Nigerian Defence Academy, Kaduna (1985-1990), University of Kansas, Lawrence, U.S.A. (1987-1988) and the University of Abuja (1990-2006) and those of my co-workers will be summarized in this lecture. The Vice-Chancellor and Chairman of this occasion and members of this distinguished audience, I wish to give some definitions of Chemistry and explain its benefits to society. This I hope will help you appreciate the relevance of chemical research to national economic development in the areas of drug production, pesticides for improved agricultural production and utilization of vegetable materials in the local tanning industry.

DEFINITIONS OF CHEMISTRY AND ITS BENEFITS TO SOCIETY

Most people view chemistry as one of those subjects that one needs to satisfy admission requirements for such professional programmes as Agriculture, Engineering, Medicine, and Pharmacy. In the eyes of the media and governments all over the world, Chemistry can only be remembered for the world’s environmental problems and major disasters such as the destruction of the Japanese city of Hiroshima during the second world war, the Bohpal (India) nerve gas leakage which left thousands dead in 1984 and the Alar Apple scarein *1989 (U.S.A.). We do not realize that Chemistry is a professionand is a*

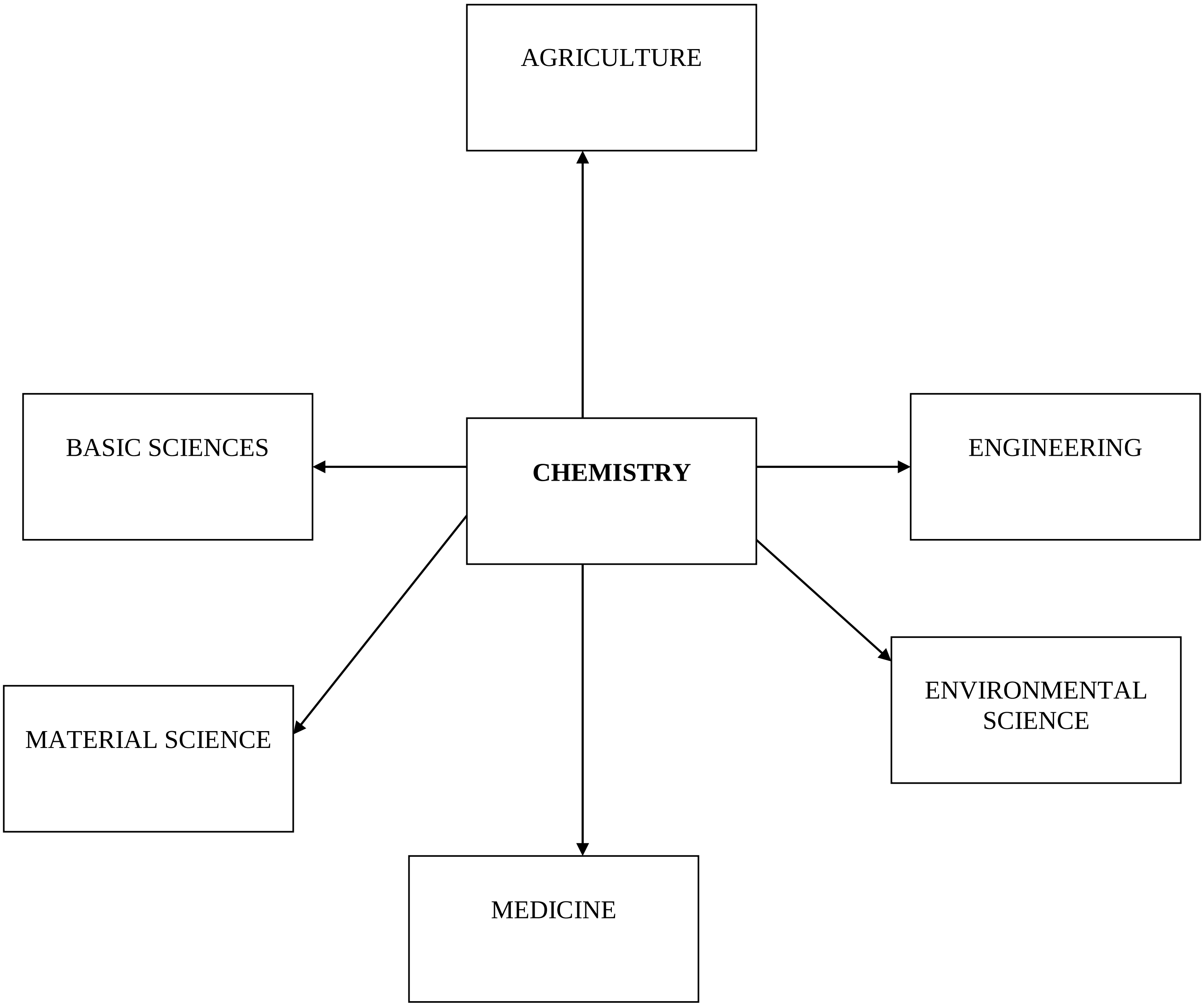


Fig. 1: The Strategic Position of Chemistry in Science and Technology.

key factor for industrial development. The strategic role of chemistry in Science and Technology is represented in Fig. 1:

What then is Chemistry and how has it influenced our lives individually and as a society? The American Chemical Society at its centennial celebration in 1976 defined chemistry as "The Science and Technology of taking things apart and putting things together". However, for the purpose of this lecture, a more basic definition is necessary. It is "the study of what things are made of". Thus, man has studied the chemical constitution of his environment and has used the knowledge to advance mankind. Chemistry has history but we do not need to go too far into history to see how much contribution Chemistry has made to the development of humanity. Modern Chemistry was realized following the development of the bleaching gas, chlorine, which led to the English Industrial revolution and the investigation of coal tar, which gave rise to a new branch of Chemistry, **Organic Chemistry.** These two developments have helped to widen the scope of Chemistry and the society has benefited tremendously from its applications in many vital sectors of the industrialized economies. The achievements of Chemistry in an industrialized economy such as the U.S.A. are well reflected in the following statements of Paul G. Gassman when he took over the presidency of the American Chemical Society in 1990:

> *Chemists and chemical engineers can take great pride in the fact that today, we live longer, we live better and we live easier than our parents did, primarily as a result of our efforts. Chemistry is a profession of which we can be proud. It is a profession that has done much for the well being of mankind. It is time that this well kept secret be let out. Almost 50% of all scientists involved in all of industrial research and development in the U.S.A. are either chemists or chemical engineers. This clearly indicates the very crucial role that our professionals play in maintaining the technological success of the United States. If we look at the chemical industry with its greater than 10 billion dollars positive balance of trade, we can see clear evidence for the importance of our professionals in helping to keep our nation financially secure.*

From the above, it is clear that chemistry is a powerful tool, for converting our natural resources, including plants into products of industrial and economic significance. The rest of this lecture will discuss efforts made to search for bioactive organic substances from plants by applying science and in particular, natural products chemistry techniques.

NATURAL PRODUCTS CHEMISTRY

Natural Products Chemistry is that aspect of organic chemistry that deals with the study of naturally- occurring organic compounds as distinct from those made by man through synthesis (Synthetic Chemistry)[1]. Natural products occur in all forms of plants and animals. They are waste products of metabolic processes and are therefore, called secondary metabolites. Natural products belong to most of the well known classes of organic compounds.

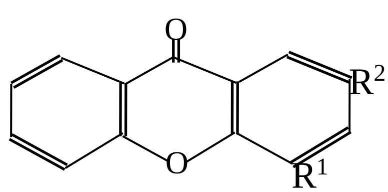
In plants, the secondary metabolites were initially considered not to be of any particular use to the plants themselves. Recently[2], they have been found to be useful to both plants and man in many ways including;

1. Protection for the plants against insects and diseases and therefore, can be used as pesticides.
2. New sources of drugs for treating human ailments such as pains/inflammations, tumors, malaria, bacterial and fungal infections, diabetes, viral conditions, e.t.c.
3. Industrially important products such as fragrant oils for the perfume industry, tannins for the leather industry, sweeteners and flavours for beverages, dyes and fibres, e.t.c.
4. Taxonomy of plants (Chemotaxonomy) in some difficult situations.

In the early days of natural products chemistry, the effort was to obtain new compounds to be added to the chemicals list but today, much attention is being given to plants with bioactivity in order to identify the active compounds and thus provide leads for further development of compounds with enhanced properties.

In Nigeria, the study of natural products chemistry started at the University of Ibadan. The first report of natural products of Nigeria[3] was probably in 1956 and it was on the poisonous material from a variety of local yam, *Dioscorea dumetorum*. This was followed much later by studies on the plant family, Meliaceae, which include the mahoganys[3,4]. Thus, at the time I joined what was then called the 'Woody' group for a B.Sc. project in 1972/73 academic session under Professor J.I.Okogun as my supervisor, a very powerful organic chemistry research group had been established. During my studies at the University of Ibadan, where I also did my Ph.D programme under the same supervisor, I was introduced to both natural products chemistry involving isolation and characterization and organic synthesis. In fact, synthesis is an important component of natural products chemistry as partial or total synthesis is critical in the confirmation of the structure of a new organic compound.

I have been involved in some major synthetic organic chemistry projects one of which was my B.Sc. project, which led to a novel synthesis of Xanthones[5], **1.**



1 $R^1 = R^2 = H$

Xanthones are now known to have anti-cancer activity and constitute an important class of antioxidants. At the time of the work, naturally occurring xanthones were rare, but today, over 200 natural xanthones have been identified[6]. The success of the B.Sc. project actually gave me the courage to pursue a postgraduate programme and an academic career.

The number of plants studied and the bioactive organic substances obtained from them is very large and cannot all be discussed within one lecture. I will therefore only highlight some of them under the following categories of bioactivity: medicinals (antimicrobials, antimalarials, anti-tumor and anti-inflammatory), tannins and pesticides.

In selecting plants for study for bioactive organic compounds, one is guided by the following;

1. Folkloric uses of plants by the natives of various parts of the world, which are passed orally from one generation to another[2].
2. Documented records of traditional practices[7,8].
3. Field surveys based on previous investigations of some families of plants.

Each of the above approaches may not necessarily give the desired result as plant species have been known to exhibit different chemical constitutions depending on geographical locations, seasonal variations, soil nutrients and time of harvest[2].

For biological and chemical evaluations of plants for bioactive substances and indeed for natural products generally, all parts of a plant can be collected for investigation. It has also been found to be more fruitful to collect plants immediately after the flowering season and from stressful environments, particularly, when searching for antimicrobial agents[9].

PREPARATION OF PLANT MATERIALS FOR BIOLOGICAL AND CHEMICAL EVALUATIONS

The plant parts to be studied are usually collected fresh and the geographical location and month of collection noted. It is advisable to collect a flowering plant to enhance identification by a qualified taxonomist. A voucher specimen should be pressed on paper, and deposited in a herbarium for future reference. The plant material is preferably, air-dried in a well- ventilated room to avoid chemical alterations. It is then milled and stored in a tightly closed polyethylene bag[10].

Fig. 2: Young Stem and Leaves of Azadirachta indica (Neem)

The powdered material may be used directly for some biological screenings (field evaluations) but for chemical evaluations, a weighed amount is extracted with an appropriate solvent, usually, 95% ethanol or water. The crude extract is subjected to various fractionation protocols depending on the chemical nature of components or the bioassay fractionation protocol[9] (Fig.3)

The crude extract and the various fractions are subjected to the appropriate biological screening protocol to determine the location as well as the degree of activity.

Usually, activity increases from the crude to the fractions, to the pure extractives, except where there may be synergistic or antagonistic elements in the crude extract or fractions, which, may disappear with fractionation or purification.

In order to identify the component responsible for a particular activity, the crude extract or the fractions need to be separated into pure substances by various chromatographic techniques[11]. These include

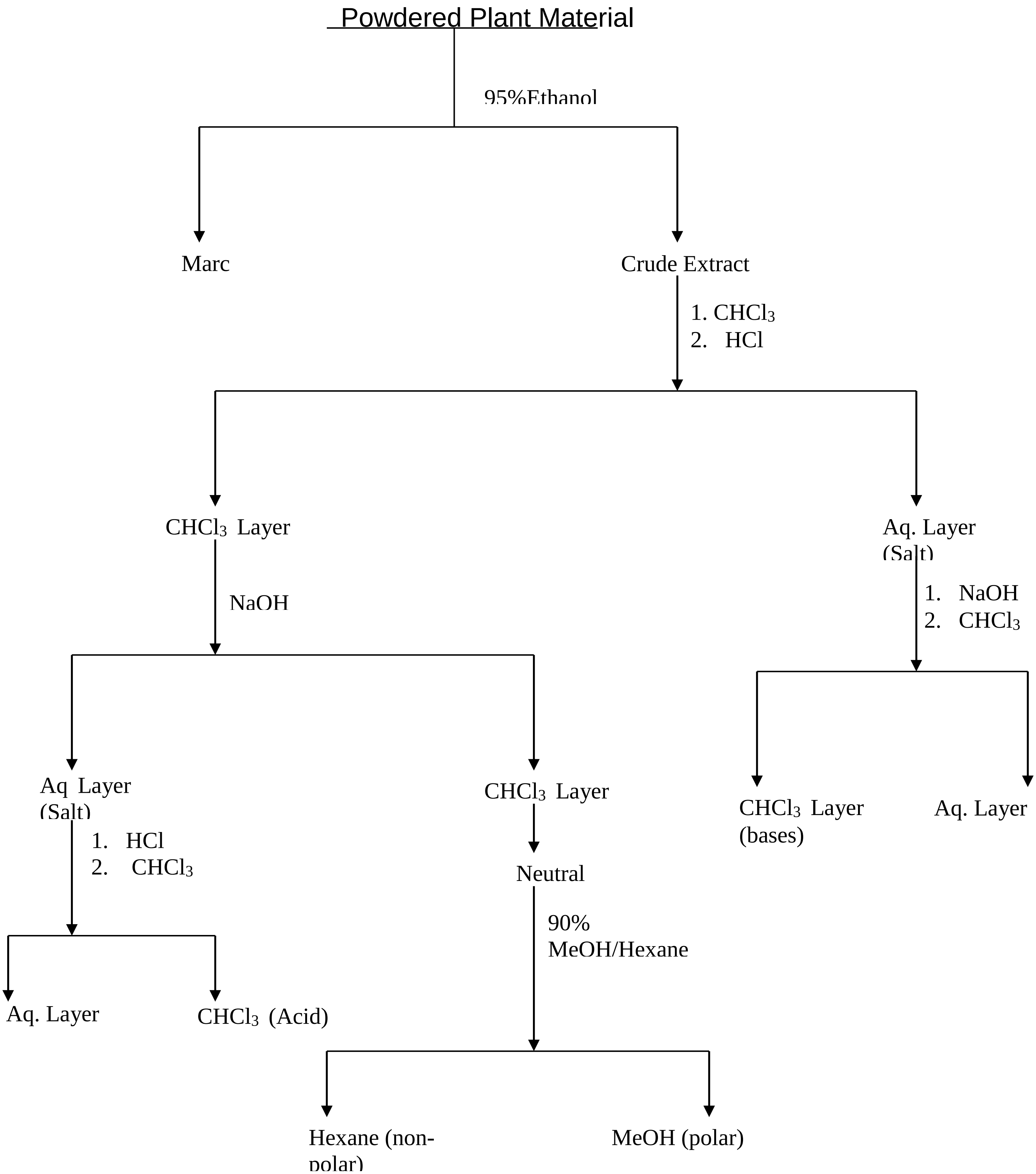


Fig. 3: Bioassay – guided fractionation protocol

Column chromatography, Thin-layer chromatography (TLC), Paper chromatography, Ion-exchange resin, electrophoresis, high- performance liquid chromatography (HPLC), gas-chromatography (GC), e.t.c. The structures of the individual components are determined by a tedious process of characterization[12], involving spectroscopic analysis[13], chemical reactions and sometimes, synthesis. The composition of most crude extracts is usually very complex as shown for extracts of various parts of the Neem tree (*Azadirachta indica*) (Table **1)** and the quantity of pure samples obtainable from them very small (Table **2**).

Table 1: Neem (*Azadirachta indica A. JUSS.)(Meliaceae)*

Phytochemicals:	**Plant part:**
1-TIGLOYL-3-ACETYL-11-METHOXY-AZADIRACHTININ	***Bark***:
17-BETA-HYDROXYAZADIRDIONE	***Seed***:
17-EPIAZADIRADIONE	***Seed***:
1ALPHA-METHOXY-1,2-DIHYDROAZADIRADIONE	***Seed***:
1BETA,2BETA-DIEPOXY-AZADIRADIONE	***Seed***:
22,23-DIHYDRO-23BETA-METHOXY-AZADIRACHTIN	***Seed***:
3-ACETYL-7-TIGLOYL-LACTONE-VILASININ	***Leaf***:
3-DESACETYL-3-CINNAMOYL-AZADIRACHTIN	***Leaf***:
3-DESACETYL-SALANIN	***Leaf***:
3-DESACETYLSALANNIN	***Seed***:
3-TIGLOYLAZADIRACHLOL	***Seed***:
4-EPINIMBIN	***Seed***:
4ALPHA,6ALPHA-DIHYDROXY-A-HOMO-AZADIRADIONE	***Leaf***:
6-ACETYL-NIMBANDIOL	***Seed***:
6-DESACETYLNIMBINENE	***Bark***: ***Leaf***: ***Seed***:
6-O-ACETYL-NIMBANDIOL	***Plant***:
7-ACETYLNEOTRICHILENONE	***Seed***:
7-DESACETYL-7-BENZOYL-AZADIRADIONE	***Seed***:

7-DESACETYL-7-BENZOYLEPOXY-AZADIRADIONE	***Seed***:
7-DESACETYL-7-HYDROXY-AZADIRADIONE	***Fruit***:
7-DESACETYL-GEDUNIN	***Seed***:
ARACHIDIC-ACID	***Fruit***
AZADIRACHTANIN	***Leaf***:
AZADIRACHTANIN-A	***Leaf***:
AZADIRACHTIN	***Seed***:
AZADIRACHTOL	***Fruit***:
AZADIRADIONE	***Seed***:
AZADIRONE	***Seed***:
BEHENIC-ACID	***Fruit***
BETA-SITOSTEROL	***Flower***: ***Leaf***:
DESACETYLNIMBIN	***Stem Bark***:
EPOXYAZADIRADIONE	***Seed***:
GEDUNIN	***Seed***:
HYPEROSIDE	***Leaf***:
ISOAZADIROLIDE	***Leaf***:
ISOMARGOSINOLIDE	***Plant***:
ISONIMBINOCINOLIDE	***Plant***:
ISONIMBINOLIDE	***Stem Bark***:
ISONIMBOCINOLIDE	***Leaf***:
ISONIMOLICINOLIDE	***Fruit***:
KAEMPFEROL	***Flower***
LIGNOCERIC-ACID	***Fruit***
LINOLEIC-ACID	***Fruit***
MARGODUNOLIDE	***Plant***:
MARGOSINE	***Stem Bark***:
MARGOSINOLIDE	***Plant***:
MELDENIN	***Seed***:
MELIANTRIOL	***Seed***:
MYRICETIN	***Flower***
MYRISTIC-ACID	***Fruit***
NIMBAFLAVONE	***Leaf***:
NIMBANDIOL	***Leaf***: ***Stem***:
NIMBIDIN	***Seed***: ***Stem Bark***
NIMBIN	***Stem Bark***
NIMBINENE	***Bark***: ***Leaf***: ***Stem***:
NIMBININ	***Stem Bark***
NIMBINONE	***Stem Bark***:
NIMBIOL	***Bark***:
NIMBIONE	***Stem Bark***:
NIMBOCINOLIDE	***Plant***:
NIMBOCINOME	***Plant***:
NIMBOLIDE	***Leaf***:

NIMBOLIN-A	***Wood***:
NIMBOLIN-B	***Wood***:
NIMBOSTEROL	***Stem Bark***
NIMOCINOL	***Fruit***:
NIMOLICINOIC-ACID	***Fruit***:
NIMOLICINOL	***Seed***:
NIMOLINONE	***Fruit***:
NONACOSANE	***Flower***:
OLEIC-ACID	***Fruit***
PALMITIC-ACID	***Fruit***
QUERCETIN	***Flower Leaf***:
QUERCITRIN	***Leaf***:
RUTIN	***Leaf***:
SALANNIN	***Seed***:
SALANNOLIDE	***Plant***:
SCOPOLETIN	***Plant***:
STEARIC-ACID	***Fruit***
SUGIOL	***Bark***:
VEPININ	***Seed***:
VILASANIN	***Leaf*****:**

Table 2: Percentage of Natural Products based on dry plant

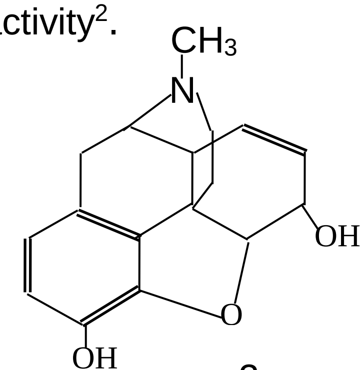
NATURAL PRODUCT	PLANT DRY WEIGHT %
1. Baccharin	2.0×10^{-2}
2. Bruceantin	1.0×10^{-2}
3. Ellipticine	3.2×10^{-5}
4. Maystasine	1.8×10^{-5}
5. Taxol	6.4×10^{-1}
6. Vinblastine	1.0×10^{-3}
7. Vincristine	5.0×10^{-3}

Having gone through the basic steps of natural products chemistry, I now wish to discuss some results of biological and chemical studies on plants that have medicinal, pesticidal and industrial significance.

MEDICINAL AGENTS

From the 11th –18th century, a dogma known as "*The Doctrine of Signatures*" was the means by which man attributed medicinal value to certain plants[2]. The dogma held that, the colour, shape, habitat and other characteristics of a plant were indicative of its medicinal properties. Thus, a worm-shaped fruit is suggestive of its ability to treat worm infestations while a yellow leaf or fruit may indicate its ability to handle liver problems. Some of these attributes still exist in our various communities today.

The importance of plant-derived medicinals in modern medicine is often under estimated; yet, compounds such as morphine, **2**, codeine, **3**, and cocaine, **4**, have long been known to have broad and representative bioactivity[2].



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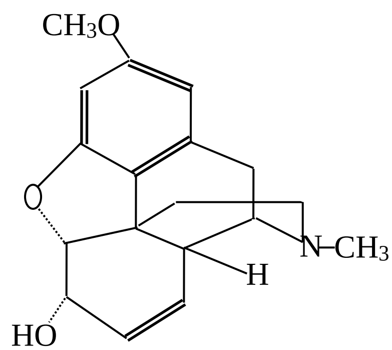

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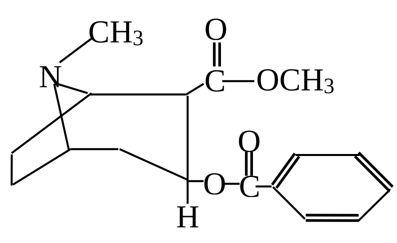

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In fact, as far back as 1961, it has been shown that over 47% of some 300million new prescriptions by physicians contained as one or more ingredients a drug of natural origin[2]. Thus, the knowledge of the biological activities and chemical constituents of plants is desirable for the discovery of new drugs and therefore boost the drug industry and the economy.

Antimicrobial Agents

The practical use of antimicrobial substances in higher plants in the prevention and cure of diseases was first demonstrated by a group of Russian workers who found that onion and garlic were highly effective in the treatment of infected wounds in rabbits and human beings. They also established that when guinea pigs were injected intra-peritoneally with amounts as large as 85mg at pH 7.3, no immediate or delayed objective reactions were observed[2].

One of the early studies on the antimicrobial activity of indigenous Nigerian plants was the screening of some selected Nigerian folk remedies[14]. However, no individual plant was screened. As a result of the new global interest to search for new anti-infective agents from natural sources partly as a result of the development of resistant strains and because, over 90% of the world population today rely on this method of healthcare, many more Nigerian higher plants have recently been investigated than previously. Over 1000 plants including some Nigerian plants, have been screened against 7 pathogenic micro-organisms of industrial significance (Table 3). The agar – streak dilution or agar-disc technique in combination with bioautography were used in the screening[15] (Figs. 4-6).

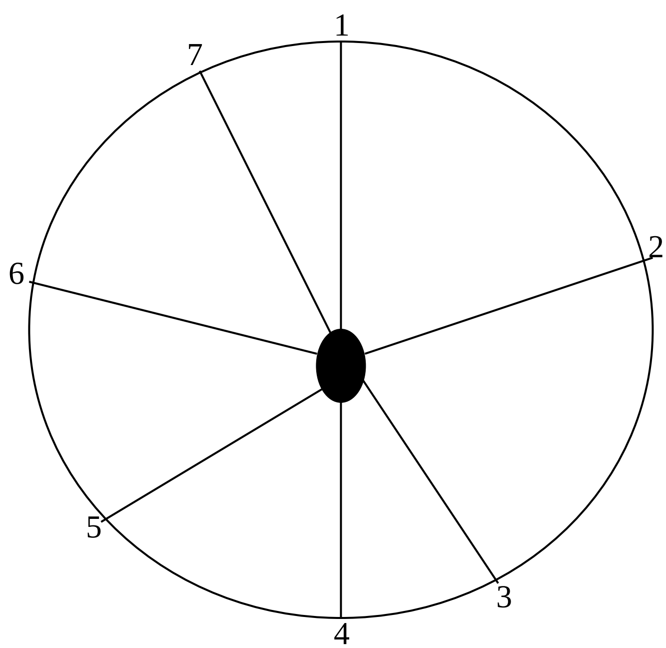


Fig. 4: Schematic of Agar-streak dilution assay. (Numbers refer to the organisms in Table 3)

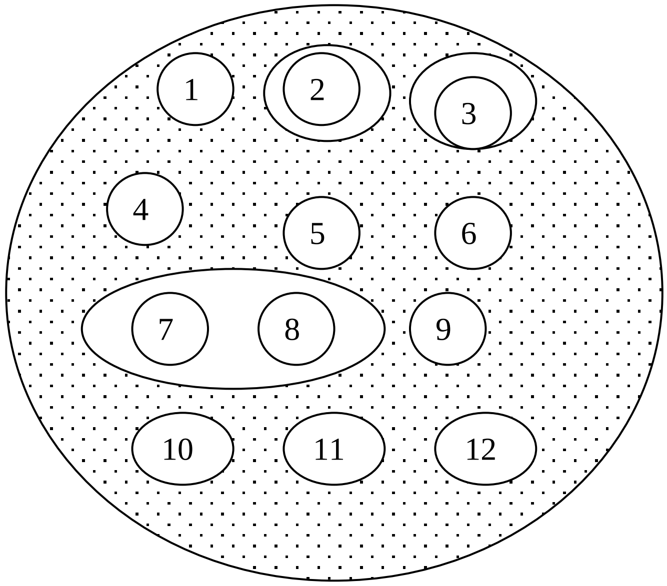


Fig. 5: Schematic of Agar-disc assay. (Discs 2, 3, 7, and 8 are active, while 7 and 8 are the most active)

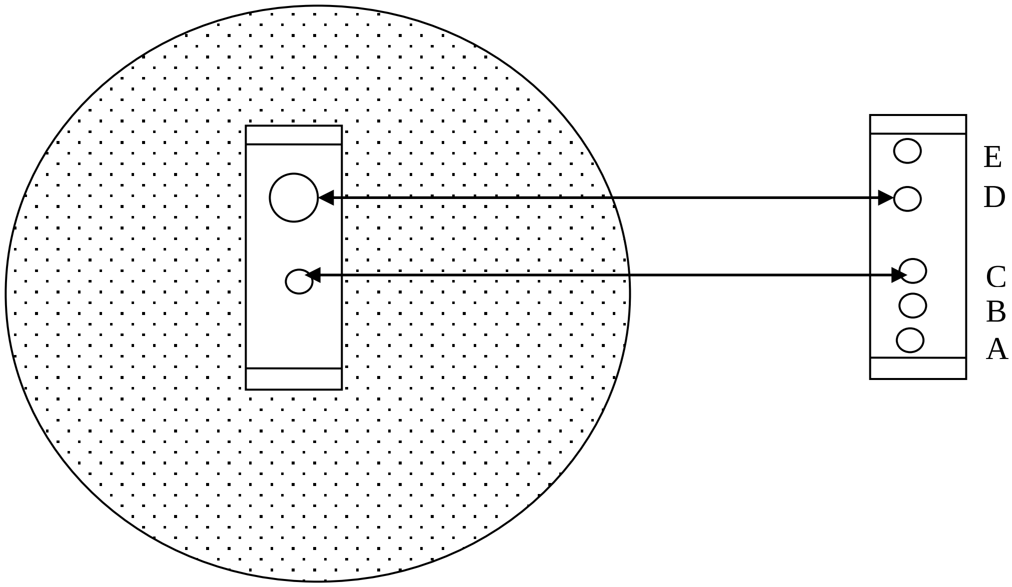


Fig. 6: Schematic of Bio-autography. (Spots **C** and **D** are the active components)

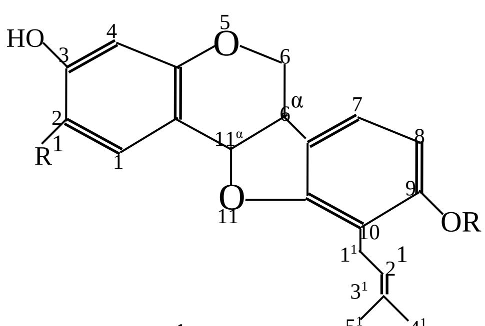
Table 3: Antimicrobial test results on some Nigerian plants

95% Ethanol extract	Plant part	*Micro–organisms/mic (μg/ml) 1	2	3	4	5	6	7
Boscia senegalensis	Stem bark	1000	-	100	-	-	-	1000
Commiphora africana	Root	-	-	-	-	100	-	-
Detarium senegalense	Bark&leaves	1000	-	-	-	1000	1000	-
Lannea acida	Bark	1000	-	-	-	-	1000	-
Piliostigma thonningii	Root bark	-	-	-	-	-	100	-
Erythrina mildbraedii	Root	100	-	-	-	100	-	-
Pterocarpus erinaceus	Root bark	2000	-	-	-	2000	-	-
Teclea verdoorniana	Root bark	2000	-	-	-	2000	-	-
Lawsonia inermis	Leaves	1000	1000	-	-	-	-	-
Dalbergia saxatilis	Bark	250	1000	-	-	-	-	1000
Dalbergia saxatilis	Leaves	1000	-	-	-	-	-	-

*Micro-organisms: 1. *Staphylococcus aureus* ATCC 13709
2. *Escherichia coli* ATCC 9637
3. *Salmonella gallinarium* ATCC 9184
4. *Klebsiella pneumoniae* ATCC 10031
5. *Mycobacterium smegmatis* ATCC 607
6. *Candida albicans* ATCC 10231
7. *Pseudomonas aeruginosa* ATCC 27853
(-) = Inactive
ATCC= American-Type Culture Collection

Crude extracts with minimum inhibition concentration (MIC) values of 1000 μg/ml and below and fractions with MIC values of 100 μg/ml and below are considered promising for further work.

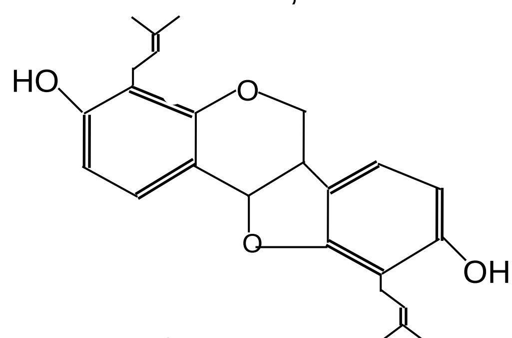
Extensive work has been done on the antibacterial plant, *Erythrina mildbraedii* (Hausa= *mijiriya*) collected from Zaria, Nigeria[9,16,17]. The 95% ethanol extract of the root showed antimicrobial activity against *Staphylococcus aureus* (MIC=100μg/ml) and *Mycobacterium smegmatis* (MIC=100μg/ml) (Table **3**). In an effort to identify the constituents responsible for the activity, the polar fraction (Fig.3) was subjected to flash column chromatography to obtain the following pterocarpans; erythrabyssin-II, **5,** erybraedins A-E, **8**-**12,** and isoneorautenol, **13** which were further screened (Table **4**).



5 R=H,R^1 = Prenyl

6 R=CH_3, R^1 = Prenyl

7 R=CH_3,R^1 = H



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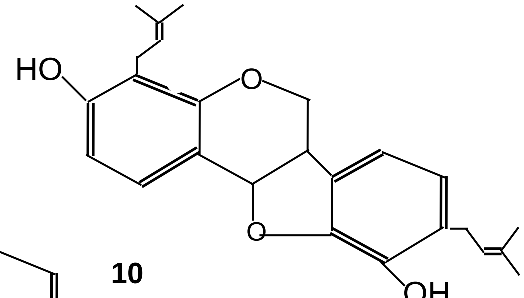

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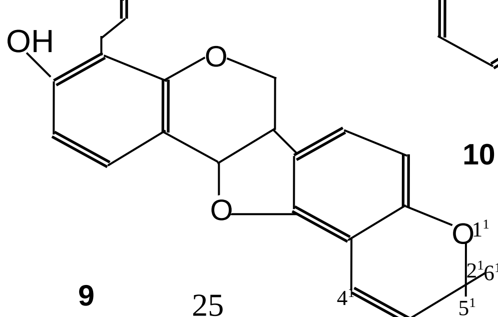

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Table **4**: **Structures and Antibacterial activity (MIC) of pterocarpans against *Staphylococcus aureus* and *Mycobacterium smegmatis***

Pterocarpans	Substituents on aromatic Rings								mic(μg/ml)	
	1	2	3	4	7	8	9	10	S.aureus	M.smegmatis
Erythrabyssin-II **5**	H	prenyl	OH	H	H	H	OH	prenyl	3.12	0.78
Erycristin **6**	H	prenyl	OH	H	H	H	OCH_3	prenyl	6.25	6.25
Sandwecensin **7**	H	H	OH	H	H	H	OCH_3	prenyl	-	-
Erybraedin-A **8**	H	H	OH	prenyl	H	H	OH	prenyl	12.5	6.25
Erybraedin-B **9**	H	H	OH	prenyl	H	H	(chromene)		12.5	12.5
Erybraedin-C **10**	H	H	OH	prenyl	H	prenyl	OH	H	12.5	12.5
Erybraedin-D **11**	H	H	OH	prenyl	H	(chromene)		H	100.0	25.0
Erybraedin-E **12**	H	furan		H	H	H	OH	prenyl	25.0	-
Isoneurautenol **13**	H	H	OH	H	H	(chromene)		H	25.0	25.0
Phaseollin **14**	H	H	OH	H	H	H	(chromene)		12.5	-
Phaseollidin **15**	H	H	OH	H	H	H	OH	prenyl	50.0	-
Streptomycin SO_4									5.0	1.25

(-) = inactive at 100 μg/ml in MIC

Of perhaps industrial significance is erythrabyssin-II, **5**, which showed stronger activity than a standard antibiotic, Streptomycin. Structure-activity relationship (SAR) studies[18] for the pterocarpans have revealed the critical role of the presence and position of the prenyl and the hydroxyl groups on aromatic rings A and B as well as the planarity of the system.

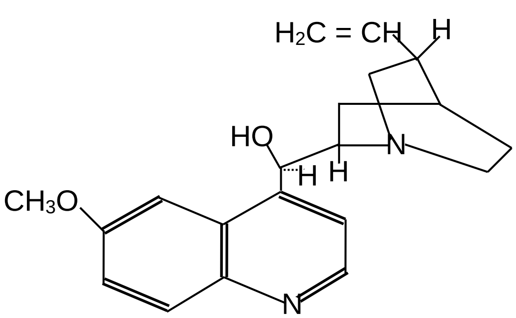
The pterocarpans from studies are generally active against Gram-positive bacteria but inactive against the Gram-negative. This has been explained on the basis of their lipophillic character arising from the presence of the prenyl group, which enhances their permeability of the cell wall of Gram-positive bacteria, which are known to possess low lipid content. The reverse is true for the Gram-negative bacteria, which have high lipid content and therefore are capable of trapping the pterocarpans and rendering them ineffective. It has also been observed that the pterocarpans possess varying degrees of activity and can therefore be deployed for use in a range of industrial products, from antibiotic drugs, to use in the home as disinfectants.

From the above results, it has been revealed that certain families of plants and those located in certain environments are more likely to be associated with anti-microbial activity than others[9]. For instance, plants of the Rutaceae, Leguminosae and the Compositae families and those from stressful environments such as the desert have been found to be particularly useful in searching for anti-microbial agents. Such observations serve as useful guides in the collection of plants for laboratory research studies.

Antimalarial Agents

Malaria is a disease of importance in many parts of the world today and it is necessary to ensure the availability of safe and effective drugs for the treatment of the condition. Recent reports indicate that the malaria parasite has developed a degree of resistance making it necessary to return to the quinine alkaloids. Future needs will therefore require a continuation of surveys for active plants[19,20].

Quinine, **16**, the original antimalarial drug was obtained from the bark of the Peruvian tree, *Cinchona officinalis* (Rubiaceae) in 1820 by J.B. Caventou and P.J. Pelletier. It was synthesized by R.B. Woodward and W. Doerming in 1944 and until World War 1, was the only effective treatment for malaria[2]. A number of examples can be found in folklore concerning plants useful for the treatment of malaria infections, “fevers”, and for use as “anti-periodics”.



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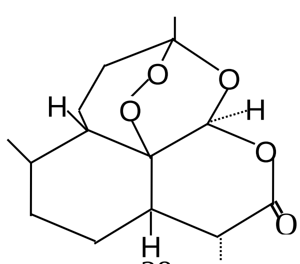

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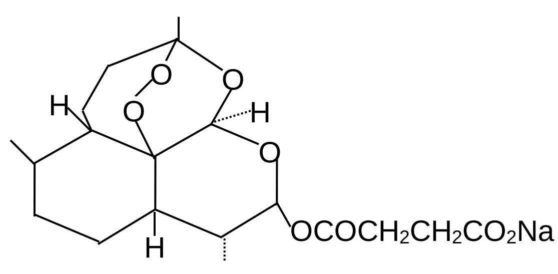
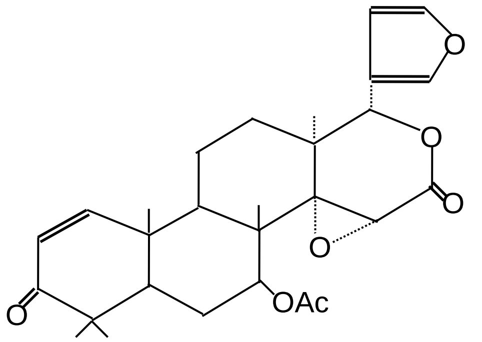


18

The first extensive survey of plants with antimalarial properties was reported by Spencer and co-workers[2] who studied over 600 plant species. One of the recent successes in the effort to find new anti-malarial drugs from plants was the isolation of artemisinin,**17,**a sesquiterpene lactone, from the Chinese shrub, *Artemisia annua* (Asteriaseae) used in Chinese traditional medicine[21]. It is used to treat multi-drug resistant strains of *falciparum* malaria. The activity is known to reside in the endo-peroxide and lactone groups. A more potent derivative, which is more soluble in water by conversion of artemisinin to the sodium salt, artesunate, **18**, has recently been developed. It has become one of the most preferred antimalarial prescriptions in recent times.

Recently, the leaves of the Neem tree (*Azadirachta indica*)(Hausa=*dogonyaro*) containing the limonoid, gedunin, **19** and some derivatives have been found to possess strong antimalarial activity[22]. The Neem tree is commonly found in the tropical areas of the world such as India and Africa and it has been suggested that the gedunin content can be used to standardize the crude drug[22].



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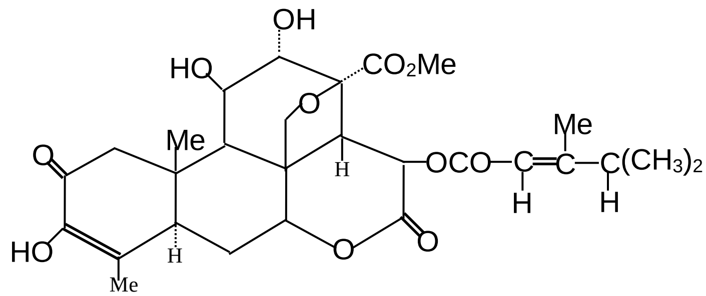

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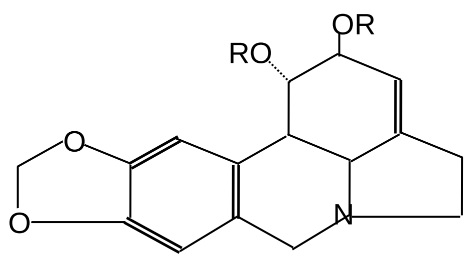


21, R = H

22, R = -$COCH_3$

Also the activity of the Asian plant, *Brucea javanica* (Simaroubaceae) fruits against chloroquine-resistant *Plasmodium falciparum in vitro* and against *Plasmodium berghei in vivo* has been reported[23]. The activities have been attributed to a number of quassinoids, the most potent being bruceantin, **20** which has gone through clinical trials in the U.S.A.

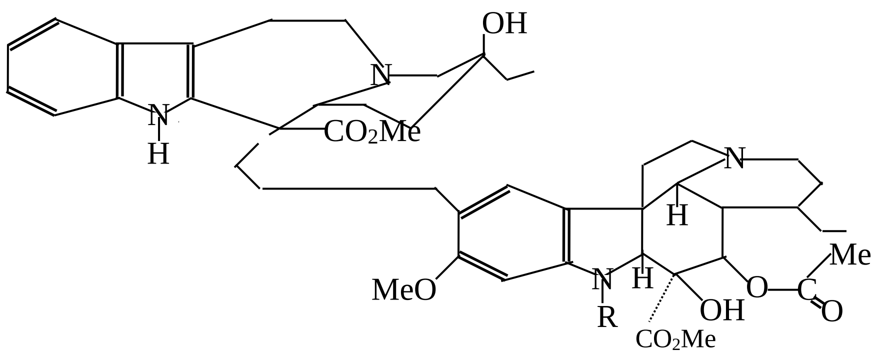
The alkaloids from the bulbs of the South African plant, *Brunsvigia littoralis* (Amaryllidaceae) have been screened for antimalarial activity against both chloroquine-sensitive and chloroquine-resistant strains of *P. falciparum*. Among the four alkaloids isolated from the ethanolic extract, liccorine, **21** and liccorine diacetate, **22** were found to have moderate activity[24].

From the work done so far, it is not clear whether particular families of plants are most likely to possess antimalarial activity or not. However, as a class, alkaloids (N-containing compounds) are more likely to possess significant anti-malarial activity. We therefore have to rely on folkloric uses of plants in our effort to discover new antimalarial drugs.

Antitumor/Anti-inflammatory agents

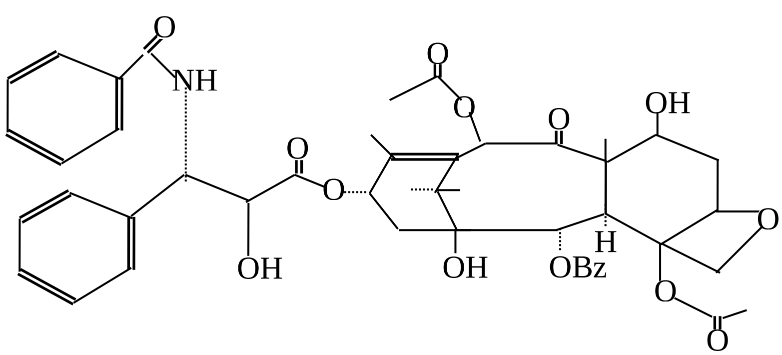
The plant kingdom has been described as the most attractive source of novel anti-tumor agents. Since 1950, the American National Cancer Institute has been involved in intensive screening of about 110,000 plant extracts for over 21 years and identified about 150 various potent compounds including, vinblastine, **23**, vincristine, **24** from *Catharanthus roseus* (Apocyanaceae), which have been found to have activity against leukaemia and solid tumors and taxol[25] **25**, isolated from the bark of *Taxus brevifolia,* is one of the most exciting compounds. Taxol was first marketed in 1992. Due to low concentration (0.01-0.03%, dry plant), low growth rate of plant and accumulation pattern that is highly susceptible to geographical or environmental conditions, the effort to synthesize it was intensified. The bio-renewable source of the drug has been found in the form of 10-deacetyl-baccatin-III, **26**. Taxol, a diterpene amide is obtained by coupling baccatin-III with the appropriate side chain. Taxol is known to be active against resistant cases of advanced ovarian and breast cancer[25].

Recently, tylophorine analogs[26], ***27*** were found to possess a novel mode of action different from known anti-tumor drugs. Tylophorine was isolated from *Tylophora asthmatica* (Asclepiagaceae), traditionally used in India as asthmatic and anti-allergic medication. The National Cancer Institute tumor screen showed them to have a fairly uniform and potent inhibition of cell growth against Hep-G2 and KB cells. Tylophorine also has a very strong anti-inflammatory action[26].



23 R = CH_3

24 R = CHO



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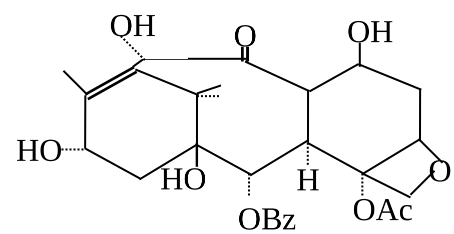

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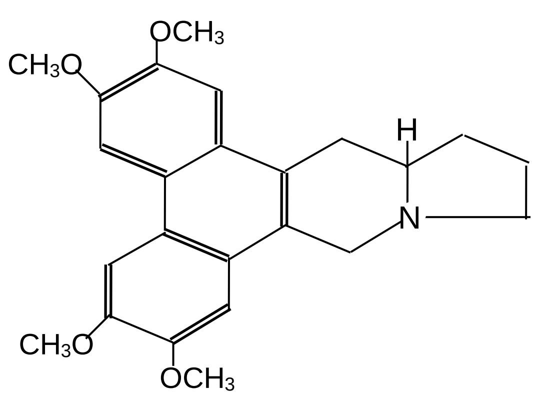
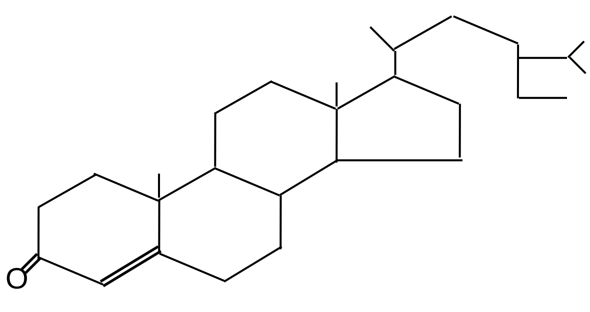


27

Some Nigerian plants have been investigated for anti-inflammatory activity and cytotoxicity[27]. A plant, *Commiphora africana* (Caesalpiniaceae) (Hausa= *dashi*) has a resin which when burnt, is used to fumigate the home against mosquitoes and to disinfect the environment in the Northern part of Nigeria. The 95% ethanol extract of the root was found to be strongly antimicrobial against *M. smegmatis* (Table **3)**. From the n-hexane fraction a highly cytotoxic compound, β-sitostenone**, 28** was isolated which was also reported from the stem bark of the Taiwanese plant, *Annona Montana* (Annonaceae) along with the highly cytotoxic compound, annoquinone-A[28], **29**.



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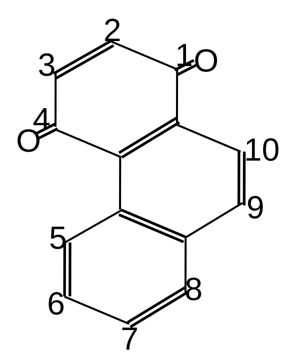


29

Newbouldia laevis (Bignoniaceae) (Edo=*ikhimi,* Hausa=*aduruku*, Yoruba=*akoko,* Ibo=*ogilishi*) has also shown activity against fresh egg albumen- induced paw oedema in rats[29] and the activity compared to that of acetyl salicylic acid (aspirin) (Fig. **7**).

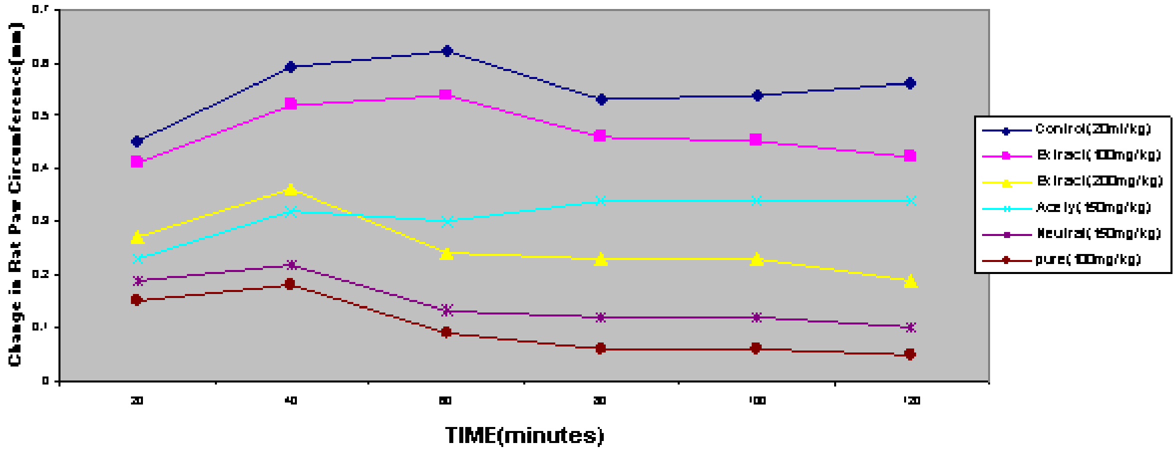
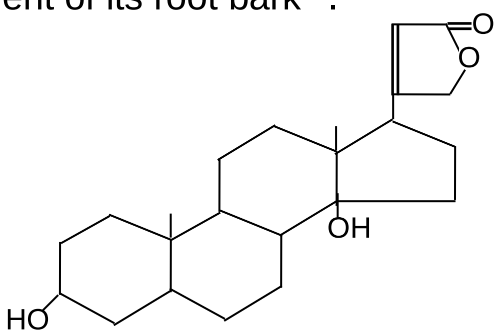


Fig. 7: Average Inflammation (mm) of the Right Hand Paw

Some findings have associated cytotoxicity with the unsaturated lactone of cardenolides and related compounds such as digitoxigenin[2], **30**. Thus, the folkloric use of *Bauhinnia thonningii* (Hausa=*kalgo*) as an anti-inflammatory agent and its highly significant activity against *Candida albicans* may be associated with the presence of griffonilide, **31,** which is a constituent of its root bark[30].



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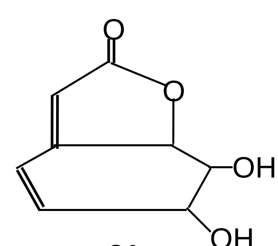


31

Tanning Agents

Tannins are polyphenols with the characteristic of binding and precipitating proteins[31]. They act as a defense mechanism in plants against pathogens, herbivores and hostile environment. They occur in fruits such as grapes, tea, legumes, foliages and trees. They are responsible for the astringent taste of wines, unripe fruits and the enhancing of colours of flowers. They are generally soluble in water[32,33].

One property of tannins, which is of immense economic importance is their ability to convert hides and skins to leather. Tanning which originally was believed to be a physical process is now known to involve a combination of the astringent phenolic compounds (tannins) in the plant extract with the animal skins giving a product called leather which has greater resistance to heat, bacteria and abrasion[31].

Tannins occur commonly in the following families of plants: Leguminosae, Anarcardiaceae, Combretaceae, Phizophoraceae, Myrtaceae and Polinaceae[32,33]. Nigeria has abundant flora, which is yet to be exploited as sources of tannins. The vegetable tanning material (mimosa) used by commercial tanneries in the country are imported. The only indigenous vegetable tanning material commonly in use in Nigerian leather industry is *Acacia nilotica* var. *adansonii* (Hausa=*bagaruwa*)[34]. There is therefore need to investigate the tanning properties of many more species of the above families of plants. This has prompted the study of the Nigerian plant, *Anogeissus schimperii* (Combretaceae) (Hausa=*marke*) which is a graceful tree growing in the Savannah region. This represents the first major work on tannins in Nigeria.

Various tissues of the plant have been investigated for tannins, non-tannins and other characteristics of the leaves such as the keeping quality, effect of seasonal variation on the quantity of tannin and the peak of tannin production by the plant[35] (Tables **5-8)**.

Table 5: Analysis of various parts of *Anogeissus schimperii*

1 Plant tissue	2 Types of tannins	3 Total solubles %	4 Insolubles %	5 Tannins %	6 Non-tannins %	7 pH of analytical infusion	8 Colour of anal. Infusion (1.0cm cell) Y	R	B	9 Weak acids meq/100g TS	10 Salts of weak acids meq/100g TS	11 Total salts meq/100g TS
V.Y.L	Mixed	31.00	68.00	20.02	10.98	4.50	29	9	1	68.58	113.97	121.99
M/L	Mixed	28.72	71.28	16.50	12.22	4.70	27	7	1	-	-	-
O/L (1)	Mixed	25.58	74.42	15.37	10.21	4.80	20	6	1	-	-	-
O/L (2)	Mixed	22.05	77.95	11.29	10.76	4.70	20	6	1	-	-	-
T/B	Mixed	15.87	84.13	10.23	5.64	4.15	19	12	1	-	-	-
Bark	Mixed	12.44	87.56	7.80	4.64	4.40	12	28	1	-	-	-
H/W	Mixed	8.94	91.06	5.67	3.27	6.55	23	29	1	-	-	-
S/W	Hydroly-sable	4.13	95.87	2.87	1.26	4.35	21	11	1	-	-	-

Note: V. Y. L. = very young leaves; M/L = Medium leaves; O/L = Old leaves; T/B= Twig bark; H/W = Heartwood; S/W = Sapwood
Data represent averages of monthly analysis of leaves, twig bark and bark for three years (1982, 1983 and 1984) and those for sapwood and heartwood during one year (1983).
Results in Columns (3) to (6) are expressed on moisture – free basis.

Table 6: Analysis of very young leaves of *Anogeissus schimperii*

1 Month	2 Total solubles %	3 Insolubles %	4 Tannins %	5 Non-tannins %	6 pH of analytical infusion	7 Colour of analytical Infusion (1.0cm cell) Y	 R	 B	8 Remarks
March	32.70	67.30	23.20	9.68	4.50	26	7	1	
April	31.79	68.21	22.29	9.50	4.50	29	7	0	
May	33.93	66.07	22.17	11.76	4.50	29	7	1	
June	34.28	65.72	21.76	12.52	4.65	29	8	0	
July	33.44	66.56	21.66	11.78	4.50	28	8	0	
August	32.12	67.88	21.12	11.00	4.40	23	11	0	
September	32.18	67.82	20.60	11.58	4.70	29	9	1	
October	34.97	65.03	20.56	14.41	4.20	26	7	0	
November	31.73	68.27	19.82	11.91	4.60	24	6	1	
December	-	-	-	-	-	-	-	-	Leaves are shed during this period
January	-	-	-	-	-	-	-	-	
February	-	-	-	-	-	-	-	-	

Note: Analytical figures represent monthly averages for two years (1982 and 1983). Results in columns (2) to (5) are expressed on moisture – free basis.

Table 7: Monthly Analysis of Composite Leaves of *Anogeissus schimperii*

1	2	3	4	5	6	7			8
Month	Total solubles %	Insolubles %	Tannins %	Non-tannins %	pH of analytical infusion	Colour of analytical Infusion (1.0cm cell)			Remarks
						Y	R	B	
June	25.82	74.18	17.41	8.41	4.55	29	5	0	
July	26.83	73.17	17.35	9.48	4.90	22	10	1	
August	21.75	78.25	12.30	9.45	4.60	17.4	4.8	0.6	
September	24.14	75.86	13.10	11.04	4.85	21	4	1	
October	22.10	77.90	12.59	9.51	4.60	24	3	1	
November	22.69	77.31	11.27	11.42	4.70	27	6	1	
December	23.18	76.82	11.65	11.53	4.70	27	6	1	
January	22.63	77.37	10.63	12.00	4.60	22	7	1	
February	21.15	78.85	10.75	10.40	4.60	20	6	1	
March	-	-	-	-	-	-	-	-	Emergence of new leaves and absence of old leaves
April	-	-	-	-	-	-	-	-	
May	-	-	-	-	-	-	-	-	

Note: Analytical figures represent monthly averages for two years (1983 and 1984). Results in columns (2) to (5) are expressed on moisture – free basis.

Table 8: Monthly Storage on the Characteristics of Composite Leaves of *Anogeissus schimperii*

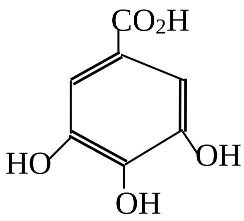
1 Month	2 Total solubles %	3 Insolubles %	4 Tannins %	5 Non-tannins %	6 pH of analytical infusion	7 Colour of analytical Infusion (1.0cm cell) Y	 R	 B
July	27.33	72.67	17.85	9.48	4.90	22	10	1
August	29.23	70.77	16.99	12.24	4.75	20	9	1
September	25.86	74.14	16.93	8.93	4.75	23	7	0
October	25.58	74.42	16.88	8.70	4.70	27	7	0
November	26.29	73.71	16.72	9.57	4.80	20	7	1
December	27.12	72.88	16.67	10.45	4.80	27	8	1
January	27.33	72.67	16.53	10.80	4.80	23	9	1
February	26.35	73.65	16.53	9.82	4.70	25	11	1
March	26.71	73.29	16.52	10.19	4.60	26	7	0
April	25.02	74.98	15.75	9.27	4.50	25	8	1
May	25.23	74.77	15.40	9.83	4.70	26	8	1
June	25.67	74.33	14.49	11.18	4.80	25	7	1

Results in columns (2) to (5) are expressed on moisture – free basis.

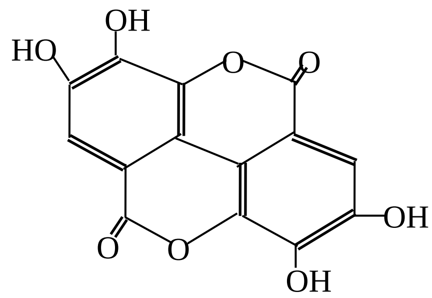
It has been established that the very young leaves possess the highest amounts of tannins and that the peak of production is in June for the composite leaves. Also, the composite leaves have very good shelf life (very minimal loss of tannin during storage).

Phytochemical work[36,37] on the various parts of the plant has led to the isolation of a number of polyphenols, prominent among which are gallic acid, **32**, ellagic acid, **33**, 3,3^1,4^1-tri-0-methylflavellagic acid, **34**, 3,3^1-di-0-methylellagic acid, **35** and a galloylated tannin, schimperiin, **36.**

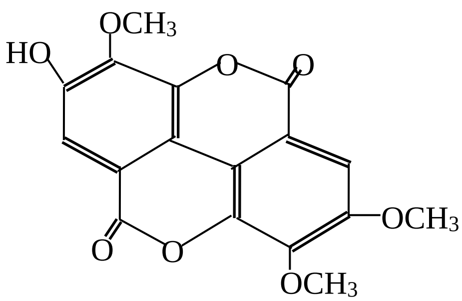
3,3^1,4^1-tri-0-methylflavellagic acid was isolated from a natural source for the first time and its co-occurrence with 3,3^1-di-0-methylellagic acid in the bark of *A. schimperii* supports the suggestion that biogenetically, hydroxylation and methylation processes take place sequentially. The presence of these polyphenols accounts for the tanning properties of *A. schimperii* and should provide a good alternative to *A. nilotica* as a vegetable tanning material.


CO2H
HO
OH
OH

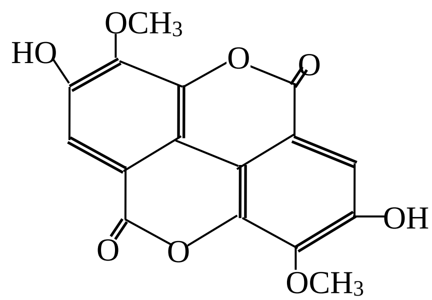
32


OH
HO
O
O
O
O
OH
OH

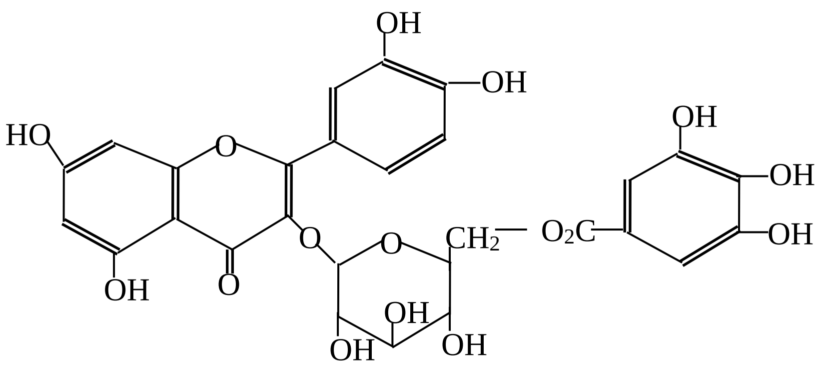
33


OCH3
HO
O
O
O
O
OCH3
OCH3

34


OCH3
HO
O
O
O
O
OH
OCH3

35


OH
OH
HO
O
OH
O
O
O
CH2
O2C
OH
OH
OH
OH
OH
OH

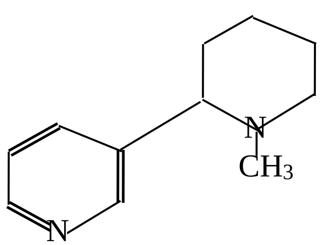
36

Acid hydrolysis of schimperiin, **36** gave gallic acid, glucose, and quercetin[37]. Quercetin is a well-known anti-oxidant[38] and thus tannins in addition to their use in the production of leather materials provide health benefits in wines and fruits.

PESTICIDAL AGENTS

The major local industries in Nigeria are expected to increase their capacity to generate industrial raw materials from local agricultural products. The Federal Government has also recently embarked on a campaign for massive production of cassava with the aim of converting it to starch and other products of industrial and economic significance such as ethanol. That means that the agricultural sector must achieve an output far beyond what is normally required directly as food. The problem however, has been the inability of that sector to generate enough primary products for conversion into intermediate industrial products due to poor yield resulting from poor soil fertility and destruction of crops on the farms and in storage by pests. The agricultural sector therefore needs a lot of input in the form of fertilizer and chemicals for improved yields and post-harvest crop protection and preservation. While efforts have been made to improve soil fertility through increased use of chemical fertilizer as well as humus manure, little effort has been made in the area of local sourcing of pests and disease control agents. Although, the development of pest and disease-resistant species and the use of biological control are technological breakthroughs and quite effective, they are, however, difficult to achieve. Thus, the use of chemicals will continue to be the major method of pest and disease control in agriculture worldwide in spite of its many disadvantages, especially environmental pollution.

There is therefore, a strong need to search for local sources of pesticidal agents for agricultural use to reduce dependence on importation. The search for new pesticidal agents is further prompted by the fact that insects develop resistant strains after long periods of exsposure to one type of chemical compounds. The folkloric use of higher plants as pesticidal materials by the natives in several parts of the world is well known[2,7,8]. Perhaps, one of the early plants so recorded as an effective pesticidal agent was tobacco (*Nicotiana tabacum*)[39]. The use of tobacco infusions to kill aphids led to the isolation of nicotine, **37** in 1828. Also recorded was the use of the powdered root of the derris plant (tuba-root) (*Derris elliptica*) by the Singapore Chinese as an insecticide against insect pests in 1848[39]. Later, many plants with fish-poisoning properties such as the *Milletia* and *Tephrosa* were also found to be insecticidal[39]. The chemical investigation of the Japanese plant, Roh-ten (*Rhododendron hortense*) in 1902 showed rotenone, **38** as the active constituent[39]. Thus, terrestrial higher plants have long been recognized to have the capacity to manufacture organic substances, which act as protective agents against attack by insects and infective agents. Some of these have been found to possess significant properties and may serve as lead compounds for the development of new generations of chemicals, which will find use in Veterinary medicine and in combating plant diseases and pests[40].



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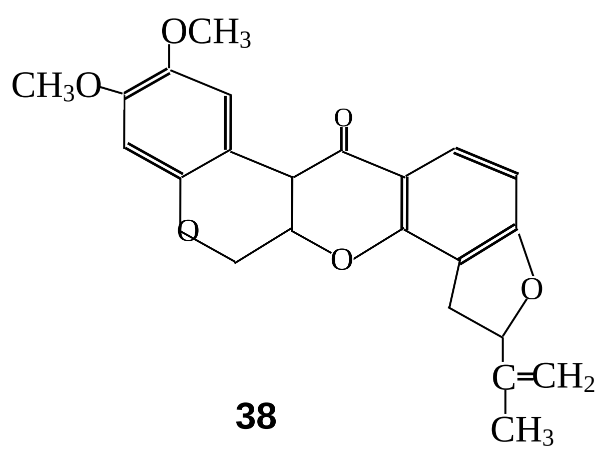


38

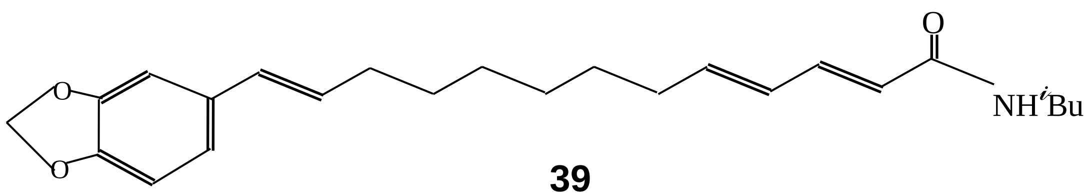
A number of Nigerian plants are known to be used traditionally as pesticidal materials[7,8]. In the past three decades, some of them have been screened biologically and phytochemically not deliberately for use in agriculture though their extracts or pure constituents had shown significant activity (Table **9**).

Table 9: Biological and Phytochemical screening results on some Nigerian pesticidal plants.

Family Species	Parts screened	Form	Activity	Organisms	Compounds
Annonaceae *Dennettia tripetala*[41,42]	Leaf	Extract	Protectant	Weevils	β-phenyl-nitroethane & terpenes
Fabaceae *Dalbergia saxatilis*[43,44]	Stem bark & leaf	Extract Powder	Insecticidal Insecticidal	Mosquitoes Housefly	Unidentified
Melliceae *Azadirachta indica*[45,46]	Seeds	Powder	Protectant	25 species of plant pests	Limonoids
Mimosoidae *Tetrapleura* tetraptera[47]	Root & stem bark	Extracts	Molluscicidal	Snails	Saponins
Amaranthaceae *Alternanthera sessilis*[48]	Leaf	Extracts	Molluscicidal	Snails	Triterpenes
Piperaceae *Piper guineense*[49,50,51]	Fruits Fruits	Powder Extract	Insecticidal Insecticidal	Weevils Grasshoppers	Alkaloids Alkaloids
Rutaceae *Clausena anisata*[52,53,54]	Leaf Root Root	Extract Extract Extract	Insecticidal Anti-feedant Molluscicidal	Grasshopper Armyworm Snail	Alkaloids Coumarins

The list of indigenous plants that have been screened for pesticidal activity is relatively short. This situation has been due probably to the fact that investigations so far have been based on folkloric use of these plants and not through the conscious effort of investigators to screen plants systematically for bioactivity. Also, among the plants studied, only in very few cases was the activity traced to the presence of specific constituents.

The most prominent among the plants so far studied for pesticidal properties is *Piper guineense* (Piperaceae) (Hausa=*masoro*, Yoruba=*iyere*, Ibo=o*ziza,* Edo=*ighere*)[49]. It is a semi-cultivated climber found in the forest of the Southern parts of Nigeria. The fruit is an important component of many traditional herbal preparations as well as a spice in local foods. The powdered dry fruits are used as insecticidal materials when placed among clothing[7]. Bioassay studies of the fruit extracts using cage experiments have revealed that both the petroleum ether and chloroform extracts were active against the garden insect, *Zonocerus variegatus* (L) (grasshopper).[50] The powdered fruit has also been reported to give protection to cowpea seeds, *Vigna unguiculata* (L) Walp against the adults of the cowpea bruchid, *Callosobruchus maculatus* (F) causing a mortality rate of 96% in 48 hours[51]. In these studies a piperine-type amide, guineensine[49], **39** was found to be the insecticidal agent, and piperine, **<u>40</u>** as the synergist in the crude extract[50] (Table **10**).



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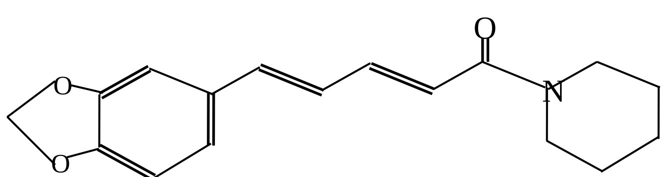

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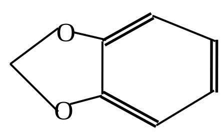
Table 10: Percentage of insects dead or moribund in 1 hour of treatment with extracts and extractives from *Piper guineense.*

Sample	Concentration %	**%** Dead or moribund
Petroleum ether extract	0.1	20.0
Chloroform extract	0.1	30.0
Guineensine	0.05	35.0
Piperine	0.5	50.0

While the synergistic role of piperine is not very obvious, the direct influence of solvents employed in the extraction of the plant material on the degree of potency of extract is evident.

To confirm the structure as well as make it more accessible, the total synthesis of guineensine was undertaken[55,56]. It involved the conversion of methylene – 1, 2 - dioxybenzene, **41** to an important intermediate, piperolein B acid, **42** via the ester, **43.** Gas chromatography (Fig**.8**), of the ester and its photolysis product, **45** as well as comparison of their spectra and melting points of their corresponding acids led to the revision of the structure of guineensine which was thought to be sylvatine,**46** as proposed by some workers[57]. The work also reviewed the Wittig synthesis of the ethylenic bond employed in the synthesis of piperolein B acid and confirmed that the stereochemistry reported[58] was cis, as expected from previous studies[59,60].



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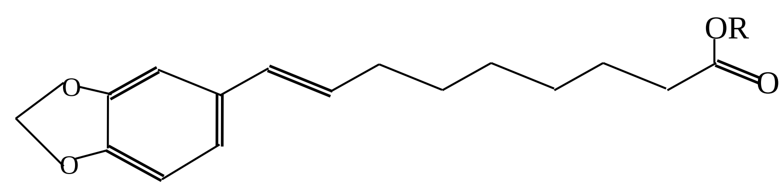
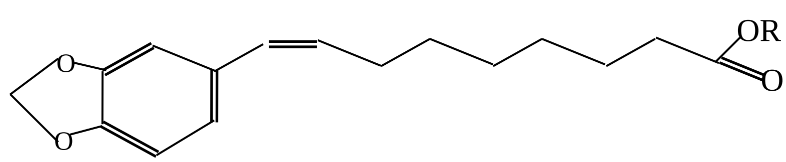


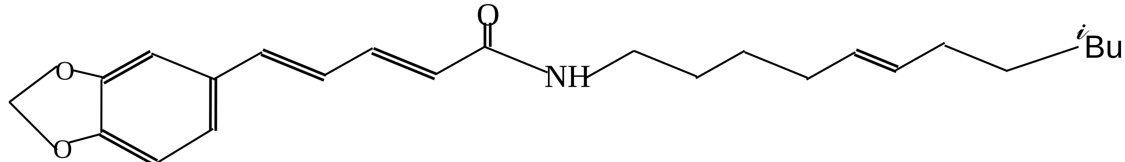
42 R = H (m.p. 80 – 81º, lit. 50 – 52)

43 R = Me



44 R = H (m.p. 49 – 52º)

45 R = Me



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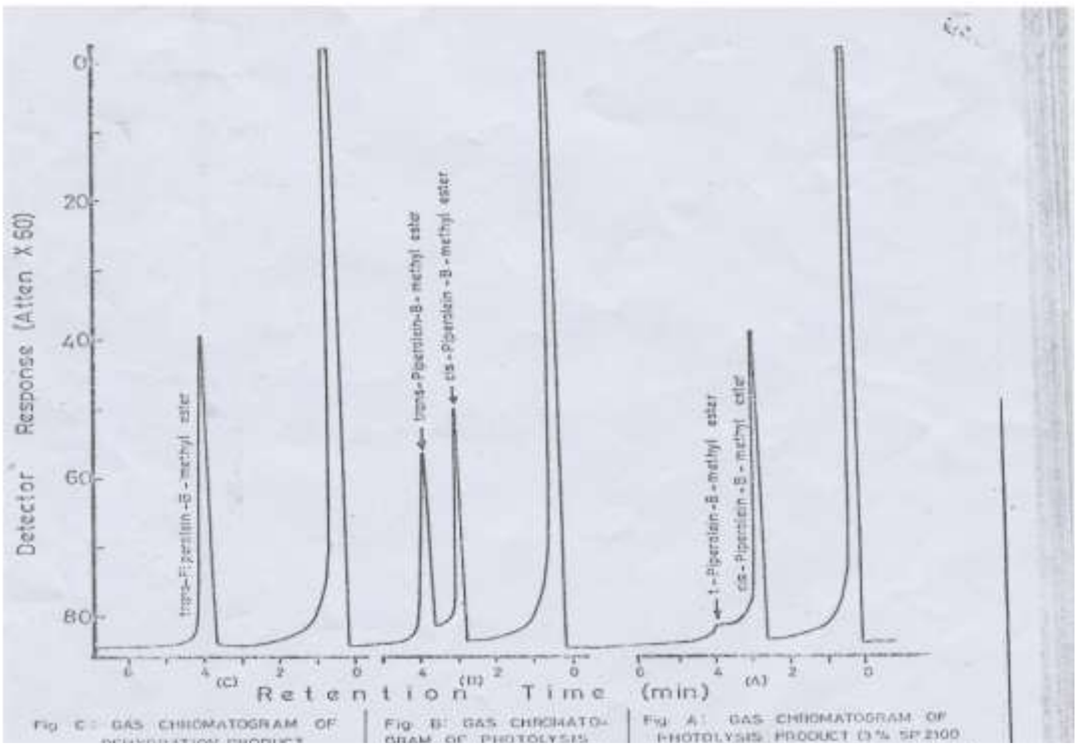


Fig. 8: Gas chromatograms of dehydration and photolysis products (43 and 45).

Some of the Nigerian native plants are known to keep off flies and mosquitoes and thus are repellents. Among such plants are the species *Clausena anisata* (wild) Oliv. (Rutaceae) found around Ile-Ife[52,53,54] and *Dalbergia saxatilis* (Hook-F) (Fabaceae), (Hausa=*ma'karfo*) located in Zaria, Kano and Sokoto areas[43]. Biological studies have shown that the volatile oil of *C. anisata* which is known to possess a very strong sweet odour and rich in alkaloids was toxic to the third nymphal stage of *Z. variagatus* (L), while the root extract is reported to show anti-feeding activity against the larvae of the African armyworm, *Spodoptera exempta* (Walker)[53,54]. Mupamine, **47** and coumarins such as xanthoxyletin, **48** have been implicated. In an experience the powdered dry leaves of *D.saxatilis* kept in a closed room not only killed the houseflies (*Musca domestica*) but appeared to have attracted them. A heavy mass of dead flies was found in the room overnight. Thus, the leaves have dual pesticidal activity, attractant and insecticidal. The bark extract has also been found to be insecticidal against mosquitoes[43] (Fig.**9**).

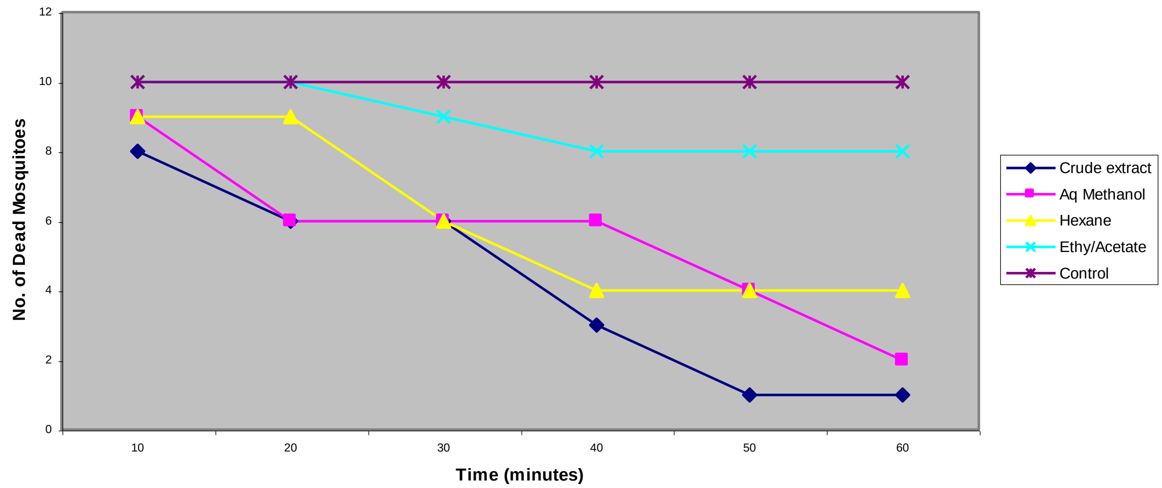
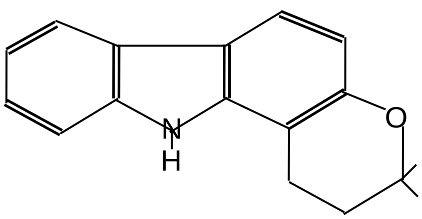


FIG.9: Mortality Rate of Mosquitoes Exposed to Solutions of the Crude Extract and Fractions of *Dalbergia saxatilis*



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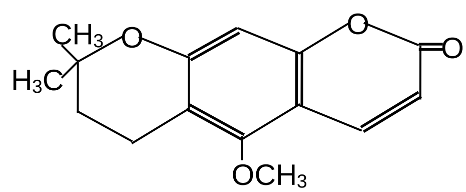

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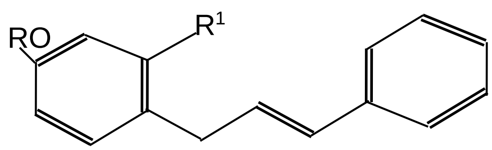
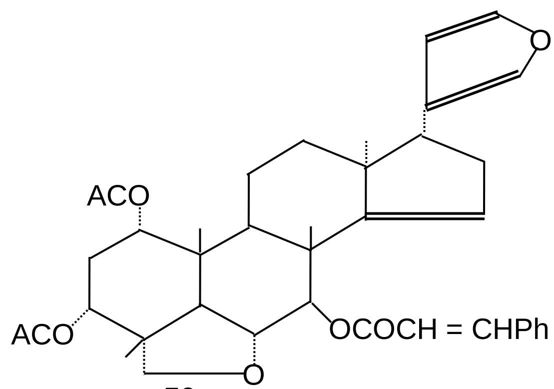
Plants belonging to the genus *Dalbergia* are known to be rich in cinnamylated phenols **49** which have been found to have sterilizing effect on flies[61].

A plant of great promise for its desirable pesticidal characteristics is the African, Central American and Indian Neem or margosa tree (*Azadirachta indica*)(L) (Meliaceae)(Hausa=*dogonyaro*). The seeds have been found to prevent damage by at least 25 species of economic pests to agricultural crops and stored products with low mammalian toxicity, no mutagenic activity and highly biodegradable[62]. The Nigerian species has yielded some meliacin cinnamates including nimbolin A, **50** and B, **51** from the trunk wood[45] but these have not been associated with any specific pesticidal activity. However, the meliacins (limonoids) have been associated with anti-feeding properties and the furan and the epoxy moieties have been found to be responsible as in limonin[63], **52.**



49, R[1]= R= H



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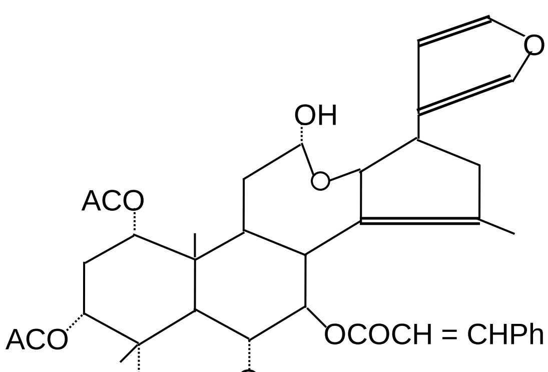

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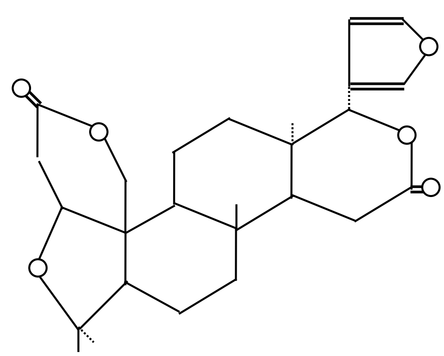

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CONCLUSION AND RECOMMENDATIONS

The terrestrial higher plants are indeed, potential sources of bioactive organic substances, which can be harnessed for use in agriculture and medicine. The cost of developing new drugs and pesticides to WHO and FAO standards are very high but the application of inter-disciplinary techniques such as bioassay-directed fractionation to the study of terrestrial higher plants traditionally used in agriculture and medicine will definitely lead to the development of local pesticides and drugs with comparable potency to those we import. The effort is to screen biologically and identify the active principle and standardize either the crude extract or the fractions. Thus, pharmacologists, agricultural scientists, biologists and natural products chemists should emphasize collaborative research in this area. Those plants that have shown good promise in primary and secondary screens should be formulated in consultation with NAFDAC and other relevant agencies in such ways that Nigerian farmers and herbal medicine practitioners can utilize them as cheap pesticides and drugs. In addition, plant-derived agents generally have been found to have some advantages over synthetic agents as they provide nutrients for the body especially when taken as part of our food and have been found to be safe and biodegradable in agricultural applications. Thus, they have economic and health values and are, environmentally friendly.

For large-scale field or storage utilization of botanic agricultural chemicals and for regular availability of drugs from plant sources, there must be adequate supply of candidate-plants. This means that since plants grow well usually in areas of natural habitat, effort must be made to encourage large-scale cultivation of such plants in their various localities as is the practice in China, Kenya and Japan.

To achieve the desired objectives of utilizing botanic materials in agriculture and medicine, the effort to have a compendium of Nigerian bioactive plants must be encouraged and funded by the Federal Government. In addition, research institutes such as the National Institute for Pharmaceutical Research and Development (NIPRD), Idu, the National Research Institute for Chemical Technology (NARICT), Zaria, the Sheda Science and Technology Complex (SHESTCO), Sheda, the International Institute for Tropical Agriculture (IITA), Ibadan and the research laboratories in the universities be adequately funded and staffed for research into the bioactive potentials of the Nigerian flora.

These institutions should establish botanical gardens as one of their key facilities for breeding and preserving plant species of economic importance. The bioactive organic substances may be our hope for the future health and food security of our people and one of the key factors in our struggle for economic recovery and development.

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