OBAFEMI AWOLOWO UNIVERSITY, ILE-IFE, NIGERIA.

Inaugural Lecture Series 204

NATURAL PRODUCTS CHEMISTRY : THE RECENT TRENDS AND IMPACT ON THE SOCIETY

By

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Professor of Pharmacognosy

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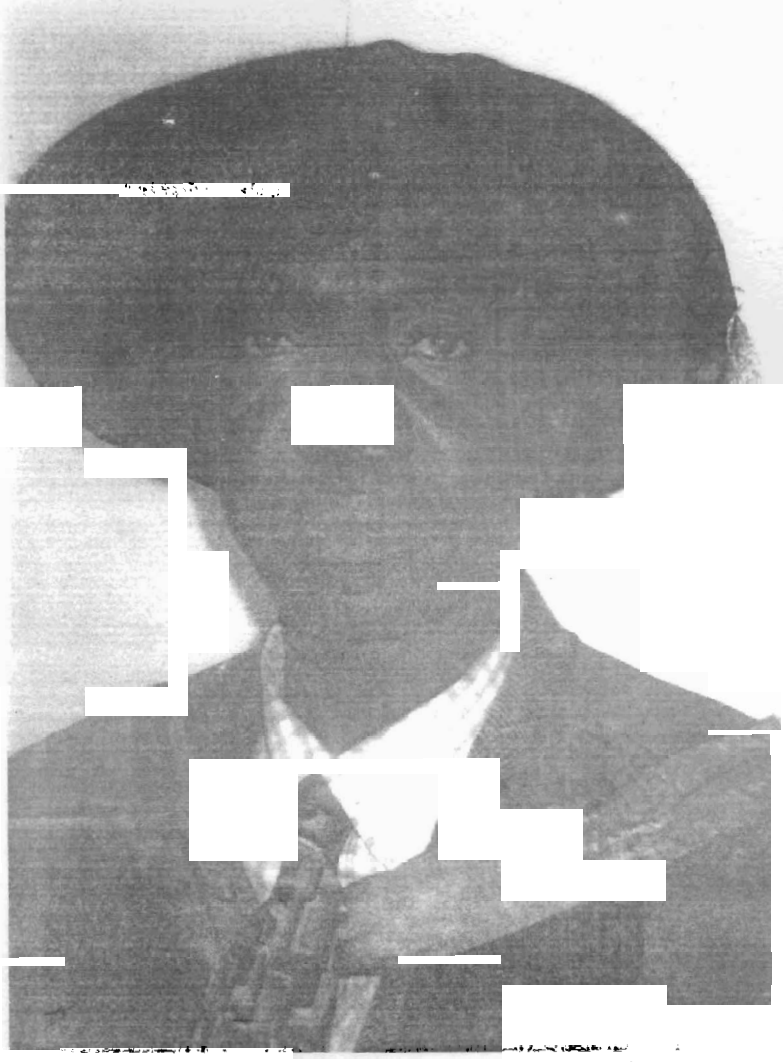

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An Inaugural Lecture Delivered at Oduduwa Hall
Obafemi Awolowo University
Ile-Ife, Nigeria

On Tuesday 11th September, 2007

Inaugural Lecture Series 204

ISSN 0189-7848

Printed by
Obafemi Awolowo University Press Limited
Ile-Ife, Nigeria.

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INTRODUCTION

Mr. Vice-Chancellor, Sir, distinguished ladies and gentlemen, I want to start my Lecture by refering to some records of the relevance and impact of natural products on man and her society by God himself. The creation of heaven and earth is recorded in the Holy Bible (Genesis 1-2) and on the third day then God said, "let the land produce vegetation: seed-bearing plants and trees on the land that bear fruit with seed in it, according to their various kinds" (Genesis 1: 11). This was done ever before the creation of mankind, also in Genesis 1: 29-30, God said, "I give you every seed-bearing plant on the surface of the whole earth and every tree that has fruit with seed in it... I give every green plant for food." God created all forms of life on earth, - plants, animals, parasites and mankind, as attested by the Bible. There are also references on the vegetation with healing properties e.g. use of poultice applied, to the ulcer of King Hezekiah (2 Kings 20: 7), leaves of fruit trees growing along river bank that "their fruit will serve for food and their leaves for healing" (Ezekiel 47: 12). My very first dive into the sea of Natural Products Chemistry (NPC) or Phytochemistry was about four decades ago during my Higher School Certificate (H.S.C.) final year practical examination. Then, we were doing the TLC of acetone extract of dried leaves with reference compounds in order to ascertain its constituents This inspired my taking NPC as a career. This was followed by a summer 1978 pre-doctoral study visit to Dr. E. A. Sofowora's (now Prof. A.Sofowora) laboratory that resulted in University of Ife (now Obafemi Awolowo University) scholarship for the completion of my Doctoral studies.

The subject Pharmacognosy includes Ethnomedicine (traditional medicine), Phytochemistry and Natural Products Chemistry

Ethnomedicine -The World Health Organization (1978b) has defined traditional medicine as the total combination of knowledge and practices whether explicable or inexplicable, used in diagnosing, preventing or eliminating a physical, mental or social diseases. These knowledge and

the practices may rely exclusively on past experiences and observations handed down from generation to generation verbally or in writing. The practices are predicated on the original concepts of nature which include the material world, the sociological environment whether living or dead and the metaphysical forces of the universe (WHO, 1978b).

Pharmacognosy -derived from two Greek Words,"pharmakon" or drug, and "gnosis" or knowledge. Like many contemporary fields of science, Pharmacognosy has undergone significant change in recent years and today represents a highly interdisciplinary science which is one of five major areas of pharmaceutical education. Its scope therefore includes the study of physical, chemical, biochemical and biological properties of drugs, drug substances, or potential drugs or drug substances of natural origin as well as the search for new drugs from natural sources. Thus, research problems in pharmacognosy now include studies in the areas of phytochemistry, microbial chemistry, biosynthesis, biotransformation, chemotaxonomy, and other biological and chemical sciences (The American Society of Pharmacognosy Webmaster, 2002).

Phytochemistry – is simply the study of the.chemistry of the constituents of plants, with the aim of identification, isolation and characterization of biologically active compounds, evaluation of their effects in animals and human (clinical trials).

Natural Products Chemistry – has a greater or wider scope than phytochemistry, and is the chemistry of plants, animals, fungi, bacteria, viruses, marine plants and animals, rocks, and other life forms as well as minerals and soils.

Therefore, Pharmacognosy as centre point of these five areas is very indispensable in my work and as is the link between or at the interphase of biology and chemistry and between nature and drugs.

Mr. Vice-Chancellor Sir, this Inaugural Lecture Series 204 titled "Natural Products Chemistry: The Recent Trend and Impact on the Society" attempts to give the account of my about 30 years of work in the above mentioned five major areas of medicinal natural products research.

Natural products from plants in human history have been used as medicines, fragrances, food additives and pesticides. Through the use of plants, human beings have taken advantages of the defensive, attractive and medicinal compounds present in leaves, flowers, roots, sap and bark of species around the World (Evans, 1989). Even though very large numbers of plants are constantly being screened for their possible pharmacological value, it is estimated that only about one percent of Nigerian medicinal plants has been subjected to scientific evaluation for potential chemotherapeutic value (Inyang, 2004).

Today, plants are the almost exclusive source of drugs for the majority of the world's population. In the industrialized countries, substances derived from higher plants constitute exactly 25% of prescribed medicines (Farnsworth and Bingel, 1977).

PHYTOCHEMICAL METHODS

The screening process all over the world has shown that plants contain hundreds or thousands of metabolites. Thus, any 'phytochemical investigation' of a given plant will reveal only a very narrow spectrum of its constituents. The process that leads from the plant to a pharmacologically active, pure constituent is very long and tedious, and requires a multidisciplinary collaboration of botanists, ethnobotanists, traditional healers, pharmacognosists, chemists, pharmacologists and toxicologists. This approach involves the following steps (Fig. 1) (Hamburger and Hostettmann, 1991).

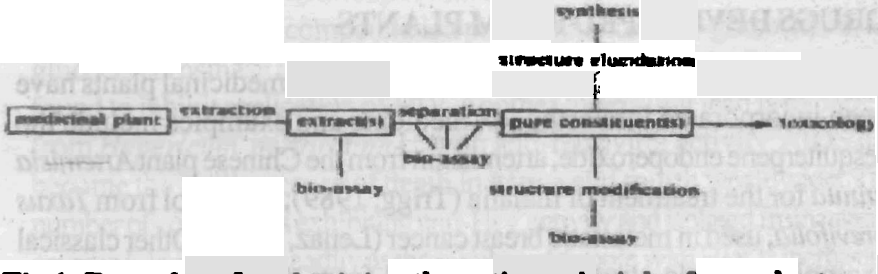


Fig 1: Procedure for obtaining the active principles from plants.

- Information of folkloric use by traditional healers and other custodian of this knowledge.
- Collection, proper botanical identification and drying of the plant material.
- Preparation of appropriate extracts and preliminary chromatographic analysis by TLC and HPLC.
- Biological and pharmacological screening of crude extracts.
- Several consecutive steps of chromatographic separation, where each fraction obtained has to be submitted to bioassays in order to follow the activity (activity-guided fractionation).
- Verification of the purity of the isolated compounds.
- Structure elucidation by chemical and physicochemical methods.
- Partial or total synthesis.
- Preparation of derivatives/analogues for the investigation of structure – activity relationships.
- Large scale isolation for further pharmacological and toxicological tests.

Major areas in current research on bioactive plants and current trends can be identified by a survey of current publications by Hamburger and Hostettmann, 1991; Cordel, 1995; from Singh *et al.*, 2005: Furia, 1997, Olaniyi, 1981, 1992.

DRUGS DEVELOPED FROM PLANTS

Less than 100 years ago, therapeutic agents from medicinal plants have been incorporated into orthodox medicine and examples include the sesquiterpene endoperoxide, artemisinin from the Chinese plant *Artemisia annua* for the treatment of malaria (Trigg, 1989); and taxol from *Taxus brevifolia*, used in metastatic breast cancer (Lenaz, 1993). Other classical examples include atropine, an alkaloid from *Atropa belladonna* as ophthalmics and synthetic spasmolytics, morphine and paraverine from

Papaver somniferum for the synthesis of analgesic and spasmolytics: quinine and quinidine from *Cinchona succirubra* bark, for malaria and antiarrythma, and digitoxin, most important cardiotonic drug in orthodox medicine from *Digitalis purpurea* for semi-synthetic cardiac glycosides. Cocaine from *Erythroxylum coca* for synthetic local aenesthetics. Ephedrine from *Ephedra sinica* for synthetic sympathomimetics; Reserpine, ajmaline and other alkaloids from *Rauwolfia serpentina* for synthetic antihypertensives and antiarrythmics. Strophantin from Strophantus seeds, emetine from Ipecac, anthraquinone glycosides from Cassia leaf, etc are also used clinically.

From podophyllotoxin, isolated from *Podophyllum peltatum* used as cathartics in folklore medicine, was developed etopside and teniposide as potent drugs used in the treatment of small-cell lung cancer, testicular cancer, lymphomas and leukeamia (Stahelin *et al.*, 1991).

A strong effort has been the search for novel anticancer agents since the early 1950s led to the first clinically useful anticancer compounds. Isolation of *Catharanthus roseus* G. Don alkaloids, bis-indole alkaloids vinblastine, vincristine, leurosine and leurosidine between late 1950 and early 1960s. Two of them, vinblastine and vincristine, have been developed as commercial drugs, for the treatment of patients with Hodgkin's disease, non-Hodgkin's lymphomas, and renal, testicular, head and neck cancer.

The identification of the human immunodeficiency virus (HIV) as the causative agent of AIDS has stimulated the search for novel antiviral agents. Two plant derived compounds have emerged as: castanospermine and hypericin from *Castanospermum australe* A. Cunn et Fras. (Leguminosae). The compound is a potent inhibitor of â-glucosidase, â-glucocerebrosinase and lysosomal á- and â-glucosidases. It is recently found to inhibit replication of HIV. Another interesting lead is hypericin from *Hypericum perforatum* L. with anti-retroviral activity. AIDS has become the leading cause of death in Africa and fourth worldwide. The number of compounds exhibiting anti-HIV activity and isolated from natural sources is increasing steadily as the number of people with HIV is increasing at an alarming rate in India and Southeast Asia. Examples are Calanolide

A, a coumarin isolated from *Callophyllum lanigerum*, and two other natural product-derived molecules which are phase II clinical candidates (Singh *et al.*, 2005).

A novel plant-derived cardiovascular drugs, forskolin was isolated from *Coleus forskolii* Brig. (Lamiaceae). It's main physiological and biochemical effects are:

(a) Vasodilatatory activity

(b) positive inotropic action on the heart

(c) decreased intraocular pressure

(d) inhibition of platelet aggregation.

The toxicity of forskolin is low and the clinical studies have so far focused on cardiovascular and bronchospasmolytic effects and on the treatment of glaucoma.

Sickle Cell Disease (SCD) is genetic disorder found in Africans, Turks, Greeks, Saudi Arabians, Egyptians, Iranians, Italians, Latin Americans and Asiatic Indians. Nigeria has the highest sickle cell disease population in the world estimated at between four and six million sufferers, roughly three to five percent of the country's population. The Fagara (*Zanthoxylum zanthoxylodes* (Lam.) Waterm. (Rutaceae) popularly known "Orin ata" in Yoruba language the root is used as chewing sticks in Western Nigeria from which a number of anti-sickling compounds were isolated (Sofowora *et al.*, 1975; Elujoba *et al.*, 1985). A drug named NIRISAN/ NICOSAN™ (HEMOXIN) has been developed and found very effective in treating SCD for which there is no non-toxic drug in the market (Wambebe *et al*, 2001;Pandey *et al. 2002*).

Another natural product for sickle cell disease named Ciklavit has been developed by Neimeth International Pharmaceuticals Plc, Lagos from an extract of *Cajanus cajan* "Otili" beans, in collaboration with the Department of Paediatrics, College of Medicine, University of Lagos, Nigeria (Akinsulie *et al.*, 2005).

From the venom of the pit viper *Bothrops jararaca* was discovered angiotensin converting enzyme. This eventually led to the development of the potent antihypertensive drug, captopril and enalapril (Feirera *et al.*, 1970).

There are indeed many reviews on the potential of medicinal plants as sources of new therapeutic gents (Soejarto and Farnsworth, 1989; Hamburger and Hostettmann, 1991; Balandrin *et el.*, 1995. Cordell 1995, 2000; Clark, 1996 Mukherjee et al, 2001)

As a result of what is already in literature, it is very obvious that scientists, phytochemists and/or natural products chemists and pharmacognosists must continue to screen our endowed medicinal plants for biological activities with the use of advanced bioactivity directed isolation and characterization of active compounds. Our University has found itself to be the leader in Traditional Medicine and Natural Products Research in Nigeria as attested to by the recent compilation of work done on plants from 1970 – 2005 (Okujagu *et al.*, 2005).

The last fifty years has seen much activity in this area and many thousands of novel compounds have been isolated and characterized. The research for drugs from plants should focus on tropical countries, because over 50 percent of the estimated (250,000) plants species found on earth come from tropical forests, which are currently being destroyed at very alarming rate, to give way for construction and or mineral development or exploitation. (Verpoorte, 1998).

Recent Trend, Challenges, Impact and Future Trend

Recently, there has been a renewed interest in natural product research due to the failure of alternative drug discovery methods to deliver many lead compounds in key therapeutic areas such as immunosupprerssion, anti-infectives, and metabolic diseases.

As I have reviewed the previous trends of over four decades, discussed the current trend, it is also appropriate to highlight some insight into the future of natural product chemistry research. The scientific professionals must face the very enormous challenges of the 21st century with

determination and open mindedness, awareness for increased collaboration in a multidisciplinary world for faster, meaningful and better drug research and development from nature. Traditional medicine must be integrated in consonance with globalization by reassessing and opening itself to the requirements of scientific rationalization which requires the use of modern medicinal diagnostic methods and therapies. Natural products have long been our single most important source of medicines. Each plant is a chemical factory capable of synthesizing unlimited number of highly complex and unusual compounds with structures that otherwise escape the imagination of man forever. There are at least 120 distinct chemical substances derived from plants that are considered important drugs currently in clinical use in the world, while several other drugs are simple synthetic modifications of these natural products (WHO, 2002). The completion of human genome project and role of genomic and proteomics have revolutionized natural products based drug discovery. Over 50% of the best – selling pharmaceuticals in use today are derived from natural products (Editorials, 2003).

In natural product drug discovery, the conventional approach of extraction, isolation, separation, identification, characterization and test for the desired biological activity suffers from problems like low yields, dereplication, difficulty in separation and inconsistent biological activity. However, the introduction of innovative technologies like high throughput screening (HTS) and recent advances in extraction like Supercritical Fluid Extraction (SFE) using fluid such as $C0_2$, ethane, NO_2 and ethylene has made significant positive impact on natural product discovery. It has been used successfully in combination with enzyme immunoassay analysis, anion exchange disk sorption and gas chromatography (Bruni, 2002). Computerization and automation of extraction processes have accelerated the pace of natural product drug discovery while chromatography, electrophoresis and spectroscopy has revolutionized the entire natural products research. Recently, traditional analytical methods are replaced by modern methods, which include hyphenation techniques, high throughput technologies, miniaturization, robotics, pharmacophore, modelling, virtual screening, docking and neural networking to efficiently access the bioactive

metabolites. These techniques facilitate rapid and efficient screening of extracts and their online characterization, being automated and highly sensitive, they require very less amount of sample and save analysis time (Kube, 2003). For a rapid phytochemical investigation of plant extracts and to perform efficient screening of extracts, the combined techniques such as HPLC coupled to UV photodiode array detection (LC/UV) and to mass spectrometry (LC/MS or LC/MS/MS) or LC/NMR or LC/TPS – MS-MS is appropriate (Hostettmann *et al.*, 1997). Separation and detection efficiency of present methods can be greatly enhanced by using combinations like HPLC – electro spray ionization – MS-MS analysis (Hoi *et al.*, 2003), HPLC-UV and HPLC-positive – EST –MS analysis (Bicchi *et al.*, 2001).

As advances in biotechnology progress, various genetically modified cell lines, cultures and organisms have become available for screening purposes that have shortened the screening time (Houghton, 2000). Capillary electrophoresis (CE) is a versatile micro/macro analytical technique gaining widespread usage for the separation and analysis of natural substances. It has several advantages over the conventional thin-layer, gas and high performance liquid chromatographies, such as low capillary cost, reduced operational costs, small sample size, low production of waste materials, short analysis time, complete automation in sample handling and data treatment. It is anticipated that this hyphenated technique could have a considerable expansion in the coming years (Bossi *et al.*, 2000).

One key challenge to natural products chemistry research in the very near future is the loss of presently cheap and ready availability of our medicinal plants to the present rate of destruction of vegetation to make way for human development and economic exploitation. Therefore, the cultivation and conservation of medicinal plants in the world, especially Nigerian biodiversity, has never been more important and urgent than now. The Convention on Biological Diversity has provision for medicinal plants conservation and this should be vigorously undertaken for the benefit of mankind. A procedure should be developed to compensate the custodians of traditional medicines (Herbalists) for the utilization of their knowledge

and their biological resources. It is equally important that all medical programmes include the recognition of traditional healers and the incorporation of traditional health practices that enhance the health status of the populations as it is currently being practice in China, India etc. The recent trend in support for traditional medicine and natural products researches in Nigeria is very encouraging. The Federal Government has declared its commitment to this cause. Recently, the Nigeria government, may be in response to the WHO call on the developing world to institutionalize traditional medicine, has taken major steps to boost research into traditional medicine in an effort to preserve the country's indigenous medical knowledge. A book has been published, which is a collection of 1,050 research efforts by Nigerian Scientists or Traditional Medicine Scholars, published in 1,020 reputable international journals from 1970 to 2004 (Okujagu *et al., 2005*). The former President, Chief Olusegun Obasanjo has also expressed his desire by setting up the National Council for Traditional Medicine, (Presidential Initiative Committee) that will set up a training and research institute in the field, which would improve Nigeria's "negligible" contribution to the global $60 billion dollar traditional medicine market. This High profile council which will help to develop, promote and commercialise traditional medicine products, could help Nigeria earn at least $1 billion over its first ten years (Sci.Dev.Net., 2006). It is worthy of note and in confirmation of OAU leadership in this area, that one of us, the one and only, Professor Abayomi Sofowora has been named to be the Vice-Chairman of the Council.

NATURAL PRODUCTS CHEMISTRY – MY CONTRIBUTION

Mr. Vice Chancellor, Sir, from my bird's eye view, after a review of literature and my contribution to scientific knowledge in the area of Natural products chemistry, biological and pharmacological activities are highlighted below:

It is in the pursuance of this noble objective that I chose today's lecture, highlighting my career contribution to this position of eminence of natural products chemistry and phytochemistry in our lives.

As a Chemist, I started with phytochemistry, limiting myself then to isolation and characterization. However, I got caught up with the vogues of

determining the character of the isolates. Now, I am solely onto activity-directed isolation of bioactive drugs.

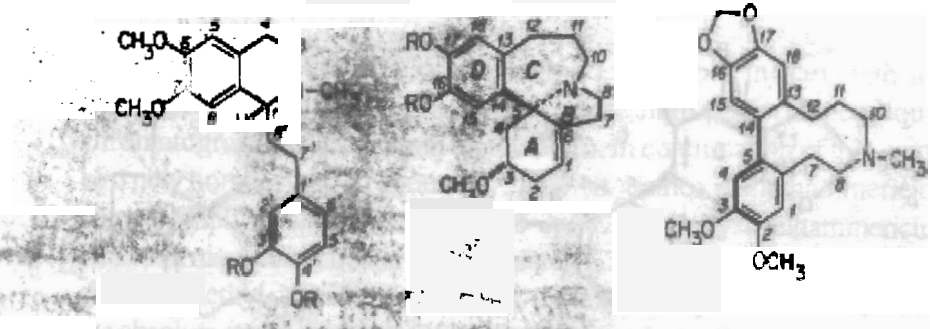
A. Phytochemistry (Isolation and Characterization) of Alkaloids, Terpenoids, Flavonoids, volatile oils and Coumarins,

B. Biological and Pharmacological Activities of Anti-infective (antimicrobial), cardiovascular, molluscicidal/trypanocidal, antimalarial, CNS (smooth muscle contraction), insecticidal, antioxidant, antidiabetic, fertility regulation (anti-implantation).

A. PHYTOCHEMISTRY – ISOLATION AND CHARACTERIZATION

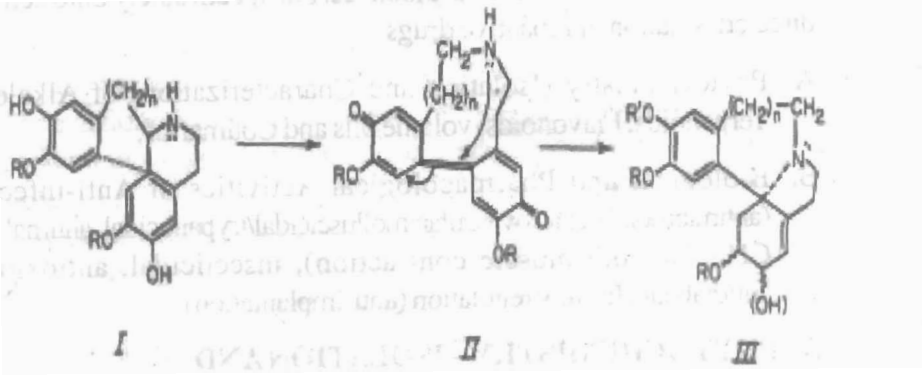
ALKALOIDS -: We have isolated and identified a variety of groups of alkaloids from many plants and some of them are highlighted-

a) *Dysoxylum lenticellare* Gillespie (Meliaceae) – A Fiji plant is used as fish poison and for alleviating aches and pains. After some years of active but vigorous work, two new alkaloids possessing the 1-phenyl ethyltetrahydroisoquinoline skeleton, Dysoxyline, and S- (+) Homolaudanosine were isolated from the chloroform partitioned fraction of the leaf methanol extract, along with known homoerythrina alkaloids 3-epischelhammericine and 2,7-di-hydrohomoerysotrine.



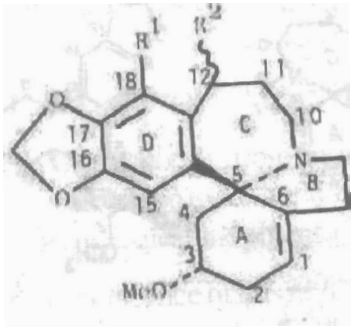
R, R = $-CH_2-$ (Dysoxyline), R, R = $-CH_2-$ (3-epischelhammericine), Dysazecine

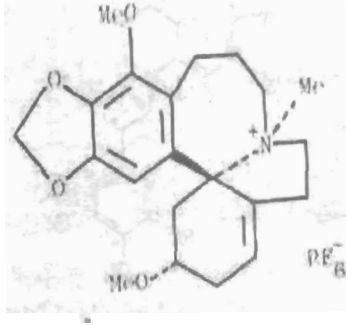
R = – CH_3 (Homolaudanosine), R= – CH_3 (2,7-dihydrohomoerysotrine),



Scheme 1: Biogenesis of Erythrina and Homoerythrina Alkaloids

Also isolated was a novel dibenz [d, f] azecine skeleton named Dysazecine, which represents the trapping of a biosynthetic intermediate in the postulated conversion of the phenyl ethylisoquinoline skeleton to the homoerythrina skeleton (scheme 1). These alkaloid skeletal was new in plants of the Meliaceae, which may be a good marker in chemotaxonomy (Aladesanmi *et al.*, 1983). They are proven to have cardioactive, molluscicidal, analgesic properties (Aladesanmi and Adewunmi, 1990; Aladesanmi et al, 1988; Aladesanmi and Ilesanmi, 1987; Adewunmi and Aladesanmi, 1988; Aladesanmi and Adewunmi, 1995).





$R^1 = R^2 = H$ (Schelhammericine),
$R^1 = H$, $R^2 = OH$ (3-epi-12-hydoxyschelhammericine)
$R^1 = OMe$, $R^2 = H$ (Dyshomerythrine),

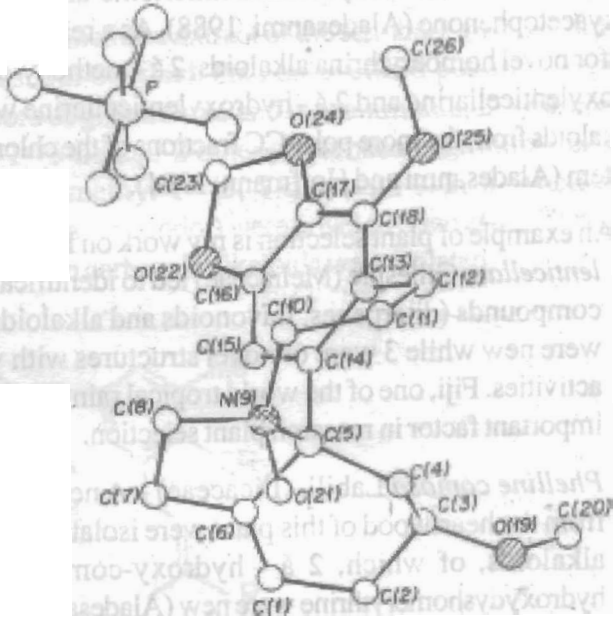


Fig 2. Molecular conformation and numbering scheme for N-methyldyshomerythrinium hexafluorophosphate.

The isolation of the alkaloids was made possible in part with my development of a unique reversed – phase high performance liquid chromatography (Aladesanmi *et al.*, 1986). In continuation of this work, two new homoerythrina alkaloids, 3-epi-18-methoxyschelhammericine named simply Dyshomerythrine and 3-epi-12-Hydroxyschelhammericine , first as a mixture but quaternization of the mixture allowed the purification of the N-methyl derivative of above as its hexafluorophosphate salt, which the absolute stereo structure (3S, 5S) and the conformation was established by its X-ray analysis (Aladesanmi *et al.*, 1984) (Fig. 2). From the stem was isolated, a total of five alkaloids – 3-epischelhammericine, 2, 7-dihydrohomoerysotrine and 3-epi-18-methoxyschelhammericine,

previously isolated from the leaf and two new alkaloids – lenticellarine and 3-epi-2, 18-di-methoxyschelhammericine along with known p-hydroxyacetophenone (Aladesanmi, 1988). As a result of my continued search for novel homoerythrina alkaloids, 2 á - methoxy-comosivine, 2 á - methoxylenticellarine and 2 á - hydroxylenticellarine were isolated as new alkaloids from the more polar CC fractions of the chloroform fraction in the stem (Aladesanmi and Hoffmann, 1994).

a) An example of plant selection is my work on Fiji plant *Dysoxylum lenticellare* Gillespie (Meliaceae) led to identification of over 20 compounds (diterpenes, flavonoids and alkaloids) of which 10 were new while 3 were of novel structures with various potent activities. Fiji, one of the world tropical rain forests, validates an important factor in research plant selection.

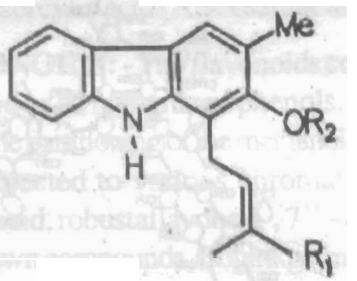
b) *Phelline comosa* Labill. (Ilicaceae) – A new Caledonia plant, from the heartwood of this plant were isolated 6 homoerythrina alkaloids, of which, 2 á - hydroxy-comosivine and 2 á - hydroxydyshomerythrine were new (Aladesanmi and Hoffmann, 1990; Aladesanmi *et al.*, 1991). They showed various degree of antimicrobial activity (Adebajo et al, 1991).

c) *Newbouldia laevis*- This was a project of my M.Sc. student, Mr. R. Nia and also my work in 1995 in Germany. The rootbark of N. *laevis*, used in the treatment of enlarged spleen, dysentery, worm infestation, migraine, earache, conjunctivitis, and various forms of orchitis, afforded six alkaloids - withasomnine, 4´– hydroxywithasomnine, 4´– methoxywithasomnine, newbouldine, 4´- hydroxynewbouldine and 4´– metghoxynewbouldine. New alkaloids, 4´ – methoxywithasomnine and 4´ – methoxynewbouldine were also identified (Aladesanmi *et al.*, 1998).

d) *Murraya koenigii* (L.) Spreng. (Rutaceae) – This was the work of my first Ph.D student, Dr. Adebajo. It is natural to Central and Southeast Asia and cultivated in Nigeria. Medicinal applications

include as tonic, stomachic, carminative, antidysentry, stimulant, febrifuge, anti-periodic and anti-vomiting agents.

The dichloromethane extract of the stembark gave six carbazole alkaloids, out of which the non-cyclized possible biogenetic precursors of girinimbine and mahanimbine, 2-hydroxyl – 3 – methyl-1- (3-methyl-2-butenyl) carbazole (girinimbilol) and 2-hydroxyl-3-methyl-1- (3, 7-dimethyl – 2, 6 – octadienyl) carbazole (mahanimbilol) were novel (Reisch *et al.*, 1994). In all, about thirteen carbazole alkaloids were isolated.



R_1 = Me, R_2 = II , (Girinimbilol)
R_1 = $(CH_2)_2CH=CMe_2$, R_2 = II (Mahanimbilol)

TERPENOIDS: - This group of compounds were isolated from 2 plants. Terpenoids form the largest group of plant products and are the most common ingredient in volatile oils.

a) *D. lenticellare* – From the pentane soluble fraction of the leaves, were isolated two diterpenes, phyllocladene and 8-hydroxysandaracopimarene while major quantities of the known diterpenes, phyllocladene , 8- â–hydroxysandaracopimarene and p- hydroxysandaracopimarene were identified. This was the first time of their isolation from Meliaceae which may be of chemotaxonomic significance (Aladesanmi *et al.*, 1986). From the n-hexane partition fraction of the stem of *D. lenticellare* were isolated

three diterpenes, phyllocladene, hydroxy-sandaracopimarene and a new compound named 8 â-methoxysandacopimarene (Aladesanmi, 1988).

Minor quantities of Ferruginol and 10-nonacosanol were also identified while a new, unusual bis-diterpene, Ferrubietolide (Fig. 3) was also isolated and X-ray diffraction analysis was used to established its structure and stereo-chemistry with moderate antimicrobial activity (Aladesanmi and Adewunmi, 1995; Onan *et al.*, 1985).

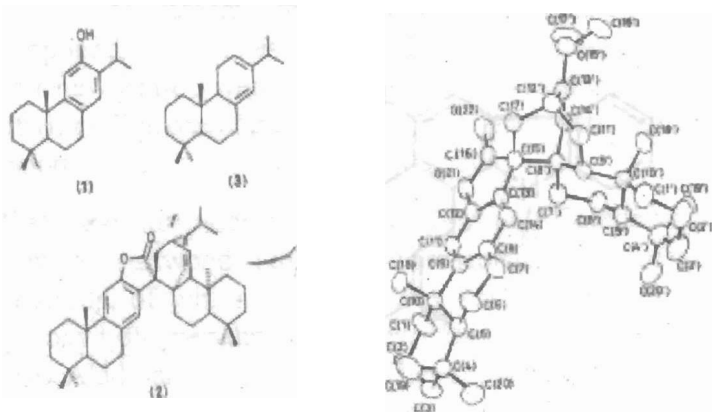


Fig 3: A view of the molecular structure of (2) with thermal ellipsoids at the 50% probability level (ORTEP) and the molecular numbering scheme. Hydrogen atoms have been omitted for clarity.

b)

Cowainea mexicana D. Don (Rosaceae) – As part of my search for biologically active compounds from desert plants, I did this work as Senior Research Associate at the University of Arizona. The plant has the history of use as a topical anti-infective agent by the Native Americans of the region. The methanol extract yielded a soluble fraction, which when subjected to silica gel CC and MPLC, triterpene ursolic acid and the three known derivatives, pomolic, 2 á - hydroxyursolic, and 2 – epi- tormentic acids were isolated.

Tormentic acid was reported to be an effective topical antibiotic against *Streptococcus mutans*; pomolic and 2 á - hydroxyursolic acids were reported to have cytotoxic and potential antitumour activity (Hoffmann *et al.*, 1994).

c) **Trichilia heudelotti** Planch ex Oliver (Meliaceae)- The purification of the n-hexane fraction led to the isolation of nimbiol, isopimarinol, ketoferruginol and a new diterpene named 12 â-hydroxysandaracopimar-15-ene while the ethylacetate fraction yielded protocatechuic acid, 4-hydroxybenzoic acid, 2-methylprotocatechuic acid and a new compound named 2-propionoxy- â-resorcylic acid (Aladesanmi and Odediran, 2000).

FLAVONOIDS: - The flavonoids constitute about one-half of the eight-thousand or so recognized phenols. A yellow precipitate (27g) formed during the partitioning of the methanol extract of the leaves of *D. leuticellare* was subjected to various chromatographic systems to give a novel biflavonoid, robustaflavone 4', 7''– dimethyl ether (Fig. 4) in addition to two known compounds, isoginkgetin and bilobetin. Their structures were established by spectroscopic data and chemical modifications (He *et al.*, 1996). This was the work of a Ph.D. student of mine in U.S.A.

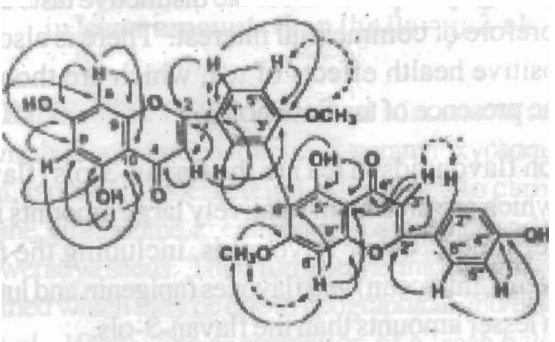


Fig 4: HMBC correlations (solid arrows) and NOE correlations (dotted arrows) for Robustaflavone.

This is a work I did in 2001/2002 as a Consultant Natural Products Chemist at the Jean Mayer United States Department of Agriculture Human Nutrition Research Center on Aging at Tufts, Tufts University Friedman School of Nutrition Science and Policy, Boston, Massachusetts, U.S.A., in collaboration with seven other International scientists, which researched into major flavonoids in dry tea. Teas are used as beverages worldwide, although consumers very in their preferences for the degree of fermentation, taste and colour.

Green tea, the non-fermented tea, is widely consumed in China and Japan, and health benefits such as cancer risk reduction have been suggested.

Oolong tea, which is partially fermented by endogenous enzymes in the tealeaf, is drunk in many countries.

Black tea, the most highly fermented, is popular in Western countries and dominates the market economically.

Pu'er tea, a rare tea, fermented by anaerobic bacteria rather than the enzymatic fermentation processes that characterize the other teas, is consumed almost exclusively in Asia.

The flavonoids are largely responsible for the distinctive taste and colour of tea, and are therefore of commercial interest. There is also growing interest in the positive health effects of tea, which are thought to be associated with the presence of tea flavonoids.

The most common flavonoids in tea are the flavan-3-ols (flavanols or flavans) (Fig. 5) which are present in relatively large amounts in tea and low levels in other foods. Other flavonoids, including the flavonols (quercetin, kaempferol, myricetin) and flavones (apigenin and luteolin) are also present but in lesser amounts than the flavan-3-ols.

Total catechins were 13.6g/100g in green and 4.2g/100g dry weight in black tea. Various methods to calculate the flavonoid content in tea were presented (Peterson *et al.*, 2005).

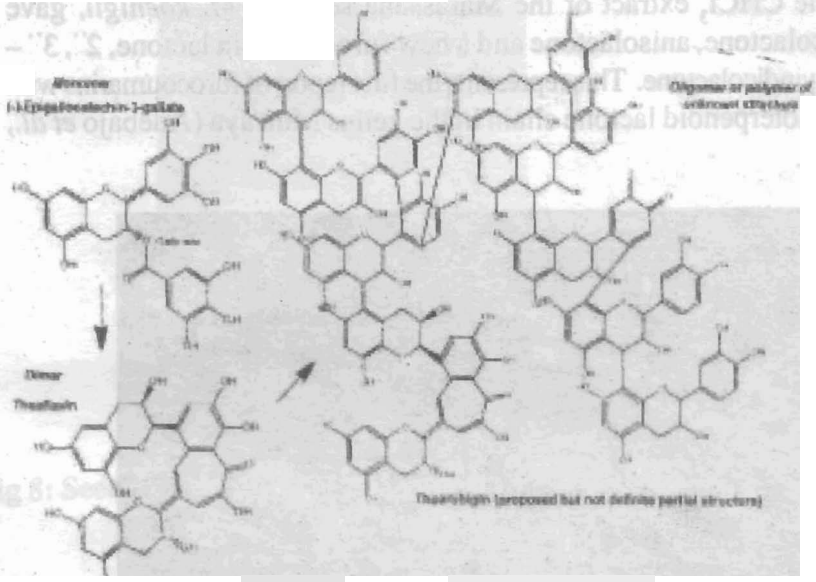


Fig. 5: Structure of significant flavan-3-0l in tea. The arubigins are oligomers of unknown structure. Other flavonoids, including the flavonols (quercetin, kaempferol, myricetin) and flavones (apigenin and luteolin), are also present but in lesser amounts than the flavan-3-ols.

COUMARINS:- The $CHCl_3$ extract of Marassana seeds of *Murraya koenigii* furnished only furocoumarins, 8-geranyloxypsoralene, imperatorin, heraclenin, isosaxalin, heraclenol as opposed to carbazole alkaloids, mahanimbine, girinimbine, koenimbine, isomahanine and mahanine isolated from Nikaweratiya seeds. Their furocoumarinic or carbazolic chemotypes was confirmed which may be due to geographical and/or genetic properties (Reisch *et al.*, 1994). The examination of a fresh batch of Marassana plant seeds resulted in the isolation of isoheraclenin, isoimperatorin, oxypeucedanin, isopimpinellin and bergapten minor constituents. The presence of furo-and pyrano-coumarins may provide additional useful

chemotaxonomic data for the genus (Reisch *et al.*, 1994). Further work on the $CHCl_3$ extract of the Marassana seeds of *M. koenigii*, gave indicolactone, anisolactone and a new furocoumarin lactone, 2'', 3'' – epoxyindicolactone. This represents the first report of furocoumarins with a monoterpenoid lactone chain in the genus Murraya (Adebajo *et al.*, 1997).

Fig 6: *Trichilia heudelotti* leaves and flowers in its natural habitat.

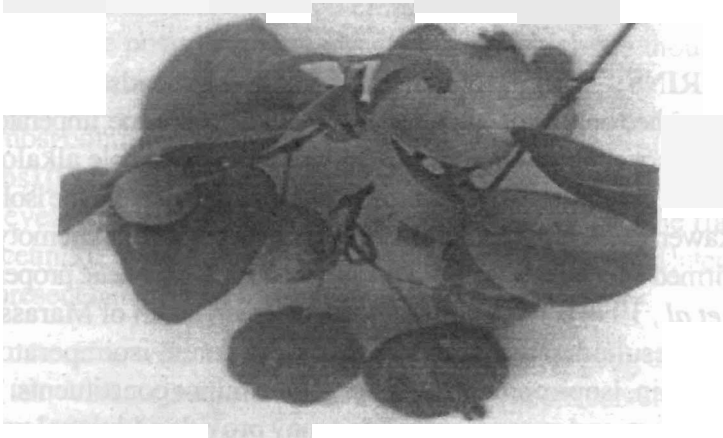


Fig 7: *Eugenia. Uniflora* L. showing both ripe and unripe fruits.

Fig 8: Seedlings of *Murraya koenigii* collected in Sri Lanka.

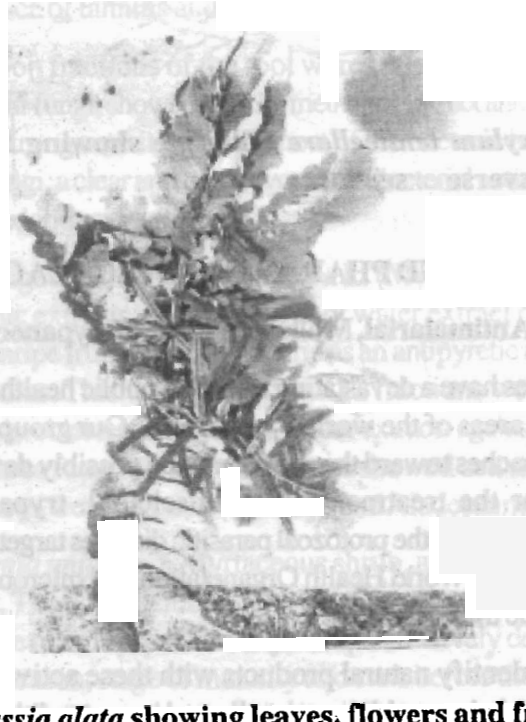


Fig 9: *Cassia alata* showing leaves, flowers and fruits.

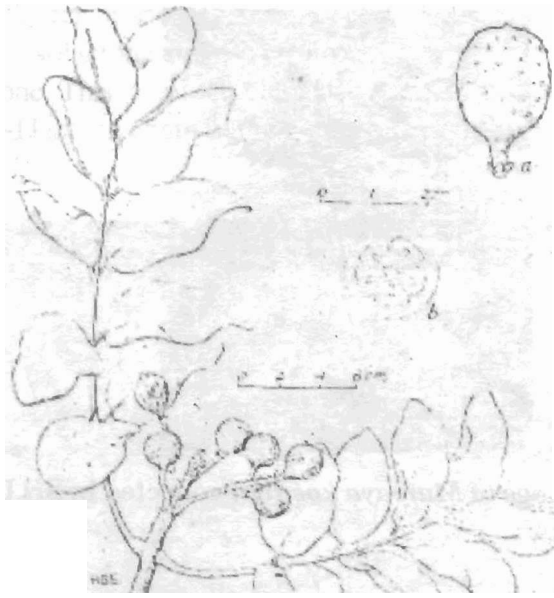


Fig 10: ***Dysoxylum lenticellare*** **Gillespie showing fruit and its transverse section.**

B. BIOLOGICAL AND PHARMACOLOGICAL ACTIVITY

Anti-infective/Antimalarial, Molluscicidal and Trypanocidal Activity

Parasitic diseases have a devastating effect on public health in especially the developing areas of the world e.g. Nigeria. Our group has devoted efforts on approaches toward the discovery and possibly development of new agents for the treatment of molluscicidal, trypanosomiasis, trichomoniasis, malaria, the protozoal parasitic diseases targeted for control or eradication by the World Health Organization and microbial infections which still plague the third world.

In an effort to identify natural products with these activities, we have worked on several plants which are implicated in our traditional folklores.

1. Antimicrobial Activity

(i) A total of ten ethanolic extracts from two plants, *Pleioceras barteri* Bail. (Apocynaceae), "pariomoda" in Yoruba, and *Marsdenia latifolia* Schum. (Asclepiadaceae); "ewurodo" in Yoruba (varieties *M. condurango* Benth and *Gongronema latifolium* Benth) decoction of stem and fruits is used as laxative, for digestive problems and as stomachic in dyspepsia. The stem is used as chewing stick to cure toothache while the powdered leaf is swallowed against malaria. *Pleioceras barteri* is used as emmenagogue and abortifacient and alkaloids are present in the rootbark, fruits and seeds. The extracts were tested against seven bacteria and 66.7% were considered active but most of the extracts, particularly *P. barteri*, were active against the gram positive. The rootbark extract proved the most active due to the presence of tannins and flavonoids (Aladesanmi *et al.*, 1986).

(ii) Partition fractions of the root were tested against nine bacteria and four fungi, showed that the methanol extract and all the fractions have strong activity against most of the bacteria but none against any fungi, a clear and unequivocal antibacterial activity of *P. barteri* (Agbedahunsi *et al.*, 1993).

(iii) Investigation of *Eugenia uniflora* L. (Myrtaceae) examined four organic extracts of the leaf. A hot water extract of the fresh leaf and unripe fruit is used in Nigeria as an antipyretic and antimalaria remedies. This was purified and 12 fractions were subjected to antimicrobial test along with the four extracts against seven bacteria and three fungi. Only two extracts showed activity while only 2 fractions were inactive (Adebajo and Aladesanmi, 1989).

(iv) *Eugenia uniflora*, a Myrtaceous shrub, a volatile oil-containing plant. The composition of the Nigerian *E. uniflora* leaf and fruit volatile oils vary qualitatively and quantitatively depending on the time, season, stage of maturity and state before the collection and extraction. The antimicrobial efficacy of the essential oils collected

at different times and their microbial transformed products were assessed against 8 bacteria and 3 fungi. The very consistent and significant activity obtained is a biological confirmation of the variation in the composition of the oils. Perhaps the most significant aspect of this work is that the fastidious *Pseudomonas aeruginosa* was the most susceptible bacterium while *T. mentagrophytes* was the most susceptible fungus. The results have provided a scientific explanation for the folkloric uses of *E. uniflora* against digestive tract disorders (Adebajo and Aladesanmi. 1989).

The contractile effects of the organic extracts and volatile oil of the fresh leaves of *E. uniflora* was assessed on isolated rat duodenum. Though they all showed considerable activity but only the ethylacetate extract yielded higher contractile responses than the reference acetylcholine. The contractile activity was absent in the oil, again, this has further confirmed the basis for using it in our traditional medicine to treat intestinal disorders such as constipation (Gbolade *et al.*, 1995)

(v) ***Phelline comosa*** Labill. (Aquifoliaceae), the heartwood was gradiently extracted and tested against 3 bacteria and 2 fungi. The most active ethylacetate extract was purified and bulked fractions obtained showed profound activity against *Bacillus subtilis* and *Streptococcus faecalis*, no activity against the fungi (Adebajo et al, 1991).

(vi) *Laportea aestuans* (Linn.) Chev., syn. *Fleurya aestuans* Gaud. (Urticaceae) fresh aerial parts, used in Nigeria for the treatment of burns and whitlow (inflammation). This was extracted and partitioned, tested against five bacteria and two fungi. The results showed the fractions to be active which may be helpful in preventing microbial infections in the case of burns and in inflammation, validating the use of *Laportea aestuans* in Nigerian traditional medicine. (Adebajo *et al.*, 1991).

(vii) *Cassia alata Linn.* (Caesalpinaceae) – In Nigerian traditional medicine, it is used in the treatment of parasitic skin diseases and pustular while the dried leaf infusion is used as a purgative. The leaves were gradiently extracted and tested for activity against five bacteria and five fungi. The extracts were active against all the microorganisms and thus purified and fractions were very active and compared favourably with phenol and bacitracin. This work valides the use of *C. alata* in Nigerian ethnomedicine for the treatment of skin diseases and also corroborates the findings on Indian species (Ogunti *et al.*, 1991).

(viii) *Crinum jagus* (Thomps.) Dandy (Amaryllidaceae) is used locally in anticonvulsant preparations and the treatment of open sores. Activity-directed fractionation of C. *jagus* bulbs, used in traditional medicine as an antibacterial agent gave four alkaloids, lycorine, hamayne, crinamine and 6-hydroxcrinamine. Only crinamine showed strong antibacterial activity. The possession of strong antibacterial activity has justified the use of *Crinum jagus* in the traditional treatment of open sores (Adesanya *et al.*, 1992).

(ix) *Trichilia heudelotti* Planch ex Oliver (Meliaceae) – The crude methanol and gradient extracts of the leaves showed antimicrobial activity, to be concentrated in the ethylacetate fraction, but none was active against any fungi. *T. heudelotti* leaves can therefore be regarded as having moderate antimicrobial properties (Aladesanmi and Odediran, 2000).

(x) *Antimicrobial and Antioxidant Activities*

Oxidants (Free radicals) – These are highly reactive molecules that can damage important cellular molecules such as DNA, lipids or other parts of the cell. The body uses antioxidants to destroy, neutralize or deactivate the free radicals. Antioxidants are abundantly available in fresh, organic, vine ripened fruits and vegetables, especially where growers have re-mineralised the soil. Commercial food processing however destroys the antioxidants available in freshly harvested raw fruits and vegetables.

Ten Nigerian plants were studied based on their ethnomedical uses to possess antimicrobial and possibly antioxidant activities. Their methanol extracts were tested against four bacteria and three fungi at four different concentrations along with thirteen antibiotics. The results showed *Markhamia tomentosa* and *Trichilia heudelotti* leaf extracts were very active even against *E. coli* and *P. aeruginosa*. The extracts were partitioned into n-hexane, $CHCl_3$, EtOAc, and aqueous fractions and tested against fifty bacteria clinical isolates along with thirteen antibiotics. At ≤5mg/ml, the $CHCl_3$, and aqueous fractions of *T. heudelotti*, $CHCl_3$, and EtOAc of *M. tomentosa* gave the highest inhibition that was stronger than their corresponding methanol extracts. The radical scavenging abilities of the methanol extracts of the ten medicinal plants using rapid DPPH tlc screening was carried out; again *M. tomentosa* and *T. heudelotti*, gave very impressively strong antioxidant activities. *Massularia acuminata* with the highest antioxidant activity showed no antimicrobial activity. The results showed that *M. tomentosa* and *T. heudelotti* could be further exploited for chemotherapeutic agents that could be used against infections caused by multiple antibiotic resistant strains, very common in Nigeria. These activities justified the ethnomedical uses of these plants (Aladesanmi *et al.*, 2007).

2. Cardiovascular Activity

It has been established unequivocally that cardiovascular, heart disease or precisely heart attack is the number one killer of both male and female and the incidence is rising at alarming rate. This prompted our screening of plants for biological activities on the cardiac muscle which was supported with OAU Grant 1427BK: "Phytochemical and Pharmacological Studies on some selected Cardioactive Nigerian Medicinal Plants". In this connection,

(i) The cardiac effects of ten Nigerian medicinal plants with twenty six extracts were examined on isolated, electrically-driven and spontaneously-beating atrial muscles of the rat, guinea-pig and lizard. The extracts (100-800 ìg/ml) induced either positive or negative concentration-dependent inotropic and/or chronotropic responses. Twenty-two out of the twenty-

six extracts demonstrated significant ($P < 0.05 - 0.001$) cardioactivity, acting directly on the cardiac muscle. The effects of most of the extracts are inhibitory on both the amplitude and frequency of atrial contraction. Only extract of *Morinda lucida* leaves and root produced pronounced excitatory effects on the amplitudes of contraction. The results obtained with *Pleioceras barteri* rootwood and *Thevetia neriifolia* kernel showed a significant inhibitory effect followed by cardiac arrythmia and finally cardiac arrest (Ilesanmi *et al.*, 1988; Aladesanmi *et al.*, 1986).

(ii) Dysoxylum lenticellare, the cardiac effects of the leaf methanol extract and ten isolated pure compounds of *Dysoxylum lenticellare* Gillespie were examined *in vitro* on isolated, spontaneously beating, a trial muscles of rat. The extract (8×10^{-4} g/ml) induced negative chronotropic and positive inotropic responses. It demonstrated significant ($P < 0.05$-0.01) cardio activity. Of the ten compounds tested, Dysoxyline, homolaudanosine (new isoquinoline alkaloids) and 3-epi-12-Hydroxy-schelhammericine demonstrated significant cardiac effects. (Aladesanmi and Ilesanmi, 1987).

(iii) This experiment was repeated in the following year (Adewunmi and Aladesanmi, 1988), *in vivo* in cats with the use of phyllocladene as reference compound because it was found in our earlier experiment (Adewunmi and Aladesanmi, 1988) to be a very active cardio depressant agent on *B. glabrata*. The cardio-depressant effects produced by phyllocladene and the methanolic extract of *D. lenticellare* were antagonized by atropine, suggesting that these effects may be mediated through cholinergic mechanism. The extract (200 ìg/kg, i.v.) significantly ($P < 0.05$) reduced the arterial blood pressure of anaesthetize cats (Adewunmi and Aladesanmi, 1988).

3. Molluscicidal, Trypanocidal Activity

Molluscicides are agents toxic to snails (Molluscs). Although generally harmless to humans, some snails, most notably of the genera *Biomphalaria, Bulinus* or *Oncomelania*, are directly implicated in the transmission of schistosomiasis (bilharzia). This parasitic disease

is endemic throughout South America, Africa and the Far East, affecting more that 200 million people in over 70 countries (Marston and Hostettmann, 1985).

(i) Schistosomiasis is perhaps second to malaria as a health problem in Africa out of the six TDR (WHO/World Bank sponsored Project on Tropical Diseases Research) diseases. About 141 million people on the African continent are infected with this tropical disease caused by water borne parasites. Research into finding cheap molluscicides led to a look at plants and several plants have been screened all over Africa for molluscicidal activity. Noteable amongst them are the Endod, *Phytolacca dodecandra*, *Swartzia madagascariensis* and *Tetrapleura tetraptera* (Aridan) (Sofowora, 1993, Aladesanmi, 2007).

(ii) In realization of the importance of molluscicides in this society, therefore I began work on *Dysoxylum lenticellare* Gillespie (Meliaceae). First, the leaves and stem were extracted with methanol and tested for activity. The methanolic extract of the leaves produced 100% mortality to *B. glabrata* at 100mg/L while that of the stem gave 60% mortality. The 2 terpenes, 7 alkaloids and a phenone isolated (Aladesanmi *et al*, 1983) were tested and p-Hydroxy-acetophenone was the most active (100% at 6ppm), followed by 2,7-dihydrohomoerysotrine (90% at 6ppm), while dysazecine has the least activity (0% at 8ppm and 50% at 20ppm). All the compounds were found to possess cardiodepressive properties (Adewunmi and Aladesanmi 1988).

(iii) In continuation of the work, a novel homoerythrina-derived alkaloid with molluscicidal activity, named lenticellarine, along with 7 other alkaloids were isolated from the leaves of *D. lenticellare*. Lenticellarine proved to be moderately molluscicidal against the snail *Biomphalaria glabrata*, LC_{75} = 100ppm, LC_{50} = 40ppm within 24 hours (Fig. 11) while others showed stronger activity but were known (Aladesanmi *et al.*, 1988).

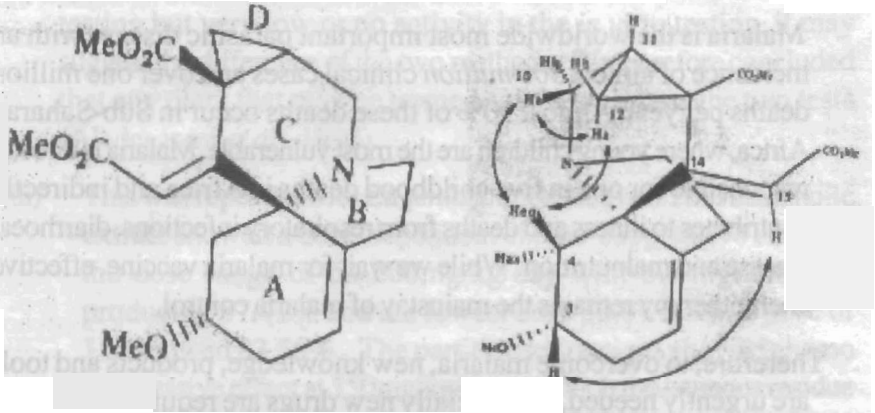


Fig 11: Nuclear Overhauser enhancements used to determine stereochemistry of the cyclopropane ring and the Ä 14-15 double bond of Lenticellarine, from 2D-NOE spectrum.

(iv) The work on the stem of *D. lenticellare* in which the methanolic extract was reported to give 60% mortality to *B. glabrata* at 100mg/L was further purified. Two new alkaloids. 3-epi-2, 18-dimethoxy-schelhammericine and lenticellarine and a new diterpene, 8â – methoxysandaracopimarene were isolated and tested against *B. glabrata* Say and fouind to possess molluscicidal activity though highest with 3-epi-2, 18-dimethoxyschelhammericine and lowest in lenticellarine, a decrease which may be due to the disruption of the homoerythrina skeleton (Aladesanmi and Adewunmi, 1990).

(v) A novel spiroketal (fused) diterpene, ferrubietolide isolated from the leaves of *D. lenticellare* and tested for molluscicidal activity against *B. glabrata,* activity which compared favourable with niclosamide. It was concluded that the activity of the *D. lenticellare* leaves extract is due to the presence of ferrubietolide and its congeners (Aladesanmi and Adewunmi, 1995). In the same vein, the alkaloids isolated from *D. lenticellare* to date represent the first alkaloids to have molluscicidal activity.

4. Antimalarial Activity

Malaria is the worldwide most important parasitic disease with an incidence of almost *300 million* clinical cases and over one million deaths per year. Almost 90% of these deaths occur in Sub-Saharan Africa, where young children are the most vulnerable. Malaria is directly responsible for one in five childhood deaths in Africa and indirectly contributes to illness and deaths from respiratory infections, diarrhoeal disease and malnutrition. While we wait for malaria vaccine, effective chemotherapy remains the mainstay of malaria control.

Therefore, to overcome malaria, new knowledge, products and tools are urgently needed, especially new drugs are required.

(i) With a Research Grant 1427BM – "Search for new sources of antimalarial drugs of plant origin", from the University Research Committee (URC), we embarked on the *in vivo* and *in vitro* screening of the different parts of nine Nigerian medicinal plants for their antimalarial activities (Aladesanmi *et al.*, 1988). Seven plant methanolic extracts were evaluated *in vivo* against N. strain of *Plasmodium berghei berghei* in a four day suppressive test in mice and had an ED_{50} values of 100-500mg/kg/day. Another twenty one plant extracts were tested *in vitro* utilizing the inhibition of intake of (G-^3H) – hypoxanthine into the multi-drug resistant, K – 1 strain of *Plasmodium falciparum* cultured in human blood.

On an early (*in vivo*) infection, *Alstonia congensis, congensis, Ocimum gratissimum,* (Efinrin) *Sarcocephalus latifolia,* (Igbesi) and *Gossypium arboreum,* (Owu) were effective in suppressing malaria infection while *Newbouldia leavies* (Akoko) failed with uninfected washed red blood cells. In the *in vitro* test, activity was more pronounced in the stem of *S latifolia* than the leaf. *A. congensis* possessed the highest activity while *Newbouldia leavies* showed the lowest activity. Our findings indicated that *Gongonema latifolium* (Ewurodo) was the most active followed by *Azadirachta indica* (Dogoyaro) while *S. latifolia* showed the least activity (>500

ig/ml). As the activity of *S. latifolia* was appreciable in the *in vivo* testing but very low or no activity in the *in vitro* testing, it may suggest the difference of the two methods. We therefore concluded that any plant that may be termed active must pass the two tests (Aladesanmi *et al.*, 1998).

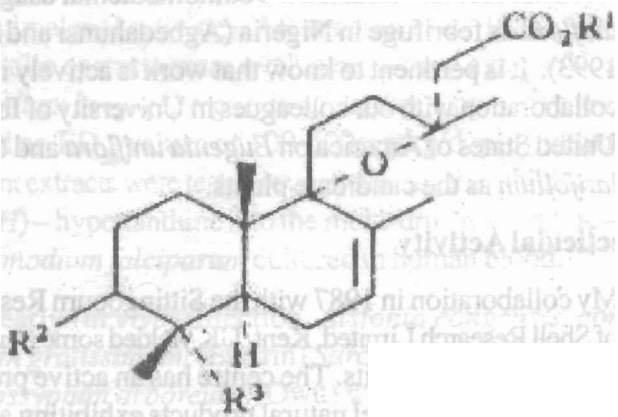
(ii) This was repeated with *Eugenia uniflora* leaves. The methanolic extract showed a dose-dependent chemo-suppressive effect in the dose range of 50-200mg/kg/day with the highest dose producing 87.42% and the lowest dose 39.87% while dose of 150 showed 83.56%. The partitioned fractions showed chemo suppressive effect at 150mg/kg/day in which the aqueous residue produce 88.53%, ethylacetate (63.47%), chloroform (43.55%) and petroleum ether showed no activity at all. The chemo suppressive activity of the plant is a function of the polarity and that the anti-malarial principle must be polar compound(s). This work has further validated the ethnomedicinal usage of *Eugenia uniflora* as febrifuge in Nigeria (Agbedahunsi and Aladesanmi, 1993). It is pertinent to know that work is actively in progress in collaboration with our colleagues in University of Ibadan and the United States of America on *Eugenia uniflora* and *Gongronema latifolium* as the candidate plants.

5. Insecticidal Activity

(i) My collaboration in 1987 with the Sittingbourn Research Centre of Shell Research Limited, Kent, UK yielded some mutual scientific and economic benefits. The centre has an active programme on the discovery of novel natural products exhibiting agrochemical activity. My work here involved the screening of six new and novel alkaloids, 18 - Methoxy – 3 – epi-Schelhammericine, Lenticellarine,12 – Hydroxy – 3 – epi-schelhammericine, Dysazecine, Dysoxyline and Homolaudanosine (Aladesanmi *et al., 1983, 1984, 1988 and* Aladesanmi and Hoffmann, *1994)*, isolated from the leaves and stem of *Dysoxylum lenticellare*

Gilespie, were found to be active against vine downg mildew though at low level.

(ii) I had the opportunity of spending my 1989/90 sabbatical leave at the University of Arizona, Office of Arid Lands Studies, Bioresources Research Facility, Tucson, Arizona, U.S.A. during which I worked on arid/desert land plants for insecticidal activity. In a collaboration on natural insecticides with a Japanese Company, I worked on *Grindelia camporum* (Asteraceae) and isolated several compounds of which grindelic acid was the most active. In order to potentate its activity, microbial transformation of grindelic acid by a culture of *Aspergillus niger* produced new 3-ketogrindelic acid and the known grindelanes (8-hydroxygrindelic acid, 7 á – 8 á - epoxy grindelic acid and methyl-3- â-hydroxygrindelate (Aladesanmi and Hoffmann, 1991).



R^1	R^2	R^3	
Me	P%O	Me	(3-ketogrindelic acid)

CONCLUSION

Natural products still play a major role as drugs, and as lead structures for the development of synthetic molecules. About 50% of the drugs introduced to the market during the last 20 years are derived directly or indirectly from small biogenic molecules. Screening for new drugs in plants implies the screening of extracts for the presence of novel compounds and an investigation of their biological activities. It is currently estimated that approximately 420,000 plant species exist in nature. For the purpose of lead discovery, or for scientific validation of a traditional medicinal plant or a phytopharmaceutical active principles in complex matrices, phytochemistry needs to be centered. Therefore, the interfacing of biological and chemical assessment becomes the critical issue.Drug discovery from plants can be guided by new isolation technologies and epidemiologic studies facilitated with computer assisted HPLC micro-fractionation and microplate technology. Epidemiologic studies have shown that high dietary flavonoid intake may be associated with decreased risk for cardiovascular disease.

Although a lot of research to discover new, effective and cheap drugs is in progress in the disease endemic developing countries, it is not yet possible to fully develop leads and drug candidates from natural products, hence, people in these countries continue to rely on traditional medicines. Poor economies and technological capabilities, lack of human resources (experts), and good management and possibly government non chalant attitude or policy in these countries are the major constraints to progress in research and development work for new drugs (Nyigo and Malebo, 2005; Okujagu *et al.*, 2005).

During my about three decades of search in the jungles of Fiji and Nigerian forest in my phytochemical pursuit to date, I have worked on 40 plants from which I have isolated, characterized and identified 108 compounds (alkaloids, terpenes, flavonoids, coumarins and phenolic acids), out of which 28 are new while 7 are novel bioactive natural products. This has provided the scientific template for the exploitation of some medicinal

plants for future development as anti-infective, anti-malarial, cardiovascular, insecticidal and molluscicidal agents.

I have equally been widely published in science journals around the world, as many (32) of my publications in form of reprints and/or authentic samples were requested for by various scientists all over the world. I think I can now answer to a Traditional Medicine Scientist amongst the 49 of such in Obafemi Awolowo University. This has been made possible by scholarships, fellowships and research grants received, which include the Federal Government of Nigeria, Obafemi Awolowo University, Ile-Ife, University of Arizona, Tucson, U.S.A. and Deutscher Akademischer Austauchdienst (DAAD). In the course of my career, I have produced two Ph.Ds. (Drs. C. A. Adebajo and Khan He) and six M.Sc. graduates of this University now in different positions while currently training two Ph.D, two M.Phil. and one M.Sc. students.

I thank God for the opportunity to be alive today to give this inaugural lecture and that my modest contribution is possible through the co-operation of these students as listed in Table 1.

In order to appreciate and complement the frantic efforts of our scientists, it is hoped that the Nigerian Institute for Pharmaceutical Research and Development (NIPRD), Abuja will take its rightful place in the area of natural products and drug development by forming effective collaboration with Nigerian Scientists and other stakeholders, otherwise, the volume of isolated bioactive compounds would only be good as archieve materials. With advances in technology, biotechnology, plant tissue culture and separation techniques, it may not be too long when random sampling combined with automated high-throughput screen (HTS) may come to the forefront in drug design, enabling extensive libraries of active compounds to be built up as an entire rain forest can be screened at pharmaceutical industry's laboratories and rendering our ethnobotanical, local knowledge of fauna and flora largely irrelevant.

Table 1: Present position of Trained Postgraduate Students

NO.	PG STUDENT	DEGREE	YEAR	PRESENT POSITION
1.	Mr. O. J. Femi-Ola	M Sc.	1988	Chief Pharmacist, State Hospital, Ado-Ekiti and a Ph.D. candidate, Faculty of Administration O.A.U. Ile-Ife.
2.	Dr. C. A. Adebajo	M Sc. Ph.D.	1988 1997	ReaderDepartment of Pharmacognosy, O.A.U., Ile-Ife.
3.	Mr. S. A. Odediran	M Sc.	1988	Chief Pharmacist, Health Centre, O.A.U., Ile-Ife.
4.	Mr. E. O. Ogunti	M Sc.	1990	U.S.A.
5.	Dr. Rene Nia	M Sc.	1994	Senior LecturerDepartment of Pharmacognosy, University of Uyo, Uyo, Akwa- Ibom State.
6.	Dr. Khan He	Ph.D.	1995	Professor of Pharmacognosy, Purdue University, West Lafayetta, IN, U.S.A.
7.	Dr. K. K. Ajibesin	M.Sc.	1996	LecturerDepartment of Pharmacognosy, University of Uyo, Uyo, Akwa- Ibom State.

Therefore, training programmes in modern drug design and development should very urgently become an integral part of both Universities and national policy of developing economies of the world.

Hence, in conclusion, a multidisciplinary approach to drug discovery involving the generation of truly novel molecular diversity from natural product sources, combine with total and combinatorial synthetic methodologies provides the best solution to increase the productivity in drug discovery and development (Vuorela *et al.*, 2004; Peterson *et al.*, 2005).

Mr. Vice-Chancellor, Sir, Principal Officers, distinguished guests, ladies and gentlemen, in the course of my lecture, I have reviewed the past-covering about five decades, the current trend and insight into the future of natural products chemistry, my three decades of humble contribution to this field of scientific innovation, medical and economic impact of this unique multi-facet science known as natural products chemistry. I have also proffered some solutions as a way forward. It is therefore my hope that the stakeholders will begin to appreciate the pains, frustrations and sacrifices of a developing world natural products chemist and of course, all scientists, in drug research, design and development to tackle the plague of the human race. I want to conclude by leaving you with, in the words of late Professor Varro E. Tyler of Purdue University, U.S.A., an internationally renowned expert in the field of Pharmacognosy and Botanical Medicine in his review of Medicinal Plant Research 1953 – 1987 (188), "the most productive period of medical plant research lies ahead of us somewhere, perhaps under our very noses, lies that one plant, the constituent of which will certainly cure cancer, AIDS, or even protect against the affliction of old age".

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