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FROM GREENS INTO MEDICINE: TAKING A LEAD FROM NATURE

By

Abiodun Oguntuga Ogundaini
Professor of Pharmaceutical Chemistry

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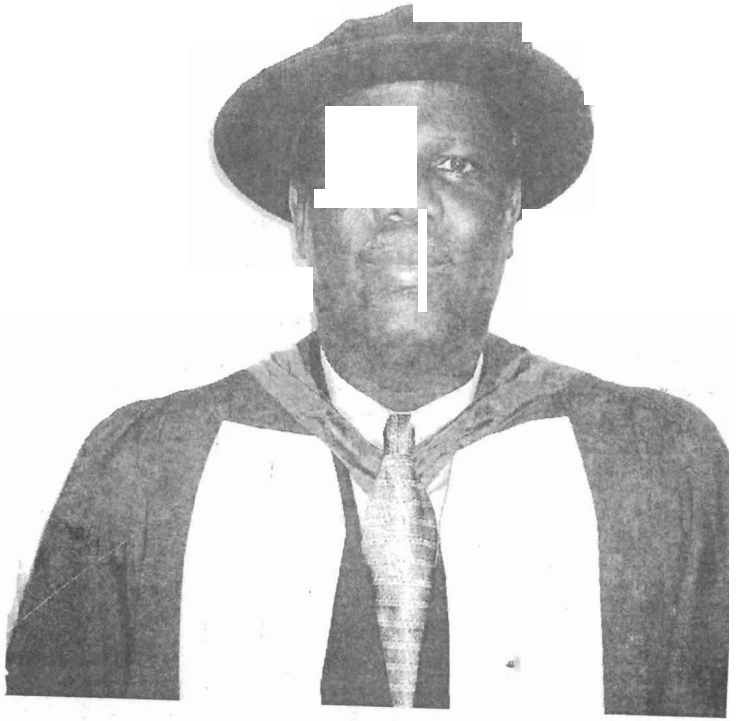

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INTRODUCTION

It is with great pleasure that I stand before this gathering today to deliver the 2nd Inaugural Lecture emanating from the Department of Pharmaceutical Chemistry, Faculty of Pharmacy of this university, albeit in a different area of specialisation from the first lecture. According to Prof. Halstead at the fourth in the series of Inaugural Lectures in Ife, "an Inaugural Lecture is an occasion to survey one's field, to explain what it is one does, to demonstrate its relevance and to place one's own contribution into their general perspective". Therefore, Mr. Vice-Chancellor, permit me to once again remind the audience what medicinal chemistry is, and the different areas in which a practitioner may function.

Medicinal chemistry is the chemistry of drug substances used in medicine. The chemistry of drugs embrace its development from natural or synthetic sources, its chemical properties which affects the formulation, mode of action, qualitative and quantitative analysis, identification and preparation of its metabolic products and the relationship between its molecular structure and biological action. It is an interdisciplinary subject requiring a sound knowledge of several contributing sciences. Hence, a practitioner may function in one or more of the following different areas.

Synthetic medicinal chemistry – This is an area of practice where chemists prepare and/or select appropriate compounds for biological evaluation, which if found to be active, could serve as lead compounds. A lead compound is a chemical structure or series of structures that show activity and selectivity in a pharmacological or biochemically relevant screen. Having secured a lead, analogous compounds are prepared and evaluated with regard to their *in vitro* and/or *in vivo* efficacy and safety, for a Structure-Activity-Relationship (SAR) study, to maximize the desired activity. SAR is the correlation of structural features with the activity of compounds in a given biological assay. A recent development in synthetic medicinal chemistry is combinatorial chemistry. This is an integral part of the drug discovery process, which aims at preparing libraries of compounds by combinatorial variation of building blocks that is, elaborating the common core (structures responsible for activity) by

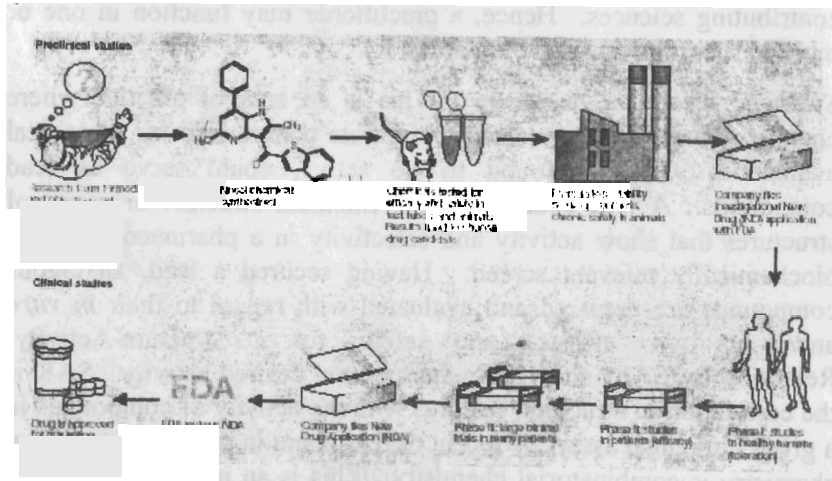
attaching combination of fragments to reactive sites in the core's periphery.

Natural Product Chemistry – This involves bioprospecting, isolation and characterisation of biologically active compounds from different natural sources such as plants, animals, marine organisms, microbes, etc.

Pharmacokinetics and Drug metabolism – This area, which was the subject of the first Inaugural Lecture in the department of Pharmaceutical Chemistry (Ogunbona, 1995), dealt with the processes of absorption, distribution, metabolism and elimination by the body, of administered drugs.

Pharmaceutical Analysis – an area in which appropriate analytical methods, are applied to determine the amount of active ingredients in raw materials and finished drug products, as well as, detect impurities. This is as much a separate field as it is a component of the other areas in medicinal chemistry.

All the above-mentioned areas are essential for drug development as shown in Scheme 1.



Scheme I – Necessary steps in Drug Development {from *Nature Reviews-Drug Discovery* (2004) **3**, 854}

Mr. Vice Chancellor, I have functioned mostly in the areas of Natural Product and Synthetic Medicinal Chemistry, which belong to the very first stages in the drug discovery and development process. Hence, the title of this lecture "*From greens into medicine: Taking a lead from nature*". The lecture will describe, using examples from my research, the biological activities of plants used locally in the treatment of diseases and, the isolation and characterisation of bioactive compounds from them. Examples will also be given of synthetic modifications to bioactive compounds from nature, towards understanding their mode of action and optimising their reported biological activities.

The Role of Nature in Health Care Delivery

For thousands of years, the products of nature supplied the only medicines for human ills and most of these remedies were obtained from higher plants. Plants, in reaction to stress, infection, danger or environmental changes, produce a wide range of diverse chemicals, secondary metabolites, which are not essential for their primary metabolism. Many of these complex molecules have therapeutic potential for a number of human ailments and are useful as medicines. Classical examples include, morphine obtained from the latex of the poppy, *Papaver somniferum*; quinine from *Cinchona* bark, atropine from *Atropa belladonna* and digitoxin from *Digitalis purpurea*. More recent examples include artemisinin from the Chinese plant *Artemisia annua* (Trig, 1989) for the treatment of malaria, and taxol, which is used in the therapy of metastatic breast cancer, from *Taxus brevifolia* (Lenaz, 1993).

In spite of the influence of modern medicine, about 80% of the rural population in Nigeria depends on herbal medical care for their health needs. The country is blessed with a great variety of medicinal plants, but unlike in India, China and Vietnam where traditional medicine has been researched, developed and integrated with the formal health care system, the situation in Nigeria is that many of the plants/remedies utilised in traditional medicine have not been subjected to any scientific study to validate their uses. Thus, the thrust of my research is to establish the scientific basis for the ethnomedicinal use of plant

materials prevalent in the local environment, especially in the treatment of infection. The focus on anti-infective agents has been deliberate because infections constitute the most frequent cause of morbidity and mortality in developing countries, such as Nigeria. Within this focus, I have investigated the antimicrobial, anti-inflammatory and antioxidant activities of plant extracts and isolated bioactive and other compounds of interest. The ultimate objective is not primarily to isolate compounds that will enter the pharmaceutical industry as new lead compounds, but to make it possible for plants and plant products to be effectively utilised within the health care delivery system through the formulation of materials with acceptable toxicity level into stable, and affordable pharmaceutical dosage forms. Where possible, isolated compounds, could serve as pointers or leads in the syntheses of superior agents, or as markers in the quality control of herbal drugs. For example, high quality *Gingko biloba* extract, used for treatment of various disorders is normally standardized to 24% gingko flavone glycosides and 6% terpene lactones.

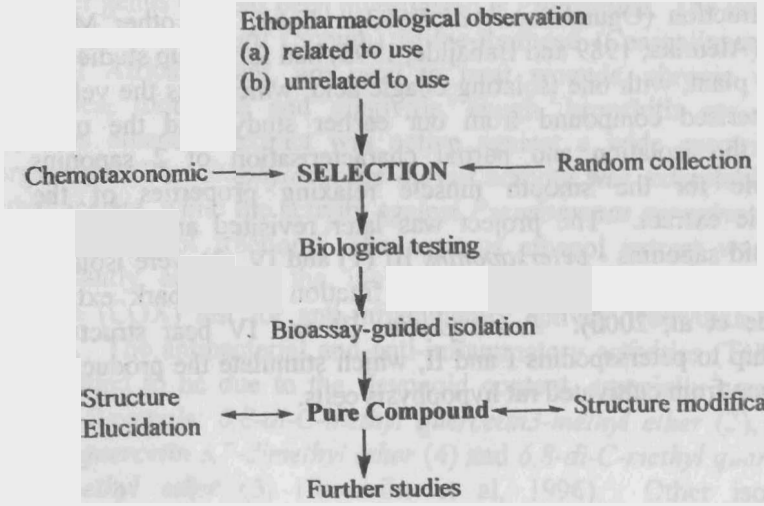
Biological screening

In order to validate activity and isolate/characterise the compounds responsible for activity from medicinal plants, it is crucial that suitable biological tests for monitoring the required effects are used. Such tests should ideally be simple, rapid, reproducible and inexpensive. Thus, the initial step necessitates that many potential plants be evaluated against a biological assay or panel of assays, and those which achieve a certain criterion for activity are moved to the next phase.

Since plants used against infection are the main focus in my research, tests that kill, or at least inhibit the growth of, microorganisms and/or stimulate the immune system are used to assess their value. Extracts of plants used in ethnomedicine in the local environment to treat infections were screened *in vitro* for antimicrobial activity, against type organisms and clinical isolates, using the classical cup-plate method and/or bioautographic techniques. Since the exquisitely modulated defense systems used by higher animals to ward off infections are inflammation, fevers and acquired immune responses,

the panel of assays has also been extended to the search for anti-inflammatory and antioxidant principles from these plants. Thus, the bioassay modelled on the inhibition of the cyclooxygenase (COX) enzymes, and the carragenin-induced oedema of the rat paw, have been employed to screen for anti-inflammatory activity. The rapid 1, 1-diphenyl-2-picrylhydrazyl (DPPH) and β-carotene thin layer chromatographic (tlc) methods were used for antioxidant activity.

The approach adopted in my research is to collect and extract plant materials based on ethnomedicinal information and then screen them for potential biological activity (antimicrobial, anti-inflammatory and antioxidant activities). About 300 plant species belonging to over 30 genera, used within the local environment to treat infections were screened over the last 20 years. Plants with promising activities based on comparative ranking were studied and are currently being studied in detail, using bioactivity-guided fractionation to isolate the compounds responsible for the observed activities (Scheme II). Some of the results and contributions from the study of such plants are now presented.

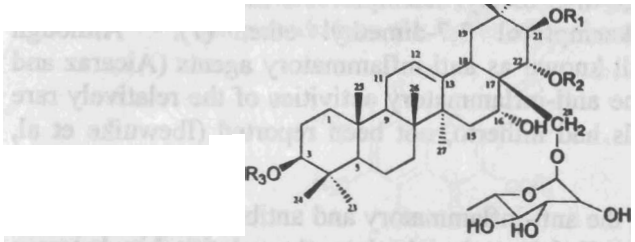


Scheme II Scheme for isolation of bioactive compounds from plant

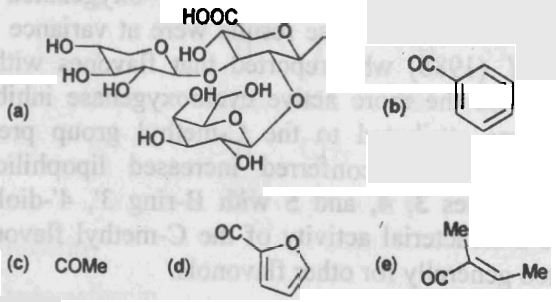
A. CONTRIBUTIONS TO NATURAL PRODUCTS WITH BIOLOGICAL ACTIVITIES

My introduction to natural product chemistry was in the year 1978 when I embarked on my M. Phil. degree project in this university, under the mentorship of Dr. Wolde Ab-Yisak, a dedicated and astute scientist. I worked on the stem bark of *Combretodendron macrocarpum* (P. Beauv) Keay {synonyms: *Combretodendron africanum* (Welw ex. Benth) Exell and *Petersianthus macrocarpus* (P. Beauv) Liben}, family Lecythidaceae.

The aqueous extract of the stem bark is traditionally used in the treatment of constipation, haemorrhoids, venereal diseases and as an abortifacient. It has also been reported that the ethanolic extract of the stem bark also produced hypotensive effects (Sandberg and Cronlund, 1982.). The objective of our study was to conduct a phytochemical study of the plant with special reference to the hypotensive principles. With the limited experience I had then, some compounds were isolated - β-sitosterol, octacosan-1-ol, an unsaturated dicarboxylic fatty acid and a yellow uncharacterised compound, which displayed hypotensive properties with little effect on the heart rate from the butanol fraction (Ogundaini *et al*, 1983). Later, two other M.Sc. students (Alemika, 1989 and Babajide, 1995) had follow-up studies on the same plant, with one isolating ellagic acid, which was the yellow uncharacterised compound from our earlier study, and the other reported the isolation and partial characterisation of 2 saponins responsible for the smooth muscle relaxing properties of the methanolic extract. The project was later revisited and two new triterpenoid saponins - *petersaponins* III (**1**) and IV (**2**) were isolated and characterised from the *n*-butanol fraction of the bark extract (Olugbade et al, 2000). *Petersaponins* III and IV bear structural relationship to petersaponins I and II, which stimulate the production of hormone from cultivated rat hypophysis cells.



1. R_1 = b, R_2 = a, R_3 = a
2. R_1 = d, R_2 = e, R_3 = a

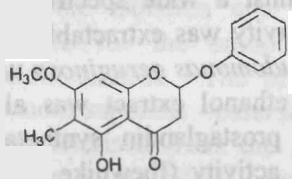


Another genus that has been investigated is *Piliostigma*. The leaves of *Piliostigma thonningii* (Schum) Milne-Redhead (Ceasaplinaceae), a tropical African plant, are used to treat wounds, chronic ulcers, diarrhoea, toothache and gingivitis, cough, bronchitis etc. The aqueous ethanolic extract was active against a wide spectrum of organisms. The *Staphylococcus aureus* activity was extractable into ethyl acetate, while the activity against *Pseudomonas aeruginosa* was in the *n*-butanol fraction. The aqueous ethanol extract was also significantly active in the inhibition of prostaglandin synthetase enzyme (COX) test for anti-inflammatory activity (Ibewuike et al, 1997a). The antibacterial and anti-inflammatory activities (Table 1) were found to be due to the flavonoid content, especially novel C-methyl flavonols: *6,8-di-C-methyl quercetin3-methyl ether* (**3**), *6-C-methyl quercetin 3,7-dimethyl ether* (**4**) and *6,8-di-C-methyl quercetin 3,7-dimethyl ether* (**5**) (Ibewuike et al, 1996). Other isolated flavonoids contributing to activity include quercetin, quercitrin, 6-C-methyl quercetin 3-methyl ether, 6-C-methyl quercetin 3,3,3'-

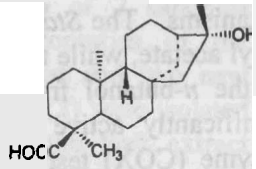
trimethyl ether, 6,8-di-C-methyl kaempferol 3-methyl ether (**6**) and 6,8-di-C-methyl kaempferol 3,7-dimethyl ether (**7**). Although flavonoids are well known as anti-inflammatory agents (Alcaraz and Jimenez, 1988), the anti-inflammatory activities of the relatively rare C-methyl flavonols had hitherto, not been reported (Ibewuike et al, 1997b).

A detailed look at the anti-inflammatory and antibacterial activities of these compounds offered an insight into the relationship between structure and observed biological activities in these series of compounds. The compounds with B-ring 3', 4'-diol group (**3, 4, 5**) were generally more potent than the 4'-oxygenated derivatives (Ibewuike et al, 1997b). These results were at variance with that of Moroney *et al.* (1988) who reported that flavones with B-ring 4'-oxygenation were the more active cyclooxygenase inhibitors. This discrepancy was attributed to the C-methyl group present in our compounds and which conferred increased lipophilicity on the flavonoid molecules **3**, **4**, and **5** with B-ring 3', 4'-diol group. In contrast, the antibacterial activity of the C-methyl flavonols parallel those reported generally for other flavonols.

Additional two new compounds, *piliostigmin* (**8**), the first ever C-methyl phenoxy chromone reported in literature and *16α-hydroxy-kauran-18-oic acid* (**9**), a diterpene, were also isolated from *P. thonningii* (Ibewuike et al, 1996: Martins et al, 1997).

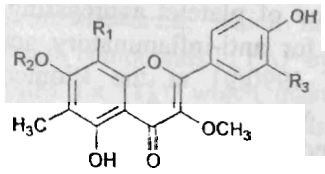


8. Piliostigmin (a phenoxychromone)



9. 16α-hydroxy-(-)-kauran-18-oic acid (a diterpene)

TABLE 1 Antibacterial and anti-inflammatory activities of isolated compounds from the leaves of *P. thonningii*.

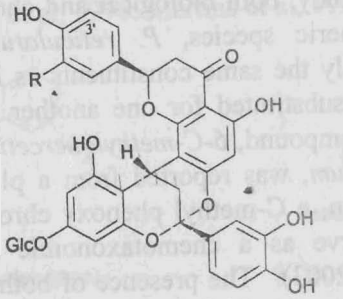


COMPOUNDS	R_1	R_2	R_3	IC_{50} (μM)	MIC (mM)
3	H	CH_3	OCH_3	4.53	-
4	H	H	OH	55.42	0.031
5	CH_3	H	OH	23.08	0.125
6	H	CH_3	OH	25.99	1
7	CH_3	H	H	-	0.125
Aspirin				953	-
Indomethacin				0.246	-
Chlorocresol				-	0.125

A comparative study, both biological and chemical, on the leaves of the only co-generic species, *P. reticulatum*, revealed that they contained basically the same constituents as *P. thonningii* and could be conveniently substituted for one another in ethnomedicine. An additional new compound, *6-C-methylquercetin-3,3',4'-trimethyl ether* from *P. reticulatum*, was reported from a plant source for the first time. Piliostigmin, a C-methyl phenoxy chromone common to both plants, could serve as a chemotaxonomic marker for the genus (Aderogba et al, 2003). The presence of both anti-inflammatory and antimicrobial flavonoids in both plants may explain their utility in treating infections, wounds and fever, as well as inflammatory conditions such as toothache and gingivitis.

My exposure to bioassays modelled on the inhibition of the cyclooxygenase (COX) enzymes, carragenin-induced oedema of the rat paw and inhibition of platelet aggregating factor (PAF)-induced exocytosis, as tests for anti-inflammatory activity, was during my sabbatical leave of 1990/91 at the Biomedical Centre, Uppsala University, where I worked on *Sarcophyte piriei*. The tests were subsequently included in our battery of screening tests and we had since acquired a plethysmometer for measuring oedema of the rat paw in our laboratory.

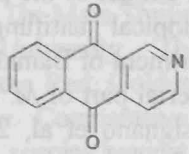
Sarcophyte piriei Hutch (Balanophoraceae; vernacular name, *diinsi*) is a parasitic plant that grows on the root of *Acacia* species. A decoction of its underground tuber is a popular folk remedy against bruises, toothache, sore throat and abdominal pain in Somalia. Preliminary evaluation of the aqueous extract showed that it has anti-inflammatory activity both *in vivo* in carragenin-induced oedema of the rat paw and, *in vitro* in the inhibition of prostaglandin synthesis, with activity comparable to aspirin. Two new flavano-flavanone glycosides, *diinsininol* (**10**), (5,7,3',4'-tetrahydroxyflavanyl-7-O-β-glucosyl-(4β-8;2β-O-7) eriodictyol and *diinsinin* (**11**) (5,7,3',4'-tetrahydroxy-flavanyl-7-O-β-glucosyl-(4β-8;2β-O-7) naringenin were isolated as being responsible for the anti-inflammatory activity (Ogundaini et al., 1996).



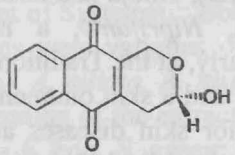
10. Diinsininol, R = OH
11. Diinsinin, R = H

Diinsininol and diinsinin exhibited IC_{50} values of 9.20μM and 13.14μM, respectively in the inhibition of prostaglandin synthesis assay compared with indomethacin, which had an IC_{50} value of 0.56μM. The IC_{50} for both compounds in PAF-induced exocytosis was 49μM for (**10**) and 39μM for (**11**), which makes them more potent inhibitors than the known PAF antagonist, ginkgolide BN 52021 (IC_{50} of 80μM), a terpene lactone, isolated from the tree *Ginkgo biloba* with similar ethnomedicinal uses to diinsi.

Mitracarpus scaber Zucc. (Rubiaceae) is a weed widely employed in traditional medicine in West Africa for headaches, toothaches, hepatic diseases etc. The juice of the plant is also applied topically for the treatment of skin diseases – infectious dermatitis, eczema and scabies. From the extract *of M. scaber* we have isolated six compounds including the alkaloid benz[g]isoquinoline-5,10-dione (**12**), psychorubrin (3-hydroxy 1H-3, 4-dihydronaphtho [2,3-c] pyran-5, 10-dione) (**13**) and pentalongin (Ogundaini, 1999; Houghton et al, 2000).



12. Benz[g]isoquinoline-5,10-dione



13. Psychorubrin

The isolated compounds and their Minimum Inhibitory Concentration (MIC) values against *Staphyloccocus aureus* NCTC 6571 are shown in Table 2. To date, benz[g]isoquinoline-5, 10-dione is the only 2-azaanthraquinone isolated from higher plants although some derivatives have been isolated from fungal cultures. Naphthoquinones are known to possess a wide range of biological activities including antibacterial and antifungal activities, and their presence in *M. scaber* may account for its traditional use in the treatment of fungal skin infections.

TABLE 2: MIC values of compounds isolated form *M. scaber* against *S. aureus*.

COMPOUND	MIC (µg/ml)*
Benz[g]isoquinoline-5,10-dione	12.5
Psychorubrin	3.125
3-O-Ethylpsychorubrin	6.25
Pentalongin	12.5
Tectoquinone	>25
2-Hydroxynaphthoquinone	>25
Gentamicin (control)	0.5

* in 10% methanol

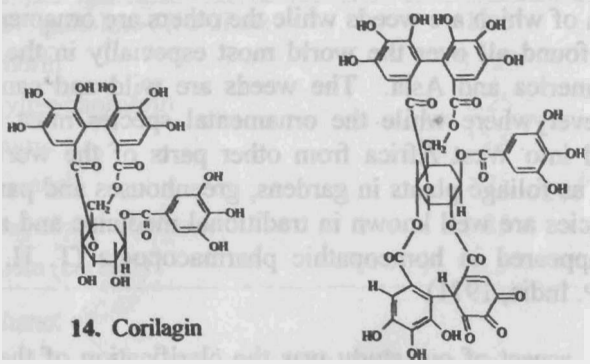
In fact, unknown to us at the time of the study was the fact that the National Institute for Pharmaceutical Research and Development (NIPRD), Abuja had already formulated an extract of the plant into a cream, *Niprifan*®, a highly effective topical antifungal agent. Similarly, at the Traditional Medicine Department of Bamako, Mali, a lotion and a skin ointment made with the aerial part of *M. scaber* are used for skin diseases and infections (Bisignano et al, 2000). *M. scaber* has also been reported to have radical scavenging properties as shown by its reaction with 1, 1-diphenyl-2-picrylhydrazyl radical (EC_{50} = 41.64±1.5µg/ml). No wonder a decoction of its aerial part was reported to have a significant hepatoprotective effect against carbon tetrachloride induced liver injury, both *in vivo* and *in vitro* (Germano et al., 1999). The ointment of *M. scaber* has also found use in veterinary medicine; when applied topically to chronic crusty or acute lesions of dermatophilosis in infected animals, cure is effected without recurrence (Ali-Emmanuel et al, 2003). The isolated active compounds could serve as markers for the quality control of these useful formulations.

Acalypha wilkesiana Muell Arg (family Rubiaceae) is variously administered in the treatment of bacterial and skin fungal infections. The expressed juice or boiled decoction, is used to treat *Pityriasis versicolor, Impetigo contagiosa, Tinea versicolor* and similar skin

infections, which affect the back, chest and the axillae of many infants in Nigeria (Oliver, 1959). These diseases are characterised by branning scales, itching, inflammation and lesions. The genus *Acalypha* comprises about 570 species (Riley, 1963), a large proportion of which are weeds while the others are ornamental plants. They are found all over the world most especially in the tropics of Africa, America and Asia. The weeds are wild and can be found growing everywhere while the ornamental species must have been introduced into West Africa from other parts of the world and are cultivated as foliage plants in gardens, greenhouses and parks. Some of the species are well known in traditional medicine and a few have actually appeared in homeopathic pharmacopoeia (T. H. P., USA, 1941; H. P. India, 1971)

The initial aspect of our study was the clarification of the botanical identity of *Acalypha* species locally available in Nigeria. This was achieved through the assistance of the Forestry Research Institute of Nigeria, and Dr. Mats Thulin of the Department of Systematic Botany of Uppsala University. The identified species were varieties of *A. wilkesiana* (the Red, Golden yellow and Lace), *A. ciliata, A. hispida* and *A. indica*. Comparative antimicrobial screening of the extracts of the six local species against typed organisms - *E. coli, S. aureus, Ps. aeruginosa, B. subtilis* and *C. pseudotropicalis*, showed that *A. wilkesiana* (Red Acalypha variety) and *A. hispida* demonstrated a broad spectrum of antibacterial and antifungal activities to warrant further studies. Subsequently, bioactivity-directed fractionation of the two Acalypha species revealed two ellagitanins, *corilagin* **(14)** and *geranin* **(15)** as the active principles (Adesina et al, 2000). Since corilagin could be a breakdown product of geranin, its natural occurrence in the plants was confirmed by thin-layer chromatographic examination of fresh leaves. Corilagin has been reported to show several biological activities, such as antifungal, antiviral, and antihypertensive effect in rats (Shimizu et al, 2001). In addition, Shimizu et al (2001), after isolating corilagin as the effective antimicrobial compound from *Arctostaphylos uva-ursi* (the leaves and extracts are described as medicine in the Japanese Pharmacopoeia), showed that it potentiates the activity of β-lactam antibiotics against methicillin resistant *Staphylococcus aureus* (MRSA). MRSA

infections are a recurring problem in hospitals, nursing and care homes, even in developed countries, where solutions to the problem are continuously being sought.



14. Corilagin

15. Geraniin

In pursuit of our objective of developing this abundant plant species into a standard pharmaceutical product of therapeutic value, an ointment of *A. wilkesiana* (red variety) was clinically evaluated in the treatment of superficial fungal infections in collaboration with Prof. A. O. Oyelami of the Department of Paediatrics and Child Health and Dr. O. Onayemi of Department of Dermatology and Venerology, both of the College of Health Sciences.

Superficial fungal infections are common in most tropical areas and developing countries with uncontrolled population growth, inadequate provision of accommodation and unsanitary living conditions. Most of the patients affected are from the socio-economic group that can ill afford imported antifungal creams, thus justifying the need for inexpensive and easily available alternatives. The clinical study was conducted at the General Outpatient Department, the Children Welfare Clinic and the Dermatology Unit of the Wesley Guild Hospital Section of the Obafemi Awolowo University Teaching Hospitals Complex between November 1996 and July 1997. The ointment of *A. wilkesiana* (red variety) was shown to be effective against some superficial fungal diseases such as *Tinea corporis* (Figures I and II), *Tinea pedis*, *Pityriasis versicolor* and *Candida intetrigo*. The overall

clinical response of patients to the ointment ranged between 54% and 100%. With the exception of *Tinea corporis*, all the patients had 100% cure rate. Those with *Tinea pedis* returned for the ointment until the lesions finally cleared, 6 months after the commencement of the treatment. One patient had an adverse reaction to the ointment and the drug was discontinued when excoriation became intolerable. Otherwise, in the study, there was no noticeable toxicity of the *Acalypha* ointment (Oyelami et al, 2003). All that is left for us to do is to develop a monograph for the quality control of the ointment, using the isolated active polyphenols as markers.

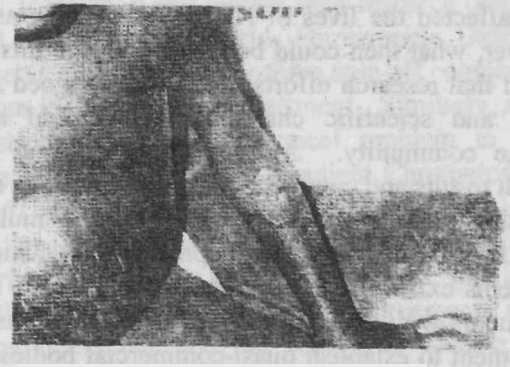


Figure 1. Patient with kwashiorkor and *Tinea corporis* before treatment.

Similar studies that had been carried out or are in progress in our laboratories include those on *Alchornea* species (Lamikanra et al. 1990; Okeke et al., 1999 and Adeloye, 2001); *Ficus* species (Adewumi, 1999 and Taiwo, 2004) and, lately, commonly available weeds used in ethnomedicine for which a University Research Committee (URC) grant was secured in 2002.

As a matter arising from all I have presented above, the logical question to ask is "how have the findings affected the lives of ordinary Nigerians?" Such a question is quite legitimate and deserves to be addressed on an occasion such as this. My answer to this question is that, it has not affected the lives of Nigerians as much as it should. Given this answer, what then could be done to bridge this gap? It is generally agreed that research efforts should be designed not only to meet academic and scientific challenges but should also be of relevance to the community. At present, a yawning gap exists between research results and commercialisation efforts. In most cases, the well-established pharmaceutical industries, usually multinationals, have a different focus in their drug development effort, which does not tally with problems existing locally. On the other hand, researchers are not entrepreneurs with capacity for development. Thus, there is a need for government to establish quasi-commercial bodies to take up the slack in order to encourage indigenous technological growth. In Nigeria, such established bodies include the Raw Materials Research and Development Council (RMRDC) and the National Institute for Pharmaceutical Research and Development (NIPRD). Their mandate is to commercially exploit research results on a pilot scale to assess the feasibility of mass production with the ultimate goal of getting entrepreneurs to take up production on a large scale. But, how far have they fulfilled this mandate? NIPRD has developed some plant based medicines which are in various stages of clinical trials: *Niprisan* (capsules and syrup) for the management of sickle cell disease; *Nipripan*, an antiulcer preparation and *Niprifan*, a highly effective topical antifungal agent, while RMRDC has sponsored some projects. The benefits of the government's massive investments in these bodies are yet to reach the masses and have also not been extended in concrete terms to Nigerian universities. It is my belief that encouragement of fruitful collaboration and joint ventures by these

bodies with Nigerian universities can serve in the long run as positive feedback for the supply of the much needed funds for research, if the products emanating from the relationship turn out to be successes.

Secondly, Nigerian business entrepreneurs are not assisting enough to translate research outputs from our universities and research institutes into tangible products for the use of Nigerians through investments on them. This is not limited to the pharmaceutical field, but common to all fields of research in the universities/research institutes.

Thirdly, another way out is to encourage researchers to establish spin off companies to develop and market their research output as done in the developed countries of the world. For example, Oxford University has an impressive record of twenty-three spin off companies with four emanating from the Chemistry Department. Similarly, a chemist, Dr. Peter Baeckstrom, to solve a practical problem in his research, developed the famous Accelerated Gradient Chromatography (AGC) assembly used routinely for separation in our laboratory. A company, Baeckstrom Separo, is now producing and marketing the AGC assembly worldwide. It must be stated, however, that at the point of setting up these companies, adequate agreement involving the university, the researcher and the source of finance are properly worked out with respect to the split in equity according to the inputs and contributions of the partners.

On a cheering note, however, a collaborator on the *Acalypha* project, Prof. Oyelami, has been improvising "*Acalypha* ointment" in the successful treatment of fungal skin diseases in his practice. I do hope that in the near future we will have him share the benefits of his experiences with us.

B. CONTRIBUTIONS TO SYNTHETIC MEDICINAL CHEMISTRY

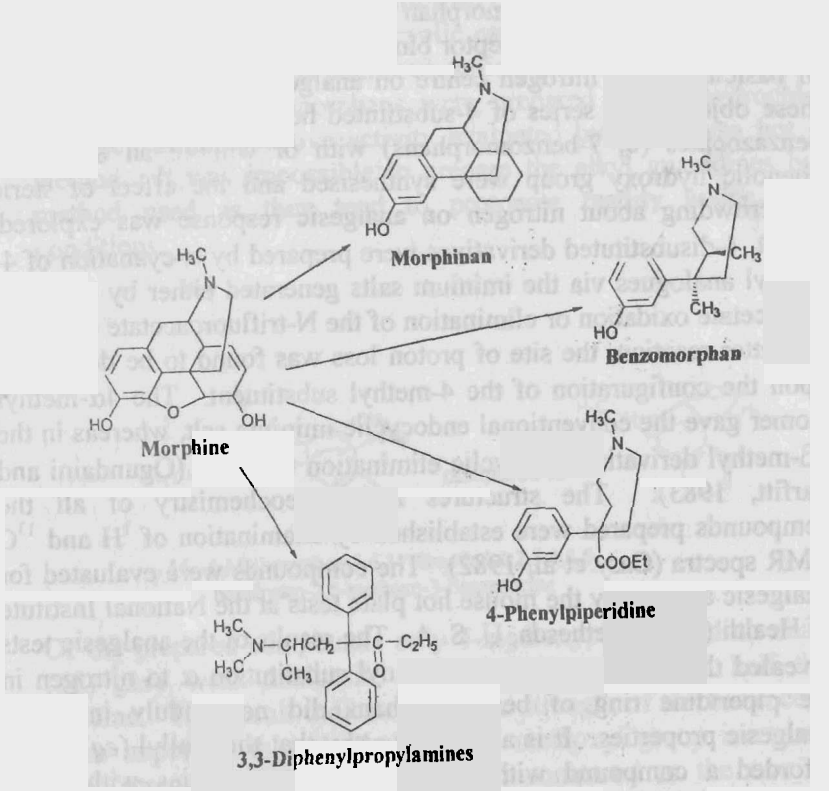
As the science of medicinal chemistry evolved, it became possible to isolate the active components from nature and modify then chemically to optimise the desired activity. Aspirin was the first successful example of using nature as a lead for new synthetic drug. Gradually synthetic chemistry became more important for developing new drugs

and no class of compounds typifies this development as much as the opiate analgesics.

No pain reliever has stood the test of time in a manner comparable to opium – the dried exudates from the unripe seed capsules of the poppy, *Papaver somniferum* L. It is known that the Sumerians, who lived in Mesopotamia, West Asia, about 4000 BC, recorded the medicinal values of opium on cuneiform tablets. The ancient Greeks and Romans also used opium as a soporific and painkiller, and in Europe in the early 19th century opium preparations, such as the pill and laudanum, were widely used. In 1805, a German chemist, Sertuner, isolated the main active compound, morphine. Morphine is a powerful analgesic, but with serious side effects: respiratory depression, constipation and dependence liability. Thousands of analogues (related to morphine or simplification of the molecule) have been synthesised to find analgesics with lower incidence of the side effects. Such analogues include **derivatives of morphine** such as codeine and heroin, **morphinans** e.g. levallorphan, **benzomorphans** e.g. pentazocine, **4-arylpiperidines**, e.g. pethidine and the **3, 3-diphenylpropylamine derivatives** e.g. methadone (Scheme III). The opiates are useful drugs in obstetrics and in terminal care patients, e.g. those with cancers. Though controlled under international and federal laws for good reasons, the policy on narcotic analgesics in Nigeria is ripe for a review, as they are now virtually non-existent in our hospitals for patients who are in dire need of them. There is an urgent need to address the role conflict among relevant regulatory agents such as NAFDAC, NDLEA and PCN to ensure that no undue obstacle is placed on the procurement and distribution processes.

My initiation into synthetic medicinal chemistry was in 1980, when with the award of a Commonwealth Scholarship tenable at the School of Pharmacy, University of Bath, UK, I joined the duo of Prof. R. T. Parfitt (my supervisor) and Dr. A. F. Casy (a mentor and guru of narcotic analgesic chemistry) in their continued effort to find narcotic analgesics without the side effects associated with morphine. My friend and colleague, the Late Prof. F. O. Ogungbamila, was already working on the reversed esters of pethidine while my own work was on the 6, 7-benzomorphans, projects that won the Janssen Prize for the

best research students in the School for both of us in the 1980/81 and 1981/82 sessions respectively.



Scheme III - Groups of Opiates from simplification of Morphine

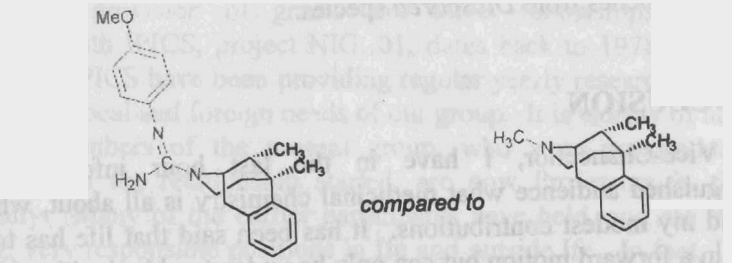
Beckett and Casy in 1958 first drew attention to the overall structural similarities of opiate agonists *viz.* the presence of an aromatic ring, a basic nitrogen centre and an hydrocarbon portion of the piperidine ring between the aromatic ring and the nitrogen centre (Scheme III) and the implications for receptor binding. They speculated on the nature of receptor-based structural requirements for analgesia. A receptor surface was formulated, which possessed a flat lipophilic surface binding the aromatic ring, a cavity to accommodate the hydrocarbon portion of the piperidine ring and anionic amine binding site (Beckett and Casy, 1958). The existence of opiate receptors was

unequivocally demonstrated in 1971, thirteen years after Goldstein et al, 1971).

My contributions to benzomorphan chemistry were on the influence of molecular geometry on receptor binding and assessment of the effects of basicity of the nitrogen centre on analgesic activity. To achieve these objectives a series of 4-substituted hexahydro-6-methano-3-benzazocines (6, 7-benzomorphans) with or without an 8-position phenolic hydroxy group were synthesised and the effect of steric overcrowding about nitrogen on analgesic response was explored. The 4, 4-disubstituted derivatives were prepared by α-cyanation of 4-methyl analogues via the iminium salts generated either by mercuric (II) acetate oxidation or elimination of the N-trifluoroacetate ester. In the latter reaction, the site of proton loss was found to be dependent upon the configuration of the 4-methyl substituent. The 4α-methyl isomer gave the conventional endocyclic iminium salt, whereas in the 4β-methyl derivative, exocyclic elimination occurred (Ogundaini and Parfitt, 1983). The structures and stereochemistry of all the compounds prepared were established by examination of ^{1}H and ^{13}C NMR spectra (Casy et al, 1982). The compounds were evaluated for analgesic activity by the mouse hot plate tests at the National Institute of Health (NIH), Bethesda, U. S. A. The results of the analgesic tests revealed that alkyl; aralkyl and alkenyl substitution α to nitrogen in the piperidine ring of benzomorphans did not unduly influence analgesic properties. It is also noteworthy that the 4-allyl (*eq*) group afforded a compound with good analgesic properties without an antagonist component, suggesting that the allyl group does not substitute spatially for an N-allyl function (Ogundaini and Parfitt, 1985).

Variation of the substituent on nitrogen in 2, 6-methano-3-benzazocine analgesics often result in dramatic changes in pharmacological responses. Analgesics related to morphine are believed to interact with their receptors by binding through the molecules' nitrogen centres either as the cation or the free base form (Casy and Parfitt, 1986). The examination of benzomorphans bearing amidino nitrogen substituent facilitated a comparison of the antinociceptive actions of compounds bearing a conventional tertiary

amine group with those bearing a novel guanidine basic centre. The idea was that 3-amidino-2, 6-methano-3-benzacocines will possess a more bulky basic pharmacophore with a shift in charge centre from an endocyclic nitrogen to an exocyclic carbon. In addition, guanidines are often stronger bases than their tertiary amine counterparts. Three aryl guanidino-benzomorphans were prepared as the hydrochloride and their antinociceptive activity evaluated by the mouse hot plate method. It was impossible to prepare the alkyl guanidines by the method used as they tend to protonate readily under reaction conditions.



16. 4-Methoxyphenyl-6,11-dimethyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine

Of the prepared compounds only 4-methoxyphenylamidino analogue (**16**) gave weak analgesia, ED_{50}, 22.1 mg/kg, about half that of codeine. This result indicated that the strength of the basic centre is more important than the bulk as the methoxyl group increased the basic strength of the guanidine (**16**) compared to the two others (Ogundaini and Parfitt, 1984).

Stilbenes and their dihydro-analogues, bibenzyls, occur naturally and under stress conditions in various plants, where the yields are often small after lengthy extraction processes. As a follow up on the bioactive stilbenes isolated by a colleague, Prof. Adesanya, in his research, we synthesised some bibenzyls alcohols, stilbenes and bibenzyls substituted only on one benzene ring. The compounds were evaluated for lethality to *Artemia salina* Leach nauplii (Brine shrimps) and inhibition of the germination of *Sorghum bicolor* L. seeds. The activities of the synthesised compounds were in both instances compared to that of dihydropinosylvin. 3-Hydroxy- and 4-hydroxy-

stilbenes were the most lethal to brine shrimp with LC_{50} of 1.48 and 1.03µg/ml respectively, whilst the bibenzyls were moderately active and the alcohols the least active. Dihydropinosylvin and its methylated derivative were the most active in the inhibition of seed germination tests ED_{50} of 0.33µg/ml and 0.67µg/ml respectively. Other bibenzyls, 4-hydroxybibenzyl (0.86µg/ml) and 4-methoxybibenzyl (0.88µg/ml) were also active. We concluded that for the stilbenes and bibenzyls a 3- and/or 4-hydroxyl group is important for activity (Sogbaike et al, 2002). Inhibition of seed germination may have implication for dormancy as reported for some dihydrostilbenes from *Dioscorea* species.

CONCLUSION

Mr. Vice-Chancellor, I have in the last hour informed this distinguished audience what medicinal chemistry is all about, what I do and my modest contributions. It has been said that life has to be lived in a forward motion but can only be understood by looking back. Looking back on my academic odyssey will necessitate making some observations that will assist that forward motion.

During the course of my lecture, I had already touched on the problems associated with translating research findings into tangible benefits for the masses of this country. In addition, there is the need to address the issue of resources available for research work: human, material and financial. A Kenyan colleague once said, "Nigeria has the human resources in all fields to service the whole of Africa". How very true this statement is, but the question is, what is the level of capacity utilisation of this resource? I daresay not up to 25% and the reasons for this are not far fetched. The financial resources available locally for research are not adequate to jump-start, for example, the once thriving and vibrant research culture of this university. To the extent that when staff members learn newer techniques and processes, as they normally should, they are hamstrung in applying the knowledge locally due to dearth of funds. The same problem of lack of funds affects equipment procurement, maintenance and repairs. The few laboratories that are able to conduct any meaningful research

are those supported by International Funding Agencies. Herein lies the challenge for all of us. We have to look inwards, to governments, industries, endowments etc for the financial input to optimally utilise our vast human resources.

It is appropriate at this juncture to acknowledge the various contributions of bodies like the International Program in Chemical Science (IPICS), University of Uppsala, Sweden and the International Foundation for Science (IFS), for sustaining our research group through the provision of grants and travel fellowships. Our association with IPICS, project NIG. 01, dates back to 1978. Since about 1990, IPICS have been providing regular yearly research grants to meet both local and foreign needs of our group. It is worthy of note that four members of the present group, who were postgraduate students when the relationship started, are now Professors in this University. Many of the earlier participants have held, and are still holding, very responsible positions in Ife and outside Ife. In fact, Dr. Wolde Ab-Yisak, who initiated the link, was the President of the University of Asmara, Eritrea, after a fruitful stint at the Astra Zeneca laboratories in Sweden. IPICS funds had trained a total of twenty-nine (29) students (M.Phil., 4; M.Sc., 19; Ph.D., 6) and generated an output of about sixty (60) publications over a period of sixteen years. Six other students, (one M.Sc and five Ph.D.) are currently at various stages of their research within the project. IPICS has enabled the group to establish enduring links with collaborators both within Africa and beyond. We have also established functional laboratories, which we are sure will be sustained beyond the period of our association.

Finally Mr. Vice-Chancellor, Stephen Covey in his book, The 7 Habits of Highly Effective People wrote, "Interdependence is a higher value than independence". I wish to say a big thank you to my teachers, my postgraduate students and especially my colleagues in IPICS NIG. 01, who have cooperated with me and combined their talents and abilities with mine to create something greater than any of us could individually achieve.

I also wish to express my gratitude to this distinguished audience who have listened patiently throughout this lecture.

Thank you and God bless.

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