FROM THE LAB BENCH THROUGH THE GARDENS TO THE APOTHECARY: JOURNEY SO FAR

BY

PROF. PATIENCE OGOAMAKA OSADEBE

The Vice-Chancellor, Prof Bartho N. Okolo
Principal Officers of the University
My Lords, Spiritual and Temporal
Dean, Faculty of Pharmaceutical Sciences, Prof Vin Okore
Deans of Faculty
Former Inaugural Lecturers of the University
Honourable Members of the University Senate
Former Dean of Engineering and a strong Associate of the Faculty of Pharmaceutical Sciences, Rev. Prof N. N. Osadebe (My better half)
Distinguished Invited Guests
Lions and Lionesses
Ladies and Gentlemen

It is my profound pleasure to have the honour to stand before you today to deliver the 69th inaugural lecture of this great citadel of learning. I want to thank our visionary Vice-chancellor for this awesome opportunity. I would be gainsaying if I stand here to tell you I am surprised that a day like this would come in my life. For, from my youth, I knew I was set for an academic life. Right back in 1983, in my final year in the then University of Ife (UNIFE, now

OAU), I set a goal for myself, (not guided by the flesh but I believe, by the Holy Spirit of God), that I would like to be an academic (a University Lecturer), marry an academic and settle in a University. The orderly and systematic manner in which things were done at UNIFE, coupled with the beautifully landscaped campus environment of that University campus was an additional motivation. My choice, besides the fact that it is linked to my destiny (God's purpose for me) was informed by a decision not to be part of the disgusting level of chaos and lawlessness I saw and encountered in life outside the University in those days. The undefined and chaotic level of pharmacy practice in Nigeria then also played a part. My desire to go to where I thought I belonged, was accentuated, when for two years I served at AMAKU General Hospital Awka, under the direct supervision of my senior colleague, Pharmacist P.O.Otegbulu (current Director of Pharmaceutical Services, Enugu State), I spent my life and time writing out doctors' prescriptions as out-of-stock (O/S) for the patient to go elsewhere to purchase. Most of the drug stores available then were patent medicine stores, usually stocked from Headbridge, Onitsha. My dream was penned down in a letter to my benefactor maternal uncle, Mr. B. C. Madiebo of blessed memory. I remember my uncle recalling this part of my letter to him, a year later, when my husband came seeking for his blessing to have me as his life partner, "*So, you are the University lecturer with whom my niece will settle in a University as a lecturer?"* Then, Rev. Prof. N.N. Osadebe was a Lecturer II and Acting Head of Department of Civil Engineering at the then Anambra State University of

Science and Technology (ASUTECH), Awka Campus. After our wedding and at the instance of Bulgarian Government Scholarship in 1985, I traveled to the Peoples Republic of Bulgaria where I did a Master's Degree in Medicinal Chemistry (Organic Synthesis). We returned to the country in late 1988. Motivated still by a resident drive for academics, I came to UNN, purchased a Ph D form in 1989 and got admitted in 1990. My employment as Lecturer II also came in February, 1990, marking the beginning of my career in the University of Nigeria, Nsukka and the fulfillment of my life dream and goal.

APPRECIATIONS AND ACKNOWLEDGEMENT

My Vice-Chancellor Sir, permit me in few minutes before I get into the lecture proper, to appreciate those who have played a part in one way or the other in the success story we are gathered here to celebrate.

God Almighty saved me at a critical time in my youth and stirred the boat of my life to the predestined/divinely appointed direction. He did not allow any human to confuse His will for me. God, you forgave me much. I have not loved you as much as you forgave me at my salvation and even after.

> ***Unto you, Lord, be all glory great things you have done.***
> ***Unto You, Lord, be all glory, great things you have done***

Eternal Rock of Ages, (twice)
I worship you and adore you
Eternal Rock of Ages

Excellent Oh Lord (twice)
Your name is excellent, Oh Lord

Father, your Spirit is the Spirit of wisdom, power, revelation, light, excellence, counsel, honour, life, and majesty.
Who shall not revere you, Oh Lord? Who shall not give glory to your name? You alone art worthy, Alleluia. Issues pertaining to life and death are in your hands. You show mercy to whom you will. Thou that take the fatherless and poor from grass to grace, be exalted forever and ever, Amen!

I want to welcome and thank every one of you here coming from far and near to witness this occasion. I want to say, point blank here and now, that you are the success of this inaugural lecture. If you did not gather, I will be mad to be talking to an empty hall.
My appreciations also go to the Chairman of the University of Nigeria Senate, Our Vice-Chancellor, Professor Bartho .N. Okolo, the Chairman of the Senate Ceremonials Committee, our own dynamic young Professor Obi Njoku and the entire Senate of the University for making this inaugural lecture a possibility, and for sustaining the vibrancy of this academic culture. Obviously, It is one sure way to be like other sister universities. I had the opportunity to stumble into a compilation of inaugural lectures of

Nigerian Universities by NUC covering the period from 2000-2002. I must confess that I saw little or nothing from UNN. I am eagerly looking forward to when the scheduling will be according to professorial seniority from Faculty to Faculty. It is in the compulsion that academic discipline comes in.

I owe deep appreciation to my parents – Mr. K. C. Nwofor and Mrs R. M Nwofor (Nee Madiebo) (both late). Anytime my mobile phone callsong rings, “Sweet mother, I will never forget you----------,” I will recall how my mother suffered as a widow for several years and still did not live long to reap fully the fruit of her labour. We are still grateful to God that he kept her long enough to see us through the critical periods of childhood and adolescence .God knows the best.

I want to appreciate in a special way my uncles, Late Mr. D. O. Madiebo, a one-time Commissioner for Police, Cross River State, and Late Mr. B. C. Madiebo (MD/CEO, B.C.M Insurance Company, Victoria Island Lagos). These uncles were great people. They took over the responsibilities of father with the absence of our father by reason of death and saw me through my secondary and university education.

My maternal grandmother, late Mrs Hannah Madiebo (Ero eje ogu) deserves to be remembered at a time like this. I spent greater part of my childhood period living with her. She was actually the physical mediator and advocate between us and her sons (our maternal uncles). She was

also a woman of ardent faith in Christ who would persevere in reading the Scriptures even though she would have to spell every word before pronouncing.

I can think of no better way to pay tribute to my husband, mentor and discipler than to properly acknowledge him in this august gathering. My husband, Rev. Prof N. N. Osadebe by reason of marriage in 1984, took over my mentorship. It is in his "Kingdom" and under his direct leadership that I grew from a girl of 24 years to a grandmother of 52 years, from a first degree Pharmacist of 1983 to a University Professor in 2004. Nkem, I remain loyal. Your husbandly love is unmatchable and your french policy of total assimilation in the spirit of Genesis -Chapter - two marriage (as it was in the beginning) is the reason for the obvious success of our union. I owe you a debt of gratitude for your tireless commitment to the cause of our union. In Proverbs 20:6, the Bible asked,. "A faithful man, who can find?" You are a rare breed. "*Esimone kali ina kodu na uwa nka ma obulu na mu ezuro gi we bulu nyunwe gi.*" In this generation filled with people who are deceiving and being deceived, you have proved to be a faithful man and a disciple of our Lord Jesus, following in his footstep. You are my HERO.

My siblings, Mrs Ifeoma Nnaemeka, Mrs Nkechi Uzoka, Mrs Ifeatu Okafor, Mrs Adaeze Osakwe, Mrs, Eunice Chukwuweogo, Mr K. C. Nwofor, Mr. Ifeanyi Nwofor, Mr.

Chukwudi Nwofor, and spouses, I am grateful for your ever-green love and support of years.
My heart-felt gratitude also goes to all my biological children, Uche, Amala (and Chinedu), Olisaemeka, Oluchukwu, Chukwujindu, Onyinye (Lady). You are all great and precious in my sight. Having an academic mother is a sacrifice of its own. My grand children, Chimamaka (Ifeatu) and Onyinyeomachi (Joy), take 'High Five'. You are rubies and arrows.

Of singular mention is Engr. Osakwe, I must not fail to appreciate especially the elder brother role he has been playing in my life since we became related by your marriage to my elder Sister. I want to prophecy that it shall be well with you, Amen. Mrs Helen, A Osakwe, I appreciate the motherly role you have been playing since the demise of our mum. Our good God will keep you

I wish to pay a tribute to my father in - law, Late Mr. Victor Osadebe. Stories of his acts of adherence to strict principles are retold everyday. Long after his transition, these acts are evergreen.
My *de facto* father-in-law, Chief A.C. Osadebe (Akagbologu I of Ogbunike) is highly appreciated. You are an able replacement of Pa Victor Osadebe. Of special note is your inherent passion for overseeing and defending your siblings and the entire extended family.
My able mother –in-law, Mrs Eunice Ifeoma Osadebe (mother of faith) is highly appreciated. She is a woman with a very large heart and deep persuasions. God will keep her

to continue the wonderful work of coordinating the entire family.

I appreciate the rest of my brothers and sisters – in – law: Tochukwu, Ijeoma, Chika, Ngozi, Chiebonam, Nnabuike and their respective spouses

I appreciate especially, Engr. Tochukwu Osadebe, the UNN Director of Works Services, who for the 28th years I have spent in Osadebe's family, has shown himself an ardent brother and friend to my husband. From you, I came to understand that there could be friendship in brotherhood. I have enjoyed the family, full of very interesting people, a family of military, disciplined and principled men.

I want to appreciate all those who did supervise me at various levels of my academic pursuit:

1) Prof. Liliana – Trenkova – Natova of the Higher Institute of Chemical Technology, Sofia, Bulgaria. She inspired my interest in Medicinal Chemistry by introducing me to her area of research involving Structure – Activity – Relationship studies on synthesized y-piperazinyl derivatives during my Masters programme

2) Dr. Segun Komolafe, then of Department of Pharmaceutical Chemistry, University of Ife. He was my undergraduate project Supervisor who impacted spiritually in my life as a staunch S. U. man.

3) Prof. C. O. Okafor (FAS), my Ph. D Supervisor. Prof was kind and understanding during the period of my programme. He read my thesis in few days. When I drifted into Community Pharmacy practice in the days of lean salary and was not serious with academic work, it took me almost a year to effect his recommended corrections. He

kept worrying my husband to encourage me to round up. Prof, I am grateful.

4) My co-supervisor for the Ph.D programme, Prof. P. A. Akah. You were wonderful. Those days I would set up experiment in Pharmacology laboratory, only to disappear for a long time for a new pregnancy and maternity, you did not lose your temper but would rather crack jokes about such. Moreso, rounds of pregnancies and deliveries were also taking place in your own house at the same time span.

I must also thank God for Prof O. K. Udeala, former Vice-Chancellor of University of Nigeria, Nsukka and current Dean of the Faculty of Pharmaceutical Sciences, University of Port Harcourt. He was instrumental to my joining the academic staff of the Faculty of Pharmaceutical Sciences, in 1990 when he was serving as Dean. Prof, I admire your astuteness and "Oyibomanness." Your reward will be here on earth and also in heaven. Even at the peak of your academic achievement as a Vice-Chancellor, you had deep respect for the relationship you had with my humble family. You have shown that the blood of the Lord Jesus Christ is thicker .than any water of sectionalism and statism. You are one of the prides of pharmacy profession in Nigeria-the first pharmacist to attain the position of a University Vice-Chancellor.

I would like to sincerely appreciate the immediate past Vice-chancellor of this University, Ven (Prof) C. O. Nebo for his legendary contributions towards the advancement of our beloved University. During his five-year tenure, he literally brought a new life to every facet of the University system (from seeming disfunctionality to full functionality.

Worthy of singular mention is his demystification of the process of professional assessment. My professorship was announced during his time.

I doff my cap also for the current Vice-Chancellor for his unalloyed efforts towards transforming UNN to No. 1 University.
He has worked so hard to change the entire landscape of the University campus.
He has proved himself worthy alumnus of the great University of Ife(OAU), which is known for years for its environmental beauty and order.
In my faculty in particular we are joyous that after many decades of patching up in prefabs, we will finally be moving into our purpose- built Faculty complex soon

I would also like to also acknowledge Professor Stephen Byrn of the University of Purdue, USA, Professor Joseph Fortunak of Howard University, USA and Sr Zita Ekeocha of Kilimanjaro School of Pharmacy, Moshi, Tanzania, for their avowed determination to ensure that the state – of – the - art knowledge of science of drug discovery, regulatory affairs and drug manufacture is transferred to Africans for the industrialization of Africa. It is regrettable that as at now, there is no truly African drug (except **Nicosan***) when one considers drug development from discovery to marketing. These three were the key facilitators/lecturers at the UNIDO –sponsored Industrial Advanced Pharmacy Training(IPAT) I just concluded at the Kilimanjaro school of Pharmacy, Tanzamia. I thank the Vice-Chancellor for partial Sponsorship of the programme.

I feel obliged to pay tribute to the fallen academic heroes of my department- Dr George Okide of blessed memory, who would have been the premier Professor of the department but was cut short by ill-fate. His memory remains evergreen; Dr U. Ajali, a scientist whose pen was that of a ready writer; Pharmacist Ernest Kenechukwu David- What a short sojourn in the department. Could his death on that fateful day have been prevented by his leaving earlier on his return journey to Enugu or by not coming to work at all that day?

The entire members of the academic board of my Department, I salute you. Prof. Mba, a strict and no-nonsense academic, God bless you. All of you in Pharm. Chem are appreciated. I enjoy the peculiar idiosyncrasies of everybody's personality that make my department alive, doing and moving. I want to specially appreciate Pharm. Justus Nwaoga. Justus, who has been a family friend.Thank you for your support all these years. To me, you are a technical genius. I have always believed that, "*agwu* invention *mara gi*". How would you have grown from a departmental technologist to a pharmacist and then to an internationally acclaimed inventor/innovator except by unmerited PROVIDENCE?

I salute the Faculty of Pharmaceutical Sciences, especially the senior members, able co-labourers in the business of turning out well-baked pharmacist products. With our motto of "Quality by Design", all probabilities of poor products mingling with our quality products will totally be brought to zero. I give you 'High Five'. All the former and current

Deans of Faculty of Pharmaceutical Sciences, take my salute. I remain loyal. Of singular mention is Prof. Vin Okore, current Dean of the Faculty of Pharmaceutical Sciences, who served as an able Associate Dean during my tenure that ended a month ago. Vin, I knew you were going to give me unalloyed support. I have been proved right. It is said that good leaders are found among good followers. You will do better than me (Amen). Prof E.C Ibezim, my faithful brother that is always there for me- thank you for going through the manuscript of this lecture. Prof A. A Attama (a meek man), Dr K.C Ofokansi (Iguedo), Prof G. Onunkwo (Nwadim), Dr Mathew Okonta - These men were my henchmen during my deanship. They answered me at any slightest call. God bless you.

I doff my cap also for my brilliant Ph.D. supervisees. I regard them as collaborators. One grace I have enjoyed as an academic is the number of outstandingly brilliant students I have had to supervise. Their prudence and hardwork made supervision light and interesting. They include:

-Dr Uzochukwu Ikem, Senior Lecturer and Associate Dean, Faculty of Pharmaceutical Sciences, my first sole Ph.D. student. I appreciate him for the readiness with which he carried out any assignment. Even after concluding his work, he still holds me in high esteem. We have published together a total of 17 articles, mainly on mistletoe

-Dr. Uchenna Estellamaris Odo, Senior Lecturer and Head, Department of Pharmacognosy, University of Nigeria, Nsukka. I enjoy your goodnaturedness, Keep it up.

-Dr. Ngozi Nwodo, Senior Lecturer and Immediate past Acting Head of Department of Pharmaceutical and Medicinal Chemistry, University of Nigeria, Nsukka, my only sister female academic staff member in Pharm. Chem. I appreciate your peace-loving and easy going lifestyle. I am happy that we have developed a cooperative relationship as against what is usually obtained with women. Your introducing me to GA Society brought a phenomenal advancement in my academic life

-Dr. W. Obonga, Senior Lecturer and Head of Department of Pharmaceutical and Medicinal Chemistry. I enjoy your radical and reactionary approach to problem- solving. Your research took you to where the joneses could not reach - A Ph.D work on *Cannabis sativa*. I had wished that your primary supervisor, Dr. Okide, was alive to see the findings you got from the work.

-Dr Edwin Omeje, a dogged and resilient academic. You are an academic strength to me, ever ready to accept delegated responsibility. I am deeply persuaded that you will go to places in

the academic world. Keep it up. With Omeje, I have published nearly 10 articles on mistletoe plant. Some of the articles were published in classic (first –rate) impact-factored journals of very long standing. An article on mistletoe from his Ph.D work won International Travel Grant of the International Society for Medicinal Plant Research, in Berlin, 2010. The article was chosen by the organizers for oral presentation and was orally presented at that conference. Our work was the only African work so honoured. The cash award was presented during the Conference Closing Ceremony in Berlin, Germany. He is currently out in India on a CV Raman Postdoctoral Fellowship.

-Another budding hands-on, world - class scientist, Dr. FBC Okoye, Senior Lecturer at Nnamdi Azikwe University, Awka, an Alexander von Humbolt Scholar, talented academic and my collaborator, with whom I have published over 10 articles in national and international journals in the field of natural product research such as Planta Medica, Ethnopharmacology, Natural Product Research, etc. Dr. Okoye's Ph.D work also won travel grant for his participation at the annual conference of the International Society for Medicinal Plant Research in 2008 and 2009. Thank you for your choice of pharmaceutical and medicinal chemistry for specialization.

The rest of my ex-masters, current Masters' and Ph.D supervisees, you are wonderful.
My class mates of 1983 set in UNIFE who remained in academics, namely, Prof Cy Usifoh, Prof C.P. Babalola, Prof A. Adebayo, you are great. Thank you for the unspoken inspiration I draw anytime I remember the exploits you have made and are still making in the world of academics.

It has been a very wonderful and heart-touching experience and privilege to have collaborated with so many wonderful colleagues, supervisors, friends and mentees over many years and I thank them all for contributing to making my career most rewarding. I look forward to continuing to interact and collaborate with people I regard as some of the finest brains in the world.

I would like to acknowledge those that have impacted my christian life at one time or the other: Rt. Rev and Mrs J. U. Ilonuba ; Rt Rev & Mrs A. E. Agbo, my visionary Bishop whom God used to take us to a new realm of ministry in His vineyard(my lord Bishop , God bless you the more), Brother and Sister Gbile Akanni and his team of dogged kingdom generals, Dr and Dr (Mrs) Willy and Vicky Onu; and Rev & Sister Luke Nnaji, Bro & Sis Linus Okoro and S.U. family of all strata, Ven (Prof) Chinedu and Ify Nebo, Ven & Mrs G. Nnamani, Ven & (Dr) Mrs Stephen Dimelu, Ven & (Dr) Mrs Theo Madueme, Bro (Prof) Emma & Sis Rose Agonmuo, Bro (Prof) & Sis (Dr) Mosto Onuoha, Prof Sam & Ejiugo

Enibe,Rev. & Mrs Joe Ndefo, Ven. & Mrs Theo Ugwuisiwu, Mrs Suzzana Anikwenze(Onodu-Ugo), Mrs Obi Nwala, Prof & Mrs Ik Onwurah, Mr & Mrs Jim Ezeibe(Men & brethren), Prof & prof(Mrs) HillyBen Osisioma and a host of others. I have drawn spiritual inspiration at one time or the other by associating with these ones. All the members of the House of Clergy (and wives) of Diocese of Nsukka, remain blessed. All members of the Action and Outreach Unit of the Diocesan Women Ministry, God bless you

I must not close this appreciation session without saying thank you to Peter Okafor, Philip Uzoh and Mr Asogwa for their role in the preparation of the script

INTRODUCTION

Overview of Drug development process

Mr Vice-Chancellor Sir, the main objective of the pharmaceutical research that cuts across various departments of pharmaceutical sciences is the discovery, design and development of new drug substances and products that could serve as better replacement or substitutes for older ones in terms of efficacy, toxicity and specificity. The classical model of drug development is composed of three phases: Discovery, Development, and Marketing (Mcchesney, 2000)

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Drug discovery breaths hope and relief to millions of patients, but the entire process of discovery, development and registration of a pharmaceutical is an immensely

expensive one. It requires immense resources- the best scientific minds, good technology (update) and complex project management. It also demands persistence and at times, mere luck. It takes about 10-15 years to develop one new medicine from the time of discovery to when it is available for treating patients, and costs an average of US$ 800 million (DiMass *et al*., 2003). Each successive step is more expensive than the previous. It is known that for every 5000-10000 compounds specifically synthesized and isolated in the research and development pipeline as a potential therapeutic agent, only an average of 250 will show sufficient promise for further evaluation using laboratory tests, mice and other test animals, about 10% will qualify for tests on humans (Stratman, 2010) and only 21.5% of the drugs that start phase 1 trials will eventually receive approval to be marketed as drug (Medical marketing and Media, 2003; PRMA; http//en.wikipepedia.org/wiki/drug_development). This is known as drug candidate attrition. Attrition of compounds is brought about by toxicity or lack of tolerance, lack of efficacy and lack of bioavailability of the active moiety in humans. This makes it more needful that non-promising candidates drop out early in the developmental process, allowing for concentration of more efforts on compounds with highest probability of reaching the market.

The main aims of pharmaceutical research and development (R&D) are to identify and validate biological targets which the potential new drugs might be able to affect, discover the right molecule (potential drug) to

interact with the target chosen, test the new compound in the laboratory and clinic for safety and efficacy, and gain approval to get the new drug into the hands of doctors and patients. In order words, before any potential new medicine can be discovered, research scientists must work to understand the diseases to be treated as much as possible and to understand the underlying cause of the condition. For example, to be able to effectively design and develop any anti malarial drug, one must understand the lifecycle of malaria parasite from the point of a mosquito bite till the clinical manifestations that result from destruction of the human red blood cells, and be able to predetermine the points of attack by antimalarial drugs. Scientists must try to understand how the disease alters the genes and how altered condition of the genes affect the protein they encode. They also try to know how the proteins interact with each other in the living cell, and how the affected cell changes the specific tissue they are in and finally how the diseases affect the entire patient. This is the premise upon which treating the problem (therapeutics) is based. It was Paul Erlich (1854-1915) that initially developed the concept that in order for a chemical to produce an effect on a biological system, the chemical must react with or become affixed to some component of the biological system. Initially, the identity of these sites are not known and were cleverly refered to by Langley as “receptive substance’, but now, they are generally refered to as “receptors”. Research results from government, academia and industry all contribute to this understand-the-disease knowledge base.

This stage takes many years of hard work to turn the basic knowledge of what causes a disease into a new treatment.

It is this whole process that takes an average of 10-15 years. Many of the drugs that came into the market today were in the early stages of discovery fifteen years before (say 1992).

Drug Development Stages

Target Identification in drug discovery: This involves choosing a biomolecule to target with a drug. In this sense, a target is a single molecule, such as a gene or protein which is involved in a particular disease (receptors). In this design stage, it is expedient that a target that can interact with and be affected by a drug molecule be identified. This stage presupposes that a good understanding of the underlying cause of the disease has been gained.

Target Validation stage: At this stage, the researcher verifies/demonstrates that a particular target is relevant to the disease under study. This is achieved through complex experiments performed both in living cells and in animal models of the disease. At the end, scientists show that the target or receptor is actually involved in the disease and can be affected by the drug.

Drug discovery: This involves finding a promising molecule that could become a drug. It is often technically refered to as lead compound. By this stage, a good understanding of the disease is already grasped. The

researchers begin to look for a molecule that may act on their target to alter the disease course. Drug discovery is the first of the three basic phases involved in the development of a new drug product.It is made up of two essential parts-drug discovery and drug design. It involves the isolation, purification, identification and structural optimization in consideration of the molecule's biological activity profile. Drug optimization or design is done to minimize toxicity and maximize therapeutic value, efficacy and pharmacokinetic characteristics

Methods of 'lead' discovery

Nature: Up till recent past, nature used to be a first resort to find interesting compounds to fight diseases, e.g., bacteria found in soil and moldy plants and phytoconstituents isolated from plants. Till today, nature (plant) serves as a ready source of retinue of structures that serve as lead for drug discovery e. g. morphine, a narcotic analgesic from *Papaver somniferum* was a lead compound to other synthetic derivatives like naloxone and buprenorphine; benzypenicillin from *Penicillium notatum* or *P. chrysogenum* to the semi-synthetic penicillins of improved acid stability (phenoxylpenicilllin)

Natural Plant products as source of new drugs

Nature has provided mankind with products for good health since the beginning of time. For thousands of years, medicine and natural products have been closely linked through the use of traditional medicines and natural poisons (Newman *et al.,* 2000). Plants hold a prominent

position in the available sources of natural bioactive molecules. Clinical, pharmacological, and chemical studies of traditional medicines, derived predominantly from plants, were the basis of most early medicines such as aspirin, digitoxin, morphine, quinine, emetine, and pilocarpine. Approximately 25 per cent of the drugs prescribed worldwide come from plants, whereas 11 per cent of the 252 drugs considered as basic and essential by the World Health Organization (WHO) derive their origin exclusively from plants. Prescription drugs containing phytochemicals were valued at more than US$ 30 billion in 2002 in the US alone. Eighty percent of the people in developing countries rely on traditional medicines for primary health care. Development of phyto-therapeutic agents during last few decades has evolved into a science itself and is undergoing further change (Spainhour, 2005). After a natural product has been screened for biological activity, isolated, purified, its structure identified and pharmacological profile refined, it becomes a lead (prototype) compound. However, it may turn out to be too complex for further immediate progress in the development. Indeed when compared to a purely man - made synthetic alternative, the natural product compound is quickly eliminated from further consideration because of issues of time and potential costs of synthetic production of it.

High-throughput screening- The last two decades have witnessed astonishing discoveries in technology that have brought a paradigmatic change from manual, low speed screening (which used to be uneconomical in terms of the

huge materials and animals usually expended) to an automated, microprocessor- controlled robotic process as High Throughput Screening (HTS). HTS is actually a blend of chemistry, biology, engineering and informatics. It is currently the most common way of finding leads. Here, research takes advantage of advances in **robotics** and computational technology to test hundreds of thousands of compounds against the target to identify any that might be promising. Traditional molecular modeling methods deal with single or fewer numbers of molecules for structural properties at high resolution. Modern computational chemistry or chemoinformatics tends to deal with massive amount of molecules or compounds for their biological behaviours at lower resolution. This is achieved by using high throughput virtual screening techniques or 3D database search techniques. Real- time experimental HTS of drug accelerates drug discovery by biologically screening large libraries of compounds against targets (enzymes and receptors) at the rate of thousands of compounds per week. However, industries and academic institutes are not able to cope with accruing cost of $1,000,000 being the cost of screening 500,000 compounds per week (Langauer, 2004). Before the advent of robotics and computational technology, many chemical compounds are synthesized in series and tested one by one for activity against the target in experimental animals. Based on such results, several lead compounds are selected for further studies. During the era of routine screening, which was the time most of my own works were done, this stage used to take a longer time and energy and

used to involve the sacrifice of huge number of experimental animals. Nowadays, animals are only killed for further testing of successfully selected 'hit' compounds.

This innovation has aided in speeding up conventional sluggish process to such an extent that now 50, 000 – 100, 000 compounds can be screened per week against the validated biological target. Even newer advancements are making possible the screening of 10, 000-100,000 compounds within 24 hours. Next to this is also the development of High Throughput Synthesis. If the syntheses of our products that were carried out in the late 80's are to be done now, the approach would have been different. The science of new drug discovery is a very dynamic one.

Combinatorial Chemistry approach

Combinatorial chemistry is the ability to make a large number of chemical variants all at one time to test them for bioactivity and then to isolate and identify the most promising compounds for further development (Borman, 1996). It has its origin from peptides. The large number of biologically active compounds obtained is known as combinatorial Library. It is the exhaustive recombination of sets of reagents and it is synonymous with any process that allows for synthesis of arbitrarily large sets of different compounds. It is used when the ligand and the receptor (target) are unknown. It is a virtual approach and provides a maximum range of drug-like compounds and increases the potential of finding active lead compounds. The science of combinatorial chemistry resulted from two paradigm-changing ideas of solid-supported synthesis and molecular

biology. These and robotic automation and computer - aided molecular design have significantly impacted the development of combinatorial chemistry. The development of the Library of Combinatorial Chemistry has been published (Spellmeyer and Grootenhuis, 1991; Oprea, 2000)

Ligand –based approach

This is when the receptor is unknown and the ligand is known (Dror *et al.*, 2004),. This is commonest and is an extension of the quantitative structure-acitivity relationships. It is also known as pharmacophore-based design. Pharmacophore is an ensemble of steric and electronic features that enables a molecule to exhibit a specific biological activity.

De novo discoveries

Here, medicinal synthetic chemists create molecules from the scratch through prudent assemblage of simpler molecules via organic synthesis. At times they simulate chemical substances native to the human body that are known to elicit known effects in the body. At other times, they target to produce molecules that are similar enough to the natural body chemical transmitter substances to interact with same target but to produce opposite effect (antagonism). These days, with recent advances in technology, computer modeling is used to predict what type of molecule may work. De novo design is used when the receptor structure is known and the ligand structures are unknown (Schneider & Fechner, 2005). Here, there is

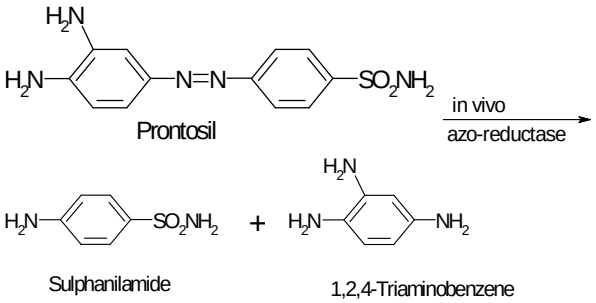
available information about the target receptor, but no existing leads to interact with the active receptor sites. De novo design is then used to propose ligands that are complimentary to the active receptor sites. De novo uses 3D searching of large data base to identify small molecules fragments that can interact with specific sites on the receptor. An example of De novo programme is GROW (Moon & Howe, 1990).

Biotechnology

This is defined as the use of microorganisms, plants, animals, or parts thereof for the production of useful compounds. Pharmaceutical biotechnology is the use of tissue cultures, living cells, or cell enzymes to make a drug or diagnostic e.g. Recombinant Human Insulin.In this approach, living systems are genetically engineered to produce disease fighting biomolecules. The products are proteins used for therapy.

Application of a hypothesis

A hypothesis by Erhlich that toxic dyes kill microorganisms but leave the host cells unaffected led to development of prontosil. This hypothesis proved real and led to the development of antibacterial sulponamides.

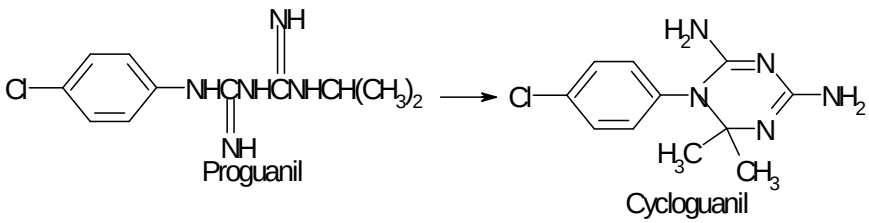


Serendipity discovery

This refers to lead discovery by chance or accidentally. Many important drugs have been discovered by careful observation and reasoning while the researcher was busy with another thing. For instance, it was chance that caused the Trefonels to add a reducing agent to prontosil in *in vitro* experiment but they had the intuition and experience to know the significance of reduction of the prontosil structure. Slidenafil citrate (Viagra) was originally designed as an antihypertensive but now used in the treatment of erectile dysfunction.

Drug metabolite approach

Drug metabolite is new chemical entity obtained from a drug after its transformation in the body. Drug metabolite approach is based on the discovery that many drugs elicit bioactivity not because they themselves are active, but because they are converted inside the body to metabolic products (metabolites) that are active. Such parent drugs are known as prodrugs. The active metabolites when isolated can serve as a lead to new drugs.



Side effects of drugs

Capitalizing on the side effects of existing drugs can lead to development of new drugs. Eg the diuretic side effects of sulphonamides have been exploited in the development of new diuretics like acetazolamide. Also the observation that the antihistaminic substance, promethazine, produces sedative central effect prompted molecular modification to enhance this property. This led to discovery of chlorpromazine and other phenothiazine tranquilizers.

Trial-and error screening and rational drug design

In this approach, all available chemical substances are subjected to variety of tests in the hope that some useful action may be discovered. All biological actions are regarded as potential source of lead in drug design. This is really a trial-and-error approach and is seemingly wasteful, uneconomical, time – consuming and unrewarding. This has been totally replaced by rational design where identifying a lead is based on molecular understanding of the drug, its properties and its receptor (target). A great majority of drugs have been discovered, developed and

marketed by a mixture of trial and- error, rational design, hardwork and pure luck.

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Lead optimization stage: Here, the chemical structures of lead compounds are altered to improve pertinent drug properties. Slight changes in structure of potential drug molecules have been known to affect activity, toxicity, physico-chemical properties and side-effects. Even at this stage, researchers often begin to think of how the drug will be presented (made) or formulated for consumption.

Early Safety Tests: Here, tests are performed on lead compounds to provide an early assessment of the safety of the lead compound. The lead is subjected to ADMET tests (pharmacokinetics). It is expected that a successful drug must be able to be absorbed into the bloodstream, distributed to proper site of action in the body; metabolized effectively and efficiently, successfully excreted from the body and should be shown to be non-toxic.

Pre-Clinical Testing: In this stage, laboratory and animal testings are performed to determine if the drug is safe for human testing.

In vitro and *in vivo* tests are carried out on the drug. Here also, techniques of scale-up production are devised to get enough of the drug for clinical testing.

At the end of the discovery stage which usually lasts for 3-4 years, 1-2 drug candidates usually emerge out of about 5000-10,000 entry products.

Development process (from 4th-10th year)

Drug Development is the blanket term used to define the process of bringing a new drug to the market once a lead compound has been identified through the process of drug discovery. It includes pre-clinical research (with microorganisms or animals) and clinical trials (on humans) and may also include the step of obtaining regulatory approval to market the drug. The development phase is made up of preclinical studies and clinical studies (Mcchesney, 2000); Craig, 2001; Newman, 2001; Lee, 1999). This stage is designed to eliminate undesirable compounds and to ensure the safety and efficacy of compounds that will pass through the developmental furnace and eliminate or at least minimize the hazard and risk of exposure to humans.

Preclinical New Chemical Entities (NCEs) or new molecular entities (NMEs) are compounds that successfully emerge from the process of drug discovery. These would usually have been confirmed to have a promising activity against a particular biological target thought to be important in the disease. However, little will be known about safety, toxicity, pharmacokinetics, metabolism of the NCE in humans. It is the function of drug development to assess these parameters prior to human clinical trials. Drug development is also set to make recommendations of the dose and the schedule to be used in human clinical trial usually called the first- in –man (FIM) or the first human

dose (FHD). In addition, drug development stage is expected to establish the physico-chemical properties of the NCE, its chemical make-up, stability and solubility. The process by which the chemical entity is made is optimized so that from being made on the bench in milligram scale by a synthetic chemist, it can be manufactured in the kilogram and then in the tonne scale. It is also further examined for suitability to be made into dosage forms like capsules, tablets, etc. The whole processes in preclinical development are known as Chemistry, Manufacture and Control (CMC). The major aspects of drug development are concerned with regulatory requirements of drug licensing authorities. These requirements are usually in form of battery of tests designed to determine the major toxicities of a new compound prior to first use in man, which usually include assessment of major organ toxicities, like liver, heart, kidney and digestive system and the effect on the other parts of the body like the skin. It is the information gathered from pre-clinical testings and CMC that are submitted to regulatory authorities as investigational new drug application (IND) before initiation of clinical trials (PRMA, 2007)

Clinical testings: These last between the 7th – 10th year and must be done before a drug is registered by a regulatory body like NAFDAC or FDA. It is made up of four phases:

Phase I: This represents the first exposure of the drug to humans and examines the effects of single and multiple increasing doses in 20-80 human subjects. Here toxicity is

generally studied using healthy volunteers. Tolerance is also evaluated. Basic pharmacokinetic studies are performed to aid in the determination of later dosage regimens and to fully characterize the routes of metabolism, excretion and elimination and assess the presence and amounts of active and inactive or toxic metabolites.

Phase II: This involves testing a drug candidate for efficacy in humans, while still monitoring for safety and tolerance concurrently. Studies that are usually done here include pharmacokinetics and dosing in patients. The studies involve up to 200-300 subjects and provide the first indications of potential benefit of the drug as compared to its risk of exposure. Different dose- range- finding studies are performed to optimize the dose of the drug, maximize its efficacy and minimize any compound related intolerance

Phase III: The studies in this phase involve the utilization of drug candidate at the optimum dose in the target patient population and in exactly the same fashion that the drug will be used if eventually approved and marketed. They are intended to verify efficacy and detect adverse reactions and contraindications: This involves a very large study of efficacy of product composed of hundreds to thousands of volunteer patients (1000-3000) depending upon the therapeutic indications. Phase III studies are the last series of studies that are performed before submitting a complete information package for regulatory approval. If approved, the drug is registered, manufactured on a larger scale and introduced to the

public. This takes place around the 11th year of the development lifespan of a drug.

Phase IV: This involves product –marketing surveillance on people conducted after a drug has been approved for sale. The studies involve adverse reaction reporting, surveys and general sampling, testing and evaluations.

Rationale for new drug discovery research

One may ask, 'why do Pharmaceutical companies continue to spend billions on searching for new drugs, when there are drugs all over the place? Actually, so many medicines have been discovered and are being used to treat many diseases but there are still many major unmet medical needs. In USA alone, according to National Vital Statistics Report (2009), from about 2.4 million deaths recorded in 2009,, 616067 were caused by diseases of the heart, 562,875 by malignant neoplasms, 141- 075 chronic lower respiratory diseases, 133,750 cerebrovascular diseases, 123,706 accidents, 74.632 Alzheimer's disease, 71,382 diabetes mellitus, 52,847 influenza and pneumonia, 46095 nephritis and others, 34,851 septicemia (Byrn, Fortunak & Ekeocha, 2012). For the rest of the world especially the developing African countries, simple and opportunistic intections continues to ravage. Malaria alone affects over 350 million people, hepatitis, A,B,C affects about 500-700 million people, AIDS, 34 million (over 30 million are already killed by the disease since 1983.There is also a worrisome resurgence of tuberculosis, and the need for

breakthrough in vaccine research remains there. Moreover, there is the problem of poor assessibility of existing drugs to all and sundry. A WHO statistical fact has it that 15% of the world population consumes 91% of all medicines (WHO Millenium Report, 2005). In other words, about 5.5 of the world 6.5 billion people do not have access to modern medicines. It may also interest you to know that there approximately 1600 medicinal molecules or products listed in US, EUr, BP and international pharmacopoeia which affect only 500 separate targets(proteins, enzymes, hormone-replacements, signaling processes, antibiotics, antivirals. However, the human genome, made up of about 28,000 genes is estimated to contain roughly 15,000 druggable targets (Byrn, Fortunak & Ekeocha, 2012). A greater percentage of what could be good sources of new drugs are unharnessed. So many orphan diseases, many of which affect mainly people in Africa do not yet have medical solution and the pharmaceutical companies do not delve into research on them for economic reasons.

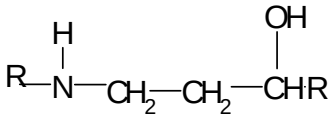
Mr Vice-Chancellor Sir, the pharmaceutical and medicinal chemists are majorly involved in the drug discovery stage which deals with identification, designing, modification and characterization of isolated or synthesized chemical entities. They are also involved with quality assurance and control of active pharmaceutical ingredients and finished formulated pharmaceutical products.

I am pleased to inform the Vice-Chancellor, that this is the aspect of drug development I have been involved in for the past 26 years as a Medicinal Chemist. As a young

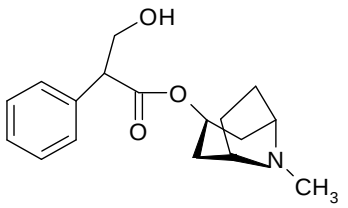
pharmacist, as I mentioned earlier, I made up my mind that I was going to be part of the drug discovery world and I showed interest early enough in medicinal and analytical pharmaceutical chemistry. I decided that I was going to undertake a pensive adventure "**From the Laboratory Bench through the Gardens to the Apothecary".** The story of the extent, and rate of this journey, I am here to tell today. **From the Lab bench** component will describe part of the researches that I carried out in synthesis laboratories and the successes made; **through the gardens** describes the aspect of my research efforts that were centred on exploitation of biodiversity in the discovery of lead drug compounds and herbal medicines, while **To the Apothecary** connotes the final destination of the new drug formulation - to the **Pharmacist** (as the custodian of drug) for dispensing to patients from Doctor's prescription.

At the Laboratory Bench (Synthetic Drug Discovery)

Mr. Vice-Chancellor Sir, while I was in the Peoples Republic of Bulgaria, courtesy of a Bulgaria Government Scholarship for Post – graduate specialization programme (Masters level), I had Prof Liliana Trenkova-Natova as my supervisor. At that time, she was working on some biologically active di-substituted piperazine derivatives. I came to understand from literature and from interaction with her that chemical entities having the γ – amino alcohol moiety in their molecules usually exhibit anti- spasmodic properties, e.g., atropine.



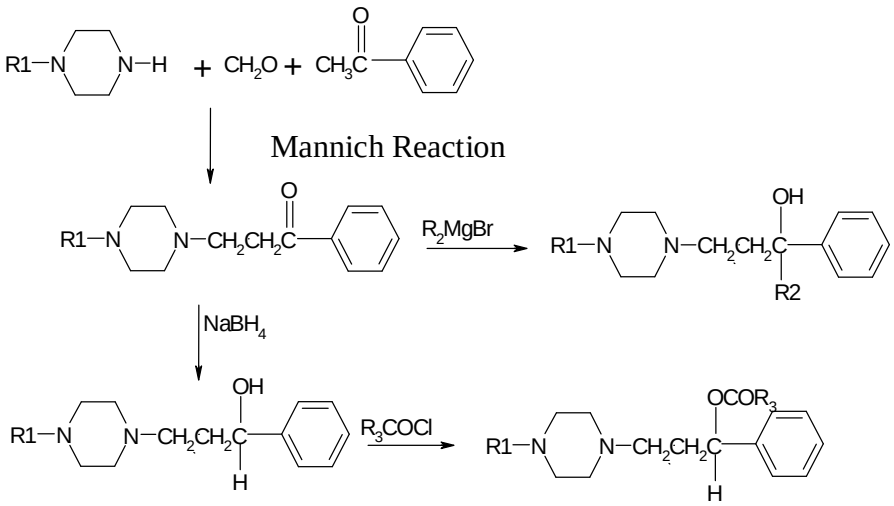
(I)



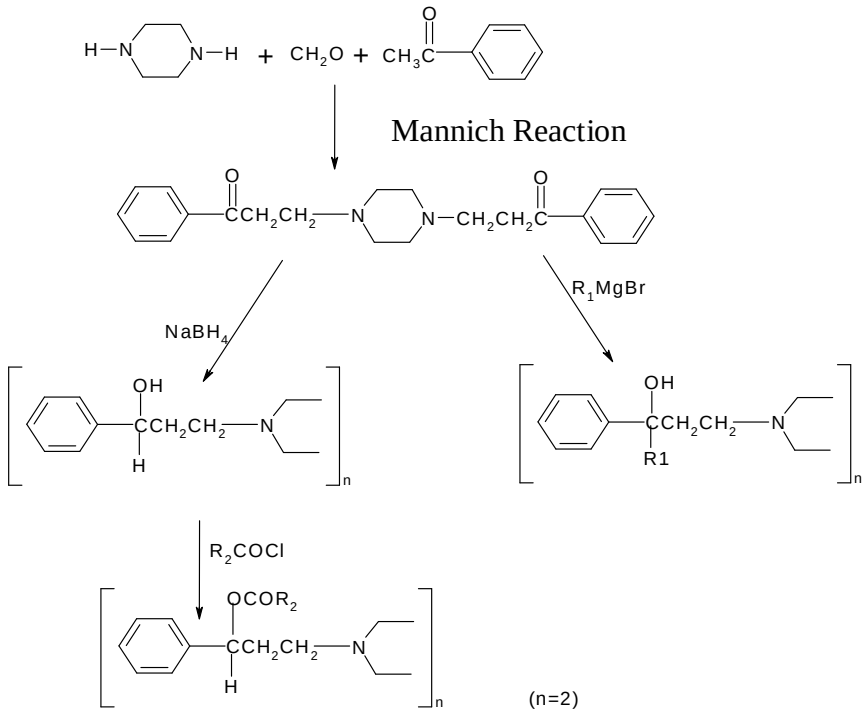
Atropine

(II)

That is to say, that the moiety is needful for antispasmodic effect. Anti -spasmodic drugs are drugs that act to antagonize or oppose acetylcholine-induced smooth muscle spasm (spontaneous contraction), thereby producing muscle relaxation. We proceeded to prepare a series of structurally- related compounds with a view to identify the optimal structure from the lot. This is shown in Schemes 1 and 2.


R1
N
N
H
+
CH2O
+
CH3C
O
Mannich Reaction
R1
N
N
CH2CH2C
O
R2MgBr
R1
N
N
CH2CH2C
OH
R2
NaBH4
R1
N
N
CH2CH2C
OH
H
R3COCl
R1
N
N
CH2CH2C
OCOR3
H

Scheme 1

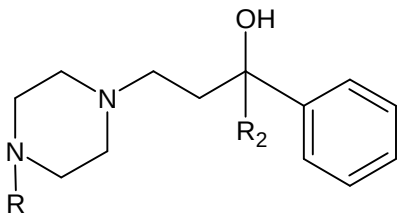


Scheme 2

As at the time of our going to laboratory, the Mannich bases, β – amino ketones were already known in literature for their antispasmodic and analgesic effects. These transformations were carried out to see which structure is optimal from the group. About 22 compounds were prepared and isolated from the two schemes. However, poor solubilities hindered the quantitative biological testings on some of the derivatives with bulky and hydrophobic side-groups.

The biological effect elicited by a drug molecule depends on the chemical structure of the substance, to such an extent that little changes in the basic structure of the biologically active molecule usually lead to changes in a specified biological effect (Loomis, 1978). This relationship holds even when toxicity or side effect is the biological end point. Due to importance of toxicity studies in determining the safety of biologically active molecules and also in structure-activity –relationship studies, we investigated the acute toxicity profiles of the synthesized γ- piperazinyl (amino) propanols with general structure (see below). In toxicology, the higher the LD_{50} value, the lower the toxicity of the drug molecule. It is evident how substitution of alkyl, arylalkyl and aryl side -chain altered toxicity profile greatly in a series. The most toxic turned out to be the only secondary alcohol derivative in the series, A88 (where R = CH_2Ph R_2=H) and the least toxic was A14 (where R = $PhCH_2$ and R_2 = Ph) (Osadebe, 2001). We also studied the effect of altered structure on the antihistaminic properties of same group, and the result is shown in Table 1.

Table 1



Compd	R_1	R_2	ID_{50}(ng)	LD_{50}(mg/kg)
A8	CH_3	Ph	220.68	126.40
A51	CH_3	$PhCH_2$	1527.48	113.69
A13	$PhCH_2$	C_2H_5	163.22	127.72
A14	$PhCH_2$	Ph	533.56	268.62
A53	$PhCH_2$	$PhCH_2$	459.44	215.66
A18	$(CH_2)_{2-}$ $C(OH)R_2Ph$	CH_3	797.62	134.99
A88	$phCH_2$	H	-	89.74

Legend: Ph =C_6H_5; LD_{50} =Dose of the drug that kills 50% of the population of test animals; ID_{50} = Dose of the drug that brought about 50% inhibition of histamine –induced contraction.

TI = Therapeutic Index= $\frac{LD_{50}}{ID_{50}}$

This is an indication of the margin of safety

For a drug under discovery, low margin of safety is undesirable, because it brings about a situation of seamlessness between effective dose that brings about desired pharmacological effect and the dose that causes toxicity, and poses a big problem in dosage design. In terms of the therapeutic index, the optimal structure in the

series was found to be the A14. The compounds as a whole were moderately toxic. Their toxicity was found to decrease with increase in the hydrophobic nature of the substituents on R_1 and R_2. Theoretically, it is known that whereas hydrophobicity is essential for the compounds to pass through the lipophilic membrane of internal tissues and organs, optimum hydrophilicity (polarity) ensures that enough of the molecules dissolve in the extra cellular aqueous layer in enough concentration to elicit the desired action.

Mr. Vice-Chancellor Sir, you can see how the drug candidate attrition takes place in drug discovery, the best structure(s) of all the compounds in the table above is chosen while others fall out. As shown in Scheme I, four new derivatives of γ- (4 – benzhydryl-l piperazinyl) α-phenyl propanols were also prepared by Grignard reduction reaction. Solubility issues hindered further quantitative biological testings on them (Osadebe, 2001b). Qualitatively, they exhibited antispasmodic and anti-histaminic effects.

A major breakthrough by our group was when we worked out a method for the preparation of new ester derivatives of the previously synthesized γ- piperazinyl propanols (Natova and Osadebe, 1988; Natova and Osadebe, 1989; Osadebe, 2001). We could not get a clue from literature for they have not been synthesized before. We came across a work by Szeja on phase -transfer catalyzed (PTC) synthesis of some esters of simple carboxylic acids. In his work, less reactive tertiary alcohols were prepared in good yield under the condition of liquid-solid phase transfer

catalysis using anhydrous sodium carbonate as solid phase, chloroform or dichloromethane as organic solvents and benzyl triethylammionium chloride as catalyst. We applied the principles of PTC in the preparation of esters of γ - (4-substituted 1- piperazinyl - α - phenyl propanols. Two Bulgarian patents on method of preparation of these ester derivatives were obtained (Natova and Osadebe, 1988; Natova and Osadebe, 1989.) Benzyl piperazine series of the some unsymmetrical ester derivative of γ- (4 substituted piperazin-l-yl) α - phenyl propanol were successfully prepared by the said PTC method, and were shown to possess potent antispasmodic activity (Osadebe *et al.*, 2004). Of the compounds evaluated, the ethyl ester of γ – (4 – benzylpiperazin-l-yl) α - phenyl propanol elicited the best antispasmodic activity. These esters, at the tail end of the drug development process, could really function as pro-drug and at the same time as drug by their own right. Drugs formulated in their esters form are known to be labile and easily destroyed by acid hydrolysis in the stomach or by basic hydrolysis in the intestine.

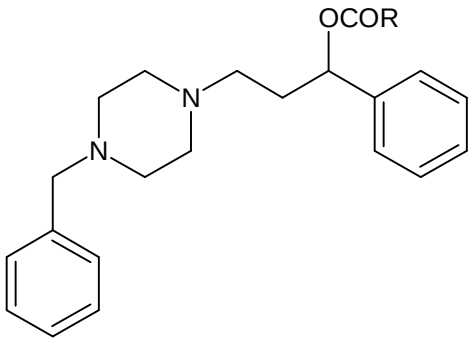
Analgesic Properties of γ-piperazinyl propanols and their ester derivatives.

By serendipity, while working on a synthesized γ-piperazinyl propanol derivatives, (Osadebe, **2001**) we observed a close structural similarity of our synthesized compounds to phenyl piperidine group of narcotic analgesics in possessing an amino group, an aromatic ring and a central carbon atom, but differing only in one of the valences of the central carbon atom still attached to

hydrogen. We therefore subjected four previously synthesized derivatives of γ-(4-benzyl-1-piperazinyl) -1-phenyl propanol to screening for analgesic activity in albino mice using a variation of the Eddy and Lambach hot plate method. The result showed that the most significant analgesic effect was elicited by the parent secondary 3-piperaziny propanol, namely γ-(4-benzyl-1-paperazingl)-α-phenyl propanol. Its esterification product with propanoyl, benzoyl and phenylacetyl chlorides exhibited reduced analgesic properties. However, the percentage maximum protection against thermal pain produced by Aspirin (71.43%) was twice as high as that produced by the most active of the four derivatives (42.65%).

For purposes of structure activity relationship studies, we determined the reversed phase thin – layer chromatographic parameter (Rm) of a series of γ-(4-substituted -1- piperazinyl) -α- substituted -1- phenyl propanol for various concentrations of acetone in water (Osadebe, 2004**).** The conventional method of assessment of partition coefficient using octanol-water is usually tedious and often presents practical difficulties, especially when working with compounds of low or poor solubility in either of the solvent phases. The extrapolated Rm values of the piperazinyl propanols were correlated with LD_{50} (acute toxicity index) values obtained from 24 – hour acute toxicity studies in albino mice (Osadebe, 2004). The extrapolated Rm values correlated parabolically with LD_{50}.

Table 2: ***Extrapolated R_m values of the esters of 3-(4-benzyl-1-piperazinyl)-1-phenyl propanol and their LD_{50} values***



Com-pound	R	Regression equation	Regression Coefficient	Rm_{aq}	LD_{50} (mg/kg)
A88	OH(parent)	Y=-0.017x+0.809	0.9851	0.809	89.74
E97	CH_3	Y= -0.0377x+2.457	0.9433	2.457	99.46
E98	CH_2CH_3	Y=0.0378x+2.6302	0.9921	2.602	118.48
E99	C_6H_5	Y=-0.0406x+2.9818	0.9643	2.9818	242.37
E100	$C_6H_5CH_2$	Y=-0.0394x+2.772	0.9643	2.7712	159.33

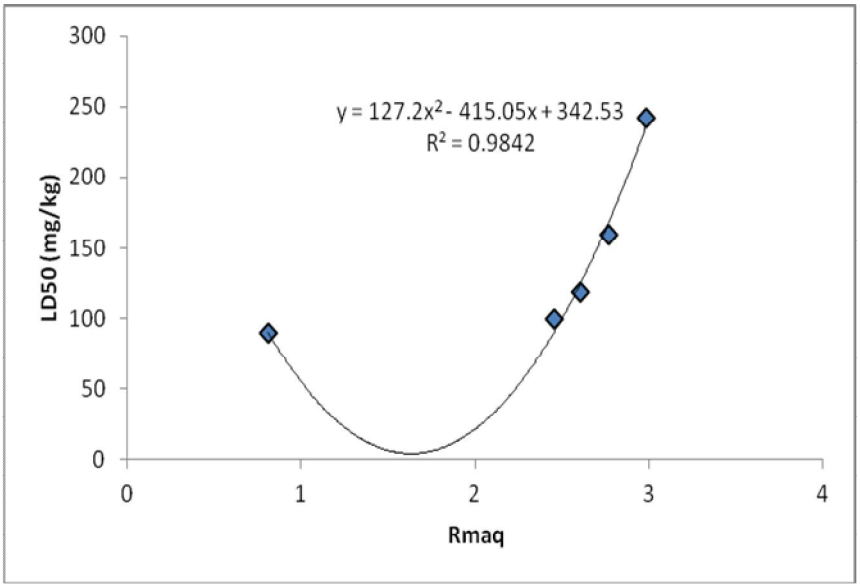


Figure 1: ***Correlation of Rm_{aq} with LD_{50} of esters of 3-(4-benzyl-1-piperazinyl)-1-phenyl propanol***

. Partition coefficient is one of the many physico- chemical parameters that affect how far a drug molecule would go in the journey to its site of action in the living organism. It is usually given mathematically as.

$$P = \frac{\text{Concentration of a Solute in oil (Co)}}{\text{Concentration in water (Cw)}}$$

Hansch and co-workers (1964) proposed a general mathematical relationship between the penetration of molecules into cells and a substituent constant Π

$$\Pi = \text{Log } P_x - \text{Log } P_H$$

where P_H is the partition coefficient of parent drug molecule and Px is that of the derivative, Π is the hydrophobic constituent constant.

The reversed phase chromatography parameter, Rm, is given by

$$Rm = \log (1/_{Rf} - 1)$$

The substitutability of R_m parameter and Π resides in the fact that the same principle that operates in octanol – water partitioning process also governs the distribution of molecules between the liquid stationary phase and the liquid polar mobile phase in partition chromatography.

The close linear relationship that exists between Π and ∆Rm is given by,

$$\Pi = -1.103\ R_{m} + 0.647$$

This is the basis of the substitution of ∆Rm values with Π in quantitative structure-activity- relationship studies designed to study the effect of substituents of varying polarity/hydrophobicity. The significance of the finding from our work is that LD_{50} and/or any biological activity of new members could be estimated/calculated from the regression equation without having to slaughter experimental animals. The new members can also be fixed from theoretically pre-determined substituent constants.

A Shift to the Gardens (Nature)

My adventure in the field of drug discovery took me from the lab bench to the Gardens and the Wilds. The gardens in the title of the lecture represent the biodiversity. During the last few decades, public interest in natural therapies has increased tremendously around the world and natural

bioresource as therapeutic source has evolved into a science and is undergoing faster changes. Recently, there has been great demand for medicinal plants in the drug industry. This resulted from the growing popularity of herbal drugs and wide use of plant –derived phytomedicines. The traditional medicines are slowly being integrated into modern medicine in the form of dietary and nutritional supplements and the scientific community is challenged to address the issues of utility, safety, quality, efficacy and standardization.

Natural products are rated as the most successful source of lead for development of biologically active metabolic by- product. It is known that out of 520 new drugs developed and approved by FDA between 1983 and 1994, 39% of them were either natural products or their derivatives (Cragg *et al*., 1997). More recent data put natural products as contributing to over 51% of successful new chemical entities (Donald, 2000). The WHO estimates that about 80 % of world's population relies primarily on traditional medicines as sources for their primary health care. A more current statistics based on prescription data from 1993 in United States show that 50% of the most prescribed drugs had a natural product either as the drug or as the starting point in the synthesis or the design of the actual end chemical substance (Newman *et al*., 2007). The above development and facts informed my shift to the biodiversity in search of new drug candidates.

Preliminary screening of some plants

While in the garden, and on the basis of folkoric and oral information, I paused and harvested the following plants and screened them accordingly depending on their traditional uses. The results are shown in Table 3

Table 3- Summary of various plants screened for various bioactivity

Plant material (botanical name)	**Local /generic name**	**Screened medicinal properties**	**Positive or negative**	**Ref. of publication**	**Part of plant**
Bucholzia coriaceae	-	Antimicrobial	+	Osadebe *et al*., 2011	Leaves
Hibiscus asper	Weed sorrel, Ileagu	Antimicrobial Anti-Inflammatory	+	Osadebe *et al.,* 2010	Leaves
Holarrhena africana	Mba	Anti-trypanocidal	+	Nwodo *et al*., 2007	Leaves
Detarium microcarpum	Ofo tree	Haematological studies, serum chemistry		Odoh *et al*., 2007	
Alchornea floribunda	Agbarugba Iporuru	Anti-inflammatory	+	Okoye & Osadebe (2010)	Leaves
Nauclea latifolia	Uvuru ili	Antimicrobial, Antiinflammatory	+	Osadebe *et al*., 2010	Leaves, Stem bark

Pterocarpus erinaceus	Uturukpa oji	Proximate analysis	-	Odoh, Ezegwu, Osadebe,(2009)	Leaves
Mucuna flagellipes	Ukpo	Haematologi-cal studies	Safe	Odoh & Osadebe, 2010	Seeds
Cannabis sativa	Indian hemp	Hepatotoxicit y evaluation		Obonga *et al*., 2006	Leaves
Euphobia hirta	Asthma plant	Platelet response	-	Omeje *et al*., 2007	leaves
Phyllanthus niruri	Okwonwan azu	Anti-diabetic	+	Odoh *et al*., 2010	leaves
Jatropha curcas	Oriogwu	Analgesic Antioxidant	+ +	Odo *et al*., 2009	leaves
Aloe barbadensis	Aloe vera -	Anti-diabetic	+	Osadebe *et al*., 2001	Leaves
Alstonia boonei	Egbu -	Analgesic Anti inflammatory	+ +	Osadebe, 2003a Osadebe, 2002c	Root bark Root bark
Pluumbago zeylanica	Ceylon leadworth	Antimicrobial	+	Osadebe *et al*., 2001	Leaves
Cymbopogon citratus	Lemon Grass	Antimicrobial	+	Osadebe & Ajali, 2003	Leaves(oil)
Alchornea floribunda	Iporuru	Anti-inflammatory Anti-microbial	+ +	Okoye & Osadebe, 2009	Leaves
Landolpha owerienssis	Utu	Hepatoprotec tive effect	+	Okonkwo & Osadebe 2012	Fruits

Loranthus micranthus	Mistletoe Ovegbe	Antimicrobial Anti inflammatory Anti diabetic Immunomodulatory	+ + +	Osadebe & Akabogu, 2006 Osadebe *et al*., 2004	Leaves
Acanthus montanus	Agamsoso agamevu	Antiinflammatory Anaglesic Antioxidant	+ +	Odoh *et al*., 2010	Leaves
Jatrova curcas	Oriogwu	Antioxidant	+	Odoh *et al*., 2009	leaves
Morinda lucida	Ogere	Toxicity	-	Osadebe, 2002a	Leaves, stem and root

After these preliminary screening works done at various times on various plants, my attention was particularly drawn to *Loranthus micranthus* and *Alchornea cordifolia* because of the numerous interesting medicinal properties possessed by the plants. My attention to mistletoe was first drawn by Mr. Emma Efegwo of blessed memory, who was using the plant then for lowering of blood pressure, sugar and for other health benefits. Scientific studies, especially on the European mistletoe have shown that composition or activities of mistletoe are dependent on the host tree,

species and harvesting period (Fukunaga *et al*., 1989; Obatomi *et al.*, 1994; Scheer *et al.,* 1992; Wagner *et al.,* 1996). We reasoned that different species of mistletoes sourced from various host trees may also vary in the macromolecular and micromolecular components. We carried out screening on mistletoes collected from Nsukka in Eastern Nigeria and confirmed them to be good and safe for lowering of blood sugar levels in diabetics (Osadebe *et al.*, 2004, 2006). Since then, we have carried out many scientific investigations into the numerous activities of mistletoe. One popular herbalist (Kafaru, 1994), who is now late, described mistletoe as an all-purpose herb and a panacea.

Studies on Mistletoe

Mistletoes are semi-parasitic ever-green plants which depend on their host tree for minerals and water only but photosynthesize their carbohydrate by means of their green leaves (Griggs, 1991). They grow on a variety of evergreen and deciduous host trees all year round. Over 700 species of the mistletoe plants are known world-wide (Gill, 1973). The name mistletoe is used for several plants that may belong to several genera such as *Viscum* (60 species),

Loranthus, Tapinanthus etc. and can grow on a variety of host trees.

Types of Mistletoe Plants

Mistletoe plants include the

European mistletoe	(*Viscum album* Linn),
Korean mistletoes	(*Korthalsella japonica),*
Japanese mistletoe	(*Viscum album coloratum*),
Australian mistletoe	(*Ligaria cuneifolia* R. et T.),
American mistletoe	(*Phoradendron flavescens*
New Zealand mistletoes	(*Alepis flavida, Peraxilla tetrapetela)*
Spanish mistletoe	(*Arceuthobium oxycedri*)

Types of African Mistletoes

(*Loranthus bengwensis, Viscum capense, V. rotundifolium, Moquinella rubra, V. obscurum, V. crassulae, V. minimum, Tapinanthus oleifolius, Tapinanthus vittatus*, *Loranthus micranthus, Viscum engleri,Viscum fischeri* and *Phragmanthera dschallensi, (*Gill, 1973; Osadebe *et al.,* 2004*)*

Host trees of Mistletoe

Each species of mistletoe can grow on a variety of host trees.

Several host trees of mistletoe have been cited around the world. For example,*Viscum album* Linn. grows on several host trees including fir, pine, apple, oak, wild pear, willow, maple, elm, birch, spruce, populus, rubber, apricot, and

eucalyptus among others. The host trees of the African mistletoe include cocoa, coffee, custard, apple, guava, hevea, shea tree and citrus fruits, avocado, kola tree, oil bean and bread fruit tree. The Northern Nigerian species, *L. bengwensis*, may parasitize *Citrus limon, Vernonia amygdalina, Jatropha curcas* and guava (Obatomi *et al.,* 1994; Obatomi *et al.,* 1997).

Traditional Names of Mistletoe

Mistletoe has several traditional names in different parts of the world. These include:

1. Ibo (Nigeria): Owube or Awurisi
2. Yoruba (Nigeria): Afomo onisana
3. Hausa (Nigeria): Kauchin
4. Mende (Sierra Leone): Ngulu-ngolo-ei
5. Temne (Sierra Leone): E-Lifa
6. English (United Kingdom): Childrens' matches or golden bough

Stories/Mysteries/mythologies/folkores about Mistletoe

Mistletoe has been used in different cultures for centuries in a variety of medicinal and non-medicinal purposes (American Cancer Society, 1983; Dalziel, 1955; Warren-Davis,1988). Mistletoe was described as an all-purpose plant (Kafaru, 1993).

Before now when scientific investigations and studies have aided in demystification of mistletoe, it has existed all along as a plant of much wonder. The ancient Celtic Druids and the Norseman hold mistletoe as sacred**.** The Druid priesthood in a very special ceremony used mistletoe. In

the Scandinavian antiquity, it was regarded as a plant of peace. Among them, it was believed that if enemies met by chance beneath it in a forest; they laid down their arms and maintained a truce until the next day. The plant is distributed to the people, who hung them over doorways as protection against thunder, lightning and other evils. The folklore, and the magical powers of this plant, blossomed over the centuries. A sprig placed in a baby's cradle was believed to protect the child from fairies. Giving a sprig to the first cow calving after New Year would protect the entire herd. Kissing under the mistletoe is an ancient English custom, originating from the Norse mythology. These magical powers of mistletoes, whether real or imagined existed in the belief pattern of the peoples concerned.

Mistletoe is the State flower of Oklahoma in the United States of America, reportedly chosen because it was once used to decorate a settler's gravesite when no other flowers were available (Geobiological Survey, 2001). Magical preparations are prepared by Hausa hunters from the ground berries, Shear butter and a kind of rock salt (Hausa gallo). Eating of the magical preparation every morning is believed to make the hunted game drowsy and easy to kill.

The raging controversies

- The summary of the myths and facts of mistletoe can be seen in the words of the book preface written by *Lao Tzu* (Bussing, 2000),

- "***Mistletoe is still a controversial plant. Growing between heaven and earth, never touching the ground, and not accepting the seasons. Even discussing its clinical impacts results in polarization: Rejected by clinical oncologists but used by practitioners and cancer patients. It is applied as a remedy to treat a broad spectrum of different diseases, such as epilepsy, diabetes, hypertension, athrosis, hepatitis, HIV infection, labour pains, and cancer***".

Traditional Uses of Mistletoes

In French Guinea, a species with hairy leaves is used for skin diseases. In Senegal, mistletoe growing on *Acacia seyal* is used to treat chest diseases. The leaves are regarded as purgative, beneficial in colds and chest complaints, especially if collected from *Detarium senegalense*. In Gold Coast, pregnant women are given decoctions of mistletoe. In Sierra Leone, the treatment for rheumatism and boils consists of grinding up the ashes of the plant with palm oil. Some fowl droppings are added before burning the mistletoe to ashes. The preparation is applied to the skin. In Hausa communities, Loranthus parasitic on Shear butter (Kauchin Ka'de) or *Vitex cienkowskii* (Kauchin 'Dunya) are used in prescriptions for Leprosy along with washings of the Koran (drunk along). In the Benue region of Nigeria, Loranthus parasitic on *Calotropis* is specially valued. *Loranthus ophiodes* that grows chiefly on symphonia is a violent poison. (Dalziel, 1955). In Nigeria and some other parts of Africa, it is

believed that the aqueous extract of mistletoe (Loranthus) species consumed over a long time will bid farewell to the cause of hypertension, diabetes and other metabolic diseases (Kafaru,1994). It is used in folk medicine to cure many illnesses. North American Indians used it for toothache, measles and dog bites.

The ethnobotanical uses of mistletoe include the treatment of hypertension, diabetes mellitus, chronic cramp, cardiovascular disease**,** epilepsy, headache, menopausal symptoms, infertility, arthritis, rheumatism, convulsion distemper, haemorrhages, prevention of pregnancy (berries), cancer and a variety of 177 nervous system disorders, stroke, stomach problems, palpitation of the heart, difficulties in breathing, hot flushes, as an antispasmodic, emetic, narcotic tonic and nervine (Kafaru, 1994). It is therefore no surprise that mistletoe appears in legends and folklore as a cure all (panacea) (Samuelson, 1961).

Phytochemistry

Several chemical substances have been isolated and identified in non - African mistletoe plants. These include ML1, ML11, ML111 and chitin binding agglutinins. Steroids, triterpenoids, flavonoids (free and glycosylated quercetins, catechin, proanthocyanidins), acids etc, have been isolated from various foreign mistletoes (Wagner *et al.,* 1996; Fukunaga *et al*., 1989).

Because of existence of variabilities in phytoconstituents of mistletoe found in different geographical locations, even

though the European and other foreign mistletoes have been exhaustively researched, there is still no guarantee that same would be found in the our mistletoe, hence our interest on the plant

Pharmacological Activities

Scientific studies, especially of the European mistletoe have shown that composition and activities of mistletoes are host tree-, species- and harvesting period- dependent (Fukunaga *et al*., 1989; Obatomi *et al*., 1994; Scheer *et al*., 1992; Wagner *et al*., 1996). The macromolecular and micromolecular components of different mistletoes species sourced from different host trees may also vary. Hence we set out to investigate these effects on the Eastern Nigeria specie, *Loranthus micranthus.*

Our works on mistletoe

Safety of mistletoe

Mistletoes have been used for centuries without adverse effect. We studied the acute toxicity of mistletoe leaves sourced from five host trees, namely, *Persea americana* (Avacado tree), *Baphia nitida(*Abosi*)*, *Kola acuminata* (kolanut tree), *Azadirachta indica* (Neem tree) and *Pentaclethra macrophylla* (Oil bean, Ukpaka) (Osadebe *et al.,* 2004; Osadebe and Omeje, 2009). These studies show that the plant is practically safe. LD_{50} of 5900 to 11650 mg/kg are reported for *L. micranthus*. Two of the studied host trees, *Persea americana and Baphia nitida gave LD50 of* 116500 mg/kg each while *Kola acuminata*, *Pentaclethra macrophylla* and *Azadiracta indica* gave 5900 mg/kg

each.The host tree where mistletoe is parasitizing has tremendous influence on toxicity.

Anti- diabetic Activities of Mistletoes

Diabetes is a multi-systemic affliction that has impact on nearly every body organ. As a disease, it kills more individuals on an annual basis than AIDS and breast cancer combined (Shapiro and Gong, 2002). The impact on the quality of life of an individual from Diabetes is profound. There are a number of natural products currently existing that demonstrate hypoglycemic activity. There are approximately 800-1200 plants that exhibit hypoglycemic activity (Spainhour, 2005). Research and development efforts thus far are limited to traditional medicines uses.

Loranthus micranthus is used traditionally to lower blood sugar level in the management of diabetes. This was first scientifically investigated and documented by Obatomi and others (Obatomi,1994) on the northern Nigerian variant, *Loranthus begwensis* Obatomi and group demonstrated the verity of the anti- diabetic and anti -hypertensive use of *Loranthus begwensis* (mistletoe of Northern Nigeria). They gave hint as to the variability of these effects with different host-tree of the mistletoe (Obatomi, 1996). We designed our study of the antidiabetic effect of the Eastern Nigeria specie to assess its antihyperglycemic and hypoglycaemic effect in normoglycemic and alloxan-induced diabetes in albino rats(Osadebe et al, 2004). The five host trees utilized include: *Persea Americana* (Avocado tree), *Baphia nitida* (Abosi) *Kola acuminata* (Kolanut tree), *Azadirachta indica* (Neem tree) a*nd Pentaclethra macrophylla* (Oil bean,

Ukpaka). We intended that from the study, the host tree of the mistletoe with the highest anti- diabetic effect will be identified for more rational use in herbal medicinal practice. From our study(Table 4), it became evident that *Loranthus micranthus* possesses good anti- diabetic activity. The variation in the anti- hyperglycemic effect followed the order: *Kola acumunata* > *Azadirachta indica* >*Baphia nitida* > *Persea Americana* ≥ *Pentaclethra macrophylla*. In alloxan – induced diabetic rats, methanolic extracts from *Kola acumunata* and *Azadirachta indica* produced hypoglycemic effect depicted as percentage reduction in blood sugar levels of 83.2 and 84% respectively at 3 h of administration, which values were found to be statistically comparable to that of 82.05% produced by the standard drug, glibenclamide at the same time. However, the effect of extract of mistletoe from *Kola acuminata* was sustained, giving a slightly elevated effect at the 4^{th} hr and attaining a maximum reduction effect at 24 hr after administration. On the other hand, the effect of mistletoe parasitic on *Azadirachta indica* was maximum with the % reduction of 84.8 and dropped to 69.8% at the 4^{th} hour reducing to 66.9% at 24 hr. From the above result, we recommend that mistletoe intended for management of hyperglycemias should be preferentially sourced from *Kola acuminata* and *Azadirchta indica*. However, where longer duration of action is desirable to avoid repetitive dosage, the specie from *Kola accuminata* should be preferred.

Table 4

Percentage reduction in blood sugar level of normal and alloxan-induced diabetic rats by extracts of Lorathus micranthus at corresponding times

Dose of extract of *Loranthus micranthus*	*Percentage reduction in blood sugar level at corresponding times (h)*									
	1h		2h		3h		4h		24h	
	AI	Nor	AI	Nor	AI	Nor	AI	Nor	AI	Nor
Persea americana (200 mg/kg)	1.33	8.36	2.39	14.43	12.17	25.77	12.36	25.77	22.80	30.00
Persea americana (400 mg/kg)	21.25	13.81	37.79	22.18	58.12	26.00	58.59	27.89	82.59	35.99
Baphia nitida (200 mg/kg)	5.6	1.90	15.4	13.0	18.2	19.60	21.6	13.0	46.4	24.3
Kola acuminata (200 mg/kg)	35.9	7.30	37.3	13.8	83.2	24.3	84.2	28.4	84.7	47.5
Pentaclethra macrophylla (200 mg/kg)	5.3	13.1	10.8	24.9	19.1	26.2	13.2	24.5	13.2	33.6
Azadirachta indica (200 mg/kg)	59.9	1.7	79.9	14.4	84.8	22.8	69.8	16.1	66.9	27.9
Glibenclamide (10 mg/kg)	63.31	29.75	81.26	43.77	82.98	48.49	82.67	50.85	83.34	53.21

Percentage reduction = (BGL at time) x 100, where BGL = blood sugar concentration, Nor = normoglycaemic rats; AI = alloxan-induced rats.

As a follow-up of our preliminary work on the anti-diabetic activities of mistletoe, and with isolation of active principles in mind, we prepared four solvent fractions of *Loranthus micranthus* crude extract based on acid- base principles as described by Olaniyi and Ogungbamila (1998) and Osadebe *et al*., 2008). We separated the components of the crude mixture into neutral, basic, weakly acidic and strongly basic fractions denoted, by A, B, C, D respectively. The anti-diabetic activity resides manly in fraction C. Fraction C contains glycosides, steroids, terpenoids and carbohydrates. Animals treated with fraction A experienced continuous increase in blood glucose concentration, which

indicates prolongation of alloxan-induced hyperglycemia. This signifies a complete absence of any inhibitory effect on hyperglycemia by the alkaloid fraction. The alkaloids of *Loranthus micranthus* were found not to be responsible for its anti-diabetic effect.

The result of a comparative study (Uzochukwu and Osadebe, 2007) carried out with an extract containing mainly flavonoids (termed flavonoid rich extract) and a crude methanol extract (CME) showed that the former gave percentage blood sugar reduction in rats of 76.8% and 84.48% for 100 mg/kg and 200 mg/kg respectively while the latter gave 68.44% and 85.40% for 100 mg/kg and 200 mg/kg respectively. This indicates that the anti-diabetic effect resides also in the flavonoid content of the leaves of mistletoes

Anti-microbial activities of mistletoe

Mistletoe is reported to be used in local traditional medicine as an anti-infective agent (oliver-Bever B, 1986). From our study on mistletoe collected in November 2000, all the extracts, namely methanol, ethanol, chloroform and petroleum ether exhibited antibacterial activity (Osadebe and Akabogu, 2004). However, the standard drugs used namely nystatin and Gentamycin exhibited anti-microbial activities which were significantly higher than those of all the extracts. We went further to study the influence of season of harvest on the antimicrobial activity and phytochemical constituents of mistletoe extract (Osadebe *et al*., 2008). The result we obtained did not show any particular trend in the distribution of phytochemical

constituents across seasons. However, judging from the intensity of the colour of phytochemical reactions, the extract of the leaves harvested in January, April and July could be said to contain more tannins than that harvested in November. Flavonoids were more in July and November extracts while alkaloids were detected only in April and July. The antimicrobial activity of LM may be attributed to the presence of tannins, terpenoids and alkaloids. In fact, tannins and alkaloids are plant metabolites frequently reported to be responsible for the antimicrobial properties of most medicinal plants (Khwaja *et al*., 1996).

The two major seasons in the tropics, the rainy and the dry seasons are known for sharp differences in environmental factors like temperature, rainfall, radiation, daylight, evaporation, etc (Evans, 1993). These factors must probably affect the availability of certain precursors needed for the biosynthesis of plant secondary metabolites. The rate and extent of the bioreaction therefore vary from season to season. These variations as demonstrated from our study, exist from host tree to host tree (Osadebe and Ukwueze, 2004). We did a comparative study of phytochemical and anti-microbial properties of leaves of *Loranthus micranthus* harvested from six host trees namely:*Irvingia gabonensis*, *Pentaclethra macrophylla*, *Kola acuminata*, *Baphia nitida*, *Persea americana*, *Azadirachta indica*. The result showed marked variations in phytochemical constituents and anti-microbial activities of the extracts from the different host trees. Extracts from *K. acuminata* and *P. americana* showed a marked broad

spectrum of activity against bacteria and fungi, and compared well with standard antibiotics used as control.

Table 5: ***Results of the anti-microbial screening of extracts of mistletoe from six different host plants (MIC Determination***)

Host tree	Minimum inhibitory concentrations (MIC, µg/ml)					
	S. aureus	*B. subtilis*	*P. aeruginosa*	*S. typhi*	*A. niger*	*C. albicans*
I. gabonensis	4.31 ± 0.17*	3.53± 0.84	5.53 ±2.34	5.55 ±0.55	-	-
P. macrophylla	3.76 ± 0.25*	4.13 ± 0.59*	7.97 ± 1.81	-	-	-
K. acuminate	6.08 ± 0.23	4.19 ± 0.30**	7.16 ± 1.21	6.48 ± 0.68	5.06 ±0.14[a]	7.98 ± 1.86
A. indica	4.45 ± 0.20*	3.99 ± 0.19***	7.41 ± 1.21	-	-	-
P. americana	5.76 ± 1.27	7.11 ± 1.49	6.16 ± 0.49***	4.94 ± 0.20	4.63 ± 1.0	6.05 ± 0.32
B. nitida	7.28 ± 0.50	7.70 ± 1.38*	10.32 ± 0.32	-	-	-
(Control 1) Amoxycillin	6.95 ±0.64	1.19 ± 0.04	9.05 ± 0.74	2.43 ± 0.49	-	-
Control 2) Ketoconazole	-	3.86 ± 0.62	-	-	2.44 ± 0.07	4.26 ± 2.05

Each value represents the mean ± s.e.m, n = 3, *P < 0.02; ***P < 0.01 significantly different compared with control, Ketoconazole, Blank spaces indicate no observable inhibition (i.e. lack of sensitivity).

Table 6: Results of sensitivity tests of 10 mg ml $^{-1}$ petroleum ether extracts of Loranthus micranthus leaves

(Inhibition zone diameter (mm) Mean±SEM)

Months	*Staph aureus*	*Bacillus subtilis*	*Salmonella kapemba*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Candida albicans*	*Aspergilus niger*
Jan	14.7±0.67	13.3±33** *	10.7±0.67***	16.0±0.58	18.3±0.88	-	-
April	16.7±1.67	17.0±0.58	20.7±0.67	17.3±0.67	16.0±0.58	12.7±0.8	-
July	16.7±1.67	18.0±0.00	19.7±0.33	16.0±0.58	19.0±0.58	-	-
Nov.	14.7±0.33	16.3±0.33*	18.7±0.33*	16.0±01.0	14.7±0.33	-	-

Each value represents the Mean±SEM, n=3, *p<0.05**, p<0.01 significantly lower when compared with values obtained at the other months

Table 7: Results of sensitivity tests on 10 mg ml $^{-1}$ of different solvent fractions of Loranthus micranthus leaves

Inhibition zone diameter (mm + SEM

Fractions	*Staph aureus*	*Bacillus subtilis*	*Salmonella kapemba*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Candida albicans*	*Aspergilus niger*
A	20.7±0.33	18.0±1.00	15.3±0.58	18.0±1.0	14.5±0.88	16.0±1.0	-
B	13.5±0.25*	14.5±0.25 *	19.0±1.00	15.0±1.0	16.0±0.00	10.0±0.0*	-
C	-	-	15.0±1.00	-	-	-	-
D	14.0±0.0*	10.0±0.0^{b}	16.7±0.33	-	15.0±1.00	-	12.5±0.3*
Chlor	26.0±0.0	20.0±0.0	17.0±0.00	17.0±1.0	-	-	-
Nist	-	12.0±0.0	-	-	-	17.0±1.0	22.0±2.0

Each value represents the Mean±SEM, n=3, *p<0.05**, p<0.01 significantly lower when compared with the control drug, chloramphenicol and nystatin: A= Petroleum ether fraction, B = Chloroform soluble fraction, C = Ethyl acetate soluble fraction, D = Ethyl acetate insoluble. Chlor = Chloramphenicol, Nist = Nystatin

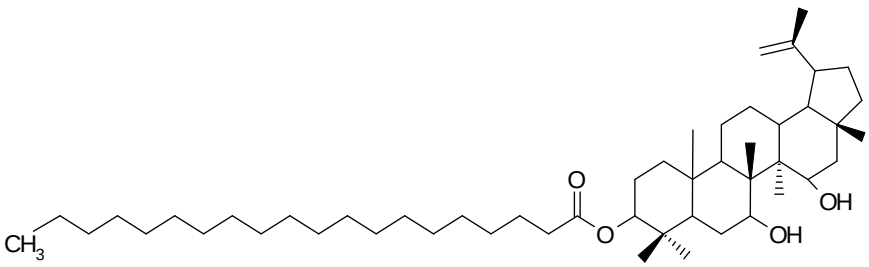
Alkaloids were found to be abundant in mistletoes parasitic on *K. acuminata*, *P. americana* and *I. gabonensis*. The preponderance of alkaloids in the extracts of the above mentioned hosts could be suggestive of a relationship between alkaloidal content and the antimicrobial activity. In summary, significant variations in antimicrobial activity was shown by extracts of the leaves of LM harvested at the different seasons and from different host trees. Extracts of the leaves harvested in April and July showed better activities. In practice therefore, mistletoe used for non-specific infections may be preferentially harvested both at the onset and peak of the rainy season and from *Kola acuminata*, *Persea Americana* and *I. gabonensis* (Osadebe *et al*., 2008).

Immunomodulatory Potentials of Mistletoe

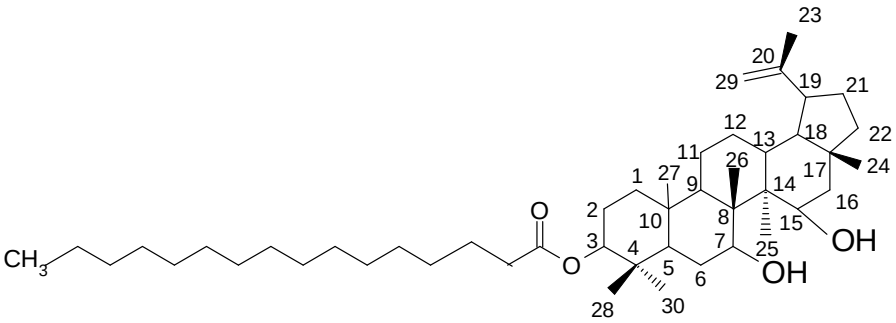
Based on the knowledge that stimulation of defense mechanistic pathways could be a possible means of inhibiting disease progression without necessarily eliciting harmful effect, and that the European species known as *Viscum album* possesses an established and pronounced immunostimulatory and anti-cancer activities, we opined that *Loranthus micranthus*, the local mistletoe, could also exhibit similar activity. We therefore evaluated the effect of mistletoe on the immune system (Osadebe and Omeje, 2009). The study showed that n-hexane , methanol and aqueous extracts elicited immunostimulatory effect following the use of three models; the total leukocytes and differential leukocytes count (TLC and DLC), delayed-type

hyper sensitivity reactions (DTHR) and antibody titration. Each model was performed by administering three different dose levels of 100, 200 and 400 mg/kg of each extract against standard control. However, the hexane extract did not produce observable stimulation of the humoral-mediated antibody titration response. Extracts of *Loranthus micranthus* caused release of leukocytes and lymphocytes in mice at a level almost twice that of the control in healthy mice, indicating potential immunomodulatory activity.

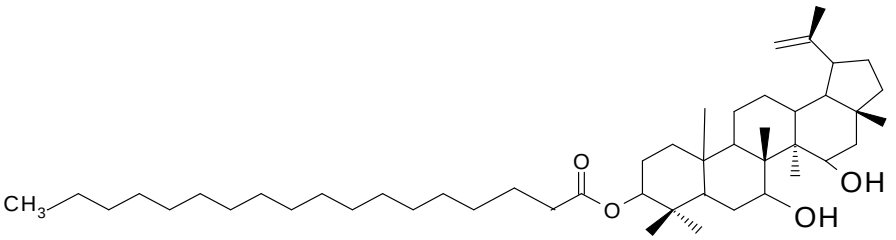
Three potential immunomodulatory isolates were obtained from the LM. (Omeje *et al*., 2011) They are lupeol-based triterpenoid esters and were isolated from an active hexane fraction of LM parasitic on kola tree namely:



III: Structure of 7, 15-dihydroxy-lup-20(29)-en-3β-O-decadecanoate



IV: Structure of 7, 15-dihydroxy-lup-20-(29)-en-3β-O-palmitate



V: Structure of 7, 15-dihydroxy-lup-20(29)-en-3β-O-stearate

When evaluated using the standard experimental methods, compound III showed some enhancement of the splenocytes at the tested doses of 5, 25 and 100 µg/ml but caused inhibition of the IL – 8 receptor expression at doses higher than 5 µg/ml. There is convincing evidence that the triterpenoid esters are good candidates for immune modulation. Similar compounds related to the three above have been reported in plants of other classes. Our report is

the first time these compounds were reported in the Eastern Nigeria mistletoe. The results are shown in Tables 8 and 9.

Table 8
Proliferation potentials of compound III on C57B1/6 Spleenocytes.

Drug	Dose (µg/ml)	% proliferation
Compound III	5	18.34 ± 1.56
Compound III	25	20.08 ± 0.83
Compound III	100	24. 44 ± 2.58
LPS	10	34.61 ± 0.44
Con A	2	34.01 ± 0.32
Control	Vehicle	7.69 ± 0.41

Table 9: ***Proliferation potentials of compound III on CD69 cells.***

Drug	Dose (µg/ml)	Stimulation	% yield stimulation
Compound III	5	2.45 ± 0.07	33.14
Compound III	25	2.71 ± 0.06	60.36
Compound III	100	3.16 ± 0.06	86.98
LPS	10	5.42 ± 0.11	220.71
Con A	2	5.27 ± 0.08	211.83
Control	Vehicle	1.69 ± 0.05	-

Mistletoe harvested from kolanut was the overall most potent in terms of immunostimulation and antioxidation with enhanced macrophage activation and cell proliferative abilities. *Bio- assay guided solvent fractionation of the*

crude extract using DTHR model showed the potency to flow in this order

Chloroform fraction >> ethylacetate fraction > n-hexane fraction > methanol fraction >acetone fraction.

DTHR is mediated by interferon-gamma (IFN – 7) (producing CD4 + TH1 or CD8 + TC1) T cells and usually takes 24-72 hr to develop and involves activation of T cells which result in mobilization of monocytes and lymphocytes to areas requiring immune stimulation. It is known to be initiated by reaction between antigen – specific cells and the antigen which results in the release of lymphokines that affects a variety of cell types especially macrophages (Omeje *et al*., 2011). Hence DTHR is an enhancement of lympho-proliferative response.

However, we observed that fractionation and purification of n-hexane extract produced single pure compounds that failed to strongly enhance certain cell types involved in the mediation of immunological reactions.

Anti-motility effects of mistletoe

Anti-motility agents are drugs used in the management of diarrhoea because of their ability to slow down excessive movement of the bowel usually characterizing diarrhoeal condition. Many antimotility agents had been used in the management of diarrhoea but none has found a place in the routine management of the illness due to their side effects after prolonged use (Gale, 2009). The search for an alternative remedy among developing countries from traditional herbal medicine was introduced by WHO to overcome the side effect of existing

anti-motility agents. Several plants have been reported to be useful in the management of diarrhoea. We investigated the anti motility effect of extracts and solvent fractions of mistletoe from six host trees. Results obtained showed that mistletoe has good anti-diarrhoeal properties. The effect varied among the different host trees. Extracts of LM parasitic on *Persia americana*, *Citrus simensis*, and *Pentacletra macrophylla* showed the highest inhibitory effect, even higher than the standard drug, atropine. Solvent fractionation led to reduced effect. All the fractions at a dose of 150 mg/kg exhibited inhibition of defeacation at degrees, comparable to that of Loperamide. The n-hexane and methanol fractions exhibited the highest activity. The difference in the anti motility effect is attributed to relative difference in the secondary metabolites in the host trees. (Osadebe *et al*., 2012). The anti -motility effect was earlier found to be dose-dependent (Osadebe & Uzochukwu, 2006).

Assay of Herbal Medicinal Products (HMP) of Mistletoe

Standardization and quality control of herbal medicinal products (HMPs) is an issue of current WHO concern. There have been evidences of unscrupulous adulteration of herbal medicines. Some vendors harvest medicinal plants at undesirable seasons and prepare them for sale not minding the quality in terms of desired therapeutic effect. Although WHO adopted a resolution (WHA 40.33) urging member states to ensure quality control of drugs derived from traditional plant remedies by using modern techniques and applying suitable standard,

this is yet to be actualized in most developing countries. The growing use of medicinal plant materials in the management of disease has created a corresponding need for reliable quality control methods for medicinal plant products.

The problem of adulteration is as serious an issue in HMPs as it is in orthodox medicines, even more with HMPs. Unscrupulous dealers even market exhausted plant materials as herbal remedies, scientifically proven inactive species are usually marketed as genuine just to sustain market and lucre.

Because of the rich traditional uses of mistletoe and the various variabilities associated with it, and to check adulteration, we undertook to develop and validate a method for the assay of the powdered leaves, extracts and formulations of *Loranthus micranthus* for the purposes of quality assurance and control. It is already accepted that, in such cases where the isolation and characterization of an active constituent need not be done or have not been done, the whole plant extract may be considered as one active constituent, in which case, the assay of one active marker substance may be adopted for its assay (EMEA, 2001). In actual sense, there could really be instances where the whole plant extract is responsible for the true activity of a phytomedicine. In such cases, fractionation and isolation had led to either loss of activity or diminished effect. It has been recommended that if a reproducible ultraviolet (UV) spectro-photometric fingerprint of the authentic herbal plant can be determined, such fingerprint can serve as a good identification and quantification

premise, and can be adopted for overall assay method for the plant material (EMEA, 2001).

We had in an earlier study found that the antidiabetic activity of *L. micranthus* may be attributed to the weakly acidic flavonoids content (Osadebe *et al*.,2006). Premised on this knowledge, we employed the method of complexation of the flavonoid (polyphenols) of *L. micranthus* with methanolic aluminum nitrate solution in the assay of its powdered leaves, its extracts and formulations. We found that while the crude methanolic extract absorbed maximally at 275 nm, the formed complexes showed strong absorption maxima at 300 nm.

Flavonoids are polyphenols containing highly conjugated systems, hence show intense absorption in the U. V. region of the electromagnetic spectrum (Harbourne, 1984). The bathochromic shift of this band to 300 nm on complexation with methanolic aluminum nitrate is highly characteristic and lends itself to UV- Vis spectrophotometer identification and assay of *L. micranthus* leaves, extracts and formulations. In literature, plant flavonoids such as quercetin, myricetin, morin, kaempferol and isorhamnetin have been chelated with methanolic aluminum nitrate and the resulting complexes subsequently detected fluorimetrically (Crozier *et al*., 2000)

The developed method was validated using accuracy, precision, repeatability and linearity testing procedures. We found the method to be simple, precise, reproducible and analytically suitable for the assay of powdered leaves, extracts and formulations of *Loranthus micranthus* sample.

Table 10: Result of optical characteristics of the complexation method for mistletoe assay

Parameter	Value
Wavelength	300 nm
Slope	0.0738±0.0042
Bears Law Limits	0.4 – 3.6 mg%
Intercept	0.2340±0.0108
Correlation Coefficient	0.9913±0.0010
Limit of detection	0.04 mg%
Limit of quantization	0.12 mg%

A careful perusal through the recently introduced Afrcan Herbal Pharmacopoeia revealed that in spite of the rich folkloric pharmaceutical and medicinal use of mistletoe, it is yet to be gazetted. We are proposing a complete monograph for mistletoe.

Challenges of Mistletoe Cultivation

A major issue with mistletoe is its parasitic nature which is a clear setback to its cultivation and use in preparation of phytomedicinals. It is always produced by seed and cannot be cultivated in the earth like other plants. Hence the ancients regard it as an ***excrescence***. It is grown by robbing the berries on the smooth bark of the underside of the branches of the tree till they adhere or by inserting them in the cleft made for the purpose (Grieve, botanical.com)

Alchornea cordifolia and *A. floribunda* Plants

Alchornea cordifolia, and *Alchornia floribunda* Schum-Thron (family, Euphorbiaceae) are shrubs usually found growing luxuriantly along the coastal regions of West Africa. The two plant species are traditionally referred to as IPORURU and are widely used in ethnomedicine for the management of a variety of inflammatory disorders found along the coastal regions of West Africa. *Alchornea cordifolia* is an important crude drug in the indigenous system of medicine for the management of pain, rheumatism, arthritis, pile, toothache and some other inflammatory disease states. In all the conditions, the ground leaves are applied to the aching places and wounds. Crushed leaves of *Alchornea castaneifilia* are rubbed on painful joints as an analgesic and beaten into a paste and applied to painful wounds. The leaf decoction of *Alchornea cordifilia* is used as an eye lotion and as an antibacterial in the treatment of common cold, cough and diarrhoea (VanMedendach de Roy, 1996). A decoction of the leafy twigs is applied as a wash for feverish chills, rheumatic pains and sores, and as an application for sore feet as lotion. The young leaves are applied with pepper and white clay as an enema and to prevent abortion (Bennett, 1950). *Alchornea florinbunda* is used traditionally as a local remedy for arthritis and muscular pain. The leaves are used to increase female fertility and are also highly regarded as a remedy for impotence. It is also used as an aphrodisiac and also for reducing sugar in the blood and urine. The powdered leaves are mixed with palm wine for the treatment of gonorrhoea. The root and stem bark

are used in the treatment of jaundice. The dry leaves are used to prepare hypoglycaemic infusions that are drunk after meals. The leaves are used internally for the management of gastrointestinal, respiratory and urinary tract infections and externally for wounds (Iwu, 1983).

Anti-Inflammatory properties of Alchornea cordifolia

Steroids are usually used for management of inflammation but they are usually associated with a myriad of untoward side effects. As a result, many non-steroidal anti-inflammatory agents (NSAIDs) have been prepared and marketed (Olaniyi, 2000) and have been used in the management of various inflammatory conditions like rheumatism, arthritis and breast pain. However, these drugs are known to provoke gastrointestinal irritation. This makes them widely unacceptable, especially in the elderly where the disease is more prevalent, hence the search for alternative anti-inflammatory drugs and medicines among the bounties of natural herbs (the biodiversity). Following from the ethnotherapeutic information already discussed above, we investigated the anti-inflammatory activity of *Alchornea cordifolia*.

Some constituents of the plant, *Alchornea cordifolia*, have been identified, mainly tannins, alkaloids and epoxyacids (Bennett, 1950). The pharmacological activities already investigated include anti-microbial activity, anti-amoebic, antidiarrhoeal and spasmolytic effects (Ebi, 2001; Tona *et al*., 2000). Hitherto, there is no scientific study validating the traditional anti-inflammatory use.

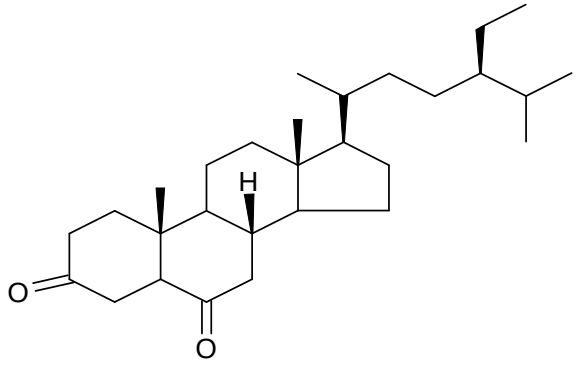
We confirmed the claim of its being beneficial in the management of different inflammatory disease states. The aqueous methanolic extract was found to exhibit anti-inflammatory activitiy. The terpenoid fractions and the tannin containing multi-component fractions were found to be responsible for the anti- inflammatory activities

Anti – Inflammatory effect of Alchornea floribunda leaves

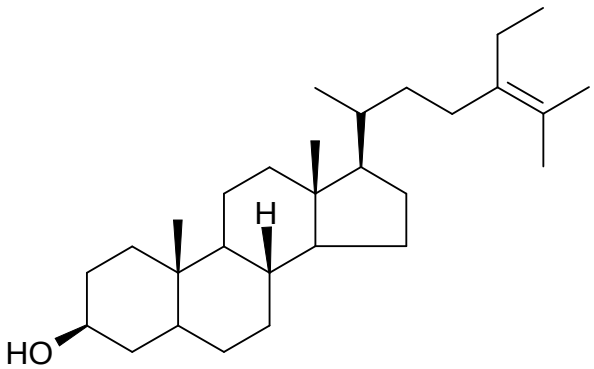
Okoye and Osadebe (2008) investigated the anti-inflammatory effects of the leaf extracts and fractions of *Alchornea floribunda* in experimental animal models of acute and chronic inflammation. The leaves of *Alchornea floribunda* were found to possess anti-inflammatory activity in acute and chronic inflammation. The n-hexane (HE) and ethyl acetate (EF) fractions were found to be the most active from the mechanistic studies. The mechanism of action may be a combination of inhibition of leucocytes migration and prostaglandin synthesis. Phytochemical investigation of the two most active fractions revealed the presence of terpenoid.(volatile oils, triterpenes and steroids in HE and flavonoids, tannins and saponins in EF)

Isolates from Alchornea floribunda

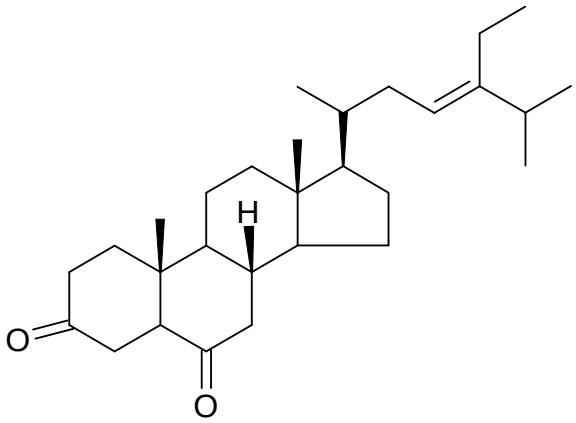
In 2008, we reported the isolation and characterization of three anti-inflammatory stigmastane steroids from the n-hexane extract of *Alchornea floribunda* leaves (Okoye, Osadebe, Esimone, Proksch and Nworu, 2008). Their structures are shown below



1; (24R)-5α-stigmast-3, 6-dione) **VI**



2: 3β-hydroxyl-5α-stigmast-24-ene **VII**



3; (5α-stigmast-23-ene-3, 6-dione), **VIII**

In the said work, compound I exhibited anti-inflammatory activity comparable to that of prednisolone while those of 2 & 3 were lower. Because the systemic use of steroids is usually accompanied by adverse effects, we chose rather to evaluate the potential of the isolated compounds as topical anti-inflammatory agents. The compounds caused significant inhibition of xylene-induced ear oedema in mice in a dose – dependent manner. Compounds 1 and 2 were respectively, 2.9 and 3.5 times more active than indomethacin used as positive control. This study by Okoye, Osadebe and others (Okoye and Osadebe, 2009; Okoye et al, 2009) is the first report on the isolation and characterization of anti-inflammatory stigmastane steroids from *Alchornea floribunda* leaves. However, some anti-inflammatory compounds which included a stigmastane steroid, ß – sitosterol were previously isolated from a related species, *Alchornea cordifolia* (Mavar-manga, 2008).

These isolated compounds have exhibited great promise as potential anti-inflammatory agents and can serve as lead structures for the discovery and development of better therapeutic molecules targeted towards some specific inflammatory diseases.

In our avowed determination to exhaust this plant with a view to discover suitable lead structures, we also isolated and characterized one new flavonol glycoside from ethyl acetate fraction of the methanol leaf extract. The structure was elucidated as 3, 5,7,3' – tetrahydroxy flavone – 3 – 0 – α – L – rhamnoside using joint spectral analysis involving UV, IR, ID and 2D (COSY) 1H – NMR spectroscopy. The compound showed significant inhibition of the rat paw oedema in a dose – dependent fashion. It is partially responsible for the observed anti-inflammatory activity of *A. floribunda* leaves (Okoye & Osadebe, 2010). The compound was first confirmed to be flavonoid from preliminary phytochemical and UV analysis. This work reported for the first time the isolation and characterization of this flavonol glycoside from nature.

Membrane -stabilizing effect of isolated flavonoid

The structure of the human red blood cells has been reported to be similar to that of lysosomal membrane components (White, 1999). We investigated the effects of the compounds on the integrity of the membranes of the human RBC *in vitro* (Okoye and Osadebe, 2008, Okoye et al). They were found to exhibit a membrane-stabilizing effect on human erythrocytes. The compounds significantly

inhibited heat- induced lysis of human erythrocytes in a dose-dependent manner.

Hepatoprotective and anti oxidant property of *Alchornea cordifolia*

We investigated the hepatoprotective and anti oxidant activities of *Alchornea cordifolia*. The anti-oxidant activity of leaf of *A. cordifolia* was determined using the DPPH free radical scavenging essay Osadebe et al., 2012). There is a lack of satisfactory liver protective drugs in orthodox medical practice for serious liver disorder. The liver is a major organ involved in metabolism, detoxification and excretion of various endogenous and exogenous substances such as xenobiotics. Such physiological activity of the liver results in the generation of highly reactive free radicals which covalently bond with membrane lipids causing lipid peroxidation. Lipid peroxidation is known to alter membrane permeability and cause tissue damage. The free radicals are implicated in diseases such as heart disease, diabetes, gout and cancer. Even though inbuilt anti oxidant systems in the body such as superoxide dismutase, tissue glutathione protect the tissues from free radical attack, excessive release of reactive oxygen species overcome this system in organ damage. This is where strengthening of inbuilt protective mechanisms and/or use of exogenous antioxidants come into play. Herbal drugs are known to play a role in the management of various liver disorders by speeding up the natural healing process of the liver. From the investigation we found out that *A. cordifolia* exerts significant protection

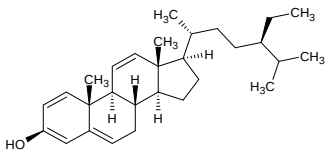
against CCl_4 – induced hepatotoxicity by its ability to ameliorate the lipid peroxidation through free radical scavenging activity. This may be attributed to the presence of antioxidants.

Hepatoprotective effect of *Landolphia owerіensis*

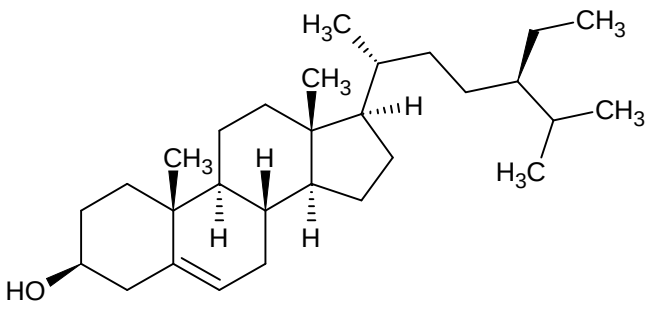
Landolphia owerіensis, locally known as “UTU”. *Landolphia owerіensis* P. Beauv. is a tropical plant economically important for latex/rubber and folklore medicine. It is used to cure so many diseases in traditional medicine, and its stringy seed pulp is freely eaten by man and animals. *Landolphia owerіensis* P. Beauv. is commonly known as white rubber vine or vine rubber. The root or green fruits are decocted in Côte d’ Ivoire, to make a steam bath to treat fever pains. The decoction of leaves is used as a purgative and as a cure for malaria. The stem bark is also reported to be a vermifuge; while in parts of Ivory Coast, the latex forms an ingredient of arrow poison. The latex is also used as a natural preservative (Anthony, 1995). There has been existing reports of the high content of anti-oxidants in *Landolphia owerіensis* which conferred to it some analgesic and anti- inflammatory properties.

We investigated the effect of this plant on the liver and found it to possess some hepatoprotective effect (Okonkwo and Osadebe, 2012). The hepatoprotective principles were isolated and characterized using spectral methods and identified as Hexadehydro β-sitosterol (IX), 3β-Sitosterol(X), 3β –simiarenol(XI) and ascorbic acid(XII). The isolated compounds marginally reversed thioacetomide- induced elevation of alanine transaminase (ALT), aspartate

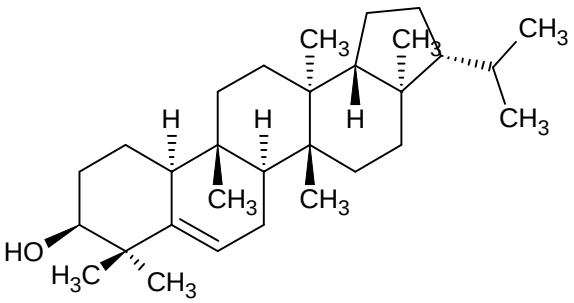
transaminase and alkaline phosphatase (ALP) compared to silimarin positive control, as well as reduced the hepatotoxin-induced rise of serum albumen (ALB, total protein (TP) and total bilirubin (both direct and indirect). Hepatohistology also confirmed mild hepatoprotective effect. Two papers from this were presented at the just concluded International Conference on Natural Products Research, held in Grand Hyatt Hotel, New Yok City, USA. Hepato-histology of the treated and control animals, further confirmed the mild hepatoprotective effect of *1, 2, 3, 4, 11, 12*-hexadehydrositost-*5*-en-*3β*-ol. Taken together, *1, 2, 3, 4, 11, 12*-hexadehydrositost-*5*-en-*3β*-ol is minor contributor to the confirmed hepatoprotective properties of *Landolphia oweriensis* P. Beauv stringy seed pulp; and is suspected to possess cholesterol lowering effect in animal models.



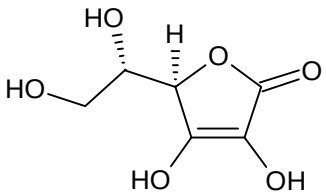
: *1, 2, 3, 4, 11, 12*-Hexadehydrositost-*5*-en-*3β*-ol (Hexadehydro-*3β*-sitosterol) **IX**



3*β*-sitosterol (X)
LOSP/CF-3



3*β*-Simiarenol
LOSP/CF-2 (XI)



(5*R*)-5-[(1*S*)-1,2-dihydroxyethyl]-3,4-dihydroxyfuran-2(5*H*)-one

This study has for the first time, isolated and elucidated the chemical structure of these important medicinal compounds from *L. oweriensis* P. Beauv. stringy seed pulp. It rationally indicated that consumption of this local snack is associated with great health benefits.

Mr. Vice – Chancellor Sir, beyond this lead discovery stage which has culminated in the isolation, purification and characterization of new natural compounds, and their testing against the target bioactivity, the next stage should be lead optimization. Semi-synthetic analogues of these compounds may turn out more active, less toxic and with few side effects. The best of such analogues are chosen to enter into preclinical trial state of drug development. Others will fall out of the development pipeline.

Major challenges of drug sourcing from nature

Do remember, Sir, I mentioned that in the drug development process, subsequent stages are usually more expensive. Natural products are usually too bulky for laboratory synthesis. Relying on biodiversity for continuous supply is often not expedient because of the danger of exhaustion and geographical variation as one moves from one bush to the other. Owing to various reasons, particularly because of habitat destruction and shrinking of forest area, it is no longer possible to meet the requirement of medicinal plants from wild or natural sources. These reasons stand against natural product drug discovery. Careful cultivation is the option but it usually may take years and there may be scarcity of land.

Herbal /traditional medicines

Originally, drugs used for therapy of disease were extracts of herbal origin. Pharmacopeoa of such era were containing preparations of therapeutic plants and minerals. However, nineteenth century brought a great expansion in knowledge of chemistry and ushered in a period of massive isolation and characterization of plant principles, structural modification of isolated compounds and from the scratch synthesis of medicinal compounds. Interest on herbal medicines has rekindled since the late 20th century and the dawn of the 21st century in developing countries like Nigeria and in the western world where it is believed that about 50% of the population use herb-derived preparations for treatment of ailments. The World Health Organization estimates that approximately 80 % of the world population relies primarily on traditional medicines as sources for their primary health care (Farnworth et *al*., 1985). Medications used in Africa and other developing countries involve both orthodox and herbal medicines, Greek and Roman medicinal practices as preserved in the script of Hippocrates advocated the use of few simple herbal drugs in conjunction with fresh air, rest and proper diet. On the other hand, Galen advocated the use of large doses of drug mixtures-including plant, animal and mineral ingredients (Falodun and Imieje, 2011). The current worldwide need of alternative medicine and growth of natural product restored the traditional systems of medicine into the market.

The traditional, complementary and the alternative medicine is attracting more and more attention within the context of health care provision and health sector reform. Their components are already being used in food as dietary ingredients, in traditional system of medicine for different ailments or as both food and medicine. The food substances are considered to be safe and nourishing, but

for those having medicinal properties and are prescribed for treatment of specific ailments, proper procedure to eliminate adulteration, contamination and toxic side effects are needed.

Since new diseases as well as drug-resistant strains of known pathogens continue to emerge, the search for novel compounds in combating many diseases and conditions is continuing globally. The scientific integration of herbal medicine into modern medical practices must take into account the interrelated issues of quantitative and qualitative assessment of bioresource, mass production and its appropriate use. The bottomline question is, if these herbs have been used for ages as medicinal remedies without adverse reports, why would they have to be subjected to years of testings and documentation before we harness their beneficial effects? The current worldwide trend towards the utilization of natural remedies has created an enormous need for information about the properties and uses of natural resources.

There has been a steady influx of herbal remedies into Nigerian market, claimed to have slimming effect. As a show of our social responsibility as research academics, and following from a report that a Ghanaian couple became diabetic while taking a slimming herbal product, we undertook to investigate the metabolic effect and phytochemical constituents of one such slimming remedy marketed in Nigeria known as Slimming Herb^{R} [German Herb (Thai) Company]. The plant is purported to be indicated for use by overweight or obese persons who do not want to control food intake. As at the time of our research in 2006, the product was not registered with National Agency for Food and Drug Administration and Control (NAFDAC).

The acute toxicity studies revealed the LD_{50} to be greater than 5000 mg/kg, meaning that the slimming herb

is safe for all practical purposes. The phytochemical analysis showed the presence of carbohydrates, flavonoids, steroids, resins, glycosides, terpenes and alkaloids.

Table 11: ***Effect of Slimming herb on blood sugar, total serum protein and serum cholesterol in rats calculated as percentage of baseline***

Test	Group	Percentage of baseline value (%)			
		Day 0	Day 1	Day 4	Day 7
Blood sugar	A	100.00±0.19	101.00±0.26	100.50±0.19	100.00±0.23
	B	100.00±0.19	103.10±0.20	*107.00±0.2	*112.30±0.20
	C	100.00±0.10	109.40±0.14	9	*120.80±0.15
	D	100.00±0.27	104.40±0.22	117.20±0.10	*123.80±0.14
				*107.90±0.2	
				1	
Total serum protein	A	100.00±0.01	100.00±0.01	100.80±0.02	104.50±0.02
	B	100.00±0.01	101.70±0.01	92.30±0.00	98.30±0.01
	C	100.00±0.00	*92.20±0.01	*69.50±0.01	*56.00±0.01
	D	100.00±0.00	*89.50±0.00	87.90±0.01	91.90±0.01
Serum cholesterol	A	100.00±0.01	102.10±0.01	105.30±0.01	107.40±0.01
	B	100.00±0.01	*91.40±0.01	*88.20±0.01	*63.40±0.00
	C	100.00±0.01	86.60±0.01	*21.20±0.00	*45.00±0.01
	D	100.00±0.01	*67.90±0.01	*41.90±0.01	*47.79±0.01

Value are expressed as mean±SEM, n=3, $p<0.05$, (0 day vs x day) was considered significant

Table 12: Effect of Slimming herb on fluid intake, food consumption and body weight in rats

Test	Group	Percentage of baseline value (%)				
		Day 0	Day 1	Day 3	Day 5	Day 7
Fluid intake	A		100.0	91.8	107.1	88.0
	B		100.0	76.8	61.0	70.4
	C		100.0	81.1	57.9	63.3
	D		100.0	69.1	58.8	51.9
Food consumption	A		100.0	105.7	83.4	97.9
	B		100.0	56.8	61.4	59.0
	C		100.0	67.3	59.2	61.2
	D		100.0	75.7	72.8	69.9
Body weight	A	100.00±8.5	101.18±8.8	99.4±11.4	99.9±12.5	100.9±13.4
	B	100.00±3.7	*92.8±2.2	**90.1±2.7	**88.5±2.7	**87.6±2.7
	C	100.00±13.0	**88.0±11.7	*77.7±9.8	*75.7±8.8	*74.6±8.4
	D	100.00±8.3	**88.3±6.8	*79.7±6.8	**76.2±6.4	**74.1±6.3

Value for body weight is expressed as means ± SEM. Values for fluid intake and food consumption are single point determinations.
*P < 0.05, (0 day vs x day) was considered significant **P < 0.05, (0 day vs x day) was considered significant

The results of the effect of Slimming Herb infusion on blood sugar, total serum protein and serum cholesterol in groups of rats that received the extract are shown in Tables 11 and 12 above

The slimming herb may be adjudged to be gluconeogenic. It is lipotropic, causing the breakdown of lipid and may have converted the broken down cholesterol and protein to glucose. The upshot of blood glucose caused by the herb may have activated a protein kinase, which has been proposed as a mechanism in the development of vascular diabetes complication. The slimming herb may aggravate disease conditions of diabetic patients and should be contraindicated in such patients. On a good note, it actually has a place in weight reduction. The mechanism may be by appetite suppression. A purgative side effect was also observed in rat which is common with most of the herbal slimming remedies. Further evaluation of the herb is recommended. However, I must point out that the use of

herbal remedies for weight loss purposes is not new and examples abound in the market

What used to be hindrances to drug sourcing from natural products using the traditional activity- guided approach are the usual problems associated with isolation and identification of the active ingredients, the long process of ensuring their pharmacological activities, seasonal, regional, geographical and taxonomical variations and processing methods have been overcome with the advent of two dimensional high performance isolation for much parallel HPLC. One can now load up to 5 gram of a natural product (NP) extract and isolate all compounds within 24 hrs and in sufficient amount for and in format amenable for direct HTS (Bindseil *et al.*, 2001). This revolutionary change in NP chemistry and discovery is changing the entire landscape of medicine development. Modern technology has revolutionalized the drug discovery process, and every day, new assays and techniques are being developed to facilitate and fast- track drug development research. With the advent of high throughput screening technology, combinatorial chemistry and biotechnology there will be a cutdown in the huge losses incurred by attrition in clinical trails.

Quality by design has been greatly advanced by the application of material science involving many pre-formulation calculations that allow for a high level of predictive and preemptive assurance of quality, thereby eliminating the traditional presumptive approaches that lead to product rejection at the end of production and manufacture**.**

Post-marketing product surveillance of multisourced generic products

Generic drug approvals are given by regulatory bodies based on the understanding that they have been manufactured in such a way that they will have similar pharmacokinetic properties as the innovator product. In practice, we have found out that it is not always the case. As certified public analyst, I have carried out the comparative in vitro bioavailability studies on a number of drugs. These generic alternatives are produced to be substitute of the original products in order to lower costs

We have done analyses on drugs like ciprofloxacin, metformin, piroxicam, lisinopril, etc. (Osadebe et al, 2003;Osadebe and Akabogu, 2004;Osadebe et al , 2011; Osadebe and Esimone, 2003, Okorie, et al, 2011a Osadebe et al, 2011b) The summary is that bioequivalence is not always achieved, which puts switchability of such with the innovator product in question. Caution must be exercised especially with the generics from India and China. Pharmacists in charge of drug stores and supplies should go extra mile to carry out tests to establish acceptable equivalence before stocking of generics to take the place of innovator products. On the other hand, availability of generic drug products have aided a great deal in making essential medicines available to large population of the average and poor people in the developing countries, in accordance with the expectation of the World Heallth Organisation.

Conclusion

My widow's mite, no doubt, has contributed in no small measure to further knowledge and discovery of medicinal products. We have not for now developed any product to the point of registration and marketing (I have not reached the **Apothecary)**. However, efforts will be made beyond this stage to cultivate one or two of these plants with a view to make herbal medicines from them available to the people. Herbal products and medicines are not as innocent as they are assumed. Hence, informed use of professionally packaged mistletoe and Alchornea extracts, fractions and formulations will be of great benefit to public health. Lack of financial resources may be a challenge but I believe God will make a way.

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Nigeria, Which way to go?

Nigeria is a country blessed with astounding resources. Yet it is a country of great lack. It is now cynically referred to as a country of paradoxes. For me, if I am to diagnose the disease plaguing this nation, I would say, it is the cankerworm of LAWLESSNESS. A country that does not respect rule of law and order cannot go far, no matter its perceived riches. Why should Nigeria be perambulating instead of maintaining a steady growth? Is it that the barber does not know how to barb or that the scissors is not sharp? In my own assessment**, I** do not see any physical reason why by this second decade of the 21st century, Nigeria cannot boast of potable water for all, good road networks and steady supply of power. When I think of the wantom destruction of human lives that take place daily on Nigerian highways because of lawlessness, I feel depressed. What baffles me most is why even the constructed roads last only for two years. It wets my eyes to see billions of Naira spent to build roads only for the

same to be destroyed within few years by uncontrolled and unguttered surface run-offs. Are we to believe that necessary engineering calculations and professional designs are not done before construction? May God deliver our beloved nation! Do we not have leaders who will lead us to agree to evolve a civilized and reliable society? As far as I am concerned, judging by what I see daily, we are not too far from the jungle. I have prayed to God to keep me alive to witness the dawn of a civilized era in Nigeria.

A major challenge of the pharmaceutical world in Nigeria is to see if we can research to have a truly African drug - discovered and developed in Africa. NICOSAN has been developed amd registered but it is not in circulation There is the need for industry- academic collaboration for the purpose of translation of the thousands of the research findings in the various academic and research institutions to marketable products. Some of the medicinal plants with validated activities will need to be cultivated in large expanse of lands for industrial exploitation. This is the only way steady supply of such can be sustained and industrial development of products from them worthwhile. What we purchase today as food supplements from GNLD, Forever Living Products, etc, are results of years of careful research, large-scale cultivation and development. I thank God for pockets of efforts I see here and there.
Once again, I want to thank God and our Vice-chancellor for this golden opportunity, and everybody here for the rapt attention.

Long live Nigeria
Long live University of Nigeria
Long live the great and noble profession of Pharmacy

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   Title: the Crisis in the Social Sciences: The Nigerian Situation
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   Title: Economic Science, Imperialism and Nigerian Development
3. **Prof. K. S. Hegde, Vet. Medicine – 1977**
   Title:
4. **Prof. D. I. Nwoga – 1977**
   Title: Visions Alternatives: Literary Studies in a Transitional Culture
5. **Prof. J. A. Umeh – 1977**
   Title: Land Policies and Compulsory Acquisition of Private Land for Public Purposes in Nigeria
6. **Prof. D. C. Nwafo – 1984**
   Title: The Surgeon as an Academic
7. **Prof. G. E. K. Ofomata – 1985**
   Title: Soil Erosion in Nigeria: The views of a Geomorphologist
8. **Prof. E. U. Odigboh – 1985**
   Title: Mechanization of cassava production and processing: A Decade of Design and Development
9. **Prof. R. O. Ohuche – 1986**
   Title: Discovering what Learners have attained in Mathematics
10. **Prof. S. C. Ohaegbulam – 1986**
    Title: Brain surgery: A luxury in a Developing Country like Nigeria
11. **Prof. I. C. Ononogbu – 1998**
    Title: Lipids: Your Friend or Foe

12. **Prof. V. E. Harbor-Peters – 2001**
Title: Unmasking some Aversive Aspects of Schools Mathematics and Strategies for averting them.

13. **Prof. P. O. Esedebe – 2003**
Title: Reflections on History, Nation Building and the University of Nigeria

14. **Prof. E. P. Nwabueze – 2005**
Title: In the Spirit of Thespis: The Theatre Arts and National Integration.

15. **Prof. I. U. Obi – 2006**
Title: What have I done as an Agricutlural Scientist? (Achievements, Problems and Solution Proposals)

16. **Prof. P. A. Nwachukwu – 2006**
Title: A Journey through the Uncharted Terrain of Igbo Linguistics

17. **Rev. Fr. Prof. A. N. Akwanya – 2007**
Title: English Language learning in Nigeria: In search of an enabling principle

18. **Prof. T. Uzodinma Nwala – 2007**
Title: The Otonti Nduka Mandate: From Tradition to Modernity

19. **Prof. J. A. Ibemesi – June 2007**
Title: From studies in Polymers and Vegetable oils to Sanitization of the Academic System

20. **Prof. Obi U. Njoku – June 2007**
Title: Lipid Biochemistry: Providing New Insights in our Environment

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Title: Re-inventing the Study of International Relations: From State and State Power to Man and Social Forces

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Title: Affluence and Affliction: The Niger Delta as a Critique of Political Science in Nigeria

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