CHEMOPREVENTIVES: UNTAPPED GENII THAT COMPROMISE THE SCIENCE OF THE "KILLERS"

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UNIVERSITY OF IBADAN

'CHEMOPREVENTIVES: UNTAPPED GENII THAT COMPROMISE THE SCIENCE OF THE "KILLERS"

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By

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The Vice-Chancellor, Deputy Vice-Chancellor (Administration), Deputy Vice-Chancellor (Academic), The Registrar and other Principal Officers, Provost of the College of Medicine, Dean of the Faculty of Basic Medical Sciences, Dean of the Postgraduate School, Deans of other Faculties and of Students, Distinguished Ladies and Gentlemen.

As I give this lecture on behalf of the Faculty of Basic Medical Sciences of the College of Medicine, I exalt, glorify and magnify the Almighty God, the King of kings, the Lord of lords; the One who was, who is and who is to come, the Giver and Preserver of life, the Source of wisdom and knowledge and whose inspiration gives men understanding. This lecture is coming up about ten years since I was promoted to the grade of a Professor of Biochemistry of this University. I am grateful to the Dean of our Faculty for giving me the opportunity to stand on this podium today to address the Vice-Chancellor and this distinguished audience within and outside the discipline of Biochemistry.

The first inaugural lecture from the Department of Biochemistry titled 'Power House of the Living Cell' was delivered by Professor Enitan Abisogun Bababunmi in 1982. The second lecture was delivered by my academic father, Professor Godwin Onyenoro Emerole, with the title 'Xenobiotics in Biochemical and Cellular Dysfunction'. Ten years later, Professor Anthony Osaigbovo Uwaifo delivered the third lecture titled, 'Cancer: A consequence of Cellular Break-down of Law and Order'. Professor Olufunso Olabode Olorunsogo delivered the fourth lecture in 2010 with the title 'From Power House to Pumps: Memoirs of a Mitochondriac'. Today with all sense of humility, I present the 5th inaugural lecture titled, "Chemopreventives: Untapped genii that compromise the science of the "Killers".

Introduction

My journey into Biochemistry and subsequently making academic a career was by divine arrangement. I graduated as

the best student at both the BSc and MSc levels in Biochemistry and as such had the option in the 80's of working in companies and industries with better pay as against my initial salary of less than ₦500 per month when I joined the services of this University. I recall that the Head of Department at that time, Professor Anthony Uwaifo, while descending the staircase of the old Biochemistry building, met me around 5 pm in the month of December 1989 and said, "Farombi, I'm going to recommend you for a job in the Department". I replied and said, "Sir, I did not apply for any job". He told me that the Departmental Academic Board just had a meeting and I was adjudged the best MSc student and that it is the tradition of the Department to always retain the best. I was thrilled and speechless about this comment. After sleeping over the information, it was impressed on me by the Spirit to take the job. I stand tall before you today to the glory of God Almighty, I have no iota of regret for venturing into the discipline of Biochemistry and making academics a career. As stated in the Holy Bible in Jeremiah 10: 23, "*The way of a man is not in himself, it is not in man that walk to direct his steps*".

Mr. Vice-Chancellor Sir, since joining the Department twenty six years ago I have supervised and trained one hundred and fifty MSc students, nineteen PhD students and several BSc students. Two of my former students are Professors, another is an Associate Professor and many others occupy senior positions in various industries, research institutes and oil companies across the country and abroad.

The Department of Biochemistry, University of Ibadan has been very outstanding in teaching, research and administration since its inception. Being a service Department, it occupies a prominent position in the College of Medicine and the University. The research capacity of the Department was further enhanced in 1979 when four research sections were created namely Membrane Biochemistry, Cancer Research, Nutritional and Industrial Biochemistry and Drug Metabolism and Toxicology Units. Over the years these four Units have advanced research in their specialized areas. I have the

opportunity of being trained by one of the older generation and a foremost Biochemist in the person of Professor Godwin Emerole in the area of Drug Metabolism and Toxicology. Today, I shall present some aspects of research conducted in this field.

Toxicology of Therapeutic Drugs

Plasmodium malaria, caused by *Plasmodium falciparum*, *Plasmodium vivax, Plasmodium ovale* or *Plasmodium malariae* is a serious disease affecting most of tropical Africa. About 3.3 billion people are at risk of malaria worldwide and about 215 million cases occur yearly with an estimated mortality of about 1 million (WHO 2013). Today, the efforts directed at controlling malaria are met with a series of daunting setbacks. While antimalarial drugs are becoming increasingly resistant to emerging strains of *Plasmodium*, vaccines so far developed have not been able to confer sufficient protection against the parasite. Nonetheless, chemotherapy, which is relatively cheap and accessible to most patients, still remains the most reliable remedy against the infection.

Amodiaquine and Chloroquine which belong to the class of 4-amino quinolines are widely used in the malaria endemic tropical regions of the world in the prophylaxis and treatment of malaria. Chloroquine in particular has wide therapeutic properties including analgesic, antipyretic and anti-inflammatory activities. These properties endeared chloroquine as the drug of choice to a number of countries in the tropics where malaria is endemic.

The current use of combinations of drugs to eradicate infection has raised serious concerns about the possibility of drug-drug interaction, which may potentiate toxicity. This development, therefore, necessitates judicious and efficient management of the few available antimalarial drugs. Both chloroquine and amodiaquine have still not left Nigeria market for chemosuppression and radical cure of malaria because they are cheap, rapidly effective and readily

available. Mefloquine, a quinoline methanol and halofantrine (HF), a phenanthrene methanol are two antimalarials introduced into the market after chloroquine and amodiaquine. Both have advantageous pharmacologic actions that require fewer doses thereby enhancing compliance.

Due to the multidrug resistant strains of *Plasmodium falciparum* that have emerged worldwide in recent times, all these antimalarial drugs have lost their potency and ability to radically cure malaria especially when used singly. Therefore, WHO recommended the use of Artemisinin Combination Therapy (ACT) as first line drugs for treating malaria even though some resistance to these drugs have also been reported in certain parts of the world especially South East Asia. The antimalarials are known to affect a wide range of biochemical processes in the living cell.

Our research unit in Biochemistry Department, named Drug Metabolism and Toxicology Research Laboratories, which recently metamorphosed to Molecular Drug Metabolism and Toxicology Research Laboratories, is reputed for its unique research and contribution to the Toxicology of Therapeutic Drugs. Following the earlier report of Emerole and Thabrew in 1983 on the interference of Chloroquine on drug metabolism, we investigated the changes in microsomal drug oxidizing enzymes, and microsomal lipids in rats treated with therapeutic doses of three structurally-related antimalarial drugs, Amodiaquine, Halofantrine and Mefloquine. We reported that these drugs inhibited the selected phase 1 drug oxidizing enzymes aniline hydroxylase, p-nitroanisole O-demethylase and pentoxyresorufin O-dealkylase (fig. 1) and interfered with microsomal lipids to varying extents, and this was related to the structural differences in the compounds (Farombi et al. 2000a).

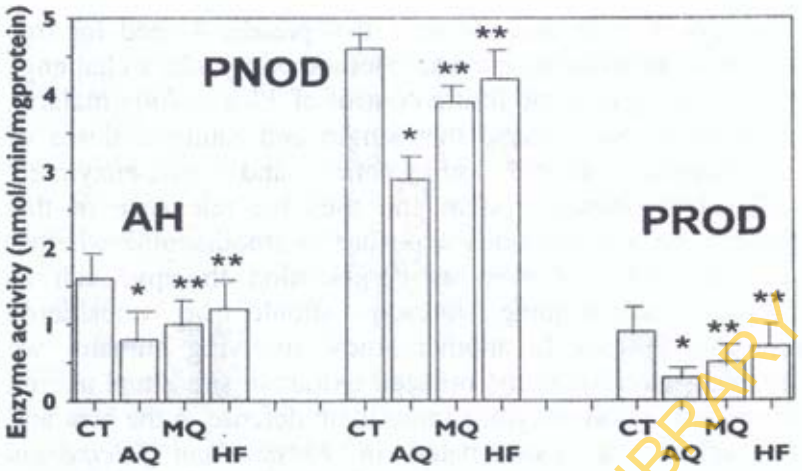


Fig. 1: Effects of therapeutic doses of antimalarial drugs on the activities of rat microsomal aniline hydroxylase, p-nitroanisole O-demethylase and pentoxyresorufin O-dealkylase activities. * Significantly different from control, P<0.001; **significantly different from control, P<0.005; CT, control; AQ, amodiaquine; MQ, mefloquine; HF, halofantrine; AH, aniline hydroxylase; PNOD, p-nitroanisole O-demethylase; PROD, pentoxyresorufin O-dealkylase. *Source*: Farombi et al. 2000.

A major event in malaria infection is increased production of highly Reactive Oxygen Species (ROS) (Wozencraft et al. 1984). A number of studies have demonstrated the susceptibility of erythrocytes infected with the human malarial parasite *P. falciparum* to oxidant-mediated damage (Wozencraft et al. 1984). Increased production of ROS in the whole blood was observed in *Plasmodium vinckei*-infected mice. Based on the ability of Fe^{2+}, ascorbate and H_2O_2 via Fenton and Haber-Weiss reactions to generate ROS, we investigated the role of these species in amodiaquine, halofantrine and mefloquine-induced oxidative damage in rats. We reported that the three antimalarial drugs induced lipid peroxidation and the effect was exacerbated in the presence of ROS (Farombi et al. 2001). This observation suggests that antimalarial drugs could exacerbate lipid peroxidation especially in conditions that result in an

elevation of ROS and the data also present a need for free radical control during malaria chemotherapy and a challenge for drug design in the future control of *Plasmodium* malaria. In addition, we showed that single and multiple doses of amodiaquine altered enzymatic and non-enzymatic antioxidant defense system and thus the relevance of this observation to continuous exposure to amodiaquine whether as single drug or even as combination therapy such as artesunate-amodiaquine therapy should be considered (Farombi 2000a). In another study involving humans, we showed that chloroquine induced oxidative stress and altered enzymic and non-enzymic antioxidant defense in the host and this effect was exacerbated in *Plasmodium falciparum* infected patients administered with the drug (Farombi et al. 2003). The implication of this study on the tissues, especially in malaria patients undergoing chloroquine treatment on a prolonged basis, warrants caution and supplementation with dietary antioxidant regimen.

Antimalarials and Genotoxicity

A number of studies have indicated the possibility of chemotherapeutic agents to induce mutagenicity apart from damaging tissue lipids and proteins. For instance, Fasunon and Uwaifo (1989) reported induction of prophage in *E. coli* D21 and D22 and chloroquine was demonstrated to induce frame shift mutation in *E. coli* and *Salmonella typhimurium* (Obaseki-Ebor and Obasi 1986). During my second post doctoral exposure at the Department of Pharmacology, Panum Institute, University of Copenhagen, Denmark with Dr. Lars Dragsted and Professor Stefen Loft as my Preceptors, I was introduced to a novel technique called "Comet assay" for assessing genotoxicity of environmental chemical compounds including therapeutic drugs. Following my interest in the toxicology of antimalarial drugs, I decided to set up experiments to investigate the possible genotoxic potential of the antimalarials, which we have studied at the cellular level.

The comet assay, or single-cell gel electrophoresis, is a popular tool for the measurement of DNA damage in individual cells. It has many applications, including measuring chemically-induced DNA damage and predicting the genotoxicity of potentially mutagenic and carcinogenic substances (Hartman and Speit 1995). It is also used for detecting DNA double-strand breaks, alkali-labile sites such as apurinic/apyrimidinic sites and DNA–protein crosslinks (Tice et al. 2000). In this connection, we investigated the genotoxic potentials of chloroquine using DNA strand breaks as endpoints in rat liver cells evaluated by the comet assay (figs. 2 and 3). Also, the genotoxicity of amodiaquine, halofantrine and mefloquine was evaluated. We also assessed the role of oxidative DNA damage in the genotoxicity by employing DNA repair enzymes endonuclease III (Endo III), which converts oxidized pyrimidines into strand breaks and formamidopyrimidine-DNA glycosylase (FPG), which removes specific modified bases from DNA to create apurinic or apyrimidinic sites that can be detected by the comet assay. Finally, we studied mechanisms underlying the genotoxic action of the drugs, by exploring role of free radical scavengers.

Our results showed that chloroquine, amodiaquine, halofantrine and mefloquine induced genotoxicity to varying extents and that ROS might play a role in DNA-damaging activities of the drugs (Farombi 2005, 2006). These data are very significant and will be important in considering the relative value of chemically-related antimalarials that are under development for radical cure of malaria in endemic zones of the world. According to WHO and subsequent adoption by Nigeria government on the use of artemisinin-based drugs as drug of choice owing to drug resistance, our recent studies on artemisinin especially at overdose warrants caution and regulation on its use. For instance, we showed that artemisinin decreased sperm quantity and quality with oxidative damage in the epididymis of rats treated with overdose of the drug (Farombi et al. 2014).

This study draws caution on the indiscriminate use, abuse and patients' noncompliance to normal prescription of artemisinin and its derivatives and as such healthcare providers in fertility clinics should advise patients to adhere to artemisinin prescription to reduce the risk of infertility especially in malaria-endemic countries. In the female rats, artemisinin in the absence of malarial parasite infection induced hormonal imbalance (decreased follicle-stimulating hormone and increased progesterone levels) and oxidative damage in erythrocytes and uterus but spared the ovary of rats (Farombi et al. 2015). Mr. Vice-Chancellor Sir, it is easily seen from our series of mechanistic studies on the antimalarials that these drugs are known to 'kill' malaria parasites but host cells are not exempted in their activities.

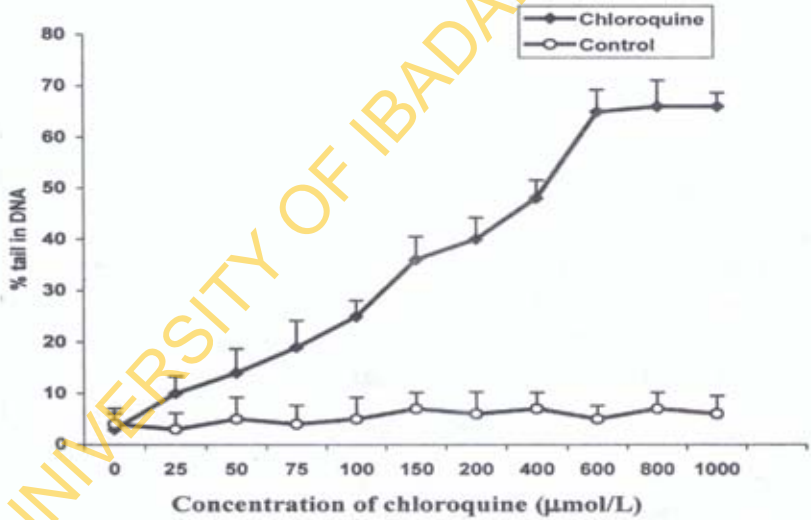


Fig. 2: Dose-dependent effect of chloroquine and no treatment (control) in rat liver cells. DNA damage (strand breaks) was measured as the percentage of tail DNA in the alkaline comet assay in rat liver cells treated with chloroquine (0–1000 µmol/L) compared with untreated cells (control). Values are mean ± SD of 5 determinations. *Source*: Farombi 2006.

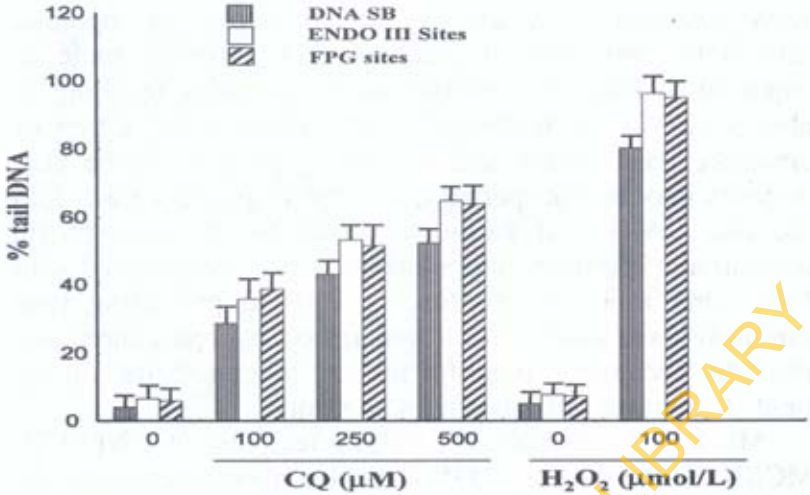


Fig. 3: DNA damage in rat liver cells exposed to chloroquine (CQ) at 37°C with post treatment with endonuclease III (ENDO III) and formamidopyrimidine-DNA glycosylase (FPG). DNA damage was measured as percentage of tail DNA. SB is strand breaks. Values are mean ± SD of 5 determinations. Hydrogen peroxide (H_2O_2) at a concentration of (100 μmol/L) was used as positive control. *Source*: Farombi 2006.

Environmental Toxicology Research

Diesel Exhaust Particles and Lung Cancer

Air pollution caused by diesel engine exhaust is a potential environmental risk factor for human health. Diesel exhaust particles (DEP) have a diverse mixture of chemicals including various Polycyclic Aromatic Hydrocarbons (PAHs), and nitrated PAHs adsorbed to the particle surface possess mutagenic and carcinogenic potentials (SCF 2002). Diesel exhaust (DE) has been shown to be a pulmonary carcinogen in experimental animals following inhalation (Mauderly et al. 1987). PAHs and nitro-PAHs adsorbed to the particle surface can form bulky DNA adducts and an increased level of DNA adducts in rat lung following inhalation exposure to DE. Also, DNA strand breaks can be induced by PAHs. The carcinogenic effect has been associated with an inflammatory response provoked by particle overload. DNA adducts and

ROS generated by DE are also thought to play an important role in the induction of mutations. The primary route of exposure to DEP is inhalation of the particles resulting in absorption via the respiratory tract. Through the action of clearance mechanisms and depending on size, shape etc., particles may be transported out of the respiratory tract, into the oral cavity and swallowed. Due to the atmospheric deposition of particles, crops may also be contaminated with DEP. Oral route of exposure to DEP in promoting lung carcinogenesis was not well understood by researchers and this later became an issue for me and other scientists in the field of chemical carcinogenesis, to resolve.

Mr. Vice-Chancellor Sir, I was a recipient of UNESCO-MCBN Fellowship in 2001 following recommendation by Professor GB Ogunmola of Chemistry Department to Professor Angelo Azzi, who was the International Chairman of the Fellowship Board at that time. I recollect that it took a long time after I had applied and was recommended before the fellowship was finally approved. Then, destiny took me to Mauritius in July 2001 as one of the speakers at the Society for Free Radical Research (SFRR-Africa) Conference where I met in person Professor Angelo Azzi. It was during breakfast one morning where I sat close to the Professor that I interacted with him and discussed the application. After the discussion, he gave me his complimentary card and told me to remind him about the application after the conference. He further told me he was very pleased with my presentation at the SFRR conference and that he would give further support to my research. Four months after meeting Angelo Azzi, I received an award letter to travel to the Institute of Food Safety and Toxicology, Soborg, Denmark. I had planned to work on another project but my host Professor Lars Dragsted who later became my very good friend introduced me to the project funded by the Danish Research Council and the Danish Ministry of Health, Research Center for Environmental Health on the role of oral exposure to DEP in lung cancer. **It was a great delight for me to be among the**

early researchers who investigated gastrointestinal exposure to DEP in lung carcinogenesis. Working with three giants in the field of chemical carcinogenesis—Dr. Lars Dragsted at Soborg, Professor Steffen Loft at Panum Institute, Copenhagen and Professor Herman Autrup of Aarhus University, Denmark whom I met for the first time in 1999 at the Pan African Environmental Mutagen Society (PAEMS) conference in Harare ably organized by Professor Julia Hasler, we investigated whether the lung is a particularly sensitive organ for DNA damage following gastrointestinal exposure to DEP. Employing the Comet assay, ^{32}P-post labeling technique and mutation analysis, we reported that the level of DNA strand breaks increased significantly at all dose levels of DEP exposure while the level of DNA adducts increased significantly only at the intermediate dose levels (fig. 4a).

Similarly, the number of oxidized DNA bases measured as endonuclease III and fapyguanine glycosylase (FPG) sensitive sites increased at the intermediate dose levels while the induction of DNA damage by DEP exposure did not increase the expression of the repair genes OGG1 and ERCC1 at the mRNA level (fig. 4b) (Muller, Farombi et al. 2004). Our study indicated that the lung is a sensitive target organ for primary DNA damage following oral exposure to DEP. The results of the study caution on the human exposure to environmental pollution resulting from carcinogenic compounds in exhaust particles from worn out engines.

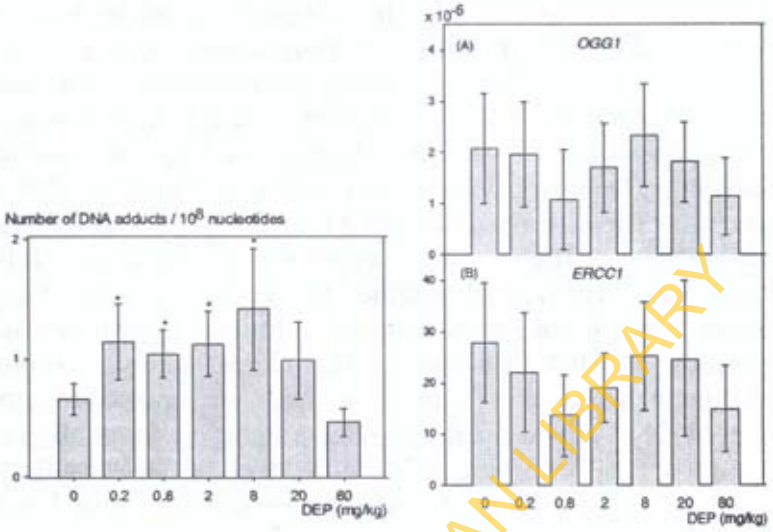


Fig. 4: (a) Level of DNA adducts in lung of Big Blue® rats after oral administration of DEP for 21 days. Values are shown as mean ± S.D. (n = 6). $P < 0.05$ as compared to control; (b) The expression of (A) OGG1 and (B) ERCC1 mRNA in lung of Big Blue® rats after oral administration of DEP for 21 days. Values are shown as mean ± S.D., n = 6. The expression are normalized to 18S or mRNA level. *Source*: Muller et al. 2004.

Environmental Chemicals and Reproductive Toxicity

On returning to Nigeria in 2002, my interest was further stimulated in research activities involving environmental compounds and how they affect specific target organs. First, my attention was drawn to the recent scientific findings on human reproduction which revealed that infertility may affect 15–20% of couples in industrialized countries (Oehninger 2001) compared with 7–8% of couples during the early 1960s and which has become a global health concern in recent decades following reports of the adverse effects of certain environmental chemicals on reproductive function. Male-factor infertility accounts for up to half of all cases of infertility and affects one in twenty men in the general population (McLachlan and de Krester 2001). Giwa-Osagie (2003) reported that of adult couples in African countries, 10–

25% are subfertile, and male-factor infertility accounts for 30–40% of these cases. According to his report, Nigeria has approximately 12 million infertile persons. Based on the avalanche of information on the possible role of environmental chemical compounds in male reproductive dysfunction, I engaged two MSc students Mr. Isaac Adedara and Mr. Sunny Abarikwu to study in my laboratory the influence of di-n-butylphthalate, a compound widely used as a plasticizer in cellulose plastics, as a solvent for dye, and for a variety of consumer products on male rats. I am happy to report that these two gentlemen who are now established investigators in the field of reproductive toxicology earned PhD degrees under my supervision and they came out excellently well. For instance we published 9 articles in highly focused and specialized international journals in Andrology from the thesis of Dr. Abarikwu. These publications are reference points today on Atrazine reproductive toxicity. Dr. Adedara is a Lecturer 1 with me in UI and Dr. Abarikwu is presently a Senior Lecturer in the University of Port Harcourt. In collaboration with my good friend, Professor Oyeyemi of Veterinary Reproduction and Surgery, we reported the testicular toxicity of Di-butylphtalate in male rats (Farombi et al. 2007).

Bonny Light Crude Oil Toxicity

Our next series of research works involved the reproductive toxicity of Nigerian Bonny light crude oil produced in the Niger Delta basin of Nigeria. Accidental or occupational pollution of the environment with petroleum is of great health concern especially in the Niger Delta region of Nigeria. Significant data have been collected from monitoring the effects of unintentional oil spills, providing ''real-world'' environmental information. Both animals and humans may be exposed directly or through the food chain. In actual fact, one of my PhD students, now Head of Department of Biochemistry in one of the South Eastern Nigerian universities, Dr. Ebokaiwe showed that humans can be

exposed to BLCO via the food chain (Ebokaiwe 2013). Interestingly, humans can be exposed to BLCO deliberately via oral route as some people believe in its folkoric use in the treatment of gastrointestinal disorders and convulsion in children.

Preliminary report of Orisakwe et al. (2004) implicated BLCO in testicular toxicity but information regarding its mechanisms of reproductive toxicity was lacking until we demonstrated for the first time that BLCO exposure induced significant reduction in testes weights, epididymal sperm counts, testicular sperm number, daily sperm production with increased oxidative stress (fig. 5) and sperm abnormality (Farombi et al. 2010). The quantification of tissue concentrations of biometals revealed bio-accumulation of toxic metals, including nickel, lead, copper and iron, in testes of rats (fig. 6) exposed to BLCO (Adedara et al. 2013a). Thus, ROS generation in tandem with heavy metal bioaccumulation (especially in the testes) through our data have been implicated in BLCO testicular toxicity.

In order to elucidate the mechanism of reproductive toxicity of BLCO, we investigated the influence of BLCO on steroidogenesis, hypothalamic-pituitary-testicular axis and pituitary-thyroid axis functions in BLCO-treated rats. This was the first study to evaluate the effects of BLCO on the endocrine system. Using Western blot technique, we showed that BLCO exposure suppressed the expression of steroid acute regulatory protein which mediates the rate-limiting step in steroid hormone biosynthesis by facilitating cholesterol transfer from the outer to the inner mitochondrial membrane, and androgen-binding protein expression, a secretory product of Sertoli cells which regulates spermatogenesis by specifically binding to testosterone with high affinity (fig. 7). This protein is considered as a biological marker for Sertoli cell function.

The effect of BLCO on these proteins was accompanied with concomitant decrease in 3β-hydroxysteroid dehydrogenase (HSD) and 17β-hydroxysteroid dehydrogenase

activities (figs. 8a and b) and decreased plasma concentrations of follicle-stimulating hormone, luteinizing hormone, prolactin and intratesticular testosterone and elevated thyrotropin, triiodothyronine and thyroxine (Adedara et al. 2014a, Ebokaiwe et al. 2015a). Our recent report showed that the interference of BLCO on endocrine function is accompanied by generation of ROS in testicular system thereby enhancing oxidative stress (Ebokaiwe et al. 2015a). The data indicate that undue exposure to BLCO has an inhibitory effect on testicular steroidogenesis and may involve its disruptive effect on the brain-pituitary-testicular axis thus highlighting the potential risk to public health for a population where, unfortunately, oil spillage occurs frequently.

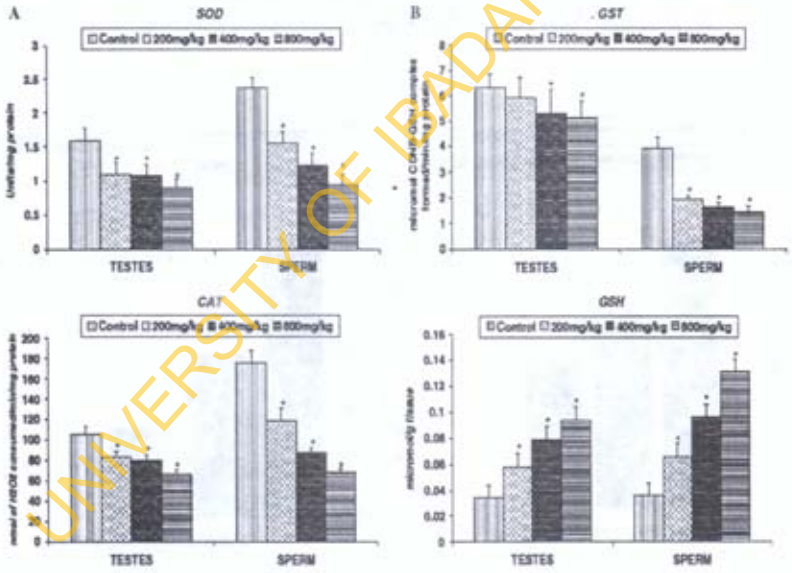


Fig. 5: Effect of BLCO on the activities of SOD, CAT, and GST and GSH level in rat after 7 days. Each bar represents mean ± SD of 12 animals. *Values differ significantly from control ($p<0.05$). *Source*: Farombi et al. 2010.

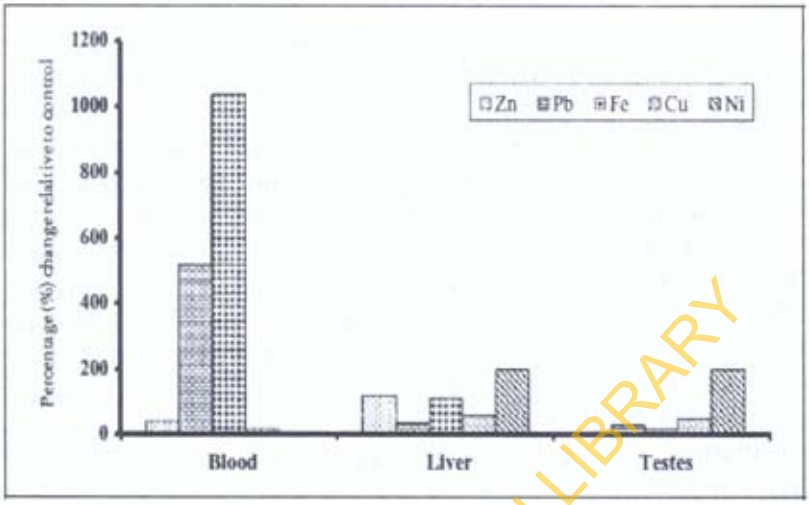


Fig. 6: Relative percentage change in metal concentrations in the tissues of rats exposed to bonny light crude oil. *Source*: Adedara et al. 2013.

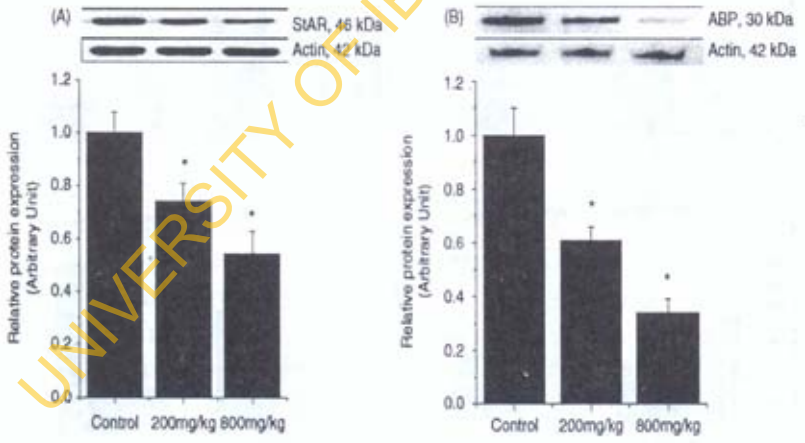


Fig. 7: Effects of BLCO on StAR (A) and ABP (B) expression in adult male rats (n.7). Data are expressed as mean ± SD. *Values differ significantly from control ($p<0.05$). *Source*: Adedara et al. 2014a.

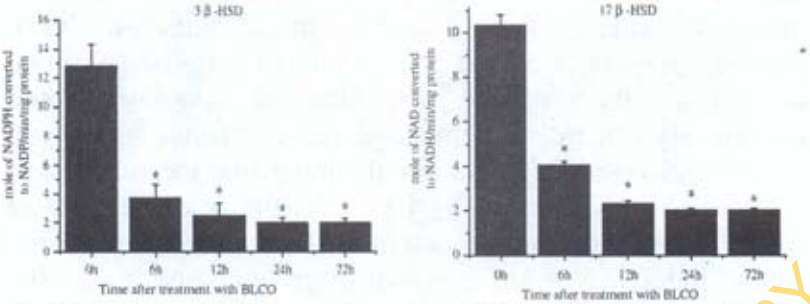


Fig. 8: (a) Effect of BLCO on the activity of 3ß -HSD in the testis of adult rats over different time points. (n=4) per time point. *; statistical significance at $p<0.05$; (b) Effect of BLCO on the activity of 17ß -HSD in the testis of adult rats over different time points. (n=4) per time point. *; statistical significance at $p<0.05$. *Source*: Adedara et al. 2014a.

In order to fully comprehend the toxicity profile of BLCO, we carried out reversibility studies in the liver of rats, knowing the ability of the adult liver to restore its function and mass after injury or extended resection. Thus, considering the defence capacity of the body, the question then arises as to whether hepatic damage resulting from exposure to BLCO is transient or permanent. In rats treated with BLCO for 21 days and treatment withdrawn for another 21 days, there was significant hepatotoxicity and increased oxidative stress, which was not reversible upon withdrawal of treatment within the time course of investigation in male rats (Adedara and Farombi 2012). These results are novel and have significant implications for human health especially, if extrapolated to individuals using BLCO as folklore medicine.

BLCO and Apoptosis

Cell death by apoptosis is a part of normal development and maintenance of testicular homeostasis. During various stages of spermatogenesis, an adequate amount of germ cells are eliminated via the process of apoptosis in order to maintain a precise germ cell population in compliance with the supportive capacity of the Sertoli cells. The two divergent

pathways of testicular apoptosis namely, the receptor mediated Fas/FasL pathway and the mitochondrial-mediated pathway play an important role in maintaining the germ cell population. Inappropriate activation of apoptosis could enormously jeopardize spermatogenesis and hence fertility. In order to gain further insight into the molecular mechanisms of gonadal toxicity induced by BLCO, using a single dose of BLCO (800 mg/kg), we determined the levels and time-course induction of stress response proteins and apoptosis-related proteins like cytochrome c, caspase 3, procaspase 9, Fas–FasL, NF-κB and TNf-α to assess sequential induction of apoptosis in the rat testis and DNA damage assessed by TUNEL assay. We showed that single dose exposure of BLCO to rats resulted in a significant increase in the levels of stress response proteins and apoptosis-related proteins and DNA damage as revealed by time-dependent increase in the TUNEL positive cells of testicular cells as early as 6 h (fig. 9) (Ebokaiwe et al. 2015b). The data demonstrate that single dose exposure of rats to BLCO induced apoptosis via FasL and mitochondria-mediated apoptosis pathways in testis of adult rats.

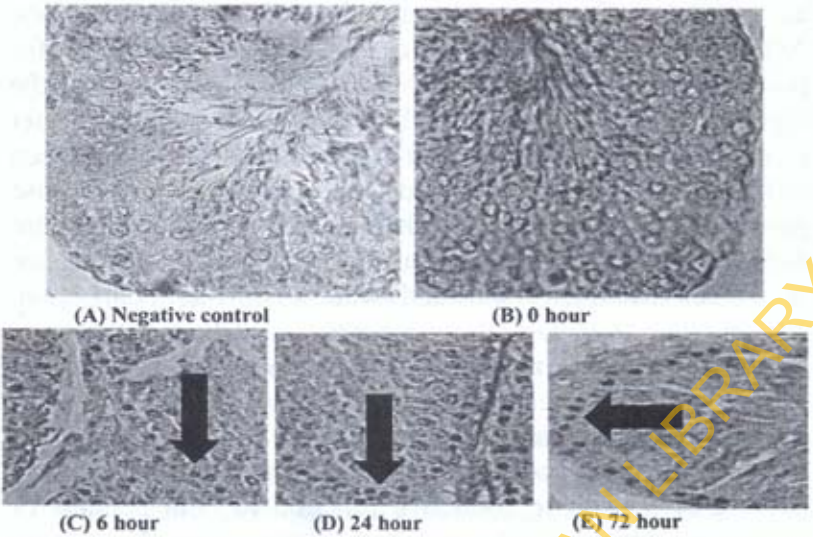


Fig. 9: BLCO-induced germ cell death in the testis of rats as revealed by TUNEL assay. Representative images for TUNEL staining in negative control (a), control (b), 6 h (c), 24 h (d) and 72 h (e) post-treatment groups. The TUNEL-positive cells (arrows) are found in the peripheral region near the basement membrane of the seminiferous tubules. A time-dependent increase in the number of apoptotic cells in the testis of BLCO-treated rats may be noted. *Source*: Ebokaiwe et al. 2015b.

Atrazine Toxicity

In continuation of our works on 'killer' environmental pollutants and contaminants as they affect human health, we carried out a series of research works on biochemical and molecular mechanisms of action of Atrazine in rodent models. The herbicide Atrazine (ATZ) (2-chloro-4-(ethylamino)-6-(isopropylamino)- s-triazine) is a widely used broad-spectrum pesticide with selective application in pre- and post-emergent control of weeds in corn and sorghum fields. It has been estimated that 76.4 million pounds of ATZ is used annually in the United States alone (Stoker et al. 2002). Besides its widespread use in the control of broadleaf and grassy weeds in a variety of crops, ATZ is a potential contaminant for surface and ground water sources (Koskinen

and Clay 1997). United States Environmental Protection Agency has classified ATZ as "priority A" chemical for potential ground water contamination and it was ranked the highest of 83 pesticides for potential ground water contamination (Abarikwu and Farombi 2012). It has been estimated that between two and three million people who use ground water as the source of their primary drinking water are exposed to Atrazine contamination because of its persistence in the environment (soil and water). In this connection, atrazine and its metabolites have been identified in the urine of occupationally-exposed males (Buchholz et al. 1999).

Atrazine and Reproductive Dysfuntion

Atrazine has been considered an endocrine disruptor, causing adverse effects on reproductive function in both genders of several mammalian and non-mammalian species (Friedmann 2002; Spano et al. 2004). For instance, the alterations in hormone levels by atrazine have resulted in a number of reproductive and developmental effects, including delay in vaginal opening in the females, altered estrus cyclicity, decreased fertility, increased pre-implantation and post-implantation loss in animal models, inflammation of the prostate, and possible implications for breast cancer in women (Stoker et al. 1999). Previous studies reported the testicular toxicity of ATZ. However, none of the previous studies examined the mechanisms of its toxicity. We reported for the first time, the spermatogenesis and morphological changes of testicular and epididymal sperms in ATZ-treated rats and that these changes occurred via mechanisms involving oxidative stress (Abarikwu et al. 2010; Farombi et al. 2013).

Prior to our mechanistic studies on ATZ-mediated cytotoxicity, the cellular and molecular events involved in ATZ-induced infertility were poorly understood. We therefore investigated ATZ-induced transcriptional changes in selected markers of steroidogenesis in primary cultures of rat interstitial Leydig cells. We reported for the first time, a

dose dependent induction in the levels of mRNA expression of genes of steroidogenic acute regulatory protein (STAR), cytochrome P45011A1, 3β-hydroxysteroid dehydrogenase (3β-HSD) and other steroidogenic proteins in cells exposed to ATZ using quantitative Real time PCR (Abarikwu et al. 2011a). In addition to these genes, the mRNA expression of CYP17A1, inhibin-α (INH-α), androgen receptor (AR), estrogen receptor-α (ER-α), and luteinising hormone receptor (LHR) also increased (Abarikwu, Pant and Farombi 2013) (fig. 10).

Steroidogenesis starts with the transfer of cholesterol by STAR into the mitochondria to the site of action of CYP11A1 which then converts cholesterol to pregnenolone. Pregnenolone is converted to progesterone by 3β-HSD and the conversion of progesterone to androstenedione is catalyzed by CYP17A1 (Payne and Youngblood 1995). The main control of this process occurs through the binding of luteinising hormone to its receptor (LHR) on the Leydig cell membrane, which is also coupled to the cyclic-AMP signaling pathway, to stimulate the production of testosterone de novo from cholesterol. However, we observed increased gene expressions of the tested genes either in the presence or absence of cyclic-AMP in the medium suggesting that ATZ may not always require cyclic-AMP signalling to up-regulate the expressions of steroidogenesis genes. Our data are novel and significant and suggest the application of these selected marker genes of steroidogenesis as indicators of short term exposure of ATZ-induced testicular toxicity in rats interstitial Leydig cells (ILCs).

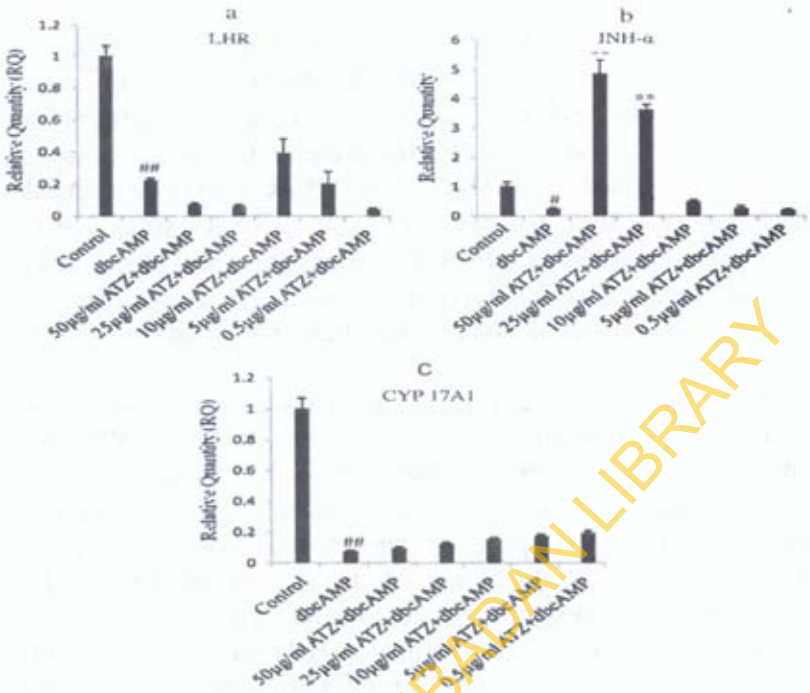


Fig. 10: Real-time quantitative RT-PCR analyses of Leydig cell mRNA for (a) luteinising hormone receptor (LHR), (b) inhibin alpha (INH-a), (c) cytochrome P450 17A1 (CYP17A1) from control and atrazine-exposed (0.5–50 lg/ml) interstitial Leydig cells at 2 h post treatment. *Source*: Abarikwu, Pant and Farombi 2013.

Atrazine and Neurodegenerative Diseases

The contribution of environmental contaminants to the aetiology of neurodegenerative diseases, such as Parkinson's disease (PD), is now being broadly recognized (Di Monte 2003). Of importance, a recent twin study for PD incidence indicated that genetic factors do not play a major role in causing adult onset PD (Tanner et al. 1999). While several environmental factors have been implicated in the aetiology of PD, the evidence for a positive relationship between PD incidence and pesticide exposure is increasing (Lockwood 2000; Le Couteur et al. 1999). Specifically, atrazine was reported to work as a potential contributory risk factor for Parkinson's disease and other neurological disorders where

dopamine levels were depleted (Filipov et al. 2007). Many of the toxicological studies conducted so far have focused primarily on the effects of ATR on the endocrine and reproductive systems. Neurotoxic potential of ATR, especially the underlying molecular mechanism, was poorly understood. In this connection, we selected the SH-SY5Y human neuroblastoma cell line as a model system to define the mode of cell death-induced by ATR in a human dopaminergic system by exploring novel markers of oxidative damage and apoptosis. We reported in SH-SY5Y cells that ATR induced generation of reactive oxygen species (ROS), cell death and cell proliferation.

Furthermore, ATZ increased leakage of lactate dehydrogenase (LDH), inhibited cellular LDH activity, mediated nuclear changes associated with apoptosis; including nuclear fragmentation, condensation, DNA laddering, increased caspase-3 activity and changes in the expressions of p53, Bax, Bcl-2, p21, and mRNA levels of caspase-3 and caspase-9 (Abarikwu, Farombi and Pant 2011). Our data demonstrate that ATZ mediates apoptosis by mechanisms involving ROS generation mediated through the Bax/Bcl-2 ratio and caspase-3-dependent pathway (Abarikwu and Farombi 2015). Using Flow cytometry, we confirmed the involvement of ROS in ATZ-induced apoptosis in PC12 cells (a rat pheochromocytoma), another cell possessing most of the functional expressions of neuronal cells used extensively in neurobiology studies (Abarikwu, Farombi, Kashyap and Pant 2011).

Municipal Landfill Leachates and Toxicity

Hazardous wastes are those that hold a substantial potential risk to human health or environment when improperly treated, stored, transported, disposed off or otherwise managed. Waste could be classified as industrial, biomedical and municipal solid waste (Bhargav et al. 2008). The increasing solid waste generation in and around major urban centres in Nigeria now (especially in Lagos metropolis,

Ibadan and Kano) due to industrial growth and rural-urban migration, has been one of the biggest environmental challenges (Farombi et al. 2012). Landfilling is a common method for the management of municipal solid waste in many developing countries. For instance, Olushosun landfill—a site situated at an excavated site North of Lagos metropolis in Ojota, Lagos State, has been identified. The site is surrounded mostly by middle-density residential areas with pockets of low and high-density residential areas and has been reported to receive more commercial and mixed industrial wastes than any other landfills in Lagos (Olorunfemi 2011).

A major problem arising from uncontrolled landfill/waste dumpsites is the generation of leachates caused by bio-chemical decomposition of organic or biodegradable portion of the wastes and the percolation of rainwater through the wastes (Farombi et al. 2012). Leachates resulting from uncontrolled landfill sites are often a common source of pollution for groundwater aquifers and surface waters. For example, the groundwater sources within 2 km radius of the Olushosun landfill has been reported to be contaminated by heavy metals which was largely associated with the dispersion of chemical constituents from leachate produced at the landfill (Oyeku and Eludoyin 2010).

We reported that the physicochemical characteristics including total alkalinity, total acidity, total hardness, biochemical oxygen demand and chemical oxygen demand, as well as the concentrations of copper, lead, cadmium, arsenic, cobalt, chromium and mercury of Olushosun municipal landfill leachates (OMLL) were higher than acceptable limits by international regulatory authorities (Farombi et al. 2012) and when administered to rats at different doses significant hepato-toxicity was observed. The toxic chemicals such as heavy metals and organic compounds that are present in leachates could be assimilated by aquatic species, pass through the food chain and bioaccumulate upon long-term exposure with potential implication for humans who depend on aquatic products as sources of food. The

deleterious influence of leachates from landfills on aquatic and human health is underscored by our studies on Ogun River, which flows in Ogun State of Nigeria and located to two heavily industrialized cities Lagos and Sango-Ota in Nigeria. The river serves as sources of drinking water, fishing and other domestic uses for the population.

Using Bulk Scientific Atomic Absorption Spectrophotometer, we reported marked accumulation of the metals in the organs of African cat fish (*Clarias gariepinus*) from the Ogun River. Heavy metal accumulation was associated with alteration in the antioxidant enzymes of the fish and induction of lipid peroxidation (Farombi et al. 2007). This study therefore provides a rational use of biomarkers of oxidative stress in biomonitoring of aquatic pollution. Mr. Vice-Chancellor Sir, I am pleased to report that this paper published in International Journal of Environmental Research and Public Health based in Basel, Switzerland has been cited up to 500 times excluding self citations and remains a reference paper for most researchers worldwide in Aquatic toxicology. Subsequently we reported OMLL spermatotoxicity in vitro (Adedara et al. 2013b).

Further insight into the mechanism of action of OMLL in living system was revealed by our studies wherein we reported testicular toxicity with testicular biometal accumulation of lead, cadmium, nickel, iron, copper, (fig. 11) oxidative stress and increased activities of marker enzymes of testicular function with altered circulatory concentrations of reproductive/endocrine hormones (fig. 12) (Adedara et al. 2015). The deleterious effects of OMLL within 28 days of exposure indicated lack of reversibility of its toxicity as most of the assessed parameters persisted after treatment withdrawal (Adedara et al. 2014). The data if extrapolated to humans, present significant health implications for individuals exposed to leachate-contaminated substances.

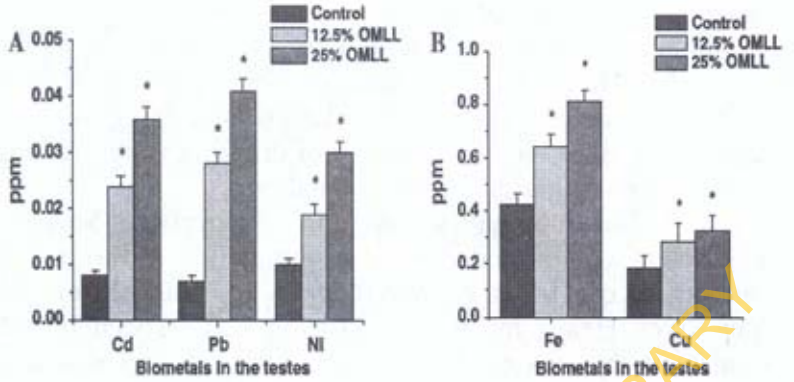


Fig. 11: Levels of Cd, Pb, Ni, Fe, and Cu in testes of rats after 7 days of exposure to OMLL. Each bar represents mean ± SD of 10 rats. *Values differ significantly from the control ($p<0.05$). *Source*: Adedara et al. 2013.

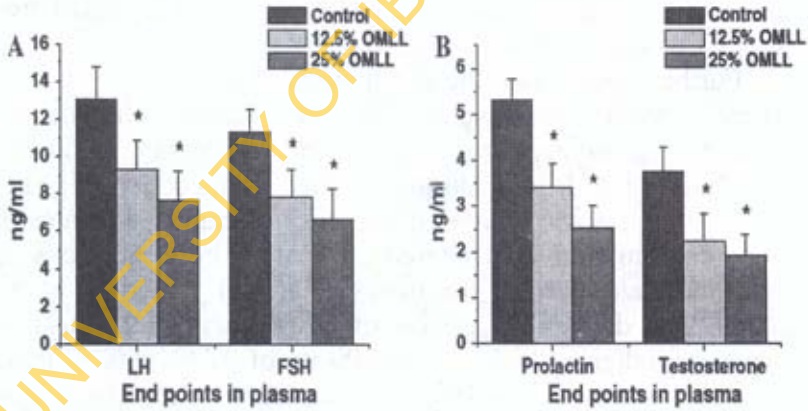


Fig. 12: Plasma concentrations of LH, FSH, prolactin, and testosterone in rats after 7 days of exposure to OMLL. Each bar represents mean ± SD of 10 rats. *Values differ significantly from control ($p<0.05$). *Source*: Adedara et al. 2015.

Chemoprevention

Mr. Vice-Chancellor Sir, from the series of studies on the science of the 'killers', it is unequivocally clear that humans are exposed to myriad of toxic and dangerous chemical compounds. The questions are: Is there hope for man? Is there respite for the cells these chemical compounds kill? Is there room for prevention of chemically-mediated diseases? Is longevity and increase in life span a possibility in the face of overwhelming killer chemical compounds? Finally, judging from the influence of the killers on humans, is there light at the end of the tunnel? In the next series of studies, I will attempt to answer these questions.

Dietary factors continue to play a complex and multifaceted role in the aetiology of many diseases such as diabetes, cardiovascular disorders and cancer (Farombi 2004). For instance, apart from cigarette smoking and chronic inflammation and infection, nutrition accounts for up to one third of the total cause of cancer (Sugimura 2002). Richard Doll and Richard Peto in 1981 reported, based on statistical and epidemiological data, that 10–70% (average 35%) of human cancer mortality is attributable to diet. In light of the considerable complexity of dietary substances, it is not surprising that in addition to mutagenic and carcinogenic components present in the diet, there may exist anti-carcinogenic and antimutagenic substances (Farombi 2004).

Recently, attention has been focused on phytochemicals—non-nutritive components in the plant-based diet that possess cancer-preventive properties (fig. 13). There is also accumulating evidence from population as well as laboratory studies to support an inverse relationship between regular consumption of fruits and vegetables and the risk of specific cancers. The results of more than 250 population-based studies, including case-control and cohort studies indicate that people who eat about five servings of fruit and vegetables a day have approximately half the risk of developing cancer.

In the United States, these observations led to the development of public-health campaigns such as the 'Five-a-Day for Better Health' programme designed to increase the

ingestion of fruits and vegetables. For a global extension of the 'Five-A-Day' concept of boosting increased consumption of fruit and vegetables, the WHO organized the third Biennial 'Five-A-Day' International Symposium on January 14–15 2003 in Berlin, Germany. At that meeting, Derek Yach, the WHO Executive Director of Non-communicable Diseases and Mental Health, said "Increasing the consumption of fruit and vegetables is a necessary part of the effort to reduce the growing global burden of chronic diseases including cancer." The guidelines stated, "choose most of the foods you eat from plant sources". Ever since, many clinical trials on the use of nutritional supplements and modified diets to prevent cancer and other life-threatening diseases are ongoing. It is conceivable that in the future people might only need to take specially formulated pills that contain substances derived from edible plants to prevent cancer or delay its onset.

Michael Sporn was the first to coin the term **'chemoprevention'** in the mid-1970s and described the strategy of blocking or slowing the onset of premalignant tumours with relatively nontoxic chemical substances. Chemoprevention therefore is defined as the use of agents (especially naturally occurring) to inhibit, mitigate, delay, reverse or retard multistage process of chronic diseases including cancer.

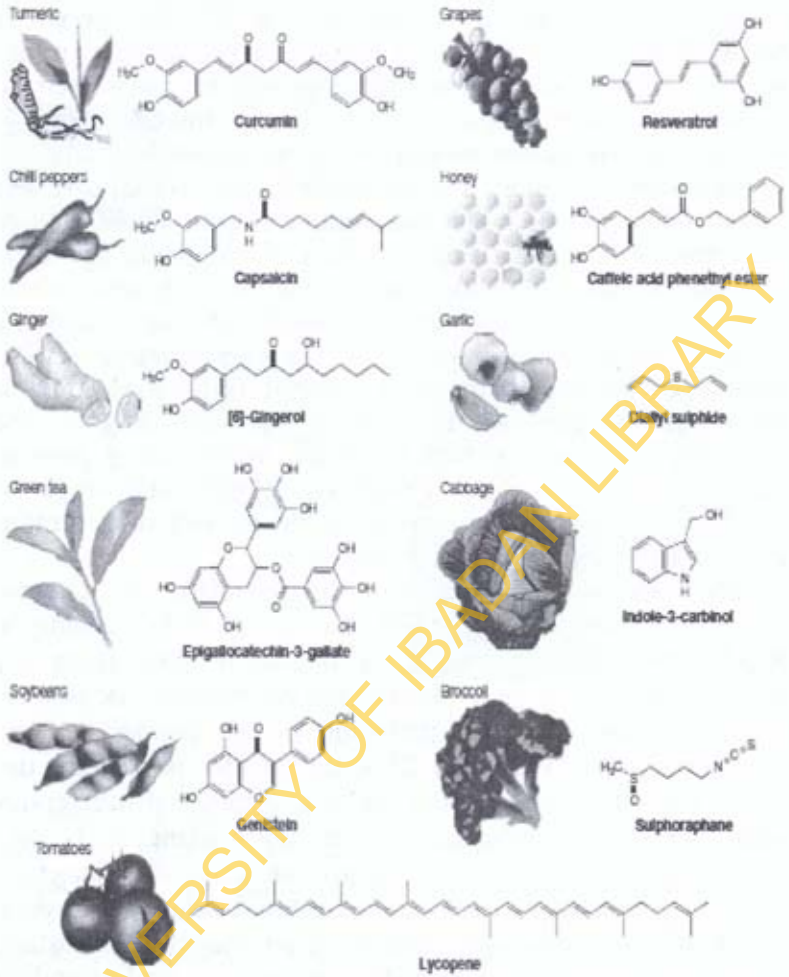


Fig. 13: Representative chemopreventive phytochemicals and dietary sources. *Source*: Surh 2003.

Mechanisms of Chemoprevention

Chemoprevention is a term that was originally applied to cancer development. However, in the last two decades chemoprevention has been extended to other chronic degenerative diseases. For the purpose of this lecture, I shall explain the mechanism of chemoprevention by focusing on

cancer. Carcinogenesis is generally recognized as a multistep process in which distinct molecular and cellular alterations occur. From the study of experimentally-induced carcinogenesis in rodents, tumour development is considered to consist of several separate, but closely linked, stages—**tumour initiation, promotion and progression** (fig. 14).

Initiation is a rapid and irreversible process that involves a chain of extracellular and intracellular events. These include the initial uptake of or exposure to a carcinogenic agent, its distribution and transport to organs and tissues where metabolic activation and detoxification can occur, and the covalent interaction of reactive species with target-cell DNA, leading to genotoxic damage. In contrast to initiation, tumour **promotion** is considered to be a relatively lengthy and reversible processes in which actively proliferating preneoplastic cells accumulate. **Progression**, the final stage of neoplastic transformation, involves the growth of a tumour with invasive and metastatic potential.

Mr. Vice-Chancellor, my involvement in chemoprevention dates back to 1989 during my PhD training in Biochemistry Department as a paradigm shift from the research on environmental toxins and carcinogens focused on by my mentors in the Department. In this connection, my research activities in the last 25 years have focused on the use of naturally-occurring agents (dietary agents and indigenous plant-based phytochemicals) with antioxidant and anti-inflammatory properties to prevent or delay the onset of several diseases such as cardiovascular disorders, reproductive dysfunction, cancer (gastrointestinal, prostate, liver), and neurological disorders, as well as understanding their molecular mechanisms with emphasis on signal transduction network. This area of research has enabled me to interact and collaborate with world-class experts in the field in countries spanning 4 continents of the world.

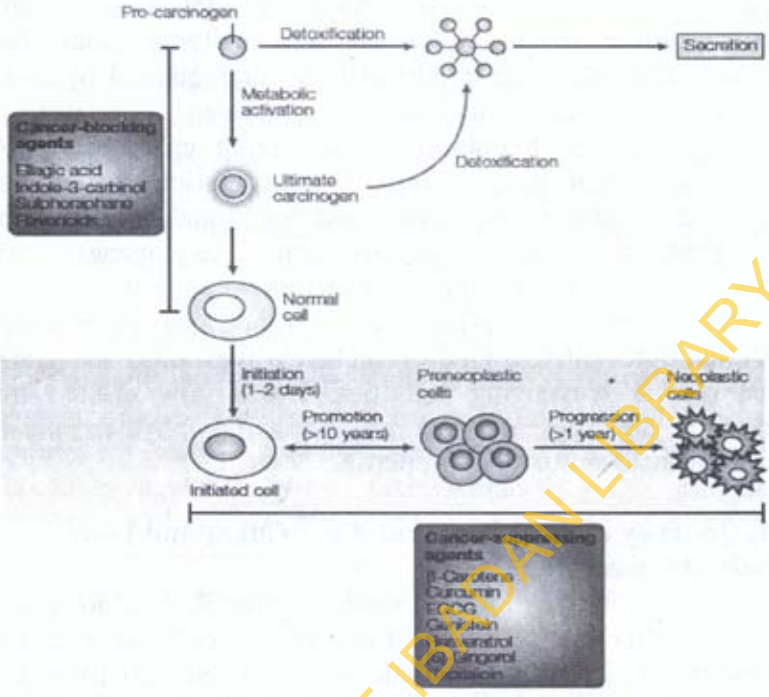


Fig. 14: Dietary phytochemicals that block or suppress the multistage carcinogenesis. *Source*: Surh 2003.

Classes of Chemopreventives

According to the conventional classification originally proposed by Lee Wattenberg, chemopreventives are subdivided into two main categories—**blocking agents and suppressing agents** (fig. 14) (Wattenberg 1985). Blocking agents prevent carcinogens from reaching the target sites, undergoing metabolic activation or subsequently interacting with crucial cellular macromolecules (for example, DNA, RNA and proteins).

Suppressing agents, on the other hand, inhibit the malignant transformation of initiated cells, in either the promotion or the progression stage. Chemopreventive phytochemicals can block or reverse the premalignant stage (initiation and promotion) of multistep carcinogenesis. They

can also halt or at least retard the development and progression of precancerous cells into malignant ones. The cellular and molecular events affected or regulated by these chemopreventives include carcinogen activation/ detoxification by xenobiotic metabolizing enzymes; DNA repair; cell-cycle progression; cell proliferation, differentiation and apoptosis; expression and functional activation of oncogenes or tumour-suppressor genes; angiogenesis and metastasis; and hormonal and growth-factor activity.

Several mechanisms have been advanced for the activities of chemopreventives. One of such involves antioxidant and free radical scavenging activities. I will now discuss my research activities on naturally-occurring phytochemicals with intrinsic antioxidant properties.

My Journey into the World of Antioxidant and Free Radical Research

I started my journey into the world of Free Radical Research in 1988 after interacting with one of my colleagues in the Department, Dr. W.G Okunade who just returned from a 3 month British Council Fellowship to the Laboratory of Professor Catherine Rice Evans of the Royal Guy Hospital London, a lady I later met in April 1996 at the 658th conference of the Biochemical Society in Liverpool (UK), and who offered me the opportunity to work with her but I chose to go elsewhere. It was actually during my first Post-doctoral training in the Laboratory of Dr. George Britton at the Department of Biochemistry, University of Liverpool that I delved actively into this area of Research after reading a fresh PhD thesis written by Dr. Alan Woodall on 'Carotenoids as Antioxidants and Free Radical Scavengers'. After reading this thesis, I became interested and discussed with my Preceptor who agreed that I could work on carotenoids even though my PhD Supervisor Professor Emerole wanted me to continue our work on the characterization of active components in brown yam flour, which was the thrust of my PhD thesis. Given my background

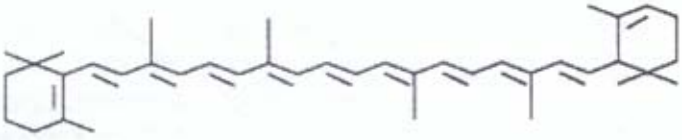
training at Ibadan to work very hard and late into the night in the laboratory, I decided to handle the two projects simultaneously, which at the end was a very successful endeavour. After spending about three weeks in the laboratory, one day Dr. Britton asked 'Tunde, you are from Nigeria and I have read from literature that your country produces and consumes a lot of red palm oil. How can we get red palm oil from Nigeria because studies showed that red palm oil is rich in α- and β-carotenes?'

As at that time no one really knew about α-carotene as an antioxidant though some studies revealed β-carotene as a potent antioxidant. At that time, I remember I took two bottles of palm oil along with me but for the purpose of cooking vegetable soup to take 'Amala' my favourite meal. Without wasting time I decided to give away the two bottles of red palm oil for the purpose of research. This sacrifice has been really rewarding and has launched me into prominence in this important field of research.

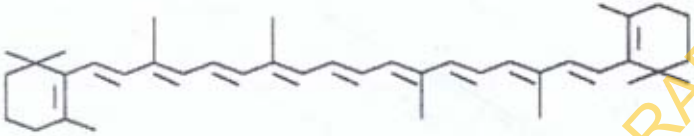
My Contributions to Antioxidant Redox Biochemistry (Antioxidant and Free Radical Research)

My first task was to isolate and characterize α and β-carotenes (which exist in the same concentrations in human plasma-($0.1\pm0.2\mu ml^{-1}$) from Nigeria red palm oil using chromatographic, HPLC and spectroscopic methods. Antioxidant potency of other potential dietary antioxidants, which exist in human plasma such as lycopene, lutein, zeaxanthin and β-cryptoxanthin had been examined but little information existed about the potency of α-carotene. Figure 15 depicts the structures of some carotenoids. Thus, we examined and compared for the first time the antioxidant potency of α-carotene and β-carotene from red palm oil in organic solution. We showed that in organic solution containing peroxyl radicals; α-carotene was a better antioxidant than β-carotene (fig. 16) (Farombi and Britton 1999a).

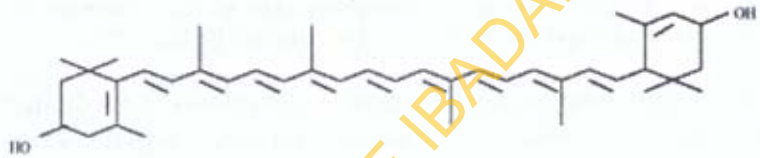
Furthermore, using azo-initiated peroxyl radical peroxidation of egg-yolk phosphatidylcholine, a membrane model, we confirmed the superiority of α-carotene as antioxidant over β-carotene (Farombi and Britton 1999b). Based on the chemical configuration of the two compounds it was deduced that the cis configuration on the β-ionone ring of α-carotene makes it a better antioxidant compared with β-carotene. Sir, since my return to Nigeria in 1996, **our Laboratory has remained a consulting and collaborative centre for colleagues in various Departments in the University and outside for antioxidant research activities.** Thus, with Professor J.O. Moody of Pharmacognosy Department and his first PhD student Dr. Yemisi Ogundipe, we reported the antioxidant activities of extracts of *Mallotus oppositifolium* in model systems (Farombi et al. 2001). Again, with the same group and two of my MSc students we reported for the first time, using the ferric thiocyanate method, horseradish peroxidase catalyzed reactions and β-carotene linoleate model system the antioxidant activities of the leaf and root extracts of *Alchornea laxiflora*, a plant used locally for the preservation of food items in Nigeria. Thus, qualifying the use of the leaves in the food industry for preservation of lipid food products, which are prone to rancidity and oxidation (Farombi et al. 2003).



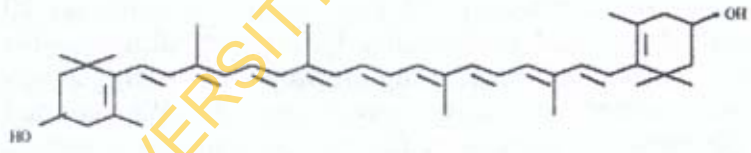
α - Carotene



β - Carotene



Lutein



Zeaxanthin

Fig. 15: Structures of carotenoids. *Source*: Farombi and Britton 1999.

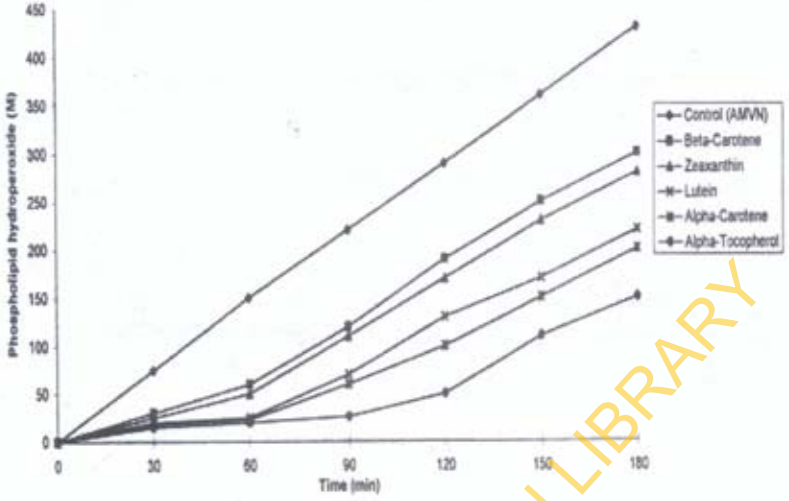


Fig. 16: Effect of carotenoids and alpha-tocopherol on AMVN-induced phopspholipid hydroperoxide formation. The points represent the means of four experiments. *Source*: Farombi and Britton 1999a.

Bioprospecting for novel natural antioxidants in medicinal plants and vegetables that may be relevant in pathologies involving ROS as well as preservation of food substances in food industries, together with one of my former PhD students Dr. Akinmoladun who is now a Senior Lecturer in Federal University of Technology (FUTA) Akure, we screened 10 selected plants used traditionally for various ailments—for antioxidant and radical scavenging properties—using seven different methods and assays involving ROS. We reported that the methanol extracts of the studied plant parts possess significant antioxidant and radical scavenging activities due to the phytochemical contents of the plants and as such make them potential candidates as natural chemoprophylactic agents (Akinmoladun et al. 2010a). Subsequently, we considered and reported in isoproterenol treated rat model the cardioprotective properties of one of the promising plants, *Spondias mombin*, used traditionally in the management of diabetes mellitus, the treatment of psychiatric disorders and to gain and retain good memory (Akinmoladun et al. 2010b). Also, we reported the antioxidant and radical scavenging

properties of *Hibiscus sabdariffa* L (Malvaceae) used in making 'Sobo', a local popular drink in Nigeria. It is shown to lower both the systolic and diastolic blood pressures in patients presenting with essential hypertension (Herrera-Arellano et al. 2004).

Further, we demonstrated its antigenotoxic properties in bone marrow micronuclei assay (Farombi and Fakoya 2005). I must point out that in recommending a dietary substance or any plant-based phytochemical as a potential antioxidant, it is necessary to establish its antioxidant and/or pro-oxidant properties *in vivo*, as well as its general safety because pro-oxidant effects of fruits and vegetable products have been observed repeatedly in humans (Young et al. 2002).

In collaboration with Dr. Lars Dragsted of Institute of Food Safety and Toxicology, Soborg, Denmark, we demonstrated both anti and pro-oxidant properties of Bowman-Birk inhibitor (BBI), a well characterized soy-derived 8 kDa protease inhibitor (Farombi et al. 2004). Using protein oxidation biomarkers as indices of biological protection afforded by dietary antioxidants, we demonstrated pro-oxidant effects of BBI protease inhibitor at high dose as reflected by marked increase in plasma protein oxidation biomarkers whereas half the dose was not able to elicit this (pro-oxidant) effect and even acted as an antioxidant in support of antioxidant properties of BBI.

This study shows that a plant-based phytochemical or nutraceutical can act as both antioxidant (especially at low dose) and/or pro-oxidant (at high dose) thus drawing caution on the use of antioxidative agents generally. So in the words of Paracelus, the father of Toxicology, the dose determines toxicity. Our modest contributions on Kolaviron from *Garcinia kola* as antioxidant will be considered later in this lecture. Mr. Vice-Chancellor Sir, I am happy to report that my contributions on Free Radical Chemistry and novel plant-based phytochemicals as antioxidants led to the award and my induction as Fellow of the Royal Society of Chemistry (FRSC) of the United Kingdom in 2010 and this was cited and published in the popular British newspaper "The Times".

Chemoprevention with Selected Chemopreventives

Convincing and compelling evidences arising from both preclinical and clinical investigations indicate that plant-based diet rich in a wide variety of fruits and vegetables are effective in preventing or reversing health-threatening diseases including cancer. Thus, search for novel chemo-preventive agents, acting on specific and/or multiple molecular and cellular targets, holds promise as a rational strategy to the control of these diseases. In the last 20 years, I have chosen to work in-depth on some selected chemo-preventives, understanding their pharmacological mechanisms of actions at the cellular and molecular levels. Collaborating with Dr. Takuji Tanaka of the Department of Oncologic Pathology, Kanazawa Medical University, Japan, we examined and reviewed certain chemopreventives abundantly present in our daily fruits and foods. They are Auraptene (7-geranyloxycoumarin), a coumarin derivative obtained from citrus fruits such as grapefruits (*Citrus paradise*); Nobiletin, a polymethoxyflavonoid occurring exclusively in citrus fruits (*Citrus depressa*); Zerumbone, a monocyclic sesquiterpene occurring in rhizomes of *Zingiber zerumbet* Smith (Zingiberaceae) and 1'-Acetoxychavicol acetate (ACA) present in the seeds and rhizomes of *Languas galangal* (Zingiberaceae), used as a ginger substitute, as stomach medicine and traditional condiment in Thailand and other countries in Southeast Asia (Farombi and Tanaka 2007). Other selected chemopreventives are Curcumin from Turmeric, Epivernodalol and its phenolics from *Vernonia amygdalina* (bitter leaf), Soybean polyphenols from Soybeans, Quercetin from onions, 6-Gingerol from Ginger and our favourite Kolaviron from *Garcinia kola* (bitter kola). For the purpose of this lecture I will discuss some of our findings on the use of some selected chemopreventives isolated and characterized from these plants in the prevention and management of diseases.

Curcumin

Curcumin is a favourite chemopreventive phytochemical to many investigators especially in the area of cancer biology worldwide. It is derived from turmeric. Because of its brilliant yellow colour, curcumin is used as a food additive, particularly in making curry.

It is used to treat various common ailments including stomach upset, flatulence, dysentery, ulcers, jaundice, arthritis, sprains, wounds, skin and eye infections (Singh 2007). It is an age-old spice with modern target and relevance. Its use in biliary diseases was documented in 1937 (67 patients treated), its antibacterial action in 1949 and its ability to decrease blood sugar levels in human subjects (i.e. its use as an antidiabetic) in 1972 (Aggarwal and Sung 2008). Our gain in knowledge about curcumin has been exponential over recent years. For instance, we reported its ability to attenuate Gentamicin-mediated nephrotoxicity and reverse phthalate-induced testicular damage via its intrinsic antioxidant properties (Farombi and Ekor 2006, Farombi et al. 2007). Several studies have also revealed that curcumin has antioxidant, antibacterial, antifungal, antiviral, anti-inflammatory, antiproliferative and pro-apoptotic effects (Aggarwal et al. 2007).

One of the most well-defined mechanisms underlying chemopreventive effects of curcumin is suppression of tumor promotion. My contribution to understanding of the underlying molecular mechanisms of chemoprevention of liver toxicity and cancer by curcumin was during my sojourn in the Laboratory of Molecular Carcinogenesis and Cancer Chemoprevention, Seoul National University, South Korea (2005-2006) as a Visiting Professor working with Professor Young-Joon Surh, the 2006 best Korean Scientist and a pre-eminent Scholar in Cancer chemoprevention. Actually, I had dreamt and prayed to work with this man since July 2001 given his profound contribution in the field when I first met him at the International Conference of the Society for Free Radical Research in Mauritius. The prayer was answered in 2005 when he invited me on a Ministry of Science and

Engineering, Korea Grant. We investigated while in Seoul the mechanisms by which curcumin elicits hepatoprotective and other chemopreventive effects in association with heme oxygenase-1 (HO-1), a stress-responsive enzyme widely distributed in many mammalian tissues (Farombi and Surh 2006) and the role of a transcription factor Nuclear erythroid related factor-2 (Nrf2) which plays a pivotal role in the activation of Antioxidant Response Element (ARE)-driven antioxidant gene expression (fig. 17). We demonstrated and documented for the first time that curcumin protects against Dimethylnitrosamine-induced liver injury through HO-1 expression and activation of Nrf2 signaling (Farombi et al. 2008) (figs. 18a and b) in rat liver *in vivo*. These mechanistic studies provided clear understanding of the liver chemopreventive properties of curcumin.

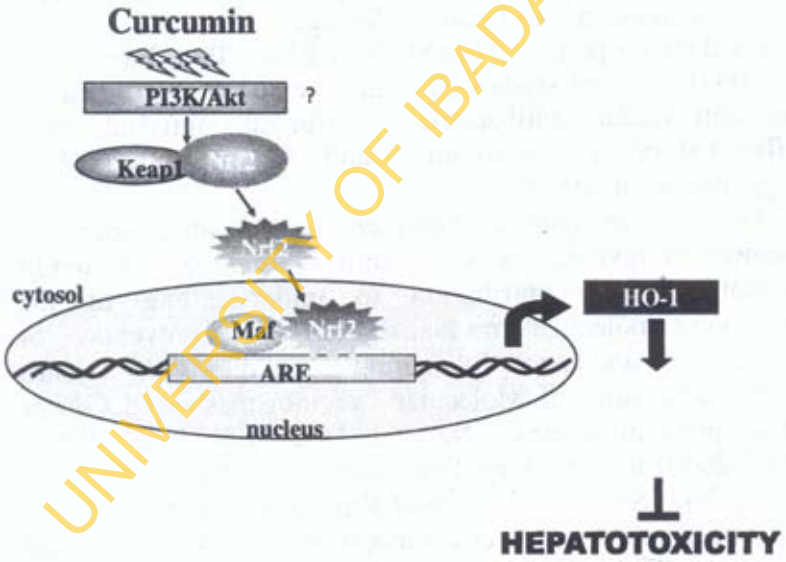


Fig. 17: Mechanism of hepatoprotection by Curcumin via HO-1 mediated NrF2 activation. *Source*: Farombi and Surh 2006.

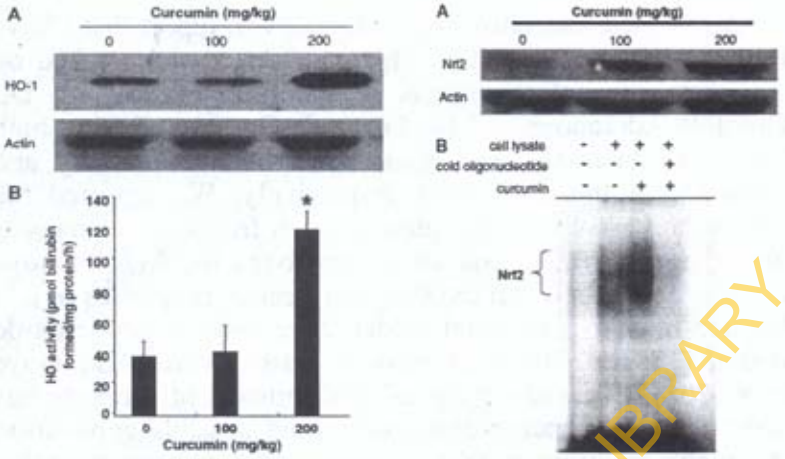


Fig. 18: (a) Effects of curcumin treatment on HO-1 expression (A) and activity (B) in rat liver. Values are means ± SD (n = 6). *significantly different from the vehicle control ($p < 0.001$). (b) Activation of Nrf2 by curcumin in rat liver. (A) Effects of curcumin on the nuclear levels of Nrf2. (B) Effect of curcumin (200 mg/kg) on the ARE-binding activity of Nrf2 in rat liver. *Source*: Farombi et al. 2008

Vernonia amygdalina (Asteraceae)

Vernonia amygdalina, a member of the Asteraceae family is commonly called "*bitter leaf*" because of its bitter taste. It is known as *Ewuro* in Yoruba, *Onugbu* in Igbo language, *Oriwo* in Bini and *Chusar daki* in Hausa. The leaves are used as green leafy vegetables and may be consumed either as a vegetable (leaves are macerated in soups) or aqueous extracts used as tonics for the treatment of various illnesses (Igile et al. 1995). In the wild, chimpanzees have been observed to ingest the leaves when suffering from parasitic infections (Huffman and Seifu 1989; Huffman 2003). Traditionally, the leaf extracts are used in the treatment of varieties of ailments ranging from emesis, nausea, loss of appetite, dysentery and other gastrointestinal tract problems to sexually-transmitted diseases and diabetes mellitus among others (Argheore et al. 1998; Farombi and Owoeye 2011). Some of these and other uses have been verified experimentally and documented by various workers, thus providing scientific evidence to support many of these claimed health benefits (Izevbigie et al. 2004; Farombi and Owoeye 2011).

Mr. Vice-Chancellor Sir, I am happy to report that I have trained and supervised two PhD candidates who worked on the chemopreventive aspects of bitter leaf. They are Dr. Omolola Adesanoye and Dr. Olatunde Owoeye who are both Senior Lecturers in the Departments of Biochemistry and Anatomy of this University respectively. We reported the antioxidant activity of the phenolic-rich fraction of *Vernonia amygdalina* using several assays involving ROS (Adesanoye and Farombi 2014) and the chemoprotective properties of this fraction in an experimental model of tert-butyl hydroperoxide (t-BHP)-induced human erythrocyte lysis in vitro (Adesanoye et al. 2013). The advantage of this antioxidant property has been revealed in neurotoxic studies and possible application in patients receiving radiotherapy for cancer treatment. In this connection, Owoeye and colleagues reported the neuro-protection of the cerebellum by the methanolic extract of *Vernonia amygdalina* leaves on the gamma-irradiated brain of Wistar rats (Owoeye et al. 2011). Subsequently, we demonstrated that *Vernonia amygdalina* protected against carbon tetrachloride and 2-acetylaminofluorene-induced liver injury by mechanisms involving scavenging of reactive free radicals generated by these carcinogens and induction of phase 2 drug metabolizing enzymes (Adesanoye and Farombi 2010; Adesanoye et al. 2016). In pursuance of good science and breaking new grounds in the *Vernonia amygdalina* story, a man had to sell his Mercedes Benz to add to the money raised for him to travel outside of the country in order to carry out an important aspect of his PhD work. Thus, Owoeye in collaboration with experts at the Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Pakistan isolated and characterized a Sesquiterpene lactone compound named **Epivernodalol (C20H24O8) for the first time** from this plant using spectroscopic methods (Owoeye et al. 2010). He subsequently showed that Epivernodalol was active against skin melanoma cell line (HT-144) demonstrating its potential anticancer property against human skin cancer (table 1).

Other investigators including my friend and collaborator Professor Ernest Izevbigie formerly of Jackson State

University, USA and now Vice-Chancellor of Benson Idahosa University, Benin City showed that certain fractions of *Vernonia amygdalina* inhibited cultured human breast tumour cells (MCF-7) growth (Izevbigie 2003; Izevbigie et al. 2004) and acted as DNA-damaging anti-cancer agent against breast cancer (Yedjou et al. 2008). These studies raise the potential application of *Vernonia amygdalina* (bitter leaf) in the management and possible treatment of human breast cancer. Happily, certain phytochemicals from bitter leaf have been formulated into pills now used in the management of breast cancer.

Table 1: Activity of Vernonia Amygdalina Del. Extract, Fractions, Epivernodalol and Doxorubicin against HT-144 (skin melanoma) Cell Line

Code	GI_{50} (μg/ml)	TGI (μg/ml)	LC_{50} (μg/ml)
MEVA (extract)	86 ± 1.3	141.3 ± 4.7	199 ± 10.8
VAD (fraction)	3.3 ± 0.3**	6.3 ± 0.3**	10.6 ± 0.8**
VAP (fraction)	9.7 ± 2.3*	21.2 ± 5.4*	37.7 ± 4.4*
Epivernodalol	1.76 ± 0.3**	7.33 ± 0.55**	22 ± 1.2**
Doxorubicin	0.01 ± 0	0.07 ± 0.03	0.48 ± 0.1

Each value represents the means ± SD of three independent experiments. * Significantly different from MEVA ($p < 0.05$).** Significantly different from MEVA ($p < 0.01$). GI_{50} = Growth inhibition of 50% of the cells; TGI = Total growth inhibition. LC_{50} = Lethal concentration of the compound/extract that kills 50% of the cells. MEVA: methanolic extract of *Vernonia amygdalina*; VAP: petroleum ether fraction; VAD: dichloromethane fraction. *Source*: Owoeye et al. 2010.

Soybeans

Flavonoids continue to draw attention as possible, very useful therapeutic agents for combating pathologic states associated with free radicals. The role of dietary flavonoids in the prevention of several chronic diseases has been the subject of

intense research interest and the soy phenolics have been the focus of particular attention. Furthermore, there is increasing evidence that dietary phytoestrogens present primarily in soybeans as isoflavones have a beneficial role in chronic renal disease (Ranich et al. 2001). Nutritional intervention studies have shown that consumption of soy-based diet owing to intrinsic polyphenolic antioxidants (Ekor 2009) reduces proteinuria and attenuates renal functional or structural damage in animals and humans with various forms of chronic renal disease (Ranich et al. 2001).

Our search revealed that the clinical use of Gentamicin, one of the most important aminoglycoside antibiotics used widely for the treatment of serious and life-threatening infections is limited by its nephrotoxicity (Mingeot-Leclercq and Tulkens 1999). In this connection, we investigated and reported the protective effect of phenolic-rich fraction of soybean in a rat model of gentamicin-mediated kidney damage (Ekor et al. 2006). This effect was ascribed to the rich antioxidant polyphenolic content of the soybean. In continuation of enhancing the therapeutic indices of clinical drugs with undesirable side effects, we therefore hypothesized that the antioxidant polyphenolic compounds in soybean with demonstrable anti-tumor activity (Barnes et al. 1990) may provide the protective benefit in cisplatin-mediated nephrotoxicity. We expressed the optimism that the anticarcinogenic effect of soybean may synergize with that of cisplatin while at the same time protecting the kidney from damage by the latter. This would enhance the therapeutic efficacy and clinical utility of cisplatin. We reported that the polyphenol-rich fraction of soybean via antioxidant and anti-inflammatory actions offered protective benefit against cisplatin-mediated acute toxic injury to the kidney (fig. 19) (Ekor et al. 2010).

These findings have implications in translational medicine and clinical applications in patients receiving amino-glycosides and chemotherapeutic drugs like cisplatin. **Mr. Vice-Chancellor Sir, the PhD thesis that emanated from this novel and translational science was adjudged to be the best PhD thesis in Basic Medical Sciences in Nigeria Universities by NUC in the year 2009.**

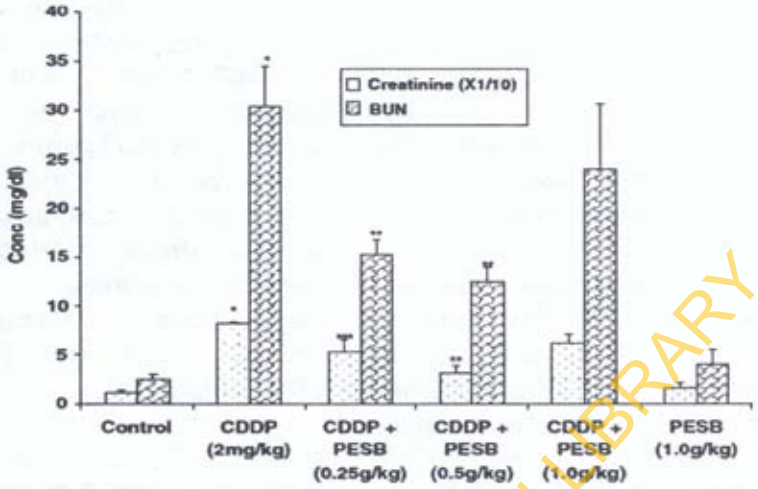


Fig. 19: Effect of the phenolic extract of soybean (PESB) on serum creatinine (CREA) and blood urea nitrogen (BUN) of normal and cisplatin (CDDP)-treated rats. *p < 0.001 when compared with control. **p < 0.05 and ***p < 0.001 when compared with CDDP group. *Source*: Ekor et al. 2010

Ginger (Zingiber officinale Roscoe, Zingiberacae)

Ginger (*Zingiber officinale* Roscoe, Zingiberacae), another interesting chemopreventive spice is a medicinal plant that has been widely used all over the world, since antiquity, for a wide array of unrelated ailments that include arthritis, rheumatism, sprains, muscular aches, pains, sore throats, cramps, constipation, indigestion, vomiting, hypertension, dementia, fever, infectious diseases and diabetes (Awang 1992; Wang and Wang 2005). The pungent principles of ginger include gingerols, shogaols, paradols, and zingerone (Surh et al. 1999). These pungent phenolics of ginger possess antioxidant, anti-inflammatory and anticarcinogenic activities.

Currently, there is a renewed interest in ginger, and several scientific investigations have been initiated aimed at isolation and identification of active constituents of ginger, scientific verification of its pharmacological actions and of its constituents, and verification of the basis of the use of ginger

in some of several diseases and conditions. Our interest is in 6-Gingerol, a major pungent principle in gingerol owing to its strong anti-inflammatory and antioxidant properties and the role of these activities in various diseases. Thus, we examined 6-gingerol from ginger in inflammation-associated colitis and colon cancer. One of my PhD students, Mr. Jide Ajayi took on the arduous task of extracting, isolating and characterizing 6-gingerol from ginger, a feat we initially considered impossible given our limited facilities but he worked so hard and today, we have established in my laboratory a simple procedure for characterizing this compound from first principle. Figure 20 depicts the HPLC chromatogram of 6-gingerol isolated from ginger.

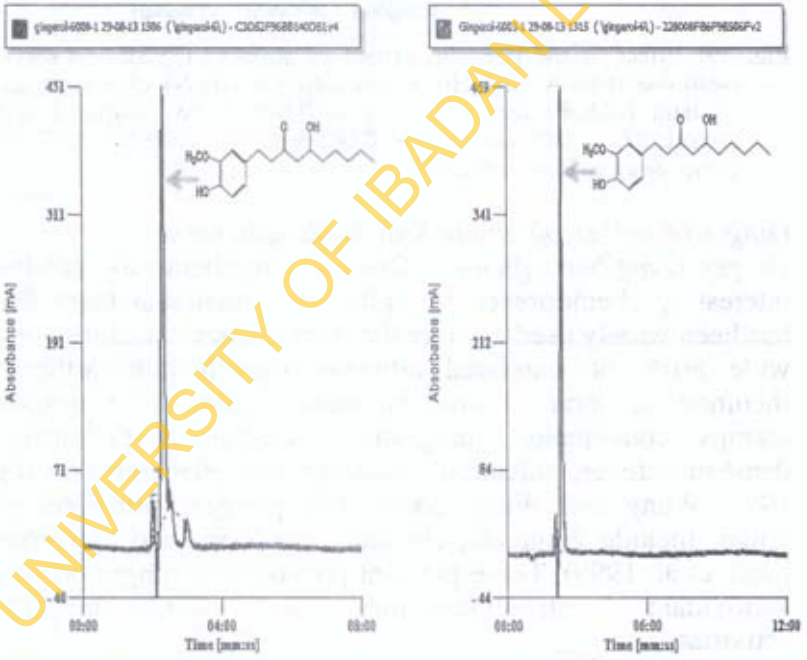


Fig. 20: HPLC chromatogram of isolated 6-gingerol from rhizomes of *Zingiber officinale* (A). HPLC chromatogram of standard 6-gingerol (B). This figure is available in colour online at *wileyonlinelibrary.com/journal/ptr*. *Source*: Ajayi et al. 2015.

Using Dextran sulphate sodium-induced colitis experimental model known to mimic the pathological features of human colitis, we showed that 6-Gingerol suppressed the induction of colonic oxidative damage and circulating concentrations of pro-inflammatory cytokines in mice (table 2) as well as preneoplastic lesion in distal colon of mice (fig. 21) (Ajayi et al. 2015). Furthermore, in our chronic ulcerative colitis model, using sulfasalazine (anti-colitis drug) as positive control, 6-gingerol reversed the clinical features of chronic colitis ranging from diarrhea, shortening of the colon to rectal bleeding. Using immunohistochemical technique, we further showed that 6-gingerol attenuated markers of oxidative and nitrosative stress and abrogated a panel of pro-inflammatory genes and certain transcription factors expressed in chronic ulcerative colitis. Our preliminary data shows its effect on colon cancer and experiments are ongoing in my laboratory to establish the veracity of this claim. In totality, these studies qualify 6-gingerol as anti-colitis drug and a lead compound in the possible management of human colon cancer.

Table 2: Effects of 6-gingerol on Levels of Interleukin-1β, Tumor Necrosis Factor Alpha, Nitric Oxide Concentration, and Myeloperoxidase Activity in DSS-exposed Mice

	Control	6-GR alone	DSS alone	DSS + 6-GR1	DSS + 6-GR2	DSS + 6-GR3
IL-1β	91.21±4.06	90.32±5.08	118.7±4.21[a]	92.57±4.08[b]	91.14±5.08[b]	88.89±4.08[b]
TNF-α	19.24±2.51	19.46±2.27	34.71±2.25[a]	18.84±2.07[b]	19.6±2.07[b]	21.1±2.07[b]
NO	2.32±0.25	2.36±0.28	3.78±0.23[a]	2.48±0.45[b]	2.40±0.39[b]	2.45±0.23[b]
MPO	1.49±0.16	1.45±0.35	2.11±0.21[a]	1.52±0.34[b]	1.46±0.32[b]	1.51±0.27[b]

IL-1β, interleukin-1β (pg/mL); TNF-α, tumor necrosis factor alpha (pg/mL); NO, nitric oxide (units/mg protein); MPO, myeloperoxidase (units/mg protein); DSS, dextran sulphate sodium. 6-GR1, 6-GR2, and 6-GR3 denote 50, 100, and 200 mg/kg of 6-gingerol, respectively. Each bar represents mean ± SD of seven mice. [a]Values differ significantly from control ($p<0.05$). [b]Values differ significantly from DSS group ($p<0.05$). *Source*: Ajayi et al. 2015.

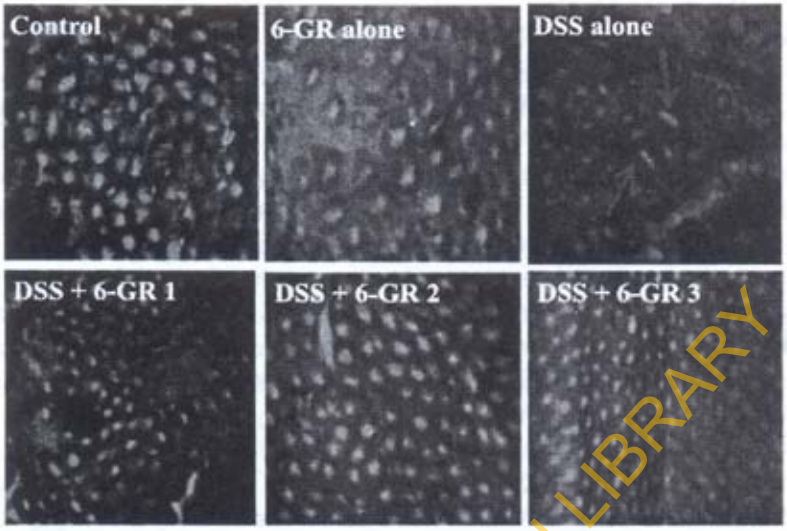


Fig. 21: Effects of 6-gingerol on DSS-induced preneoplastic lesion in mice distal colon. Control and 6-gingerol alone (6-GR) showing normal architecture without suspicious focus. Colons of mice treated with DSS alone have enlarged ulceration with several aberrant crypt foci. Dextran sulphate sodium-treated mice administered with 6-gingerol at 50 mg/kg (6-GR1) and 100 mg/kg (6-GR2) showing normal architecture. Dextran sulphate sodium mice administered with 6-gingerol at 200 mg/kg (6-GR3) showing normal histological structure but with mild ulceration and a very few aberrant foci (red arrow). Original magnification of 160X. *Source*: Ajayi et al. 2015.

Garcinia kola Heckel (Guttiferae)

Another interesting chemopeventive and our favourite in Biochemistry Department is *Garcinia kola*, a tropical flowering plant found in western and central Africa, which produces large, orange fruits and brown, nut-like seeds embedded in an orange-coloured pulp. It is popularly known as bitter kola because of its bitter taste. It is called various names in different parts of Nigeria: *Orogbo* (Yoruba), *Edun* (Edo), *Namiji ngooro* (Hausa), *aku ilu, ugugolu* (Igbo). Bitter kola plays pivotal role in traditional hospitality and ceremony. For instance bitter kola and other components like sugar cane, kolanut and honey are usually presented during naming ceremony of babies and the officiating elder uses the

seed to pray for the child, with the believe that properties of longevity and pleasant living will be conferred on the baby. The elders after chewing the seed pray thus "*Orogbo l'o ni kio gbo, obi nii bi ibi danu, nire nire laa soro ataare, ladun-ladun la aba ile oniyo, adun ni toyin, adun ni tireke*," meaning bitter kola (*orogbo*) says you should grow to old age, kolanut (*Obi*) wards away evil, table salt (*Iyo*) is always found with sweetness, honey is renowned for sweetness, sugar cane is renowned for sweetness too.

Apart from the cultural use of bitter kola, it plays a very important role in African ethno-medicine. The seed is employed as a general tonic, and is believed to cure impotence. Traditionally, the seeds are used in the treatment of inflammatory disorders and liver disease. For instance, extracts of the seeds led to remarkable improvement of liver function in patients with chronic hepatitis and cholangitis after treatment for 14 days at a Nigerian herbal home (Iwu 1982). The seeds are used medicinally to treat parasitic, microbial, and viral infections as well as treatment of bronchitis, throat infections, chest colds, and coughs. Some of these claims have been verified by experimental findings. For instance Mr. Ifeoluwa Awogbindin, one of my PhD students, under the mentoring of myself and Professor David Olaleye of our Virology Department, demonstrated that bioflavonoid fraction from *Garcinia kola* protected BALB/c mice against influenza A/Perth/H3N2/16/09 (Pr/H3N2) virus infection (Awogbindin, Olaleye and Farombi 2015). This study indicates that this fraction is effective for delaying the development of clinical symptoms of influenza virus through a mechanism unrelated to those deployed by the existing anti-influenza drugs but closely associated to its antioxidant and immunomodulatory properties.

Phytochemical studies on *Garcinia kola* revealed the presence of complex mixtures of phenolic compound triterpenes and benzophenones. Subsequently, **Kolaviron** (biflavonoid complex containing GB1, GB2 and kola-flavanone), a deffated fraction of alcoholic extract of *Garcinia kola* seeds was isolated (Iwu 1985) (fig. 22). Other

researchers have isolated some other compounds from bitter kola. For example, one of my PhD students Dr. Ademola Oyagbemi, while collaborating with my friend late Professor Johan Esteryhyse of the Cape Peninsular University of Technology, Cape Town South Africa isolated and characterized for the first time Squalene, a novel antioxidant, anticancer and cholesterol lowering phytochemical and Rugulosin which has antibiotic and antimycotic properties and acts as HIV-1 integrase inhibitor.

Mr. Vice-Chancellor, our interest in *Garcinia kola* research, especially the characterized bioflavonoid termed **Kolaviron,** dates back to 23 years in Biochemistry Department. The interest in the research was facilitated by my mentor and PhD Supervisor, Professor Godwin Emerole. Today, we have graduated over 50 MSc students, 6 PhD students and currently another PhD student is on the project. Under the training of Professor Emerole and my humble self, Dr. O.A. Adaramoye whose promotion to the grade of Reader was announced a few days ago, was the first PhD student on *Garcinia kola.* We have also collaborated with world experts on chemoprevention on the project in countries spanning 4 continents of the world. In other words, we have taken research on this wonderful seed beyond the shores of this country. Our systematic and mechanistic experimental findings at the cellular and molecular levels have lent credence to the therapeutic value of this seed earlier alluded to by traditional elders. Although some do not know the value of this seed and therefore it has remained untapped as a novel chemopreventive and therapeutic agent, just like the Nigerian Juju musician, King Sunny Ade in 1973 released a musical album on this seed and said "*Ki lan fani Orogbo, Kilan fani Orogbo, Ohun ta pa ti o lawe, eyi ta je to tun koro, Kilan fani Orogbo*----". It was later in 1977, I guess elders who understood the real value of bitter kola corrected him and he released another album and sang thus: "*Mojorogbo, Kiohun mi le gbo, mo jogede, ki ohun mi le de, mo je kukundu ku olohun areree*---".

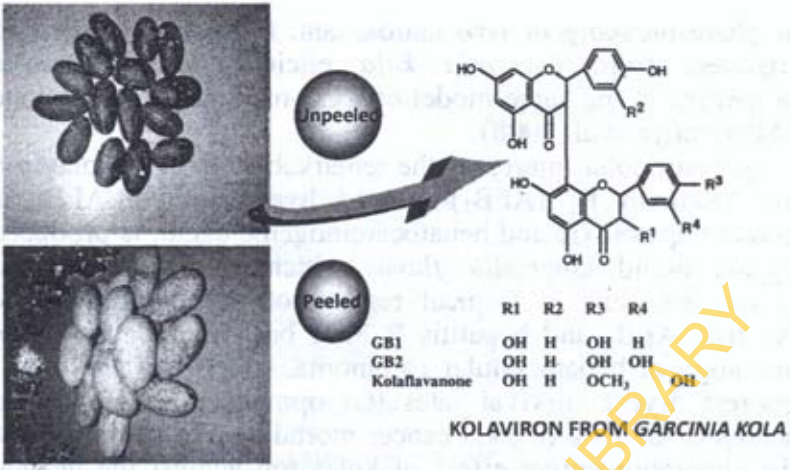


Fig. 22: *Garcinia kola* and isolated bioflavonoid termed Kolaviron.

I shall now summarize some of our humble contributions to knowledge on *Garcinia kola* and its isolated bioflavonoid, Kolaviron, as novel chemopreventive agent.

Kolaviron as Liver Chemopreventive Agent

Garcinia kola seeds and seed extracts have been shown to be of benefit to human health, and relevant in the management and chemoprevention of life-threatening diseases. The effects range from antidiabetic, immunomodulatory, antiviral, anti-inflammatory, and antioxidant activities to strong hepatoprotective properties. Kolaviron and other isolates of *Garcinia kola* seeds were shown to protect against CCl_4–induced liver injury, reduce significantly CCl_4-induced increases in serum aminotransferases and sorbitol dehydrogenases, and protect against CCl_4-mediated liver damage by modulating the cholesterol:phospholipid ratio as well as the toxic onslaught imposed on liver microsomal marker enzymes (Farombi 2000). Kolaviron given orally to rats prior to challenge with 2-acetylaminofluorene reversed its effects on ornithine carbamyltransferase and other biochemical indices of hepatic damage (Farombi et al. 2000). The protective effect of kolaviron was comparable to the effect of butylated hydroxylanisole, indicating that kolaviron may act

as chain-breaking *in vivo* antioxidant. Furthermore, purified fractions from *Garcinia kola* elicited hepatoprotective properties in the same model of CCl_4-mediated liver damage (Adaramoye et al. 2008).

Of particular interest is the remarkable effect of kolaviron on Aflatoxin B_1 (AFB_1)-induced liver damage. AFB_1, a potent hepatotoxic and hepatocarcinogenic agent, is produced by the mould *Aspergillus flavus*, which contaminates cereal grains and nuts in tropical regions of the world such as Nigeria. AFB_1 and hepatitis B have been implicated in the aetiology of hepatocellular carcinoma, which has one of the poorest 5-year survival rates (Groopman et al. 1992) and accounts for 15% of total cancer mortality. We demonstrated the chemopreventive effect of kolaviron against the hepatic oxidative damage (fig. 23) and genotoxicity (fig. 24) induced by AFB_1 in rats (Farombi et al. 2005) by mechanisms involving induction of phase 2 xenobiotic metabolizing enzymes capable of detoxifying toxic aflatoxin metabolites. We showed also that Kolaviron protected against Dimethyl nitrosamine (DMN)-mediated liver toxicity and histological changes in rats (fig. 25) (Farombi et al. 2009).

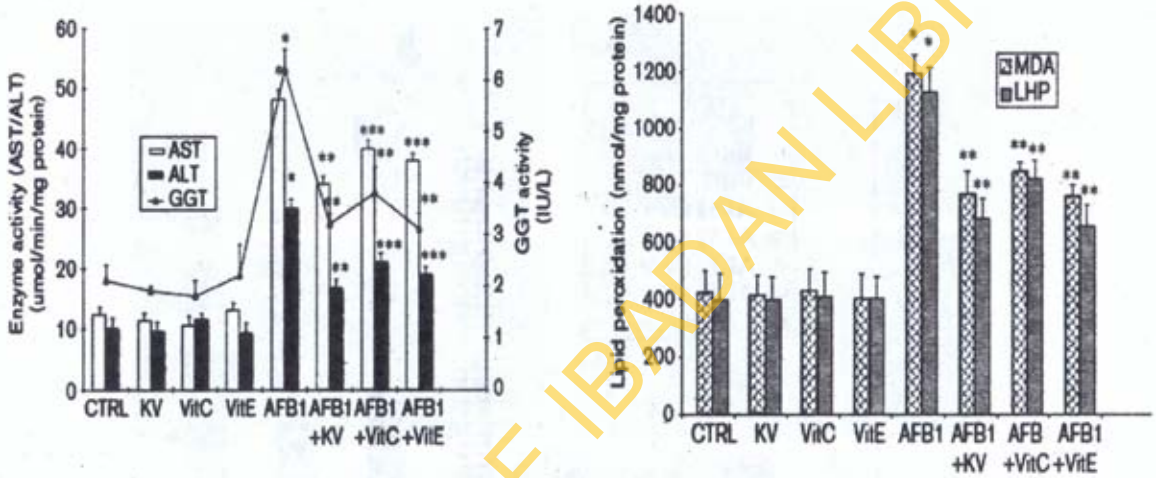


Fig. 23: Effects of kolaviron, vitamins C and E on (A) the activities of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma glutamyltransferase (γ-GT), (B) malondialdehyde (MDA) and lipid hydroperoxide (LHP) of rats treated with aflatoxin B_1 (AFB_1). *P<0.001 significantly different from control; values are mean±SD for five rats in each group. **P<0.01 significantly different from AFB_1 group; ***P<0.05 significantly different from AFB_1 group. *Source*: Farombi et al. 2005.

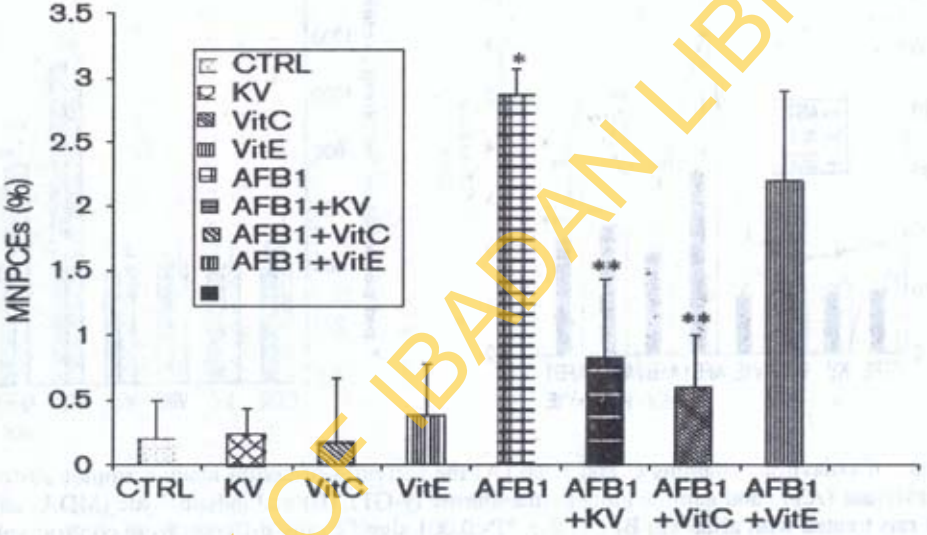


Fig. 24: Effects of pretreatment with kolaviron, vitamins C and E on the frequency of occurrence of micronucleated polychromatic erythrocytes (MNPCEs) in rats treated with aflatoxin B_1 (AFB_1). Values are mean ± SD for five rats in each group. *P<0.001 significantly different from control; **P<0.01 significantly different from AFB_1 group. *Source*: Farombi et al. 2005.

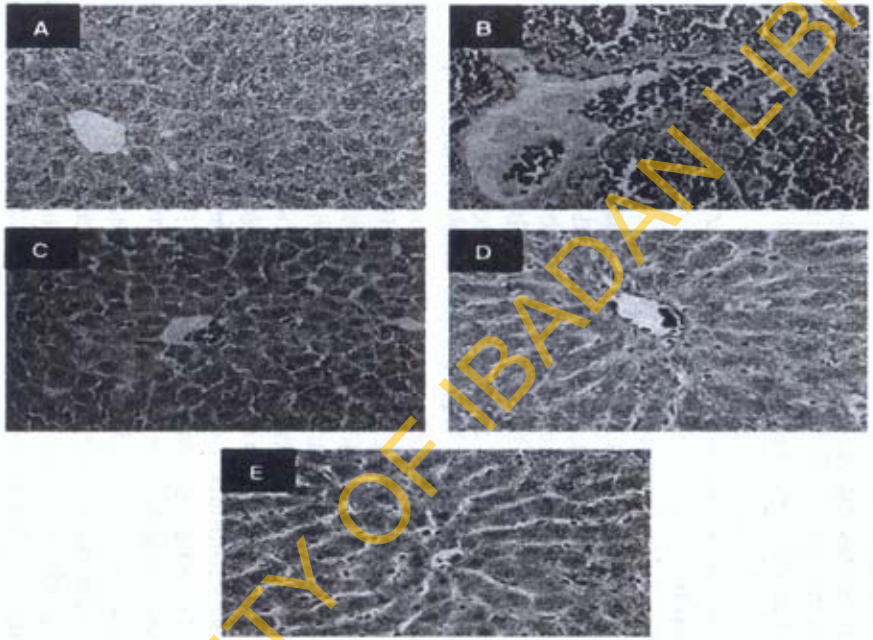


Fig. 25: Effects of kolaviron and curcumin on DMN-induced histological changes in the livers of rats. (A) Liver from a vehicle treated rat, (B) DMN-treated rat liver, (C) liver from the rat treated with kolaviron (100 mg/kg) plus DMN, (D) liver from a rat treated with kolaviron (200 mg/kg) and DMN, (E) liver from a rat treated with curcumin (200 mg/kg) and DMN. Liver sections were stained with hematoxylin and eosin. X400. *Source*: Farombi et al. 2009.

Biochemical Basis for the Chemopreventive Action of Kolaviron

Earlier hypotheses regarding the biochemical mechanisms of the hepatoprotective effect of kolaviron stated that it protected against carcinogen-induced liver injury by stabilizing the membrane, and by interfering with the distortion of the cellular ionic environment associated with xenobiotic treatment; also possibly by the interference of kolaviron with hepatic drug metabolism (Braide 1991). These studies, however, did not elucidate the hepatoprotective mechanism of action of kolaviron.

Kolaviron modulates Xenobiotic Metabolizing Enzyme Complex System

We investigated the hepatoprotective action of kolaviron using CCl_4 as a model compound. Our data showed that kolaviron treated with CCl_4 in rats preserved the activities of certain phase 1 enzymes, especially aniline hydroxylase, a representative CYP 2E1 enzyme (Farombi 2000), while administration of kolaviron alone did not alter the activity of these enzymes. This result was further corroborated by our recent observation that kolaviron did not influence the constitutive expression of CYP 2E1, determined by western blot. Our results further showed that treatment of rats with kolaviron resulted in a marked elevation in the activity of major phase 2 conjugation enzymes (Farombi 2000; Farombi et al. 2005) (fig. 26), demonstrating that kolaviron protects against carcinogen-induced damage to tissues by stimulating the activities of phase 2 enzymes to detoxify toxic reactive metabolites generated by the carcinogens.

Following CCl_4 administration to rats, the cholesterol:phospholipid ratio was increased, suggesting a decrease in membrane fluidity with a resultant alteration in membrane function (Farombi 2000). Co-administration of kolaviron with CCl_4 reversed the CCl_4-induced elevation in the cholesterol:phospholipid ratio and preserved some microsomal marker enzymes, suggesting that kolaviron may protect biomembranes against damage, maintain membrane fluidity (Farombi 2000), and stabilize the drug metabolizing enzyme complex.

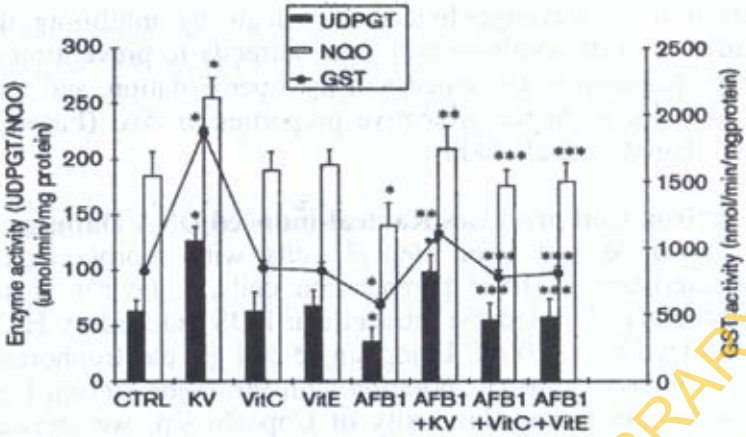


Fig. 26: Effects of kolaviron, vitamins C and E on the activities of uridyl glucuronosyltransferase (UDP-GT), NADH:quinone oxidoreductase (NQO) and glutathione S-transferase (GST) of rats treated with aflatoxin B_1 (AFB_1). Values are mean±SD for five rats in each group. *P<0.001 significantly different from control; **P<0.01 significantly different from AFB_1 group; ***P<0.05 significantly different from AFB1 group. *Source*: Farombi et al. 2005.

Kolaviron as a Potent Antioxidant and Free Radical Scavenger

One of the mechanisms of chemoprevention is the anti-oxidative activity of chemopreventive agents; thus, the ability of natural compounds to reverse or mitigate carcinogen-induced tissue damage may be related to their intrinsic antioxidant properties.

Using several *in vitro* chemical models involving the generation of reactive oxygen species, we evaluated the antioxidant properties of kolaviron. Kolaviron showed significant reducing power, and a dose-dependent inhibition of oxidation of linoleic acid (Farombi et al. 2002). In our model system, Kolaviron inhibited H_2O_2, and was more effective than butylated hydroxyanisole and β-carotene, but comparable in activity with α-tocopherol, a radical chain-breaking antioxidant. Kolaviron also significantly scavenged superoxides generated by phenazine methosulfate and NADH. Furthermore, kolaviron scavenged hydroxyl radicals by inhibition of the oxidation of deoxyribose. The ability of

kolaviron to scavenge hydroxyl radicals by inhibiting the oxidation of deoxyribose may relate directly to prevention of the propagation of the process of lipid peroxidation, and may account for its hepatoprotective properties *in vivo* (Farombi 2000; Farombi et al. 2000).

Kolaviron Compromises Radical-induced DNA Damage

In human-derived liver HepG2 cells with morphological characteristics of liver parenchyma cells, kolaviron dose-dependently inhibited the intracellular ROS induced by H_2O_2 (Nwankwo et al. 2000). Using single cell gel electrophoresis ("Comet assay") in collaboration with Professor Steffen Loft of Panum Institute, University of Copenhagen, we showed that kolaviron concentration-dependently decreased H_2O_2-induced DNA strand breaks, and oxidized purine and pyrimidine bases in both human lymphocytes and rat liver cells (table 3) (Farombi et al. 2004). These data show that kolaviron is effective against oxidative modification of DNA and supports the role of kolaviron as an antioxidant, and a candidate for the chemoprevention of chemically-induced DNA damage.

Table 3: Effect of Kolaviron on H2O2-induced Oxidized DNA bases in Human Lymphocytes

Treatment	DNASB (% of tail DNA)	ENDO III sites (% of tail DNA)	FPG sites (% of tail DNA)
DMSO	8.0±4.1	2.3±4.6	1.7±2.8
H_2O_2	82.1±6.2	16.7±3.2	17.8±3.4
Kolaviron (30 µmol/L)	7.8±3.1	2.8±3.7	1.9±2.5
Kolaviron (30 µmol/L) + H_2O_2	58.2±4.7*	10.2±2.8*	9.1±3.6*
Kolaviron (60 µmol/L	8.2±4.2	2.5±2.7	1.9±2.4
Kolaviron (60 µmol/L + H_2O_2	47.1±5.2**	6.2±3.8**	5.6±3.7**
Kolaviron (90 µmol/L)	7.2±4.7	2.0±2.5	1.5±2.5
Kolaviron (90 µmol/L) + H_2O_2	28.1±3.6**	5.4±3.0**	4.3±3.1**

Percentage of tail DNA (FPG) and ENDO III sites. FPG= formamidopyrimidine glycosylase; ENDO III= endonuclease III enzyme; DNASB- DNA strand breaks. Values are mean ± SD of 5 determinations. *p< 0.05; **p< 0.01, refers to difference between H_2O_2 (100umol/L)v treated lymphocytes preincubated with or without kolaviron. *Source*: Farombi et al. 2004.

Kolaviron Decreases LDL Oxidation and Affects Biomarkers of Oxidative Stress

Oxidation of low density lipoprotein (LDL) is generally believed to promote atherosclerosis primarily by leading to an increased uptake of oxidized LDL (ox-LDL) by macrophages, and subsequent foam-cell formation. Therefore, attempting to inhibit or reduce the process of LDL oxidation by anti-oxidants, which may slow the progression of atherosclerosis, appears to be a rational and pragmatic approach to preventing cardiovascular diseases. Thus, in rats treated with kolaviron for 7 days, lipoprotein resistance to copper-induced oxidation was highly improved, as shown by a significant increase in lag time, and a decrease in the area under the curve (AUC) and the slope of propagation (Farombi & Nwaokeafor 2005). Markers of lipid oxidation significantly decreased in the kolaviron-treated rats, with an attendant significant increase in the total antioxidant activity compared to control.

Additionally, kolaviron inhibited the Cu^{2+}-induced oxidation of rat serum lipoprotein in a concentration-dependent manner, and elicited a significant chelating effect on Fe^{2+}. Furthermore, kolaviron effectively prevented microsomal lipid peroxidation induced by iron/ascorbate in a concentration-dependent manner (Farombi & Nwaokeafor 2005). In totality, the results demonstrate that kolaviron protected against the oxidation of lipoprotein by mechanisms involving metal chelation and antioxidant activity, and, as such, might be of importance in relation to the development of atherosclerosis and cardiac dysfunction as reported in similar works (Adaramoye et al. 2005; Adaramoye & Lawal 2015).

Molecular Mechanisms Underlying Chemopreventive Action of Kolaviron

Kolaviron Compromises Stress Response and Inflammatory Proteins

The role of inflammation in carcinogenesis has been extensively investigated and well documented. Many bio-chemical processes that are altered during chronic

inflammation have been implicated in tumorigenesis. These include shifting cellular redox balance toward oxidative stress; induction of genomic instability; increased DNA damage; stimulation of cell proliferation, metastasis, and angiogenesis; deregulation of cellular epigenetic control of gene expression; and inappropriate epithelial-to-mesenchymal transition. Thus, inadequate resolution of inflammation and uncontrolled inflammatory reactions can evoke a state of chronic inflammation, which is a common etiologic factor for various human ailments including cancer (Balkwill et al. 2005; Aggarwal et al. 2006). Using DSS-induced colitis (gastrointestinal inflammatory disorder) in rats, we showed that Kolaviron suppressed the DSS-mediated increase in colonic nitric oxide concentration and myeloperoxidase activity, and significantly prevented the increase in inflammatory mediators, interleukin-1β and tumour necrosis factor alpha in the colon of DSS-treated rats (fig. 27) (Farombi et al. 2013). Professor S.B. Olaleye of Physiology Department, another lover of *Garcinia kola*/Kolaviron research, demonstrated that both crude extracts of *G. kola* and kolaviron have the capacity to attenuate gastrointestinal inflammatory disorders (Olaleye et al. 2000; Olaleye et al. 2010).

Recently one of my protégés, Dr. Abarikwu demonstrated further the anti-inflammatory property of kolaviron via inhibition of interleukin-6 (IL-6) secretion in lipopolysaccharide stimulation of macrophages (Abarikwu 2014). Like other early-response gene products, Cycloxygenase-2 (COX-2) can be induced rapidly and transiently by pro-inflammatory mediators, endotoxins as well as carcinogens (Kim et al. 2005). Inducible nitric oxide synthase (iNOS) is another inducible enzyme that causes the overproduction of nitric oxide during inflammation and tumor development (Aggarwal and Shishoda 2004; Chung et al. 2007). Therefore, suppression of the induction and activity of COX-2 and/or iNOS has been considered a new paradigm in cancer chemoprevention in several organs (Chung et al. 2007;

Neergheen et al. 2010). Collaborating with Professor Young-Joon Surh while in Korea, our findings on the molecular mechanisms underlying hepatoprotective action of kolaviron indicate that it can suppress certain pro-inflammatory genes whose expression have been shown to be regulated by transcription factors. We demonstrated that kolaviron abolished the expression of COX-2 and iNOS proteins in dimethylnitrosamine (DMN)-treated rat liver (fig. 28) and confirmed by immuno-histochemical staining (fig. 29), suggesting that kolaviron may be important not only in alleviating liver inflammation but probably for the prevention of liver cancer (Farombi et al. 2009). These data suggest that kolaviron compromises inflammation and oxidative stress (as reported before) which are "co-conspirators" in the science of the "killers" and as such is a strong anti-inflammatory chemopreventive relevant in the management of inflammation-associated diseases.

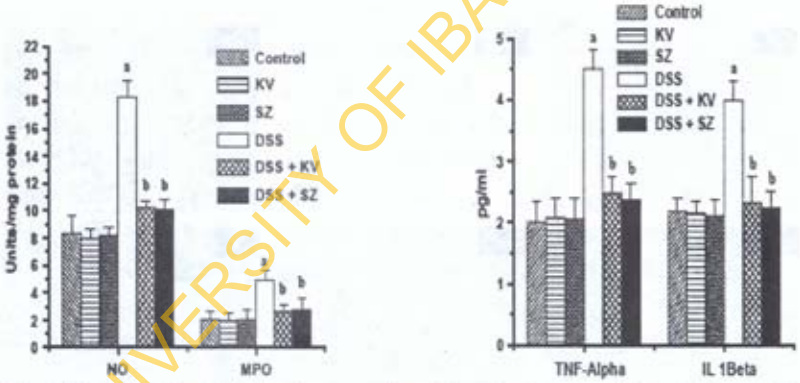


Fig. 27: Effects of kolaviron and sulfasalazine on (A) nitric oxide concentration and myeloperoxidase activity; (B) tumour necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β) levels in colons of DSS-exposed rats. Each bar represents mean ± S.D. of 6 rats. [a]Values differ significantly from control ($p<0.05$). [b]Values differ significantly from DSS group ($p<0.05$). DSS, Dextran Sulphate Sodium; KV, Kolaviron; SZ, Sulfasalazine. *Source*: Farombi et al. 2013.

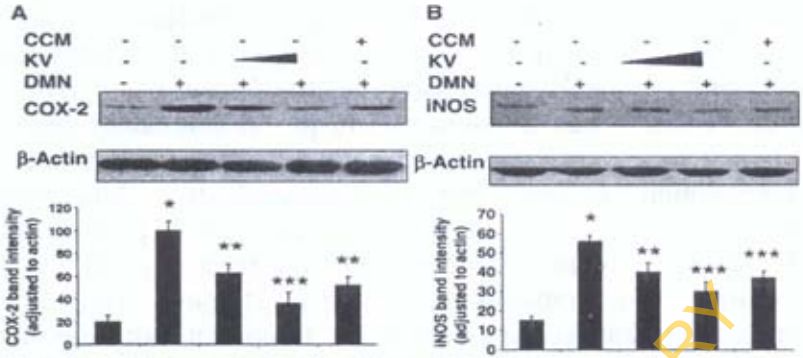


Fig. 28: Inhibitory effect of kolaviron and curcumin on DMN-induced COX-2 expression in rat liver. Quantifications of COX-2 (A) and iNOS (B) immunoblots were normalized to that of actin followed by statistical analysis of relative image density in comparison to control. Lane 1, control; lane 2, DMN-treated; lane 3, kolaviron (100 mg/kg) plus DMN; lane 4, kolaviron (200 mg/kg) plus DMN, lane 5, curcumin (200 mg/kg) plus DMN. (*P<0.001 compared with lane 1; **P<0.05 compared with lane 2; ***P<0.01 compared with lane 2. *Source*: Farombi et al. 2009.

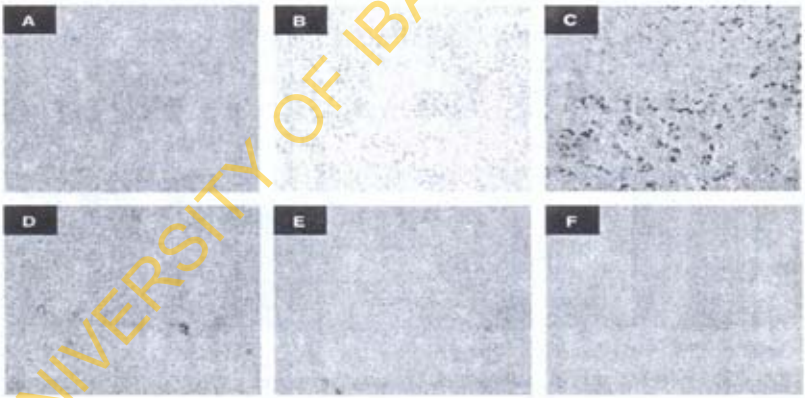


Fig. 29: Immunohistochemistry of COX-2 in the liver of kolaviron and curcumin-treated rats. Treated rat livers were used for immunohistochemical analysis of COX-2, using rabbit polyclonal anti-rat COX-2 antibody as a primary antibody. Positively stained COX-2 staining yielded a brown-colored product. Vehicle treated control rat, X100 (A). DMN-treated, X100 (B); DMN-treated, X400 (C); kolaviron (100mg/kg) plus DMN-treated, X100 (D); kolaviron (200mg/kg) plus DMN-treated, X100 (E); curcumin (200 mg/kg) plus DMN-treated, X100 (F). *Source*: Farombi et al. 2009.

Kolaviron Down Regulates Inflammation-Associated Redox-regulated Transcription Factors

Nuclear factor kappa B (NF-κB) is a ubiquitous transcription factor that resides in the cytoplasm as a heterodimer consisting of p50, p65 and IκBα subunits. Upon activation, it trans-locates to the nucleus where it induces gene transcription (Nanji et al. 2003). On activation, IκBα undergoes phosphorylation and ubiquitination-dependent degradation by 26S proteosomes, thus exposing nuclear localization signal on p50-p65 heterodimer, leading to its nuclear translocation. In the nucleus, it binds to a specific consensus sequence in the DNA (5'-GGGACTTTC-3') called kB binding site. On activation, NF-κB induces expression of more than 200 genes including COX-2. The transcription factors NF-κB and AP-1 have been reported to be key regulators of inflammatory protein such as COX-2 and iNOS (Nanji et al. 2003). Using gel shift Electrophoretic Mobility Shift Assay (EMSA) and Western blot analysis, we showed that kolaviron abrogated the DNA binding activity of NF-κB and AP-1 induced by DMN (Farombi et al. 2009) (fig. 30). Agents that can suppress NF-κB and AP-1 have the potential of preventing the onset of cancer (Aggarwal et al. 2004). Therefore the inhibition of DMN-mediated DNA binding of these transcription factors and expression of pro-inflammatory proteins by kolaviron explains the molecular basis of the hepatoprotective effect of kolaviron.

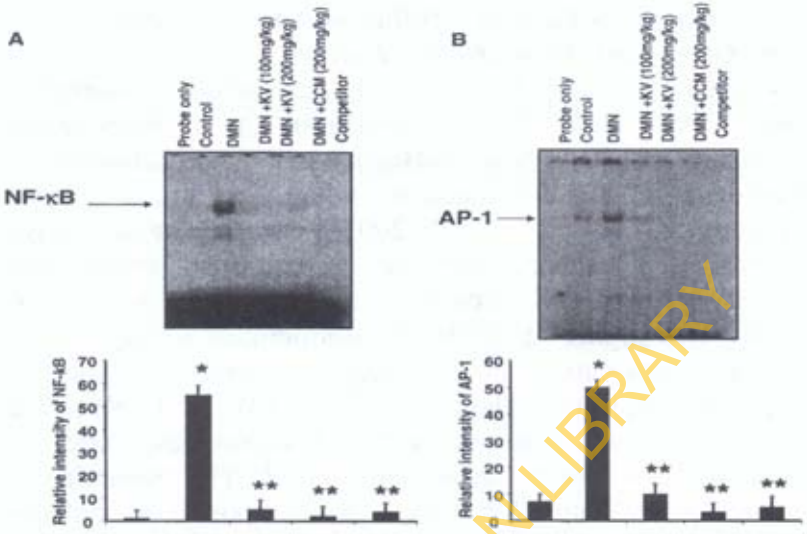


Fig. 30: Inhibitory effects of kolaviron and curcumin on DMN-induced activation of NF-κB (A) and AP-1 (B) in rat liver. Lane 1, free probe; lane 2, control; lane 3, DMN alone; lane 4, kolaviron (100 mg/kg) plus DMN; lane 5, kolaviron (200 mg/kg) plus DMN; lane 6, curcumin (200 mg/kg) plus DMN; lane 7, competitor. *P<0.001 compared with lane 2; **P<0.001compared with lane 3. *Source*: Farombi et al. 2009.

Kolaviron Abrogates Apoptosis and Related Caspases

In pursuance of additional mechanisms of chemoprevention with kolaviron, Dr. Adedara my former PhD student, during his doctorate programme on a John D. and Catherine T. MacArthur Foundation-funded Fellowship, carried out some aspects of his research with Professor Premendu Mathur, one of our collaborators in the Department of Biochemistry & Molecular Biology, Pondicherry University, India. Dr. Adedara was able to elucidate other chemopreventive mechanisms of action of kolaviron in models of testicular cell death induced by two environmental compounds—Ethylene glycol monoethyl ether (EGEE), a widely used industrial solvent and a component of many cleaning agents, paints and hydraulic fluid, and Carbendazim (CBZ), a broad-spectrum and systemic fungicide. Immunoblot analysis revealed significant increase in stress-inducible protein levels, protein

expression of active caspases, Fas and Fas-L, accompanied by elevation of cytosolic cytochrome c level in the testes of EGEE-treated rats (figs. 31 and 32).

In addition, the observation from immunofluorescence staining was consistent with the increased apoptotic bodies as revealed by TUNEL-positive nuclei in the testes of EGEE-treated rats (Adedara, Mathur and Farombi 2013c). Interestingly, carbendazim similarly mediated apoptosis involving both the mitochondria- and FasL-mediated pathways (fig. 33) (Adedara, Mathur and Farombi 2013d). Our results showed that kolaviron not only protected the testes against damage but also abolished apoptosis in the two models of testicular death induced by these environmental toxicants. Thus Kolaviron, may provide additional therapeutic approach to testicular dysfunction resulting from exposure to environmental compounds by its anti-apoptotic properties.

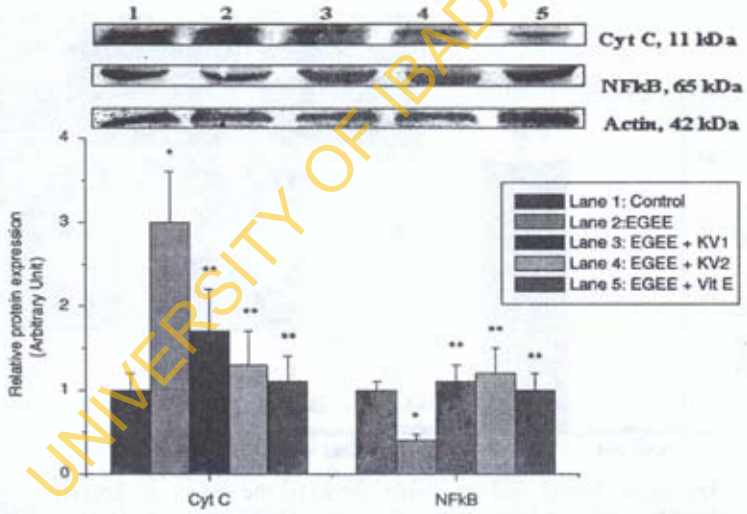


Fig. 31: Effect of kolaviron and vitamin E on cytosolic levels of cytochrome c release and NF-kB in EGEE-exposed rats. The data are expressed as mean + S.D.; n=5. *: Values differ significantly from control ($p<0.05$). **: Values differ significantly from EGEE ($p<0.05$). *Source*: Adedara et al. 2013c.

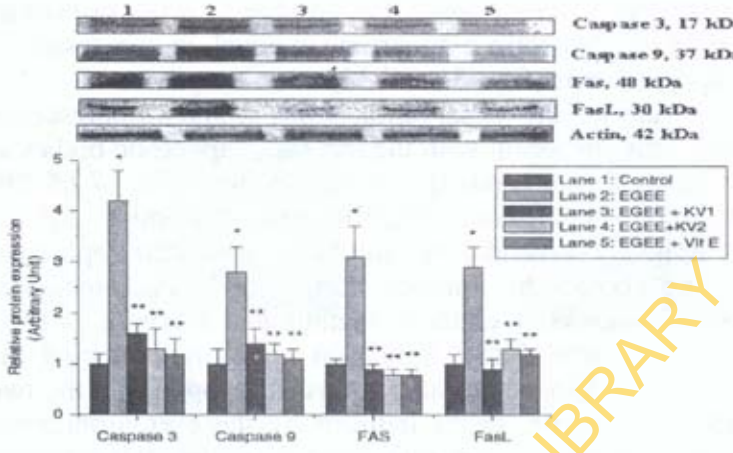


Fig. 32: Effect of kolaviron and vitamin E on caspases, Fas and FasL in EGEE-exposed rats. The data are expressed as mean+S.D.; n=5. *: Values differ significantly from control ($p<0.05$). **: Values differ significantly from EGEE ($p<0.05$). *Source*: Adedara et al. 2013c.

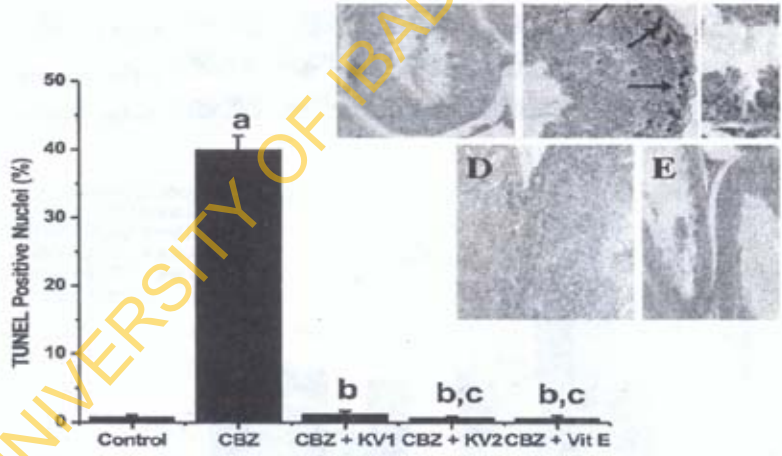


Fig. 33: Testis histopathology guide showing the effect of kolaviron and vitamin E on seminiferous tubules with TUNEL-positive nuclei in CBZ-treated rats. Control (A) 100X, CBZ alone (B) 200%, CBZ + KV1 (C) 100X, CBZ + KV2 (D) 200X And CBZ + Vitamin E (E) 100X. Arrowheads identify TUNEL-positive nuclei. Increased number of TUNEL-positive nuclei, mainly spermatogonia and spermatocytes, are seen in testis sections of CBZ-exposed rats. The data are expressed as mean±S.D. [a]Values differ significantly from control ($p<0.05$). [b]Values differ significantly from CBZ ($p<0.05$). [c]Values differ significantly from CBZ + KV1 ($p<0.05$). *Source*: Adedara et al. 2013d.

Neuroprotective Mechanisms of Kolaviron-Implications for Parkinson Disease

We reported for the first time the anti-apoptotic activity of Kolaviron in PC12 cells, a rat pheochromocytoma, exposed to endocrine disruptoratrazine. In the PC-12 cells, kolaviron reversed atrazine-induced generation of reactive oxygen species detected by Flow cytometric analysis. Furthermore, kolaviron treatment elicited significant restoration in atrazine-induced alterations in the expression of apoptosis markers viz. p53, Bax, Bcl2, caspase-3, caspase-9, cyclooxygenase-2 (COX-2) as well as c-Jun and c-fos (fig. 34) (Abarikwu et al. 2011a). In order to find a possible therapeutic intervention by application of natural compounds to degenerative diseases, we selected the SH-SY5Y human neuroblastoma cell line, a reliable neuronal model system for apoptosis to elucidate the underlying signal transduction pathway(s) involved in kolaviron-mediated protection. Thus, we demonstrated for the first time unequivocally that kolaviron blocked atrazine-mediated nuclear changes associated with apoptosis (fig. 35); including nuclear fragmentation, condensation, DNA laddering (fig. 35), and increased caspase-3 activity. Interestingly, kolaviron, prevented atrazine-induced changes in the expressions of p53, Bax, Bcl-2, p21, and mRNA levels of caspase-3 and caspase-9 (fig. 36) (Abarikwu et al. 2011b). These data suggest that kolaviron possesses potential therapeutic properties against chemical-induced apoptotic cell death in the neuronal system and *therefore opens up a new therapeutic window in progressive neurodegenerative diseases such as Parkinson's disease.* Mr. Vice-Chancellor Sir, I am happy to report that our new research on preclinical evaluation of Kolaviron as an anti-parkinsonian lead drug has been supported by a recently awarded TETFUND National Research Fund (NRF) Grant. Figure 37 summarizes how Kolaviron, a novel chemopreventive agent compromises the science of the "killers".

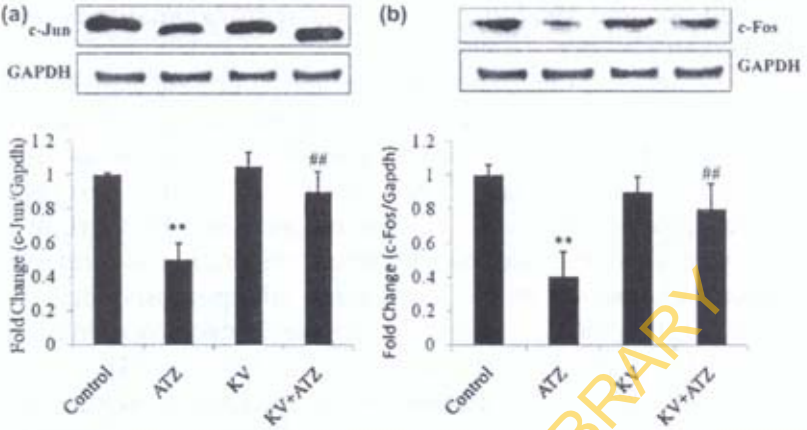


Fig. 34: Protective effect of kolaviron (KV) on atrazine (ATZ)-induced alterations in the protein expression of c-Jun and c-Fos (A, B) in PC12 cells. *Source*: Abarikwu et al. 2011a.

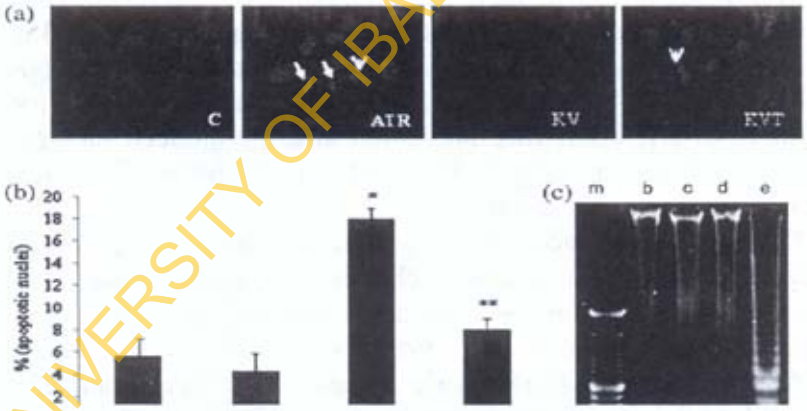


Fig. 35: Kolaviron (KV) prevents atrazine (ATR)-induced apoptosis. SH-SY5Y cells, with or without simultaneous treatment with KV were exposed to ATR for 48 h, microscope (magnification, X400). Arrow heads indicated condensed nuclei and arrow indicated fragmented nuclei (a), quantification of abnormal nuclei after exposure to ATR in the presence or absence of KV. *Source*: Abarikwu et al. 2011b.

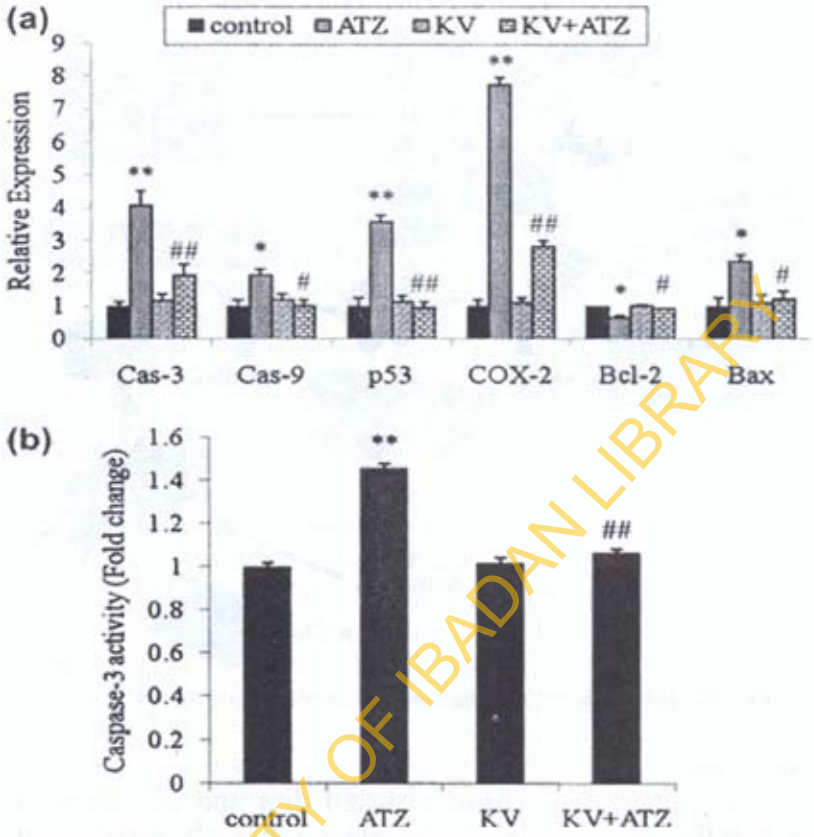


Fig. 36: Real-time quantitative-PCR analyses of mRNA expression of caspase-3 (cas-3), caspase-9 (cas-9), p53, cyclooxygenase-2 (COX-2), Bcl-2 and Bax genes in PC12 cells exposed to kolaviron (KV) and atrazine (ATZ) alone or in combination for 6 h (A). Caspase activity (B). *Source*: Abarikwu et al. 2011b.

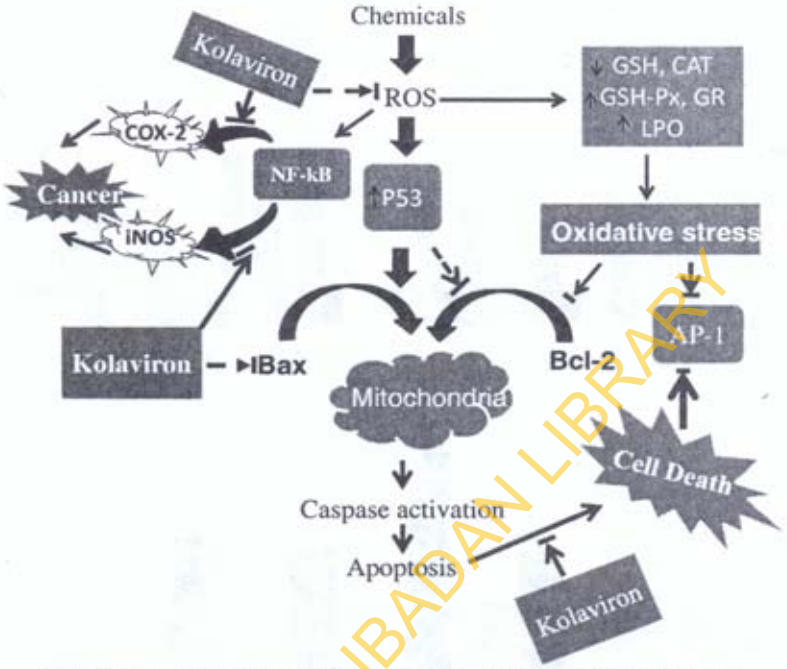


Fig. 37: How kolaviron compromises the science of the "Killers".

Conclusion

Mr. Vice-Chancellor, distinguished ladies and gentlemen, I have in the course of this lecture shown through our series of studies that humans are advertently and inadvertently exposed to environmental toxicants especially through diet. Also, therapeutic drugs especially when taken at overdose are capable of damaging tissues. Through excessive generation of free radicals, the tissue defence mechanism can be compromised and overwhelmed leading to oxidative stress. Inflammation especially unresolved, is another mechanism of initiating disease conditions such as cancer. I have also shown that providentially in our diet, certain protective factors are inherent in them and capable of preventing, delaying or reversing diseases caused by these chemicals. In this connection, chemopreventives with potent antioxidant and anti-inflammatory properties can compromise the two co-conspirators employed as veritable tools by the 'killers' in

initiating cell dysfunction and death. Therefore, if we invest in eating these naturally occurring chemopreventive agents, there is hope that humans can be spared from certain health-threatening diseases and longevity can be achieved. In actual fact, there has been a paradigm shift in many countries (including the USA) from the use of conventional medicine to naturally-occurring phytochemicals and it has been predicted that the doctors of the future will prescribe pills made of phytochemicals and chemopreventives to patients given their beneficial principles. I will conclude with the words of wisdom from Hippocrates a celebrated Greek Physician and adjudged "father of Western medicine" who said **"Let medicine be thy food and food be thy medicine" and "You are what you eat".**

Recommendations

In the course of my training and development of my academic career, I have by the Grace of God and His Mercy worked in various world-class laboratories and worked with international experts in my field of research. I had postdoctoral training three times in three different laboratories around the globe and I have been invited to conduct research in many laboratories abroad as Visiting Scholar and Visiting Professor. My doctoral students as well as junior colleagues have also leveraged on this and I have connected them to my friends and collaborators aboard. Some of them have conducted certain parts of their PhD work outside the country. Hence, I have been able to present the information contained in this lecture to you all. During these visits, I learnt so many things in terms of research, academic culture and best practices. The common denominator is actually the commitment of the government to high quality research and engagement of scientists to highly competitive and globally-relevant research. For instance as a Visiting Professor in Seoul National University, Korea my friend Professor Young-Joon Surh disclosed that so many Korean Scientists who trained in the USA were recruited back to the country to replicate and do the 'wonders' in Korea while they were in

the USA. They were given space, grants and enabling environment to do research and compete globally. Mr. Vice-Chancellor, ladies and gentlemen within a short period of time the dividend of this investment started showing. In certain fields of research endeavour and technological innovations, South Korea is on top today. This country was at par with Nigeria in the 1960s! This is another opportunity of calling on the government to invest in quality research. Thank God the awareness is there as the past Nigerian Government instituted the National Research Fund scheme under TETFUND. We need more of this at this time.

Another lesson I learnt while in those institutions abroad is also the issue of the universities and their focus on certain specialized research. They have not attempted to shine in all areas of research but they have strived to be known in certain focused specialized areas. Many researchers in our universities are just conducting what I call 'survival' or racking research, only for the purpose of promotion and to gain high scores during the usual scoring of papers exercise. Unfortunately, this will not take us anywhere. I am using this medium to call on the University management to examine our research activities critically and focus on certain impactful research areas that can showcase the University, taking into consideration the strength and comparative advantage of researchers in Departments and Faculties.

While the effort to centralize certain equipment may be good, serious efforts should be made to develop laboratories based in various departments and equip them with a state-of-the-art facilities. Most of the equipment we centralize in the central research laboratories are usually placed on the corridors of personal laboratories of colleagues abroad. To my esteemed colleagues especially the younger ones, it is highly imperative to do away with 'survival' research and go beyond mere publishing only for the purpose of promotion. Rather, we should be engaged in cutting-edge research, highly competitive hypothesis-driven proposals that can attract international grants to do globally-relevant research. It is only by engaging in this kind of research that the gown can effectively impact the town.

For researchers working in the field of natural product, I encourage you to dig deeper and stop scratching the problem on the surface. While the use of extracts may provide some preliminary information on the therapeutic use of a plant, it is only isolated and well-characterized compounds that can be useful in investigating and understanding the underlying pharmacological basis of action of these plants. Hence, multi-disciplinary approach involving Biochemists, Chemists, Pharmacognosists, Toxicologists, Pharmacologists and Microbiologists is highly needed at this time.

Judging from what I have presented today you will all agree with me that there is a lot to be done between biomedical scientists and clinicians. Translational medicine is actually the future of molecular medicine. The University should encourage and support translational research through research funding—taking research products from 'bench to the bedside'. As a Fellow of the Nigerian Academy of Science, in the month of September 2015, Professor Fola Esan (retired Professor of Hematology) and I were privileged to represent Nigeria and the Academy in Beijing, China on Inter academy programme. In China, we were exposed to a lot of translational research and many products actually developed in the laboratory facilitated by the government and various universities are useful in Chinese Traditional Medical Hospitals in treating many health-threatening ailments including cancer. No wonder, China continues to be a major exporter of traditional medicinal products to the world market through well-organized and articulated translational research.

Toxicology is a cross-cutting research field and there is actually a dearth of trained and qualified toxicologists around the African continent. Toxicology plays an important role in detecting poisons, fake drugs, hazardous chemical compounds, genotoxic agents and dangerous herbal products. Before taking any natural product to the market, it must have passed through series of toxicity testing and found not to be toxic. There is the need for the University to establish viable and weil-equipped toxicity screening center to serve the nation. In addition, University of Ibadan should have a Toxicology programme at the postgraduate level to train and

increase manpower and build capacity in this important field. During my one-month visit to the Indiana State University, Bloomington, USA (April, 2014), I discussed this extensively with the leadership of Society of Toxicology (SOT), USA and International Union of Toxicology (IUTOX) when I was honoured with the globally competitive award of the SOT Global Senior Toxicology Fellowship. Happily, we have the support of these esteemed organizations and experts in the field. We need the support of the University management to actualize this for our University, Nigeria and Africa at large.

Finally, research on chemoprevention should be encouraged given the role it plays in preventive medicine and health care delivery system. The Government through the Ministry of Health should promote and facilitate chemopreventive initiatives just like many governments abroad have done in recent years. For instance, a number of government programmes have been created in the United States and in Europe to increase vegetable consumption and plant-based phytochemicals—in order to decrease cancer incidence and other life-threatening diseases. These include the following: 'Savor the Spectrum' an initiative that urges all Americans to eat five to nine servings of colourful fruit and vegetables a day for better health based on current research showing that phytonutrients from different colour groups are powerful disease fighters that help our body fight off cancer and heart diseases.

European Prospective Investigation of Cancer and Nutrition (EPIC) is one of the most important multicentre prospective cohort studies ever launched worldwide involving more than half a million (520,000) participants recruited by 20 centres in 10 countries under the coordination of the International Agency for Research on Cancer (IARC) and partly funded by the 'Europe Against Cancer' programme of the European Commission, as well as by the participating countries. EPIC focuses on identifying the dietary determinants of cancer, and is aimed at expanding the presently limited knowledge of the role of nutrition and other lifestyle factors in the aetiology and prevention of cancer and

other life-threatening diseases. These initiatives in place in Nigeria, will facilitate longevity and accentuate our average life span, which is currently one of the lowest in the world.

Acknowledgements

For this cause I bow before the Father of light, the Creator of the ends of the earth, the 'Elohim' of Israel for the avalanche of grace, mercy and favour bestowed on me without measure. He is the Lifter up of my head, my Succorer, Standby and One who causes me to triumph in every situation and make manifest the savour of His knowledge in every place. Glory be to His Holy name!

I am highly indebted to my late father Chief Emmanuel Oyetunji Farombi for his investment in my education and support all the way. In nostalgia, I remember he used to quote to me regularly Proverb 22:8 "*Seest thou a man diligent in his business? he shall stand before kings; he shall not stand before mean men*". Today, the fulfillment of this scripture has come to pass. I am eternally grateful to my mother Mama Comfort Adegbenle Farombi who is seated here today to witness this occasion. I thank her for motherly care, love, concern, affection and constant prayers. Mama may you live long for more years to come! Amen.

12th century theologia Salisbury said in 1159: *"We are like dwarfs sitting on the shoulders of giants. We see more, and things that are more distant, than they did, not because our sight is superior or because we are taller than they, but because they raise us up, and by their great stature add to ours."*

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References

Abarikwu, S.O. (2014) Kolaviron, a natural flavonoid from the seeds of Garcinia kola, reduces LPS-induced inflammation in macrophages by combined inhibition of IL-6 secretion, and inflammatory transcription factors, ERK1/2, NF-κB, p38, Akt, p-c-JUN and JNK. *Biochimica et Biophysica Acta,* 1840: 2373–2381.

Abarikwu, S.O., Adesiyan, A.C., Oyeloja, T.O., Oyeyemi, M.O. and Farombi, E.O. (2010) Changes in Sperm Characteristics and Induction of Oxidative Stress in the Testis and Epididymis of Experimental Rats by a Herbicide, Atrazine. *Archives of Environmental Contamination and Toxicology,* 58: 874-882.

Abarikwu, S.O. and Farombi, E.O. (2012) Evaluating the reproductive toxicities and tumor-promoting properties of the chloro-S-triazine herbicide, atrazine in the vertebrates male and female animals. In: A.D. Justin (Ed.), *Advances in Environmental Research.* Hauppauge, New York: Nova Science Publishers. pp 459-486.

_____ (2015) Atrazine induces apoptosis of SH-SY5Y human neuroblastoma cells via the regulation of Bax/Bcl-2 ratio and caspase-3-dependent pathway. *Pesticide Biochemistry and Physiology,* 118:90-8.

Abarikwu, S.O., Farombi, E.O., Kashyap, M.P. and Pant, A.B. (2011a) Atrazine induces transcriptional changes in steroidogenesis marker genes in primary cultures of rat Leydig cells. *Toxicology in Vitro,* 25(8): 1588-95.

Abarikwu, S.O., Farombi, E.O., Kashyap, M.P. and Pant, A.B. (2011b) Kolaviron protects apoptotic cell death in PC12 cells exposed to Atrazine. *Free Radical Research,* 45(9): 1061-73.

Abarikwu, S.O., Farombi, E.O. and Pant, A.B. (2011c) Biflavanone-kolaviron protects human dopaminergic SH-SY5Y cells against atrazine induced toxic insult. *Toxicology in Vitro,* 25(4): 848-858.

Abarikwu, S.O., Pant, A.B. and Farombi, E.O. (2013) Quercetin decreases steroidogenic enzyme activity, NF-κB expression, and oxidative stress in cultured Leydig cells exposed to atrazine. *Molecular and Cellular Biochemistry,* 373(1-2):19-28.

Adaramoye, O.A., Farombi, E.O., Nssien, M., Idowu, S.O., Ademowo, O.G. and Adeyemi, E.O. (2008) Hepatoprotective activity of purified fractions from *Garcinia kola* seeds in mice intoxicated with carbon tetrachloride. *Journal of Medicinal Foods,* 11(3):544-50.

Adaramoye, O.A. and Lawal, S.O. (2015) Kolaviron, a biflavonoid fraction from Garcinia kola, protects against isoproterenol-induced injury by mitigating cardiac dysfunction and oxidative stress in rats. *J Basic Clin Physiol Pharmacol.,* 26(1):65-72.

Adaramoye, O.A., Nwaneri, V.O., Anyanwu, K.C., Farombi, E.O. and Emerole G.O. (2005) Possible anti-atherogenic effects of kolaviron (*Garcinia kola* seed extract) in hypercholesterolemic rats. *Clinical & Experimental Pharmacology & Physiology,* 32 (1-2): 40-46.

Adedara, I.A., Awogbindin, I.O., Adesina, A.A., Oyebiyi, O.O., Lawal, T.A. and Farombi E.O. (2015) Municipal Landfill Leachate-Induced Testicular Oxidative Damage is Associated with Biometal Accumulation and Endocrine Disruption in Rats. *Archives of Environmental Contamination and Toxicology,* 68(1): 74-82.

Adedara, I.A., Ebokaiwe, A.P. and Farombi, E.O. (2013a) Tissues distribution of heavy metals and erythrocytes antioxidant status in rats exposed to Nigerian bonny light crude oil. *Toxicology and Industrial Health,* 29(2): 162-8.

Adedara, I.A. and Farombi, E.O. (2012) Hepatic oxidative damage following withdrawal of Nigerian bonny light crude oil treatment in rats. *Cell Biochemistry and Function,* 30(6): 480-6.

Adedara, I.A., Lawal, T.A., Adesina A.A. and Farombi, E.O. (2013b) Involvement of oxidative stress in municipal landfill leachate-induced toxicity in boar sperm. *Environmental Toxicology and Pharmacology,* 36(3): 972-8.

Adedara, I.A., Mathur, P.P. and Farombi, E.O. (2013c) Kolaviron, a natural biflavonoid of *Garcinia kola* seed prevents ethylene glycol monoethyl ether-induced testicular apoptosis via down-regulation of stress proteins, Fas/Fas-L and Caspases expressions in rats. *Toxicology Mechanisms and Methods,* 23(9): 689-96.

Adedara, I.A., Vaithinathan, S., Jubendradass, R., Mathur, P.P. and Farombi, E.O. (2013d) Kolaviron, a *Garcinia kola* biflavonoid, prevents carbendazim-induced steroidogenic dysfunction and apoptosis in testes of rats. *Environmental Toxicology and Pharmacology,* 35: 444-453.

Adedara, I.A., Ebokaiwe, A.P., Mathur, P.P. and Farombi, E.O. (2014a) Nigerian Bonny light crude oil induces endocrine disruption in male rats. *Drug and Chemical Toxicology,* 37(2): 198-203.

Adedara, I.A., Lawal, T.A., Adesina, A.A., Oyebiyi, O.O., Ebokaiwe, A.P. and Farombi, E.O. (2014b) Sperm functional parameters and erythrocytes oxidant-antioxidant imbalance during municipal landfill leachate treatment withdrawal in rats *Environmental Toxicology and Pharmacology,* 37(1): 460-467.

Adesanoye, O.A. and Farombi, E.O. (2010) Hepatoprotective effects of *Vernonia Amygdalina* (Compositae) in rats treated with Carbon tetrachloride. *Experimental and Toxicologic Pathology,* 62: 197-206.

Adesanoye, O.A., Molehin, O.R., Delima, A.A., Adefegha, S.A. and Farombi, E.O. (2013) Modulatory Effect Of Methanolic Extract Of *Vernonia Amygdalina* (Meva) On Tert- Butyl Hydroperoxide-Induced Erythrocyte Hemolysis. *Cell Biochemistry and Function,* 31(7): 545-550.

Adesanoye, O.A. and Farombi, E.O. (2014) In Vitro Antioxidant Properties of Methanolic Leaf Extract of Vernonia Amygdalina Del. *Niger J Physiol Sci.,* 29(2): 91-101.

Adesanoye, O.A., Adekunle, A.E., Adewale, O.B., Mbagwu, A.E., Delima, A.A., Adefegha, S.A., Molehin, O.R. and Farombi, E.O. (2016) Chemoprotective Effect of *Vernonia Amygdalina Del.* (Astereacea) against 2-Acetylaminofluorene-induced Hepatotoxicity in Rats. *Toxicology and Industrial Health,* 32(1): 47-58.

Aggarwal, B.B. and Shishoda, S. (2004) Suppression of the nuclear factor κB activation pathway by spice-derived phytochemicals: Reasoning for the seasoning. *Ann NY Acad Sci* 1030: 434-441.

Aggarwal, B.B., Shishodia, S., Sandur, S.K., Pandey, M.K. and Sethi, G. (2006) Inflammation and cancer: How hot is the link? *Biochem Pharmacol,* 72: 1605-1621.

Aggarwal, B.B., Sundaram, C., Malani, N. and Ichikawa, H. (2007) Curcumin: The Indian solid gold. *Adv Exp Med Biol*, 595: 1-75.

Aggarwal, B.B. and Sung, B. (2008) Pharmacological basis for the role of curcumin in chronic diseases: An age-old spice with modern targets. *Trends in Pharmacological Sciences,* Vol. 30 No.2, 85-94.

Ajayi, B.O., Adedara, I.A. and Farombi, E.O. (2015) Pharmacological Activity of 6-Gingerol in Dextran Sulphate Sodium-induced Ulcerative Colitis in BALB/c Mice. *Phytotherapy Research,* 29: 566-72.

Akinmoladun, A.C., Obuotor, E.M., Barthwal, M.K., Dikshit, M. and Farombi, E.O. (2010) Ramipril-Like Activity of Spondias Mombin Linn against NO-Flow Ischemia and Isoproterenol-Induced Cardiotoxicity in Rat Heart. *Cardiovascular Toxicology,* 10(4): 295-305.

Akinmoladun, A.C., Obuotor, E.O. and Farombi, E.O. (2010) Antioxidant and Free radical scavenging capacities of some medicinal plants from Nigeria: A comparison of seven methods. *Journal of Medicinal Foods*, 13(2): 444-51.

Argheore, E.M., Makkar, H.P.S. and Becker, K. (1998) Feed value of some browse plants from the central zone of Delta State Nigeria. *Trop Sci,* 38: 97-104.

Awang, D.V.C. (1992) Ginger. *Can. Pharm. J.,* 125: 309-311.

Awogbindin, I.O., Olaleye, D.O. and Farombi, E.O. (2015) Kolaviron Improves Morbidity and Suppresses Mortality by Mitigating Oxido-Inflammation in BALB/c Mice Infected with Influenza Virus. *Viral Immunology,* 28(7): 367-77.

Balkwill, F., Charles, K.A. and Mantovani, A. (2005) Smoldering and polarized inflammation in the initiation and promotion of malignant disease. *Cancer Cell,* 7: 211-217.

Barnes, S., Grubbs, C., Setchell, K.D.R. and Carlson, J. (1990) Soybean inhibits mammary tumours in models of breast cancer. In: *Mutagens and carcinogens in the diet.* Wiley-Liss, pp. 239-253.

Bhargav, B., Singh, M.P., Murthy, R.C., Mathur, N., Misra, D., Saxena, D.K. and Chowdhuri, D.K. (2008) Toxic potential of municipal solid waste leachates in transgenic *Drosophila melanogaster* (hsp70-lacZ): hsp70 as a marker of cellular damage. *Ecotoxicol Environ Saf,* 69: 233-245.

Braide, V.B. (1991) Antihepatotoxic biochemical effects of kolaviron, a biflavonoid of *Garcinia kola* seeds. *Phytotherapy Research,* 5: 35-37.

Buchholz, B.A., Fultz, E., Haack, K.W., Vogel, J.S., Douglas-Gilman, S., Gee, S.J., Hammock, B.D., Hui, X., Wester, R.C. and Maibach, H.I. (1999) HPLC-accelerator MS measurement of atrazine metabolites in human urine after dermal exposure. *Anal Chem,* 71: 3519-3525.

Chung, W.Y., Park, J.H., Kim, M.J., Kim, H.O., Hwang, J.K., Lee, S.K. and Park, K.K. (2007) Xanthorrhizol inhibits 12-O-tetradecanoylphorbol-13-acetate-induced acute inflammation and two-stage mouse skin carcinogenesis by blocking the expression of ornithine decarboxylase, cyclooxygenase-2 and inducible nitric oxide synthase through mitogen-activated protein kinases and/or the nuclear factor-kappa B. *Carcinogenesis,* 28: 1224-1231.

Di Monte, D.A. (2003) The environment and Parkinson's disease: is the nigrostriatal system preferentially targeted by neurotoxins? *Lancet Neurol,* 2: 531-538.

Doll, R. and Peto, R. (1981) The causes of cancer: Quantitative estimates of avoidable risks of cancer in the United States today. *J. Natl Cancer Inst.,* 66: 1191-1308.

Ebokaiwe, A.P., Ramesh, P., Mathur, P.P. and Farombi, E.O. (2015a) Transient Effect of Single Dose Exposure of Nigerian Bonny-Light Crude Oil on testicular steroidogenesis in Wistar rats is accompanied by oxidative stress. *Drug and Chemical Toxicology,* 38(4): 428-35.

Ebokaiwe, A.P., D'Cruz, C.S., Jubendradass, R., Amala Rani, J.S., Mathur, P.P. and Farombi, E.O. (2015b) Nigerian Bonny-Light Crude Oil induces alteration in Testicular Stress response Proteins and caspase-3 dependent Apoptosis in Albino Wistar Rats. *Environmental Toxicology (USA),* 30(2): 242-52.

Ekor, M. (2009) Modulation of Gentamicin- and Cisplatin-induced Nephrotoxicity and Acute Renal Failure by Methanolic Extracts of Soybean (*Glycine Max (L.) Merr.*) in Rats. PhD Thesis, University of Ibadan.

Ekor, M., Emerole, G.O. and Farombi, E.O. (2010) Phenolic Extract of Soybean (*Glycine max*) Attenuates Cisplatin–induced Nephrotoxic Acute Renal Failure in rats. *Food and Chemical Toxicology,* 48: 1005-1012.

Ekor, M., Farombi E.O and Emerole, G.O. (2006) Modulation of Gentamicin-induced renal dysfunction by phenolic compounds in Soybean (*Glycine maxima). Fundamental and Clinical Pharmacology,* 20: 263-271.

Emerole, G.O. and Thabrew, M.I. (1983) Changes in some rat hepatic microsomal components induced by prolonged administration of chloroquine. *Biochem. Pharmacol.* 32: 3005-3009.

Farombi, E.O. (2000a) Influence of amodiaquine treatment on microsomal lipid peroxidation and antioxidant defense systems of rats. *Pharmacology & Toxicology,* 87: 249-254.

_____ (2000b) Mechanisms for the hepatoprotective action of kolaviron: Studies on hepatic enzymes, microsomal lipids and lipid peroxidation in carbon tetrachloride-treated rats. *Pharmacological Research,* 42: 75-80.

_____ (2003a) African Indigenous Plants with Chemo-therapeutic Potentials and Biotechnological Approach to the Production of Bioactive Prophylactic Agents. *African Journal of Biotechnology,* 2(12): 662-671.

_____ (2003b) Locally Derived Natural Antioxidant Substances in Nigeria: Potential Role as New Chemotherapeutic Agents. In: T. Bahorun and A. Gurib-Fakim (Eds.), *Molecular and Therapeutic Aspects of Redox Biochemistry.* London: OICA International (UK) Limited. pp. 207-226.

_____ (2004) Diet-related cancer and prevention using anticarcinogens. *African Journal of Biotechnology,* 3(12): 651-661.

_____ (2005) Evaluation of the Genotoxic effects of Amodiaquine, Mefloquine and Halofantrine in Rat Liver cells. *Environmental Mutagens and Carcinogens,* 25(3): 97-103.

_____ (2006) Genotoxicity of Chloroquine in rat liver cells: Protective role of Free radical scavengers. *Cell Biology and Toxicology,* 22 (3): 159-167.

_____ (2009) Biochemical and Molecular Mechanisms of Hepatoprotection by Kolaviron, a natural antioxidant biflavonoid from *Garcinia kola* seed. In: *Nutritional antioxidants in cancer and degenerative diseases.* Kerala: Research Sign Post.

Farombi, E.O. (2011) Bitter kola (*Garcinia kola*) seeds and hepatoprotection. In: V.R. Preedy, R.R. Watson, V.B. Patel (Editors), *Nuts & seeds in health and disease prevention* (1st Edition). London, Burlington, San Diego: Academic Press (Elsevier). pp. 221-228.

Farombi, E.O., Abarikwu, S.O., Adedara I.A. and Oyeyemi, M.O. (2007) Curcumin and Kolaviron ameliorate Dibutyl phthalate-induced testicular toxicity in rats. *Basic and Clinical Pharmacology and Toxicology,* 100: 43-48.

Farombi, E.O., Abarikwu, S.O., Adesiyan, A.C. and Oyejola, T.O. (2013) Quercetin Exacerbates The Effects of Subacute Treatment of Atrazine on Reproductive Tissues Antioxidant Defense Systems, Lipid Peroxidation and Sperms Quality of Rats. *Andrologia,* 45(4): 256-65.

Farombi, E.O., Abolaji, A.O., Adedara, I.A., Maduako, I.C. and Omodanisi, I.E. (2015) Artemisinin induces hormonal imbalance and oxidative damage in the erythrocytes and uterus, but not in the ovary of rats. *Human and Experimental Toxicology,* 34(1): 83-92.

Farombi, E.O., Adedara, I.A., Abolaji, A.O., Anamelechi, J.P. and Sangodele, J.O. (2014) Sperm characteristics, antioxidant status and hormonal profile in rats treated with artemisinin. *Andrologia,* 46(8): 893-901.

Farombi, E.O., Adedara, I.A., Ajayi, B.O., Ayepola, O.R. and Egbeme, E.E. (2013) Anti-oxidative and anti-inflammatory effects of kolaviron on Dextran sulphate sodium-induced colitis in rats. *Basic and Clinical Pharmacology and Toxicology,* 113(1): 49-55.

Farombi, E.O., Adedara, I.A., Ebokaiwe, A.P., Teberen, R. and Ehwerhemuepha, T. (2010) Nigerian Bonny Light Crude Oil Disrupts Antioxidant Systems in the Testes and Sperm of Rats. *Archives of Environmental Contamination and Toxicology,* 59(1): 166-74.

Farombi, E.O., Adelowo, O.A. and Ajimoko, Y.R. (2007) Antioxidant status and heavy metal levels as biomarkers of environmental pollution in Nigerian Ogun River cat fish (*Clarias gariepinus*). *International Journal of Environmental Research and Public Health,* 4(2): 158-165.

Farombi., E.O., Adepoju, B.F., Ola-Davies, O.E. and Emerole, G.O. (2005) Chemoprevention of aflatoxin B1-induced genotoxicity and hepatic oxidative damage in rats by Kolaviron, a natural biflavonoid of *Garcinia kola* seeds. *European Journal of Cancer Prevention,* 14: 207-214.

Farombi, E.O., Adoro, S. and Uhunmwangho, S. (2001) Antimalarial drugs exacerbate Rat Liver Microsomal Lipid Peroxidation in the Presence of Oxidants. *Bioscience Report,* 21(3): 353-359.

Farombi, E.O., Akanni, O.O. and Emerole, G.O. (2002) Antioxidative and scavenging activities of kolaviron in vitro. *Pharmaceutical Biology,* 40: 107-116.

Farombi, E.O., Akintunde, J.K., Nzute, N., Adedara, I.A. and Arojojoye, O. (2012) Municipal landfill leachate induced hepatotoxicity and oxidative damage in rats. *Toxicology and Industrial Health,* 28(6): 532-41.

Farombi, E.O. and Britton, G. (1999a) Antioxidant activity of Palm oil carotenes in organic solution: Effects of structure and chemical reactivity. *Food Chemistry,* 64(3): 315-321.

_____ (1999b) Antioxidant activity of Palm oil carotenes in peroxyl radical-mediated peroxidation of phosphatidyl choline liposomes. *Redox Report (Communications in Free Radical Research),* 4 (1/2): 61-68.

Farombi, E.O. and Ekor, M. (2006) Curcumin attenuates Gentamicin-mediated renal oxidative stress in rats. *Food and Chemical Toxicology (UK),* 44: 1443-1448.

Farombi, E.O. and Emerole, G.O. (1998) Interference of common antimalarial drugs with some hepatic microsomal components and drug metabolism: Potential implications for toxicity. *South African Journal of Science,* 94: 303-304.

Farombi, E.O. and Fakoya, A. (2005) Free radical scavenging and antigenotoxic activities of natural phenolic compounds from dried flowers of *Hibiscus sabdariffa* L. *Molecular Nutrition and Food Research,* 49(12): 1120-1128.

Farombi, E.O., Hansen, M., Ravn-Haren, G., Moller, P. and Dragsted, L.O. (2004) Commonly consumed and naturally occurring dietary substances affect biomarkers of oxidative stress and DNA damage in healthy rats. *Food and Chemical Toxicology,* 42(8): 1315-1322.

Farombi, E.O., Moller, P. and Dragsted, L.O. (2004) Ex-vivo and in vitro protective effects of kolaviron against oxygen-derived radical-induced DNA damage and oxidative stress in human lymphocytes and rat liver cells. *Cell Biology and Toxicology,* 20(2): 71-82.

Farombi, E.O. and Nwaokeafor, I.A. (2005) Antioxidant mechanisms of action of kolaviron: Studies on serum lipo-protein oxidation, metal chelation and oxidative microsomal membrane damage in rats. *Clinical and Experimental Pharmacology & Physiology,* 32: 667-674.

Farombi, E.O., Ogundipe, O.O. and Moody, J.O. (2001) Antioxidant and anti-inflammatory activities of *Mallotus oppositifolium* in model systems. *African Journal of Medicine & Medical Sciences,* 30 (3): 213-215.

Farombi, E.O., Ogundipe, O.O., Uhunwangho, E.S., Adeyanju, M.A. and Moody, J.O. (2003) Antioxidant Properties of Extracts from *Alchornea laxiflora* (Benth) Pax and Hoffman. *Phytotherapy Research,* 17 (7): 713-716.

Farombi, E.O., Olowu, B.I. and Emerole, G.O. (2000) Effect of three structurally related antimalarial drugs on liver microsomal components and lipid peroxidation in rats. *Comparative Biochemistry and Physiology (Part C-Comparative Pharmacology & Toxicology),* 126 (3): 217-224.

Farombi, E.O. and Owoeye, O. (2011) Antioxidative and Chemopreventive Properties of *Vernonia amygdalina* and *Garcinia* Biflavonoid. *International Journal of Environmental Research and Public Health,* 8: 2533-2555.

Farombi, E.O., Shrotriya, S. and Surh, Y.J. (2009) Kolaviron inhibits dimethyl nitrosamine-induced hepatotoxicity by suppressing COX-2 and iNOS expression: NF-kB and AP-1 as potential molecular targets. *Life Sciences,* 84: 149-155.

Farombi, E.O., Shyntum, Y.Y. and Emerole, G.O. (2003) Influence of chloroquine treatment and malaria infection on some enzymatic and non-enzymatic antioxidants in humans. *Drug and Chemical Toxicology,* 26(1): 59-71.

Farombi, E.O., Tahnteng, J.G., Agboola, O., Nwankwo, J.O. and Emerole, G.O. (2000) Chemoprevention of 2-acetylaminofluorene-induced hepatotoxicity and lipid peroxidation in rats by kolaviron, a Garcinia kola seed extract. *Food and Chemical Toxicology,* 38: 535-541.

Farombi, E.O. and Surh, Y.J. (2006) Heme oxygenase-1 as a Potential Therapeutic Target for Hepatoprotection. *Journal of Biochemistry and Molecular Biology,* 39(5):479-491.

Farombi., E.O. and Tanaka, T. (2007) Cancer chemoprevention with Zingiberaceae and citrus-derived phytochemicals: Biochemical and molecular mechanisms. In: T. Tanaka (Ed), *Cancer: Disease progression and chemoprevention*, Kerala: Research Sign Post. pp. 167-183.

Fasunon, O.D. and Uwaifo, A.O. (1989) Prophage induction by 4 antimalaria drugs (Daraprim, Fansidar, Nivaquine and Camoquine) and in combination with aflatoxin B1. *Mutation Research,* 222: 311-6.

Filipov, N.M., Stewart, M.A., Carr, R.L. and Sistrunk, S.C. (2007) Dopaminergic toxicity of the herbicide atrazine in rat striatal slices. *Toxicology,* 232: 68-78.

Friedmann, A. (2002) Atrazine inhibition of testosterone production in rat males following peripubertal exposure. *Reprod Toxicol,* 16: 275-279.

Giwa-Osagie, O.O. (2003) Nigeria has twelve million infertile persons. *Pharma News,* 25: 48-49.

Groopman, J.D., Dematos, P., Egner, P.A, Love-Hunt, A. and Kensler, T.W. (1992) Molecular dosimetry of urinary aflatoxin-N7-guanine and serum aflatoxinalbumin adducts predicts chemoprotection by 1,2-dithiole-3-thione in rats. *Carcinogenesis,* 13: 101-106.

Hartmann, A. and Speit, G. (1995) Genotoxic effects of chemicals in the single cell gel (SCG) test with human blood cells in relation to the induction of sister-chromatid exchanges (SCE). *Mutat Res* 346: 49-56.

Herrera-Arellano, A., Flores-Romero, S., Chávez-Soto, M.A. and Tortoriello, J. (2004) Effectiveness and tolerability of a standardized extract from Hibiscus sabdariffa in patients with mild to moderate hypertension: a controlled and randomized clinical trial. *Phytomedicine,* 11:375-82.

Huffman, M.A. (2003) Animal self-medication and ethno-medicine: Exploration and exploitation of the medicinal properties of plants. *Proc Nutr Soc,* 62: 371-381.

Huffman, M.A. and Seifu, M. (1989) Observations on the illness and consumption of a possibly medicinal plant, *Vernonia amygdalina* (Del.), by a wild chimpanzee in the Mahale Mountains National Park, Tanzania. *Primates,* 30: 51-63.

Igile, G.O., Oleszek, W., Burda, S. and Jurzysta, M. (1995) Nutritional assessment of *Vernonia amygdalina* leaves in growing mice. *J Agr Food Chem,* 43: 2162-2166.

Iwu, M.M. (1982) Flavonoids of *Garcinia kola* seeds. *Journal of Natural Products* 45: 650-651.

_____ (1985) Antihepatotoxic constituents of *Garcinia kola* seeds. *Experientia,* 41: 699-700.

Izevbigie, E.B. (2003) Discovery of water-soluble anticancer Agents (Edotides) from a vegetable found in Benin City, Nigeria. *Exp Biol Med,* 228: 293-298.

Izevbigie, E.B., Bryant, J.L. and Walker, A. (2004) A novel natural inhibitor of extracellular signal-regulated kinases and human breast cancer cell growth. *Exp Biol Med,* 229: 163-169.

Kim, S.O., Kundu, J.K., Shin, Y.K., Park, J.H., Cho, M.H., Kim, T.Y. and Surh, Y.J. (2005) [6]-Gingerol inhibits COX-2 expression by blocking the activation of p38 MAP kinase and NF-kappaB in phorbol ester-stimulated mouse skin. *Oncogene*, 24: 2558-2567.

Koskinen, W.C., Clay, S.A. (1997) Factors affecting atrazine fate in north central U.S. soils. *Rev Environ Contam Toxicol* 151: 117-165.

Le Couteur, D.G., McLean, A.J., Taylor, M.C., Woodham, B.L. and Board, P.G. (1999) Pesticides and Parkinson's disease. *Biomed Pharmacother,* 53:122-130.

Lockwood, A.H. (2000) Pesticides and Parkinsonism: is there an etiological link? *Curr Opin Neurol,* 13:687-690.

McLachlan, R. and de Krester, D. (2001) Male infertility: The case for continued research. *Med J Aust,* 174:116-117.

Mauderly, J.L., Jones, R.K., Griffith, W.C., Henderson, R.F. and McClellan, R.O. (1987) Diesel exhaust is a pulmonary carcinogen in rats exposed chronically by inhalation *Fundam Appl Toxicol,* 9: 208-221.

Mingeot-Leclercq, M.P. and Tulkens, P.M. (1999) Aminoglycoside nephrotoxicity. *Antimicrob Agents Chemother,* 43: 1003-1012.

Müller, A.K., Farombi, E.O., Møller, P., Autrup, H.N., Vogel, U., Wallin, H., Dragsted, L., Loft, S. and Binderup, M.L. (2004) DNA damage in lung after oral exposure to diesel exhaust particles in Big Blue® rats. *Mutation Research (Fundamental and Molecular Mechanisms of Mutagenesis)* 550 (1-2); 123-32.

Nanji, A.A., Jokelainen, K., Tipoe, G.L., Rahemtulla, A., Thomas, P. and Dannenberg, A.J. (2003) Curcumin prevents alcohol-induced liver disease in rats by inhibiting the expression of NF-kappa B-dependent genes. *Am J Physiol Gastrointest Liver Physiol,* 284: G321-327.

Neergheen, V.S., Bahorun, T., Taylor, E.W., Jen, L.S. and Aruoma, O.I. (2010) Targeting specific cell signaling transduction pathways by dietary and medicinal phytochemicals in cancer chemoprevention. *Toxicology,* 278: 229-241.

Nwankwo, J.O., Tahnteng, J.G. and Emerole, G.O. (2000) Inhibition of aflatoxin B1 genotoxicity in human liver-derived HepG2 cells by kolaviron biflavonoids and molecular mechanisms of action. *European Journal of Cancer Prevention,* 9: 351-361.

Obaseki-Ebor, E.E. and Obasi, E.E. (1986) Aspects of chloroquine mutagenicity. *Mutat Res,* 175:51-9.

Oehninger, S. (2001) Strategies for the infertile man. *Semin Reprod Med,* 19: 231-237.

Olaleye, S.B., Farombi, E.O., Adewoye, E.A. and Onasanwo, S.A. (2000) Analgesic and anti-inflammatory effects of kolaviron (a *Garcinia kola* seed extract). *Afr J Biomed Res,* 3: 171-174.

Olaleye, S.B., Onasanwo, S.A., Ige, A.O., Wu, K.K. and Cho, C.H. (2010) Anti-inflammatory activities of kolaviron: Inhibition of nitric oxide, prostaglandin E2 and tumor necrosis factor-alpha production in activated macrophage-like cell line. *Afr J Med Med Sci,* 39S: 41-46.

Olorunfemi, F.B. (2011) Landfill development and current practices in Lagos metropolis, Nigeria. *J Geogr Reg Plan,* 4: 656-663.

Orisakwe, O.E., Akumka, D.D., Njan, A.A. and Afonne, O.J. (2004) Testicular toxicity of Nigerian bonny light crude oil in male albino rats. *Reprod Toxicol,* 18: 439-442.

Owoeye, O., Yousuf, S., Akhtar, M.N., Qamar, K., Dar, A., Farombi, E.O., Onwuka, S.K. and Choudhary, M.I. (2010) Another anticancer elemanoide from *Vernonia amygdalina* Del. *International Journal of Biological and Chemical Sciences,* 4: 226-234.

Owoeye, O., Farombi, E.O. and Onwuka, S.K. (2011) Gross morphometric reduction of rats' cerebellum by gamma irradiation was mitigated by pretreatment with *Vernonia amygdalina* leaf extract. *Romanian Journal of Morphology and Embryology,* 52(1): 81-8.

Oyeku, O.T. and Eludoyin, A.O. (2010) Heavy metal contamination of groundwater resources in a Nigerian urban settlement. *Afr J Environ Sci Tech,* 4: 201-214.

Payne, A.H. and Youngblood, G.L. (1995) Regulation of expression of steroidogenic enzymes in Leydig cells. *Biol Reprod.,* 52(2): 217-25.

Ranich, T., Bhathena, S.J. and Velasquez, M.T. (2001) Protective effects of dietary phytoestrogens in chronic renal disease. *J Ren Nutr,* 11: 183-193.

SCF (2002) Opinion of the Scientific Committee on Food on the risks to human health of polycyclic aromatic hydrocarbons in food. European Commission.

Singh, S. (2007) From exotic spice to modern drug? *Cell,* 130: 765-768.

Spano, L., Tyler, C.R., van Aerle, R., Devos, P. and Mandiki, S.N. (2004) Effects of atrazine on sex steroid dynamics, plasma vitellogenin concentration and gonad development in adult goldfish (*Carassius auratus*). *Aquat Toxicol,* 66: 369-379.

Stoker, T.E., Guidici, D.L., Laws, S.C. and Cooper, R.L. (2002) The effects of atrazine metabolites on puberty and thyroid function in the male Wistar rat. *Toxicol Sci,* 67: 198-206.

Stoker, T.E., Robinette, C.L. and Cooper, R.L. (1999) Maternal exposure to atrazine during lactation suppresses suckling-induced prolactin release and results in prostatitis in the adult offspring. *Toxicol Sci,* 52: 68-79.

Sugimura, T (2002) Food and Cancer. *Toxicology,* 181-182: 17-21.

Surh, Y-J., Park, K.K., Chun, K.S., Lee, L.J., Lee, E. and Lee, S.S. (1999) Anti-tumor-promoting activities of selected pungent phenolic substances present in ginger. *J Environ Pathol Toxicol Oncol,* 18: 131-139.

Tanner, C.M., Ottman, R., Goldman, S.M., Ellenberg, J., Chan, P., Mayeux, R. and Langston, J.W. (1999) Parkinson's disease in twins: An etiologic study. *JAMA,* 281: 341-346.

Tice, R.R., Agurell, E., Anderson, D., et al. (2000) Single cell gel/comet assay: Guidelines for in vitro and in vivo genetic toxicology testing. *Environ Mol Mutagen,* 25: 206-21.

Wang, W.H. and Wang, Z.M. (2005) Studies of commonly used traditional medicine-ginger. *Zhongguo Zhong Yao Za Zhi,* 30: 1569-1573.

Wattenberg, L.W. (1985) Chemoprevention of cancer. *Cancer Res.,* 45: 1-8.

WHO (2013) *World malaria report 2013. Global malaria programme.* Geneva: World Health Organization.

Wozencraft, A.O., Dockrell, H.M., Taverne, J., Targett, G.A. and Playfair, J.H. (1984) Killing of human malaria parasites by macrophage secretory product. *Infect Immun,* 43: 664-669.

Yedjou, C., Izevbigie, E. and Tchounwou, P. (2008) Preclinical assessment of *Vernonia amygdalina* leaf extracts as DNA damaging anti-cancer agent in the management of breast cancer. *IJERPH,* 5: 337-341.

Young, J.F., Dragsted, L.O., Haraldsd_ottir, J., Daneshvar, B., Kall, M.A., Loft, S., Nilsson, L., Nielsen, S.E., Mayer, B., Hyunh-Ba, T., Hermetter, A. and Sandstr€om, B. (2002) Green tea extract only affects markers of oxidative status postprandially: Lasting antioxidant effect of flavonoid-free diet. *Brit. J. Nutr.*, 87: 343-355.

BIODATA OF
PROFESSOR EBENEZER OLATUNDE FAROMBI

Ebenezer Olatunde Farombi was born in Osogbo, Osun State to the family of Late Chief Emmanuel Oyetunji Farombi and Chief (Mrs.) Comfort Adegbenle Farombi. After his primary education, he attended Akinorun Grammar School, Ikirun where he obtained the West Africa School Certificate with Division 1 and he was the Library Prefect. He had his A' Levels at the Polytechnic Ibadan. Thereafter, he proceeded to the University of Ibadan to study Biochemistry and graduated as the only candidate with Second Class Upper Division and was the best student in his graduating class. After the compulsory NYSC, he returned to the University for postgraduate studies for which he was awarded the Federal Government of Nigeria Scholarship. He obtained his MSc degree in Biochemistry and again he was the overall best student and the only candidate with PhD grade in his graduating class.

His academic career in the University began in 1988 as practical class demonstrator in Biochemistry, Graduate Assistant in 1989, and Assistant Lecturer in March 1990. During his doctorate programme, he enjoyed two fellowships Bassir Thomas Research Fellowship and Cadbury Plc Postgraduate Fellowship and he was the first to receive the prestigious Award. He rose steadily and consistently through the ranks of the promotion ladder of the University. He became Lecturer II in 1993, Lecturer I in 1997, Senior Lecturer in 2000, Reader in 2003 and Professor of Biochemistry on October 1, 2006.

After his PhD in 1995, he proceeded to the University of Liverpool, England for postdoctoral training with Dr. George Britton as his preceptor. He had another postdoctoral training in Denmark between 2001 and 2002 where he worked with three giants in the field of chemical carcinogenesis—Dr. Lars Dragsted of the Institute of Food Safety and Toxicology, Soborg, Professor Steffen Loft, Panum Institute, University of Copenhagen and Professor Herman Autrup of the Department

of Environmental Health, University of Aarhus, Denmark. He was at different times Visiting Professor to the National Research Laboratory of Molecular Carcinogenesis and Chemoprevention, Seoul National University, South Korea (2005/2006); the Department of Nutritional Toxicology, Friedrich-Schiller University of Jena, Germany (2007); College of Science, Engineering and Technology, Jackson State University, Jackson, Mississippi, USA (2009, 2010); Cape Peninsular University of Technology, Cape Town, South Africa (2011); University of Chicago Medical School, USA (2011); Indiana University, Bloomington, USA (2014) and China Academy of Chinese Medical Sciences, Beijing China (2015).

Worthy of note, his scientific impact nationally and globally has been recognized. For instance in 2005, he was cited and listed among top 10 productive researchers in University of Ibadan who contributed research articles within a 10 year frame (1995-June 2005)- (SESRTCIC, *http://sesrtcic.org/statisticstate*) and ten years later, following the February 2015 Webometric Ranking of Nigerian Scientists, he was top-rated (ranked number 1 Nigerian scientist) with h-index of 35, i10-index of 86 and 4,156 citations. He is a recipient of several International Fellowships and Grants including: UNESCO/MCBN (1998); IUBMB (1998, 2003); WHO/TDR (1998) Fellowships; Danish Research Council Grant (2002); Lady Bank-Anthony Cancer Research Grant (2004), Seoul National University, Korea Visiting Professorship Grant (2005), the MacArthur Foundation Grant for Multidisciplinary Team Research on Chemoprevention (2009), The MacArthur Foundation Grant for Specialized Linkages in the special area of Biotechnology and Medicinal Chemistry (2008, 2009) and 2012 IUTOX Fellowship. Professor Farombi was the winner and recipient by open international competition of the 2014 SOT Global Senior Toxicology Award for his outstanding contribution to the Science of Toxicology.

A very effective, productive and innovative researcher, supervisor and mentor, he has supervised 150 MSc

dissertations and 19 PhD theses in Biochemistry and Toxicology and several BSc students' projects. He is the supervisor of the adjudged best PhD Thesis in the discipline of Basic Medical Sciences within the Nigeria University system during 2009 assessment by NUC. He has edited a book on Cancer Chemoprevention and has published 165 scientific articles in reputable international journals, 12 chapters in books, and has given over 100 scientific lectures in countries spanning four continents of the world. He is the Foundation Editorial Board Chairman of the Archives of Basic and Applied Medicine (ABAM) and Foundation Editor-in-Chief of Toxicology Digest, the official journal of West Africa Society of Toxicology (WASOT).

He has held several administrative positions including: Sub-Dean Postgraduate, Faculty of Basic Medical Sciences (2006-2008), Head of Biochemistry Department, (February 1st, 2008- 31st July, 2010), Coordinator, Zonal Committee, National Biotechnology Development Agency (NABDA) Zonal Biotechnology Centre (October 2008-2009), Leader, University of Ibadan Biotechnology Center of Excellence Project (November 2009-2010), Dean, Faculty of Basic Medical Sciences (2010-2014), Acting Director, Institute for Advanced Medical Research and Training (IAMRAT) (1st May-31st July 2011) and Acting Provost, College of Medicine, University of Ibadan (2010-2014) (on several occasions).

In the course of his scientific career, he has been honoured with prestigious professional awards: He is a Fellow of the Royal Society of Chemistry (FRSC) UK, Fellow Nigerian Academy of Science (FAS), Fellow Academy of Toxicological Sciences (FATS) of the USA and recently, he was admitted to the Fellowship of the African Academy of Science (FAAS), being the first Nigerian Biochemist to be so honoured. He is happily married to Dr. (Mrs.) Temitope Farombi a Senior Registrar, University College Hospital, Ibadan and they are blessed with three children.

NATIONAL ANTHEM

Arise, O compatriots
Nigeria's call obey
To serve our fatherland
With love and strength and faith
The labour of our heroes' past
Shall never be in vain
To serve with heart and might
One nation bound in freedom
Peace and unity

O God of creation
Direct our noble cause
Guide thou our leaders right
Help our youths the truth to know
In love and honesty to grow
And living just and true
Great lofty heights attain
To build a nation where peace
And justice shall reign

UNIVERSITY OF IBADAN ANTHEM

Unibadan, Fountainhead
Of true learning, deep and sound
Soothing spring for all who thirst
Bounds of knowledge to advance
Pledge to serve our cherished goals!
Self-reliance, unity
That our nation may with pride
Help to build a world that is truly free

Unibadan, first and best
Raise true minds for a noble cause
Social justice, equal chance
Greatness won with honest toil
Guide our people this to know
Wisdom's best to service turned
Help enshrine the right to learn
For a mind that knows is a mind that's free