UNIVERSITY OF ILORIN

THE TWO HUNDRED AND SIXTIETH (260TH)
INAUGURAL LECTURE

"IN SICKNESS AND GOOD HEALTH: PHARMACOLOGY AS SYSTEMS MEDICINE RESEARCH PRIMER"

By

PROFESSOR OLUFUNKE ESAN OLORUNDARE

B.Sc Pharm (Zaria); M.Sc., Ph.D. (Wisconsin-Madison, USA), Cert. Biotechnology, Cert. Stem Cell Technologies (Madison College WI, USA)

DEPARTMENT OF PHARMACOLOGY AND THERAPEUTICS,
FACULTY OF BASIC CLINICAL SCIENCES,
COLLEGE OF HEALTH SCIENCES,
UNIVERSITY OF ILORIN, NIGERIA

THURSDAY, 13TH JUNE, 2024

This 260th Inaugural Lecture was delivered under the Chairmanship of:

The Vice Chancellor

Professor Wahab Olasupo Egbewole SAN
LL.B (Hons) (Ife); B.L (Lagos); LL.M (Ife); Ph.D. (Ilorin); FCArb; Fspsp

13th June, 2024

ISBN: 978-978-8556-66-4

Published by:

The Library and Publications Committee,
University of Ilorin, Ilorin, Nigeria

Printed by
Unilorin Press, Ilorin, Nigeria

PROFESSOR OLUFUNKE ESAN OLORUNDARE

B.Sc Pharm (Zaria); M.Sc., Ph.D. (Wisconsin-Madison, USA), Cert. Biotechnology, Cert. Stem Cell Technologies (Madison College WI, USA)

DEPARTMENT OF PHARMACOLOGY AND THERAPEUTICS,
FACULTY OF BASIC CLINICAL SCIENCES,
COLLEGE OF HEALTH SCIENCES,
UNIVERSITY OF ILORIN, NIGERIA

BLANK

Courtesies

The Vice Chancellor,
Deputy Vice Chancellor (Academic),
Deputy Vice Chancellor (Management Services),
Deputy Vice Chancellor (Research, Technology and Innovation),
The Registrar,
The Ag. Bursar,
The University Librarian,
The Provost, College of Health Sciences,
The Dean, Faculty Basic Clinical Sciences,
Deans of other Faculties, Postgraduate School and Student Affairs,
Directors of various Units,
Professors and other Members of the Senate,
Ag. Head of Department of Pharmacology and Therapeutics,
Heads of other Departments,
Academic and Non-teaching Staff,
Distinguished Invited Guests,
Students of the Faculty of Basic Clinical Sciences,
Great Students of the University of Ilorin,
Gentlemen of the Press,
Distinguished Ladies and Gentlemen.

Preamble

Vice Chancellor, sir, it is with gratitude to God and to you, sir, that I stand to deliver this Inaugural lecture today before this distinguished audience. This lecture should have been delivered a few years after my husband delivered his inaugural lecture several years ago, but I got involved with helping to develop and to establish, the research and training aspect of the University of Ilorin, Stem Cell Research programme. Following the signing of the memorandum of understanding (MOU) between the University of Ilorin and the University of Wisconsin-Madison, USA, on Stem Cell Research and training, I went back to school at Madison College, Madison, WI, USA, with two other colleagues, from the University. This was a prelude to our preparation for undertaking the Stem Cell

Research training at the University of Wisconsin-Madison, WI, USA. The 2 semesters coursework at Madison College resulted in the award of a Certificate in Biotechnology and Certificate in Stem Cell Technologies. I must quickly add that I am grateful to the University of Ilorin under the leadership of Professor A. G. Ambali for sponsoring this academic exercise. I enjoyed every bit of it as it afforded me the opportunity to go back to formal classes, sit for quizzes and examinations with those students who are the age of my children and even younger. Indeed, I have always loved learning. The other impediment that stood in my way of delivering this lecture earlier than now, was the protracted sickness of my very beloved younger brother who finally passed on two years ago (May God bless his gentle soul!). His death dealt a major blow on me, which took some time for me to overcome. I, therefore, have every reason to thank God that I can stand before this great audience today to deliver this lecture which is the 260th in the series.

What is Pharmacology?

Pharmacology is a field of biomedical science that encompasses drug composition and properties, functions, sources, synthesis and drug design, molecular and cellular mechanisms, organ/systems mechanisms, signal transduction/cellular communication, molecular diagnostics, interactions, chemical biology, therapy, and medical applications and antipathogenic capabilities; and consisting of two main areas, namely, pharmacodynamics and pharmacokinetics (Vallance and Smart, 2006) .

My Journey into Pharmacology

During my final year at the Faculty of Pharmacy, Ahmadu Bello University, Zaria, the elective I chose for my final year project was in Pharmacology. I had the priviledge of watching with admiration Prof. Charles Wambebe (of blessed memory) who at that time was carrying out his Ph.D. research study, which involved implanting electrodes into the brain of animals, for brain recordings. This formed a strong pull for me to opt for Pharmacology as my elective research area. I was

attached to Dr. A. A. Diallo as my project supervisor. Even at the undergraduate level, I learnt to implant electrodes to the brain of rodents. My project involved the measurement of brain waves, electroencephalogram, (EEG), of rat brains, and to evaluate the influence of drugs with stimulant and depressant activities on Pentobarbital sleeping time. With contributions into my academic life from such great teachers, I concluded my undergraduate programme with a First-Class Honours degree in Pharmacy from the Ahmadu Bello University, Zaria.

I went to the University of Wisconsin-Madison, U.S.A., for my postgraduate studies, utilising the University of Ilorin staff development award. Although my initial interest was to conduct my postgraduate research in the field of Cancer Pharmacology, I discovered that my would-be supervisor was a heavy smoker. In those days, the University was not declared a smoke-free environment, I, therefore, concluded that I would not work under his supervision, so that I do not end up with smoke-related health problems. Hence, the most obvious next step was to go for Central Nervous System Pharmacology, a very familiar terrain for me from my undergraduate days. For my M.Sc. in the U.S.A., I used similar stereotaxic stage and rat atlas, that I used in Nigeria, to implant cannulas into different regions of the brain for drug microinjection.

My Journey Through Pharmacology Research

1. Brain Research

How Do We Develop Fever?

The generation of fever involves pyrogens, initiating the fever cycle. Endotoxins of gram-negative bacteria, with their pyrogenic component lipopolysaccharide, is the most potent exogenous pyrogen. Fever is also a common finding in malaria, hypersensitivity reactions, autoimmune diseases and malignancies. Exogenous pyrogens initiate fever by inducing host cells (mainly macrophages) to produce and release endogenous pyrogens such as interleukin 1. Endogenous pyrogens are transmitted to the hypothalamic thermoregulatory centre where they induce synthesis of prostaglandins, (of

prostaglandins of the E series). An abundance of evidence has shown that pyrogen-induced fever is mediated ultimately by an action in the brain of cyclooxygenase products. Brain mapping studies in which E series prostaglandins injected into the anterior hypothalamus preoptic region (AH/PO) produced hyperthermia (fever) demonstrating the importance of this region of the brain in the control of body temperature (Ackerman, D. and Rudy T. A. 1980). Prostaglandins raise the thermostatic set point in the brain to initiate the febrile response. The preoptic anterior hypothalamus region of the brain contains "warm receptors" for warmth, as well as "cold receptors" that respond to cold. When peripheral warm receptors are activated by a rise in ambient temperature, adrenergic warm receptors in the hypothalamus are stimulated by the increase in temperature. The preoptic area contains neurons that are sensitive to small changes in core or hypothalamic temperature. Preoptic thermosensitive neurons also receive somatosensory (sensory input from the skin and spinal thermoreceptors. In this way, preoptic neurons in the hypothalamus compare and integrate peripheral and central thermal information.

Vice Chancellor, sir, my M.Sc. Research focused on finding other regions of the brain aside from the already established/known preoptic region of the hypothalamus that controls body temperature to cause hyperthermia (fever). This is based on the fact that previous studies in monkeys in which the AH/PO had been completely destroyed bilaterally, experienced strong pyrexia after intra-cerebroventricular injection of bacterial endotoxin or PGE_1 or intravenous injection of endogenous pyrogen. Thus, showing that prostaglandins may produce pyrexia through an action at a site or sites outside the AH/PO (Lipton and Trzcinka, 1976). Therefore, I mapped the subdiencephalic rat brain for sites capable of mediating prostaglandin-induced pyrexia. In conscious rats, PGE_1 was injected unilaterally into 412 sites between the mid-mesencephalon and the caudal medulla, and core temperature was measured using a thermistor probe inserted into the colon. I implanted cannulas into these regions of the rat brain through which microinjections of prostaglandins were administered to

the rats, (since prostaglandins are the endogenous mediators of fever in the brain).

My findings, **Olorundare,** and Rudy (1986a) (Fig. 1) showed that the reactive sites where unilateral micro-injection of prostaglandin E_1 produced fever (pyrexia), were found in the hippocampus (5 sites) and in the vicinity of the cochlear nuclei (7 sites). Since the dose of prostaglandin administered in this study was greater than that required to produce hyperthermia when injected into the AH/PO region, we safely concluded these extra-AH/PO sites are less sensitive to PGE than the AH/PO region. PGE_1 injections into the hippocampus produced pyrexia with less reliability than injections near the cochlear nuclei, while the cochlear nuclei injections produced pyrexia with good reliability. However, the cochlear nuclei have no known involvement in normal thermoregulation or in fever production. In addition, the cochlear nuclei protrude into the subarachnoid space, increasing the likelihood that injectate could enter the cerebrospinal fluid and be carried forward to the established region known for temperature regulation in the brain, the AH/PO. Because of this possibility relating to the putative cochlear nucleus site of action, the study was extended to further map the responsiveness of the cochlear nucleus region more extensively to PGE_1-induced pyrexia. Various sites tested included: the anterior hypothalamic/preoptic region, dorsal third ventricle/cerebral aqueduct junction, the interpeduncular cistern and the cochlear nuclei region. My findings, **Olorundare,** and Rudy (1986b) (Fig. 2) showed that micro-injection of PGE_1 into or near the cochlear nuclei reliably produced a core temperature increase, or that the cochlear nuclei region provided a unique access portal to AH/PO tissue by which prostaglandins released in the cochlear nuclei region and contiguous tissue and/or present in the cerebrospinal fluid near the acoustic tubercle mediate fever. The cochlear nucleus is the first processing station in the brain for auditory information and has hitherto not been associated with the fever pathways. Findings from both

publications, therefore, suggest that an extra-anterior hypothalamic preoptic region (AH/PO) site for prostaglandin action in the brain is involved in the mediation of fever.

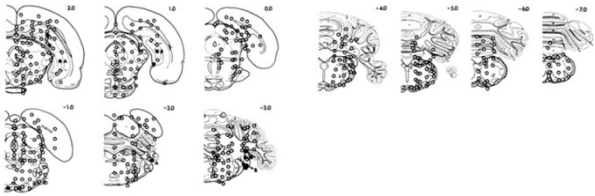


Fig. 1: Frontal sections of the rat brain illustrating the approximate positions of the PGE, injection sites. Open circles: unresponsive sites. Filled circles: responsive sites (which produced fever in response to PGE_1 microinjection). Olorundare and Rudy (1986a)

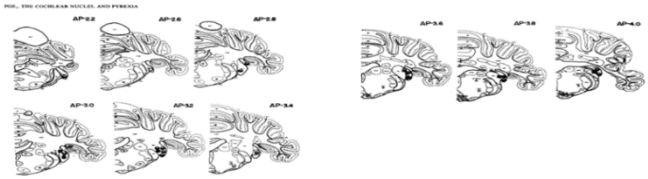


Fig. 2: Frontal sections of the rat brain illustrating the approximate positions of CN injection sites. Also indicated is the intensity of the hyperthermia evoked by 100 ng PGE_1 injected into each site. Intensity is quantified on the basis of the maximum increase in colonic temperature, δTc, observed within the first 60 min after injection. Filled symbols: ΔTc>I.0°C; half-filled symbols: ΔTc=0.55-1.0°C; open symbol: ΔTc=0.45°C. Circles: latency to onset of hyperthermia=0--3 min; squares: latency=4--10 min. Olorundare and Rudy (1986b)

2. My Doctoral and other Research Efforts on Human Blood Platelets

Human Blood Platelets, how they are made in the Body and their Significance to our Well Being

Platelets circulate in the blood as biconvex discs of about (2–4 μm in diameter) numbering 150 to 350 x 10^9/L in

healthy individuals. They are anucleate blood cells with a short lifespan, circulating in blood for 7–10 days in humans before they are eliminated in the spleen and liver. Thrombopoiesis (the production of platelets) occurs primarily in the bone marrow and is preceded by the differentiation of haematopoietic stem cells into polyploid megakaryocytes, which shed numerous cytoplasmic protrusions called proplatelets (Phillips and Agin, 1977; George, Nurden and Phillips 1984, **Olorundare**, 2000a).

Under physiological conditions, platelets are unactivated, they are discoid shaped as they circulate in the body. Under this condition, the endothelial cell lining the blood vessels is resistant to interactions with platelets and coagulation factors, and this prevents thrombosis (clotting). Also, prostacyclin (PGI_2) and nitric oxide among other antithrombotic substances in the body suppress most platelet activation processes, including adhesion, pseudopod formation (shape change), secretion, aggregation, and procoagulant activity, to keep our blood flowing freely in the blood vessels. When endothelial continuity is disrupted (as when a cut is made on the skin or when there is an injury) and the underlying matrix is exposed. A coordinated series of events are set in motion to seal the defect (primary haemostasis). Haemostasis is the process by which the body seals off leaks of the circulatory system to prevent loss of content. There are three equally important components in the maintenance of haemostasis: vascular integrity, platelets, and coagulation factors. Bleeding results from defects in one or more of these elements. The ability of platelets to adhere to an injured vessel wall, form aggregates, resulting in the initial/primary plug has been well described by many authors George, Nurden and Phillips 1984, **Olorundare,** 2000a, Janus-Bell, and Mangin 2023). Activation of resting platelets leads to a shape change response that involves a major reorganization of the cytoskeletal elements (Loftus and Albrecht 1984; Albrecht, **Olorundare,** and Simmons 1988; Waples, **Olorundare,** *et al.,* 1992). The sequence of events during shape change has been divided into clearly defined stages which represent a continuum of morphological forms ranging from discoid (resting,

unactivated) to pseudopodial or dendritic, to spread dendritic, to flattened/spreading and fully spread and this activation of platelets to plug leaking vessels is accompanied by the release of various proteins within the granules of the platelet ((Loftus and Albrecht 1984; Albrecht, **Olorundare,** and Simmons 1988; Waples, **Olorundare,** *et al.,* 1992).

Platelets contain three types of secretory organelles: the dense granules, the alpha granules, and the lysosomes. Proteins and ions contained inside platelet granules are released when there is injury (or a cut) to the body, and these help the body to stop bleeding. These include vonWillebrand factor, fibrinogen, fibronectin among others, in addition to divalent cations including calcium and magnesium (Phillips and Agin 1977; George, Nurden and Phillips 1984, **Olorundare,** 2000a; Gremmel *et.al., 2016*). Platelets interact with the endothelium and with each other via many surface glycoproteins known as the integrins (**Olorundare,** 2000a; Janus-Bell, and Mangin 2023). The integrins are a large family of transmembrane, noncovalent αβ-heterodimeric receptor proteins that are crucial for cell attachment to extracellular matrices. Some integrins also mediate important cell-cell adhesion of platelets by binding the fibrinogen molecule, which can bridge between adjacent platelets. On platelets, integrins play a central role in adhesion and aggregation on sub-endothelial matrix proteins of the vascular wall, to ensure hemostasis.

My Research Contributions to How Platelets Function in Haemostasis

My contribution in the field of thrombosis and haemostasis started with my Ph.D. research under Professor Ralph Albrecht. The research focused on investigating the internal reorganisation which underlies the continuum of platelet shape change upon activation of resting platelets, to start off release of platelet granule contents, aggregation (platelet-platelet clumping together) and platelets ability to form the primary platelet plug, thus sealing up leaky blood vessels. In addition, the study also included the events within platelets that bring about platelet-platelet interaction (what happens when platelets recruit

other platelets) which results in a permanent seal to the leaky vessel or the injury (Albrecht, **Olorundare,** *et al.*, 1987; Albrecht, **Olorundare** and Simmons 1988). I employed three microscopic methods (video-enhanced differential interference contrast light microscopy (VDIC), high voltage electron microscopy (HVEM) and low voltage-high resolution scanning electron microscopy (LV-HR-SEM) in conjunction with colloidal gold, or other inert metals conjugated to fibrinogen or other platelet proteins to track internal and surface biological events in human platelets as they go through the stages of shape change to bring about thrombosis. With VDIC one can monitor, in real time, by video enhanced light microscopy, what happens to platelets obtained from human blood, when they become activated and participate in thrombosis. The same platelets examined under enhanced light microscopy are subsequently prepared for electron microscopy by the critical point procedure and examined under HVEM to investigate what happened within the platelet ultrastructure, and also examined the same platelets specimens by LV-HR-SEM to understand platelet receptor (integrins) activities on the surface of the platelets. The study evaluated platelet proteins including fibrinogen, vonWillebrand factor and their interactions with the integrins (platelet receptors) that are involved in platelet function in causing thrombosis. My findings showed that platelet activation involves mechanisms that increase polymerization of monomeric actin to actin filaments and engagement of actin filaments with myosin filaments culminating in platelet cytoskeletal reorganization and continuum of platelet shape change, in conjunction with platelet fibrinogen receptor (αIIbβ3) reorganization which enables platelet -platelet interactions and formation of platelet plug or thrombi (Figs, 3 and 4). My research conclusively demonstrated the contractile activities that underlie thrombosis and by extension clot retraction during wound healing. In addition, the involvement of calcium ions in the platelet-platelet interactions was established (**Olorundare,**. *et al.,* 1988; **Olorundare** *et al.,* 1992; **Olorundare,** *et al.,* 1993).

After my Ph.D. I continued to collaborate in platelet research study, in the laboratory of Professor Ralph Albrecht, in conjunction with Lisa Waples and Dr. Quetin Lai, from the

Material Science Program and the Department of Chemical Engineering, at the University of Wisconsin-Madison, U.S.A, respectively, to investigate different polymers (materials used for artificial valves, stents and prosthetic devices) for their thrombogenic potentials. Several individuals with coronary vessel blockades, aortic valve blockades, breast implants, etc. are dependent on prosthetic devices implanted into their organs for optimal day to day functioning. It is very important that such devices are tested for their thrombogenicity before they are marketed by the companies that make them. With respect to studies of the interaction of platelets with polymers, we reported that intracellular Ca^{2}+ levels of platelets increased with surface-induced activation, (as in when platelets contact artificial materials) and that platelet-platelet contact (as is the case when initial platelets at the site of injury recruits other platelets) leads to intracellular Ca^{2}+ transients. We also identified the types of polymers which will not cause thrombosis when they are used possibly as prosthetic materials. (Waples, **Olorundare**, *et al.*, 1992; Waples, **Olorundare** *et al.,* 1996).

Correlative microscopy involves imaging the same sample by multiple imaging modalities. The interaction of platelets with the materials can be viewed simultaneously by light microscopy, using both epifluorescence and asymmetric illumination contrast (AIC), or VDIC microscopy, to monitor and record, in real time the biological events. Same specimens are subsequently observed by both HVEM and LV-HR-SEM. Professor Albrecht's laboratory has pioneered the use of small labels (eg 3nm, 5nm and 18nm colloidal gold label) conjugated to platelet proteins to track the distribution and movement of the platelet receptors in resting platelets, after platelet activation and in platelet-platelet interactions. With such small probes (labels conjugated to platelet proteins) the interaction of these proteins with their respective receptors can be precisely tracked (Albrecht, **Olorundare,** *et al.,* 1987; Albrecht, **Olorundare,** *et al*., 1992).

In biological systems, identification of the various molecular species participating in cellular function vis-à-vis their

physical/spatial relationship to one another and to the surface structure and ultrastructure is essential. Over the years, Professor Ralph Albrecht's laboratory was at the forefront of developing protocols and methodologies using immunogold labelling (including labelling with other inert materials such as palladium and platinum) which are currently being used by other laboratories globally for labelling ligands, antibodies, antibody fragments and receptors, for correlative light and electron microscopy. Thus a crucial understanding of the molecular interactions in a macromolecular environment is revealed (Albrecht, **Olorundare,** *et al.,* 1992; Albrecht, **Olorundare** *et al*., 2011; Albrecht, Meyer and **Olorundare** 2013).

During my sabbatical leave in 1999-2000, I worked at the laboratory of Professor Dean Mosher, of the Department of Medicine and Physiological Biochemistry, University of Wisconsin-Madison, USA, where I continued my research on other important platelet proteins (fibronectin, vitronectin and laminin) and their involvement in thrombosis, and clot and retraction. Fibronectin (FN) is a major cell-adhesion glycoprotein found in high concentrations in plasma and other body fluids and in an insoluble fibrillar form in the fibrin clot, connective tissues, and basement membranes. Lysophosphatidic acid (LPA) and sphingosine-1-phosphate (S1P) are agonists of the endothelial differentiation gene (Edg) family of G-protein–coupled receptors and both agonists are generated by platelet activation during blood coagulation.

Findings from my study demonstrated that LPA, thrombin, adenosine diphosphate, and S1P induce adherent platelets to bind to fibronectin matrix and point to the fact that platelets may contribute to early deposition of fibronectin matrix after vascular injury. The results further suggested that both fibronectin assembly by activated adherent platelets and factor XIIIa–mediated cross-linking to the fibrin clot result in insolubilisation of fibronectin after wounding. Factor XIIIa is an enzyme in the blood coagulation pathway and is important in wound healing following injury (**Olorundare** 2000b; **Olorundare**, *et al.*, 2001).

Cytochalasin D and E: Effects on Fibrinogen Receptor Movement and Cytoskeletal Reorganization in Fully Spread, Surface-Activated Platelets: A Correlative Light and Electron Microscopic Investigation.

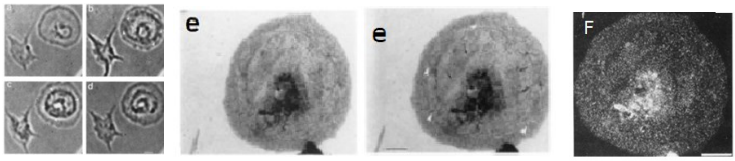


Fig. 3: (a-d) VDIC-LM micrographs showing the effect of cytochalasin on fibrinogen receptor redistribution. (a) The platelet before incubation with Fgn-Au. (b and c) At **3** minutes and **10** minutes after addition of label show progressive redistribution of the ligand-receptor complexes in the plane of the platelet membrane (arrowheads).

The label is seen to concentrate (dark band) on the membrane overlying the cytoskeletal inner filamentous zone which surrounds the granulomere. Treatment of the specimen with cytochalasin E, 5×10^{-5} mol/L, for **10** minutes resulted in dispersion of the previously redistributed receptor sites (as evidenced by the decreased intensity of the dark band of label surrounding the granulomere and the resultant irregular "gray" areas [label] on the membrane over the peripheral web) (d) at 7 minutes after addition of cytochalasin E. Bar = 1μm. (e) HVEM stereo pair whole mount of the same platelet seen in (a through d). The IF2 is disrupted (compare with **le)** and the platelet lacks distinct ultrastructural zones normally seen in fully spread platelets. Gold label, dark dots represents Fgn-Au-receptor complexes. Some of these remain more concentrated on the membrane around the central granulomere region, over the partially organized IF2 and remaining microfilament bundles (arrows). However, many have moved out to more peripheral location overlying the remnant OF2 (arrowheads). Bar = **1**pm. ***(1)*** **20** keV LV-HR-SEM of same platelet as in (e). Beam penetration at this voltage produces atomic number contrast from the dense gold particles. Therefore, the label appears very bright and can be clearly identified. As in the HVEM, some of the Fgn-Au-receptor complexes remain concentrated around the granulomere; however, many have moved out to other locations on the platelet surface. Bar = 1.35μm.

Olorundare O. E. *et al***,** Blood 79 (1): 99-109, 1992.

Fig. 4: Platelets treated with cytochalasin E, 5 x 10^{-6} mol/L, then allowed to activate on formvar-coated grids for a total of 15 minutes. Most of the platelets are either discoid or spherical. (b) Platelets pre-treated with 0.1% DMSO in Lagas buffer (control) before surface activation on formvar-coated grids for 15 minutes. Many platelets have reached the fully spread stage (arrowheads). Bar = 15µm (Olorundare O. E. et al., Blood 79 (1):99-109, 1992.

3. My Research Contributions to Cardiometabolic Diseases

What is known as cardiometabolic syndrome (CMS)?

Cardiometabolic syndrome (CMS) is a complex interaction between metabolic dysregulation or metabolic breakdown, cardiovascular disease (CVD), and diabetes risk factors. This syndrome has a global prevalence (Saljoughian M 2017, Cho N. *et al.,* 2018).

What are the common characteristics of Cardiometabolic Syndrome?

Cardiometabolic syndrome encompasses a group of interrelated abnormalities including abdominal obesity, (with obesity triggering metabolic disturbances), insulin resistance, impaired glucose tolerance, dyslipidemia, hyperuricemia, hypertension and other cardiovascular diseases (Kirk and Klein 2009; Saljoughian 2017). Individuals with CMS are two times more likely to die from coronary heart disease and three times more likely to have a heart attack or stroke, than those who do not have the syndrome (Kirk and Klein 2009; Saljoughian 2017). CMS has far-reaching clinical implications, extending beyond CVD and diabetes to conditions such as non-alcoholic fatty liver disease, cancer, and sleep apnea.

What are some of the Trigger Factors?

1. Genetic predisposition which interacts with environmental factors.
2. Sedentary lifestyles and poor diets which amplify obesity, visceral adiposity and insulin resistance.
3. Hormonal imbalances.

Highlights of some of my research contributions to addressing Cardiometabolic Syndrome

This study was carried out by one of my previous M.Sc. students; Ms. Fatimoh Ojuade (Ojuade, **Olorundare** *et al.,* 2021) and investigated the antidiabetic potentials of *Parquetina nigrescens* (Afzel) (Asclepiadaceae) plant, known in Yoruba language as 'Ogbo", "Kwankwanin" in Hausa, "Mgbidimgbe" in Igbo, in the management of type 2 diabetes mellitus (T2DM). We conducted biochemical evaluation of fasting glucose levels, hepatic glucose metabolising enzymes and glycogen content, serum insulin, leptin, adiponectin and lipase levels. In addition, assessment of serum lipid, atherogenic index (AI) and coronary risk index (CRI) and insulin resistance were measured. A pathohistological evaluation of the liver and pancreatic acinar was also conducted (Ojuade Fatimoh, **Olorundare** *et al.,* 2021). The findings of the study revealed that aqueous extract of Parquetina nigrescens reduced fasting blood glucose, improved glucose tolerance, insulin resistance, leptin and adiponectin in diabetic rats. Adiponectin is a fat protein from adipose tissue and has been shown to have cardioprotective effects. Experimental models have confirmed that adiponectin has anti-inflammatory and anti-atherogenic properties. Low levels of adiponectin have been found in patients with diabetes, dyslipidemia, and obesity. The leaf extracts reduced lipid profile, coronary risk index and atherogenic index in diabetic rats. Administration of the different doses of the extract conferred protection to both the liver and pancreas through the varying degrees of regeneration of the damaged organs. This study provided possible mechanisms of the ameliorative potentials of *Parquetina nigrescens* in type 2 diabetic rats. Aqueous extracts of *Parquetina nigrescens* showed a dose-dependent antidiabetic and anti-hyperlipidemic activity and

hence can ameliorate T2DM and some of the coronary events associated with T2DM. This study opens an avenue for prospecting the plant for bioactive phytochemicals which can be developed into drugs for the management of T2DM.

The second study I want to bring to the attention of this audience is another one carried out by another previous M.Sc. student, Mr. Joy Folahan. This study examined estradiol (an important hormone among the female gender) in conjunction with selected antihyperlipidemic drugs used singly or in combination for their atheroprotective potentials in ovariectomised rats fed with thermoxidized oil diet (Folahan and **Olorundare,** *et al.,* 2023). There is a noticeable increase in risk for cardiovascular diseases (CVDs) including atherosclerosis in postmenopausal women when estrogen levels decline. A synergy of mechanisms which confer cardioprotective potentials to premenopausal women in the presence of estrogen, invariably leads to a myriad of cardiac pathologies in postmenopausal women with very low levels of estrogen (Davezac *et al.,* 2021). Several risk factors of cardiovascular disease are altered following the menopausal transition, resulting in a significant increase in the risk for myocardial infarction and cerebrovascular disease. These factors include hypertension, dyslipidemia, inflammation, and hemostatic factors (Hodis *et al.,* 2019). Thermoxidation of edible oil through fat frying at high temperatures results in the generation of several oxidized products that promote lipid peroxidation and reactive oxygen species (ROS) production when eaten (Ng *et al.,* 2014). Intermittent deep frying of edible oils is a common food processing practice in homes, food vendors, restaurants, and industries. This is a practice adopted to reduce costs and improve taste. In deep-fat frying, the oil is usually heated to an extreme temperature of 180 °C and higher in the presence of moisture and air, which results in an array of chemical reactions known as lipid oxidation (Falade and Oboh 2015). Thermal oxidation of dietary oils destroys essential fatty acids and generates products such as aldehydes peroxides, hydroperoxides, and many other potentially hazardous non-volatile polar compounds are retained in the thermoxidised oil

and when consumed repeatedly increase the risk for cardiovascular diseases (Ng *et al.,* 2014).

The study involved surgically removing the ovaries of rats of litter bearing age, to simulate menopause and the rats were allowed to recover from the surgery under antibiotic cover. The animals were then fed for three months with thermoxidized oil diet. Estradiol, (to replace estrogen lost due to ovariectomy) or single or combinations of atorvastatin, and ezetimibe (both being antihyperlipidemic drugs used in clinics) were administered to some groups of the rats over the period of 3 months.

Our assessment of lipid profile in conjunction with evaluation of various biochemical markers of oxidative stress, inflammation, and histopathological evaluation of the ascending and thoracic aorta, showed that palm and soya oils supplemented diets fed to ovariectomized rats significantly increased atherogenic dyslipidemia. Both oils decreased the high-density lipoprotein/low density lipoprotein ratio, while also elevating the atherogenic index and coronary risk index significantly. The atherogenic index is a strong marker for assessing the risk of atherosclerosis and coronary heart disease in vessels. Aortic nitric oxide was examined as an indicator of vascular integrity. Both oils in the diet fed to ovariectomized rats, reduced aortic nitric oxide levels. Diminished nitric oxide is associated with endothelial dysfunction and predisposes the vessel to atherosclerosis. In addition, evaluation of tumour necrosis factor alpha (TNF-α), an inflammatory marker, showed a significant increase in the tissues of the rat thoracic aorta. Treatment with antihyperlipidemic drugs and estradiol reversed indices of atherogenic dyslipidemia in ovariectomized rats fed with palm and soya oil-supplemented diets Figs. 5, 6 and 7 (Folahan, **Olorundare** *et al.,* 2023).

Oxidised dietary lipids induce vascular inflammation and atherogenesis in postmenopausal rats: Estradiol and selected antihyperlipidemic drugs restore vascular health in vivo (Folahan, **Olorundare** *et al.,* 2023).

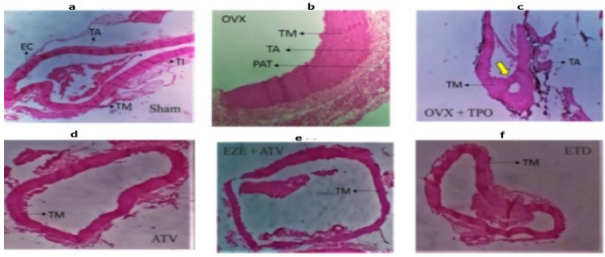


Fig. 5: Photomicrographs of the effects of estradiol and selected antihyperlipidemic drugs on the ascending aorta of ovariectomized Wistar rats fed with thermoxidized palm oil diet. (a) Sham (b) OVX (c) OVX + TPO (d) ATV (e) EZE + ATV (f) ETD.
Note the thickening of the tunica media indicated by TM and aortic recanalization indicated by the yellow arrow in OVX + TPO. Note the reduced amount of red blood cells in the luminal aspect of the aortic wall an d the preservation of the elastic laminae of the tunica media indicated by TM in ATV, EZE + ATV and ETD treatment groups. H&E staining of the rat aorta (x100 magnification)OVX – ovariectomy; TPO – thermoxidised palm oil; EC – endothelial cells; TM – tunica media; TI – tunica intima; TA – tunica adventitial; PAT – peri-adventitial fat; ATV – atorvastatin; EZE – ezetimibe; ETD – estradiol.

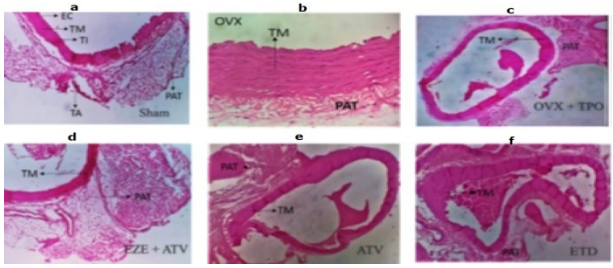


Fig. 6: Photomicrographs of the effects of estradiol and selected antihyperlipidemic drugs on the thoracic aorta of ovariectomized Wistar rats fed with hermoxidized soya oil diet. (a) Sham (b) OVX (c) OVX+TSO (d) ATV (e) EZE+ATV (f) ETD. Note the accumulation of

large amount of red blood cells indicated by the yellow arrow; thickness of tunica media and complete disruption of the elastic laminae indicated by the white arrow and increased deposition of peri-adventitial fat (PAT) indicated by the red arrow in (c). Note the preservation of the elastic laminae of the tunica media, indicated by TM in (d-f). H&E staining of the rat aorta (x100 magnification) OVX – ovariectomy; TSO – thermoxidized soya oil; EC – endothelial cells; TM – tunica media; TI – tunica intima; TA – tunica adventitia; PAT – peri-adventitial fat; ATV – atorvastatin; EZE – ezetimibe; ETD – estradiol.

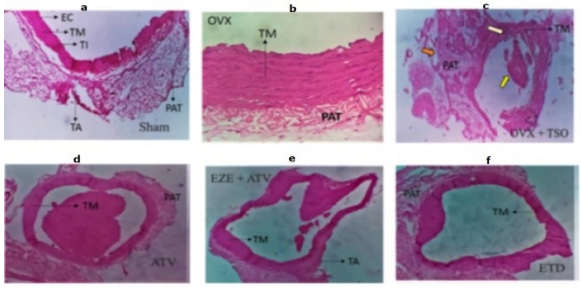


Fig. 7: Photomicrographs of the effects of estradiol and selected antihyperlipidemic drugs on the thoracic aorta of ovariectomized Wistar rats fed with thermoxidized palm oil diet. (a) Sham (b) OVX (c) OVX+TPO (d) EZE+ATV (e) ATV (f) ETD

Note hypertrophy of the peri-adventitial adipose tissue indicated by the black arrow in (OVX+TPO). Note the preservation of the elastic laminae of the tunica media, indicated by TM in all treatment groups. H & E staining of the rat aorta (x 100 magnifications)

OVX – ovariectomy; TPO – thermoxidized palm oil; EC – endothelial cells; TM – tunica media; TI – tunica intima; TA – tunica adventitia; PAT – peri-adventitial fat; ATV – atorvastatin; EZE – ezetimibe; ETD – estradiol

4. Cancer Chemoprevention using African Medicinal Plants

Based on recent estimates of global mortality data, more than three-quarters of the 20.4 million premature deaths (occurring between the ages of 30-70 years) are due to noncommunicable diseases (WHO 2020). Cardiovascular disease (CVD) and cancer were the leading causes in 127 countries. Cancer is a major epidemiological burden in both developed and developing countries. It ranks as a leading cause of death and an

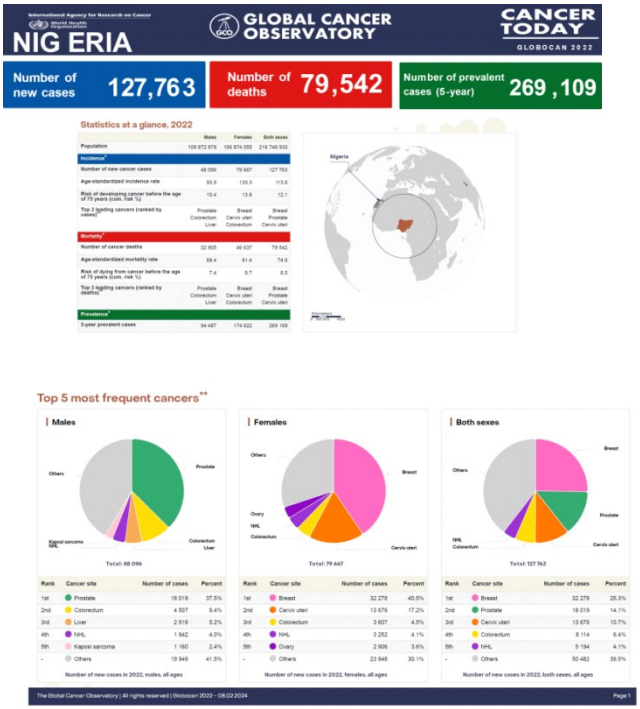
important obstacle to increasing life expectancy in every country of the world (Bray *et al.,* 2021 and Fadelu and Rebbeck 2021).

What is Cancer

Carcinogenesis is a long-term process of cellular growth, division and clonal expansion of initiated cells exemplified by 3-steps known as initiation, promotion and metastasis (Gupta and Mukhtar 2002). It is a multistep process, whose initiation and progression occur through a range of defects that develop both within and outside the cancer cell. Various environmental carcinogens (such as cigarette smoke, gasoline vapours, industrial emissions, waste, and exposure to radiation) are known to activate the different stages of cancer (Aggarwal and Shishodia 2006). Defects in cell-signaling pathways allow cancer cells to alter their normal programmes of proliferation, transcription, growth, migration, differentiation and death. Environmental carcinogens are known to activate the different stages of cancer development. Despite a better understanding of cancer, the advancement of modern technology and the advent of rationally targeted drugs, the incidence and cure rate of some cancers have not improved. A hint to improving cancer statistics lies in the epidemiology of the disease. Epidemiological data has revealed that certain cancers are more common among people of some countries than others (Kolonel *et.al.,* 2004). Cancer of the colon, lung, prostate and breast are very common in western countries, while cancer of the head, neck and of the cervix are most common in India, and stomach cancer is most prevalent in Japan. According to the WHO cancer fact sheet for Nigeria (2022) (Figs. 8 and 9) the 3 leading cancers in men are prostrate, colorectal and liver cancers, while in the female gender; breast, cervical and colorectal cancers are the 3 top cancers (2022). It is estimated that 75-85% of all chronic diseases are linked to lifestyle and cannot be explained by differences in genetic make-up (Hussain *et al.,* 2003). Over one third of cancer deaths worldwide are due to potentially modifiable lifestyle risk factors (Weiderpass, 2010). For example, tobacco smoking is strongly associated with lung, mouth and throat cancers. Alcohol drinking is associated

with some increase in oral, esophageal, breast and other cancers. Diet low in fruits and vegetables are associated with increased risk of colon, breast and possibly other cancers, while populations that consume food rich in fruits and vegetables have a lower incidence of cancers (Willett, 1994; Aggarwal and Shishir, 2006). To reduce the incidence of cancer, one promising approach is its prevention. Chemoprevention provides a practical approach to identify potentially useful inhibitors of cancer development and affords excellent opportunities of studying the mechanism of carcinogenesis. The intervention of cancer at the promotion stage seems to be the most appropriate and practical because tumor promotion is a reversible event at the early stages (Bickers and Athar 2000).

Figs. 8 and 9: WHO Cancer Fact Sheet for Nigeria (2022).



Fruits and vegetables are excellent sources of fibers, vitamins and minerals. They are also known to contain several micronutrients and other compounds such as alkaloids, polyphenols, terpenes etc., that provide health benefits beyond basic nutrition (Aggarwal and Shishodia 2006; Noratto *et al.,* 2010).These natural products from fruits and vegetables may be used alone or in combination with conventional chemotherapeutic drug regimens to prevent the occurrence and spread of cancer, through their anticancer, anti-inflammatory, immune-modulatory and anti-angiogenic activities (Masuda *et al.,* 2002).

My initial desire to conduct research in the field of cancer pharmacology still laid dormant in my long-term memory. So, while on sabbatical leave in Prof. Deane Mosher's laboratory, I got connected to Prof. Hasan Mukhtar. His laboratory was on the same floor as Prof. Mosher's, and his research focused on cancer chemoprevention. I started collaborative studies with him, which led us to write a collaborative cancer research proposal together.

Mr. Vice Chancellor, in November 2014, TETFUND gave a National Research Fund award (NRF) to **Olufunke E. Olorundare**, Joseph Adebayo Abiola, S. Babatunde and Phillip Manma Kolo, in collaboration with Professors Ralph M. Albrecht and Hassan Mukhtar of the University of Wisconsin Madison, U.S.A. This NRF award was for conducting research in cancer prevention and therapy using phytochemicals. Before the research work commenced, I came across Prof. Mamoru Koketsu of the Gifu University, Gifu, Japan, who also collaborated with us in this research. The study entailed isolation of fractions and characterisation of phytochemicals from African vegetables and medicinal plants for the purpose of evaluating their anticancer activity and delineating their mechanisms of action- (i.e. evaluating their effects on markers of cancer initiation, progression and metastasis). We identified three indigenous Nigerian plants: *Polyalthia longifolia,* Gongronema *latifolium,* and *Clerodendrum volubile* to start off this research, using the leaves of these plants. Funds from this award were utilized in the training of two postgraduate students

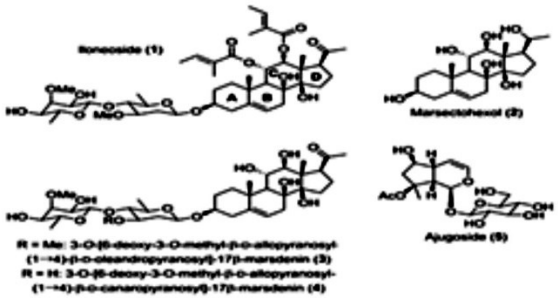
(one from my laboratory and one from Professor Adebayo's laboratory) for their Ph.D. research work and one student from my laboratory for his M.Sc research work. The research resulted in the discovery ground-breaking, isolated and characterised phytochemicals, with anticancer activities.

1. As a result of our research our collaboration with Professor Mamoru Koketsu, we reported for the first time, the isolation of a rare Tetranorditerpene from *Polyalthia longifolia* (masquerade tree) and a methyl ester derivative of the isolated tetranorditerpene was synthesised in the laboratory. The tetranorditerpene and its methyl ester derivative showed antileukemic activity, although the derivative was more potent against human leukemia HL-60 cells. This work resulted in the discovery of new anticancer agents (Afolabi, **Olorundare**, *et al.,* 2017a; Afolabi, Gyebi, Agede, Njan and **Olorundare** *et al.,* 2021). Acute leukemia accounts for approximately 30% of all childhood malignancies and is the most common cancer in children (Ward *et al.,* 2014). Leukemia is particularly a severe problem in Africa, and despite significant advances in the chemotherapeutic management of leukemia, many children and adults still die of this disease. Thus, there is an unmet need for agents with higher efficacy and reduced side effects, that are affordable in low-middle income countries, to serve either as chemopreventive therapies or cytotoxic drugs. In this area, our derivatised compound could be useful in fulfilling this gap in the treatment of leukemia.
2. In furtherance of our objectives in the bioprospecting of useful molecules for human health, especially anticancer compounds from naturally occurring indigenous plants, and in conjunction with Prof. Mamoru Koketsu, we explored the anticancer potentials of another indigenous plant, *Gongronema latifolium* Benth (*Asclepiadaceae*) an edible-green-leafy vegetable that is traditionally used as spices, vegetables and for various medicinal purposes in the South East (where it is known as "Utazi") and

South West parts of Nigeria (Arokeke, Marugbo or Eweta) and among the people of the South -South region (as Obenetete).

This research led to the isolation of a new pregnane glycoside: Iloneoside 3-*O*-[6-deoxy-3-*O*-methyl-β-D-allopyranosyl-(1→14)-β-D-oleandropyranosyl]-11,12-di-*O*-tigloyl-17β-marsdenin. Since we were the first to isolate this compound, we were accorded the right to name it "Iloneoside" after Ilorin where our university is situated. This ditigloylated pregnane glycoside (Iloneoside) is cytotoxic, with anticancer potentials against human leukemia HL-60 cells (Fig.10) (Gyebi, Adebayo and **Olorundare** *et al.,* 2018). Vice Chancellor, sir, herein we report the isolation and characterization of a lead compound, which carries the name of the University and is ready to be further explored for the management of leukemia.

Fig. 10: Iloneoside: A cytotoxic ditigloylated pregnane glycoside from the leaves of Gongronema latifolium Benth. Gyebi, Adebayo and **Olorundare** *et al.,* 2018.

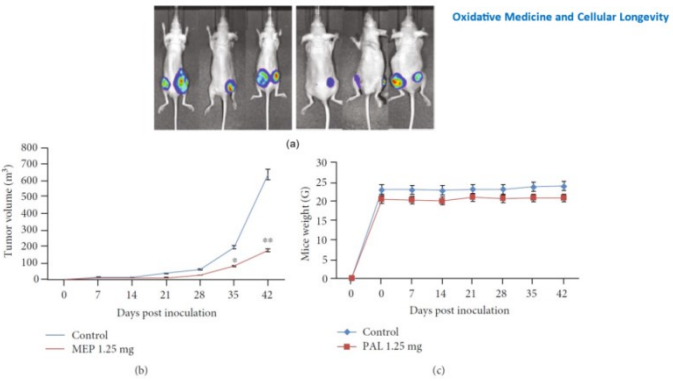


Chemical Structures of Isolated Compounds

3. Even with the advent of better treatment options, prostate cancer (PCa) remains the second most common cancer globally and a leading cause of cancer-related deaths in men in Nigeria (WHO globocan 2022). In collaboration with Prof. Hasan Mukhtar, we continued our study of Polyalthia longifolia on other types of

cancers aside from Leukemia. We evaluated the anticancer potentials of *Polyalthia longifolia* on various types of prostate cancer cell lines, which represent human forms of clinically aggressive and mild types. The investigation was conducted both by in- vitro analysis on prostate cancer cell lines and in- vivo study in xenograft animal models of prostate cancer using tumor-bearing athymic nude mice.

Fig. 11: *Polyalthia longifolia* methanolic leaf extract inhibits the growth of metastatic PC3M-LUC-C6 tumors in athymic nude mice. (a) Representative bioluminescence of PC3M-luc-6 tumor-bearing mice after 6 weeks of treatment. (b) Line graph showing tumor growth determined by weekly measurements of the tumor volume. (c) Line graph showing the animal weight. Each value in the graph is the mean ± SD from 6 mice. ∗p < 0:05 and ∗∗p < 0:01 were considered statistically significant. – (Afolabi, **Olorundare** *et al.,* 2019a).



Our findings showed that *Polyalthia longifolia* exhibited high efficacy against prostate cancer cell lines and in the PCa xenograft mouse model with significant inhibition of tumor growth and reduced tumor burden. We also elucidated the biochemical mechanisms by which this plant caused inhibition of prostate cancer to be due to induction of apoptosis (programmed cell death) in prostate cancer cells (Afolabi; **Olorundare**, *et al.,* 2018; Afolabi, **Olorundare**, *et al.,* 2019a).

4. We also evaluated *Clerodendrum volubile* P. Beauv known as ' obenetete' among the itsekiri tribe and 'eweta' among the Ilaje people of Nigeria (Erukainure *et al.,* 2014) for anticancer activity against prostate cancer cells. We reported the mechanisms by which the leaf extract of this plant exerts its cytotoxic activity. (A). Our study was the first reported study to show the cytotoxic potential of *Clerodendrum volubile* leaf extracts on prostate cancer and the possible mechanistic pathways for this anticancer activity (Afolabi, **Olorundare** *et al.,* 2019b).

   Our studies provided the first evidence of the growth inhibitory potential of the extract and identifies signaling pathways altered in *Clerodendrum volubile* -treated prostate cancer cells to be due to modulation of the cell cycle, via increased expression of Cyclin Dependent Kinase inhibitor (p21), suggesting an effect of the extract on the cell cycle machinery. Consistently, treatment of prostate cell lines with *Clerodendrum volubile* leaf extract resulted in induction of cancer cell death (Afolabi, **Olorundare** *et al.,* 2019b).

5. Currently, and in collaboration with Professor Jean Christopher Chamcheu of the Louisiana state University, USA, and one of my former M.Sc, Students, in Prof. Chamcheu's laboratory, we are exploring fractions of *Garcinia Kola* (the African bitter kola) for its anti-cancer potentials on Melanoma and Keratinocyte carcinoma, both of which are very common skin cancers in the United States. Our study has identified ethyl acetate subfraction of kolaviron, (the active component of bitter kola) to contain potent anti-cancer phytochemicals for both forms of skin cancer. This fraction exerts its anticancer activity via the modulation of autophagy-related genes leading to in cancer cell death (Folahan, **Olorundare** and Chamcheu 2024).

Management of Toxicities due Anticancer Drugs

Recent advances in anticancer therapy have reduced mortality of some malignant tumours. However, tumour-associated cardiotoxicity has increased patients' morbidity and

mortality and limited the therapeutic usefulness of these anticancer regimens, as well as cause dose-limiting toxicities, which limit the doses of chemotherapeutic drugs that can be administered to the cancer patients. These cardiovascular toxicities pose great threats to the well-being of cancer survivors and patients. Tumour-associated cardiovascular disease has become the second leading cause of death after tumour recurrence and has received increasing attention for management in recent years (Barthur *et al.,* 2017; **Olorundare** *et al.,* 2021; Adeneye, **Olorundare** *et al.,* 2021a). Therefore, we extended our study to exploring the phytochemicals from African vegetables and medicinal plants for the remediation of cardiac toxicities caused by anticancer cytotoxic drugs. We evaluated the potentials of extracts of edible plant seeds and vegetables as possible antidotes to toxicities of chemotherapeutic drugs used in clinical practice. These studies focused on the potential use of extracts from plants of African origin, namely *Clerodendrum volubile*, *Irvingea gabonensis* (African bush mango) and *Ocimum gratissimum* Linn. as possible antidotes to toxicities due to anticancer drug treatment. We directed our attention to ameliorating the toxicities of two clinically used anticancer drugs: Doxorubicin, a versatile, highly used drug, which features in many chemotherapeutic cocktails/regimens and Trastuzumab, a gold standard monoclonal antibody against breast and gastric cancers. (Blackwell *et al.,* 2010).

Doxorubicin is a broad-spectrum antibiotic anthracycline with wide applications in the clinical chemotherapeutic management of solid tumors such as breast, lung, ovarian, uterine cancers and blood cancers such as leukemias and Hodgkins's lymphoma (Tacar *et al.,* 2013). Despite its incontrovertible efficacy, doxorubicin is notorious for its life-threatening toxicity profile such as cardiotoxicity, neurotoxicity, hepatotoxicity, and hematologic toxicity. Life-threatening cardiomyopathy represents the cumulative dose-limiting toxicity of the drug.

Our findings showed that *Clerodendrum volubile leaf* extract offered protection against doxorubicin-induced cardiotoxicity which was mediated via free radical-scavenging activity/antioxidant mechanisms, and we reported improvements

in the cardiovascular disease risk indices (**Olorundare** *et al.,* 2020a). We also reported the vasorelaxant potentials of this leaf extract against doxorubicin cardiac toxicity (Akinsola, Adeneye, **Olorundare** *et al*., 2022). We investigated the ameliorative potential of Clerodendrum volubile leaf extract on doxorubicin-induced hepatorenal toxicities in rats. Our study demonstrated that Clerodendrum volubile leaf extract offered protection against doxorubicin-induced hepatorenal toxicities which were mediated via suppression of oxidative stress, free radical scavenging activity and/or antioxidant mechanisms (Adeneye, **Olorundare** *et al.,* 2021b).

Trastuzumab, a monoclonal antibody targeted against the human epidermal growth factor receptor 2 (HER 2) is employed in the clinical management of HER 2 positive metastatic breast and gastric cancers, gastro-esophageal adenocarcinoma, and colorectal carcinoma, has been limited by its off-target toxicities which include, significant dose-limiting cardiac and lung toxicities, and these toxicities have no effective treatment, in either their prevention or amelioration.

We investigated the protective and therapeutic potentials of *Clerodendrum volubile* (CVE) leaf extract and *Irvingia gabonensis* (IGE) seed extract pretreatments in trastuzumab treated Wistar rats. Overall, the findings from this study (**Olorundare** *et al.,* 2020b) highlighted the promising therapeutic potential of both extracts against trastuzumab-induced cardiac. Their cardio-protective activities are mediated via free radical scavenging, antioxidant, and antithrombotic mechanisms, thus, highlighting the therapeutic potential of *CVE* and *IGE* in the management of trastuzumab-induced cardiotoxicity. Regarding trastuzumab-induced hepatorenal toxicities, we reported that both extracts ameliorated trastuzumab toxicities either partly or wholly via their free radical scavenging and antioxidant potentials (Adeneye, **Olorundare**, *et al.,* 2021c).

In our quest to provide effective and affordable therapeutic option(s) for treating trastuzumab-induced cardiotoxicity, we evaluated the possible therapeutic potential of *Ocimum gratissimum* Linn. leaf extract and fractions in acute trastuzumab-induced cardiotoxicity in Wistar rats. We compared the effects of this extract and fractions with a fixed-dose combination of clinically used antihypertensive drugs, -

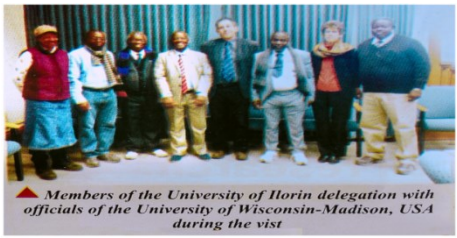
Valsartan-lisinopril. Our findings highlighted the promising therapeutic potential of *Ocimum gratissimum* in significantly reducing trastuzumab-induced cardiotoxicity mediated via abrogation of cardiomyocyte apoptosis and antioxidant mechanisms (Adeneye, **Olorundare**, *et al.,* 2023; **Olorundare**, *et al.,* 2024). We also evaluated the chemopreventive/ therapeutic effect of *Ocimum gratissimum* against pulmonary toxicities due to Trastuzumab. Our findings showed that the extracts and fractions from this plant abrogated trastuzumab-induced lung fibrosis via antioxidant and anti-apoptotic mechanisma (Ajayi, **Olorundare** *et al.,* 2023).

Stem Cell Research:

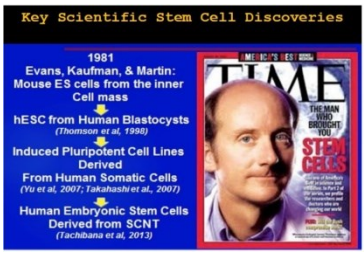
My journey into Stem cell research was at the instance of Prof. Sulyman Kuranga and Prof. A. G Ambali, the University Vice Chancellor at that time. Following my appointment as Coordinator of the University Stem cell research programme, and to overcome my apprehension of this new responsibility, I decided to undertake a 5-days crash programme of lectures and laboratory training with Life Technologies, U.S.A. under the supervision of Dr. Nirupama Shevde, the global training manager for Life Technologies stem cell programme at that time. This was to enable me acquire some knowledge about human stem cells. I paid out of pocket for this training. Following this training at Life Technologies, U.S.A. and with the assistance of my Ph.D. supervisor, Prof. Ralph Albrecht and under the leadership of Prof. A. G. Ambali a visit of the University of Ilorin Stem cell research team to the University of Wisconsin-Madison was arranged. This visit culminated in the signing of a memorandum of understanding (an MOU) with the University of Wisconsin-Madison on Stem cell research, training, and future development at Ilorin. (see Figs. 12 a and b: attached photos of the visit). It is noteworthy that in 1998, Prof. James Thompson of the University of Wisconsin-Madison, for the first time, in a landmark breakthrough research generated stem cells from human embryonic cells (Fig. 13 a and Thomson J.A. *et al.,* 1998). In August 2015, **Olufunke Olorundare**, Abiola Samuel Babatunde and Ibrahim Raufu resumed at Madison College as students to undertake the mandatory 2-semester coursework in Biotechnology and Stem cell Technology. This programme was

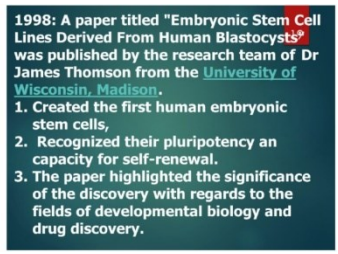
fully paid for by the University of Ilorin. We came back to Nigeria in June 2016, with the expectation to return to the USA for the real research training at the University of Wisconsin-Madison. This expectation did not come through as the University was no longer able to provide funds for the follow-up research training at the laboratories in the University of Wisconsin-Madison. In January 2018, as the immediate past Director of the Stem cell research centre, and with the endorsement of the immediate past Vice Chancellor, Prof. Sulyman Age, Abdulkareem, I made a presentation to the management of TETFUND on what we learnt during our 2-semester training at Madison College. This presentation resulted in the approval of the sum of ₦247,141,725 by TETFUND to the University for Stem cell research training of academic and technological staff at the University of Wisconsin-Madison. This award enabled us to go back to UW-Madison in 2020 to start the Stem cell research training.

Figures 12a and b: Professor A. G. Ambali, former Vice Chancellor University of Ilorin, and former Chancellor Rebecca Blake of the University of Wisconsin, WI, U.S.A.



Figures 13a and b: The Man Who Brought You Stem Cells





Stem Cell Titbits

1. What defines a 'stem cell'? Fig. 14a

- Stem cells capable of replication and self-renewal---they are capable replication, and they can undergo unlimited cell division.
- Cell Potency: They are undifferentiated and can be induced to differentiate into multiple cell types, ie. they can change to one or several different cell types differentiate under proper conditions.
- Stem Cell are Dynamic: They are undifferentiated "master" cells that do not yet have a specific function.

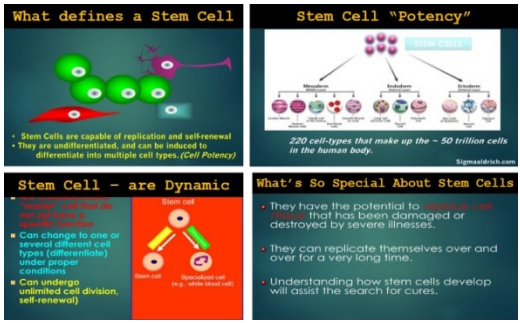
2. **The Science of Stem Cells: Fig 14b and c**

- Stem cells have the ability to continually reproduce while maintaining the capacity to give rise to other more specialized cells.
- Stem cells are found at all stages of development, from embryonic stem (ES) cells that can differentiate into all specialized cells found in the human body, to adult stem cells capable of regenerating their tissue of origin.
- Stem cells occur from the earliest stages of development and provide the starting material for every organ and tissue.

3. **What's so special About Stem Cells? Fig.14d**

- They have the potential to replace cell /tissue that has been damaged or destroyed by severe illnesses.
- They can replicate themselves over and over for a very long time.

- Understanding how stem cells develop will assist the search for cures.



Figures 14a, b, c, d: Characteristics of Stem Cells

4. **Types of Stem Cells? Fig. 15a**

- Embryonic (also called "pluripotent") stem cells can develop into all the cell types of the body.
- Adult stem cells are less versatile
- But can be reprogrammed: Adult stem cells Induced Pluripotent Stem Cells (IPSC).

5. **Sources of Stem cells: Fig. 15b**

- Stem cells may be derived from autologus, allogeneic or xenogenic sources.
- Histocompatibility is a prerequisite for transplantation of allogeneic stem cells.
- Fetal tissue is the best current tissue source for human neural stem cells, however this is not without issue.

6. **Xenogenic - Stem Cells. Fig. 15c.**

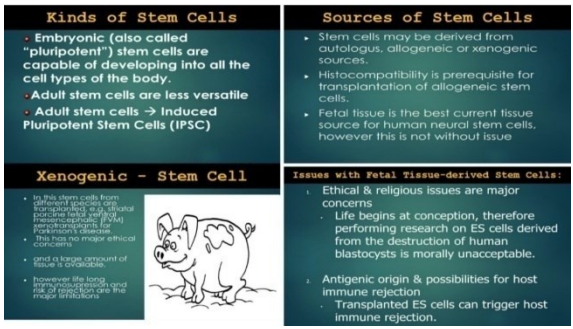
- In this stem cells from different species are transplanted, e.g. striatal porcine fetal ventral mesencephalic (FVM) xenotransplants for Parkinson's disease.
- This has no major ethical concerns, and a large amount of tissue is available,
- However, lifelong immunosupression and risk of rejection are the major limitations.

7. **Embryonic Stem Cells**

- During embryonic development, specialized cells (e.g., muscle or immune cells) arise from a common stem cell that differentiates via a series of cellular changes triggered by specific gene expression patterns.
- All our body parts originally came from one source of cells (es) cells**.**
- Scientists can recover these embryonic stem (ES) cells from embryos and manipulate them in vitro to study early development.
- Scientists can also differentiate ES cells into cell types that are useful for therapeutic purposes, such as transplantation.

8. **Issues with Fetal tissue-derived stem cells: Fig. 15d.**

- Ethical & religious issues are major concerns.
- Life begins at conception, therefore performing research on ES cells derived from the destruction of human blastocysts is morally unacceptable.
- Antigenic origin & possibilities for host immune rejection.
- Transplanted ES cells can trigger host immune rejection.



Figs. 15 a, b, c, d. Types and Sources of Stem Cells. Issues with Embryonic Stem Cells.

9. **Hence, the Significance of IPSC-derived Stem Cells from Adult Tissues: This is using Self to Repair or Treat Self**

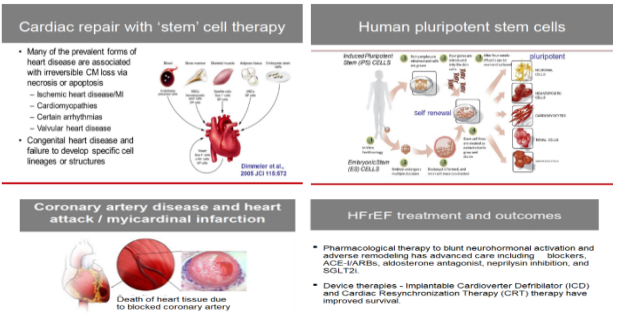
- Pluripotent stem cells (IPSCs) have the ability to differentiate into almost all cell types.

- The issues with using ES cells are largely resolved by using IPSC from somatic cells which can be recovered from an adult source.
- If the same cells are recovered from a human donor, who will also later receive the differentiated cells, this also largely mitigates any immune reaction encountered during transplantation.
- programing of Induced Pluripotent Stem Cells (iPSC) from adult humans

10. **Major Progress in Several Important Health problems:**
    a. *Alzheimer's disease*
    b. Parkinson's disease
    c. *Spinal cord injury*
    d. Heart disease
    e. Diabetes
    f. Stroke
    g. Severe Burns

11. Currently stem cell research and therapy is directed towards reprogramming of somatic cells from adult humans, which overcomes issues arising from use of embryonic stem cells and is also mainly devoid of the complications which accompany the use of embryonic and xenogenic stem cell (Figs.16 a. b, c, d).

Figs. 16a, b. IPSCs for Cardiac Therapy from Autologous Source**.**



Figs. 16 c, d. http://www.knowabouthealth.com/wp-ontent/v uploads/2009/06/myocardial-infraction.jpg

My Research Contribution to Stem Cell Technology

I had my stem cell research training in 2 laboratories, Prof. Timothy Kamp's laboratory which is involved in research into cardiac cell regeneration via manipulation of the Leucine-rich repeat containing 10 protein (LRRC10) gene, a gene discovered to cause regeneration in some fishes and tadpoles. The adult human heart shows little regenerative capacity as most frequently demonstrated by myocardial infarction (heart attack) causing replacement of contractile cardiac muscle by fibrotic scar. In contrast, some species of fish and amphibians undergo adult heart regeneration in response to injury. In addition, neonatal mice and neonatal pigs exhibit a brief time window after birth in which the heart can regenerate after an induced myocardial infarction. The teleost fish, Astyanax mexicanus has two populations, the surface dwelling and cave dwelling types. The surface fish show robust cardiac regeneration, but little regeneration occurs in the cave-dwelling fish. Comparison of gene expression profiles following injury in the surface fish and cave fish revealed that LRRC10 is more highly expressed in regenerating surface fish. The conserved nature of regulation of LRRC10 across species and the expression of LRRC10 in human heart led to this investigative study on the essential role of LRRC10 in human cardiac regeneration. The laboratory is also involved in developing protocols for repairing cardiomyopathies e.g. Brugada syndrome.

My second laboratory belonged to Prof. Ruben Alexanian. The laboratory focused on developing stem cell protocols to repair valvular heart disease. Heart valves play a critical role by ensuring unidirectional blood flow through the cardiovascular system. In the developing world, a common cause of aortic valve disease is rheumatic fever while in developed countries, calcified aortic valve diseases are the main cause of valvular insufficiency. Drug-based treatments slow down the process and valve replacement surgery are inevitable, with mechanical or biological prostheses being the options for valve replacement. Endocardial cells play a pivotal role in heart development, as they are responsible for inducing the first

functional population of cardiomyocytes (heart cells)- the trabecular cardiomyocytes. Besides promoting trabecular development, the embryonic endocardium serves as the source of progenitors of several other cell types in the heart including the endothelium that makes up part of the coronary vasculature, and the valves of the heart.

We developed a monolayer based, small molecule induced, hPSC-derived endocardial progenitor cells. This differentiation protocol holds great potential for cardiac and valvular heart disease modeling, given the central role of the endocardium in heart development and pathophysiology. For hPSC Culture and endocardial progenitor cells (EPC) differentiation, HES3-NKX2.5$^{eGFP/w}$ reporter line was used and cultured in RPMI 1640 + B27 supplement without insulin augmented with CHIR99021 (WNT activator) for 24 – hours, and was followed by addition of various small molecules that enhance differentiation until day 9, to generate endocardial progenitor cells. Porcine aortic valve leaflets were decellularized and endocardial cell progenitor cells at day 9 of differentiation were plated on hydrogels obtained from decellularized porcine aortic valves in endothelial-mesenchymal transition differentiation media for 48-96 hours. and qRT-PCR was performed. Flow Cytometry and quantitative RT-PCR were performed throughout the differentiation of the cells and after co-culturing. From our results, we conclude that hydrogels from decellularized aortic valve promote endothelial-mesenchymal transition of endocardial progenitor cells, a crucial process in valvular development. (Walters, North, **Olorundare,** *et al.,* 2023).

Brugada syndrome (BrS) is an inherited cardiac arrhythmia characterized by a pattern of coved ST-segment elevation on the electrocardiogram in the right precordial leads and an increased risk of ventricular fibrillation and sudden cardiac death. Loss-of-function mutations in *SCN5A* gene have been associated with BrS in about 20% of patients. The primary manifested pathology in BrS occurs in the right ventricle outflow tract with areas of low voltage and scar and associated repolarization abnormality.

Under the direction of Dr. Jianhua Zhang, we worked on differentiating heart cells from a patient with heterozygous mutation for the defective gene (*SCN5A*). The differentiated heart cells are being used to study how this defect affects the heart cells. The study will also include the use of "patch clamp" to study the electrophysiology of the heart cells generated from the patient's heart cells (Fig. 17 a and b) (Zhang, Saito, Kim, Jenkins, **Olorundare,** *et al.,* 2022).

Research study into the role of leucine-rich repeat containing 10 protein (LRRC10) and cardiac regeneration led me to use LRRC10 KO hPSCs (LRRC10 knock out cell line) to generate day 15 cardiomyocytes (differentiated and beating heart cells). The cells were purified, to remove those cells that were not heart cells and treated with various agonists of cellular proliferation including neuregulin, IL-11 and CHIR 99021. Preliminary results obtained from this study suggests that LRRC10 does not seem to be required for baseline proliferation and nucleation of IPSC-cardiomyocytes (**Olorundare** *et al.,* 2023).

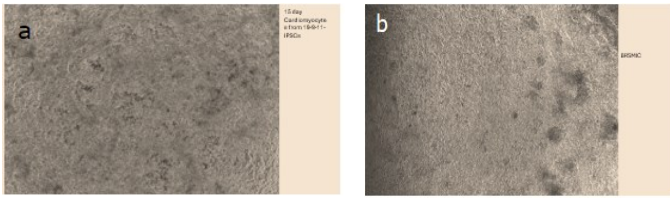


Fig. 17 a and b: Day 15 cardiomyocytes (after GiWi) beating heart generated from hPSC made from wild type 19-9-11 hPSC (a) and the day 15 cardiomyocytes generated from the hPSC of a Brugada syndrome patient.

Human Development

Besides teaching Pharmacology to medical students over the years, I pioneered the postgraduate degree at the Department of Pharmacology and Therapeutics from which 34 M.Sc. and 3 Ph.D. students have graduated. Presently, we have 10 Ph.D. and 2 M.Sc. students in the Department.

Community Service at the National Level

In 2014, the Raw Materials Research and Development Council (RMRDC), Abuja gave a seed grant to a team of researchers from this University to carry out study on *Moringa oleifera* seeds with the purpose of elucidating the safety and toxicology profile of *Moringa oleifera* seed extract and to characterise the active phytochemical constituents that are responsible for toxicity of the seed. The team of researchers included:

a. Olufunke E. Olorundare, Dept. of Pharmacology and Therapeutics, College of Health Sciences.
b. A. A, Njan, Dept. of Pharmacology and Therapeutics, College of Health Sciences.
c. S. A. Biliaminu, Dept. of Chemical Pathology and Immunology, College of Health Sciences.
d. O. Atolani, Dept. of Chemistry, Faculty of Physical Sciences

Here, I provide a summary of our findings from the study on the seeds of *Moringa Oleifera*.

Moringa oleifera seeds are widely accepted as a nutritional supplement in this country as well as other countries of the world. In North Central Nigeria, pregnant women use *Moringa* seeds as food supplement due to its milk producing property. The seeds are consumed and are sold on the shelf of nature, herbal shops, pharmacies and supermarkets and are consumed as herbal remedy for various diseases.

We evaluated the acute and sub-acute toxicity of defatted extract of *Moringa oleifera* seed in albino rats using standard methods. Biochemical assays and histopathology showed that the extract at doses above 400mg/kg caused kidney damage by inducing widespread necrosis of the tubular epithelial cells and revealed that grave consequences attend the chronic consumption of *Moringa oleifera* seeds as this could lead to kidney damage. Therefore, indiscriminate use of moringa seeds should be discouraged (**Olorundare**, *et al.,* 2016).

Next, we determined if oral administration of seed extract of *Moringa oleifera* was developmentally toxic to pregnant Wistar rats. In our assessment, laparohysterectomies

were performed on pregnant rats one day before the expected parturition of half of the dams. We evaluated the following: implantations, uterine weight, foetal resorptions foetal death, viability, among other tests. The remaining pregnant rats were allowed to birth the litter, and offspring parameters were assessed. This study revealed that M*oringa oleifera* ethanolic seed extract may adversely affect pregnancy in the female rats at high doses (Anoka, Atolani, **Olorundare**, *et al.,* 2017a).

The reversibility studies carried out on rats exposed chronically to *Moringa oleifera* seed extract showed that the seed could cause infertility in male rats due to decreased semen pH. Our results also showed that the extract may be hepatotoxic due to persistent high level of liver enzymes, even after cessation of exposure to the extract, this is also consistent with the histopathological results which showed hepatic necrosis associated with chronic exposure to the seed extract (Njan, Atolani, **Olorundare**, *et al.*, 2017 b)

We carried out studies to determine the toxicants in the Moringa seeds. Findings from this study implicated niazinin triacetate and trivaccenin component of the seed as possible immunotoxic, carcinogenic, and mutagenic compounds, thus demonstrating the need to exercise caution in the consumption of the moringa seeds (Atolani, **Olorundare***, et al.,* 2020).

We also screened the oil of Moringa seed and the protein component of the seed for antioxidant and anti-inflammatory potential (Olubunmi, **Olorundare**, *et al.,* 2018). The oil and extracts of *Moringa oleifera* seed exhibited prominent antioxidant and free radical scavenging activities. This finding would be of immense use to nutritionists and nutraceuticals scientists for the purpose of formulating antioxidant-rich therapeutic diets. Our study also evaluated the isolated seed protein of *Moringa oleifera* for possible anti-bacterial, anti-fungal activity and cytotoxicity, against both 3T3 and MDA-MB-231 breast cancer cell lines (Atolani, **Olorundare**, *et al.,* 2021) The assays and *in silico* toxicity result indicted that the peptides isolated from the seed are not immunotoxic, carcinogenic or mutagenic.

Community Service at the Local Level

I have served as Ag. Head of Department and Head of the Department of Pharmacology and Therapeutics for many terms over the years. I have also served on various University boards including the Library and Publications Committee, University Printing Press and as a member of the University Students Accommodation Committee (1994-1997), in addition to being a hall mistress serving Amina Hall and later the female medical students' hostel. I was the Coordinator of the University of Ilorin Stem Cell Research program from (2013-2014) and the director of University Stem Cell Research program/ Centre from (2014-2017). During my tenure, the stem cell research program became a recognised unit of the University of Ilorin, on the international level and the University was subsequently designated by TETFUND as a centre of excellence for Stem Cell Research.

Since 2019, I have been conducting research for the Biofare group (in conjunction with some colleagues and postgraduate students). The Biofare group is headed by Professor Samuel Ibiyemi (our retired Professor of Chemistry). The Biofare group is endowed with 50-hectares of land in Edidi, in Isin local Government area of Kwara State, for the cultivation of *Moringa Oleifera* because of its nutritional function in health, and for creating wealth, as this venture creates jobs for the youths. My research contribution to this group (all gratis) has evaluated the toxicity profile of their proprietary herbal supplement, sold under the name moringa plus (containing powdered *Moringa* leaves plus some herbs). The result of the study has been published (Afolabi, **Olorundare** *et al.,* 2023). We have also evaluated the biochemical profile of Moringa plus herbal supplement for its antioxidant, immune boosting and health improving attributes. Presently, I am working with the group in conjunction with Dr. Olubunmi Atolani of the Department of Chemistry and one of my postgraduate students, to evaluate their new food product, of herbal fortified yam and soya beans flour. The safety profile, and other necessary investigations that will permit NAFDAC listing and subsequent registration of the product will also be conducted. This is also being done, gratis. The goal of the Biofare group is to support youths in Kwara State to key into the production of this foodstuff for economic development.

Conclusion

Vice Chancellor, sir, from my research studies across the body systems, I have made the following summarised conclusions: in the brain, my research work has discovered the cochlear nuclei regions as another site in the brain aside from the established anterior hypothalamus preoptic region for the mediation of pyrexia. My research studies on the blood has delineated the ultrastructural processes and receptor movements/ redistributions which take place in the human platelets that brings about formation of the primary haemostatic plug and subsequent platelet-platelet interactions which take place to stop leaks in blood vessels and some of the processes which take place in the platelet to bring about clot retraction during wound healing. At the level of cardiometabolic syndrome, my research studies have demonstrated the deadly relationship between postmenopausal syndrome and consumption of thermoxidized oils, in the generation and progression of atherosclerosis. In the quest of seeking an end to the scourge of cancer, my research studies have identified seeds and leaves of African origin with potential anticancer attributes and have even gone as far as obtaining a pure compound named after the University of Ilorin, with potent anticancer properties. In addition, my research studies in this area have identified African vegetables and seeds that can abrogate or ameliorate the toxicities of some cancer chemotherapeutic drugs. More recently, in the area stem cell research and regenerative medicine, my study has shown that hydrogels from decellularized aortic valves promote endothelial-mesenchymal transition of endocardial progenitor cells, a crucial process in valvular development. Pharmacology was at work before we were born. I am sure that we all started taking drugs from the time we were in our mother's wombs, as our mothers during antenatal care had to swallow haematinics, and anti-malarials tablets, some of which crossed the placenta to the foetus, pharmacology was at work then in the development of safe drugs for the growing foetus. As we all grew up, pharmacology kept pace with us, as a faithful partner, in sickness to restore us back to homeostasis; and in health to help organs in our bodies maintain homeostasis.

I do sincerely hope that this inaugural lecture has convincingly demonstrated that pharmacology has a special role in medical research and in the promotion of health and well-being. I dare say that pharmacology is the "sinoatrial node" (heartbeat) of medicine, if not its "left ventricles".

Recommendations

Mr. Vice Chancellor, the following are my humble recommendations:

1. It is imperative for TETFUND to devote attention to funding the purchase and maintenance of equipment for laboratories in our various universities for basic science teaching and research at the undergraduate level. This directly derives from my personal experience and exposure to research in my undergraduate days, which enabled me to effortlessly fit into the research culture, during my postgraduate studies at the University of Wisconsin-Madison, U.S.A, TETFUND has done marvelously in the area of providing buildings for most of our tertiary institutions, and must be commended for the accomplishment in this area. The time has come for TETFUND to prioritize providing funds to equip these magnificent empty buildings to make our universities real universities. TETFUND must insist on obtaining major equipment directly from the overseas manufacturers, who must not only install the equipment and make sure that they function at the delivery stage, but also enter into maintenance agreements with these companies for the equipment. A situation where middlemen and contractors who know very little about the functioning of the equipment they supplied, and sometimes supply equipment that will never be put to use beyond a few weeks/months, is a deplorable waste of government resources and deeply frustrating for researchers.

2. Academics in the Medical and Sciences fields must as a matter of urgency collaborate across research disciplines, for robust and comprehensive research output. Research studies which impact societal needs will easily be published in visible journals. This also directly attracts funding for future research from international funding bodies. Aside from this, such interdisciplinary collaborations enable academicians to have broad understanding of other related disciplines aside from their own narrow area.

3. Electricity should be improved in Nigerian universities. Nigerian universities vice chancellors need to have an urgent discussion on their platform on this matter and to seek the

intervention of TETFUND, companies, philanthropists' and state governments to arrest this situation of 'darkness in the universities". There is an urgent need to invest in solar-generated power supply in all Federal and State Universities. The logistics of getting this done can be worked out such that within the next 5 years all these Universities will be lit-up. This will revolutionise the research and academic environment of our Universities.

4. Accessing articles published from international journals is a major problem for many researchers in the Medical and Natural Sciences. A situation where what a researcher has access to, is the abstract of a published journal article is not helpful for scientific understanding and knowledge, of current happenings in one's field of research. Many good journals will require one to login through the institutional library to access the full article or else pay for such articles in foreign currencies. It is imperative for the University librarians to look forward to finding a solution to this problem. A few Universities can pull resources together to subscribe to these journals for the use of academics.

5. The University of Ilorin has made a major stride under successive leadership, in staff training for stem cell research and biotechnology. This field of research is the future of medical research. Regenerative medicine, gene editing and gene therapy, for health and plant gene editing for food sufficiency are the directions for the future of man and should be sustained. The University administration must not permit the Stem cell research centre to go into coma. I am confident in the ability of our dynamic Vice Chancellor, Prof. W. O Egbewole, to do all that is needed to bring this research centre to the level of excellence commensurate with what obtains in overseas countries. Nigeria is waiting and the world is waiting for our university in this regard.

6. Bioprospecting of African medicinal plants and herbs should be made a pivotal agenda of the Universities, TETFUND, NAFDAC and the Federal Ministry of Health. China is at the forefront of this endeavour.

Acknowledgements

First and foremost, my gratitude goes to the Almighty God Who deserves all my worship and to my Saviour and Lord, Jesus Christ through Whose shed blood and redemptive work, I am alive today, standing before you all. He is my hope and trust for eternal salvation at the end of my race on earth.

Special appreciation goes to my late Dad, Reverend Canon Johnson Olajide Fagboyegun (fondly called Reverend JOF) who was extremely dear to me in all aspects of my life, from my early education, in my secondary school days at St Annes School, Molete, Ibadan, where many of my classmates know him as 'Funke Fagboyegun's dad'. He was always there for me. Through my University days in Zaria, when he always called on Sundays, and I would go to the University telephone room/booth to receive phone calls from home, to my marital life, when he would call every evening, just to 'say hello'. I missed him dearly when he passed on in July 2008. I also acknowledge my mother, Mrs. Florence Olawumi Fagboyegun and my siblings: Rtd. Hon. Justice Olanrewaju Akeredolu, Mr. Olatunji Olumide Fagboyegun (of blessed memory) Lawyer Olusegun Ayodapo Olugboyegun, Pastor Olurotimi Akintunde Fagboyegun, Mrs. Omolola Olufunlola Adekeye, Ekundayo Aderogba Olugboyegun and their families. I want to use this opportunity to recognise Pa Reuben Fasoranti, who is the head of my dad's family, and his daughter, Funmilayo Fasoranti, her twin brothers, and Mr. Boye Iwajomo, Pa Fasoranti's grandson. I acknowledge late Mrs. Funke Olakunri for her frankness and love for the 'big family; she was always open and warm. My appreciation also goes to mommy, Mrs. Florence Morenike Saraki.

I want to express my appreciation to the past and present administrations of this University, starting with Professors S. O. O. Amali and I. O. Oloyede who were Vice Chancellor and Deputy Vice Chancellor at the time of my appointment as Professor, and to their families. I thank Professor A.G. Ambali who was the Vice Chancellor who approved my invitation to the University of Ilorin Stem cell research program and to Professor

S. A. Kuranga and their families. I appreciate Professor S. A. Abdulkareem during whose tenure the University obtained TETFUND funding for the Stem cell Research training in the USA. A big 'thank you" to my current Vice Chancellor, Professor W. O. Egbewole for his passion to see that the building of Stem Cell Research Centre in this University becomes a reality, and for his drive for excellence in this University. I thank the past Registrar Dr. F. Olowoleni and the current Registrar Mr. M. A. Alfanla for their excellent office ethics and drive for excellence. My special appreciation goes to Prof. A. A. Adeoye, the Chairman, Library and Publications Committee for his dedication and efforts on this manuscript.

My special thanks go to all my present and past teachers. My secondary school principal, late Mrs. Christine Groves-Bullock to my teachers at the undergraduate level, especially Prof. Charles Wambebe (of blessed memory). I appreciate Professor Thomas Rudy who supervised my M.Sc. thesis, and Professors Paul Bass, William Mellon, Richard Peterson who were some of my Pharmacology teachers at the University of Wisconsin-Madison. I specially appreciate one of my neuroanatomy teachers, Prof. John Harting, and my appreciation goes to many of my teachers at the University of Wisconsin-Madison who I cannot mention here because space. I also appreciate my lecturers at Madison College during my academic training in Stem cell technology, I specially thank Dr. Thomas Tubon, the Stem Cell Director and Mary Ellen Kraus, the Biotechnology Director.

My deep appreciation goes to my Ph.D. supervisor, Professor Ralph Muehl Albrecht, who was not only a mentor, but became part of my family, and his wife Dr. Chris Erickson and daughter, Amber Albrecht. I want to use this opportunity to specially acknowledge my colleagues in Professor Albecht's laboratory, Lisa Waples, Daryl Meyers, Drs. Steve Goodman and Quentin Lai. I appreciate Professors Julie Oliver and her husband, Douglas Steeber, I also appreciate Professor Albrecht's laboratory manager during my Ph.D. programme, Scott Simmons and his wife and Paul Sims and his family. I appreciate late Professor Hans Ris who taught me how to use the critical point

dryer to prepare biological specimens with excellent ultrastructure for observations under the high voltage electron microscope, and to Rick Noll who taught me how to use the Scanning electron microscope. I thank Professor Jim Pawley who taught me how to use the high voltage electron microscope, and was always there to assist, and Mr. Alan Kutchera at the University of Wisconsin-Madison Integrated Microscopy. I appreciate Professor Deane Mosher of the Department of Medicine and Biomolecular Chemistry, for providing a space in his laboratory for my sabbatical leave and his wife, Dr. Fran Fogerty, for making their home available to me. I acknowledge my colleagues in Professor Deane Mosher's laboratory, Doug Annis, Dr. Bianca Johansson and her husband, Dr. Mats Johansson and their family. I also appreciate Mr. Lance Rodenkirch, who is presently the Director of the Optical Imaging Core, University of Wisconsin-Madison, who taught me while I was in Professor Mosher's laboratory how to use the confocal microscope.

. I thank Professor Timothy Kamp of the Department of Medicine, and the Department of Cardiac Arrythmias and Regenerative Medicine, for providing a space for me to undergo training in stem cell research in his laboratory. Special thanks to my colleagues in Professor Timothy Kamp's laboratory; Dr. Jianhua Zhang, Dr. Natthaphat Siri-Angkul and Lisette Jenkins. I want to specially thank Yukun Li, and Gina Kim, who was a research specialist in Professor Kamp's laboratory who taught me how to differentiate human pluripotent stem cells into excellent cardiomyocytes. Gina is the daughter of my postgraduate school colleague, Professor Youngsook Lee. I want to specially thank Dr. Ruben Alexanian for allowing me into his laboratory to learn how to differentiate human pluripotent cells into progenitors of heart valves. I am grateful to Ryan North with whom I worked in the Alexanian laboratory, for his amiable nature, and also to Janay Walters, who was the research trainee in the Alexanian laboratory at that time.

My special appreciation goes to Professor Krishanu Saha and to Sarah Caroline Gomes DeLima, who came from Brazil for short research training in the laboratory of Professor

Krishanu Saha at the Wisconsin Institute of Discovery, who was the first person who introduced me to laboratory practical on gene editing. Special thanks go to Dr. Dustin Rubinstein, Director of Genome editing, University of Wisconsin Biotechnology Centre who gave me tutorials in gene editing and partnered with Professor Timothy Kamp for me to learn gene editing using the SCN5A mutational correction of Brugada cell line. I say a 'big shout out to' Dr. Jennifer Kushner, Director of CALS Global, University of Wisconsin-Madison who hosted the stem cell research collaboration between the University of Ilorin and the University of Wisconsin-Madison, for the excellent work she did to make the programme a huge success.

I say a big "thank you" to my international collaborators, Professor Mamoru Koketsu of Gifu University Japan. He hosted two Ph.D. students that I sent to his laboratory. Special appreciation goes to Prof. Hasan Mukhtar, Dr. Deeba Syed, Prof. Mukasa Ntambi, and Prof. Jean Christopher Chamcheu, all from the University of Wisconsin-Madison, U.S.A. Professor Chamcheu has since relocated to Louisiana State University at Baton Rouge. To my Nigerian collaborators; I am profoundly indebted to Prof. Adejuwon Adeneye of the Lagos State University, and special thanks goes to Prof. Sunday Soyemi, of the Lagos State University and Dr. Abayomi Ajayi, Dr. Theophilus Jarikre and Prof. T. Omobowale, all of the University of Ibadan, Dr. O. Atolani of the University of Ilorin, Prof. Oyewopo, for their hard work and excellent research contributions to our publications. I am grateful for collaboration with RMRDC, Prof. H. Ibrahim. My appreciation also goes to the following previous and current colleagues: Professor Ayo Soladoye, Professor Ayoola Olatunde (my former Head of Department), Professors A. B. O. Omotoso, Olu Obafemi, M. O. Buhari, Bolade Eyinla, Lawrence Olatunji and his wife and to Professor Victor Owoyele. I also thank the following; Professors Olugbenga Mokuolu, Kolade Ernest, Hannah Olawumi, O.T. Adedoyin, Omotayo Adesiyun, Abayomi Fadeyi, Oluwole Akinola, Akeem Shittu, Bernard Enaibe, Ade Stephen Alabi, Gabriel Omotoso and Dare Akintade. I appreciate Professors Victoria Alabi, Ibraheem Katibi and his wife Dr. Dolapo Katibi,

and my thanks go to Professors Luke Edungbola and Bashiru Okesina.

My appreciation goes to my colleagues at the Department of Pharmacology and Therapeutics: Professor Anoka Njan, Dr. Mary Ologe, Dr. Olalekan Agede, Dr. Saheed Afolabi, Dr. Alli Oluwafuyi. I say thank you to Dr. Matthew Bello, Mr. Femi Adesua and Mrs. Oni, and other the laboratory staff, and also to the secretarial staff of the Department and to my past and present postgraduate students. I use this opportunity to thank the members of the College of Health Sciences, the Provost, the Deans of Basic Medical Sciences, Basic Clinical Sciences and Clinical Sciences and all the subdeans for their excellent work and for making the College of Health Sciences a conducive environment for work. My special appreciation goes to the CMD UITH, Prof. Yussuf and his family.

To my Pastors, I say 'a big thank you" The General Overseer of Mountain and Fire Ministries; Dr. Daniel Kolawole Olukoya and his wife Dr Shade Olukoya. I appreciate Pastor Wale AdeOlumuyiwa and his family. I appreciate Pastors Samuel Oladejo and his family and other regional overseers and pastors in Kwara State. I thank Pastor Moses Adekunle and his family for their prayers, same goes for Pastor Morenikeji Jesushina, and Pastor Taiwo of the Mountain of Fire and miracles ministry, Lagos headquarters.

Finally, I specially thank and appreciate members of my nuclear family; my husband Professor Adekunle Solomon Olorundare, and my children Dr. Israel Olorundare, Engineer David Olorundare and my appreciation goes to my daughter Dr. IfeOluwa Ojemakinde and Architect Funminiyi Ojemakinde her husband and their family, for their love and support. I am grateful to you all for your love, understanding and prayers. I want to appreciate the in-laws of my daughter and their families for their love for my daughter. To God be all the glory!

References

Ackerman, D. & Rudy T. A. (1980). Thermoregulatory characteristics of neurogenic hyperthermia in the rat. *Journal of Physiology,* 307, 59-70.

Adeneye, A. A., **Olorundare, O. E.,** Akinsola, A. O., Sanni, D. A., Okoye, I. I., Ntambi, J. M & Mukhtar, H. (2021b). Ameliorative Potential of Clerodendrum volubile Ethanol Leaf Extract on Doxorubicin-Induced Hepatorenal Toxicities in Rats. *Pharmacology and Toxicology of Natural Medicines,* 1(1), 1-13. DOI: 10.52406/ptnm. v1i1.8).

Adeneye, A. A., **Olorundare, O. E.,** Omobowale, T. O., Akinsola, A. O., Kolo, P. M., Albrecht, R. M. A, & Crooks, P. A. (2021a). Selected antihypertensive agents and their fixed-dose combinations effectively ameliorate trastuzumab-mediated cardiac dysfunction in rats. *Nigerian Journal of Physiological Sciences*, 36(1), 57-65.

Adeneye, A., **Olorundare, O**, Ajayi, A, Akinsola, A.; Atolani, O ; Soyemi, S., Mgbehoma, A . (2023). Antidotal potential of ocimum gratissimum linn. leaf extract and fractions against trastuzumab-mediated cardiotoxicity in rats. British Journal of Pharmacology (IUPHAR): P1037.

Adeneye, A., **Olorundare, O.**, Akinsola A., Soyemi, S., Mgbehoma A., Okoye, I., Albrecht, R., Ntambi J. & Mukhtar H. (2021c). Experimental therapeutic evaluation of the African vegetables (Clerodendrum volubile leaf and Irvingea gabonensis seed extracts in Trastuzumab-mediated hepato-renal dysfunction in Wistar rats. *Asian Journal of Pharmaceutical and Clinical Research*, 14(1), 147-157. DOI: http://dx.doi.org/10.22159/ ajpcr.2021.v14i1.40118}.

Afolabi S, Gyebi G., Agede O., Njan A., **Olorundare O.** & Koketsu M. (2021). Screening of Selected Nigerian Medicinal Plants/Seeds for Growth Inhibitory Activity against Human Leukemia HL-60 Cells and DPPH Radical Scavenging Activity. *African Journal of Biomedical Research*, 24, 421- 426.

Afolabi, S. O., **Olorundare, O. E.,** Akanbi, O. B., Bello, M. K., Njan, A., Agede, O. A. & Ibiyemi, S. (2023). GC/MS Analysis and a 30-day Toxicological Evaluation of a Nigerian Immunomodulatory Polyherbal Supplement (PHS). *Pharmacology and Toxicology of Natural Medicines (ISSN: 2756-6838)*, *3*(2), 1-14.

Afolabi, S. O., **Olorundare, O. E**., Babatunde, A., Albrecht, R. M., Koketsu, M., Syed, D. N., & Mukhtar, H. (2019a). Polyalthia longifolia extract triggers ER stress in prostate cancer cells concomitant with induction of apoptosis: Insights from in vitro and in vivo studies. *Oxidative medicine and cellular longevity*, *2019*(1), 6726312. Doi.org/10.1155/2019/6726312.

Afolabi, S. O., **Olorundare, O. E**., Gyebi, G., Syed, D. N., Mukhtar, H., & Albrecht, R. (2019b). Cytotoxic potentials of Clerodendrum volubile against prostate cancer Cells and its possible proteomic targets. *J. Clin. Nutr. Food Sci*, *2*, 46-53.

Afolabi, S. O., **Olorundare, O. E.,** Ninomiya, M., Babatunde, A., Mukhtar, H. & Koketsu, M. (2017). Comparative antileukemic activity of a tetranorditerpene isolated from Polyalthia longifolia leaves and the derivative against human leukemia HL-60 cells. *Journal of Oleo Science*, *66*(10), 1169-1174.

Aggarwal, B. B., & Shishodia, S. (2006). Molecular targets of dietary agents for prevention and therapy of cancer. *Biochemical pharmacology*, *71*(10), 1397-1421.

Ajayi, A., **Olorundare, O**., Adeneye, A., Soyemi, S., Mgbehoma, A., Akinsola, A., Okoye, I., Albrecht, R. & Mukhtar H. (2023). Ocimum gratissimum leaf extract and fractions alleviate trastuzumab-induced lung toxicity in Wistar rats via antioxidants and anti-apoptotic mechanisms. *British Journal of Pharmacology (IUPHAR) P0456*. DOI: 10.1111/bph.16111.

Akinsola, A. A., Adeneye, A. A., **Olorundare, O. E**., Salahdeen, H.M., Murtala B. A. & Albrecht Ralph M. (2022). Vasorelaxant mechanism(s) of Clerodendrum Volubile ethanol leaf extract in normal and doxorubicin-treated endothelium intact aortic rings. *Asian Journal of Pharmaceutical and Clinical Research*, 15(7), 1-9.

Albrecht RM, Meyer DA, Olorundare OE (2013). High resolution labeling for correlative microscopy. In: Scanning Electron Microscopy for Life Sciences. Advances in Microscopy and Microanalysis. Heide Schatten (editor). Pp. 83-98. Cambridge University Press, New York.

Albrecht RM, **Olorundare O.E**, Oliver JA, and Meyer DA (2011). Nanoparticle labels for co- localization and correlative imaging at high spatial resolution. Microscopy and Microanalysis, 17 (Suppl 2), 358-359.

Albrecht, R M.; **Olorundare, O. E**. and Simmons. S. R. (1988). Fibrinogen Receptor Movement in the surface membrane of Adherent fully Spread Platelets. In: Fibrinogen Biochemistry, Biological Functions, Gene Regulation and Expression. {M. W. Mosseson, D. L. Amrani, K. R Siebenlist, and J. Dioro (eds).}, pp. 211-214, Excerpta Medical. Elsevier, Amsterdam.

Albrecht, R M.; Olorundare, O. E., Simmons, S. R; Loftus, J. C. and Mosher, D. F (1992). Use of correlative Microscopy with colloidal gold labeling to demonstrate platelet receptor distribution and movement. In: Methods in Enzymology. (Hawiger Ed.) Vol. 215, Chapter 39,456-479. NY: Academic Press, Inc.

Albrecht, R. M., **Olorundare, O. E**. & Simmons. S. R. (1988). Fibrinogen Receptor Movement in the surface membrane of Adherent fully Spread Platelets. In: *Fibrinogen Biochemistry, Biological Functions, Gene Regulation and Expression.* {M. W. Mosseson, D. L. Amrani, K. R Siebenlist, and J. Dioro (eds).}, pp. 211-214, Excerpta Medical. Elsevier, Amsterdam.

Albrecht, R.M.; Olorundare, O.E.; Bielich, H.W. and Simmons, S.R. (1987). Correlative video enhanced DIC-LM, HVEM and Low-Voltage High Resolution SEM in the study of surface and internal ultrastructure. Proceeding of Electron Microscopy Society of America, 45: 556 – 559.

Athar, M., Back, J. H., Tang, X., Kim, K. H., Kopelovich, L., Bickers, D. R., & Kim, A. L. (2007). Resveratrol: a review of preclinical studies for human cancer prevention. *Toxicology and applied pharmacology*, 224(3), 274-283.

Atolani, O., **Olorundare, O. E**., Anoka, A. N., Osin, A. O. & Biliaminu, S. A. (2018). Antioxidant, proteinase inhibitory and membrane stabilization potentials of Moringa oleifera seed oil. *FABAD Journal of Pharmaceutical Sciences*, 43(2), 1-13.

Atolani, O., **Olorundare, O. E**., Banerjee, P., Adeyemi, O. S. & Preissner, R. (2021). Moringa oleifera Seed Protein: MALDI-TOF and TANDEM-Mass Spectrometry Characterisations, Anti-cancer, Cytotoxicity, in silico Toxicity and Anti-microbial Evaluations. *Periodico Tche Quimica,* 18(38), 214-223.

Atolani, O., **Olorundare, O. E.**, Banerjee, P., Osin, O. A., Preissner, R. & Njan, A. A. (2020). Isolation, characterisation and in silico toxicity evaluations of thiocarbamates, isothiocyanates, nitrile, glucosinolate and lipids from Moringa oleifera Lam. seed. *Journal of the Turkish Chemical Society Section A: Chemistry*, *7*(1), 233-242.

Barthur, A., Brezden-Masley, C., Connelly, K. A., Dhir, V., Chan, K. K., Haq, R. & Yan, A. T. (2016). Longitudinal assessment of right ventricular structure and function by cardiovascular magnetic resonance in breast cancer patients treated with trastuzumab: a prospective observational study. *Journal of Cardiovascular Magnetic Resonance*, 19(1), 44.

Bickers, D. R., & Athar, M. (2000). Novel approaches to chemoprevention of skin cancer. *The Journal of dermatology*, *27*(11), 691-695.

Blackwell, K. L., Burstein, H. J., Storniolo, A. M., Rugo, H., Sledge, G., Koehler, M. & O'Shaughnessy, J. (2010). Randomized study of Lapatinib alone or in combination with trastuzumab in women with ErbB2-positive, trastuzumab-refractory metastatic breast cancer. *Journal of clinical oncology*, 28(7), 1124-1130.

Bordbar, M., Jam, N., Karimi, M., Shahriari, M., Zareifar, S., Zekavat, O. R. & Mottaghipisheh, H. (2023). The survival of childhood

leukemia: An 8- year single- center experience. *Cancer Reports*, *6*(4), e1784.
Bray, F., Laversanne, M., Weiderpass, E. & Soerjomataram, I. (2021). The ever- increasing importance of cancer as a leading cause of premature death worldwide. *Cancer*, 127(16), 3029-3030.
Cho N,Shaw J.E, Karuranga S., Huang Y, da Rocha Fernandes J.D., Ohlrogge A.W. Malanda B, (2018). IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045, Diabetes Res. Clin. Pract. 138 (1): 271–281.
Davezac, M., Buscato, M., Zahreddine, R., Lacolley, P., Henrion, D., Lenfant, F. & Fontaine, C. (2021). Estrogen receptor and vascular aging. *Frontiers in aging*, *2*, 727380.
Dinarello, C. A. & Wolff, S. M. (1982) Molecular basis of fever in humans. *American Journal of Medicine*, 72, 799-819. DOI: 10.1111/bph.16111.
Erukainure, O. L., Ebuehi, O. A., Choudhary, I. M., Adhikari, A., Hafizur, R. M., Perveen, S., & Elemo, G. N. (2014). Iridoid glycoside from the leaves of Clerodendrum volubile beauv. shows potent antioxidant activity against oxidative stress in rat brain and hepatic tissues. Journal of dietary supplements, 11(1), 19-29.
Fadelu, T., & Rebbeck, T. R. (2021). The rising burden of cancer in low– and middle–Human Development Index countries. *Cancer*, 127(16), 2864-2866.
Falade, A. O., & Oboh, G. (2015). Thermal oxidation induces lipid peroxidation and changes in the physicochemical properties and β- carotene content of arachis oil. *International Journal of Food Science*, 2015(1), 806524.
Folahan J. T., **Olorundare, O. E.** & Chamcheu J. C. (2024). A bioguided fraction of Kolaviron induces cell death in melanoma and keratinocyte carcinoma in vitro: Involvement of Autophagy. 22nd LBRN (Louisiana Biomedical Research Network) Annual Meeting. Held on January 19-20, 2024, at the Baton Rouge Marriott, Baton Rouge, LA, USA.
Folahan, J. T., **Olorundare, O. E**., Ajayi, A. M., Oyewopo, A. O., Soyemi, S. S., Adeneye, A. A., Okoye, I. I., Afolabi, S. O. & Njan, A. A. (2023). Oxidized dietary lipids induce vascular inflammation and atherogenesis in post-menopausal rats: estradiol and selected antihyperlipidemic drugs restore vascular health in vivo. *Lipids in Health and Disease*, 22(1), 107.
George, J. N., Nurden, A. T. & Phillips, D. R. (1984). Molecular defects in interactions of platelets with the vessel wall. *New England Journal of Medicine*, 311(17), 1084-1098.
Gremmel, T., Frelinger III, A. L., Michelson, A.D. (2016). Platelet Physiology. Semin Thromb Hemost. 42:191–204.

Gupta, S. & Mukhtar, H. (2002). Chemoprevention of skin cancer: current status and future prospects. *Cancer and Metastasis Reviews*, 21, 363-380.

Gyebi, G. A., Adebayo, J. O., Olorundare, O. E., Pardede, A., Ninomiya, M., Afolabi, S. O. & Koketsu, M. (2018). Iloneoside: a cytotoxic ditigloylated pregnane glycoside from the leaves of Gongronema latifolium Benth. *Natural product research*, *32*(24), 2882-2886.

Hodis, H. N., Mack, W. J., Henderson, V. W., Shoupe, D., Budoff, M. J., Hwang-Levine, J. & Azen, S. P. (2016). Vascular effects of early versus late postmenopausal treatment with estradiol. *New England Journal of Medicine*, 374(13), 1221-1231.

Hussain, S. P., Hofseth, L. J. & Harris, C. C. (2003). Radical causes of cancer. *Nature Reviews Cancer*, 3(4), 276-285.

Janus-Bell, E. & Mangin, P. H. (2023). The relative importance of platelet integrins in hemostasis, thrombosis and beyond. *Haematologica*, 108(7), 1734.

Kirk, E. P., & Klein, S. (2009). Pathogenesis and pathophysiology of the cardiometabolic syndrome. *The Journal of Clinical Hypertension*, *11*(12), 761-765.

Kolonel, L. N., Altshuler, D. & Henderson, B. E. (2004). The multiethnic cohort study: exploring genes, lifestyle and cancer risk. *Nature Reviews Cancer*, 4(7), 519-527.

Lipton, J. M. & Trzcinka, G. P. (1976). Persistence of febrile response to pyrogens after PO/AH lesions in squirrel monkeys. *American Journal of Physiology-Legacy Content*, 231(6), 1638-1648.

Loftus, J. C. & Albrecht, R. M. (1984). Redistribution of the fibrinogen receptor of human platelets after surface activation. *The Journal of cell biology*, 99(3), 822-829.

Masuda, T., Toi, Y., Bando, H., Maekawa, T., Takeda, Y. & Yamaguchi, H. (2002). Structural identification of new curcumin dimers and their contribution to the antioxidant mechanism of curcumin. *Journal of agricultural and food chemistry*, 50(9), 2524-2530.

Ng, C. Y., Leong, X. F., Masbah, N., Adam, S. K., Kamisah, Y. & Jaarin, K. (2014). Heated vegetable oils and cardiovascular disease risk factors. *Vascular pharmacology*, *61*(1), 1-9.

Njan, A. A., Atolani, O., **Olorundare, O. E.**, Afolabi, S. O, Ejimkonye, B. C., Crucifix, P. G., Salami, B., Olajide, J. O. & Oyewopo, A. O. (2017a): Chronic Toxicological Evaluation and Reversibility Studies of Moringa oleifera Ethanolic Seed Extract in Wistar Rats. *The Tropical Journal of Health Sciences*, 25 (1), 57-67.

Njan, A. A., Atolani, O., **Olorundare, O. E**., Afolabi, S. O., Ejimkonye, B. C., Crucifix, P. G., Salami, B., Olajide, J. O. and Oyewopo, A. O. (2017b). Assessment of Developmental Toxicity of Moringa oleifera (Seed Extract) in Pregnant Wistar rats. *Centrepoint Journal (Science Edition),* 23(1), 1-18.

Noratto, G. D., Bertoldi, M. C., Krenek, K., Talcott, S. T., Stringheta, P. C. & Mertens-Talcott, S. U. (2010). Anticarcinogenic effects of polyphenolics from mango (Mangifera indica) varieties. *Journal of agricultural and food chemistry*, 58(7), 4104-4112.

Ojuade, F. I., **Olorundare, O. E**., Akanbi, O. B., Afolabi, S. O. & Njan, A. A. (2021). Antidiabetic and antihyperlipidemic effects of aqueous extract of Parquetina nigrescens in streptozotocin–nicotinamide induced type 2 diabetic rats. *Heliyon*, 7(6).

Olorundare O.E. (2000a). Human blood platelets. In: Journal of Phytomedicine and Therapeutics (Journal of Pharmaceutical Research and Development, NIPRD, Abuja, Nigeria 5(2): 60-71.

Olorundare, O. E. (2000b). Lysophosphatidic acid (LPA) and Sphingosine -1-phosphate (S-1-P)" An emerging class of lysophospholipd mediators, *Journal of Pharmaceutical Research and Development, NIPRD, Abuja, Nigeria* 5(1): 1-14.

Olorundare, O. E., & Rudy, T. A. (1986a). Examination of the subdiencephalic rat brain for sites mediating PGE1-induced pyrexia. *Pharmacology Biochemistry and Behavior*, 25(2), 347-351.

Olorundare, O. E., & Rudy, T. A. (1986b). Studies on the pyrexic effect of PGE1 injected into the region of the cochlear nuclei. *Pharmacology Biochemistry and Behavior*, 25(2), 353-358.

Olorundare, O. E., Adeneye, A. A., Akinsola, A. O., Ajayi, A. M., Atolani, O., Soyemi, S. S. & Albrecht, R. M. (2024). Anti-apoptotic and antioxidant mechanisms may underlie the abrogative potential of Ocimum gratissimum Linn. Leaf extract and fractions against trastuzumab-induced cardiotoxicity in Wistar rats. *Toxicology Reports*, 12, 200-214.

Olorundare, O. E., Adeneye, A. A., Akinsola, A. O., Ajayi, A. M., Agede, O. A., Soyemi, S. S. & Crooks, P. A. (2021). Therapeutic potentials of selected antihypertensive agents and their fixed-dose combinations against trastuzumab-mediated cardiotoxicity. *Frontiers in Pharmacology*, 11, 610331.

Olorundare, O. E., Adeneye, A. A., Akinsola, A. O., Sanni, D. A., Koketsu, M., & Mukhtar, H. (2020a). Clerodendrum volubile Ethanol Leaf Extract: A Potential Antidote to Doxorubicin- Induced Cardiotoxicity in Rats. *Journal of Toxicology*, 2020(1), 8859716.

Olorundare, O. E., Adeneye, A., Akinsola, A., Soyemi, S., Mgbehoma, A., Okoye, I. & Mukhtar, H. (2020b). African Vegetables (Clerodendrum volubile Leaf and Irvingia gabonensis Seed Extracts) Effectively Mitigate Trastuzumab- Induced Cardiotoxicity in Wistar Rats. *Oxidative Medicine and Cellular Longevity*, 2020(1), 9535426.

Olorundare, O. E., Bello, M. K., Biliaminu, S. A., Babatunde, A. S., Ibrahim, O. K. & Njan, A. A. (2015). Acute and subacute toxicities of defatted ethanolic extract of Moringa oleifera seed in albino rats. *West African Journal of Pharmacology and Drug Research*, 30, 46-51.

Olorundare, O. E., Nezhaad, N. R. Armbruster, J., Baherawala, S. and Kamp, T. (2023). Investigating the role of LRRC10 in IPSc human cardiomyocyte proliferation. Cardiovascular Research Centre Summit, April 2023 (Poster) University of Wisconsin-Madison, USA**.**

Olorundare, O. E., Peyruchaud, O., Albrecht, R. M. & Mosher, D. F. (2001). Assembly of a fibronectin matrix by adherent platelets stimulated by lysophosphatidic acid and other agonists. *Blood, The Journal of the American Society of Hematology*, *98*(1), 117-124.

Olorundare, O. E., Simmons, S. R. & Albrecht, R. M. (1992). Cytochalasin D and E: effects on fibrinogen receptor movement and cytoskeletal reorganization in fully spread, surface-activated platelets: a correlative light and electron microscopic investigation. *Blood*, 79 (1), 99-109.

Olorundare, O. E., Simmons, S. R. & Albrecht, R. M. (1993). Evidence for two mechanisms of ligand-receptor movement on surface-activated platelets. *European journal of cell biology*, 60(1), 131-145.

Olorundare, O. E.; Goodman, S. L. and Albrecht, R. M. (1988). Trifluoperazine inhibition of fibrinogen receptor redistribution in surface activated platelets: Correlative video-enhanced differential interference contrast light microscopic, High Voltage Electron Microscopic and Scanning Electron Microscopic Studies. Scanning electron microscopy. In: Albrecht, R. M. and Hodges, G. M. (Eds). Biotechnology and Bioapplications of Colloidal Gold. Scanning Microscopy International, Chicago, pp. 87-94.

Phillips, D. R. & Agin, P. P. (1977). Platelet membrane defects in Glanzmann's thrombasthenia: evidence for decreased amounts of two major glycoproteins. *The Journal of clinical investigation*, 60(3), 535-545.

Saljoughian, M. (2017). Cardiometabolic syndrome a global health issue. *US PHARMACIST*, *42*(2), HS19-HS21.

Tacar, O., Sriamornsak, P. & Dass, C. R. (2013). Doxorubicin: an update on anticancer molecular action, toxicity and novel drug delivery systems. *Journal of pharmacy and pharmacology*, 65(2), 157-170.

Thomson, J. A., Itskovitz-Eldor, J., Shapiro, S. S., Waknitz, M. A., Swiergiel, J. J., Marshall, V. S. & Jones, J. M. (1998).

Embryonic stem cell lines derived from human blastocysts. *science*, 282(5391), 1145-1147.

Vallance P., Smart T.G. (2006). The future of Pharmacology. *British Journal of Pharmacology* 147 (Suppl 1): S304-S307.

Walters, J. K., North, R., **Olorundare, O. E**., Aaron, S., Christofi, V. P., Zhang, J., & Alexanian, R. A. (2023). Differentiation of endocardial progenitor cells from human pluripotent stem cells using robust small molecule-based protocol. *Journal of the American College of Cardiology*, 81(8_Supplement), 1953-1953.

Waples, L. M., Olorundare, O. E., Goodman, S. L. & Albrecht, R. M. (1992). Changes in intracellular Ca2+ and structure in platelets contacting synthetic substrates. *Cell and Materials*, 2, 299-308.

Waples, L. M.; **Olorundare ,O. E.**; Goodman, S. L.; Lai, Q. J. and Albrecht, R. M. (1996). Platelet-polymer interactions: Morphologic and intracellular free calcium studies of individual human platelets. Journal of Biomedical Materials Research, John Wiley & SonsInc. USA. 32:65-76.

Weiderpass, E. (2010). Lifestyle and cancer risk. *Journal of preventive medicine and public health*, 43(6), 459-471.

WHO cancer fact sheet (2022). https://gco.iarc.who.int/media/ globocan/factsheets/populations/566-nigeria-fact-sheet.

Willet, W. C. (1994). Diet and health: what should we eat? *Science,* 264(5158):532-537. Doi: 10.1126/science.8160011.

World Health Organization (2020). Global Health Estimates 2020: Deaths by Cause, Age, Sex, by Country and by region, 2000-2019. https://gco.iarc.who.int/media/globocan/factsheets/ populations/566-nigeria-fact-sheet.pdf

World Health organization (2020). Global health estimates: Leading causes of death. https//www.WHO. int.>data > global. health. Estimates.

Zhang, J. Saito, Y. Kim, G. Jenkins, L. **Olorundare, O. E**, Siri-Angkul, N. Walters, J. Orland, K, Eckhardt L, Kamp, T. J (2022). Development of Second Heart Field-derived Right Ventricle/Outflow Tract Cardiomyocytes from Human Pluripotent Stem Cells for Brugada Syndrome Disease Modeling. Cardiovascular Research Centre Summit, October 21, 2022, University of Wisconsin-Madison, USA.