FEDERAL UNIVERSITY OF TECHNOLOGY MINNA

THERAPIES FOR DIABETES MELLITUS: MY ROLE

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INAUGURAL LECTURE SERIES 62

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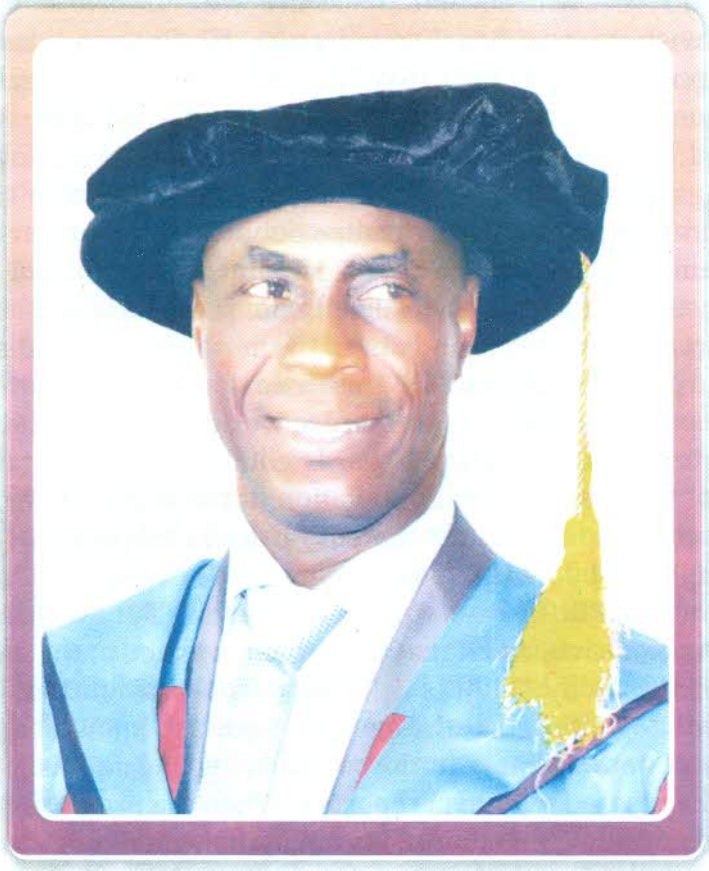

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INTRODUCTION

I wish to commence my lecture by first and foremost appreciating **ALLAH (SWT)** for his mercies and making it possible for me to witness this special day in my life which I tagged "Inaugural Lecture day" .Indeed, this day is special to me having attained the peak of my carrier in the University. Today, I will present my inaugural lecture publicly as a member of the academia which to me is a dream accomplished. Most interestingly, the lecture will dwell extensively on therapies with respect to a worrisome and one of the most devastating diseases known globally - **DIABETES**. This disease attracted my attention because as the fourth killer disease worldwide, any attempt to educate and find solution towards eliminating it will save the lives of the much desired population of the diabetics. Mr. Vice-Chancellor, Sir. Spiritually, there is no doubt that diseases exists as supported by Hadith (Sayings and deeds of the Holy Prophet Mohammed, PBUH) where prophet said that "For every disease there is medicine, and if that medicine is applied to the disease, he will recover by ALLAH's will "And prophet said further" Allah has sent down the cure; the one who knows it, knows it and the one who doesn't know it, doesn't know it." Again, Aisha (May Allah be pleased with her) reported: When the prophet (PBUH) visited any ailing member of his family, he would touch the sick person with his right hand and would supplicate-O Allah! The Robb (Sustainer) of mankind! Remove this disease and cure (him/her).You are the great curer. There is no cure but through you which leaves behind no disease" (Al-Bukhari and Muslim). In view of the title of this lecture and for better understanding, it is pertinent to define the word" **DISEASE**". Therefore, a disease as captured from the Oxford Advanced Learners Dictionary, is

defined to be "a disorder of structure or function in a human, plant or animal especially one that produces specific symptoms or that affects a specific location and is not simply a direct result of physical injury". There are mainly two forms of structural or functional disorders viz: The communicable diseases (**CDs**) and the non communicable diseases (**NCDs**). The former refers to diseases that are caused by microorganisms and consequently invade tissues while the latter are diseases not caused by infectious agents (non infectious or non transmittable). A clear example of CDs include: Malaria, Trypanosomiasis, HIV, Tuberculosis etc. while examples of NCDs include: Diabetes, Hypertension, Cardiovascular diseases, Obesity etc. Thus, this lecture will avail me the opportunity to educate the town and gown on the disease (Diabetes), its treatment and my contribution towards addressing the menace as it affects the diabetics.

DIABETES AS A DISEASE

Essentially, diabetes is a non – communicable disease of endocrine origin and metabolic disorder that affects both adults and children of all races. It is commonly associated with markedly increased morbidity and mortality rates which results in significant financial burden e.g. 92 billion dollars per year in United States (Forster, 1994). Seemingly everywhere, the prevalence of diabetes has increased steadily over the past several decades.

In Nigeria, the literature relating to prevalence of the disease is scarce. However, it was reported that over 5 million people are affected as at 2008 (Daily Trust, September 4th, 2009).

In Port-Harcourt for example, it was found to be as high as 23.4% among the high socio – economic group and 16% among the low socio – economic group (Nwafor and Owhoji, 2001). Thus, it

became the most challenging NCD disease of the 21st Century. The Centre for Disease Control and Prevention estimates that 30 million people worldwide had diabetes in 1985. A decade later, the global burden of diabetes was estimated to be 135 million. Although, changes in the definition of diabetes may have affected the number (Acog, 1986). The World Health Organization (WHO) estimate for the number of people with diabetes, worldwide in 2000 was about 177 million. Two major concerns are that, much of this increase will occur in developing countries, due to population growth, ageing, unhealthy diets, obesity, sedentary life-styles and that there will be growing incidence of the disorder. By 2030, while most people with diabetes in developed countries will be aged 65 years or more, in developing countries, the majority will be in the 45 – 65 years age (WHO, 2002). In the United States alone, there are 20.8 million children and adults with diabetes and from the number; 14.6 million have been diagnosed while 6.2 million are unaware that they have the disease. Based on death certificate data, diabetes contributed to 224,092 deaths in 2002 and studies indicate that diabetes is generally under-reported, particularly in cases of older people with multiple chronic conditions such as heart disease and hypertension. As a result, the toll of diabetes is believed to be much higher than officially reported. The total estimated cost of treatment of diabetes in 2007 was 174 billion dollars (Janghorbani *et al*, 2007). Available WHO report as at 2016 indicated that about 422 million people have diabetes worldwide and more than 14 million live in sub-Saharan Africa and by 2040, the figure will double. In Nigeria, more than 1.56 million cases of diabetes was documented only for 2015.

CLASSIFICATION OF DIABETES

It is quite clear that diabetes is not a single disease, but a syndrome (a group of symptoms which consistently occur together) which may be produced by a number of different

factors. It is common practice to generally classify diabetes into two major groups viz: **Diabetes mellitus** and **Diabetes Insipidus**. The World Health Organization recognizes three main forms of diabetes mellitus namely: Type 1, Type 2 and Gestational Diabetes (WHO, 1999). Type 1 diabetes Mellitus is also referred to as juvenile –onset diabetes while type 2 is referred to as adult-onset or maturity-onset diabetes. Recently, a third type has been identified which was formally referred to as "Other types". Gestational diabetes is similar to type 2 in that it involves insulin resistance which a times disappears with child delivery

TYPE 1 DIABETES MELLITUS (INSULIN DEPENDENT DIABETES MELLITUS, IDDM)

Type 1 diabetes mellitus or juvenile-onset diabetes is characterized by loss or destruction of the insulin-producing beta cells of the islets of Langerhans in the pancreas, leading to a total deficiency of insulin. The main cause of this beta cell loss is a T-cell mediated autoimmune attack (Rother, 2007). There is no known preventive measure that can be taken against type 1, diabetes.

TYPE 2 DIABETES MELLITUS (NON INSULIN DEPENDENT DIABETES MELLITUS, NIDDM).

Type 2 diabetes mellitus arises due to insulin resistance or reduced insulin sensitivity, combined with reduced insulin secretion. The defective responsiveness of body tissues to insulin almost certainly involves the insulin receptor in cell membranes. In the early stage, the predominant abnormality is reduced insulin sensitivity, characterized by elevated levels of insulin in the blood. At this stage, hyperglycemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce glucose production by the liver. As the disease progresses, the impairment of insulin worsens and therapeutic replacement of insulin often becomes necessary. Type 2 diabetes may go unnoticed for years because visible

symptoms are typically mild, non-existent or sporadic, and usually no ketoacidotic episodes. However, severe long-term complications can result from unnoticed type 2 diabetes, including renal failure due to kidney damage, vascular disease, vision damage, loss of sensation or pain due to diabetic neuropathy, and, and liver damage from non-alcoholic steatohepatitis.

GESTATIONAL DIABETES

Gestational diabetes mellitus (GDM) resembles type 2 diabetes in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. Although, gestational diabetes may be transient, if untreated, the health of the foetus or the mother may be terribly affected. Risks to the baby may include macrosomia (high birth weight), congenital cardiac and central nervous system abnormalities, and skeletal muscle malformations. Increased foetal insulin may inhibit foetal surfactant production and cause respiratory distress syndrome. Hyperbilirubinemia may result from red blood cell destruction. In severe cases, death may occur most commonly as a result of poor placental profusion due to vascular impairment. A cesarean section may be performed if there is marked foetal distress or an increased risk of injury associated with macrosomia (Baron, 1982).

TYPE 3 DIABETES

There are several rare cases of diabetes mellitus that do not fit into type 1, type 2 or GDM but accounts for up to 5% of all cases of diabetes. They are recently termed type 3 diabetes mellitus (Type 3A-3E). In the past, attempts to classify them became controversial. Type 3A may arise as a result of genetic defect in beta cells while 3B may be due to genetically related insulin resistance type 3C and 3D may also arise due to diseases of the pancreas and hormonal defects respectively. Type 3E may be induced by chemicals or drugs (DCCTRG, 1993).

DIABETES INSIPIDUS

This is a condition in which large amounts of very dilute urine sometimes as much as 25 litres per day is secreted. It is entirely unrelated to diabetes mellitus. It may be sub-classified as primary, secondary and nephrogenic. Both secondary and primary diabetes insipidus results from failure of the post-posterior lobe of the pituitary gland to secret anti diuretic hormone (ADH), which encourages the reabsorption of water by the kidney tubule. In nephrogenic diabetes insipidus, adequate ADH is present but the kidney tubule does not respond to its signal to reabsorb water from the urine. Nephrogenic diabetes – insipidus is a sex-linked recessive disorder. All forms of the disease are characterized by extreme polyuria and polydipsia but no polyphagia (Alice, 1997).

AETIOLOGY OF DIABETES

Heredity and diet are believed to play a major role in the development of diabetes. Diabetes results when the pancreas produces insufficient amounts of insulin to meet the body's needs. It may also arise when the pancreas produces insulin but the cells are unable to efficiently use it (insulin resistance). The excess sugar remains in the blood and its subsequently removed by the kidneys (Edell, 2001). There is at present no universally accepted explanation of the cause for spontaneous diabetes but a variety of factors have been implicated as being of causal importance in the development of diabetes. These include: heredity, virus infections, diet, immunological damages, etc.

HEREDITY:

Heredity plays a prominent role in determining one's risk of diabetes, but only as a predisposing factor and not an absolute determinant. Genetic factors play a much more important role in the Type 2 than the Type 1 diabetes e.g. the identical twin of a person who develops Type 2 diabetes after the age of 40 is almost

100% certain to develop the disease, but someone whose identical twin has the Type 1 diabetes runs only a 52% risk of also becoming diabetic. Parents with Type 1 diabetes face only a 2% risk of having a child with the disease, whereas the risk to the offspring of type 2 diabetic is about 10%. Genetic predisposition is apparently stronger in the case of Type 2 diabetes of the young with a 50% chance that the child of such a diabetic will also develop the disease (Harris *et al*, 1998).

VIRAL INFECTION

The evidence that viral infection might cause some forms of human insulin dependent diabetes mellitus is derived from epidemiological studies and isolated case reports. Studies in mice have shown that viruses can induce diabetes by two distinct pathogenic mechanisms. Destruction of pancreatic beta cells by direct cytolysis results from infection with the D variant of the EMC virus, Mengo virus 2T and coxsackie B4 virus, while induction of an autoimmune destructive process results from infection with reo virus Type 1 and rebella virus. The ability of virus, to induce diabetes in mice is dependent on the genetic background of the host as well as on the genetic make-up of the virus (Amer. Diabetes Assoc., 1997).

DIET

Dietary factors have been quoted as possible genesis for the rising incidence of insulin dependent diabetes mellitus in Northern Europe and North America. There are no direct available data relating diet after weaning to the development of diabetes in genetically susceptible children. However, two reports have provided circumstantial evidence supporting the proposition that dietary factors may at least in certain circumstances influence the development of human diabetes mellitus. Thus, an unusually high incidence of diabetes in boys born in the month of October in Iceland has been linked to the

high nitrosamine content of a smoked mutton traditionally consumed. In the second report, anti-gliadin antibodies were reported in 54% of children less than two years of age. In addition, studies using the spontaneously diabetic insulin dependent rats suggest that certain components of the diet may be essential for the expression of clinical diabetes in diabetes prone animals. Wheat and milk protein have been shown to have the strongest diabetogenic effect and are evidently capable of triggering the string of events which results ultimately in destruction of pancreatic islet insulin-secreting cells (Amer. Nat. Diabetes Data group, 1995).

IMMUNOLOGICAL DAMAGES:

Auto-immune reactions are also suggested as a cause for the beta cell destruction of the Type 1 diabetes. An immune response may be expressed by T-lymphocytes or by soluble antibodies in the blood or by both. Thus, these reactions may arise spontaneously or by a viral infection of the pancreas that leaves the islet tissues modified for attack (Dagogo *et al*, 1997). It is also clear that in both man and animals with spontaneous insulin dependent diabetes, the immune system retains the capacity to recognize and destroy transplanted insulin secreting cells indefinitely. The information below summarizes the evidence that insulin dependent diabetes is a slow autoimmune disease:

- Special gene linked genetic predisposition.
- Association with other autoimmune disorders.
- Circulating islet cell cytoplasmic and surface insulin auto-antibodies in new cases.
- Manonuclear cell infiltration of pancreatic islets resulting in selective destruction of insulin-secreting cells.
- Recurrence of insulin and selective destruction of insulin secreting cells in pancreas.

SYNTHESIS OF INSULIN

The immediate precursor of insulin is a molecule named proinsulin. It consists of insulin itself and a peptide loop that runs from A chain to the B chain. The loop is referred to as connecting peptide or C-peptide. The final step involves the clipping of the C-peptide form the proinsulin molecule. The synthesis of pre and pro insulin occurs on the rough endoplasmic reticulum and the folding is accompanied by disulphide bond formation shortly after synthesis. The newly synthesized polypeptide is then transferred via an energy dependent process from the rough endoplasmic reticulum to the golgi apparatus at which site cleavage to insulin begins (Makinson, 1980).

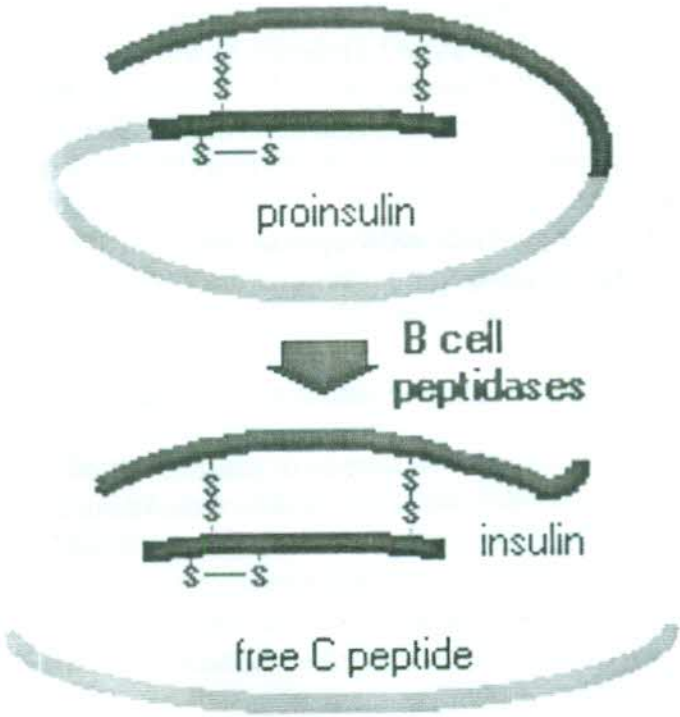


Fig. 1: Synthesis of Insulin (Source: Yudkin and Offord, 1980)

INSULIN SECRETION:

Insulin and the C-peptide are secreted in essential equimolar quantities and each is present in human serum. The secretion occurs at the surface of plasma membrane in an energy-dependent process in which the granule contents are liberated at the cell surface. The small amounts of proinsulin detectable in normal serum could lead to significant elevation of insulin in persons with normal pancreatic beta cells (White *et al.*, 1978). When the levels of glucose rise, the beta cells releases pulses of insulin which increases in frequency with increasing concentrations of glucose. These events are underpinned by cycles of change in electric potential across the cell membrane which in turn generates oscillations in the concentration of free calcium inside the cell. When the levels of calcium rise, insulin-containing granules move to the cell membrane and release their contents into the bloodstream. Under resting conditions, the membrane potential in beta cells is kept negative by potassium ion channels. These funnels through the plasma membrane allow potassium ions out of the cell. The exit of potassium ions allows the membrane to become depolarized (becomes less negative) and voltage – dependent calcium channels open. In this manner, the potassium – ATP channels control the set-point of beta-cell electrical activity and their modulation has direct bearing on the regulated release of insulin (Mark, 1999).

MECHANISM OF INSULIN ACTION

Insulin supplied to the blood occurs in a free state or as bound plasma proteins. Free insulin exerts influence on the metabolism of all insulin-sensitive tissues, while the bound insulin, acts on fat tissue only. Insulin sensitive tissues include muscular and connective tissues (fat tissue is a variety of connective tissue).The liver is less sensitive to insulin; nervous tissues are also less sensitive to insulin too. Mammalian insulin receptors of glycoprotein nature have been found in tissues. Thus, they are numerous in the cells with a more pronounced susceptibility to

metabolic insulin influence. The insulin-receptor complex is capable of drastically changing the cell membrane permeability for glucose, amino acids, Ca^{2+}, K^{+}, and Na^{+} or to be more precise, of accelerating the transport of glucose, amino acids, K^{+} and Ca^{2+} into the cell. A major cause of this effect is a membrane-oriented action of insulin on active transport systems and the influence of this hormone on the generation of second messengers. At present, it is believed that the effects due to insulin are mediated by one or more peptide second messengers. The cAMP(ubiquitous compound) play a role of second messenger and transmits the chemical signals through cascade of reactions (Fajan, 1971).

These peptides stimulate the transport of Ca^{2+} and glucose. The most distinctive feature of insulin is its ability to intensify the active transport of glucose to the cells of hormone-sensitive tissues. The mechanism of insulin-stimulated glucose transport, into the cells is far from being clear. Presumably, insulin either directly interacts with the protein made up of glucose channels in the membrane and opens "pores for glucose passage" or directly through cyclic nucleotides which affects phosphorylation of membrane, proteins and thereby the membrane permeability for glucose. The activation of Na^{+}/K^{+} pump which leads to increased Na^{+}/K^{+} membrane gradient facilitation , transport of amino acids into cell and fat tissues presumably favours glucose transport too (Stroev, 1989).

DIAGNOSIS OF DIABETES

Diabetes is detected by:

a. A fasting plasma or serum glucose test which measures blood glucose after at least 8 hours without eating. The test is used to detect diabetes.

b. An oral glucose tolerance test which measures blood glucose after at least 8 hrs without eating and 2 hrs

after drinking a glucose oral dose. This test can be used to diagnose diabetes or pre-diabetes.

c. A random plasma or serum glucose test, the blood glucose level is determined in relation to when the last meal was taken.

In all cases, the positive results are confirmed by repeating the fasting plasma or serum glucose and oral glucose tolerance tests on a different day. Diagnosis is usually prompted by onset symptoms of excessive urination (polyuria) and excessive thirst (polydipsia) often accompanied by weight loss. These symptoms typically worsen over days to weeks.

Another test being developed for type 1 diabetes detects some specific "Antibodies" (proteins of the immune system that attack foreign substances).This test may detect type 1 diabetes at an early stage reducing the risk of complications from the disease (NIH, 2005). Table 1 showed the FPG tests and diagnosis.

The diagnosis of other types of diabetes is usually accomplished in other ways. These include health screening, detection of hyperglycemia during other medical investigations; and secondary symptoms such as vision changes or unexplainable fatigue (WHO, 1999).

Table 1: Fasting Plasma Glucose Test (FPG)

Plasma Glucose (mg/dl)	Diagnosis
99 and below	Normal
100 to 125	Pre-diabetes
126 and above	Diabetes

Confirmed by repeating the test on a different day

Source: NIH publications, January, 2005.

COMPLICATIONS OF DIABETES

Diabetes mellitus of whatever type if left untreated may cause life threatening complications. Type 1 diabetes mellitus can result in diabetic coma (a state of unconsciousness caused by extremely high levels of glucose in the blood) or death. In both type 1 and 2 diabetes mellitus, complications may include among others blindness, kidney failure and heart diseases; it is primarily these complications that account for the heavy burden the disease inflicts on society and make it the third leading cause of death in the World. The most common complications are:

RETINOPATHY

Diabetics are twenty-five times more likely to become blind than non-diabetics for two reasons. Firstly, they are strongly predisposed to develop cataracts probably because the excess glucose in their blood polymerizes and is deposited in the lens of the eye (Arky, 1979). Secondly, because of the growth of tiny and poor-quality new blood vessels in the retina as well as macula, the blood flow and oxygen supply are impaired. This can lead to severe vision loss or blindness (Weiss, 2006)

NEPHROPATHY

In long-standing diabetes, the smallest blood vessels of nephrons (the functional filtration units of the kidney) frequently suffer the same type of damage as the blood vessels of the retina; this condition is called diabetic nephropathy. Severe diabetic nephropathy commonly leads to kidney failure and approximately 50% of people with type 1 diabetes die of kidney failure within 25yrs of the onset of diabetes (Drash, 1979). Diabetes mellitus is the most common cause of adult kidney failure worldwide.

PREMATURE ATHEROSCLEROSIS

Atherosclerosis (hardening of the arteries) is a condition in which arteries become progressively occluded (obstructed) by accumulation of cholesterol containing plaque. Although, it is

common in older non-diabetics, the diabetics tend to develop it earlier and in a more severe form. The most common effects of atherosclerosis are coronary artery diseases and stroke, which result when the blood supply to the heart muscle or the brain is obstructed by a plague within an artery. Coronary artery disease is the leading cause of death in long-term diabetics accounting for 75% of fatalities. Also, because of atherosclerosis and restricted blood flow, diabetics develop gangrene. (Kolata, 1979).

NEUROPATHY

Diabetic neuropathy symptoms may include muscle weakness, pain, local paralysis, urinary incontinence, sexual impotence (erectile dysfunction) and sensation of cold or heat in various parts of the body (Richard *et al;* 1990). Much evidence indicates that most of the complications of diabetes are caused by the great variations in blood glucose levels common in this disease. Even diabetics who take regular insulin injections exhibit wide fluctuations in their blood glucose levels in-marked contrast to the tightly controlled blood glucose levels observed in normal people. According to the prevalent hypothesis, the more a diabetic succeeds in controlling his or her blood glucose to a near-normal level, the less risk there will be of developing any complications of diabetes mellitus disease.

EPIDEMIOLOGY OF DIABETES MELLITUS

Diabetes mellitus is by far the most common of the endocrine disorders worldwide. It is widely distributed and the incidence of both types (IDDM and NIDDM) is on the increase throughout the world. However, the prevalence of both varies considerably in different parts of the world. This seems to be due to differences in both genetic environmental factors. Therefore, diagnostic criteria are arbitrary (Eugene, 2004). Population studies involving Pima Indians in Arizona and civil servants in Whitehall have shown that hyperglycemia represents an independent risk

factor for the development of disease of small and large blood vessels respectively. The current diagnostic criteria for diabetics of hyperglycemia have been shown to be associated with a significantly increased risk of disability and death from vascular disease irrespective of the basic cause of hyperglycemia.

The prevalence of the disease in Britain is between 1% and 2% but almost 50% of diabetes worldwide are non insulin dependent diabetes mellitus. In Europe and North America, the ratio of NIDDM: IDDM is 7:3. Thus, in Central and South America, Africa and parts of Asia, the prevalence rates are skyrocketing. It should not be surprising that this same issue is occurring not only in developed countries but increasingly within the developing world too (Eugene, 2004). The America Diabetes Association reported in the 2003 assessment of the National Centre for Chronic Disease Prevention and Health Promotion that 1 in 3 Americans born after 2000 develop diabetes in their lifetime (Narayan, 2003).

DIABETES MELLITUS THERAPY

Once diabetes is diagnosed, treatment consists of controlling the amount of glucose in the blood (normalization of glucose in blood) and preventing complications. The immediate goals of treatments are to stabilize the metabolism, restore normal body weight and eliminate the symptoms of high glucose. The long-term goals are to prolong life, improve the quality of life, relieve symptoms and prevent long-term complications through careful dietary management, weight control, medication, physical activity (exercise), self-testing and education (Bevier *et al;* 1995).

DIETARY MANAGEMENT

This is one of the most effective ways for treating or managing diabetes through meal planning. The meal planning involves choosing healthy foods, eating the right amount of food, and

meals at the right time. The American Diabetes Association and American Dietetic Association developed six food exchange lists for the purpose of people with diabetes. The lists include: starch or bread, meat and substitutes, vegetables, fruits, milk or dairy and fat and calories for the recommended daily intake. The exchange list also show the number of food choices that can be eaten at each meal. Using the foods on the list, the distribution of calories can be controlled throughout the day so that food and insulin function will be balanced (Encyclopedia of Diabetes, 2001).

Meal plans differ depending on the type of diabetes. Within IDDM (Type 1), consistency in the time of meals eaten and the amounts, types of food intake is important to allow food and insulin drug to work so as to regulate the blood glucose levels (Edell, 2001).

MEDICATION

There are three main approaches available as medications for the management or treatment of diabetes mellitus viz: Insulin Therapy, Oral drug therapy and phytotherapy.

INSULIN THERAPY

Insulin is available in a variety of formulations. These preparations differ from one another with respect to time course of action, route of administration, concentration, source of insulin and degree of purity. There are six basic preparations of insulin: natural insulin and five modified insulin. The modified ones are slower in onset than native insulin and have longer duration of action. The time course of the modified insulin has been extended by two processes viz: complexing insulin with a protein and altering the physical state of insulin itself (Richard *et al*, 1990). When classified according to time course of action, the basic insulin preparations fall into three groups: rapid-acting, intermediate-acting and long-acting. Regular insulins are rapid-acting preparations (6-16hrs) while isophane insulin

suspensions are intermediate acting insulin (24hrs). The long-acting insulin are protamine zinc insulins (36hrs).

The principal treatment of type 1 diabetes, even from the earliest stage, is replacement of insulin combined with careful monitoring of blood glucose levels; using blood testing monitors. Without insulin, diabetic ketoacidosis can develop and may result in coma or death.

DRUG THERAPY

Medications to control blood sugar are pills usually taken once or twice per day and there are many new drugs on test. These medications generally work by preventing the body from releasing sugar into the bloodstream, when insulin is not working properly; more than required insulin is released into bloodstream thereby clearing glucose from bloodstream into the cell. Novel oral drugs such as sulfonylreas, biguanides, glycosidase inhibitors and thiazolidinediones (TZDs) are also in various stages of testing (Bailey, 1999). The first insulin sensitizers are already in use (Evan and Rusan, 1999).

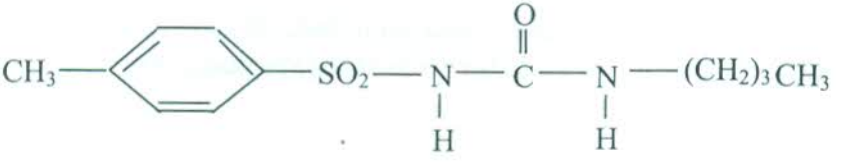
Recent studies into how insulin is released from pancreatic cells have led to the development of several new drugs that enhance this process. Some of these, like repaglinide, are already available with many others still in development. The success of insulin sensitizers like the biguanides and thiazolidinediones have lead to the discovery of new type of insulin sensitizers that work slightly in different ways. The discovery that thiazolidinediones work by activating a protein called gamma PPAR (gamma peroxisome proliferators-activated receptor) has spurred several companies to develop drugs that activate gamma PPAR in different ways (Bailey, 1999).

A number of drug options are available for treating type 2 diabetes but are not effective for type 1 patients. They are:

a. Sulfonylurea

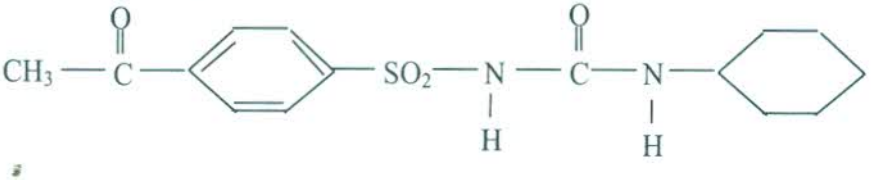
The sulfonylureas are derivatives of the sulfonamide antibiotics but lack antimicrobial activity. They are subdivided into first generation and second generation agents. The principal difference between the two groups lies with their potencies: the first generation drugs are much more effective than the second generation drugs. However, although differences in potency are large, such differences are of minimal clinical significance.

Tolbutamide is an example of first generation sulfonylurea. It produces its initial effects by simulating release of insulin from pancreas. With prolonged use, tolbutamide offers the additional benefits of enhancing cellular sensitivity to insulin. Although the mechanism of this effect is not known, one hypothesis is that chronic tolbutamide increase the number of insulin receptors (Shinkai, 1999).

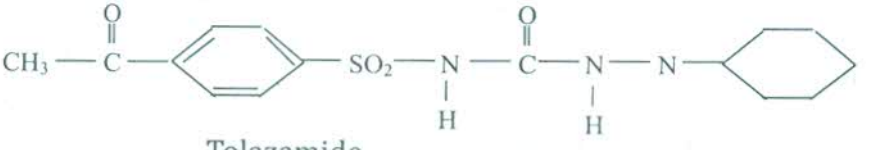


Tolbutamide (Orinase)

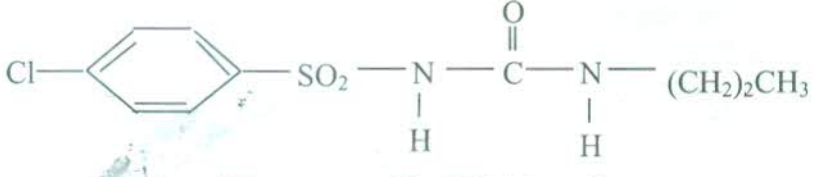
(1^{ST} Generation)



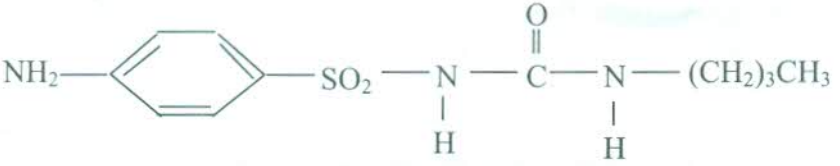
Acetohexamide (Dymelor) (1^{ST} Generation)



Tolazamide

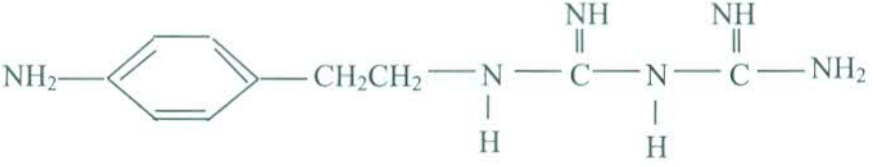


Chlorpropamide (Diabinese)



Carbutamide

b. Biguanides: Metformin (Glucophage) and phenformin are in this category. They inhibit the production and release of glucose from liver. Their advantage is that they tend to cause less weight gain than other drugs. Side effects include a metallic taste in mouth, nausea, pain and diarrhea. Others include lactic acidosis and impaired kidney function (Shinkai, 1999).



Phenformin

c. Alpha-glycosidase inhibitors: These drugs blocks the action of enzymes in the digestive tract that breakdown carbohydrates hence sugar is absorbed slowly into bloodstream. Drugs in this category include acarbose, miglitol. Side effects include diarrhea and liver damage (Vinik *et al*, 2004).

d. Thiazolidinediones (TZD)

These drugs make the body tissues more sensitive to insulin and prevent liver from overproducing glucose. Side effects include

swelling, weight gain and fatigue. A far more serious potential side-effect includes diarrhea and liver damage (Vinik *et al*; 2004).

DRUG COMBINATION

Drugs from different classes are combined to effectively control the blood sugar levels. In this case, newer medications such as Glucovance were developed. The drug contains both glyburide and metformin. Again towards the same direction, there is considerable interest in discovering drugs that could block the auto-immune responses. Such drugs are useful in the treatment as well as management of type 1 diabetes mellitus. The drugs are also useful in the control of auto-immune diseases such as multiple sclerosis and rheumatoid arthritis. The principal goal of the drug action is to delay the progression of the full-blown disease (Rosen and Evan 2001).

EMERGING THERAPIES FOR DIABETES MELLITUS

It is clear that no method now available for treating diabetes really restores the metabolic pattern to nearly normal. The precise control of metabolism provided by the interlocking secretion of insulin, glucagon, growth hormone, corticosteroids and catecholamine cannot be reproduced even roughly by the parental administration of insulin or the oral hypoglycemic agents as they are now used. Recognition of the inadequacy of current treatment regimens with respect to the persistence of metabolic abnormalities as well as the increasing frequency of long-term complications of diabetes has led to a search for new approaches to treatment. Efforts are directed at five possible modalities: use of implantable insulin pumps, insulin inhalers, islet cell transplantation, phytotherapy and gene therapy (Rosen and Evan, 2001).

IMPLANTABLE INSULIN PUMP

Researchers are working hard to develop an implantable insulin

pump that can measure sugar levels and deliver the exact amount of insulin required. This will make it possible to mimic the action of natural insulin delivery. However, the major problem remains the development of a glucose sensor which may be implanted under the skin. Other studies have shown that pre-programmed continuous infusion procedures may be effective in the absence of a glucose sensor. Most recently, normalization of blood glucose has been achieved in juvenile diabetes with a portable insulin infusion pump with which insulin is administered subcutaneously (Edell, 2001).

INSULIN INHALERS

Although daily insulin injection will still be needed, inhaled insulin is currently in clinical trials and these inhalers are about the size of a flash light and uses rapid action insulin. The sprayed insulin passes quickly into the bloodstream to exert its effects (Edell, 2001)

NEW INSULINS

In the past few years, three new formulations of insulin emerged which were designed to offer the advantages of simpler regimens and better glucose control for people whose cases must be treated absolutely with insulin.

Glargine:- (from Averitis Co) is a basal insulin, offering a more continuous activity with much less of a action than natural insulin. It can be used with very rapid acting insulin such as lispro or aspart to provide a flatter basal amount of insulin. Until now, this development has been possible with twice daily injections of the basal rate of insulin pump. Glargine application tries to permit a more normal meal-time pattern.

Aspart:- (from Nov Nordick Co) is a very rapid acting insulin that can be injected 15mins prior to eating. Its fast action also allows

more freedom in the timing of meals and the amount of food eaten.

A 75/25 lispro mixture:- (from Eli Lilly Co) contains Lily's very rapid acting lispro and a novel human insulin analog. It is designed for those who need better control after meals and want to use an insulin pen. (Edell, 2001)

ISLET CELL TRANSPLANTATION

Islet cells of the pancreas are the insulin-secreting cells. While whole pancreas transplantation continued to be used in certain circumstances, the shortage of suitable organs and the risks of lifelong immunosuppressant (which leaves the patient vulnerable to serious infections) have prevented this procedure from being widely used. Attempts at pure islet cell transplantation in the past have been disappointing but a recent study has renewed excitement in this procedure. To this end, several procedures for isolating, culturing and implanting islet cells have been worked out but improvements are still needed. Perhaps the most exciting technology of recent is the use of **stem cells derived from pancreatic ducts.** Stem cells are immature cells that can be renewed indefinitely and can be induced to form mature pancreatic beta cells. Thus, they would provide unlimited source of beta cells for transplantation. There have been recent successes with this technology in reversing the type 1 diabetes in mice. (Rosen and Evan, 2001).

GENE THERAPY

Two recent reports described research into gene therapy for different aspects of diabetes. These reports are in the forefront of research outcome from decoding of the human genome.

a. Scientists have identified a gene called ship 2 that appears to regulate insulin. Such findings make ship 2 a potential gene therapy target for the treatment of

type 2 diabetes aimed at improving the individual's insulin regulation.

b. A protein that blocks the overgrowth of blood vessels in the eye is being studied as possible gene therapy for diabetic retinopathy. A recent study showed that treatment with the protein called pigment epithelium derived factor (PEDF) prevented excessive new blood vessel formulation in an animal model. It may also be used to treat muscular degeneration (Rosen and Evan, 2001).

PHYTOTHERAPY

Recently there has been an explosion of research concerning the health benefits of phytochemicals in herbs especially the medicinal herbs and it was concluded that, the higher the consumption of fruits and vegetables, the lower the risk of having any chronic disease such as cancer and diabetes mellitus. Conversely, those who ate few fruits and vegetables are more likely to die prematurely. Many phytochemicals which are biochemically active belongs to the group known as flavonoids, saponins, alkaloids, lignins and tannins. These compounds are usually bitter and so horticulturists have investigated these compounds over the years (Duke, 1998). Thus, many of the phytochemicals are hypoglycemic agents. Many of such phytochemicals are available with us today as herbal medical remedies (Farnsworth, 1994). Saidu *et al,* (2012c) also had similar findings on the effect of aqueous extract of A. occidentale leaf in Normoglycemic rats. Another work by Saidu *et al* (2012d, 2014a and 2014b) indicated that Blighia sapida root bark extract, Azadirachta indica leaf and Cucumis sativas fruit pulp are reach in phytochemicals and were found to possess antidiabetic properties.

The majority of the plants has moderate action and can be useful in mild cases of diabetes, perhaps combined with a diet poor in

anti diabetic agents. In some cases, their prolonged use might delay the establishment of a more serious diabetic disease. In more severe cases, the plants can be used as an accessory treatment, making it possible to reduce the frequency and the dosage of insulin or other orthodox drugs.

PROMISING ANTI-DIABETIC HERBS

Investigations have been carried out on over 60 herbal extracts in a special cell culture to determine how much a particular compound stimulates the update and utilization of glucose. While these tests are not substitutes for human or animal studies, they are important because they identify safe compounds that act directly on the metabolism of cells. Plenty of plants and their phytochemicals can lower blood sugar levels but may accomplish it by imposing toxic effects on the body. From the investigations, Cinnamon was by far one of the most effective extract followed by Haxelgreen and black tea, from the extract of commercial cinnamon; new phytochemicals called chalcone polymers were identified. These polymers increase glucose metabolism in the cell 20 folds or more. Chalcone polymers are also anti-oxidants that strongly inhibit the formation of reactive oxygen species in activated blood platelets. Thus, they are also applicable to diabetic complications. The Goatsrue (*Galega officinallis*) has been tested in humans and was found very effective but still under toxicological investigations. It contains a guanidine derivative that is similar to the synthetic pharmaceutical hypoglycemic biguanide medications (Duke, 1998). While hypoglycemic herbs may offer promise in the treatment of diabetes in their combined effect with insulin, treatment is inherently disruptive a times and extreme caution must be taken in order to promote a smooth transition, maintain suitable sugar levels. Some of the promising hypoglycemic herbs are presented in Table 2 below:

Table 2: Promising Antidiabetic Plants

Scientific Name	Common Name	Use
Agrimonia pitosa	Hairy Agrimony	Hypoglycemic
Alisma plantageaquatica	Great water plantain	Hypoglycemic
Allium cepa	Onion	Hypoglycemic
Allium sativa	Garlic	Hypoglycemic
Allium cepaaggrefatum	Potato onion	Hypoglycemic
Allium cepaascalonicum	Shallot	Hypoglycemic
Allium cepaproliferum	Tree Onion	Hypoglycemic
Adiantum capillus-veveris	Adiantum plant	Hypoglycemic
Anacardium occidentale	Cashew leaves	Hypoglycemic
Andrographis paniculata	Kirata leaves	Hypoglycemic
Arctium lappa	Burdock roots	Hypoglycemic
Atriplex halimus	Salt Bush leaves	Hypoglycemic
Argyreia cuneata	River	Hypoglycemic
Anemarrheria asphodeloides	Zhi Mu	Hypoglycemic
Arctin minus	Lesser Burdock	Hypoglycemic
Astragalus membranaceuos	Huang Qi	Hypoglycemic
Astratylodes japonica	Japanese Atractylodes	Hypoglycemic
Bideus pilosa	Acestilla Plant	Hypoglycemic
Blighia sapida	Akee apple plant	Hypoglycemic
Brassica oleracia	Cabbage	Hypoglycemic
Cecropia optusitolia	Guarumo Leaves	Hypoglycemic
Coccima grandis	Coccinia roots	Hypoglycemic
Coccina indica	Ivy gourd	Hypoglycemic
Corchorus olitorius	Jute leaves	Hypoglycemic
Cautarea latifkra	Copalchi root	Hypoglycemic
Outarea sativus	Cucumber fruit	Hypoglycemic
Cumimum cyminium	Cumin Seed	Hypoglycemic
Cichorium intybus	Chicory	Hypoglycemic
Cirrsium ochrocentrum	Yellow thistle	Hypoglycemic
Coix lacrymajobu	Jobis Tears	Hypoglycemic
Cenyea canadensis	Canada Fleabane	Hypoglycemic
Cynara scolymus	Globe Artichoke	Hypoglycemic
Drosera rotundifolia	Sundew	Hypoglycemic
Elentherococcus senticosus	Siberian Ginseng	Hypoglycemic
Epimedium grandiflorum	Barrenwirt	Hypoglycemic
Eucalyptus globules	Tasmanian	Hypoglycemic
Euonymus alatus	Winged Spindle Tree	Hypoglycemic
Galega officinalis	Goats Rue	Hypoglycemic

Gynostemme peutaphyllum	Sweet Tea Vine	Hypoglycemic
Gymnema sylvsetre	Gymnena leaves	Hypoglycemic
Hordeum vilgare	Barley	Hypoglycemic
Hydrophila auriculata	Barleria Plant	Hypoglycemic
Hydrastis canadensis	Goldenseal root	Hypoglycemic
Honhuynia cordata	Tsi	Hypoglycemic
Inula helenuim	Elecanpane root	Hypoglycemic
Lablab purpureus	Hyacinth bean	Hypoglycemic
Lactuca sativa	Lettuce	Hypoglycemic
Latus corniculatus	Birds foot Trefoil	Hypoglycemic
Lotus albus	White Lupin	Hypoglycemic
Lycium barbarum	Box Thorn	Hypoglycemic
Lycium chinere	Chinere Boxthorn	Hypoglycemic
Lycopus virginicus	Bugleweed	Hypoglycemic
Lythrum salicaria	Purple Loose strife	Hypoglycemic
Morus alba	White mulberry	Hypoglycemic
Morus nigra	Black Mulberry	Hypoglycemic
Musa sapientum	Banana flowers & roots	Hypoglycemic
Nymphaea lotus	Lotus roots	Hypoglycemic
Nasturtium officinale	Watercress	Hypoglycemic
Nasturtium x sterile	Brown watercress	Hypoglycemic
Ocimium sanctum	Sacred basil plant	Hypoglycemic
Oleo europaea	Olive	Hypoglycemic
Opuntia spp	Pear stems and fruit	Hypoglycemic
Panax ginseng	Ginseng	Hypoglycemic
Panax pseuduginseng	San Q1	Hypoglycemic
Phaseolus vulgaris	French bean	Hypoglycemic
Phellodendran amurense	Amur cork tree	Hypoglycemic
Phellodendran chinese	Chinese cork tree	Hypoglycemic
Platycodan grandiflorus	Balloon flower	Hypoglycemic
Polygonatum odoratum	Solomon's seal	Hypoglycemic
Potentilla erecta	Tormentil	Hypoglycemic
Rehmania glutinosa	Chinese foxglove	Hypoglycemic
Rosa multiflora	Japanese rose	Hypoglycemic
Scoparia dulcis	Sweet brain leaves	Hypoglycemic
Syzygium jambolanum	Jambul seeds	Hypoglycemic
Spinacia oleracea	Spinach leaves	Hypoglycemic
Tecoma stans	Tronadora leaves	Hypoglycemic
Trigonella foenumgraecum	Fenugreek	Hypoglycemic
Triticum sativum	Wheat leaves	Hypoglycemic

Urtica pilulifera	Roamn nettle	Hypoglycemic
Urtica dioica	Stinging nettle	Hypoglycemic
Urtica urens	Annual nettle	Hypoglycemic
Vaccinium caepitosum	Dwarf bilberry	Hypoglycemic
Vaccinium membranaceum	Mountain huckleberry	Hypoglycemic
Vaccinium ovalifolium	Black huckleberry	Hypoglycemic
Vaccinium ovatum	Evergreen huckleberry	Hypoglycemic
Vaccinium parvifolium	Red bilberry	Hypoglycemic
Vaccinium scoparium	Grouse berry	Hypoglycemic
Vaccinium uliginosum	Bog bilberry	Hypoglycemic
Vitis vulpine	Frost grape	Hypoglycemic
Xanthium strumerium	Cackle bur	Hypoglycemic
Zea mays	Sweet corn	Hypoglycemic

Source: WHO Technical Report Series 727, Geneva, 1985

MY ROLE

In view of the foregoing, it is pertinent that diabetes mellitus had become a devastating disease that needed much attention with respect to research into alternative ways of managing it especially by screening potent plants or herbs that are efficacious and can be used as possible candidates for drugs in future. Therefore, the urge for therapeutic solutions for diabetics has made me to expend my time on diabetes research which will be highlighted in the remaining part of my lecture. To accomplish my desire, my attention was drawn to the plants that abound all over the places that may have antidiabetic potentials. In this study, we began by screening for hypoglycemic properties in Six (6) plants as presented in Table 3 below:

Table 3: List of Plants Analysed

S/N	Plant Scientific Names	Local Name			Part used
		Hausa	Yoruba	Igbo	
1	*Zyzzipus spinachristi*	Kurna	Ekannase-adie	Ogirili	Leaf
2	*Artemisia herba-alba*	Tazargade	Eemo	Akidi muo	Leaf
3	*Terminalia glaucescens*	Baushe	Idi Odan	Edo	Leaf
4	*Moringa oleifera*	Zogale	Ewe-ile	Okwe Oyibo	Leaf
5	*Blighia sapida*	Gwanja kusa	Isin	Okpu	Leaf
6	*Anacardium occidentale*	Yazawa	Kaju	Kausu	Leaf

In order to probe into the medicinal potentials of the plants chosen, it is important to screen the plants for possible phytoconstituents. Thus, the findings are presented in table 4 below:

The Phytochemicals in Different Plant Extracts

The results of phytochemicals detected in different plant extracts are as presented in Table 4. All the six plants showed presence of some phytochemicals.

Table 4: Phytochemicals detected in the different plant extracts

Plants	Alkaloid	Anthraquinones	Tannias	Saponins	Phlobatannins	Resins	Vol. oils	Flavonoids	Terpenes	Cardiarc glycosides	Indole alkaloids	Cyanophoric	Balsams
Zizzypus spinachristi	-	++	+++	++	-	+	+	+++	+++	-	-	-	-
Artemisia herba-alba	++	++	++	++	-	-	-	++	-	-	+	+	-
Terminalia glaucescens	++	++	++	-	-	-	+	++	-	-	++	-	-
Moringa oleifera	+++	++	+++	++	-	-	-	+++	-	-	+	+	-
Blighia sapida	++				-	-	-	+	+	+	+	-	-
Anacardium occidentale	++	++	++	++	+	-	+	+	++	+	+	+	-

Keys: +++ = Highly positive - = Negative.

++ = Moderately positive

+ = Faintly positive

Analyses of the Crude Plant Extracts

The percentage aqueous crude extracts yield of the six plants analyzed are given in Table 5. The values ranged from 20% to 70%. The lowest yield (20%) was obtained from *Zizzipus spinachristi* while the highest (70%) was obtained from the Anacardium *occidentale* Leaf.

Table 5: Percentage Aqueous Crude Extract Yield of the Plants used

Plant Extracts	Crude extract yield %
Zizzypus spinachristi	20
Artemisia herba-alba	60
Terminalia glaucesceus	55
Moringa oleifera	50
Blighia sapida	40
Anacardium occidentale	70

The crude extract was obtained from the leaves of the plants.

Safe Doses and Clinical Observations at Higher Doses

The safe doses and clinical observations at higher doses are as shown in Table 6. The aqueous extract of *A. occidentale* leaf had the lowest safe dose (300mg/kg bwt) while the aqueous extract of *Zizzypus spinachristi* leaves had the highest safe dose (900mg/kg bwt). At safe doses, the rats showed no apparent clinical adverse side effects when orally administered. However, at higher doses, similar clinical manifestations were observed for all the extracts.

Table 6: Safe Dose and Clinical Observations of Aqueous Leaf Extracts of the Plants in rats

Plant leaf (Aqueous extract)	Safe doses (mg/kg b.wt p.o)	Observation at higher doses (mg/kg bwt)
Zizzypus spinachristi	900	At>1000 weakness, drowsiness, mortality
Artemisia herba-alba	525	At>650 Weakness, intense drowsiness, mortality
Terminalla glaucesceus	550	At>600 Weakness, drowsiness, mortality
Moringa oleifera	500	At>600 Weakness, salivation, mortality
Blighia sapida	400	At>500 Weakness, diarrhea, mortality
Anacardium occidentale	300	At>300 Weakness, intense drowsiness

BW = Body Weight P.O = Per-Oral

The Percentage Glucose Reduction of Different Plant Aqueous Extract

The results of the glucose reduction ability of different plant extracts tested on alloxan induced rats are indicated in Table 7. The aqueous extract of *Anacardium occidentale* and *Moringa oleifera* leaves had the highest percentage glucose reduction of 74.2% and 74.0% respectively, while *Artemisia herba-alba* had the lowest percentage glucose reduction (43.4).

Table 7: Percentage Glucose Reduction of Aqueous Leaf extracts of the Plants in Alloxan induced rats

Plant (Aqueous Extract)	% glucose reduction (Alloxan-induced models)
Zizzypus spinachristi	43.7
Artemisia herba-alba	43.4
Terminalia glaucesceus	44.3
Moringa oleifera	74.0
Blighia sapida	51.2
Anacardium occidentale	74.2

The aqueous extract of the A. occidentale leaf indicated a promising antidiabetic potential. Thus, the ethanol extracts (200mg and 300mg/kgbwt) were further subjected to bioassay guided fractionation for a pure and potent fraction(s). The findings are as presented in Table 8 below:

Hypoglycemic Effect of Column Fractions of *A. occidentale* leaf

Table 8 below showed the percentage glucose reduction of the column fractions of *Anacardium* at varying doses. Ethylacetate fraction at both 200mg and 300mg showed high percentage glucose reduction (54.1 and 59.6) when compared to the oral hypoglycemic drug-metformin (500mg/kg b. wt). The

ethylacetate fraction at 300mg/kg b.wt had a higher activity than the metformin drug.

Table 8: Hypoglycemic Effect of Column Fractions of *Anacardium occidentale* Leaf

Fractions/Drug	% glucose reduction
Ethylacetate Fractions (300mg)	59.6
Ethylacetate Fractions (200mg)	54.1
Ethylac: Ethanol Fractions (300mg)	53.5
Ethylac: Ethanol Fractions (200mg)	50.2
Ethanol Fractions (300mg)	0.72
Ethanol Fractions (200mg)	0.33
Metformin (500mg)	54.1

To further confirm the efficacy of the ethanol extract, rats were administered higher doses (2000,4000,6000mg/kg.bwt) for a period of six weeks and results were as shown in Table 9:

Biochemical Parameters of Rats Administered ethanol Extract of *A. occidentale* Leaf

Table 9 below showed biochemical parameters namely ALT, AST, total protein, creatinine and urea of rats administered ethanol extract of *A. occidentale* leaf. The ALT and AST activity decreased for all the groups at the end of 6 weeks study period while the total protein decreased at the end of 6 weeks study period for all the groups. The creatinine and urea levels increased for all the groups.

Table 9: Biochemical Parameters of Rats Administered Ethanol Extract of *A. occidentale* leaf

Parameters	Control		Group I		Group II		Group III	
	0	42	0	42	0	42	0	42
ALT (U/L)	49.94±0.2	49.73±0.3	50.12±0.5	48.27±0.2*	49.93±0.8	46.39±0.2**	50.49±0.4	41.88±0.9+
AST (U/L)	52.8±0.4	53.4±0.1	53.0±1.2	51.7±0.5*	52.5±2.0	48.2±0.6**	52.6±1.6	44.5±0.6+
Total protein (g/dl)	6.76±0.01	6.74±0.04	6.84±0.04	6.29±0.04	6.79±0.207	6.36±0.05	6.82±0.05	6.39±0.09
Creatinine (mmol/l)	10.3±0.1	14.5±0.2	15.3±0.21	17.2±0.12*	15.1±0.31	16.8±0.118**	18.5±0.21	19.1±0.22+
Urea (mmol/l)	32.1±0.21	35.3±0.11	30.4±0.2	34.3±0.41*	36.2±0.21	37.2±0.2**	39.1±0.22	40.1±0.11+

Source: Saidu *et al*, 2012a

The Values are expressed as mean ± SEM

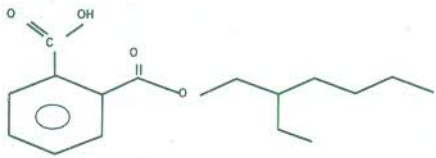
Group I (rats fed 2000mg) Vs Control
Group II (rats fed 4000mg) Vs Control
Group III (rats fed 6000mg) Vs Control

Spectral Analyses of Ethylacetatate (300mg/kg.bwt) Fraction of A. *occidentale* leaf Gas Chromatography-Mass Spectroscopy and Infra Red

The spectral analyses of the most active hypoglycemic fraction (ethyl acetate) of *A. occidentale* leaf are presented in Figs 4.67 and 4.68. The GC-MS and IR spectral techniques indicate the presence of an ESTER as the likely active principle (Fig. 4.67). The ester found in the fraction had the following structure based on the National Institute of Science and Technology library Database search (Saidu *et al*, 2012b). The Maytenus senegalensis also revealed the presence of esters as the major phytoconstituents and antidiabetic principles (Mann *et al*, 2014).

1. 1, 2 - Benzenedicarboxylic acid, mono (2-ethylhexyl) ester-MEHP
2. $C_{16}O_4$

3. M.wt = 256.1688
4. Cas No = 4376-20-9

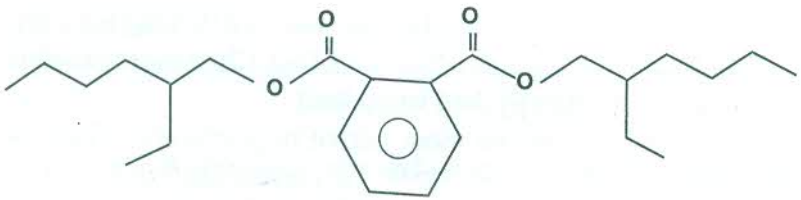


1,2 – Benzenedicarboxylic acid, mono(2 - ethyl)ester

Formula	$C_{16}H_{22}O_4$
Molecular wt.	278
CAS No.	4376 - 20 - 9

Another ester found is:

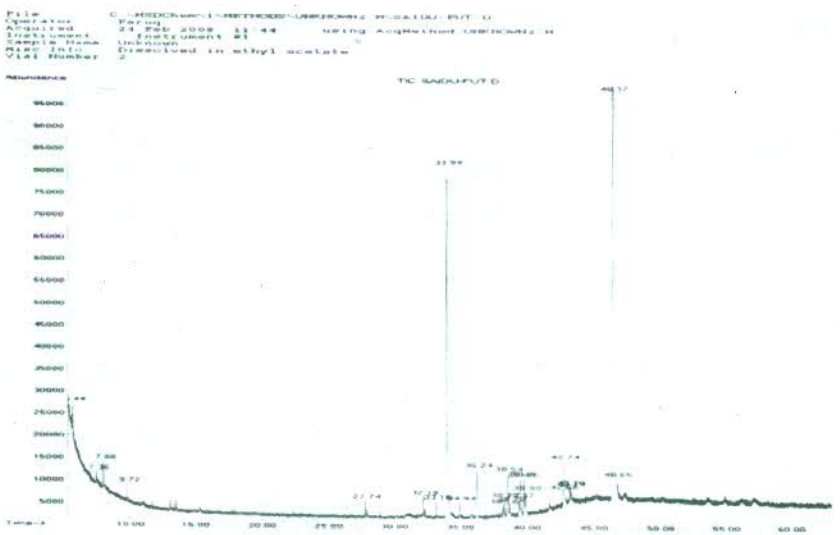
1. Bis (2-ethylhexyl) phthalate – DEHP
2. $C_{24}H_{38}O_4$
3. M.wt = 390.5561
4. CAS No 117-81-7



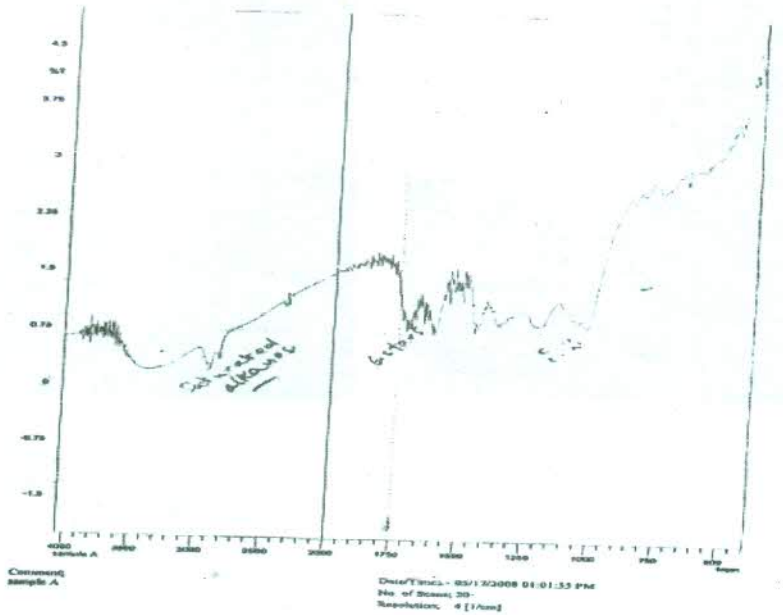
Bis (2-ethylhexyl) phthalate

Formula	$C_{24}H_{38}O_4$
Molecular wt.	390
CAS No.	117-81-7

Source: Saidu *et al*, 2012b)



GC-MS spectrum



IR SPECTRUM

Histopathology of Organs (Liver and Kidney)

Plates I - IV showed the micrographs of liver. Plate I showed the control with the portal triad and sinuses unaltered. The hexagonal structures of the hepatic cells as seen are noticeable. Plates II, III, IV depict rats administered crude ethanol extract of *A. occidentale*. There was degeneration of hepatic cells.

Plates V - VIII depicts the micrographs of kidney. Plate V indicates the control with normal distributions of glomeruli tubules and vascular channels. Plates VI, VII and VIII showed kidney micrographs of rats fed crude ethanol extract of A. occidentale. There was intense necrosis and glomerular tubular damage.

Plate I: Liver section from control rat (x100) Typical normal portal area with portal Vein and hepatic arteria. Hepatic lobule with central vein are clear. No obliteration of *canaculi* spaces

Plate II: Liver section from rat treated with 2000 mg/kg bwt of ethanolic extract A. *occidentale* for 42 days (x100). Cellular edema seed, cell necrosis and degeneration observed

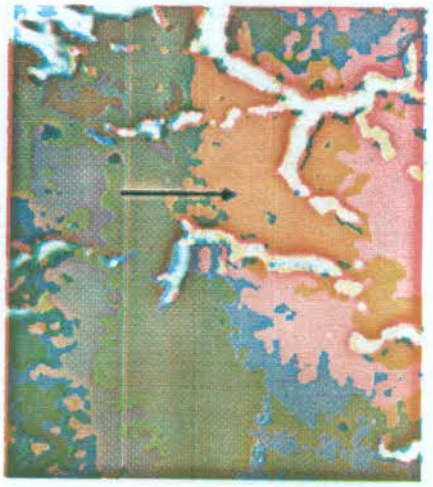


Plate III: Liver section from rat treated with 4000 mg/kg bwt of ethanol extract A. *occidentale* for 42 days (x100). Necrosis more pronounced

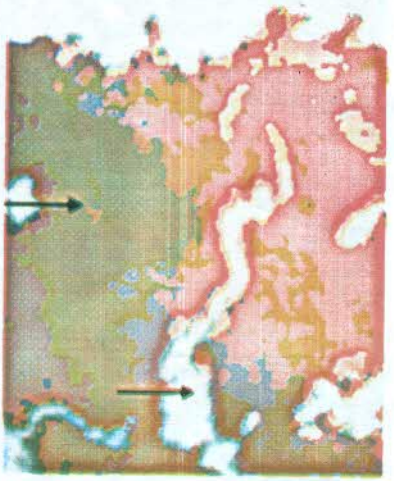


Plate IV: Liver section from rat treated with 6000 mg/kg bwt of ethanolic extract A. *occidentale* for 42 days (x100). Mesangial expansion observed

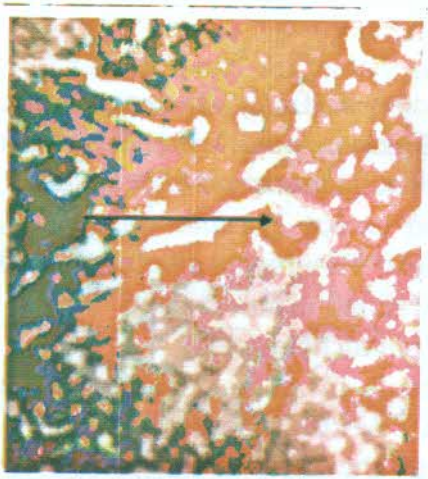


Plate V: Kidney section from control rat (x100). Numerous tubules clearly lie adjacent to glomerulus

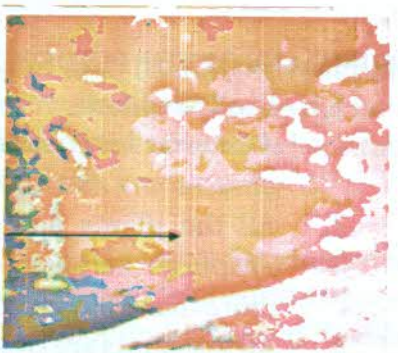


Plate VI: Kidney section from rat treated with 2000mg/kg bwt of ethanol extract of *A. occidentale* for 42 days (x100). Patches of tubular necrosis seen in medulla interstition space

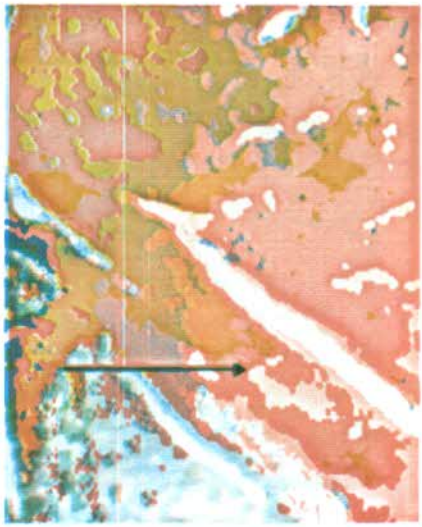


Plate VII: Kidney section from rat treated with 4000 mg/kg bwt of ethanol extract of *A. occidentale* for 42 days (x100). Necrosis more

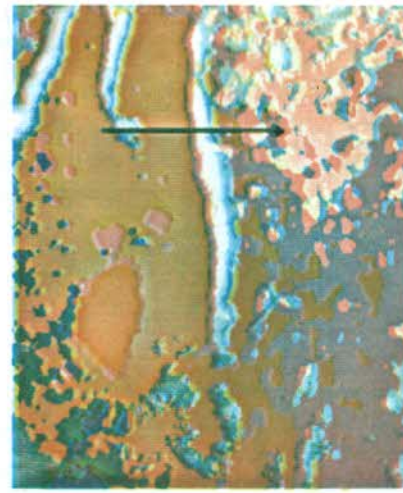


Plate VIII: Kidney section from rat treated with 6000mg/kg bwt of ethanol extract of *A. occidentale* for 42 days(x100). Mesangial expansion observed

SUMMARY OF THE FINDINGS

1. In all, six plants were analyzed namely: *Moringa oleifera, Artemisia herba-alba, Zyzzipus spinachristi, Terminalia glaucescens, Anacardium occidentale* and *Blighia sapida.*
2. All the plants analyzed except *Zyzzipus spinachristi, Artemisia herba alba* and *Terminalia glaucesens* had more than 50% glucose reduction potentials.
3. All the plants are rich in phytochemicals.
4. The bioactive components in *A. occidentale* contain esters which are known to be insulin sensitizers.
5. The mode of action of the active principles is by activation of gamma peroxisome proliferator receptors (gamma-PPARs) which facilitates insulin recognition by receptors.

6. Histopathology of the kidney and liver tissues revealed pronounced lesions at *A. occidentale* doses ≥ 2000mg/kg bwt indicating its toxic effects.
7. *A. occidentale* posses the highest significant antidiabetic activity compared to other plants. Hence could be exploited as a phytocandidate for sustainable healthcare.

CONCLUSION

In conclusion, diabetes mellitus is a medical condition which can be proficiently managed by the application of purified phytoconstituents derivable or harvested from potent hypoglycemic plants.

RECOMMENDATIONS

From the findings of this research, it is clear that a lot needed to be done in the area of medicinal plants research so as to further exploit the available natural endowment for a sustainable healthcare. Consequently, I recommend as follows:

1. There is need for policy makers and health intervention agencies to refocus on a workable or realizable policy on the non communicable diseases as against the current trend where the focus is mainly on communicable diseases.

2. Diabetes as a disease undermine output in the society in terms of service delivery and may lead to undesirable ill effects hence the need for synergy between relevant bodies like World Health Organisation (WHO), International Diabetes Foundation (IDF) and World Diabetes Foundation (WDF).

3. For sustainable healthcare, the pharmaceutical industries should partner with Universities in the area of antidiabetic drug development.

4. The Nigerian Government should as a matter of urgency set up Medicinal plant hubs at different locations in the country to boost the research in alternative medicine like India and China.

These recommendations if fully implemented will address the challenges faced by diabetics and a sustainable healthcare driven policy will be achieved.

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have in me as your staff. I humbly congratulate you for a very successful tenure (2012-2017) with huge landmark achievements.

I wish to express my profound appreciation to my brothers, Alh. Mohammed Mohammed, Mal. Yahaya Kudu Saidu, Barr. Baba Saidu, Mal. Alfa Saidu, Alh. Sani Abubakar, my amiable sisters and others too numerous to mention. Your support is strongly acknowledged.

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A BRIEF PROFILE OF THE INAUGURAL LECTURER

Prof. Abubakar Ndaman Saidu was born on 1st September, 1963 in Bida to the family of Alhaji Saidu and Mallama Aminat. The little Abubakar attended North Primary School (now Masaba), Bida from 1969 to 1976. On completion, he gained admission into the famous and prestigious Government College, Bida where he had his post-primary education from 1976 to 1981. He then proceeded to University of Sokoto in 1981 and graduated with a Bachelor of Science (B.Sc) degree in Biochemistry in 1986. Abubakar, as a young graduate was deployed to Ondo State for his National Service during the 1986/87 National Service year. Thus, he served with Apoi National High School, Igbotu, Ondo State.

After his National Service, he remained at home for only five months before joining the services of Federal University of Technology, Minna as a **Graduate Assistant** in the then newly established Department of Biochemistry on 4th January, 1988. As a result, he was the first to be appointed as Graduate Assistant in the Department and among the first three in the University. Due to his zeal and determination as an academic trainee, he proceeded to University of Jos for his Master of Science Degree (M.Sc) in Biochemistry which he completed successfully in 1991. His Master of Science Degree earned him promotion to the rank of **Assistant Lecturer** in the same year. In order to fit into his chosen career properly, he then enrolled for a Doctor of Philosophy (PhD) at Federal University of Technology, Minna and completed in 2010.

Professor A.N. Saidu rose through all the academic cadre ranks as follows:- **Lecturer II** (1999 - 2002), **Lecturer I** (2002 - 2008), **Senior Lecturer** (2008 - 2012), **Associate Professor** (2012 -

2015). The experienced academic by all standards and scholar of repute became a **PROFESSOR** of Biochemistry as approved by the University Council effective 1st October, 2015.

Professor A. N. Saidu has held many positions in the University among which are:- Departmental Examination Officer, CPES Examination Officer, CPES Coordinator, Departmental Registration Officer, Project/Seminar Coordinator, Postgraduate Coordinator, Deputy Dean (SSSE) and Dean, Students Affairs Division (2013 - 2017). He served as a member of numerous committees of the University: Committee of Deans, Students Disciplinary Committee, University Health Services Board, Tertiary Institutions Social and Health Insurance Programme among others and currently, a Council member, Federal University of Technology, Minna. He is a member of professional bodies such as Nigerian Society of Biochemistry & Molecular Biology (NSBMB), Fellow of African Scientific Institute (ASI), African Network for Drugs and Diagnostics Innovation (ANDI), etc.

As a mentor, he has supervised over eighty undergraduate projects, more than five Masters theses and currently with some PhD students. In addition, he has served as external examiner to some tertiary institutions and attended many conferences within and outside Nigeria and had over fifty scholarly publications in reputable Journals and Book of Proceedings. His research interest is **DIABETES**, a worrisome non-communicable killer disease. Professor A. N. Saidu is married with children.