Article title: HYPOGLYCEMIC EFFECTS OF ETHANOLIC FRUIT & LEAVE EXTRACTS OF *Solanum incanum* (GARDEN EG)
STREPTOZOTOCIN-INDUCED DIABETIC WISTAR RATS

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HYPOGLYCEMIC EFFECTS OF ETHANOLIC FRUIT & LEAVE EXTRACTS
OF *Solanum incanum* (GARDEN EGG) IN STREPTOZOTOCIN-INDUCED DIABETIC WISTAR
RATS

A RESEARCH PROPOSAL

BY
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CHAPTER ONE

1.0 INTRODUCTION

Diabetes Mellitus is a serious metabolic disorder characterized by hyperglycemia and various life-threatening complications. Despite enormous preventive efforts, diabetes mellitus is one of the fastest growing chronic disorders across the world. In 2010, an estimated 285 million people worldwide suffered from diabetes mellitus, and the number of people with diabetes mellitus is expected to rise to 439 million or 7.7% of the global adult population aged 20–79 yr by 2030.

Although no cure is yet available for diabetes mellitus, various pharmacologic agents have been developed and are being used to enable blood glucose control. However, the current pharmaceuticals for diabetes mellitus have a number of limitations, such as having adverse effects and high rates of failure in long-term glycemic control. This has led to research for alternative or complementary approaches, such as natural products or botanicals, which have some degrees of efficacy and mostly are without the troublesome side effects associated with the conventional pharmacologic treatments. Furthermore, earlier intervention for glycemic control is being emphasized for prevention or delay of diabetes mellitus in the management of patients with prediabetes which include the use of alternative approaches such as natural products to provide additional strategies for the early management of diabetes mellitus or prediabetes.

1.2 Aim

To assess the hypoglycemic effect of the ethanolic leave and fruit extracts of *Solanum incanum* in streptozotocin-induced diabetic wistar rats.

1.3 Objectives

To assess the anti diabetic effect of the ethanolic fruit extract of *Solanum incanum* (garden egg) in streptozotocin induced wistar rats.

To assess the anti diabetic effect of the ethanolic leaf extract of *Solanum incanum* [garden egg] in streptozotocin induced wistar rats.

To assess the anti hyperlipidemic effect of the fruit and leaf extracts in streptozotocin induced wistar

rats.

To assess the anti diabetic combined effect of the leaf and fruit ethanolic extracts in streptozotocin induced wistar rats.

To assess the lipid profiles (serum levels of total cholesterol, triglyceride, High Density Lipoproteins (HDL) and Low Density Lipoprotein (LDL) in the diabetic treated wistar rats.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Diabetes Mellitus

Diabetes is one of the oldest diseases of human kind whose devastating effect is increasing by the day and severity almost at epidemic level (Wide, et al., 2004). It is a disease of disordered metabolism of carbohydrate, that also affect protein and fat which is caused by complete or relative insufficiency of insulin action (Mycek, 2000). There are three types of diabetes: Type1 diabetes called Insulin-Dependent Diabetes Mellitus (IDDM), Type 2 diabetes called Non-Insulin Dependent Diabetes Mellitus (NIDDM) and Gestational Diabetes Mellitus (GDM). The number of people with diabetes is increasing due to population growth, aging, urbanization, increasing prevalence of obesity and decrease physical activity (King and Rewers, 1993; Ramachnadran et al.,1999). The early symptoms of diabetes include elevated blood sugar levels (glycosuria), dehydration, weight loss, blurred vision (Mycek, 2000).

Diabetes mellitus is a pathophysiological condition in which there is excessive glucose in the blood. It is a disease in which homeostasis of carbohydrate, protein and lipid metabolism is improperly regulated by the hormone insulin after elevation of postprandial (after-feeding) blood glucose level (Dewanjee et al., 2008; Twari and Rao, 2002). The effect of DM include long term damage, dysfunction and failure of various organs especially the eyes, kidney, nerves, heart and blood vessels (CDA,2006).symptoms of DM include polyuria, polydipsia and weight loss. Impairment of growth and susceptibility to certain infections may also accompany chronic cases while in acute, life threatening situation of hyperglycemia with ketoacidosis or non ketotic hyperosmolar state may develop leading to stupor, coma and even death in the absence of effective treatment (Potawel et al, 2008). Diabetes mellitus is the commonest non-communicable endocrine disease and is considered one of the living cause of death all over the world; affecting over 135 million people worldwide (Medical Surveillance Monthly Report (MSMR) 2004). Long-term complications of diabetes include retinopathy leading to blindness; neuropathy with risk of foot ulcer, amputation and Charcot joint: and autonomic neuropathy

causing gastrointestinal, genitourinary, cardiovascular syndrome and sexual dysfunction (Kengne et al., 2005). Patients with DM have an increased incidence of atherosclerosis and peripheral arterial cerebrovascular disease. Hypertension and abnormalities of lipid metabolism are often found with people with diabetes (Rani & Khuller, 2004).

2.2 AETIOLOGY AND CLASSIFICATION

2.2.1 Type 1 Diabetes Mellitus

Interleukin 1 (IL-1) is a protein cytokine which is the principal trigger of all immune responses (Menser, et al., 1978). This substance is produced by macrophages as a result of antigen processing. Interleukin mobilizes B and T cells and stimulates T-helper cells to produce IL-2; another cytokine important to the immune response. Most significantly, the pancreatic islets of diabetic animals have been shown to contain inflammatory cells incorporating IL-1 and incubation of islets with IL-1, selectively destroys β -cells (Menser, et al., 1978). Moreover, development of type 1 diabetes normally occurs over a period of a few weeks, and in a few instance where this was spotted very early and the patients treated with immune suppressants such as cyclosporine, the diabetic process was ameliorated (Menser, et al., 1978). These facts indicate that type 1 diabetes probably results from an autoimmune process involving IL-1. There are a handful of cases (Menser, et al., 1978) in which viruses have been implicated in development of type 1 diabetes. One of the most convincing evidence involved a previously healthy young boy who suddenly developed very severe diabetes and died after 7 days (Pak, et al., 1988). Coxsackie B4 virus was cultured from his body fluid, which produced diabetes when injected into animals.

2.3 CAUSES OF DIABETES

2.3.1 Causes of Type 1 Diabetes Mellitus

(a) Type 1 diabetes usually develops due to an autoimmune disorder. This is when the body's immune system behaves inappropriately and starts seeing one of its own tissues as foreign.

(b) The islet cells of the pancreas that produce insulin are seen as the “enemy ” by mistake. The body then creates antibodies to fight the “foreign ” tissue and destroys the islets cells ability to produce insulin. The lack of sufficient insulin thereby results in diabetes.

(c) It is unknown why this autoimmune diabetes develops. Most often it is a genetic tendency; sometimes it follows a viral infection such as mumps, rubella, cytomegalovirus, measles, influenza, encephalitis and polio (Menser, et al., 1978). Certain people are more genetically prone to this happening although why this occurs is not known.

(d) Other less common causes of type 1 diabetes include injury to the pancreas from toxins, trauma, or after the surgical removal of the majority (or all) of the pancreas.

2.4 Type 2 Diabetes Mellitus

Etiology of type 2 diabetes is less clearly understood. There are many root causes of the diseases;

(a) Impaired insulin release – basal secretion of insulin is often normal, but the rapid release of insulin is greatly impaired, resulting in failure of normal handling of carbohydrate load.

(b) Insulin resistance – A defect in the tissue response to insulin is believed to play a major role. This phenomenon is called insulin resistance and is caused by defective insulin receptors on the target cells.

There is a much stronger genetic link in this condition than in type 1 diabetes (Nurup et al., 1994).

There is also a most intriguing suggestion that mutations in the gene for the enzyme glycosidase represent the genetic defect in a form of type 2 diabetes known as maturity onset diabetes of the young (Nurup et al, 1994). This type 2-like condition is quite rare, but very strongly genetically linked in affected families.

(c) Genetic predisposition seems to be the strongest factor.

(d) Obesity and high caloric intake

(e) Twenty percent of people with this type 2 diabetes have antibodies to their islet cells, which are detectable in their blood resulting in the possibility of incomplete islet cell destruction. These patients often tend to respond early to oral drugs to lower blood sugar but may need insulin at some point.

2.5 BIOCHEMISTRY AND PATHOGENESIS OF DIABETES: ROLE OF INSULIN

Insulin is secreted in response to elevated serum glucose levels, by the β -cells of the pancreatic islets of Langerhans. Alpha Islet-cells secrete glucagons, a hormone with actions nearly opposite those of insulin, the delta-cells also secrete somatostatin, and the F-cells secrete pancreatic polypeptide. The role of insulin is to stimulate the GLUT-4 glucose transporter. GLUT-4 is the most important of the glucose transporter molecules and by insertion into the muscle and adipose cell membranes serves to facilitate glucose delivering into these cells.

Under normal circumstances, liver and muscle cells take up glucose and convert any excess to the storage form glycogen. If insulin is absent, these three types of cells will undergo “starvation, in the midst of plenty”, and have to resort to last-ditch methods, once glycogen is exhausted, to obtain glucose, which is required as an energy source by the cells (Dewanjee et al., 2008). Insulin is also involved in uptake of amino acids by muscle cells.

2.5.1 Complications of Diabetes

Diabetic complications include:

I. . Ocular problems

In diabetic retinopathy, the epithelia cells undergo hyperplasia, so that the basement membrane may become three times as thick as normal. This produces vascular lesions which in turn promote the growth of small, fragile blood vessels in the retina. These are easily ruptured, producing retinopathy, for which the only treatment is laser photocoagulation. Sorbitols also cause cataracts by producing an osmotic over hydration of eye tissue (Dewanjee et al., 2008).

II. . Diabetic Nephropathy

Excess sorbitol causes lesions in small blood vessels similar to those seen in the eye. Hypertension appears to exacerbate the condition, and recently it has been found that angiotensin converting enzyme (ACE) inhibitors not only prevent development of diabetic nephropathy but alleviate this condition, even if systemic hypertension is not present (Lewis et al., 1993). The proposal is that ACE inhibitors reduce possible renal hypertension.

III. Atherosclerosis and other Vascular Complications

Hardening of the arteries is very apparent in diabetics, and is associated with an increased risk of stroke, heart attack, and other complications.

Blood vessel deterioration is also associated with reduction in nitric oxide level, platelet adhesion, sorbitol production. Compromised circulation in the legs can lead to non healing leg ulcers with gangrene, sometimes requiring amputation of the affected limbs. Skin infections, especially those due to *Candida albicans*, are also commonly observed in diabetics requiring amputation of the affected limbs (Lewis et al., 1993).

2.5.2 Role of hormones other than insulin in diabetes

i. Glucagon

Glucagon is a 29-residue peptide, produced by the Alpha islet-cells of the pancreas. The role of glucagon is to prevent hypoglycemia. It interacts with specific receptors in liver to trigger glycogenolysis and an increased gluconeogenesis through cAMP related events. It is thought that glucagon antagonist may be helpful in reducing serum glucose levels in type 2 diabetes (Livingstone and Schoen, 1999).

ii. Somatostatin

It is produced by the delta-cells of the pancreas and is known to affect the release of other pancreatic hormones. It inhibits the release of both insulin and glucagon and when administered to untreated diabetic patient ameliorates elevation in both the postprandial and fasting serum glucose levels. It has also been shown that administration of somatostatin causes a reduction in the dose of insulin necessary to maintain type 1 diabetic patients (Lewis et al., 1993).

iii. Pancreatic Polypeptide

These small peptides, also produced by the pancreas, appear to have a role in the control of insulin secretion and possibly of glucose metabolism.

2.6 ANTI-DIABETIC AGENTS

2.6.1 Anti-diabetic herbs

Despite the significant achievements in treatment modalities and preventive measures of diabetes, its prevalence has risen exponentially in the last decade. Because of these limitations, there is continued need for new and more effective therapies which would improve diabetic control and reduced associated risk factors like hyperlipidemia, and hypertension. A lot of alternative therapies have emerged with herbal medicine inclusive. This is why the use of herbs has more than tripled over the last ten years (Eisenberg et al., 1988).

The field of herbal medicines research has gained significant importance in the last few decades and the demand to use natural products in the treatment of diabetes is increasing worldwide. Available literature reports shows that there are more than 400 plant species showing antidiabetic activity (Rai 1995; Mukherjee, 1981). The effects of these plants have been shown to delay the development of diabetic complications and correct some metabolic abnormalities. In the past few years some of the new bioactive drugs isolated from hypoglycemic plants showed antidiabetic activity with more efficacy than oral hypoglycemic agents used in clinical therapy (Mahamed et al., 2006). Moreover, a large number of medicinal plants possess some degree of toxicity. For example, it was reported that about one third of

medicinal plants used in the treatment of diabetes are considered to be toxic (Marles and Fransworth, 1994). Some of them significantly suppressed the rise in peripheral glycemia, both in the basal (fasting) state and after glucose intake (rats rendered glucose intolerant by tetracycline-induced fatty liver). Suppression of basal blood glucose output indicated a lowering effect of the plant extract on hepatic glucose output (Nicola et al., 1996). Single doses of unroasted seeds of *Cajanus cajan* Mill sp. (Pigeon Pea) caused a significant reduction in serum glucose levels 1-3 h after oral administration to healthy and alloxanized mice. In contrast, roasted seeds caused a significant increase in serum glucose levels during the 3 h experimental period. This shows that roasting of *Cajanus cajan* seeds at high temperature for 30 min resulted in the total loss of the hypoglycaemic component (Amalraj and Ignacimuthu, 1998).

Vernonia amygdalina (bitter leaf) is a common medium sized shrub with abundant bitter principles in every part of the plant. It is a widely used local plant.

Solanum incanum and *Solanum melongena* (Solanaceae) are both shrubs or trees found in the sub-Saharan Africa and the Middle East. Both are called “gauta” among the Hausa community of Northern Nigeria and “Tarku” among the Bura/Babar speaking people of Southern Borno of North Eastern Nigeria. They are widely used in traditional medicine for the treatment of pain related illnesses such as sore throat, angina, stomach-ache, colic, headache, painful menstruation, liver pain and pain caused by onchocerciasis, pleurisy, pneumonia and rheumatism. Microscopic, chemo-microscopic, quantitative evaluative and thin layer chromatographic (TLC) studies were carried out on the leaves of both plant species using standard pharmacognostic procedures. Elemental analysis using Instrumental Neutron Activation Analysis (INAA) technique was also carried out on the two plant species. Organoleptically, leaves of both plants were green in colour and distinct in odour, but *Solanum incanum* had a more bitter taste than *Solanum melongena* (Chanda, 2014).

2.6.2 Anti-diabetic Drugs

Anti diabetic drugs are mediations that work to lower blood glucose concentrations, or the amount of sugar in the blood. Anti diabetic drugs exert their useful effects through:

- (1) Increasing insulin level in the body.
- (2) Increasing the body's sensitivity (or decreasing its resistance) to insulin.

(3) Decreasing glucose absorption in the intestines.

The hypoglycemic effect of salicylates have been known for 100 years. The mechanism was never established with certainty, although it appears that salicylates enhance insulin secretion. Clinical use of salicylates was not feasible since the very large doses required produced intolerable side effects.

The hypoglycemic effects of the thiadiazole sulfonamide known as IPTD, used to treat typhoid fever in the 1940s were also noted. This drug produced many deaths which were subsequently attributed to prolonged drug-induced hypoglycemia. At about the same time these effects were noted, the synthesis of sulfonylureas such as carbutamide, an active hypoglycemic agents was reported (Groop, 1992). Since then about 12,000 sulfonylureas have been tested, and about 10 are currently on the market (Groop, 1992).

The hypoglycemic effects of guanidine were reported in 1918 but toxic effects prevented its use. The guanidine derivatives synthalin A and synthalin B were introduced into therapy in the 1929s, but chronic toxicity forced their abandonment in the 1930s. The widely used biguanides phenformin and metformin were prepared in the 1950s, and the later is still in widespread use. Other classes of hypoglycemic agents, the thiazolidinediones, have been introduced more recently.

In the long history of the world, plants have been used medicinally. A large and increasing number of patients use medicinal herbs or seek the advice of their physician regarding their use (O ' Hara et al., 1998). It has been estimated roughly, that presently more than half of the total population of the world use herbal drugs (Chang, 1987). Increasing interest in medicinal herbs has increased scientific scrutiny of their therapeutic potentials and safety thereby providing physicians with data to help patients make wise decisions about their use (O ' Hara et al, 1998).

CHAPTER THREE

3.0 MATERIALS AND METHODS

3.1 Materials

Materials/Apparatus: Fresh fruits of *Solanum incanum*, fresh leaf of *Solanum incanum*, Lipid Profile auto analyzer, mortar and pestle, distilled water, glass bottle, American Society for Testing and Materials (ASTM) 60 mesh, water bath, thermometer, Accu-check glucometer, test strips, cages for rats, weighing balance, micro pipette, centrifuge, dessicator, glucose, 70 male and female albino rats of wistar strain, will be used for this study.

Chemicals/Reagents utilized: Streptozotocin, Glibenclamide (Daonil; Aventis Pharma. Ltd., India), Cholesterol reagent (Teco Diagnostics., USA), TriglycerideGPO reagent (Teco Diagnostics., USA) and HDL Cholesterol reagent (Agappe Diagnostics., Switzerland) will be obtained from a distribution company in Abuja.

Location of the study: The entire study will be carried out at the University of Abuja Animal House. The plant extraction, acclimatization of rats, induction of diabetes, treatment of diabetes, biochemical analysis and statistical analysis will all be carried out at both the Biochemistry Laboratory and at the animal house respectively.

Plant sample collection: Fresh fruits and leaf of *Solanum incanum* (garden egg) will be obtained from the research farm of the University of Abuja, after proper identification by a certified Botanist, after which they will then be washed and dried for further use.

Experimental animals: Healthy adult male and female wistar albino rats weighing about 140-180 g will be obtained from the research farm, University of Abuja and allowed to acclimatize at the College of Health Science animal house for 15 days. The animals will be housed in a standard well ventilated cages at room temperature and provided with water and top feed growers pellets, rat diet and water.

3.2 Methodology

Experimental procedures for plant sample preparation:

The collected fresh fruits and leaf of *Solanum incanum* will be washed and chopped into small pieces, partially sun dried for one week to extract the powdered form of the plant after which they will be shade dried for another one week. The dried pieces will then be pounded gently into powder using mortar and pestle after which the extract will then be prepared from the powder.

Experimental procedures for aqueous extract preparation:

200g of each of the powder of fruit and leaf will be dissolved in 1600 ml of ethanol in a glass bottle respectively for a period of 48 hours with intermittent vigorous shaking. The solution will be filtered with, ASTM (American Society for Testing and Materials) 60 mesh size while the filtrate will be collected and evaporated at 45°C using water bath. The dried concentrate (extract) will then be stored in a sealed transparent bottle for subsequent use.

Experimental procedures for diabetes induction:

Diabetes will be induced by a single intraperitoneal injection of streptozotocin (120 mg/kg body weight) after 18 hours fast while 5% glucose solution will be administered orally so as to prevent the drug induced hypoglycemic effect of streptozotocin. After 72 hours of streptozotocin injection, blood samples will be collected by tail snip method to determine the blood glucose concentrations to confirm the development of Diabetes Mellitus. Albino rats with fasting blood glucose concentration of greater than 126 mg/dl will be considered hyperglycemic and will be selected for the study.

3.3 Experimental design:

The animals will be randomly divided into nine groups each containing five wistar rats while each

wistar rat will be marked using black stain; Group A will receive a mark on the head, Group B will receive a mark on the body, Group C will receive a mark on the tail, Group D1 will receive a large mark on both tail and ear, Group D2 will receive a slim mark on both tail and ear, Group E1 will receive large marks on both the abdomen and thigh, Group E2 will receive slim marks on both the abdomen and thigh while Group F1 will remain unmarked, Group F2 will be marked at the tail end. Each cage will be identified by a label comprising the cage number, the dose of streptozotocin/treatment to be received by the animal, and the numbers and weight of the animals in each cage. After the grouping is done, blood samples will be collected from each group members for lipid profile and blood glucose tests respectively before and after Diabetes induction and treatment.

Non-Diabetic group:

Group A: (NORMAL CONTROL/Non-Diabetic Wistar Rats): Will be administered 0.5 ml normal saline only. On the 7th and 14th days of treatment, the blood glucose levels of the wistar rats will be determined using accu-check glucometer, the animals will then be weighed to determine the effect of the plant extract on their body weights. The results obtained will then be expressed in g of body weight and mg/dl of blood respectively.

Diabetic groups:

Group B: (NEGATIVE CONTROL/Untreated Diabetic Wistar Rats): These will Serve as diabetic control; receiving 0.5 ml normal saline/day/rat.

Group C: (POSITIVE CONTROL/Diabetic Wistar Rats): Will be administered Glibenclamide (10 mg/kg b.wt./day) in 0.5 ml normal saline as a fine aqueous suspension orally.

Group D 1: (TEST CONTROL Ia /Diabetic Wistar Rats): Will be administered a daily low dose of ethanolic fruit extract of *Solanum incanum* as a fine aqueous suspension orally in 0.5 ml normal saline

Group D 2: (TEST CONTROL Ib /Diabetic Wistar Rats): Will be administered a daily high dose of ethanolic fruit extract of *Solanum incanum* as a fine aqueous suspension orally in 0.5 ml normal saline

Group E 1: (TEST CONTROL IIa /Dabetic Wistar Rats): Will be administered a daily low dose of ethanolic leaf extract of Solanum incanum as a fine aqueous suspension orally in 0.5 ml normal saline

Group E 2: (TEST CONTROL IIb /Dabetic Wistar Rats): Will be administered a daily high dose of ethanolic leaf extract of Solanum incanum as a fine aqueous suspension orally in 0.5 ml normal saline

Group F 1: (TEST CONTROL IIIa /Diabetic Wistar Rats): Will be administered a low dose of combined ethanolic leaf and fruit extracts of Solanum incanum as a fine aqueous suspension orally in 0.5 ml normal saline

Group F 2: (TEST CONTROL IIIb /Diabetic Wistar Rats): Will be administered a high dose of combined ethanolic leaf and fruit extracts of Solanum incanum as a fine aqueous suspension orally in 0.5 ml normal saline

Collection and treatment of sample:

The extracts will be reconstituted in normal saline water and administered orally on daily basis. The extract group will be treated with high and low doses of the leaf and fruit ethanolic extracts respectively, while the diabetic control and the normal control will be given 0.5 ml of saline water for a period of 14 days. At the end of 14 days, the fasting blood glucose levels of all the animals will be taken, after which the animals will be weighed and anaesthetized using chloroform and bled by cardiac puncture 24 h after the last treatment. The blood sample will then be collected in plain bottles, allowed to clot and the serum separated by centrifugation for 10 min, which will then be collected and stored at 37 and finally subjected to biochemical analysis.

Biochemical analysis: The serum levels of total cholesterol, triglyceride, High Density Lipoproteins and Low Density Lipoprotein will be determined by a lipid profile auto analyzer.

Statistical analysis: Data will be expressed as mean $\pm$ standard deviation. Comparative analyses between and amongst variables will be done using analysis of variance (ANOVA). A post hoc comparison (LSD) test will be performed to further ascertain significant differences between means. Statistical significance will be set at $P < 0.05$. All statistical analysis will be done using SPSS.

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