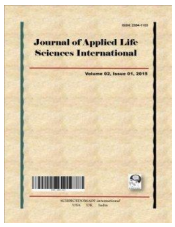

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Hypoglycaemic and Hypolipidaemic Potentials of *Senna alata* and Its Effect on the Pancreas of Alloxan-Diabetic Induced Albino Rats

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Authors' contributions

This work was carried out in collaboration between both authors. Author BMO designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author FCA managed the analyses of the study and the literature searches. Both authors read and approved the final manuscript.

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ABSTRACT

This study evaluates the anti-diabetic and anti-lipidemic potentials of oral administration of ethanolic leaf extracts of *Senna alata* on alloxan-induced diabetic albino rats. Forty rats were grouped into eight groups (five per group) based on average body weights. Diabetes similar to that of type I in human was induced by a single intra-peritoneal injection of alloxan monohydrate a diabetogenic agent (160 mg/kg). The fasting blood sugar (FBS) level of the rats was checked before alloxan injection and after 120 hours of alloxan injection, the rats from group 2 to group 8 were confirmed diabetic with an increase in glucose levels >8.7 mmol/L. Group 1 served as normal control, Group 2 was treated with a standard diabetic drug, "metformin", which serves as positive control while Group 3 (diabetic and untreated negative control) and Groups 4 to 8 were diabetic and treated with the extract of *S. alata*. The extract was administered twice daily for 21 days at doses of 500 mg kg^{-1} – 2500 mg kg^{-1} in Group 4 to 8 based on average body weight. Group 3 (negative control) remain diabetic with increased glucose, total cholesterol (HDL), triglyceride (TAG) level, low-density

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lipoprotein (LDL) levels and reduction in high-density lipoprotein (HDL) level throughout the experiment. Glucose assay was carried out on the 7th, 10th, 14th and 21st day while CHOL, triglyceride, LDL and HDL were assayed on the 21st day. A significant reduction ($p<0.05$) in the FBS levels of rats in Group 4-8 was observed when compared to the normal control. A significant increase ($p<0.05$) in HDL level were observed in groups treated with the extract and metformin group when compared to Group 1 (normal control) and also a significant decrease ($p<0.05$) were observed in CHOL, TAG and LDL levels in groups treated with extract and metformin group when compared to the normal control with an associated rapid decrease in glucose level. The study has demonstrated that the extract exhibits anti-lipidemic and anti-diabetic properties because of the significant regeneration and repair of damage beta cells in alloxan-induced diabetic rats as captured in the photomicrographs.

Keywords: Senna alata; anti-diabetic; antilipidemic; pancreas; photomicrographs.

1. INTRODUCTION

Plants extract or pure compounds or standardised extracts are a natural product which provides unlimited opportunities for new drug discoveries because of the unmatched availability of chemical diversity [1]. According to the WHO [2], a medicinal plant is any plant which, in one or more of its organs, contains substances that can be used for therapeutic purposes, or which are precursors for chemo-pharmaceutical semi-synthesis. When a plant is designated as medicinal, it is implied that the said plant is used as a drug or therapeutic agent or an active ingredient of a medicinal preparation. The therapeutic treatment of disease with the use of herbs began long ago. Methods of folk healing throughout the world commonly used herbs as part of their tradition. The practice of using herbs to treat diseases is very common among many non-developed societies. It is sometimes easier to get than purchasing expensive modern pharmaceuticals. Plants used for traditional medicine contain a wide range of substances that can be used to treat chronic as well as infectious diseases. Due to the development of adverse effects and microbial resistance to the chemically synthesised drugs, men turned to ethnopharmacognosy. They found literally thousands of phytochemicals from plants as safe and broadly effective alternatives with less adverse effect. Many beneficial biological activities, such as anti-cancer, anti-microbial, anti-oxidant, anti-diarrheal, and wound healing activity were reported. In many cases the people claim the good benefit of certain natural or herbal products [1].

All forms of diabetes have very serious effects on health. In addition to the consequences of abnormal metabolism of glucose, there are a number of long-term complications associated with the disease. Coronary artery disease, caused by lipid abnormalities is commonly associated particularly in those with type 1 diabetes, and is the most common cause of death. These lipid abnormalities include hypertriglyceridemia, high level of low-density lipoprotein (LDL), high level of cholesterol and reduced high-density lipoprotein (HDL) levels. While lipid abnormalities typically improve with better glycermic control, normalisation does not usually occur. Although glycermic control may decrease the risk of developing this complication, diabetes remains a very significant cause of social, psychological and financial burdens in populations worldwide [3,4].

A lipid profile is a measurement of various lipids that are found in the blood. This kind of blood test is often used to assess the risk of heart disease, associated with diabetes mellitus. There are two common concerns about lipids in our diet. One is their high caloric value, which may lead to undesired weight gain. The other is their association with high total cholesterol level, which is a risk factor for cardiovascular disease. One reason the USA recommends that 100% or fewer of one's calories come from saturated fat is because the amount of saturated fat in one's diet correlates strongly with cholesterol level. A lipid profile contains information about several different types of lipids that normally circulate in the blood. Values are numerical, but in order to simplify the explanation, ranges of numerical values are often placed into categories such as "low risk" or "high risk" associated with diabetes mellitus [5].

The pancreas is a vital endocrine-exocrine organ that produces several hormones and enzymes. Its enzymes help in the digestion of carbohydrates, fats, and proteins whereas its hormones such as insulin regulate carbohydrate metabolism in the body and maintain passage of glucose across the cell membrane [6]. Therefore,

any change in the function of the organ may directly affect the physiological function of the body.

Nature provides an abundant source of medicinal plants which are known to be used in the treatment of a wide range of diseases right from the word go. In Africa and elsewhere, plant extracts are still widely used in the treatment of diabetes and other ailments and up to 80% of the African population use traditional medicines for primary health care [7]. *Senna alata* is a tropical perennial herb of medicinal value. Studies have reported the use of *S. alata* leaves in treating abdominal pain, constipation, and liver abnormalities [8]; others include eczema, skin inflammation, rashes on the skin, athlete's foot, and ringworm (from where the name 'ringworm shrub' was gotten) [9]. This research work was designed to evaluate the hypoglycaemic and hypolipidaemic potentials of *S. alata* and its effect on the pancreas of alloxan diabetic-induced albino rats.

2. MATERIALS AND METHODS

2.1 Plant Material and Preparation of Extract

Fresh leaves of *Senna alata* (Fig. 1) were obtained from herbarium; University of Port Harcourt Rivers state, Nigeria. Identification and authentication of the plant were done by Dr. Eke, Chimezie of the department of Plant Science and Biotechnology. The voucher specimen UPH/V/1225 was kept in the Plant Science and Biotechnology Laboratory of the University of Port Harcourt, Rivers State. The leaves were subsequently cleaned, air-dried under a room temperature of 27 ±1°c for 14 days.

2.2 Ethanolic Extraction of *Senna alata*

The leaves of the plant were air dried and triturated in a mechanical mill and then wrapped in a filter paper and put inside the soxhlet extraction thimble and heated under reflux until the reflux was clear. The filtrate was concentrated on a rotary evaporator at 45°C and the extract was then kept in a sterile bottle under a refrigerated condition at 4°C throughout the experiment. The resulting solution was filtered into a clean screw-cap bottle and store in the refrigerator throughout the experiment. Metformin, an anti-diabetic drug, used as a reference drug in this study was bought from a pharmacy shop by University of Port Harcourt Teaching Hospital, East-West Road, Port Harcourt.

Fig. 1. *Senna alata* plant

2.3 Preparation of Chemicals

All laboratory reagents used were of analytical grade and were freshly prepared. Fresh distilled water was used when required. For normal saline, 0.9 g of sodium chloride (NaCl) was dissolved in 10 ml of distilled water; the solution was made up to 100 ml and stored in clean, dry, screw-cap bottle. One thousand, five hundred mg of alloxan was weighed and dissolved in 10 ml of normal saline, stirred and the solution made up to 100 ml.The required volume of alloxan to induce diabetes was calculated with respect to the average body weight of each group of the animals.

3. EXPERIMENTAL DESIGN

3.1 Sources of Animals

Forty (40) albino rats of Wistar strain weighing 160 to 280 g body weight (B. WT), were obtained from the font Scientific Laboratory Animal Farm, No. 200 Uniport Road, University of Port-Harcourt Choba, Port Harcourt, Nigeria. These animals were maintained under laboratory conditions of temperature (22 to 24°C), humidity (40 to 60%) and 12 hour light/12 hour dark regime at University of Port-Harcourt Animal House. They were exposed to both food and water ad libitum for the entire duration of the study. All animals used for this study were maintained according to the rules and regulations outlined in accordance with NIH Guide for the care and use of laboratory animals; NIH Publication revised (1985) NIPRD Standard Operation Procedures (SOPs). They were grouped into 8 of 5 rats each, based on average

body weights. This study was carried out following the approval from the Departmental Ethical Committee on the care and use of Experimental Animals for Research.

3.2 Induction of Diabetes

The albino rats of Wistar strain were allowed to fast overnight but had free access to water and few hours prior to the administration of alloxan, a fasting blood glucose test was conducted to obtain a baseline result. All the animal groups except the normal control group were induced by intraperitoneal administration of 160 mg kg-1 body weight alloxan monohydrate in normal saline. The diabetic status of the rats was confirmed 120 hours after administering the alloxan, which showed an insulin-dependent diabetes mellitus (known as Alloxan Diabetes), with characteristics similar to type 1 diabetes in human.

3.3 Administration of Leave Extract and Treatment of the Animals

The experimental animals were grouped as follows:

- Group 1: Normal control - These non-diabetic rats were well-fed with conventional rat feed throughout the course of the experiment.
- Group 2: Positive Control - Diabetic rats that were treated with 500 mg kg^{-1} body weight metformin (a standard anti-diabetic drug)
- Group 3: Negative Control - Diabetic rats that were not treated.
- Group 4-8: Diabetic rats that were treated with leaf extract of concentrations 500, 1000, 1500, 2000 and 2500 mg kg^{-1} body weight respectively.

All experiments animals were conducted in compliance with NIH guide for the care and use of laboratory animals (pub No: 85-23 Revised 1985) and divided into 8 groups of 5 rats each. Treatment of animal was carried out according to the dosage required for each group and once daily in full dose. Administration of Metformin into Group 2 and various concentrations of the extract to Group 4 - 8 was by oral intubation twice daily for 21 days. In addition, each rat was also adapted to the commercial feed and water for 21 days during the study period. Rats in Group 1 (normal control) and Group 3 (negative control) were given commercial feed and water without the leaf extract or reference drug. All the rats were not under stress as mobility was not restrained within their cages moreover, they all had free access to food and water. The fasting glucose level for the rats in each group was carefully monitored at 7- day interval.

3.4 Method of Blood Collection for Glucose Determination

After 120 hours of induction of alloxan, the blood collection for glucose estimation was by vein puncture technique. A sterile lancet was used to puncture the tail vein of the rats. A drop of blood from the tail of the rat was placed in glucometer test strip to deduce the diabetic states. The result observed and was recorded accurately.

3.5 Estimation of Blood Glucose Level

The fasting blood glucose level of blood samples drawn from the tail vein puncture was determined using a one-touch ultra-easy glucometer. A drop of blood from the tail of the rat was placed in glucometer test strip, inserted into the glucometer which automatically displayed the level of glucose in the blood. Blood glucose level was monitored throughout the experiment.

3.6 Collection of Blood Sample for Lipid Analysis

On the 21st day, FSB was carried on all the animals to determine the glucose level. The animals from each group were sacrificed, and the blood collected into lithium heparin bottles to determine plasma lipid level. Total CHOL, HDL, LDL, and TAG were analysed by kinetic methods kits from Randox, (United Kingdom) using a double-beam spectrophotometer. Only those rats with established fasting blood glucose >8.5 mmol/l were included for subsequent treatment.

3.7 Collection of Tissue Sample for Histology

The animals to be sacrificed were first anaesthetized with chloroform (inhalational anaesthesia) followed by cervical dislocation. Each animal was placed on a dissecting slab and then cut along the thorax down the abdominal region; freshly dissected pancreas from each animal was fixed in buffered neutral formalin (10%). The tissues were subjected to standard routine histological procedures [10]. The slides were viewed using the light microscope and

observations were recorded at X40 magnification identifying both normal and degenerated pancreatic islet.

4. RESULTS

4.1 Statistical Analysis

The result of the study was reported as a mean ± standard error of the mean (SEM) of triplicate determination. Data were analysed using one-way analysis of variance (ANOVA) and differences were considered significance at $p<0.05$.

Baseline results obtained 96 hr after administration of alloxan showed a significant increase ($p<0.05$) in fasting blood sugar above 9.9mmol/l in groups 2 – 8 when compared with group 1 which is the control group. A significant ($p<0.05$) rise in fasting blood glucose level was observed in negative control which is the untreated group when compared to normal control group. Aqueous leave extract of *Senna alata* (500, 1000, 1500, 2000, 2500mg/kg) exhibited a dose-dependent significant ($p<0.05$) antiglycaemic activity on day 7, 10, 14 and 21 of treatment. The aqueous leave extract of *S. alata* was found to be more effective than that of the reference standard drug, Glucophage. Glucophage produced a significant ($p<0.05$) reduction in blood glucose level compared to normal control.

4.2 Histology Results

Photomicrographs of the pancreas of rats from groups 1 – 8 are presented in Plate 1 (A-H).

Table 1. The effect of ethanolic leaf extract of *S. alata* monitored after the 7th, 10th, 14th and 21st days of treatment of alloxan diabetic-induced rats

Groups	Fasting blood glucose level				
	Baseline result (mmol/L)	7^{th} Day (mmol/L)	10^{th} Day (mmol/L)	14^{th} Day (mmol/L)	21^{st} Day (mmol/L)
1	5.12 ± 0.47	5.31 ± 0.27	5.11 ± 0.02	5.45 ± 0.35	4.82 ± 0.25
2	9.94 ± 0.53*	6.95 ± 0.95	3.25 ± 0.15*	3.77 ± 0.20*	3.19 ± 0.50*
3	9.84 ± 0.48*	9.95 ± 0.66	10.73 ± 0.22	12.33 ± 0.26	14.64 ± 0.15
4	9.94 ± 0.58*	5.80 ± 0.20*	3.75 ± 0.25*	3.66 ± 0.55*	3.22 ± 0.10*
5	10.14± 0.20*	6.60 ± 0.40*	4.55 ± .45*	3.14 ± 0.25*	3.20 ± 0.10*
6	9.97 ± 0.40*	6.03 ± 0.89*	3.35 ± .87*	2.92 ± 0.10*	3.26 ± 0.30*
7	10.84 ± 0.35*	6.50 ± 0.50*	3.72 ± .40*	3.42 ± 0.40*	3.15 ± 0.30*
8	10.89 ± 0.22*	7.55 ± 0.45*	3.77 ± .52*	2.29 ± 0.15*	2.28 ± 0.50*

Value of fasting blood glucose levels, expressed in mmol/L and all are represented as Mean ± S.D; n=3, p<0.05 established a significant different when compared to non-diabetic group

Table 2. Effect of oral administration of ethanolic leaf extract of *S. alata* on the lipid level of diabetic –induced albino rats

Groups	Cholesterol (CHOL) (mg/dL)	Triglycerides (mg/dL) (TG)	Low density lipoprotein (LDL) (mg/dL)	High density lipoprotein (HDL) (mg/dL)
Normal	3.36 ± 0.18	1.53 + 0.05	2.62 + 0.16	0.20+ 0.26
Positive control	3.61 ± 0.15	1.39 + 0.02	2.56 + 0.26	0.41 + 0.30
Negative control	4.77 + 0.02	1.79 + 0.20	3.66 + 0.02	0.16 + 0.02
Group 4	4.36 ± 0.16	1.74 + 0.57	3.32 + 0.39	0.28 + 0.00
Group 5	3.89 ± 0.75	1.38 + 0.12	3.21 + 0.69	0.39 + 0.01
Group 6	3.77 ± 0.39	1.27 + 0.12	2.93 + 0.46	0.42 + 0.02
Group 7	3.14 ± 0.24	1.19 + 0.05	2.88 + 0.02	0.45 + 0.00
Group 8	2.60 + 0.10	0.95 + 0.25	0.55 + 0.26	0.49 + 0.10

Values are shown in mean ± standard deviation, n = 3

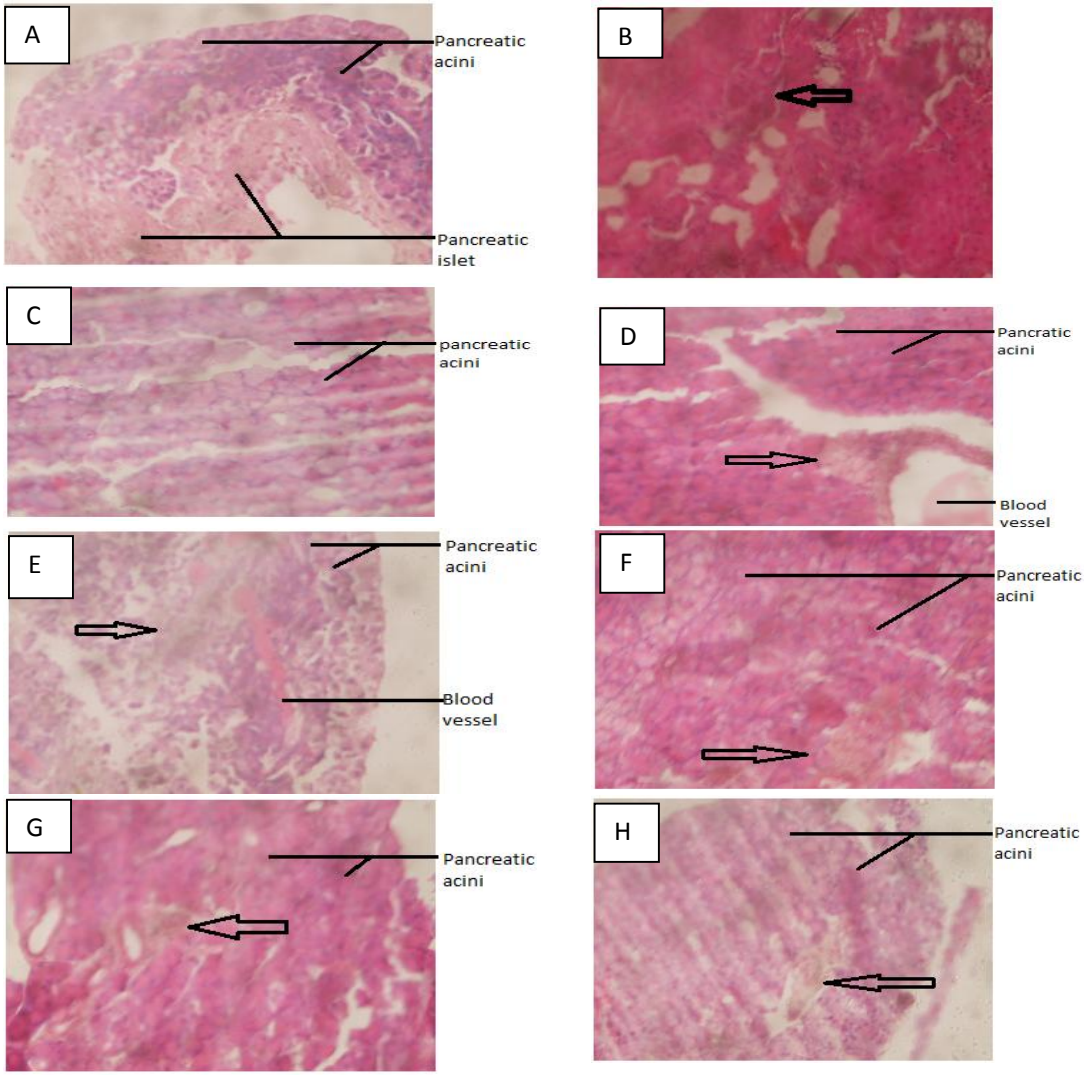

Plate 1. Photomicrograph of the pancreas of rats. A: Group 1 showing normal pancreatic acini and islet. B: Group 2 showing pancreatic acini, inter lobular and intra lobular ducts. Pancreatic islets of Langerhans (arrowed) appears atrophic with few cells. C: Group 3 showing only pancreatic acini with pancreatic islet not seen. D: Group 4 showing normal pancreatic acini with distorted and atrophic pancreatic islets close to the blood vessel. E – H: Groups 5 – 8 showing distorted (arrowed) pancreatic islets cells and acini

5. DISCUSSION AND CONCLUSION

The currently available drug regimens for management of diabetes mellitus have certain drawbacks and therefore, there is a need to find safer and more effective anti-diabetic drugs [11]. Diabetes mellitus of long duration is associated with several complications such as atherosclerosis, myocardial infarction, nephropathy etc. These complications have long been assumed to be related to chronically to the elevated glucose level in blood [12]. Alloxan causes a massive reduction in insulin release by the destruction of b-cells of the islets of Langerhans and thereby induces hyperglycemia [11,13]. Apart from the necrotic effect on the pancreas, it also adversely affects other organs of the experimental animals leading to alterations in the haematological parameters and biochemical parameters of organ function that eventually culminate into hampering the normal function indices of these organs. Intraperitoneal administration of 150 mg/kg of Alloxan monohydrate induced hyperglycaemia in rats

after 92 hours. Alloxan has been reported to induce diabetes mellitus by forming highly reactive superoxide radicals which destroy the insulin-producing beta cells in the pancreas [14]. Medicinal plants have been used as an alternative to orthodox medicine in many countries including Nigeria. Despite their widespread use, few scientific studies have been undertaken to ascertain the efficacy of traditional remedies [15]. In line with the recommendations of the WHO Expert Committee on diabetes mellitus, it is important to investigate and ascertain the hypoglycaemic action of plants which are traditionally used in traditional medicine [16].

Daily administration of aqueous extracts of *S. alata* for 21 days had resulted in a decrease in blood glucose level in alloxan diabetic induced albino Wister rats. Oral administration of standard drug (Metformin), 500, 1000 and 1500, 2000 and 2500 mg/kg of the ethanolic leaf extract of *S. alata* led to significant reduction ($p<0.05$) in blood glucose levels in alloxan induced diabetic rats when compared to the diabetic negative control rats after the period of treatment. Similar effects have been documented in other studies using the leaves and stems of other plants from the same family [17] who reported the antidiabetic effect of *Cassia auriculata* bark extract and Elaikim-Ikechukwu et al. [18] who reported the effect of *Cassia alata* leaf extract in diabetic Wistar rats. Stalin et al. [19] and Subrahmanyam et al. [20] also found Metformin to significantly reduce blood glucose which is in agreement with the observation made in this present study. In this study it was observed that at the highest dose (2500 mg/kg) there was a less but significant reduction on the blood glucose level of the rats. This result was in agreement with the previous reports in the literature [21,22]. Karau et al. [21] in their work hypoglcaemic effect of aqueous and ethyl acetate extracts of *Senna spectalis* in alloxan induced diabetic male mice observed that on administration of the ethyl acetate fraction of the stem of the plant used at 50 mg, 100 mg and 200 mg/kg, highest activity was observed at 50 mg/kg and the activity was seen to decline with increased concentration which was explained to be as a result of the extract at higher concentrations could inhibit its absorption by saturating the cells in the gastrointestinal tract. Similarly, Karau et al. [23] observed that the ethylacetate extract of both the leaf and stem bark of *Pappea capensis* in alloxan induced diabetic BALB/c mice at doses of 100 mg and 200 mg/kg induced hypoglycaemia in a dose-independent manner. Several mechanisms have been proposed by which plant extracts are able to exert their hypoglycaemic effect which include; stimulation of insulin release from beta cells [24], decreasing hepatic glucose production [25], decreasing the utilisation of ingested carbohydrate [26] and increasing peripheral tissue utilisation of glucose [27]. More so Metformin is amongst the group of anti-diabetic drugs called insulin sensitizers as a result of its ability to stimulate insulin release. It was reported that plants exert their hypoglycaemic effect by interfering with carbohydrate absorption [28].

Results obtained showed, a dose-dependent decrease in total cholesterol, triglyceride and LDL levels and an increase in HDL levels in diabetic rats treated with the extract while similar results were observed in the group treated with Metformin. This result agrees with the observation [3,29] that lipid abnormalities are commonly associated with diabetes, particularly in those with type 2 diabetes. The report stated that most common lipid abnormalities in these patients include hyper-triglyceridemia and reduced high-density lipoprotein (HDL) cholesterol levels. While lipid abnormalities typically improve with better glycemic control, normalisation does not usually occur. The result of this study also agrees with the findings of other researchers [30,31] who reported that many plants extracts have potential therapeutic value in combating atherosclerosis which is one of the major complications of diabetes by lowering serum lipid particularly total cholesterol, triglyceride and low-density lipoproteins. The anti-lipidemic activity of *S. alata* is the important finding of this research and support the traditional use of the plant in the management of lipid-related problems and diabetes**.** Similarly, Onyegeme-Okerenta and Essien [32] reported that leaf extract of *M. aboensis* has anti-diabetic and anti-lipidemic properties and can be used in the management of diabetes induced by alloxan since it was capable of controlling the glucose level in the blood in a way similar to the reference drug which works by decreasing the amount of glucose produced by the liver and increases the uptake of glucose by the cells of the body.

Photomicrographs of the pancreas of the normal control group showed normal pancreatic islets. Groups 2, 4, 5-8, showed significant damage to the beta cells of the islets of Langerhans as compared to group one. Group 3 which was left

untreated had a complete loss of function and the islets of Langerhans was not shown. At the end of the treatment period, there was no significant regeneration of the pancreatic cells due to the duration of the experiment and the lack of a long wash-off period where the animals are free of drugs and have access to water and food, *ad libitum*. The majority of islet cells is formed by beta cells which are responsible for producing insulin. Depletion of beta cells will therefore result in insulin deficiency which will lead to a disorder in carbohydrate, protein and fat metabolism with a resultant hyperglycaemia. In this study, Alloxan which selectively destroys beta cells of the islet was used to induce type 1 diabetes mellitus. Insulinitis and loss of beta cells were observed which may be seen in type 1 DM. insulinitis is evidenced by heavy lymphocytic infiltration in and around the islet. This is commonly seen in islets containing residual beta cells and it supports the possibility of a specific, immunologically mediated destruction of beta cells as the cause of type 1 DM. There is no evidence of immune involvement in the pathogenesis of type 2 DM. Insulinitis was seen in the group treated with 2500 mg/kg/day of plant extract showing that some of the scanty cells seen in the islet are β cells. Large deposits of a homogenous eosinophilic material largely occupying the islet and around blood vessels are seen in the diabetic control group. This could be a localised amyloidosis which has been documented to occur in the pancreas in many diabetics. This is deposited extracellularly and first appears in the walls of small vessels. It is also deposited in reticulin fibres and basement lamina. When present in large amount, it induces pressure atrophy of the surrounding cells. It is not surprising therefore that scanty atrophic cells are found in this group making worse the situation. This is related to the chronic inflammatory disorder. Islet cells of Group 4 treated with 500 mg/kg/day of plant extract has regenerated considerably suggesting the presence of stable cells in the islets with the ability to regenerate. This also suggests that the plant extract at this dose has the ability to induce the quiescent cells to proliferate to replace the lost cells. The exact mechanism is not known but it has been documented that the flavonoid fraction of this plant extract decreases blood glucose and increases the number of β cells [33]. In conclusion, the reduction of blood glucose levels shows that the aqueous leaves extract of *S. alata* have antidiabetic activities in alloxan-induced diabetic Wistar albino rats. Metformin used in treating group 2 when compared to groups 4-8 treated with the aqueous leaves extract showed a similar mode of action by decreasing the amount of glucose produced by the liver and increasing the uptake of glucose by the cells of the body. *S. alata* had no significant effect on the pancreas and thus the pancreas was distorted. The study has demonstrated that ethanolic leaf extract of *Senna alata* exhibits anti-lipidemic and anti-diabetic properties because of the significant regeneration and repair of the damaged cell of islets of Langerhans (beta cell) and pancreatic functions in alloxan-induced diabetic albino rats as captured in the photomicrographs and can therefore be used in the management of diabetes.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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