

# Hypoglycemic and Hypolipidaemic Effect of Allium Cepa in Streptozotocin-Induced Diabetes

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**ABSTRACT:** Type 2 diabetes is a global public health crisis that threatens the economies of all nations, particularly developing countries. It is generally characterized by hyperglycaemia and hyperlipidaemia culminating in severe morbidities. Epidemiologic studies and randomized clinical trials show that type 2 diabetes is largely preventable through diet and lifestyle modifications without major recourse to pharmacological measures. This study aimed to assess the antidiabetic and antilipidaemic activities of Allium cepa (onions) in streptozotocin-induced diabetic male Wistar rats. Adult male Wistar rats were randomly divided into eight (8) groups of five rats each (n=5). Groups 1a and 2a served as the control groups. Diabetes was induced in the rats by an intraperitoneal injection of streptozotocin (60mg/kg). The normoglycaemic groups (1b, 1c and 1d) and the streptozotocin-induced diabetic groups (2b, 2c and 2d) were treated with graded doses of A. cepa extract (ACE) (0.4g/100gbw, and 0.6g/100gbw) and metformin (0.5g/100gbw) respectively 28days. The body weights and fasting glucose level of the animals were monitored weekly. At the end of the experiment the rats were sacrificed, blood samples were centrifuged to obtain the serum for biochemical analysis. The pancreases were excised for histological study. Data obtained were analyzed using SPSS statistical tool and expressed as mean±SEM. Results show that ACE caused an increase in the average weight at the end of the experiments in all non-diabetic animals treated with varying doses of Allium cepa. Fasting blood glucose levels of diabetic rats was reduced by 50.00% and 35.05% on administration of 0.4g/100gbw and 0.6g/100gbw of Allium cepa respectively. Treatment with Allium cepa significantly (p<0.05) decreased the total cholesterol level (0.4gm/100gm [230.22±15.79], 0.6gm/100gm [220.75±21.06] in a dose dependent manner. The levels of triglycerides (180.10±15.64), high density lipoprotein (80.15±2.97) and low density lipoprotein (224.22±32.88) were significantly (p<0.05) higher in the streptozotocin-induced diabetic rats studied. Histology of the pancreas showed evidence of aplastic islet cells that were not healed by the Allium cepa or metformin. In conclusion, Allium Cepa (EXTRACT) demonstrated significant antidiabetic and antilipidemic activities in diabetic rat, but the mechanism needs to be established.

**Keywords:** Allium cepa, Diabetes, Streptozotocin, Metformin

## INTRODUCTION

Humans are afflicted by various diseases, which have different causes. These diseases include diabetes mellitus, which is a metabolic disease. Dietary factors play a key role in the development of these diseases [1]. Despite the understanding about the usefulness of insulin in the management of diabetes mellitus, for obvious reasons (such as availability, poverty, accessibility, and proper storage), there has been unending efforts in searching for substitutes, either in synthetic forms or from plant sources, for the treatment of diabetes mellitus [13]. It is for this and other reasons that the search for safer and more effective drugs in the treatment of diabetes is directed towards the use of herbal therapy.

Medicinal plants continue to provide valuable therapeutic agents, both in the modern and the traditional system. It is fascinating to observe how cultures that never came into contact with one another came to the same conclusions about

the role of onions (Allium cepa) and garlic (Allium sativa) in health and disease states. If folk wisdom is not ignored, it may teach us valuable lessons. In ancient Chinese medicine, garlic was prescribed to aid respiration and digestion, and also for diarrhea and worm infestation [17].

Onions (Allium cepa) are highly valued herbs possessing culinary and medicinal value. Some of their beneficial properties are seen after long-term usage. Liberal use of onions can play a protective role against the development of many health problems in addition to adding flavour to our food. For medicinal purposes, onions (Allium cepa) may be used both internally and externally. Onion (Allium cepa) and other alliaceous vegetables are similar in many respects to garlic. Consumption of onion (Allium cepa) increases circulation and stimulates warmth in the body [9]. Onion (Allium cepa) is effective against many bacteria including Bacillus subtilis, Salmonella, and E. coli.. Externally, onion is used in the form of poultices (a soft substance, spread on a cloth, sometimes heated, and put on the skin to reduce pain or swellings) for tumours and ear aches[9], [3]. The tear-evoking lachrymatory chemical released when onion bulb is crushed or cut, has a stimulating effect on the mucosa and secretory glands of the eyes and nose, and it is for this that onion has been used in the treatment for respiratory problems [16]. Though many research reports [3], The George Mateljan Foundation, [16] have implicated onions (Allium cepa) in the control of blood glucose levels and dyslipidaemia, studies on the effect of onions in diabetes mellitus is scanty. It is for this reason that the current study examines the effect of onion consumption in diabetes mellitus, especially as it concerns plasma glucose level and lipid profile. The aim of the study was to determine the alteration in plasma glucose level and lipid profile in Streptozotocin-induced diabetes mellitus

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treated rats, following the administration of *Allium cepa* (onions).

## MATERIALS AND METHOD

### Chemicals and Reagents used for the Study

The various chemicals (analytical grade) that were used for this study were purchased from Rovet Scientific Ltd. 1, Wire Road, Benin city, Edo State. All the reagents for the assays were commercial kits and products of Randox Laboratories Ltd, Antrim, United Kingdom.

Metformin (Glucophage) was purchased from a local Pharmacy in Abraka. The tablets were dissolved in distilled water to get the appropriate concentrations (0.5gm/100g) that were administered to the rats, using the formula: rat dose = (human dose/average BW) x 7.

### Plant Material and Preparation of Extracts

The *Allium cepa* (onions) bulb that were used for the study were purchased from a local Market, Abraka, Ethiope-East, Local Government Area, Delta State, Nigeria, and were authenticated and identified to the species level by a taxonomist, Dr Ezenwa Kingsley of the Department of Medical plant, University of Benin, Benin city Edo State. A voucher specimen of *Allium cepa* was kept in the herbarium. Fresh onions (*Allium cepa*) were cut into small pieces and mashed, and the fluid squeezed out of the resultant slurry on daily basis. The extracted juice was administered to the rats at the dose of 0.4gm/100gm and 0.6gm/100gm body weight. Similar dosages have been applied in studies with *allium cepa* [2]. One millilitre of *allium cepa* extract/100gm body weight is equivalent to 0.4gm/100gm body weight [2].

### Experimental Animals

Mature Wistar rats, bred in the laboratory animal unit of the Emma-maria Scientific Research Laboratory, Abraka, Delta State, were used for the experiment. They were housed in an environment of normal ambient temperature and the lighting period was about 12h daily. The relative humidity was between 40%- 60%. The weight of the rats varied between 150grams-200grams. The rats were kept in wooden cages supplied with clean drinking water and fed ad libitum with commercial pellet feed (Animal Care, Asaba, Delta State). Ethical conditions governing the conduct of experiments with life animals were strictly observed. The experimental protocol was approved by the institutions ethical committee for the use of laboratory animals.

### Experimental Design

The rats were divided randomly into eight (8) groups of five (5) rats each and all rats were weighed before the start of the experiment and every other day for the duration of the experiment, using a digital weighing balance.

### Drug Preparation and Administration

Streptozotocin with Batch number 4572, Mat date 04-09-2010 to exp date 04-09-2016 was purchased from Uche Scientific Co Ltd. 21, Iga-idunganran Street, Idumota, Lagos State. Streptozotocin was dissolved in saline solution (0.9% sodium

chloride, pH 7) to get the appropriate concentration that was administered to the rats.

Diabetes was induced by administration of Streptozotocin dissolved in 0.9% sodium citrate buffer, (pH 7), intraperitoneally, at a dose of 60mg/kg body weight [2]. The rats in the control group were administered with equal volume of 0.9% sodium chloride, pH 7 (that was used to prepare the Streptozotocin solution).

Thereafter, the rats were fed with normal feed and water. Two days (48 hours) after induction, diabetes was confirmed with a random blood glucose level of  $\geq 200$ mg/dl, using the ACCUCHEK glucometer [15].

### Animal grouping

The experimental rats were grouped as follows:

Group 1a (control): not induced with Streptozotocin; not administered onions (*Allium cepa*) and received normal feed and water ad libitum for the duration of the experiment.

Group 1b (Non-diabetic rats): treated with 0.4g/100g BW onions (*Allium cepa*) extract and received normal feed and water ad libitum for the duration of the experiment.

Group 1c (Non-diabetic rats): treated with 0.6g/100g BW onions (*Allium cepa*) extract and received normal feed and water ad libitum for the duration of the experiment.

Group 1d (Non-diabetic rats): treated with standard oral hypoglycaemic drug, metformin and received normal feed and water ad libitum for the duration of the experiment.

Group 2a (Diabetic rats): untreated with neither metformin nor onion (*Allium cepa*) extract, but received normal feed and water ad libitum for the duration of the experiment.

Group 2b (Diabetic rats): treated with 0.4g/100g BW onions (*Allium cepa*) extract and received normal feed and water ad libitum for the duration of the experiment.

Group 2c (Diabetic rats): treated with 0.6g/100g BW onions (*Allium cepa*) extract and received normal feed and water ad libitum for the duration of the experiment.

Group 2d (Diabetic rats): treated with standard oral hypoglycaemic drug, metformin and received normal feed and water ad libitum for the duration of the experiment.

### Duration of the Experiment

The total duration of the experiment was six (6) weeks, as stated below:

Acclimatization period: 14 Days (maximum of 2 weeks).

Experimental period: 28days (4 weeks).

### Sample Collection

The blood glucose level was checked every seven (7) days (weekly), using the ACCUCHEK glucometer. Blood was taken from the tail vein of the rats on each occasion, [11].

After an overnight fast on the last day of the experiment, a final blood glucose check was done. The preparation for the sacrifice of the animals started with anesthetizing using light ether anaesthesia. Cotton wool soaked in diethyl ether was placed in transparent (desiccators) airtight container; the rats were put individually into the container and the lid replaced until they became anaesthetized. Each rat was placed its

dorsal surface, and a laparotomy was carried out to expose the internal organs, and blood was collected by cardiac puncture, using 5ml syringes and 21G needle into blood sample containers. The blood samples were centrifuged at a rate of 4000 rpm for 10 minutes and the serum was collected and stored in a refrigerator at 40°C for analysis of the lipid profile levels. Stored serum sample were analyzed for serum (HDL)-cholesterol, triglycerides (TG), and total cholesterol (TC) concentrations as determined by enzymatic determination, using the kits purchased from Randox laboratories Ltd, United Kingdom. Low Density Lipoprotein (LDL) was calculated from the Friedewald formula ( $LDL = Total\ cholesterol - [HDL + 0.46 - TG]$  mmol/l).

### Preparation of the Pancreas for Histological Examination

Tissue sample (pancreas) collected after sacrificing of the rats, on the completion of 28 days treatment with drug or extract, was fixed in 10% formal saline for 24h. They were washed in ascending grades of ethanol, cleared with xylene, embedded in paraffin wax, sectioned with a microtome and stained with hematoxylin and eosin (H and E) and mounted on Canada balsam (Sigma-Aldrich, St Louis, MO). All the sections were examined under a light microscope at different magnifications photomicrographs of lesions were taken with a digital microscopic eyepiece SCOPTEK DCM 500, 5.0 MEGA PIXELS connected to USB 2.0 computer at University of Benin Teaching Hospital (UBTH), Benin City, and Edo State.

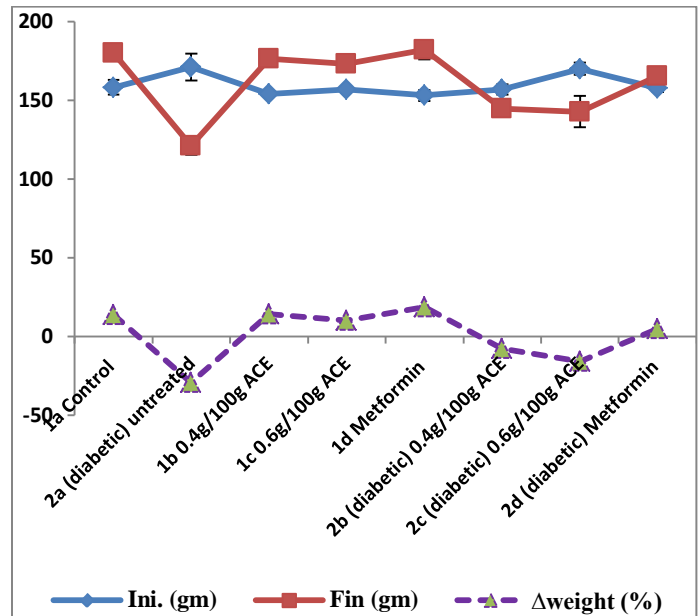
### Statistical Analysis

The results were expressed as Mean ± SEM (standard Error of the Mean). Data obtained were statistically analysed using the Student's t-Test statistics, one way analysis of variance (ANOVA), followed by post Hoc Fisher's test for multiple comparison, using the software, Statistical Package for Social Science (SPSS) version 20 windows software. Significance level was at p values < 0.05, while p values > 0.05 was considered to be statistically non-significant.

## RESULTS

### Effect of ACE on the Body Weight of Experimental Rats

The effect of administration of ACE on the body weight of normoglycaemic, diabetic rats and the percentage weight change is represented in the figure 1 below;



From Fig. 1, the mean final body weight of the control rats (normoglycaemic), was significantly ( $p < 0.05$ ) greater than the mean of their initial body weight at the beginning of the experiment. Similarly, the mean final body weights of the normoglycaemic rats (groups 1b, 1c and 1d) treated with various doses of ACE and metformin respectively were significantly ( $p < 0.05$ ) greater than the means of their respective initial body weights. The body weight of diabetic rats treated with various doses of ACE was significantly lower than the control group. However, the percentage decrease in the body weight of the diabetic rats treated with ACE when subjected to multiple comparison was significantly lower those of the untreated diabetic rats.

### Effect of ACE on the Fasting Blood Glucose of Experimental Rats

The effect of administration of ACE on the Fasting Blood Glucose of normoglycaemic, diabetic rats and the percentage change in fasting blood glucose is represented in the figure 2 below;

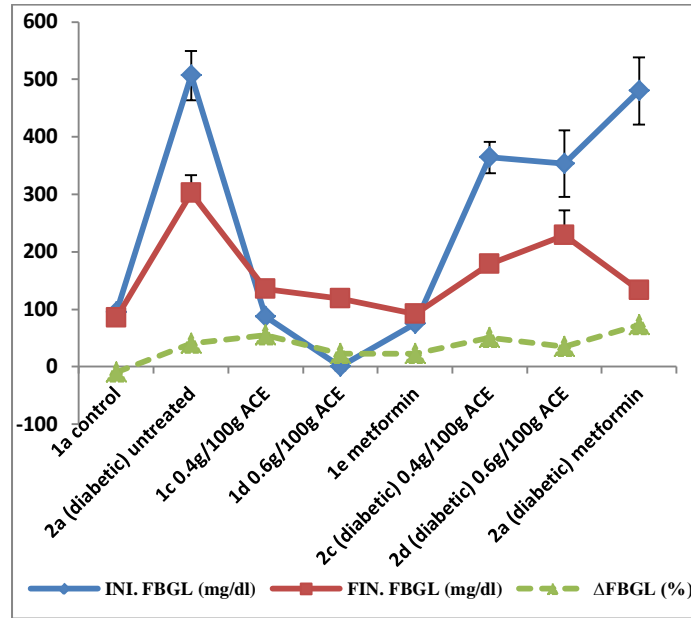
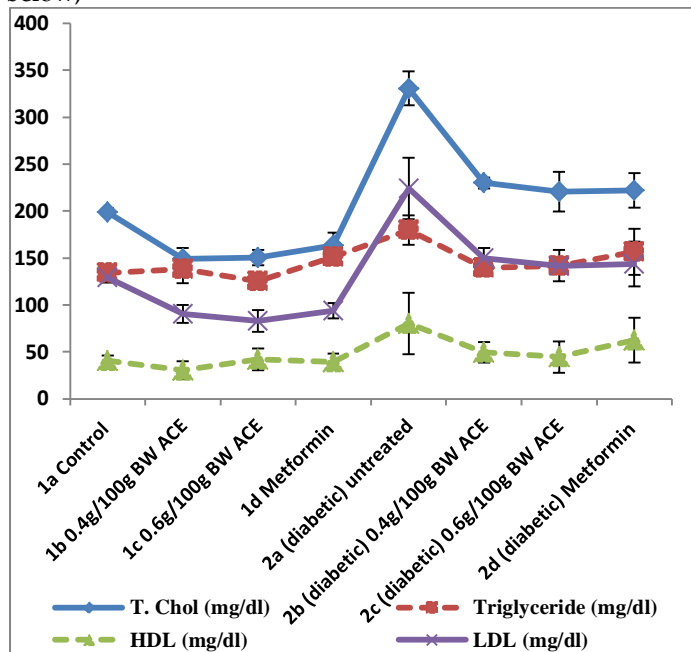


Fig. 2 shows that the mean final fasting blood glucose levels of the treated, normoglycaemic, rats increased when compared to the final mean value of the untreated, normoglycaemic (control) rats. The final mean values of the fasting blood glucose levels of the normoglycaemic rats, treated with 0.4g/100g BW and 0.6g/100g BW A. cepa respectively were significantly ( $p < 0.05$ ) greater than that of the untreated, normoglycaemic (control) rats. This was not the case with respect to the normoglycaemic rats, treated with metformin or 0.2g/100g BW A. cepa; in which their final blood glucose levels were not significantly different from the control level.

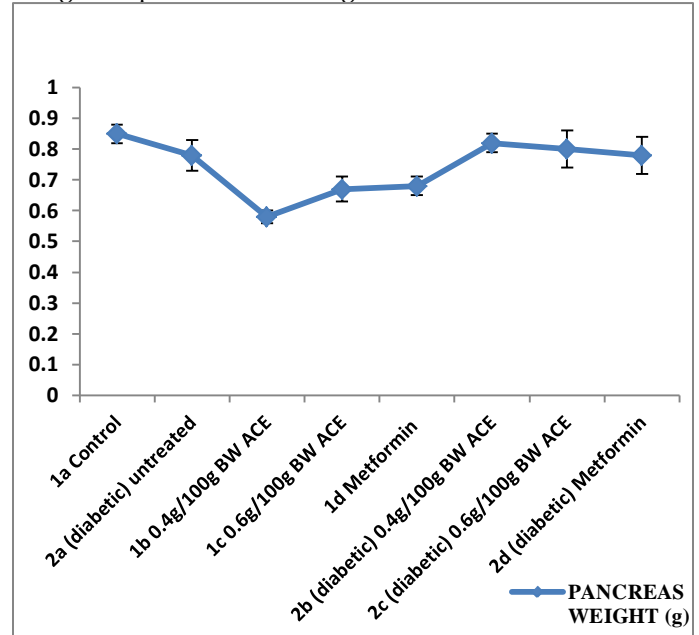
### Effect of ACE on the Lipid Profile of Experimental Rats

The effect of administration of ACE on the Lipid profile of normoglycaemic, diabetic rats is represented in the figure 3 below;



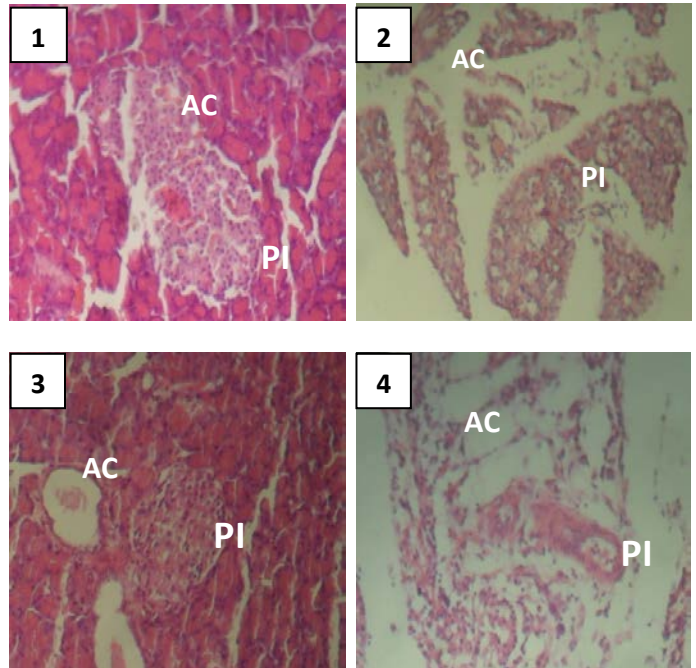
### Effects of ACE on the weight of the Pancreas

The effect of administration of ACE on the pancreas weight of normoglycaemic, diabetic rats and the percentage weight change is represented in the figure 4 below;



### Effect of ACE on the Histological features of diabetic and normoglycaemic rats

Histological effect of Treatment with A cepa and metformin on the pancreas of the experimental rats are shown in the micrographs below.



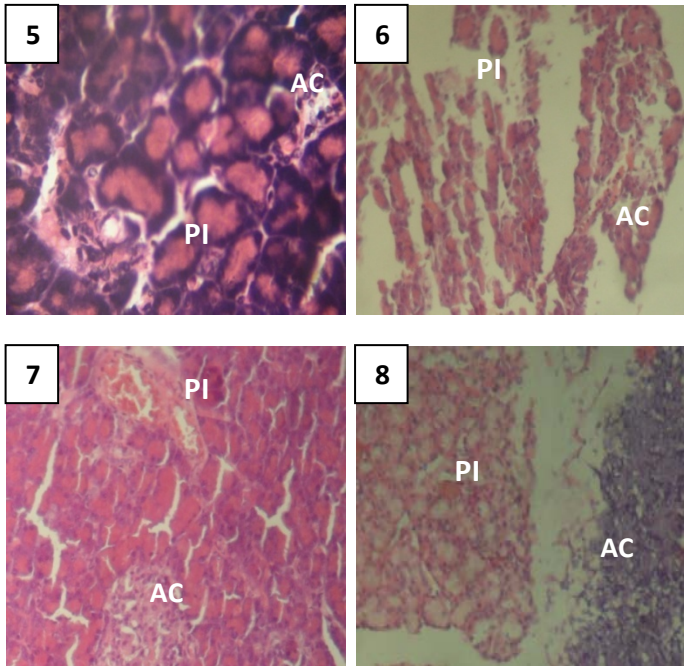


Plate 1: Pancreas of the normoglycaemic rats (control); (H and E x 400) represents sections of the pancreas, showing the exocrine parenchyma disposed in lobules within which are acini composed of cuboidal cells and lumina filled with eosinophilic material. Few ductules, blood vessels are seen. Scant clusters of pancreatic islets are also present within the exocrine parenchyma. Few fat lobules are present in the periphery of the pancreatic tissue. Diagnosis: Features are in keeping with a NORMAL PANCREAS.

Plate 2: Pancreas of the non-diabetic rats, treated with 0.4g/100g BW A. cepa; (H and E x 400) represents sections of the pancreas showing exocrine pancreas disposed in lobules which are composed of acini lined by cuboidal cells and lumen filled with eosinophilic material. The endocrine pancreas is composed of several clusters of islet cells disposed within the exocrine pancreas. The cells are more abundant than in the previously viewed sections. Diagnosis: Pancreatic biopsy- features are in keeping with MILD ISLET HYPERPLASIA.

Plate 3: Pancreas of the non-diabetic rats treated with 0.6g/100g BW A. cepa; (H and E x400). The islet cells are composed of moderately sized clusters of cells with round to oval nuclei. Coarse chromatin is prominent within the nucleus and the surrounding cytoplasm is eosinophilic. Diagnosis: Pancreatic biopsy- features are in keeping with a NORMAL PANCREAS.

Plate 4: Sections of the pancreas of the non-diabetic rats treated with metformin; (H and Ex 400) represents sections of the pancreas showing the exocrine pancreas disposed in lobules which are composed of acini lined by cuboidal cells and lumen filled with eosinophilic material. The endocrine pancreas is composed of several clusters of islet cells disposed within the exocrine pancreas. The islet cells are composed of moderately sized clusters of cells with round to oval nuclei. Coarse chromatin is prominent within the nucleus and the

surrounding cytoplasm is eosinophilic. Diagnosis: Pancreatic biopsy- features are in keeping with a NORMAL PANCREAS.

Plate 5: Section of the pancreas of the diabetic rats untreated (Group 3); (H and Ex 400) represents sections of the pancreas showing markedly distorted pancreatic islets with abundant lobules of adipose tissues. There is extensive loss of cytological details in the few parenchymas that is present. Diagnosis; pancreatic biopsy- Features are in keeping with PANCREATIC ATROPHY.

Plate 6: Sections of the pancreas of the diabetic rats treated with metformin (Group2a); (H and E x 400) showing the exocrine pancreas appears as in control. The islets are abundant and hyperplastic. Diagnosis: Pancreatic biopsy; features are in keeping with MILD PANCREATIC ISLET HYPERPLASIA.

Plate 7: Sections of the pancreas of the diabetic rats, treated with 0.4g/100g BW A. cepa (Group 2c); (H and E x 400) showing the exocrine pancreas as described for control. Islet cell clusters are present but appear hypoplastic in character. Diagnosis: pancreatic biopsy is in keeping with PANCREATIC ISLET HYPOPLASIA.

Plate 8: Pancreas of the diabetic rats treated with 0.6g/100g BW A. cepa (Group 2d); (H and E x 400) represents sections of the exocrine pancreas as described for normal exocrine pancreas. No islet cells seen. Diagnosis: Pancreatic tissue biopsy; Features are in keeping with PANCREATIC ISLET APLASIA.

## DISCUSSION

From the results of the present study, treatment with Allium cepa caused an increase in the overall weights, at the end of the experiments, in both untreated, non-diabetic (control) Wistar rats and non-diabetic rats treated with metformin or varying doses of Allium cepa. The increase in weight is unlikely to be as a result of treatment with either metformin or Allium cepa, as the increase in weight observed in the treated non-diabetic rats was not significantly different from the increase in weight observed in the untreated non-diabetic rats. This is irrespective of the dose of Allium cepa administered to the rats.

In the case of the diabetic rats, while treatment with metformin caused an increase in the body weights of the rats, treatment with the three doses of Allium cepa studied caused loss of body weight, suggesting that the mechanisms involved in the hypoglycaemic effect of metformin and Allium cepa may not be similar. Metformin has been shown to increase the sensitivity of peripheral tissues to insulin thereby increasing glucose uptake by the tissues that is translocation of glucose transporters in muscle and adipose tissue to increase their glucose uptake and the inhibition of release of free fatty acids into the circulation due to suppression of the activity of hormone-sensitive lipase and a simultaneous increase in their clearance from the circulation.

An important observation from the experiment with the normoglycaemic rats, treated with metformin or different doses of Allium cepa is that Allium cepa increased the fasting

blood glucose in the rats, suggesting that they have hyperglycaemic property in the non-diabetic state, following prolonged administration. However, the increased levels of fasting blood glucose observed were within the normoglycaemic range (blood glucose levels  $\leq 200$ mg/dl is normoglycaemic in experimental Wistar rats, [15].

Allium cepa has been shown to reduce blood glucose levels in a dose dependent manner with the highest reduction being at 300mg/kg [10], [14]. The results of this study are in agreement with those of previous studies. While 0.2g/100g BW of Allium cepa caused only about 2.85% decrease in fasting blood glucose level, it was about 50.00% and 35.05% with respect to 0.4g/100g BW and 0.6g/100g BW of Allium cepa.

Dyslipidaemia, is a common feature in diabetes mellitus [5] and its occurrence has been shown to increase the risk of coronary heart disease [7], [8]. The marked hyperlipidaemia in diabetes mellitus has been attributed to the uninhibited actions of lipolytic hormones on the fat depots [4].

Specifically, hypercholesterolaemia has been reported in Streptozotocin induced diabetic rats [14], [12]. In the present study, there was a significant ( $p < 0.05$ ) increase in the serum total cholesterol level in the untreated Streptozotocin induced diabetic rats, but treatment with Allium cepa significantly ( $p < 0.05$ ) decreased the cholesterol level in a dose dependent manner. The serum cholesterol lowering ability of Allium cepa extract was observed to be better than that of metformin, especially at 0.4g/100g BW and 0.6g/100g BW doses respectively. Similar dose dependent effect of Allium cepa was reported by Ozuogwu [10].

With respect to triglycerides, high density lipoprotein and low density lipoprotein levels, their serum levels were significantly ( $p < 0.05$ ) higher in the Streptozotocin induced diabetic rats studied (Tables 6; 10 and 12) when compared with the levels in the untreated non-diabetic control rats. However, just as in the case of serum total cholesterol, treatment with Allium cepa caused significant ( $p < 0.05$ ) reduction in their levels in a dose dependent manner. In line with this finding was the reported observation that dietary dehydrated onion significantly lowered the level of low density lipoproteins in hypercholesterolaemic rats. Also Ozuogwu [10] reported a significant dose dependent lowering of serum total lipid levels in Streptozotocin induced diabetic rats treated with Allium cepa. While they suggested that the hypolipidaemic effect of Allium cepa may be related to its active ingredient, allyl propyl disulphide, [6] implicated S-methyl cysteine sulphoxide (SMCS) as being contributory to the hypolipidaemic effect of Allium cepa.

The histology of the pancreas of the animals treated with Allium cepa in this study showed very little change in the atrophic islet cells. A similar histological finding was made in the animals treated with metformin. The pancreatic Islet cells of the untreated diabetic rats were atrophic, suggesting lack of secretory activity in the Islet cells.

Streptozotocin induces diabetes by destroying the beta-cells of islet of Langerhans in the pancreas, leading to reduction in the synthesis and release of insulin [15]. The observation

from the histological experiments of the current study also supports this fact, that is, that the pancreatic Islet cells of the Streptozotocin-induced diabetic rats were atrophic.

Another important finding from the histology of the pancreas in this study is that with the maximal dose of Allium cepa (0.6g/100g BW) used in the study, the pancreatic Islet cells were aplastic. This might explain the poorer blood glucose control observed with respect to the diabetic rats treated with that dose of Allium cepa. Though it is not clear by which way Allium cepa at the dose of 0.6g/100g BW produced a suboptimal control of blood glucose level, the observation from the study will suggest that beyond a certain dose of Allium cepa extract, the control of blood glucose level in the Streptozotocin-induced diabetic rats will be suboptimal. Based on the results of the present study, the optimal dose may be about 0.4g/100g BW of the extract.

Treatment of the diabetic rats with Allium cepa or metformin did not significantly alter the weights of the pancreas suggesting that the treatments targeted specific cells, possibly the beta cells; hence they did not have overwhelming effect on the weights of the pancreas. However, it is difficult to explain why similar treatments of the non-diabetic rats caused significant ( $p < 0.05$ ) decrease in the pancreatic weights.

## CONCLUSION

This study has shown that Allium cepa has potent hypoglycaemic and hypolipidaemic effects in the diabetic state, and therefore, has the ability to ameliorate possible complications associated with diabetes mellitus, such as atherosclerosis, diabetic retinopathy, neuropathy and renal diseases. Also, Allium cepa has immense therapeutic prospects against the development, progression and complications of diabetes mellitus.

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