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HISTOPANCREATIC ARCHITECTURE IN DIABETES MELLITUS WISTAR RATS TREATED WITH EXTRACT OF BEETROOT

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ABSTRACT

This study assessed the effects of Aqueous Beetroot extract on the pancreas of diabetes mellitus Wistar rats by evaluating histo-architecture. Thirty male Wistar rats, aged 8 to 10 weeks and weighing 160-200 g, were divided into five groups: A-normal control, B-diabetic only, C-diabetic treated with beetroot, D-diabetic treated with metformin, and E-beetroot extract only. Diabetes was induced via a single intraperitoneal injection of streptozotocin (STZ) at a dose of 70 mg/kg. After 72 hours of diabetes, the rats received aqueous beetroot and Metformin (500mg/kg and 100 mg/kg bodyweight respectively) orally, daily for four weeks. Body weight and blood glucose levels were measured weekly, and at the end of the treatment, relative pancreas weight and histological evaluations were performed. Results indicated significant differences ($p<0.05$) in body weight, blood glucose levels, and relative pancreas weight between the diabetic+beetroot and diabetic+metformin groups compared to the diabetic group. Histological findings revealed normal pancreatic histoarchitecture with numerous islet cells in the normal control and beetroot-only groups, while the diabetic group showed reduced islet cell mass. The diabetic+beetroot and diabetic+metformin groups exhibited minimal damage. The normal control and beetroot-only groups had normal reactions to Periodic acid-Schiff (PAS), while the diabetic control group showed positive results. Some PAS positivity was noted in the diabetic+beetroot and diabetic+metformin groups. Overall, aqueous beetroot extract demonstrated protective effects on pancreatic health, mitigating the damage induced by diabetes mellitus.

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INTRODUCTION

Diabetes Mellitus is a chronic metabolic disorder marked by persistent hyperglycaemia, posing a significant public health issue globally due to its severe complications when poorly managed [1]. Many patients struggle to keep up with medication schedules and dietary recommendations, despite the high costs of care [1]. The disorder is defined by persistent hyperglycaemia measured on two or more occasions, resulting from either reduced insulin secretion, increased insulin resistance, or both. Around 10% of diabetes cases are due to Type 1 diabetes mellitus, characterised by insufficient or absent insulin production caused by autoimmune destruction of the pancreatic beta cells. In contrast, about 90% of diabetes cases are classified as Type 2 diabetes mellitus, involving relative insulin deficiency due to peripheral insulin resistance and inadequate compensatory insulin production [2].

There are also other forms like gestational diabetes mellitus and maturity-onset diabetes [3]. The significance of plants in our daily lives is profound, with many classified as edible or therapeutic, offering various uses and benefits [4]. Medicinal plants are those utilised for treating diverse diseases. Several plants, often marketed as Chinese herbal medicine, have been studied for their antihypeglycemic effects in both animal and human research [4]. However, most herbal medicines have not yet been rigorously evaluated for their advantages or potential adverse effects on body tissues and organs [4]. One notable plant is Beetroot, widely used in cooking and traditional medicine [5]. It is employed to address several health issues, including anaemia and diabetes, by potentially lowering blood sugar levels in diabetic patients [5]. Beetroot is also beneficial for heart disease, digestive issues, kidney problems, and gallbladder concerns. It aids in preventing cataracts, treating respiratory problems, and improving blood circulation [5].

As a member of the Chenopodiaceae family, it is celebrated as one of the healthiest vegetables and is rich in sucrose, making it a good alternative to tropical sugarcane. Given its nutrient density, beetroot is undoubtedly considered a 'super-food' [5]. This study explored the beneficial effects of aqueous beetroot extract on the pancreas of Wistar rats with diabetes mellitus by examining histo-architecture.

MATERIALS AND METHODS

Plant Materials: The beetroot was harvested from the Livingstone district, Southern Province of Zambia. Before the study, identification of the beetroot was conducted at the University of Zambia's School of Natural Sciences under the Department of Biological Sciences. The beetroot was air-dried, pounded, and then ground and sieved to obtain a homogeneous powder. Extraction was performed using lyophilisation methods [6].

Animals and Animal Management: Thirty adult Wistar rats (*Rattus norvegicus),* presumed healthy, were used. The rats, aged between 8 to 10 weeks and weighing between 160-200 g, were housed in five cages (6 rats per cage) in the animal holdings of the Department of Anatomy, Mulungushi University School of Medicine and Health Sciences. They were maintained on standard pelleted feeds (Wealth-gate pelletized feeds) and had free access to clean water and feed (*ad libitum*).

Induction of Diabetes: Diabetes was induced using streptozotocin (STZ). After a baseline glucose level was established from fasting overnight, the rats were injected with STZ at a dose of 70 mg/kg body weight [7]. Following the injection, the rats were returned to their normal feeding cycle. Diabetes was confirmed 72 hours post-STZ administration by measuring fasting blood sugar levels using a tail vein puncture, with a glucometer. Animals were considered diabetic if fasting blood glucose levels exceeded 10 mmol/l (≥ 250 mg/dl).

Experimental Design: The 30 Wistar rats were randomly divided into five groups (6 rats per group): - Group A: normal control - Group B: diabetic control - Group C: diabetic + beetroot - Group D: diabetic + metformin - Group E: beetroot extract only.

Beetroot Mode of Administration: The dosage of aqueous extracts of beetroot used was based on reports of Refaat and El-Nassag [8]. Beetroot was dissolved in physiological saline and administered orally via an orogastric cannula to Group C (n=6) at a dose of 500 mg/kg body weight daily at 9:00 – 10:00 a.m. for up to four weeks. Group E (n=6) also received the aqueous extract at the same dosage, while Group D rats (n=6) were treated with metformin at 100 mg/kg body weight. Group A (n=6) received no treatment with STZ or beetroot extract.

Measurement of Blood Glucose Levels: Blood glucose levels were evaluated in overnight-fasted rats from 9:00 to 10:00 hours using the glucose oxidase method with One Touch Ultra 2 glucometers (Accu-Chek Compact Plus). Blood was collected from the median caudal vein of the tail. Blood glucose levels were monitored weekly for one week prior to diabetes induction and during four weeks of treatment [9].

Measurement of Body Weight (g): Body weight (g) of the rats was recorded weekly during a one-week acclimatisation period before diabetes induction and continuously during the four weeks of the experimental treatment, using a weighing scale (Venus VT 30 SL) [10].

The Relative Pancreas Weight (%): The relative pancreas weight was calculated as the ratio of the pancreas weight to the terminal body weight of each respective rat, recorded as a percentage using a sensitive weighing balance (Sonyf3g brand) [11].

Histological Process: At the study's conclusion, the animals were sacrificed via euthanasia. Each rat was positioned supine on a dissecting board and pinned through the fore and hind paws. The abdomens were dissected with Scalpel and surgical blade, and pancreas were carefully removed and weighed. Tissues were fixed in freshly prepared formol saline for 72 hours and processed for routine histological examinations, stained with Hematoxylin and Eosin (H&E) to observe cellular morphology changes and Periodic acid-Schiff (PAS) staining was used to checked for the presence of the glycogen.

Photomicrography: Photomicrographs of the histological sections of the prefrontal cortices were captured with an Olympus microscope (New York, USA) in the Department of Human Anatomy, Mulungushi University School of Medicine and Health Sciences, Livingstone Campus, Zambia.

Statistical Analysis: Data were presented as mean ± standard error of the mean (mean ± SEM) and analysed using one-way ANOVA. All graphs were created using Excel (Microsoft Corporation, USA). P values less than 0.05 ($p < 0.05$) were considered statistically significant.

RESULTS

Average Body weight on weekly basis (g): Figure 1 demonstrates changes in the weekly body weight changes of Wistar rats across different experimental groups. Initially, during acclimatization (week -1) and after induction (week 0), there were no significant weight changes in comparison to the control group ($p>0.05$). However, by week 3, a notable decrease in weight was observed in the diabetic group compared to the control, diabetic + beetroot, and beetroot only groups, which was statistically significant ($p<0.05$). By week 4, the diabetic group recorded the lowest bodyweight which also showed statistically significant differences ($p<0.05$) when compared to the other groups.

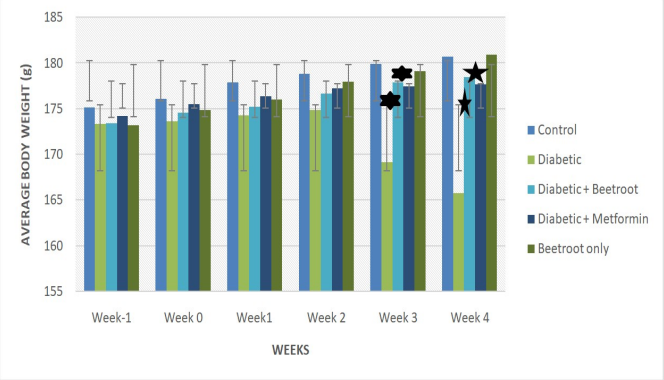

Figure 1. Average bodyweight on weekly basis (g) Data was expressed as mean ± SEM ($p<0.05$)

Blood Glucose Level on Weekly Basis (mg/dl): Figure 2 demonstrates the blood glucose levels taken weekly in various groups of Wistar rats. The blood glucose levels of multiple groups were normal in the acclimatisation week (week-1), with no significant change compared to the control group. However, during induction (week 0), there was an increase in blood glucose in the diabetic, diabetic + beetroot, and diabetic + Metformin groups. A significant decline in blood glucose was noted after treatment in week 1 for the diabetic + beetroot group when compared to the diabetic and diabetic + Metformin groups, with a significance level of $p<0.05$. The diabetic + beetroot group continued to show a significant decline ($p<0.05$) in blood glucose levels until week 4 of treatment. By week 4, the diabetic + beetroot group had reached normal blood glucose levels, which was not statistically significant compared to the control and beetroot groups, but was significant when compared to the diabetic-only group. The diabetic + Metformin group also reached normal glycemic levels in week 4, although it was slightly higher compared to the diabetic + beetroot group.

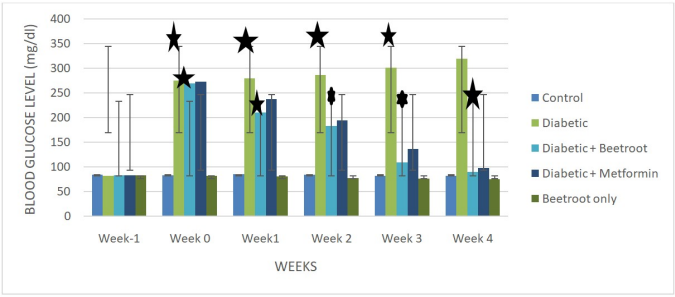

Figure 2. Blood Glucose Levels of Wistar rats on weekly basis (mg/dl). Data was expressed as mean ± SEM (p<0.05)

Relative Pancreas Weight (%): Figure 3 illustrates the relative weight of the pancreas across different groups of Wistar rats. Notably, the diabetic group exhibited a significant reduction in pancreas weight compared to the control group, as well as the diabetic + beetroot, diabetic + Metformin, and beetroot-only groups. While the diabetic + beetroot group showed a decrease in pancreas weight compared to the control and beetroot-only groups, this change was not statistically significant (p>0.05). Similarly, the diabetic + Metformin group also demonstrated a reduction in pancreas weight in comparison to the control and beetroot-only groups, though this result was also not significant (p>0.05) and slightly lower than that observed in the diabetic + beetroot group.

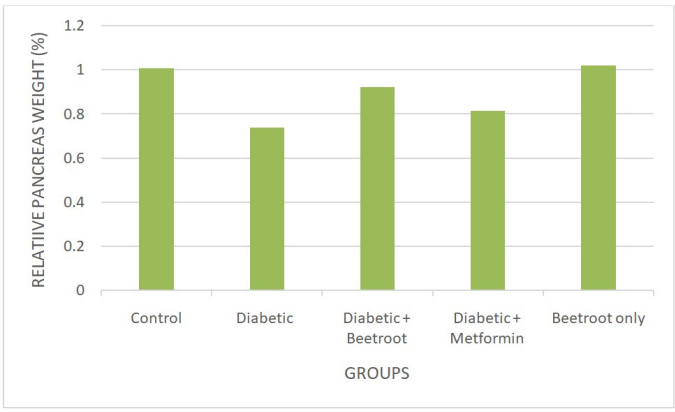

Figure 3. Relative Pancreas Weight (%). Data was expressed as mean ± SEM (p<0.05)

Histological Findings: The photomicrographs revealed that the normal histoarchitecture of pancreatic islets was well-preserved in both the normal control and beetroot-only groups (Figures 4A and 4E). In contrast, the untreated diabetic group displayed a significant reduction in the cell mass of the pancreatic islets (Figure 4B).

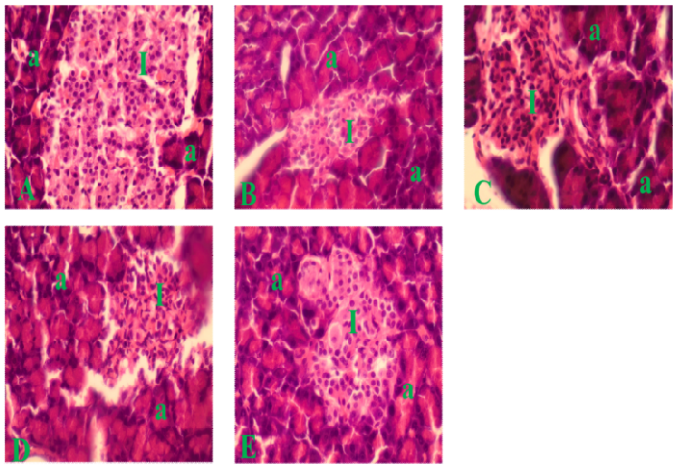

Figure 4. Photomicrograph showing the Pancreatic islet at day 28. H&E X400. A- Normal control, B – Diabetic, C – Diabetic+ Beetroot, D – Diabetic+Metformin and E- Beetroot only. I- Pancreatic islet, a-Acini

Interestingly, the diabetic groups that received beetroot and Metformin treatments maintained normal histoarchitecture of the pancreatic islets (Figures 4C and 4D). Furthermore, the acini from the normal control and beetroot-only groups showed a negative reaction to the Periodic Acid-Schiff (PAS) staining (Figures 5A and 5E). Conversely, the diabetic control group exhibited positive reactions to PAS staining (Figure 5B). The diabetic + beetroot and diabetic + Metformin groups displayed varying degrees of positive reactions in their histoarchitecture (Figures 5C and 5D).

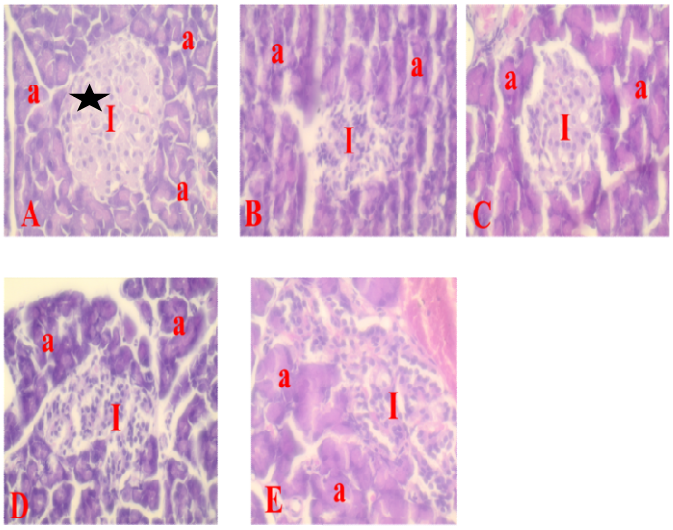

Figure 5. Photomicrograph showing the Pancreatic islet at day 28. PAS X400. A- Normal control, B – Diabetic, C – Diabetic+Beetroot, D – Diabetic+Metformin and E- Beetroot only. I- Pancreatic islet, a-Acini

DISCUSSION

Beetroot, which is rich in antioxidants and nitrates, has the potential to lower blood glucose levels and could serve as an alternative approach in diabetes management [6]. This study illustrated the protective effects of aqueous beetroot extract on body weight, blood glucose levels, relative pancreas weight, and the histoarchitecture of the pancreas in diabetic Wistar rats. As shown in Figure 1, the diabetic group experienced significant weight loss during weeks three (3) and four (4) compared to the control and beetroot-only groups. This weight loss can be attributed to insufficient insulin production, which prevents body cells from utilising glucose as an energy source, leading to the breakdown of adipose tissue and muscle for energy. Consequently, a rapid loss of body weight occurred in the Wistar rats [11]. Similarly, Yusuf et al. [7][8] reported significant weight loss in the diabetic control group compared to the control group, resulting from disturbed metabolism of fat, protein, and carbohydrates due to oxidative stress induced by diabetes. These findings align with those of the current study. The diabetic + beetroot group did not show significant weight loss compared to the control and beetroot-only groups. This can be explained by the antioxidant and anti-inflammatory properties of beetroot, attributed to compounds such as betalains, which helped prevent further destruction of beta cells in the pancreatic islets and facilitated insulin production. This led to the suppression of gluconeogenesis and enhanced energy metabolism across several organs [2]. Furthermore, research indicated that beetroot provides bioactive compounds with antioxidant activity against oxidative stress-related diseases, including diabetes mellitus, which supports the current findings [9]. The diabetic + metformin group similarly exhibited no significant weight loss compared to the control and beetroot groups, likely due to the activation of Adenosine Monophosphate-activated protein kinase, which enhances insulin sensitivity and increases glucose uptake and utilisation in peripheral tissues [10]. In Figure 4.2, all groups induced with streptozotocin exhibited elevated blood glucose levels (p<0.05) after 72 hours from the baseline.

The diabetic group showed a significant increase in blood glucose levels from induction (week 0) through week four compared to the control and beetroot-only groups. This increase is a result of a combination of insufficient insulin production by the pancreas, insulin resistance, and inappropriate glucagon secretion [11]. This is corroborated by the study conducted by Yusuf et al. [7],[8], which found that the diabetic control group experienced significant increases in blood glucose levels due to damage to beta cells resulting in low insulin production. In the diabetic + beetroot group, there was a notable decline in blood glucose levels after one (1) week of treatment. By week four (4), blood glucose levels in the diabetic + beetroot group reached normal levels, which were not statistically significant compared to the control and beetroot-only groups, but significant when compared to the diabetic-only group. Studies have shown that beetroot may improve the body's response to insulin sensitivity and reduce the risk of insulin resistance, attributed to its high nitrate and betalain content that promotes antioxidant properties key to lowering insulin resistance [5][12]. This aligns with findings from earlier research, which concluded that beetroot treatment significantly improved blood glucose levels in diabetic albino rats due to its antioxidant properties [13]. The diabetic + metformin group also demonstrated a significant decline in blood glucose levels during the first week of treatment and reached normal glycemic levels by week four. Notably, the diabetic + metformin group showed slightly higher blood glucose levels compared to the diabetic + beetroot group, highlighting the effectiveness of beetroot extract in glucose control. The hypoglycemic effect of metformin is attributed to reduced hepatic glucose production, decreased intestinal glucose absorption, and enhanced insulin sensitivity, which increases peripheral glucose uptake and utilisation [14].

Figure 3 illustrates that the diabetic group exhibited a significant decline in relative pancreas weight compared to the control, diabetic + beetroot, diabetic + metformin, and beetroot-only groups. This decline is linked to either beta-cell destruction or insulin resistance, leading to beta-cell dysfunction and subsequent apoptosis [15]. Yusuf et al. [7] also reported a significant decrease in relative pancreatic weight in the diabetic control group compared to the control group, attributed to cell death from DNA fragmentation due to oxidative stress and the release of oxygen radicals, resulting in islet fibrosis. Their results are consistent with those observed in the current study. In contrast, the diabetic + beetroot group did not show a significant decline in relative pancreas weight compared to the normal and beetroot-only groups. This can be attributed to the presence of betalains in beetroots, which help alleviate the reactive oxygen species (ROS) generated during hyperglycemia-induced oxidative stress, thus preserving beta-cell integrity and function. A study focusing on beetroot's protective effects on glucose-damaged organs reported that treatment with a high dose of beetroot extract reversed alterations in oxidants, inflammatory, and apoptotic markers while also reducing fasting circulatory glucose [16], reinforcing the findings of this current study. Similarly, the diabetic + metformin group exhibited no significant decline in relative pancreatic weight compared to the normal and beetroot-only groups. However, relative pancreas weight in the diabetic + metformin group had decreased more than in the diabetic + beetroot group, suggesting the efficacy of beetroot extract in preserving relative pancreatic weight. The protective effects of metformin stem from its ability to inhibit gluconeogenesis and protect pancreatic beta cells from glucotoxicity, thereby preserving their integrity [17].

Histological investigations assessed the normal histoarchitecture and the presence of numerous pancreatic islets in both the normal control and beetroot-only groups (Figures 4A and 4E). However, the diabetic group exhibited disrupted histoarchitecture with reduced cell mass in the pancreatic islets (Figure 4B). Persistent hyperglycemia results in poorly functioning beta cells that de-differentiate and undergo apoptosis. Hyperglycemia induces apoptosis through oxidative stress, where free radicals damage cellular lipids, proteins, and DNA [18]. Normal histoarchitecture was maintained in the pancreatic islets of the diabetic + beetroot and diabetic + metformin groups (Figures 4C and 4D). Betalains in beetroot have been shown to alleviate oxidative and nitrative stress by scavenging free radicals, preventing DNA damage, and reducing low-density lipoprotein (LDL) levels [19]. The ameliorative effects of beetroot observed in this study align with earlier findings that highlighted the regeneration and improvement of pancreatic tissue and enhanced insulin secretion following treatment with betanin in diabetic rats [20]. The acini of the normal control and beetroot-only groups showed a negative reaction to the Periodic Acid-Schiff (PAS) staining (Figures 5A and 5E), indicating a normal balance between glycogen synthesis and degradation. Conversely, the diabetic control group displayed a positive PAS reaction (Figure 5B), indicative of excess glycogen accumulation within cells due to persistent hyperglycemia and increased glycogen synthesis. A study by Ravikumar et al. [21] on cytological intracellular glycogen evaluation using PAS staining observed that diabetic subjects exhibited cytoplasmic PAS positivity due to increased glycogen accumulation ($P < 0.05$), with a greater number of glycogen-containing cells. Duration of diabetes had less impact on intracellular glycogen accumulation ($P > 0.05$), reinforcing the current findings. The diabetic + beetroot and diabetic + metformin treated groups exhibited varying levels of positive PAS staining in their histoarchitecture (Figures 5C and 5D) due to improved insulin sensitivity and secretion, resulting in a balanced insulin and glucose homeostasis following treatment. A study examining the effect of bioactive compounds in beetroot juice on insulin and glucose regulation reiterated these findings [22].

CONCLUSION

The present study confirms the antihyperglycemic effect of aqueous beetroot extract, demonstrating its capability to mitigate damage to the histoarchitecture of the pancreas in streptozotocin-induced diabetic Wistar rats.

Conflict of interest: no conflict of interest reported.

Statement of ethical Consideration: The ethical approval and permission for the study was obtained from Mulungushi University School of Medicine and Health Sciences Research ethic committee.

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