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CARDIO PROTECTIVE EFFECT OF AN AQUEOUS EXTRACT OF BEETROOT ON DIABETIC WISTAR RATS

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ABSTRACT
Beetroot is a medicinal plant used for the treatment and management of numerous ailments including diabetes mellitus. This study investigated the cardio-protective effects of beetroot extract on diabetic Wistar rats. Thirty male rats (160–200 g) were divided into five groups (n=6): normal control, diabetic only, diabetic + beetroot (500 mg/kg), diabetic + metformin, and beetroot only. Diabetes was induced with streptozotocin of 70 mg/kg body weight. After 72 hours of confirmation of hyperglycemia, treatments were administered orally for four weeks. Blood glucose levels and body weights were measured weekly, and relative organ weights were recorded after sacrifice. Results showed significant reductions in blood glucose levels, improved body weight and relative heart weights in treated groups compared to the diabetic-only group ($p<0.05$). Histology revealed preserved cardiomyocytes in treated groups, while diabetic group rats showed degeneration. PAS staining indicated reduced glycation in treated groups compared to diabetic group rats. Beetroot extract demonstrated protective effects against diabetic cardiac tissue damage.

KEYWORDS: Heart, Hematoxylin and Eosin stain, Diabetes mellitus, Metformin, Beetroot.

1. INTRODUCTION

Diabetes is a metabolic disease that involves inappropriately raised blood glucose levels, which affect how proteins, lipids, and carbohydrates are metabolized.[1][2] It is defined as an increase in blood sugar following any food. According to Modak M *et al*.[2] diabetes is caused by either inadequate or dysfunctional insulin.

According to data, this disease currently affects 2.8% of the world's population of humans, and by 2025, that percentage is expected to reach more than 5.4%.[3] Early detection, diagnosis, treatment, and lifestyle changes are required for diabetes. The fifth-largest cause of death in the 21st century is diabetes, a condition that affects a lot of individuals.[4]

Diabetes' destructive effects and consequences all highlight the urgent need for qualified medical care and effective therapies. Diabetes can now be managed with a variety of therapies, including insulin therapy, medication, and nutrition therapy. Various kinds of glucose-lowering medications have distinct anti-diabetic effects. The medications sulfonylurea and meglitinides may increase insulin secretion, biguanides and thiazolidinediones may increase glucose marginal absorption, alpha-glucosidase may delay the assimilation of carbohydrates from the intestines, and biguanides may reduce hepatic gluconeogenesis.[5]

Despite significant progress in diabetes management over the past fifty years, the results of diabetes treatment are still far from optimal. These remedies might come with some risks, such as toxicity, pharmacological problems, and drug resistance (loss of efficacy). For instance, 44% of individuals have sulfonylurea potency loss after 6 years of medication. It is hypothesized that medications to reduce blood sugar cannot treat hyperlipidemia.[6]

Medical professionals must also carefully consider the side effects of medications and their effects on one another in ex vivo. Many treatments using medicinal plants are currently highly recommended.[7] Carotenoids, flavonoids, terpenoids, alkaloids, and glycosides are present in almost all plants and frequently have anti-diabetic properties.[8]

The anti-hyperglycemic effects of plant therapy are frequently a result of their capacity to enhance pancreatic tissue function, which is accomplished by augmenting insulin secretions or reducing the bowel assimilation of glucose. The diabetic population today has been growing and raising concerns in the medical professional space and the public. The purpose of this research is to know whether an aqueous extract of beetroot can protect the heart from damage caused by diabetes in Wistar rats.

2. MATERIALS AND METHODS

Plant materials

Beetroot was harvested from the Livingstone District in the Southern Province of Zambia. Before the study, the plant material was authenticated at the University of Zambia, School of Natural Sciences, under the Department of Biological Sciences. The harvested Beetroot was air-dried, pounded, and ground into a fine powder, which was then sieved to obtain a homogeneous mixture. Extraction was performed following the method described by Borjan et al.[9]

Animals and Animal management

Thirty (30) adult male Wistar rats (Rattus norvegicus), presumed healthy and aged between 8 to 10 weeks (body weight: 160–200 g), were used for this study. The animals were housed in five cages (6 rats per cage) in the animal holding facility of the Department of Anatomy, Mulungushi University School of Medicine and Health Sciences. They were maintained on standard pelletized feed (Wealth-gate®) with ad libitum access to clean water and feed.

Induction of diabetes

Diabetes was induced using streptozotocin (STZ). After an overnight fast, baseline glucose levels were measured, and the rats were injected intraperitoneally with STZ at a dose of 70 mg/kg body weight, followed by a return to their normal feeding regimen.[10] Diabetes was confirmed 72 hours post-STZ administration by measuring fasting blood glucose levels via tail vein puncture using a glucometer. Rats with blood glucose levels ≥ 10 mmol/L (≥ 250 mg/dL) were considered diabetic and included in the study.

Experimental design

The 30 Wistar rats were randomly divided into five groups (n=6 per group):

Group A (Normal control): Non-diabetic, untreated.

Group B (Diabetic control): STZ-induced, untreated.

Group C (Diabetic + Beetroot): STZ-induced + 500 mg/kg beetroot extract.

Group D (Diabetic + Metformin): STZ-induced + 100 mg/kg metformin.

Group E (Beetroot only): Non-diabetic + 500 mg/kg beetroot extract.

Beetroot administration

The dose of the aqueous extracts of Beetroot used in these studies was adopted from the report of Al-Harbi *et al.*,[11] Beetroot was dissolved in physiological saline daily and was administered orally with the use of an oro-gastric cannula to Group C rats (n=6) at 500 mg/kg bw (at 9.00 – 10.00 a.m. each day) for a maximum period of four weeks, Group D (n=6) at 500 mg/kg bw, Group E rats (n=6) were administered 500 mg/kg bw of beetroot extracts. Group A rats (n=6) received neither STZ nor Beetroot extract.[12]

Measurement of blood glucose levels

Blood glucose levels were monitored weekly using a glucometer (Accu-Chek® Compact Plus) via tail vein puncture after an overnight fast. Measurements were taken during a two-week acclimatization period before diabetes induction and continued for four weeks post-treatment.[12]

Measurement of body weight

Body weight (g) was recorded weekly using a digital weighing scale (Venus VT 30 SL) during the acclimatization period and throughout the four-week experimental period.[12]

Relative heart weight (%)

The relative heart weight of the rat was evaluated as the ratio of respective weight of the heart and the terminal body weight of the same rat, the unit was recorded as percentage (%) using sensitive weighing balance (SonyF3G brand).[12]

Histological processing

At the end of the study, rats were euthanized, and their hearts were excised, weighed, and fixed in 10% formo saline for 72 hours. Tissues were processed for paraffin embedding, sectioned, and stained with hematoxylin and eosin (H&E) and periodic acid schiff (PAS) for microscopic evaluation.

Photomicrography

Histological sections were examined under an Olympus microscope (USA) equipped with a digital camera at the Department of Human Anatomy, Mulungushi University School of Medicine and Health Sciences, Livingstone Campus, Zambia.

Statistical analysis

Data were expressed as mean ± standard error of the mean (SEM) and analyzed using one-way ANOVA. Graphical representations were generated using Microsoft Excel (Microsoft Corp., USA). A p-value less than 0.05 ($p<0.05$) was considered statistically significant.

RESULTS

Average Body Weight on a Weekly Basis (g)

Figure 1 shows the changes in the body weight of Wistar rats across different groups in the experimental design every week. During the acclimatization week (Week -1), the body weights of the rats were measured and found to be normal, with no significant differences compared to

the Control group (p>0.05). From Week 1 to Week 4, there was an increase in body weight in the control and beetroot-only groups. However, in Week 3, the Diabetic group showed a significant (p < 0.05) decline in weight compared to the other groups, while the Control, Diabetic + Beetroot, Diabetic + Metformin, and Beetroot-only groups continued to exhibit an increase in average body weight. By Week 4, the Diabetic group experienced a further decline in weight. In contrast, the Control, Diabetic + Beetroot, Diabetic + Metformin, and Beetroot-only groups showed significant differences (p < 0.05) compared to the Diabetic group.

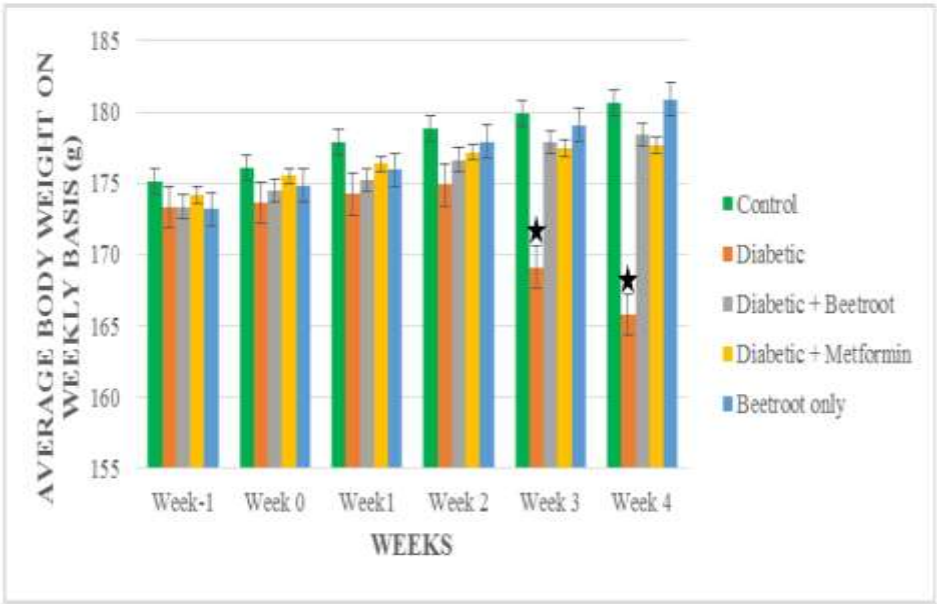


Figure 1: Average body weight on weekly basis (g). Data was expressed as mean ± SEM (p<0.05) *asterisk means significance at p<0.05.

Average Blood Glucose on a Weekly Basis (mg/dl)

Figure 2 illustrates the weekly blood glucose levels measured in the various groups of Wistar rats. During the acclimatization week (Week -1), blood glucose levels were normal, with no significant differences compared to the Control group. In the induction week (Week 0), the Diabetic, Diabetic + Beetroot, and Diabetic + Metformin groups exhibited a significant increase in blood glucose levels compared to the Control group. After treatment began in Week 1, the Diabetic + Beetroot group showed a significant (p < 0.05) decline in blood glucose levels compared to the Diabetic and Diabetic + Metformin groups, and this trend continued until Week 4. Throughout the treatment period, the Diabetic group remained significantly different (p < 0.05) from the other groups.

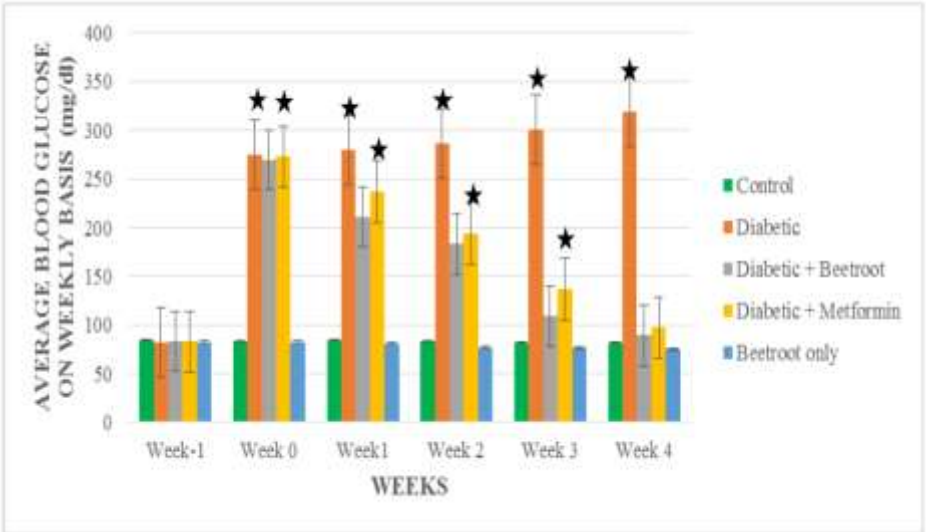


Figure 2: Blood glucose of Wistar rats on weekly basis (mg/dl). Data was expressed as mean ± SEM (p<0.05) * asterisk means significance at p<0.05.

Relative heart weight (%)

Figure 3 displays the relative heart weight in the different groups of Wistar rats. The Diabetic group showed a significant ($p < 0.05$) decline in heart weight compared to the Control group. The Diabetic + Beetroot group also exhibited a decline in heart weight compared to the Control and Beetroot-only groups, but this difference was not significant ($p > 0.05$). Similarly, the Diabetic + Metformin group showed a decrease in heart weight compared to the Control group, but this was also insignificant ($p > 0.05$).

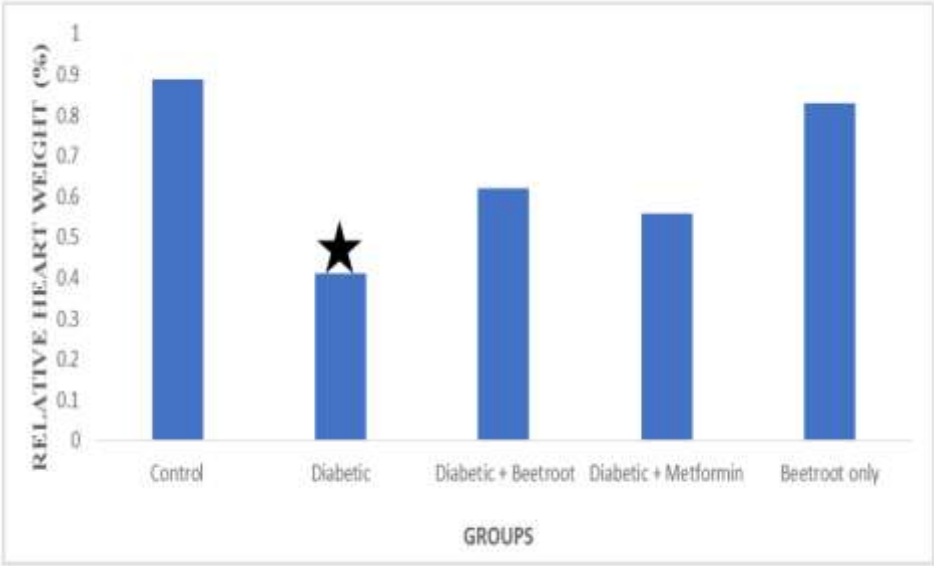
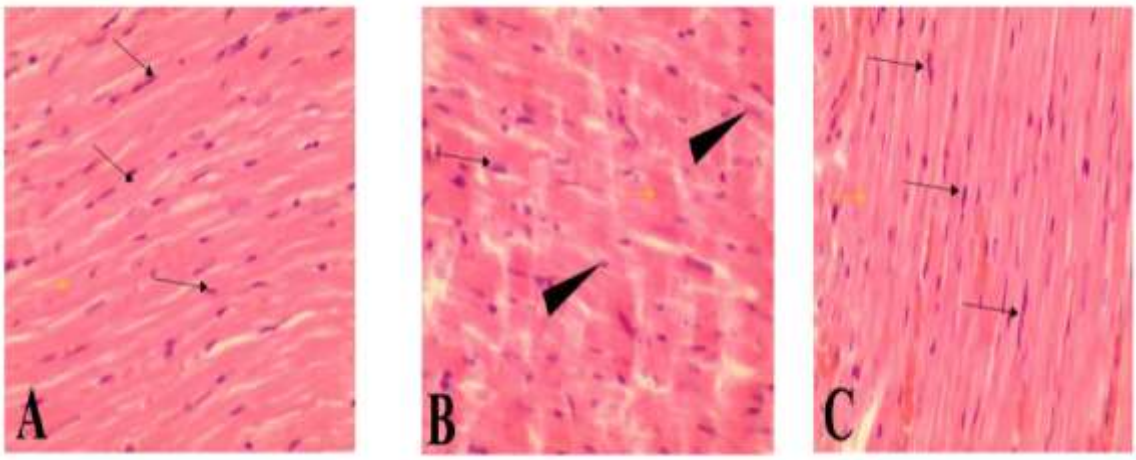


Figure 3: Relative heart weight (%). Data was expressed as mean ± SEM ($p<0.05$) * asterisk means significance at $p<0.05$.

Histology of the heart

The hearts of the Normal Control and Beetroot-only groups displayed normal histoarchitecture, with numerous intact cardiomyocytes (Figures 4A and E). In contrast, the Diabetic group showed disrupted histoarchitecture, with numerous degenerating cardiomyocytes (Figure 4B). The Diabetic + Beetroot and Diabetic + Metformin groups exhibited minor disruptions in histoarchitecture, with a mix of normal and degenerating cardiomyocytes (Figures 4C and 4D).

In the Periodic Acid-Schiff (PAS) staining results, the Normal Control and Beetroot-only groups showed normal reactions (Figures 5A and 5E). The Diabetic group displayed a positive reaction to PAS (Figure 5B). The Diabetic + Metformin group appeared similar to the Control group (Figure 5C), while the Diabetic + Beetroot group showed a slightly positive reaction to PAS (Figure 5D).



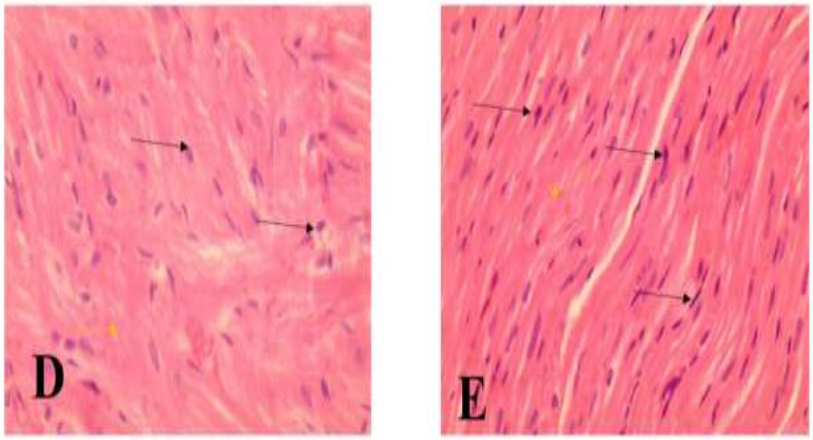


Figure 4: Photomicrograph showing the Heart at day 28. H&E stain X400. A- Normal control, B – Diabetic, C – Diabetic+ beetroot, D – Diabetic+ Metformin and E- beetroot only. Black arrow – cardiomyocyte, Arrow head – degenerating cardiomyocyte, black arrow – myocardial fibers.

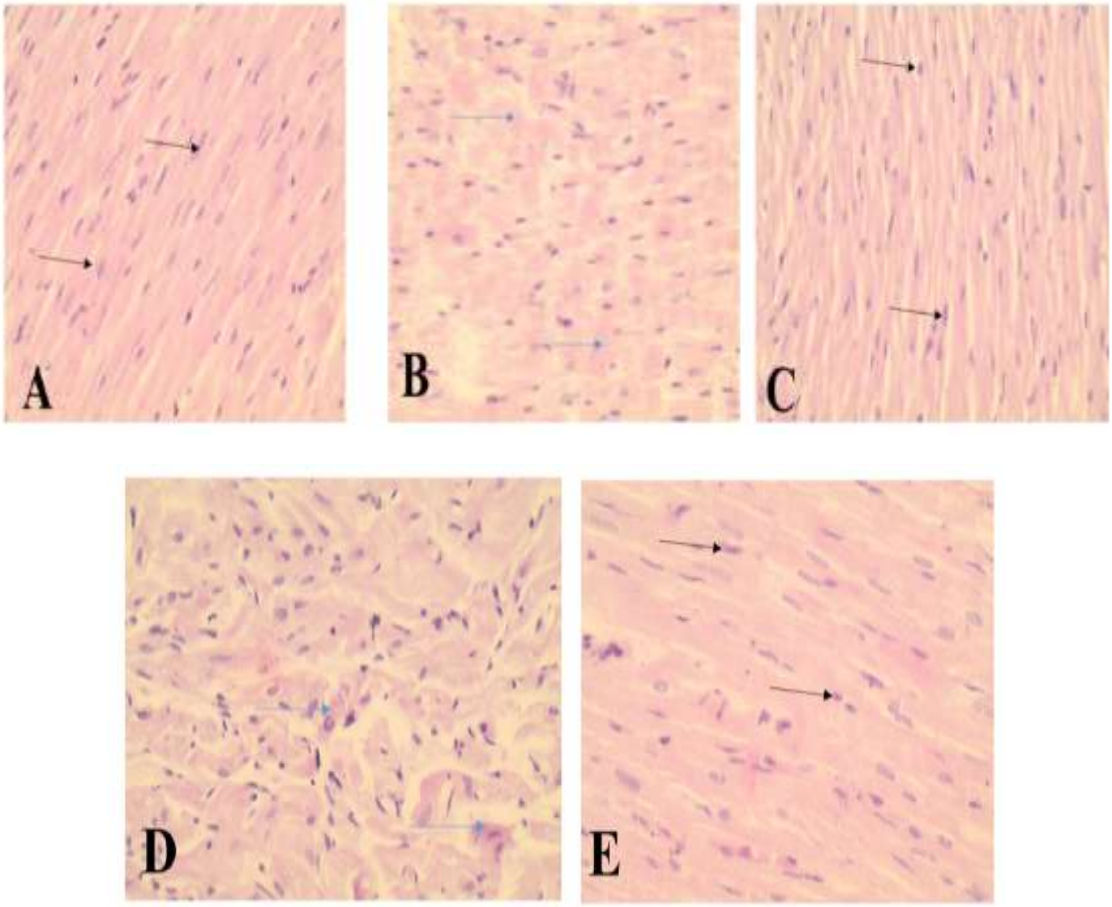


Figure 5: Photomicrograph showing the Heart at day 28. PAS stain X400. A- Normal control, B – Diabetic, C – Diabetic+ beetroot, D – Diabetic+ Metformin and E- beetroot only. Black arrow – cardiomyocyte, Blue arrow – PAS reaction.

DISCUSSION

Beetroot is widely recognised for its anti-hyperglycemic and anti-diabetic properties, making it a staple in traditional and complementary therapies for managing diabetes mellitus.[13] This study explores the potential therapeutic effects of aqueous beetroot extract on the diabetic heart in Wistar rats, providing valuable insights into its mechanisms of action and comparative efficacy with conventional treatments like metformin.

The diabetic group exhibited significant weight loss by the third week, attributed to insulin deficiency, which forced the body to utilise adipose tissue for energy due to impaired glycogenolysis and gluconeogenesis.[14] In

contrast, the Diabetes + Beetroot group showed weight gain, likely due to the presence of antioxidants such as betalains (betacyanins and betaxanthins), flavonoids, polyphenols, saponins, and inorganic nitrate (NO3). These compounds may protect pancreatic β-cells from further damage, thereby preserving insulin production.[15] The Diabetes + Metformin group also maintained body weight, though less effectively than the beetroot group, by suppressing gluconeogenesis, enhancing glucose uptake in peripheral tissues, and activating AMP-activated protein kinase (AMPK) to improve energy metabolism.[16] Beetroot's rich mineral content (e.g., potassium, magnesium, and iron) further supports metabolic health, while its betalain pigments exhibit potent antioxidant, anti-inflammatory, and chemopreventive properties.[15,17]

The diabetic group displayed marked hyperglycemia due to insulin resistance and impaired β-cell function.[18] The Diabetes + Beetroot group exhibited a significant reduction in blood glucose levels, likely mediated by beetroot's ability to enhance insulin secretion, inhibit intestinal glucose absorption, and modulate postprandial glucose responses. These effects are linked to its bioactive compounds, including betalains and polyphenols.[15,19] Metformin also reduced hyperglycemia but with a milder effect, primarily by suppressing hepatic gluconeogenesis and improving insulin sensitivity.[13,19] Studies by Dhananjayan et al.[20] corroborate these findings, showing that beetroot-derived betanin restores glycolytic enzyme activity (e.g., glucokinase) and reduces gluconeogenic enzyme activity (e.g., glucose-6-phosphatase), thereby normalising plasma glucose and Hba1c levels.

The diabetic group showed decreased relative heart weight, indicative of cardiomyocyte apoptosis and oxidative stress driven by hyperglycemia-induced reactive oxygen species (ROS).[21] The Diabetes + Beetroot group demonstrated cardioprotective effects, likely due to betalains' ability to enhance antioxidant enzyme activity (e.g., superoxide dismutase and peroxidase) and mitigate nitrative damage.[15] Metformin also reduced heart weight, though less significantly, by activating Adenosine monophosphate-activated protein kinase (AMPK) and improving endothelial function.[22,23] Histological analysis revealed that beetroot preserved cardiomyocyte integrity, whereas the diabetic group exhibited cellular degeneration due to advanced glycation end products (AGES) and lipotoxicity.[24] Beetroot's nitric oxide (NO)-boosting properties further improved endothelial function and reduced oxidative stress, aligning with findings that dietary nitrate decreases NADPH oxidase activity and ROS production.[25] Periodic acid-Schiff (PAS) staining confirmed glycogen accumulation in diabetic cardiomyocytes, a hallmark of glucotoxicity.[26,27] The Diabetes + Beetroot and Diabetes + Metformin groups showed reduced PAS positivity, reflecting improved glucose metabolism. Beetroot's nitrate content may further protect against glycogen storage disorders by enhancing NO bioavailability and reducing oxidative stress.[24,28]

CONCLUSION

This study highlights beetroot's multifaceted benefits in managing diabetes and its cardiovascular complications. Its effects on weight management, glucose homeostasis, and cardiac health are comparable to or superior to metformin in some aspects, underscoring its potential as a complementary therapy. Future research should explore optimal dosing, long-term effects, and the synergistic potential of beetroot with conventional antidiabetic drugs.

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