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Research article

Rebalancing hepatic carbohydrate metabolism: Effects of *Dalbergiella welwitschii* (Baker) Baker f. (Fabaceae) under diabetic conditions

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Abstract: This study evaluated the effects of an alkaloid-rich leaf extract of *Dalbergiella welwitschii* (Baker) Baker f. on hepatic carbohydrate metabolism in streptozotocin-induced diabetic rats. Diabetes was induced in rats, which were then treated with low (50 mg/kg) and high (100 mg/kg) doses of the extract, or metformin (200 mg/kg), for 20 days. Key hepatic enzymes—glycogen phosphorylase, glucose-6-phosphatase, lactate dehydrogenase, fructose-1,6-bisphosphatase, glycogen synthase, and hexokinase—along with hepatic glycogen and insulin levels were measured. Treatment with the extract significantly restored enzyme activities, increased insulin levels, and enhanced glycogen content. These results indicate that *D. welwitschii* extract can modulate hepatic carbohydrate metabolism and may have potential therapeutic benefits for diabetes management.

Keywords: alkaloids; diabetes mellitus; hepatic enzymes; phytotherapy; west African blackwood

1. Introduction

Diabetes mellitus is a chronic metabolic disorder marked by persistent hyperglycemia, primarily resulting from deficient insulin secretion, impaired insulin action, or a combination of both [1]. Prolonged elevation in blood glucose levels is associated with severe complications such as nephropathy, retinopathy, and cardiovascular diseases [2].

The global burden of diabetes continues to rise at an alarming rate. According to the International Diabetes Federation (IDF) Diabetes Atlas [3], 11.1% or 1 in 9 of the adult population (20–79 years) is living with diabetes, with over 4 in 10 unaware that they have the condition. This number is expected to increase to 643 million by 2030 and to 783 million by 2045. More recent estimates from 2023 suggest that over 800 million people are currently living with the condition, indicating a faster-than-anticipated increase. This upward trend is especially concerning in low- and middle-income regions such as Africa and Asia, where the incidence is projected to double in the coming decades [3].

Although several pharmacological interventions exist for the management of hyperglycemia, many are associated with adverse effects or limited efficacy, prompting increasing interest in safer, plant-based therapeutic alternatives [4,5], particularly in Africa and, more specifically, in Nigeria.

Among natural compounds, alkaloids have drawn considerable attention due to their broad pharmacological potential. They constitute a significant class of known plant secondary metabolites and are well-documented for their anti-inflammatory, anticancer, antiviral, cardioprotective, and antidiabetic properties [6,7]. These bioactive molecules modulate key molecular mechanisms, including enzyme inhibition, antioxidant activity, and enhancement of insulin secretion and sensitivity [8]. Alkaloids have historically served as important leads in drug discovery derived from plants, highlighting their continued relevance in pharmacology [9].

Numerous studies have reported the hypoglycemic potential of alkaloid-rich extracts from medicinal plants, underscoring their promise as therapeutic agents in diabetes management [8,10,11]. However, to the best of our knowledge, there is currently no direct evidence supporting the antidiabetic activity of *Dalbergiella welwitschii* (Baker) Baker f., commonly known as West African blackwood and locally referred to as Elemosho in southwestern Nigeria. Previous investigations on this plant have largely focused on its anti-inflammatory and anthelmintic properties [12,13].

D. welwitschii, a climbing shrub belonging to the family Fabaceae, is widely distributed in riverine and deciduous forests throughout West Africa. In traditional medicine, its roots, bark, and leaves are used in the treatment of infections, rheumatism, arthritis, and gastrointestinal disorders, and are also employed as ecbolics and abortifacients [13,14]. Notably, recent findings by Ajiboye et al. [15] demonstrated that alkaloids isolated from *D. welwitschii* attenuated hepatic damage in streptozotocin-induced diabetic rats, further highlighting the plant's therapeutic potential.

However, the effects of *D. welwitschii* on hepatic carbohydrate metabolism remain largely unexplored. Given the central role of hepatic carbohydrate-metabolizing enzymes in the regulation of glucose homeostasis, the objective of this study was to evaluate the modulatory effects of an alkaloid-rich extract from *D. welwitschii* leaves on key hepatic enzymes involved in glycolysis, gluconeogenesis, and glycogen metabolism in a diabetic rat model.

2. Materials and methods

2.1. Chemicals and reagents

All chemicals, including streptozotocin (STZ), were purchased from Sigma-Aldrich (Steinheim, Germany); all reagents used were of analytical grade. Enzyme assay kits were obtained from Randox Laboratory (Crumlin, UK).

2.2. Plant material and extraction

Leaves of *D. welwitschii* were obtained from the Federal Research Institute of Nigeria (FRIN) in Ibadan, Oyo State. Identification was carried out by a professional taxonomist at FRIN, based on voucher number FHI: 113156. The leaves were air-dried at room temperature for two weeks before being ground into powder using an electric blender.

The alkaloid-rich extract was prepared following the method of Harborne [16], with slight modifications by Ademiluyi and co-authors [17]. Powdered leaves were defatted with *n*-hexane (24 h). Ten grams of the defatted material was extracted with 100 mL of 10% acetic acid in ethanol (24 h). The mixture was filtered through muslin cloth and filter paper and concentrated under reduced pressure at 45 ℃; the alkaloids were precipitated by adding concentrated ammonium hydroxide. The precipitate (2 g) was collected and stored at 4 ℃ until use.

2.3. Animals and experimental design

Forty male Wistar rats (100–130 g, two months old, age selected due to the toxicity profile of STZ) were sourced from the Animal Holding Unit, Ekiti State University, Nigeria. Animals were housed in groups of five under standard laboratory conditions (22 ± 2 ℃, 12-h light/dark cycle) and

fed standard pellet chow with 20% w/v fructose water for one week before experiments, following Salau et al. [18] with a little modification. Diabetes was induced by intraperitoneal injection of STZ dissolved in citrate buffer (pH 4.5) at 45 mg/kg body weight after overnight fasting. Control rats received citrate buffer only. Rats with fasting blood glucose ≥250 mg/dL were included and randomly divided into five groups (n = 8 each), as described in Table 1.

Treatment was administered orally daily between 10 and 11 am via oral gavage using a needle and intubator.

Table 1. Experimental groups of rats.

Group	Description	Acronym
I	Normal rats, no diabetes induction	NC
II	Diabetic rats, no treatment	DC
III	Diabetic rats treated with low dose (50 mg/kg b.w.) of *D. welwitschii* alkaloid-rich extract	DL
IV	Diabetic rats treated with high dose (100 mg/kg b.w.) of *D. welwitschii* alkaloid-rich extract	DH
V	Diabetic rats treated with metformin (200 mg/kg b.w.)	DM

2.4. Sample collection and biochemical analysis

After 21 days of treatment, rats were anesthetized (halothane) and sacrificed by cervical dislocation. Blood was collected via cardiac puncture and allowed to clot, and serum was separated by centrifugation. Livers were excised, rinsed with saline, blotted dry, weighed, and homogenized in 0.1 M potassium phosphate buffer (pH 6.5) for biochemical analyses [15].

2.5. Parameters studied

2.5.1. Determination of hepatic glucose

This was carried out using a commercial kit. Briefly, using a micropipette, 10 µL of appropriately diluted sample, standard, and distilled water were pipetted into clean test tubes labeled as sample, standard, and blank, respectively. 100 µL of working glucose reagent was added to the solution, mixed, and left undisturbed for 10 min at room temperature. The absorbance of the sample and standard was measured against the blank within 60 min at 505 nm.

2.5.2. Determination of serum insulin

An aliquot (0.05 mL) of the standard solution, control, and serum samples was placed in appropriate wells. Exactly 0.01 mL of the insulin reagent was dispensed into each well, and the microplates were swirled gently for 20 s. The wells were washed three times with 0.35 mL of working washing solution per well and aspirated using a micropipette. A known volume (0.1 mL) of the working substrate was added to each well and incubated at 25 ℃ for 15 min. Exactly 0.05 mL of the stopping reagent was placed into each well and mixed gently for 20 s. The plate was read on a microplate reader at 450 nm within 30 min after the addition of the stopping reagent.

2.5.3. Determination of hepatic glycogen

Glycogen concentration in the liver homogenate was determined as glucosyl units following acid hydrolysis [19]. Supernatant from the homogenization of liver (0.1 mL) was hydrolyzed with 0.5 mL of 1 M HCl for 2 h at 95 ℃. The reaction mixture was neutralized with 0.5 mL of 1 M NaOH. Glucose concentrations of the hydrolyzed samples were determined using the glucose reagent as previously described. Hepatic glycogen concentration was then calculated.

2.5.4. Determination of glycogen synthase and phosphorylase

2.5.4.1. Glycogen synthase activity

The micro-ELISA plate provided in this kit was pre-coated with an antibody specific to glycogen synthase. Standards or samples were then added to the wells and allowed to bind with the immobilized antibody. Subsequently, a biotinylated detection antibody specific for glycogen synthase and an avidin–horseradish peroxidase (HRP) conjugate were added sequentially and incubated. After each step, unbound components were removed by washing.

Next, the substrate solution was added to each well. Wells containing glycogen synthase, the biotinylated detection antibody, and the avidin–HRP conjugate developed a blue coloration. The enzyme–substrate reaction was terminated by the addition of sulfuric acid, resulting in a yellow color. The optical density (OD) was then measured spectrophotometrically at 450 nm ± 2 nm.

2.5.4.2. Glycogen phosphorylase

Briefly, 100 μL each of the standard dilutions, blank, and samples were added into the appropriate wells, covered with a plate sealer, and incubated for 1 h at 37 ℃. After incubation, the liquid in each well was removed, and 100 μL of detection reagent A working solution was then added to each well. The plate was resealed, and incubation continued for another 1 h at 37 ℃. The solution was aspirated, and the wells were washed three times with 350 μL of wash solution per well, allowing 2 min for each wash. After the final wash, residual buffer was completely removed by decanting, inverting the plate, and blotting it against absorbent paper.

Next, 100 μL of detection reagent B working solution was added to each well. The plate was sealed and incubated for 30 min at 37 ℃. Following this, 90 μL of substrate solution was added to each well, the plate was covered with a new sealer, and incubation continued for 10–20 min at 37 ℃.

Finally, 50 μL of stop solution was added to each well, resulting in a color change to yellow. The contents were mixed gently by tapping the plate. If the color change was not uniform, the plate was tapped again to ensure thorough mixing. Wells were checked to confirm the absence of air bubbles, droplets, or fingerprints on the plate bottom. The optical density (OD) was immediately measured using a microplate reader at 450 nm. The optical density (OD) was then measured spectrophotometrically at 450 nm ± 2 nm.

2.5.5. Determination of fructose-1,6-bisphosphatase activity

Following Gancedo and Gancedo [20], the assay mixture in a final volume of 2 mL contained 1.2

mL of Tris-HCl buffer (0.1 M, pH 7.0), 0.1 mL of substrate (fructose-1,6-bisphosphate, 0.05 M), 0.25 mL of magnesium chloride (0.1 M), 0.1 mL of potassium chloride solution (0.1 M), 0.25 mL of ethylenediaminetetraacetic acid (0.001 M) solution, and 0.1 mL of enzyme homogenate. The incubation was carried out at 37 °C for 5 min. The reaction was terminated by the addition of 10% trichloroacetic acid. The suspension was centrifuged, and the supernatant was used for phosphorus estimation by the method of Fiske and Subbarow [21]. The supernatant was made up to a known volume. To this, 1 mL of ammonium molybdate was added, followed by 0.4 mL of amino naphtholsulphonic acid. The blue color developed after 20 min was read at 680 nm.

2.5.6. Determination of glucose-6-phosphatase activity

Following Erukainure et al. [22], tissue lysates were incubated with 50 mM ATP, 0.25 M glucose, 5 mM KCl, and 0.1 M Tris-HCl buffer in a shaker for 30 min at 37 ℃. Water and 1.25% ammonium molybdate were used to stop the reaction. Freshly prepared 9% ascorbic acid was added to the reaction mixture and further incubated for 30 min. Absorbance was read at 660 nm. Glucose-6-phosphatase activity was extrapolated from a standard curve of inorganic phosphate and reported as the amount of inorganic phosphate (Pi) released/min/mg.

2.5.7. Determination of glucose-6-phosphate dehydrogenase

Briefly, 2.0 mL of buffer was added to 0.1 mL of NADP and 1.0 mL of liver homogenate. The mixture was thoroughly mixed and incubated at 37 ℃ for 10 min. Subsequently, 0.05 mL of substrate was added, mixed gently, and the absorbance was measured at 340 nm.

2.5.8. Determination of hexokinase activity

The total reaction mixture had a final volume of 5.3 mL and contained the following components: 1.0 mL of 0.005 M glucose solution, 0.5 mL of 0.072 M adenosine triphosphate (ATP) solution, 0.1 mL of 0.05 M magnesium chloride solution, 0.4 mL of 0.0125 M potassium dihydrogen phosphate solution, 0.4 mL of 0.1 M potassium chloride solution, 0.4 mL of 0.5 M sodium fluoride solution, and 2.5 mL of Tris-HCl buffer (0.01 M, pH 8.0). The mixture was pre-incubated at 37 ℃ for 5 min.

The reaction was initiated by adding 2.0 mL of liver supernatant. Immediately after initiation, 1.0 mL of the reaction mixture was transferred into a tube containing 1.0 mL of 10% trichloroacetic acid (TCA), which served as the zero-time control. A second aliquot was withdrawn after 30 min of incubation at 37 ℃ and deproteinized with 10% TCA. The protein precipitate was removed by centrifugation, and the residual glucose in the supernatant was estimated according to the method of Trinder [23]. Absorbance was measured spectrophotometrically at 340 nm.

2.5.9. Determination of lactate dehydrogenase

Briefly, 1.0 mL of the reconstituted reagent (prepared by mixing 3 mL of buffer with one vial of NADH; R1a and R1b) was added to 0.2 mL of the sample. For the blank, the sample was replaced with distilled water. The mixture was thoroughly mixed, and absorbance was measured at 340 nm.

2.6. Data analysis

Data are presented as mean ± standard deviation (SD) of eight replicates. Statistical comparisons were performed using one-way ANOVA followed by Tukey's post hoc test with GraphPad Prism 7 software. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Regulation of hepatic glucose levels by alkaloid-rich extract in diabetic rats

Figure 1 shows that hepatic glucose was significantly reduced in DL and DH rats compared to DC ($p < 0.05$). Both doses of *D. welwitschii* extract lowered glucose levels to values approaching those observed in metformin-treated rats (DM) and close to normal controls (NC).

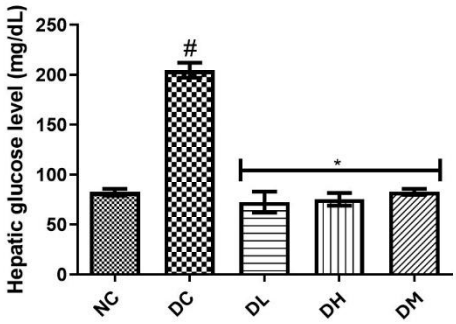

Figure 1. Hepatic glucose levels in STZ-induced diabetic rats treated with alkaloid-rich D. *welwitschii* leaf extract. Values are expressed as mean ± SD (n = 8). #$p < 0.05$ vs. NC; *$p < 0.05$ vs. DC. NC: normal control rats, DC: diabetic control rats, DL: diabetic rats treated with low dose (50 mg/kg b.w.) of *D. welwitschii* alkaloid-rich extract, DH: diabetic rats treated with high dose (100 mg/kg b.w.) of *D. welwitschii* alkaloid-rich extract, DM: diabetic rats treated with metformin (200 mg/kg b.w.).

3.2. Regulation of serum insulin and hepatic glycogen concentrations by alkaloid-rich extract in diabetic rats

Figure 2 shows the effects of *D. welwitschii* extract on serum insulin and hepatic glycogen. Insulin levels increased markedly in DL and DH ($p < 0.05$), with DL reaching values similar to NC and DH slightly lower but still significantly above DC. DM served as a reference, indicating that both extract doses approached standard treatment efficacy (Figure 2A). Hepatic glycogen showed a similar trend: DL and DH exhibited clear recovery, with values near NC and comparable to DM ($p < 0.05$) (Figure 2B).

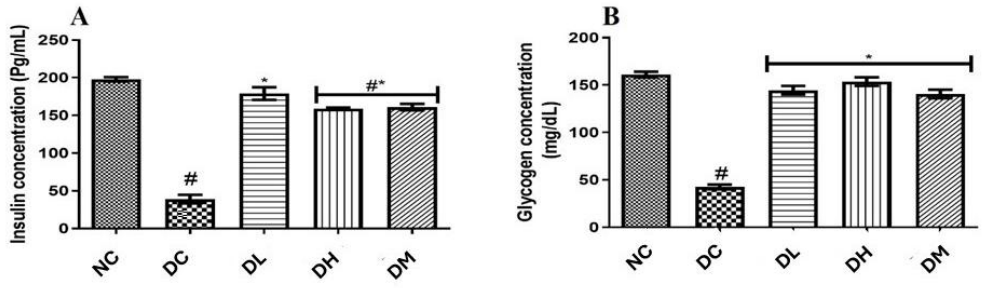

Figure 2. Serum insulin and hepatic glycogen levels in STZ-induced diabetic rats treated with alkaloid-rich *D. welwitschii* leaf extract. Values are expressed as mean ± SD (n = 8). #$p < 0.05$ vs. NC; *$p < 0.05$ vs. DC. NC: normal control rats; DC: diabetic control rats; DL: diabetic rats treated with low dose (50 mg/kg b.w.) of *D. welwitschii* alkaloid-rich extract; DH: diabetic rats treated with high dose (100 mg/kg b.w.) of *D. welwitschii* alkaloid-rich extract; DM: diabetic rats treated with metformin (200 mg/kg b.w.).

3.3. Regulation of hepatic glycogen synthase and phosphorylase activities by alkaloid-rich extract in diabetic rats

Figure 3 shows hepatic glycogen synthase and phosphorylase activities. Glycogen synthase, reduced in DC, increased significantly in DL and DH ($p < 0.05$), reaching values comparable to NC and approaching DM levels (Figure 3A). Glycogen phosphorylase, elevated in DC, decreased in DL, while remaining above NC, whereas activity normalized in DH, with levels similar to DM and NC ($p < 0.05$) (Figure 3B).

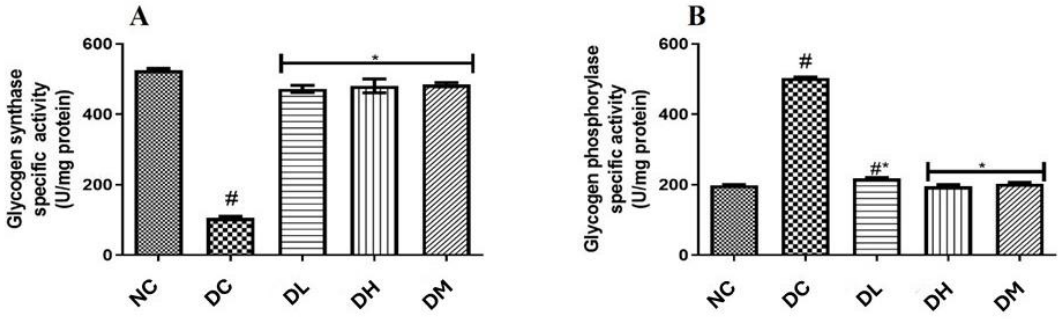

Figure 3. Hepatic glycogen phosphorylase and synthase activities in STZ-induced diabetic rats treated with alkaloid-rich *D. welwitschii* leaf extract. Values are expressed as mean ± SD (n = 8). #p < 0.05 vs. NC; *p < 0.05 vs. DC. NC: normal control rats; DC: diabetic control rats; DL: diabetic rats treated with low dose (50 mg/kg b.w.) of *D. welwitschii* alkaloid-rich extract; DH: diabetic rats treated with high dose (100 mg/kg b.w.) of *D. welwitschii* alkaloid-rich extract; DM: diabetic rats treated with metformin (200 mg/kg b.w.).

3.4. Regulation of carbohydrate-metabolizing enzyme activities by alkaloid-rich extract in diabetic rats

Figure 4 presents the effects of *D. welwitschii* extract on key hepatic carbohydrate-metabolizing enzymes. The activities of fructose-1,6-bisphosphatase (F16BP) and glucose-6-phosphatase were elevated in DC. These activities were significantly reduced in DL, while a greater reduction was observed in DH, restoring levels to values comparable with or lower than those observed in DM and NC ($p < 0.05$) (Figure 4A, B).

Glucose-6-phosphate dehydrogenase (G-6-PDH) and hexokinase, which were decreased in DC, were restored in both DL and DH to levels, comparable with DM and, in some cases, NC ($p < 0.05$) (Figure 4C, D).

Lactate dehydrogenase (LDH), elevated in DC, decreased to near-normal levels in DL and DM ($p < 0.05$). In contrast, DH exhibited significantly higher LDH activity than NC rats ($p < 0.05$) (Figure 4E).

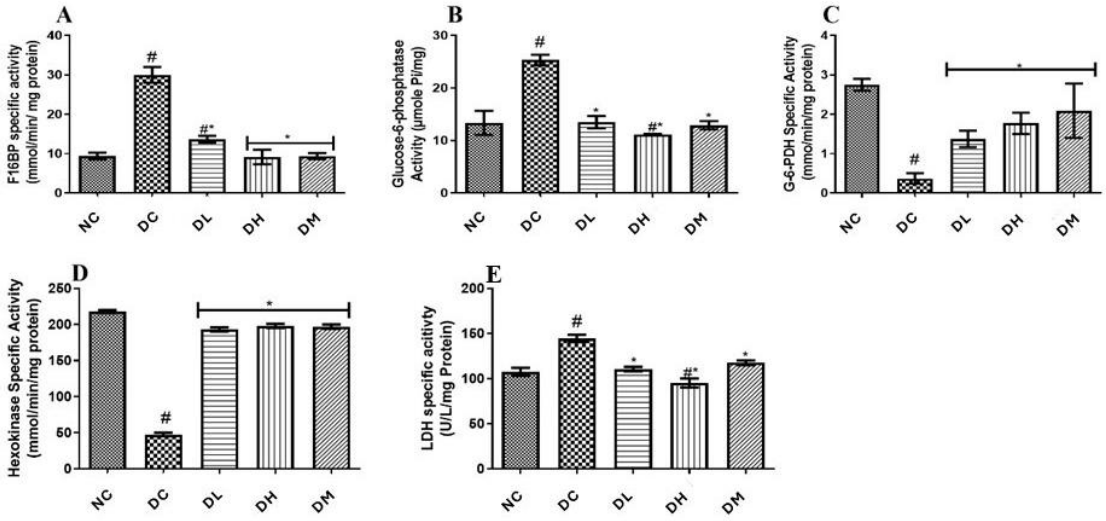

Figure 4. Carbohydrate-metabolizing enzyme activities in STZ-induced diabetic rats treated with alkaloid-rich *D. welwitschii* leaf extract. Values are expressed as mean ± SD (n = 8). #$p < 0.05$ vs. NC; *$p < 0.05$ vs. DC. NC: normal control rats; DC: diabetic control rats; DL: diabetic rats treated with low dose (50 mg/kg b.w.) of *D. welwitschii* alkaloid-rich extract; DH: diabetic rats treated with high dose (100 mg/kg b.w.) of *D. welwitschii* alkaloid-rich extract; DM: diabetic rats treated with metformin (200 mg/kg b.w.); F16BP: fructose-1,6-bisphosphatase; G-6-PDH: glucose-6-phosphate dehydrogenase; LDH: lactate dehydrogenase.

4. Discussion

In this study, the DC group exhibited significantly elevated hepatic glucose and reduced insulin levels, indicative of hyperglycemia and insulin resistance, characteristic of type 2 diabetes mellitus [24,25]. The inverse relationship between hepatic glucose and insulin reflects the deterioration of

insulin-mediated regulation of carbohydrate metabolism [26,27]. STZ induces diabetes by reducing insulin levels and altering liver glycogen metabolism, leading to hyperglycemia [28,29].

Administration of an alkaloid-rich *D. welwitschii* leaf extract effectively reduced hepatic glucose levels while increasing insulin and glycogen concentrations in diabetic rats, which may suggest improved pancreatic function and enhanced insulin action. Glycogen metabolism enzymes, glycogen synthase and glycogen phosphorylase, which are dysregulated in diabetes, were restored toward normal activity, with the high dose showing more pronounced effects than the low dose. This indicates a dose-dependent amelioration of hyperglycemia in diabetic rats.

Key gluconeogenic enzymes, fructose-1,6-bisphosphatase and glucose-6-phosphatase, were elevated in DC rats and significantly reduced in DL and DH rats, with DH achieving greater normalization, aligning with the observed improvements in hepatic glucose levels. Similarly, glucose-6-phosphate dehydrogenase (G-6-PDH) and hexokinase, which were suppressed in DC rats, were restored by both extract doses to levels comparable to DM and, in some cases, NC rats.

Lactate dehydrogenase (LDH), elevated in DC rats, decreased to near-normal levels in DL and DM rats, while DH exhibited higher LDH activity than NC rats, reflecting tissue-specific effects of the high-dose extract. These enzymatic changes collectively indicate that *D. welwitschii* extracts normalize hepatic carbohydrate metabolism, supporting their hypoglycemic potential.

5. Conclusions

Alkaloid-rich extracts of *D. welwitschii* leaves improve hepatic carbohydrate metabolism in streptozotocin-induced diabetic rats by modulating insulin levels, glycogen storage, and key metabolic enzymes. These findings support its potential role in the management of hyperglycemia.

Author contributions

All authors contributed to the conception and design of the study, performed the experiments, analyzed the data, drafted the manuscript, and approved the final version for publication.

Use of Generative-AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

The authors declare no conflict of interest.

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