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Mechanistic Evaluation of Dose-Dependent Antidiabetic, Antioxidant, and Hepatoprotective Effects of Hydro-ethanol (3:2) Extract of Commelina benghalensis Linn. Aerial Parts

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Abstract

Diabetes mellitus is a complicated metabolic disease characterized by β-cell dysfunction, oxidative damage, and hyperglycemia. This study evaluated the dose-dependent antidiabetic, antioxidant, and hepatoprotective effects of hydro-ethanol (3:2) extract of *Commelina benghalensis* (HEECB) aerial parts (2.5, 5, 10 mg/100 g b.w./day) in STZ-induced diabetic rats to assess its efficacy in regulating glucose metabolism and oxidative stress and hepatic enzyme activities. A single intramuscular injection of streptozotocin (STZ) (4 mg/0.1 M citrate buffer/100 g body weight) was used to induce diabetes. Treatment of HEECB was then started orally for 28 days. Fasting blood glucose (FBG), serum insulin, carbohydrate metabolic enzymes (hexokinase and glucose-6-phosphatase), oxidative stress markers such as catalase, superoxide dismutase (SOD), and thiobarbituric acid reactive substances (TBARS) along with acid phosphatase (ACP) and alkaline phosphatase (ALP) were examined from concerned samples. The STZ-induced diabetic rats showed a significant ($p < 0.05$) decrease in serum insulin, hexokinase, catalase, and SOD activities, along with a significant ($p < 0.05$) increase in FBG, TBARS, glucose-6-phosphatase, ACP, and ALP activities. Treatment with mentioned doses of HEECB, significantly ($p < 0.05$) increased insulin levels, improved antioxidant defense by raising catalase and SOD activities and lowering lipid peroxidation and levels, and normalized glucose metabolism by increasing hexokinase and suppressing glucose-6-phosphatase activity. The extract also demonstrated hepatoprotective effects by normalizing ACP and ALP activities. The finding suggest that hydro-ethanolic extract of *Commelina benghalensis* aerial parts (HEECB) showed optimal efficacy at 1 mg, exerting potent antihyperglycemic, antioxidative, and hepatoprotective effects via β-cell protection, insulin sensitization, and enzyme modulation against diabetic complications.

Keywords: Streptozotocin; Antidiabetic; Antioxidative; Hepatopretective; Commelina benghalensis; Phytotherapeutic

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1. Introduction

Diabetes mellitus is a rapidly growing global health concern, with adult prevalence rising dramatically and projections indicating that over 700 million adults would have diabetes by 2045 (Sun et al., 2022). Chronic hyperglycemia is a hallmark of this metabolic condition, which is often caused by both insulin resistance and beta-cell malfunction. One of the main causes of these anomalies is oxidative stress, a state caused by an imbalance between the generation of reactive oxygen species (ROS) and the effectiveness of antioxidant defences (Caturano et al., 2023). Increased lipid peroxidation, non-enzymatic protein glycation, and mitochondrial dysfunction all contribute to elevated ROS levels in diabetics (Jomova et al., 2023). These factors all enhance insulin resistance and harm cellular structures, laying the groundwork for serious diabetic consequences (Mana et al., 2022).

There are numerous biological mechanisms that link oxidative stress to diabetes. The polyol, hexosamine, protein kinase C (PKC), and advanced glycation end-product (AGE) pathways are important pro-oxidative pathways that are elevated in hyperglycemic situations. These processes are used to metabolize excess glucose, which results in an excess of radical species. Glyceraldehyde-3-phosphate build up in particular is crucial because it activates PKC and triggers the AGE pathway, which promotes detrimental protein changes and increases oxidative stress, inflammation, and vascular damage (Giacco and Brownlee, 2010).

The antidiabetic potential of medicinal plants has been extensively studied in an attempt to combat diabetes and its consequences. White mulberry (*Morus alba*) (Shin et al., 2016), fenugreek (*Trigonella foenum-graecum*) (Sarker et al., 2024), cinnamon (*Cinnamomum verum*), ginger (*Zingiber officinale*) (Alam et al., 2022) and amada (*Curcuma amada*) (Mitra et al., 2019) are notable examples with scientific support. These plants frequently include bioactive substances including flavonoids, alkaloids, and saponins that work in a variety of ways, including increasing glucose absorption, boosting insulin secretion, preventing the absorption of carbohydrates, and reducing oxidative stress through antioxidant activity.

Commelina benghalensis (Linn.), popularly referred to as "Kanshira," is a member of the Commelinaceae family and is found all across India. Along with a number of other pharmacological activities, such as anti-inflammatory, anti-microbial anti-oxidant, hepatoprotective, anti-cancer, and infertility management effects, this traditional herb. However, its antidiabetic potential and mechanistic role in glucose metabolism and oxidative stress regulation have not been sufficiently investigated. Because of this gap, comprehensive experimental validation of its effectiveness in diabetes settings is required (Orni et al., 2018).

The anti-diabetic properties of various extracts from the aerial parts of *Commelina benghalensis* (Linn.) were recently reported by our laboratory. These extracts were found to lower plasma glucose levels, improve glucose tolerance, and enhance glycolytic activity in diabetic animals, with the hydro-ethanol extract showing the highest potency (Das et al., 2024). Therefore, the present study aims to evaluate the dose-dependent efficacy and safety profile of the hydro-ethanol (60:40) extract of *Commelina benghalensis* (Linn.) (HEECB) aerial parts in streptozotocin-induced diabetic rats. The necessity to ascertain the minimum effective dose, the dose that produces the greatest therapeutic benefit without toxicity, and to comprehend

the connection between the dose and physiological responses, such as glucose regulation and antioxidant activity, makes dose-dependence crucial in these kinds of investigations.

2. Materials and Methods

2.1. Collection of plant material

A taxonomist from Vidyasagar University's Department of Botany verified the aerial parts of *Commelina benghalensis* (Linn.), which were gathered from fields in the Purba Medinipur district of West Bengal (Ref no: *C. benghalensis/VU/Bio/09/22*). The samples were cleaned, chopped into tiny pieces, allowed to air dry at room temperature for three to four days, and then ground into a fine powder using an electric grinder.

2.2. Preparation of the hydro-ethanolic (60:40) extract of the aerial parts of *Commelina benghalensis* (Linn.)

The hydro-ethanolic (3:2) extract of the aerial parts of *Commelina benghalensis* (Linn.) was prepared using our laboratory's standard procedure. Fifty grams of the powdered material were extracted with a solvent mixture containing water (480 mL) and ethanol (320 mL) at room temperature (25–28 °C) for 48 hours with intermittent stirring. The extract was then filtered through Whatman No. 3 filter paper and concentrated using a rotary evaporator. The dried residue was stored at 2–8 °C for further studies (Pal et al., 2024). As previous pilot study indicated this extract out of other extracts was effective considering fasting blood glucose parameter for diabetes management so, this extract was used here to investigate its mechanism of action in this concern.

2.3. Chemicals

Streptozotocin (STZ), nicotinamide adenine dinucleotide phosphate (NADP), adenosine triphosphate (ATP), thiobarbituric acid (TBA), trichloroacetic acid (TCA), and HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid), along with other chemicals, were obtained from Sigma Aldrich Diagnostics Ltd., Maharashtra, India. All reagents used in this study were of analytical grade. The toxicity assessment kits were supplied by Meril Diagnostics Ltd., India.

2.4. Animal selection and maintenance

The study used thirty Wistar male rats weighing 120 ± 10 g and three months old. After 15 days of acclimatization, they were kept in standard laboratory settings (25 ± 2 °C, 12-hour light/dark cycle), with free access to water and a meal high in protein. Each clean polypropylene cage was used for six rats.

2.5. Ethical statement

Animal care and maintenance followed the guidelines of the Institutional Animal Ethics Committee (IAEC) under approval no. *VU/IAEC/CPCSEA/7/7/2022* (dated 22/11/2022), in accor-

dance with the regulations of the Committee for Control and Supervision of Experiments on Animals (CCSEA), Government of India.

2.6. Diabetes mellitus induction in rats

Single intramuscular injection of streptozotocin (STZ, Sigma-Aldrich, USA) at a dose of 4 mg/100 g body weight, diluted in 0.1 M citrate buffer (pH 4.5), was used to induce diabetes. Rats with fasting blood glucose levels between 300 and 350 mg/dL after seven days of STZ injection were identified as diabetics and chosen for the study (Bera et al., 2013).

2.7. Experimental design

Control group ($n = 6$): After receiving a single intramuscular injection of citrate buffer (0.1 M/100 g body weight), the rats were given distilled water (0.5 mL/100 g body weight) orally every day for 28 days.

Diabetic group ($n = 6$): The rats were injected with STZ (4 mg/100 g body weight) diluted in 0.1 M citrate buffer to induce diabetes. After that, they were given distilled water orally (0.5 mL/100 g body weight/day) for 28 days.

2.5 mg dose treated group ($n = 6$): Diabetic rats received the HEECB (3:2) aerial parts with dose of 2.5 mg/0.5 mL distilled water/100 g body weight/day by oral gavage for 28 days in the fasting state.

5 mg dose treated group ($n = 6$): The HEECB (3:2) aerial parts (5 mg/0.5 mL distilled water/100 g body weight/day) was given orally to diabetic rats for 28 days during fasting state.

10 mg dose treated group ($n = 6$): Diabetic rats were treated orally with HEECB (3:2) aerial parts (10 mg/0.5 mL distilled water/100 g body weight/day) for 28 days while fasting.

Rats were sacrificed by euthanasia in accordance with CPCSEA rules on the 29th day (considering the day of STZ injection as day one). As STZ-induced diabetes stabilizes within the first week, a 28-day treatment strategy was used, and a four-week period enables assessment of prolonged antidiabetic efficacy rather than immediate effects. This time frame is enough to evaluate dose-dependent safety, restoration of antioxidant defenses, modulation of carbohydrate-metabolizing enzymes, and chronic glycemic management while also maintaining consistency with well-established experimental diabetes models. For the estimation of insulin level and evaluation of toxicity, blood was drawn from the dorsal aorta, and serum was separated by centrifugation ($3000 \times g$, 5 min). Tissues from the liver, kidney, and skeletal muscle were removed, cleaned with saline, blotted, and kept at -20 °C for biochemical evaluation. To evaluate functional and structural alterations, antioxidant measures, and hepatic and muscle enzyme activity were investigated.

2.8. Fasting blood glucose (FBG) level measurement

A glucometer was used to measure the levels of FBG by drawing blood from the tail vein. The FBG level was measured at the time of grouping and then every seven days after that. The results were represented in mg/dL (Bera et al., 2013).

2.9. Serum insulin level estimation

Serum insulin levels were analyzed using a RayBio Rat Insulin ELISA kit (Norcross, GA, USA) and reported in μIU/mL (Bürgi et al., 1988).

2.10. Hexokinase activity assessment

Tissue homogenates (50 mg/mL in 0.1 M phosphate buffer, pH 7.4) were treated with a test combination including $MgCl_2$, glucose, thioglycerol, HEPES buffer, and ATP. Absorbance was measured at 340 nm. The measurement of the enzyme activity was μg/mg tissue (Das et al., 2024).

2.11. Glucose-6-phosphatase activity assessment

A conventional procedure was used to measure the activity of glucose-6-phosphatase in the liver and skeletal muscle. Maleic acid buffer (pH 6.5) and glucose-6-phosphate were added to tissue homogenates (50 mg/mL) and incubated for 15 minutes at 37 °C. Enzyme activity was measured as mg inorganic phosphate/g tissue after the reaction was halted with 10% TCA and centrifuged at $3000\times g$ for 10 minutes (Das et al., 2024).

2.12. Evaluation of oxidative stress markers

The activity of superoxide dismutase (SOD) and catalase in the liver and kidney were measured spectrophotometrically using established methods. Thiobarbituric acid-reactive compounds (TBARS) were measured at 535 nm to evaluate lipid peroxidation (Mitra et al., 2019).

2.13. Toxicity markers assessment

Standard diagnostic kits were used to quantify the activities of acid phosphatase (ACP) and alkaline phosphatase (ALP) in serum (Vanha-Perttula and Nikkanen, 1973).

2.14. Statistical analysis

Data were expressed as mean $\pm$ SEM. Statistical significance among groups was determined using one-way ANOVA followed by Multiple Comparisons Student's two-tail *t*-test (Das et al., 2024).

3. Results and Discussion

Diabetes's metabolic network is a complicated web in which oxidative stress and hyperglycemia combine to produce a vicious loop. Excessive reactive oxygen species (ROS) produced by long-term blood glucose rise cause oxidative damage, β-cell malfunction, and insulin resistance, all of which are exacerbated by one another. The current study assessed the antihyperglycemic, antioxidative, and hepatoprotective properties of the hydro-ethanolic (3:2) extract of *Commelina benghalensis* (HEECB) aerial parts in STZ-induced diabetic rats, a model in which STZ, which

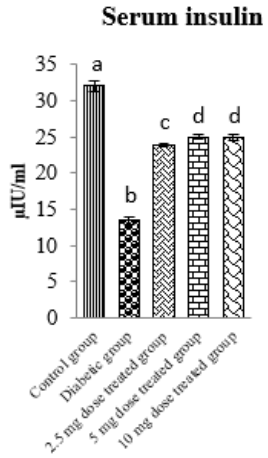


Figure 1: Recovery in the serum insulin and fasting blood glucose levels after treatment at different doses of hydro-ethanol extract of aerial parts of C. benghalensis (Linn.) in diabetic rat. Values were expressed as Mean ± SEM, $n = 6$, ANOVA followed by "Multiple comparison student's two tail-t-test." Bars with different superscripts (a-d) differ from each other significantly, $p < 0.05$.

is produced by *Streptomyces achromogenes*, causes diabetes by selective β-cell cytotoxicity and DNA strand breakage (Das et al., 2024). The STZ-induced diabetic rat exhibited significant ($p < 0.05$) increase (Table 1) in fasting blood glucose (FBG) level and decrease in serum insulin levels (Figure 1), indicating β-cell dysfunction. Following treatment with the extract, insulin levels were restored and FBG was reduced, indicating improved pancreatic function and insulin sensitivity. This suggests that the phytochemicals in the extract increased peripheral glucose uptake and promoted β-cell regeneration or protection (Rad et al., 2022; Das et al., 2024).

Table 1: Effect of HEECB on FBG levels (mg/dL) in STZ-induced diabetic rat

Day	**Control group**	**Diabetic group**	**2.5 mg dose treated diabetic group**	**5 mg dose treated diabetic group**	**10 mg dose treated diabetic group**
On the day of STZ injection	72.1 ± 2.6^a	74.5 ± 2.5^a	72.0 ± 2.5^a	70.5 ± 2.3^a	72.0 ± 2.4^a
1st day (Treatment started)	74.3 ± 2.2^a	335.0 ± 4.8^b	342.0 ± 4.5^b	316.7 ± 4.5^b	330.0 ± 4.5^b
7th day	70.6 ± 2.5^a	342.6 ± 3.5^b	250.0 ± 4.2^c	222.4 ± 3.5^d	116.4 ± 3.4^d
14th day	71.6 ± 2.1^a	340.0 ± 4.5^b	242.0 ± 4.9^c	202.4 ± 4.5^d	204.0 ± 4.9^d
21st day	74.3 ± 2.5^a	346.0 ± 4.9^b	233.3 ± 4.2^c	130.6 ± 4.9^d	132.0 ± 4.5^d
29th day	71.0 ± 2.4^a	349.0 ± 4.5^b	226.6 ± 4.5^c	102.6 ± 4.8^d	104.1 ± 4.9^d

Treatment was initiated on day 1 following STZ injection, and animals were sacrificed on day 29. Data represent Mean ± SEM ($n = 6$), ANOVA followed by Multiple Comparison Student's two-tail *t*-test. Bars with different superscripts (a–d) differ from each other significantly, $p < 0.05$.

The carbohydrate metabolizing enzyme also demonstrated the metabolic adjustment. Hexokinase activity was inhibited significantly ($p < 0.05$) in diabetic rats, which reduces glycolysis, whereas glucose-6-phosphatase activity was elevated significantly ($p < 0.05$), favouring the release of glucose from the liver (Figure 2). Improved glucose absorption and reduced gluconeogenesis were shown by the phytomolecules in the said extract through significant in-

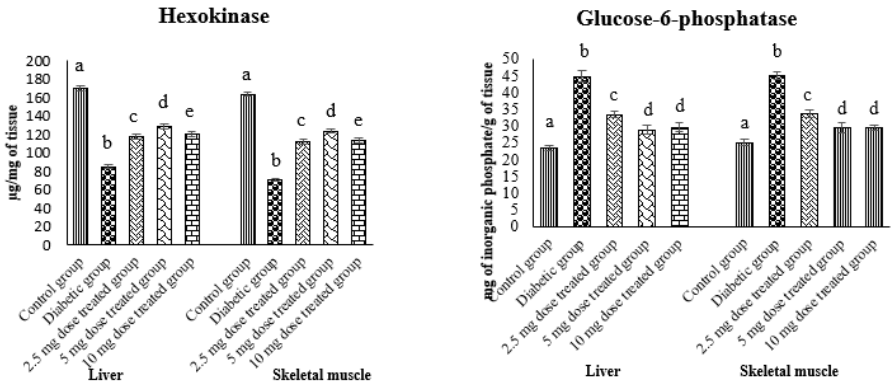


Figure 2: Effect of hydro-ethanolic extract of aerial parts of *C. benghalensis* (Linn) at different doses on the activities of hexokinase and glucose-6-phosphatase in the liver and skeletal muscle in experimental diabetic rat. Values were expressed as Mean $\pm$ SEM, n = 6, ANOVA followed by "Multiple comparison student's two tail-t-test." Bars with different superscripts (a– e) differ from each other significantly, $p < 0.05$.

creases in hexokinase and decreases in glucose-6-phosphatase activity (Alam et al., 2022). In hepatic and renal tissues, STZ-induced diabetic rats showed enhanced TBARS levels and significantly ($p < 0.05$) reduced catalase and SOD activity, indicating increased oxidative stress and metabolic disruption (Figure 3). These results confirm that diabetes causes increased lipid peroxidation and ROS production.

The phytoconstituents were essential in restoring redox equilibrium by boosting the activity of intrinsic antioxidant enzymes, binding metal ions that catalyze oxidation, and scavenging dangerous free radicals. Accordingly, the treatment with HEECB aerial parts effectively reduces TBARS levels and normalizes antioxidant enzyme activity (Mitra et al., 2019; Muralikrishnan et al., 2012; Phillips et al., 2004).

Furthermore, diabetic rats exhibited a significant ($p < 0.05$) increase in the activities of serum acid and alkaline phosphatases, indicating tissuebdamage and metabolic stress (Figure 4). Treatment with the extract markedly normalized these enzyme levels, suggesting restoration of tissue architecture and metabolic integrity (Ahmad et al., 2017). These data indicated a multi-targeted mechanism of action for HEECB aerial parts. It enhances antioxidant defenses to counteract oxidative stress, controls important metabolic enzymes to balance glucose flow, protects hepatic tissues from metabolic toxicity, and reduces hyperglycemia through β-cell protection and insulin stimulation. The extract shows promise as a natural, phytomolecule-based therapeutic candidate for managing diabetes and its complications by successfully breaking the oxidative stress–diabetes vicious cycle through these synergistic pathways.

4. Conclusion

The hydro-ethanolic extract of *Commelina benghalensis* (HEECB) aerial parts demonstrated significant antidiabetic efficacy in STZ-induced diabetic rats through a multi-targeted mechanism. Among the tested doses, 5 mg considered as the threshold dose, whereas 2.5 mg con-

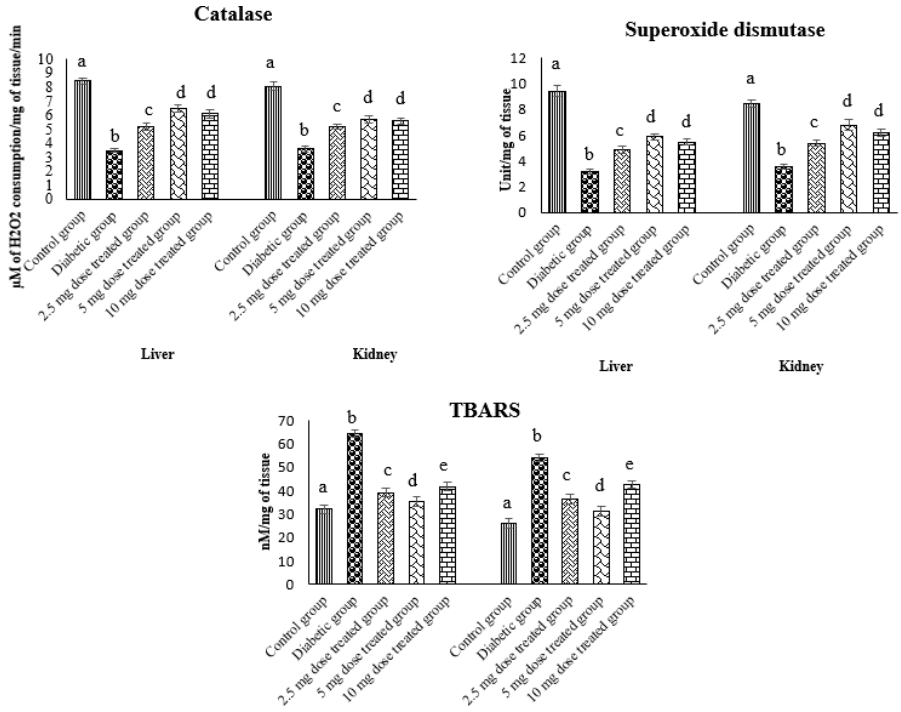


Figure 3: Antioxidative effects of different doses of the hydro-ethanolic extract of *C. benghalensis* (Linn.) aerial parts in the liver and kidney of diabetic rats. Data are presented as Mean ± SEM (n = 6). Statistical analysis was performed using ANOVA followed by multiple comparison two-tailed t-test. Superscripts (a–e) indicate significant differences, $p < 0.05$ among groups.

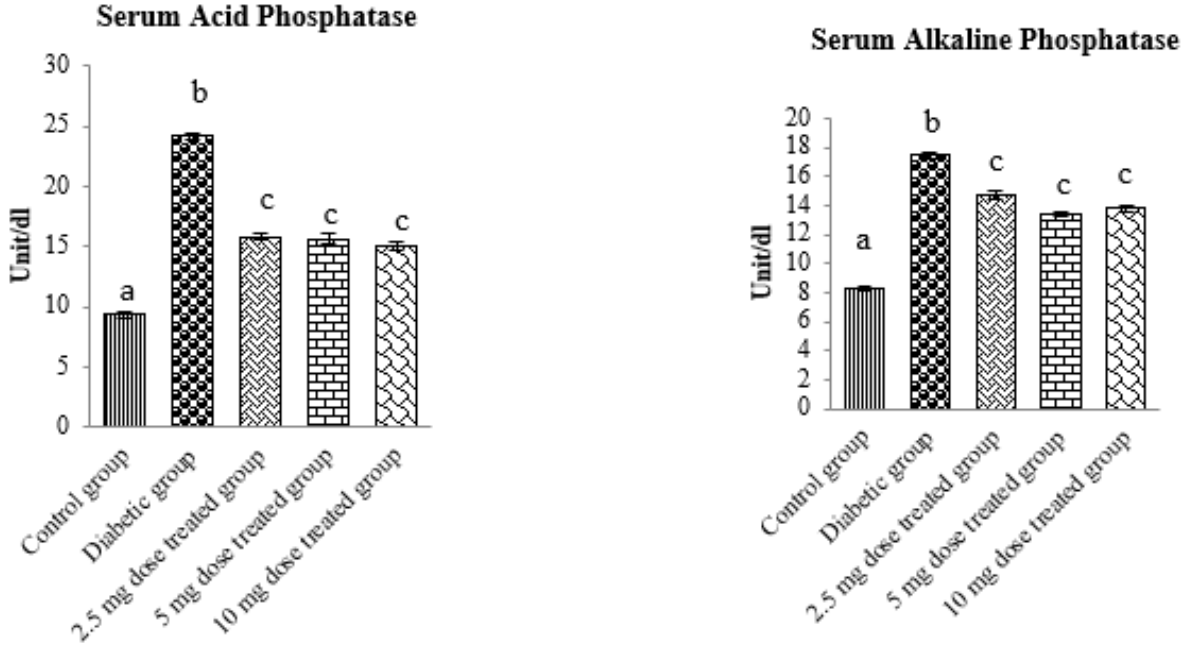


Figure 4: Toxicity assessment in serum after treatment at different doses of hydro-ethanol extract of aerial parts of *C. benghalensis* (Linn.) in diabetic rat. Values were expressed as Mean ± SEM, n = 6, ANOVA followed by "Multiple comparison student's two tail-t-test." Bars with different superscripts (a–c) differ from each other significantly, $p < 0.05$

sidered as sub-threshold activity and no additional benefit was seen at 10 mg, may be due to receptor saturation. Overall, HEECB effectively alleviated STZ-induced hyperglycemia, oxidative stress, and hepatic dysfunction through β-cell protection, improved insulin sensitivity, antioxidant restoration, and modulation of key metabolic enzymes, highlighting its strong multi-targeted antidiabetic potential.

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Conflict of interest

The authors have no conflict of interest.

Ethical statement

This study was ethically permitted from Institutional Animal Ethics Committee VU/IAEC/CPCSEA/7/7/2022 (dated 22/11/2022).

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