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Research Article

In vitro and *in vivo* studies of the antidiabetic activities of *Albizia lebbeck* (L.) Benth (Fabaceae) aqueous leaf extract

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ABSTRACT

Diabetes mellitus is a growing worldwide health issue that requires effective and safe therapeutic interventions. In recent years, plant-derived antidiabetic agents have gained a lot of interest due to their safety, efficacy and affordability. *Albizia lebbeck*, traditionally been used in diabetes management, lacks sufficient scientific evidence, especially with regard to its aqueous leaf extract. Therefore, the present study evaluated the antidiabetic efficacy of aqueous leaf extract of *Albizia lebbeck* (ALEAL) through *in-vitro* α-amylase and α-glucosidase inhibitory assays and *in-vivo* studies using alloxan-induced diabetic Wistar rats, at doses of 100, 250 and 500 mg/kg body weight, followed by biochemical, enzymatic, oxidative stress, and histopathological assessments. Phytochemical screening of ALEAL revealed the presence of phenols, flavonoids, tannins, alkaloids, saponins, coumarins, and terpenoids. ALEAL exhibited significant enzyme inhibitory activity against α-amylase and α-glucosidase, with IC_{50} values of 137.7 µg/ml and 115.2 µg/ml, respectively. Treatment of diabetic rats with ALEAL significantly reduced blood glucose levels (36.6% reduction at the highest dose) and enhanced insulin secretion. In addition, ALEAL improved lipid profile, attenuated hepatic and renal dysfunction markers, and reduced oxidative stress by decreasing malondialdehyde levels while increasing antioxidant enzymes, including GSH, SOD, CAT, GPx, and GR. Furthermore, ALEAL enhanced glucokinase activity, increased hepatic glycogen content, and suppressed glucose-6-phosphatase activity. Histopathological analysis confirmed restoration of pancreatic architecture. Collectively, these findings suggest that ALEAL exerts potent antidiabetic effects through modulation of glucose metabolism, carbohydrate-hydrolyzing enzyme inhibition, antioxidant defense, and pancreatic protection, supporting its potential as a promising natural therapeutic agent for diabetes management.

Keywords:
Antidiabetic; Alloxan; *Albizia lebbeck*; Oxidative stress; Pancreas

1. INTRODUCTION

Diabetes mellitus is a global epidemic metabolic disease characterized by elevated blood glucose with abnormal carbohydrate, fat and protein metabolism that occurs due to defective insulin production, impaired peripheral action or both [1]. Hyperglycemia is generally accompanied by symptoms like polyuria, polyphagia, polydipsia, ketoacidosis, weight loss, blurred vision and also increased susceptibility to infectious illnesses. The impact of persistent hyperglycemia may also result in severe life-threatening health complications such as cardiomyopathy, neuropathy, nephropathy and retinopathy [2]. The prevalence of diabetes is swiftly increasing with

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the global rise in obesity, sedentary lifestyles and unhealthy eating habits. It has been estimated that around 463 million adults are suffering from diabetes worldwide and the figure is expected to worsen to 578 million by 2030 and 700 million by 2045 [3]. Also, "The International Diabetes Federation" (IDF) reported that 10.5% of adults worldwide suffer with diabetes and the number is expected to rise to 12.2% by 2045 [4]. The rising prevalence and the complications associated with diabetes, necessitates continuous medical care with multifactorial risk-reduction strategies beyond glycemic control.

The current management of diabetes includes diet, exercise, insulin injections, and oral hypoglycemic agents. Although synthetic oral hypoglycemic drugs alongside insulin are the main route for controlling diabetes, they fail to reverse the course of its complications completely and further demonstrated to have prominent side effects including weight gain, diarrhea, nausea, and lactic acidosis, highlighting the limitations of current pharmacotherapy [5]. Conversely, plant-based medicines for diabetes management are gaining popularity worldwide due to their perceived efficacy, safety, cultural acceptability and cost-effectiveness [6]. In fact, traditional medicinal practitioners from different parts of the world claim to cure diabetes or at best reduce its major symptoms and progression through the administration of plant-based medicines [3]. In view of the side effects associated with modern pharmacotherapy, the World Health Organization (WHO) has also emphasized the use of ethnomedicine in diabetes management.

Albizia lebbeck (L.) Benth. (Family: Fabaceae) is commonly known as Vakai in Tamil, Siris/Shiris in Hindi and *Lebbeck* tree in English, and is mainly distributed in tropical and subtropical areas of India, tropical Africa, Asia and northern Australia. Traditionally, it has been used as an anti-asthmatic, anti-inflammatory, anti-fertility, anti-diarrhoeal, antiseptic, anti-dysenteric and antitubercular remedy [7]. It has also been used in the treatment of ringworms and wounds by washing the affected areas, gonorrhea, leucorrhoea, bronchitis, leprosy, paralysis, helminthic infection and other genital diseases. The phytoconstituents reported in the plant, such as melacacidin, D-catechin, β-sitosterol, *albizia*hexoside, amyrin, betulinic acid and echinocystic acid glycosides are responsible for various potent physiological and pharmacological activities [8]. Traditionally the whole plant has been used as a hypoglycemic agent; however, to the best of our knowledge, no scientific study has yet validated this traditional claim with respect to its aqueous leaf extract. Thus the present study was designed to evaluate the antidiabetic potential of aqueous leaf extract of *Albizia lebbeck* (ALEAL) using alloxan-induced diabetic rats, thereby providing scientific evidence for its use in diabetes management. This plant may provide a safe, affordable, and effective alternative for diabetes management, particularly in low-resource settings.

2. MATERIALS AND METHODS

2.1. Plant material and preparation of extract

Fresh leaves of *Albizia lebbeck* (L.) Benth. were collected from in and around Tiruchirappalli, Tamil Nadu, India. The plant material was identified using *Flora of the Presidency of Madras* and authenticated by comparison with the herbarium specimen deposited at the Rapinat Herbarium, St. Joseph's College, Tiruchirappalli, Tamil Nadu (voucher specimen number: RHT 65293).

The fresh leaves were shade-dried and coarsely powdered using a kitchen blender. 200 g of powdered plant material was mixed with 1200 ml of water and allowed to boil with frequent stirring. Boiling was continued until the contents were reduced to one third. Then it was filtered using muslin cloth and the filtrate obtained was evaporated to dryness using a water bath. The paste form of the extract obtained was subjected to preclinical screening.

2.2. Preliminary phytochemical screening

Preliminary phytochemical screening of ALEAL was performed using standard protocols reported in the literature [9] to detect saponins (froth test), phenols (Folin–Ciocalteu test), flavonoids (Shinoda test), alkaloids (Dragendorff's and Mayer's tests), tannins (lead acetate test), terpenoids (Noller's test), steroids and triterpenes (Liebermann–Burchard test), coumarins (sodium hydroxide test), quinones (sulfuric acid test), sugars (Fehling's test), and glycosides (anthrone test).

2.3. *In vitro* α -amylase inhibition assay

The *in vitro* α-amylase inhibition assay was performed using the 3, 5-dinitrosalicylic acid (DNSA) method [10]. The ALEAL was dissolved in a minimum amount of 10% DMSO and was further dissolved in sodium phosphate buffer [Na_2HPO_4/ NaH_2PO_4 (0.02 M), NaCl (0.006 M), pH 6.9] to give concentrations ranging from 10 to 500 µg/ml. A volume of 200 µl of α-amylase solution (2 units/ml) was mixed with 200 µl of the extract and incubated for 10 min at 30 °C. Thereafter 200 µl of the 1% starch solution was added to each tube and incubated for 3 min. The reaction was terminated by the addition of 200 µl of DNSA reagent (12 g of sodium potassium tartrate tetrahydrate in 8.0 ml of 2 M NaOH and 20 ml of 96 mM DNSA solution) and the mixture was boiled for 10 min in a water bath

at 85-90 °C. The mixture was cooled to ambient temperature and was diluted with 5 ml of distilled water, and the absorbance was measured at 540 nm using a UV-Visible spectrophotometer. The blank with 100% enzyme activity was prepared by replacing the plant extract with 200 µl of buffer. A positive control sample was prepared using acarbose (10 to 500 µg/ml) and the reaction was performed similarly to that of the plant extract as mentioned above. All tests were performed in triplicate. The percentage inhibition of α-amylase was calculated using the following formula:

$$\% \text{ Inhibition} = \frac{\text{Absorbance of the control - Absorbance of the test sample}}{\text{Absorbance of the control}} \times 100$$

2.4. *In vitro* α-glucosidase inhibition assay

Plant extract was evaluated for α-glucosidase inhibitory activity according to the method given by Bhatia et al., [11]. Plant extract (50 µl) at varying concentrations (10 to 500 µg/ml) was incubated with 10 µl of α-glucosidase enzyme solution (1 U/ml) for 20 min at 37 °C with an additional 125 µl of 0.1 M phosphate buffer (pH 6.8). After 20 min, the reaction was started with the addition of 20 µl of 1 M pNPG (*p*-nitrophenyl-α-D-glucopyranoside) as substrate and the mixture was incubated for 30 min. The reaction was terminated with the addition of 0.1 N of Na_2CO_3 (50 µl) and final absorbance was measured at 405 nm using spectrophotometer. Acarbose was used as a positive control at varying concentrations (10 to 500 µg/ml). All tests were performed in triplicate. The percentage inhibition of α-glucosidase was calculated using the following formula:

$$\% \text{ Inhibition} = \frac{\text{Absorbance of the control - Absorbance of the test sample}}{\text{Absorbance of the control}} \times 100$$

2.5. Experimental animals

Healthy adult Wistar strain albino rats of both sexes, aged two to three months and weighing 150-200 g were obtained from Tamil Nadu Veterinary and Animal Sciences University, Chennai. The animals were allowed to acclimatize under laboratory conditions for a period of 10 days prior to the experiment. The animals were housed in standard polypropylene cages. Six animals were housed per cage, so as to provide them with sufficient space, and to avoid unnecessary morbidity and mortality. The animals were maintained under standard conditions, with a 12: 12-h light/ dark cycle and at an ambient temperature of 23 ± 2 °C and relative humidity of 65 ± 5%. The animals were fed standard rat chow pellets obtained from Sai Durga Foods and Feeds, Bangalore, India and provided water *ad libitum*. All studies were conducted in accordance with the ethical guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) after obtaining necessary clearance from the committee (Approval No: 790/03/ac/CPCSEA).

2.6. Experimental design

2.6.1. Induction of experimental diabetes

Diabetes mellitus was induced in normoglycemic albino rats after fasting them overnight by intraperitoneal administration of alloxan monohydrate freshly prepared in physiological saline, at a dose of 150 mg/kg bw. To prevent alloxan-induced hypoglycemia resulting from the massive release of insulin from pancreatic β-cells, the rats were provided with a 5% glucose solution in their drinking bottles for the next 24 h. After 72 h of alloxan administration, the blood glucose levels of the rats were determined using a glucometer. The rats with blood glucose levels greater than 200 mg/dl were considered diabetic and were selected, grouped, and used for further studies.

2.6.2. Treatment groups

Experimental animals were divided into six groups (Group I–VI) of six rats each. Group I comprised normal rats and served as the normal control, while Groups II–VI comprised of diabetic rats and were treated as follows: Group II rats served as the diabetic control and were administered with normal saline only. Group III, IV, and V diabetic rats were treated with ALEAL at doses of 100, 250, and 500 mg/kg bw, respectively. Group VI diabetic rats received the standard drug, Glibenclamide (10 mg/kg bw). All treatments were administered orally using a cannula once daily at 24 h intervals for a period of 30 days. Animals had free access to standard pellet chow and water ad libitum throughout the experimental period (Figure 1).

At the end of the experimental period of 30 days, the animals were fasted overnight for 12 h, anaesthetized with diethyl ether, and sacrificed by cervical dislocation. Blood was collected, and serum was separated by centrifuging at 3000 rpm for 10 min. The liver, kidney and pancreas were dissected out and washed in ice-cold saline. Liver and kidney tissues were homogenized in 0.1M phosphate buffer, pH 7.4, and used for studying various parameters. Part of the pancreatic tissue was processed for histopathological studies.

2.6.3. Parameters studied

The initial body weights of the rats were recorded on day 1, and subsequent changes in body weight

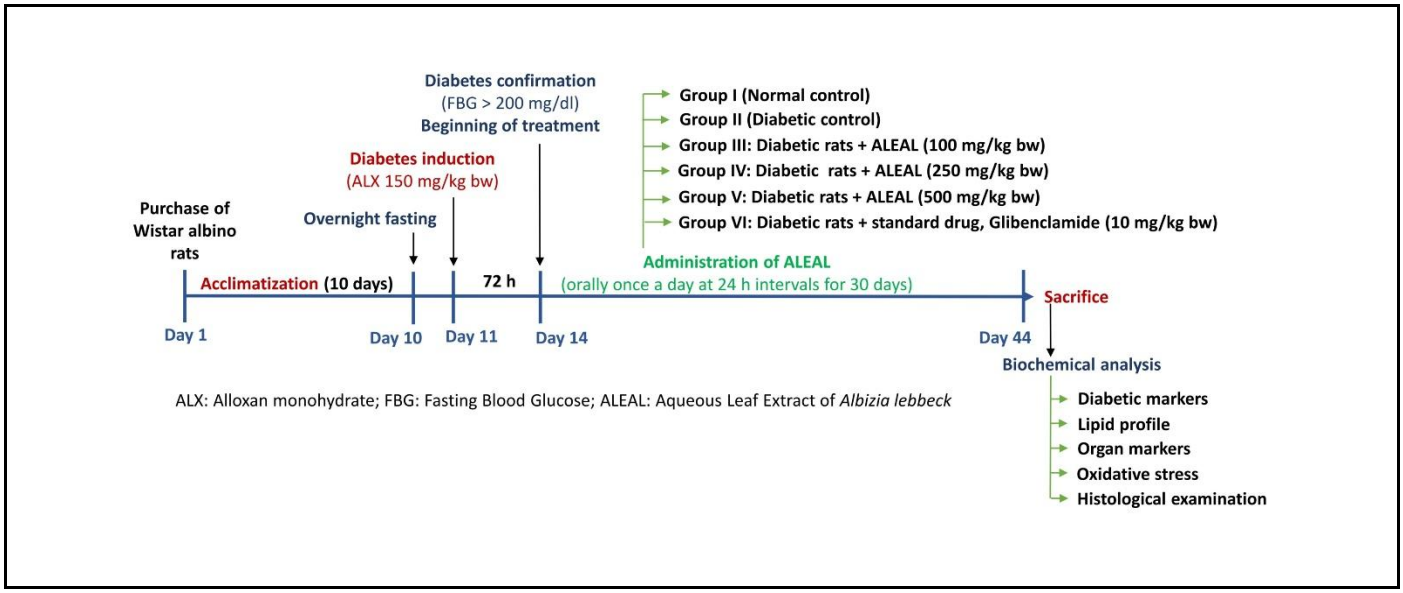


Figure 1. Schematic representation of study design**.**

were recorded once every 10 days. Serum insulin levels were measured by the ELISA method using a commercial kit (Sigma-Aldrich, USA). Blood glucose and serum lipid profile such as triglycerides (TG), total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C) were estimated using commercially available kits (Biosystems, TN, India). Low density lipoprotein cholesterol (LDL-C) was calculated using Friedewald's formula [12]. The activities of hepatic marker enzymes, including alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP), as well as kidney function markers such as urea and creatinine, were determined using commercial kits (Biosystems, TN, India). Liver glycogen, serum/tissue protein, glucose-6-phosphatase **(**G6Pase**)**, and glucokinase (GK) were estimated using standard protocols. Lipid peroxidation (LPO), the antioxidant status, including reduced glutathione (GSH), glutathione reductase (GR), glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT) in hepatic and renal tissues were also analyzed using standard methods.

2.7. Statistical analysis

All the results were expressed as mean ± S.E.M. The data were statistically analyzed by one -way analysis of variance (ANOVA), and P values < 0.05 were considered statistically significant.

3. RESULTS

3.1. Preliminary phytochemical screening

The preliminary phytochemical analysis of ALEAL revealed the presence of phenols, flavonoids, tannins, alkaloids, saponins, coumarins, and terpenoids.

3.2. *In vitro* α -amylase and α – glucosidase inhibitory activities

The results of α-amylase and α-glucosidase inhibition by ALEAL and acarbose, are presented in Figure 2. The crude extract ALEAL significantly ($p < 0.05$) enhanced the inhibition of α-amylase and α-glucosidase in a concentration-dependent manner. Notably, ALEAL exhibited an IC_{50} of 137.7 µg/mL against α-amylase and 115.2 µg/mL against α-glucosidase, indicating its substantial inhibitory potency. Meanwhile, the standard drug, acarbose, exhibited near-complete enzyme inhibition at medium and high concentrations, with IC_{50} values of 34.4 µg/mL against α-amylase and 28.5 µg/mL against α-glucosidase.

3.3. Effect of ALEAL on body weight

Animals were observed for changes in body weight every 10 days throughout the experiment and the results are summarized in Figure 3. Initially, there were no significant differences in body weights among the groups as the animals were evenly segregated based on their body weight into each group. After induction of diabetes, statistically significant differences in the body weights between normal and diabetic rats were observed ($p < 0.05$). The normal control rats showed an approximately 23% increase in body weight as compared to their initial weight, while the diabetic control rats showed a 25% decrease in body weight at the end of the experiment. However, a significant increase in body weight was observed in diabetic animals treated with 10 mg/kg of glibenclamide (15%) and 500 mg/kg of ALEAL (9%) for 30 days. There was a decrease in body weight in the 100 mg/kg (7%) and 250 mg/kg (1%) of ALEAL-treated rats; however

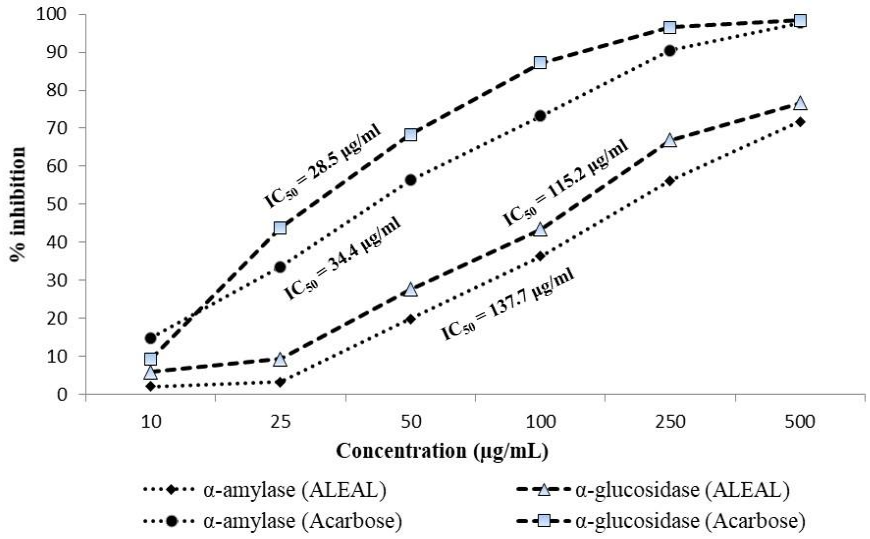


Figure 2. α-amylase and α-glucosidase inhibition by ALEAL and acarbose.

the decrease was much lower than that observed in the diabetic control group.

3.4. Effect of ALEAL on blood glucose and insulin levels

The effects of ALEAL on blood glucose and insulin levels in normal and diabetic rats are depicted in Figure 4. Alloxan-induced diabetic rats exhibited a significant increase in blood glucose levels and a decrease in plasma insulin levels in comparison to normal rats. Treatment with ALEAL significantly ($p < 0.05$) reduced blood glucose levels in alloxan-induced diabetic rats at all tested doses (100, 250, and 500 mg/kg), showing reductions of 11.68%, 27.36%, and 36.6%, respectively, compared with the diabetic control group. Similarly, treatment with glibenclamide (10 mg/kg) also produced a significant ($p < 0.05$) reduction in blood glucose levels, with a 45.97% decrease compared with the diabetic control group. On the other hand, a significant ($p < 0.05$) increase in plasma insulin levels was noted in diabetic rats treated with glibenclamide or ALEAL in a dose-dependent manner.

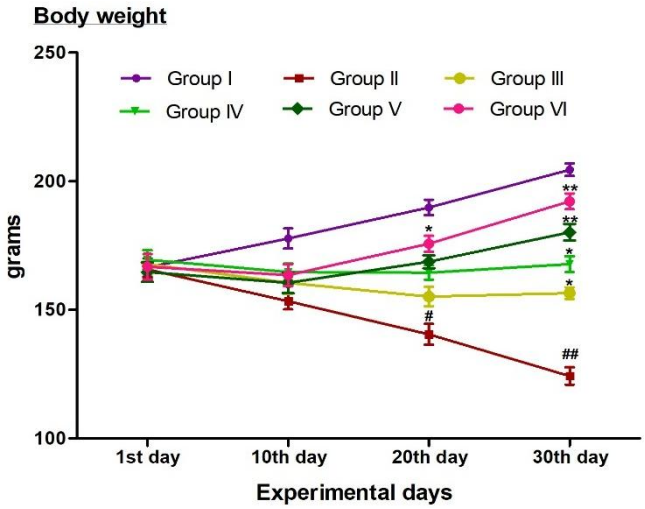


Figure 3. Effect of ALEAL on body weight of experimental animals. Values are mean ± S.E.M of 6 rats; #p< 0.05, ##p< 0.01, significantly different from group I; *p< 0.05, **p< 0.01, significantly different from group II. Group I: normal control, Group II: diabetic control, Group III: alloxan + ALEAL (100 mg/kg), Group IV: alloxan + ALEAL (250 mg/kg), Group V: alloxan + ALEAL (500 mg/kg), Group VI: alloxan + glibenclamide (10 mg/kg).

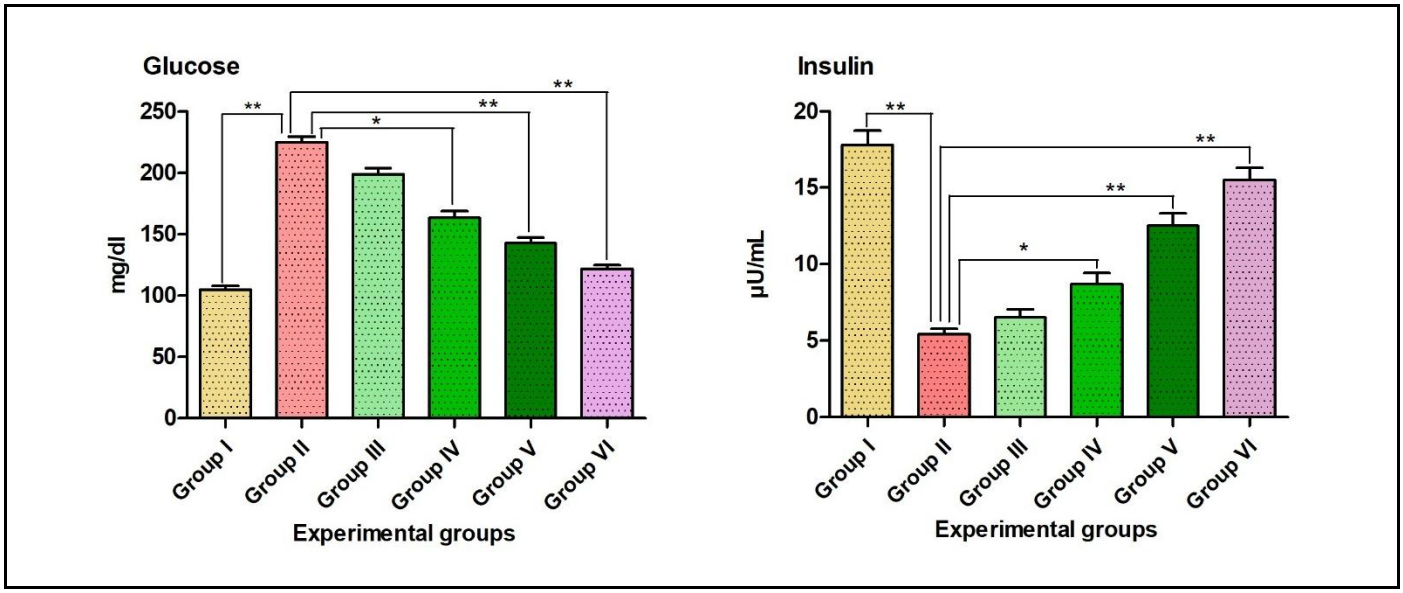


Figure 4. Effect of ALEAL on blood glucose and insulin levels in experimental animals**.** Values are mean ± S.E.M of 6 rats; *p< 0.05, **p< 0.01**;** Group I: normal control, Group II: diabetic control, Group III: alloxan + ALEAL (100 mg/kg), Group IV: alloxan + ALEAL (250 mg/kg), Group V: alloxan + ALEAL (500 mg/kg), Group VI: alloxan + glibenclamide (10 mg/kg).

3.5. Effect of ALEAL on lipid profile

The effect of ALEAL on the lipid profile of diabetic rats is given in Table 1. In diabetic rats, the levels of TG, TC, and LDL-C were significantly increased, whereas the HDL-C level was decreased. However, in the ALEAL-treated groups (100, 250 and 500 mg/kg), TG, TC and LDL-C levels were significantly reduced ($p < 0.05$), while HDL-C levels were significantly increased ($p < 0.05$) compared with those of the diabetic control rats. These effects were comparable to those observed in the glibenclamide-treated (10 mg/kg) group.

3.6. Effect of ALEAL on organ markers

The effect of ALEAL on liver and kidney function markers in diabetic rats is shown in Table 2. Diabetic rats exhibited significantly elevated levels of liver enzymes (ALP, ALT, and AST) and kidney markers (urea and uric acid). However, treatment with ALEAL at doses of 100, 250, and 500 mg/kg resulted in a dose-dependent normalization of these altered markers. Additionally, ALEAL treatment restored total protein levels to normal values.

3.7. Effect of ALEAL on levels of tissue enzymes and glycogen

Table 3 demonstrates the changes in the activities of carbohydrate-metabolizing enzymes and glycogen content in the liver of control and experimental rats. The activity of GK was significantly ($p < 0.01$) decreased by 31.4%, whereas the activity of G6Pase was significantly ($p < 0.01$) increased by 78.4% in diabetic rats compared with normal control rats. Upon treatment of diabetic rats with ALEAL, the activities of GK and G6Pase were normalized. Diabetic animals also showed a marked decline in liver glycogen content. Conversely, oral treatment of diabetic rats with ALEAL partially restored the glycogen level to a level near that of normal control rats.

Table 1. Effect of ALEAL on serum lipid profile in experimental animals.

Groups	Triglycerides (mg/dL)	Cholesterol (mg/dL)	HDL-Cholesterol (mg/dL)	LDL-Cholesterol (mg/dL)
Group I	74.5 ± 1.04	135.3 ± 2.39	30.67 ± 0.32	89.57 ± 1.08
Group II	245.7 ± 2.91$^{\#}$	291.9 ± 3.64$^{\#}$	15.21 ± 0.73$^{\#}$	227.45 ± 2.46$^{\#}$
Group III	215.8 ± 3.46*	263.1 ± 3.26*	19.46 ± 0.56*	199.06 ± 2.53*
Group IV	183.8 ± 2.78*	232.6 ± 3.26*	22.41 ± 0.75*	173.26 ± 2.21*
Group V	105.6 ± 1.89**	185.2 ± 2.51**	26.06 ± 0.23**	138.2 ± 1.96**
Group VI	86.2 ± 1.25**	141.9 ± 2.52**	28.51 ± 0.18**	96.26 ± 1.48**

Values are mean ± S.E.M of 6 rats; $^{\#}$p< 0.01, significantly different from group I; *p< 0.05, **p< 0.01, significantly different from group II. Group I: normal control, Group II: diabetic control, Group III: alloxan + ALEAL (100 mg/kg), Group IV: alloxan + ALEAL (250 mg/kg), Group V: alloxan + ALEAL (500 mg/kg), Group VI: alloxan + glibenclamide (10 mg/kg)

Table 2. Effect of ALEAL on serum liver and kidney markers in experimental animals.

Groups	Total Protein (g/dL)	ALP (IU/L)	ALT (IU/L)	AST (IU/L)	Urea (mg/dL)	Creatinine (mg/dL)
Group I	6.73 ± 0.41	98 ± 1.42	22.73 ± 0.91	44.45 ± 0.36	29.63 ± 0.92	0.91 ± 0.09
Group II	4.02 ± 0.34$^{\#}$	288 ± 1.89$^{\#}$	92.31 ± 1.09$^{\#}$	125.68 ± 2.13$^{\#}$	58.56 ± 0.88$^{\#}$	2.06 ± 0.12$^{\#}$
Group III	4.78 ± 0.36	239.53 ± 2.36	76.47 ± 1.33	104.66 ± 2.33	52.11 ± 1.41	1.91 ± 0.33
Group IV	5.63 ± 0.42*	166.03 ± 2.08*	46.16 ± 0.66*	78.03 ± 1.25*	43.36 ± 1.28*	1.53 ± 0.26*
Group V	6.05 ± 0.37**	120.56 ± 1.93**	30.07 ± 0.86**	58.61 ± 1.07**	35.89 ± 1.04**	1.26 ± 0.33**
Group VI	6.51 ± 0.33**	104.18 ± 1.69**	28.85 ± 0.59**	52.53 ± 0.95**	32.13 ± 0.93**	1.16 ± 0.09**

Values are mean ± S.E.M of 6 rats; $^{\#}p< 0.01$, significantly different from group I; *p< 0.05, **p< 0.01, significantly different from group II. Group I: normal control, Group II: diabetic control, Group III: alloxan + ALEAL (100 mg/kg), Group IV: alloxan + ALEAL (250 mg/kg), Group V: alloxan + ALEAL (500 mg/kg), Group VI: alloxan + glibenclamide (10 mg/kg).

3.8. Effect of ALEAL on oxidative stress markers

The effects of ALEAL treatment on LPO and both enzymatic and non-enzymatic antioxidant status in hepatic and renal tissues of diabetic rats are given in Figure 5. The observed data showed that LPO levels were significantly elevated in diabetic rats compared to the control group. However, treatment with ALEAL significantly reduced LPO levels. GSH levels, which were depleted in alloxan-induced diabetic rats, were restored following ALEAL treatment. Furthermore, the activities of enzymatic antioxidants, including GR, GPx, SOD, and CAT, were markedly reduced in the liver and kidney tissues of diabetic rats. Administration of ALEAL significantly restored the activities of these antioxidant enzymes in a dose-dependent manner.

3.9. Effect of ALEAL on pancreatic histopathology

Photomicrographs of hematoxylin and eosin-stained sections of the pancreas of experimental animals are shown in Figure 6. The Group I rats showed a normal pancreatic architecture that was uniform throughout the tissue. The islets of Langerhans were well-defined, compact, and contained centrally located β-cells, surrounded by normal exocrine acinar cells, with no evidence of cellular degeneration. In contrast, pancreatic islet cells in untreated alloxan-induced diabetic rats (Group II) revealed significant deterioration, characterized by necrosis, inflammatory cell infiltration, and loss of islet integrity. However, treatment with ALEAL (Groups III–V) and glibenclamide (Group VI) markedly ameliorated alloxan-induced pancreatic damage. These groups displayed improved islet architecture with increased cellularity and reduced inflammatory infiltration compared to the diabetic control group.

4. DISCUSSION

Medicinal plants are known to contain a wide range of bioactive phytoconstituents with diverse therapeutic properties, including antioxidant and antidiabetic activities. In the present study, preliminary phytochemical screening of the aqueous leaf extract of *A. lebbeck* (ALEAL) revealed the presence of flavonoids, alkaloids, saponins, tannins, glycosides, and phenolic compounds, which is in agreement with previous findings [13]. Earlier studies have reported that medicinal plants possessing both antidiabetic and antioxidant activities are often rich in polyphenolic compounds such as flavonoids, tannins, terpenoids, and steroidal glycosides [14,15]. These phytoconstituents are known to play a crucial role in reducing oxidative stress and regulating glucose metabolism, thereby contributing to the antidiabetic potential of ALEAL.

Table 3. Effect of ALEAL on tissue enzymes and glycogen in experimental animals

Groups	Glucose-6- phosphatase (U/mg tissue/min)	Glucokinase (U/mg tissue/min)	Liver glycogen (mg/g tissue)
Group I	23.5 ± 0.38	1.336 ± 0.04	19.18 ± 0.27
Group II	41.92 ± 0.48$^{\#}$	0.916 ± 0.05$^{\#}$	6.03 ± 0.58$^{\#}$
Group III	38.41 ± 0.46*	1.015 ± 0.01*	12.19 ± 0.19*
Group IV	35.67 ± 0.26*	1.075 ± 0.02*	14.33 ± 0.36*
Group V	28.05 ± 0.64**	1.168 ± 0.01**	17.35 ± 0.28**
Group VI	25.66 ± 0.51**	1.375 ± 0.17**	18.95 ± 0.21**

Values are mean ± S.E.M of 6 rats; $^{\#}p< 0.01$, significantly different from group I; *p< 0.05, **p< 0.01, significantly different from group II. Group I: normal control, Group II: diabetic control, Group III: alloxan + ALEAL (100 mg/kg), Group IV: alloxan + ALEAL (250 mg/kg), Group V: alloxan + ALEAL (500 mg/kg), Group VI: alloxan + glibenclamide (10 mg/kg)

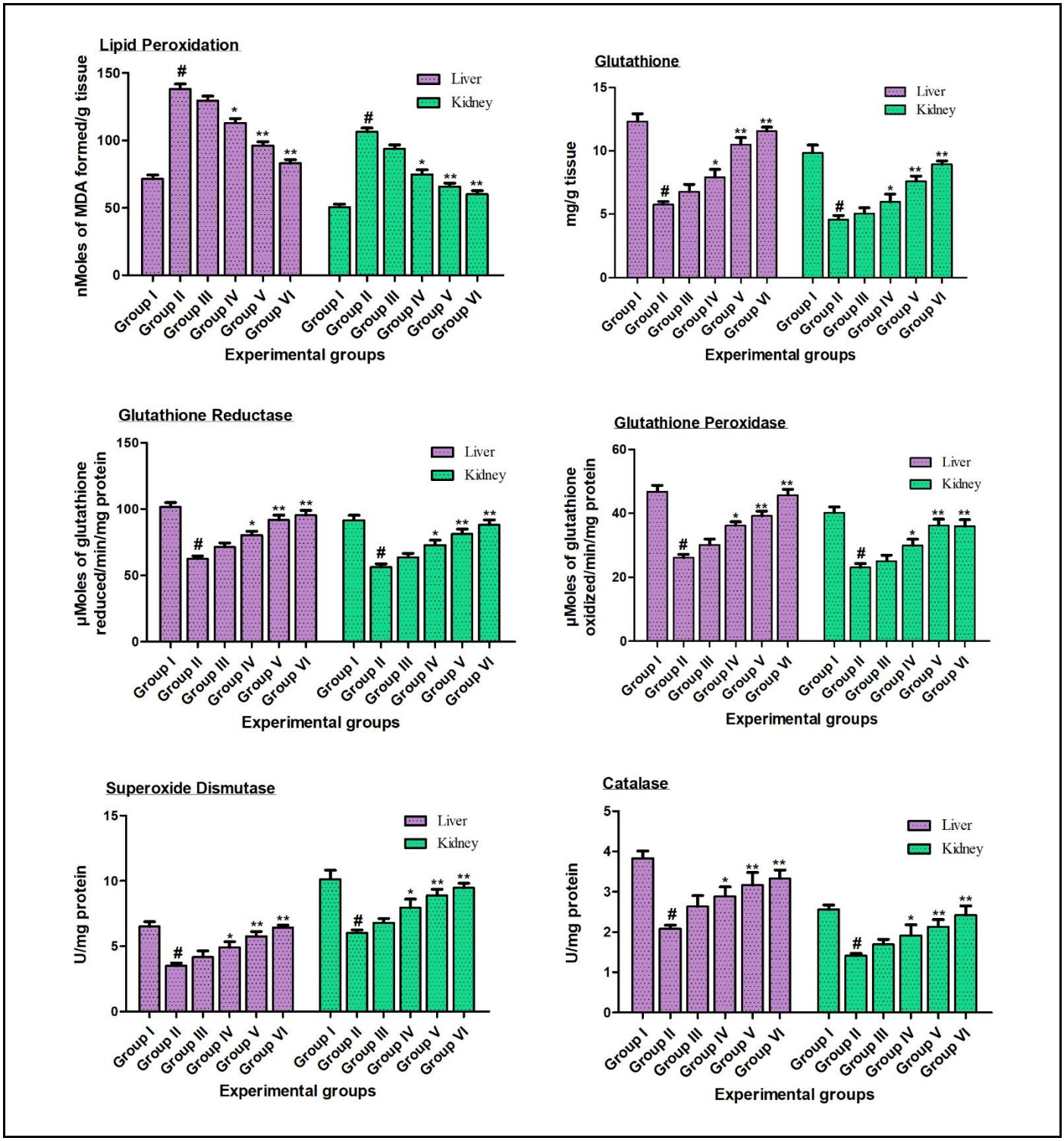


Figure 5. Effect of ALEAL on enzymatic and non-enzymatic antioxidant status of liver and kidney. Values are mean ± S.E.M of 6 rats; #p< 0.01, significantly different from group I; *p< 0.05, **p< 0.01, significantly different from group II. Group I: normal control, Group II: diabetic control, Group III: alloxan + ALEAL (100mg/kg), Group IV: alloxan + ALEAL (250mg/kg), Group V: alloxan + ALEAL (500mg/kg), Group VI: alloxan + glibenclamide (10mg/kg).

One of the modern therapeutic approaches for controlling postprandial hyperglycemia in diabetic conditions is to reduce carbohydrate absorption after food intake. Complex carbohydrates such as starches, oligosaccharides, and disaccharides must be broken down into monosaccharides before absorption into the bloodstream, a process mainly mediated by the enzymes α-amylase and α-glucosidase. α-Amylase hydrolyzes starch into smaller oligosaccharides consisting of maltose, maltotriose, and maltooligosaccharides. These products are further degraded into glucose by α-glucosidase, after which they are absorbed into the bloodstream [16]. Therefore, inhibition of these enzymes can delay carbohydrate digestion and reduce the rate

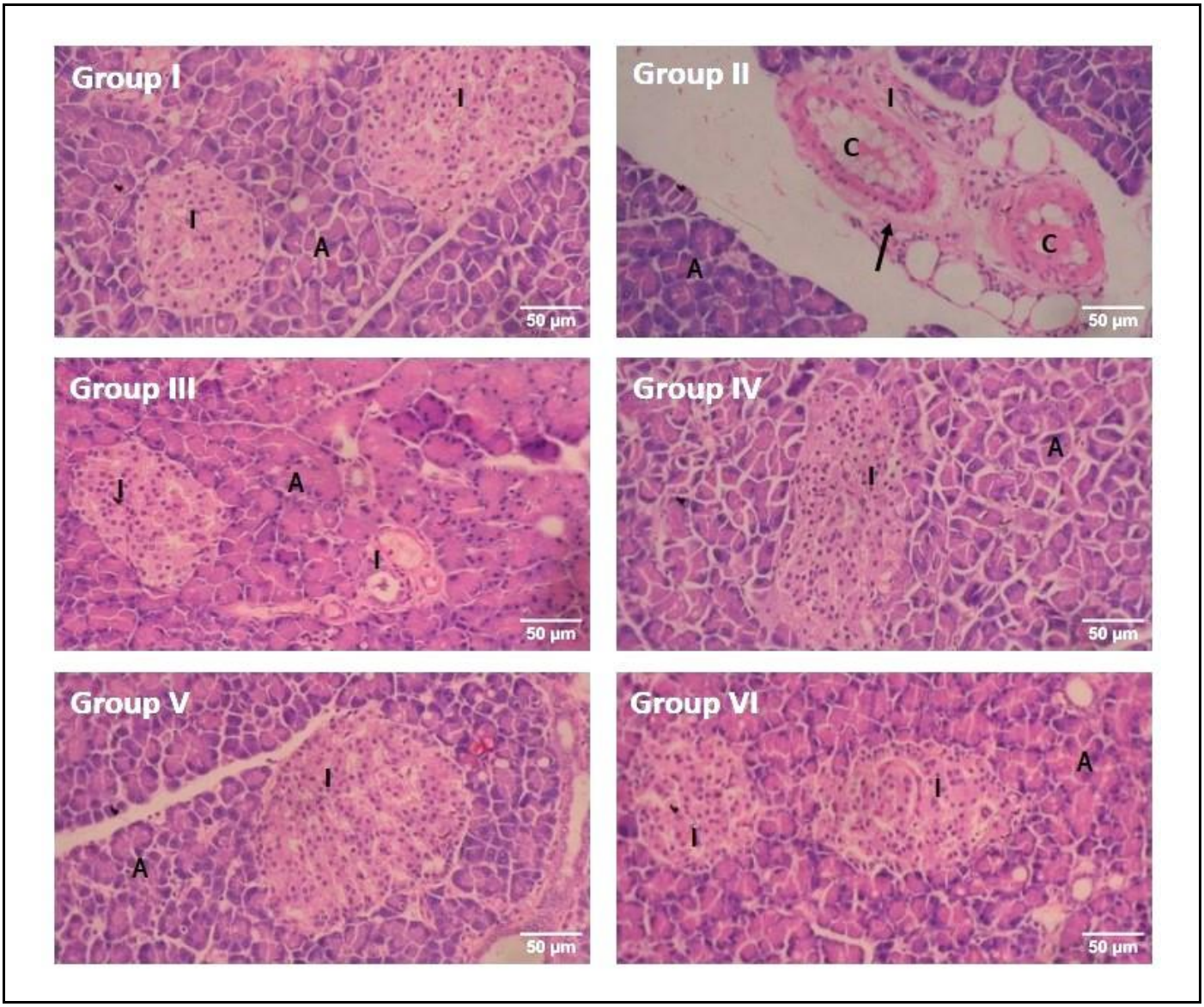


Figure 6. Photomicrographs of hematoxylin and eosin (H&E; x100) – stained sections of the pancreas of experimental rats. Group I shows normal pancreatic architecture with compact islets (I) surrounded by exocrine acinar (A) cells. Group II exhibits marked degeneration of pancreatic islet cells (black arrow), with congestion in blood vessels (C). Groups III, IV, V, and VI show varying degrees of pancreatic protection and restoration. Group I: normal control, Group II: diabetic control, Group III: alloxan + ALEAL (100 mg/kg), Group IV: alloxan + ALEAL (250 mg/kg), Group V: alloxan + ALEAL (500 mg/kg), Group VI: alloxan + glibenclamide (10 mg/kg).

of glucose absorption, thereby lowering postprandial blood glucose levels. Inhibition of α-amylase and/or α-glucosidase is thus considered an important therapeutic strategy for the management of type 2 diabetes mellitus (T2DM). Currently, only three α-glucosidase inhibitors, namely acarbose, miglitol, and voglibose are used in clinical practice. However, these drugs are associated with side effects such as malabsorption, diarrhea, abdominal pain, and flatulence, resulting in high discontinuation rates [17]. Additionally, these agents are not recommended for individuals with renal impairment or hepatic disease. Therefore, there is increasing interest in identifying novel inhibitors with improved efficacy and safety. Compounds with α-glucosidase inhibitory activity are widely distributed in medicinal plants. In the present study, ALEAL also significantly inhibited α-amylase and α-glucosidase enzymes (Figure 2), which may be attributed to its various bioactive phytoconstituents. Similar findings have been reported in previous studies on *A. lebbeck*, where flavonoids such as geraldone, luteolin, and isookanin isolated from methanolic bark extracts demonstrated considerable inhibitory activity against carbohydrate-hydrolyzing enzymes [18]. In addition, studies on other *Albizia* species, such as *A. procera* [19] and *A. antunesiana* [20], have also reported varying degrees of α-amylase and α-glucosidase inhibitory activities, suggesting that members of the genus *Albizia* possess promising antidiabetic potential. Furthermore, several plant-derived phytoconstituents, including terpenes, alkaloids, quinones, flavonoids,

phenols, phenylpropanoids, and steroids, have been reported to exhibit potent inhibitory activity against these carbohydrate-hydrolyzing enzymes [21,22].

Diabetes mellitus is also characterized by loss of body weight, possibly due to the inability of cells to utilize glucose, increased lipolysis in adipose tissue, and protein breakdown leading to skeletal muscle wasting. Body weight reduction resulting from metabolic imbalance is commonly associated with diabetes [23]. Similarly, in the present study, alloxan administration caused a significant loss of body weight in the diabetic control group. This weight loss was ameliorated by ALEAL at all tested doses (100, 250, and 500 mg/kg) (Figure 3). Although slight reductions in body weight were still observed in the 100 and 250 mg/kg ALEAL-treated groups, the magnitude of weight loss was markedly lower than that of the diabetic control group, suggesting partial protection against diabetes-induced muscle wasting and tissue degradation. Interestingly, rats treated with 500 mg/kg ALEAL exhibited an increase in body weight, indicating a dose-dependent improvement in metabolic homeostasis. The protective effect of ALEAL on body weight may be associated with improved glycemic control and restoration of metabolic balance, thereby reducing excessive protein catabolism and lipid mobilization commonly observed in diabetic conditions [24].

Alloxan-induced diabetes is primarily mediated through the selective destruction of pancreatic β-cells via the generation of reactive oxygen species (ROS), resulting in insulin deficiency and persistent hyperglycemia. In the present study, Group II diabetic control rats showed significantly elevated fasting blood glucose levels accompanied by reduced insulin concentrations (Figure 4), confirming the successful induction of β-cell dysfunction. These findings are in line with alloxan's known diabetogenic effect, which impairs endogenous insulin secretion, thereby compromising glucose homeostasis [25]. However, administration of ALEAL markedly ameliorated hyperglycemia and restored serum insulin levels in a dose-dependent manner, suggesting a protective and regenerative effect on pancreatic β-cells (Figure 4). The antihyperglycemic activity of ALEAL may be attributed to its rich phytochemical composition, including flavonoids, phenolic compounds, saponins, terpenoids, and alkaloids. Saponins have been reported to reduce fasting blood glucose levels by enhancing insulin secretion and improving peripheral glucose utilization, while terpenoids stimulate insulin release or mimic insulin action at target tissues [26]. Furthermore, flavonoids and phenolic compounds may enhance glucose uptake by upregulating glucose transporter activity and promoting β-cell regeneration. Compounds such as catechins and related derivatives have been reported to improve insulin sensitivity and cellular glucose utilization [27]. Additionally, the strong antioxidant capacity of ALEAL (Figure 5) may help reduce oxidative stress, a key factor in β-cell apoptosis and diabetes progression, thereby protecting pancreatic architecture and supporting endogenous insulin production [24].

Hyperglycemia accompanied by dyslipidemia is a hallmark feature of diabetes mellitus and plays a central role in the development of cardiovascular complications [28,29]. Chronic elevation of blood glucose significantly impairs lipid metabolism, leading to characteristic abnormalities in circulating lipoproteins. In the present study, alloxan-induced diabetic rats demonstrated significant hypercholesterolemia, hypertriglyceridemia, elevated LDL-C, and reduced HDL-C levels. These alterations in serum lipid profiles are well-recognized contributors to atherogenesis and substantially increase the risk of coronary heart disease under diabetic conditions [29]. The observed dyslipidemia may be attributed to insulin deficiency resulting from alloxan-mediated destruction of pancreatic β-cells. Under normal physiological conditions, insulin plays a key role in maintaining lipid homeostasis by stimulating lipoprotein lipase, thereby promoting TG hydrolysis and enabling lipid clearance from the circulation [30]. Reduced insulin secretion disrupts this regulatory mechanism, leading to the accumulation of TGs and cholesterol in the plasma. Treatment with ALEAL markedly improved the lipid profile in diabetic rats, as evidenced by significant reductions in TC, TG, and LDL-C levels, along with a concomitant increase in HDL-C concentration (Table 1). These hypolipidemic effects may result from the modulation of cholesterol absorption and biosynthesis, improved lipoprotein metabolism, and restoration of pancreatic β-cell function [28].

Alloxan-induced insulin deficiency generally leads to alterations in carbohydrate metabolism. In the present study, untreated diabetic rats exhibited a significant elevation in hepatic G6Pase activity along with noticeable reductions in GK activity and hepatic glycogen content. These findings are consistent with the metabolic disturbances reported in earlier experimental diabetes models [32]. G6Pase catalyzes the terminal step of hepatic glucose production by converting glucose-6-phosphate into free glucose. Thus, the elevated G6Pase activity observed in diabetic control animals indicates enhanced hepatic gluconeogenesis and glycogenolysis, which contribute to persistent hyperglycemia. Insulin deficiency is known to upregulate G6Pase expression, thereby increasing endogenous glucose output [33]. Treatment with ALEAL significantly reduced G6Pase activity toward near-normal levels, suggesting suppression of excessive hepatic glucose production. Conversely, GK activity was significantly decreased in untreated diabetic rats (Table 3). GK plays a crucial role in hepatic glucose utilization by phosphorylating glucose to glucose-6-phosphate, thereby facilitating

glycolysis and glycogen synthesis and promoting the clearance of glucose from circulation. Because insulin positively regulates GK expression, its reduction in diabetic animals reflects impaired insulin signaling [34]. Restoration of GK activity following ALEAL treatment suggests enhanced insulin sensitivity and improved metabolic handling of circulating glucose. Hepatic glycogen content was markedly depleted in diabetic control animals (Table 3), consistent with impaired glycogenesis and enhanced glycogen breakdown under insulin-deficient conditions [33]. The significant restoration of glycogen stores in ALEAL-treated groups further supports improved insulin-mediated glucose storage. Collectively, the coordinated normalization of G6Pase, GK, and hepatic glycogen levels indicates that ALEAL exerts a dual regulatory effect on hepatic carbohydrate metabolism by suppressing glucose overproduction while enhancing glucose utilization. These beneficial effects may be attributed to the phytoconstituents present in ALEAL, such as alkaloids, polyphenols, or flavonoids, which are known to enhance insulin secretion, improve insulin sensitivity, and regulate carbohydrate-metabolizing enzymes through activation of intracellular signaling pathways, as reported in experimental diabetes models [35].

Oxidative stress plays a central role in both the development and progression of diabetes and its complications. Chronic hyperglycemia enhances the generation of ROS through multiple mechanisms, including glucose autoxidation, non-enzymatic protein glycation, and activation of the polyol pathway, leading to the impairment of endogenous antioxidant defense systems [36]. In the present study, diabetic control animals exhibited a significant elevation in malondialdehyde (MDA), a key biomarker of LPO, along with a marked decline in both enzymatic and non-enzymatic antioxidants, including GSH, GR, GPx, SOD, and CAT in hepatic and renal tissues (Figure 5). These findings indicate enhanced oxidative stress under diabetic conditions.

Persistent hyperglycemia induces oxidative stress–mediated cellular damage, which is largely driven by LPO [37,38]. LPO causes the oxidative degradation of polyunsaturated fatty acids (PUFAs), thereby generating several reactive and cytotoxic end products that contribute to oxidative stress and the depletion of key antioxidant enzymes, particularly SOD and CAT, which constitute the first line of defense against ROS. Reduced activities of these enzymes may result from excessive superoxide generation, H_2O_2 accumulation, and glycation-induced enzyme inactivation [37]. The glutathione redox system also plays a crucial role in maintaining cellular redox balance, where GSH serves as a cofactor for GPx in detoxifying peroxides, while GR regenerates reduced GSH using NADPH [37,38]. Consequently, the GSH level and activities of GPx and GR become compromised under diabetic conditions. In the current study, treatment with ALEAL significantly restored GSH levels, and upregulated the activities of SOD, CAT, GPx, and GR compared with untreated diabetic animals (Figure 5). These findings indicate a strong antioxidant potential of ALEAL, likely mediated through both direct free radical scavenging and the enhancement of endogenous antioxidant defenses. The protective effects may be attributed to phytoconstituents such as flavonoids, phenolic compounds, and other antioxidant metabolites capable of neutralizing ROS, chelating transition metal ions, and potentially upregulating antioxidant gene expression [39].

The biochemical changes observed in the present study were further validated by significant histopathological changes in the pancreatic tissues of experimental animals. For instance, the group II animals demonstrated a marked reduction in the size and number of the endocrine islets of Langerhans, accompanied by extensive degeneration of islet cells. In several sections, the islets appeared shrunken and poorly defined due to the substantial loss of structural organization, confirming severe pancreatic damage to β-cells caused by alloxan-mediated oxidative stress and lipid peroxidation [40]. These histopathological alterations are consistent with earlier reports in alloxan-induced diabetic models, where oxidative stress–mediated β-cell destruction resulted in shrinkage and degeneration of pancreatic islets [3]. In contrast, rats treated with ALEAL and glibenclamide showed marked improvement in pancreatic histology (Figure 6), with preserved islet morphology comparable to the normal control, indicating a protective effect on β-cell survival and function.

5. CONCLUSION

Collectively, the results demonstrate that ALEAL exhibits significant antidiabetic activity through multiple mechanisms, including an insulin secretagogue action, inhibition of carbohydrate-metabolizing enzymes, antioxidant defense, and regeneration of pancreatic β-cells. This multi-targeted pharmacological activity highlights its promise as a potential phytopharmaceutical candidate for the management of diabetes mellitus. The present study also provides scientific evidence supporting the traditional use of *Albizia lebbeck* in the management of diabetes and its associated complications. Nevertheless, further studies focusing on the characterization of the extract, isolation of bioactive compounds, elucidation of molecular mechanisms, and comprehensive pharmacological validation are necessary to facilitate the development of *A. lebbeck* derived phytotherapeutics.

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Author contribution

All authors contributed to the completion of this study. Kumaraswamy Athesh, Gunasekaran Shobana, and Thillaivasan Prabhash performed the pharmacological assays, conducted the literature review, and prepared the manuscript. Kumaraswamy Athesh and Nayagam Agnel Arul John supervised the experimental work, interpreted the results, and critically reviewed the manuscript. All authors approved the final version of the manuscript.

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Conflict of interest

None to declare.

Ethics approval

All animal experiments were conducted in accordance with the guidelines of the committee for the purpose of control and supervision of experiments on animals and were approved by the Institutional Animal Ethics Committee (Approval No: 790/03/ac/CPCSEA).

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