A Comparative Study of Egyptian Bee Pollen and Propolis Extracts: Impacts on Metabolic Profile, Liver, and Kidney Functions in Diabetic Rats Induced by Streptozotocin

Abram B. Emil[1]*, Neven H. Hassan[1], Sally Ibrahim[2], Sara E. Ali [1]

1. Department of Physiology, Faculty of Veterinary Medicine, Cairo University, Giza, Egypt
2. Department of Animal Reproduction and AI, Veterinary Research Institute, National Research Centre, Dokki, Giza, Egypt

* Corresponding author: Abram B. Emil, E-mail: abram.emil@cu.edu.eg

1. Abstract

Diabetes impairs metabolic profile and liver and kidney functions due to oxidative stress. Bee pollen and propolis are known for their antioxidant properties. Therefore, the current study aims to compare the potential effects of Egyptian bee pollen extract (PoE) and propolis extract (PrE) against diabetes-induced metabolic, liver, and kidney dysfunction in rats. Sixty male rats were randomly assigned to six groups. Group 1 was the control group. Groups 2 and 3 received oral PoE and PrE (100 mg/kg bwt). Groups 4, 5, and 6 received streptozotocin (55 mg/kg bwt) as a single intraperitoneal dose to induce diabetes. Group 4 was the untreated diabetic group, while Groups 5 and 6 were diabetic rats treated with PoE and PrE. After 60 days, insulin hormone levels, metabolic profiles, as well as liver and kidney function tests, were evaluated. The metabolic profile analysis included measurements of blood glucose, total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL). Liver function was assessed by measuring alanine transaminase (ALT) and aspartate transaminase (AST) levels, total protein, and albumin. Kidney function was evaluated through measurements of creatinine and uric acid concentrations. Our results revealed that Diabetes significantly impaired insulin levels, metabolic profiles, and liver and kidney functions. However, treatment with PoE and PrE resulted in a notable improvement. In conclusion, PoE and PrE are promising adjunct treatments for diabetes complications due to their antioxidant properties. Bee pollen extract has a superior impact in addressing these complications than bee propolis water extract.

Keywords: Propolis; Bee pollen; Diabetes; Oxidative stress; Male rats.

2. Introduction

Diabetes mellitus (DM) is a complex metabolic disorder characterized by elevated blood glucose levels.[1]. Diabetes significantly impacts metabolism by disrupting the body's ability to process and use glucose, the primary energy source for cells, and this disruption extends to liver and kidney function as well as lipid metabolism, contributing to oxidative stress. [2]. In a healthy metabolism, insulin, a hormone produced by the pancreas, facilitates the uptake of glucose from the bloodstream into cells, where it is used for energy or stored as glycogen in the liver and muscles. [3]. However, in diabetes, the body either doesn't produce enough insulin (Type 1 diabetes) or becomes resistant to insulin (Type 2 diabetes), resulting in glucose remaining in the bloodstream and causing high blood sugar levels (hyperglycemia) [4]. This Chronic hyperglycemia strains the liver, which plays a central role in glucose metabolism and can lead to the development of non-alcoholic fatty liver disease (NAFLD), where excess glucose is converted into fat and accumulates in the liver. [5] Furthermore, high blood sugar levels can damage the delicate filtering units in the kidneys, leading to diabetic nephropathy, a leading cause of chronic kidney disease and kidney failure [6]. Chronic hyperglycemia also promotes oxidative stress, a condition where an imbalance between free radicals and antioxidants leads to cell and tissue damage [7]. Oxidative stress further exacerbates liver and kidney dysfunction, contributing to the progression of NAFLD and nephropathy [8].

In addition to its effects on glucose metabolism, diabetes significantly disrupts lipid metabolism, contributing to oxidative stress [9]. Insufficient insulin prevents cells from efficiently using glucose for energy, forcing the body to rely more heavily on the breakdown of fats and proteins as alternative energy sources [10]. This increased lipolysis results in elevated levels of free fatty acids in the blood, which can lead to dyslipidemia, a condition marked by abnormal lipid levels, such as high triglycerides and low HDL cholesterol [11]. As the body breaks down fats for energy, it produces ketone bodies—acetoacetate, beta-hydroxybutyrate, and acetone [12]. These ketone bodies can accumulate to dangerous levels, leading to diabetic ketoacidosis, a serious condition that can further harm the kidneys and other organs [13]. Moreover, the altered lipid metabolism and increased fat storage, especially in the abdominal region, as seen in Type 2 diabetes, exacerbate insulin resistance, creating a vicious cycle that worsens both glucose and lipid metabolism [1]. The accumulation of excess lipids, ketone bodies, and glucose in cells generates more free radicals, intensifying oxidative stress and leading to cellular damage [14]. Over time, the combined effects of

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chronic hyperglycemia, disrupted lipid metabolism, oxidative stress, and kidney dysfunction can lead to severe complications, including cardiovascular disease, a leading cause of mortality in individuals with diabetes [15]. Additionally, they can cause damage to blood vessels, nerves, and organs, leading to complications such as neuropathy, nephropathy, and retinopathy [16].

Antioxidants are beneficial in treating diabetes mellitus (DM) as they help combat complications associated with reactive oxygen species (ROS) [15]. Natural antioxidants are crucial in managing DM, particularly in developing countries [17]. Honeybee products, such as bee pollen and propolis, are believed to be valuable in controlling DM by targeting reactive oxygen species (ROS) [18]. These natural substances may help delay the development of diabetic complications, address metabolic disturbances, and protect against oxidative stress and free radical damage [19]. Bee pollen, rich in proteins, carbohydrates, vitamins, and minerals, offers antioxidant, antibacterial, anti-inflammatory, and liver-protective effects [20]. Its diverse nutrients help reduce oxidative stress and inflammation, improve lipid profiles, and support liver and kidney health [21]. Propolis, a sticky resin produced by honeybees from plant resins, is known for its antioxidant, antibacterial, antidiabetic, anti-inflammatory, liver-protective, and immunomodulatory properties [22]. With over 300 components, including phenolic compounds and flavonoids, propolis enhances antioxidant enzymatic functions, reduces lipid peroxidation, and inhibits harmful radicals [23]. This study aims to compare the impact of propolis and bee pollen on metabolism and their ameliorating effects on liver and kidney function in STZ-induced diabetic male rats.

3. Materials and Methods

3.1. Chemicals

Bee pollen and propolis were purchased from the Agriculture Research Center. Streptozotocin (98% purity, CAS No. 18883-66-4) and citrate buffer solution (10 mmol/L, pH 4.5) were procured from Sigma-Aldrich Co.

3.2. Preparation of ethanolic bee pollen extract (PoE):

For the bee pollen extract preparation, the mixture, with a ratio of approximately 1:35 of Egyptian bee pollen to ethanol, was heated to 40 °C using an ultrasonic bath to extract active compounds. The mixture was then ultrasonicated, centrifuged at 6000 x g, adjusted to a final volume of 50 mL, and dried in a freeze dryer for 48 hours [24].

3.3. Preparation of aqueous propolis extract (PrE):

To prepare propolis aqueous extract, crude Egyptian propolis was

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mixed with deionized water in a 1:10 ratio and allowed to sit at room temperature for six hours. The mixture was then filtered through a syringe filter. The extract was subsequently dried using a freeze dryer for 48 hours [25].

3.4. Animals:

Sixty male Sprague Dawley rats, weighing between 200 and 240 grams and aged 8-10 weeks, were procured from VACSERA, Egypt. Rats were housed at the Faculty of Veterinary Medicine, Cairo University, in standard polypropylene cages under controlled conditions: a temperature of 22±3 °C, humidity of 55±5%, and a natural 12-hour light/dark cycle. The rats had unrestricted access to food and water.

3.5. Induction of diabetes:

To induce diabetes, streptozotocin (STZ) was dissolved in cold citrate-buffered saline (CBS) at 0.1 M and pH 4.5. The rats were fasted overnight and then received a single intraperitoneal injection of freshly prepared STZ at a dose of 55 mg/kg body weight [26]. Three days post-injection, blood samples were obtained from the tail vein to assess fasting blood glucose levels using a glucometer (Accu-Check, Roche Diagnostics, Pvt. Ltd.) [27]. Rats with glucose levels exceeding 250 mg/dL were considered diabetic. [28].

3.6. Experimental Design:

The Animal Use Protocol (Vet CU 25122023856) has been followed, and the experimental protocol was authorized by the Institutional Animal Care and Use Committee (IACUC) of Cairo University's Faculty of Veterinary Medicine. The rats were acclimated for 2 weeks and then randomly divided into six groups of 10 animals each for 2 months, based on the following treatment protocol:

- **Group 1 (C)**: The control group received an intraperitoneal injection of citrate-buffered saline (CBS) (0.1 M; pH 4.5) and was given normal saline orally day after day.
- **Groups 2 (PoE) and 3 (PrE)**: rats were treated orally on alternate days with 100 mg/kg of bee pollen and propolis extracts [29,30].
- **Groups 4, 5, and 6 were diabetic rats** receiving a single intraperitoneal injection of streptozotocin (STZ) at 55 mg/kg body weight on the first day.
- **Group 4 (D):** The diabetic untreated group was given normal saline orally on alternate days.
- **Group 5 (D + PoE) and Group 6 (D + PrE):** Diabetic rats were given 100 mg/kg of bee pollen and propolis extract orally on alternate days.

3.7. Sampling:

At the end of the experiment, the rats were fasted overnight and

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euthanized. Blood samples were collected using the orbital sinus puncture technique. The samples were centrifuged at 4000 rpm for 15 minutes to separate plasma (with fluoride as an anticoagulant) or serum (without anticoagulant).

3.8. Hormonal analysis:

Insulin hormone levels were assessed with a rat-specific ELISA kit from Elabscience (Catalog No. E-EL-R0048, China) following the manufacturing instructions.

3.9. Evaluation of metabolic profile:

Serum metabolic parameters, including blood glucose levels, lipid, and protein profiles, were measured using spectrophotometric methods with commercial kits from Spectrum Diagnostics Egyptian Company for Biotechnology, following the manufacturer's instructions (UV-2100 Spectrophotometer, USA).

Blood glucose levels were measured by enzymatically oxidizing glucose with glucose oxidase to produce hydrogen peroxide. This hydrogen peroxide then reacts with phenol and 4-amino antipyrine in the presence of peroxidase to generate a red violet quinone imine dye, measured at 546 nm [31].

Lipid profile components such as total cholesterol, triglycerides, and HDL (high-density lipoprotein) cholesterol were assessed using established methods [32–34]. LDL (low-density lipoprotein) and VLDL (very low-density lipoprotein) cholesterol levels were calculated with the following formulas:

- VLDL cholesterol = triglycerides/5 [35]
- LDL cholesterol = total cholesterol - (HDL + VLDL) [35]

The cholesterol assay involves enzymatically breaking down cholesterol esters into cholesterol and free fatty acids, then oxidizing cholesterol to produce cholesterol-4-en-3-one and hydrogen peroxide [37]. Lipoprotein lipase (LPL) converts triglycerides into glycerol, which is then phosphorylated and oxidized to yield hydrogen peroxide. This peroxide reacts with phenol and 4-aminoantipyrine, catalyzed by peroxidase, to form a dye measured at 546 nm. HDL cholesterol is quantified by precipitating LDL and VLDL, leaving HDL in the supernatant for measurement. Protein levels, including total protein and albumin, are measured calorimetrically.

The total protein is quantified using the biuret reaction [38], while albumin is measured by its binding to bromocresol green. Globulin is calculated as the difference between total protein and albumin, and the albumin-to-globulin (A/G) ratio is derived [39].

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3.10. Measurement of liver function markers:

Both alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities were measured using kits obtained from Biomed Company in Egypt. The kinetic methods for determining these enzymes have been optimized following the previous protocol [40].

For AST, the enzyme catalyzes the conversion of o-ketoglutarate and L-aspartate into L-glutamate and oxaloacetate. This oxaloacetate is then reduced to malate-by-malate dehydrogenase (MDH) and its coenzyme NADH, which becomes oxidized in the process. The decrease in NADH observed as a reduction in extinction over time is directly proportional to AST activity in the sample.

Similarly, the method for ALT involves the enzyme catalyzing the reaction between L-alanine and oxoglutarate to produce pyruvate and L-glutamate. The pyruvate then reacts with NADH and a proton (H^+) in the presence of lactate dehydrogenase (LDH) to yield L-lactate, NAD^+, and water. The reduction in NADH, monitored as a decrease in extinction over time, reflects the ALT activity in the sample.

3.11. Measurement of kidney function markers:

Both creatinine and uric acid levels in the blood were measured using spectrophotometric methods with commercial kits provided by Spectrum Diagnostics Egyptian Company for Biotechnology, following the manufacturer's guidelines (UV-2100 Spectrophotometer, USA) [41].

For creatinine measurement, it reacts with picric acid in an alkaline solution to form a colored complex. The reaction between creatinine and picrate in the presence of NaOH produces a yellow-red complex, which is detected by a spectrophotometer.

The uric acid measurement is carried out using a modified Trinder peroxidase assay, which involves 3,5-dichloro-2-hydroxybenzenesulfonic acid (DCHB). In this process, uricase first oxidizes uric acid to allantoin, generating hydrogen peroxide as a byproduct. The hydrogen peroxide then reacts with 4-aminoantipyrine and DCHB in the presence of peroxidase, leading to the formation of a quinoneimine dye.

3.12. Statistical analysis:

The results were presented as means ± standard error and statistically analyzed by a one-way analysis of variance (ANOVA) followed by the Tukey post-hoc test using SPSS statistical analysis software (Version

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20) to determine significant differences between groups. A p-value of less than 0.05 was considered statistically significant.

4. Results

4.1. Hormonal analysis:

The findings of this study revealed a significant reduction in serum insulin levels in diabetic rats compared to the control group ($p \leq 0.05$). Nevertheless, both the D + PoE and D + PrE groups showed a marked improvement in insulin levels relative to the untreated diabetic group ($p \leq 0.05$). Notably, the D + PoE group exhibited a greater increase in insulin levels than the D + PrE group (Fig. 1).

4.2. Metabolic profile:

The study's results showed that diabetic rats had significantly higher blood glucose levels compared to control rats ($p \leq 0.05$). Both the D + PoE and D + PrE groups exhibited a significant reduction in blood glucose levels relative to the diabetic control group ($p \leq 0.05$). The (D + PoE) group demonstrated a more significant decrease in blood glucose levels compared to the (D + PrE) group (Fig. 2). Additionally, diabetic rats had significantly elevated levels of cholesterol, triglycerides, LDL cholesterol, and VLDL cholesterol, along with a marked reduction in HDL cholesterol compared to control rats ($p \leq 0.05$). In contrast, the D + PoE and D + PrE groups showed significant reductions in cholesterol, triglycerides, LDL cholesterol, and VLDL cholesterol, with a notable increase in HDL cholesterol levels compared to the diabetic control group ($p \leq 0.05$). The (D + PoE) group exhibited a more pronounced improvement in cholesterol, triglycerides, LDL, and VLDL levels and a more significant rise in HDL levels compared to the (D + PrE) group (Fig. 3).

Furthermore, the current results indicated a significant decrease in total protein, albumin, globulin, and the A/G ratio in diabetic rats compared to control rats ($p \leq 0.05$). Conversely, both the D + PoE and D + PrE groups showed a significant increase in total protein, albumin, globulin, and the A/G ratio compared to the diabetic control group ($p \leq 0.05$). The (D + PoE) group demonstrated a marked improvement in total protein, albumin, globulin, and the A/G ratio compared to the (D + PrE) group (Fig. 4).

4.3. Liver function markers:

The diabetic rats had significantly elevated levels of ALT and AST compared to normal rats ($p \leq 0.05$). However, administering PrE and PoE to the diabetic group resulted in a significant reduction in ALT and AST levels compared to the untreated diabetic group ($p \leq 0.05$). Notably, the D + PoE group demonstrated a more significant improvement in ALT and AST levels compared to the D + PrE group (see Fig. 5).

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4.4. Kidney function markers:

The study revealed a significant rise in creatinine and uric acid levels in the diabetic group compared to the normal group ($p \leq 0.05$). On the other hand, administering Pr and PO to the diabetic group significantly lowered both creatinine and uric acid levels when compared to the untreated diabetic group ($p \leq 0.05$). Interestingly, the D + PoE group showed a statistically significant improvement in creatinine and uric acid levels compared to the D + PrE group (Fig. 6).

5. Discussion

Diabetes significantly disrupts the metabolic profile, leading to a cascade of complications [42]. Over time, these metabolic disturbances can damage various organs and systems, resulting in complications such as cardiovascular disease, neuropathy, nephropathy, and retinopathy [43]. This interplay of factors highlights the importance of effective diabetes management to mitigate the risk of long-term health issues [44]. Our data demonstrated a significant disturbance in the metabolic profile of the diabetic group compared to the control groups. This result aligned with previous studies [5,45]. I/P injection of STZ at 55 mg/kg in rats caused a significant decrease in serum insulin levels, along with a marked increase in blood glucose levels in the diabetic group compared to the control group; this finding was consistent with earlier research [26]. That may be attributed to the destruction of insulin-producing beta cells in the pancreas, leading to insulin deficiency [46]. Insulin deficiency reduces cellular glucose uptake, especially in muscle and fat tissues, so glucose accumulates in the bloodstream rather than being used for energy [47]. Additionally, the liver continues to produce glucose through gluconeogenesis and glycogenolysis, which exacerbates hyperglycemia [48]. Hormonal imbalances, including elevated levels of counter-regulatory hormones such as glucagon, cortisol, and epinephrine, further contribute to higher blood glucose levels by promoting glucose release from the liver and inhibiting its uptake by cells [49]. Diabetes impairs glucose regulation, leading to excessive glucose synthesis and chronic hyperglycemia [50].

Our findings showed that supplementation with Egyptian bee pollen and propolis extract in diabetic rats significantly improved serum insulin and glucose levels compared to untreated diabetic rats. These results were in line with previous findings reporting that bee pollen lowered blood glucose levels and oxidative stress in diabetic STZ-induced rats [51]. Additionally, it has been reported that propolis administration significantly decreases blood glucose levels in diabetic rats [52]. This effect is attributed to a reduction in oxidative stress and an enhancement of antioxidant activity, primarily due to the phenolic and flavonoid compounds in

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bee pollen and propolis [51,53] These compounds increase insulin secretion by mitigating diabetes-induced oxidative stress, indicating their potential antidiabetic and antioxidant effects. As a result, pancreatic beta cell function improves, leading to lower serum glucose levels [51].

Moreover, there was a disruption in lipid metabolism, as shown by a significant increase in triglycerides, LDL, and VLDL levels, along with a marked reduction in HDL levels in diabetic rats compared to the control rats. This finding aligned with previous studies [54–57]. This may occur through several interconnected mechanisms. One of the main problems in diabetes is insulin deficiency, which disrupts normal lipid metabolism as insulin helps regulate fat metabolism by suppressing lipolysis [58]. So insulin deficiency leads to increased lipolysis and higher levels of free fatty acids in the bloodstream [59]. Then the liver processes these excess free fatty acids into triglycerides, which are transported in the blood as VLDL particles [60]. The increased production of VLDL is a major factor in hypertriglyceridemia, commonly seen in diabetes [61]. Additionally, VLDL particles serve as precursors to LDL particles, so elevated VLDL levels also result in higher LDL cholesterol levels [62]. These are more likely to contribute to the formation of atherosclerotic plaques in blood vessels, increasing cardiovascular risk [63]. Diabetes also affects the activity of lipoprotein lipase (LPL), an enzyme that breaks down triglycerides in VLDL particles [64]. Normally, insulin activates LPL to help clear triglycerides from the bloodstream and allow tissues to use free fatty acids [65]. In diabetes, reduced insulin activity or resistance lowers LPL activity, leading to increased triglyceride and VLDL levels [66].

Furthermore, insulin deficiency, along with chronic high blood sugar, can impair the liver's ability to produce LDL receptors, which are essential for removing LDL cholesterol from the blood [67]. This reduction in LDL receptor activity results in higher LDL cholesterol levels. Chronic high blood sugar also promotes de novo lipogenesis, the conversion of excess glucose into fatty acids and then triglycerides in the liver [68]. These triglycerides are incorporated into VLDL particles, further increasing triglyceride and VLDL levels [54].

Simultaneously, the rise in triglyceride-rich lipoproteins like VLDL is linked to a decrease in HDL cholesterol. This occurs because cholesteryl ester transfer protein (CETP) facilitates the exchange of triglycerides from VLDL with cholesteryl esters from HDL [69]. This exchange causes HDL particles to become triglyceride-rich and more prone to degradation by hepatic lipase, leading to a reduction in functional HDL particles and lower HDL cholesterol

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levels [70]. Insulin deficiency also hinders the production of Apolipoprotein A-I (apoA-I), a key protein needed for HDL synthesis, which further reduces HDL levels [71]. These combined effects—insulin deficiency, increased VLDL production, impaired triglyceride clearance, formation of small, dense LDL particles, decreased LDL receptor activity, enhanced de novo lipogenesis, and altered HDL metabolism—result in the dyslipidemia commonly observed in diabetes, significantly raising the risk of cardiovascular disease.

Treatment with Egyptian bee pollen and propolis extract in the current study resulted in a marked improvement in the lipid profile of the treated diabetic groups when compared to untreated diabetic ones. Specifically, there was a significant reduction in the levels of triglycerides, total cholesterol, LDL, and VLDL. At the same time, the levels of HDL were notably increased in the treated groups compared to the untreated diabetic group. These findings are consistent with the study, which demonstrated that bee pollen administration significantly improved the lipid profile in diabetic groups[72]. These may be attributed to the rich content of phenolic and flavonoid compounds in bee pollen and propolis [73]. These bioactive compounds enhance the activity of lipoprotein lipase (LPL) and apolipoprotein A-I involved in lipid metabolism, leading to decreased levels of LDL, VLDL, and triglycerides while increasing HDL levels [74]. Additionally, their antioxidant properties help prevent lipid peroxidation, contributing to an improved overall lipid profile. This improvement in lipid profile suggests that propolis and bee pollen not only help manage blood glucose levels but also offer protective benefits against cardiovascular complications commonly associated with diabetes.

Additionally, diabetes disrupted the protein profile, as our data revealed a significant decrease in total protein, albumin, globulin, and the albumin-to-globulin (A/G) ratio in the diabetic group compared to the control group. These findings aligned with previous studies [75,76] .This result may be due to various mechanisms. In type 1 diabetes, insulin deficiency can lead to increased protein breakdown as the body degrades muscle protein to supply amino acids for glucose production, thereby lowering total protein levels in the blood [77]. Additionally, chronic high blood sugar and insulin deficiency can impair liver function, which affects its ability to produce proteins [78]. Since the liver is responsible for generating many plasma proteins, including albumin and globulins, its dysfunction can result in decreased levels of these proteins [79]. Kidney damage, which is common in diabetes due to diabetic nephropathy, can also contribute to reduced protein levels [80]. In this condition, the kidneys fail to effectively filter proteins, causing

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protein loss in the urine and resulting in lower total protein, albumin, and globulin levels in the blood [81]. Furthermore, liver dysfunction related to diabetes can reduce albumin production, as albumin is primarily made by the liver [82]. Inflammatory processes associated with diabetes can alter globulin levels since globulins include immunoglobulins and transport proteins that may be affected by inflammation [83]. The A/G ratio is influenced by these changes, as a decrease in albumin levels without a corresponding decrease in globulins can lower the ratio [84]. These combined effects led to a significant decrease in total protein, albumin, globulin, and the albumin-to-globulin (A/G) ratio, reflecting the complex relationship between metabolic disturbances, organ function, and inflammation in diabetes.

The administration of Egyptian bee pollen and propolis extracts enhances protein profiles, leading to a significant increase in total protein, albumin levels, globulin, and the A/G ratio in treated diabetic rats compared to untreated diabetic rats. These findings are consistent with a previous study that demonstrated that bee pollen administration significantly increased total protein, albumin levels, globulin, and the A/G ratio in diabetic rats [51]. Also, it has been reported that propolis administration significantly increased total protein, albumin levels, globulin, and the A/G ratio in diabetic rats [9]. These effects are attributed to their antioxidant and anti-inflammatory properties that protect proteins from oxidative damage, leading to better maintenance of total protein levels [85]. Additionally, the bioactive compounds in propolis and bee pollen, such as flavonoids and phenolics, support liver function, which is crucial for the synthesis of albumin and globulins [21].

In addition, the findings of this study revealed an increase in ALT and AST enzymatic activity, which are liver function markers, in the diabetic group compared to the control group. This is consistent with earlier research [3,45,86,87]. This may be linked to several mechanisms: insulin deficiency, a key feature of T1DM, impairs the liver's ability to regulate glucose and fat metabolism, causing the accumulation of fatty acids in the liver [88]. This buildup can result in non-alcoholic fatty liver disease (NAFLD), leading to cellular stress and damage, which increases AST and ALT levels [89]. Additionally, chronic hyperglycemia associated with diabetes can lead to elevated production of reactive oxygen species (ROS), causing oxidative stress and damage to liver cells, thereby raising AST and ALT levels [90]. Chronic inflammation, common in diabetes, involves inflammatory cytokines that promote liver inflammation and damage, contributing to elevated enzyme levels [91]. Direct liver damage from fat accumulation, oxidative stress, or inflammation can cause the leakage of AST and ALT into

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the bloodstream [92]. Prolonged diabetes can also result in diabetic hepatopathy, where sustained high blood sugar levels and metabolic disturbances cause liver cell damage, further increasing AST and ALT levels [93]. Impaired insulin signaling in diabetes disrupts various metabolic pathways in the liver, contributing to liver dysfunction and higher levels of these enzymes as the liver struggles to maintain normal function.

Administering the extracts of Egyptian bee pollen and propolis enhances liver function, leading to a significant decrease in ALT and AST levels in treated diabetic groups compared to untreated diabetic groups. Our results are consistent with those of previous studies [94] that demonstrated that bee pollen administration significantly reduced ALT and AST levels in diabetic rats. Also [9] reported that propolis administration significantly decreased ALT and AST levels in diabetic rats. These are primarily through their antioxidant and anti-inflammatory properties [95]. These natural substances help reduce oxidative stress and inflammation in the liver, which are common in diabetes and can lead to liver damage [96]. By protecting liver cells from damage, bee pollen and propolis promote healthier liver function, resulting in more stable and potentially normalized ALT and AST levels. Additionally, their bioactive compounds support the regeneration of liver tissue and enhance the overall metabolic functions of the liver, further contributing to improved ALT and AST levels in diabetic patients [97].

Similarly, the findings of this study showed an increase in the creatinine and uric acid levels in the blood, which are markers of kidney function, in the diabetic group compared to the control group. This is consistent with previous research [98–102]. This may be due to diabetic nephropathy, which damages the glomeruli, the kidney's filtering units, reducing their efficiency in filtering waste, and thereby causing creatinine and uric acid to build up in the bloodstream [103]. Chronic high blood sugar leads to thickening of the glomerular basement membrane, which lowers the glomerular filtration rate (GFR) [104]. As GFR decreases, creatinine clearance diminishes, resulting in higher blood creatinine levels [105]. In the early stages of diabetes, the kidneys might undergo hyperfiltration, where the glomeruli are overworked to filter the blood, but this eventually leads to glomerular damage and a subsequent drop in kidney function, further raising creatinine levels [106]. Additionally, the elevated pressure within the glomeruli due to systemic hypertension, which is common in diabetes, worsens kidney damage and increases creatinine levels [107]. Insulin deficiency hampers the kidneys' ability to excrete uric acid by increasing its reabsorption in the renal tubules, leading to higher uric acid

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levels in the blood [101]. As diabetic nephropathy advances and GFR decreases, the kidneys become less effective at filtering uric acid, causing its accumulation in the blood. Moreover, diabetes is linked to oxidative stress and chronic inflammation, which result in endothelial dysfunction, impacting the renal blood vessels and impairing kidney function, thereby contributing to elevated levels of creatinine and uric acid [106]. The increased production of reactive oxygen species (ROS) can damage kidney cells, further hindering renal function and raising the levels of waste products like creatinine and uric acid in the blood [101]. High blood pressure, often associated with diabetes, causes microvascular damage in the kidneys, reducing their function and leading to elevated levels of creatinine and uric acid [108]. Early signs of kidney damage in diabetes include microalbuminuria, which can progress to proteinuria as nephropathy worsens, and this progression is linked to declining kidney function and increased blood levels of creatinine and uric acid [109]. Diabetes can also alter protein metabolism, leading to increased production of creatinine, a byproduct of muscle metabolism, and uric acid, a byproduct of purine metabolism [43]. These combined effects led to a significant increase in creatinine and uric acid concentrations in the blood.

Furthermore, administering Egyptian bee pollen and propolis extract significantly improved kidney function, resulting in a marked reduction in creatinine and uric acid concentrations in the blood of treated diabetic groups compared to untreated diabetic groups. Our findings are consistent with the study revealing that bee pollen administration significantly lowered creatinine and uric acid levels in rats with ethylene glycol-induced nephrotoxicity [110]. Also, it was found that administering propolis significantly reduced creatinine and uric acid levels in diabetic rats [29]. These effects may be attributed to their antioxidant, anti-inflammatory, and nephroprotective properties [110]. The bioactive compounds in propolis and bee pollen help reduce this oxidative stress and inflammation, thereby protecting kidney function. Additionally, these natural substances may enhance blood flow to the kidneys and support the repair of damaged kidney tissues, leading to improved filtration efficiency [110].

So, the administration of Egyptian bee pollen and propolis extracts to diabetic rats led to significant improvements in their insulin levels, metabolic profiles, as well as liver and kidney functions when compared to untreated diabetic groups. Notably, the diabetic rats treated with bee pollen extract showed greater enhancements in all evaluated parameters, including serum insulin, blood glucose, lipid profiles, protein levels, liver enzymes, and kidney markers, than those treated

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with propolis extract. This superior effect of bee pollen is likely due to its higher concentrations of gallic acid, quercetin, catechin, naringenin, luteolin, epicatechin, α-catechin, and 3,4-dimethoxycinnamic acid, as revealed in the phytochemical analysis previously reported [111]. These compounds are known for their strong antidiabetic, liver-protective, kidney-protective, and metabolism-boosting effects.

6. Conclusion

The administration of Egyptian bee pollen and propolis demonstrates beneficial effects in mitigating complications associated with diabetes, particularly in relation to disturbances in insulin levels, metabolic profiles as well as liver and kidney dysfunction. However, the emphasis on bee pollen is notable due to its unique chemical composition, which contributes to its superior efficacy in addressing these issues

Conflict of interest

The authors declare no conflict of interest.

7. References

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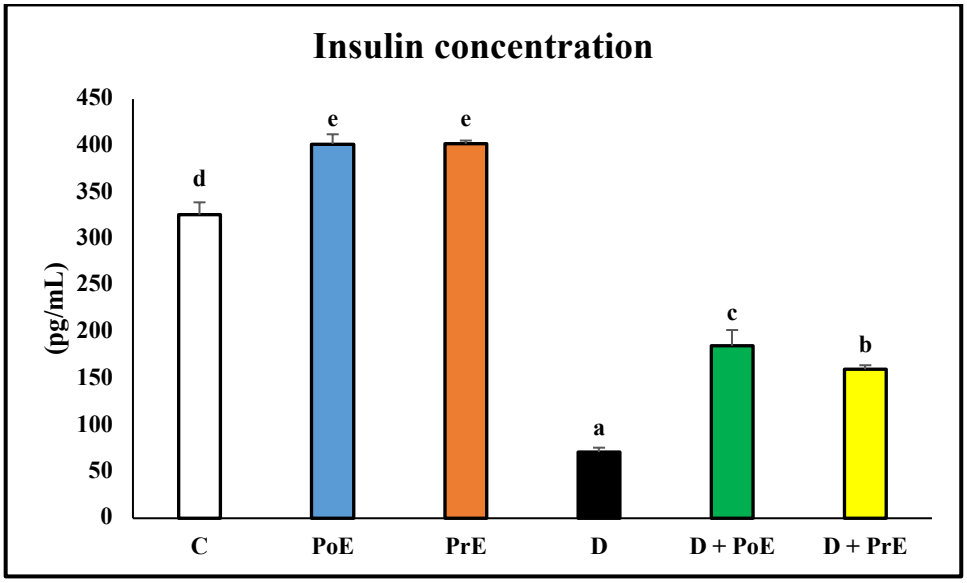


Fig. 1. Insulin levels in different experimental groups. Each value is expressed as mean ± standard error (n = 6 rats/group). The columns having different letters are significantly different ($P \leq 0.05$).

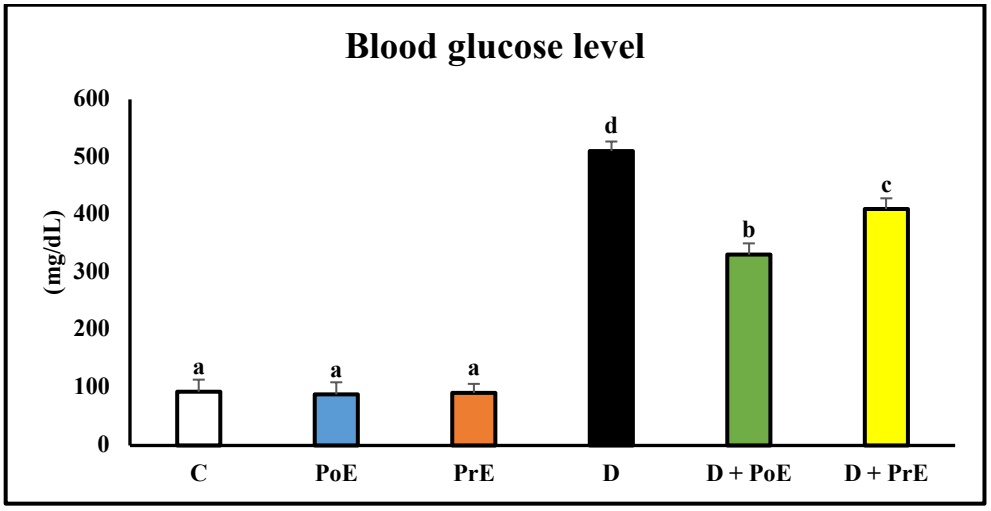
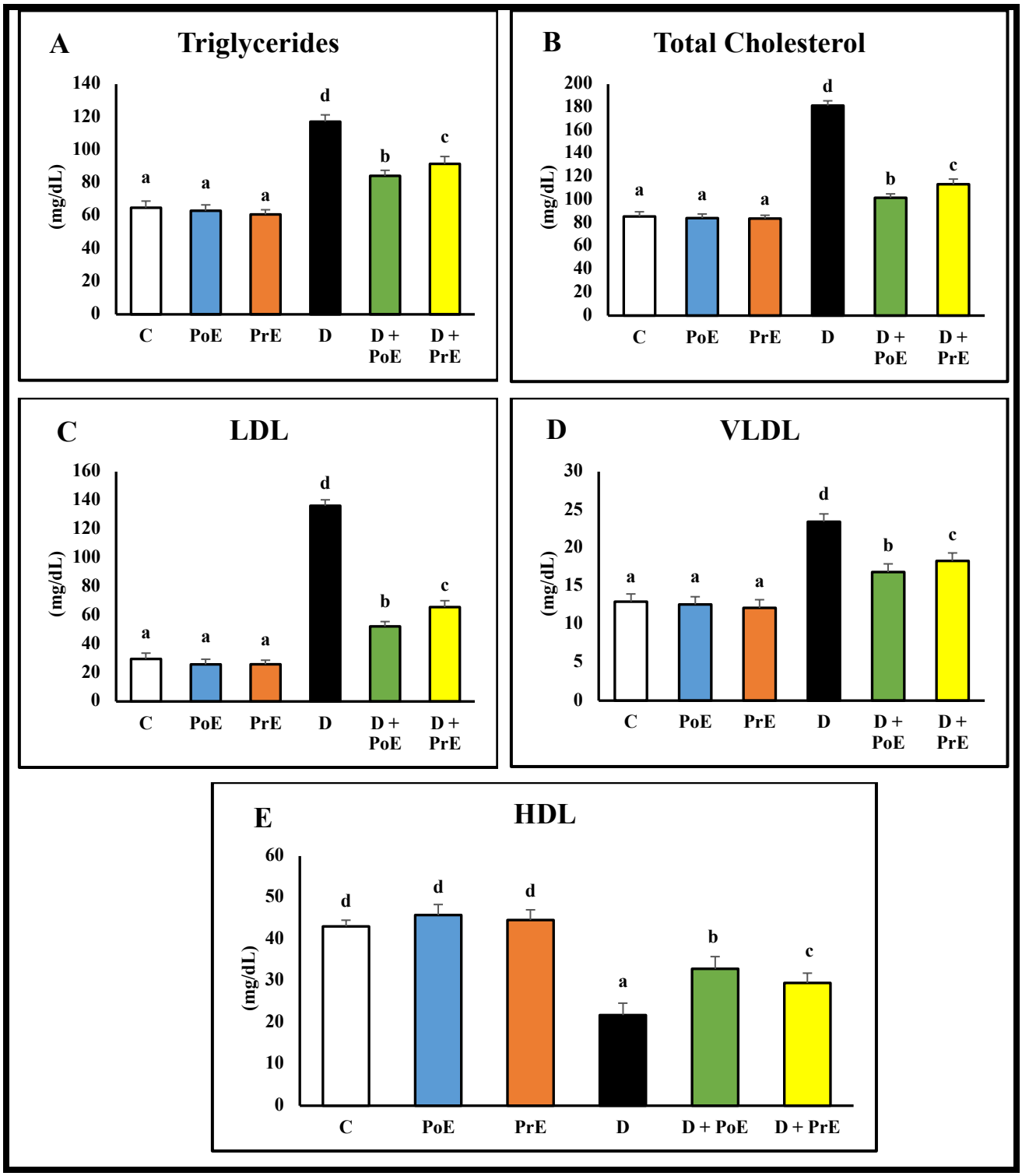


Fig. 2. Blood glucose levels in different experimental groups. Each value is expressed as mean ± standard error (n = 6 rats/group). The columns having different letters are significantly different ($P \leq 0.05$).



Figs. 3. Lipid profile levels in different experimental groups: (A) Triglyceride, (B) Total cholesterol, (C) LDL (low-density lipoprotein), (D) VLDL (very low-density lipoprotein), and (E) HDL (high-density lipoprotein). Each value is expressed as mean ± standard error (n = 6 rats/group). The columns having different letters are significantly different ($P \leq 0.05$).

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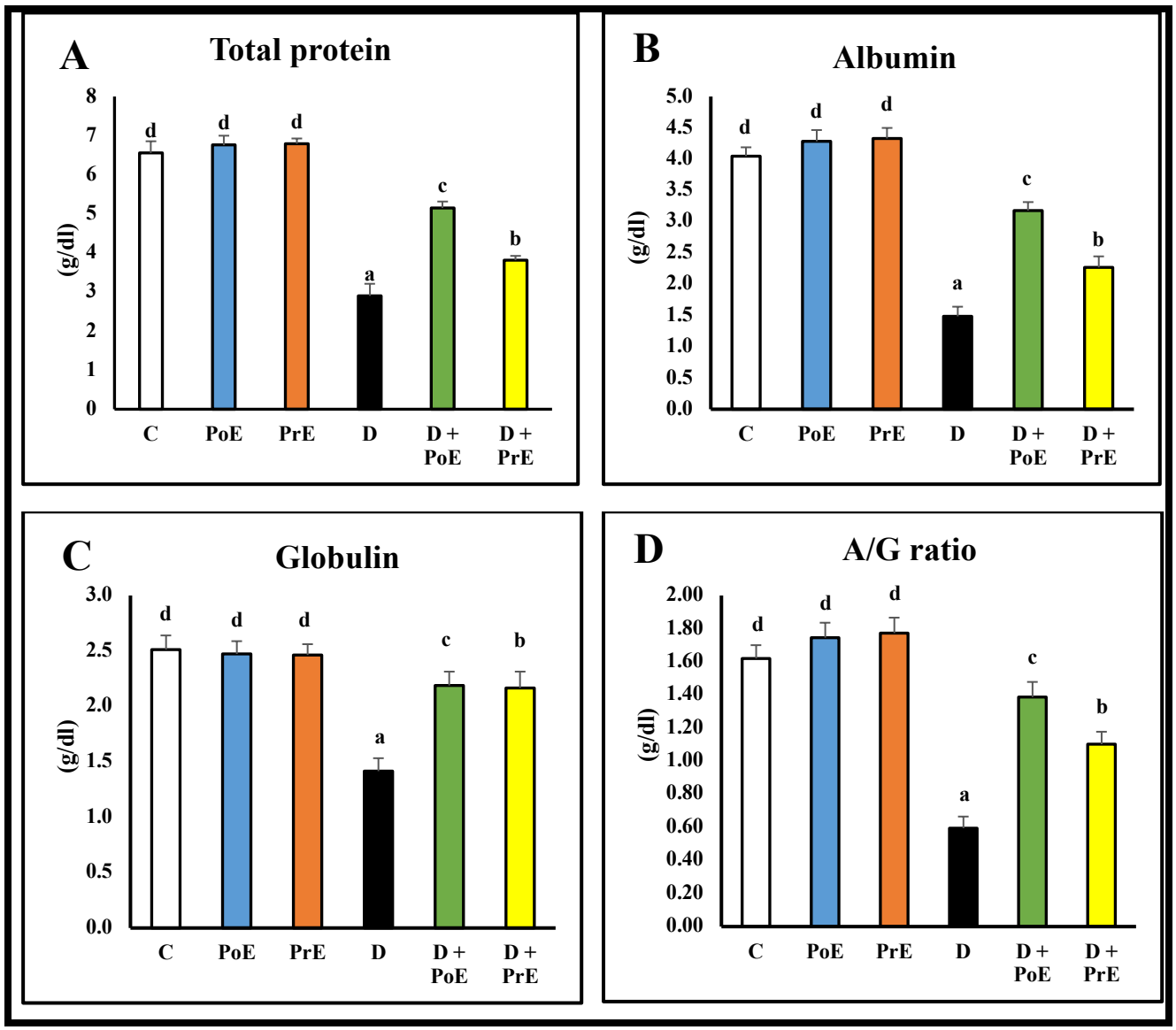

Figs 4. Protein profile levels in different experimental groups, (A) total protein, (B) albumin, (C) globulin, and (D) A/G ratio (Albumin/Globulin ratio). Each value is expressed as mean ± standard error (n = 6 rats/group). the columns having different letters is significantly different ($P \leq 0.05$)

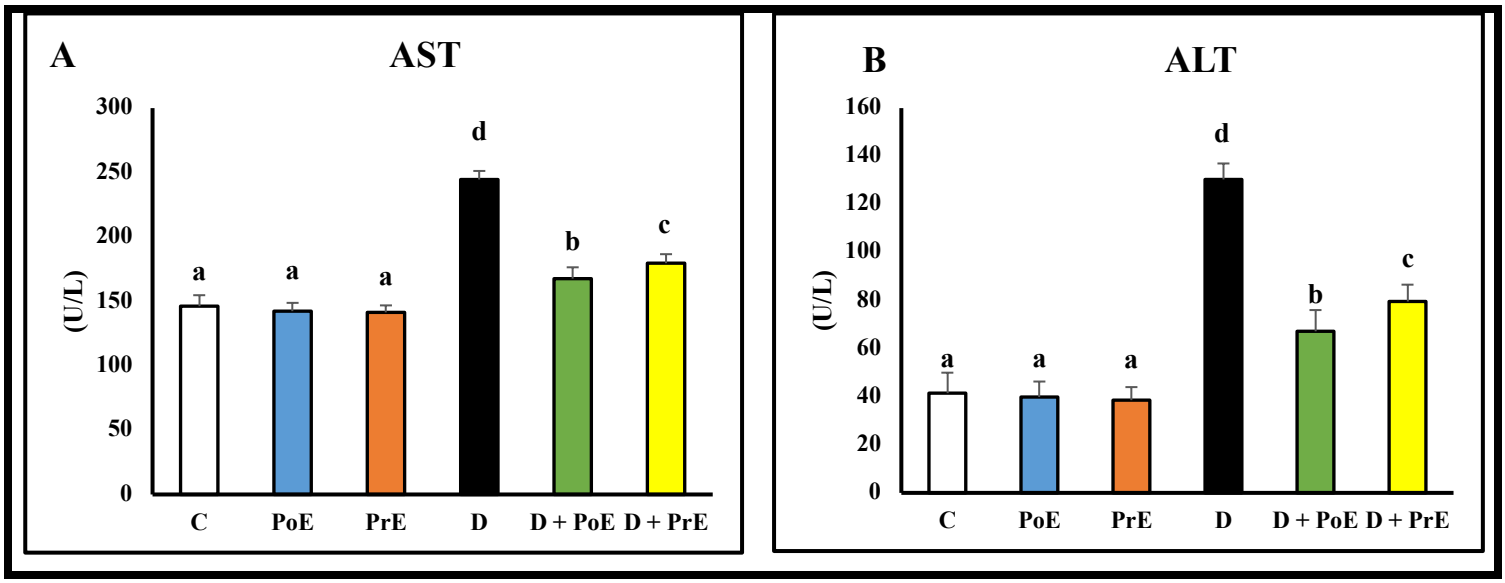

Fig. 5. The liver function marker levels in different experimental groups: (A) AST concentration (aspartate aminotransferase concentration), (B) ALT concentration (alanine aminotransferase concentration). Each value is expressed as mean ± standard error (n = 6 rats/group). The columns having different letters are significantly different ($P \leq 0.05$)

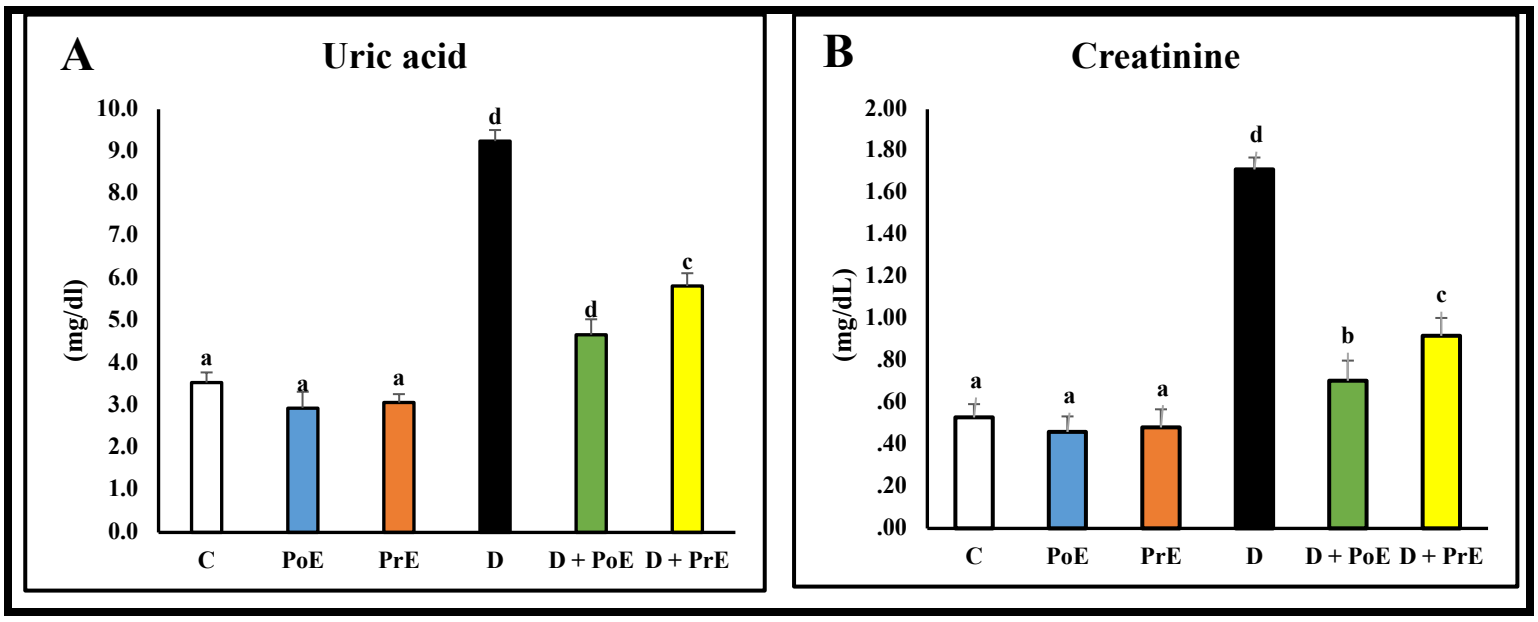

Fig. 6. The kidney function marker levels in different experimental groups, (A) uric acid concentration, and (B) creatinine concentration. Each value is expressed as mean ± standard error (n = 6 rats/group). The columns having different letters are significantly different ($P \leq 0.05$)