



Evaluating the Efficacy of Metformin and Camel Milk on Streptozotocin-nicotinamide Induced Diabetic Albino Rats

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ABSTRACT

Background: This study was intended to evaluate the anti-diabetic activity of metformin and camel milk solely or in combination in streptozotocin- nicotinamide induced type II diabetic albino Wistar rats.

Methods: Thirty albino Wistar rats were induced with type II diabetes through streptozotocin (60 mg/kg), followed by the administration of nicotinamide (120 mg/kg) after 15 min. The rats were randomly divided into control, diabetic control, metformin-treated (100 mg/kg), camel milk-treated (50 ml/rat/day) and metformin + camel milk-treated groups for 30 days. For this study, rats with blood glucose levels higher than 250 mg/dL were included. Blood glucose levels and body weight were measured at the beginning of the study and at regular intervals throughout the experiment. Furthermore, histopathological examination of liver, kidney and pancreatic tissue was conducted to determine the effects of metformin and camel milk on these organs.

Result: The results showed that treatment with metformin, camel milk, or a combination of both significantly reduced fasting blood glucose levels and improved body weight compared to the diabetic control group. Morphological improvements were also observed in the histopathological examination of liver, kidney and pancreatic tissue. The results of this study are consistent with previous research showing the anti-diabetic effects of metformin and support the emerging role of alternative therapies such as camel milk. However, further research is needed to explore the potential mechanisms underlying the observed effects.

Key words: Camel milk, Metformin, Nicotinamide, Streptozotocin, Type II diabetes.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by several anomalies in the metabolism of carbohydrates, fats and proteins (American Diabetes Association, 2014). The number of people with diabetes increased from 536.6 million in 2021 to 783.2 million in 2045, with 90% of cases being type II diabetes (Sun *et al.*, 2022; Lancet, 2023). Insulin resistance, hyperinsulinemia and hyperglycemia are typical symptoms of type II diabetes mellitus. Further more, aberrantly elevated hepatic gluconeogenesis and deterioration of pancreatic β cells is a key component in the emergence of hyperglycemia in type-II diabetes mellitus (Perriello *et al.*, 1997). Additionally, compared to normal individuals, COVID-19 patients with type II diabetes had much higher rates of morbidity and mortality, which raises concerns for public health and medical costs (Hadjadj *et al.*, 2021). Metformin is the first line of treatment among individuals with type II diabetes. It works by improving insulin-mediated regulation of hepatic glucose production and insulin-stimulated absorption of glucose by skeletal muscles, which reduces hyperglycemia and hyperinsulinemia. Nonetheless, adverse effects from the antidiabetic medications including lipohypertrophy, headaches, abdominal pain, anaphylactic reactions and hypoglycemia have been observed by patients (Hays *et al.*, 2008). To treat and manage diabetes mellitus, there is a rising need for natural substances with antidiabetic effects. The use of camel milk in complementary and alternative medicine for the treatment of diabetes has been the subject of extensive

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research in recent years. Numerous studies have demonstrated the possible benefits of camel milk and its use as a substitute treatment for various kinds of diseases (Radwan *et al.*, 2020). Camel milk boasts substantial concentrations of minerals such as Na, Cu, K, Fe, Zn and Mg, as well as vitamins, particularly A, B2, C and E, along with immunoglobulins G and A. Moreover, camel milk has several antioxidant constituents, such as caseins, bioactive peptides, lactic acid bacteria, whey proteins and lactoferrin (Khan *et al.*, 2021, Yadav *et al.*, 2015). A study found that persons who routinely and consistently drink camel milk in the northern region of west India have a zero percent diabetes prevalence (Agrawal *et al.*, 2007). Type II diabetic patients utilize camel milk to control the intricacies associated with their diseases and diminish complications (Radwan *et al.*, 2020). The utilization of camel milk

therapies among patients with type II diabetes has varied, with prevalence rates ranging from 17% to 73% (Fabian *et al.*, 2011; Chang *et al.*, 2007). The potential of whey protein hydrolysates from camel milk to lower hyperglycemia and hyperlipidemia and inhibit important metabolic enzymes such as α -amylase, α -glucosidase and dipeptidyl peptidase-IV (DPP-IV) presents a promising avenue for the development of functional foods or supplements to manage metabolic disorders. A further study revealed that camel milk contains additional proteins called lactoferrin, which, given its long-standing bioactivity and relation to diabetes, may make a promising candidate for milk's antidiabetic properties. Camel milk lowers the risk of type II diabetes through maintaining the blood sugar and also significantly enhances the body's insulin resistance (Hussain *et al.*, 2021 Khan *et al.*, 2022). However, most of the observations of the anti-diabetic properties were recorded in type I diabetes with both animal and human models (Breitling, 2002). On the other hand, there is insufficient research that consistently shows how camel milk affects type II diabetes (Agrawal *et al.*, 2011). The impetus of this experiment was to reveal the morphological and physiological effects of the administration of metformin and camel milk solely and, in combination in streptozotocin-nicotinamide induced type II diabetic rats.

MATERIALS AND METHODS

Institutional Animal Ethics Committee (IAEC) approval was obtained for the experimental investigation. Wistar rats (150-200 g) were obtained from the Disease-Free Small Animal House, LUVAS, Hisar, Haryana. The room in which they were kept had a 12-hour light-dark cycle, a temperature of $22 \pm 2^\circ\text{C}$ and a relative humidity of around 60%. Standard additive-free food and unlimited tap water were given to the rats. The research was conducted in the Department of Zoology, Maharshi Dayanand University, Rohtak, from 2022-2023.

Streptozotocin, nicotinamide bought from Himedia and Sigma-Aldrich. Every day, sterilized bottles of camel milk were bought from a local farmer. Rats that had fasted all night were given a single intraperitoneal injection of streptozotocin (60 mg/kg) to induce type II diabetes. Nicotinamide (120 mg/kg) was then injected intraperitoneally into the rats after 15 minutes. Nicotinamide and streptozotocin were dissolved in normal saline and citrate buffer (pH 4.5), respectively. Elevated fasting blood glucose measured 72 hours later verified the presence of hyperglycemia. Rats with glucose levels more than 250 mg/dL were considered diabetic rats and were divided into five groups (Fig 1). Group I: Healthy control group (n= 6): rats were injected with citrate buffer only. Group II: Diabetic control group (n= 6): For one month following the onset of diabetes, no additional medical intervention or dietary changes were made. Group III: Metformin group (n= 6): rats administered 100 mg/kg of metformin orally (Ojuade *et al.*, 2021). Group IV: Camel milk group (n= 6): rats administered 50 ml/rat/day fresh camel milk orally. (Elattar *et al.*, 2017). Group V: Metformin+Camel milk group (n = 6): rats were subjected to metformin (100 mg/kg) and 50 ml/rat/day fresh camel milk. The body weights of each group were measured daily during the experiment. The glucose levels were measured every five days (0, 5, 10, 15, 20, 25 and 30) during the treatment. Before sacrificing the rats, an oral glucose tolerance test (OGTT) was carried out. Giving a glucose solution (2 g/kg) orally was used to assess OGTT. Glycemic readings were taken at 0,30,60,90 and 120 minutes before and after the loading of glucose (Meena *et al.*, 2016). The kidney, liver and pancreas were preserved in 10% formalin for histological examination (Raj *et al.*, 2023). The collected data were statistically examined using ANOVA (two-way) and Tukey's post hoc test at a significance level of $p < 0.05$.

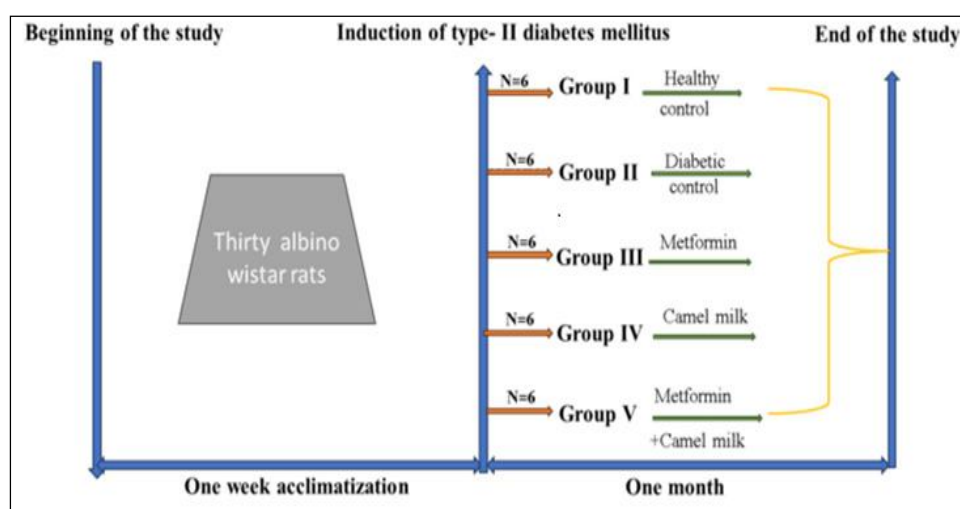


Fig1: Experimental design of the study.

RESULTS AND DISCUSSION

Bodyweight

The body weight of treatment groups was evaluated routinely (Fig 2). The healthy control group exhibited increased body weight significantly ($p < 0.05$) from day 0 to day 30, rising from 155.6 ± 5.31 g to 174.3 ± 11.09 g. On the other hand, after type II diabetes was induced, the average body weight decreased significantly ($p < 0.05$) from 159.6 ± 9.22 g on day 0 to 120 ± 9.85 g on day 30 throughout the experiments that were perceived in previous studies (Ojuade *et al.*, 2021; Abdulmalek *et al.*, 2019;). The body weight loss observed in diabetic control rats was significantly ($p < 0.05$) ameliorated by metformin, camel milk and metformin+camel milk administration, resulting in an average body weight gain from 162.3 ± 3.12 g, 162.1 ± 8.79 g, 160 ± 3.84 g on day 0 to 195 ± 6.48 g, 190.6 ± 4.47 g, 183.3 ± 10.80 g on day 30. Camel milk contains bioactive compounds such as insulin-like proteins

(58.67 IU/L), which may contribute to its antihyperglycemic effects (Mullaicharam *et al.*, 2014; Agrawal *et al.*, 2005). The high zinc content in camel milk stimulates the pancreas to release insulin. Previous studies have shown that diabetic rats given camel milk had improvements in their body weight (Sboui *et al.*, 2022; Kotb *et al.*, 2022).

Glycemic level

Glycemic levels of blood were monitored every 5th day during the study (Fig 3). In comparison to the healthy control group, which had blood glucose levels of 149.5 ± 9.28 mg/dL on day 0 and 141.5 ± 9.89 mg/dL on day 30, the diabetic control group's blood glucose levels were consistently ($p < 0.05$) high, measuring 497.6 ± 143.9 mg/dL on day 0 and 524.8 ± 79.06 mg/dL on day 30 as was observed in the previous finding of Ojuade *et al.*, 2021. After the diabetic rats received metformin, camel milk and metformin+camel milk their glucose levels decreased significantly ($p < 0.05$) from

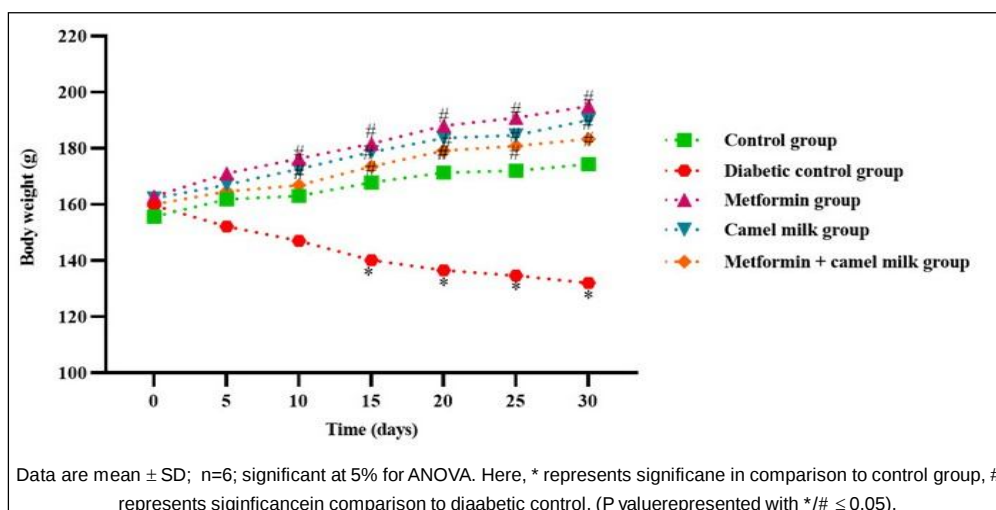


Fig 2: Graphical representation of average body weight pattern of the animals' post-treatments of camel milk and metformin individually or in combination during the study period.

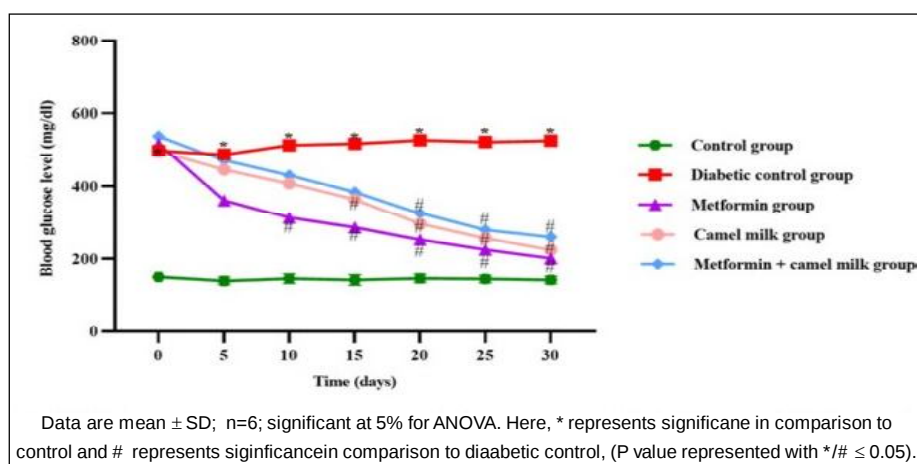


Fig 3: Effect of metformin and camel milk solely and in combination on blood glucose levels (mg/dL).

516.1±85.82 mg/dL, 495±72.80 mg/dL, 536.6±56.89 mg/dL on day 0 to 201.8±61.53 mg/dL, 224.8±23.67 mg/dL, 260.8±33.31 mg/dL on day 30 of the treatment. Previous research has suggested that in rat models of type-II diabetes, metformin significantly alters the insulin signalling pathway

by inhibiting gluconeogenesis and enhancing insulin-mediated glucose elimination, possibly through increased insulin-receptor affinity (Alavi *et al.*, 2017). Recent investigations on both humans and animals have demonstrated that camel milk and probiotics work better

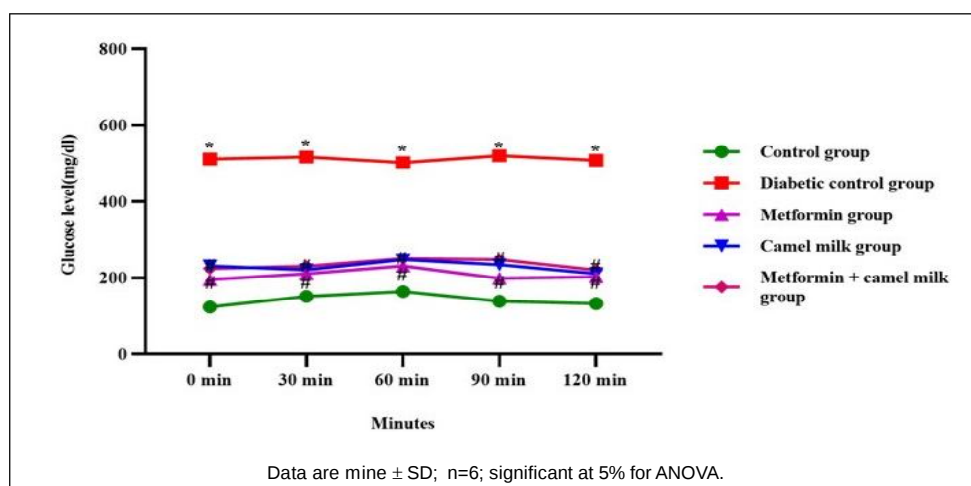


Fig 4: Effect of metformin and camel milk solely and in combination on oral glucose tolerance test.

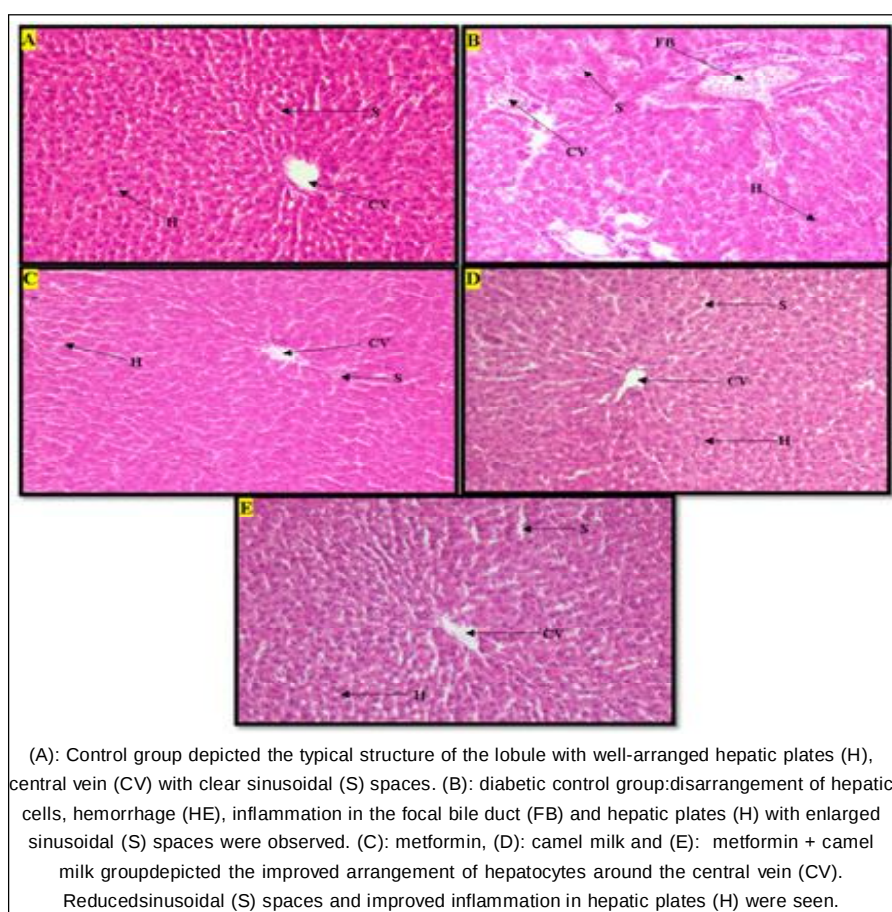


Fig 5: Histopathological observation of the liver section of different animal groups.

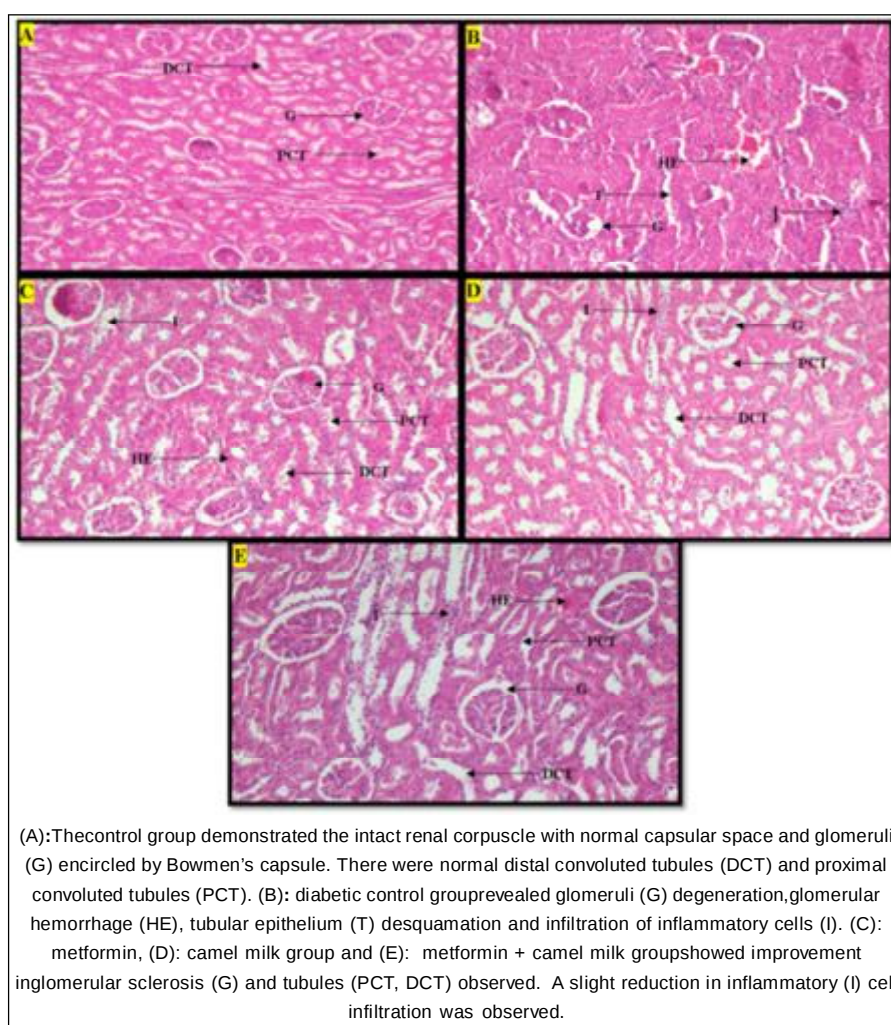


Fig 6: Histopathological structure of the kidney of different treatment groups.

together to manage type II diabetes (Tiderencel *et al.*, 2020; Widodo *et al.*, 2019). Camel milk exosomes can significantly increase glucose consumption in L6 cells by inhibiting mitochondrial respiratory chain complex I (Yang *et al.*, 2023).

Oral glucose tolerance test

The diabetic control group exhibited hyperglycemia during the oral glucose tolerance test comparison with the control group ($p < 0.05$) (Fig 4). A remarkable glucose regulation was observed in the metformin, camel milk and metformin + camel milk treated group in comparison to the diabetic control group ($p < 0.05$) similar to the findings of (Raj *et al.*, 2023).

Histological study

Liver

The liver section of the control group showed, a normal arrangement of the hepatic cells circularly around the central vein. Hepatic plates are well-spaced with adequately arranged sinusoidal spaces (Fig 5). In the diabetic control

group, distorted lobule with disorganized hepatic cells around the central vein and enlarged hepatic sinusoids were observed. Necrosis, degeneration and inflammation in the focal bile duct and hepatic plates with enlarged sinusoidal spaces were observed. All these histopathological changes were improved in the metformin, camel milk and metformin + camel milk treated group. Hepatocyte arrangement around the central vein and sinusoid area was ameliorated in these treatment groups as was observed in previous findings of Ojuade *et al.* (2021). The consumption of camel milk may lower insulin requirements and improve glycemic levels. Camel milk proteins have the potential to stimulate and increase insulin secretion through three different mechanisms: (i) stimulating insulin secretion mediated by glucose; (ii) inhibiting glucagon secretion by pancreatic α -cells and its function in the liver and/or (iii) inhibiting key enzymes, such as dipeptidyl peptidase IV (DPP), that indirectly control insulin secretion (Andersen *et al.*, 2018). Recent

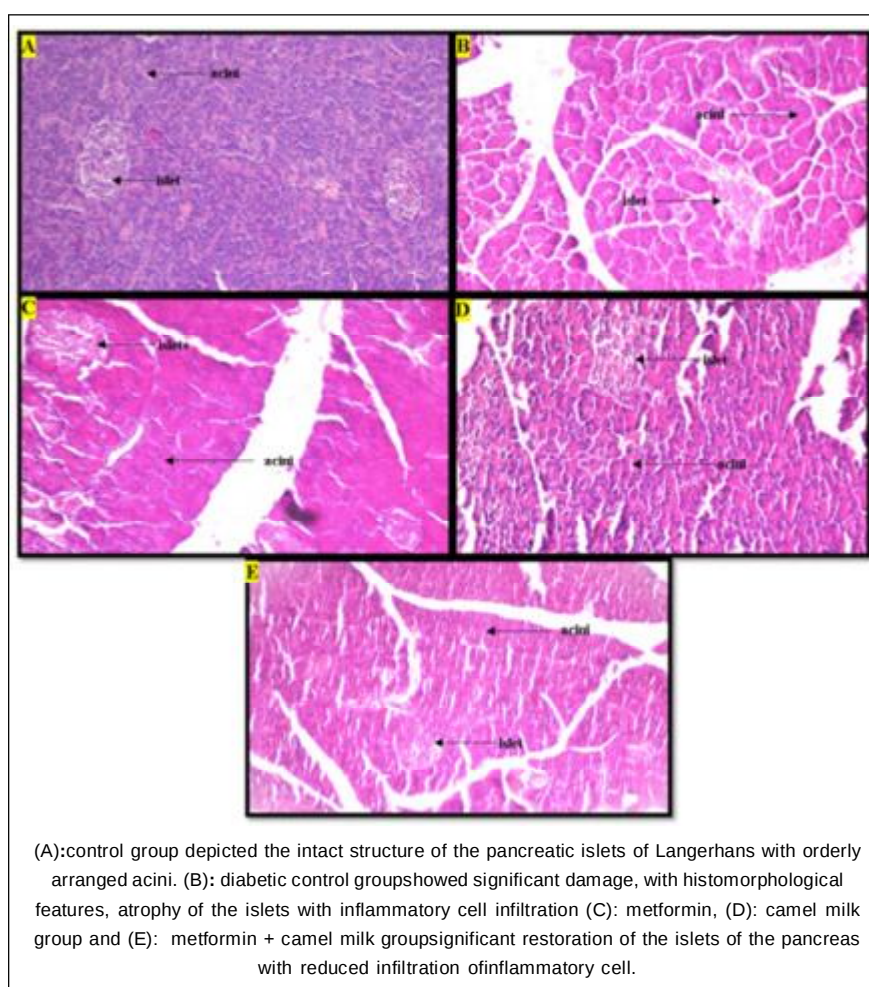


Fig 7: Histopathological examination of the pancreas of different study groups.

investigations employing hydrolysates of camel milk whey protein revealed a variety of bioactive peptides that inhibited DPP-IV activity in vitro to varying degrees [Mudgli *et al.*, 2018]. It also lessens oxidative stress, which lessens the effects of diabetes on conditions including retinopathy, nephropathy, high cholesterol and liver damage (Shori *et al.*, 2015).

Kidney

The control group showed intact renal corpuscles with normal proximal and distal convoluted tubules in addition to glomeruli encircled by Bowman's capsules with sufficient capsular space (Fig 6). The diabetic control group had a distinctly enlarged Bowman capsule along with glomerular sclerosis and mesangial hyperplasia. This included tubular epithelium desquamation and glomeruli vacuolar degeneration, as well as a noticeable presence of inflammatory cells. The metformin, camel milk and metformin + camel milk treated group exhibited improvement in the structure of the renal tubules (PCT, DCT), infiltration of

inflammatory cells and renal corpuscles as well as mesangial hyperplasia. The kidney's histology showed a marked improvement after treatment with camel milk+exosomes either separately or in grouping. Glomerular sclerosis was absent (Shaban *et al.*, 2022). Metformin-treated diabetic rats showed improved morphological alterations in the kidney, pancreas and liver (Almuttairi, 2023).

Pancreas

The pancreatic tissue of the healthy control group had normal islets with intact acini. In the diabetic control group atrophy of the islets with damaged acinar architecture and inflammatory cell infiltration was observed (Fig 7). In diabetic animals, streptozotocin causes oxidative stress that deteriorates the pancreatic tissue and, as a result, raises fasting blood glucose levels. The morphological study of the pancreas of the metformin-treated groups showed regeneration with increased hyperchromasia of the acinar and islet cell nuclei and abundant cytoplasm. The camel

milk-treated group showed an improved structure of the pancreatic islet and acinar cell with increased hyperchromasia. Histopathological findings in the combined group (metformin + camel milk) were improved, with an orderly arrangement of pancreatic islet cells and acini similar results noticed in previous studies (Khowailed *et al.*, 2018).

CONCLUSION

This study set out to find if streptozotocin-nicotinamide-induced type II diabetes in albino rats could be effectively treated with camel milk and metformin, either separately or together.

The study found that both metformin and camel milk, when administered individually, or in combination significantly reduced fasting glycemic levels and improved glucose regulation in diabetic rats compared to the diabetic control group. Morphological deformities were also improved in metformin and camel milk-treated groups. The results of this study have shed important light on the possible advantages of camel milk and how it affects type II diabetes mellitus glycemic management. Further research in this field may result in the development of novel therapeutic drugs or dietary interventions for people with metabolic diseases, which might serve as supplements or substitutes for already available therapies. It's crucial to remember that although in vitro and in vivo studies offer insightful information, human clinical trials are required to verify the effectiveness and safety of these therapies.

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Conflict of Interest

The authors declare no conflict of interest.

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