Diabetes, Metabolic Syndrome and Obesity

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ORIGINAL RESEARCH

Potential Effect of Curcumin in Lowering Blood Glucose Level in Streptozotocin-Induced Diabetic Rats

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Purpose: The prevalence of diabetes mellitus has significantly increased, with 537 million individuals living with diabetes in 2021. Curcumin, a natural compound present in turmeric, has anti-inflammatory and antioxidant properties that aid in controlling diabetes. Curcumin can lower blood glucose levels, increase pancreatic cell function, and reduce insulin resistance. The pathophysiology of diabetes involves oxidative stress and endoplasmic reticulum stress, which can lead to cell death. This study aimed to evaluate the antidiabetic activity of curcumin in rats by administering it for a month and evaluating pancreatic tissue histology.

Patients and Methods: STZ-induced diabetic rats were fed a high-fat diet containing glibenclamide, 200 mg/kg body weight (BW) curcumin, 400 mg/kg BW curcumin, or a placebo for 4 weeks. After intervention, blood glucose levels were measured, and the pancreatic tissue was examined. Blood glucose levels were measured at 0, 2, 4, 6, and 8 h.

Results: One-way ANOVA was performed to measure the mean difference among the groups at 0, 2, 4, 6, and 8 h of observation, which reported a statistically significant difference ($p < 0.05$). The blood glucose levels decreased after 4 h in the group receiving curcumin. Histological evaluation of the pancreas showed slight hydropic degeneration after 4 weeks of curcumin treatment.

Conclusion: Our study indicates that curcumin has a beneficial effect in diabetic rats by reducing blood glucose levels and a protective effect on the pancreas.

Keywords: curcumin, diabetes, blood glucose, antidiabetic, antioxidant, insulin resistance

Introduction

The number of adults aged 20–79 years diagnosed with diabetes mellitus has significantly increased from 151 million in 2000 to 463 million in 2019. In 2021, 537 million people were estimated to be living with diabetes, and this number is expected to rise to 643 million by 2030 and 783 million by 2045.[1] Diabetes mellitus is one of the most prevalent diseases in the world and has become a significant public health challenge in the 21st century. Additionally, it can lead to serious health complications.[2] In recent decades, the World Health Organization has acknowledged the value of traditional medicine, particularly medicinal plants, in enhancing individual and community health. Traditional medicine is believed to be more cost-effective and less harmful than insulin and oral medications, which may be inadequate and result in additional complications.[3,4]

Curcumin is a natural compound found in turmeric. Its diverse biological effects may aid in the management of diabetes. The antidiabetic effects of curcumin primarily stem from its anti-inflammatory and antioxidant properties, considering that inflammation significantly disrupts the structural integrity of β-cells.[5] Curcumin can lower blood glucose

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levels by decreasing glucose synthesis in the liver, lowering the inflammatory state induced by hyperglycemia, increasing cellular glucose uptake, and activating various enzymes and proteins that modulate insulin secretion and sensitivity. In addition, curcumin can increase pancreatic cell function and reduce insulin resistance.[6] Curcumin has also been reported to play an important role in modulating the activation of cholinergic and insulin receptors and the glucose transport mechanism via glucose transporter 3 (GLUT3).[7] Another study found that curcumin at a dose of at 150 mg/kg body weight can lower blood glucose and plasma lipid levels in rats administered a high-fat diet plus streptozotocin (STZ) in a 7-week intervention.[8] Curcumin enhances glucose and fatty acid oxidation via the LKB1-AMPK pathway, which lowers insulin resistance.[8] The pathophysiology of diabetes involves oxidative stress and endoplasmic reticulum (ER) stress. If these stresses persist longer and become more severe, they may lead to cell death. Previous studies have revealed reduced pancreatic β-cell mass in patients with type 1 and type 2 diabetes mellitus. Pancreatic cells are susceptible to oxidative damage owing to the overproduction of reactive oxygen species (ROS) within the cell, as hyperglycemic conditions lead to protein glycosylation and glucose autooxidation.[9–11] Type 1 diabetes mellitus produces oxidative stress in rat animal models by decreasing antioxidant activity, increasing malondialdehyde (MDA) and total oxidative status (TOS), and modifying total antioxidative capacity (TAC) and total thiol (SH) levels.[12] Additionally, it elevates the concentrations of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β.[12]

Previous research showed the relationship between curcumin and its mechanism in managing diabetes. Those studies used curcumin in experimental animals for 4 to 8 weeks to demonstrate its hypoglycemic effects.[13–15] Furthermore, curcumin, given intraperitoneal, improved C-peptide levels and reduced pro-inflammatory cytokines in rats with STZ-induced diabetes.[16] In order to evaluate curcumin's effect on blood glucose levels and on pancreatic tissue, we administered 200 mg/Kg BW and 400 mg/Kg BW of curcumin for 4 weeks, and their pancreatic tissue histology was evaluated. Glibenclamide was used as a positive control to validate the efficacy of curcumin.

Material and Methods

Experimental Animals

This study used 20 Wistar rats (*Rattus norvegicus*) aged 12–15 weeks and weighing 200–250 g. All rats were healthy males with no disabilities. The rats were placed in cages of adequate size and kept under a temperature of 28°C and humidity of 40–60%. The rats had access to food and water and were fed according to their needs during the experiments. The rats were acclimatized for 2 weeks.

During acclimatization, rats were fed a high-fat diet. For the first 3 days, they were fed a basic mixed high-fat diet at a 1:1 ratio to aid digestion. On the 4th day, the proportion of high-fat diet was steadily increased to induce type 2 diabetes. Food and water were provided *ad libitum* twice a day.

After acclimatization, a diabetic rat model was established. Rats were fasted overnight to induce non-insulin-dependent diabetes mellitus. STZ was administered at a dose of 45 mg/kg BW as a single intraperitoneal injection.

The recommended dosage of streptozotocin for a typical adult weighing 70 kg is 45 mg. The conversion factor from humans to mice is 0.018. Therefore, for a rat weighing 300 grams, the appropriate dose of streptozotocin would be 0.81 mg.[17] After 72 h (3 days), hyperglycemia was confirmed by higher glucose levels in the plasma of the rats. For this study, rats with a blood glucose level > 200 mg/dL were selected.[18] In a diabetic animal model, STZ was used due to its superior efficacy in developing diabetes mellitus and its higher tolerance in rats compared with another inducer, alloxan. STZ has been demonstrated to be more efficacious than alloxan in causing diabetes mellitus in earlier comparative trials.[19]

Diabetic rats were randomly assigned to four groups of five using an online random team generator. Rats in group A were treated with glibenclamide (5 mg/kg BW) as a positive control. Group B rats were administered curcumin at a dose of 200 mg/kg BW. Rats in group C were administered with 400 mg /kg BW curcumin. Rats in group D rats received sodium carboxymethyl cellulose (Na-CMC; placebo) as a negative control (1 mL orally). All interventions were administered using a nasogastric sonde once daily for 4 weeks. Na-CMC was employed as a suspension to generate a colloidal substance extract because the colloid can improve the solubility and stability of the active substance, resulting

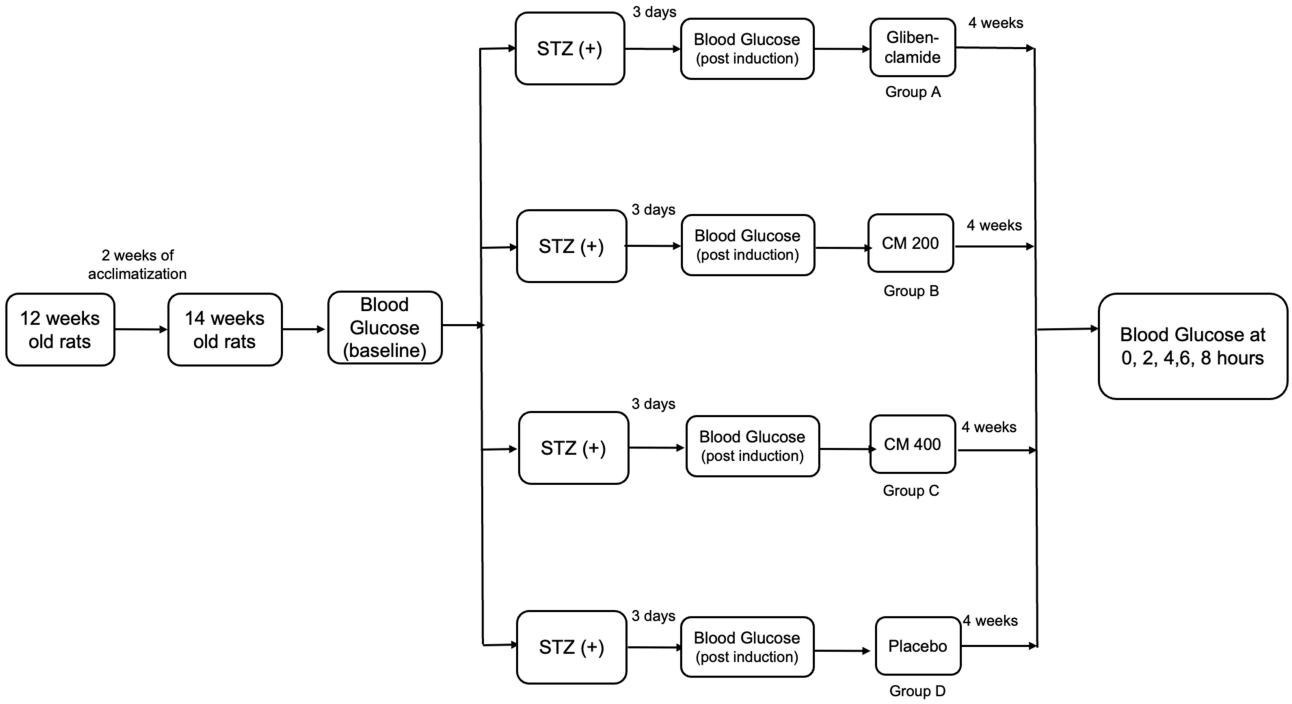

Figure 1 Schematic diagram of in vivo experimental protocol.

in higher bioavailability and easier absorption in the intestines.[12] The schematic diagram of the in vivo experimental protocol is shown in Figure 1.

This study was conducted in accordance with the ARRIVE guidelines for in vivo experiments. This study was approved by the Health Research Ethics Committee of the Faculty of Medicine and Health Sciences at Universitas Muhammadiyah Makassar (registration number 468/UM.PKE/I/45/2024; January 2024) following international guiding principles for biomedical research involving animals.[20]

Curcumin Preparation

Curcumin, also known as 1,7-bis (4-hydroxy-3-methoxyphenyl)-1.6-heptadiene-3,5-dione, turmeric yellow, or diferuloylmethane, was purchased from Merck, PT Merck Chemicals and Life Sciences (chemical formula [4-(OH)-3-$(CH_3O)C_6H_3CH{=}CHCO]_2CH_2$), Jakarta, Indonesia. Curcumin was dissolved in normal saline solution to obtain the 200 and 400 mg/kg doses. The dose administered to rats was calculated by applying a conversion factor of 0.0026. Group B received 200 mg/kg BW curcumin daily for 30 days, whereas group C received 400 mg/kg BW curcumin. According to the previous study, curcumin is chemically unstable in alkaline aqueous solutions (pH > 7.0) and crystallizes in acidic aqueous solutions (pH < 7).[21] We utilized saline because of its neutral pH (about 7.4), which is close to the physiological pH of the body. This is important for curcumin, as it can degrade under acidic or highly alkaline conditions.

Blood Glucose Measurement

All diabetic rats were fasted overnight. Fasting blood glucose levels were measured using a pre-standardized glucometer and reagent strips using the glucose oxidase method. Blood samples (0.5–1.5 µL) were collected from the tail veins of the rats, and their glucose levels were measured using an Easy Touch® glucometer (Bioptik EasyTouch-GCU ET-301) from Bioptik Technology Inc, Taiwan. Blood samples were collected seven times: first before the intervention (baseline), second post-induction with STZ, and the remaining times at the end of the intervention (at 0, 2, 4, 6, and 8 h) (Figure 1).

Previous studies used curcumin in experimental animals for 4 to 8 weeks to demonstrate its hypoglycemic effects.[13–15] Blood glucose levels were measured at 0, 2, 4, 6, and 8 hours after the period of weeks intervention to demonstrate the function of curcumin in improving insulin resistance and glucose tolerance in the STZ-induced diabetic animal model.

Histopathological Preparations of Rat Pancreatic Tissue

After 30 days of intervention, rats were sacrificed and pancreatic tissues were harvested. The tissue fragments were fixed in 10% neutral formalin solution, embedded in paraffin, and then stained with hematoxylin and eosin.

Histopathological preparations of pancreatic tissue were conducted using 10% formalin buffer neutral solution for 2×24 h. The specimens were cut and placed in a plastic container. The fixed tissue was then cut using a sharp, sterile scalpel. After trimming, the tissues were placed in a cassette. Tissue samples in the cassette were further dehydrated using 70%, 80%, and 90% alcohol for 1 day. Tissue dehydration was performed to remove all the fluid present in the fixed tissue so that it can be filled with paraffin or other substances to prepare blocks. This was followed by clearing the samples using xylol I and II for 1 h each. Generating tissue blocks serves to preserve each part of the tissue, preventing alterations, particularly in the early stages of cutting through tissue embedding. In this study, anti-rust molds or base molds were used to manufacture paraffin blocks, and liquid paraffin at a temperature of 70°C was used. Thereafter, the tissue samples were sliced to a thickness of 3–5 μm using microtomes. Subsequently, the tissues were stained using hematoxylin and eosin. Staining is the procedure of imparting color to cut tissues to facilitate tissue identification and microscopic observation.

Statistical Analysis

The data are presented as mean±standard error (SEM) and analyzed using the SPSS 26 software (IBM Corporation, NY, USA). Statistical analyses with repeated measures and one-way ANOVA were used to compare the numerical mean differences among the groups, followed by *post-hoc* Dunn-Bonferroni analysis. $p < 0.05$ was considered statistically significant. We adjusted the p-value with Bonferroni correction by comparing 4 pairs of groups.

Results

At baseline, there were no statistically significant differences in age and BW among the different groups. Additionally, blood glucose levels at baseline and post-induction with STZ did not have any statistically significant differences in mean (Table 1).

Repeated measures ANOVA showed that blood glucose levels did not significantly differ among the different time points in all groups ($p > 0.05$). However, one-way ANOVA performed to measure the mean difference among the groups at 0, 2, 4, 6, and 8 h observation showed a statistically significant difference ($p < 0.05$). Group B (CM200) had decreased blood glucose levels from 0 to 6 and 8 h (225.0±39.11 vs 128.80±16.46 and 139.20±10.17 mg/dL, respectively). Similarly, in group C (CM400), blood glucose levels decreased from 0 to 6 and 8 h (192.80±42.28 vs 154.40±12.46 and 127.60±9.63 mg/dL, respectively) (Table 2).

Table 1 Characteristics of Animals Used in the Experiment

Variables	Groups				p-value*
	Group A (Glibenclamide)	Group B (CM200)	Group C (CM400)	Group D (Placebo)	
Mice age (in weeks)	12.60±0.40	13.40±0.51	13.00±0.44	12.80±0.37	0.61
Mice body weight (g)	242.60±16.36	244.40±18.61	248.60±21.74	242.0±18.09	0.99
Blood glucose measurement at baseline (mg/dL)	89.60±3.31	86.40±2.89	87.80±2.59	88.00±3.28	0.93
Blood glucose post-induction with STZ (mg/dL)	352.40±49.19	338.80±56.14	369.20±55.00	399.60±23.64	0.82

Notes: *Comparison of mean among groups using one-way ANOVA, n=5, $p < 0.05$ was considered significant. CM, curcumin.

Table 2 Mean Blood Glucose Level After Four Weeks of Intervention at 0, 2, 4, 6, and 8 h

Groups	Blood Glucose level (mg/dl)					p-value*
	0 h	2 h	4 h	6 h	8 h	
Group A (glibenclamide)	82.20±17.26	87.20±3.69	88.0±5.28	85.40±3.17	84.40±2.78	0.989
Group B (CM200)	225.0±39.11	233.0±57.89	216.20±23.40	128.80±16.46	139.20±10.17	0.110
Group C (CM400)	192.80±42.28	218.40±47.61	133.40±13.37	154.40±12.46	127.60±9.63	0.187
Group D (placebo)	432.80±28.66	440.60±26.19	435.80±23.14	459.00±20.41	468.00±22.58	0.850
p-value**	0.000	0.000	0.000	0.000	0.000	

Notes: *Comparison of mean among groups using repeated measures ANOVA. **Comparison of mean using one-way ANOVA. N=5; $p < 0.05$ was considered significant. CM, curcumin.

Abbreviations: BW, body weight; ER, endoplasmic reticulum; GLUT, glucose transporter; HO-1, heme oxygenase-1; Na-CMC, sodium carboxymethyl cellulose; ROS, reactive oxygen species; SEM, standard error; STZ, streptozotocin; SUR1, sulfonylurea receptor 1.

The Dunn-Bonferroni post-hoc test revealed a significant difference in blood glucose levels between intervention group B (CM200) and group C (CM400) compared to group D (placebo) at 2 hours of blood glucose measurement. The difference was 207.600 mg/dL in group B (95% CI, −376.70 to −38.50, p=0.012) and 222.200 mg/dL in group C (95% CI, −391.30 to −53.10, p=0.007).

Further post-test using Dunn-Bonferroni revealed that at 4 h, blood glucose measurement reported a significant difference between group B (CM200), group C (CM400), and group D (placebo). There was a significant blood glucose difference from 216.20±23.40 mg/dL in group B (CM200) compared to group D (placebo) with 435.80±23.14 mg/dL, a difference of 237.600 (95% CI, −314.02 to −161.18, p=0.000). We also reported a significant blood glucose difference from 133.40±13.37 mg/dL in group C (CM400) compared to group D (placebo) with 435.80±23.14 mg/dL, a difference of 320.400 (95% CI, −396.82 to −243.98, p=0.000).

The Dunn-Bonferroni post-hoc test revealed a significant difference in blood glucose levels between group B (CM200) and group C (CM400) compared to group D (placebo) at 6 hours of blood glucose measurement. The difference was 330.200 (95% CI, −392.34 to −268.06, p=0.000) in group B and 304.600 (95% CI, −366.74 to −242.46, p=0.000) in group C.

Furthermore, the Dunn-Bonferroni post-hoc test also revealed a significant difference in blood glucose levels between group B (CM200) and group C (CM400) compared to group D (placebo) at 8 hours of blood glucose measurement. The difference was 328.800 (95% CI, −385.65 to −271.92, p=0.000) in group B and 340.400 (95% CI, −397.25 to −283.55, p=0.000) in group C.

Figure 2 shows that blood glucose levels decreased in groups B (CM200) and C (CM400) compared with group D (placebo), with wide differences in their means. Blood glucose levels decreased at 4 h in the curcumin-treated group.

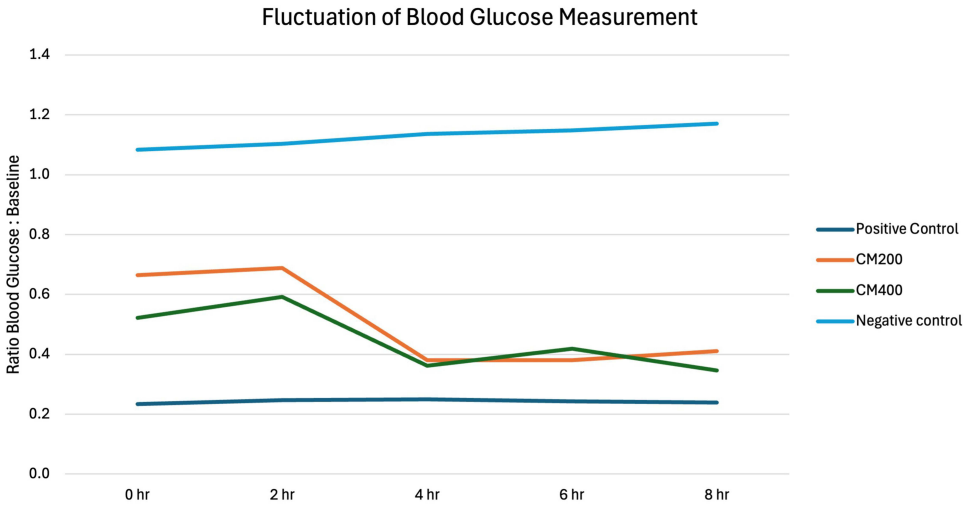

Figure 2 Changes in blood glucose measurement at the observation time points (0, 2, 4, 6 and 8 h) after 30 days of intervention. CM200: group that received curcumin at a dose of 200 mg/kg body weight. CM400: group that received curcumin at a dose of 400 mg/kg body weight. Positive control group was treated with glibenclamide. Negative control group received a placebo.

Discussion

Curcumin, a primary constituent of turmeric, has been demonstrated to modulate blood glucose levels through many pathways. Research suggests that curcuminoids do not directly impact the activity of receptor tyrosine kinase or glucose metabolism in the intestines. However, they do decrease hepatic gluconeogenesis via suppressing enzymes like phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase). Furthermore, curcuminoids increase the phosphorylation of AMP-activated protein kinase (AMPK) and its downstream target acetyl-CoA carboxylase (ACC), implying a role in mediating the glucose-lowering action.[22] In our finding, curcumin demonstrated notable antidiabetic properties in rats at doses of 200 and 400 mg/kg BW. At a dosage of 400 mg/kg BW, it caused a decrease in blood glucose levels from 218.40±47.61 to 127.60±9.63 mg/dL (Table 2). Curcumin had a hypoglycemic impact after 4 hours (Figure 2), indicating that its antidiabetic action is similar to glibenclamide in diabetic rats induced by STZ. This suggests that curcumin could be considered as an alternative or adjunct therapy for diabetes treatment.

A previous study reported that curcumin significantly enhances glucose tolerance in diabetic rats.[8] Based on a previous study, the blood insulin levels of rats administered curcumin increased by 42.5% compared with the diabetic group. This finding suggests that curcumin supplementation can reduce hyperglycemia and insulin resistance in diabetic rats by enhancing lipid and glucose metabolism in skeletal muscles and preserving pancreatic islet cells.[8] Curcumin supplementation enhances hepatic glucokinase activity, which aids in glucose metabolism. It decreases the activities of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase, two important enzymes involved in gluconeogenesis, resulting in reduced glucose synthesis.[15] Curcumin reduces the activity of enzymes involved in lipid metabolism and diminishes lipid peroxidation by restoring normal antioxidant enzyme activity.[15]

STZ is toxic to pancreatic β-cells because its molecular structure permits glucose to enter the cells through low-affinity GLUT2 on the plasma membrane.[23] Our findings are consistent with this explanation. Following STZ induction, we measured the blood glucose levels in rats and found that the glucose levels were significantly increased in all groups compared with the baseline measurements (Table 1). Previous studies reported that STZ is an immunosuppressive agent that causes autoimmune destruction of the insulin-producing beta cells in the pancreas, leading to a significant increase in blood glucose levels.[24]

In the negative control group (placebo), hypertrophy of acinar cells, hydropic degeneration, and accumulation of hemosiderin were observed, which are indications of bleeding (Figure 3). Previous studies have shown that pancreatic histological damage due to diabetes is characterized by changes in the shape of the pancreas, such as narrowing and reduction in the size of the Langerhans islands,[25] as well as vacuolization of the cytoplasm.[26] A faint cytoplasm suggests an insulin deficiency, which results in cytoplasmic vacuolization.[27] Another study reported necrosis and hydropic degeneration of islet cells, atrophy in Langerhans cells and vasodilatation in veins capillary in diabetic induced rats with STZ.[28]

Our study found that the group that received 200 mg/kg BW curcumin showed slight hydropic degeneration, while acinar formation appeared normal. Meanwhile, the group that had been treated with 400 mg/kg BW curcumin showed normal and degenerated acinar cells, indicating curcumin's positive and protective effects on pancreatic structure (Figure 3). There is evidence that reported the efficacy of curcumin in exhibiting a defensive impact on pancreatic tissue in models of diabetes. A previous study has demonstrated that applying curcumin can effectively reduce fasting blood glucose levels and restore pancreatic function in rats with type 2 diabetes.[29] In another study with type 1 diabetes models, a new curcumin derivative (NCD) reduced plasma glucose and increased plasma insulin and C-peptide levels, improving pancreatic function. Histopathological examination showed pancreatic islet regeneration and the presence of insulin-positive cells, indicating NCD's potential to enhance pancreatic islet regeneration.[30]

Previous research has demonstrated that administering curcumin at a dose of 100 mg/kg BW for eight weeks can protect pancreatic islets in diabetic rats, implying that curcumin can alleviate stress-induced inflammation and apoptosis in diabetes.[31] The efficacy of curcumin as an antioxidant and anti-inflammatory drug has been demonstrated by its ability to reduce the generation of ROS, enhance cellular antioxidant defense systems, and modulate inflammatory cytokines. Curcumin activates heme oxygenase-1 (HO-1) and suppresses the NF-κB signaling pathway via the PI3K/Akt pathway, which is crucial for inflammatory responses.[31] Curcumin protects cells against apoptotic death by decreasing

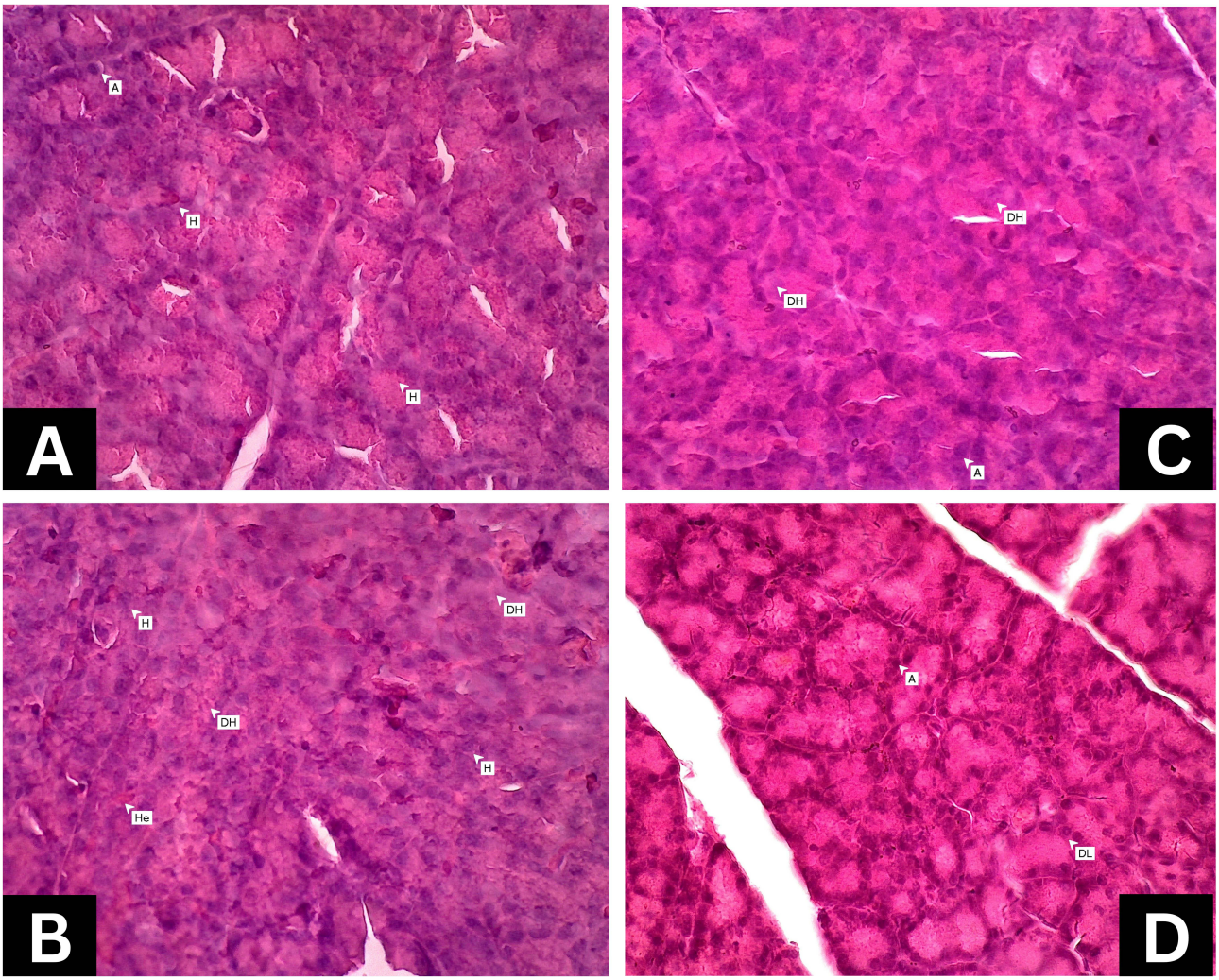

Figure 3 Histological presentation of pancreatic tissue stained with hematoxylin and eosin dye.(**A**) Positive control: pancreatic section from rats treated with glibenclamide (x400). Acinar cells (A), hemosiderin (H), HE 400X. (**B**). Negative control: pancreatic section from rats treated with placebo (x400). Hypertrophy (H) of acinar cells, hydropic degeneration (DH), and accumulation of hemosiderin (He) are indications of bleeding. HE 400X. (**C**). CM200: pancreatic section from rats treated with curcumin at a dose of 200 mg/kg body weight after diabetic induction (x400). The pancreatic region exhibiting slight hydropic degeneration (DH), while the formation of acinar cells appears to be normal. HE 400X.(**D**) CM400: pancreatic section from rats treated with curcumin at a dose of 400 mg/kg body weight after diabetic induction (x400). Appearance of normal acinar cells (A) and acinar cells experiencing degeneration (DL). HE 400X.

inflammatory responses and blocking both ER/mitochondria-dependent and -independent apoptotic pathways and their interactions.[31] Another study has demonstrated that the administration of small amounts of curcumin causes minimal cellular damage, characterized by pyknotic and apoptotic nuclei. However, the majority of cells in both the outer and inner zones of the pancreatic islets remains undamaged. High doses of curcumin disrupt a few cellular elements and cause pancreatic islets to lose cellular features, with many cells remaining intact with vesicular nuclei. Oral curcumin treatment has resulted in slight vacuolar alterations in the pancreatic islets and minor congestion of the blood capillaries.[32] Our results demonstrate the beneficial effect of curcumin on diabetic rats through a protective effect on the pancreas and reduction of blood glucose levels. Curcumin has the potential to be developed as an herbal product for the treatment of diabetes. Evidence from other studies suggests that Curcumin regulates blood glucose by inhibiting hepatic gluconeogenesis, enhancing AMPK phosphorylation, and activating PPAR-gamma.[22,33]

Our study's limitation is the absence of continuous monitoring of blood glucose changes throughout the four-week intervention period with curcumin. In addition, our investigation did not include the evaluation of biomarkers that indicate oxidative stress and inflammatory diseases related to diabetes mellitus. Further experiments could provide insights into the efficacy of different curcumin doses or formulations and their effects on pancreatic function and

systemic pro-inflammatory cytokine profiles in experimentally induced diabetes mellitus. Therefore, curcumin, a natural chemical, has the potential to be a future therapeutic option for diabetes mellitus.

Conclusion

Our study findings suggest that curcumin has beneficial effects on diabetes and provides protection for pancreatic tissue. We observed a decrease in blood glucose levels after administering 200 mg/kg and 400 mg/kg of curcumin for 4 weeks.

Data Sharing Statement

The data that support of this study are available from the corresponding author upon request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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