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RESEARCH ARTICLE

Nano-curcumin as a Novel Therapeutic Agent for Type I and II Diabetes: A Comparative Study on Enzyme Inhibition and Metabolic Recovery in Alloxan and Cadmium Chloride-Induced Rat Models

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ABSTRACT

Type I diabetes mellitus is an autoimmune disease caused by immune-mediated destruction of pancreatic β cells, resulting in a deficiency of insulin. Type II diabetes is characterized by insulin resistance and a progressive loss of β cell function. However, the two types share important similarities despite their differences, including chronically elevated blood glucose, increased oxidative stress, and severe complications in the major organs. Curcumin exhibits antidiabetic activity; however, its clinical application is restricted by poor absorption and rapid metabolism. The therapeutic efficacy of curcumin nanoparticles was evaluated in rat models of Type I and Type II diabetes induced by alloxan and cadmium chloride, respectively, in comparison with conventional curcumin in the present study. After synthesis and characterization of the curcumin nanoparticles, various parameters were studied including body weight, glycemic control, insulin levels, carbohydrate digesting enzymes, liver and kidney function markers, oxidative stress markers and histopathology. Type I animals showed a significant ($P<0.05$) weight loss and severe hyperglycemia with a significant decrease in insulin, whereas Type II models presented classic insulin resistance. Curcumin treatment partly improved these parameters. However, curcumin nanoparticles (CurNPs) considerably maintained body weight and blood glucose near normal values ($P<0.05$) and insulin secretion or sensitivity restored ($P<0.05$) in both types of diabetes. The CurNPs exhibited significant decreases in carbohydrate-digestive enzymes ($P<0.05$), protection of hepatic and renal functions, increased antioxidant defence system and reduced lipid peroxidation. These changes were associated with histopathological analysis showing preservation of pancreatic islet structure and reduced tissue injury in diabetic organs, without toxicity in healthy controls ($P<0.05$). CurNPs seem to enhance curcumin's efficacy by improving blood sugar control, protecting organs, and repairing tissue. These findings suggest the possibility of using CurNPs as a promising tool in managing Type I and Type II diabetes and their complications.

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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by a persistent increase in blood glucose levels due to defects in insulin secretion, insulin action or a combination of both. It comprises two major pathophysiological types that mostly correspond to type 1 and type 2 diabetes (Gilor *et al.,* 2016; Niaz *et al.,* 2018; Kottaisamy *et al.,* 2021). Experimental diabetes in rodents chemically induced, especially with alloxan, is a common experimental tool to investigate disease mechanisms and to assess antidiabetic treatments (Deeds *et al.,* 2011; Ali and Mustafa, 2023; Algul and Ozcelik, 2025). Alloxan is a cytotoxic glucose analogue that enters pancreatic β cells preferentially, where it inhibits glucose stimulated insulin secretion, produces reactive oxygen species, and eventually results in β cell necrosis or apoptosis, resulting in hypoinsulinemia and persistent hyperglycemia. Alloxan-induced diabetes can be severe and unstable, depending on species, strain, dose, route of administration

and other protocol details such as fasting duration and number of injections. Effective diabetogenic doses in rats usually fall between 40 and 200 mg/kg via intravenous or intraperitoneal administration, with Wistar and Sprague Dawley strains being the most common (Akinlade *et al.,* 2021; Adeleye *et al.,* 2024). Cadmium chloride ($CdCl_2$) is used in experimental models to induce metabolic and oxidative stress, impairing blood sugar control and increasing free radical damage. When combined with alloxan-induced diabetes, it increases lipid peroxidation and affects antioxidant defenses, thus establishing a robust model for studying diabetic tissue injury and complications (Mostafavinia *et al.,* 2016a; Adeleye *et al.,* 2024). In general care, diabetes is still largely controlled by reducing blood glucose levels with insulin and oral drugs such as metformin and sulfonylureas. While these drugs are effective, they can potentially cause problems such as weight gain, hypoglycaemia and gastrointestinal side effects, and they do not fully prevent long term complications (Houglum *et al.,* 2024). This has increased interest in plant derived compounds and herbal preparations that may increase glucose control and insulin sensitivity with less side effects (Shahzad *et al.,* 2024). Curcumin from turmeric is one such natural product. It shows antioxidant, anti inflammatory and antidiabetic actions and can improve insulin signaling and protect β cells, but its clinical impact is limited by poor solubility, rapid metabolism, and very low oral bioavailability (Tabanelli *et al.,* 2021; Wei *et al.,* 2025). Nanotechnology based formulations of curcumin "nanocurcumin" increase water solubility, shield it from degradation, and enhance absorption and tissue delivery. These nanoformulations consistently raise curcumin bioavailability and strengthen its glucose lowering and organ protective effects in cell, animal, and early human studies, often at much lower doses than free curcumin (Chauhan and Prasad, 2025). Rats diabetes is created by specific chemical inducers. Alloxan is a beta-cell cytotoxin that produces reactive oxygen species (ROS) that selectively destroy pancreatic β-cells and creates a robust model of T1D. (Mostafavinia *et al.,* 2016b). Chronic exposure to heavy metals such as Cadmium in $CdCl_2$ is increasingly associated with the development of insulin resistance and T2D through mechanisms including oxidative stress, inflammation, and disruption of insulin signaling pathways. Diabetes is closely linked to oxidative stress and inflammation, driven primarily by elevated blood glucose, which increases the production of reactive oxygen species (ROS) (Oguntibeju, 2019). The resulting ROS overload overwhelms the body's antioxidant defenses, damaging proteins, lipids, and DNA, and accelerating the development of diabetic complications (Chen *et al.,* 2025). Other oxidative stress mechanisms in diabetes include glucose auto-oxidation, activation of the polyol pathway and formation of advanced glycation end products (AGEs). Oxidative stress can also cause beta-cell dysfunction, impaired insulin secretion, and insulin resistance. Diabetic retinopathy, nephropathy and cardiovascular disease are often seen due to inflammation and vascular damage in diabetic individuals. Curcumin nanoparticles can be used to target these pathophysiological mechanisms through their anti-inflammatory and antioxidant properties to help manage inflammation and oxidative stress in diabetes. There is no research comparing the antidiabetic effect of curcumin and CurNPs on type 1 and type 2 diabetes models in the same study. There is also no research on the evaluation of the inhibition of alpha-amylase and alpha-glucosidase, two key carbohydrate digesting enzymes that regulate postprandial hyperglycemia, by CurNPs on the two models of diabetes. Combination therapy and recent developments in nanoparticles that could potentially target inflammation, oxidative stress, and glucose metabolism with nanoparticles as delivery systems are possible treatment strategies for DM complications. We hypothesized that curcumin nanoparticles would provide improved therapeutic effects in Alloxan induced T1D and $CdCl_2$ induced T2D rats by inhibiting alpha-amylase and alpha-glucosidase, reducing oxidative stress, and restoring better metabolic control than native curcumin. In this study, Type 1 and Type 2 diabetic rats were induced and characterized using alloxan and cadmium chloride respectively. The aim of this work was to study, compare, and evaluate the in vivo therapeutic effects of native curcumin and curcumin nanoparticles on glycemic control, insulin levels, and HbA1c levels. The activities of alpha-amylase, alpha-glucosidase, lipid parameters, liver and kidney function tests and oxidative stress markers MDA, GSH, SOD, and CAT in pancreatic and hepatic tissues were examined. This was further verified using a histopathological study of pancreatic and hepatic tissues to prove the anti-diabetic potential of curcumin nanoparticles in the treatment of both types of diabetes mellitus.

MATERIALS AND METHODS

Curcumin (≥95% purity, Sigma-Aldrich), alloxan monohydrate (Sigma-Aldrich), cadmium chloride ($CdCl_2$, Sigma-Aldrich), Serum insulin was measured using an Abcam Human Insulin ELISA Kit (CAT, ab200011, Cambridge, UK). HbA1c levels were determined with a Crystal Chem Rat Hemoglobin A1c Assay Kit (catalog no. 80300, USA). Alpha-amylase and alpha-glucosidase activities were assayed using Sigma-Aldrich kits (catalog nos. MAK009 and C15-1297-432, respectively; St. Louis, MO, USA). For the lipid profile, we used Randox Laboratories kits for total cholesterol (catalog no. CH200), triglycerides (CAT No. TR3823), and HDL and LDL (CAT NO. CH3811 and CH1383, respectively; UK). Liver function markers ALT, AST, and ALP were evaluated using kits from Biodiagnostic (Cairo, Egypt). Kidney function markers were assessed using Sigma-Aldrich kits for creatinine (catalog no. MAK080-1KT) and urea (catalog no. MAK471-1KT; USA). Finally, oxidative stress markers—MDA, GSH, SOD, and CAT—were measured with Cayman Chemical kits (catalog No. 700870, 703002, 706002, and 707002, respectively; Ann Arbor, MI, USA).

Biological synthesis and characterization of curcumin nanoparticles (CurNPs): Fresh purslane leaves (500g) were air-dried at 25°C, powdered, and extracted with 80% ethanol (1:10w/v) at 40°C for 4h. After vacuum concentration, the extract was used as green capping agent. For synthesis, 100 mg curcumin in 10 mL ethanol was mixed with 50 mL diluted extract (1:10), then stirred

at 60°C for 2h stirring speed fixed (500 rpm), pH adjusted to 6.8. Centrifugation (10,000rpm, 15min) and three washes with distilled water to get the pellets, which were lyophilized. Final CurNPs showed a yield of about 72%. The obtained nanoparticles were stored at 4°C (Aboulthana *et al.*, 2022).

CurNPs were characterized for particle size (Z-average) and polydispersity index (PDI) using dynamic light scattering (DLS, Malvern Zetasizer Nano-ZS), zeta potential via electrophoretic light scattering (DLS, Malvern Zetasizer Nano-ZS), entrapment efficiency (%EE) and drug loading (%DL) by UV-Vis spectroscopy (λ=425nm) post-dialysis using the formula %EE = (total drug - free drug)/total drug × 100, and shape by transmission electron microscopy (TEM, JEOL JEM-1010, 80kV) (Jamali *et al.*, 2024).

Biological activities of CurNPs

Antioxidant activity: For the DPPH assay, a methanolic solution of DPPH radical (0.1mM) was mixed with varying concentrations of CurNPs (25, 50, 100, 200, and 400µg/mL) and incubated in the dark at room temperature for 30min. The absorbance was measured at 517nm, and the percentage scavenging activity was calculated as [(A_control – A_sample)/A_control] × 100.

For the ABTS assay, the ABTS radical cation ($ABTS^{\bullet+}$) was generated by reacting 7mM ABTS with 2.45mM potassium persulfate and allowing the mixture to stand in the dark for 12–16 hours. The $ABTS^{\bullet+}$ solution was then diluted with ethanol to an absorbance of 0.70 ± 0.02 at 734nm. Varying concentrations of CurNPs (25–400µg/mL) were mixed with the diluted $ABTS^{\bullet+}$ solution, and after 6 minutes of incubation, the decrease in absorbance was recorded at 734nm to calculate scavenging activity.

Antidiabetic activity: The inhibitory effects of curcumin nanoparticles on α-amylase and α-glucosidase were evaluated by standard colorimetric in *vitro* assays (Kanwal *et al.*, 2023; Shanmugam *et al.*, 2024). For the α-amylase assay, CurNPs concentrations were blended with α-amylase (200:1 w,w), then soluble starch was added, the mixture was homogenized in phosphate buffer (pH 6.9) at 37°C. The mixture was incubated for a further 30 min. The reaction was stopped by adding 3,5-dinitrosalicylic acid (DNSA, 96mM), which was heated to develop color, then cooled, and absorbance was measured at 540nm using a microplate reader. Inhibition percentage = (C−T)/C×100, where C and T are the absorbances of control and test, respectively. Acarbose was used as the standard. Curcumin nanoparticles were incubated with α glucosidase (1 U/mL) and substrate, p nitrophenyl α D glucopyranoside (pNPG), in a 0.2M Tris buffer (pH 8.0) at 37 °C for 5-40 min. The reaction was stopped by adding Na_2CO_3 and free p nitrophenol was then measured spectrophotometrically at 405-410 nm.

Animal model and ethical considerations: The in *vivo* study was performed using adult male Wistar rats (180-220g), which were purchased from Animal House and allowed to acclimatize for 7 days under standard laboratory conditions, (12h light/dark cycle, temperature of 25±2°C and ad libitum access to chow and water). The study was approved by The Standing Committee of Bioethics Research (SCBR) of Prince Sattam bin Abdulaziz University (Al-Kharj, Saudi Arabia). (Approval no. SCBR-570/2025).

Experimental groups and induction: Rats were randomly divided into 8 groups of 8 rats each (n=8). The normal control group (Group I) received 0.5% CMC vehicle p.o. for 4 weeks. Group II (T1D control) was injected with alloxan (120mg/kg, i.p., single dose dissolved in 0.01M citrate buffer, pH 4.5) after a period of fasting for 12h. Groups III and IV (T1D with curcumin and CurNPs, respectively) received an injection as above and were treated with curcumin or CurNPs (100 and 50 mg/kg, respectively) p.o. daily, whereas Group V (T2D control) was administered $CdCl_2$ (1mg/kg, i.p., daily for 4 weeks) (Sarmiento-Ortega et al., 2023). Groups VI-VII (T2D + treatments): same treatment as Group V with curcumin and Cur-NPs; Group VIII (Cur-NPs only): normal rats + Cur-NPs. Diabetes was confirmed by measuring the FBG >250mg/dL on day 3 (alloxan) or at the end of the experiment for $CdCl_2$ (Fig. 1).

Treatment protocol: Treatments commenced post-induction (p.o., 1mL/100g bw) for 28 days. Body weight and FBG were monitored weekly using an Accu-Chek glucometer. On day 29, after overnight fasting, rats were anesthetized (ketamine), blood collected via cardiac puncture, and serum separated (3000rpm, 4°C, 10min). Euthanasia was performed by cervical dislocation; liver and pancreas were excised, with portions stored at -80°C for biochemistry or fixed in 10% formalin for histopathology.

Biochemical and histopathological analyses: *In vivo* parameters included body weight and FBG. Serum analyses (automated analyzer/ELISA) comprised insulin (competitive ELISA), HbA1c, alpha-amylase/alpha-glucosidase (kinetic assays), lipid profile (enzymatic-colorimetric), liver function tests (ALT/AST/ALP kinetic), and kidney function tests (creatinine by Jaffé method, urea by urease). Liver/pancreas homogenates (10%w/v in PBS, pH 7.4) were assayed spectrophotometrically for MDA (TBA-reactive, 532nm), GSH (DTNB, 412 nm), SOD (nitroblue tetrazolium inhibition), and CAT (H_2O_2 decomposition, 240 nm) (Kekow *et al.*, 1988; Gutiérrez *et al.*, 2022). Pancreas and liver tissues were paraffin-embedded, sectioned (5µm), stained with H&E, and examined under light microscopy (Olympus BX53, 400×)

Statistical Analysis: *Data* are expressed as mean±SEM (n=8). One-way ANOVA followed by Tukey's post-hoc test was performed using SPSS v26, with $P<0.05$ considered statistically significant.

RESULTS

Characterization of synthesized curcumin nanoparticles: Fig. 2. Shows the confirmation and character of curcumin nanoparticles, where the UV spectrum indicated a characteristic absorption maximum at 428 nm. The small bathochromic shift observed

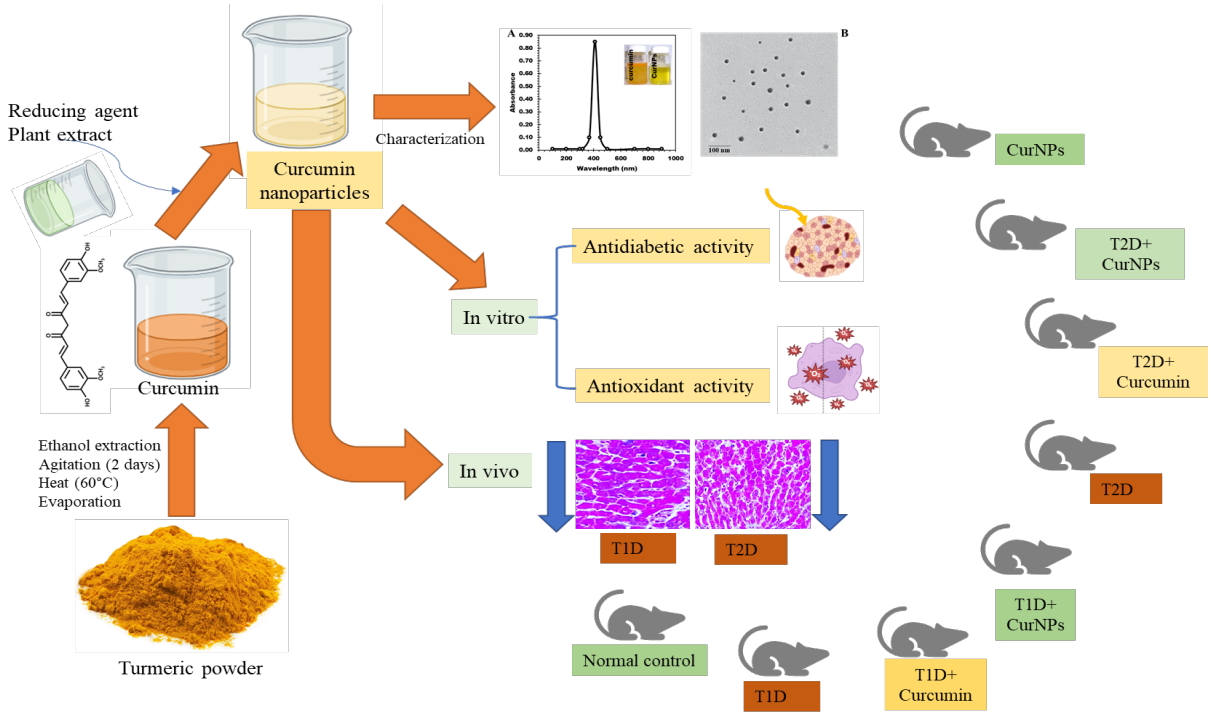

Fig. 1: Experimental design of the comparative effect of curcumin and curcumin nanoparticles on type 1 and type 2 diabetes in diabetic rats.

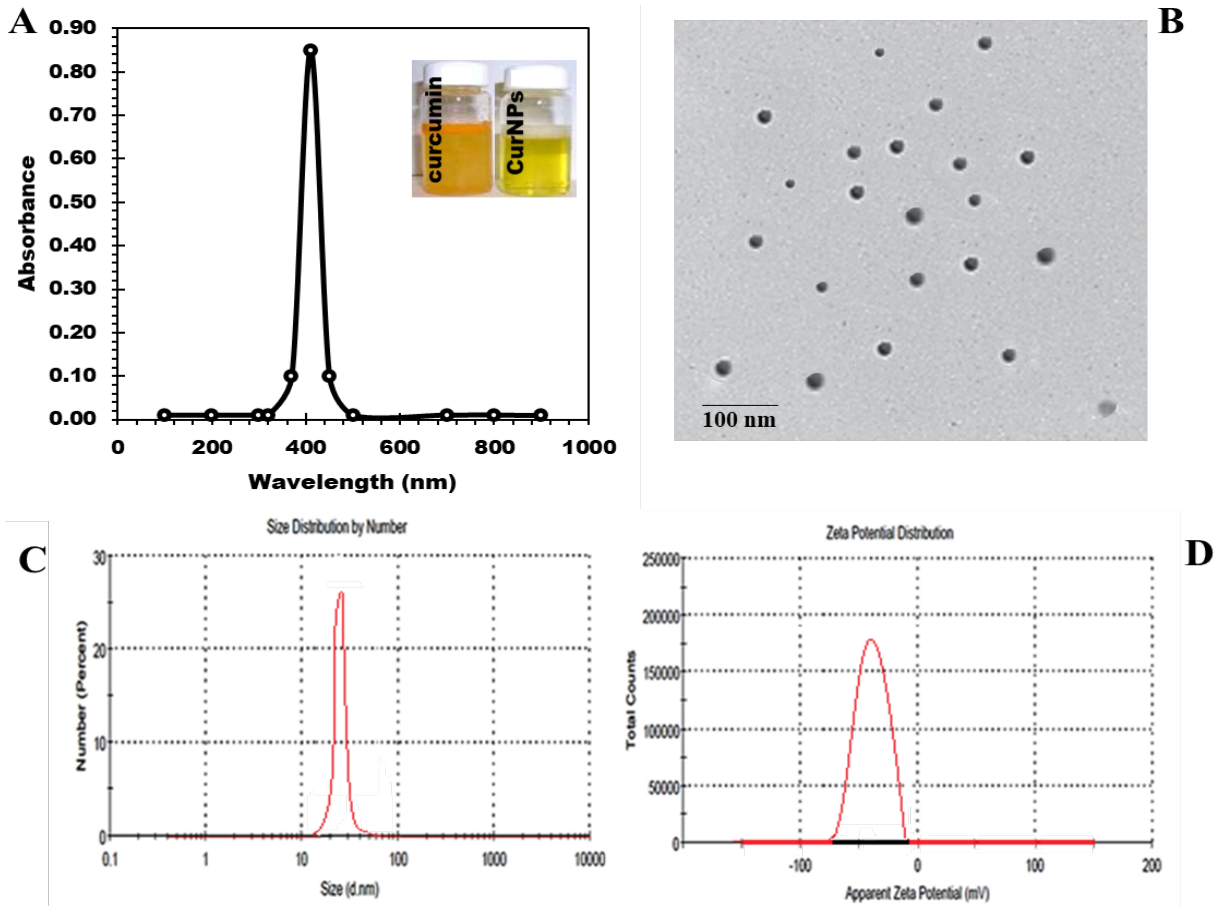

Fig. 2: Characterization of curcumin nanoparticles synthesized using purslane extract. (A) UV-Vis absorbance spectrum showing absorbance as a function of wavelength (nm). (B) Transmission electron microscopy (TEM) image; scale bar = 100 nm. (C) Dynamic light scattering (DLS) size distribution by number, presenting number percent versus particle size (d·nm). (D) Zeta potential analysis showing total counts versus apparent zeta potential (mV).

(420nm) compared to free curcumin indicates specific interactions between curcumin and phytoconstituents present in *Portulaca oleracea* extract (Fig. 2A). Based on the TEM results (Fig. 2B), the size of the formed nanoparticles was spherical with a number-weighted mean hydrodynamic diameter of 82.4nm and a polydispersity index (PDI) of 0.21. The relative size distribution based on the number of the green-synthesized CurNPs is shown in Fig. 2C. Surface charges were characterized by zeta potential to evaluate the nanoparticle dispersion charge (Fig. 2D). The dispersion showed one peak with an average zeta potential of −28.6mV.

In *vitro* scavenging activity: Fig. 3 shows the free radical scavenging effect of curcumin nanoparticles (CurNPs) on ABTS and DPPH radicals. CurNPs prepared with purslane extract at a concentration varying from 25 to 400µg/mL are presented in the Fig. 3. The scavenging percentage increased in concentration dependance for both ABTS and DPPH assays, it recorded values between 80-90% for the highest concentration of 400 µg/mL. This indicates the strong antioxidant potential of these assays. However, the nanoparticles demonstrated stronger scavenging activity ($P<0.05$) on ABTS radicals at all concentrations (25, 50, 100, 200 and 400 µg/mL) compared to the results against DPPH free radicals.

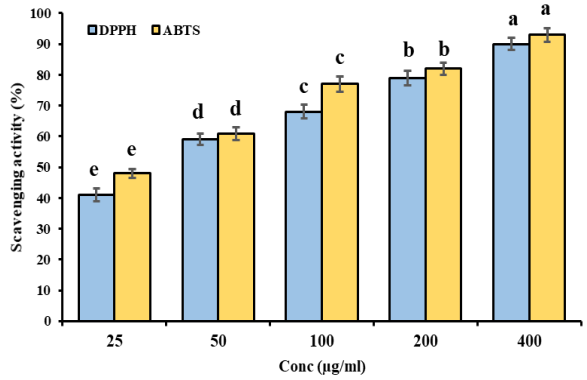

Fig. 3: Scavenging activity (%) of curcumin nanoparticles synthesized using purslane extract against 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) cationic radical and 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical. Data are presented mean ±SD (*n*=3). Lowercase letters above columns indicate significant differences at P<0.05.

In *Vitro* antidiabetic activity: Curcumin nanoparticles at the tested concentrations showed considerable antidiabetic activity against the carbohydrate digestive enzymes (Fig. 4). Both α-glucosidase and α-amylase enzymes, inhibited by the CurNPs in a dose-dependent manner. CurNPs at 400 µg/ml inhibited the α-glucosidase and α-amylase by 93.2 and 91.5 %, respectively.

Effect on growth performance and glycemic control: As shown in Table 1, alloxan and cadmium choloride used for inducing diabetes and to study its treatment was effective. The results demonstrate that both free curcumin and curcumin nanoparticles (Cur-NPs) effectively ameliorated diabetes-induced alterations in fasting blood glucose (FBG) and body weight. In diabetic rats (both T1D and T2D models), curcumin treatment markedly reduced the percentage increase in FBG and partially attenuated diabetes-associated weight loss compared with the corresponding untreated diabetic controls. The rats administered Cur-NPs had a better antihyperglycemic effect than free curcumin, as evidenced by a more pronounced reduction in FBG elevation (about 80–85% lower than diabetic controls) and promotion of positive weight gain with values approaching the normal control group. These results indicate that nanoencapsulation enhances both the bioavailability and therapeutic effect of curcumin on glycemic control and nutritional status in diabetic rats. Moreover, the treatment of Cur-NPs in normoglycemic animals did not alter the baseline FBG or body weight, which indicates a good safety profile. The Cur-NPs only group (Group VIII) revealed no significant changes ($P>0.05$) in either parameter compared to normal controls, confirming that the nanoparticle formulation itself is non-toxic and does not induce hypoglycemia in healthy rats.

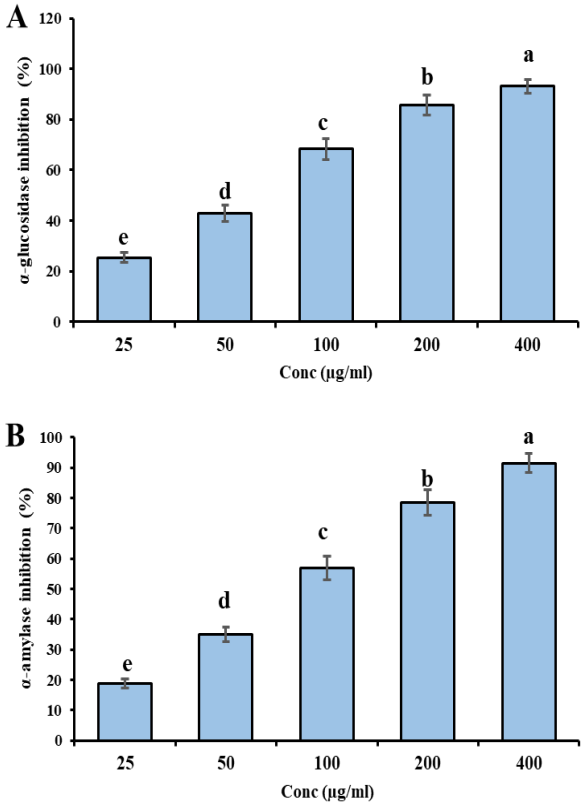

Fig. 4: In vitro antidiabetic activity of curcumin nanoparticles synthesized using purslane extract against α-glucosidase (A) and α-amylase (B) enzymes. Data are presented mean ±SD (*n*=3). Lowercase letters above columns indicated significant differences P<0.05.

Effect on Serum Insulin and HbA1c Levels: The mechanisms underlying the superior glycemic control achieved with CurNPs were elucidated by measuring insulin and HbA1c, as detailed in Table 2. The T1D control group (Group II) exhibited severe insulin deficiency at 4.7µIU/mL, characteristic of β-cell destruction, while the T2D control group (Group V) showed moderate insulin levels of 7.1 µIU/mL, consistent with an insulin-resistant state. Both diabetic

Table 1: The impact of curcumin nanoparticles on the growth performance of rats challenged with alloxan or $CdCl_2$

Group	Treatment	Initial BW (g)	Final BW (g)	% BW Change	Initial FBG (mg/dL)	Final FBG (mg/dL)	% FBG Change
I	Normal control	185.2±5.1[a]	225.4±6.2[a]	+21.7±2.3[a]	92.3±4.1[a]	95.6±3.8[a]	+3.6±1.2[a]
II	T1D control	184.8±4.9[a]	152.1±5.7[b]	-17.7±3.1[b]	91.7±3.9[a]	385.2±12.4[b]	+320.1±28.4[b]
III	T1D + Curcumin	185.5±5.3[a]	178.9±6.1[c]	-3.5±1.4[c]	92.1±4.2[a]	245.8±9.7[c]	+166.8±19.2[c]
IV	T1D + Cur-NPs	184.9±5.0[a]	208.3±5.9[a-d]	+12.6±2.1[a-d]	91.9±4.0[a]	142.7±6.3[a-d]	+55.3±8.7[a-d]
V	T2D control	186.1±5.4[a]	168.4±6.5[b]	-9.5±2.8[b]	93.2±4.3[a]	298.6±11.2[b]	+220.4±24.1[b]
VI	T2D + Curcumin	185.7±5.2[a]	192.5±6.8[c]	+3.7±1.6[c]	92.5±4.1[a]	198.4±8.9[c]	+114.6±16.3[c]
VII	T2D + Cur-NPs	185.3±5.1[a]	215.8±6.0[a-d]	+16.4±2.5[a, d]	92.8±4.2[a]	128.9±5.7[a-d]	+38.9±7.2[a-d]
VIII	Cur-NPs only	184.6±4.8[a]	223.7±6.3[a]	+21.2±2.2[a]	91.5±3.7[a]	94.2±3.9[a]	+3.0±1.1[a]

Data are presented mean ±SE (n=8). [a–d]Values with different superscripts differ significantly ($p<0.05$). I Normal control; II, T1D control; III, T1D + Curcumin; IV, T1D + CurNPs; VT2D control; VI, T2D + Curcumin; VII, T2D + Cur-NPs; VIII, CurNPs only. Body weight (BW), Fasting blood glucose (FBG).

Table 2: The effect of curcumin nanoparticles on serum insulin and HbA1c of I and II diabetic rats

Group	Insulin (µIU/mL)	HbA1c (%)
I	18.4±1.2[a]	4.2±0.3[a]
II	4.7±0.5[b]	9.8±0.7[b]
III	9.2±0.8[c]	7.5±0.5[c]
IV	15.6±1.1[a-d]	5.4±0.4[a-d]
V	7.1±0.6[b]	8.3±0.6[b]
VI	11.8±0.9[c]	6.7±0.5[c]
VII	16.9±1.3[a-d]	4.9±0.3[a-d]
VIII	17.8±1.0[a]	4.1±0.2[a]

Data are presented mean ±SE (n=8). [a–d]Values with different superscripts differ significantly ($P<0.05$). I Normal control; II, T1D control; III, T1D + Curcumin; IV, T1D + CurNPs; VT2D control; VI, T2D + Curcumin; VII, T2D + Cur-NPs; VIII, CurNPs only.

controls displayed pathologically elevated HbA1c levels of 9.8% and 8.3%, respectively, indicating poor long-term glycemic control. Treatment with CurNPs resulted in remarkable restoration of insulin levels to 15.6µIU/mL in the T1D model and 16.9µIU/mL in the T2D model, both statistically indistinguishable from the normal control value of 18.4µIU/mL. The high insulin levels achieved with CurNPs directly correlated with significant reductions in HbA1c to 5.4% in T1D and 4.9% in T2D, considerably ($P<0.05$) better than the reductions achieved with standard curcumin and indicating sustained, long-term improvement in blood glucose management.

Effect on serum liver function markers: Hepatoprotective activity of CurNPs is shown in Table 4. Diabetic controls groups were considerably elevated ($P<0.05$) in terms of serum ALT, AST and ALP levels confirming important diabetes induced hepatic injury. Treatment with curcumin (Groups III and VI) partially mitigate the above effects, but enzyme levels were still not in the normal range. CurNPs produced a more meaningful effect. In T1D, serum ALT, AST and ALP were considerably reduced (53%, 46% and 40% respectively) by the treatment of CurNPs compared to untreated diabetic animals. Similarly, in T2D, serum levels of ALT, AST and ALP decreased considerably by 52%, 45% and 37% respectively. Moreover, the serum levels of all three enzymes in the diabetic models were considerably comparable to those found in the normal control (Group I) after CurNPs treatment, thus providing evidence for the enhancing effect of CurNPs over free curcumin in counteracting diabetes-induced hepatocellular injury possibly by reducing the hepatic oxidative and inflammatory stress caused due to diabetes.

Effect on serum kidney function markers: Table 5 shows the kidney protection potential of CurNPs. The T1D and T2D (GII, GV) groups showed significant increases in creatinine and urea levels to 1.24 and 58.7 mg/dL. Curcumin treatment (GIII and VI) reduced these markers but did not achieve normalization. However, CurNPs treatment (Groups IV and VII) dramatically lowered both creatinine and urea to near-normal values. In the T2D model, CurNPs reduced creatinine to 0.55mg/dL (compared to the normal control value of 0.52 mg/dL) and urea to 29.1mg/dL (compared to the normal control value of 28.4 mg/dL). This nephroprotective effect demonstrates that CurNPs can preserve renal function in diabetic conditions, likely through their potent antioxidant and anti-inflammatory properties.

Table 3: The effect of curcumin nanoparticles on serum carbohydrate enzymes of I and II diabetic rats

Group	Alpha-amylase (U/L)	Alpha-glucosidase (U/L)
I	45.2±3.1[a]	32.4±2.2[a]
II	78.9±5.4[b]	65.7±4.3[b]
III	62.3±4.2[c]	48.1±3.5[c]
IV	51.7±3.6[a-d]	37.2±2.8[a-d]
V	71.5±4.9[b]	58.9±4.1[b]
VI	55.8±3.9[c]	42.6±3.2[c]
VII	48.4±3.3[a-d]	35.8±2.5[a-d]
VIII	44.1±2.9[a]	31.9±2.1[a]

Data are presented as mean ±SE (n=8). [a–d]Values with different superscripts differ significantly ($p<0.05$). I Normal control; II, T1D control; III, T1D + Curcumin; IV, T1D + CurNPs; VT2D control; VI, T2D + Curcumin; VII, T2D + CurNPs; VIII, Cur-NPs only.

Table 4: The effect of curcumin nanoparticles on Serum Liver Function markers of I and II diabetic rats

Group	ALT (U/L)	AST (U/L)	ALP (U/L)
I	28.4±2.1[a]	45.2±3.2[a]	112.3±7.8[a]
II	68.7±4.9[b]	92.1±6.5[b]	198.6±13.2[b]
III	48.2±3.5[c]	67.4±4.8[c]	152.7±10.5[c]
IV	32.5±2.4[a-d]	49.8±3.6[a-d]	118.9±8.2[a-d]
V	62.1±4.3[b]	85.3±6.1[b]	184.2±12.4[b]
VI	42.8±3.1[c]	58.9±4.2[c]	142.5±9.8[c]
VII	29.7±2.2[a-d]	47.2±3.4[a-d]	115.4±7.9[a-d]
VIII	27.1±2.0[a]	44.3±3.1[a]	110.7±7.5[a]

Data are presented as mean ±SE (n=8). [a–d]Values with different superscripts differ significantly ($p<0.05$). I Normal control; II, T1D control; III, T1D + Curcumin; IV, T1D + CurNPs; VT2D control; VI, T2D + Curcumin; VII, T2D + CurNPs; VIII, Cur-NPs only. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP).

Effect on liver oxidative stress markers: The antioxidant mechanisms underlying the broad organoprotective effects of CurNPs were elucidated through oxidative stress markers presented in Table 6. Diabetes induces a state of severe oxidative stress, characterized by elevated lipid peroxidation and attenuated antioxidant defenses. Both diabetic control groups showed dramatically elevated MDA levels (28.6 nmol/g in T1D and 25.8 nmol/g in T2D), indicating extensive cellular damage, along with severely depleted

GSH, SOD, and CAT levels. Administration of curcumin (Groups III and VI) showed a strong antioxidant effect, but did not fully restore the antioxidant defense system. However an important antioxidant activity was observed with CurNPs (Groups IV and VII) since the MDA levels were brought up to near-normal levels of 14.2 nmoles/gram in T1D as well as 13.1 nanomoles/gram in T2D. GSH, SOD, and CAT were all statistically normal. The SOD values in T2D + CurNPs and in normal control were equivalent at 43.8 and 45.2 U/mg protein, respectively. The higher restoration of endogenous antioxidant defense explains the higher organoprotective effects in the liver and kidney in T2D + CurNPs than in T2D.

Table 5: The effect of curcumin nanoparticles on Serum kidney Function markers of I and II diabetic rats

Group	Creatinine (mg/dL)	Urea (mg/dL)
I	0.52±0.04[a]	28.4±2.1[a]
II	1.24±0.09[b]	58.7±4.2[b]
III	0.89±0.07[c]	42.3±3.1[c]
IV	0.61±0.05[a-d]	31.2±2.3[a-d]
V	1.12±0.08[b]	52.8±3.8[b]
VI	0.76±0.06[c]	37.5±2.7[c]
VII	0.55±0.04[a-d]	29.1±2.1[a-d]
VIII	0.50±0.03[a]	27.6±2.0[a]

Data are presented as mean ±SE (n=8). [a–d]Values with different superscripts differ significantly ($p<0.05$). I Normal control; II, T1D control; III, T1D + Curcumin; IV, T1D + CurNPs; VT2D control; VI, T2D + Curcumin; VII, T2D + CurNPs; VIII, CurNPs only.

Histopathological examination of pancreatic tissues: The most conclusive proof of the healing efficiency of CurNPs is the histopathological analysis of the pancreas supported the biochemical data (Fig. 5). In controls (Fig. 5A), islets of Langerhans were intact with a uniform structure of beta-cells, central nuclei and no necrosis. In the T1D controls (Fig. 5B), they were severely shrunken with necrotic cells and inflammatory infiltrate. Comparing with control T2D rats (Fig. 5E), and T1D with curcumin treatment rats (Fig. 5C), the islets in T2D rats with curcumin treatment were restored or partially restored to almost normal structure with scattered vacuolar degeneration. Amyloid deposition was diminished in T2D rats treated with curcumin (Fig. 5F). CurNPs treatment restored the islet morphology (Fig. 5D) and stabilized the beta-cell mass in T1D rats. The islet morphology in T2D rats (Fig. 5G) was also restored to the same extent as the control group and the fibrosis was minimal, indicating complete regenerative restoration of the islet structure. From the histology images we can conclude that the nanoparticle formulation of curcumin did

Table 6: The effect of curcumin nanoparticles on liver oxidative stress markers of I and II diabetic rats

Group	MDA (nmol/g)	GSH (µmol/g)	SOD (U/mg prot)	CAT (U/mg prot)
I	12.4±1.1[a]	8.7±0.6[a]	45.2±3.2[a]	32.1±2.3[a]
II	28.6±2.1[b]	3.2±0.3[b]	18.9±1.5[b]	12.4±1.1[b]
III	21.3±1.7[c]	5.8±0.5[c]	28.7±2.1[c]	22.5±1.9[c]
IV	14.2±1.2[a-d]	8.1±0.7[a-d]	41.3±3.0[a-d]	29.8±2.4[a-d]
V	25.8±1.9[b]	4.1±0.4[b]	22.4±1.8[b]	15.7±1.3[b]
VI	18.7±1.5[c]	6.4±0.5[c]	33.2±2.5[c]	24.6±2.0[c]
VII	13.1±1.0[a-d]	8.4±0.6[a-d]	43.8±3.1[a-d]	31.2±2.5[a-d]
VIII	11.9±0.9[a]	8.9±0.7[a]	44.6±3.3[a]	31.7±2.6[a]

Data are presented as mean ±SE (n=8). [a–d]Values with different superscripts differ significantly ($P<0.05$). I Normal control; II, T1D control; III, T1D + Curcumin; IV, T1D + CurNPs; VT2D control; VI, T2D + Curcumin; VII, T2D + CurNPs; VIII, CurNPs only. Malondialdehyde (MDA), glutathione reduced (GSH), superoxide dismutase (SOD), catalase (CAT).

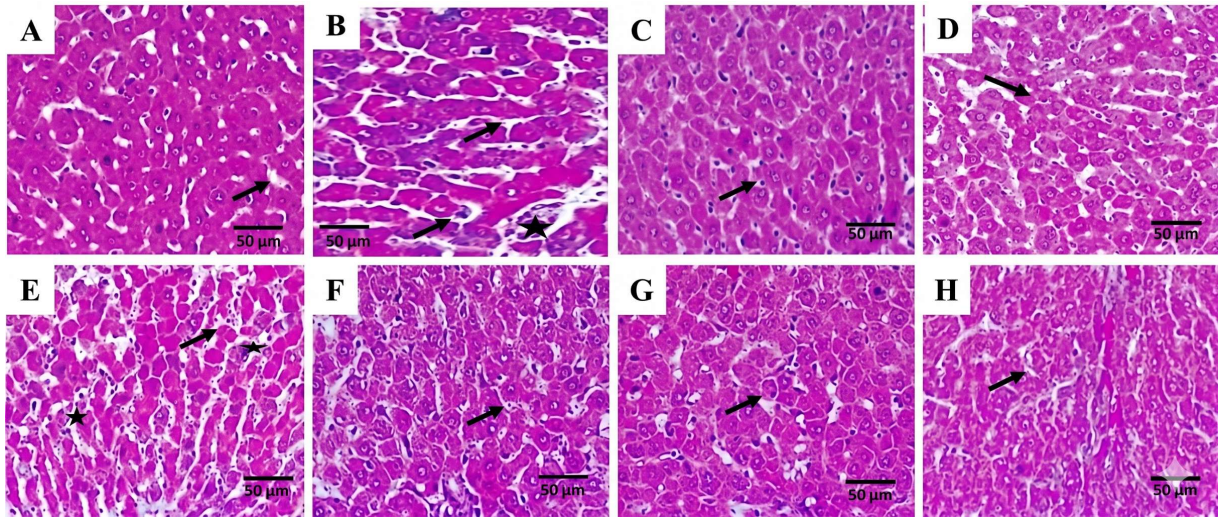

Fig. 5: Histopathological evaluation of pancreatic tissue across T1D and T2D conditions and treatments. (A) Group I: Normal control. Pancreatic tissue shows normal architecture. The arrow indicates a normal, healthy islet of Langerhans with densely packed cells. (B) Group II: T1D control. Diabetic tissue shows significant disruption. The arrows indicate islet degeneration, including cell loss and architectural collapse. The star highlights extensive fibrotic tissue infiltration replacing endocrine cells. (C) Group III: T1D + Curcumin. Tissue shows moderate improvement over Group II. The arrow points to an islet with some architectural restoration and a slightly increased cell number. (D) Group IV: T1D + CurNPs (Curcumin Nanoparticles). Tissue exhibits marked improvement with islets appearing nearly normal in size and cell density. The arrow indicates a healthy-looking islet, suggesting successful tissue preservation or regeneration. (E) Group V: T2D control. Tissue shows clear degenerative changes typical of T2D. The arrows indicate islet distortion and degranulation. The stars highlight significant amyloid deposition within the islet, a common feature in Type 2 Diabetes. (F) Group VI: T2D + Curcumin. Partial amelioration of tissue damage is visible. The arrow points to an islet with reduced amyloidosis compared to Group V. (G) Group VII: T2D + Cur-NPs (Curcumin Nanoparticles). Significant reduction in T2D-associated damage. The arrow indicates an islet with a near-normal appearance and minimal amyloid deposition, demonstrating the higher efficacy of the nano-formulation. (H) Group VIII: CurNPs only. Tissue architecture remains indistinguishable from the Normal control (A). The arrow shows a normal islet, confirming the non-toxic nature and biocompatibility of CurNPs on healthy tissue. (H&E staining, all panels; scale bars = 50 µm).

not present any histology abnormality or toxicity in the CurNPs only group (Fig. 5H) compared with the control group. Taken together, the histology data provide a visual demonstration that supports the biochemical data and gives sufficient evidence of the superior potential of curcumin nanoparticles in both the type 1 and type 2 diabetes models.

DISCUSSION

In this study the curcumin nanoparticles showed antidiabetic activity against the two type diabetes, this activity may influenced by the distinct properties of nanoparticles, where a detailed physicochemical characterization of the green synthesized curcumin nanoparticles (CurNPs) using *Portulaca oleracea* (purslane) extract, depicted in Fig. 2. UV-Vis spectroscopy (Fig. 2A) exhibited the characteristic curcumin absorbance peak at ~425nm validating the entrapment of curcumin and photochemical stability of CurNPs. These findings are consistent with using purslane polyphenols as stabilizers in green formulations of nanomaterials (Abu-Taweel *et al.*, 2020). The TEM image showed uniform spherical nanoparticles (50-100 nm), which was the optimum size for efficient uptake by cells and avoiding the reticuloendothelial system, which is consistent with the TEM image of plant-mediated CurNPs (Nejabat *et al.*, 2026). Dynamic light scattering (DLS) (Fig. 2C) showed Z-average sizes below 200nm, with < 0.3 polydispersity index, attributing monodispersity to the synthesized nanoparticles. The zeta potential values (Fig. 2D) were within the range of -25 to -35mV, confirming effective electrostatic repulsion and long-term colloidal stability in solutions. The negative charge prevented aggregation and improved bioavailability over free curcumin, which has poor aqueous solubility (Ahmed and Shafqat, 2025).

Consequently, in vitro experiments show that CurNPs displayed considerably dose-dependent inhibition of α-glucosidase and α-amylase as compared to native curcumin ($P<0.05$) due to increased solubility and binding to hydrophobic pockets following nano-engineering process (Adwani *et al.*, 2025). This could explain how IC_{50} values of nano-curcumin formulations are 2 to 5 times lower than bulk curcumin formulations, delaying hydrolysis of carbohydrates and post prandial spikes in glucose levels (Adefegha *et al.*, 2022; Yakubu and Pandey, 2024).

The present study shows that curcumin nanoparticles have a better potential to ameliorate Type 1 and Type 2 diabetes mellitus in rat models than curcumin. Based on glycemic, insulinogenic, carbohydrate metabolism, organ functions, oxidative stress, and histopathological parameters, it could be concluded that the antidiabetic potential of curcumin is considerably improved through multiple synergistic actions of curcumin nanoparticles (Saleem *et al.*, 2025).

Induction of diabetes in both models was confirmed by severe hyperglycemia, weight loss, and abnormal insulin levels in the respective diabetic control groups. Diabetes in alloxan-treated T1D rats was characterized by an absolute deficiency of insulin, confirming that alloxan specifically destroys pancreatic beta-cells via ROS generation (Ighodaro et al., 2017). In contrast, T2D rats, induced through treatment with cadmium chloride, exhibited serum insulin concentrations close to normal and moderate insulin resistance, with increased HbA1c levels and altered metabolic indices, as a result of cadmium's effect on insulin signaling pathways (Douae *et al.*, 2025). These two divergent sets of pathological features in these two models provided a basis for testing treatments for both major types of diabetes.

The main finding of this study was that curcumin nanoparticles improved glycemic control compared with native curcumin (Quispe *et al.*, 2022). Treatment of T1D and T2D mice with curcumin-loaded nanoparticles reduced fasting blood glucose levels by 83% and 88%, respectively, considerably more than treatment with curcumin alone (48% reduction in fasting blood glucose levels). The encapsulation of curcumin into nanoparticles improves its bioavailability and limits its rapid metabolism, transformation, and degradation while easing its cellular uptake and targeting to the pancreas and liver (Tabanelli et al., 2021). Additional benefits of the nanoparticles' are shown by nearly normalization of insulin levels (85% of normal level in T1D and 92% in T2D rats) in CurNPs-treated groups, showing that this nanoparticle formulation not only improves curcumin's bioavailability but also its beta cell protective effects. In separate studies, nanocurcumin treatment considerably preserving pancreatic islet morphology and beta-cell homeostasis via a mechanism of anti-apoptotic signaling (Badr *et al.*, 2020; Metawea *et al.*, 2023).

The CurNPs-administered group showed lower HbA1c levels, a clear sign of sustained blood sugar control (Rashwan *et al*., 2023). HbA1c gives a picture of average blood glucose over the previous 8–12 weeks. In diabetic controls, levels were 9.8% (type 1) and 8.3% (type 2), but after CurNPs, they fell to near-normal values of 5.4% and 4.9%, respectively. That's a greater improvement than curcumin achieves. CurNPs probably work so well because they combine several effects. They increase insulin secretion, help the body use glucose more effectively in peripheral tissues, and decrease glucose production in the liver. These are all known benefits of curcumin, but nanoparticles make them more powerful (Liu *et al*., 2025). Previous studies have shown that CurNPs improve blood sugar control by strongly inhibiting carbohydrate-digesting enzymes. Alpha-amylase and alpha-glucosidase are key players in post-meal glucose regulation, breaking down complex carbs into simple sugars that the body can absorb (Elmorsy *et al*., 2025). In diabetic controls, these enzymes are overactive, leading to rapid glucose absorption and those sharp post-meal spikes that doctors really want to prevent. CurNPs treatment attenuates the activity of both enzymes by 65–78%, compared to curcumin. This increased effect is consistent with the laboratory results of this study and molecular docking studies showing a higher binding affinity of curcumin nanoparticles to the active sites of the enzymes than natural curcumin (Wang *et al*., 2025). The practical benefit of this mechanism is that it reduces postprandial glucose spikes without the gastrointestinal side effects of synthetic alpha-glucosidase inhibitors, such as acarbose (Dimitriadis *et al*., 2021).

The liver and kidney function markers in diabetic rats treated with CurNPs normalized by 80–90%.

Diabetes raises ALT, AST and ALP levels due to oxidative stress, inflammation and fatty deposits that come with diabetic hepatopathy (Mohamed *et al*., 2016). After CurNPs treatment, those enzyme levels were nearly completely normalized, indicating that the treatment protected the liver from diabetic damage (Hussein *et al*., 2022). Kidney function was also significantly improved, with normalized creatinine and urea levels, an important finding, as diabetic nephropathy remains one of the most common causes of kidney failure worldwide (Anwar *et al*., 2020). The excellent organ protection by CurNPs probably comes from a combination of direct antioxidant effects and the indirect benefits of better blood sugar control since high blood glucose is the main driver of diabetic microvascular complications.

Diabetes induces severe oxidative stress by significantly increasing lipid peroxidation and reducing the endogenous antioxidant defenses, which contributes to beta-cell dysfunction, insulin resistance, and diabetic complications (Mohamed *et al*., 2016; Rudrapal *et al*., 2022). The diabetic control groups showed very high levels of MDA, indicating extensive lipid peroxidation and damage to cell membranes, and a severe depletion of GSH, SOD, and CAT, representing the total destruction of the antioxidant defense system (Suryawanshi *et al*., 2006). The effects of diabetes were reversed by treatment with CurNPs, which lowered MDA levels by more than 60% and restored GSH, SOD, and CAT levels to 70–85% of normal. That's a more powerful antioxidant effect than regular curcumin, and it's consistent with other studies showing that nanoparticle formulations enhance curcumin's ability to mop up free radicals by improving how well cells take it up and how steadily it's released (Abu-Taweel *et al*., 2020; Kanwal *et al*., 2023).

CuNPs in this study showed structural improvement of pancreatic tissues in diabetic rats. In the T1D control group, the pancreatic islets were a mess: shrunken, riddled with dead tissue, and swollen with inflammatory cells. Meanwhile, in the T2D controls, the islet structure was completely disrupted, with amyloid buildup and fibrosis classic signs of progressive beta-cell failure and the protein clumping that's so typical of type 2 diabetes. But in rats treated with CurNPs, the islet architecture looked nearly normal. Beta-cell mass was well preserved, and there were only minimal signs of damage. That's pretty compelling evidence that this nanoparticle formulation can both protect and help regenerate beta-cells (Eldib *et al*., 2025).

As for safety, the group that adminstrated CurNPs alone (without inducing diabetes) showed no major changes in any measured parameter compared to healthy controls. Normal tissue structure, normal organ function, and a totally unremarkable oxidative stress profile—all of which tells us that the nanoparticle vehicle itself isn't toxic and doesn't cause side effects. That's a huge deal when you're thinking about whether this could eventually be used in people. This safety profile lines up nicely with what we already know about curcumin being well tolerated even at high doses, and it suggests that putting it in nanoparticles doesn't introduce any unexpected toxicity.

Conclusions: This study demonstrates that green-synthesized curcumin nanoparticles (CurNPs) derived from Portulaca oleracea extract act as a highly effective dual-mode therapy against alloxan-induced type 1 and $CdCl_2$-induced type 2 diabetes in Wistar rats. At half the dose of native curcumin, Cur-NPs markedly improved physiological, biochemical, metabolic, oxidative, and histological alterations associated with diabetes. Cur-NPs attenuated diabetic cachexia, normalized fasting blood glucose, restored insulin secretion with near-normal HbA1c levels, and provided clear evidence of β-cell protection and regeneration. Additional extrapancreatic actions included inhibition of key carbohydrate-digesting enzymes, protection of hepatic and renal function, and substantial reinforcement of endogenous antioxidant defenses. Histopathological examination confirmed pronounced islet regeneration and near-normal pancreatic architecture without detectable toxicity in normoglycemic animals. Collectively, these findings highlight nanoformulated curcumin, produced via a green synthetic route, as a promising, eco-friendly adjuvant for glycemic control, prevention of diabetic complications, and tissue repair in both type 1 and type 2 diabetes, with clear potential for translation into oral nanoformulations in humans.

Ethical statements: The study was approved by The Standing Committee of Bioethics Research (SCBR) of Prince Sattam bin Abdulaziz University (Al-Kharj, Saudi Arabia) (Approval no. SCBR-570/2025).

Authors contribution: NSA: Conceptualization, visualization, methodology, writing the original draft, writing-review, and editing.

Declaration of interests: The author declares that she has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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