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Therapeutic Effects of Curcumin-Loaded Nanoparticles on Glycemic Control and Insulin Regulation in STZ-Induced Diabetic Mice

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Abstract: *Streptozotocin (STZ)-induced diabetes is characterized by profound metabolic derangements, including persistent hyperglycemia, impaired insulin secretion, body weight loss, and alterations in vital organ weights, largely driven by oxidative stress and metabolic dysregulation. Curcumin is known for its potent antioxidant and antidiabetic properties; however, its clinical applicability is limited by poor bioavailability. To address this limitation, curcumin-loaded nanoparticles (CNPs) were formulated using the solvent emulsion evaporation method and characterized by particle size analysis and zeta potential measurements, which confirmed uniform size distribution and colloidal stability. Mice were randomly allocated into four groups: Control, Diabetic (STZ, 45 mg/kg, i.p.), Glibenclamide-treated (5 mg/kg, oral), and CNP-treated (80 mg/kg). Treatments were administered daily for 15 days following diabetes induction. STZ-induced diabetic mice exhibited significantly elevated blood glucose levels, reduced serum insulin concentrations, marked body weight loss, increased liver weight likely associated with lipid accumulation and decreased pancreatic weight indicative of tissue degeneration. CNP administration significantly attenuated hyperglycemia and improved serum insulin levels compared with untreated diabetic mice. In addition, CNPs effectively minimized diabetes-induced body weight loss, reduced the abnormal increase in liver weight, and promoted recovery of pancreatic weight. The therapeutic outcomes observed with CNPs were comparable to those achieved with glibenclamide treatment. Overall, these findings demonstrate that curcumin-loaded nanoparticles exert curative effects on glycemic status, serum insulin levels, and diabetes-associated body and tissue weight alterations, supporting their potential as a promising nanotherapeutic strategy for diabetes management.*

Keywords: Curcumin-loaded nanoparticles, Streptozotocin-induced diabetes, Body and tissue weight changes, Blood glucose and serum insulin levels

I. INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia, impaired insulin secretion or action, enhanced oxidative stress, and progressive cellular injury affecting multiple organs [1]. Streptozotocin (STZ) induced diabetes is a well-established experimental model that selectively damages pancreatic β-cells, thereby reproducing key pathological features of diabetes, including hypoinsulinemia, sustained hyperglycemia, and systemic metabolic dysregulation [2]. Diabetic state is frequently associated with pronounced body weight loss and marked alterations in liver and pancreatic weight indices, which arise from enhanced protein catabolism, increased hepatic gluconeogenesis, and compromised nutrient assimilation [3]. These metabolic derangements promote tissue wasting, organ atrophy, and functional impairment, thereby providing a relevant framework for evaluating therapeutic

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interventions aimed at restoring glycemic control, improving insulin secretion, and preserving body and tissue integrity in diabetes. Body weight loss observed in diabetic conditions is closely linked to insulin deficiency, enhanced muscle protein breakdown [4,5]. In parallel, chronic hyperglycemia promotes lipid accumulation and oxidative injury in the liver, leading to hepatomegaly [6], while pancreatic tissue undergoes degeneration and loss of mass due to β-cell destruction. Together, these changes serve as reliable indicators of disease severity and therapeutic response in experimental diabetes models.

Curcumin, a bioactive polyphenol derived from *Curcuma longa*, has attracted considerable attention due to its potent antidiabetic, antioxidant, and anti-inflammatory properties [7]. Numerous studies have demonstrated its ability to improve glycemic control, enhance insulin sensitivity, and protect tissues against oxidative damage. However, the clinical and experimental utility of curcumin is substantially limited by poor aqueous solubility, rapid metabolism, and low systemic bioavailability [8]. To overcome these limitations, nanotechnology-based delivery systems have been developed to enhance curcumin stability and therapeutic performance.

Curcumin-loaded nanoparticles (CNPs) provide several pharmacological advantages, including improved absorption, sustained release, enhanced cellular uptake, and targeted tissue distribution. These features collectively result in superior modulation of metabolic pathways involved in glucose homeostasis and tissue protection [9]. Mechanistically, curcumin has been shown to activate the PI3K/Aktsignaling pathway, a critical regulator of insulin signaling, glucose metabolism, and cell survival, thereby supporting the maintenance of organ integrity under diabetic stress [10]. Nano-scale formulation further amplifies these effects by preventing premature degradation and enhancing intracellular delivery, leading to more sustained biological activity.

Given the central role of hyperglycemia and insulin deficiency in driving body weight loss, organ weight alterations, and tissue degeneration in diabetes, simultaneous evaluation of glycemic status, serum insulin levels, and anthropometric indices is essential for a comprehensive assessment of therapeutic efficacy. Therefore, the present study was designed to evaluate the protective effects of curcumin-loaded nanoparticles on blood glucose levels, serum insulin concentrations, body weight, and tissue weights (liver and pancreas) in STZ-induced diabetic mice. This integrated approach aims to elucidate the potential of CNPs in mitigating diabetes-associated metabolic deterioration, cachexia, and organ dysfunction, thereby supporting their development as a promising nanotherapeutic strategy for diabetes management.

II. METHODS AND MATERIALS

2.1 Material

Curcumin and Poly(lactic-co-glycolic acid) (PLGA) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Streptozotocin (STZ) was obtained from SRL (Sisco Research Laboratories Pvt. Ltd., Mumbai, India). Polyvinyl alcohol (PVA) was bought from HiMedia Laboratories Pvt. Ltd. (Mumbai, India).

2.2 Experimental Animal

Male albino mice (*Mus musculus*), aged three months and weighing between 40 and 50 g, were used in the study. Mice were housed in the departmental facility (Reg. No. 1825/PO/EReBi/S/15/CCSEA) under standard conditions (12 h light/dark cycle, 26 ± 2 °C) with free access to a standard diet (Nutrinix STD-1020, Nutrivet Life Sciences, Pune) and water *ad libitum*. All procedures were approved by the Institutional Animal Ethics Committee (IAEC) and followed CCSEA guidelines, Government of India.

2.3 Experimental Design

2.3.1 Diabetes induction.

Diabetes was induced in mice by intraperitoneal injection of freshly prepared STZ (40 mg/kg b.w.) in 0.15 M citrate buffer (pH 4.5) once daily for 4–5 days [11]. Blood glucose was measured using an Accu-Chek Active glucometer

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(Roche Diagnostics, Germany), and diabetes was confirmed 72 hours post-injection when blood glucose levels exceeded 250 mg/dL.

2.3.2 Animal Groups

A total of 24 male albino mice were randomly divided into four groups (n = 6 each): Control, receiving 0.15 M citrate buffer (pH 4.5, i.p.); Diabetic, induced with STZ (40 mg/kg b.w., i.p.); Glibenclamide-treated, diabetic mice given glibenclamide (5 mg/kg b.w., oral) [12] for 15 days; and Cur-PLGA-NPs-treated, diabetic mice administered Cur-PLGA-NPs (80 mg/kg b.w.) for 15 days. The 80 mg/kg b.w. Cur-NPs dose was selected based on prior optimization studies testing 20,40,60,80,100,120,140 mg/kg b.w. doses to determine the most effective and safe concentration.

2.3.3 Synthesis and Characterization of Curcumin-Loaded PLGA Nanoparticles (CNP)

CNP were prepared using the solvent emulsion evaporation method [13]. Curcumin (20 mg) and PLGA (200 mg) were dissolved in 2 mL ethyl acetate (organic phase) and emulsified dropwise into 4 mL of 1% PVA under vortexing, followed by probe sonication on ice to form a fine O/W emulsion. The emulsion was added to 100 mL of 0.5% PVA and stirred for 12–18 h for solvent evaporation. The suspension was filtered, centrifuged (15,000-20,000 g, 20 min, 4 °C), washed three times with distilled water, and lyophilized for storage. The CNP were characterized using dynamic light scattering (Nano ZS 90 ZEN 3696, Malvern) for particle size distribution and polydispersity index (PDI), zeta potential and electrophoretic mobility to assess surface charge and colloidal stability.

2.3.4 Assessment of Blood Glucose, Serum Insulin, Body Weight, and Tissue Weights

At the end of the experimental period, mice were fasted overnight, and fasting blood glucose levels were measured using a glucometer. Body weight of each animal was recorded prior to sacrifice to evaluate treatment-induced changes. Animals were then euthanized and organs, including the liver and pancreas, were carefully excised, and weighed immediately using a precision analytical balance.

For biochemical analysis, blood samples were collected by cardiac puncture, allowed to clot at room temperature, and centrifuged at 3000 rpm for 10 minutes to obtain serum. Serum insulin levels were measured using a commercially available murine ELISA kit according to the manufacturer's protocol. Absorbance was read with a microplate reader, and insulin concentrations were determined using a standard calibration curve.

III. RESULT AND DISCUSSION

3.1 Synthesis and Characterization of Curcumin-Loaded Nanoparticles (CNPs)

The nanoparticle formulation is crucial to this therapeutic outcome. Curcumin-loaded PLGA nanoparticles were successfully synthesized using the solvent emulsion-evaporation method, yielding a stable and uniformly dispersed nanocarrier system. Scanning electron microscopy (SEM) analysis revealed that the CNPs possessed a predominantly spherical morphology with smooth surface characteristics and minimal aggregation, further confirming successful nanoparticle formation (Fig.1A). The particle size distribution graph generated from SEM micrographs revealed that the curcumin-loaded nanoparticles were predominantly within the 120–140 nm (Fig.1B) range. X-ray diffraction (XRD) patterns of CNP (Fig1C) exhibited diffused peaks, indicating reduced crystallinity and successful encapsulation of curcumin within the PLGA matrix. The FTIR spectrum of curcumin-loaded nanoparticles (Fig.1D) shows a broad band at ~3324 cm^{-1} (O–H stretching of phenolic groups), a prominent peak at ~1636 cm^{-1} (C=O and conjugated C=C stretching of curcumin), and characteristic aromatic bands at ~976–866 cm^{-1}. Particle size analysis showed that CNPs possessed an average hydrodynamic diameter of approximately 137nm (Fig.1E) indicating efficient nanoscale formulation suitable for enhanced cellular uptake and systemic circulation [14]. The smallest particle size observed in this study enhances the potential therapeutic efficiency of CNPs, as nanoparticles below 100 nm are reported to exhibit improved tissue penetration, higher systemic circulation time, and enhanced cellular internalization through endocytosis mechanisms [15]. The preservation of these peaks indicates successful encapsulation of curcumin without

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chemical degradation. Curcumin shows very low solubility in water, whereas curcumin nanoparticles (CNP) exhibit significantly improved aqueous solubility due to their reduced particle size and enhanced dispersion. The polydispersity index (PDI) 0.165, reflected narrow size distribution, confirming uniform nanoparticle dispersion. Zeta potential evaluation demonstrated a surface charge of −26.1mV (Fig.1F), signifying strong colloidal stability and reduced risk of particle agglomeration due to sufficient electrostatic repulsion. The negative charge additionally reflects successful PLGA encapsulation and PVA stabilization, both of which contribute to improved shelf-life and controlled drug release behaviour [16]. Over time, curcumin nanoparticles remained stable, showing no aggregation or loss of solubility, indicating good formulation stability.

Nanoparticles with surface charge values more negative are known to resist aggregation due to electrostatic repulsion, improving shelf-life and biological compatibility [17]. The negative charge also prevents rapid opsonization and clearance by the mononuclear phagocyte system, supporting prolonged systemic circulation and enhanced therapeutic outcomes [18,19]. The low PDI value falls within the acceptable range (<0.30) for monodisperse nanoparticle systems, ensuring reproducibility and predictable biological behaviour [20]. Such uniformity is crucial for consistent drug release kinetics and biodistribution. The nanoscale diameter enhances curcuminbiodistribution and absorption by overcoming its intrinsic limitations such as poor solubility and rapid metabolic breakdown. Collectively, the small particle size, optimal PDI, and negatively charged zeta potential confirm that the formulated CNPs possess ideal physicochemical characteristics for therapeutic application.

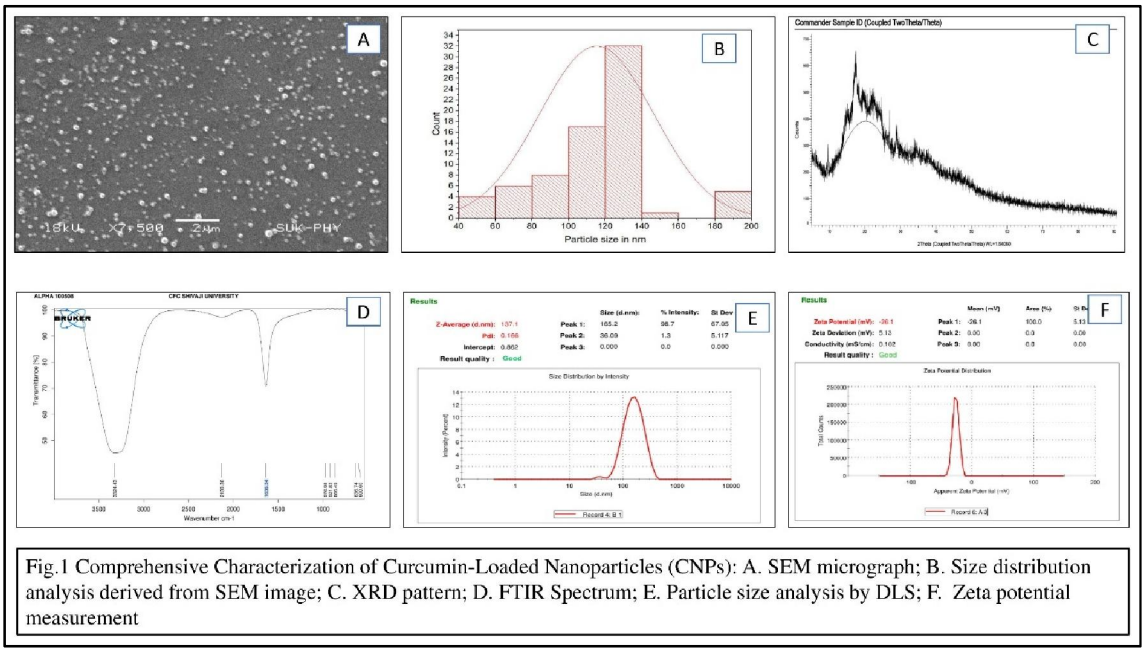

Fig.1 Comprehensive Characterization of Curcumin-Loaded Nanoparticles (CNPs): A. SEM micrograph; B. Size distribution analysis derived from SEM image; C. XRD pattern; D. FTIR Spectrum; E. Particle size analysis by DLS; F. Zeta potential measurement

3.2 Effect of CNP on body weight alterations:

The mean body weight of control mice was 40.13 ± 2.15 g, whereas a significant decline was observed in STZ-induced diabetic mice (29.54 ± 3.43 g, $P < 0.001$), confirming diabetes-associated weight loss. Glibenclamide-treated mice showed significant increase in body weight (33.87 ± 3.15 g, $P < 0.01$ vs. diabetic), while curcumin-loaded nanoparticles (CNP) demonstrated a marked improvement (38.67 ± 2.68 g, $P > 0.05$) with nonsignificant difference when compared with control group (Fig.2A). CNP-treated animals displayed near-normal weight recovery, indicating better systemic metabolic restoration compared to conventional drug treatment.This protective effect is consistent with earlier reports that nano-formulations of curcumin (Cur-NPs) can prevent metabolic deterioration associated with diabetes and support maintenance of body weight [21]. The weight recovery seen in CNP-treated mice suggests that CNP does not just

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prevent further weight loss, but actively promotes recovery toward normal body mass. Importantly, previous work has shown that conventional curcumin (non-nano) often has limited efficacy due to poor bioavailability and rapid metabolism, which undermines its therapeutic potential [22].

3.3 Evaluation of Hepatic and Pancreatic Weight Variations

The mean liver weight in control mice was 2.47 ± 0.144g, whereas diabetic mice showed a marked increase to 2.79 ± 0.106g ($P < 0.01$ vs. control), indicative of diabetes-associated enlargement of hepatic tissue. Glibenclamide treatment resulted in partial recovery (2.61 ± 0.129g, $P < 0.05$ vs. diabetic), while CNP administration produced a more pronounced effect (2.52 ± 0.124g, $P > 0.05$ vs. control), with values comparable to those of the control group. Relative pancreatic weight in control mice was 0.288 ± 0.087g. STZ-induced diabetes caused a significant decline to 0.203 ± 0.098g ($P < 0.001$ vs. control). Glibenclamide treatment improved pancreatic weight to 0.263 ± 0.084g ($P < 0.01$ vs. diabetic), while CNP-treated mice showed further restoration (0.249 ± 0.065g, $P < 0.001$ vs. diabetic), approaching control values and indicating enhanced pancreatic weight preservation (Fig.2B).

Induction of diabetes resulted in a noticeable alteration in organ mass. Interestingly, liver weight showed an increase in the diabetic group relative to the healthy controls, indicating diabetes-associated hepatomegaly. In contrast, pancreatic tissue weight was significantly reduced, reflecting tissue destruction. CNP administration confers strong protective and restorative effects on these tissues. The observed increase in liver weight in diabetic mice is indicative of hepatic hypertrophy commonly associated with metabolic burden, hepatic lipid accumulation, and inflammatory insult under chronic hyperglycemia [23]. CNP treatment effectively normalized liver weight, suggesting mitigation of hepatic stress, reduction in accumulated lipids, and stabilization of hepatocyte architecture. Restoration toward normal mass reflects recovery of metabolic homeostasis and resolution of diabetes-driven hepatocellular enlargement.Contrary to hepatic response, pancreatic tissue demonstrated marked atrophy in diabetic mice that might be due to distruction of both endo and exocrine part of pancreas. CNP administration resulted in significant improvement in pancreatic weight, highlighting its ability to protect and support tissue regeneration. Collectively, normalization of liver hypertrophy alongside recovery of pancreatic mass clearly demonstrates the dual protective role of CNPs in diabetes. Liver weight adjustment signifies correction of metabolic overload and oxidative imbalance, while pancreatic restoration affirms cytoprotection of insulin-producing cells. These outcomes strongly support the therapeutic promise of CNPs in reversing pathological organ remodelling associated with diabetic progression.

3.4 Effect of CNP on blood glucose and serum insulin levels

In the control group, blood glucose levels were 98 ± 5.08 mg/dL. STZ-induced diabetic mice showed a significant elevation in blood glucose (286 ± 7.70 mg/dL; $P < 0.001$ vs. control), confirming successful induction of hyperglycemia. Treatment with glibenclamide significantly reduced blood glucose levels to 162 ± 8.53 mg/dL compared with the diabetic group ($P < 0.001$). Administration of CNPs also significantly lowered blood glucose to 149 ± 6.80 mg/dL relative to untreated diabetic mice ($P < 0.001$). (Fig.2C)

STZ-induced diabetic mice showed a pronounced decline in serum insulin levels (94.34 ± 4.8020) compared with the control group (193.54 ± 5.8557; $P < 0.001$), indicating severe β-cell impairment. Treatment with glibenclamide significantly elevated serum insulin levels (145.762 ± 5.3380) relative to the diabetic group ($P < 0.001$). Similarly, curcumin-loaded nanoparticle (CNP) treatment resulted in a significant increase in serum insulin levels (158.303 ± 4.5830) compared with untreated diabetic mice ($P < 0.001$). However, insulin levels in the CNP-treated group remained significantly lower than those of the control group ($P < 0.01$). (Fig.2D)

Previous investigations by Potphode*et al*. (2018) demonstrated the antidiabetic potential of nanocurcumin, reporting a significant reduction in blood glucose levels at a relatively high dose of 150 mg/kg b. w. [24]. In contrast, the present study achieved a comparable and pronounced hypoglycemic effect at a substantially lower effective dose of 80 mg/kg body weight, as determined through a systematic dose-optimization study. This finding highlights the improved therapeutic efficiency of the formulated CNP, suggesting enhanced bioavailability and glucose-lowering potency at

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reduced dose. Importantly, unlike earlier reports, the current investigation directly compared the efficacy of CNP with glibenclamide, a standard synthetic antidiabetic drug. The comparable glycemic control observed between nanocurcumin and glibenclamide underscores the potential of nanocurcumin as an effective alternative or adjunct to conventional therapy, while possibly minimizing dose-related adverse effects associated with higher drug exposure.

A critical finding of this study is that while CNP treatment significantly increased serum insulin levels, indicating a partial restoration of β-cell function, it also markedly reduced elevated blood glucose levels in STZ-induced diabetic mice. This dual effect demonstrates that CNPs not only support insulin secretion but also improve glycemic control. The improvement in glycemic control and insulin secretion observed with CNP treatment may be attributed to the enhanced bioavailability and cellular uptake of curcumin in nanoparticle form. Curcumin is known to exert protective effects on pancreatic β-cells through its antioxidant, anti-inflammatory, and anti-apoptotic properties, thereby preserving insulin production and secretion [7]. Our findings align with previous studies where nanoformulations of curcumin, administered at different doses, demonstrated significant glucose-lowering effects and increased serum insulin levels in diabetic models [25-29].

Our results corroborate previous work demonstrating that nano-encapsulation of curcumin in carriers like poly (lactic-co-glycolic acid) (PLGA) or chitosan or Poly (lactic acid)-Poly (ethylene glycol) (PLA-PEG) copolymer nanoparticles significantly enhance its pharmacokinetic profile, cellular uptake, and therapeutic efficacy in diabetic models [30,31,32].

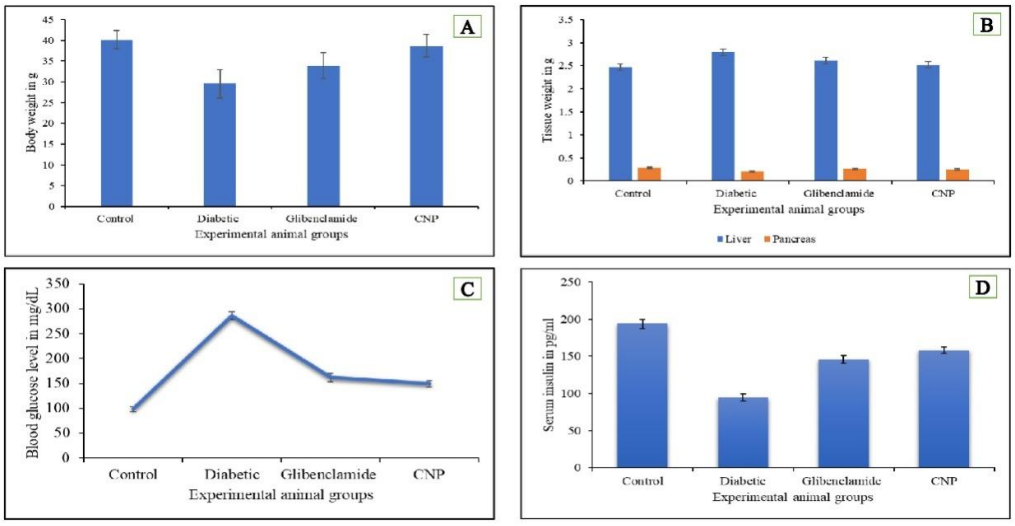

Fig.2 Effect of CNP on A. body weight; B. tissue weight; C. blood glucose levels; D. serum insulin levels

IV. CONCLUSION

Curcumin-loaded nanoparticles effectively mitigated STZ-induced metabolic disturbances, as reflected by improved body weight, normalized hepatic and pancreatic indices, reduced blood glucose levels, and enhanced insulin secretion. Physicochemical characterization confirmed successful synthesis with stable, uniform nanosized particles. The improved bioavailability of the nanoformulation likely underlies its superior metabolic and glycemic regulation, supporting its therapeutic potential in diabetes management.

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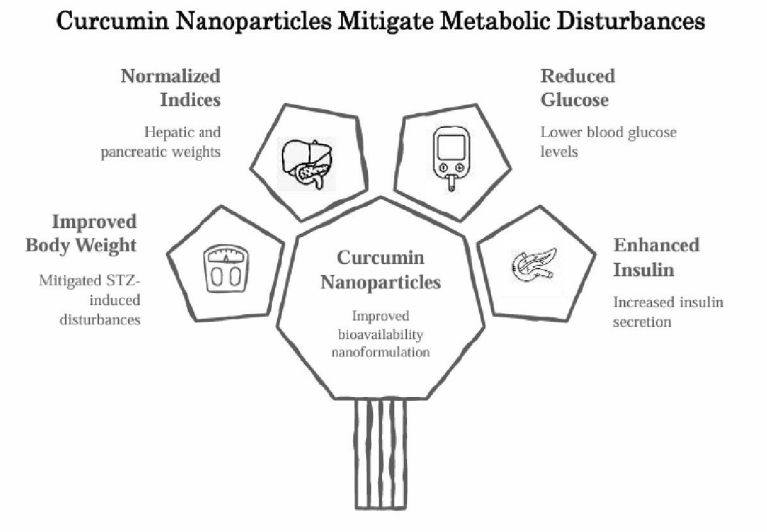

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CONFLICT OF INTEREST: The authors have no conflicts of interest regarding this investigation**.**

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