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Research article

Chia Seed Extract Attenuates Streptozotocin-Induced Pancreatic Beta-Cell Dysfunction in Diabetic Rats: Evidence from Functional and Oxidative Stress Biomarkers

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Abstract: Diabetes mellitus has a global prevalence of more than 422 million cases, with progressive beta-cell dysfunction marked by pancreatic dysplasia. This paper appraised the protective influences of chia seed extract (CSE) on beta-cell dysfunction induced by streptozotocin (STZ) in diabetic rats. In this experiment, Wistar rats (160g) were separated into four groups (normal control, diabetic control, and two CSE-treated diabetic groups (250 and 500 mg/kg body weight)). The separation lasted 8 weeks, during which 32 male rats were used. STZ (40mg/kg) was injected intraperitoneally to induce diabetes. The measured parameters included fasting glucose, HbA1c, serum insulin, HOMA-IR, pancreatic enzymes, and oxidative stress markers. CSE treatment dose-dependently lowered fasting glucose (59% reduction at high dose, $p<0.001$), augmented insulin secretion ($p<0.001$), diminished HOMA-IR (62% reduction, $p<0.001$), and highly inhibited oxidative imbalance in pancreatic tissue. The CSE 500mg/kg concentration suppressed malondialdehyde by 59 percent and replenished glutathione by 105 percent. These results indicate that the chia seed extract has strong antidiabetic and antioxidant effects, suppressing STZ-induced pancreatic beta-cell dysfunction by reducing oxidative stress.

Keywords: Chia seed extract; pancreatic beta-cells; streptozotocin; diabetes mellitus; oxidative stress

1. Introduction

Diabetes mellitus is among the greatest problems of global public health, and the International Diabetes Federation estimates 700 million people will have diabetes by 2045 [1]. The central influence on diabetic pathogenesis is progressive beta-cell damage, which occurs through either autoimmune destruction in type 1 diabetes or through slow deterioration and insulin resistance in type 2 diabetes [2,3]. Streptozotocin (STZ) is a natural antibiotic synthesized by Streptomyces achromogenes and has been utilized in diabetes research for more than 40 years [4]. STZ selectively concentrates in pancreatic beta-cells via GLUT2-mediated uptake, induces cytotoxicity via DNA methylation and DNA fragmentation, and ultimately leads to apoptosis and necrosis [5]. Such specificity makes STZ-induced models useful for studying beta-cell injury mechanisms and potential treatment interventions [6]. Oxidative imbalance, with excessive ROS generation and impaired antioxidative defense, is a high-priority intermediary in STZ-mediated beta-cell dysfunction [7]. Pancreatic beta-cells have the lowest regulation of antioxidant enzymes, making

them highly susceptible to oxidative damage [8]. This weakness indicates the therapeutic benefits of antioxidant-based interventions to protect beta-cells. Chia seeds (Salvia hispanica L.) have an outstanding plant-derived composition with substantial amounts of polyphenolic substances (chlorogenic acid, caffeic acid, kaempferol, quercetin), omega-3 and omega-6 (PUFAs), nutritive fibers, and micronutrients [9-11]. Plant polyphenols have shown attenuating effects against STZ-induced beta-cell damage by suppressing oxidative stress, anti-inflammatory signaling, and apoptosis [12]. Nevertheless, the research on the influences of chia seed extract on beta-cell protection is not thorough. This research was conducted to measure the cytoprotective influence of chia seed extract on STZ-induced injury to pancreatic beta-cells, using glycemic control, insulin activity, pancreatic integrity, and oxidative stress parameters in a diabetic rat group.

2. Materials and Methods

2.1 Preparation of Materials

2.1.1 Chia Seed Extract

Chia seeds (Salvia hispanica L.) were sourced from certified farming vendors and botanically verified. The seeds were subjected to drying at 40 °C

over a period of 24 hours and finely ground. Maceration extraction was carried out via 70% ethanol (1:10 w/v seed-to-solvent ratio) at room temperature, with mixing every 12 hours. To prepare the extract, it was filtered (Whatman Grade 1), evaporated under decreased pressure at 45 °C by rotary evaporation, and finally stored at -20 °C. To administer it, the dried extract was resuspended in distilled water with 0.5% carboxymethyl cellulose (CMC).

2.1.2. Streptozotocin Preparation

Streptozotocin (Sigma-Aldrich, USA) was diluted in a newly formulated 0.1 M citrate buffer (pH 4.5) prior to its treatment. The solutions were kept on ice and consumed within 30 minutes to avoid degradation.

2.2 Experimental Animals

Male Wistar rats (n=36, 160+10 g) were kept in polypropylene cages in a well-controlled conditions (25 +2 C, 55 +5 humidity, 12 light and dark period). Ad libitum provision was made for a standard rodent pellet diet and filtered water. Animals were acclimatized for one week before experimentation. The Institutional Animal Ethics Committee approved all the protocols and complied with regulations for the care and handling of laboratory animals.

2.3 Diabetes Induction and Experimental Design

After acclimatization, STZ (40 mg/kg body weight) in 0.1 M citrate buffer (pH 4.5) was given by a single intraperitoneal injection, causing diabetes. The 40 mg/kg dose was chosen to ensure partial, rather than total, beta-cell destruction, leaving sufficient residual secretory activity to permit assessment of extract-mediated cytoprotection, in line with previous studies that used the same dose range in Wistar rats. The animals were starved the night before injection, whilst being free to drink water. To avoid post-injection episodes of hypoglycemia, 5% glucose solution was administered after the injection over 24 hours. Fasting blood glucose was quantified 72 hours post-STZ administration by tail-vein puncture utilizing a glucometer (Accu-Check Active, Roche Diagnostics). Rats with fasting glucose >250 mg/dL were deemed diabetic. This threshold represents the established criterion for confirming reliable STZ-induced beta-cell injury at partial-destruction doses and is consistent with published protocols. Four rats failed to achieve the diabetic threshold (fasting glucose >250 mg/dL at 72 h post-STZ) and were excluded from all groups and humanely euthanized in accordance with institutional ethics protocols. No re-dosing was performed. Successfully diabetic rats (n=28) plus normal controls (n=8) were apportioned into four groups (n=8/group): G1 (Normal Control) - non-diabetic given vehicle; G2 (Diabetic Control) - diabetic given vehicle; G3 (CSE Low Dose) - diabetic given 250 mg/kg CSE; G4 (CSE High Dose) - diabetic given 500 mg/kg CSE. Animals were treated daily using oral gavage at a dose of 10 mL/kg for 8 weeks. Body weight was recorded weekly for dose adjustment.

2.4 Physiological and Biochemical Measurements

Weekly monitoring was conducted of body mass, food, and water consumption. Blood was collected after 6 hours of fasting via the tail vein and measured weekly as fasting blood glucose. The blood specimens were taken after the experiment by cardiac puncture under the influence of isoflurane anesthesia and cervical dislocation. Serum was centrifuged at 3000×g for 15 min at 4 °C, then maintained at -80 °C until analysis. HPLC was used to measure the glycated hemoglobin (HbA1c) levels. Serum insulin levels were determined using a commercial ELISA kit (Mercodia Rat Insulin ELISA; sensitivity 0.1 mIU/L). Insulin resistance was determined using the HOMA-IR formula: HOMA-IR = [fasting insulin (mIU/L) × fasting glucose (mmol/L)/22.5]. Spectrophotometric measurements of serum amylase and lipase activities were done using diagnostic kits (Randox Laboratories, UK). Pancreatic tissues were thoroughly scraped, mixed in potassium phosphate buffer (0.1 M, pH 7.4; 1:10 w/v), and separated by centrifugation at 10,000xg at 4 o C. The degree of lipid peroxidation was measured as the concentration of malondialdehyde (MDA) utilizing the thiobarbituric acid–based lipid peroxidation assay, with absorbance measured at 532 nm. The levels of reduced glutathione (GSH) were ascertained as per the method of Ellman, in which the absorbance was recorded at 412 nm. The Bradford assay measured the total protein amount to normalize the biochemical readings.

2.5 Statistical Analysis

The findings are displayed as mean ± SE, with eight animals per group (n = 8). Normality of the observations was analyzed using the Shapiro–Wilk test, whereas variance homogeneity was analyzed using the Levene test. The ANOVA (one-way analysis of variance) was employed to evaluate differences among experimental groups, and the post hoc multiple-comparison test was conducted using the Tukey test. A p-value of below 0.05 was taken to be substantial.

3. Results

3.1 General physiological parameters

CSE administration significantly ameliorated diabetic physiological disturbances. Diabetic controls (G2) exhibited severely attenuated weight gain compared to normal controls (G1) (195.0 ± 7.3 vs. 285.0 ± 8.6 g, $p<0.001$). CSE treatment dose-dependently improved body weight, with high-dose achieving 37% improvement (268.0 ± 7.1 g, $p<0.01$ vs. G2). Untreated diabetic rats developed severe hyperglycemia (385.0 ± 12.4 mg/dL at week 8 vs. 92.0 ± 5.1 mg/dL in controls, $p<0.001$). High-dose CSE demonstrated superior efficacy, reducing fasting glucose by 59% to 156.0 ± 8.2 mg/dL ($p<0.001$ vs. G2), while low-dose achieved 43% reduction (218.0 ± 9.8 mg/dL, $p<0.01$). Characteristic diabetic polyphagia and polydipsia were markedly attenuated by CSE treatment in a dose-dependent manner (Table 1). Figure 1 should follow Table 1 directly. The sentence above integrates with the existing paragraph that ends with the water intake data (G4: 28.5 ± 2.1 mL/day, $p < 0.001$ vs. G2).

Table 1. Impact of CSE on general physiological indicators in diabetic rats

Parameter	G1	G2	G3	G4
Final Body Weight (g)	285.0 ± 8.6	195.0 ± 7.3***	238.0 ± 6.8**	268.0 ± 7.1**
Week 8 Fasting Glucose (mg/dL)	92.0 ± 5.1	385.0 ± 12.4***	218.0 ± 9.8**	156.0 ± 8.2***
Food Intake (g/day)	18.3 ± 1.5	32.5 ± 2.1***	25.4 ± 1.9*	21.8 ± 1.6*
Water Intake (mL/day)	22.4 ± 1.8	58.6 ± 3.2***	42.3 ± 2.6*	28.5 ± 2.1***

Data presented as Mean±SEM. Significance vs. Diabetic Control (G2): *p<0.05, **p<0.01, ***p<0.001. G1: Normal Control; G2: Diabetic Control; G3: Diabetic+CSE (250 mg/kg); G4: Diabetic+CSE (500 mg/kg).

3.2. Biochemical parameters and pancreatic function

CSE administration produced significant dose-dependent improvements in glycemic control and markers of pancreatic function. Untreated diabetic rats exhibited severely elevated HbA1c (9.8 ± 0.4% vs. 4.2 ± 0.3%, $p<0.001$) and profoundly depressed serum insulin (2.3 ± 0.4 vs. 8.6 ± 0.5 mIU/L, $p<0.001$). High-dose CSE reduced HbA1c by 40% to 5.9 ± 0.4% ($p<0.001$ vs. G2) and restored insulin to near-normal levels (6.8 ± 0.5 mIU/L, $p<0.001$). The HOMA-IR index confirmed severe insulin resistance in diabetic controls (8.4 ± 0.6 vs. 2.1

± 0.3, p<0.001), which was dose-dependently reversed by CSE treatment, with the high dose achieving a 62% reduction (3.2 ± 0.4, p<0.001). Elevated pancreatic enzymes in diabetic rats (amylase: 156±8.2 U/L; lipase: 142 ± 7.6 U/L) were effectively normalized by high-dose CSE treatment (Table 2). Figure 2 should follow Table 2 directly. The sentence above integrates with the existing paragraph that ends with the serum lipase result (G4: 91 ± 4.9 U/L, p < 0.001 vs. G2).

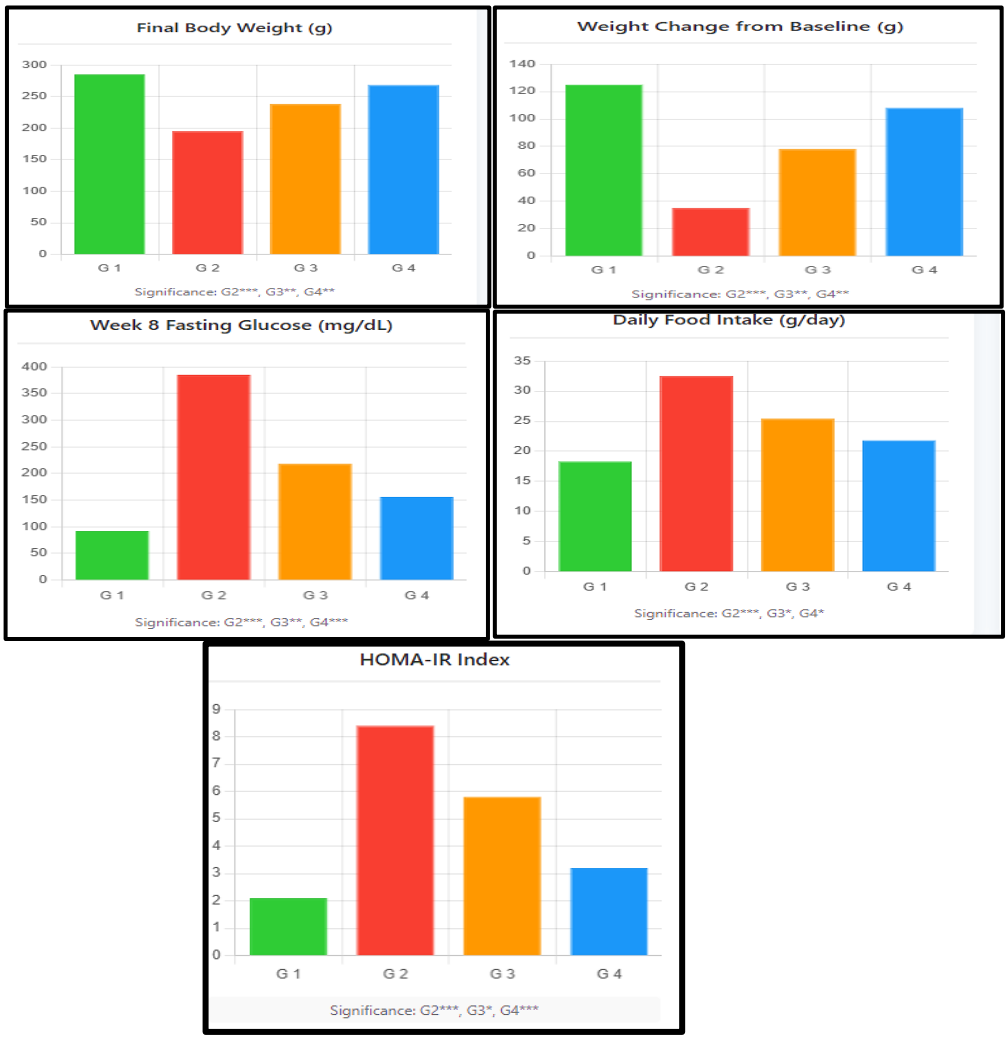


Figure 1. Impact of chia seed extract (CSE) on general physiological indicators in streptozotocin (STZ)-induced diabetic rats over eight weeks of treatment. (A) Final body weight (g) at week 8. (B) Total body weight change from baseline (g). (C) Week 8 fasting blood glucose (mg/dL). (D) Average daily food intake (g/day). (E) Average daily water consumption (mL/day).

Table 2. Effects of CSE on Biochemical Parameters and Pancreatic Function

Parameter	G1	G2	G3	G4
HbA1c (%)	4.2 ± 0.3	9.8 ± 0.4***	7.1 ± 0.5**	5.9 ± 0.4***
Serum Insulin (mIU/L)	8.6 ± 0.5	2.3 ± 0.4***	4.2 ± 0.6*	6.8 ± 0.5***
HOMA-IR Index	2.1 ± 0.3	8.4 ± 0.6***	5.8 ± 0.5*	3.2 ± 0.4***
Serum Amylase (U/L)	98 ± 6.1	156 ± 8.2*	118 ± 7.4*	104 ± 5.8***
Serum Lipase (U/L)	82 ± 5.3	142 ± 7.6*	112 ± 6.8*	91 ± 4.9***

Data displayed as Mean±SEM. Significance vs. G2: *p<0.05, **p<0.01, ***p<0.001.

3.3. Oxidative stress markers in pancreatic tissue

CSE demonstrated remarkable antioxidant effects in pancreatic tissue. Diabetic controls exhibited pronounced oxidative damage, with MDA levels 3-fold higher (6.8 ± 0.4 vs. 2.1 ± 0.2 nmol/mL, $p<0.001$). High-dose CSE reduced MDA by 59% to 2.8 ± 0.2 nmol/mL ($p<0.001$), approaching normal values. Pancreatic GSH was severely depleted in diabetic rats (12.3 ± 1.2 vs. 28.4 ± 1.8 µg/mL, $p<0.001$). High-dose CSE restored GSH by 105% to 25.2 ± 1.6 µg/mL ($p<0.001$), nearly normalizing antioxidant defenses (Table 3).

Table 3. Effects of CSE on oxidative stress markers in pancreatic tissue

Parameter	G1	G2	G3	G4
MDA (nmol/mL)	2.1 ± 0.2	6.8 ± 0.4***	4.9 ± 0.35**	2.8 ± 0.2***
GSH (µg/mL)	28.4 ± 1.8	12.3 ± 1.2***	18.6 ± 1.5**	25.2 ± 1.6***

Data presented as Mean±SEM. MDA: malondialdehyde; GSH: reduced glutathione. Significance vs. G2: *p<0.05, **p<0.01, ***p<0.001.

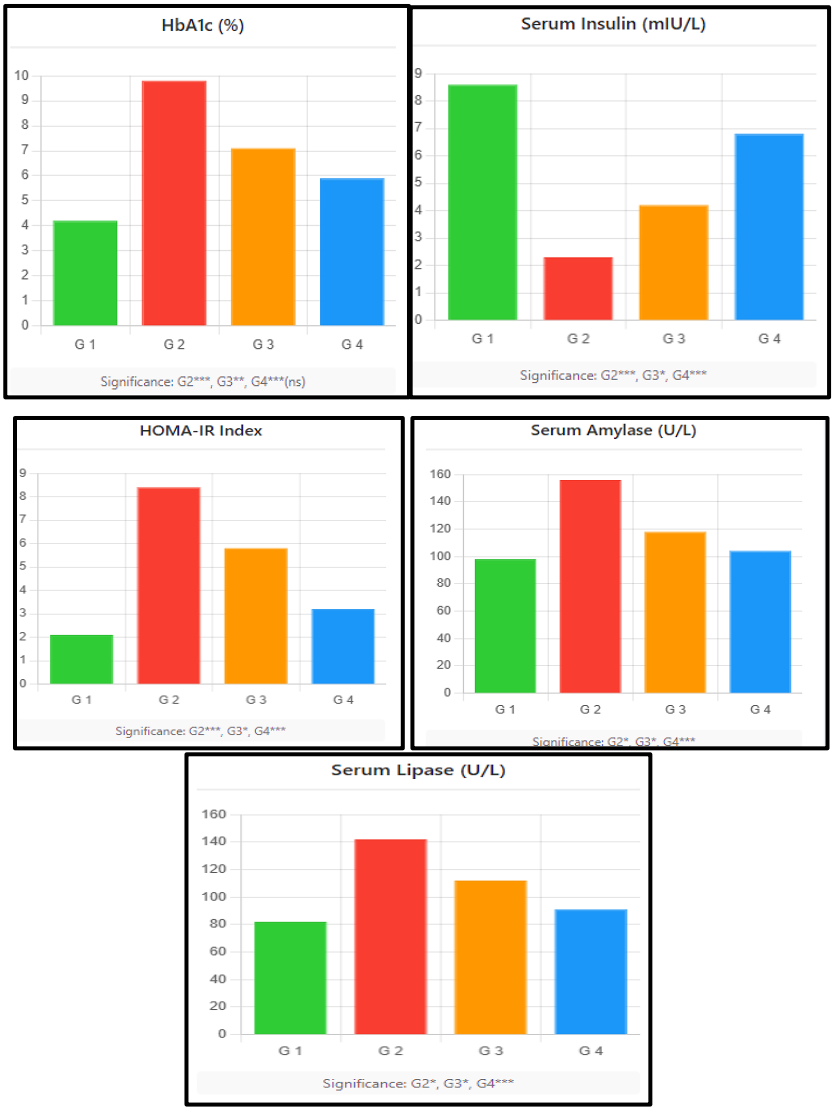


Figure 2. Influences of chia seed extract (CSE) on biochemical indicators of glycaemic control, insulin activity, and pancreatic enzyme activity in streptozotocin (STZ)- triggered diabetic rats after eight weeks of intervention. (A) Glycated haemoglobin (HbA1c, %). (B) Serum insulin level (mIU/L). Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) index (C). (D) Serum amylase level (U/L). (E) Serum lipase level (U/L).

4. Discussion

This research has shown that chia seed extract significantly reduces functional and oxidative stress markers of STZ-induced pancreatic beta-cell dysfunction through dose-dependent mechanisms that include alleviation of oxidative stress and recovery of beta-cell secretory activity. These results can greatly contribute to knowledge of phytochemical-based therapeutic interventions for diabetic pathologies. The CSE produced a strong hypoglycemic effect, reducing fasting glucose by 59% compared with similar experimental studies of polyphenol-containing extracts in these models [15], indicating a particularly strong hypoglycemic effect. The 40% decrease in HbA1c is cumulative glycemic management over 8 weeks and evidence that it is effective beyond acute glycemic control. Such a close approach to normal HbA1c levels (5.9±0.4% vs. 4.2±0.3% in controls) is clinically significant, as it is well known that HbA1c is correlated with diabetic complications in humans [16]. Recovery of serum insulin levels (2.3 to 6.8 mIU/L with high dose CSE) implies either maintenance of residual beta-cell secretory capacity or increased insulin secretion of remaining beta-cells. The polyphenolic compounds can regulate insulin secretion in several ways, such as by regulating calcium channels, activating protein kinase C, and increasing mitochondrial ATP production [17]. The fact that CSE allowed near-normal insulin levels to be maintained despite beta-cell impairment in the initial stages of the disease shows that CSE could either promote the secretory capacity of the remaining beta-cells or inhibit additional cell death.

This extraordinary decrease in HOMA-IR (62% with high-dose CSE) indicates increased systemic insulin sensitivity, possibly through direct actions of CSE polyphenols on peripheral insulin signaling pathways. Chia seeds contain flavonoids, especially quercetin, which stimulates the PI3K signaling and autophosphorylation of insulin receptors [18]. This enhanced peripheral insulin sensitivity would lower compensatory secretory requirements in the remaining beta-cells, thus preserving beta-cell function. Most mechanistically important findings are on pancreatic oxidative stress markers. The threefold increase in MDA in diabetic controls is indicative of intense oxidative injury on pancreatic lipids, which is congruent with the oxidative stress-based beta-cell toxicity of STZ [21]. The 59% MDA reduction at high doses of CSE suggests that it is a very strong inhibitor of oxidative radical production or that it increases scavenger mechanisms. The fact that pancreatic GSH is almost fully restored (105% increased, close to normal levels) requires CSE to have the ability to restore antioxidant defenses, which may be due to direct antioxidant activity or the induction of GSH synthesis via stress-response mechanisms [23]. Those protective properties can be explained by the high phytochemical content of chia, especially polyphenols (chlorogenic acid 2-3% dry weight, caffeic acid, kaempferol, quercetin) [24]. These flavonoids work by direct free radical scavenging, pro-oxidant metal chelation, and the activation of endogenous antioxidant enzymes [25]. The omega-3 fatty acid content could also be highly protective of membranes and anti-inflammatory by blocking the production of eicosanoids [26].

The strong dose-response association (500 mg/kg better than 250mg/kg) shows that the protective effects are concentration-dependent, as antioxidant pharmacology predicts. Nevertheless, such doses are significant compared to the dietary intake of chia, which limits direct clinical extrapolation. Moreover, oral gavage administration is reliable for dosing, although it might not be comparable to dietary bioavailability owing to hepatic first-pass metabolism and intestinal differences in absorption. Mechanistic understanding would be enhanced by future studies on the tissue disposition of CSE polyphenols using pharmacokinetic approaches. The study's limitations include the 8-week treatment duration, adopted due to the importance of a sustained treatment effect and practical limitations. In the long term (12-16 weeks), it may be decided whether the CSE protective effects are maintained or decreased, and whether prolonged treatment can prevent further diabetic complications. Also, histopathological analysis of pancreatic tissue and immunohistochemical evaluation of beta-cell mass would serve as direct structural indicators of beta-cell cytoprotection. A notable limitation of this work is the absence of histopathological (H&E staining) and immunohistochemical (insulin/glucagon immunostaining) examination of the pancreatic tissue. The current data are limited to functional and biochemical measures of beta-cell protection; without such data, it is not possible to prove structural preservation of islet architecture and beta-cell mass. These histopathological endpoints should be included in future research to give extensive evidence of cytoprotection. CSE employed in this research was not characterized by batch-specific using HPLC or GC-MS phytochemical methods, nor was the total

polyphenol content (Folin-Ciocalteu) or overall flavonoid concentration (aluminum chloride colorimetric method) determined. This is a major limitation, as the polyphenol content would vary greatly among extraction batches, seed origins, and solvent conditions. TPC and TFC quantification will become the norm in all subsequent studies using this extract, and HPLC profiling will be used to confirm the presence and relative abundance of chlorogenic acid, caffeic acid, kaempferol, and quercetin.

5. Conclusions

This paper shows that chia seed extract has a significant impact on the functional biomarkers of STZ-induced pancreatic beta-cell dysfunction, alleviating dose-related oxidative stress and reversing beta-cell dysfunction. The high-dose CSE (500 mg/kg) achieved a 59% reduction in fasting glucose, a 40% reduction in HbA1c, a 62% improvement in HOMA-IR, and a 105% improvement in GSH. The results have a scientific basis for the possible application of chia seeds in the suppression and control of diabetes. The attenuation of oxidative stress and the beta-cell protection demonstrated should be the focus of further translational and clinical studies that test the use of CSE supplementation in prediabetic and recently diagnosed diabetic patients. The enhanced clinical potential refers to other oxidative-stress-mediated pancreatic pathologies, such as acute pancreatitis. Future studies ought to examine molecular processes, conduct dose-optimization trials, and determine the long-term effectiveness and safety of its use in humans.

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