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Protective Effects of Citrullus Mucosospermus Fruit Extract Against Streptozotocin-Induced Diabetic Mice Through Regulation of Hyperglycemia and Inflammatory Cytokines

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1. Abstract

Citrullus monospermous has long been used as a functional food and traditionally used medicinal plant; however, its antidiabetic effects remain largely unknown. This study investigated the protective effects of Citrullus monospermous fruit extract (CM) against streptozotocin (STZ)-induced diabetes and investigated the underlying mechanisms associated with glucose homeostasis, tissue protection, and inflammatory regulation. Freeze-dried fruits of C. monospermous were extracted with distilled water, and the extract had been previously characterized by HPLC, revealing cucurbitacin E and cucurbitacin E-2-O-glucoside as its major phytochemicals. Experimental diabetes was induced by intraperitoneal injection of STZ (50 mg/kg). Diabetic mice were orally administered CM (50, 100, or 200 mg/kg/day) or metformin (125 mg/kg/day) for 37 days. Body weight, food and water intake, fasting blood glucose, oral glucose tolerance, serum biochemical parameters, insulin receptor levels, histopathological alterations, and hepatic inflammatory cytokine expression were evaluated. CM slightly improved body weight loss and reduced excessive water intake in diabetic mice. Fasting blood glucose and glucose intolerance were ameliorated in a dose-dependent manner, with the 200 mg/kg group exhibiting effects comparable to those of metformin during the oral glucose tolerance test. CM also reduced serum glucose and lactate dehydrogenase activity while partially improving lipid metabolic parameters. Insulin receptor levels were significantly restored by CM treatment, particularly at 100 and 200 mg/kg. Histopathological analysis revealed that CM markedly attenuated STZ-induced pancreatic, renal, and hepatic damage. Furthermore, CM significantly suppressed the hepatic mRNA expression of IL-6, IL-1β, IL-10, and TNF-α in a dose-dependent manner, indicating potent anti-inflammatory activity. CM exerts protective antidiabetic effects through improving glucose homeostasis, restoring insulin receptor levels, alleviating diabetes-associated tissue injury, and suppressing hepatic inflammatory cytokine expression. These findings suggest that C. Mucosospermus fruit extract may serve as a promising natural therapeutic candidate for the prevention and management of diabetes mellitus.

2. Introduction

Diabetes mellitus (DM) is one of the most prevalent chronic metabolic disorders worldwide and is characterized by persistent hyperglycaemia resulting from impaired insulin secretion, insulin resistance, or both [1-3]. Chronic hyperglycaemia disrupts glucose homeostasis and contributes to the development of severe complications, including cardiovascular disease, diabetic nephropathy, neuropathy, and retinopathy, thereby imposing a substantial global health burden [4-6]. Consequently, there is an increasing demand for safe and effective natural products that can improve glucose metabolism and prevent diabetes-associated complications [7,8].

From the perspective of Traditional Chinese Medicine (TCM), diabetes corresponds to Xiaoke disease (Wasting-Thirst), which is characterized by excessive thirst (Drink plenty of fluids), ex-

cessive hunger (Overeating), frequent urination (Polyuria), fatigue, and progressive depletion of body fluids [7,9]. According to TCM theory, Xiaoke is primarily caused by Yin deficiency (Yin deficiency) accompanied by internal heat (heat), dysfunction of the lung (lung), spleen (spleen), and kidney (kidney) systems, and impairment of Qi (gas) transformation [10]. Therefore, nourishing Yin (Nourish Yin), clearing heat (Clear heat), promoting body fluid production (Promote the production of body fluids), and restoring metabolic balance are considered fundamental therapeutic principles [11]. In recent years, numerous medicinal plants traditionally used in TCM have been scientifically validated for their antioxidant, anti-inflammatory, hypoglycaemic, and insulin-sensitizing activities, providing pharmacological evidence supporting their traditional applications [7]. Plant-derived natural products have attracted increasing attention as complementary therapeutic agents for diabetes because they contain diverse bioactive compounds capable of regulating glucose metabolism through multiple mechanisms [12,13]. Polyphenols, flavonoids, phenolic acids, alkaloids, and terpenoids have been shown to improve insulin sensitivity, inhibit α-glucosidase and α-amylase activities, suppress oxidative stress, reduce inflammatory responses, and protect pancreatic β-cells, thereby contributing to glucose homeostasis [14,15].

Among medicinal plants, members of the Cucurbitaceae family have received considerable attention because they are rich sources of polyphenols, flavonoids, cucurbitacin's, carotenoids, vitamins, dietary fibre, and essential minerals [16,17]. Numerous Cucurbitaceae species exhibit antioxidant, anti-inflammatory, hepato-protective, anti-obesity, and antidiabetic activities [18,19]. Furthermore, several cucurbit species have been reported to suppress carbohydrate-digesting enzymes and improve postprandial glucose metabolism, suggesting their potential as functional foods for metabolic disorders [16]. Citrullus monospermous (Egusi water-melon) is an indigenous African cucurbitaceous crop that has traditionally been consumed as both a food and medicinal resource [20]. The seeds are rich in proteins, unsaturated fatty acids, tocopherols, minerals, dietary fibre, and phenolic compounds, contributing to their high nutritional value [21]. Previous studies have demonstrated that C. monospermous possesses antioxidant, anti-inflammatory, lipid-lowering, and hepato-protective activities, indicating its potential as a functional ingredient for preventing metabolic diseases [18,19].

Our research group has recently provided additional evidence supporting the metabolic benefits of C. monospermous. We demonstrated that its aqueous extract significantly reduced body weight gain, adipose tis-sue accumulation, dyslipidaemia, and obesity-associated inflammation in high-fat diet-induced obese mice, indicating its anti-obesity potential [18]. Subsequently, we reported that the same extract effectively attenuated methionine- and choline-deficient diet-induced non-alcoholic steatohepatitis (NASH) by reducing hepatic lipid accumulation, inflammatory cytokine production, oxidative stress, and liver injury [19]. Since obesity, insulin resistance, non-alcoholic fatty liver disease, and diabetes share common pathological mechanisms in-volving oxidative stress, chronic inflammation, and metabolic dysfunction, these findings strongly suggest that Citrullus species may also possess antidiabetic activity [22].

Oxidative stress and chronic inflammation are recognized as major contributors to the progression of diabetes and its complications [23,24]. Persistent hyperglycaemia stimulates excessive production of reactive oxygen species (ROS), activates NF-κB signalling, and increases the expression of pro-inflammatory cytokines, including tumour necrosis factor-α (TNF-α), interleukin (IL)-1β, and IL-6, ultimately leading to pancreatic β-cell dysfunction and insulin resistance [25]. Therefore, natural products possessing both antioxidant and anti-inflammatory activities are considered promising candidates for diabetes management [26,27].

Streptozotocin (STZ) is a pancreatic β-cell-selective toxin widely used to establish experimental diabetic models [28]. STZ induces DNA alkylation, nitric oxide production, mitochondrial dysfunction, and excessive ROS generation, resulting in β-cell destruction, impaired insulin secretion, and persistent hyperglycemia resembling human diabetes mellitus [29,30]. Consequently, STZ-induced diabetic mice have become one of the most reliable experimental models for evaluating the efficacy and mechanisms of natural products against diabetes [31]. Although increasing evidence supports the beneficial effects of C. monospermous against obesity and non-alcoholic steatohepatitis, its antidiabetic efficacy has not yet been comprehensively investigated. In particular, the effects of its aqueous extract on glycaemic control, serum biochemical parameters, pancreatic and hepatic histopathology, insulin signalling, and inflammatory cytokine regulation in STZ-induced diabetic mice remain largely unknown. Moreover, its therapeutic potential has not been evaluated from the perspective of integrative medicine and Traditional Chinese Medicine [32].

Therefore, the present study aimed to investigate the protective effects of the water extract of Citrullus monospermous in streptozotocin-induced diabetic mice. Fasting blood glucose, oral glucose tolerance, serum biochemical parameters, insulin receptor concentrations, hepatic and pancreatic histopathological changes, and inflammatory cytokine expression were comprehensively analysed to elucidate the antidiabetic mechanisms of CM.

3. Methods and Materials

3.1. Chemicals and Reagents

Streptozotocin (STZ) and metformin hydrochloride were purchased from Sigma-Aldrich (St. Louis, MO, USA). All other chemicals and reagents used in this study were of analytical grade.

3.2. Preparation of Citrullus Mucosospermus Fruit Extract (CM)

Citrullus mucosospermus (Egusi watermelon) fruits used in this study were cultivated at the experimental farm of Pusan National University (Miryang, Republic of Korea). Seeds were sown

in mid-April, and fully mature fruits were harvested and freeze-dried using a freeze-dryer (Ilshin Biobase Co., Dongducheon, Re-public of Korea). The dried fruits were pulverized into a fine powder and passed through a 30-mesh sieve to obtain a uniform particle size.

For extraction, 10 g of the powdered sample was mixed with distilled water at a solid-to-solvent ratio of 1:10 (w/v) and extracted using an ultrasonic extractor (JAC Ultrasonic Co., Seoul, Republic of Korea) for 1 h at room temperature. The extract was filtered through Whatman No. 2 filter paper (GE Healthcare, Maidstone, UK), concentrated under reduced pressure using a rotary evaporator (Heidolph Instruments GmbH, Schwabach, Germany), and subsequently freeze-dried to obtain a powdered extract. The resulting aqueous extract was designated as C. mucospermus extract (CM) and stored at −20 °C until use. Prior to animal administration, CM was freshly dissolved in distilled water to the desired concentrations for oral gavage (Figure 1A).

3.3. Induction of Diabetes

After a one-week acclimation period, diabetes was induced by intraperitoneal injection of streptozotocin (STZ; Sigma-Aldrich, St. Louis, MO, USA) freshly dissolved in 0.1 M citrate buffer (pH 4.5) at a dose of 50 mg/kg body weight for five consecutive days. On the day following the final STZ injection, fasting blood glucose (FBG) levels were measured from tail vein blood using a Care Sens II blood glucose monitoring system (i-SENS, Seoul, Republic of Korea). Mice with FBG levels of ≥250 mg/dL were considered diabetic and included in the subsequent experiments.

3.4. Animals and Experimental Design

All animal procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of Pusan National University (Approval No. PNU-2021-0072) and conducted in accordance with the relevant guidelines for the care and use of laboratory animals.

Seven-week-old male ICR mice were obtained from Samtako BioKorea Inc. (Osan, Republic of Korea). The animals were housed at the Laboratory Animal Resource Center of Pusan National University, which is ac-credited by the Ministry of Food and Drug Safety (Certification No. 000231) and the Association for Assessment and Accreditation of Laboratory Animal Care International (AAALAC International; Accreditation No. 001525).

The mice were maintained under controlled environmental conditions (23 ± 2 °C, 50 ± 10% relative humidity) with a 12-h light/12-h dark cycle (lights on at 08:00 and off at 20:00). Animals had free access to sterilized water and a standard irradiated laboratory diet (Samtako Bio Korea Inc., Osan, Republic of Korea) containing 20% crude protein, 4.5% crude fat, 6.5% crude fiber, 7.5% crude ash, 0.5% calcium, and 1.0% phosphorus.

After confirmation of diabetes, mice with fasting blood glucose levels ≥250 mg/dL were randomly assigned to five groups (n = 8 per group): diabetic control (DC; STZ + distilled water), CM50 (STZ + CM, 50 mg/kg/day), CM100 (STZ + CM, 100 mg/kg/day), CM200 (STZ + CM, 200 mg/kg/day), and metformin (Met; STZ + metformin, 125 mg/kg/day). Age-matched non-diabetic mice served as the normal control group (NC, n = 8).

CM and metformin were freshly dissolved in distilled water and administered by oral gavage once daily at 10:00 a.m. for 4 weeks. To minimize potential bias, the order of administration was randomized daily. The treatment doses were selected based on previous studies and preliminary experiments. No animals were excluded from the final analysis. Animal husbandry and experimental procedures were performed by different investigators to reduce experimental bias.

At the end of the experimental period, the mice were fasted overnight (12 h), and fasting blood glucose levels were measured using blood collected from the tail vein. The animals were then euthanized by carbon dioxide (CO_2) inhalation, and blood, liver, pancreas, and kidney tissues were immediately collected for subsequent biochemical, histopathological, and molecular analyses (Figure 1B).

3.5. Measurement of Body Weight, Food Intake, and Water Consumption

Body weight was measured daily before oral administration using an electronic balance (Mettler Toledo, Greifensee, Switzerland) throughout the experimental period. Food intake and water consumption were recorded daily by measuring the amounts of diet and water provided and the remaining amounts after 24 h. These parameters were assessed to evaluate the effects of CM treatment on metabolic alterations associated with STZ-induced diabetes.

3.6. Oral Glucose Tolerance test (OGTT)

The oral glucose tolerance test (OGTT) was performed one day before the end of the experimental period. After 4 h of fasting, baseline blood glucose levels were measured using blood collected from the tail vein. Glucose was freshly dissolved in distilled water and orally administered at a dose of 2 g/kg body weight. Blood glucose levels were measured at 1, 30, 60, and 120 min after glucose administration using a glucometer (Accu-Chek Performa; Roche Diagnostics, Mannheim, Germany).

3.7. Serum Biochemical Analysis

At the end of the experimental period, blood samples were collected from the abdominal vein of each mouse and transferred into serum separation tubes (BD Vacutainer, Franklin Lakes, NJ, USA). The samples were allowed to clot at room temperature for 30 min and then centrifuged at 1,500 × g for 15 min to obtain serum.

Serum levels of glucose (Glu), total cholesterol (TC), triglycerides (TG), lactate dehydrogenase (LDH), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured using an automated biochemical analyser (BS-120 Automatic Chemistry Analyzer, Mindray, Shenzhen, China) according to the manufacturer's instructions.

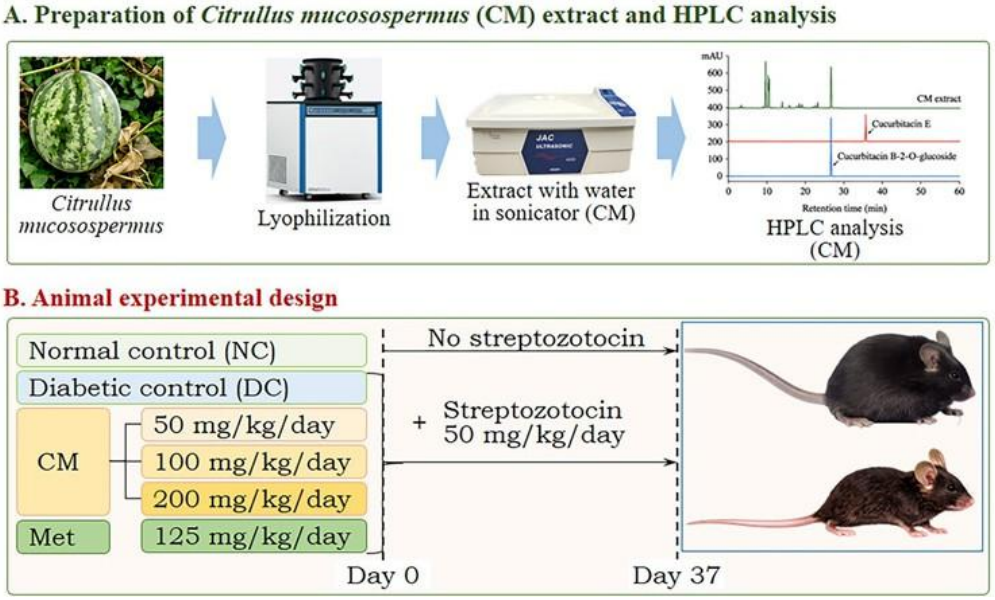

Figure 1: Experimental design for the preparation of water extract of Citrullus mucosospermus (CM) (A) and evaluation of its antidiabetic effects in streptozotocin-induced diabetic mice (B).

3.8. Insulin Receptor ELISA

Insulin receptor levels in liver tissues were determined using a mouse insulin receptor ELISA kit (ABIN7012860, antibodies-online, Aachen, Germany) according to the manufacturer's instructions. Briefly, liver tissues were homogenized in ice-cold phosphate-buffered saline (PBS; 1:9, w/v) and centrifuged at 5,000 × g for 10 min at 4 °C. The supernatants were collected for analysis, and absorbance was measured at 450 nm using a microplate reader. Insulin receptor concentrations were calculated from a standard curve.

3.9. Histopathological Analysis

Pancreatic, renal, and hepatic tissues were excised and fixed in 10% neutral-buffered formalin for 48 h. The fixed tissues were embedded in paraffin, sectioned at a thickness of 4 μm using a microtome (Leica Microsystems, Bannockburn, IL, USA), mounted on glass slides, and dried overnight. The sections were deparaffinized in xylene (Dae Jung, Gyeonggi-do, Republic of Korea), rehydrated through a graded ethanol series (100–70%), and stained with hematoxylin and eosin (H&E; Sigma-Aldrich, St. Louis, MO, USA) according to standard histological procedures. Histopathological changes were examined and photographed using a Leica microscope equipped with Leica Application Suite software (Leica Microsystems, Heer brugg, Switzerland).

3.10. Quantitative Reverse Transcription Polymerase Chain Reaction (RT-qPCR) Analysis

The hepatic mRNA expression levels of inflammatory cytokines, including interleukin (IL)-6, IL-1β, IL-10, and tumour necrosis factor-α (TNF-α), were analysed by quantitative reverse transcription polymerase chain reaction (RT-qPCR) as previously described [33].

Total RNA was extracted from liver tissues using RNAzol reagent (Tel-Test Inc., Friendswood, TX, USA) according to the manufacturer's instructions. RNA concentration and purity were determined using a Nano Drop spectrophotometer (Bio Spec-nano, Shimadzu Biotech, Kyoto, Japan). Complementary DNA (cDNA) was synthesized from 5 μg of total RNA using oligo(dT) primers and Super Script II reverse transcriptase (Invitrogen, Carlsbad, CA, USA). Quantitative PCR was performed using 2× Power SYBR Green Master Mix (Toyobo Co., Osaka, Japan) with gene-specific primers (Supplementary Table S1). The amplification conditions were 95 °C for 15 s, 55 °C for 30 s, and 70 °C for 60 s. Relative mRNA expression levels were calculated using the 2^−ΔΔCt method with β-actin as the internal reference gene.

Supplementary Table S1: Primer sequences for RT-qPCR.

Primer name	Sequence (from 5' to 3')	Product size (bp)
IL-6		134
Forward	TTCCA TCCAG TTGCC TTCTT G	
Reverse	GGGAG TGGTA TCCTC TGTGA AGTC	
IL-1β		94
Forward	CTACA GGCTC CGAGA TGAAC AAC	
Reverse	TCCAT TGAGG TGGAG AGCTT TC	
IL-10		105
Forward	CAGCC GGGAA GACAA TAACT G	
Reverse	CCGCA GCTCT AGGAG CATGT	
TNFα		61
Forward	ATCCG CGACG TGGAA CTG	
Reverse	ACCGC CTGGA GTTCT GGAA	

3.11. Statistical Analysis

All data are presented as the mean ± standard deviation (SD) (n = 8). Statistical analyses were performed using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA). Differences among groups were analysed by one-way analysis of variance (ANOVA), followed by Tukey's post hoc test for multiple comparisons. A value of $P < 0.05$ was considered statistically significant. Statistical significance is indicated as ##$P < 0.01$ and ###$P < 0.001$ versus the normal control (NC) group, and **$P < 0.01$ and *** $P < 0.001$ versus the diabetic control (DC) group.

4. Results

4.1. Extraction and Phytochemical Analysis of Citrullus Mucosospermus

The experimental procedure used in the present study is described as follows. Briefly, fruits of CM were freeze-dried, powdered, and extracted with distilled water using an ultrasonic extractor to obtain the CM (Figure 1A). The phytochemical composition of CM was previously characterized by HPLC analysis in our recent study [33]. Cucurbitacin E and cucurbitacin E-2-O-glucoside were identified as the two major cucurbitacins, with concentrations of 0.048 ± 0.001 mg/g and 2.145 ± 0.188 mg/g extract, respectively. Among these, cucurbitacin E-2-O-glucoside was the predominant cucurbitacin in the aqueous extract. Therefore, the present study employed this chemically characterized extract to evaluate its antidiabetic activity in streptozotocin (STZ)-induced diabetic mice (Figure 1B).

4.2. Body Weight and Food Intake in STZ-Induced Diabetic Mice Treated with CM

Body weight, food intake, and water consumption were assessed to determine the effects of CM on physiological parameters in STZ-induced diabetic mice.

As shown in Figure 2A, body weight increased steadily throughout the experimental period in the normal control (NC) group, whereas streptozotocin (STZ)-induced diabetic mice exhibited a marked reduction in body weight gain. At the end of the experiment (day 37), the body weight of the diabetic control (DC) group remained significantly lower than that of the NC group ($p < 0.05$). Administration of CM at doses of 50, 100, and 200 mg/kg slightly attenuated body weight loss compared with the DC group. However, no statistically significant differences were observed among the CM-treated groups and the DC group during the experimental period. The final body weight measurements are presented in Figure 2B. CM administration tended to mitigate these alterations, particularly in the CM200 and Met group as positive control.

Food intake was significantly higher in STZ-induced diabetic mice than in normal mice ($p < 0.05$), indicating the development of diabetic polyphagia. Administration of CM at all tested doses did not significantly alter food intake compared with the DC group, and metformin treatment similarly had no significant effect (Figure 2C).

Water consumption was markedly increased in the DC group compared with the NC group ($p < 0.01$), reflecting the characteristic polydipsia associated with diabetes mellitus. CM-treated groups exhibited a tendency toward reduced water consumption compared with the DC group, particularly at 200 mg/kg, although the differences were not statistically significant. Likewise, metformin treatment showed a similar decreasing trend without statistical significance (Figure 2D).

These results indicate that CM administration may improve diabetes-associated physiological abnormalities, particularly excessive water consumption, in STZ-induced diabetic mice.

4.3. Glucose Homeostasis in STZ-Induced Diabetic Mice Treated with CM

The effects of CM on glucose homeostasis were evaluated by measuring fasting blood glucose levels and performing an oral glucose tolerance test (OGTT). As shown in Figure 3A, Fasting blood glucose levels were significantly elevated in the diabetic control (DC) group compared with the normal control (NC) group ($p < 0.001$), confirming successful induction of hyperglycemia by STZ administration. CM treatment reduced fasting blood glucose in a dose-dependent manner, with the CM200 group showing the lowest level. Metformin also decreased fasting blood glucose compared with the DC group; however, neither CM nor metformin treatment produced statistically significant differences relative to the DC group.

Basal glucose levels were significantly elevated in all STZ-treated groups compared with the NC group. Following oral glucose administration, blood glucose levels peaked at 30 min in all groups. The NC group showed a gradual decline in glucose levels, returning toward baseline by 120 min, whereas the DC group maintained elevated glucose concentrations throughout the test period, indicating impaired glucose tolerance. CM treatment improved glucose clearance in a dose-dependent manner, with the CM200 group exhibiting the greatest reduction at 60 and 120 min, comparable to the metformin-treated group. Although CM treatment attenuated hyperglycemia, glucose levels remained higher than those of the NC group at all measured time points (Figure 3B).

Collectively, these findings indicate that CM fruit extract partially improved glucose homeostasis in STZ-induced diabetic mice. Although the reduction in fasting blood glucose was modest, CM administration, particularly at 200 mg/kg, enhanced glucose clearance during the OGTT, suggesting improved glucose utilization and amelioration of glucose intolerance.

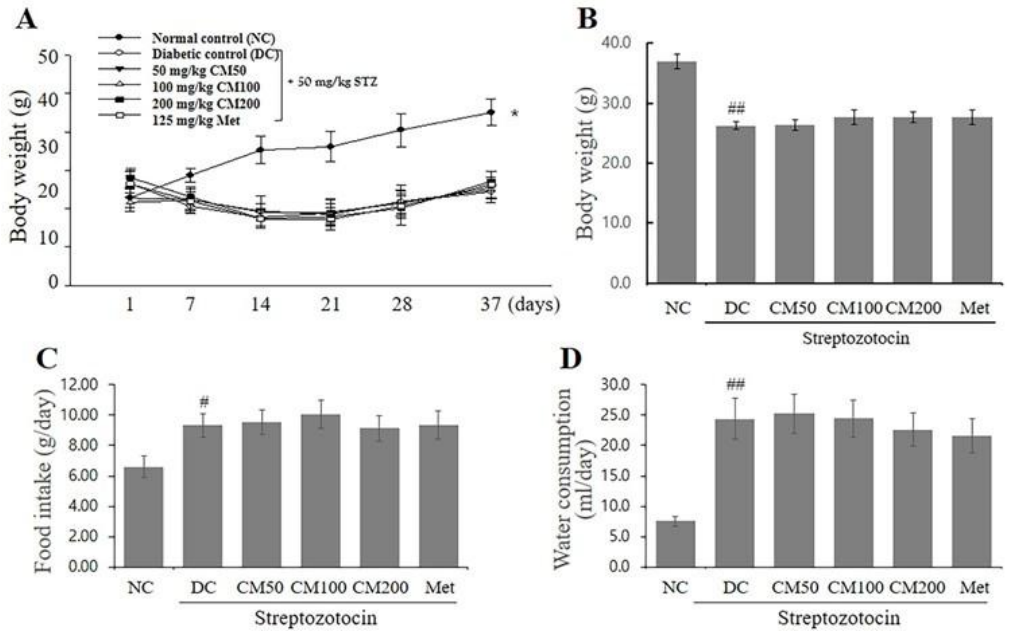

Figure 2: Effects of *Citrullus mucosospermus* fruit extract (CM) on body weight change (A), body weight (B), food intake (C) and water consumption (D) in streptozotocin-induced diabetic mice. Diabetes was induced by streptozotocin (STZ, 50 mg/kg). Experimental groups included normal control (NC), diabetic control (DC), metformin-treated group (Met, 125 mg/kg), and CM-treated groups (CM50, CM100, and CM200 mg/kg body weight). Data are presented as mean ± standard deviation (SD) (n = 8). Statistical analysis was performed using one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison test. $^{\#\#}p < 0.05$ and $^{\#\#\#}p < 0.001$ versus the NC group; $^{**}p < 0.01$ and $^{***}p < 0.001$ versus the DC group.

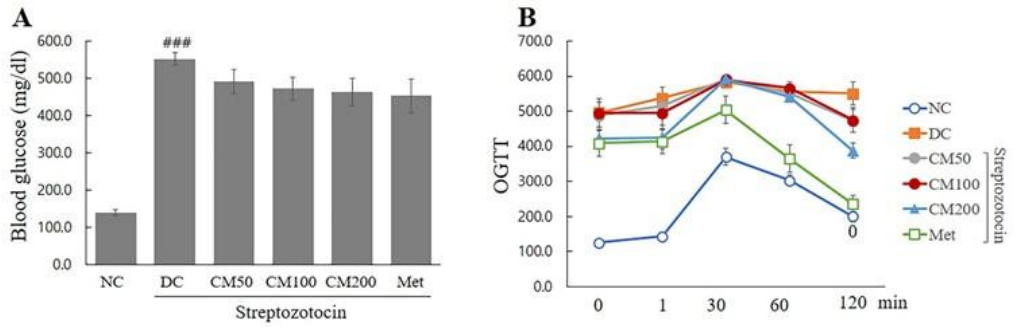

Figure 3: Effects of *Citrullus mucosospermus* fruit extract (CM) on Fasting blood glucose levels measured after 12 h fasting (A) and oral glucose tolerance test (OGTT) (B) in streptozotocin-induced diabetic mice. Blood samples were collected and centrifuged at 3000 rpm for 10 min. Diabetes was induced by streptozotocin (STZ, 50 mg/kg). Experimental groups included normal control (NC), diabetic control (DC), metformin-treated group (Met, 125 mg/kg), and CM-treated groups (CM50, CM100, and CM200 mg/kg body weight). Data are presented as mean ± standard deviation (SD) (n = 8). Statistical analysis was performed using one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison test. $^{\#\#}p < 0.05$ and $^{\#\#\#}p < 0.001$ versus the NC group; $^{**}p < 0.01$ and $^{***}p < 0.001$ versus the DC group.

4.4. Serum Biochemical Parameters in STZ-Induced Diabetic Mice Treated with CM

The effects of CM on serum biochemical parameters in streptozotocin (STZ)-induced diabetic mice are presented in Table 1. Serum glucose (Glu) levels were markedly elevated in the DC group compared with the NC group, confirming the successful induction of severe hyperglycemia by STZ. Treatment with CM reduced blood glucose levels at all tested doses compared with the DC group, with the CM50 and CM200 groups showing relatively greater reductions. The metformin-treated group exhibited the lowest serum glucose level among all experimental groups.

TC levels were decreased in the DC group compared with the NC group, whereas CM administration resulted in a dose-dependent increase in TC levels, with the CM200 group reaching levels comparable to those of the metformin-treated group. TG levels were also lower in the DC group than in the NC group. CM50 and CM100 treatments showed a tendency to restore TG levels, while CM200 and metformin treatment significantly reduced TG concentrations compared with the DC group.

Serum lactate dehydrogenase (LDH), a biomarker of tissue injury, was markedly elevated in the DC group compared with the NC group. CM administration reduced LDH activity in a dose-dependent manner, with the greatest reduction observed in the CM200 group. However, LDH levels remained higher than those in the NC group, indicating that CM partially alleviated tissue injury associated with diabetes. Serum HDL-C and LDL-C levels showed differences among the experimental groups, indicating that CM administration may influence lipid metabolic

profiles in STZ-induced diabetic mice.

Collectively, CM attenuated hyperglycemia, reduced serum LDH activity, and improved lipid metabolic parameters in STZ-induced diabetic mice. The CM200 group showed the most pronounced effects, suggesting that higher-dose CM treatment may alleviate diabetes-associated metabolic disturbances and tissue injury.

4.5. Insulin Receptor Levels in STZ-Induced Diabetic Mice Treated with CM

Insulin receptor concentrations were significantly reduced in the diabetic control (DC) group compared with the normal control (NC) group ($p < 0.05$), indicating impaired insulin signalling following STZ induction. CM administration increased insulin receptor levels in a dose-dependent manner. While the CM50 group showed no significant change, the CM100 and CM200 groups exhibited significant increases compared with the DC group ($p < 0.001$), with levels comparable to those of the NC group. The metformin-treated group also showed a significant increase in insulin receptor concentration, with no significant differences observed among the CM100, CM200, and metformin groups. These findings suggest that CM, particularly at 100 and 200 mg/kg, may restore insulin receptor expression and improve insulin signalling in STZ-induced diabetic mice (Figure 4).

Table 1: Effects of Citrullus mucosospermus fruit extract (CM) on serum biochemistry in streptozotocin-induced diabetic mice.

	NC	DC	CM50	CM100	CM200	Met
Glu(mg/dl)	159.4±8.0	534.6±41.9	422.5±34.5	497.5±44.1	426.8±61.9	411.6±72.6
TC (mg/dl)	150.3±2.7	101.9±6.9	74.7±4.3	90.8±8.0	108.4±7.2	112.0±7.9
TG (mg/dl)	68.0±7.7	30.0±3.2	35.3±4.0	45.3±3.0	19.6±4.7	15.4±3.5
LDH (U/L)	538.8±24.6	1136.1±64.2	1118.3±47.9	1012.8±59.7	782.3±45.4	943.0±69.5
HDL (mg/dl)	118.6±3.3	81.7±5.2	61.1±4.0	60.3±4.0	81.8±3.3	87.3±3.3
LDL (mg/dl)	15.6±1.5	10.7±1.7	6.0±0.9	12.2±2.0	12.4±1.4	13.6±1.0

Blood samples were collected and centrifuged at 3000 rpm for 10 min. Serum levels of glucose (Glu), total cholesterol (TC), triglyceride (TG), lactate dehydrogenase (LDH), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were analyzed. Diabetes was induced by streptozotocin (STZ, 50 mg/kg). Experimental groups included normal control (NC), diabetic control (DC), metformin-treated group (Met, 125 mg/kg), and CM-treated groups (CM50, CM100, and CM200 mg/kg body weight). Data are presented as mean ± standard deviation (SD) (n = 8). Statistical analysis was performed using one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison test. ##$p < 0.05$ and ###$p < 0.001$ versus the NC group; **$p < 0.01$ and ***$p < 0.001$ versus the DC group.

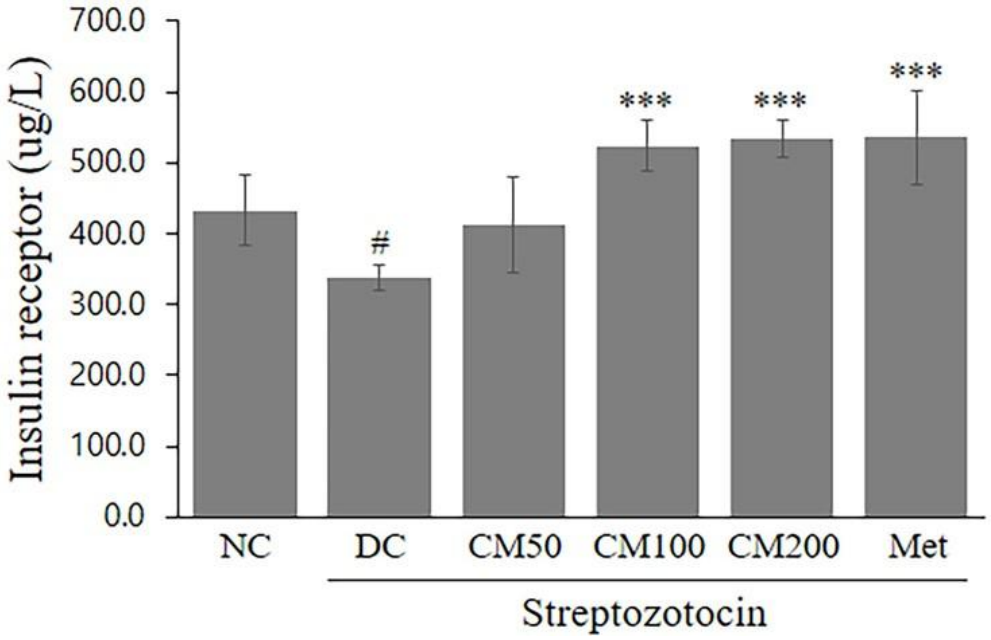

Figure 4: Effects of *Citrullus mucosospermus* fruit extract (CM) on insulin receptor concentration in streptozotocin-induced diabetic mice. Diabetes was induced by streptozotocin (STZ, 50 mg/kg). Experimental groups included normal control (NC), diabetic control (DC), metformin-treated group (Met, 125 mg/kg), and CM-treated groups (CM50, CM100, and CM200 mg/kg body weight, respectively). Data are presented as mean ± standard deviation (SD) (n = 8). was determined using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test. $^{\#\#}p < 0.05$ versus the NC group; $^{***}p < 0.001$ versus the DC group.

4.6. Histopathology in STZ-Induced Diabetic Mice Treated with CM

Histopathological examination was performed to evaluate the protective effects of CM against diabetes-induced tissue injury in the pancreas, kidney, and liver (Figure 5). The NC group exhibited normal histological architecture in all examined tissues. In contrast, the DC group showed marked pathological alterations following STZ administration.

In the pancreas, STZ-induced diabetic mice exhibited severe degeneration of the islets of Langerhans, characterized by reduced islet size, irregular islet morphology, decreased cellular density, and partial destruction of the endocrine tissue. These pathological alterations were progressively ameliorated by CM treatment, particularly in the CM100 and CM200 groups, in which pancreatic islet morphology and cellular organization were largely preserved and appeared comparable to those observed in the metformin-treated group.

In the kidney, the DC group showed pronounced renal injury characterized by tubular epithelial degeneration, tubular dilatation, vacuolar changes, and widening of the Bowman's space. These abnormalities were markedly attenuated following CM administration in a dose-dependent manner, with the CM100 and CM200 groups exhibiting improved tubular architecture and reduced renal lesions.

Hepatic sections from the DC group demonstrated hepatocellular vacuolar degeneration, ballooning change, and disruption of hepatic cord organization, indicating diabetes-associated liver injury. Treatment with CM substantially reduced these pathological changes and restored hepatic morphology, with the higher-dose groups showing nearly normal hepatic architecture comparable to that of the metformin-treated mice.

Collectively, these findings demonstrate that CM effectively attenuated STZ-induced histopathological damage in multiple target organs, suggesting a protective effect against diabetes-associated tissue injury.

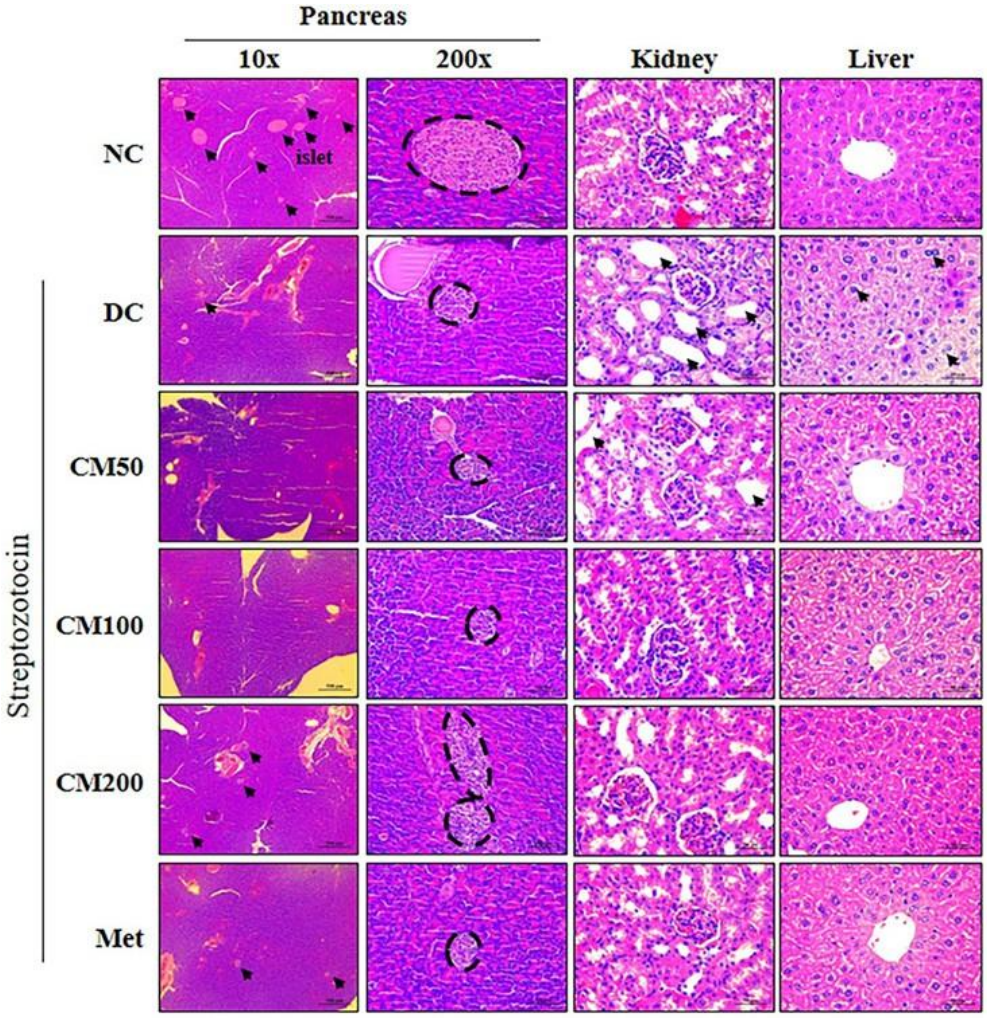

Figure 5: Histopathologic changes of the pancreas, kidney, and liver (H&E stain, scale bar=25 μm) in streptozotocin-induced diabetic mice. Diabetes was induced by streptozotocin (STZ, 50 mg/kg). Experimental groups included normal control (NC), diabetic control (DC), metformin-treated group (Met, 125 mg/kg) as positive control, and CM-treated groups (CM50, CM100, and CM200 mg/kg body weight).

4.7. Hepatic Inflammatory Cytokine Expression in STZ-Induced Diabetic Mice Treated with CM

Hepatic mRNA expression of inflammatory cytokines was evaluated to determine the anti-inflammatory effects of CM in STZ-induced diabetic mice (Figure 6). The expression levels of IL-6, IL-1β, IL-10, and TNF-α were significantly elevated in the DC group compared with the NC group ($p < 0.001$), indicating enhanced hepatic inflammatory responses following STZ induction. CM treatment significantly reduced the expression of all examined cytokines in a dose-dependent manner. Among the CM-treated groups, the CM200 group showed the greatest inhibitory effects, with cytokine levels approaching those of the NC group. The metformin-treated group also exhibited significant reductions in inflammatory cytokine expression. These findings suggest that CM attenuates diabetes-associated hepatic inflammation in STZ-induced diabetic mice.

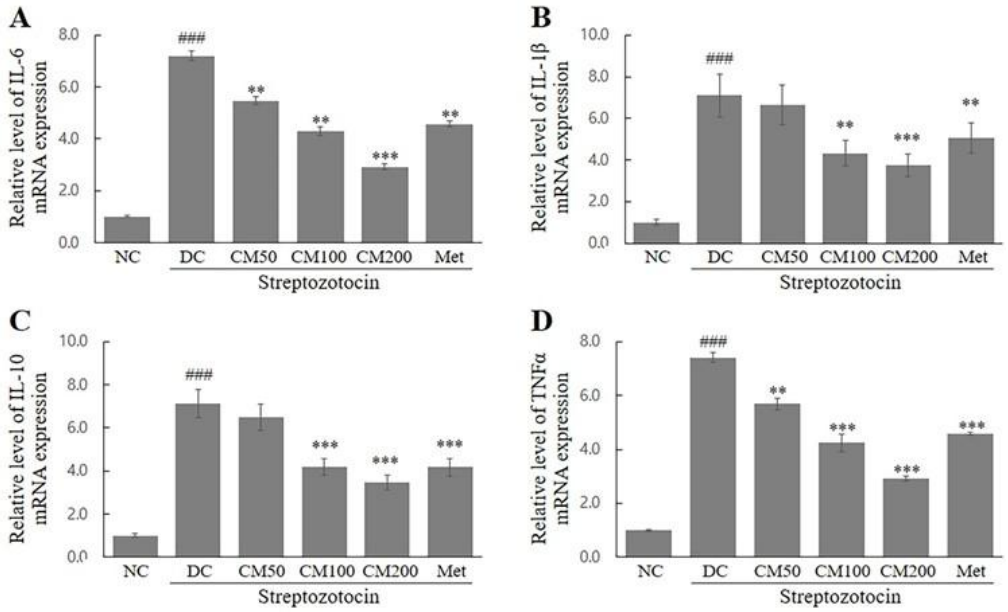

Figure 6: Effects of *Citrullus mucosospermus* fruit extract (CM) on the expression of inflammatory cytokines (IL-6, IL-1β, IL-10, and TNF-α) in the liver tissues of streptozotocin-induced diabetic mice. Diabetes was induced by streptozotocin (STZ, 50 mg/kg). Experimental groups included normal control (NC), diabetic control (DC), metformin-treated group (Met, 125 mg/kg), and CM-treated groups (CM50, CM100, and CM200 mg/kg body weight). Relative mRNA expression levels of IL-6, IL-1β, TNFα, and IL-10 were measured by RT-qPCR. Data are presented as mean ± standard deviation (SD) (n = 8). Statistical analysis was performed using one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison test. $^{\#\#}p < 0.05$ and $^{\#\#\#}p < 0.001$ versus the NC group; $^{**}p < 0.01$ and $^{***}p < 0.001$ versus the DC group.

5. Discussion

The present study demonstrated that Citrullus mucosospermus fruit extract (CM) exerted protective effects against STZ-induced diabetes by improving glucose homeostasis, restoring insulin receptor expression, reducing tissue injury, and suppressing hepatic inflammatory responses. Although CM did not significantly affect body weight, food intake, or water consumption, it consistently ameliorated diabetes-associated bio-chemical, histopathological, and molecular abnormalities, suggesting that its antidiabetic effects are mainly mediated through regulation of metabolic and inflammatory pathways. Previous studies have similarly re-ported that medicinal plants improve diabetic metabolic dysfunction without significant changes in body weight or energy intake, indicating that metabolic and inflammatory regulation may occur independently of general physiological alterations [34,35]. Collectively, these findings suggest that CM improves diabetes-associated metabolic dysfunction through coordinated regulation of glucose metabolism, insulin signaling, tissue protection, and inflammatory responses.

STZ induces pancreatic β-cell dysfunction via DNA alkylation, excessive ROS, and nitric oxide, causing insulin deficiency and hyperglycemia [29,30]. In the present study, STZ-treated mice exhibited typical diabetic features, including hyperglycemia, impaired glucose tolerance, pancreatic degeneration, dyslipidemia, elevated LDH activity, and increased hepatic inflammatory cytokine expression, confirming successful establishment of the diabetic model.

Previous studies have shown that plant-derived polyphenols and triterpenoids improve glucose metabolism by enhancing peripheral insulin responsiveness and glucose utilization with limited effects on basal hepatic glucose production [15,36]. Improved postprandial glucose disposal without complete normalization of fasting glucose is considered an indicator of enhanced peripheral insulin sensitivity rather than direct inhibition of hepatic gluconeogenesis [37,38]. Consistent with these findings, CM improved glucose tolerance in STZ-induced diabetic mice, particularly at 200 mg/kg with an efficacy comparable to metformin. These results suggest that CM enhances glucose utilization and exerts antihyperglycemic effects primarily through improvement

of peripheral insulin sensitivity and glucose handling.

Improved glucose metabolism was accompanied by restoration of insulin receptor expression. CM treatment significantly recovered STZ-induced reductions in insulin receptor levels, particularly at 100 and 200 mg/kg. The insulin receptor activates the IRS-1/PI3K/Akt signaling pathway, which regulates GLUT4 translocation and cellular glucose uptake [38-40]. Since reduced insulin receptor expression contributes to insulin resistance and metabolic dysfunction [41,42], the recovery observed after CM treatment suggests improved insulin signaling, although further studies on downstream pathways are required.

In the present study, CM treatment improved several biochemical abnormalities associated with STZ-induced diabetes. CM reduced serum glucose levels and decreased LDH activity in a dose-dependent manner, with the greatest effect observed at the high dose, while partially improving diabetes-associated lipid abnormalities. These changes were accompanied by reduced tissue injury and improved insulin-related metabolic function, suggesting restoration of metabolic homeostasis. Previous studies have identified LDH as a sensitive marker of cellular damage caused by oxidative stress, inflammation, and chronic hyperglycemia [43,44], with elevated LDH levels associated with diabetic tissue injury and disease progression [44]. Dyslipidemia, a major complication of insulin deficiency and resistance, is also closely linked to cardiovascular risk in diabetic patients [45]. Consistent with these findings, CM appears to alleviate diabetes-associated metabolic disturbances by reducing cellular damage and improving glucose and lipid metabolism.

In the present study, histopathological analysis revealed that STZ administration induced severe structural damage in the pancreas, kidney, and liver, including pancreatic islet degeneration, renal tubular injury, and hepatic tissue damage. However, CM treatment, particularly at 200 mg/kg, markedly attenuated these pathological changes. These improvements were accompanied by reduced LDH activity and restored insulin receptor expression, suggesting that CM protects diabetic tissues through metabolic and protective mechanisms. Previous studies have demonstrated that preservation of pancreatic islet architecture is essential for maintaining insulin secretion and delaying diabetes progression [46]. In addition, hyperglycemia-induced oxidative stress and chronic inflammation are major contributors to diabetic renal and hepatic injury [6]. Consistent with these findings, CM preserved pancreatic islet integrity and reduced renal and hepatic damage, indicating that its protective effects involve attenuation of oxidative and inflammatory injury as well as improvement of insulin-related metabolic function.

CM administration significantly attenuated hepatic inflammatory responses in STZ-induced diabetic mice. STZ increased hepatic expression of IL-6, IL-1β, TNF-α, and IL-10, whereas CM treatment markedly reduced these cytokine levels. The suppression of inflammatory markers was associated with improved glucose metabolism, restored insulin receptor expression, and reduced tissue injury, suggesting that regulation of inflammatory signaling contributes to the beneficial effects of CM. Previous studies have identified chronic low-grade inflammation as a key mechanism underlying insulin resistance and diabetic complications [47], [48]. Pro-inflammatory cytokines such as IL-6, IL-1β, and TNF-α activate NF-κB and JNK pathways, impair IRS-1-mediated insulin signaling, and promote β-cell dysfunction and insulin resistance [23,49]. In addition, NLRP3 inflammasome contributes to diabetes-associated inflammation and metabolic dysfunction [50,51]. Although IL-10 is generally anti-inflammatory, its elevation during chronic inflammation may represent a compensatory response to excessive inflammatory stimulation [52,53]. Therefore, the reduction of inflammatory cytokines and normalization of IL-10 expression by CM suggest restoration of inflammatory homeostasis, contributing to improved insulin sensitivity and protection against diabetic tissue injury.

The biological effects of CM are likely attributed to its phytochemical constituents. HPLC analysis identified cucurbitacin E and cucurbitacin E-2-O-glucoside as major compounds, with cucurbitacin E-2-O-glucoside being predominant [19]. C. mucosospermus contains cucurbitacins, phenolics, flavonoids, and other antioxidant phytochemicals with reported antioxidant, anti-inflammatory, hepatoprotective, and antidiabetic activities [19], [54]. Cucurbitacins have been shown to regulate NF-κB, MAPK, and JAK/STAT signaling, reduce oxidative stress, and improve insulin responsiveness [17], [54- 56]. Thus, the restoration of insulin receptor expression and suppression of hepatic inflammatory cytokines by CM are consistent with the known biological activities of Citrullus-derived phytochemicals. However, further studies are required to determine the specific active components and molecular targets, particularly the role of cucurbitacin E-2-O-glucoside in CM-mediated antidiabetic effects.

The present study demonstrates that CM exerts multifaceted protective effects against STZ-induced diabetes through coordinated regulation of glucose metabolism, restoration of insulin signaling, suppression of oxidative and inflammatory responses, and preservation of tissue integrity. CM treatment improved glucose homeostasis, restored insulin receptor expression, reduced hepatic inflammatory cytokine production, and attenuated pathological alterations in the pancreas, kidney, and liver. These findings indicate that the antidiabetic effects of CM extend beyond glucose-lowering activity and involve comprehensive regulation of metabolic dysfunction, insulin sensitivity, inflammatory homeostasis, and protection against diabetes-associated tissue damage.

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