RESEARCH PAPER

Protective Effects of Serinolamide A against Streptozotocin-Induced Diabetes Mellitus in Rats

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ABSTRACT
Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia and is associated with oxidative stress, inflammation, and progressive organ damage. The present study aimed to evaluate the protective effects of Serinolamide A against streptozotocin (STZ)-induced diabetes mellitus in rats. Experimental diabetes was induced by a single intraperitoneal injection of STZ (55 mg/kg), and diabetic rats were treated orally with Serinolamide A (1, 5, and 10 mg/kg) for 28 consecutive days. Metformin (70 mg/kg, p.o.) was used as the standard drug. Fasting blood glucose, body weight, serum biochemical parameters, liver glycogen content, oxidative stress markers, pro-inflammatory cytokines, and histopathological changes were evaluated. Treatment with Serinolamide A significantly ameliorated hyperglycemia and improved body weight in diabetic rats. Furthermore, Serinolamide A restored liver glycogen levels, enhanced antioxidant defense by increasing superoxide dismutase, catalase, and reduced glutathione activities, and reduced lipid peroxidation. The treatment also attenuated inflammatory responses by decreasing tumor necrosis factor-α and interleukin-6 levels. Histopathological examination revealed marked protection against diabetes-induced renal damage. The observed effects were dose-dependent, with the 10 mg/kg dose showing effects comparable to those of metformin. These findings suggest that Serinolamide A possesses significant antidiabetic and protective effects, which may be attributed to its antioxidant and anti-inflammatory properties, and could represent a promising therapeutic candidate for the management of diabetes mellitus and its associated complications.

Keywords: Serinolamide A, Diabetes mellitus, Streptozotocin, Oxidative stress, Inflammation, Antidiabetic activity.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from defects in insulin secretion, insulin action, or both[1]. The increasing prevalence of diabetes and its associated complications, including nephropathy, neuropathy, retinopathy, and cardiovascular diseases, have become major global health concerns[2-5]. Although several antidiabetic drugs are available, their long-term use is often associated with adverse effects and limited efficacy, necessitating the development of safer and more effective therapeutic agents[6-8].

Natural bioactive compounds have gained considerable attention for their potential in the management of diabetes. Serinolamide A, a marine-derived fatty acid amide structurally related to endocannabinoids, exhibits selective cannabinoid receptor type-2 (CB2) agonistic activity and possesses anti-inflammatory and cytoprotective properties[9-11]. Emerging evidence suggests that modulation of the endocannabinoid system plays an important role in regulating glucose homeostasis, insulin sensitivity, and inflammatory responses associated with diabetes[12-14].

Streptozotocin (STZ)-induced diabetes is a widely used experimental model that mimics the pathological features of diabetes through selective destruction of pancreatic β-cells, resulting in hyperglycemia and metabolic disturbances[15-18]. Therefore, the present study was designed to evaluate the protective effects of Serinolamide

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A against STZ-induced diabetes mellitus in rats and to investigate its potential as a novel therapeutic agent for diabetes management.

MATERIALS AND METHODS

Animals

Thirty-six male wistar rats weighing between 150-200gm were selected for experimental design. Animals were procured from Institutional Animal house [Reg. No. 651/PO/Re/S-2002/CPCSEA]. All animals were maintained under ambient conditions as well as under temperature and humidity of 25±2ºC with normal light dark cycle of 12hr. the animals are feed with pellets and water as ad-libitum procured from Research Diet pune. The experimental protocol was reviewed and approved by the Institutional Animal Ethics Committee [Approval No. CPCSEA/IAEC/650/PO/Re/S-2002/2026/18].

Drug and chemicals

Serinolamide-A was procured from Hunan Mclob Tech Co. Ltd., China. Streptozotocin (STZ) was obtained from Sigma-Aldrich, USA. Commercial diagnostic kits for creatinine, urea, albumin were purchased from ERBA Diagnostics Pvt ltd. All other chemicals and reagents used were of analytical grade.

Acute Oral Toxicity Study

Acute oral toxicity of Serinolamide-A was evaluated according to OECD guideline 423. Female Wistar rats were divided into three groups (n = 6) and administered 0.5% CMC (control), 300 mg/kg, and 2000 mg/kg of Serinolamide-A orally. Animals were observed continuously for the first 4 h and daily for 14 days for mortality and signs of toxicity. At the end of the study, gross pathological examination of major organs was performed. No mortality or treatment-related toxic effects were observed up to 2000 mg/kg, indicating that Serinolamide-A is safe within the tested dose range[19-22].

Induction of Diabetes

Diabetes was induced by a single intraperitoneal injection of streptozotocin (55 mg/kg) prepared in freshly prepared citrate buffer (pH 4.0). After 48 h, rats with fasting blood glucose levels above 250 mg/dL were considered diabetic and used for the study[23-25].

Experimental groups

All animals were randomly divided into six groups (n = 6). Group I: Normal control and received 0.5% CMC.

Group II: Disease Control and received streptozotocin (STZ, 55 mg/kg, i.p.).

Group III: Standard received STZ (55 mg/kg, i.p.) followed by metformin (70 mg/kg, p.o.) and served as the standard group.

Groups IV, V, and VI: Treatment Group- received STZ (55 mg/kg, i.p.) and were treated with Serinolamide-A at doses of 1, 5, and 10 mg/kg, respectively, by oral administration for 28 consecutive days. Metformin and Serinolamide-A suspensions were prepared in 0.5% CMC. At the end of the study, all animals were anesthetized with urethane (1.4 g/kg, i.p.), and blood samples were collected and centrifuged at 5000 rpm for 10 min at 4°C to obtain serum for biochemical analysis.

Animals were then sacrificed, and both kidneys were excised. Pancreases homogenates (10%, w/v) were prepared in ice-cold phosphate-buffered saline (50 mM, pH 7.4) and centrifuged at 10,000 rpm for 10 min at 4°C. The resulting supernatant was used for the estimation of antioxidant parameters and pro-inflammatory cytokines[25].

Estimation of Liver Glycogen Content

At the end of the experimental period, animals were euthanized, and the liver was excised and washed with ice-cold normal saline to remove adhering blood. Liver tissue was minced and homogenized in 80% ethanol at a concentration of 100 mg/mL and centrifuged at 10,000 rpm for 15 min. Subsequently, distilled water and 52% perchloric acid were added to the residue, and the resulting mixture was thoroughly extracted. The extract was centrifuged at 9,500 rpm for 15 min to obtain the supernatant.

An aliquot of 0.2 mL of the supernatant was mixed with 1 mL of distilled water and anthrone reagent. The reaction mixture was heated in a boiling water bath, cooled to room temperature, and the absorbance was measured spectrophotometrically at 630 nm. A standard curve was constructed using glucose solutions of known concentrations, and the liver glycogen content was calculated accordingly and expressed as mg glycogen/g tissue[25].

Biochemical Estimation in Pancreases Homogenates

At the end of the treatment period, rats were individually housed in metabolic cages for 24 h for urine collection and evaluation of renal function. Blood samples were collected by retro-orbital puncture and centrifuged to obtain serum. Fasting blood glucose levels were determined by the glucose oxidase-peroxidase method, while serum creatinine, blood urea nitrogen (BUN), albumin, total protein, total cholesterol, and triglyceride levels were estimated using commercially available diagnostic kits (Erba Diagnostics, India) according to the manufacturer's instructions[25].

Antioxidant Estimation in Pancreases Homogenates

Pancreases tissues were homogenized in ice-cold phosphate-buffered saline (50 mM, pH 7.4) and centrifuged at 10,000 rpm for 10 min at 4°C. The resulting supernatant was used for the estimation of antioxidant parameters. Reduced glutathione (GSH), superoxide dismutase (SOD), and lipid peroxidation (LPO) levels were determined using commercially available assay kits according to the manufacturer's instructions. Catalase (CAT) activity was determined spectrophotometrically by monitoring the decomposition of hydrogen peroxide at 240 nm[24, 25]. ***Estimation of Pro-inflammatory Cytokines***

The levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) in Pancreases homogenates were

quantified using commercially available ELISA kits according to the manufacturer's protocol. The concentrations of cytokines were calculated from the respective standard curves[24, 25].

Histopathological Examination

At the end of the experimental period, rats were sacrificed under urethane anesthesia (1.4 g/kg, i.p.), and kidneys were excised and fixed in 10% neutral buffered formalin. The tissues were processed, embedded in paraffin wax, and sectioned into 5-µm-thick slices. Sections were stained with hematoxylin and eosin (H&E) and examined under a light microscope (×40) for evaluation of histopathological changes, including glomerular and tubular damage associated with Diabetes[25].

RESULTS AND DISCUSSION

Effect of Serinolamide-A on Body Weight

STZ-induced diabetic rats showed a significant decrease in body weight compared with the normal control group ($P < 0.001$). Treatment with Serinolamide-A significantly restored body weight in a dose-dependent manner, with the 10 mg/kg dose exhibiting effects comparable to those of metformin (Fig. 1A and 1B), indicating its protective effect against STZ-induced diabetes in rats.

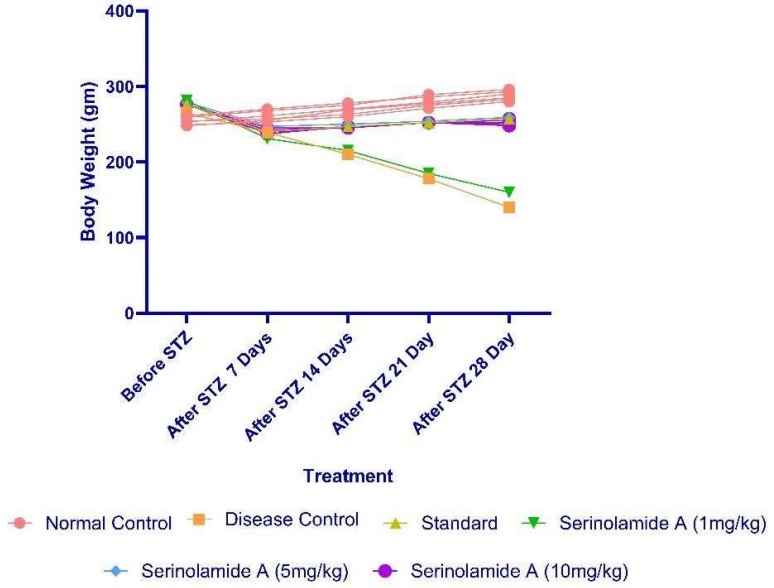


Figure 1 Effect of Serinolamide-A on Body Weight

Effect of Serinolamide-A on Liver Glycogen Level and Urine Volume

STZ-induced diabetic rats showed a significant decrease in Liver Glycogen Level and elevation in Urine Volume compared with the normal control group ($P < 0.001$). Treatment with Serinolamide-A significantly restored Liver Glycogen Level and also reduce the urine volume in a dose-dependent manner, with the 10 mg/kg dose exhibiting effects comparable to those of metformin (Fig. 2A and 2B), indicating its protective effect against STZ-induced diabetes in rats.

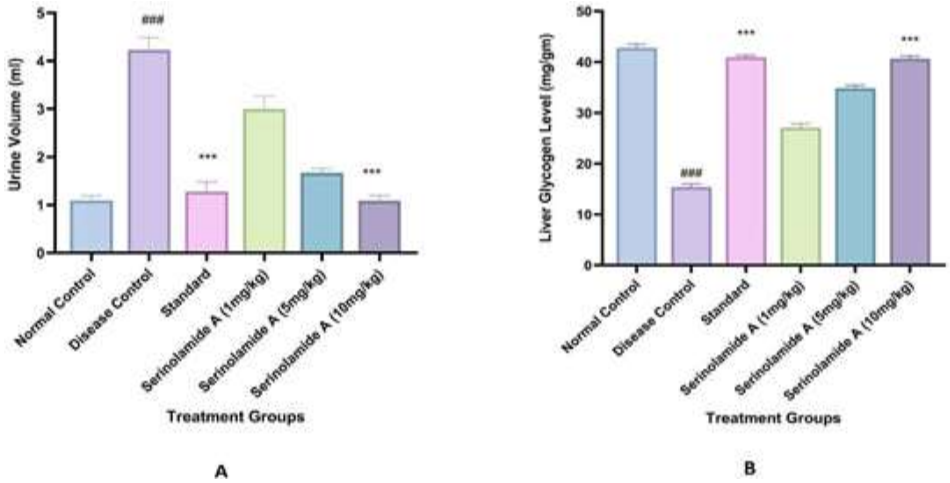


Figure 2 Effect of Serinolamide-A on Liver Glycogen Level and Urine Volume

Effect of Serinolamide-A on Serum Biochemical Parameters

STZ-induced diabetic rats exhibited significant elevations in serum creatinine, and blood urea nitrogen (BUN) accompanied by decreased serum albumin levels compared with the normal control group ($P < 0.001$). Treatment with Serinolamide-A significantly reversed these alterations in a dose-dependent manner, with the 10 mg/kg dose showing effects comparable to metformin, indicating its protective effect against STZ-induced biochemical dysfunction (Fig. 3).

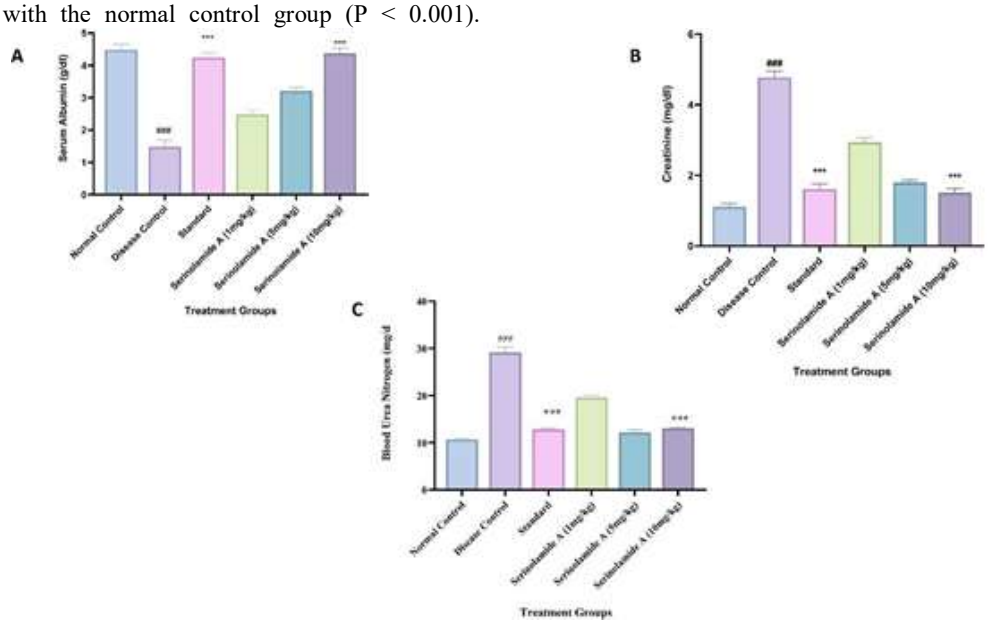


Figure 3 Effect of Serinolamide-A on Serum Biochemical Parameters

Effect of Serinolamide-A on Oxidative Stress Markers in STZ induced Diabetes in rats

STZ-induced diabetic rats exhibited significant oxidative stress, characterized by increased lipid peroxidation (LPO) and decreased superoxide dismutase (SOD), reduced glutathione (GSH), and catalase (CAT) activities compared with the normal control group ($P < 0.001$). Treatment with Serinolamide-A significantly reversed these alterations in a dose-dependent manner, with the 10 mg/kg dose producing effects comparable to metformin ($P < 0.001$) (Fig. 4).

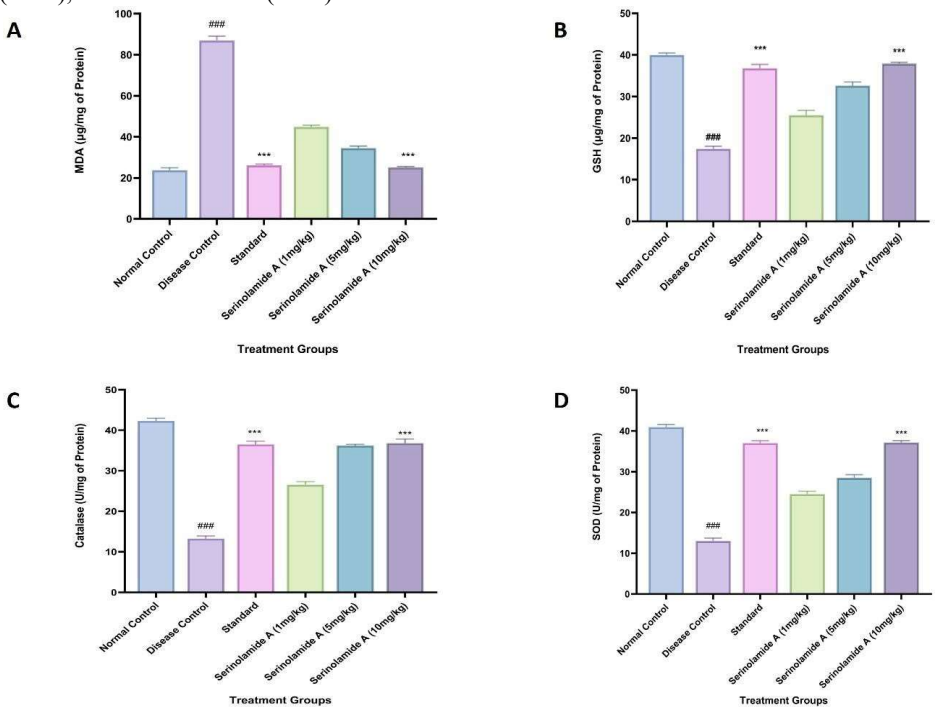
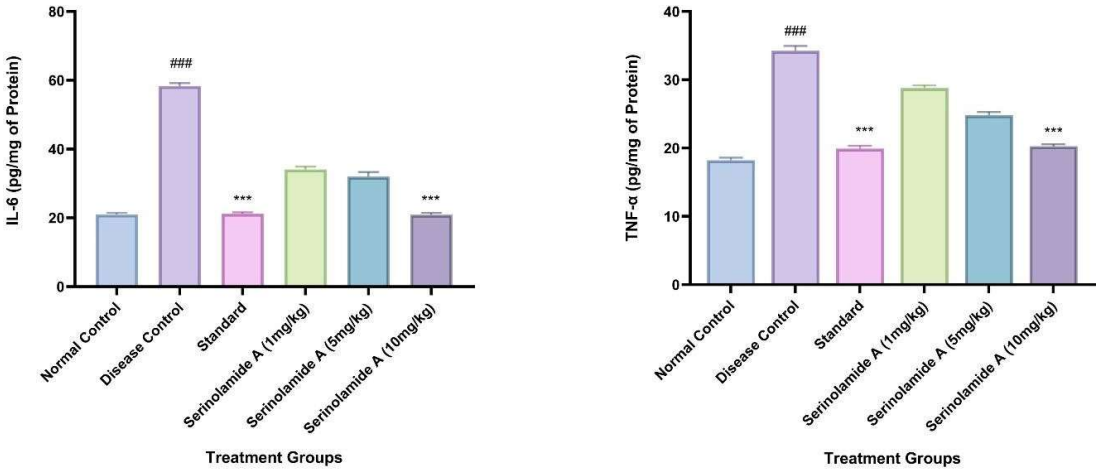


Figure 4 Effect of Serinolamide-A on Oxidative Stress Markers in STZ induced Diabetes in rats

Effect of Serinolamide-A on Pro-inflammatory Cytokines in STZ induced Diabetes in rats The levels of pro-inflammatory cytokines, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), were significantly elevated in the pancreases of STZ-induced diabetic rats compared with the normal control group ($P < 0.001$). Administration of Serinolamide-A significantly suppressed the release of these cytokines in a dose-dependent manner, indicating its anti-inflammatory potential. The reduction in TNF-α and IL-6 levels produced by Serinolamide-A was comparable to that observed with metformin treatment ($P < 0.001$) (Fig. 5).



A B

Figure 5 Effect of Serinolamide-A on Pro-inflammatory Cytokines in STZ induced Diabetes in rats

Effect of Serinolamide-A on Histopathological Alterations

Histopathological examination of Pancreases sections from the normal control group revealed normal renal architecture with intact glomeruli and tubules. In contrast, STZ-induced diabetic rats exhibited marked pathological alterations characterized by tubular necrosis, inflammatory cell infiltration, vascular congestion, interstitial edema, and glomerular damage. Treatment with metformin markedly attenuated these histopathological changes. Similarly, administration of Serinolamide-A produced a dose-dependent improvement in renal morphology, as evidenced by reduced inflammatory infiltration, decreased tubular necrosis, and restoration of normal glomerular and tubular architecture. The highest dose of Serinolamide-A demonstrated pronounced protection against STZ-induced renal tissue damage comparable to that observed with metformin treatment (Fig. 6).

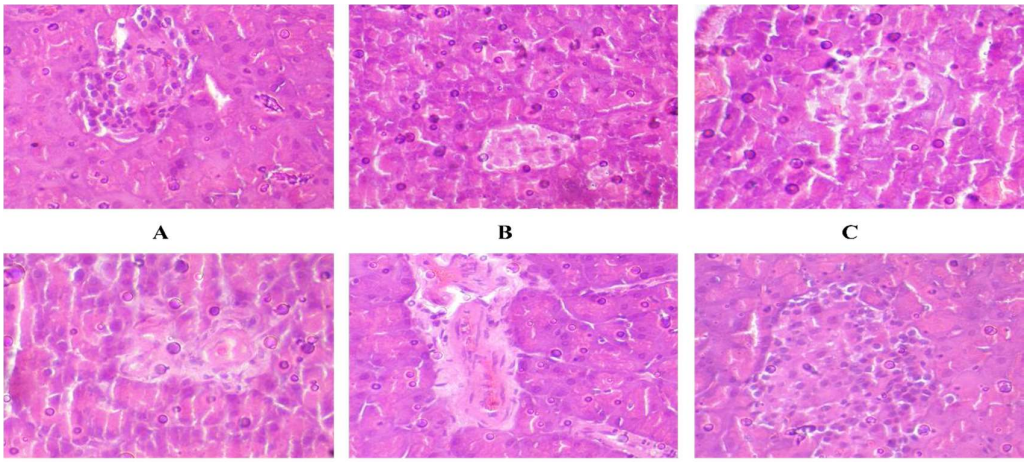


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Figure 6 Effect of Serinolamide-A on Histopathological Alterations

Diabetes mellitus is characterized by chronic hyperglycemia accompanied by oxidative stress, inflammatory responses, and progressive damage to various organs[26-28]. Streptozotocin (STZ)-induced diabetes is a widely accepted experimental model that mimics pancreatic β-cell destruction and metabolic disturbances associated with diabetes[15]. In the present study, administration of Serinolamide-A significantly attenuated diabetes-induced alterations and exhibited marked protective effects in STZ-treated rats.

STZ administration resulted in a progressive reduction in body weight, which is a common consequence of impaired glucose utilization and increased protein catabolism. Treatment with Serinolamide-A significantly restored body weight in a dose-dependent manner, suggesting improved metabolic status and enhanced utilization of glucose. The beneficial effect observed with the highest dose (10 mg/kg) was comparable to that of metformin, indicating a potent antidiabetic activity.

Liver glycogen content is an important indicator of glucose homeostasis and insulin action[29]. Diabetic rats exhibited marked depletion of hepatic glycogen stores, whereas treatment with Serinolamide-A significantly increased glycogen levels. Restoration of glycogen content suggests improved glucose uptake and enhanced glycogenesis, which may be attributed to improved insulin sensitivity or preservation of pancreatic β-cell function. Moreover, reduction in urine volume observed after Serinolamide-A treatment indicates attenuation of diabetes-associated polyuria and improved glycemic control.

Alterations in renal biochemical markers such as elevated serum creatinine and blood urea nitrogen along with reduced serum albumin are indicative of diabetic nephropathy and renal dysfunction[30]. Serinolamide-A significantly normalized these parameters, suggesting a nephroprotective effect against STZ-induced renal injury. These findings were further supported by histopathological observations showing restoration of normal tissue architecture and reduction in tubular necrosis and inflammatory infiltration.

Oxidative stress plays a crucial role in the pathogenesis of diabetes and its complications. Excessive generation of reactive oxygen species causes lipid peroxidation and depletion of endogenous antioxidant defenses[31-33]. In the present study, STZ-induced diabetic rats showed increased lipid peroxidation and significant reductions in superoxide dismutase, catalase, and reduced glutathione levels. Treatment with Serinolamide-A markedly reversed these changes, demonstrating its antioxidant potential. Restoration of endogenous antioxidant enzymes may contribute to cellular protection against oxidative damage and preserve tissue integrity.

Inflammation is another key factor involved in the progression of diabetes and associated complications[33, 34]. Elevated levels of pro-inflammatory cytokines such as TNF-α and IL-6 were observed in diabetic rats, confirming the inflammatory state induced by STZ. Administration of Serinolamide-A significantly suppressed the production of these cytokines in a dose-dependent manner. Serinolamide-A is a marine-derived fatty acid amide structurally related to endocannabinoids and acts as a selective CB2 receptor agonist. Activation of CB2 receptors has been reported to exert anti-inflammatory and cytoprotective effects through inhibition of pro-inflammatory mediators and attenuation of oxidative stress. Therefore, the observed reduction in TNF-α and IL-6 levels may be attributed to modulation of the endocannabinoid system and suppression of inflammatory signaling pathways.

Histopathological evaluation further confirmed the biochemical findings[35]. Severe pathological changes observed in STZ-induced diabetic rats, including glomerular damage, tubular degeneration, vascular congestion, and inflammatory cell infiltration, were markedly ameliorated following Serinolamide-A treatment. The highest dose produced tissue protection comparable with metformin, indicating its ability to preserve normal organ morphology.

Overall, the present findings suggest that the antidiabetic activity of Serinolamide-A may involve multiple mechanisms, including improvement of glucose metabolism, enhancement of antioxidant defense, suppression of inflammatory mediators, and protection against diabetes-induced tissue injury. These findings support the therapeutic potential of Serinolamide-A as a promising natural molecule for the management of diabetes mellitus and its associated complications. Nevertheless, further studies are warranted to elucidate the precise molecular mechanisms and signaling pathways involved and to establish its safety and efficacy in clinical settings.

The present study demonstrated that Serinolamide-A exerts significant protective effects against streptozotocin-induced diabetes mellitus in rats. It improved body weight, restored liver glycogen, reduced urine volume, normalized renal biochemical parameters, enhanced antioxidant defenses, suppressed lipid peroxidation, and reduced inflammatory cytokines (TNF-α and IL-6). Serinolamide-A also attenuated diabetes-induced histopathological changes in a dose-dependent manner, with the 10 mg/kg dose showing efficacy comparable to metformin. These findings suggest that Serinolamide-A possesses antidiabetic, antioxidant, anti-inflammatory, and tissue-protective properties, highlighting its potential as a promising therapeutic candidate for diabetes mellitus and its complications. However, further mechanistic and clinical studies are required to confirm its translational potential.

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CONFLICT OF INTEREST STATEMENT
The authors have no conflict of interest.

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