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Original Research Article

Geraniol Attenuates Oxidative Stress and Apoptosis in the Liver and Kidney of Streptozotocin-Induced Diabetic Rats

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ABSTRACT

Monoterpenes such as geraniol are known for their pharmacological properties. This study assessed geraniol's antioxidant, and antiapoptotic potentials on diabetic rat liver and kidney. Male Wistar rats (24) were assigned into four groups of 6 rats per group. Diabetic rats (18) received a single dose of streptozotocin (STZ, 60 mg/kg) intraperitoneally. Animals were classified as control, STZ, STZ+GER (geraniol 200 mg/kg), and STZ+GLI (glibenclamide 5 mg/kg) groups. Treatment lasted 21 days. Blood glucose level was assessed using a glucometer. Superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) were assayed spectrophotometrically using standard commercial kits. Cytochrome c (Cyt c), caspase 9 (C9), and caspase 3 (C3) expressions in rat liver and kidney were assessed using commercial (ELISA) kits. The glucose level in the blood was elevated in the STZ group. Significant expressions of Cyt c, C9, and C3 and reduced SOD, CAT, and GSH levels were observed in rat liver and kidney of the STZ group. Treatment with geraniol significantly reduced blood glucose levels, Cyt c, C9, and C3 expressions relative to the STZ group. Similarly, antioxidant enzyme activities were significantly increased in the rat liver both in the STZ+GER and STZ+GLI groups. Thus, this study shows that geraniol has antidiabetic, antioxidant, and antiapoptotic effects on the liver and kidneys of streptozotocin-induced diabetic rats.

Keywords: Antioxidants, Apoptosis, Cytochrome c, Diabetes, Geraniol

Introduction

Diabetes mellitus is a non-communicable disease with increasing cases globally, thus, a public health issue. This disease is characterized by alteration in the breakdown of carbohydrates, proteins, and lipids due to the inability of the pancreas to secrete sufficient insulin or reduced tissue response to insulin.[1] This condition results in high blood glucose concentration (hyperglycemia).[1,2] Hyperglycaemia causes hemoglobin glycation and the generation of reactive radicals (ROS) that are implicated in several health complications such as nephropathy, cardiomyopathy, and retinopathy.[1,2,3] Hyperglycaemia has been reported to be a major cause of organ damage.[4] High blood glucose concentration and ROS have also been reported to alter mitochondrial functions in the liver and kidney of diabetic patients.[5,6,7] Mitochondrial dysfunction is a major factor that triggers β-cell dysfunction and malfunctioning of insulin signaling pathways in the cell.[8,9] Mitochondrial dysfunction which occurs as a result of excessive ROS production is potent in inducing the opening of the mitochondrial membrane permeability pore.[10] This phenomenon causes loss of membrane potential and the release of apoptotic proteins into the cytosol from the mitochondria intermembrane space.[10,11] Once released, cytochrome c (an apoptotic protein) activates initiator caspase 9, and downstream caspase 3 causing cell death.[12] Effective management of diabetes mellitus can delay the onset of complications associated with this disease, thereby increasing the quality of life.[13]

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Drugs such as biguanides and sulfonylureas e.t.c., are used in treating diabetes. These drugs do have negative effects e.g. nausea and may prove ineffective after a long period of use [14] thus resulting in organ failure. Death occurs in extreme cases due to long-term complications associated with diabetes.[13] Therefore, the pursuit of new drugs from natural sources with little or no side effects is on the increase globally. Many diabetic patients especially in resource-poor settings such as Africa make use of plants and their compounds in managing diabetes and its complications. Plants are rich in phytochemicals and have been used as therapeutic agents in the treatment of various diseases over the years. It has been stated that A*llium cepa* and *Artemisia herba* have anti-diabetic effects with little or no negative effects.[15] Bioactive compounds such as quercetin, S-methyl cysteine sulfoxide from *Allium cepa*, tannins, and flavonoids from various plants have been reported to have anti-diabetic effects.[16,17,18] Monoterpenes such as geraniol derived from plants have been used in the treatment of some diseases. Geraniol has antioxidant,[19] anticancer,[20] anti-inflammatory,[21] antimicrobial,[22] and anti-diabetic[23] potentials. This study investigated geraniol's antioxidant and antiapoptotic effects in diabetic rat liver and kidney.

Materials and Methods

Reagents and chemicals

Geraniol was purchased from Chem Cruz (Santa Cruz Biotechnology Inc. USA, Lot E2721), cytochrome c, caspase 3, and caspase 9 kits were purchased from Elabscience Biotechnology Inc. (USA) (Cat. No: E-EL-R0006 for cytochrome c, Cat. No: E-CK-A313 for caspase 9, and Cat. No: E-CK-A311 for caspase 3). Urea (Product code: BXC0123), and creatinine (Product code: BXC0111) kits from Fortress diagnostic (United Kingdom). The other reagents were of high quality.

Experimental animals

Male Wistar rats (140g - 168g,) were obtained from the animal house, College of Medicine, University of Lagos, Idi-Araba, Lagos, Nigeria. The animals had free access to rat chow and water *ad libitum*. The rats

were kept in ventilated plastic cages. The animals were handled according to the guidelines of NIH of 1985, the CMUL Health Research Ethical Committee, and assigned the code CMUL/HREC/07/21/881. The animals were acclimatized for fourteen (14) days before the experiment commenced.

Induction of diabetes

Each rat was given a single intraperitoneal injection of streptozotocin (60 mg/kg body weight) dissolved in citrate buffer (pH 4.5) to induce diabetes. One or two drops of blood from the lateral vein of the rats were used to access blood glucose levels 72 hours after the administration of streptozotocin using a glucometer. Twenty-four animals were used in this study. Eighteen (18) rats with blood glucose levels of 200 mg/dl and above were assigned into three groups of 6 rats per group. Animals in group 1 (CTL) were used as control.

Rats in group 2 were given 60 mg/kg streptozotocin (STZ) i.p only

Each rat in group 3 was given 60 mg/kg streptozotocin only and 200 mg/kg geraniol (STZ + GER) daily for 21 days.

Each rat in group 4 was given only 60 mg/kg streptozotocin and 5 mg/kg glibenclamide (STZ+GLI) daily for 21 days.

The dosage of geraniol administered was based on a previous study by Babukumar et al.[23] The treatment lasted 21 days. The animals were euthanized on the 22nd day by cervical decapitation, dissected and samples were collected for analysis.

Determination of blood glucose level

Blood glucose levels were measured on day 0, day 7, day 14, and day 21 using an Accu-Check Active Glucometer (Mannheim, Germany).

Biochemical assays

On the 22nd day, rat blood was collected into hepatized tubes through the orbital sinus. The blood was spun at 3000 revolutions per min for 10 min. The plasma gotten was kept at -20 °C for further analysis. Urea and creatinine levels were assayed using Fortress diagnostic kits. Briefly, the assay medium contains 10 µL of plasma, and 1000 µL working buffer (Tris buffer pH 7.95, 2-Oxoglutarate, ADP, Urease, GLDH, and NADH) mixed thoroughly in a 1500 µL cuvette. Absorbance was taken 30 sec after and 120 sec later. Similarly, to determine creatinine concentration in plasma, 1000 µL of the working reagent (NaOH and Picric acid) and 100 µL of the plasma were thoroughly mixed. Absorbance was taken immediately.

Assessment of oxidative stress biomarkers

Rat kidney and liver were excised and rinsed in 1.15% potassium chloride (KCl). The samples were crushed in chilled 0.1 M phosphate buffer (pH 7.4) using a homogenizer and centrifuged for 10 min at 10,000 revolutions per min. The supernatant obtained was used for antioxidant assays. Superoxide dismutase (SOD) activity was calculated based on the method of Marklund and Marklund.[24] The principle was centered on the inhibition of pyrogallol autooxidation by SOD at 420 nm. To 50 µL of the post-mitochondrial fraction, 1 mL of the assay buffer (50 mM Tris-Cacodylate, 1 mM DTPA, and 40 µg catalase, pH 8.0), and 1 mL chromogen solution (2.6 mM pyrogallol) were mixed thoroughly. The absorbance reading was taken at 420 nm. Catalase activity was determined by the methods of Goth[25], and Hadwan and Abed.[26] Briefly, 0.2 mL of the supernatant, 1000 µL 65 µM H_2O_2 dissolved in sodium-potassium phosphate buffer (NaH_2PO_4) (60 mM, pH 7.4) were carefully mixed and allowed to stand for 60 sec. The reaction was brought to halt by adding 1000 µL 32.4 mM ammonium molybdate. Absorbance reading was taken at 405 nm. Reduced glutathione (GSH) was assessed by the method of Ellman[27.] This principle is based on the reduction of DTNB by sulphydryl groups in the tissue supernatant to form a yellow complex which is read at 412 nm. Briefly, 0.05 mL of the sample, 0.4 mL of Tris-HCl (0.4 M) pH 8.9, and 0.01 mL of DTNB (0.01 M) were thoroughly mixed. The yellow colour was measured at 420 nm.

Assessment of apoptotic markers

The expressions of apoptotic markers (Cyt c, C9, and C3) in rat liver and kidney were assessed using ELISA kits (Elabscience Biotechnology Inc. USA). Briefly, cytochrome c was determined in the post-mitochondrial fractions by adding 100 µL of the tissue fraction into a pre-coated ELISA plate. The fraction was incubated at 37°C for 1 hr 30 min. After which biotinylated detection antibody solution was added to the plate and allowed to incubate at 37°C for I hr. After decanting, the plate was washed thrice with PBS. Avidin-horseradish peroxidase conjugate was added to the plate and allowed to incubate at 37°C for 30 min, TMB was added and incubated for 15 min at 37 °C. The reaction was stopped by the addition of 50 uL sulphuric acid. The absorbance of the plate was taken at 450 nm. For the determination of caspase 9 and caspase 3, 45 µL of the liver and kidney supernatant were added into pre-coated plates, 0.05 mL of the working solution, and 5 µL of the substrate (Ac-LEHD-pNA or Ac-DEVD-pNA) were added to the plates. The solution was incubated at 37 °C for 2 hr. The absorbance of the solution was taken at 405 nm.

Statistical analysis

Triplicate data are presented as mean ± SEM using graph pad 8.1.1 software. The data were analyzed with One-way, Two-way Analysis of Variance (ANOVA), and Tukey's posthoc test. Values were considered significant at $p<0.05$.

Results and Discussion

The study investigated geraniol's antioxidant and antiapoptotic potentials on diabetic rat liver and kidney induced with streptozotocin. From Table 1, no significant ($p>0.05$) difference was observed between the initial and final body weights of rats in each of the groups. Also, there was no observable difference between rat liver weights in all the groups. However, we observed a notable increase in the kidney weight of rats in the STZ, and STZ+GER groups relative to the control (Table 1). Generally, there was no significant increase or decrease in the organ and body weight ratio of rats in all the groups. The observed increase in the kidney weight in the STZ and STZ+GER groups may be suggesting that STZ caused hypercellularity of the tissues which was not reversed by geraniol. Figure 1: shows that streptozotocin in rats caused a notable ($p<0.05$) increase in blood glucose levels. However, blood glucose level was significantly reduced in the treated groups. We observed significant ($p<0.05$) blood glucose reduction on the 8th, 15th, and 22nd day of geraniol and glibenclamide administration in the STZ+GER and STZ+GLI groups when compared to the STZ group. The reduced plasma glucose level observed after 21 days of the oral administration of geraniol to the STZ group indicates that geraniol has glucose-lowering properties. This finding is consistent with the reports of some other studies.[28,29] The kidney is responsible for filtration and electrolytes balance. Prolonged hyperglycemia may result in kidney dysfunction via dysregulated mitochondrial-dependent apoptosis and oxidative stress. In Figure 2A, a significant increase in plasma urea concentration was detected in the STZ group relative to the control group. However, geraniol reduced urea concentration in the STZ+GER group significantly. Similarly, glibenclamide lowered urea concentration in the STZ+GLI group significantly. Also, plasma creatinine concentration increased significantly in the STZ group relative to the control. There was a significant reduction in plasma creatinine concentration in the STZ+GER and STZ+GLI groups in relation to the STZ group (Figure 2B). These results, therefore, show that the observed elevated concentration of urea and creatinine in the STZ group which were lowered in the STZ+GER group suggest that geraniol may have nephron-protective potential. This result is consistent with a recent report on the nephron-protective potential of geraniol against cyclosporin A-induced kidney damage in rats.[30]

The antioxidant and anticancer properties of geraniol have been previously reported.[31] The capacity of antioxidant enzymes to scavenge reactive oxygen species produced in the cell, especially in pathologic scenarios has been documented also.[31] Table 2 showed the effect of geraniol on the antioxidant enzyme activities and reduced glutathione levels in the liver of rats from the different groups. Superoxide dismutase activity increased in the STZ+GER group relative to the STZ group. The activity of superoxide dismutase increased by 27% in the STZ+GER group than in the STZ group.

Table 1: Mean rat body weight, rat organ weight, and rat organ/weight ratio in each group

Groups	Animal weights (g)		Organ Weights (g)		Organ/weight ratio	
	Initial	Final	Liver	Kidney	Liver	Kidney
CTL	168.7 ± 9.87	176.3 ± 3.18	5.75 ± 0.54	0.48 ± 0.03	0.033	0.003
STZ	140.0 ± 2.31	131.0 ± 3.22	4.72 ± 0.46	0.93 ± 0.15*	0.036	0.007
STZ+GER	153.0 ± 12.0	165.7 ± 16.02	6.05 ± 0.43	0.86 ± 0.04*	0.037	0.004
STZ++GLI	152.3 ± 4.49	147.3 ± 4.26	4.99 ± 0.02	0.53 ± 0,02**	0.034	0.004

Values are presented as mean ± standard error of mean (n = 3). *Values are significantly different from the control. **values are significantly different from the streptozotocin group.

Table 2: Effect of geraniol on SOD, CAT, and GSH levels in the liver of rats in each group

Groups	SOD (U/mg)	CAT (µMOL/ml/mins	GSH (Mm)
CTL	0.98 ± 0.08	11.92 ± 0.39	0.75 ± 0.04
STZ	0.77 ± 0.01	10.37 ± 0.20	0.54 ± 0.01*
STZ+GER	1.27 ± 0.06**	14.78 ± 0.18**	0.72 ± 0.03**
STZ+GLI	1.35 ± 0.16**	13.71 ± 1.06**	0.89 ± 0.05**

Values are presented as mean ± standard error of mean (n = 3). *Values are significantly different from the control. **values are significantly different from the streptozotocin group.

Table 3: Effect of geraniol on SOD, CAT, and GSH in the kidney of rats in each group

Groups	SOD (U/mg)	CAT (µMOL/ml/mins	GSH (Mm)
CTL	1.00 ± 0.12	10.00 ± 0.30	0.49 ± 0.06
STZ	0.36 ± 0.08*	10.00 ± 0.09	0.36 ± 0.02
STZ+GER	0.94 ± 0.05**	13.00 ± 0.30**	0.50 ± 0.06
STZ+GLI	1.10 ± 0.19**	12.00 ± 0.39**	0.40 ± 0.01

Values are presented as mean ± standard error of mean (n = 3). *Values are significantly different from the control. **values are significantly different from the streptozotocin group.

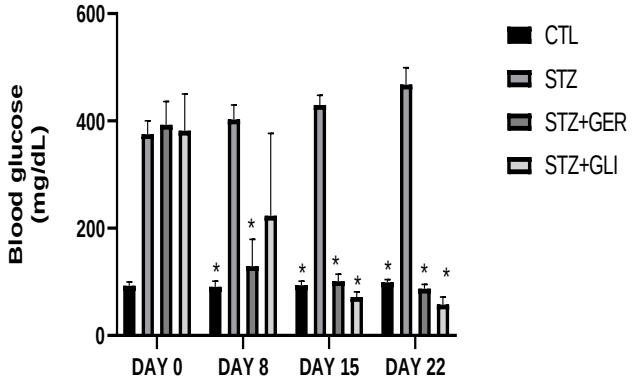

Figure 1: Effect of 21 days of oral administration of geraniol to streptozotocin-induced diabetic rats. *Values are significantly different from the streptozocin group.

Also, catalase activity increased significantly in the STZ+GER and STZ+GLI groups compared to the STZ groups. Catalase activity increased by 15% in the control than what was observed in the STZ group. Reduced glutathione levels increased notably in the STZ+GER and STZ+GLI groups compared to the STZ group. Therefore, the reduced activities of SOD and CAT observed in the tissues of the STZ group suggests that there was a depletion of the antioxidant enzymes in diabetic rat liver and kidney. However, elevated levels of these enzyme activities in the STZ+GER group suggest that geraniol probably can activate *de novo* synthesis of these enzymes in the body thereby circumventing the effect of ROS due to diabetes. Also, the observed depletion of GSH levels in rat liver and kidney of the STZ group that was further elevated in the STZ+GER group indicates the potent antioxidant potential of geraniol.

In Table 3, we observed that the activity of superoxide dismutase in the STZ group was lowered significantly relative to the control. However, SOD activity in the kidney of rats was elevated significantly in both the STZ+GER and STZ+GLI groups. Furthermore, elevated catalase activity was seen in the STZ+GER group relative to the STZ and control groups. Geraniol in the STZ+GER group however increased GSH levels by 38% relative to the STZ group. The level of GSH increased by 36% in the control relative to the STZ group. Generally, the findings are consistent with earlier reports of Erujuwa *et al.*[32] and Zhou et al.[33] The expression of cytochrome c significantly increased in the STZ group in relation to the control (Figure 3A). From the result, we observed that treatment with geraniol significantly reduced cytochrome c levels in the STZ+GER group. A similar pattern was observed in the STZ+GLI group. Caspase 9 expression was significantly elevated in the liver of rats in the STZ group, this expression was however significantly reduced in the STZ+GER and STZ+GLI groups, respectively. (Figure 3B). In Figure 3C, geraniol and glibenclamide lowered caspase 3 expressions significantly in the rat liver of the STZ+GER and STZ+GLI groups relative to the STZ group.

Furthermore, the effect of geraniol on Cyt c, C9, and C3 expressions in rat kidneys was assessed (Figure 4). From the results, treatment with STZ significantly increased tissue expression of Cyt c. This however was greatly reduced by geraniol and glibenclamide in the STZ+GER and STZ+GLI groups, respectively as shown in Figure 4A. Caspase 9 an initiator protease of the mitochondrial pathway of apoptosis was significantly elevated in the STZ group, but geraniol and glibenclamide treatments reduced caspase 9 expressions significantly in the STZ+GER and STZ+GLI groups relative to the STZ group (Figure 4B).

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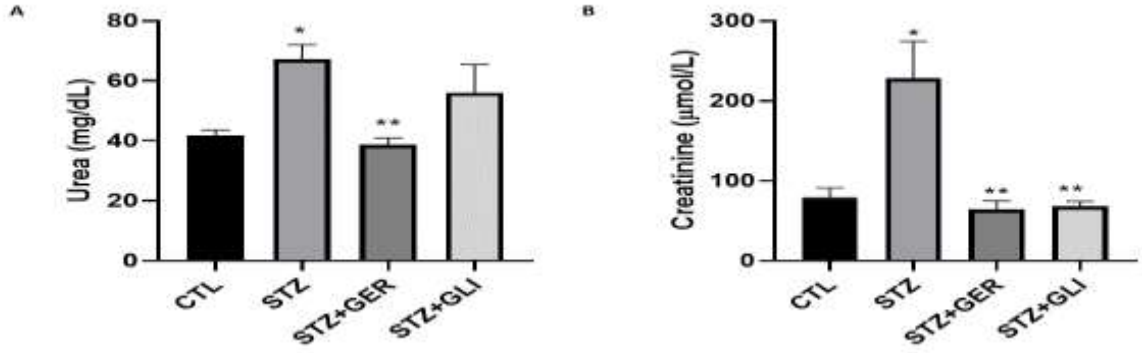

Figure 2: Effect of geraniol on urea and creatinine concentration in streptozotocin-induced diabetic rats. *Values are significantly different from the control. **values are significantly different from the streptozotocin group.

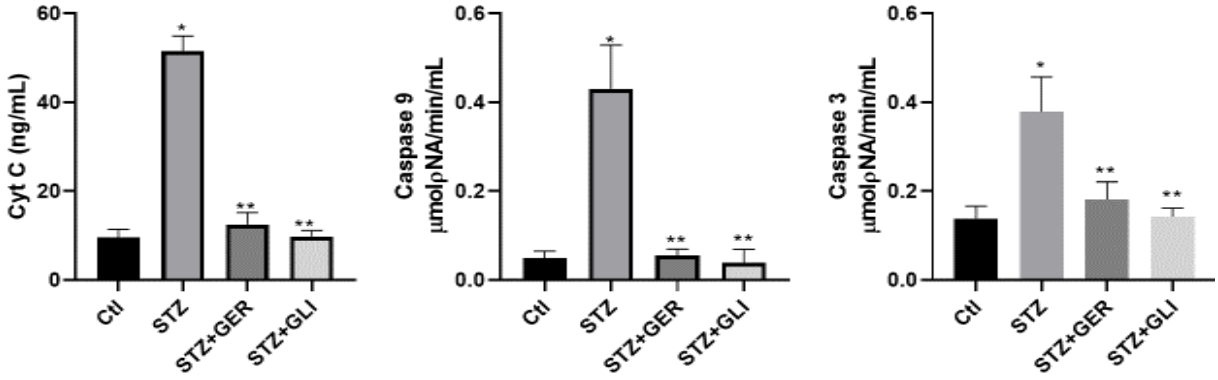

Figure 3: Effect of geraniol on cytochrome c, caspase 9 and caspase 3 in the liver of streptozotocin-induced diabetic rats. *Values are significantly different from the control. **values are significantly different from the streptozotocin group.

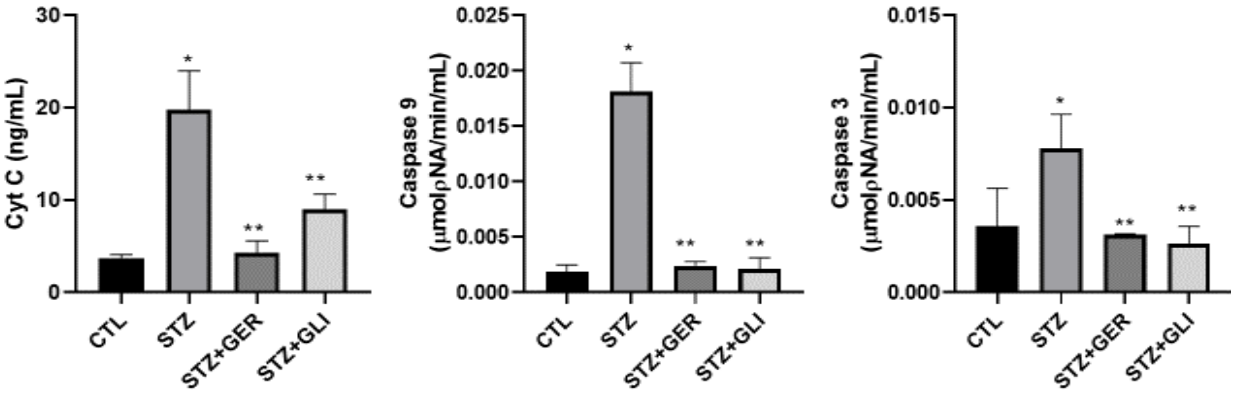

Figure 4: Effect of geraniol on cytochrome c, caspase 9, and caspase 3 in the kidney streptozotocin-induced diabetic rats. *Values are significantly different from the control. **values are significantly different from the streptozotocin group.

Caspase 9 expression was lowered significantly in the control group compared to the STZ group. Caspase 3 expression increased notably in the kidney of diabetic rats, but was greatly lowered by geraniol and glibenclamide in the STZ+GER and STZ+GLI treated groups. (Figure 4C). Previous studies have shown that hyperglycemia can induce apoptosis and the release of proapoptotic proteins into the cytosol.[34,35] Cytochrome c, a proapoptotic protein thus ensues the cell dies in a programmed fashion by activating the protease activities of C9 and C3.[36] Furthermore, high expressions of Cyt c, C9, and C3 seen in rat liver and kidney of the STZ group was significantly reduced to almost normal in the STZ+GER group. Thus, these results suggest that geraniol may be interacting easily with the mitochondrial membranes due to its lipophilic nature. This phenomenon may thus hinder the release of cytochrome c and forestalls the stimulation of caspases 9 and 3. Generally, the results from this study suggest that geraniol has great potential in ameliorating oxidative stress and mitochondrial-mediated apoptosis associated with diabetes.

Conclusion

From the findings, geraniol elicits its antidiabetic effect by reducing blood glucose levels and lowering plasma urea and creatinine levels. Overall, geraniol exhibited its antioxidant and antiapoptotic properties by increasing antioxidant enzyme activities in the STZ+Ger treated group and reducing Cyt c, caspases 9 and 3 expressions in geraniol-treated diabetic rats.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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