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ANTIOXIDANT AND ANTI-INFLAMMATORY ACTIVITIES OF *STEVIA REBAUDIANA* LEAF EXTRACT IN DIABETIC RATS

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ABSTRACT

This study explores the antioxidant and anti-inflammatory effects of *Stevia rebaudiana* aqueous leaf extract in alloxan-induced diabetic male Wistar rats. Thirty rats, comprising six normoglycemic controls (NC) and twenty-four diabetic rats were used. The diabetic rats were divided into four groups (n = 6 each): DC, diabetic rats administered distilled water; DGL, diabetic rats treated with glibenclamide; DSR_{100} and DSR_{200}, diabetic rats treated with 100 and 200 mg/kg *S. rebaudiana* extract, respectively. Treatments were administered daily via gavage for 15 days. After 15 days, animals were fasted overnight, euthanized by cervical dislocation, and blood samples collected for serum analyses. Body weight, liver weight, fasting blood glucose (FBG), and serum malondialdehyde (MDA) level were monitored. Antioxidant enzyme activities—superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx)—were also measured, alongside serum levels of pro-inflammatory cytokines interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and the anti-inflammatory cytokine interleukin-10 (IL-10). The findings revealed that *S. rebaudiana* extract significantly reduced serum MDA levels and enhanced the activities of antioxidant enzymes (SOD, CAT, and GPx) in diabetic rats. Significant ($p<0.05$) improvements in FBG, liver-to-body weight ratio, and cytokine profiles were observed in the DSR_{100} and DSR_{200} groups compared with the DC. Specifically, the extract significantly decreased IL-1β and TNF-α while elevating IL-10 level. These effects were dose-dependent, with 200 mg/kg dose showing the most pronounced benefits. In conclusion, aqueous leaf extract of *S. rebaudiana* demonstrates robust antioxidant and anti-inflammatory activities, effectively attenuating oxidative stress-induced inflammatory responses in alloxan-induced diabetic rats.

Keywords: Diabetes, *Stevia rebaudiana*, Oxidative stress, Antioxidant, Inflammation

INTRODUCTION

Diabetes is a metabolic disorder characterized by persistent hyperglycemia and disturbances in carbohydrate, fat, and protein metabolism arising from deficiencies in insulin secretion, action, or both (Zhao et al., 2023). Chronic hyperglycemia leads to glucose accumulation in the bloodstream, significantly increasing the risk of atherosclerosis, kidney damage, neuropathy, and vision loss (Prabhakar, 2024). These complications make diabetes a major contributor to global morbidity and mortality (Prabhakar, 2024). The global prevalence of type 2 diabetes (T2D) is increasing, with projections indicating that it may affect as many as 529 million people worldwide (Ong et al., 2023). This widespread condition significantly affects healthcare expenditure, patient mortality, morbidity, and overall well-being. This alarming trend correlates with an increase in associated risk factors such as obesity and overweight (Boye et al., 2023).

T2DM is characterized by increased oxidative stress and impaired antioxidant defenses, both of which play critical roles in pathogenesis and progression (Caturano et al., 2023). These imbalances are particularly pronounced in individuals with poor glucose regulation (e.g., hypoglycemia and hyperglycemia) and hypertriglyceridemia (Shibib et al., 2024). Hyperglycemia drives non-enzymatic protein glycation, producing Amadori products that undergo further oxidative modifications to form advanced glycation end-products (AGEs). AGEs contribute to oxidative stress, extracellular matrix protein expression, inflammation, and cytokine activation, which collectively exacerbate diabetic complications (Bangar et al., 2022). Additionally, metabolic stress, inflammatory mediators, and impaired antioxidant systems amplify free-radical production in diabetes (Masenga et al., 2023).

Antioxidants, which inhibit oxidation by neutralizing free radicals or preventing their formation, play a pivotal role in counteracting oxidative stress. Phenolic compounds, which are a diverse group of secondary plant metabolites, are among the most potent antioxidants. These include phenolic acids, flavonoids, diterpenes, and volatile oils, which are integral to plant defence and growth regulation mechanisms (Al-Khayri et al., 2023).

The exploration of medicinal plants as sources of natural antioxidants has garnered significant attention for drug development (Sultana et al. 2023; Adebayo et al., 2024). Many plants harbor bioactive compounds that are effective and safe in preventing degenerative diseases (Ashraf et al., 2024; Singh et al., 2023). *Stevia rebaudiana* (commonly known as stevia) has demonstrated diverse pharmacological and nutritional benefits. Ethnopharmacological studies have highlighted its potential for managing diabetes and its associated complications (Fatima et al., 2023). This study investigated the antioxidant and anti-inflammatory properties of aqueous leaf extracts of *Stevia rebaudiana* in alloxan-induced diabetic male Wistar rats with the aim of elucidating its therapeutic potential in mitigating oxidative stress and inflammation associated with diabetes.

material and methods

MATERIALS AND METHODS

Plant Material

Fresh leaves of *S. rebaudiana* were harvested from a young plant in an agroforestry area of Ipele, Ondo State (Nigeria). A Taxonomist at the Department of Plant Biology, University of Ilorin, Ilorin, Nigeria identified and authenticated the leaves. After cleaning, the stevia leaves were air-dried in the shade at ambient temperature and meticulously powdered using a kitchen blender. The powdered sample was extracted with

distilled water, maintained in the laboratory for 72 h in a percolator, and filtered using Whatman filter sheets. The extract was further purified and evaporated in a water bath for 72 h. The extract was weighed and diluted with distilled water. Before administration, all extracts were filtered using 0.22-µm pore syringe filters.

Experimental Animals

Thirty adult male Wistar rats, with an average weight ranging from 120.5 to 150.0 g, were obtained from Ibadan and housed in the Experimental Animal House, Department of Biochemistry, Landmark University, Omu-Aran, Nigeria. The subjects were maintained in stainless steel cages featuring wired floors under a 12-hour light/dark cycle, with humidity levels ranging from 25% to 35% and a temperature of 20 to 22 °C. They were provided with commercial pelletized rat chow and had ad libitum access to clean water. The research was carried out in compliance with the guidelines set forth by the Animal Care Use and Research Ethics Committee at Landmark University, Omu-Aran, Nigeria, and received approval under LUAC/BCH/2023/0004.

Animal Treatment

Rats were randomly allocated to five groups (n = 6). Group 1 (control) included normoglycemic rats administered 1 mL of normal saline via gavage. Groups 2–5 comprised alloxan-induced diabetic rats, which were rendered diabetic by a single intraperitoneal injection of 100 mg/kg alloxan monohydrate (Sigma-Aldrich). Group 2 comprised diabetic rats receiving distilled water, group 3 included diabetic rats treated with 0.07 mg/kg glibenclamide, and groups 4 and 5 consisted of diabetic rats administered 100 mg/kg and 200 mg/kg *S. rebaudiana*, respectively. The treatment was administered daily via oral gavage.

Animal Sacrifice and Sample Collection

After 15 days of treatment, the animals were weighed individually before being anesthetized with a mixture of ketamine (80 mg/kg) and xylazine (5 mg/kg), followed by sacrifice via cervical dislocation. Five milliliters (5 mL) of blood were obtained from each animal via cardiac puncture. The liver, kidney, and brain were excised, blotted with tissue paper, and free of extraneous fat before weighing.

Sample Preparation

Following a 20-min coagulation period at ambient temperature, the blood samples were transferred to centrifuge tubes and subjected to centrifugation for 15 min at 3000 rpm, resulting in the separation of their serum.

Biochemical Analyses

The fasting blood glucose level was measured using blood from the tail vein of each animal using a glucometer (Accu-Chek® Active, Roche Diagnostic, Germany). Malondialdehyde (MDA) concentration was determined using the thiobarbituric acid methos of Schmedes and Hølmer (1989). Serum interleukins (IL-1β, IL-6, and IL-10) and tumour necrosis factor-α (TNF-α) levels, were determined using their respective diagnostic kits (R&D System, Minneapolis, USA) in strict accordance with the manufacturer's instructions.

Statistical Analysis

The results are presented as the mean ± SEM of six independent determinations. Statistical analyses were performed using one-way analysis of variance (ANOVA). Mean comparisons were performed using Duncan's multiple-range test. The mean concentrations were tested for significant differences at the 95% confidence level, and a P-value of <0.05 was considered significant.

RESULTS AND DISCUSSION

Effects on Fasting Blood Glucose, Body Weight and Liver to Body Weight Ratio

Fasting blood glucose concentration was significantly higher in alloxan-induced diabetic rats compared to normoglycemic rats (NC). However, treatment with the aqueous leaf extract of *Stevia rebaudiana* significantly reduced fasting blood glucose levels after 15 days (Table 1). The elevation in fasting blood glucose in diabetic rats, indicative of rapid beta-cell destruction aligns with previous findings (Karganov et al., 2020). The reduction in fasting blood glucose levels following treatment with *S. rebaudiana* extract supports earlier studies reporting its ability to revitalize beta cells, enhance insulin synthesis, and restore hepatic glycogen storage (Elshafey et al., 2023; Abdi et al., 2023). Stevioside, a zero-calorie sweetner in the leaves of *S. rebaudiana*, has no effect on blood glucose concentration when consumed hence its usage as sugar substitute. The human body does not metabolize stevioside, and it lacks specific receptors for the compound. Stevioside is reported to exhibit antidiabetic property by counteracting α-cell hypersecretion (Hong etal., 2006).

Body weight significantly decreased in alloxan-induced diabetic rats, but significant improvements were observed following treatment with *S. rebaudiana* extract for 15 days (Table 1). This aligns with Oluba et al. (2019), who demonstrated weight loss as a consequence of alloxan induction due to compromised glucose uptake and subsequent reliance on fat and protein stores for energy. The liver-to-body weight ratio was significantly higher in alloxan-induced diabetic rats compared to NC rats, but treatment with glibenclamide (DGL) and *S. rebaudiana* extract significantly normalized this ratio (Table 1).

Liver enlargement observed in diabetic rats suggests the presence of non-alcoholic fatty liver disease (NAFLD), a common comorbidity in diabetes (Li et al., 2021). Mechanisms such as insulin resistance, hyperglycemia-induced oxidative stress, and inflammatory responses contribute to liver damage. Additionally, excessive hepatic fat accumulation can lead to NAFLD and, in severe cases, to non-alcoholic steatohepatitis, characterized by hepatic inflammation, necrosis, and fibrosis (Lian et al., 2020; Geng et al., 2021).

Table 1: FBG, body weight, liver-body weight ratio

Treatment group	FBG (mg/dL)	Body weight (g)	Liver/body weight ratio
NC	96.3 ± 5.1^{a}	203.5 ± 10.5^{c}	0.04 ± 0.00^{a}
DC	278.1 ± 10.2^{e}	111.3 ± 8.1^{a}	0.06 ± 0.00^{c}
DGL	103.1 ± 10.0^{b}	182.1 ± 6.1^{b}	0.04 ± 0.00^{a}
DSR_{100}	159.9 ± 8.6^{d}	166.2 ± 7.9^{b}	$0.05 \pm 0.00^{a,b}$
DSR_{200}	123.2 ± 10.5^{c}	173.5 ± 10.0^{b}	0.04 ± 0.00^{a}

Data are mean ± SEM of six independent determinations. Values in the same row carrying different alphabets are significant (P = .05). Note: NC, normoglycemic rats; DC, alloxan-induced diabetic rats; DGL, alloxan-induced diabetic rats treated with glibenclamide; DSR_{100}, alloxan-induced diabetic rats administered 100 mg/kg of aqueous leaf extract of *S. rebaudiana*; and DSR_{200}, alloxan-induced diabetic rats administered 200 mg/kg of aqueous leaf extract of *S. rebaudiana*.

Effects on Serum Lipid Peroxidation and Antioxidant Enzymes

Serum malondialdehyde (MDA), a marker of oxidative stress, was significantly elevated in alloxan-diabetic rats compared to normoglycemic rats. Treatment with glibenclamide normalized serum MDA levels, while *S. rebaudiana* extract significantly reduced MDA levels at both 100 and 200 mg/kg doses (Fig. 1a). Elevated MDA levels in alloxan-induced diabetes are consistent with findings by Oluba et al. (2019), highlighting oxidative stress due to an overwhelmed antioxidant defense system.

The activities of serum catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) were significantly reduced in diabetic rats compared to NC rats (Fig. 1b–d). Treatment with *S. rebaudiana* extract significantly improved these enzyme activities in diabetic rats. Antioxidant enzyme activity is crucial in mitigating oxidative stress associated with diabetes, which contributes to complications such as cardiovascular diseases and neurodegeneration (Sharifi-Rad et al., 2020; Kurek and Krejpcio, 2019).

Previous studies suggest that *S. rebaudiana* leaves, rich in steviol glycosides such as stevioside and rebaudiosides, exhibit therapeutic benefits, including antidiabetic, antioxidant, and anti-inflammatory effects (Zou et al., 2020; Kurek and Krejpcio, 2019). These glycosides pass through the body without metabolism, making *S. rebaudiana* a preferred option for managing diabetes, obesity, and cardiovascular diseases. Antioxidants are crucial in preventing and managing diabetic complications (Raina et al., 2024). For instance, Curcumin, a potent antioxidant, have been demonstrated to protect neurons against oxidative damage by regulating mitochondrial membrane potential and reducing intracellular reactive oxygen species production (Bagheri et al., 2020). Numerous studies have demonstrated the effectiveness of phytochemicals including polyphenols in alleviating diabetes and related symptoms (Kabir et al., 2021; Zhao et al., 2019). The ability of *S. rebaudiana* extract to alleviate hyperglycemia and enhance antioxidant defenses underscores its therapeutic potential.

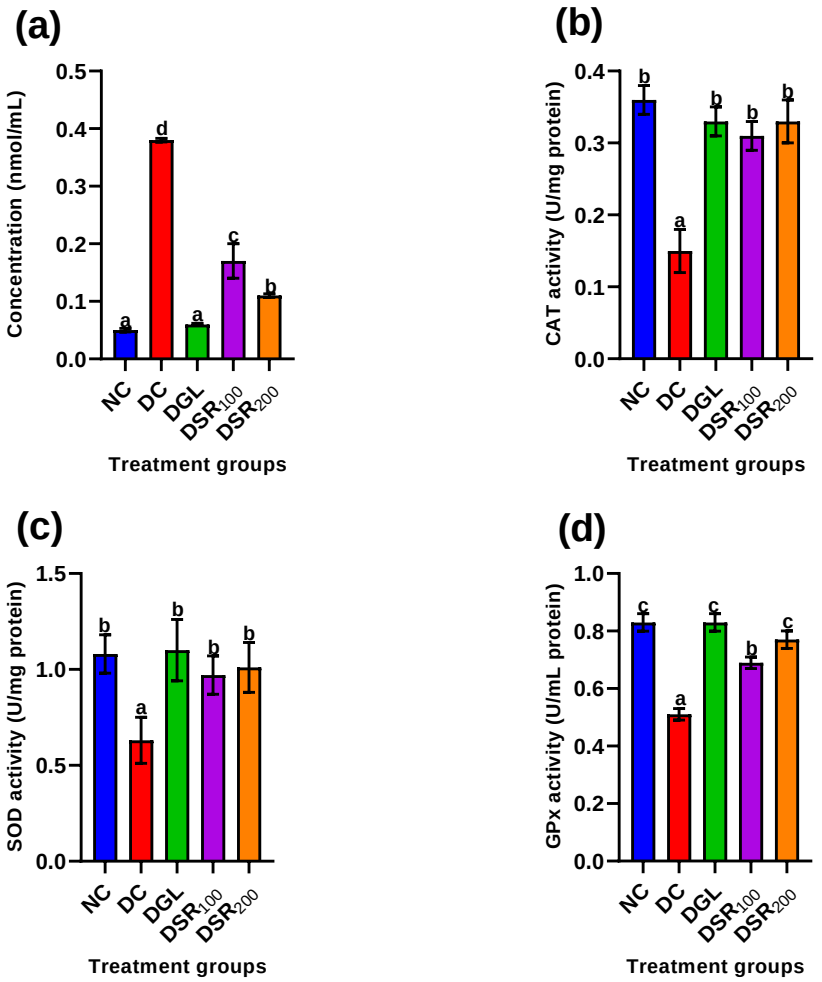

Figure 1: Serum (a) malondialdehyde concentration, (b) catalase activity, (c) superoxide dismutase activity, and (d) glutathione peroxidase activity in alloxan-induced diabetic rats administered aqueous leaf extract of *S. rebaudiana* for 15 days. Results are mean ± SEM of six independent determinations. Bars carrying different alphabets are significant (P = .05). Note: NC, normoglycemic rats; DC, alloxan-induced diabetic rats; DGL, alloxan-induced diabetic rats treated with glibenclamide; DSR_{100}, alloxan-induced diabetic rats administered 100 mg/kg of aqueous leaf extract of *S. rebaudiana*; and DSR_{200}, alloxan-induced diabetic rats administered 200 mg/kg of aqueous leaf extract of *S. rebaudiana*.

Effects on Pro-Inflammatory and Anti-Inflammatory Markers

Serum levels of pro-inflammatory markers IL-1β (Fig. 2a) and TNF-α (Fig. 2b) were significantly elevated in alloxan-induced diabetic rats compared to normoglycemic rats. Treatment with *S. rebaudiana* extract for 15 days significantly reduced IL-1β and TNF-α levels compared to untreated diabetic rats. Conversely, serum IL-10, an anti-inflammatory marker, was significantly lower in untreated diabetic rats but significantly improved following treatment with *S. rebaudiana* extract. The elevated levels of pro-inflammatory cytokines in diabetic rats reflect the pro-inflammatory state induced by diabetes, a phenomenon previously reported by Oluba et al. (2019). Oxidative stress arising from disrupted carbohydrate, protein, and lipid metabolism initiates inflammatory cascades, exacerbating diabetes-related complications (Chen et al., 2024). Treatment with *S. rebaudiana* extract mitigates this inflammation by reducing pro-inflammatory cytokines and enhancing IL-10 levels, suggesting a protective anti-inflammatory effect. A previous study reported that administering a hydroalcoholic extract of stevia leaves at a dose of 500 mg/kg inhibited inflammation and mitigated oxidative liver damage, primarily by modulating the levels of proinflammatory cytokines, including TNF-α, IL-1β, and IL-6 (Latha et al., 2017). Similarly, stevioside has been reported to suppress the secretion of pro-inflammatory cytokines in macrophages following exposure to lipopolysaccharides (Wei et al., 2021). The anti-inflammatory activity of stevioside is attributed to its ability to inhibit the mitogen-activated protein kinase and nuclear factor kappa B signaling pathways (Zou et al., 2020). The observed upregulation of the anti-inflammatory cytokine IL-10 in alloxan-induced diabetic rats highlights a novel aspect of *S. rebaudiana* extract's therapeutic potential, underscoring its efficacy in mitigating oxidative stress-induced inflammation associated with diabetes.

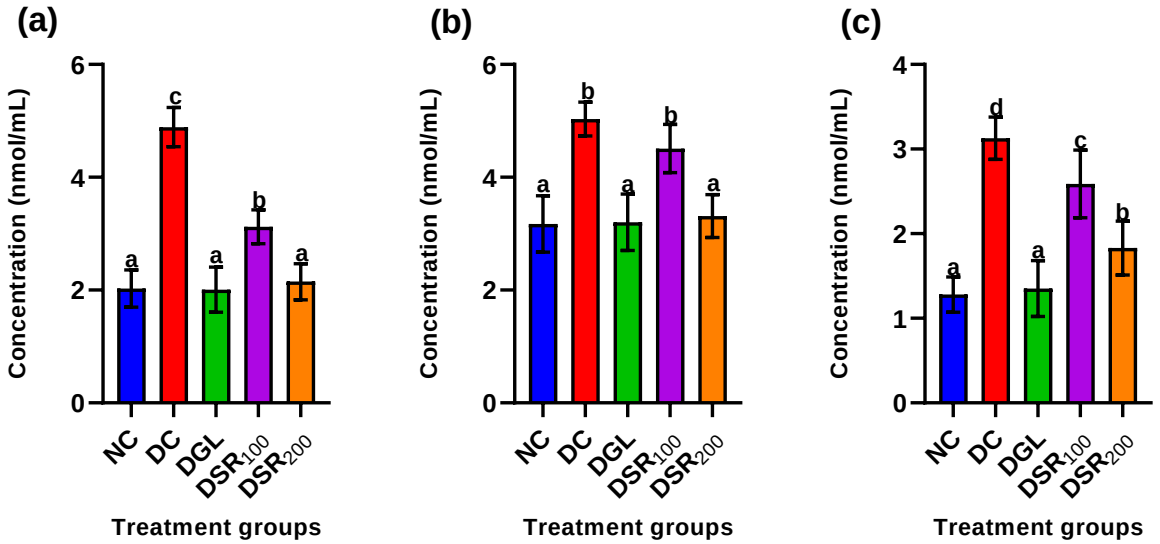

Figure 2: Serum (a) interleukin -1β (IL-1β), (b) tumour necrosis factor-α (TNF-α), and (c) interleukin-10 (IL-10) concentrations in alloxan-induced diabetic rats administered aqueous leaf extract of *S. rebaudiana* for 15 days. Results are mean ± SEM of six independent determinations. Bars carrying different alphabets are significant (P = .05). Note: NC, normoglycemic rats; DC, alloxan-induced diabetic rats; DGL, alloxan-induced diabetic rats treated with glibenclamide; DSR_{100}, alloxan-induced diabetic rats administered 100 mg/kg of aqueous leaf extract of *S. rebaudiana*; and DSR_{200}, alloxan-induced diabetic rats administered 200 mg/kg of aqueous leaf extract of *S. rebaudiana*.

CONCLUSION

This study demonstrates that aqueous leaf extract of *Stevia rebaudiana* effectively reduces alloxan-induced hyperglycemia and serum malondialdehyde while boosting serum antioxidant enzymes (catalase, superoxide dismutase, and glutathione peroxidase) activities. In addition, significant reductions in serum concentration of pro-inflammatory cytokines (IL-1β and TNF-α) and significant increase in anti-inflammatory cytokine (IL-10) were observed in the extract-treated diabetic rats. By improving serum antioxidant enzyme activity and modulating serum inflammatory markers, the extract holds promise as a therapeutic agent for managing diabetes and its associated complications.

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