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RESEARCH ARTICLE
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Physiological Heterogeneity in the Krameria Genus: Blood Glucose and Proinflammatory Effect of *Krameria Triandra* in Diabetic Rats

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia, and results in severe complications. *Krameria pauciflora* (KP) is known to exhibit antihyperglycemic effects in diabetic rats. The present study was carried out to evaluate the effects of *Krameria triandra* extract (KTE) on blood glucose and proinflammatory interleukins in diabetic rats. Twenty-four adult male rats were randomly assigned to two groups: a normal control group (n=6) and an experimental group (n=18). Diabetes was induced in rats of the experimental group by a single intraperitoneal injection of 60mg streptozotocin. The diabetic rats were subdivided into three groups (n=6 each): (1) diabetic (DM) rats treated orally with vehicle, (2) KTE diabetic (DOK) rats treated orally with KTE 100mg/kg, and (3) Metformin diabetic (DOM) rats treated orally with metformin (100mg/kg). Following the experimental period (16 days), blood samples were collected for analysis of fasting blood glucose, proinflammatory Interleukins (IL-2, IL-6, IL-1Beta), and Insulin-like Growth Factor (IGF). Initial and final body weight of rats were also recorded. The results indicated significant metabolic and immunological restructuring of KTE, characterized by increases in both fasting blood glucose and proinflammatory cytokine (IL-6), as well as suppression of IGF. This divergence of effects between *Krameria pauciflora* and *Krameria triandra* underscores the necessity for species-specific pharmacological evaluation and cautions against generalizing effects across the species of the *Krameria* genus. Further studies are warranted to elucidate the compounds and mechanisms underlying these observations and to assess the clinical relevance of KTE.

Keywords: Diabetic; *Krameria Triandra*; Proinflammatory, Streptozotocin.

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INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder of humans characterized by hyperglycemia, leading to severe complications, such as cardiovascular diseases, neuropathy, retinopathy and nephropathy (Sun, 2022; Nadhiya et al., 2024; Prabhakar, 2024). The global prevalence of diabetes continues to rise, with an estimated 537 million adults were affected in 2021, a number projected to reach 783 million by 2045 (Sun, 2022).

In individuals with diabetes, strict glycemic control is crucial, as persistent hyperglycemia adversely affects immune competence and vascular function (Ma et al., 2025). Complications from diabetes remarkably reduce quality of life and increase mortality rates. Cardiovascular diseases account for nearly 50% of diabetes-related deaths, while diabetic neuropathy also affects up to 50% of patients (American Diabetes Association, 2021). Additionally, diabetic retinopathy is a leading cause of blindness, and diabetic nephropathy contributes to the development of end-stage renal disease (Kropp et al., 2023; Kulkarni et al., 2024; Macaron et al., 2025).

Herbal products are gaining popularity for their potential role in the management of diabetes due to their bioactive compounds with antidiabetic properties. Several plant products have been shown to exhibit hypoglycemic effects by improving insulin sensitivity and reducing oxidative stress of the body (Kooti et al., 2016; Alaqeel and Al-Hariri, 2023). However, the use of these products for effective management of diabetes faces different

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challenges, such as their standardization, sustainable sourcing, and pharmacological validation (Yuan et al., 2016; Chunarkar-Patil et al., 2024; Ahmad et al., 2025). Ethnobotanical studies highlight the need for biodiversity conservation to ensure the regular availability of different medicinal plants (Sasidharan et al., 2011; Shukla, 2023; Gitima et al., 2025).

Rhatany is a hemiparasitic shrub that belongs to the family of *Krameriaceae*, a monogeneric family of 18 species native to South America. Rhatany is also known as *Krameria lappacea* or *Krameria triandra*, and traditionally has been used for the management of various health problems due to its rich contents of tannins, flavonoids, lignans, and terpenoids (Sumathi and Thomas, 2017).

The medicinal properties of Krameria triandra have been studied in different research settings and the results have shown that the plant exhibits anti-inflammatory (Baumgartner et al., 2011), antimicrobial (Velasco-Lezama et al., 2023), antioxidant, photoprotective, and radical scavenging activity and protection (Abdel-Gaber et al., 2024). Additionally, the beneficial effects of this plant against exposure to free radicals, physical, and chemical inducers have also been reported (Korać and Khambholja, 2011).

Most of the available literature regarding the antidiabetic effects of *Krameria* species relates to *Krameria pauciflora* (KP). In vivo study using methanol extracts of KP roots demonstrated an antihyperglycemic effect in diabetic rats, and this effect was comparable to that of metformin (Ramírez-Cisneros et al., 2012). However, the effect was not consistent across all extracts, and the mechanism remains unclear.

Despite its similar phytochemical profile (notably tannins and flavonoids), there is a conspicuous lack of published studies directly investigating the antidiabetic effects of *Krameria triandra* in either animal or human models. No clinical or preclinical studies could be found in the existing literature that specifically evaluated the impact of *Krameria triandra* extract (KTE) on blood glucose regulation, insulin sensitivity, or diabetic complications. This knowledge gap demands comprehensive research to explore the potential hypoglycemic effects of KTE. Therefore, the present study was planned to investigate any possible hypoglycemic and anti-inflammatory effects of KTE in a rat model.

MATERIALS & METHODS

Preparation of Plant Extract

Krameria triandra (KT) leaves (alhussainattara.com, Saudi Arabia) were dried under shade and grinded to get a fine powder (particle size of about 500µm) according to procedure described previously (Abdel-Gaber et al., 2024). A total of 25g powder was taken from this plant sample and dissolved in 500mL of water, methanol, n-hexane, and ethyl acetate for 72 hours. A 24-hour extraction in a Soxhlet apparatus was carried out to obtain the aqueous extract. The obtained extracts were concentrated under reduced pressure using a rotary evaporator, and the residues were stored in airtight containers at 4°C until further use. Prior to administration in rats, the dried extracts were freshly dissolved in 0.5% carboxymethyl cellulose suspension as the vehicle to the required concentrations.

Study Design

A total of 24 adult male rats, were selected for this study. These rats were kept under standard environmental facilities, including 24±1°C, 45±5% humidity, and 12 12-hour light/dark cycle. All animals were fed standard laboratory pellet chow and had free access to distilled water. These rats were allowed an acclimatization period of one week prior to the start of experiments.

The initial body weight of each rat was recorded before the start of treatments. Then experimental rats were randomly assigned to two groups: a normal control group (n=6), fed a standard diet, and an experimental group (n=18). Diabetes was induced in the experimental group by a single intraperitoneal injection of 60mg streptozotocin (Sigma-Aldrich; USA), as described earlier (Al-Hariri et al., 2019). Three days later, tail blood was collected, and fasting blood glucose level was measured by using a glucometer (Accu-Chek; Roche) to confirm the diabetes status. Rats showing diabetes (blood glucose level >200mg/dL) were included in the study (El Agawany et al., 2012). The diabetic rats were subdivided into three groups (n=6 each): (1); diabetic (DM) rats treated orally with vehicle (5 mL/kg), (2); KTE diabetic (DOK) rats treated orally with methanol extract of KTE 100mg/kg (oral gavage), the selected dose was based on a prior study that evaluated the hypoglycemic effects of *Krameria pauciflora* (Ramírez-Cisneros et al., 2012) and (3); Metformin diabetic (DOM) rats treated orally with metformin (100mg/kg), as described by Ramírez-Cisneros et al. (2012). These treatments were given orally to rats of the respective groups daily for 16 days.

Blood Studies

Following the experimental period (16 day), the animals were anesthetized via sevoflurane inhalation before feeding, as previously described (Alaqeel et al., 2022). Body weight of each rat of all groups was recorded and blood samples without anticoagulant were collected from the abdominal aorta for fasting blood glucose and other metabolite analyses. Blood samples were allowed to clot at room temperature, serum was separated following centrifugation and stored at -20°C for further analysis. Serum levels of proinflammatory and growth markers, including Interleukins (IL-2, IL-6, IL-1Beta) and Insulin-like Growth Factor (IGF) (elabscience, USA), were quantified using enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions.

Statistical Analysis

The data were statistically analyzed using IBM SPSS Statistics for Windows, version 24.0. Results were presented as mean±SE. Statistical assessment was carried out using a paired t-test and one-way ANOVA, followed by Fisher's Least Significant Difference (LSD) multiple comparison test. A P-value of less than 0.05 was deemed statistically significant.

RESULTS

Body Weight Change Patterns

No statistically significant differences were observed in initial body weight among rats of all study groups. However, at the end of the experiment, the analysis revealed

significant effects of treatments on final body weight (P<0.001). Control rats exhibited an average weight gain of 38.0±5.0g during the study, while all experimental groups showed significant body weight reduction at end of the study compared to initial body weight. This reduction was seen most markedly in the DM group than the treated diabetic groups [DM Group: -26.52±11.64g (13.5% decrease), DOK Group: -22.62±9.73g (10.8% decrease) and DOM Group: -15.70±21.05g (6.3% decrease)]. Meanwhile, Paired T test confirmed the significant weight gain during the study in rats of the control group, as shown in Fig. 1.

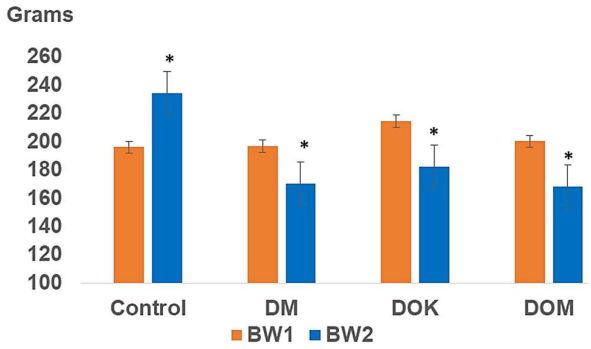

Fig. 1: Comparison of body weight of rats before and after the experiment across study groups (Paired T-test). DM: diabetes mellitus; DOK: Diabetic rats treated orally with *Krameria triandra* extract; DOM: Diabetic rats treated orally with metformin; BW1: Initial body weight; BW2: Final body weight; *: P<0.05.

Fasting Blood Glucose Levels

The statistical analysis of fasting blood glucose level revealed significant changes in all the study groups (F=3.688, P≤0.05). Fasting blood glucose levels in the normal control group were significantly less compared to all other experimental groups (P≤0.05), confirming the successful induction of the diabetic state in the treatment groups. Quantitative analysis among the treatment interventions revealed that the DOM group exhibited significantly higher reduction in fasting blood glucose (P≤0.05) compared to non-treated diabetic group (DM) and KTE treated group (DOK), suggesting a potentially higher glucose-lowering effect of the metformin treatment compared to KTE (Fig. 2).

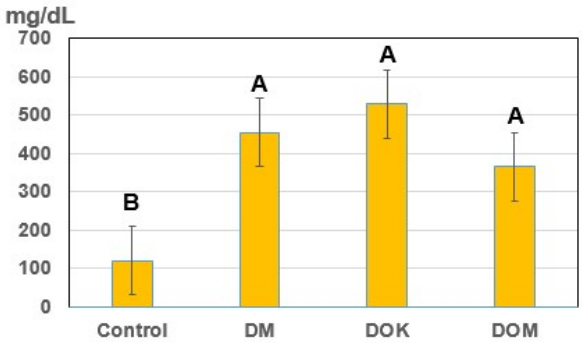

Fig. 2: Fasting blood glucose levels in all study groups at the end of the experiment (one-way ANOVA). DM: Diabetes mellitus; DOK: Diabetic rats treated orally with *Krameria triandra* extract; DOM: Diabetic rats treated orally with metformin. All treatment groups differ significantly (P<0.05) as compared to the control group.

Insulin-like Growth Factor

The ANOVA identified significant IGF variations between groups (F=3.53, P≤0.05), with specific contrasts when comparing the control vs. DOK with -3045.9pg/ml as well as DM with -2221.1pg/mL (P≤0.05) reduction, respectively, as shown in Table 1.

Table 1: Effect of *Krameria triandra* extract on the blood biomarkers in Streptozotocin-induced diabetic rats.

ParameterS	Group	Mean±SE	Significance
IGF (pg/mL)	Control	4804.5±647	
	DM	2583.4±866	*
	DOK	1758.6±450	
	DOM	3352.2±727	NS
IL-1B	Control	45.1±16	NS
	DM	15.8±4	NS
	DOK	53.2±13	NS
	DOM	213.5±110	NS
IL-2	Control	2.2±0.2	NS
	DM	1.5±0.1	NS
	DOK	2.7±0.7	NS
	DOM	2.2±0.6	NS
IL-6	Control	545.1±64	
	DM	454.7±56	*
	DOK	1336.9±433	
	DOM	402.6±30	

*: Fisher's Least Significant Difference multiple comparison; DM: Diabetes mellitus; DOK: Diabetic rats treated orally with *Krameria triandra* extract; DOM: Diabetic rats treated orally with Metformin.

Cytokine Profile Alterations

The inflammatory cytokine IL-6 levels showed significant intergroup variation (F=3.93, P≤0.05), with significant elevation in the DOK group (1336.9±433pg/mL) compared to the other study groups [control group (545.1±64pg/mL), DM (454.7±56pg/mL) and DOM (402.6±30pg/mL) respectively (Table 1). Several inflammatory markers, including IL-1 Beta (F=1.24, P≥0.05), and IL-2 (F=0.84, P≥0.05), showed statistically non-significant differences among the study groups (Table 1).

DISCUSSION

To the best of our knowledge this is the first study that highlighted the efficacy of KTE the management of diabetes mellitus in rats. Our results induced significant metabolic and immunological restructuring effect of KTE, characterized by increased both fasting blood glucose and proinflammatory cytokine (IL-6), as well as suppression of IGF in rats. These results are in contrast with reports of anti-inflammatory and antidiabetic effects from other species (Ramírez-Cisneros et al., 2012). Despite the fact that *Krameria triandra* is well recognized for its anti-inflammatory properties, attributed to its tannin contents (Baumgartner et al., 2011), 145% increase in IL-6 levels observed in the DOK group relative to control group suggests that this treatment modality elicits a distinct pro-inflammatory response.

The observed increase in IL-6 suggests that KTE may stimulate a pro-inflammatory response. These results indicate that the failure of KTE in the present study to improve glycemic control may be partly explained by IL-6–mediated inflammatory mechanisms (Devaraj et al., 2010; Yu et al., 2024).

In contrast, studies on *Krameria pauciflora* (KP) have demonstrated anti-inflammatory and antihyperglycemic effects of KP. Methanol extract of KP reduced inflammation in Carrageenan-induced rat paw edema and, at certain doses, lowered blood glucose in diabetic rats comparably to the effect of metformin (Ramírez-Cisneros et al., 2012). Notably, these effects were not observed in all extracts or at all doses, and no hypoglycemic effect was seen in normoglycemic animals. The anti-inflammatory and antidiabetic effects of KP were attributed to its flavonoid contents, particularly catechins, which are known for their antioxidant and metabolic benefits (Baranwal et al., 2022).

The absence of elevated levels of proinflammatory markers in the DM group, despite the presence of hyperglycemia, suggests that the increase in blood glucose observed in the DOK group may be due to aggravation of inflammatory response mechanisms. Some plant-derived compounds such as certain polysaccharides and tannins can act as pathogen associated molecular patterns. When these compounds are recognized by pattern recognition receptors like Toll-like receptors (TLRs), they can activate the NF-κB signaling pathway. This activation leads to the production of proinflammatory cytokines and may also influence glucose metabolism (Hou et al., 2019; Mobeen et al., 2025). Chronic activation of this pathway has been linked to insulin resistance and elevated blood glucose levels, as inflammation interferes with insulin signaling (Devaraj et al., 2010; Zeng et al., 2016).

The current study did not detect any significant changes in some proinflammatory interleukins. However, IL-1α and IL-2 may not increase during inflammation due to strong negative regulation, differences in their release and activation requirements, and the specific immune context (Evavold and Kagan, 2022). Meanwhile, cytokines like IL-6 and IL-1β are more readily induced and less tightly regulated, leading to their frequent elevation in inflammatory states (Supino et al., 2022). Additionally, IL-1β and IL-6 increase together because IL-1β directly induces IL-6 and both are central to the inflammatory response. IL-2 cytokines do not always increase in the same settings due to their specific release requirements and roles in different stages of the immune system (Chen et al., 2005).

In the present study, IGF-1 level was significant reduced across DOK and DM groups. In diabetes, IGF-1 levels decrease primarily due to insulin deficiency or resistance, which impairs hepatic IGF-1 and insulin deficiency. Additionally, increased IGF-binding protein-1 (IGFBP-1), normally suppressed by insulin, and further lowers bioactive IGF-1 by binding and inactivating it. Chronic inflammation and oxidative stress in diabetes also suppress IGF-1 signaling. These changes contribute to poor tissue repair, muscle atrophy, impaired myogenesis, and accelerated sarcopenia. Elevated levels of proinflammatory cytokines can occur due to complex regulatory interactions and disease-specific mechanisms.

Conclusion

There is a substantial gap in the literature regarding the metabolic and immunological effects of *Krameria triandra*. The finding that KTE increases proinflammatory cytokines, and blood glucose in rats contradicts the reports of anti-inflammatory and antidiabetic effects of other *Krameria* species. This divergence underscores the necessity for species-specific pharmacological evaluation and cautions against generalizing effects across the *Krameria* genus. Further studies are warranted to elucidate the compounds and mechanisms underlying these observations and to assess the clinical relevance of KTE.

DECLARATIONS

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