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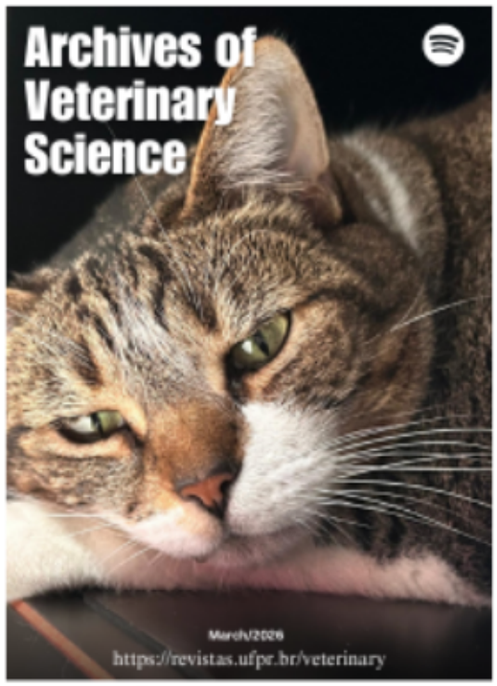

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Exploring the therapeutic potential of honeybee venom in mitigating diabetic reproductive complications: insights from *in vitro* and *in vivo* studies in rats

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Abstract: Diabetes mellitus impairs male reproductive health through oxidative stress–mediated pathways. This study investigated the antioxidant capacity and reproductive effects of honeybee venom (apitoxin) in diabetic male rats. The *in vitro* antioxidant activity of bee venom showed a DPPH radical scavenging rate of 76.85 ± 1.55%, close to that of ascorbic acid (79.29 ± 1.82%, $P < 0.001$), and a metal chelating activity of 91.69 ± 2.55% ($P = 0.227$). For *in vivo* evaluation, streptozotocin-induced diabetic Wistar rats (n = 6/group) were assigned to control (C), apitoxin-treated (A), diabetic (D), and diabetic + apitoxin (DA) groups for 28 days. Diabetic rats exhibited markedly decreased sperm motility (61.4 ± 6.9%) compared to C (78.6 ± 3.8%) and A (82.9 ± 4.9%) ($P = 0.007$), whereas apitoxin treatment in DA rats improved motility to 77.1 ± 7.6%. Epididymal, vesicular, and prostatic weights were reduced in diabetic groups ($P < 0.01$). Oxidative stress was evident with elevated MDA in D (49.3 ± 31.1 nmol/mg protein) versus DA (27.7 ± 4.4) and C (29.0 ± 3.0) ($P = 0.023$), while GSH was significantly higher in DA (54.4 ± 18.4 µmol/mg protein) compared to D (35.2 ± 4.2) ($P = 0.006$). Overall, honeybee venom ameliorated diabetes-induced oxidative damage and improved sperm quality through redox modulation. These findings highlight its potential as a natural therapeutic agent against diabetic reproductive complications.
Keywords: Honeybee venom, diabetes, oxidative stress, sperm motility, antioxidant activity.

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder that adversely affects quality of life in both humans and animals (Sharma et al., 2017). This detrimental effect primarily stems from the disruption of redox homeostasis within biological tissues, leading to an imbalance between oxidant generation and antioxidant defense (Korac et al., 2021). The excessive generation of reactive oxygen and nitrogen species (ROS and RNS) within tissues and organs disrupts metabolic pathways. It impairs cells sensitive to metabolic alterations, potentially leading to cellular and tissue demise. DM is characterized by significant disturbances in both glucose and fatty acid metabolism (Sivri, 2025). In managing DM, lifestyle modifications, dietary adjustments, and stress management strategies are recommended in conjunction with medications, including insulin tailored to the specific type of diabetes (Rosenfeld et al., 2025).

Given the established role of oxidative stress in diabetic complications, antioxidant-based interventions have gained interest, and bee venom presents a promising natural candidate due to its bioactive peptide components (Al-Hatamleh, 2020).
The male reproductive system is particularly vulnerable to diabetes-induced oxidative and metabolic alterations (Leisegang, 2022). Vascular, neural, and myopathic impairments contribute to reproductive dysfunction in males, thereby impacting sperm parameters as well. Perturbations in seminal activity parameters resulting from DM are often associated with infertility concerns (Gandhi et al., 2017). The susceptibility of spermatozoa membranes to peroxidative damage, owing to their lipid density, has been well-documented (Hwang, 2025), with previous reports outlining the effects of lipid peroxidation on semen quality in rats with experimental STZ-induced diabetes (Badejogbin, 2025).

Honeybee venom (apitoxin) from *Apis mellifera* is a complex mixture of peptides, enzymes, and bioactive molecules. Apitoxin has found therapeutic applications due to its recognized anti-inflammatory, antioxidant, and immune-modulating effects (Kasozi, 2020). Studies have indicated that administering apitoxin (0.1-0.3 mg per rabbit, subcutaneously) to male rabbits for 20 weeks enhances reproductive performance and antioxidant capacity (El-Hanoun et al., 2020). Similarly, research has shown that administering apitoxin at precise dosages, for specific durations, and via appropriate injection methods in female rats improves reproductive and immune performance (Elkomy et al., 2021). However, limited studies have examined the influence of bee venom on testicular redox balance and reproductive performance under diabetic conditions, particularly regarding semen quality, organ weights, and oxidative stress markers such as MDA, GSH, and NOx.

This study aimed to investigate the antioxidant capacity and reproductive effects of honeybee venom in diabetic male rats. Specifically, the objectives were:

1. To assess the *in vitro* antioxidant activity of honeybee venom using standard biochemical assays.
2. To evaluate the *in vivo* influence of honeybee venom administration on semen quality, testicular redox status, and reproductive organ morphology in streptozotocin-induced diabetic rats.
3. To examine the potential association between oxidative stress modulation and reproductive outcomes under diabetic conditions.

It was hypothesized that honeybee venom, owing to its bioactive constituents such as melittin and phospholipase A_2, may improve antioxidant status and testicular function by mitigating oxidative stress and supporting sperm quality in diabetic rats.

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