

Effects of orally administered aqueous extract of *Phoenix dactylifera* (date) seeds on reproductive hormones, sperm parameters, testicular oxidative stress, and histology in male Wistar rats

Blessing Francis * and Jessica Erhunmwunse

Department of Veterinary Physiology and Biochemistry, Faculty of Veterinary Medicine, University of Benin, Benin City, Nigeria.

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Abstract

Phoenix dactylifera (date) seeds are reportedly rich in phenolic compounds and flavonoids, with potent antioxidant properties, making them potentially relevant for improving reproductive and physiological health. This present study administered aqueous *P. dactylifera* seed extract to male Wistar rats, and evaluated its effects on their serum levels of male reproductive hormones, sperm counts and motility, and testicular levels of oxidative stress markers and histology. Dried date seeds were extracted with water for 48 hours, and the extract was freeze dried and refrigerated prior to use for the study. Twenty-five adult male Wistar rats were used for the study; they were randomly allocated into five groups (a control group and four treatment groups). The control group received 0.5 ml distilled water, while the treatment groups received 50, 100, 200, and 400 mg/kg body weight of aqueous date seed extract orally for 35 consecutive days. The rats were humanely sacrificed 24 hours after the final dose. Blood was collected and serum testosterone and luteinizing hormone (LH) levels were assayed. The testicles were harvested, and testicular levels of oxidative stress markers [superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and malondialdehyde (MDA)] were determined. Also the epididymis of each rat was harvested and epididymal sperm counts and motility were evaluated. Histological evaluation of the testis and epididymis were also done. Results showed that oral administration of the extract led to significantly higher ($p < 0.05$) total sperm counts in the rat groups that were given 200 and 400 mg/kg extract in a dose dependent manner. Progressive sperm motility was significantly higher ($p < 0.05$) in the rat group that was given 400 mg/kg of the extract. Plasma testosterone levels were also significantly ($p < 0.05$) higher in the rat groups given 200 mg/kg and 400 mg/kg of the extract, while LH levels were significantly ($p < 0.05$) higher in a dose dependent manner in the all the extract treated groups. Testicular SOD activity was significantly ($p < 0.05$) higher in the rat groups given 200 and 400 mg/kg extract, whereas testicular CAT and GPx activity showed no significant variations among the groups. Testicular MDA levels were significantly ($p < 0.05$) lower in the rat groups given 100, 200 and 400 mg/kg of the extract. Histological examination revealed normal testicular and epididymal architecture. It was concluded that administration of aqueous *P. dactylifera* seed extract led to significantly higher serum levels of testosterone and LH and enhanced epididymal total sperm counts and motility in the extract-treated rats, probably through improved antioxidant defense and reduced lipid peroxidation.

Keywords: *Phoenix dactylifera* seed; Aqueous extract; Male rats; Epididymal sperm counts and motility; Male hormones; Testicular oxidative stress.

* **Correspondence:** Blessing Francis; Email: blessing.francis@uniben.edu; Phone: +2348030713997

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Introduction

Infertility has affected millions of humans and animals worldwide, with male factors being implicated in 25 – 50% of the cases (Skoracka *et al.*, 2020; Torres-Arce *et al.*, 2021; Takalani *et al.*, 2023). Many environmental and genetic factors, including oxidative stress have been associated with male infertility (Bisht *et al.*, 2017; Alahmar, 2019; Torres-Arce *et al.*, 2021). Oxidative stress has been reported to be a major contributor to sperm dysfunction, impairing membrane integrity, mitochondrial activity and DNA stability in spermatozoa and causing damage to nuclear DNA and sperm epigenome among others (Aitken and Roman, 2008; Bisht *et al.*, 2017).

Due to their promising therapeutic potential and widely believed relatively low risk of adverse effects, scientists are increasingly becoming interested in therapy using natural products, particularly plant-derived substances (Najmi *et al.*, 2022). Among these, *Phoenix dactylifera* holds a unique position both as a nutritional and medicinal plant (Mahomoodally *et al.*, 2024). *Phoenix dactylifera* commonly known as the date palm and Dabino (local name), belongs to the Family Arecaceae and genus *Phoenix*. It is a perennial, monocotyledonous plant whose fruits are oblong drupes containing single elongated seeds (Al-Karmadi and Okoh, 2024; Dharajiya *et al.*, 2025). Date fruit is considered a complete diet as it has been reported to be rich with plenty of vitamins and minerals, and contains a wide range of beneficial secondary metabolites (Al-Snafi and Thuwaini, 2023).

While the date fruit is widely known for its high metabolizable energy content and antioxidant-rich properties, recent attention has turned to its often-overlooked by-product, the date seed. Khan *et al.* (2018) reported that date seed exhibited antioxidant, hepatoprotective, nephroprotective and hypolipidemic effects. Its antioxidant properties have been attributed to the

presence of phenolic compounds and flavonoids which have the potential of boosting serum levels of antioxidant enzymes, such as catalase and superoxide dismutase (Masenga *et al.*, 2023). Although date seed oil preparations have been shown to improve spermatogenesis and increase testicular antioxidant enzymes (Ben *et al.*, 2009; Al Za'abi *et al.*, 2022), no study has evaluated the dose-dependent effects of date seed aqueous extract on male reproductive hormones, sperm counts and motility, and testicular levels of oxidative stress markers. The present study administered aqueous *P. dactylifera* seed extract to male Wistar rats, and evaluated its effects on serum levels of reproductive hormones, sperm counts and motility, and testicular levels of oxidative stress markers and histology.

Materials and Methods

Plant Material: The *Phoenix dactylifera* (date) seeds that were used for the study were purchased from Oba Market, Benin City, Edo State, Nigeria, and identified by a taxonomist and deposited at the Herbarium Unit of the Department of Plant Biology and Biotechnology, University of Benin, Benin City, with Voucher Number: UBH-P420.

Extraction of Date Seed: The date seeds were manually separated from the fleshy pulp, thoroughly washed with clean water and sun-dried. The dried seeds were ground into a fine powder using a laboratory-grade electric grinder; this was then immersed in water for 48 hours after which it was filtered using a muslin cloth. The aqueous extract was then freeze dried, and the powdered extract was stored in an airtight container and refrigerated at 4°C throughout the study.

Animals: A total of 25 adult male Wistar rats (*Rattus norvegicus*), weighing between 102 – 168g, were obtained from the Animal House of the Department of Anatomy, University of Benin, Nigeria. The rats were housed in cages

floored with wood shavings. They were acclimatized for two weeks prior to the commencement of the experiment and were maintained under standard laboratory conditions in well ventilated cages with wire mesh at the top. They were kept at room temperature with 12: 12 hours light to dark cycles, and were provided with clean drinking water and rat feed, *ad libitum*. The Ethics Committee, Faculty of Pharmacy, University of Benin, Nigeria gave ethical clearance for this study (Reference Number: EC/FP/025/01).

Experimental Design: At the end of the two weeks acclimatization, the rats were randomly allocated to five groups of six rats each: A control group and four treatment groups given varied doses – 50, 100, 200 and 400 mg/kg of the extract. Individual rats in each group were weighed at the start of the experiment and at weekly intervals at the same time range in the mornings to determine new body weights for preparation of fresh stock of *Phoenix dactylifera* seed extract during the experiment. The extract was reconstituted daily with distilled water and orally administered to the experimental animals via gastric *gavage*. The four treated groups received single doses of 50, 100, 200 and 400 mg/kg of the extract, respectively, daily for 35 days, while the control group was given 0.5 ml distilled water (via *gavage*). The rats were humanely sacrificed twenty-four hours after the last treatment.

Sample collection: Blood samples were collected via cardiac puncture through the inferior vena cava, allowed to stand to clot and then centrifuged. The serum was carefully decanted and frozen until needed for testosterone and luteinizing hormone (LH) assay. The testes and epididymis were harvested. The cauda epididymis from each rat was placed in normal saline and seminal analysis (sperm count and sperm motility) was performed immediately. The testis and portions of epididymis from each rat were collected and preserved in Bouin's fluid for

histological examinations, while the second testis from each rat was frozen and later homogenized in cold normal saline in 4:1 ratio, volume of normal saline/weight. The homogenates were centrifuged at 3,000 rpm for 10 minutes, and the supernatants were used for assay of oxidative stress parameters.

Biochemical determinations: Serum concentrations of testosterone and LH were measured using commercially available enzyme linked immunosorbent assay (ELISA) kits (Monobind[®] inc., Lake Forest, CA, USA) according to the manufacturer's instructions. The testosterone test kit utilized microplates pre-coated with testosterone specific-antibodies in a competitive format. The LH kit employed a sandwich ELISA format, where the target hormone is captured by antibodies immobilized on the plate surface.

Testicular activity of superoxide dismutase (SOD) were determined according to the methods of Misra and Fridovich (1972) which is based on the principle that superoxide dismutase inhibits the auto-oxidation of adrenaline by catalysing the breakdown of superoxide anion. The degree of inhibition reflected the activity of SOD which was determined at 420 nm wavelength with the aid of a spectrophotometer. Catalase (CAT) activity was estimated by measuring the rate of decomposition of hydrogen peroxide as described by Cohen *et al.* (1970). Glutathione peroxidase (GPx) activity was determined spectrophotometrically by measuring the rate of NADPH oxidation at 340 nm wavelength according to the coupled enzyme assay system as described by Nyman (1959). Malondialdehyde (MDA) levels were determined using the thiobarbituric acid assay method as described by Buege and Aust (1978).

Total sperm count and sperm motility evaluation: The cauda epididymes were carefully dissected, and its contents were expressed into 2 ml of normal saline (0.9%

NaCl) and total sperm count was then enumerated using a manual cytometer as described by Abba and Igboke (2015). Sperm motility was immediately assessed by placing a drop (10 μ L) of sperm sample on a grease-free slide. A cover slip was put over the drop and examined under the microscope ($\times 40$ magnification) as described by Chima *et al.* (2017).

Histology of the testis and epididymis: The testes and epididymis that were fixed in Bouin's solution were processed routinely, embedded in paraffin, sectioned at 5 μ m and stained with hematoxylin and eosin (H&E) for light microscopic examination, as described by Bancroft and Gamble (2008).

Statistical Analysis: Statistical analysis was done using GraphPad prism version 8.0.2. Quantitative data generated were subjected to one-way analysis of variance (ANOVA). Variant means were separated using the least significant difference method. Significance was accepted at $p < 0.05$. Summary of the results were presented as means \pm SEM.

Results

Serum levels of testosterone in the rat groups treated with 200 and 400 mg/kg extract were significantly ($p < 0.01$) higher than that of the

untreated control group (Figure 1). Also the serum LH levels of the rat groups treated with 50, 200 and 400 mg/kg were significantly ($p < 0.05$) higher than that of the untreated control group in a dose dependent manner (Figure 1).

The testicular catalase (CAT) and glutathione peroxidase (GPx) activity of the rat groups did not significantly vary ($p > 0.05$), but the testicular superoxide dismutase (SOD) activity of the rat groups treated with 200 and 400 mg/kg extract were significantly ($p < 0.05$) higher than that of the control, while the testicular malondialdehyde (MDA) levels of the rat groups treated with 100, 200 and 400 mg/kg extract were significantly lower than that of the untreated control (Figure 2).

Mean total sperm counts of rats given 200 and 400 mg/kg extract were significantly ($p < 0.01$) higher than that of the untreated control (Figure 3), while sperm motility was highest in the rat group treated with 400 mg/kg extract, which was also significantly ($p < 0.05$) higher than that of the untreated control (Figure 4). The number of sluggish sperm cells and non-motile cells did not significantly vary across the groups, though the mean number of non-motile cells was highest in the group treated with 100 mg/kg extract (Figure 4).

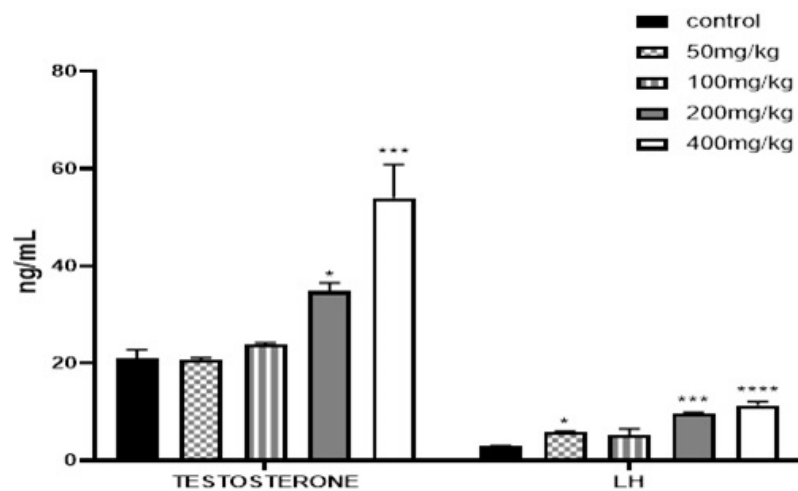


Figure 1. Serum levels of testosterone and luteinizing hormone (LH) of rat groups given varied doses of aqueous *Phoenix dactylifera* (date) seed extract for 35 days, compared with an untreated control.

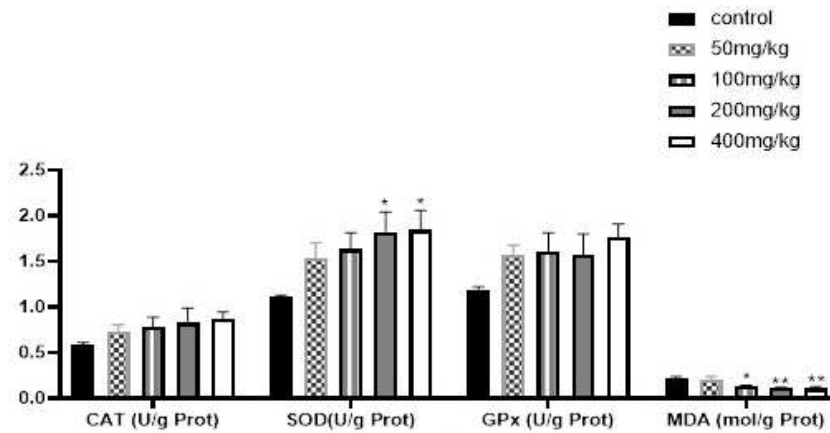


Figure 2. Testicular activity of catalase, (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) and malondialdehyde (MDA) levels of rat groups given varied doses of aqueous *Phoenix dactylifera* (date) seed extract for 35 days, compared with an untreated control.

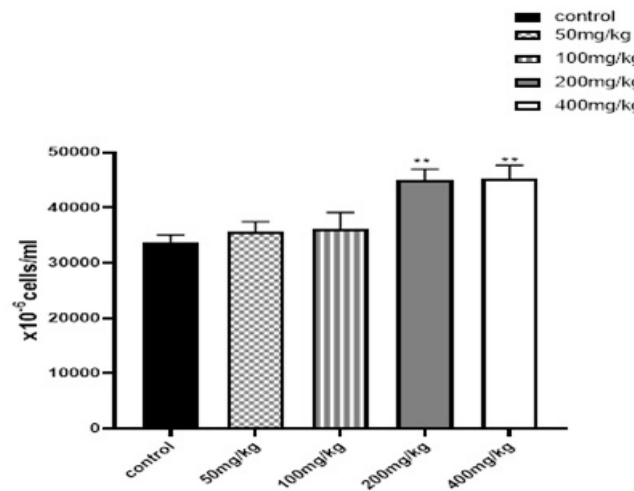


Figure 3. Total epididymal sperm counts of rat groups given varied doses of aqueous *Phoenix dactylifera* (date) seed extract for 35 days, compared with an untreated control.

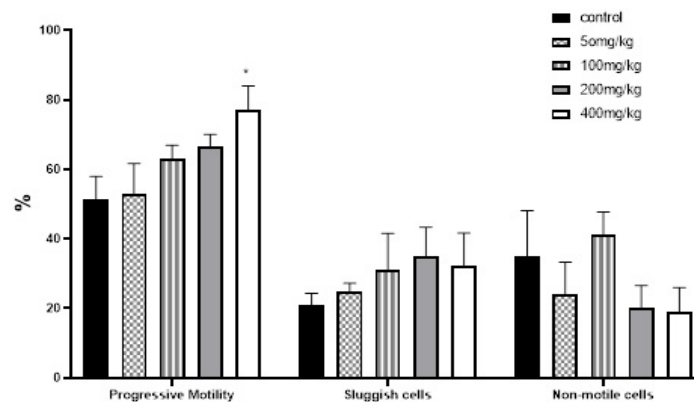


Figure 4. Percentage progressive motility, sluggish cells and non-motile cells in epididymal sperm of rat groups given varied doses of aqueous *Phoenix dactylifera* (date) seed extract for 35 days, compared with an untreated control.

Histological evaluation of the epididymis showed that no lesions in the epididymis of rats of all rat groups except the epididymis of the rat group given 200 mg/kg group which

showed depletion of spermatozoa in the ducts (Figure 5). Also, no lesions were observed in stained sections of the testis of rats in all the groups (Figure 6).

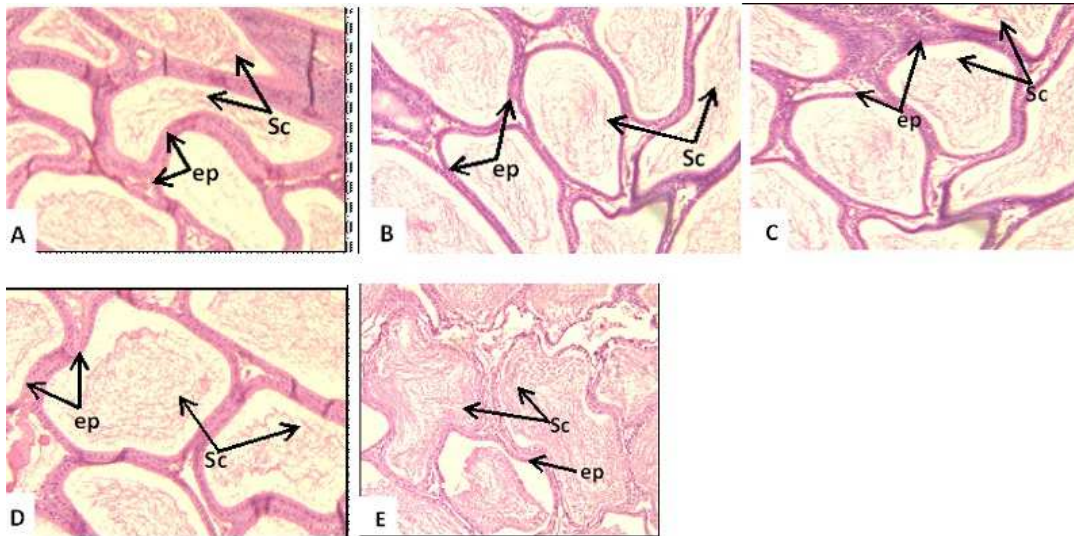


Figure 5. Section of the epididymis of rat groups given varied doses of aqueous *Phoenix dactylifera* (date) seed extract for 35 days, compared with an untreated control, showing no lesions on the epithelial linings (ep) and normal sperm density (sc) except in the group treated with 200 mg/kg extract that had lower sperm density. [A – untreated control; B – 50 mg/kg extract; C – 100 mg/kg extract; D – 200 mg/kg extract; E – 400 mg/kg extract.] H & E, $\times 100$.

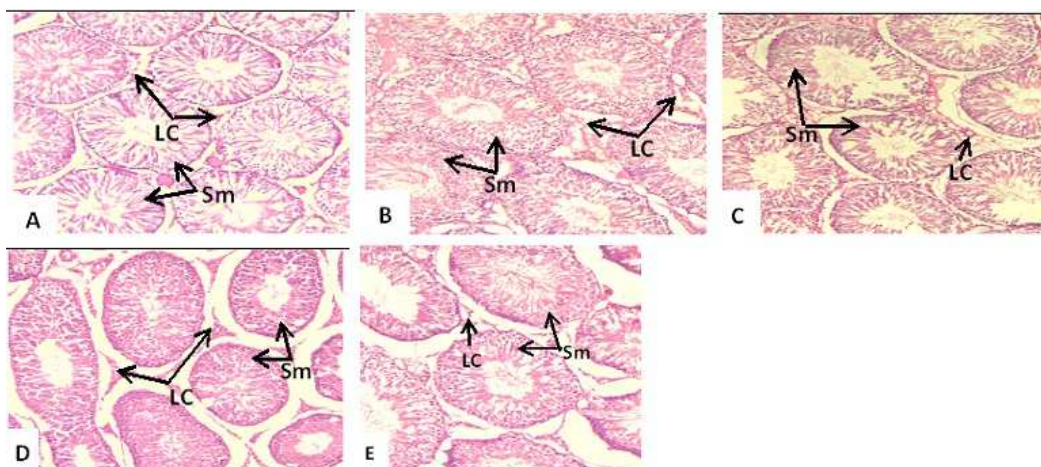


Figure 6. Section of the testis of rat groups given varied doses of aqueous *Phoenix dactylifera* (date) seed extract for 35 days, compared with an untreated control, showing no lesions: there are normal seminiferous tubules (sm) and Leydig cells (LC). [A – untreated control; B – 50 mg/kg extract; C – 100 mg/kg extract; D – 200 mg/kg extract; E – 400 mg/kg extract.] H & E, $\times 100$.

Discussion

Testosterone is directly involved in maintaining spermatogenesis (Li *et al.*, 2024), and its elevation in the present study likely contributed to the higher total sperm output recorded in the treated groups especially in the groups treated with 200 and 400 mg/kg extract. The dose-dependent higher serum levels of luteinizing hormone (LH) recorded in this study suggests activation of the hypothalamic–pituitary–gonadal axis which is important in maintaining hormonal homeostasis, and therefore probably accounts for the positive influence of the extract treatment on spermatogenesis (Lei *et al.*, 2025). Luteinizing hormone is a glycoprotein hormone secreted from the pituitary gland in response to the pulsatile release of gonadotropin-releasing hormone from the hypothalamus; it stimulates Leydig cells via cAMP-dependent pathways, promoting expression of steroidogenic acute regulatory protein (StAR), which facilitates cholesterol transport into mitochondria – the rate-limiting step in steroidogenesis (Lim and Cheon, 2025). Cholesterol is converted to pregnenolone by CYP11A1 enzyme in the inner mitochondrial membrane and subsequently undergoes structural changes to form testosterone by downstream enzymes including 3β -hydroxysteroid dehydrogenase and CYP17A1 (Choi *et al.*, 2021).

Though some earlier reports associate high serum levels of testosterone with prostate disorders, reports by Mohammed *et al.* (2023) show that date seed phenolic compounds attenuate prostate enlargement in a testosterone-induced benign prostatic hyperplasia model, suggesting that the androgenic effect of date seed consumption is unlikely to translate directly to prostrate pathology, though this requires further investigations.

Superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) constitute

the first line of enzymatic protection against reactive oxygen species (Ighodaro and Akinloye, 2018). Superoxide dismutase (SOD) serves as the primary defense against superoxide radicals as it catalyzes the dismutation of superoxide anion into hydrogen peroxide and oxygen (Wang *et al.*, 2018). Catalase (CAT) converts hydrogen peroxide into water and molecular oxygen, limiting its accumulation and preventing the formation of highly reactive hydroxyl radicals (Nandi *et al.*, 2019). Glutathione peroxidase (GPx) further detoxifies hydrogen peroxide and lipid hydroperoxides using reduced glutathione, thereby protecting cellular and lipid membranes from oxidative injury (Pei *et al.*, 2023).

The significantly higher SOD activity recorded for the rat groups given higher doses (200 and 400 mg/kg) of extract in this study indicates that the extract may have exerted a selective antioxidant effect enhancing superoxide dismutation without over-stimulating downstream enzymatic cascades such as CAT and GPx whose activities were not significantly altered in this study. The hydrogen peroxide generated through SOD activity may have been neutralized by intrinsic non-enzymatic antioxidant systems and other endogenous scavengers (Mirończuk-Chodakowska *et al.*, 2018; Witkowska, 2018).

Malondialdehyde (MDA) is a widely used biomarker of lipid peroxidation (Khoubnasab *et al.*, 2015; Merino de Paz *et al.*, 2024). The significantly lower MDA levels in the treated groups which was dose dependent provides strong evidence of minimized lipid peroxidation. Since sperm membranes are rich in polyunsaturated fatty acids, lower MDA levels indicate preservation of membrane fluidity and structural integrity (Simsek *et al.*, 2025).

Earlier reports have shown that excessive oxidative stress and lipid peroxidation stimulates inflammatory cytokine release which can suppress gonadotropin-releasing

hormone (GnRH) secretion and subsequently reduce luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, leading to testicular dysfunction, reduced spermatogenesis and infertility (Lue *et al.*, 1999; Khan and Ahsan, 2017). By minimizing oxidative stress, this extract may have suppressed inflammatory cytokines and alleviated inhibitory influences on the hypothalamus-pituitary-gonadal axis, thereby enhancing GnRH secretion and LH downstream release, which in turn enhanced spermatogenesis: this may have accounted for the findings in the present study of significant higher mean total sperm count in rat groups given 200 mg/kg and 400 mg/kg extract, and the higher progressive motility at 400 mg/kg.

Furthermore, the preserved testicular and epididymal architecture without structural abnormalities recorded in the extract treated groups concurs with the positively enhanced antioxidant status and minimized lipid peroxidation, which will ultimately lead to better testicular and epididymal function (Atig *et al.*, 2011). The higher progressive motility, total sperm count and dose-dependently higher testosterone levels in the extract treated groups, as well as preserved testicular and epididymal architecture revealed in the histological examination, are consistent with an enhanced anti-oxidative environment.

Conclusion: Oral administration of *P. dactylifera* seed extract as used in the study exerted fertility-enhancing effect by leading to significantly higher epididymal total sperm counts, sperm motility, and higher serum levels of male reproductive hormone levels in the extract treated groups, in a dose-dependent manner. These effects were believed to be strongly associated with enhanced antioxidant defenses and reduced oxidative stress in the testes. The results support the potential application of *P. dactylifera* seed as a therapeutic or supportive agent for male reproductive dysfunction associated with oxidative stress. However,

further studies are required to identify the active compound(s), and evaluate long-term safety and clinical applicability.

Conflict of Interest

The authors hereby declare that there is no conflict of interest.

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