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Modulatory Effects of Plant-Derived Stem Cell on Olanzapine-Induced Testicular Dysfunction in Male Wistar Rats

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Abstract

Olanzapine-induced testicular dysfunction contributes to male infertility by disrupting steroidogenesis, energy metabolism, and oxidative balance. Plant-derived stem cells (PDSC), with antioxidant and regenerative properties, may offer protection against such drug-induced reproductive toxicity. To evaluate the modulatory effects of PDSC on testicular reproductive parameters in olanzapine-induced spermatotoxicity in male Wistar rats. Fifty adult male Wistar rats were randomly assigned to five groups (n = 10) and treated orally for 28 days. Group I received distilled water, Group II OLZ (10 mg/kg), and Groups III–V OLZ plus PDSC (100, 200, or 400 mg/kg). Sperm parameters, reproductive hormones (FSH, LH, testosterone), oxidative stress biomarkers, DNA damage marker (8-OHdG), testicular biochemical indices, and steroidogenic enzyme activities were evaluated. OLZ significantly reduced testosterone, testicular glycogen and cholesterol, normal sperm morphology, and 17β-HSD activity, while increasing FSH, LH, MDA, and sperm motility. PDSC produced dose-dependent improvements, increasing testosterone, glycogen levels, and 17β-HSD activity while reducing gonadotropins, oxidative stress, and DNA damage, particularly at 200 mg/kg. However, PDSC did not restore testicular cholesterol or zinc levels and was associated with reduced 3β-HSD activity. PDSC mitigates olanzapine-induced reproductive toxicity through antioxidant, DNA-protective, and steroidogenic mechanisms, highlighting its potential for managing male reproductive dysfunction.

Keywords: Olanzapine; Plant-derived stem cells (PDSC); Spermatotoxicity; Oxidative stress; Male infertility.

INTRODUCTION

Infertility is clinically defined as the inability to achieve pregnancy after 12 months of consistent, unprotected sexual intercourse in couples of reproductive age (Vander Borght & Wyns, 2018). Recent research indicate that infertility affects approximately 17.5 % of adults worldwide (about 1 in 6 people during their reproductive years), with male factors contributing to 30–50 % of cases (World Health Organization, 2023). This condition imposes significant psychological, social, and economic burdens on individuals and families (Sharma et al., 2022). In Nigeria, cultural norms often attribute infertility to women, leading to underreporting of male causes, delayed diagnosis, and an increased emotional strain among couples attempting to conceive (Esan et al., 2025). Male infertility arises from various factors, including oxidative stress, hormonal imbalances, infections, environmental toxins, and idiopathic causes, all of which can compromise testicular and epididymal integrity (Sharma et al., 2021). Among modifiable risk factors, long-term use of certain medications, particularly antipsychotics, has increasingly been recognized as a concern. These drugs can disrupt the hypothalamic-pituitary-gonadal axis, induce oxidative damage, and impair spermatogenesis (Görmüş et al., 2021). Olanzapine (OLZ), an atypical antipsychotic from the benzodiazepine class, is one of the most widely prescribed agents for schizophrenia and bipolar disorder due to its broad receptor antagonism, which include dopamine D2, serotonin, muscarinic, adrenergic, and histaminergic pathways (Mlambo et al., 2023). While well-known side effects include weight gain, dyslipidemia, and insulin resistance (Oruch et al., 2025), recent studies have highlighted reproductive toxicity, including sexual dysfunction, reduced sperm quality, hormonal disruption, and testicular damage (Ardıç et al., 2021). Although treatment options such as hormone replacement therapy, infection control, and assisted reproductive technologies (ART) are available, they often fail to fully address the underlying mechanisms, depending on the cause (Kolli et al., 2023). In recent years, interest has grown in the therapeutic potential of stem cells due to their regenerative and healing properties (Zakrzewski et al., 2019). Plant-derived stem cells have gained increasing recognition in biomedical

research for their capacity to influence disease outcomes and support tissue repair through specialized growth and differentiation mechanisms (Li et al., 2025). These cells are rich in bioactive compounds, including polyphenols and flavonoids, which confer antioxidant, anti-inflammatory, and regenerative properties (Hermosaningtyas et al., 2024). Plant-derived stem cells (PDSC), particularly extracts from *Malus domestica* and *Vitis vinifera*, are characterized by continuous proliferative capacity, self-renewal ability, and a high concentration of these bioactive metabolites. These properties underpin their demonstrated benefits in models of chronic conditions such as diabetes, as well as in aging and neurodegenerative disorders (Salehi et al., 2020). Furthermore, their potential to modulate cellular responses and protect against drug-induced damage has been suggested (Siddiqa et al., 2025). However, despite these promising attributes, the role of PDSC in mitigating drug-induced reproductive toxicity remains insufficiently explored. Therefore, this study aimed to investigate the modulatory effects of plant-derived stem cells on olanzapine-induced testicular toxicity in male Wistar rats.

MATERIALS AND METHODS

Olanzapine was obtained from a local pharmacy. Plant-derived stem cell (PDSC) formulation was purchased from PhytoScience (Kuala Lumpur, Malaysia), consisting of extracts from *Malus domestica* and *Vitis vinifera* stem cells.Serum levels of testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), glutathione (GSH), malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), and 8-hydroxy-2′-deoxyguanosine (8-OHdG) were determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturers' instructions. Other biochemical parameters, including glycogen, cholesterol, zinc, and steroidogenic enzyme activities (3β-HSD and 17β-HSD), were assessed using standard colorimetric or spectrophotometric methods with commercially available reagents.

Experimental Animals

Fifty adult male Wistar rats (weighing 150–200 g) were obtained from a reputable animal breeding facility in Ibadan, Nigeria. The animals were acclimatized for 14 days prior to the commencement of the experiment. Rats were housed in standard polypropylene cages under controlled laboratory conditions (12 h light/dark cycle, temperature 24 ± 2°C, and relative humidity of 50–60%), with free access to standard pellet diet and clean drinking water *ad libitum*. The animals were maintained in a well-ventilated environment and handled in accordance with standard laboratory practices.

Experimental design

Animals were randomly allocated into five groups (n = 10 per group). Group I (control) received distilled water (10 mL/kg), while Group II received olanzapine (10 mg/kg, p.o.). Groups III–V received olanzapine (10 mg/kg) in combination with plant-derived stem cells (PDSC) at doses of 100, 200, and 400 mg/kg, respectively. All treatments were administered once daily by oral gavage at a volume of 1 mL/100 g body weight for 28 consecutive days.

Sample collection

At the end of the treatment period, animals were sacrificed by cervical dislocation. Blood samples were collected via retro-orbital puncture, allowed to clot, and centrifuged at 3000 × g for 10 min to obtain serum for hormonal and biochemical analyses. Organs including the brain, liver, kidneys, seminal vesicles, testes, and epididymis were excised, rinsed in normal saline, blotted dry, and weighed. Testicular and epididymal tissues were subsequently homogenized for further biochemical assays.

Biochemical and hormonal assays

Serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone, as well as oxidative stress markers including glutathione (GSH), malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), and 8-hydroxy-2′-deoxyguanosine (8-OHdG), were quantified using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturers' instructions. Testicular glycogen, cholesterol, and zinc levels were determined using standard colorimetric methods. Steroidogenic enzyme activities, including 3β-hydroxysteroid dehydrogenase (3β-HSD) and 17β-hydroxysteroid dehydrogenase (17β-HSD), were assessed spectrophotometrically in testicular homogenates.

Ethical approval

All experimental procedures were approved by the College of Medicine, University of Lagos Animal Care and Use Research Ethics Committee (CMUL/ACUREC/03/25/1866) and conducted in accordance with international guidelines for the care and use of laboratory animals.

Statistical analysis

Data are presented as mean ± standard error of the mean (SEM). Statistical analyses were performed using GraphPad Prism version 8.0 (GraphPad Software, San Diego, CA, USA). Group comparisons were carried out using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Effect of Plant-Derived Stem Cell on Standardized Organ Weights

Olanzapine produced a small, non-significant increase in the relative weights of the testes, kidneys and liver compared with the control group. Co-treatment with PDSC influenced these changes. OLZ+ PDSC 200 and 400 mg/kg groups showed reduced liver weights. Brain weight was reduced across all treatment groups, with the 400 mg/kg group showing the lowest value. In contrast, the weights of the epididymis and the seminal vesicles remained constant across all groups.

Effect of Plant-Derived Stem Cell on Sperm Parameters

Olanzapine treatment showed no change in sperm count compared to the control. However, it significantly increased sperm motility and decreased normal sperm morphology in the OLZ group. Co-treatment with PDSC produced dose-related changes, with the most consistent improvement in sperm count, motility and morphology observed at 200 mg/kg. In contrast, the 100 mg/kg and 400 mg/kg doses showed less improvement.

Effect Plant-Derived Stem Cell on Serum Hormone Levels

Olanzapine caused a significant decrease in testosterone and increases in FSH and LH compared to the control group. Co-administration with PDSC produced-dose related changes in the hormone levels, with the 100 mg/kg group showing the most improvement on testosterone, the 200 mg/kg group increased the FSH and the 400 mg/kg group increased both the FSH and LH when compared with the control group.

Effect Plant-Derived Stem Cell on Oxidative Stress Markers (Testes and Epididymis)

In the testes, olanzapine increased MDA and 8-OHdG, SOD, GSH and reduced CAT. PDSC at 100 mg/kg reduced MDA and 8-OHdG. PDSC increased SOD (significantly at 400 mg/kg) with a reduction in GSH and CAT at higher doses (200 and 400 mg/kg). In the epididymis, Olanzapine similarly increased MDA and reduced SOD and CAT. PDSC increased MDA at 400 mg/kg. PDSC increased SOD at 100 and 200 mg/kg, and CAT in all PDSC doses. No significant effect on GSH level.

Effect Plant-Derived Stem Cell on Steroidogenic Enzymes

Olanzapine increased 3β-HSD activity while decreasing 17β-HSD activity. PDSC reversed these changes: it decreased 3β-HSD and increased 17β-HSD, with the strongest effect at 200 mg/kg.

Effect Plant-Derived Stem Cell on Testicular Biochemical Parameters

Olanzapine reduced testicular glycogen and cholesterol levels and increased epididymal zinc. PDSC treatment further reduced cholesterol and restored glycogen levels and decreased epididymal zinc in a dose dependent manner maximal at 400 mg/kg.

Table 1. Effect of Plant- derived Stem Cell on the Standardized weight of vital organs

Parameter	Standardized weight of vital organs					
	Testes	**Epididymis**	**Seminal Vesicle**	**Kidney**	**Liver**	**Brain**
Control	1.67±0.40	0.10±0.01	0.10±0.01	0.45±0.11	4.07±0.41	1.53±0.14
OLZ	1.88±0.22	0.10±0.01	0.10±0.01	0.59±0.24	4.30±0.53	1.46±0.16
OLZ+PDSC-100	1.54±0.31	0.10±0.01	0.10±0.01	0.64±0.39	4.04±033	1.36±0.24
OLZ+PDSC-200	1.74±0.18	0.10±0.01	0.10±0.01	0.42±0.06	3.84±0.44	1.16±0.21
OLZ+PDSC-400	1.56±0.29	0.0±0.01	0.10±0.01	0.42±0.05	3.26±0.67	1.16±0.16

Values are expressed in Mean ± SEM (n = 10). Data was analyzed using One way ANOVA following Turkey's post hoc comparison. #$p< 0.05$ versus control-treated group.

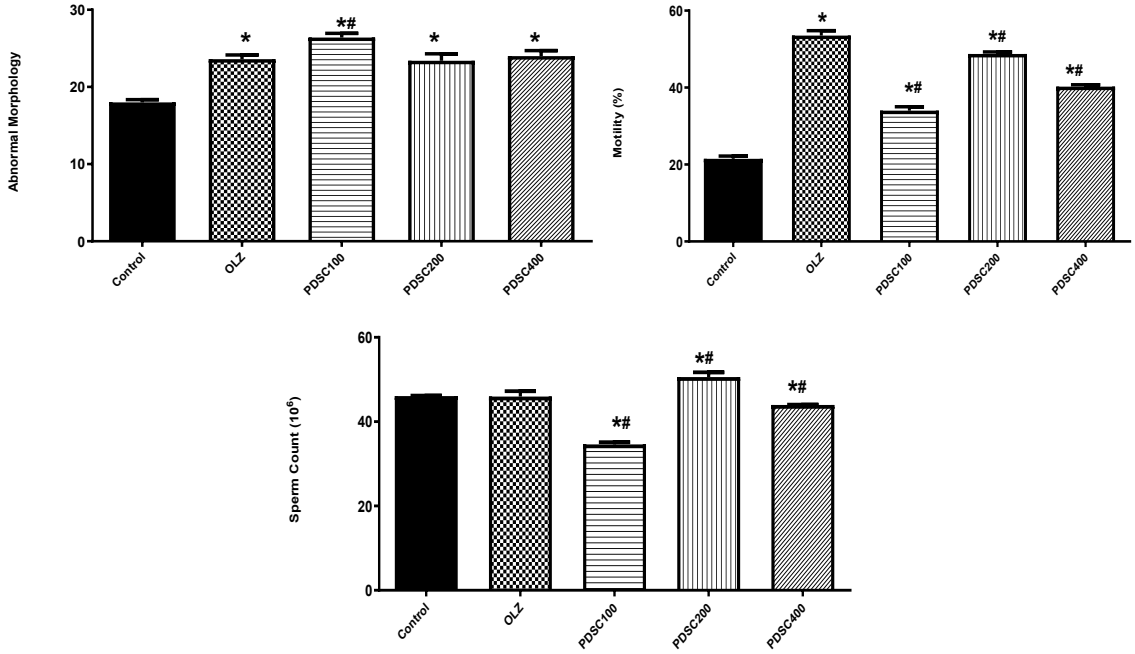

Figure 1. Effects of PDSC on sperm count, motility, and morphology in olanzapine-induced reproductive toxicity in adult male Wistar rats. Values are expressed as mean ± SEM (n = 5). Statistical significance was determined using one-way ANOVA followed by Tukey's post hoc test ($p < 0.05$).

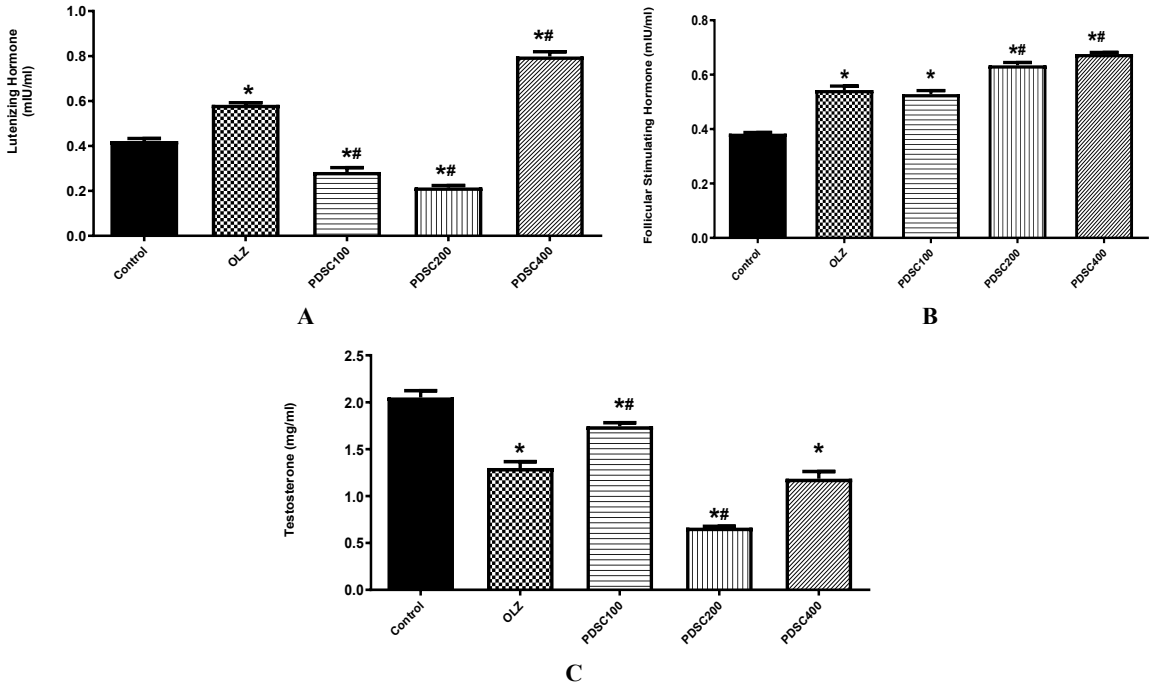

Figure 2 (A–C) Effect of Plant-derived stem cell (PDSC) on serum reproductive hormones in olanzapine-induced adult male rats. (A) Testosterone, (B) Follicle Stimulating Hormone (FSH), (C) Luteinizing Hormone (LH).

Values are expressed as mean ± SEM (n = 5). #$p < 0.05$ versus control-treated group. Statistical analysis was performed using one-way ANOVA followed by Tukey's multiple comparison test.

DISCUSSION

Plant-derived stem cells represent a novel therapeutic approach for improving reproductive outcomes in olanzapine-induced infertility in male Wistar rats. Their modulatory effects hold promise as potential therapeutic agents for enhancing reproductive health and mitigating antipsychotic-induced toxicity. Olanzapine has been shown to exert detrimental effects on the male

reproductive system, including testicular structural damage, increased oxidative stress, reduced sperm count, motility, and morphology, as well as decreased serum testosterone, luteinizing hormone, and follicle-stimulating hormone levels (Ardıç et al., 2021).

Effects on Relative Organ Weights

Olanzapine caused a mild, non-significant increase in the relative weights of the testes, kidneys, and liver, indicating minimal effect on organ enlargement within the study period. Co-administration with PDSC reduced liver weight, suggesting a possible modulatory effect on hepatic changes. Brain weight was reduced across all treatment groups, although the underlying mechanism remains unclear. In contrast, the weights of the epididymis and seminal vesicles were unchanged across groups, indicating no significant effect on these organs. Although plant-derived stem cells have been reported to exhibit weight-regulating properties (Garcia-Alvarez et al., 2016), this effect was not consistently observed.

Effects on Reproductive Hormones

Testosterone

This study demonstrated a significant reduction in testosterone levels in both the olanzapine-treated and PDSC co-treated groups compared with the control. This decline is consistent with the known inhibitory effect of olanzapine on testicular steroidogenesis and testosterone production, as previously reported (Ardıç et al., 2021). Although plant-derived supplements have been documented to enhance testosterone levels under certain experimental conditions (Edah et al., 2026), the present findings suggest that the suppressive effect of olanzapine on testosterone synthesis may override the modulatory potential of plant stem cell extracts within the study context. This indicates that PDSC did not sufficiently restore testosterone levels against olanzapine-induced endocrine disruption.

Follicle-Stimulating Hormone (FSH)

Follicle-stimulating hormone (FSH) is routinely measured in male infertility studies because it reflects Sertoli cell function and provides an indirect index of spermatogenic activity and integrity of the hypothalamic–pituitary–gonadal (HPG) axis. FSH levels were significantly elevated in both olanzapine- and PDSC-treated groups, indicating disruption of normal hypothalamic–pituitary–gonadal feedback, likely secondary to impaired testicular function and reduced testosterone-mediated inhibition. This aligns with reports that olanzapine alters gonadotropin regulation (Razdan et al., 2018), although contrasting findings of reduced FSH have also been documented (El Roghy & Mahmoud, 2024), suggesting variability in response. Overall, PDSC did not restore normal FSH regulation within the study period.

Luteinizing Hormone (LH)

LH is an important marker in male infertility studies because it reflects pituitary regulation of Leydig cell function and testosterone synthesis within the hypothalamic–pituitary–gonadal (HPG) axis. In this study, LH levels were increased in the olanzapine and high-dose PDSC co-treated groups, suggesting a compensatory HPG axis response to olanzapine-induced testicular dysfunction (Lima et al., 2023). In contrast, LH levels were reduced in the lower- and mid-dose PDSC groups, indicating a partial attenuation of olanzapine's disruptive effect and reduced need for pituitary compensation. Overall, PDSC showed a dose-dependent and inconsistent effect on LH regulation.

Effects on Sperm Characteristics

Olanzapine significantly impaired sperm quality by reducing normal sperm morphology and increasing abnormal forms, consistent with its known testicular toxic effects. Co-administration with plant-derived stem cells (PDSC) partially reversed these alterations, with an overall improvement in sperm morphology at higher treatment levels, suggesting a dose-related protective effect. Sperm motility was increased following olanzapine exposure; however, PDSC modulated this effect, with a moderate restorative influence that was most pronounced at intermediate treatment levels, although very high exposure appeared less beneficial. Sperm count showed a biphasic response, with improvement at moderate PDSC treatment but reduction at both lower and higher exposures, indicating a non-linear, dose-sensitive effect on spermatogenic output.

Effects on Steroidogenic Enzyme Activities

3β-Hydroxysteroid Dehydrogenase (3β-HSD)

3β-Hydroxysteroid dehydrogenase (3β-HSD) is a key steroidogenic enzyme involved in the conversion of DHEA to androstenedione, a critical precursor in testosterone biosynthesis, and is therefore essential for normal spermatogenesis and male reproductive function. In this study, olanzapine increased testicular 3β-HSD levels, suggesting a dysregulation of steroidogenic pathways possibly linked to compensatory alterations in androgen synthesis. However, co-treatment with plant-derived stem cells (PDSC) reduced 3β-HSD levels, indicating a lack of restoration of normal steroidogenic activity.

This finding aligns with reports of decreased steroidogenic enzyme activity following certain plant extract interventions (Qiao et al., 2019), but contrasts with studies showing restoration of 3β-HSD and improved steroidogenesis with other botanical agents (Gaikar et al., 2021), highlighting variability in phytotherapeutic effects on reproductive endocrine function.

17β-Hydroxysteroid Dehydrogenase (17β-HSD)

17β-Hydroxysteroid dehydrogenase (17β-HSD) is an enzyme responsible for the conversion of androstenedione to testosterone in the testes (Turcu et al., 2020). In this study, olanzapine administration resulted in a decrease in 17β-HSD levels. However, treatment with PDSC significantly increased 17β-HSD levels, indicating an enhanced capacity for testosterone production. This finding is consistent with Lee et al. (2024), who reported that extracts of *Sambucus nigra* increased 17β-HSD levels. In contrast, Oladipupo et al. (2025) observed a decrease in 17β-HSD levels following treatment with *Olax subscorpioidea* extracts.

Effects on Testicular Biochemical Indices

Testicular Glycogen

Testicular glycogen, which represents stored energy in the testes and supports spermatogenesis, also serves as an indicator of testicular health (Rotimi et al., 2024). A reduction in glycogen levels was observed in the olanzapine-treated group compared to the control group. However, PDSC treatment led to an increase in testicular glycogen levels. This finding aligns with Devaraj et al. (2024), who reported that antipsychotics such as olanzapine reduce glycogen levels in males. Similarly, Ante et al. (2025) observed that *Phoenix dactylifera* extracts increased testicular glycogen levels.

Testicular Cholesterol

Testicular cholesterol, a key precursor for testosterone synthesis, was also evaluated. A reduction in cholesterol levels was observed in the olanzapine group compared to the control group. PDSC treatment further reduced cholesterol levels, suggesting increased utilization of cholesterol for steroidogenesis. This finding is in agreement with Widhiantara et al. (2023), who reported improved spermatogenesis following treatment with *Blumea balsamifera*. Additionally, literature reports that *Agnus castus* extract enhanced reproductive parameters, although it was associated with increased testicular glycogen levels rather than cholesterol (Al-Enezi, 2015).

Testicular Zinc

Zinc, an essential mineral for spermatogenesis and testosterone production (Fallah et al., 2018), was also assessed. Both olanzapine and PDSC treatments resulted in increased zinc levels. This finding is consistent with Remita et al. (2023), who demonstrated increased zinc levels following treatment with *Crataegus monogyna* extracts. Similarly, Eze et al. (2025) reported that administration of *Sphenocentrum jollyanum* increased zinc levels.

Epididymal Zinc

Evaluation of epididymal zinc levels, which reflect sperm maturation, stabilization, and motility, revealed an increase in the olanzapine group compared to the control group. However, PDSC treatment resulted in a decrease in epididymal zinc levels, which may suggest impaired sperm motility. This finding is consistent with Eze et al. (2025), who also reported reduced zinc levels. In contrast, studies using *Crataegus monogyna* extracts have demonstrated increased zinc levels.

Effects on Oxidative Stress and Antioxidants

Malondialdehyde (MDA)

In this study, olanzapine administration led to an increase in testicular and epididymal malondialdehyde (MDA), a marker of lipid peroxidation (Al-Saeed et al., 2019). Treatment with plant-derived stem cells (PDSC) reduced testicular MDA levels, consistent with studies (Abd et al., 2020; Saad et al., 2024) demonstrating that plant constituents such as flavonoids and phenolic acids possess antioxidant properties.

Superoxide Dismutase (SOD)

Olanzapine slightly reduced superoxide dismutase (SOD) activity in the epididymis, indicating oxidative stress in this organ, which is critical for sperm maturation (Ardıç et al., 2021). PDSC treatment produced a modest increase in both testicular and epididymal SOD levels, suggesting enhancement of the body's primary enzymatic antioxidant defense system (Ighodaro & Akinloye, 2018).

Catalase (CAT)

Additionally, olanzapine caused a marked reduction in catalase (CAT) activity, further supporting its role in inducing oxidative stress in the testes, a key mechanism underlying drug-induced male reproductive dysfunction (Agarwal et al., 2014). PDSC treatment increased CAT activity in both the testes and epididymis, indicating its potential to enhance antioxidant defense. This is consistent with findings by Lobo et al. (2017) and Nimse and Pal (2015), which suggest that plant-derived antioxidants can upregulate key enzymatic defenses against oxidative damage.

Reduced Glutathione (GSH)

Evaluation of reduced glutathione (GSH) levels revealed no significant changes across all groups in both the testes and epididymis, indicating that neither olanzapine nor PDSC significantly influenced this parameter.

Effects on DNA Integrity

Olanzapine significantly increased testicular 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels, a well-established biomarker of oxidative DNA damage, confirming its detrimental effect on DNA integrity, as also reported by Ardıç et al. (2021). PDSC demonstrated a variable effect on 8-OHdG levels, with evidence of reduction in some instances but also increases, suggesting a complex response. This observation aligns with Lobo et al. (2017),

who reported that excessive antioxidant exposure may paradoxically increase DNA damage.

Effects on Epididymal Oxidative Stress, Zinc, and Nitric Oxide Levels

Similar patterns were observed in the epididymis, where PDSC was associated with increased MDA levels and reduced SOD activity under certain conditions. Epididymal zinc levels, which were slightly elevated following olanzapine administration, declined with PDSC treatment. This finding is noteworthy, as zinc plays a critical role in antioxidant defense and sperm integrity (Fallah et al., 2018), and its reduction may negatively impact reproductive function. This contrasts with studies such as Ebaid et al. (2025), which demonstrated that zinc supplementation ameliorates olanzapine-induced reproductive dysfunction. Epididymal nitric oxide (NO) levels were elevated following olanzapine administration and were not normalized by PDSC treatment, suggesting that PDSC may not directly regulate nitric oxide pathways.

CONCLUSION

In conclusion, this study demonstrates that olanzapine induces significant testicular and epididymal dysfunction primarily through oxidative stress, disruption of steroidogenic enzyme activity, and impairment of key biochemical parameters essential for male reproductive function. Treatment with plant-derived stem cells (PDSC) exhibited notable protective effects by enhancing antioxidant defenses, improving steroidogenic activity, and partially restoring biochemical alterations associated with spermatogenesis. However, the variable effects observed in parameters such as DNA integrity, epididymal zinc, and nitric oxide levels suggest a complex and dose-sensitive response, indicating that while PDSC holds therapeutic potential, its effects are not uniformly protective across the evaluated male reproductive indices. Overall, PDSC may serve as a promising therapeutic approach for mitigating olanzapine-induced reproductive toxicity, though further studies are required to optimize its efficacy and fully elucidate its mechanisms of action.

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Competing Interests: The authors declare that there are no competing interests.

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