

Evaluation of the Antioxidant and Testiculo-protective Effects of *Prunus domestica* leaf Ethanolic extract on Cadmium-Induced Reproductive Toxicity in Wistar Rats

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Abstract

Original Research Article

This study investigated the protective effects of ethanolic leaf extract of *Prunus domestica* against cadmium-induced testicular toxicity in adult male Wistar rats. Cadmium is a well-established reproductive toxicant known to induce oxidative stress, lipid peroxidation, hormonal imbalance and impaired spermatogenesis (Nordberg *et al.*, 2007; Waalkes, 2003). Thirty adults male Wistar rats were randomly assigned into five groups (n = 6). Cadmium chloride (2 mg/kg) was administered intraperitoneally for 21 days. Ethanolic leaf extract of (200 and 400 mg/kg) was administered orally. Cadmium significantly (P < 0.05) increased malondialdehyde (MDA) levels while reducing superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), testosterone levels, sperm count and motility. Histopathology revealed seminiferous tubular degeneration and germ cell loss. Co-administration of the extract significantly reversed these alterations in a dose-dependent manner. The findings suggest that *Prunus domestica* leaf extract mitigates cadmium-induced testicular damage through antioxidant mechanisms.

Keywords: *Prunus domestica*, cadmium toxicity, testicular damage, antioxidant activity, Wistar rats.

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1. INTRODUCTION

Cadmium (Cd) is a toxic heavy metal widely distributed in the environment due to industrial processes, cigarette smoke and agricultural contamination (ATSDR, 2012; Godt *et al.*, 2006). It accumulates in biological tissues and exerts toxic effects primarily through oxidative stress and disruption of cellular antioxidant systems (Stohs *et al.*, 2000; Valko *et al.*, 2005).

The testes are particularly susceptible to cadmium toxicity because of their high rate of cell proliferation and polyunsaturated fatty acid content (Aitken & Roman, 2008). Cadmium disrupts the blood–testis barrier, damages Sertoli and Leydig cells and impairs spermatogenesis (Mruk & Cheng, 2004; Siu *et al.*, 2009). Decreased testosterone production and reduced sperm parameters are common outcomes (Lafuente, 2013; Thompson & Bannigan, 2008).



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Oxidative stress is central to cadmium-induced reproductive damage. Cadmium increases reactive oxygen species (ROS) generation, elevates lipid peroxidation and suppresses antioxidant enzymes such as SOD, CAT and GSH (Halliwell & Gutteridge, 2015; Ognjanović *et al.*, 2010).

Prunus domestica contains flavonoids, phenolic acids, anthocyanins and vitamins known for antioxidant activity (Scalzo *et al.*, 2005; Kim *et al.*, 2003). Plant-derived antioxidants have shown protective effects against heavy metal-induced toxicity (Flora *et al.*, 2012; Kalender *et al.*, 2005).

This study evaluated the restorative effect of ethanolic leaf extract of *Prunus domestica* on cadmium-induced testicular toxicity in adult male Wistar rats.

2. MATERIALS AND METHODS

2.1 Experimental Animals

Thirty (30) healthy adult male Wistar rats (*Rattus norvegicus*), weighing between 180– 220 g and aged 10– 12 weeks, were obtained from a certified animal breeding unit. The animals were acclimatized for 14 days before commencement of the experiment under controlled laboratory conditions: temperature ($22 \pm 2^\circ\text{C}$), relative humidity (50– 60%), and a 12-hour light/12-hour dark cycle. Animals were housed in well-ventilated polypropylene cages (6 rats per cage) lined with clean wood shavings that were changed daily. Standard pellet feed and clean drinking water were provided *ad libitum*. All experimental procedures were conducted in accordance with the guidelines of the Organization for Economic Co-operation and Development (OECD, 2001) for

laboratory animal care and were approved by the Institutional Animal Ethics Committee.

2.2 Collection and Authentication of Plant Material

Fresh leaves of *Prunus domestica* were collected from a pesticide-free environment and authenticated by a taxonomist in the Department of Botany. A voucher specimen was deposited in the departmental herbarium for reference with voucher serial number: FUTO/ HERB/PD/2026/028.

2.3 Preparation of Ethanolic Leaf Extract

The collected leaves were washed thoroughly with distilled water to remove debris and air-dried under shade at room temperature ($25\text{--}28^\circ\text{C}$) for 14 days to preserve thermolabile phytoconstituents. The dried leaves were pulverized using an electric grinder into fine powder. Approximately 500 g of powdered material was macerated in 2.5 L of 95% ethanol for 72 hours with intermittent shaking (Harborne, 1998). The mixture was filtered using Whatman No.1 filter paper. The filtrate was concentrated under reduced pressure using a rotary evaporator at 40°C to obtain a semi-solid crude extract. The extract was further dried in a water bath at 40°C to remove residual solvent and stored at 4°C until use.

2.4 Induction of Toxicity

Cadmium chloride (CdCl_2) was administered intraperitoneally at 2 mg/kg for 21 days, following established reproductive toxicity protocols (El-Demerdash *et al.*, 2004; Ognjanović *et al.*, 2010).

Experimental Groups

Table 1: Showing Experimental design

Groups	Administration	Duration (Weeks)	Number of rats
A	Feed + distilled water	3	6
B	Feed + distilled water and Cadmium only	3	6
C	Feed + distilled water + 100mg/kg extract	3	6
D	Feed + distilled water and Cadmium + 200 mg/kg extract	3	6
E	Feed + distilled water and Cadmium + 400 mg/kg extract	3	6

n = 30

Source: Field work, 2025

2.5 Sample Collection

Twenty-four hours after the last treatment, animals were fasted overnight and anesthetized using ketamine (50 mg/kg). Blood samples were collected via cardiac puncture into plain tubes, allowed to clot, and centrifuged at 3000 rpm for 10 minutes to obtain serum.

Testes were carefully excised, cleared of adhering tissues, blotted dry, and weighed. One testis was homogenized for biochemical analysis, while the other was preserved for histological examination.

2.6 Biochemical Assays

Freshly excised testicular tissues were rinsed in ice-cold physiological saline to remove blood contaminants and weighed. The tissues were homogenized in 0.1 M phosphate buffer (pH 7.4) to obtain a 10% (w/v) homogenate using a chilled glass homogenizer.

The homogenates were centrifuged at 10,000 rpm for 15 minutes at 4°C, and the supernatant obtained was carefully collected and used for biochemical assays of antioxidant enzymes and lipid peroxidation.

2.7 Determination of Superoxide Dismutase (SOD) Activity

Superoxide dismutase activity was determined using the method described by Henry P. Misra and Irwin Fridovich (1972).

Principle

The assay is based on the inhibition of epinephrine auto-oxidation to adrenochrome under alkaline conditions (pH 10.2). Superoxide dismutase competes with the reaction by scavenging superoxide radicals, thereby reducing the rate of adrenochrome formation.

Procedure

The reaction mixture consisted of:
 Carbonate buffer (pH 10.2)
 Ethylenediaminetetraacetic acid (EDTA)
 Epinephrine solution.

Testicular tissue supernatant

The reaction was initiated by the addition of epinephrine. The increase in absorbance due to adrenochrome formation was monitored spectrophotometrically at 480 nm.

Expression of Results

One unit of SOD activity was defined as the amount of enzyme required to inhibit 50% of epinephrine auto-oxidation. Results were expressed as U/mg protein.

2.8 Determination of Catalase (CAT) Activity

Catalase activity was measured using the method described by Hugo Aebi (1984).

Principle

Catalase catalyzes the decomposition of hydrogen peroxide (H₂O₂) into water and oxygen. The rate of hydrogen peroxide decomposition was monitored spectrophotometrically.

Procedure

The reaction mixture contained:

Phosphate buffer (pH 7.0)

Hydrogen peroxide solution

Testicular tissue supernatant

The decrease in absorbance of hydrogen peroxide was measured at 240 nm using a UV spectrophotometer.

Expression of Results

Catalase activity was expressed as μmol of hydrogen peroxide decomposed per minute per milligram protein ($\mu\text{mol}/\text{min}/\text{mg}$ protein).

2.9 Determination of Reduced Glutathione (GSH)

Reduced glutathione levels were determined using the DTNB method.

Principle

Reduced glutathione reacts with 5,5'-dithiobis-2-nitrobenzoic acid (DTNB) to produce a yellow-colored compound, 5-thio-2-nitrobenzoic acid, which can be measured spectrophotometrically.

Procedure

The testicular homogenate was precipitated with trichloroacetic acid (TCA) and centrifuged to obtain a clear supernatant. The supernatant was then reacted with DTNB reagent, and the intensity of the yellow chromogen formed was measured at 412 nm.

Expression of Results

Results were expressed as μmol GSH/mg protein.

2.10 Determination of Lipid Peroxidation (MDA Level)

Lipid peroxidation was assessed by measuring malondialdehyde (MDA) levels using the Thiobarbituric Acid Reactive Substances (TBARS) assay described by Hiroshi Ohkawa et al. (1979).

Principle

Malondialdehyde, a major product of lipid peroxidation, reacts with thiobarbituric acid (TBA) under high temperature and acidic conditions to produce a pink chromogen measurable at 532 nm.

Procedure

Testicular homogenate was mixed with TBA reagent. The mixture was heated at 95°C for 30 minutes in a water bath.

The reaction mixture was cooled and centrifuged.

The absorbance of the supernatant was measured at 532 nm.

Expression of Results

Results were expressed as nmol MDA/mg protein.

2.11 Hormonal Assay

Serum testosterone levels were determined using a commercial enzyme-linked immunosorbent assay

(ELISA) kit based on the competitive immunoassay principle described in clinical chemistry by Norbert W. Tietz (2012).

Procedure

Microplate wells were pre-coated with anti-testosterone antibodies.

Serum samples and enzyme-labeled testosterone conjugate were added to the wells.

After incubation, wells were washed to remove unbound materials.

Chromogenic substrate was added for color development.

Absorbance was measured at 450 nm using a microplate reader.

Calculation

Testosterone concentration was determined from a standard calibration curve generated from known testosterone standards.

Sperm Analysis

Sperm parameters were evaluated using epididymal sperm obtained from the cauda epididymis.

The epididymis was minced in physiological saline at 37°C to allow sperm cells to diffuse into the medium.

Sperm Count

Sperm concentration was determined using a Neubauer hemocytometer under a light microscope at $\times 400$ magnification.

Results were expressed as million sperm cells per milliliter ($\times 10^6$ sperm/mL).

Sperm Motility

Sperm motility was assessed microscopically immediately after sperm suspension preparation. The percentage of progressively motile spermatozoa was recorded.

Sperm Morphology

Sperm smears were prepared and stained using eosin-nigrosin stain. Approximately 200 sperm cells were evaluated for structural abnormalities such as head, midpiece, and tail defects.

2.12 Histological Examination

Testicular tissues were fixed in 10% neutral buffered formalin for 48 hours. The tissues were dehydrated in graded ethanol series, cleared in xylene, and embedded in paraffin wax.

Sections were cut at 5 μm thickness using a rotary microtome and mounted on glass slides. The sections were stained with Hematoxylin and Eosin (H&E) following standard histological procedures described by John D. Bancroft and Marilyn Gamble (2008).

Microscopic examination was performed using a light microscope to evaluate structural changes in seminiferous tubules and interstitial tissues.

2.11.2 Histological Findings

Control Group

The control group exhibited normal testicular histoarchitecture. Seminiferous tubules appeared round to oval with intact basement membranes. A complete spermatogenic series was observed, including spermatogonia, primary spermatocytes, spermatids, and mature spermatozoa. The lumens of the seminiferous tubules contained abundant spermatozoa. Interstitial spaces showed normal Leydig cells with eosinophilic cytoplasm and no evidence of inflammation or vascular congestion.

Cadmium-Treated Group

Severe histopathological changes were observed in animals exposed to cadmium. These included degeneration and disorganization of seminiferous tubules, thinning and detachment of the germinal epithelium, and cytoplasmic vacuolization within Sertoli cells. Sloughing of immature germ cells into the tubular lumen was evident, accompanied by a marked reduction in spermatogenic layers.

Additionally, interstitial edema and vascular congestion were observed, with a notable decrease in Leydig cell population. Pyknotic nuclei were also present, indicating apoptotic degeneration of germ cells. These findings suggest disruption of spermatogenesis and impairment of steroidogenic function.

Extract-Only Group

Animals treated with **Prunus domestica leaf extract alone showed normal seminiferous tubular architecture comparable to the control group. Active spermatogenesis was observed with abundant spermatozoa in the tubular lumen. Leydig cells appeared normal and prominent within the interstitial spaces. No degenerative or inflammatory changes were detected, indicating that the extract did not exert toxic effects on testicular tissue.

Cadmium + 200 mg/kg Extract Group

Moderate improvement in testicular histology was observed in animals treated with cadmium and 200 mg/kg of the extract. Partial restoration of seminiferous tubule architecture was evident, with reappearance of some spermatogenic layers. Vacuolization was reduced, and mild interstitial edema persisted. Leydig cells showed improved morphology compared with the cadmium-treated group.

Cadmium + 400 mg/kg Extract Group

Animals treated with cadmium and 400 mg/kg extract exhibited near-normal testicular histoarchitecture. Seminiferous tubules appeared largely restored with a well-organized germinal epithelium and abundant spermatozoa within the lumen. Interstitial spaces showed minimal edema, and Leydig cells appeared structurally intact. These findings indicate a dose-dependent protective effect of the plant extract.

2.12 Correlation between Biochemical and Histological Findings

The biochemical results correlated strongly with the histological observations. Cadmium exposure resulted in increased lipid peroxidation, as evidenced by elevated MDA levels, accompanied by reduced activities of antioxidant enzymes such as SOD, CAT, and GSH.

Treatment with *Prunus domestica* leaf extract significantly restored antioxidant enzyme activities and reduced lipid peroxidation. These biochemical improvements were associated with restoration of seminiferous tubule architecture and recovery of spermatogenic activity.

Furthermore, normalization of serum testosterone levels corresponded with the restoration of Leydig cell morphology, indicating recovery of steroidogenic function. The protective effect of the plant extract is therefore attributed to its antioxidant properties and ability to stabilize cellular membranes against oxidative damage.

2.13 Statistical Analysis

Data were analyzed using one-way ANOVA followed by Tukey post hoc test ($p < 0.05$ considered significant) (GraphPad Prism methodology).

3. RESULTS

3.1 Effect of Ethanol Leaf Extract of *Prunus domestica* on Testicular Oxidative Stress Markers in Cadmium-Induced Toxicity

Cadmium administration significantly increased lipid peroxidation (MDA) levels while it significantly decreasing antioxidant enzyme activities (SOD, CAT, and GSH) compared to the control group ($p < 0.05$). Co-administration of ethanolic leaf extract of *Prunus domestica* significantly reversed these changes in a dose-dependent manner. The high-dose extract group showed values closer to the control group.

Table 1: Showing Effects on Testicular Oxidative Stress Markers

Groups	Control	Cadmium	Extract only	Cd + 200 mg/kg	Cd + 400 mg/kg
SOD (U/mg protein)	18.42 ± 0.56 ^a	9.37 ± 0.48 ^c	19.01 ± 0.44 ^a	14.28 ± 0.51 ^b	17.36 ± 0.47 ^a
CAT (U/mg protein)	24.15 ± 0.72 ^a	11.62 ± 0.63 ^c	25.03 ± 0.68 ^a	18.74 ± 0.59 ^b	22.80 ± 0.61 ^a
GSH (µmol/mg protein)	8.21 ± 0.31 ^a	3.74 ± 0.22 ^c	8.43 ± 0.29 ^a	6.02 ± 0.25 ^b	7.52 ± 0.28 ^a
MDA (nmol/mg protein)	2.11 ± 0.09 ^a	6.85 ± 0.18 ^c	2.03 ± 0.07 ^a	4.01 ± 0.14 ^b	2.68 ± 0.11 ^a

Values are Mean ± SEM (n = 7).

Different superscripts (a–c) across columns indicate significant difference at $p < 0.05$.

3.2 Effect on Serum Testosterone Levels

Cadmium exposure significantly reduced serum testosterone compared to control ($p < 0.05$).

Treatment with ethanol leaf extract significantly increased testosterone levels in a dose-dependent manner.

Table 2: Showing Effects on Serum Testosterone

Group	Control	Cadmium	Extract only	Cd + 200 mg/kg	Cd + 400 mg/kg
Testosterone (ng/mL)	5.82 ± 0.21 ^a	2.34 ± 0.15 ^c	6.04 ± 0.19 ^a	3.97 ± 0.18 ^b	5.21 ± 0.22 ^a

Values are Mean ± SEM (n = 7).

Different superscripts indicate statistical significance at $p < 0.05$.

3.3 Effect on Sperm Parameters

Cadmium significantly reduced sperm count and motility while increasing abnormal sperm morphology compared to control ($p < 0.05$).

Extract treatment significantly improved sperm quality parameters.

Table 3: Effect on Sperm Parameters

Group	Control	Cadmium	Extract only	Cd + 200 mg/kg	Cd + 400 mg/kg
Sperm Count ($\times 10^6/\text{mL}$)	72.41 \pm 2.11 ^a	38.75 \pm 1.96 ^c	74.18 \pm 2.34 ^a	56.83 \pm 2.08 ^b	68.92 \pm 2.15 ^a
Motility (%)	85.32 \pm 1.78 ^a	41.84 \pm 2.03 ^c	87.15 \pm 1.69 ^a	63.42 \pm 1.85 ^b	79.61 \pm 1.72 ^a
Abnormal Morphology (%)	6.41 \pm 0.34 ^a	21.67 \pm 0.91 ^c	5.92 \pm 0.28 ^a	13.28 \pm 0.67 ^b	8.74 \pm 0.41 ^a

Values are Mean \pm SEM (n = 6).

Different superscripts indicate significant difference at $p < 0.05$.

3.4 Histological Findings

Control Group {A}

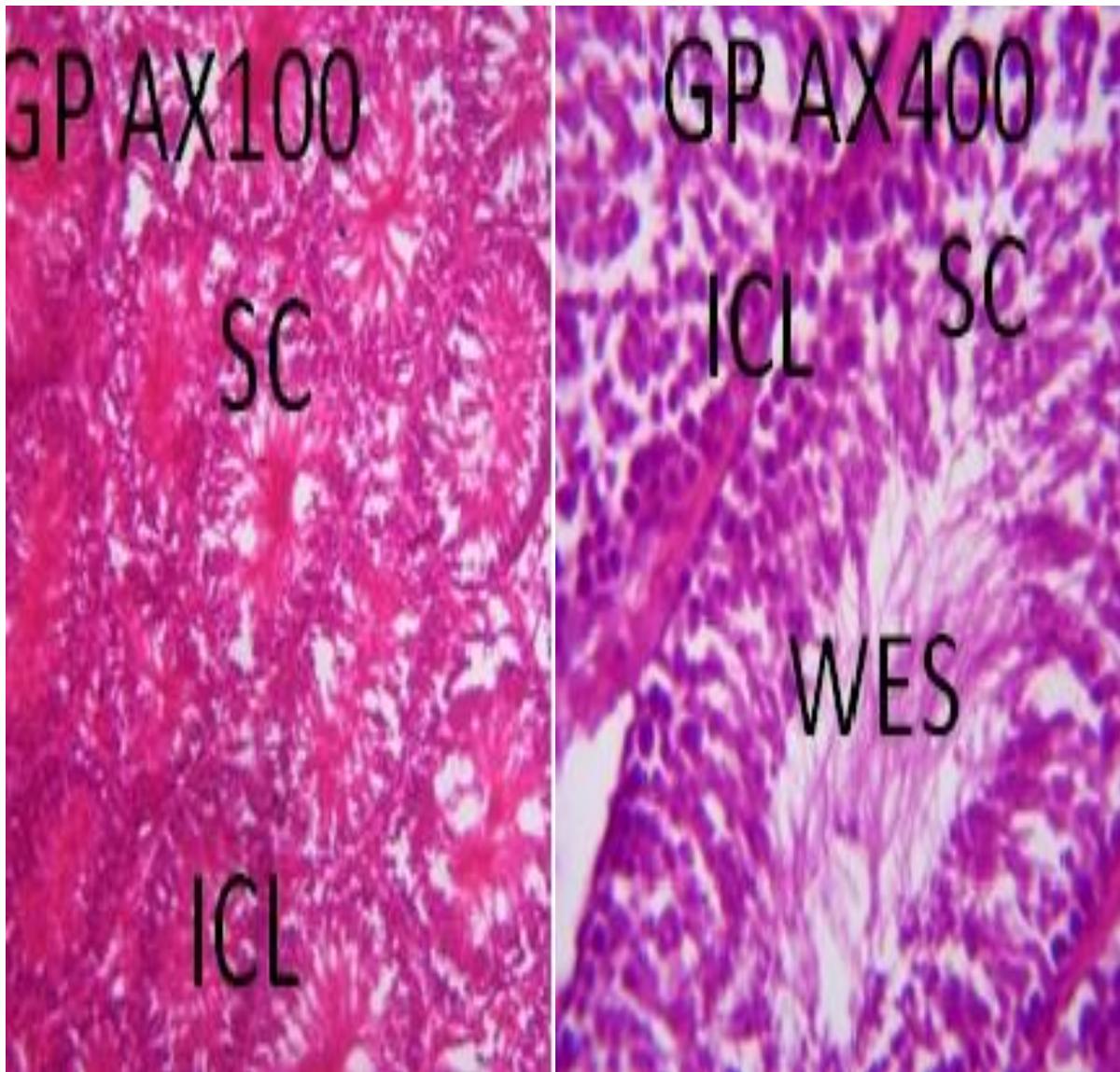


Plate 1: Photomicrographs of group A (Control) section of the testes (X100/X400 (H/E) shows normal testicular architecture with active

seminiferous tubules that are lined with interstitial cells of the Leydig (ICL), Sertoli cells (SC) and well enhanced spermatogenesis (WES).

Cadmium induced Group (B)

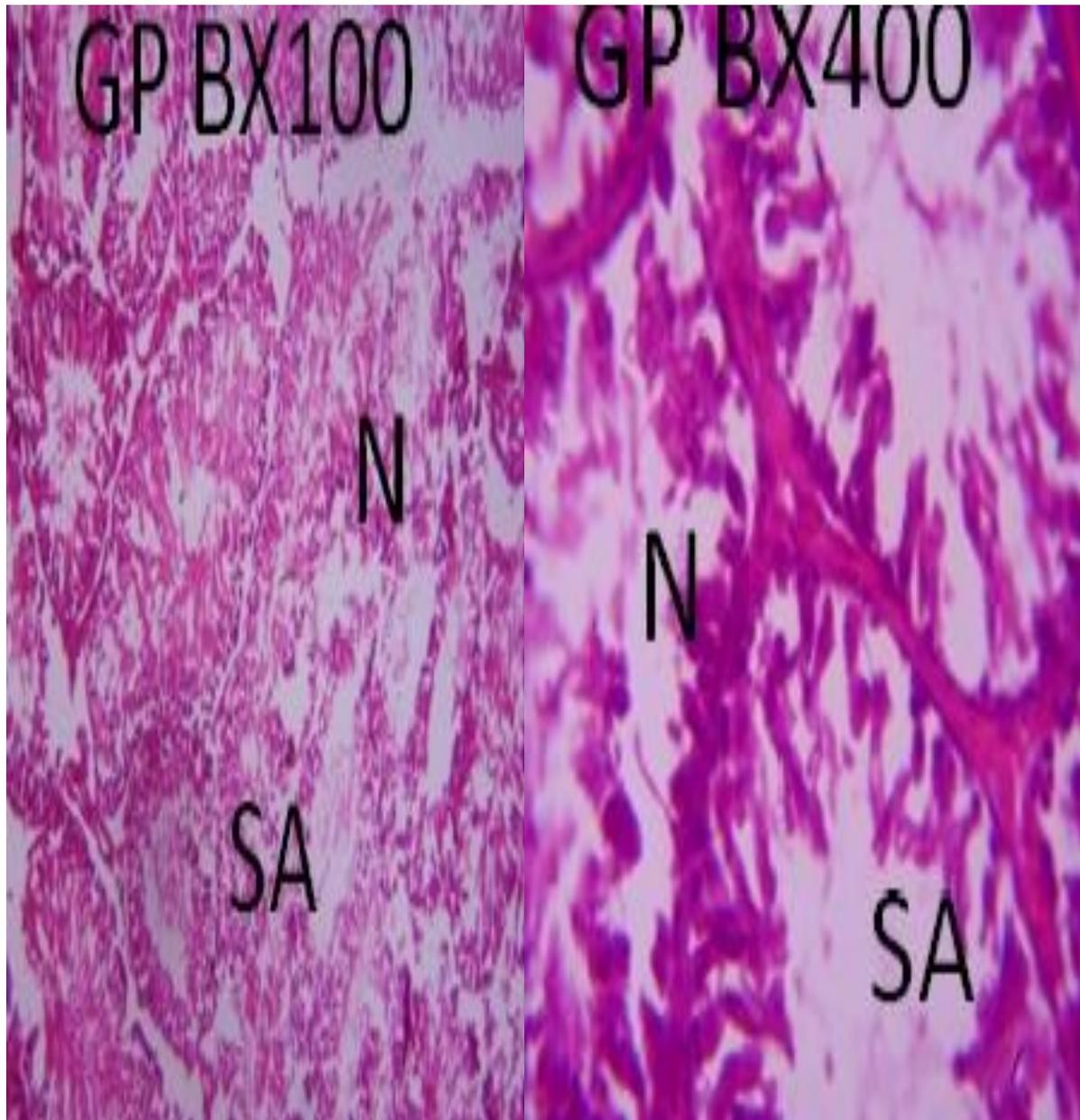


Plate 2: Photomicrograph of group B sections of the testis induced with Cadmium (X100/X400(H/E) shows severe degeneration of the

testicular tissue with severe spermatogenic arrest (SA) and severe necrosis (N) of the testicular cells.

Extract Only Group

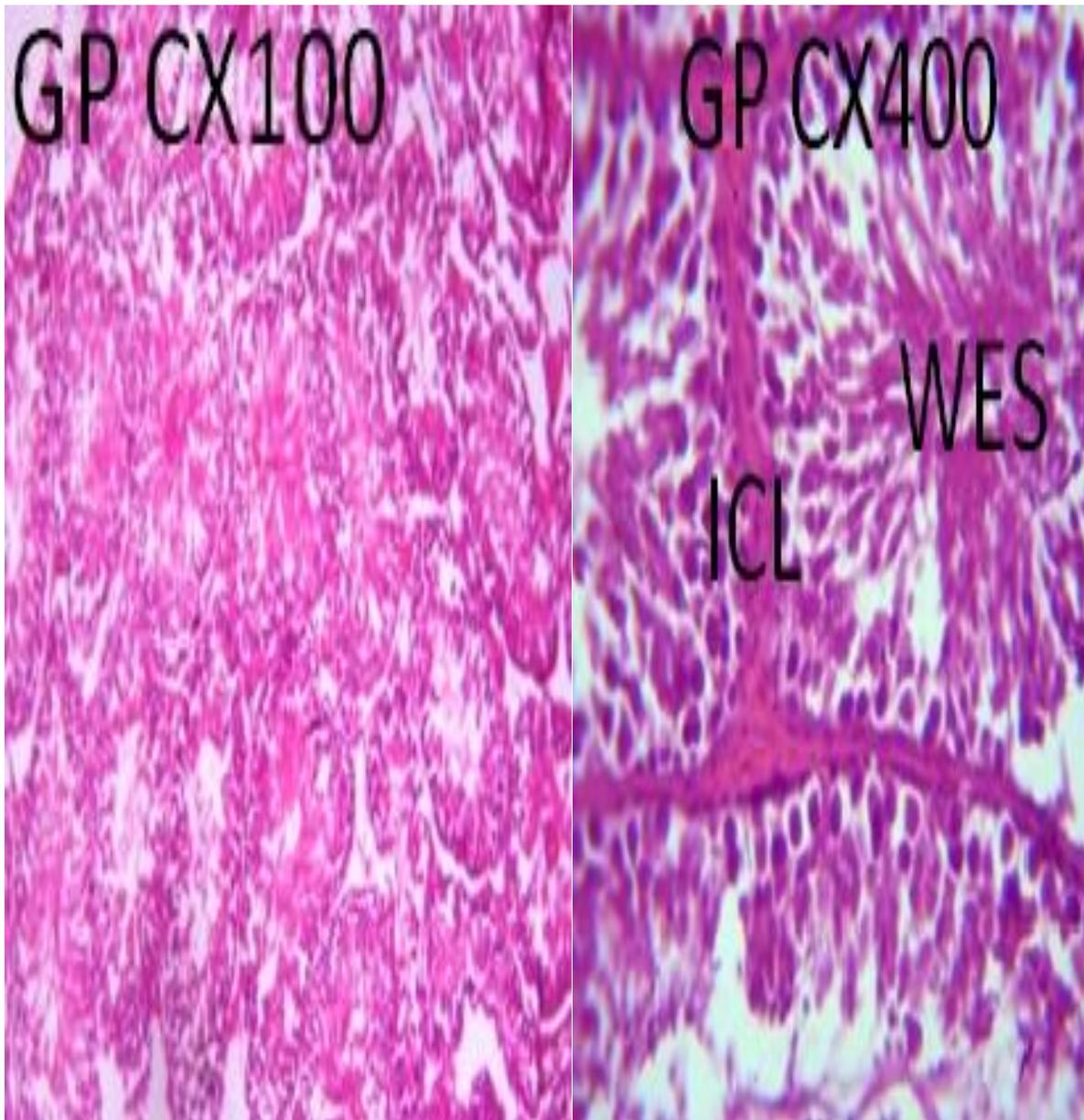


Plate 3: Photomicrograph (100x400) (H/E) of control group C section of testis administered with 100mg/kg of the extract shows testicular architecture

with active seminiferous tubules lined with distorted interstitial cells of Leydig (ICL) with Sertoli cell (SC) and well enhanced spermatogenesis (WES).

Cadmium-induced + 200 mg/kg Extract

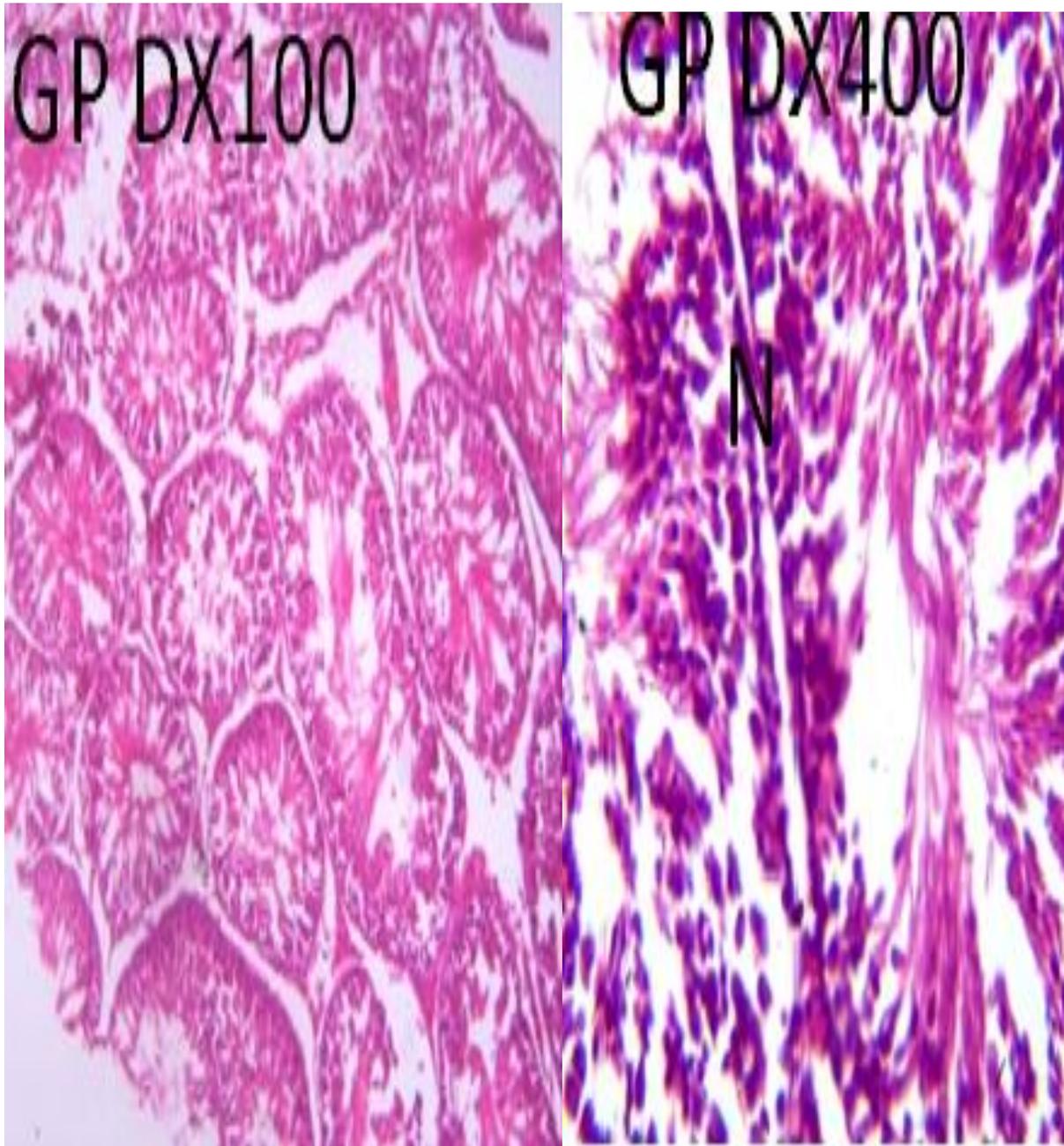


Plate 4: Photomicrograph (X100/X400(H/E) of group D section of the testis induced with cadmium and treated with 200mg/kg extract of *P.*

domestica shows moderate response with mild necrosis (N) of the testicular cells.

Cadmium-induced + 400 mg/kg Extract

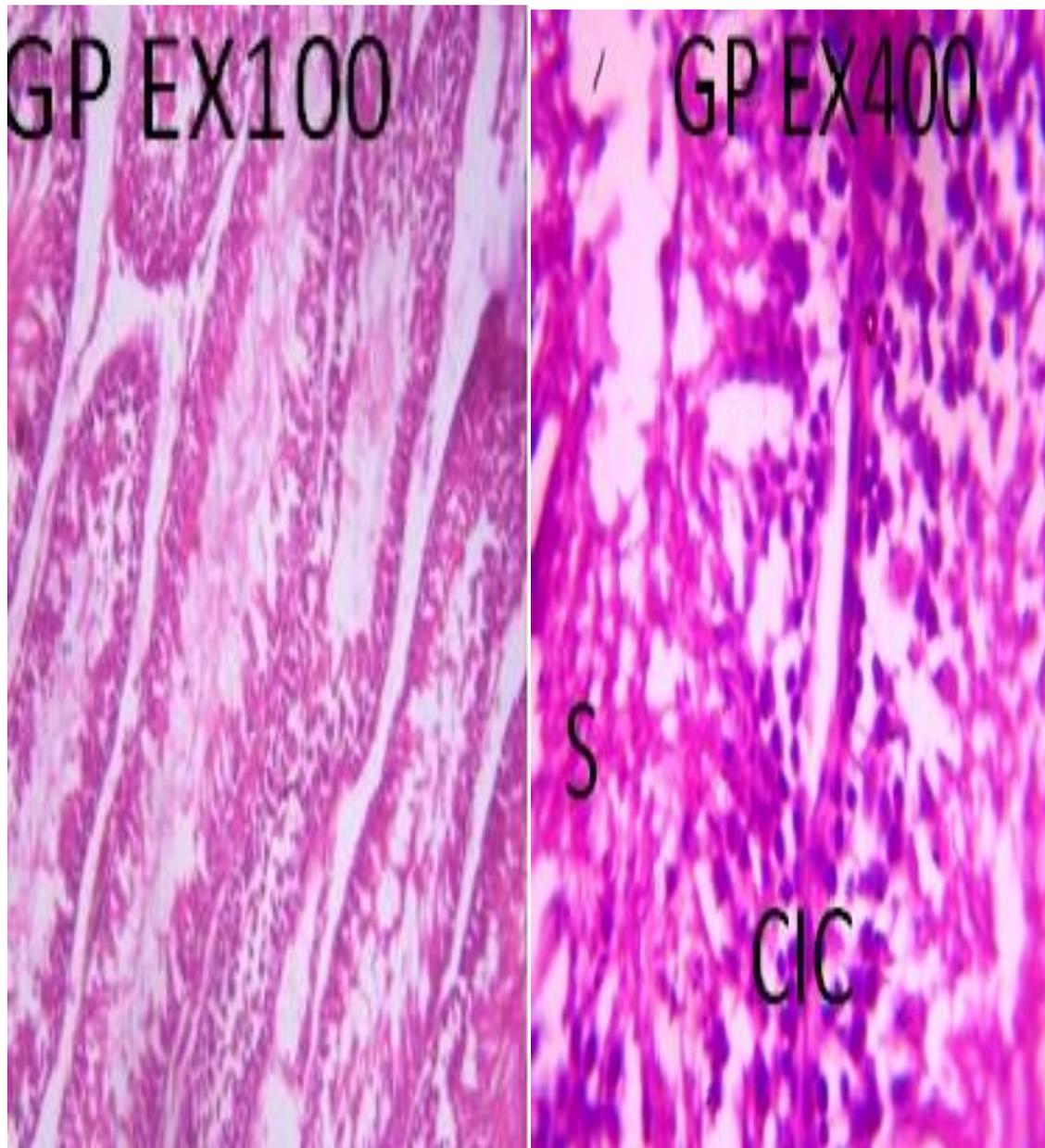


Plate 5: Photomicrograph (100/X400(H/E) of group E section of the testis induced cadmium and treated with 400mg/kg of *P. domestica* extract shows

moderate response with moderately enhanced spermatogenesis (S) and mild cluster of inflammatory cells (CIC).

3.5 Summary of Findings

Cadmium significantly induced oxidative stress in testicular tissue and also significantly reduced testosterone levels. Cadmium significantly impaired sperm quality parameters. Ethanol leaf extract of *Prunus domestica* significantly ameliorated biochemical, hormonal, and histological alterations in a dose-dependent manner.

4. DISCUSSION

This study investigated the protective effect of ethanol leaf extract of *Prunus domestica* against cadmium-induced testicular toxicity in adult male Wistar rats. The findings demonstrated that cadmium exposure significantly induced oxidative stress, hormonal imbalance, impaired sperm parameters, and histopathological alterations in the testes. However, co-administration of the ethanol leaf extract significantly ameliorated these adverse effects in a dose-dependent manner.

4.1 Effect on Oxidative Stress Markers

Cadmium administration resulted in a significant increase in malondialdehyde (MDA) levels, indicating enhanced lipid peroxidation. This finding confirms that cadmium induces oxidative damage to membrane lipids, consistent with established mechanisms of cadmium toxicity (Stohs et al., 2000; Valko et al., 2005).

Additionally, significant reductions in superoxide dismutase (SOD), catalase (CAT), and reduced glutathione (GSH) were observed in the cadmium-treated group. These antioxidant enzymes constitute the primary defense system against reactive oxygen species (ROS). Their depletion suggests that cadmium overwhelms endogenous antioxidant capacity, thereby promoting oxidative stress (Ognjanović et al., 2010).

Co-treatment with ethanol leaf extract of *Prunus domestica* significantly reduced MDA levels while

restoring antioxidant enzyme activities. This protective effect is likely attributed to the presence of flavonoids, phenolic acids, and other antioxidant phytochemicals known for free radical scavenging properties (Scalzo et al., 2005; Kim et al., 2003). The dose-dependent restoration observed in this study suggests a strong antioxidative potential of the extract.

4.2 Effect on Serum Testosterone Levels

Cadmium exposure significantly reduced serum testosterone levels compared to the control group. This reduction may be due to cadmium-induced damage to Leydig cells, which are responsible for testosterone synthesis. Disruption of the hypothalamic–pituitary–testicular axis has been reported as a key mechanism in cadmium-induced reproductive toxicity (Lafuente, 2013).

The ethanol leaf extract significantly improved testosterone levels, especially at the higher dose. This suggests that the extract protected Leydig cells from oxidative damage and restored steroidogenic activity. The improvement in hormonal status further supports the antioxidative and cytoprotective properties of *Prunus domestica*.

4.3 Effect on Sperm Parameters

Sperm count and motility were significantly reduced in the cadmium-treated group, while abnormal sperm morphology increased. These findings are consistent with previous studies reporting cadmium-induced impairment of spermatogenesis (Thompson & Bannigan, 2008).

Oxidative stress plays a major role in sperm dysfunction because sperm membranes contain high levels of polyunsaturated fatty acids, making them highly susceptible to lipid peroxidation (Aitken & Roman, 2008). The observed deterioration in sperm quality is therefore attributable to cadmium-induced ROS generation.

Treatment with ethanol leaf extract significantly improved sperm count, motility, and morphology. This suggests that the extract preserved spermatogenic integrity and enhanced sperm maturation processes. The improvement likely resulted from reduced oxidative damage and improved testosterone production.

4.4 Histopathological Findings

Histological examination of the testes in the cadmium-treated group revealed degeneration of seminiferous tubules, thinning of germinal epithelium, and interstitial edema. These structural alterations confirm the toxic effect of cadmium on testicular architecture and spermatogenic activity.

Conversely, extract-treated groups showed marked restoration of seminiferous tubule structure and spermatogenic cell layers. The high-dose extract group demonstrated near-normal histoarchitecture, indicating significant protection against cadmium-induced damage.

The histological improvements observed correlate with the biochemical and hormonal findings, further validating the protective role of the ethanol leaf extract.

5. CONCLUSION

Based on the findings of this study, it was concluded that:

Cadmium exposure induced significant oxidative stress in testicular tissue, evidenced by increased lipid peroxidation and decreased antioxidant enzyme activity. Cadmium significantly reduced serum testosterone levels and impaired sperm parameters. Histopathological examination confirmed severe degeneration of testicular architecture following cadmium exposure.

Ethanol leaf extract of *Prunus domestica* significantly ameliorated cadmium-induced biochemical, hormonal, spermatogenic, and histological alterations in a dose-dependent manner.

Therefore, ethanol leaf extract of *Prunus domestica* possesses significant protective effects against cadmium-induced testicular toxicity, primarily through antioxidant and cytoprotective mechanisms.

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