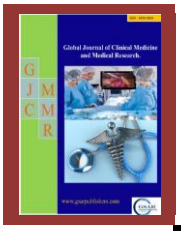

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Modulatory Effects of D-Ribose-L-Cysteine on Lead-Induced Neuro-Reproductive Toxicity in the Hypothalamic-Pituitary-Ovarian Axis of Adult Wistar Rats

By

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Abstract

Background: *A common environmental toxin, lead acetate (LA), has been linked to oxidative stress, neuroendocrine disruption, and reproductive health problems. D-ribose-L-Cysteine (DRLC) has cytoprotective and antioxidant qualities that could mitigate damage from LA. This study investigated how DRLC protected female Wistar rats exposed to LA from behavioral, hormonal, histological, and biochemical changes in the hypothalamic-pituitary-ovarian (HPO) axis.*

Methods: *Twenty adult female Wistar rats were divided into four groups (n=5): a combination group (LA+DRLC), DRLC only (100 mg/kg), LA only (0.05 w/v 1.5ml/rat in a day), and control. Hormonal assays, neurobehavioral tests, oxidative stress markers and histological evaluations were measured and performed following a 28-day oral exposure. EPM test and Sexual Performance Paradigm test was conducted to measure anxiety level and assess sexual behavior.*

Results: *Hormone (LH, FSH) and neurotransmitters (dopamine) level were altered after exposure to LA and treatment with DRLC. Elevated nitric oxide and reduced superoxide dismutase levels indicated oxidative imbalance as a result of exposure to lead acetate. Histological findings revealed vacuolization, neuronal shrinkage in the pituitary and hypothalamus, increased collagen deposition and degenerative changes in the ovary due to lead exposure. In the LA only group, immunostaining revealed strong Bax expression, which suggested heightened neuronal death. DRLC treatment ameliorated these effects, preserving tissue architecture and reducing oxidative and apoptotic markers.*

Conclusion: *DRLC exhibits potent neuro-reproductive protective effects against lead acetate toxicity by mitigating oxidative stress, preserving neuronal and ovarian histoarchitecture, and downregulating apoptotic pathways.*

Keywords: *D-Ribose-L-Cysteine, Neuro-reproductive toxicity, Hypothalamic-pituitary-ovarian axis, wistar rats.*

Introduction

Neuro-reproductive toxicity is a term used to describe a variety of adverse effects on nervous and reproductive system structure or function caused by exposure to biological, chemical, or physical agents. The neurophysiological changes induced by neurotoxic agents can include motor or cognitive symptoms and/or psychiatric and behavioral disturbances. Common neurotoxic agents include drugs, bacterial and animal neurotoxins, synthetic pesticides, and heavy metals. Compared to other environmental contaminants to which humans are regularly exposed, metals have been known to be toxic since antiquity and their toxic effects have been extensively investigated and described. However, as we will discuss later in this research article, the precise mechanisms of heavy metal toxicity are still unclear. Due to their exceptional toxicity to the nervous system at low levels, their presence in the environment has been regulated to a certain extent (Jaishankar *et al*., 2014). Despite this, millions of people continue to suffer from chronic exposures to neurotoxic

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metals via food and water consumption or through other routes of exposure such as occupational inhalation, tobacco smoking, and more recently, electronic cigarette vaping (Zhao *et al*., 2019).

One of the most prevalent environmental toxins is lead (Pb), which can have a major neurotoxic effect and consequently impair brain function (Ihuoma *et al*. 2023). Antioxidants can be utilized to counteract the negative effects of heavy metal exposure, especially lead (Pb), which is linked to severe neuronal damage through oxidative stress mediated by reactive oxygen species (Yousef *et al*. 2019). Neurotoxicity during development is caused by lead (Pb). Lead acetate exposure during development causes abnormal hippocampus neurogenesis via altering the number of neural progenitor cell (NPC) subpopulations in the rat dentate gyrus.

Lead acetate is a compound which is highly neurotoxic and is a heavy metal that negatively impacts human health with adverse effects on the nervous system. Lead acetate is an example of a neurotoxin and means that it can affect the brain and the nervous system as well as the kidneys (ATSDR, 2020). During their research Lidsky & Schneider stumbled upon the fact that lead acetate can affect synaptic transmission, cognitive abilities and neuronal development (Lidsky & Schneider, 2003). There are reports linking even minute exposure to lead with lowered IQ's, attention disorders and increased chances of degenerative diseases (Canfield *et al*., 2003).

The toxic effect of lead acetate on brain activity is explained by the fact that lead ions mimic calcium ions and block some biochemical signaling ions (Toscano and Guilarte, 2005). Lead also inhibits neurotransmitter release, changes the activity of genes and incorporates oxidative stress (Sanders *et al*., 2009). Moreover, during well-defined and crucial stages of development, let us say during exposure to brain development periods, lead could have an impact such as paralysis of normal function of the brain, thereby damaging its structure (Nelson *et al*., 2017).

In light of the properties that D-ribose-L-cysteine (DRLC) possesses, it could be a good candidate for neuro-reproductive protection and DRLC promotes the production of glutathione that helps in ameliorating oxidative stress and inflammation in neural and reproductive tissues, this compound being a strong anti-oxidant and anti-inflammatory agent. According to studies, it is effective in the reversal of oxidative damage in neurons and also in reproduction. In addition, DRLC supplementation in diabetic models has been effective in normalizing redox dysregulation while also supporting spermatogenic function, thus exhibiting dual neuro-reproductive protective effects (Ukwenya *et al*., 2020; Emokpae *et al*., 2021). D-ribose-L-cysteine (DRLC) has been reported on to possess neuro reproductive shielding capability through promotion of cellular antioxidant mechanisms particularly increasing glutathione synthesis. In neuro-applications, DRLC protected nerve cells by decreasing the levels of oxidative stress which could be toxic in neurodegenerative diseases. For instance, DRLC has been shown to lower oxidative stress and neuroinflammation in Alzheimer's-type angiopathy models (Ogunlade *et al*., 2020). Moreover, DRLC protects against the testicular and reproductive consequences of oxidative injury associated with diabetes and other toxic liabilities. This compound improves spermatogenesis and hormone homeostasis by decreasing oxidative stress and inflammatory cytokines in diabetic rats (Ukwenya *et al.*, 2020).

The aim of conducting a study on the mitigating effect of DRLC on lead acetate toxicity in the hypothalamic-pituitary-ovarian axis is to investigate potential protective and therapeutic mechanisms that could mitigate the adverse reproductive effects of lead acetate exposure. This includes understanding how DRLC, a known therapeutic supplement for its role in regulating reproductive function, may counteract or mitigate the disruptive impact of lead acetate on the hypothalamic-pituitary-ovarian axis.

Methods

Chemical and Animal Procurement

The experimental rats were acclimated to laboratory conditions for 2 weeks. Adult female wister rats with body weight (130g-190g, 8 weeks old) were procured from the research Farm, Federal University of Technology, Akure Nigeria, and were maintained at room temperature and relative humidity of 45 to 55% under 12-h light: 12-h dark cycle with free access to food pellets (Farm support Ltd., Akure, Nigeria) and water ad libitum. All chemicals and reagents used in this study were of analytical grade and sourced from reliable manufacturers to ensure consistency and reliability in experimental results. The ELIZA kits for hormone profiles was obtained from Randox Laboratories Ltd., Admore Diamond Road, Crumlin, Co., Antrim, United Kingdom. All other chemicals and reagents were purchased from Pascal Laboratory and Scientific Tools Limited Akure Ondo State Nigeria while the DRLC tablets were obtained from Pascal Pharmaceutical Nigeria Limited Akure.

Lead acetate and DRLC solution preparation

Lead acetate was prepared as a 0.05% (w/v) solution in distilled water. 50g of lead acetate was dissolved completely in 10 litres of distilled water. This solution was used to induce neuro-reproductive toxicity in the experimental animals. Lead acetate is a known environmental toxin that disrupts reproductive and neurological functions, making it a suitable agent for creating the toxic model in this study. 1.5 ml of the solution was administered orally to each rat using a ball-tip gavage for 14 days across all groups except the control group and the DRLC groups. The DRLC solution was prepared to deliver a dose of 100 mg/kg body weight of the compound to the experimental animals and the procedure began with dissolving completely a mini cup of DRLC tablets (containing 32 capsules all about 10.6667grammes) in an appropriate volume of normal saline (1000ml) to prepare a homogeneous solution and this is followed by gentle stirring to ensure complete dissolution of the compound.

The DRLC solution was prepared once and stored temporarily in a clean, labeled container at room temperature, protected

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from light and contamination to ensure maximum stability and effectiveness during administration. The DRLC solution was administered orally to the experimental animals daily with an oral cannula with the dose (1-2 ml) adjusted according to their body weight to ensure accurate delivery of 100 mg/kg for 14 days.

Experimental Design

The experiments were performed following the guidelines of the University Facility Animal Care Committee and the guidelines of the Association for Assessment and Accreditation of Laboratory Animal Care International. They were also performed in conformity with the National Institute of Health Guide for Care and Use of Laboratory Animals of National Research Council, 1985. A total number of twenty female wistar rats with body weight (130g-190g, 8 weeks old) was used for the experiment and grouped into four each group containing five rats; group A is the control group fed with feed and water only, group B were exposed to lead acetate (0.05%) w/v in their drinking water and administered 100mg/kg bw of DRLC, group C were exposed to lead acetate (0.05%) w/v in their drinking water only and group D were administered 100mg/kg bw of DRLC only.

The Elevated Plus Maze (EPM) test was employed in the study to evaluate anxiety-related behavior in the experimental animal and every observations were recorded manually or using a video tracking system for precision. The inflexion ratio of each test was calculated as time spent in the open arms divided by the total time spent in open and closed arm by each rat in every good and a higher inflexion ratio indicates lower anxiety while a lower inflexion ratio suggest higher anxiety.

A Sexual Performance Paradigm test was designed and conducted to evaluate the sexual behavior and interaction between an adult healthy male Wistar rats and adult female wistar rats exposed to lead toxicity and DRLC treatment. The test involved a single male rat interacting with multiple females to assess willingness and copulatory performance. A single adult male Wistar rat was assigned to interact with five females from each experimental group, making a total of 20 females and 4 males for the entire study. The female rats were prepared by ensuring they were in the proestrous phase, confirmed through vaginal cytology. The male rat was then introduced into the natural environment (home cage) of the females and a female rat from a group was tested with the male rat at a time, allowing approximately 25 minutes of interaction per group.

Observations were recorded automatically using video tracking for detailed analysis. After each 5-minute session, the male rat was given a resting period to recover before interacting with the next females and they were returned to their respective cages after the test to prevent prolonged stress or unintended mating. This design allowed for a comprehensive evaluation of male sexual behavior and provided valuable insights into the effects of lead toxicity and the modulatory interventions being studied.

Experimental animal sacrifice and sample collection

The animal sacrifice and sample collection were conducted under ethical guidelines to ensure the integrity of the study while minimizing animal suffering. The animals were fasted overnight with access to water to minimize variability in physiological parameters and sacrifices were carried out in a designated laboratory area under aseptic conditions to prevent contamination of the samples. Each rat was anesthetized using an appropriate dose of a ketamine-xylazine mixture to induce deep sedation, cervical dislocation followed by transcardiac perfusion was performed to ensure humane euthanasia and proper preservation of the brain tissue. Blood was collected via cardiac puncture using a sterile syringe immediately after sacrifice. The blood was transferred into plain tubes, allowed to clot, and centrifuged to obtain serum for hormonal and biochemical assays (NO, SOD, LH, FSH).

The brain was carefully excised, and the hypothalamic region was dissected and snap-frozen in liquid nitrogen. Samples were stored at -80°C for biochemical assays, including oxidative stress markers analysis. The ovaries were also removed, weighed, and inspected for gross morphological changes. Portions of the ovaries were fixed in Natural Buffered formalin for histopathological analysis, while the remaining portions were stored at -80°C for biochemical analysis. The pituitary gland was dissected, snap-frozen in liquid nitrogen, and stored at -80°C. All collected samples were labeled appropriately with unique identifiers for each animal and stored under optimal conditions to prevent degradation.

Hormonal Assay

Using a Syngenemed microwell kit and the standard Quantitative Enzyme-Linked Immunosorbent Assay (ELISA) technique, serum samples were tested for FSH, LH, estrogen, progesterone, and dopamine at both physiological and pathological levels in batches with the control sera. The assay kits' manufacturer instructions were closely followed throughout the analysis.

Histological evaluation

The ovary, pituitary, and hypothalamus tissues were carefully dissected and fixed in 10% neutral-buffered formalin for 48 hours. After fixation, tissues were dehydrated through a graded series of ethanol, cleared in xylene, and embedded in paraffin wax. Serial 5 µm-thick sections were then cut in a rotary microtome and mounted on grease-free and clean glass slides. The routine or standard procedure described by Olawuyi, (2020) was employed in processing the H and E slides of the ovaries, hypothalamus and pituitary while the modified Masson Trichrome staining technique described by Bancroft and Gamble, (2008) was further employed in processing the ovaries. Standard Cresyl fast violet Nissl staining procedure by Hammond, (2017) was also further employed in processing the hypothalamus and pituitary.

Photomicrography

A light microscope equipped with a digital camera was used to observe and capture images of stained histological slides. . Images were taken at magnifications X40 (or overall tissue architecture and structural organization), X100 (for closer

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examination of specific regions and moderate cellular details and X400 (for high-resolution visualization of cellular and subcellular structures). ToupView, a microscope imaging software, was used to capture high-quality images. The software allowed for real-time observation and focusing adjustments to ensure clarity. Brightness, contrast, and color balance were adjusted to optimize the visualization of stained sections and scale bars were added for accurate measurement and comparison

Statistical analysis

GraphPad Prism 8 was utilized for data analysis and visualization due to its robust statistical tools and user-friendly interface. All data were expressed as mean ± standard error of the mean (SEM). One-Way Analysis of Variance (ANOVA) was employed to compare means across the experimental groups. When ANOVA indicated significant differences ($p < 0.05$), a post-hoc test (e.g., Tukey's multiple comparison test) was conducted to identify specific group differences. A p-value of < 0.05 was considered statistically significant. Graphical Representation used was bar graphs and mean values with error bars representing SEM were plotted for each parameter. Statistically significant differences between groups were denoted using symbols (e.g., asterisks) or letters.

Results

Histological Observations of the Organs

Ovary: All sections of the ovary were stained with Mason Trichrome**.** The section of the ovary of the control group shows normal ovarian histology with healthy follicles and blood vessels. In contrast, section of LA only group showed high deposit of collagen indicating fibrosis and disrupted follicles with follicular atresia. DRLC only group showed moderate healthy ovarian structures with healthy blood vessels, follicles and reduced collagen deposit. The combination group of LA+DRLC presents little morphological changes in the follicle shape and size with moderate collagen deposit within the stroma.

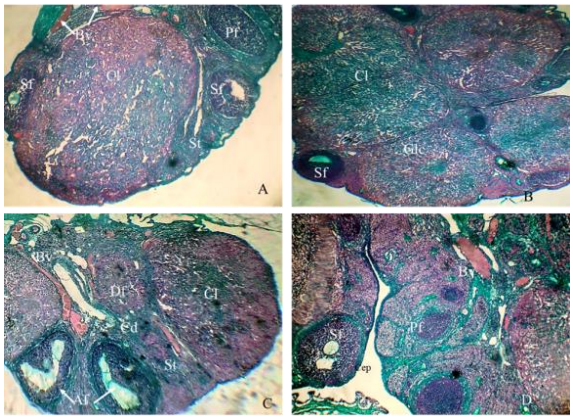

Figure 1: Photomicrographs of sections of the ovary stained with Masson Trichrome. Mag.x40. (A) Control, (B) LA+DRLC (0.05% w/v + 100mg/kg bw), (C) LA only (0.05% w/v), (D) DRLC (100mg/kg bw). Bv = blood vessel, Pf = primary follicle, Sf = secondary follicle, Cl = corpus luteum, cep = cuboidal epithelium, Df = disrupted follicle, Glc = granulosa luteal cells, Af = damaged antral follicle and St = stroma.

Hypothalamus: The sections of the hypothalamus were stained with Hematoxylin and Eosin. The hypothalamus section of the control group shows normal architecture with intact neuronal cells in the arcuate nucleus and glial structures. In contrast, LA only group presents cellular changes due to lipid accumulation and deeply stained shrunken neurons.

DRLC only group showed reduced cellularity and little vacuolization. The combination group of LA+DRLC presents preserved neuronal integrity and reduced vacuolization.

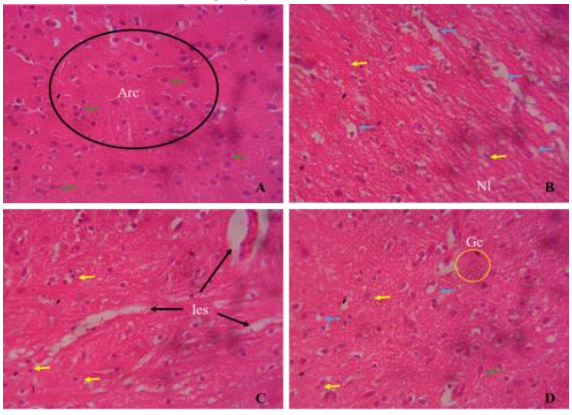

Figure 2: Photomicrographs of sections of the hypothalamus stained with Hematoxylin and Eosin. Mag.x400. (A) Control, (B) LA+DRLC (0.05% w/v + 100mg/kg bw), (C) LA only (0.05% w/v), (D) DRLC (100mg/kg bw). Arc = arcuate nucleus, Gc = glial cells, Nl = region of neuronal loss, Ies = increase extracellular space, blue arrow = vacuolization, yellow arrow = shrunken neurons, green arrow = healthy neurons

Pituitary: The sections of the pituitary were stained with Hematoxylin and Eosin. The pituitary section of the control group presents normal healthy adenohypophysis and the posterior pituitary while the LA only group showed damaged capillary network and shrunken neurons with deeply eosinophilic cytoplasm.

There is increased sinusoids noticed in LA+DRLC group and the DRLC only group presents diminished intracellular connection with increased vacuolization around neurons.

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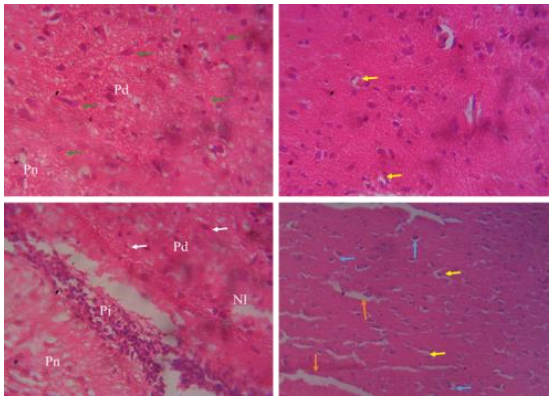


Figure 3: Photomicrographs of sections of the pituitary stained with Hematoxylin and Eosin. Mag.x400. (A) Control, (B) LA+DRLC (0.05% w/v + 100mg/kg bw), (C) LA only (0.05% w/v), (D) DRLC (100mg/kg bw). Pd = pars distalis, Pn = pars nervosa, Pi = pars intermedia, white arrow = shrunken neurons, blue arrow = vacuolization, yellow arrow = sinusoid/capillary network, green arrow = healthy neurons, Nl = region of neuronal loss and brown arrow = damaged sinusoids

Biochemical Result

Level of Nitric Oxide (NO) and Superoxide Dismutase (SOD)

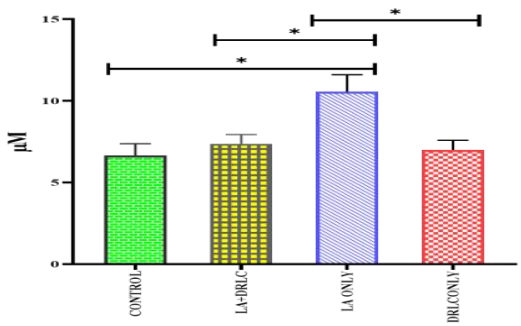
NO: From Table 1.0 below, Post Hoc comparisons using Tukey's Multiple comparison test indicated that the mean score and standard deviation for the LA only group (M = 10.560, SD = 2.336) was significantly different from Group A (CONTROL) (M = 6.651, SD = 1.619), Group B (LA+DRLC) (M = 7.368, SD = 1.276) and Group D (DRLC only) (M = 6.994, SD = 1.325). There is statistically significant change in the LA only group in comparison to the control group.

The mean (±SEM) of the nitric oxide level of group C (LA only) is the highest (10.560 ± 1.044) and that of group A (CONTROL) is the lowest (6.651 ± 0.7241). Significant increase in nitric oxide level of the LA only group was recorded when compared with the rest of the groups including the CONTROL.

Comparison	Mean Difference	Standard Error	P-Value
CONTROL vs. LA+DRLC	-0.7171	1.070	0.9069
CONTROL vs. LA ONLY	-3.908	1.070	0.0104
CONTROL vs. DRLC ONLY	-0.3435	1.070	0.9881
LA+DRLC vs. LA ONLY	-3.191	1.070	0.0396
LA+DRLC vs. DRLC ONLY	0.3735	1.070	0.9849
LA ONLY vs. DRLC ONLY	3.565	1.070	0.0199

Table 1.0: Post-Hoc comparison of the level of Nitric Oxide concentration among the study groups. Value of $p < 0.05$ was considered significant (n=5).

Figure 4: **The Level of Nitric Oxide concentration across all groups**



The LA Only group presented the highest level of nitric oxide concentration with a significant increase in concentration when compared with the CONTROL and the DRLC Only groups.

SOD: As seen in the Table 2.0 below, Post Hoc comparisons using Tukey's Multiple comparison test indicated that the mean score and standard deviation for the LA only group (M = 0.6099, SD = 0.3886) was significantly different from Group A (CONTROL) (M = 1.108, SD = 0.2117) and Group D (DRLC only) (M = 1.085, SD = 0.1573). There is statistically significant changes in the LA only group in comparison to with control group. The mean (±SEM) of the

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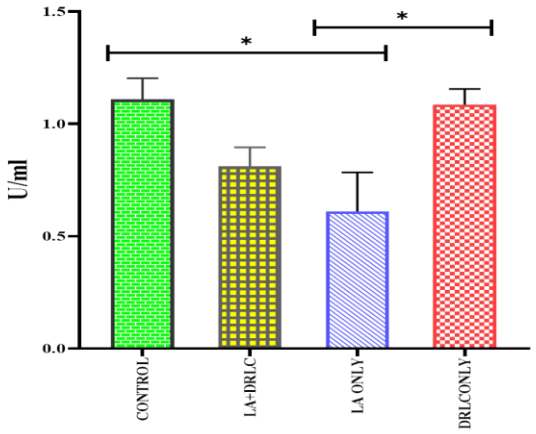
superoxide dismutase level of group A (CONTROL) is the highest (1.108 ± 0.09467) and that of group C (LA only) is the lowest (0.6099 ± 0.1738). There was a significant decrease in the level of superoxide dismutase in the LA only group when compared with the CONTROL and DRLC Only groups.

Comparison	Mean Difference	Standard Error	P-Value
CONTROL vs. LA+DRLC	0.2975	0.1601	0.2838
CONTROL vs. LA ONLY	0.4984	0.1601	0.0306
CONTROL vs. DRLC ONLY	0.02299	0.1601	0.9989
LA+DRLC vs. LA ONLY	0.2009	0.1601	0.6028
LA+DRLC vs. DRLC ONLY	-0.2745	0.1601	0.3485
LA ONLY vs. DRLC ONLY	-0.4754	0.1601	0.0405

Table 2.0: Post-Hoc comparison of the level of Superoxide Dismutase concentration among the study groups. Value of p < 0.05 was considered significant (n=5).

Figure 5: The Level of Superoxide Dismutase concentration across all groups



The CONTROL and the DRLC Only group presented the highest level of Superoxide Dismutase concentration across all groups. There was significant decrease in the concentration of SOD in the LA Only group when compare with the CONTROL and the DRLC only groups.

Hormone Profile Analysis

Level of Luteinizing Hormone (LH), Follicle Stimulating Hormone (FSH) and Dopamine

LH: Considering Table 3.0 below, Post Hoc comparisons using Tukey's Multiple comparison test indicated that the mean score and standard deviation for Group A (M = 1.241, SD = 0.007855) was significantly different from Group B (LA+DRLC) (M = 1.214, SD = 0.007586) and Group C (LA Only) (M = 1.184, SD = 0.01050). Additionally, Group B showed a significant difference compared to Group C (M = 1.184, SD = 0.01050). Group C showed a significant difference compared to Group D (DRLC Only) (M = 1.231, SD = 0.01992). There are statistically significant changes in all groups in comparison to the group A (CONTROL) except in the DRLC Only group. The mean (±SEM) of LH level of group C (LA only) is the lowest (1.184 ± 0.004696) while group A (CONTROL) is the highest (1.241 ± 0.003513).

Comparison	Mean Difference	Standard Error	P-Value
CONTROL vs. LA+DRLC	0.02710	0.007914	0.0165
CONTROL vs. LA ONLY	0.05708	0.007914	<0.0001
CONTROL vs. DRLC ONLY	0.01060	0.007914	0.5527
LA+DRLC vs. LA ONLY	0.02998	0.007914	0.0079
LA+DRLC vs. DRLC ONLY	-0.01650	0.007914	0.1999
LA ONLY vs. DRLC ONLY	-0.04648	0.007914	0.0001

Table 3.0: Post-Hoc comparison of the level of Luteinizing Hormone concentration among the study groups. Value of p < 0.05 was considered significant (n=5).

FSH: Using Table 4.0 below, Post Hoc comparisons using Tukey's Multiple comparison test indicated that the mean score and standard deviation for Group A (M = 2.077, SD = 0.008497) was significantly different from Group B (LA+DRLC) (M = 2.034, SD = 0.01498), Group C (LA Only) (M = 2.012, SD = 0.003975) and Group D (DRLC Only) (M = 2.054, SD = 0.01528). Additionally, Group B showed a significant difference compared to Group C (M = 2.012, SD = 0.003975). Group C showed a significant difference compared to Group D (M = 2.054, SD = 0.01528). There are statistically significant changes in all groups in comparison to the group A

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(CONTROL). The mean (±SEM) of FSH level of group C (LA only) is the lowest (2.012 ± 0.001778) while group A (CONTROL) is the highest 2.077 ± 0.003800). The LA only

group presents a significant decrease in the FSH level when compared to the LA+DRLC group and the DRLC only group shows significant increase in the level of FSH when compared with the LA only group.

Comparison	Mean Difference	Standard Error	P-Value
CONTROL vs. LA+DRLC	0.04330	0.007390	0.0001
CONTROL vs. LA ONLY	0.06560	0.007390	<0.0001
CONTROL vs. DRLC ONLY	0.02320	0.007390	0.0291
LA+DRLC vs. LA ONLY	0.02230	0.007390	0.0369
LA+DRLC vs. DRLC ONLY	-0.02010	0.007390	0.0653
LA ONLY vs. DRLC ONLY	-0.04240	0.007390	0.0002

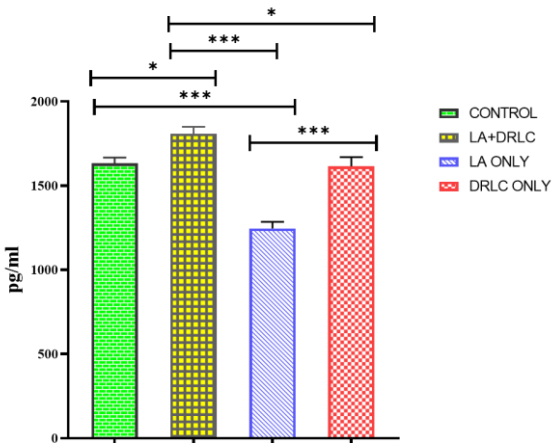
Table 4.0: Post-Hoc comparison of the level of Follicle Stimulating Hormone concentration among the study groups. Value of $p < 0.05$ was considered significant (n=5).

Dopamine: As shown in Table 5.0 below, Post Hoc comparisons using Tukey's Multiple comparison test indicated that the mean score and standard deviation for Group A (M = 1632, SD = 77.27) was significantly different from Group B (LA+DRLC) (M = 1809, SD = 90.64) and Group C (LA Only) (M = 1246, SD = 87.65). Additionally, Group B showed a significant difference compared to Group C (M = 1246, SD = 87.65) and Group D (M = 1616, SD = 121.4). Group C showed a significant difference compared to Group D (M = 1616, SD = 121.4). The mean (±SEM) of DOPAMINE level of group B is the highest (1809 ± 40.54) while group C is the lowest (1246 ± 39.20). There was a significant decrease in the dopamine level in the LA+DRLC group when compared to the LA only and DRLC only group. Additionally, the DRLC only group showed significant increase in the dopamine level when compared to the LA only group.

Comparison	Mean Difference	Standard Error	P-Value
CONTROL vs. LA+DRLC	-176.7	60.50	0.0445
CONTROL vs. LA ONLY	386.2	60.50	<0.0001
CONTROL vs. DRLC ONLY	16.59	60.50	0.9925
LA+DRLC vs. LA ONLY	562.9	60.50	<0.0001
LA+DRLC vs. DRLC ONLY	193.3	60.50	0.0260
LA ONLY vs. DRLC ONLY	-369.6	60.50	<0.0001

Table 5.0: Post-Hoc comparison of the level of Dopamine among the study groups. Value of $p < 0.05$ was considered significant (n=5).

Figure 6: Distribution of Dopamine across all groups



The LA+DRLC and DRLC Only group showed the highest distribution of Dopamine in comparison to the other groups. There was notable significant decrease in the level of Dopamine in the LA Only group compared to the other groups of animals

Behavioral Assessment Results

Elevated Plus Maze (Inflexion Ratio): Considering Table 6.0 below, Post Hoc comparisons using Tukey's Multiple

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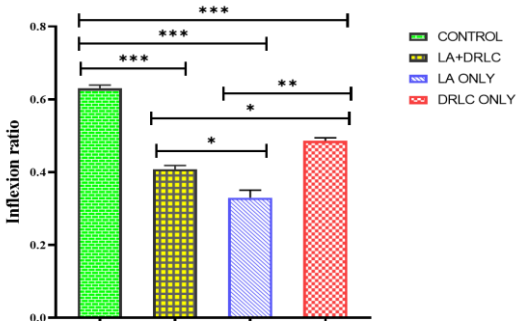
comparison test indicated that the mean score and standard deviation for Group A (M = 0.6300, SD = 0.02121) was significantly different from Group B (LA+DRLC) (M = 0.4080, SD = 0.02280), Group C (LA Only) (M = 0.3300, SD = 0.04637) and Group D (DRLC Only) (M = 0.4860, SD = 0.01817). Additionally, Group B showed a significant difference compared to Group C (M = 0.3300, SD = 0.04637) and Group D (M = 0.4860, SD = 0.01817). Group C showed a significant difference compared to Group D (M = 0.4860, SD = 0.01817). The LA only group showed significant reduction in the level of inflexion ratio when compared with the other groups while the LA+DRLC group showed significant decrease in inflexion ratio when compared with the DRLC only group of animals. The mean (±SEM) of the EPM Inflexion ratio of the CONTROL group is the highest (0.6300 ± 0.009487) and that of group C (LA only) is the lowest (0.3300 ± 0.02074).

Comparison	Mean Difference	Standard Error	P-Value
CONTROL vs. LA+DRLC	0.2220	0.01857	<0.0001
CONTROL vs. LA ONLY	0.3000	0.01857	<0.0001
CONTROL vs. DRLC ONLY	0.1440	0.01857	<0.0001
LA+DRLC vs. LA ONLY	0.07800	0.01857	0.0034
LA+DRLC vs. DRLC ONLY	-0.07800	0.01857	0.0034
LA ONLY vs. DRLC ONLY	-0.1560	0.01857	<0.0001

Table 6.0: Post-Hoc comparison of the EPM Inflexion Ratio among the study groups. Value of $p < 0.05$ was considered significant (n=5).

Figure 7: Inflexion Ration comparison across all groups



Inflexion ration in the CONTROL group is the highest compared to the other groups of animals. There was significant decrease in the inflexion ratio in all groups when compared with the control group.

Total Copulatory Period: There are statistically significant increase in all groups in comparison with the control group. From Table 7.0 below, Post Hoc comparisons using Tukey's Multiple comparison test indicated that the mean score and standard deviation for Group A (M = 8.600, SD = 0.9618) was significantly different from Group B (LA+DRLC) (M = 14.56, SD = 1.122), Group C (LA Only) (M = 18.43, SD = 1.247) and Group D (DRLC Only) (M = 10.69, SD = 0.8905). Additionally, Group B showed a significant difference compared to Group C (M = 18.43, SD = 1.247) and Group D (M = 10.69, SD = 0.8905). Group C showed a significant difference compared to Group D (M = 10.69, SD = 0.8905). The LA only group showed significant increase in the total copulatory period when compared with the LA+DRLC and DRLC only. The mean (±SEM) of the total copulatory period of the CONTROL group is the lowest (8.600 ± 0.4301) and that of group C (LA only) is the highest (18.43 ± 0.5578).

Comparison	Mean Difference	Standard Error	P-Value
CONTROL vs. LA+DRLC	-5.960	0.6732	<0.0001
CONTROL vs. LA ONLY	-9.830	0.6732	<0.0001
CONTROL vs. DRLC ONLY	-2.090	0.6732	0.0311
LA+DRLC vs. LA ONLY	-3.870	0.6732	0.0002
LA+DRLC vs. DRLC ONLY	3.870	0.6732	0.0002
LA ONLY vs. DRLC ONLY	7.740	0.6732	<0.0001

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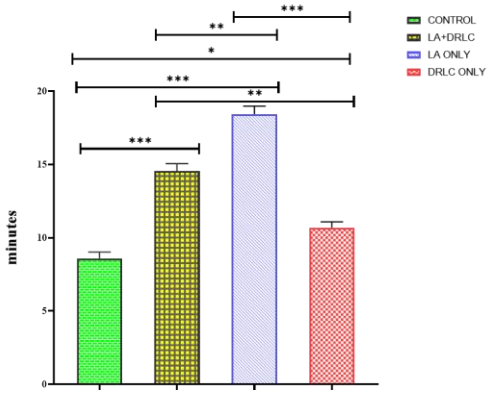
Table 7.0: Post-Hoc comparison of the Total Copulatory Period among the study groups. Value of $p < 0.05$ was considered significant (n=5).

Figure 8: Total Copulatory Period across all groups



Longest copulatory period was recorded in the groups of animal exposed to Lead acetate only while the control group presented the shortest copulatory period when compared with the rest of the experimental groups.

Discussion

In control group (A), ovarian tissue exhibited normal folliculogenesis with intact blood vessels and follicles, in accordance with normal expected physiological status and this observation serves as a baseline to compare the effects of LA and DRLC. The combination treatment LA+DRLC Group B produced marked alterations, including fibrosis of the corpus luteum, follicular morphology alteration, and antral follicle degeneration but not as prominent and pronounced as that seen in the LA only group. These findings suggest that there is a potential interactive effect between LA and DRLC, leading to structural change in the ovary. Fibrosis of the corpus luteum may indicate an inflammatory response or abnormal luteal function, which may influence reproductive capacity. Lead was also found to induce oxidative stress and inflammation, which could contribute to this fibrosis (Flora *et al*., 2012).

LA treatment only (Group C) induced more severe pathological changes, including damaged blood vessels, over-deposition of collagen in the stroma, and follicular atresia. The results show that lead acetate, when administered without DRLC, can exert significant adverse effects on ovarian vascularity and stromal integrity, suppressing normal follicular development and inducing atresia. The increased collagen deposition in the stroma may indicate an increase in extracellular matrix components, which can disrupt normal ovarian function (Hughesdon and Kumarasamy, 1999). Lead's toxicity can disrupt hormonal balance and induce apoptosis in ovarian cells, explaining the observed follicular atresia. Interestingly, DRLC presented healthy histoarchitecture of the organs as the ovaries in this group had healthy vessels, moderate stromal collagen, and even follicles, suggesting a protective role for DRLC. This observation agrees with previous findings that L-cysteine is an antioxidant and that it can mitigate heavy metal toxicity (Aebi, 1984). D-ribose, as a component of nucleic acids, can also help in cell repair and regeneration. The variations in collagen deposition between groups suggest that lead acetate and D-ribose-L-cysteine are able to influence the equilibrium of extracellular matrix components in the ovary. Excessive collagen deposition, such as in the lead acetate-treated group, can disrupt normal ovarian structure and function, with a risk of fibrosis and impaired folliculogenesis. Moderate collagen deposition in the DRLC treated group can reflect a more equilibrated extracellular matrix turnover, beneficial to normal ovarian function. The atresia and morphological changes in follicles are indicative of the potential impact of lead acetate and DRLC on the development of follicles. Follicular atresia, or the degeneration of ovarian follicles, can lead to infertility and endocrine disruption. The protective effect of DRLC on follicular atresia suggests that it has a potential role in the maintenance of ovarian reserve and reproductive function.

Histoarchitectural analysis of Hypothalamus with Hematoxylin and Eosin (H & E) staining showed obvious alterations in the experimental groups. The hypothalamus showed normal histoarchitecture with well-delineated neuronal cells in the arcuate nucleus and intact glial constituents in the control group, indicating a physiologically stable microenvironment. Lead acetate (LA) exposure, however, resulted in prominent histopathological alterations, including neuronal cell shrinkage, increased lipid accumulation, and hyperchromatic nuclei—characteristic changes of neurotoxicity and cellular stress. These are consistent with previous reports that lead induces neuronal damage through oxidative stress and inflammatory pathways (Dhar *et al*., 2019; Garza-Lombó *et al*., 2021). Interestingly, DRLC-only rats were found to have minimal structural abnormalities, reduced cellularity and mild vacuolization, suggesting that even though DRLC has a generally benign profile, its metabolic action can subtly interfere with cell density. Most importantly, the co-treatment group (LA+DRLC) had normal neuronal architecture with negligible vacuolization and nearly normal cellular profile, indicating a neuroprotective effect of DRLC against lead-induced hypothalamic pathology. This finding is in agreement with earlier evidence showing DRLC's antioxidative and anti-inflammatory actions that maintain neuronal integrity under toxic stress (Ajayi *et al*., 2022; Oyovwi *et al*., 2024) and also by a study conducted by Olawuyi *et al.*, 2020 investigating the effects of aqueous Lawsonia inermis (henna) leaf extract on aluminum-induced oxidative stress in the pituitary gland of adult male Wistar rats who found out that aqueous *Lawsonia inermis* (henna) leaf extract demonstrated antioxidant properties, mitigating the harmful effects of aluminum on the pituitary gland.

Histopathology of the pituitary gland through Hematoxylin and Eosin (HandE) staining revealed significant group-wise difference in cytoarchitecture. Adenohypophysis and neurohypophysis (posterior pituitary) of the control group were structurally normal, as indicated by the presence of well-structured glandular tissue, intact capillaries, and normal endocrine cells. Conversely, the LA alone group showed

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extensive histological damage, including impaired capillary network, neuron shrinkage, and highly eosinophilic cytoplasm—changes indicating cellular degeneration and oxidative stress. The findings agree with previous reports associating lead toxicity with vascular impairment and disruption of the cytoskeleton in neuroendocrine tissues (Zhang *et al*., 2017; Rahman *et al*., 2018). Surprisingly, in the DRLC-only group, although frank structural injury was not seen, there was some intercellular connectivity loss and perineuronal vacuolization. This can be a sign of cellular remodeling or mild metabolic adaptation secondary to stress, though it did not duplicate the extent of damage related to lead exposure. Interestingly, the LA+DRLC group had preservation of overall tissue architecture in the midst of the presence of widened sinusoidal spaces, which may suggest compensatory vascular remodeling or increased perfusion as a result of DRLC's endothelial-protective and antioxidative effects. The histological improvements are consistent with previous findings that D-Ribose-L-Cysteine enhances cellular glutathione levels, reduces oxidative damage, and sustains microvascular integrity in stressed tissues (Ajayi *et al*., 2022; Oyovwi *et al*., 2024).

In this study, the group of rats treated with DRLC only and the group exposed to LA+DRLC showed an increase in the level of SOD when compared to the group exposed to LA only indicating that DRLC may upregulate antioxidant defenses protecting the cells from damage and help counteract LA-induced oxidative damage. This finding correlates with a report by Wang and Fowler 2008 which states that D-Ribose-L-Cysteine (DRLC) upon investigation acted as a modulator of markers of oxidative stress following lead acetate exposure and also with the findings from a study by Olawuyi *et al.*, 2020 that DRLC supplementation mitigated toxic changes, significantly restoring antioxidant markers (like GSH) and normalizing hormone profiles, indicating protective effects against nicotine-induced testicular toxicity. As few direct investigations on the impacts of DRLC on levels of NO and SOD have been conducted with respect to lead-induced toxicity, research indicates DRLC augmentation of antioxidant defense. For instance, supplementation with DRLC was seen to increase brain activities of SOD, catalase, and glutathione, reduce malondialdehyde content in stressed mice, suggesting its ability to reverse oxidative damage.

Exposure to lead acetate has been shown to result in endocrine disruption, leading to significant changes in the concentrations of hormones such as estrogen, progesterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and dopamine. Such endocrine disruptions can adversely affect reproductive health and neurological function. In Wistar female rats, lead acetate exposure resulted in a significant decrease in serum FSH, LH, and progesterone concentrations. These reductions indicate potential disturbances in reproductive hormone regulation and ovarian function. Additionally, lead exposure has been associated with the inhibition of dopamine synthesis due to its effects on the dopaminergic system involved in sexual behavior and neurological function (Mokhtari and Zanboori, 2011) and this is in line with the finding of this study in which the dopamine level of the group of rats exposed to lead acetate only is relatively low when compared with the control group and this suggest that excessive free radicals from LA could impair dopamine synthesis and synthesis. The reduction could also be as a result of damage to the dopaminergic neurons by exposure to lead contributing to depressive-like behavior and eventually sexual performance anxiety. Furthermore the groups of animals exposed to DRLC and LA+DRLC have a higher level of dopamine when compared to the control group and the LA only group indicating DRLC ability to restore or enhance dopaminergic neuron functions thereby leading to reduced stress, improved mood and better sexual performance related responses in the rats and this is slightly agrees to a research by Xu *et al.* (2023) which explored the neuroprotective effect of calcitriol that shares antioxidant and neuroprotective properties with DRLC in aging mouse and it was found that calcitriol improved cognitive performance and reduces stress indicating its role in supporting dopaminergic function.

In addition, lead exposure was associated with reduced production of dopamine via its effects on the dopaminergic system which is responsible for neurological status and sexual behavior. It was revealed through research that exposure to lead reduces levels of dopamine in the brain, maybe via the inhibition of the activity of monoamine oxidase-A (MAO) (Akinyemi *et al*., 2019). In addition, DRLC exhibited neuroprotective activity in other toxicology conditions. For instance, in ethanol-treated adolescent mice, DRLC treatment modulated neurotransmitter functions, including dopamine, in the cerebellum, indicating its ability to reverse neurochemical changes (Adekomi *et al*., 2023).

Co-administration of D-Ribose-L-Cysteine (DRLC) with lead acetate has been found to exert a restorative effect on such hormonal imbalances. Studies have found that DRLC treatment significantly increased serum concentrations of FSH, LH, and progesterone in female Wistar rats that had been exposed to lead. This suggests the possibility of using DRLC to mitigate the reproductive toxicity of lead exposure (Ogunlade *et al*., 2022; Olawuyi *et al.*, 2020) as this was seen in the group of animals treated with combination of lead acetate and DRLC in which the level of LH and FSH is higher when compared to the groups of animal exposed to lead acetate only and DRLC only.

Exposure to lead acetate has also been reported to disrupt female reproductive endocrinology in a qualitative way in terms of the levels of the dominant hormones such as estrogen and progesterone. In a research by Pollack *et al.* (2011), elevated blood lead was associated with minimal changes in the reproductive hormones in premenopausal women as measured by estradiol and progesterone changes. Similarly, developmental lead exposure in female rats resulted in down-regulated circulating estradiol levels, indicating a direct impact on ovarian steroidogenesis and this supports the result of this study in which the estrogen and progesterone level of the group of animals exposed to LA only and that of the group

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treated with the combination of LA+DRLC is relatively low compared to the control and DRLC only group.

D-Ribose-L-Cysteine (DRLC) also proved to possess potential in the reversal of hormonal dysregulations due to lead toxicity. Ogunlade *et al*. (2020) demonstrated in a study that co-administration of DRLC with lead acetate in adult female Wistar rats regulated hormone levels such as progesterone and heightened ovarian toxicity. These findings point to the antioxidative action of DRLC having the potential to reverse oxidative stress caused by lead, hence normalizing regulation and synthesis of reproductive hormones.

Lead acetate exposure has been linked with sexual dysfunction, which may result in sexual performance anxiety. The mechanism underlying the dysfunction is oxidative stress and hormonal alteration. A study conducted by Besong *et al*. (2024) demonstrated that lead exposure in Wistar male rats resulted in decreased penile weight, luteinizing hormone, follicle-stimulating hormone, and testosterone levels, and nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) levels. Such changes have the potential to impair erectile function, leading to increased sexual performance anxiety and this demonstration supports the finding of this study in which lower level of LH and higher level of FSH across the groups exposed to lead acetate is a reflection of reduced stimulus for ovulation due to anxiety-induced reproductive dysfunction and attempt to compensate for impaired ovarian response.

D-Ribose-L-Cysteine (DRLC) was found to be efficient in mitigating heavy metal-induced reproductive toxicity. Falana *et al*. (2017) studied the effects of DRLC on aluminum-induced testicular damage in male Sprague-Dawley rats. The study confirmed that DRLC treatment significantly enhanced sperm parameters and increased serum testosterone levels, suggesting its potential role in the preservation of testicular function and in the mitigation of sexual performance-induced anxiety. In this study, the relatively high level of FSH in DRLC-treated suggest that DRLC supports follicular development in female rats while the decrease in LH indicates stress-related hormonal imbalance modulation and it is fairly supported by the study by Falana *et al* above.

Besides, antioxidative activities of DRLC have been demonstrated in various studies. For example, research by Falana and Adeleke (2017) showed that DRLC treatment alleviated aluminum-induced testicular toxicity by enhancing antioxidant activity. Even though the research was done on aluminum exposure, the findings suggest that antioxidative activity of DRLC will also be beneficial to suppress lead exposure-induced oxidative stress and thereby improve sexual dysfunction and associated performance anxiety as the groups of animals exposed to DRLC during the second behavioral test displayed more willingness to copulate and reduced sign of anxiety when compared to the groups of animals exposed to lead acetate only.

Lead acetate exposure has been shown to significantly alter sexual behavior in model animals. Specifically, measures such as the inflexion ratio—a measure which reflects the dynamic unfolding of sexual approach behavior—and the copulatory period, a measure of duration and effectiveness of sexual performance—are adversely affected. Research evidence shows that lead acetate exposure decreases the inflexion ratio, which reflects decreased behavioral responsiveness and motivation during sexual behavior, and prolongs the latency to initiate mating, thereby impairing the copulatory phase and this is reflected in this study where the groups of animals exposed to lead acetate (Group B and C) showed low inflexion ratio indicating high level of anxiety and increased copulatory time. These behavioral changes are proposed to be mediated by neurotoxicity caused by lead, which impacts dopaminergic transmission and the neuroendocrine regulation of sexual behavior (Zhou and Zhang 2019).

D-Ribose-L-Cysteine (DRLC) has proven to be a potential drug in reversing such deficits and because of its high antioxidant activity, DRLC reverses oxidative stress and reestablishes normal function of neural circuits involved in sexual behavior. Experimental studies have shown that co-administration of DRLC with lead acetate exposure is associated with reduction in behavioral effects (Emokpae *et al*., 2020). Specifically, administration of DRLC normalized the inflexion ratio and reduced the latency period prior to copulation, reflecting heightened sexual motivation and effectiveness. This restoration of behavioral parameters can be attributed to DRLC's ability to reduce oxidative stress and increase dopaminergic neurotransmission, thereby restoring the interference caused by lead in the neural circuitry controlling sexual performance as this is also seen in the result of this study where animals treated with DRLC shows a low period of copulation and high inflexion ratio when subjected to elevated plus maze test. (Oyovwi *et al*., 2024).

Conclusion

Lead acetate influences the HPO axis and causes differential Bax +ve cells expression in the hypothalamus, which also affects GnRH secretion and secondary reproductive function. D-Ribose-L-Cysteine (DRLC) is a therapeutic agent with antioxidative, anti-inflammatory, and neuroprotective properties. By inhibiting oxidative stress markers such as nitric oxide and superoxide dismutase and preserving histoarchitecture of the ovary, pituitary, and hypothalamus, DRLC inhibits lead-induced damage, thereby enhancing reproductive health and neuroendocrine homeostasis.

Recommendations

Clinical studies will be needed to establish the ability of DRLC to reverse endocrine equilibrium, improve fertility status, and reverse neurotoxicity. The studies will be utilized to determine the translational relevance of DRLC as a therapeutic intervention against heavy metal-caused reproductive and neurological disease.

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29. The data that support the findings of this study are available on request from the corresponding author, OAT. The data are not publicly available due to intention of maintaining privacy of the authors. This research was self-funded.

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