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Role of Carrot Leaf (*Daucus Carota*) Ethanol Leaf Extract Against Cadmium Induced Toxicity in Pituitary Gland of Adult Wistar Rats

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ABSTRACT

Background: Cadmium remains the most toxic pollutants which interferes with the endocrine function of the pituitary gland, thereby affecting gonadotropin synthesis, which is critical for maintaining male reproductive systems.

Objectives: This study investigates the role of *Daucus carota* ethanol leaf extract against cadmium induced toxicity in pituitary gland of adult Wistar rats

Materials and Methods: Forty (40) adult male Wistar rats weighing 145-178kg were randomly placed into five groups(n= 8). Cadmium chloride($CdCl_2$), *Daucus carota* ethanol leaf extract. Group I received normal rat feed and water ad libitum for 28 days and were kept as control. Group II were administered with single dose of 8mg/kg body weight cadmium chloride only ($CdCl_2$). Group III rats received 8mg/kg CdCl2 at a dose of 100mg/kg of the extract. Group IV received 8mg/kg body weight of $CdCl_2$ and 200mg/kg of the extract. Group V received 400mg/kg of the extract twice daily for 28 days. All treatment were administered through oral gavage. Blood sample was collected using retrorbital venous plexus puncture before sacrifice by cervical dislocation. The pituitary glands were harvested and then fixed in 10% formalin for histology analysis

Results: Biochemical analyses indicated that cadmium exposure significantly increased oxidative stress and decreased gonadotropin levels, while *Daucus carota* ethanol leaf extract improved antioxidant enzyme activity and reduced lipid peroxidation. Results revealed that cadmium exposure when compared to control groups A is significant($p < 0.05$).

Conclusion: Cadmium exposure significantly lowers antioxidant defense capacity. *Daucus carota* ethanol leaf extract could be a treatment strategies for individuals at risk of cadmium exposure, counteracting oxidative stress and potentially improving reproductive health

KEYWORDS: Carrot Leaf, Oxidative stress, Follicle stimulative hormone, Luteinizing hormone, Antioxidant

ARTICLE DETAILS

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INTRODUCTION

Cadmium (Cd) is a heavy metal that poses a significant threat to human health and the environment due to its high toxicity and ability to bioaccumulate in living organisms (Briffa *et al*., 2020) Exposure to cadmium occurs primarily through contaminated food, water,air, industrial pollution, cigarette smoke (Jin *et al*., 2020). It is known to cause a range of adverse health effects, particularly affecting the endocrine system (Akinyemi *et al*., 2021). The pituitary gland, a crucial component of the endocrine system, is susceptible to cadmium toxicity, which can lead to disruptions in hormonal balance and overall physiological homeostasis (Adewale *et al*., 2022; Choudhury *et al*., 2022). Cadmium exerts its toxicological effects by inducing oxidative stress, disrupting endocrine functions, and impairing reproductive health. which interferes with the synthesis of hormones and increases the production of ROS and a decrease in antioxidant defense mechanisms (Jones and Smith, 2019).It can disrupt regulation

in the pituitary gland, leading to potential health consequences (Sakai *et al*., 2023). Specifically, it has been shown to target the hypothalamic-pituitary-testicular (HPT) axis, disrupting gonadotropin secretion (Wang *et al.*,2020). Once absorbed, cadmium accumulates in the body and is poorly excreted, leading to long-term toxicity in various organs, including the testis, brain, liver, and kidneys (Godt *et al*., 2006).

One of the major effects of cadmium toxicity is its impact on the endocrine system, including the pituitary gland (Choudhury *et al*., 2022). This imbalance results in cellular damage, DNA fragmentation, and apoptosis, significantly impairing the endocrine functions regulated by the gland (Li *et al*., 2022). It can also interfere with the body's ability to regulate growth, development, metabolism, and other essential functions (Bartoli *et al*., 2024). Moreover, cadmium has been shown to interfere with the hypothalamic-pituitary axis, which controls hormonal feedback mechanisms, leading to systemic dysfunction of hormonal homeostasis (Alavi *et al*., 2023).

In response to the deleterious effects of cadmium, recent studies have explored the potential of natural antioxidants as therapeutic agents. This has necessitated the search for natural plant-based interventions with antioxidant, anti-inflammatory, and protective effects. *Daucus carota* (carrot), leaf extract is less exploited leaves. It may offer protective effects against oxidative damage. *Daucus carota* (carrot), particularly its leaves, has gained attention due to its rich bioactive components. Given the increasing environmental contamination and human exposure to cadmium, there is an urgent need for research focused on identifying effective strategies to mitigate its toxic effects. The use of natural antioxidants, such Daucus carota leaf extract, offers a promising avenue for reducing cadmium toxicity (Adebayo *et al*., 2023; Sakai *et al*., 2023).

MATERIALS AND METHODS

Materials

Fresh Daucus carota leaves, Forty wistar rats, Normal saline, Whatmann Filter paper, filter funnel, Refrigerator, Animal cages, Metal wire, Adhesive tape, Heparinized test tubes, Disposable syringes and needles, Oral gavage, Weighing scales, Dissecting kits, Laboratory coat, .Glass slides

Plant Collection and Identification

Fresh *Daucus carrot* leaves were obtained from local market(Ogbe Awusa) Abakaliki, Ebonyi State of Nigeria. The carrot leaves were Identified and authenticated by a Botanist in the Department of Science and Biotechnology in University of Nigeria Nsuka, Enugu State, Nigeria. The herbarium number is 1179b

Cadmium procurement

Cadmium Chloride ($CdCl_2$) was purchased from Zayo-Sigma Chemicals Ltd, Jos, Nigeria; an agent and Partner of Sigma-Aldrich in Nigeria. Two (20) g of $CdCl_2$ was mixed with 100 milliliters of purified water and after which preserved in refrigerator for use. LD50 of Cadmium == 88mg/kg

Preparation of *Daucus carota* Ethanol Leaf Extract

The leaves were allowed to dry under shade for two weeks to prevent direct effects of sunlight on bioactive component of the leaves. After shade drying, these leaves were ground into a powdery form using a grinding machine. The extraction process involve maceration, filtration, and concentration techniques. 100g of the ground sample was macerated in 300ml ethanol, with intermittent agitation for 24 hours. The mixture was filtered through filter paper, and the extract was concentrated on a water bath, The remaining of the sample was macerated in 600ml ethanol with constant agitation for 72 hours. The extract was collected after 72hrs , through filtration and concentrated using a water bath, The marc was resoaked in 475ml ethanol for another 72 hours, filtered, and concentrated to obtain the *Daucus carota* ethanol leaf (DCELE) extract in solid. 1800mg of cadmium was dissolved in 225ml of distilled water to obtain working solution from where various doses for Daucus carota leaf extract were calculated according to the weight of the animal.

Animal procurement

Forty (40) Male Wistar rats weighing 145kg to 180kg were procured and maintained in the animal house of the Department of anatomy of Ebonyi State university, Abakaliki . The animals were housed in metal cages, fed with standard rat feed daily and water ad libitum *with* acclimatization period of 14 days. They were maintained under conditions of 24 hours light/dark cycle at ambient temperature of 24 ± 2^{0C}.

Experimental Design

The rats were randomly placed in five (5) groups comprising of eight (8) rats. The rats were subjected to different treatments as outlined in Table below

These amounts was determined using an initial investigation indicating no signs of toxicity. 20 g of $CdCl_2$ was mixed with 100 milliliters of normal saline and after which preserved in refrigerator for use. It was given orally at 8 mg/kg body weight dose.

- Group I (control) received normal rat feed and water ad libitium for 28 days
- Group II received 8mg/kg body weight of cadmium chloride($CdCl_2$ only)for 14days
- Group II received 8mg/kg body weight of ($CdCl_2$) and100mg/kg of *Daucus carota* leaf extract for 14days
- Group IV received 8mg/kg body weight of $CdCl_2$ and 200mg/kg *of Daucus carota Leaf extract daily* for 14days
- Group V received 8mg/kg body weight of ($CdCl_2$ 400mg/kg body weight of *Daucus carota leaf extract* for 28days.

The volume administered was calculated using the formula:

$$\text{Volume (mL)} = \frac{\text{Dose (g/kg)} \times \text{Bodyweight (kg)}}{\text{Concentration (g/ml)}}$$

Animal Sacrifice and Sample Collection

After the last administration, at the conclusion of the experiment, after weighing the animals for the last time, the rats were sacrificed by cervical dislocation and the pituitary glands from each animal were harvested and then fixed in 10% formalin solution for histological analysis..

Biochemical studies

Blood was collected using a 5ml syringe through venous orbital plexus puncture and immediately transferred into heparinized test tube. The blood was kept for 24 hours after which supernactant was collected in a test tube and centrifuged for 10minutes at 2500rpm. The plasma concentration of were determined using enzymatic kits and standard reagents according to the protocol of the manufacturer The kids were supplied by NIADDK – NIH (USA). After obtaining the samples, there were homogenized and spinned in 10minutes, the resulting serum was used for the evaluation of Malondialdehyde(MDA) and Catalase (CAT) Activity.

Evaluation of oxidative stress marker

Estimation of Lipid Peroxidation (Malondialdehyde)

Lipid peroxidation in the tissue was estimated colorimetrically by thiobarbituric acid reactive substances(TBARS) using the method of Yagi (1976). A principle component of TBARS being malondialdehyde (MDA), a product of lipid peroxidation, The principle is based on the formation of a TBA pink-colored chromogens as a result of the reaction between TBA and oxidation products that can be quantified by spectrophometry. It involved 0.1 ml of tissue in Tris HCl buffer, treated with 2 ml of TBA-TCA-HCl reagent (thiobarbituric acid 0.37%, 15% TCA, 0.25 N HCl). The solution was placed in water bath for 15 minutes and cooled. The absorbance of clear supernatant was measured against reference blank at 535 nm. Concentration was calculated using the molar absorptivity of malondialdehyde which is expressed as nmol/mg protein. Thiobarbituric acid reactive substances (TBARS) method for detection of MDReaction of MDA with thiobarbituric acid at acidic pH at high temperatures

Assay of Catalase (CAT) Activity

The principle of the test is based on the determination of the H_2O_2 decay rate at 240 nm. Results were expressed as U/L. Catalase activity was measured according to the method of Aebi (1984). Tissue serum(0.1 ml) was pipetted into cuvette containing 1.9 ml of 50mM phosphate buffer, pH 7.0. Reaction was started by the addition of 1.0 ml of freshly prepared 30% (v/v) hydrogen peroxide (H_2O_2). The rate of decomposition of H_2O_2 was measured spectrophotometrically from changes in absorbance at 240 nm. Thus, the difference in absorbance over a period of time is proportional to a measure of enzyme activity. Activity of enzyme was expressed as units /mg protein

Assay of Superoxide Dismutase (SOD) Activity

Superoxide dismutase activity was measured according to the method of (Fridovich and Beauchamp,1971). Superoxide dismutase reduces superoxide to hydrogen peroxide, the theory is based on competition between SOD activity and iodonitrazoliu violet in reacting with superoxide which is generated by 603anthine oxidase reaction. Reagent preparation involved Phosphate buffer pH7.0, carbonate Buffer Ph10.2, Xanthine oxide 0.3u/ml.

Statistical Analysis

The level of homogeneity among the groups was tested using one way Analysis of Variance (ANOVA). Data obtained was expressed as mean ± SD. All groups were compared with each other for every parameter. The software for the analysis is graph pad prism version 9.0.1.5 The level of significance for all the analysis was set at ($p < 0.05$).

RESUITS

Table 4.1: Effects of *Daucus carota* ethanolic leaf extracton cadmium toxicity on animal weight change.

Groups	Initial weight (g)	Final weight (g)	Weight Change (g)	Percentage Weight Change (%)
A	150.50±3.55	162.70±6.70	12.8±3.10[a]	7.80
B	154.10±2.40	155.60±6.45	1.50±4.05[b]	1.00
C	155.50±3.40	160.30±2.50	4.8±0.90[a]	3.00
D	160.40±6.50	170.50±6.60	10.1±0.11[a]	5.92
E	165.70±8.70	173.30±4.50	7.60±4.42 [b]	4.39

Values represent Mean ± SEM. A representsa significant difference when compared to A; b represents a significant difference when compared to B.

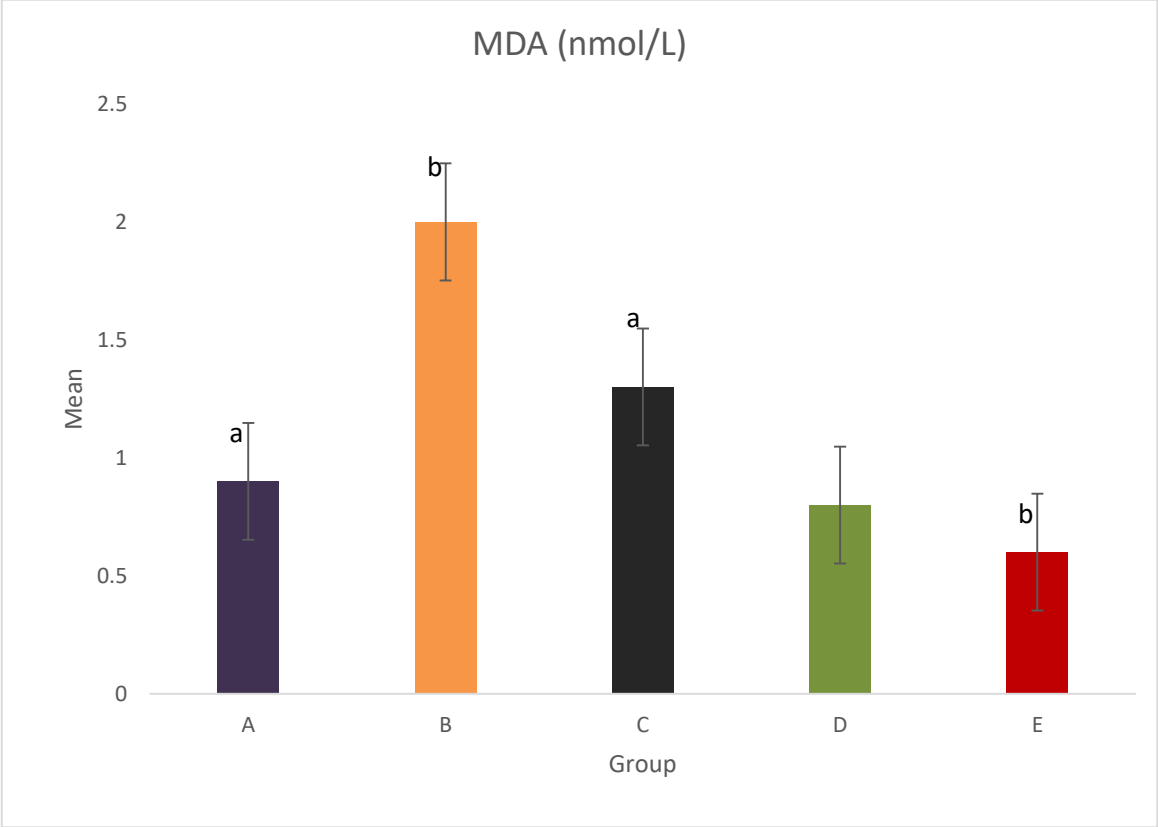

Fig. 4a: Effects of Cadmium and *Daucus carota* leaf extract on oxidative marker.

Levels of Malondialdehyde (MDA): Cadmium group significantly increased compared to control($^{a}p < 0.05$), and significantly decreased compared to treated groups($^{b}p < 0.05$).

Effects of Cadmium and Daucus carota leaf Extract on Oxidative Stress Marker

The Oxidative stress markers in this study as presented in figure(4a), Levels of Malondialdehyde (MDA) in cadmium group B significantly increased compared to control group A($p < 0.05$), and significantly decreased compared to treated groups (C, D and E) ($p < 0.05$).

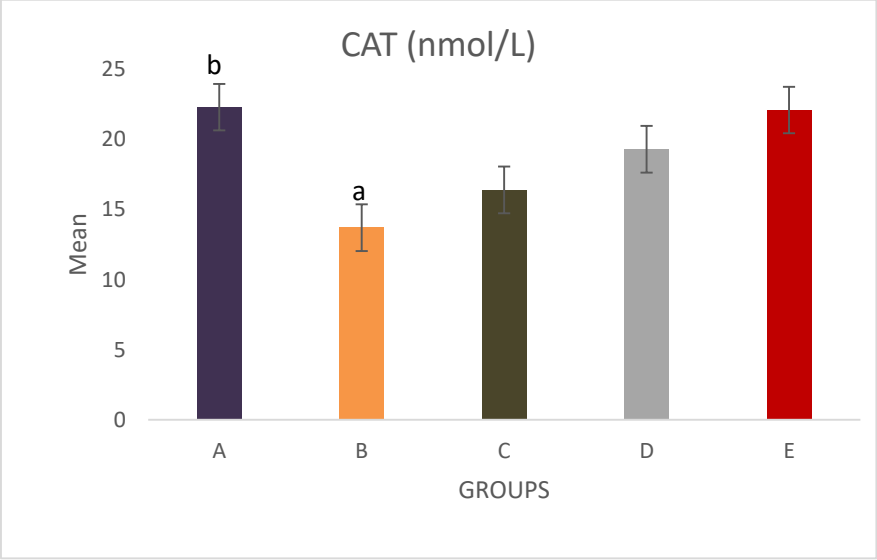

Fig 4b: Effects of Cadmium and Daucus carota Leaf Extract on Antioxidant Enzyme

Levels of catalas(CAT): Cadmium group significantly decreased compared to control ($^{b}p < 0.05$) and significantly increased compared to treated groups ($^{a}p < 0.05$).

In figure (4b), the level of catalase (CAT) in group B decreased significantly compared to group A($p < 0.05$). The treated groups (C, D and E), the levels of Catalase (CAT), progressively increased compared to group B ($p < 0.05$).

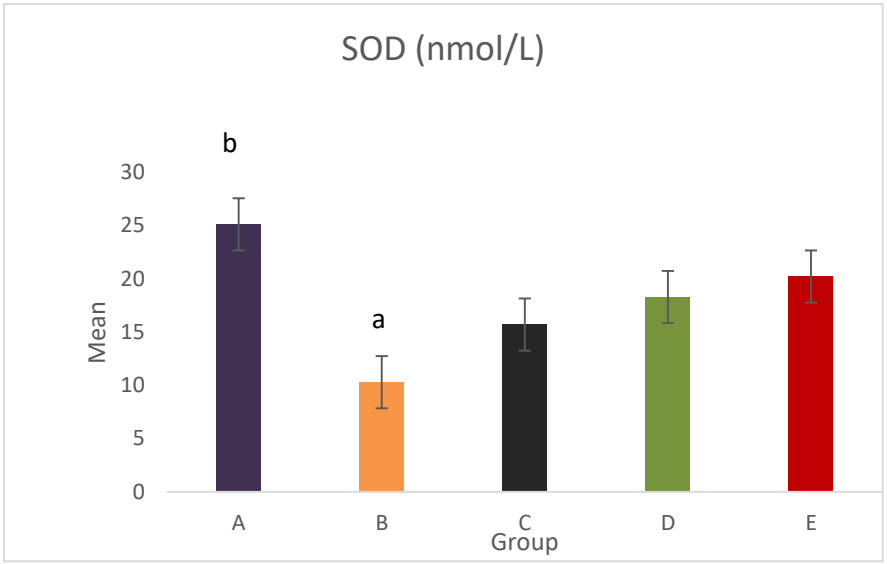

Fig 4c: Effects of Cadmium *and* *Daucus carota* Leaf Extract on Antioxidant Enzyme

Levels of Superoxide Dismutase (SOD): Cadmium group significantly decreased compared to control (($^{b}p < 0.05$) and significantly increased compared to treated groups ($^{a}p < 0.05$).

The antioxidant enzymes in this study as presented in figure(4c). the Levels of Superoxide Dismutase (SOD) in cadmium group B significantly decreased compared to control group A($p < 0.05$) and significantly increased compared to treated groups C, D and E ($p < 0.05$).

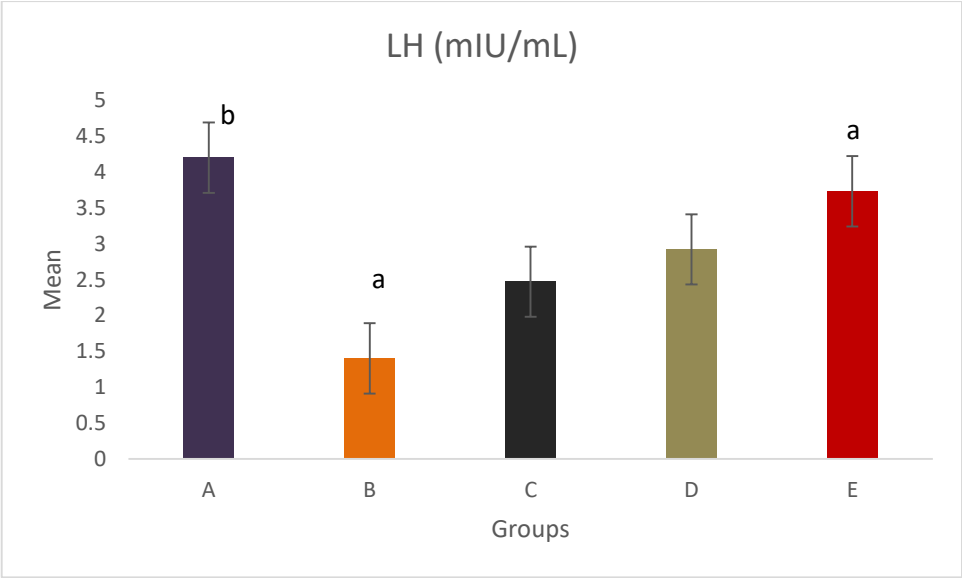

Figure 4d:Effect of *Daucus carota* Leaf Extract after Exposure to Cadmium on Luteinizing Hormone Level

Levels of luteinizing hormone (LH): Cadmium group significantly decreased compared to control (($^{b}p < 0.05$) and significantly increased compared to treated groups ($^{a}p < 0.05$).

The control group recorded the highest LH level, while cadmium exposure significantly reduced LH level ($p < 0.05$), indicating cadmium's detrimental effect on gonadotropjn synthesis. In contrast *Daucus carota* leaf extract treated groups uniformly improved LH levels compared to cadmium group ($p < 0.05$).

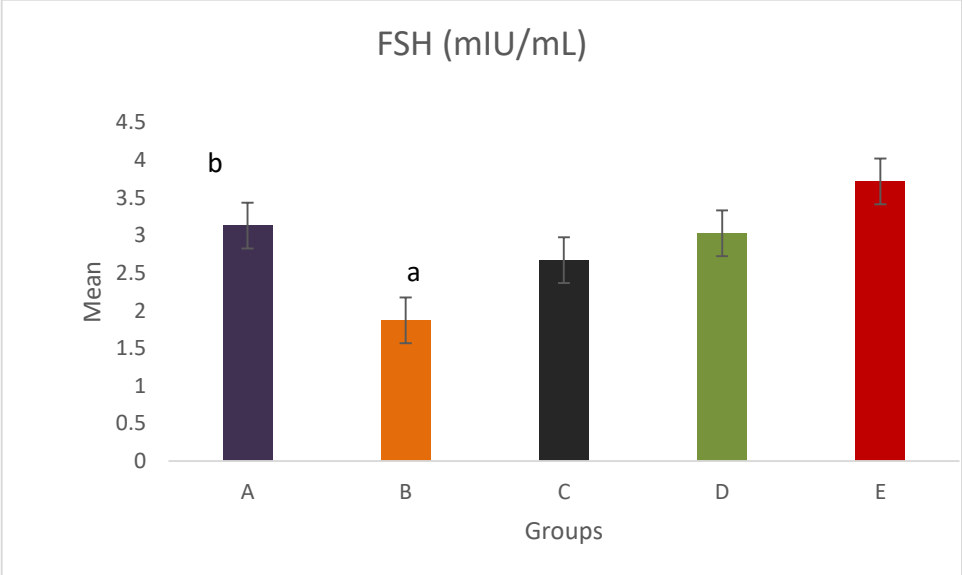

Figure 4e: Effect of *Daucus carota* Leaf Extract after Exposure to Cadmium on Follicle Stimulating Hormone(FSH) levels

Levels of follicle stimulating hormone(FSH) Cadmium group significantly decreased compared to control (($^{b}p < 0.05$) and significantly increased compared to treated groups ($^{a}p < 0.05$).

The control group recorded the highest FSH level, while cadmium exposure significantly reduced FSH level ($p < 0.05$), indicating cadmium effects. *Daucus carota* leaf extract treated groups maintained a steady non significant increase in FSH levels compared to cadmium group ($p < 0.05$).

DISCUSION

Percentage body Weight gain (PBWG)

The Percentage body weight gain is presented in table 4a, the control group (A) exhibited a high weight gain, cadmium exposure in Group B led to a significant weight drop when compared to group A, indicating toxicity-related metabolic effects. Group C, D and E treated with *Daucus carota* leaf extract, showed a weight increase, with significant different from group B. No significant difference among treated groups except group E. This result is in line with the report of cadmium exposure in rats generally leads to decreased body weight and reduced weight gain, often in a dose- and duration-dependent manner, which is accompanied by other signs of toxicity This effect is attributed to cadmium-induced internal organ damage, oxidative stress, and disruptions in metabolism (Choudhury *et al*., 2022)

Biochemical Analysis

The biochemical analysis in this study evaluated oxidative stress marker and antioxidant activity in the Pituitary gland of cadmium exposed adult wistar rats and the ameliorative effects of *Daucus carota* leaf extract. The elevated level MDA resulted to the decreased antioxidant enzyme marker Catalase (CAT)(figure 4b. Treatment with *Daucus carota* leaf extract shows declined in oxidative stress marker and enhanced antioxidant enzyme activity

Findings show that exposure to cadmium result to elevated oxidative stress, as a result of increased levels of Malondialdehyde (MDA). In the control group, in which MDA levels were recorded very high, while cadmium exposure significantly elevated MDA levels(figure4a), confirming cadmium's pro-oxidant effects and its role in promoting lipid peroxidation. This is in line with the previous study that Cd decreases antioxidant activity and increased Malondialdehyde (MDA) content of the pituitary cell, hence. Cd induced oxidative stress damage (Zhang *et al*., 2020; Liu *et al*., 2021). The *Daucus carota* leaf extract treated groups significantly reduced MDA levels indicating nature based antioxidant role to humiliate lipid peroxidation (Oboh *et al*., 2022; Kamel *et al*., 2023)

Figure4b, CAT activity decreased significantly in group B(cadmium group), indicating severe oxidative stress. This is in line with the previous study by Hassan, *et al*., (2021), reporting cadmium exposure to induces endocrine disorders, mechanisms of action and health implication. In treated groups, *Daucus carota* leaf extract, administration shows an improvement in CAT activity when compared to group B. The recovery though not fully restored when compared to group A, reflects the antioxidant's capacity to improve the body's oxidative defense mechanisms. This is in line with the result of other study of (Wang ***et al.,*** 2023), indicating the effectiveness of naturai antioxidant in combating heavy metal induced oxidative stress. Cadmium toxicity and its amelioration through chelation therapy has been reported (Singh *et al*., 2020).

In figure 4c, the activity of SOD decreased significantly in group B (cadmium group) compared to the control group A. The significant reduction in SOD levels in group B suggests that cadmium exposure enhances oxidative stress by reducing antioxidant defense activity. In the previous study, this decrease in SOD highlights the effect of cadmium on male fertility(Joseph *et al*., 2022). In contrast, groups C, D and E

which received *Daucus carota* leaf extract post-cadmium exposure, exhibited significantly increased SOD activity compared to Group B. In this study, Daucus carota leaf extract .as a antioxidant that helps stabilize cell membranes and restores SOD levels to counteract oxidative damage. This aligns with previous studies indicating that *Daucus carota* ethanol leaf can enhance antioxidant capacity against cadmium induced oxidative damage (Sun *et al.,* 2009; Jiménez-Fernández et al., 2015).

Figure 4d; effects of daucus carota leaf extract against cadmium exposure on LH level, the control group A records high level of LH compared to group B ($p < 0.05$). Cadmium exposure in group B significantly reduced LH compared to control ($p < 0.05$). Co-treatment with *Daucus carota* ethanol leaf extract in groups C, D,and E significantly improved hormone levels in a dose-dependent manner. These varying effects might be related to cadmium's impact on the feedback mechanisms between LH, and FSH within the HPG axis. LH secretion is disrupted by cadmium, which affects fertility and reproductive health. This is marks the beginning of how cadmium's endocrine-disrupting effects extend to the reproductive system , exposure to cadmium can result in notable decreases in body weight and hormone content, indicating direct harmful impacts on pituitary tissue (Minguez-Alarcon *et al*., 2019). This can lead to hormonal imbalances, reproductive disorders, and an increased risk of hormone-related cancers (Satarug *et al*., 2021).

Figure 4e; effects of *Daucus carota* leaf extract against cadmium exposure on FSH level. In the control group A showed a concentration of FSH at high level while cadmium exposure significantly reduced FSH levels compared to control group ($p < 0.05$), suggesting cadmium's interference with the regulation of FSH. Zhou *et al*., (2020) had previously reported similar toxic effects of cadmium exposure on the pituitary gland and hormone secretion. Also, (Goya *et al*., 2019), had reported cadmium-induced endocrine disruption and its effects on the pituitary gland. Further increasing the dosage of *Daucus carota* leaf extract achieved an improved FSH ($p < 0.05$) compared to cadmium group, showing Daucus carota ethanol leaf extract treatment partially restored FSH levels. However, *Daucus carota* leaf extract co-treatment alleviates these effects, with higher dosage, demonstrates better restoration of hormonal levels. This suggests a dose-dependent protective effect against cadmium-induced hormonal imbalance(Sakai *et al.,* 2023; Qian et al., 2024), In group E treated group only, shows an improvement when compared to group B ($p < 0.05$). The recovery though not fully restored when compared to group A($p < 0.05$), reflects the antioxidant's capacity to counter hormonal imbalance This is in line with the previous study by Khalid *et al*. (2021), suggests a protective, dose-dependent effect of *Daucus carota* leaf extract in mitigating cadmium-induced disruptions in hormonal balance

CONCLUSION

The results of this study provide significant insights into the effects of cadmium-induced oxidative stress on pituitary gland in Wistar rats and the potential protective role of *Daucus carota* leaf extract against cadmium induced toxicity. Cadmium is known to induce oxidative stress, which can compromise cellular and enzymatic defenses, ultimately affecting reproductive health and function

Ethical Approval

Ethical approval was sought for and obtained from the Research and Ethics Committee of the Faculty of Basic Medical Sciences (preclinicals) Ebonyi State University, Abakaliki. The ethical code of this study is MPC/2502/30/004.

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