



# Protective impacts of gallic acid against cadmium-induced oxidative toxicity in the ovary of rats

Damilare Rotimi<sup>1</sup> · Oluwafemi Adeleke Ojo<sup>1</sup> · Bright Ayomide Emmanuel<sup>1</sup> · Adebola Busola Ojo<sup>2</sup> · Tobiloba Christiana Elebiyo<sup>1</sup> · Charles Obiora Nwonuma<sup>1</sup> · Olarewaju M. Oluba<sup>1</sup>

Received: 17 February 2021 / Accepted: 25 March 2021 / Published online: 2 April 2021  
© The Author(s), under exclusive licence to Springer-Verlag London Ltd., part of Springer Nature 2021

## Abstract

This study evaluates the probable effects of induced reproductive toxicity by cadmium and its amelioration by gallic acid (GA). Adult female rats were daily administered with cadmium (CdCl<sub>2</sub>) (5 mg/kg) singly or combined with GA (20 mg/kg) for 14 days to evaluate the effect on antioxidant status and ovary function using biochemical and histological analysis. Cadmium-treated rats alone revealed a considerable increment in total body weight and ovaries' weight due to muscle wasting. However, GA + cadmium reversed considerably the trend and offered protection against cadmium-induced muscle wasting. Cadmium treatment alone decreased reduced glutathione (GSH) level, activities of superoxide dismutase (SOD), and catalase (CAT) and also increased malondialdehyde (MDA) level. Besides, the administration of GA alone or in combination mitigated the cadmium-mediated decrease in GSH, SOD, and CAT, respectively. Serum concentrations of estrogen (E), testosterone (T), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were reduced significantly in cadmium-treated rats. Histopathology of the ovaries showed a considerable reduction in follicle number. GA treatment alone and CdCl<sub>2</sub> + GA-treatment group decreased cell death of follicular cells in the ovaries of rats and increased serum reproductive hormones. Taken together, gallic acid prevented the deleterious impacts of CdCl<sub>2</sub> on the biomarkers of oxidative stress, antioxidant enzymes, and ovarian histopathological structure.

**Keywords** Antioxidant · Gallic acid · Cadmium · Oxidative stress · Reproductive hormone · Ovary

## Introduction

Gallic acid (GA) and its derivatives are found distributed in different fruits like oranges, watermelon, apple, and pineapple (Jimoh et al. 2017; Oboh et al. 2018) and therapeutic plants like *Blighia sapida* (Ojo et al. 2017a), *Senecio bialfræ* (Ajiboye et al. 2018), and *Tithonia diversifolia* (Ojo et al. 2018a) with numerous pharmacological properties. Consumption of these GA derivatives (vegetables and fruits for example cauliflower, green chicory, eggplant, mango, grapes, walnut, etc.) triggers a reversal in the incidence of numerous ailments (Kahkeshani

et al. 2019). GA is a polyphenol with numerous biological properties for example antidiabetic, anti-inflammatory, anticancer, antimicrobial, antifungal, and anti-ulcerogenic properties (Zahrani et al. 2020). Several reports have reported that GA displays its pharmacological potentials via its antiradical activities (Ola-Davies and Olukole 2018). A study relating the antioxidant properties of key phenols such as gallic acid, chlorogenic acid, vanillic acid, and protocatechuic acid documented that GA demonstrated the highest antioxidant properties (Ola-Davies and Olukole 2018). GA has also been reported to play a defensive role against ovarian oxidative stress (Li et al. 2017) as well as to have an effect on the histological and stereological ovarian index in the experimental model (Ghaedi and Edalatmanesh 2017).

Throughout the world, cadmium is one of the commonly used metals for industrial purposes and is released in large amounts into the environment (Mansour and Ramadan 2010; Xu et al. 2014). In animals and humans, the pollution caused by cadmium poses a potential health hazard (Liu et al. 2017). Cadmium can have access to the body via skin

✉ Oluwafemi Adeleke Ojo  
ojo.adeleke@lmu.edu.ng

<sup>1</sup> Medicinal Biochemistry and Biochemical Toxicology Group, Department of Biochemistry, Landmark University, Omu-Aran, Nigeria

<sup>2</sup> Department of Biochemistry, Ekiti State University, Ado-Ekiti, Nigeria

absorption, ingestion of contaminated food, water, or pediatric syrups, and inhalation of fumes (Rezaei et al. 2019). After it gets to the body, the red blood cells and albumin transport it around. Once absorbed, it is stored and accumulates within the vital organs especially the reproductive organs (Maret and Moulis 2013). Cadmium toxicity has been implicated as a cause of infertility in males and females (Kumar and Sharma 2019). The complex cycle that incorporates expansion and separation of germ cells is known as folliculogenesis. This cycle relies upon the multifaceted interactions among systemic factors for example both pituitary gonadotropins and hormones/local factors generated by ovarian somatic cells (Hernandez-Medrano et al. 2012).

Natural antioxidant systems are present in the human body to help detoxify radicals synthesized. Oxidative stress occurs as a result of exposure to numerous exogenous compounds that trigger radical generation in a way that exceeds the antioxidants synthesized (Acaroz et al. 2019). Numerous compounds, including cadmium, trigger oxidative stress in several cells and organs (Nair et al. 2013). Cadmium-induced oxidative stress was reported in organs like the liver, brain, heart, lungs, kidney, blood, testes, and ovaries (Ojo et al. 2014a, 2014b, 2014c, 2014d). Reports showed that cadmium could cause cancer and induce histological harm in testis (Massanyi et al. 2007). It also affects human systems, for instance, in the female reproductive system, it causes radical generation and upset ovarian histo-architecture, extending the estrous cycle and delayed puberty beginning (Samuel et al. 2011), decrease estradiol, progesterone, and testosterone concentrations (Monsefi and Fereydouni 2013) and reduces the affinity of gonadotropin, in this way disrupt the process of steroid biosynthesis (Nampoothiri et al. 2007). For now, reports on the impact of GA on CdCl<sub>2</sub>-induced oxidative stress in the female reproductive organs are few. This work, therefore, researched the probable mitigating role of GA on CdCl<sub>2</sub>-induced oxidative stress in female albino rats.

## Materials and methods

### Chemicals

Unless otherwise expressed, the synthetic chemicals, reagents, and kits utilized were bought from Sigma-Aldrich Co. (St. Louis, MO, USA). These comprise cadmium chloride (CdCl<sub>2</sub>), GA (C<sub>7</sub>H<sub>6</sub>O<sub>5</sub>), reduced glutathione (GSH), 1-chloro-2,4-dinitrobenzene, thiobarbituric acid (TBA), and 5', 5'-di-thiobis(2-nitrobenzoic acid) (DTNB).

### Experimental animals

Twenty (20) sexually developed female Wistar rats (170–200 g) were acquired from the Department of Biochemistry,

Landmark University. The rats were accustomed to 7 days of access to rat pellets (obtained from Ladokun feed, Omu-Aran, Kwara State, Nigeria) and water ad libitum. The animals were taken care of in compliance with the standards for the treatment of animals as set out in the ethical book of Landmark University. This work was endorsed by the Institution ethical committee on August 30th, 2020, with approval number LUAC/2020/0052B.

### Study design

The experimental animals were arbitrarily allocated to four groups of 5 rats; control, cadmium only, cadmium + GA group, and GA group. The control rats were administered orally 1 ml of distilled water daily (vehicle), second group rats got cadmium chloride (5 mg/kg/daily), third group rats were administered cadmium chloride (daily) + GA (20 mg/kg/daily) concurrently, fourth group rats were administered GA only for 2 weeks. GA and CdCl<sub>2</sub> were reconstituted in distilled water and apportioned for 2 weeks. Doses for cadmium and GA were selected based on earlier reports (El-Demerdash et al. 2004 for cadmium and Ola-Davies and Olukole 2018 for GA). It has been shown that the dose chosen induces major oxidative stress in different tissues (Ojo et al. 2014b; Ojo et al. 2018b), while GA was reported to be safe at 20 mg/kg body weight per day (Ola-Davies and Olukole 2018). Towards the end of the treatment, the rats were euthanized by cervical dislocation, ovaries were removed, homogenized with cold phosphate buffer, and kept at a temperature of -4 °C. The homogenized ovary was centrifuged at 3000g for 1800 s to collect a clear supernatant solution which was used to assess some oxidative stress parameters. Blood was collected by cardiac puncture into plain tubes, left for an hour, and the serum was separated after being centrifuged at 1300 ×g for 10 min.

### Assessing changes in body weight and relative weights of organs

The final weights of the animals were recorded before the sacrificing of the rats. The animals were euthanized with halothane anesthesia after the 14-day treatment duration. The ovaries were collected, connective tissue was cleared, and weighed with an electronic balance weight. Afterwards, the ovaries were homogenized in phosphate-buffered saline (PBS).

### Evaluation of ovarian antioxidants and non-antioxidants enzymes

The superoxide dismutase (SOD) and catalase (CAT) activities and levels of GSH in the ovarian supernatants were measured via standard assay kits (RX Daytona automated analyzer (Randox, UK) according to the producer's guidelines.

## Evaluation of malondialdehyde concentrations in the ovary

The lipid peroxidation product concentration, malondialdehyde (MDA), was evaluated utilizing Draper and Hadley (1990) protocol. The supernatant absorbance in each tube was perused against a standard blank in a spectrophotometer at 532 nm. The volume of MDA found in the samples has been calculated as nmoles of MDA formed/mg protein.

## Evaluation of some selected serum hormone concentration

The serum concentrations of estrogen, testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were evaluated utilizing the readily accessible enzyme-linked immunoassay kits (ELISA) using the producer's guidelines.

## Histopathological investigation

The ovaries for each group were set in a 10 % formalin solution. The histological assessment was achieved by utilizing the hematoxylin and eosin (H & E) strategy to conduct the histological test. Quickly, the ovaries were independently fixed in formalin solution for 4 h, dried out in ethanol, and enclosed in paraffin sheets. Tissue parts 5-mm thick were deparaffinized utilizing xylene. The cut segments were later stained and analyzed under a photomicroscope.

## Statistical evaluation

All results were analyzed via GraphPad Prism 8.0 (Version 8.0, Software Program, GraphPad Prism Inc., San Diego, CA) and displayed as mean  $\pm$  S.D. One-way analysis of variance (ANOVA) followed by a *t*-test was employed for evaluating biochemical parameters along with Tukey's post hoc test. *p*-value < 0.05 was thought to be measurably significant.

**Table 1** Impacts of gallic acid and CdCl<sub>2</sub> on body weight and relative weight of ovary

Parameters	Control	Gallic acid	Cadmium + gallic acid	Cadmium
Animal weight	183.25 $\pm$ 1.61	184.33 $\pm$ 0.33	180.5 $\pm$ 2.20*	174.67 $\pm$ 1.20**
Relative weight of ovary	0.24 $\pm$ 0.01	0.23 $\pm$ 0.02	0.18 $\pm$ 0.01*	0.13 $\pm$ 0.01**

Values are presented as mean  $\pm$  SEM, *n* = 5. Different superscripts across the row means significant difference (*p* < 0.05) relative to control

## Results

### Changes in body weight and relative weights of organ

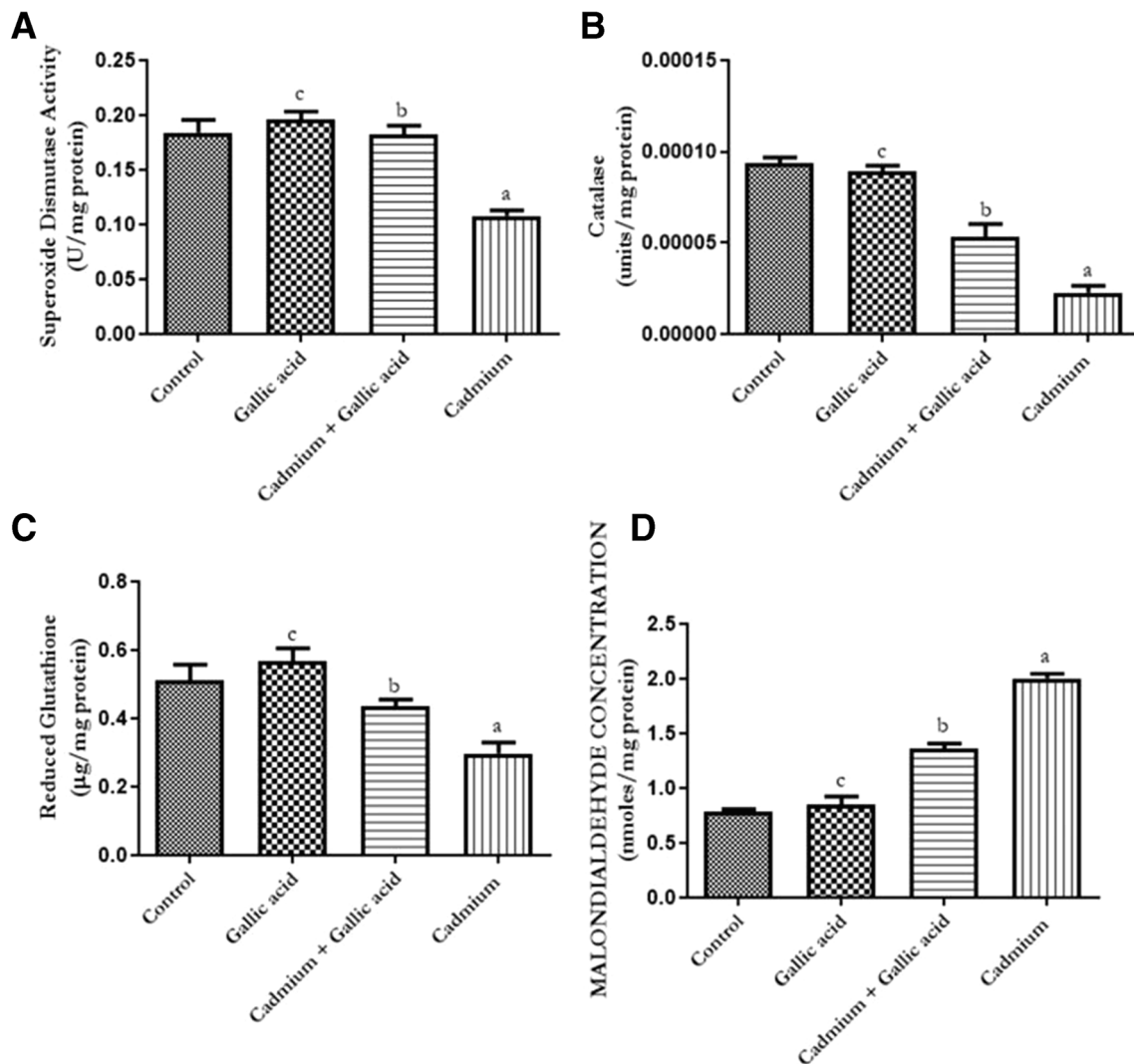
The body weight alteration of the animals was fundamentally reduced (*p* < 0.05) in CdCl<sub>2</sub>, CdCl<sub>2</sub> + GA, and GA groups, comparable to the control. The body weight was considerably elevated in GA + CdCl<sub>2</sub>, contrasted with the CdCl<sub>2</sub> group (Table 1). Furthermore, no substantial changes were observed in the relative weights of the ovaries between the control and the GA groups. In contrast, there was a considerable decrease in the relative weight of ovaries in the CdCl<sub>2</sub> group while administration of GA significantly increases the relative weight of ovaries in the CdCl<sub>2</sub> + GA groups.

### Antioxidant activity and concentration of MDA in the ovary

Ovary redox status is presented in Fig. 1. A noteworthy increase (*p* < 0.05) in the MDA level with a significant decrease in the level of GSH and SOD activity was observed in the cadmium-treated group. GA only group considerably (*p* < 0.05) increased the activities of CAT, SOD, and GSH and there was an increase observed in the MDA level when compared with control. The GA + cadmium group increased the CAT, GSH, and also MDA level when compared with the control.

### The serum concentration of sex hormones (estrogen, testosterone, LH, and FSH)

The reproductive hormones are shown in Fig. 2. The FSH, estrogen, and testosterone significantly increased in the CdCl<sub>2</sub> group. Treatment with GA shows a significant reduction in all the hormones expect LH which was a non-significant increase. However, rats administered with cadmium + GA significantly reduced the estrogen and testosterone concentration comparable to the control. In any case, no significant difference was found in testosterone concentrations between the control group and GA-treated rats with similar effects observed with estrogen and FSH levels.



**Fig. 1** Ovaries' levels of antioxidants and MDA levels in cadmium-induced oxidative toxicity treated with GA. **A** SOD, **B** CAT, **C** GSH, and **D** MDA between the control and treated groups. Values are shown as

mean  $\pm$  SD ( $n = 5$ ). a is significant at  $p < 0.05$  vs control, b is significant at  $p < 0.05$  vs cadmium, and c is significant at  $p < 0.05$  versus cadmium and CdCl<sub>2</sub> + gallic acid

### Histopathology of the ovary

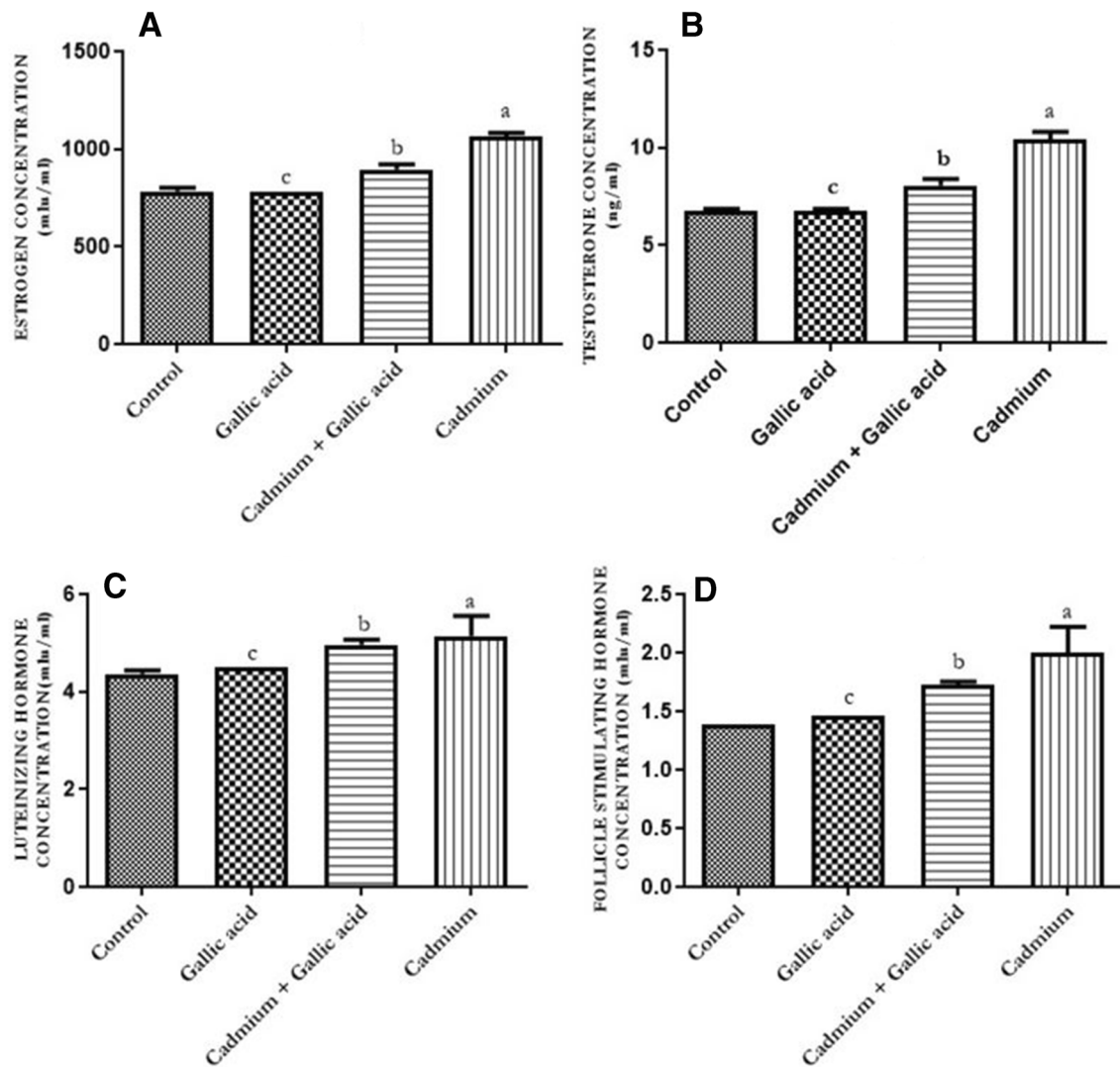
The ovaries were examined and the photomicrograph at  $\times 100$  magnification as shown in Fig. 3. The structure of the ovary in the control revealed the corpus luteum and follicles. The group treated with cadmium showed decrease follicles and distorted oocytes. On the other hand, the histology of the ovaries for the CdCl<sub>2</sub> + GA groups was comparable to that observed in control rats.

### Discussion

Environmental toxicants like cadmium are harmful chemicals that have been found to cause damages in the tissues and organ systems including the ovary by triggering oxidative stress by producing free radicals (Opwari and Henkel

2016). This study investigated the preventive and ameliorative effects exerted by GA on cadmium-induced oxidative stress in rat ovaries. The decreased bodyweight witnessed in the CdCl<sub>2</sub> groups could be added to muscle wasting while an increase in the group treated with GA proffer defense towards cadmium-induced muscle degenerating. Our findings correlate with earlier reported studies (Nampoothiri et al. 2007; Ronco et al. 2009; Samuel et al. 2011). The reduced weight of the ovaries in this study corresponds with the reports of Samuel et al. (2011) who documented a noteworthy decrease in the weight of ovaries in animals treated with CdCl<sub>2</sub>.

Several reports revealed that Cd aggregates in target organs (Ojo et al. 2018b), bringing about critical oxidative stress (Farombi et al. 2012; Ojo et al. 2017b). The redox status (MDA, CAT, SOD, and GSH) serves as a biomarker for damages in the tissues. Hence, the decrease in these parameters for example CAT, SOD, and GSH and an increase in the MDA



**Fig. 2** Serum concentration of some selected hormones in cadmium-induced oxidative toxicity treated with GA. **A** Estrogen, **B** testosterone, **C** FSH, and **D** LH. Values are mean  $\pm$  SD,  $n = 5$ . Values are presented as

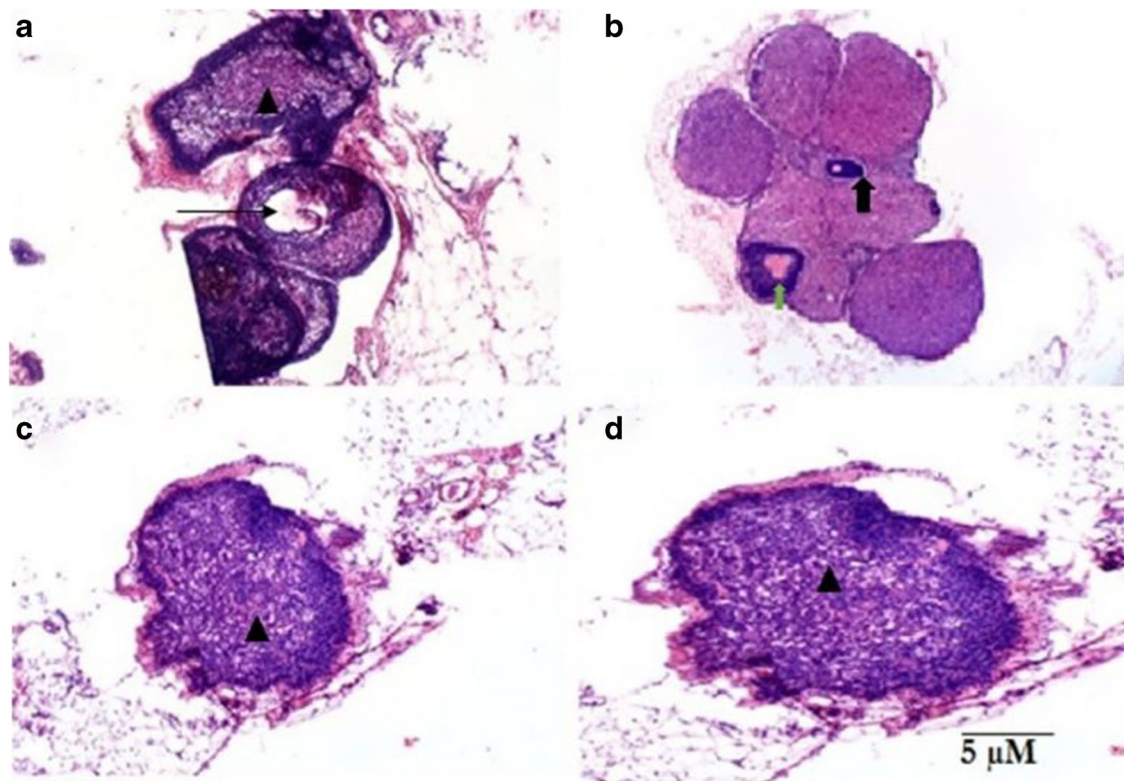
mean  $\pm$  SD ( $n = 5$ ). a is significant at  $p < 0.05$  vs control, b is significant at  $p < 0.05$  vs cadmium, and c is significant at  $p < 0.05$  versus cadmium and CdCl<sub>2</sub> + gallic acid

level from this study proved that cadmium induced oxidative injury to the ovaries of the rats. The mechanism of cadmium action as a pro-oxidative is well known as it can weaken the antioxidant system and enhance the concentration of pro-oxidant which ultimately increases the occurrence of oxidative stress (McRae et al. 2019).

SOD and CAT serves as the initial defense towards oxidative stress for the tissues upon cadmium exposure. SOD removes superoxide anion from cells, while CAT eliminates H<sub>2</sub>O<sub>2</sub> to prevent oxidative stress. GSH, a non-enzymatic antioxidant, also scavenges free radicals via its sulfanyl group interaction with reactive oxygen species (ROS) (Edge 2013). Our outcomes demonstrated a momentous reduction in SOD studied. Likewise, the GSH level reduced substantially in the CdCl<sub>2</sub> group. GSH is an antioxidant recognized to forage radicals by interacting with its functional thiol groups and acts as a substrate for both glutathione peroxidase (GPx) (Nna

et al. 2017). In this study, the ovarian MDA improved considerably in the cadmium group, inferring a probably expanded aggregation of ROS in the ovary. Our data correlate with earlier studies that reported a suppressed antioxidant defense system in the ovaries of rats treated with CdCl<sub>2</sub> (Mansour et al. 2010; Nna et al. 2017).

Estrogen (E) is an essential female sex hormone by enhancing the development and maturation of reproductive tissues (Cui et al. 2013). The synthesis of E is regulated by the gonadotropins (FSH and LH) produced by the anterior pituitary, with LH stimulating the secretion of E (Beshay and Carr 2017). A disruption in the synthesis of FSH and LH could alter the functioning of the gonadotrophin-releasing hormone (GnRH), hence interfering in the normal HPA mechanism. The reduction in estrogen concentrations in the cadmium group could be attributed to the reduced FSH and LH levels in the gonad. Decreased FSH levels have been implicated in



**Fig. 3** Impact of cadmium chloride and GA on the ovary of rats induced with cadmium. **a** Control, **b** CdCl<sub>2</sub>, **c** CdCl<sub>2</sub> + GA, and **d** GA. The black thin arrow indicates primary follicle, the big arrows specify distorted

oocyte, light green arrow indicate atretic follicle, and black triangle indicate corpus luteum. Magnification:  $\times 100$

inhibiting the growth and development of oocytes to developing follicles, thus limiting the ovulation processes and the number of corpus luteum. Low LH levels also affect the ovulation process by forming large cystic antral follicles. The observed increase in the ovarian weight could be attributed to the low LH level which leads to large cystic antral follicles. Our results revealed that GA improves the level of E, LH, and FSH.

GA exerted its inherent antioxidant and estrogenic properties which enhances it to bind to E receptors and mitigate the effects against cadmium. An observable expansion in the FSH and LH levels in rats administered with GA in cadmium-exposed rats could improve the normal operation of the hypothalamus-pituitary axis (HPA). The HPA is important in regulating the endocrine system. Elevated FSH levels might increase the number of prenatal follicle formation. An increase in LH level causes ovulation and contributes to the improvement in the corpus luteum. Thus, increasing the estrogen level. Furthermore, GA decreased the levels of testosterone in cadmium chloride-induced rats. This might be because of the presence of the phenolic ring in GA (Pietta 2020). It has been documented that this flavonoid ring exhibits the capacity to reduce sexual hormones. Administration of GA is beneficial in preserving levels of T, E, and FSH.

There were no considerable changes in the histo-architectural of the ovaries across all groups. In contrast, the structural changes observed in the ovaries might be the impact of lipid peroxidation caused by cadmium. These results might be similar to the reports obtained by Omoirri et al. (2021). Hence, these outcomes indicate that the antioxidant properties of GA are the probable approaches implicated in reducing CdCl<sub>2</sub> toxicity in the ovaries.

## Conclusion

From the data obtained, the oxidative stress observed was a result of the aggregation of CdCl<sub>2</sub> in the ovary. Hence, the reduction in FSH and LH levels might be responsible for the decline in the circling levels of hormones. Thus, these damaging impacts were impaired by GA. It is thus, concluded that GA exerts a protective role on the ovaries of rats fed with CdCl<sub>2</sub>.

**Author contribution** OAO, DR, and OMO contributed to the design of the study. BAE carried out the analysis. DR participated in data collection and statistical analysis. OAO, ABO, TCE, and DR wrote the first draft of the manuscript. OAO, DR, ABO, TCE, CON, and OMO perused and approved the final manuscript.

## Declarations

**Ethics approval and consent to participate** The animals have been treated in compliance with the standards for the treatment of animals as set out in the ethical manual of the Landmark University. This work was endorsed by the Institution committee on August 30th, 2020, with approval number LUAC/2020/0052B.

**Informed consent** Not applicable.

**Conflict of interest** The authors declare no competing interests.

## References

- Acaroz U, Ince S, Arslan-Acaroz D, Gurler Z, Demirel HH, Kucukkurt I, Eryavuz A, Kara R, Varol N, Zhu K (2019) Bisphenol-A induced oxidative stress, inflammatory gene expression, and metabolic and histopathological changes in male Wistar albino rats: protective role of boron. *Toxicol Res (Camb)*. 8(2):262–269
- Ajiboye BO, Ojo OA, Okesola MA, Akinyemi AJ, Talabi JY, Idowu OT, Fadaka AO, Boligon AA, de Campos MMA (2018) In vitro antioxidant activities and inhibitory effects of phenolic extract of *Senecio bialfrax* (Oliv and Hiern) against key enzymes linked with type II diabetes mellitus and Alzheimer's disease. *Food Sci Nut* 6(7):1803–1810
- Beshay VE, Carr BR (2017) Hypothalamic–pituitary–ovarian axis and control of the menstrual cycle. In: *Clinical reproductive medicine and surgery*. Springer, Cham, pp 1–17
- Cui J, Shen Y, Li R (2013) Estrogen synthesis and signaling pathways during aging: from periphery to brain. *Trends Mole. Med* 19(3):197–209
- Draper HH, Hadley M (1990) Malondialdehyde determination as index of lipid peroxidation. *Methods Enzymol* 186:421–431
- Edge R (2013) Radiolytic and photolytic production of free radicals and reactive oxygen species: interactions with antioxidants and biomolecules. In: *Applied photochemistry*. Springer, Dordrecht, pp 305–330
- El-Demerdash FM, Yousef MI, Kedwany FS, Baghdadi HH (2004) Cadmium-induced changes in lipid peroxidation, blood hematology, biochemical parameters and semen quality of male rats: protective role of vitamin E and b-carotene. *Food Chem. Toxicol* 42(10):1563e1571
- Farombi EO, Adedara IA, Akinrinde SA, Ojo OO, Eboh AS (2012) Protective effects of kolaviron and quercetin on cadmium-induced testicular damage and endocrine pathology in rats. *Andrologia* 44(4):273e284
- Ghaedi L, Edalatmanesh MA (2017) The effect of gallic acid on histopathological and stereological ovarian index in animal model of polycystic ovaries syndrome. *Indo Am J Pharm Sci*. 4(8):2264–2273
- Hernandez-Medrano J, Campbell BK, Webb R (2012) Nutritional influences on folliculogenesis. *Reprod Domest Anim* 47 Suppl 4(s4):274–282
- Jimoh OT, Ademiluyi AO, Oboh G, Boligon AA (2017) Phenolic extracts and amino acids content from *Cucumeropsis mannii* naudin and *Citrullus lanatus* inhibit relevant enzymes of erectile dysfunction in rat's penile tissue. *Biochem Biophysics Rep* 12:5–11
- Kakhshani N, Farzaei F, Fotouhi M, Alavi SS, Bahramsoltani R, Naseri R, Momtaz S, Abbasabadi Z, Rahimi R, Farzaei M, Bishayee A (2019) Pharmacological effects of gallic acid in health and diseases: a mechanistic review. *Iran J Basic Med Sci* 22(3):225–237
- Kumar S, Sharma A (2019) Cadmium toxicity: effects on human reproduction and fertility. *Rev Environ Health* 34(4):327–338
- Li B, Weng Q, Liu Z, Shen M, Zhang J, Wu W, Liu H (2017) Selection of antioxidants against ovarian oxidative stress in mouse model. *J Biochem Mole Toxicol* 31(12):e21997
- Liu Y, Xiao T, Perkins RB, Zhu J, Zhu Z, Xiong Y, Ning Z (2017) Geogenic cadmium pollution and potential health risks, with emphasis on black shale. *Journal of Geochemical Exploration*. 176:42–49
- Mansour SZ, Ramadan FL (2010) Antioxidant effect of pollen grains and soya lecithin on cadmium-induced biochemical and structural disorders in the ovary of female rats during estrus cycle. *J. Radiat. Res. Appl. Sci.* 3(3A):747–761
- Maret W, Moulis JM (2013) The bioinorganic chemistry of cadmium in the context of its toxicity. In: *Cadmium: from toxicity to essentiality*. Springer, Dordrecht, pp 1–29
- Massanyi P, Lukáč N, Uhrin V, Toman R, Pivko J, Rafay J, Forgacs Z, Somosy Z (2007) Female reproductive toxicology of cadmium. *Acta Biol. Hung* 58(3):287e299
- McRae NK, Gaw S, Brooks BW, Glover CN (2019) Oxidative stress in the galaxiid fish, *Galaxias maculatus*, exposed to binary waterborne mixtures of the pro-oxidant cadmium and the anti-oxidant diclofenac. *Environ Poll* 247:638–646
- Monsefi M, Fereydouni B (2013) The effects of cadmium pollution on female rat reproductive system. *J. Infertil. Reproductive Biol* 1(1):1e6
- Nair AR, DeGheselle O, Smeets K, Van Kerkhove E, Cuyppers A (2013). Cadmium-induced pathologies: where is the oxidative balance lost (or not)? *Int J Mole Sci*14(3): 6116–6143.
- Nampoothiri LP, Agarwal A, Gupta S (2007) Effect of co-exposure to lead and cadmium on antioxidant status in rat ovarian granulosa cells. *Archives Toxicol* 81(3):145e150
- Nna VU, Usman UZ, Ofutet EO, Owu DU (2017) Quercetin exerts preventive, ameliorative and prophylactic effects on cadmium chloride - induced oxidative stress in the uterus and ovaries of female Wistar rats. *Food Chem Toxicol* 102:143e155
- Oboh G, Adebayo AA, Ejakpovi II, Ogunsuyi OB, Boligon AA (2018) Phenolic profiling and in vitro antioxidant, anticholinesterase, and antimonoamine oxidase properties of aqueous extract of African star apple (*Chrysophyllum albidum*) fruit parts. *J Food Biochem*:e12568
- Ojo OA, Ajiboye BO, Oyinloye BE, Ojo AB (2014a). Prophylactic effects of ethanolic extract of *Irvingia gabonensis* stem bark against cadmium-induced toxicity in albino rats. *Advances in Pharmaceutics*. 2014a; 8: Article ID 894610, Hindawi Publishing Co-operation.
- Ojo OA, Oyinloye BE, Ajiboye BO, Onikanni SA (2014b) Neuroprotective mechanism of ethanolic extract of *Irvingia gabonensis* stem bark against cadmium-induced neurotoxicity in rats. *Br J Med Med Res*. 4(36):5793–5805
- Ojo OA, Ajiboye BO, Oyinloye BE, Ojo AB, Olarewaju OI (2014c) Protective effect of *Irvingia gabonensis* stem bark extract on cadmium-induced nephrotoxicity in rats. *Interdiscip Toxicol* 7(4):208–214
- Ojo OA, Ajiboye BO, Oyinloye BE, Ojo AB (2014d) Hematological properties of *Irvingia gabonensis* in male adult. *J Pharma Sci Innov* 3(5):434–436
- Ojo OA, Ajiboye BO, Ojo AB, Olayide I, Akinyemi AJ, Fadaka AO, Adedeji EA, Boligon AA, de Campos MM (2017a) HPLC-DAD fingerprinting analysis, antioxidant activity of phenolic extracts from *Blighia sapida* bark and its inhibition of cholinergic enzymes linked to Alzheimer's disease. *Jordan J Biol Sci* 10(4):257–264
- Ojo OA, Ojo AB, Akintayo C, Ajiboye BO, Awe J, Obafemi T (2017b) Antioxidant activity and hepatoprotective effect of *Ficus asperifolia* (Miq.) on carbon tetrachloride-induced hepatic damage in Wistar rats. *J Pharma Sci Res* 9(12):2376–2381
- Ojo OA, Ojo AB, Ajiboye BO, Olaiya O, Okesola MA, Boligon AA, de Campos MMA, Oyinloye BE, Kappo AP (2018a) HPLC-DAD fingerprinting analysis, antioxidant activities of *Tithonia diversifolia*

- (Hemsl.) A. Gray leaves and its inhibition of key enzymes linked to Alzheimer's disease. *Toxicol Rep* 25:585–592
- Ojo OA, Ojo AB, Awoyinka OA, Olayide I, Ajiboye BO, Oyinloye BE, Osukoya OA, Ibitayo AO (2018b) Aqueous extract of *Carica papaya* Linn roots potentially attenuates arsenic induced biochemical and genotoxic effects in Wistar rats. *J Trad Compl Med* 8(2): 324–334
- Ola-Davies OE, Olukole SG (2018) Gallic acid protects against bisphenol A-induced alterations in the cardiorenal system of Wistar rats through the antioxidant defense mechanism. *Biomed Pharmacother* 107:1786–1794
- Omoirri MA, Ehebha SE, Madubogwu NU, Gbagbeke KO, Uyovwiesewa AJ (2021) Ameliorative potentials of *Boerhavia diffusa* ethanolic leaf extract on cypemethrin-induced reproductive dysfunction in Wistar rats. *Magna Sci Adv Res Rev* 1(2):038–044
- Opuwari CS, Henkel RR (2016) An update on oxidative damage to spermatozoa and oocytes. *BioMed Res Int*:9540142
- Pietta PG (2020) Flavonoids as antioxidants. *J Nat Prod* 63(7):1035–1042
- Rezaei H, Zarei A, Kamarehie B, Jafari A, Fakhri Y, Bidarpoor F, Karami M, Farhang M, Ghaderpoori M, Sadeghi H, Shalyari N (2019) Levels, distributions and health risk assessment of lead, cadmium and arsenic found in drinking groundwater of Dehgolan's villages. *Iran Toxicol. Environ Health Sci* 11(1):54–62
- Ronco AM, Urrutia M, Montenegro M, Llanos MN (2009) Cadmium exposure during pregnancy reduces birth weight and increases maternal and foetal glucocorticoids. *Toxicol. Lett.* 188(3):186e191
- Samuel JB, Stanley JA, Princess RA, Shanthi P, Sebastian MS (2011) Gestational cadmium exposure-induced ovotoxicity delays puberty through oxidative stress and impaired steroid hormone levels. *J. Med. Toxicol* 7(3):195e204
- Xu M, Hadi P, Chen G, McKay G (2014) Removal of cadmium ions from wastewater using innovative electronic waste-derived material. *J Hazard Mater* 273:118–123
- Zahrani NAA, El-Shishtawy RM, Asiri AM (2020) Recent developments of gallic acid derivatives and their hybrids in medicinal chemistry: a review. *Eur J Med Chem*:112609

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.