Effect of Quercetin and Melatonin on Bisphenol A–Induced Oxidative Stress in rats Ovarian and Uterine Tissues

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ABSTRACT:

Bisphenol A (BPA), an endocrine-disrupting chemical, is widely used in industrial production. However, it is considered a ubiquitous environmental contaminant worldwide. Bisphenol-A acts like estrogen by interacting with the l estrogen receptors and is known to cause ovarian toxicity. The current investigation aimed to examine the effects of quercetin and melatonin on bisphenol-A–induced oxidative stress in ovarian and uterine tissues. Thirty-two female rats weighing (200±10 g) were divided into four groups. Group 1: intake standard diet; Group 2: bisphenol-A (120 mg/kg body weight) via oral gavage; Group 3: bisphenol-A (120 mg/kg body weight) + quercetin (50 mg/kg body weight via oral administration); and Group 4: bisphenol-A (120 mg/kg body weight) + melatonin (50 mg/kg body weight through oral). After a six-weeks experimental period, serum, ovaries, and uteruses were collected for hormonal analysis, ovarian and uterine analysis of oxidative stress biomarkers, and histopathological examination. ***The findings*** *revealed that BPA decreased serum estradiol (E2) significantly. In addition, malondialdehyde (MDA) showed a significant increase. wheares ovarian and uterine antioxidant enzyme levels, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), were significantly diminished histological abnormalities in the ovaries and uterus were observed in the BPA group. However, the administration of melatonin and quercitrin significantly inhibited the debilitating effects of BPA on the reproduction of female rats. Moreover, melatonin and quercetin exerted protective effects against oxidative stress caused by BPA. In a* ***conclusion,*** *both quercetin and melatonin had protective effects against BPA-induced ovarian and uterine oxidative stress.*

Keywords: *Bisphenol A; hormones; endocrine disruptors; ovary; uterus; oxidative stress.*

INTRODUCTION

Nowadays, industrial modernization results in the high production of hazardous chemicals. Among these chemicals, are endocrine-disrupting chemicals (EDCs) which are a diverse set of compounds of natural and synthetic origin, and could irritate biological hormones. One of the most common EDCs is bisphenol A (BPA), which is frequently used in baby bottles, medical and dental devices, and water pipes. The lipophilic nature of BPA enables it to easily pass through cell membranes and accumulate in the adipose tissues **(Yilmaz et al., 2020).**

BPA is categorized as a xenoestrogen due to its capability to cause endocrine disruption via imitating the natural estradiol. BPA caused moderate toxicity Among animals, particularly mammals. It affects the performance of insulin, prolactin, androgens, and thyroid hormones **(Renaud et al., 2019).** Furthermore, BPA was reported to affect insulin and glucose pathways, lipid and protein, and ovarian steroidogenesis, so, it could lead to metabolic endocrine disorders such as polycystic ovary syndrome (PCOS) **(Belenkaia et al., 2019).**

BPA may accumulate in human tissues and impair health via molecular pathways **(Cimmino et al., 2020).** BPA is found in blood, urine, amniotic fluid, placenta, cord blood, and human breast milk in various quantities, making BPA exposure unavoidable and potentially causing liver malfunction, chronic illnesses, obesity, cancer, reproductive damage, and diabetes **(Zhang et al., 2020).**

The ovary is responsible to produce steroid hormones. Recent research reveals that bisphenol A (BPA) may impact female reproductive function; as a result, it is essential to assess BPA's toxicity to the ovary, especially because BPA has been linked to a variety of health problems.

Polyphenolic flavonoids, such as quercetin, are present in plants such as citrus fruits, onions, and apples and are employed as antioxidants, it is well recognized for their anti-cancer, anti-inflammatory, anti-thrombosis, and anti-hypertension properties **(Kasmi et al., 2018).** Quercetin has a considerable scavenging impact on free radical formation in several

clinical conditions **(Liu et al., 2014)**.

Many studies have found quercetin to be protective against heavy metals and endocrine disruptors **[Jahan et al. 2016].** Quercetin protects tissue and boosts antioxidant **levels (Jahan et al., 2016)**.

N-acetyl-5-methoxytryptamine, or melatonin, is high in eggs and fish t in animal foods, while in plant foods, the highest content of melatonin was found in nuts, and some cereals and germinated legumes or seeds and melatonin is a natural occurring indoleamine that controls several physiological processes. Long-term melatonin supplementation reversed age-related decreases in redox status in several tissues and cells **(Martin et al., 2014)**. Melatonin's amphiphilic nature allows it to traverse all morphophysiological barriers and reach subcellular compartments, where it might alter mitochondria-related activities and increase antioxidant defense. Furthermore, Melatonin and its metabolites also scavenged free radicals. This prevented free radical damage to the electron transport chain, mitochondria, and cellular membranes **(Ramis et al., 2015; Tamura et al., 2020**).

In light of these considerations, this research was carried out in order to investigate the potential protective benefits that quercetin or melatonin could have against the ovarian and uterine oxidative stress that is related to bisphenol in female rats.

MATERIALS AND METHODS

Reagents

All chemicals including bisphenol A, Melatonin, and Quercetin were of high analytical grade and were purchased from the company Sigma-Aldrich (st. Louis, mo, united states)

Animals' housing and grouping

Thirty - two adult female rats weighing 200±10 g (from Ain Shams University's animal facility at the faculty of medicine), were employed in an entirely random experimental setup. At a temperature of 25°C, all the animals were kept in a light/dark cycle for a period of 12 hours. Additionally, free access to food and water during the investigation was guaranteed.

Experimental design

Rats were divided into four distinct groups (eight rats per group). After acclimation for one week, rates were fed a standard basal diet compliant with AIN-93 **(Reeves,1993)**.

Group 1 (NC, or normal controls): rats were fed a normal diet according to AIN-93.

Group 2 Bisphenol-A at a dose of (120 mg/kg BW.)

Group 3 Bisphenol-A (120 mg/kg BW) and Quercetin (50mg/ kg BW)

Group 4 Bisphenol-A (120 mg/kg BW) + Melatonin (50 mg/kg BW)

The doses of Bisphenol -A, Quercetin, and Melatonin used in this experiment were chosen based on earlier research by **Farombi et al., (2012); Berghian et al., (2022),** and **Sangai and Verma, (2012)** respectively.

In this study, the BPA was made ready by dissolving 120mg/kg BW in 0.5 ml of virgin olive oil.

BPA (dissolved in Olive oil), Quercetin, and melatonin (50 mg/kg BW) (dissolved in Deionized water + 2.5% ethanol) were administered via oral gavage.

After six weeks of the experimental period, the rats were anesthetized, and serum samples were collected and kept at - 70℃ for subsequent biochemical analysis. The ovaries and the uteruses were collected and were prepared for histopathological examination as explained later.

Biochemical analysis

a. Hormonal analysis.

After allowing the blood samples to clot for two hours at room temperature, they were centrifuged for fifteen minutes at 3,000 rounds/min. at room temperature. The separated collected serum was then frozen at -70 degrees Celsius until subsequent analysis. ELISA kits (Abcam Company (USA).) were used to evaluate 17-estradiol (E2) **(Jenner et al., 1972),** follicle-stimulating hormones (FSH) **(Qiu et al., 1998)**, thyroid-stimulating hormone TSH **(Frank et al., 1996),** prolactin **(Gillet et al., 1993)** luteinizing hormones (LH), and progesterone (P4) **(Aufrère and Benson, 1976).**

b.Ovarian and uterine Analysis of oxidative stress biomarkers

Tissue specimens from the uteruses and ovaries were crushed in liquid nitrogen, then frozen, the frozen, powdered tissue was placed in 500 μL of phosphate-buffered

saline, cooled to 4℃, and then homogenized. The homogenates were centrifuged for twenty minutes at 10,000× g, 20 min, and 4℃, and the resultant supernatant was used to measure the levels of malondialdehyde, and the activities of antioxidant enzymes. The concentration of total protein in the supernatant was determined by the Bradford method, with bovine serum albumin as the standard (Sigma Aldrich, St. Louis, MO, USA).

Malondialdehyde (MDA) in the ovary and uterus was measured in accordance with **Esterbauer et al., (1991),** ovarian and uterine glutathione peroxidase (GPx) was evaluated according to **Ursini et al., (1985),** ovarian and uterine Catalase (CAT) was measured as stated by **Sinha, (1972).** The amount of superoxide dismutase (SOD) in the ovary and uterus was determined as described by **Fridovich, (1997)**.

Histopathological examination of the ovaries and uterus

Tissue Preparation:

The ovaries and uteruses were cleansed of fatty material and rinsed with saline, dried using tissue paper. Uterus and ovary samples were then fixed in 10% neutral buffer formalin for forty-eight hours. Specimens of tissues were hydrated in ethanol, cleared with xylene, and embedded in paraffin., and 5-µm sections were stained with hematoxylin and eosin (H&E) **(Gamble and Wilson 2008).** Under a light microscope, ovarian and uterine tissue slides were evaluated for histological analysis.

Statistical Analyses

SPSS 28.0 was used for the statistical analysis (IBM Inc., Armonk, NY, United States). The data were presented as a mean ± standard error. One-way analysis of variance (ANOVA) was used to examine the differences between the groups, with a significance level set at $P < 0.05$ according to **Levesque (2007).**

RESULTS

Alterations to Female Hormone Balance

In this research, in comparison to the negative control group, BPA oral administration substantially increased serum gonadotrophic hormone levels including FSH and LH (Table 1) and prolactin (Table 2). However, it significantly diminished serum estradiol with no significant

change in serum progesterone (Table 2).

Melatonin-treated groups, in contrast to the BPA-administered group, exhibited an increase in estradiol levels (Table 2) to almost normal levels as compared to the BPA group and decreased prolactin (Table 2). Furthermore, FSH and LH returned to almost normal levels (Table 1) Compared with the BPA-alone control group, the BPA-plus-quercetin group shows no discernible improvement in hormone levels.

Ovarian oxidative stress Biomarkers: (Figure 1)

The results showed that Bisphenol A exposure increased reactive oxygen species levels and induced ovarian and uterine oxidative stress as denoted by elevated ovarian and uterine MDA levels (Fig.1 d& Fig. 2 d respectively) of the BPA group compared with the control group ($p < 0.05$). However, treatment with melatonin or quercetin could reverse bisphenol A-induced up-regulation of reactive oxygen species and significantly diminished MDA levels in the ovary and uterus, with a more obvious effect of melatonin over quercetin.

The expression and activities of key antioxidants, SOD, GPx, and CAT significantly declined ($P \leq 0.05$) upon Bisphenol A ingestion. Interestingly treatment with melatonin or quercetin has the capability to counter the bisphenol A-induced suppression of SOD, GPx, and CAT activities. Melatonin has a more noticeable antioxidant influence whereas quercetin also significantly increased antioxidant enzymes but to a lower degree when compared to the effect of melatonin. (Fig1 & Fig.2)

Ovarian and uterine histopathological assay:

In the Current study, melatonin-treated groups displayed normal or almost normal ovarian and uterine histological structures. On the other hand, the BPA-intoxicated group showed abnormal histopathological features including atretic follicles and ovarian follicles, which are slightly but not significantly improved upon quercetin supplementation. However, melatonin showed the capability to improve the morphology and histopathology of the uterus and ovaries

Histopathological findings of the ovary:

The structure of the ovarian tissue was found to be normal in the control group, (Fig. 3. A & B) and has a typical histological structure. Numerous follicles of various types (Graafian follicles and Corpus luteum) were noted. Also, there were normal Graafian follicles (arrow). There was a significant change in the ovarian tissue of the BPA alone group as appeared in (Fig 3. C) where the ovary of rats from the BPA group showed hyperplasia and hypertrophy of stromal interstitial cells (small arrow), interstitial connective tissue proliferation (large arrow) and atresia of the follicle (arrowhead). In addition, (Fig. 3 D): Ovary of rats from the group intoxicated with BPA showing congestion (small arrow), hemorrhage (large arrow) as well as hyperplasia and hypertrophy of stromal interstitial cells.

A slight but no significant improvement was observed in BPA -intoxicated rats treated with quercetin which may explain the accompanying insignificant impr-ovement in reproductive horm-ones. Quercetin supplementation did not exert significant change as compared to the BPA alone group where the ovaries of rats from group 3 demonstrated hyperplasia and hypertrophy of stromal interstitial cells (small arrow) with fine interstitial fibroblasts proliferation (Fig. 3E.) In addition, the ovary of rat from group 3 showing vacuolation of luteal cells (regression of corpus luteum) (Fig.3.F)

Interestingly, there was a significant improvement in the ovary tissue of the BPA+ *melatonin* group compared to that of the BPA alone group which proves the positive ameliorative impact of melatonin (Fig. 4). Where (Fig. 3 G) where the ovary of a rat from group 4 showing normal Graafian follicles (arrow) and (Fig. 3 H) where the ovary of a rat from group 4 supplemented with melatonin, showed no histopathological changes and normal follicles were noted.

Histopathological findings of the uterus:

The uterus of rats from the control negative group showed normal morphology with no histopathological changes (Fig. 4 A&B), While administration of BPA caused hyperplasia and

vacuolation of the endometrial epithelium (small arrow) and inflammatory cells infiltration in lamina propria (large arrow) (Fig.4 C). in addition, the uterus of BPA-treated rats showed inflammatory cells (eosinophils) infiltration in lamina propria (arrow) (Fig.4 D).

Despite the supplementation of quercetin improved the antioxidant status as compared to BPA - group, however, no significant improvement was noticed in quercetin-supplemented rats as shown in (Fig.4 E), where vacuolation of the endometrial epithelium (small arrow) and inflammatory cells infiltration in lamina propria (large arrow) were observed. In addition to vacuolation and apoptosis of endometrial epithelium (arrow) (Fig.4 F).

On the other hand, melatonin remarkably improved the morphology of the uterus as denoted by slight vacuolation of the endometrial epithelium (arrow) (Fig 4 G) and slight apoptosis of endometrial epithelium (arrow) (Fig.4 H) as compared to BPA only group

DISCUSSION

Fears about BPA's endocrine-disrupting effects have been voiced because of the chemical's classification as an endocrine disruptor. Diabetes, obesity, Cancer, and infertility are just some of the many adverse health outcomes linked to BPA exposure **(Ahmed and Atlas, 2016).**

Hormonal changes

According to some researchs, BPA may have a role in the etiology of female infertility. Because BPA has been found at elevated levels in infertile women, it has been speculated that it may impede normal conception. In addition, to a reduction in E2 synthesis, BPA exposure has been linked to hormone imbalance. Women with endometriosis have been shown to have higher amounts of BPA. It is possible that the reduction in the release of sex hormones that impact ovarian shape and function is connected to BPA exposure, which has been linked to the development of Polycystic Ovary Syndrom (PCOS) like abnormalities **(Pivonello et al., 2020).**

This research showed that rats given BPA had much lower levels of estradiol and higher levels of the gonadotrophic hormones FSH and LH. The hypothalamus's

gonadotropic hormones may be disturbed as a result of BPA's antagonistic activity. Histopathological analysis of the ovary and its diminished antral follicles, which may be related to reduced estrogen, further supports the findings.

The lower estradiol levels might be attributed to BPA's deleterious influence on estrogen production via changing steroidogenesis enzymes. Similar observations were reported by **Thilagavathi et al., (2018).**

The association between BPA exposure and higher prolactin levels may be caused by BPA's ability to bind to membrane estrogen receptors (α, β, γ (mER)) that may behave as nongenomic steroids **(Steinmetz et al., 1997).** The increased prolactin also could be attributed to changes in prolactin expression as a result of BPA exposure, and BPA-stimulated tissue changes in the mammary gland were found to increase prolactin levels **(Hassan et al., 2013).**

Unlike the findings of the present study, in a prior study, **Gámez et al., (2015)** discovered elevated LH and E2 levels as a result of BPA treatment. In addition, to hyperandrogenism, BPA has also been shown to have the ability to generate oxidative stress, which might impact hormone levels as a result of disturbances in the hypothalamic-pituitary-ovarian (HPO-axis) functioning and altered ovarian histology **(Ijaz et al., 2020**).

Ovarian and uterine Oxidative Stress Biomarkers and histopathology

BPA toxicity in animal models has been linked to oxidative stress for years. Bisphenol A disrupts cell redox state, causing oxidative stress. BPA injection increases mouse organ hydrogen peroxide generation, according to **(Kabuto et al., 2003).**

In this research, BPA exposure diminished SOD levels in the ovary and uterus due to cells' failure to create enough SOD due to severe cellular damage. Superoxide dismutase converts the superoxide anion radical into hydrogen peroxide, a more stable Reactive Oxygen Species (ROS), to protect tissues from oxidative stress and injury. SOD depletion increases the superoxide-free radicals, ROS, and Lipid peroxidation (LPO) processes.

Current results detected a significant drop in ovarian and uterine CAT levels in rats given BPA vs the control rats. The decline in CAT activity may be caused by the cells' inability to get rid of the hydrogen peroxide they produce. This could be because cells' excessive ROS generation inactivates enzymes.

The elevated ovarian and uterine MDA levels observed in the current research after BPA exposure suggested an increase in ROS formation, which led to enhanced LPO activity, exacerbating membrane disruption and Deoxyribonucleic Acid (DNA) damage. ROS-induced oxidative damage, such as lipid peroxidation, alters membrane structure, inactivates enzymes, and damages cellular macromolecules, contributing to pollutants' toxicity **(Murugesan et al., 2005).**

Based on the current investigation and a vast body of previous research on BPA's effects at similar and much higher doses, BPA caused oxidative stress, which might be one of BPA's genotoxic mechanisms.

Melatonin is a neurohormone engaged in diverse homeostatic processes, including reproduction and redox balance. As an antioxidant, melatonin serves as a scavenger of ROS and nitrogen species, where it increases antioxidant enzyme gene expression, preventing oxidative stress damage **(Pandi-Perumal et al., 2006).**

The administration of melatonin or *quercetin along* with BPA lead to improvement in the oxidative status and morphology of ovaries, this improvement could be due to an increase in antioxidant capability and a decrease in lipid peroxidation.

According to the findings of the current investigation, melatonin was able to increase the activity of antioxidant enzymes and protect ovarian and uterine tissue from oxidative damage. These findings are in line with previous research **(Yu et al., 2019)**. **Zhang et al., (2019)** reported that one of the primary causes of follicular cell apoptosis is oxidative stress.

Melatonin (MLT), a highly lipophilic chemical, may readily traverse cell barriers and have antioxidant and anti-apoptotic properties) **Zhang et al., 2019; Tamura et al., 2020)**. MLT may reduce BPA's harmful effects by

increasing free radical scavenging **(Olcese, 2020).** Furthermore, Melatonin was reported to reduce free radical-induced mitochondrial oxidative damage in female mice **(Song et al., 2019).**

As a natural antioxidant, Quercetin has been used to treat obesity, cardiovascular disease, cancer, chronic inflammation, and disorders of the reproductive system.

Similar results to those of the present study were shown in earlier research, which indicated that quercetin may reduce oxidative stress by controlling the PI3K / Akt / FoxO3a signaling pathway **(Zheng et al., 2022).**

Unlike current results, Quercetin was reported to improve the function and quality of the ovary (Soleimani 2021), also Quercetin was reported to alleviate PCOS by imitating estrogen's actions and having Phyto-estrogenic properties **(Soleimani et al., 2021; Khorchani et al., 2020).** Because of its propensity to alter the HPO-axis, BPA has modest estrogenic action comparable to that of E2. Clinical consequences of this disturbance include hormonal imbalance and consequent ovarian morphological abnormalities.

BPA also harms the female reproductive system. **Zhang et al. (2017)**, where BPA (100 μg/kg BW /day) for 7 days, negatively affects oocyte quality in mice. However, Melatonin (30 mg/kg BW/ day) for 7 days, increased in vitro fertilization by reducing ROS levels and inhibiting oocyte apoptosis, restoring BPA-induced changes to fertilization.

Furthermore, current histo-logical data demonstrates that melatonin protects against ovarian and uterine damage produced by BPA exposure, which is in agreement with **(Dernek et al., 2017).**

However, contrary to the present results, quercetin has been found to improve hormone production while decreasing the proliferation rate and apoptosis in ovarian cancer cells. This variation could be explained by the low water solubility and instability of quercetin.

This research confirms previous findings that quercetin protects against oxidative stress and reduces lipid peroxidation.

Ptak et al., (2017) showed that BPA has many effects on ovarian

function. Stimulating ovarian cancer cell growth, BPA binds to steroid hormone receptors and blocks endogenous ligand binding. BPA also has a secondary effect on endocrine and autocrine adipokines and receptors in ovarian cells.

The histopathology analysis revealed many histological abnormalities in the rats' ovaries after BPA treatment, including various aberrant situations such as tissue proliferation and follicular atresia.

According to **Liu et al., (2022),** rats treated with high doses of BPA exhibited histology findings that showed necrosis, hemorrhage, and the presence of a considerable number of ataractic follicles without any signs of the ovulatory process, confirming the ovotoxic nature of BPA.

The administration of melatonin caused significant improvement in the ovary and uterus tissue of the BPA+ melatonin group when compared to the BPA-only group. This restoration is due to the positive fertility effects of melatonin as well as its high antioxidant potential.

Unlike the current finding, **Qiu et al. (2020)** found normal morphology of the ovary and normal follicular development in BPA-exposed newborn rats. Exposure dose and duration are major factors for these discrepancies

The findings of the present investigation agree with those of **Takeuchi et al. (2004)** with respect to the histological alterations in the ovary.

Thus, exposure to BPA causes histologically evident alternations in ovaries and uteruses, while melatonin administration but not quercetin showed positive effects on ovarian and uterine BPA intoxication.

The significant beneficial effect of melatonin in improving the morphology of the ovary and uterus, as proven by almost normal ovarian morphology and slight histopathological changes in the uterus as compared to the BPA group, might be attributed to the high antioxidant potential, which protects the ovary and uterus from oxidative damage, and subsequently improves gonadotropic as well as reproductive hormones.

CONCLUSION

According to the findings, BPA may cause infertility due to its oxidative and hormonal effects on

the ovaries. Melatonin supplementation, taken for six weeks, decreased BPA-induced oxidative stress.

Overall, the present research showed that melatonin had a more significant effect than quercetin on improving hormone levels, morphology, and oxidative stress. Quercetin, meanwhile, demonstrated modest benefits in terms of ovarian and uterine morphology and hormone characteristics.

Future prospective:

Further research on the link between BPA and female fertility, as well as possible methods of protection and treatment, is necessary in order to raise public awareness about the health dangers associated with BPA exposure. It is also critical to discover a safe substitute for BPA.

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Conflict of Interest

There is no conflict of interest.

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Ethical statement

authors declare that the National Institutes of Health (NIH) guidelines for the care and use of laboratory animals (NIH Publication No. 85-23 received in 1985) were strictly adhered to. The experimental protocol and all producers follow the guidelines of the specified Ethical Committee, Ain shams University, Egypt.

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Table (1): Effect of BPA, Quercetin and Melatonin on serum Gonadotrophic Hormones.

Groups	Parameters	
	Follicle-stimulating hormone **FSH (mIU/ml)**	Luteinizing hormone **LH (mIU/ml)**
(G1) NC	2.14 ± 0.048 [a]	1.67 ±0.026 [a]
(G2) BPA	3.66 ± 0.082 [b]	2.32 ± 0.034 [b]
(G3) BPA+QUERCETIN	3.47 ± 0.118 [b]	2.22 ± 0.048 [b]
(G4) BPA+MELATONIN	2.54 ± 0.051 [c]	1.84 ± 0.011 [c]

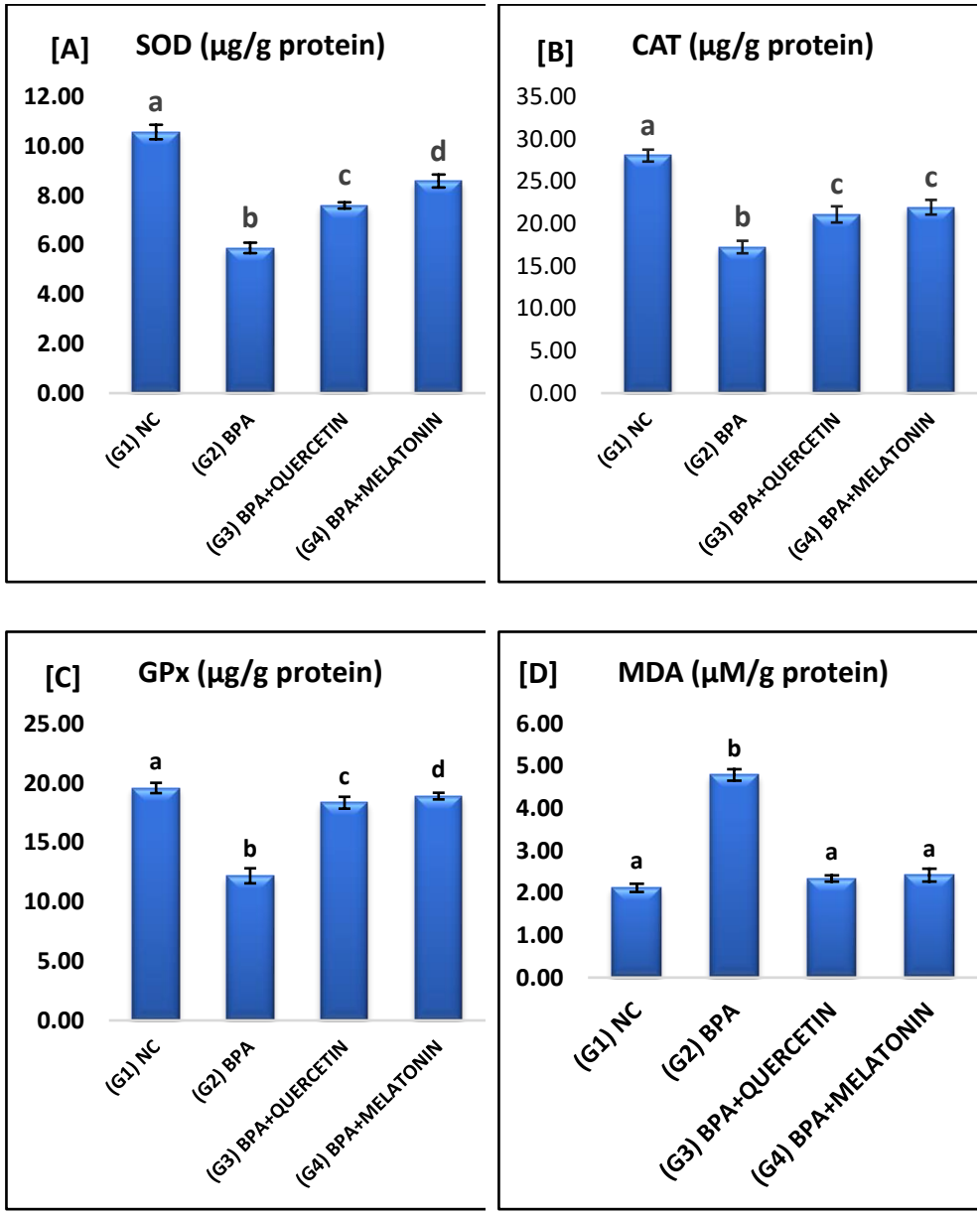
Data are expressed as Mean ± SE. There is a statistically significant difference between values that do not share a common superscript at p < 0.05

Table (2): Effect of BPA, Quercetin, and Melatonin on serum Estradiol, Progesterone, and Prolactin

Groups	Parameters		
	17β-estradiol **E2 (pg/ml)**	**Progesterone (ng/ml)**	**PRL (ng/ml)**
(G1) NC	27.84 ± 0.22[a]	21.87 ± 0.25 [a]	35.09 ± 0.19[a]
(G2) BPA	22.55 ± 0.14[b]	22.48 ± 0.22 [a,b]	38.82 ± 0.16 [b]
(G3) BPA+QUERCETIN	22.61 ± 0.17[b]	21.81 ± 0.39 [a,b]	38.68 ± 0.27 [b]
(G4) BPA+MELATONIN	26.87 ± 0.13[c]	21.76 ± 0.25 [a,b]	35.61± 0.21 [c]

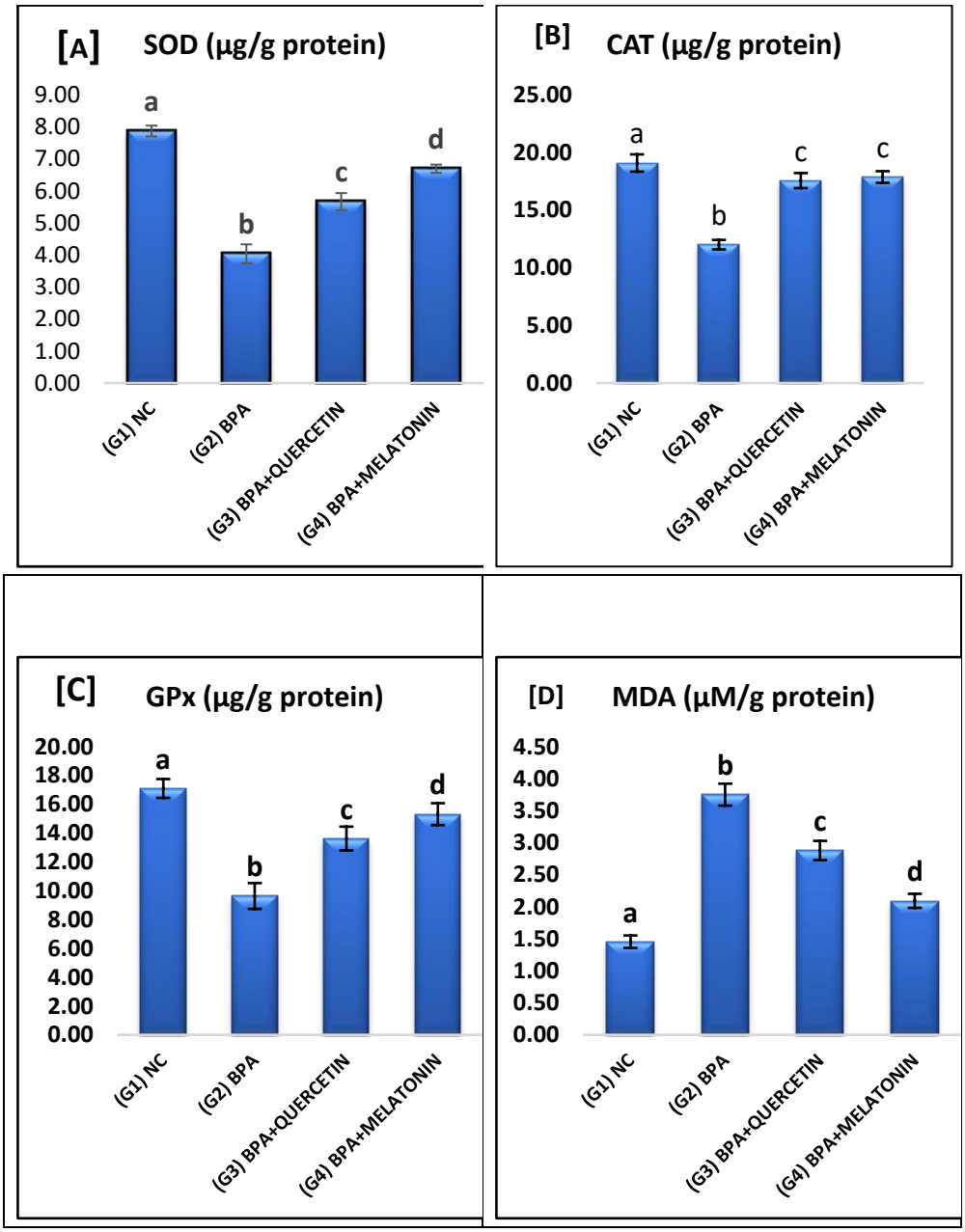
Data are expressed as Mean ± SE. There is a statistically significant difference between values that do not share a common superscript at p < 0.05

Figure (1) Effect of BPA, Quercetin, and Melatonin on Ovarian Antioxidant Status: (A) SOD; (B) CAT; (C) GPx and (D) MDA.



Data are expressed as Mean ± SE. There is a statistically significant difference between values that do not share a common letter at $p < 0.05$

Figure (2) Effect of BPA, Quercetin, and Melatonin on Uterine Antioxidant Status: (A) SOD; (B) CAT; (C) GPx and (D) MDA



Data are expressed as Mean ± SE. There is a statistically significant difference between values that do not share a common letter at $p < 0.05$

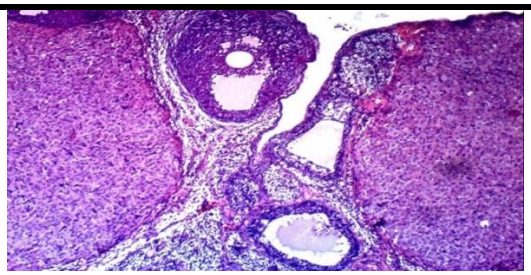
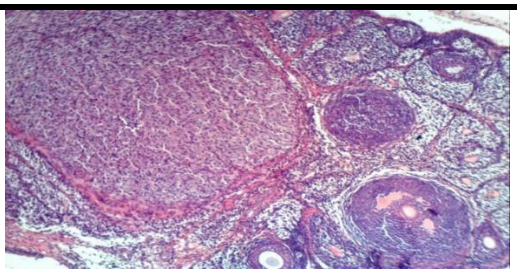


Fig.3 A



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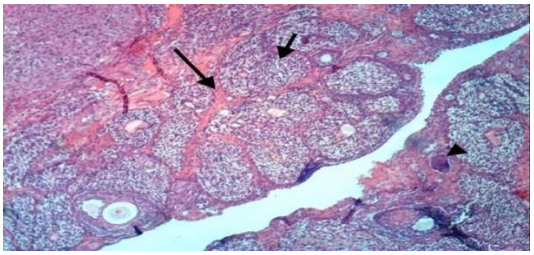


Fig.3 C

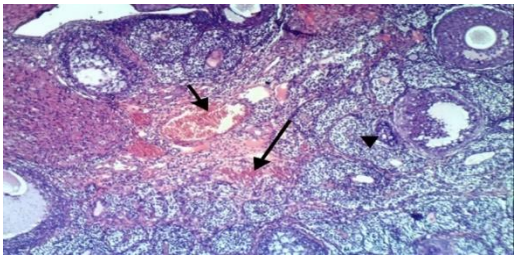


Fig.3 D

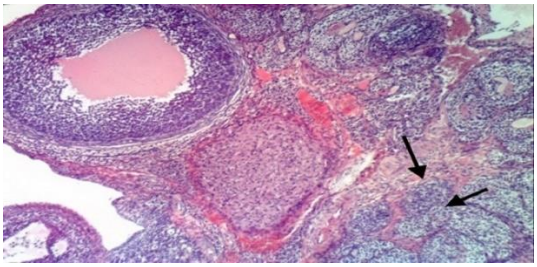


Fig.3 E

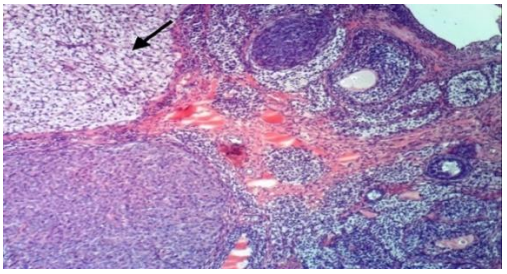
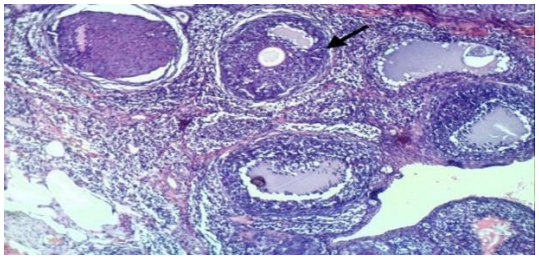


Fig3 F



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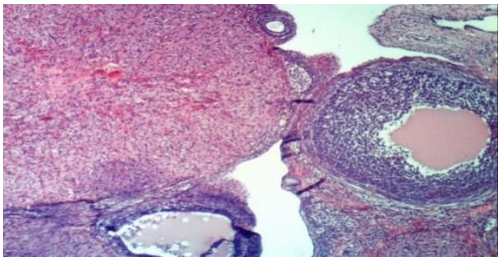


Fig.3 H

Figure 3. Ovarian histopathology of female rats. Fig. 3.A, B. Control; Fig. 3.C, D. BPA; Fig. 3.E, F. BPA & Quercetin and. Fig. 3. G, H. BPA & Melatonin (H & E X 100).

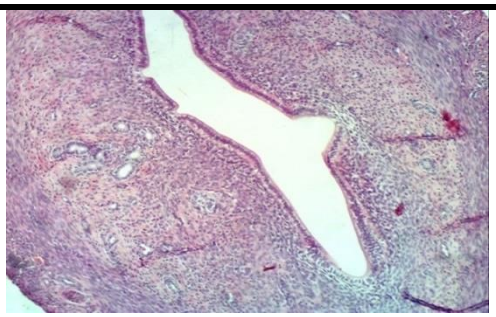
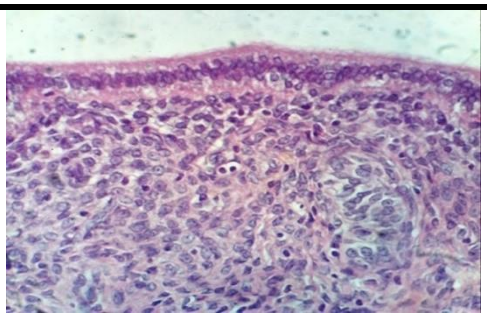


Fig.4 A



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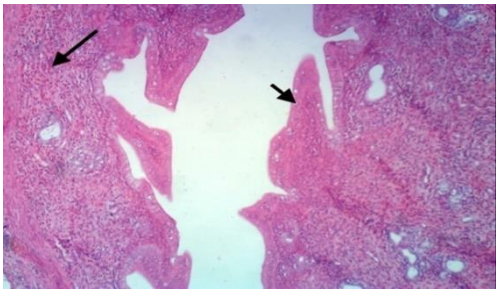

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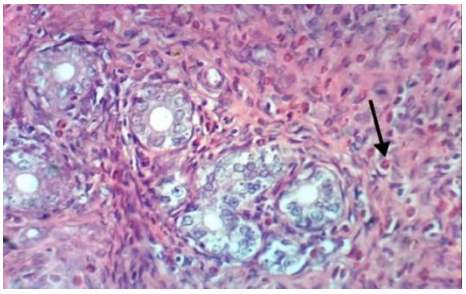

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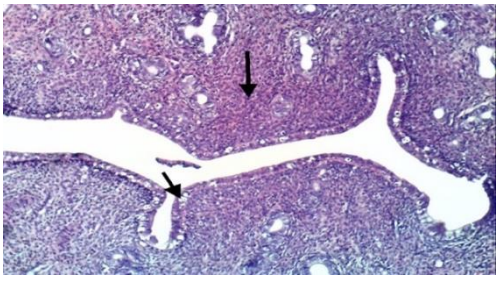

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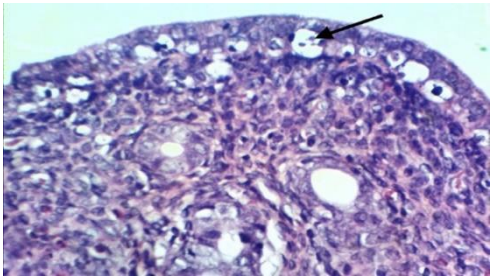

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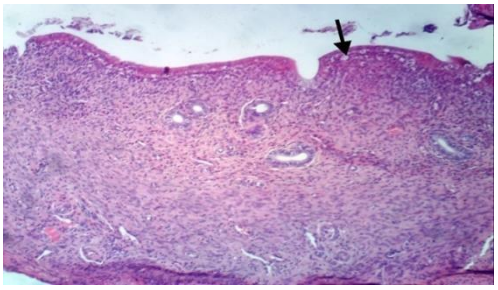

Fig.4 G

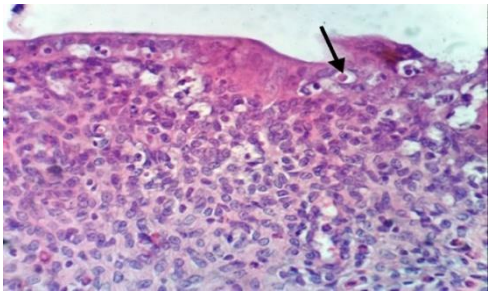

Fig.4 H

Figure 4. histopathology of the uterus of female rats. Fig. 3.A, B. Control; Fig. 3.C, D. BPA; Fig. 3.E, F. BPA & Quercetin and. Fig. 3. G, H. BPA & Melatonin (H & E X 10

تأثير الكيرسيتين والميلاتونين على الإجهاد التأكسدي الناجم عن البيزفينول -A في أنسجة مبيض ورحم الجرذان

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الملخص العربي:

*يستخدم Bisphenol-A (BPA) ، وهو مادة كيميائية معطلة للغدد الصماء ، على نطاق واسع في الإنتاج الصناعي. فيعتبر BPAملوثا بيئيا في جميع أنحاء العالم. يمارس Bisphenol-A نشاطا شبيها بهرمون الاستروجين من خلال التفاعل مع مستقبلات هرمون الاستروجين الكلاسيكية (ERα و ERβ) ومن المعروف أنه يسبب سمية المبيض. هدفت هذه الدراسة إلى تقييم آثار الكيرسيتين والميلاتونين على الإجهاد التأكسدي الناجم عن Bisphenol-A في أنسجة المبيض والرحم. اثنين و ثلاثون أنثى من الجرذان تزن 200±10 غرام قسمت إلى أربع مجموعات (كل مجموعة 8 جرذان). المجموعة 1: النظام الغذائي القياسي؛ المجموعة 2: Bisphenol-A (120 مغ/كغ من وزن الجسم) يومياً عن طريق الفم ؛ المجموعة 3: Bisphenol-A (120 مغ/كغ من وزن الجسم) + كيرسيتين (50 مغ/كغ) عن طريق الفم ؛ والمجموعة 4: Bisphenol-A (120 مغ/كغ من وزن الجسم) + الميلاتونين (50 مغ/كغ من وزن الجسم عن طريق الفم). بعد فترة تجريبية مدتها ستة أسابيع، تم جمع المصل والمبيضين والرحم للتحليل الهرموني، وتحليل المبيض والرحم للمؤشرات الحيوية للإجهاد التأكسدي، والفحص النسيجي. كشفت النتائج أن BPA أدى الى انخفاض في مستوى هرمون الاستروجين في الدم بشكل كبير. بالإضافة إلى ذلك، أظهر مالونديالدهيد (MDA) زيادة كبيرة. في حين أن مستويات إنزيمات المبيض والرحم المضادة للأكسدة، بما في ذلك السوبر أكسيد ديسميوتيز (SOD)، والكاتالاز (CAT) ، والجلوتاثيون بيروكسيديز (GPx) ، انخفضت بشكل كبير. لوحظت بعض الاضطرابات في الفحص الهستولوجي للمبيض والرحم في مجموعة BPA. وقد أظهرت النتائج ان إعطاء الميلاتونين والكيرسيترين يمنع بشكل كبير الآثار الموهنة ل BPA على تكاثر إناث الفئران. علاوة على ذلك، مارس الميلاتونين والكيرسيتين تأثيرات مخففة من وطأة الإجهاد التأكسدي الناجم عن BPA.**الاستنتاج:** كان لكل من الكيرسيتين والميلاتونين آثار مخففة من وطأة الإجهاد التأكسدي المبيضي والرحمي الناجم عن BPA.*

الكلمات المفتاحية: *Bisphenol-A ؛ الهرمونات؛ اضطرابات الغدد ؛ المبيض؛ الرحم؛ الإجهاد التأكسدي.*