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# The Effect of Quercetin Against Oxidative Stress and Possible Histopathological Changes Due to Bisphenol-A Exposure in Rat Ovary

## Sıçan Ovaryumunda Bisfenol-A Maruziyetinin Neden Olduğu Oksidatif Stres ve Olası Histopatolojik Değişimlere Karşı Kuersetin'in Etkisi

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## ABSTRACT

**Aim**: Endocrine disrupting chemicals are known to have negative effects on the reproductive system. Bisphenol A (BPA), one of these chemicals, is thought to trigger oxidative stress due to its estrogenic effects and potentially impair ovarian function, leading to decreased fertility, especially in females. In this study, we aimed to determine the possible histopathologic effects of BPA, which has endocrine disrupting properties, on the ovaries of female rats and the protective role of quercetin (Q) in reducing the oxidative stress caused by BPA exposure.

**Material and Method**: In this study, 32 female Wistar albino rats were used, and 4 groups were formed as control (corn oil, p.o.), BPA (10 mg/kg p.o.), Q (15 mg/kg i.p.) and BPA+Q. After the rats were sacrificed, histopathological changes in ovarian tissues and Malondialdehyde (MDA), Catalase (CAT), advanced oxidation protein products (AOPP), and glutathione (GSH) levels were analyzed spectrophotometrically.

**Results**: The results of the study, which lasted a total of 14 days, showed that BPA caused changes in the ovarian tissues of female rats. The results of biochemical and histopathological analysis determined that quercetin administration ameliorated the adverse effect of BPA. BPA administration showed a significant increase in the levels of MDA and AOPP, biomarkers of oxidative stress. Moreover, antioxidant enzyme levels (CAT and GSH) were increased by Q administration.

**Conclusion**: BPA may induce oxidative stress in ovarian tissues of female rats, leading to histopathologic changes. On the other hand, quercetin treatment showed a protective effect by significantly reducing the debilitating effects of BPA on the reproductive system.

**Keywords**: Ovarium, oxidative stress, bisphenol-A, quercetin, rat

## ÖZ

**Amaç**: Endokrin bozucu kimyasalların üreme sistemi üzerinde olumsuz etkileri bilinmektedir. Bu kimyasallardan biri olan Bisfenol A'nın (BPA) östrojenik etkileri nedeniyle oksidatif stresi tetiklediği ve potansiyel olarak ovaryum fonksiyonlarını bozarak özellikle dişilerde doğurganlığın azalmasına yol açtığı düşünülmektedir. Bu çalışmada, endokrin bozucu özelliği olan BPA'nın dişi sıçanların ovaryumları üzerindeki olası histopatolojik etkilerini ve BPA maruziyetinin neden olduğu oksidatif stresi azaltmada kuersetinin (Q) koruyucu rolünü belirlemeyi amaçladık.

**Gereç ve Yöntem**: Bu çalışmada 32 dişi Wistar albino sıçan kullanılmış ve kontrol (mısır yağı, p.o.), BPA (10 mg/kg p.o.), Q (15 mg/kg i.p.) ve BPA+Q olmak üzere 4 grup oluşturulmuştur. Sıçanlar sakrifiye edildikten sonra, ovaryum dokularındaki histopatolojik değişiklikler ve Malondialdehit (MDA), Katalaz (KAT), ileri oksidasyon protein ürünleri (AOPP) ve glutatyon (GSH) seviyeleri spektrofotometrik olarak analiz edildi.

**Bulgular**: Toplam 14 gün süren çalışmanın sonuçları, BPA'nın dişi sıçanların ovaryum dokularında değişimlere neden olduğunu göstermiştir. Biyokimyasal ve histopatolojik analiz sonuçları, kuersetin uygulamasının BPA'nın olumsuz etkisini iyileştirdiğini belirledi. BPA uygulaması, oksidatif stres biyobelirteçleri olan MDA ve AOPP seviyelerinde önemli bir artış göstermiştir. Ayrıca, antioksidan enzim seviyeleri (KAT ve GSH) Q uygulaması ile artmıştır.

**Sonuç**: BPA dişi sıçanların ovarium dokularında oksidatif stresi indükleyerek histopatolojik değişimlere yol açabilir. Öte yandan, kuersetin tedavisi, BPA'nın üreme sistemi üzerindeki zayıflatıcı etkilerini önemli ölçüde azaltarak koruyucu bir etki göstermiştir.

**Anahtar Kelimeler**: Ovaryum, oksidatif stres, bisfenol-A, kuersetin, sıçan

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## INTRODUCTION

Plastic production and consumption have increased significantly in recent years in parallel with the developments in the industry. Products made of plastic cause serious health and environmental problems, despite their advantages such as making our lives easier and ease of use (1). Every year more and more reports reveal the results that numerous harmful compounds from plastic products are polluting the water, soil, and air. Among the most dangerous of these products are acrylonitrile, phthalates, dioxins, polychlorinated biphenyls, and bisphenol A (BPA) (1).

One of the most widely used plastic products, BPA (2,2-bis(4-hydroxyphenyl) propane), is used in the manufacture of many plastic products, including baby bottles, dental supplies, cosmetics, medical equipment, and recycled paper. However, BPA has a xenoestrogen property that disrupts endocrine metabolism by binding to estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ) (2). This effect of BPA is closely related to disorders in the development and functioning of reproductive organs, proven by clinical results, as well as metabolic disorders, including triggering certain types of cancer (uterus, ovary, prostate), obesity, thyroid hormone disorder, and diabetes (3). Polycystic Ovary Syndrome (PCOS) is one of the most common endocrine diseases among women of reproductive age. There is also an important link between the development of PCOS-like abnormalities and BPA exposure (4).

The toxicity of BPA, especially in the reproductive system, is due to its interaction with androgen and estrogen receptors (5). Although BPA itself is not an oxidizer, it causes cellular changes that are usually mediated by lipid peroxidation (LPO) and the production of free radicals that cause oxidative stress (OS) (5). Exposure to BPA, even at low concentrations, can alter reproductive physiology and cause changes in the ovaries and uterus. It affects the decrease in sperm count and quality together with the damage in testis histology (6).

Many studies have reported negative effects of BPA exposure on fertility (7,8). Animal studies have shown that the negative effect of BPA on female fertility is due to disruption of cytoskeletal dynamics of the oocyte, induction of OS, and increased DNA damage (9). It is also suggested that BPA has effects on female reproductive functions for generations and may cause fertility disorders that are passed on to the next generations (10).

Polyphenols are compounds found naturally in the plant world with many different types and in the structure of fruits and vegetables. The disease prevention potential of polyphenolic compounds is due to their ability to reduce reactive oxygen species (ROS) levels in cells (11). Thanks to these properties, polyphenols show promise in the prevention of infections, cardiovascular and neurodegenerative diseases, diabetes, premature aging and cancer. Flavonoids are a group of polyphenols commonly found in plants as secondary metabolites (12). Quercetin (Q), one of the members of this group, can prevent cell death by scavenging free radicals, and protecting against metal ions and lipid peroxidation (13). Several studies show that Q reduces the negative effects of BPA. For example, animals receiving a mixture of quercetin and BPA showed an increase in total lipids and testosterone levels, and Q showed a protective effect against BPA-induced testicular tissue damage (14). Mahdavinia et al. (2019) determined that quercetin administration reduced OS by preventing mitochondrial damage in a rat model of BPA-induced hepatotoxicity (15). The findings of Shirani et al. (2019) showed that quercetin can reduce the toxic effects of BPA in mitochondria isolated from rat kidney tissues (16).

From past to present, different antioxidant approaches have been used to reduce or eliminate the damage caused by BPA in female and male reproductive systems. These antioxidants are intended to increase male and female fertility by reducing multiple markers of OS, lipid peroxidation, or DNA damage. Many biological activities of Q such as antioxidant, anti-inflammatory, anticancer, antiviral, and antimicrobial have been proven by previous studies (17). Considering these effects of quercetin, this study, it was aimed to investigate the histopathological effects of BPA, which has endocrine-disrupting properties, on the female reproductive system by using rat ovarian tissues and to investigate the therapeutic effects of Q on OS.

## MATERIAL AND METHOD

### Reagents and Chemicals

All chemicals including bisphenol A (BPA, Purity 99%), and quercetin (Purity 98%) were purchased from Sigma-Aldrich (St. Louis, MO, US). The appropriate amount of BPA was dissolved in corn oil to reach the desired concentrations.

### Animals

The animal material of this study was composed of 32 female Wistar albino rats. The average weights of the animals were in the range of 200-250 g. The rats were housed in polycarbonate cages and fed pellet food in rooms at 22±2 degrees, lit at a rhythm of 12 hours light and 12 hours dark. Water intake was released.

### Experimental Protocol

Rats were randomly divided into four experimental groups. Eight animals (n=8) in each group were placed in cages. The animals were administered corn oil and BPA orally (p.o.) and quercetin intraperitoneally (i.p.) for two weeks. Groups were formed as described below and sacrificed under anesthesia on the 15th day (18,19).

Group 1: Control Group (CO), (0.5 ml corn oil, p.o.),

Group 2: BPA Group (BPA), (10 mg/kg BPA p.o.),

Group 3: Quercetin Group (Q), (15 mg/kg i.p.),

Group 4: BPA (10 mg/kg/p.o.) + Quercetin (15mg/kg/i.p.)

### Histopathologic analysis

After the ovarian tissues were fixed in 10% buffered formaldehyde, they were embedded in paraffin blocks following the routine histological tissue follow-up steps. Then, 4 µm thick sections taken with a microtome were stained with hematoxylin-Eosin dye and examined under a light microscope (Olympus BX53, Japan). For histopathological evaluation, randomly selected areas of ovarian tissue sections were evaluated. According to the intensity of pathological lesions observed in the evaluated areas, it was scored as: - (no lesion), + (mild), ++ (moderate), +++ (severe) (20).

### Tissue homogenate

Cold phosphate buffer (pH: 7.4) was added at a ratio of 1:9 by weight of ovarian tissue. Tissues were rapidly homogenized with the aid of a homogenizer (ISOLAB, Türkiye). Then, the tissue homogenates were centrifuged at 10.000 rpm for 15 minutes, and the supernatants were stored at -80°C until the day of analysis.

### Biochemical analysis

In the supernatants obtained, OS markers Malondialdehyde (MDA) (21), advanced oxidation protein products (AOPP) (22), Catalase (CAT) (23), and glutathione (GSH) (24) analyses were determined using spectrophotometric (Shimadzu UV-1240, Japan) methods reported in previous studies.

### Statistical analysis

Statistical analyses were performed using SPSS 24.0 software. All data are presented as mean±standard deviation. Statistical analysis of groups was performed using one-way ANOVA followed by post hoc multiple comparisons (Tukey test) for comparative analysis between groups. p-value ≤0.05 was considered statistically significant.

## RESULTS

### Histopathology Findings

There were no pathological findings in the ovarian tissues of the groups treated with corn oil and Q (**Figure 1**). Severe hyperemia/congestion in the ovarian tissue of the BPA group and necrosis in the ovarian cells were detected. It was observed that there was a significant decrease in preantral follicles compared to the control group. Q administration significantly ameliorated BPA-induced pathological changes (**Table 1**, **Figure 1**).

**Table 1. Histopathological scores of ovaries of rats treated with BPA and Q**

| Histopathological Parameters | CO | BPA | Q | BPA+Q |
|---|---|---|---|---|
| Hyperemia/Congestion | - | +++ | - | ++ |
| Necrosis | - | +++ | - | + |
| Preantral follicle count | +++ | + | +++ | + |

CO; Corn oil, BPA; Bisphenol A, Q; Quercetin.

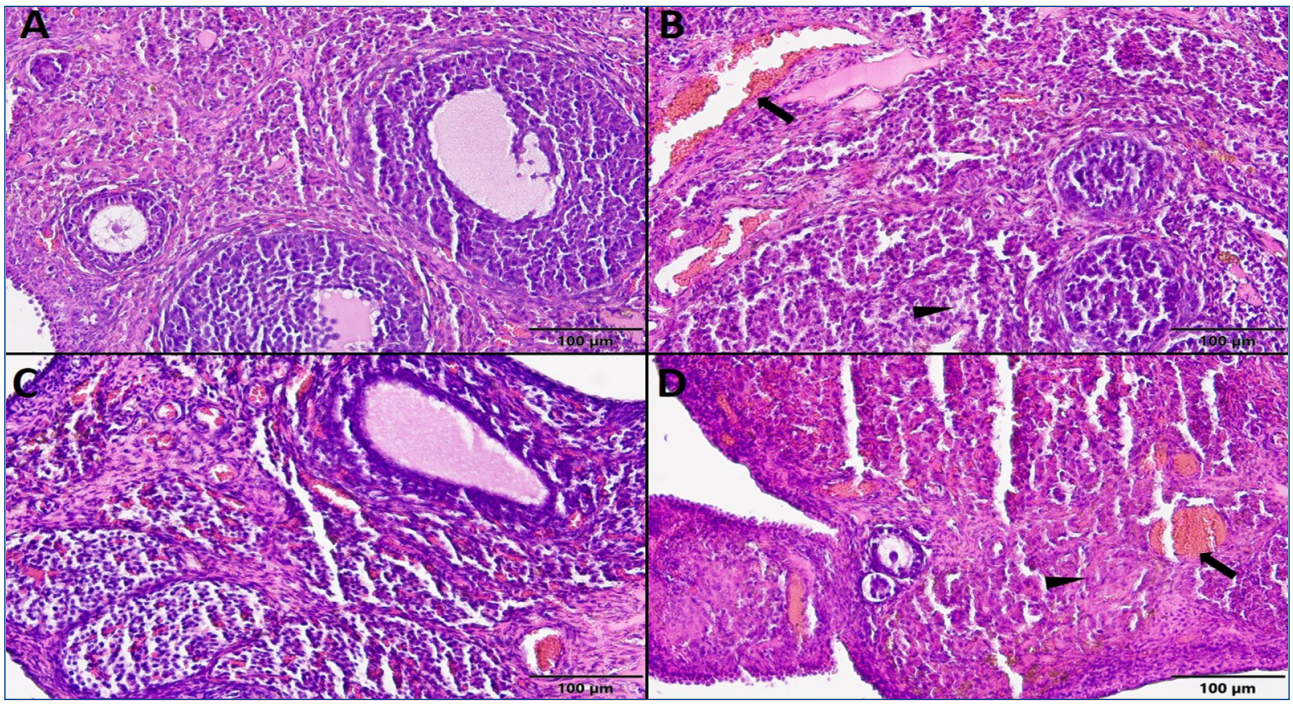


**Figure 1.** Ovarian tissue light microscopic images. A: Corn oil (CO) group, B: Bisphenol A (BPA) group, C: Quercetin (Q) group, D: BPA+Q group. CO and Q groups had healthy ovarian tissue. BPA group, intense hyperemia/conjunctivitis in ovarian tissue (arrow), necrosis in ovarian cells (arrowhead). BPA+Q group, moderate hyperemia/congestion (arrow), and low degree of necrosis (arrowhead) are observed. H&E. 20x.

**Table 2. MDA, CAT, AOPP and GSH levels in ovarian tissue of rats treated with BPA and Q.**

| Groups | Control (CO) | BPA | Q | BPA+Q |
|---|---|---|---|---|
| MDA (nmol/g tissue) | 5.95±1.41$^{b}$ | 9.40±1.50$^{a}$ | 6.63±1.21$^{b}$ | 7.59±1.06$^{b}$ |
| CAT (U/g tissue) | 296.94±74.78$^{ab}$ | 184.47±66.80$^{c}$ | 339.87±61.15$^{a}$ | 241.79±44.99$^{bc}$ |
| AOPP (mmol/gr tissue) | 16.71±2.24$^{b}$ | 20.65±1.54$^{a}$ | 17.36±1.57$^{b}$ | 19.02±1.58$^{ab}$ |
| GSH (µmol/g tissue) | 2.80±0.54$^{a}$ | 1.72±0.96$^{b}$ | 2.66±0.49$^{ab}$ | 1.89±0.99$^{ab}$ |

CO; Corn oil, BPA; Bisphenol A, Q; Quercetin, MDA (Malondialdehyde), CAT (Catalase), AOPP (Advanced oxidation protein products), GSH (Glutathione). a,b,c p: values with different letters are significant when compared with each other (p≤0.05). Data are presented as mean±SD.

## Biochemical Findings

MDA, CAT, AOPP and GSH enzyme activity levels of ovarian tissues of all groups are shown in **Table 2** and **Figure 2**. In the comparison between the groups, the MDA level of the ovarian tissue increased in the BPA group due to the increase in the ROS level ($p<0.05$). Although the control group had the lowest MDA value, the difference between them was not statistically significant when compared to the Q and BPA+Q groups ($p>0.05$). In CAT results, while CAT activity decreased with BPA application, Q treatment increased the decreased CAT levels, bringing them closer to the control group ($p<0.05$). There was an increase in AOPP values in the BPA-treated groups, but Q treatment partially reversed this situation. In the AOPP results, only the values for the CO and Q groups were significant compared to the BPA group ($p<0.05$). Although the combination of BPA+Q decreased the AOPP level numerically, the difference between them was not significant compared to the BPA group ($p>0.05$). GSH level decreased significantly in the BPA group compared to the CO group ($p<0.05$). While Q application caused an increase, albeit partially, there was no significant difference when compared to other groups ($p>0.05$).

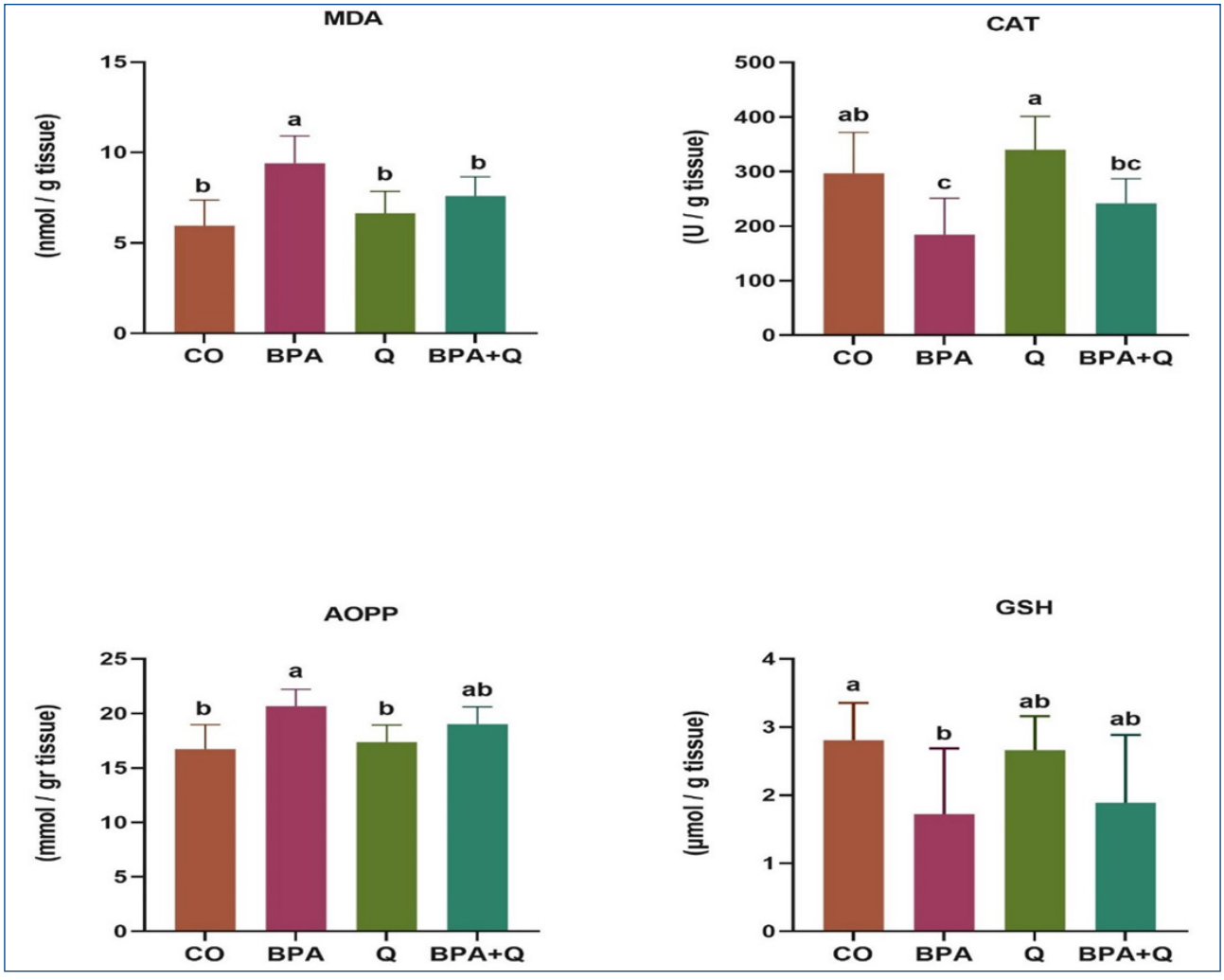


**Figure 2.** The effects of BPA and Q administered on MDA, CAT, AOPP, and GSH levels in the ovaries of rats. Data are presented as mean±SD (p≤0.05). CO; Corn oil, BPA; Bisphenol A, Q; Quercetin, MDA (Malondialdehyde), CAT (Catalase), AOPP (Advanced oxidation protein products), GSH (Glutathione). a,b,c p: values with different letters are significant when compared with each other (p≤0.05).

## DISCUSSION

Bisphenol A can have various effects on the ovaries depending on the duration of exposure. In a previous study, female rats exposed to BPA exhibited a reduction in oocyte count, an increase in uterine tissue weight, and structural changes in estrogen receptor expression in the endometrium (25). Additionally, a decrease in ovarian count due to BPA has been reported (26). These studies suggest that BPA may lead to adverse effects on the reproductive system, potentially resulting in a reduction in fertility rates. In this study, histopathology results showed improvement in the ovarian tissue of the BPA+Q group compared to the BPA group. This is thought to be due to the positive effects of quercetin on fertility as well as its high antioxidant potential. Quan et al. (2017) reported that oral BPA exposure causes histopathological changes due to increased ROS production in the testes of male offspring (27). According to Liu et al. (2022), necrosis and bleeding were detected in BPA-treated rats, while a significant number of ataractic follicles were detected without any signs of an ovulation process (28). This situation reveals the ovotoxic effect of BPA. In addition, it has been determined that quercetin significantly prevents cell viability and tissue damage due to the OS produced, and increases antioxidant capacity in the female reproductive system (29). Similar to our results, Elwakeel and El-Monem (2018) also found that Q ameliorates pathological changes in tissues exposed to BPA (30).

Excessive ROS production causes an increase in MDA levels due to lipid peroxidation of polyunsaturated fatty acids in cell membranes (31). Similar to our results, several studies are showing that MDA is increased in tissues due to exposure to BPA (32,33). Quercetin treatment reduces OS and lipid peroxidation caused by BPA. Co-administration of BPA and quercetin reversed the toxic effects of BPA in rats, restoring the lipid profile (14). It has also been stated in previous studies that quercetin can reduce OS and lipid peroxidation in tissues by scavenging free radicals (34,35). In the current study, similar to the findings in the literature, free radical formation caused by BPA showed the effect of reducing the increased MDA level in ovarian tissues with the application of Q, which has antioxidant properties.

Catalase is an important enzyme involved in the body's antioxidant defense and is found in all aerobic organisms. The decreased CAT level in the BPA group is thought to occur as a result of the cells not being able to get rid of the hydrogen peroxide (H2O2) they produce due to excessive ROS production in the cells. BPA can induce OS by reducing antioxidant enzymes. A significant decrease in ovarian and uterine CAT levels was determined in rats administered BPA compared to the control group by Fadlalla (2022) (34). Banerjee et al. (2018) reported that the CAT level was significantly reduced after nine days of intraperitoneal BPA administration in mature female rats (36). In the findings obtained from the same study, it was concluded that the detection of CAT level plays an important role in the functional integrity of ovarian granulosa cells and the detection of reproductive capacity impaired by BPA (36). Quercetin, on the other hand, has been reported to be effective in repairing the deteriorated antioxidant activity in tissues and correcting the deteriorated enzyme systems (16).

AOPP level is a new protein marker of protein damage caused by oxidation. This value increases in many chronic diseases such as chronic kidney disease, osteoporosis, and inflammatory bowel disease (37). Increased OS is the main cause of various abnormalities in BPA toxicity to the female reproductive system (38). In a study measuring the effect of OS on infertility, 2.0-3.5 times higher AOPP levels were determined in the seminal plasma of infertile individuals (39). Similar to our results, the increase in AOPP in cells and tissues in parallel with the increase in ROS, which is a product of OS, has also been proven by many previous studies (40,41). In addition to all these, antioxidants prevent OS in cells and tissues, preventing oxidation or overproduction of ROS. In recent years, many reports have shown that BPA-induced toxicity is prevented/reduced by using flavonoid compounds in various organs (42,43).

The GSH system is an enzymatic antioxidant that protects against damage caused by oxidants and is involved in the regulation of many important signaling pathways. Exposure to BPA causes a significant increase in intracellular ROS and a significant decrease in GSH levels (44). It has been reported that intraperitoneal administration of BPA to adult mice for five days resulted in a decrease in GSH due to the increase in hydroxyl radicals (45). In our study, the increase in the GSH level of the BPA+Q group was due to the neutralization of the ROS increase caused by BPA (46). It was also reported by Mahdavinia et al. (2019) that the administration of quercetin increased the level of GSH compared to the BPA group (15). It is hypothesized that the increase in GSH in the female reproductive system is effective in reducing OS either by interacting directly with ROS or by donating electrons (47).

## CONCLUSION

This study revealed the negative effect of BPA administration for 14 days on the reproductive system caused by oxidative stress in the ovarian tissues of female rats due to ROS production. In the study, it was determined that quercetin has a strong antioxidant activity and is effective in preventing histopathological damage caused by exposure to BPA. In addition, MDA and AOPP levels, which increased with BPA application, were decreased with quercetin application. It was

determined that quercetin had a significantly increased effect on the decrease caused by BPA in the antioxidant enzymes catalase and GSH. Consequently, findings indicate that the deleterious impacts of BPA on the female reproductive system, which persist despite advancements in industrial and technological practices, can be ameliorated through the utilization of quercetin, an inherent component of various dietary sources. However, more detailed and repetitive studies in the field of Pharmacology and Toxicology are needed to understand the mechanism of action of BPA exposure on the reproductive system and to elucidate the therapeutic activity of quercetin.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** Approval was granted by Van Yüzüncü Yıl University Animal Experiments Local Ethics Committee (Decision No: 2023/10-08).

**Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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