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Protective effects of panax ginseng against bisphenol a-induced testicular toxicity in rats

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Bisphenol A (BPA) is an endocrine-disrupting chemical known to cause testicular toxicity through oxidative stress and apoptosis. Panax ginseng (PG) is a natural product with anti-inflammatory effects. This study aimed to evaluate the protective effect of PG against BPA-induced testicular damage in rats. Thirty-two Wistar Albino rats aged 10–12 weeks were divided into four groups: Control, PG, BPA, and BPA + PG. BPA (50 mg/kg/day) and PG (100 mg/kg/day) were orally administered for 6 weeks. BPA significantly increased serum total oxidant status and decreased antioxidant status ($p < 0.001$, $p < 0.001$). Also, the levels of superoxide dismutase (an antioxidant enzyme) ($p = 0.0005$) and androgen receptor-mRNA (an androgen signaling marker) decreased ($p = 0.014$). However, caspase 3 (an apoptosis marker) ($p = 0.0067$), 8-hydroxy-2′-deoxyguanosine (a marker of oxidative DNA damage) ($p < 0.001$), and tumor necrosis factor-α (a proinflammatory cytokine) ($p < 0.001$) levels increased in testicular tissues. Rats treated with PG showed improvements in all oxidative and inflammatory markers and significantly restored androgen receptor expression. Histopathological examination revealed degeneration in seminiferous tubules and reduced spermatozoa in the BPA group, while the BPA + PG group showed marked improvement. These findings suggest that PG may alleviate oxidative stress-related testicular damage at both molecular and histological levels and may offer insights for future clinical studies.

IJIR: Your Sexual Medicine Journal; https://doi.org/10.1038/s41443-026-01277-w

INTRODUCTION

The growing prevalence of reproductive issues, such as lower sperm counts and infertility, has brought men's health into focus in recent years [1, 2]. Environmental factors are the main threats to impair male fertility and cause testicular damage [3]. One of the most encountered agents, Bisphenol A (BPA; 2,2-bis (4-hydroxyphenyl) propane), is an endocrine-disrupting chemical (EDC) [4, 5]. Exposure to BPA may occur via foods, beverages, inhalation, and dermal absorption routes [6]. BPA is used to produce polycarbonate plastics and epoxy resins, such as feeding bottles, food storage containers, toothpaste, and electronic devices that are widely used in daily life [7]. It has been shown to have devastating effects on metabolic functions, on solid organs, and on the reproductive system [8]. As an EDC, BPA can cause testicular toxicity by two main pathways: Estrogen/androgen receptors and oxidative stress. Studies have shown that BPA may bind to hormone receptors, potentially diminishing spermatogenesis and reducing semen quality [9]. Also, in previous experimental models, BPA is shown to generate oxidative stress and inflammation in the testicular tissues via increased ROS production, impaired antioxidant enzyme functions, down-regulation in antioxidant gene expression, and increased lipid peroxidation [10, 11]. The inflammatory process and estrogenic stimulation are closely interconnected, forming a feedforward loop that may amplify the effects of the other.

Ginseng has been used in traditional medicine for its pharmacological properties including metabolic, anti-stress, anti-inflammatory, immunomodulatory, and antiallergic effects [12]. Today, it is one of the most widely used natural products. There are two main types of ginseng: Panax ginseng C.A. Meyer (Asian or Korean) and Panax quinquefolius (American). Panax ginseng (PG) inhibits reactive oxygen species (ROS) formation by activating the Wnt/β-catenin signal pathway and enhancing antioxidant enzymes such as superoxide dismutase (SOD), catalase, glutathione peroxidase [13]. It is demonstrated to have ameliorative effects on testicular toxicity by reducing lipid peroxidation and activating the antioxidant system [14]. Moreover, it is known to enhance spermatogenesis, sperm count and vitality by supporting Leydig cell function and steroidogenesis [15].

In this experimental model based on previously validated BPA-induced testicular toxicity protocols, we aimed to demonstrate the protective role of PG via apoptotic, inflammatory, oxidative, and molecular markers, and histological analysis.

METHODS

Experimental animals

The procedures used and the care of animals were approved by the Institutional Animal Care and Use Committee (IACUC) in Marmara University (approval number: 31.2023mar). 32 male Wistar Albino rats

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Received: 30 July 2025 Revised: 19 March 2026 Accepted: 11 April 2026
Published online: 23 April 2026

(weighing 250–300 g, aged 10–12 weeks) were obtained. The number of animals was determined based on power considerations and reference to previous studies using the same model. The rats were kept at 21 °C and maintained in a 12-hour light/12-hour dark cycle. A maximum of 4 rats per cage was arranged. During the experimental period, the rats were provided food and water *ad libitum*.

Chemicals

The BPA dose and duration used in this study were selected based on previously established experimental models of BPA-induced testicular toxicity [11, 16, 17]. BPA (Sigma-Aldrich, Germany, Cat No:133027) was dissolved in %1 ethanol. PG dose was determined to be 100 mg/kg/day based on previous studies (25–200 mg/kg/day) [18–22]. PG (powder extract, standardized to NLT 30% ginsenosides, Casel İlaç Sanayi, Türkiye, Cat No: 3002147) was dissolved in water.

Experimental design

Thirty-two healthy male albino rats were randomly divided into 4 groups. Control group (C) ($n = 8$) received a standard diet. The PG group ($n = 8$) was administered PG (100 mg/kg/day, orally) for 6 weeks. The BPA group ($n = 8$) was given BPA (50 mg/kg/day, orally) for 6 weeks. The BPA + PG group ($n = 8$) was given BPA (50 mg/kg/day, orally) and PG (100 mg/kg/day, orally) for 6 weeks. At the end of the 6-week experimental period, the rats were decapitated after being anesthetized with ether. Serum samples were prepared from trunk blood. Testicular tissues were divided into 2 sets of tissues; 1 set for biochemical analysis which was kept at -80 °C and the other set of tissues was held in 10% formaldehyde solution for histopathological analysis. Biochemical and histological analyses were performed by investigators blinded to group allocation. In the present experimental study, ARRIVE guidelines (Animals in Research: Reporting In Vivo Experiments) have been followed.

Biochemical analysis

The serum total oxidant status (TOS) was determined spectrophotometrically by measuring serum ferrous ion exchangeability to ferric ion using a commercial kit (Rel Assay Diagnostics, Gaziantep, Türkiye, No: 0017). The serum total antioxidant status (TAS) was determined spectrophotometrically by measuring the ability of serum to resist free radical reactions using a commercial kit (Rel Assay Diagnostics, Gaziantep, Türkiye, No: 0024).

Commercial ELISA kits for rats were applied according to the manufacturer's protocol to analyze superoxide dismutase (SOD) (an antioxidant enzyme) ((Elabscience, the USA, Cat. No: E-BC-K022-M), tumor necrosis factor-alpha (TNF- α) (a proinflammatory cytokine) (Invitrogen, the USA, Cat. No: KRC3011), 8-hydroxy-2′-deoxyguanosine (8-OHdG) (a marker of oxidative DNA damage) (Elabscience, the USA, Cat. No: E-EL-0028), and caspase-3 (an apoptosis marker) (Elabscience, the USA, Cat. No: E-CK-A311).

Molecular analysis

Q-PCR measurements of androgen receptor gene expression (AR mRNA) were analyzed in three steps. Firstly, the commercial kit was used according to the manufacturer's instructions to isolate RNA (Intron, South Korea, Cat. No:17211). Secondly, cDNA synthesis was performed with reverse transcriptase enzyme from the RNAs isolated and used as a template. After that, Q-PCR was performed using SYBR Green PCR Master Mix (Applied Biosystems, the USA, No:4368708) with the following primers: AR Forward: CTGTGGCATGCCCC TAAAGA; AR Reverse: TCGCTCCTGCTGTCTAGTCT; GAPDH Forward: GCAAGGA TACTGAGAGCAAGAG; GAPDH Reverse: GGATGGAATTGTGAGGGAGAT. GAPDH was set as a reference gene and analyzed by 2-ΔΔCt method using StepOnePlus device (Applied Biosystems, the USA, Cat. No: 4376600). For the qPCR analyses, three independent RNA samples were used, and each experimental setup was performed in duplicate.

Histopathological analysis

Testicular tissues from all groups were fixed in 10% neutral buffered formalin for 72 h. They were dehydrated by passing through ascending alcohol series (70%, 90%, 96%, 100%), cleared in xylene, kept in paraffin in an oven at 60 °C for 4 h, and then blocked in cassettes. Approximately 4 µm-thick sections taken from the paraffin blocks were stained with Hematoxylin and Eosin for evaluation. Stained sections from each rat were evaluated under a light microscope (Olympus BX51, Japan) and photographed with a digital camera (Olympus DP72, Japan). In each section, 20 seminiferous tubules were evaluated with the modified histopathological Johnsen's score at 200x magnification [23, 24]. Histopathological evaluations were performed by experienced histologist blinded to the experimental groups. Each seminiferous tubule was scored from 10 to 1 as: 10: Complete spermatogenesis; 9: Many spermatozoa, slightly impaired spermatogenesis; 8: A few late spermatids, less than 5 spermatozoa/tubule; 7: Many early spermatids, absence of spermatozoa; 6: A few early spermatids, absence of spermatozoa; 5: Many spermatocytes, absence of spermatids and spermatozoa; 4: A few spermatocytes; 3: Only spermatogonia; 2: Only Sertoli cells, absence of spermatogonia; 1: Absence of germinal epithelium.

Statistical analyses

Statistical analysis was performed with Graphpad Prism 9.0 (Graphpad Software, San Diego, California, USA). Data are presented as mean ± SEM (Standard error of mean). ANOVA and post hoc Tukey test were used to compare data groups. $p < 0.05$ was considered significant. Johnsen's histopathological score was evaluated using the non-parametric Mann–Whitney test.

RESULTS

Effects of PG on inflammation, apoptosis and oxidative stress markers in BPA-induced testicular toxicity

In serum samples, a decrease in TAS ($p < 0.001$) and an increase in TOS ($p < 0.001$) were observed in the BPA group compared to the control group. Significant decrease in TOS and a rise in TAS were detected in the PG + BPA group ($p < 0.001$) (Table 1). In the PG + BPA group, TOS levels decreased by approximately half compared to the BPA group (24.64 ± 0.9443 µmol/L reduced to 16.37 ± 0.9328 µmol/L). In testicular tissues, a significant decline in the level of SOD ($p = 0.0005$) was observed in the BPA group compared to the control group (Fig. 1). On the other hand, caspase 3, 8-OHdG, and TNF-α levels increased ($p = 0.067$, $p < 0.001$, and $p < 0.001$, respectively) in testicular tissues of the BPA group (Fig. 2a, Fig. 2b, Fig. 3, respectively), (Table 1). Significant improvement was observed in the PG + BPA group. A higher SOD level ($p = 0.016$) and lower caspase 3, 8-OHdG, and TNF-α levels were noted ($p = 0.0132$, $p = 0.0018$, $p = 0.0002$, respectively), (Table 1).

Effects of PG on androgen receptor expression in BPA-induced testicular toxicity

As a molecular marker of androgen signaling, the AR mRNA level was lower in the BPA group compared to the control group ($p = 0.014$). Also, it was detected to be much higher in the PG + BPA group ($p = 0.0025$), (Fig. 4), (Table 1).

Effects of PG on testicular histology of BPA-induced testicular toxicity

In light microscopic examinations, a completely normal morphology was observed in the seminiferous tubules of the control and PG groups. In the seminiferous tubules, spermatogonia, primary spermatocytes, secondary spermatocytes, and spermatids were observed from basal membrane to lumen, respectively. In most of the seminiferous tubules lumen, spermatozoa were seen in the control group. Numerous degenerative seminiferous tubules were found in the BPA group. It was observed that the germinal epithelium's thickness forming the seminiferous tubules' wall became thinner and there were dilatations between the spermatogenic cells. There were fewer spermatozoa in the lumen of the seminiferous tubules. In the BPA + PG group, seminiferous tubule germinal epithelium thickness increased, dilatations between the germinal epithelial cells decreased and the number of spermatozoa in the lumen increased (Fig. 5). Histopathologic Johnsen's score of the seminiferous tubules decreased in the BPA group (score: 7.250 ± 0.12, $p = 0.0286$) compared to the control (score: 9.738 ± 0.09) and PG (score:9.663 ± 0.11) groups, and this score increased in the BPA + PG group (score: 8.775 ± 0.10; $p = 0.0286$)) compared to BPA group (Table 1).

Table 1. Comparison of the effects of BPA and PG administration on biochemical markers.

		C Mean ± SEM	PG Mean ± SEM	BPA Mean ± SEM	BPA + PG Mean ± SEM
Serum	**TOS (μmol/L)**	15.15 ± 1.035	15.57 ± 0.6698	24.64 ± 0.9443***($p < 0.001$)	16.37 ± 0.9328^{+++}($p < 0.001$)
	TAS (μmol/L)	1.91 ± 0.068	2.25 ± 0.061**($p = 0.0024$)	1.48 ± 0.035***($p < 0.001$)	2.12 ± 0.068^{+++}($p < 0.001$)
Testis	**SOD (U/g)**	4.873 ± 0.34	4.559 ± 0.29	2.890 ± 0.21 *** ($p = 0.0005$)	3.469 ± 0.35 * ($p = 0.016$)
	TNF-α (ng/g)	18.69 ± 0.68	16.88 ± 0.59	30.30 ± 2.38 *** ($p < 0.001$)	19.77 ± 1.72^{+++} ($p = 0.0002$)
	8-OHdG (ng/mg DNA)	1.923 ± 0.17	2.061 ± 0.22	3.459 ± 0.18 *** ($p < 0.001$)	2.381 ± 0.15^{++} ($p = 0.0018$)
	Caspase-3 (nmol pNA/min mg protein)	0.7771 ± 0.13	0.6586 ± 0.11	1.419 ± 0.16 ** ($p = 0.0067$)	0.8300 ± 0.13^{+} ($p = 0.0132$)
	AR mRNA(fold change)	1.017 ± 0.059	1.133 ± 0.099	0.6757 ± 0.068 *($p = 0.014$)	1.089 ± 0.059^{++}($p = 0.0025$)
	Johnsen's score	9.738 ± 0.09	9.663 ± 0.11	7.250 ± 0.12*($p = 0.0286$)	8.775 ± 0.10^{+}($p = 0.0286$)

C control group, *PG* panax ginseng control group, *BPA* BPA group, *BPA + PG* BPA + panax ginseng group, TOS total oxidant status, *TAS* total antioxidant status, *SOD* superoxide dismutase, *TNF- α* tumor necrosis factor alpha, *8-OHdG* 8-hydroxy-2'-deoxyguanosine, *AR mRNA* androgen receptor mRNA, *SEM* standard error of mean.

* : $p < 0.05$ Compared to the control group.

** : $p < 0.01$ Compared to the control group.

***: $p < 0.001$ Compared to the control group.

$^{+}$: $p < 0.05$ Compared to the BPA group.

$^{++}$: $p < 0.01$ Compared to the BPA group.

+ ++: $p < 0.001$ Compared to the BPA group.

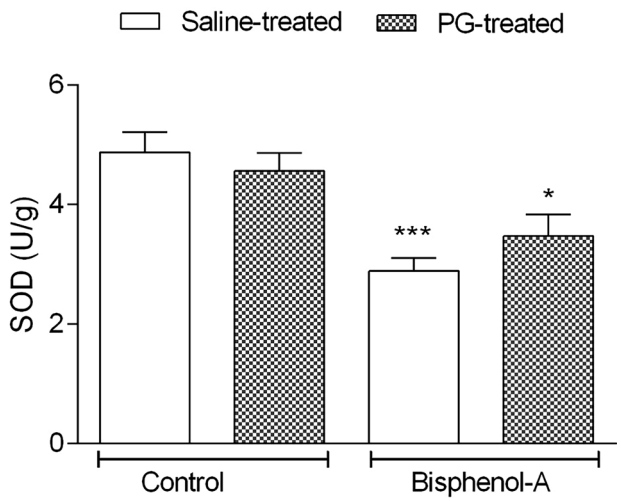

Fig. 1 Comparison of superoxide dismutase (SOD) levels in testicular tissue of rats exposed to bisphenol A (BPA) and treated with Panax ginseng (PG). $n = 8$ per group. **$p < 0.01$: Compared to the control group. + $p < 0.05$: Compared to PG group.

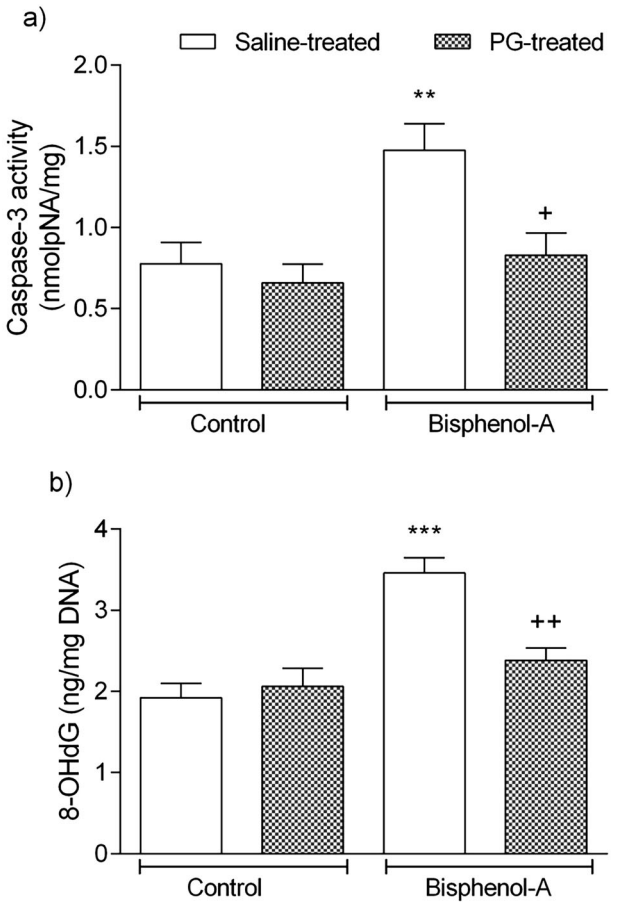

Fig. 2 Comparison of caspase 3 and 8-OHdG levels in testicular tissue of rats exposed to bisphenol A (BPA) and treated with Panax ginseng (PG). $n = 8$ per group. *$p < 0.05$: Compared to the control group. + $p < 0.05$: Compared to BPA group. ***$p < 0.001$: Compared to the control group. ++ $p < 0.01$: Compared to BPA group.

DISCUSSION

The increased toxic effects of chemicals on the reproductive system have gained great attention throughout the last decades. As an endocrine-disrupting chemical, BPA exposure has been a serious matter of research in recent years due to its widespread presence. Oxidative stress, the disruption in the balance of ROS and antioxidant enzymes (such as SOD, catalase, and glutathione reductase), has a key role in testicular toxicity. Some experimental studies have shown that BPA may cause testicular toxicity and reproductive disorders due to this aforementioned pathogenic pathway [17]. Also, due to its lipophilic nature, BPA may accumulate in the cell membrane and increase oxidative stress and inflammation [25]. Oxidative stress and apoptosis may lead to low sperm quality and histopathologic changes in testicular tissue. In the present study, increased oxidative stress was demonstrated in the BPA group via oxidative stress markers (via TOS, TAS, SOD, 8-OHdG). In addition, lower androgenic signaling (via AR mRNA),

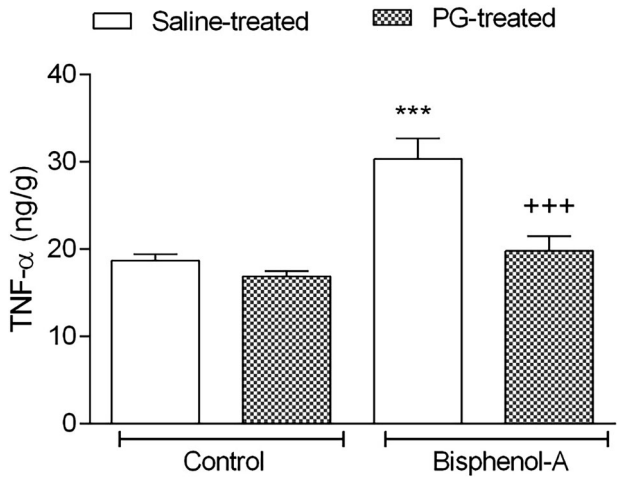

Fig. 3 Comparison of TNF-α levels in testicular tissue of rats exposed to bisphenol A (BPA) and treated with Panax ginseng (PG). $n = 8$ per group. ***$p < 0.001$: Compared to the control group. +++ $p < 0.001$: Compared to BPA group.

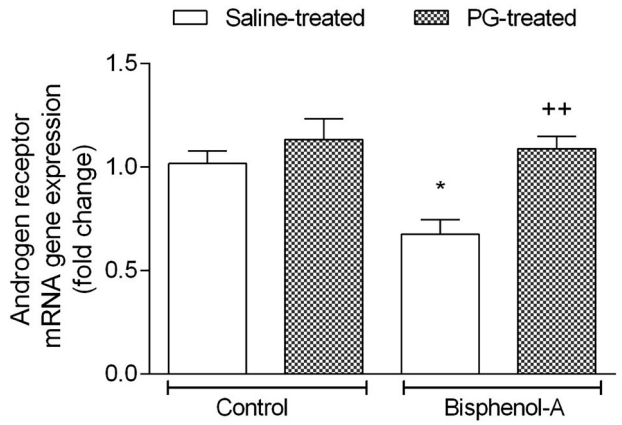

Fig. 4 Comparison of AR mRNA levels in testicular tissue of rats exposed to bisphenol A (BPA) and treated with Panax ginseng (PG). $n = 8$ per group. *$p < 0.05$: Compared to the control group. + $p < 0.05$: Compared to BPA group.

and higher apoptosis (via caspase-3) and inflammation (via TNF-α) were revealed in the same group. All markers showed alleviation with PG treatment in the BPA + PG group.

BPA is known to disrupt the seminiferous tubules and result in edema, necrosis, and germinal wall thinning in the interstitial tissue. The fact that frequently exposed chemicals cause testicular toxicity has led to the search for prevention. In this context, some antioxidant agents, such as hesperidin, zinc, and naringin, have been tested to reduce oxidative stress and prevent testicular toxicity [26–28]. Panax ginseng is one of the best-known antioxidant plants traditionally used in Asian countries. Besides its antitumor, immunomodulatory, and cognitive effects, it reduces oxidative stress and improves spermatogenesis. In the present study, we observed that germinal wall thickness and spermatozoa count were significantly reduced in the BPA group. The modified Johnsen's score was significantly lower. And treatment with PG led to marked histological improvements and a higher modified Johnsen's score.

TOS and TAS are crucial parameters used in the assessment of oxidative stress levels. Çibuk et al. observed a significant increase in TOS and a decrease in TAS after BPA (25–50 mg/kg/day) exposure [16]. In our study, BPA affected serum TOS and TAS

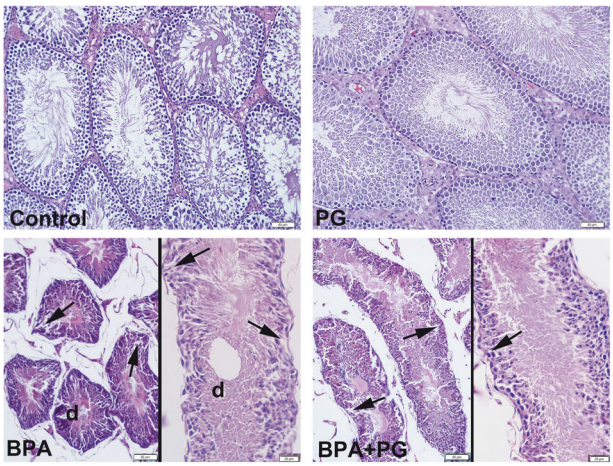

Fig. 5 Representative light micrographs of the experimental groups. Normal seminiferous tubule morphology is seen in the Control and PG groups. Numerous degenerative seminiferous tubules (**d**), thinning of the germinal epithelium lining the seminiferous tubules, and dilatations (arrow) between spermatogenic cells are seen in the BPA group. Increase of thickness of the seminiferous tubule germinal epithelium and decrease of the dilatations (arrow) between the germinal epithelial cells are seen in BPA + PG group. Hematoxylin and eosin staining. Original magnification: 200x, insets: 400x, Scale bar: 50 µm, insets: 50 µm.

levels in favor of oxidative stress with BPA at a dose of 50/mg/kg/day. In addition, Aslan et al. indicated that PG (200 mg/kg/day) may be beneficial in cisplatin-induced testicular damage with changes in TOS and TAS [19]. We demonstrated that half-dose PG may improve TOS and TAS levels against BPA exposure.

Acting as an antioxidant enzyme, SOD decreases in testicular tissue with BPA exposure. Both Xie et al. [29] and Morgan et al. [11] showed that different doses of BPA can reduce SOD levels in the testis (respectively,5–50 mg/kg/day and 25 mg/kg/day). In testicular damage with excess heat exposure, Liu et al. showed that PG may improve SOD levels [30]. Our findings similarly showed a decrease in SOD, and PG treatment reverses this decrease.

Experimental studies have demonstrated that BPA can cause alterations in DNA structure. 8-OHdG, a marker of DNA oxidation, tends to increase under conditions of oxidative stress [31]. Increased 8-OHdG indicates oxidative DNA damage, which may impair spermatogenesis. It has previously been shown that an increase in 8-OHdG may occur in oxidative damage caused by BPA (100 mg/kg/day) [17]. In a recent study, El-Shimi et al. presented that BPA caused an increase in serum 8-OHdG levels because of oxidative stress. In this study by El-Shimi et al, rats treated with PG had statistically lower serum 8-OHdG levels [18]. Furthermore, in our study, we have shown an increase in 8-OHdG with BPA exposure and a decrease with PG in testicular tissues.

TNF-α is a pro-inflammatory cytokine that plays an important role in inflammation and cell cycle, and regulates the inflammatory response [32]. Previous studies showed that agents causing testicular toxicity can induce an increase in TNF-α [33]. Elevated TNF-α reflects an inflammatory response that damages the seminiferous tubule morphology and accelerates germ cell loss. Tekin et al. found that BPA (100 mg/kg/day) increased TNF-α in oxidative testicular damage [26]. In our study, we showed that BPA caused an increase in TNF-α in testicular tissues, whereas PG could prevent testicular toxicity by decreasing TNF-α, an important proinflammatory cytokine.

Apoptosis is a natural and fundamental process by which cells undergo programmed death to maintain proper development and function. In seminiferous tubules, it routinely occurs in both spermatogenic and supportive cells. However, excessive apoptosis results in reduced sperm count and quality [34]. Caspases acting

as cysteine proteases have an important role in the regulation of apoptosis. Among them, caspase 3 is the most commonly used apoptosis marker due to its reliability and easy measurement. Li et al. showed that BPA (0–160–480–960 mg/kg/day) dose-dependently increased testicular toxicity and caspase 3 activity [35]. In our study, we observed that BPA exposure caused a significant increase in caspase 3 activity, while PG decreased it, suggesting that it may have a role in preventing oxidative tissue damage and apoptosis.

Androgens are the main hormones for the endocrinological functions of the testis. They exert their effects by binding to androgen receptors in many tissues, such as the skeletal and genitourinary systems. As a selective estrogen receptor modulator, BPA binds to estrogen receptors with lower affinity and mimics the function of 17-β estradiol [36]. Moreover, it may act as an antagonist to androgen receptors. Reduced AR expression contributes to germ cell loss and reduced fertility by disrupting spermatogenesis. Restoration of this expression with an antioxidant such as PG may indicate the recovery of fertility. Park et al. showed, by molecular docking, that BPA binds to androgen receptors, disrupts hormone signaling, and may affect the endocrine system [37]. Qiu et al. found that BPA dose-dependently decreased the expression level of ARs with qPCR [38]. Thus, BPA may cause spermatogenesis failure and fertility disorders. In an experimental study, Kopalli et al. demonstrated by Western Blot that PG increased androgen receptor proteins in doxorubicin-induced testicular damage [15]. We similarly found that AR mRNA expression may be improved with PG in BPA-induced testicular toxicity.

There are certain limitations in the present study, such as a small sample size and the absence of long-term follow-up. Also, hormonal evaluation and semen analysis, which could provide functional insight into reproductive outcomes, were not performed. Lack of dose-response analysis is another limitation, as it prevents the determination of the relationship between different BPA or PG doses and the magnitude of their effects. Additionally, investigations in other animal models or clinical studies focusing on male fertility and reproductive function would help to confirm translational relevance to humans.

This study demonstrated that BPA exposure induces significant testicular toxicity in rats, leading to oxidative stress, inflammation, apoptosis, and impaired spermatogenesis. The biochemical, molecular, and histological analyses confirmed the detrimental effects of BPA on testicular tissue and treatment with PG exhibited a protective role against BPA-induced testicular damage by mitigating oxidative stress, reducing inflammation and apoptosis, and improving androgen receptor expression. Histopathological evaluations further confirmed the beneficial effects of PG. These findings highlight PG's potential as a therapeutic agent for counteracting BPA-induced reproductive toxicity. Further studies are needed to explore the underlying molecular mechanisms and evaluate its clinical applicability in humans.

DATA AVAILABILITY

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

Conceptualization: DD, GS, KC. Data curation: DD, GS, SEP, BIA, YC, OC, FE. Formal analysis: DD, GS, TES, KC. Funding acquisition: DD, KC. Investigation: DD, GS, SEP, Methodology: DD, GS, TES, KC. Project administration: DD, KC. Resources: DD, KC. Software: GS. Supervision: GS, KC. Validation: DD, GS, TES, KC. Visualization: DD, GS, TES, KC. Writing – original draft: DD, TES. Writing – review and editing: GS, KC.

FUNDING

This experimental study was supported by the Marmara University Scientific Research Projects Committee (BAPKO-Project ID: TTU-2023-11076). Open access funding provided by the Scientific and Technological Research Council of Türkiye (TÜBİTAK).

ETHICS STATEMENT

This study was approved by the Institutional Animal Care and Use Committee (IACUC) of Marmara University, School of Medicine (Approval No: 31.2023mar). All animal experiments were conducted following the national guidelines and the relevant national laws on the protection of animals.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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