Toxicology Reports 5 (2018) 427–433

Contents lists available at ScienceDirect

Toxicology Reports

journal homepage: www.elsevier.com/locate/toxrep

Protective effects of *Asparagus officinalis* extract against Bisphenol A-induced toxicity in Wistar rats

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ARTICLE INFO

Keywords:
Asparagus Officinalis
Bisphenol A
Liver
Kidney
Rat

ABSTRACT

Asparagus officinalis is an herbal medicine with remarkable antioxidant, anti-inflammatory, and antihepatotoxic properties. The present study aimed to investigate whether Bisphenol A (BPA) could induce histopathological changes and oxidative stress in the liver and kidney tissues of male rats. In addition, we evaluated whether the co-administration of the *Asparagus officinalis* extract (AOE) could prevent the possible damages. In total, 40 adult male Wistar rats with the mean weight of 200 ± 20 grams were divided into five groups. Control subjects were placed in the first group, while group two was the vehicle (5 ml/kg bwt/day). Subjects in group three were administered with 400 mg/kg of AOE (bwt/day), group four received 10 mg/kg of BPA (bwt/day) dissolved in 5 ml/kg of olive oil, and group five received oral BPA and AOE daily for eight weeks. After the experiments, the blood, liver, and kidneys of the animals were collected and examined. Biochemical results showed a significant elevation in the levels of liver and kidney biomarkers in the BPA group ($P \leq 0.05$). Moreover, malondialdehyde was observed to increase, while thiol protein and total antioxidant capacity decreased. Histopathological results of the BPA group indicated dilated and congested central and portal veins and inflammatory areas in the liver. In addition, renal test results showed casts in the urinary tubules and acute tubular necrosis. According to the results, the co-administration of AOE and BPA could increase the total antioxidative capability, thereby improving the function and structure of the liver and kidney tissues. Therefore, AOE is a potential protective agent against oxidative stress, liver, and kidney damage.

1. Introduction

Environmental pollution increases the level of hazardous chemicals, which adversely affect humans and wildlife. Numerous chemicals have been associated with oxidative stress, and the subsequent pathogenesis leads to the production of unregulated free radicals and reactive oxygen species (ROS); these cytotoxic agents induce cell death [1].

Bisphenol A (BPA) is a potential endocrine-disrupting chemical, which is a frequent component found in plastic baby bottles, as well as food and beverage containers [2]. Humans are at an increasing risk of exposure to BPA since it can leach out of polymers and enter food and water sources [3]. BPA has been detected in the solid and liquid fractions of canned foods, with a higher concentration in the solid fractions compared to liquid fractions [4]. BPA has been reported to have widespread accumulation in human body [5]. Some researchers have found BPA even in human head hair [6]. Highest concentration (1–104 ng/g of tissue) of BPA has been recorded in the placenta and fetus [7]. Exposure to BPA during the embryonic/fetal period and infancy is associated with tissue oxidative stress and peroxidation, which leads to the underdevelopment of certain organs, such as the reproductive system [8,9].

BPA is a xenoestrogen, which imitates the action of natural estrogen and causes adverse health consequences. Apart from its estrogenic activity, BPA has been shown to dysregulate the cytokines and induce oxidative stress in the brain, liver, and kidneys [10]. BPA has renal excretion and builds up in the case of reduced glomerular filtration rate. Moreover, increased plasma levels of BPA have been reported in patients with chronic kidney disease [11].

According to the literature, natural compounds extracted from medicinal herbs have significant protective and preventive effects against pathological conditions. Plants such as *Terminalia muelleri* [12], *Trigonella foenum graecum* [13], and *Spirulina* [14] exert protective

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https://doi.org/10.1016/j.toxrep.2018.02.010
Received 24 October 2017; Received in revised form 25 February 2018; Accepted 27 February 2018
Available online 09 March 2018

effects on the kidneys and liver against the oxidative damage induced by environmental pollutants. *Asparagus officinalis* is used in salads, vegetable dishes, and soups, while it has numerous applications in the traditional herbal medicine of Europe and Asia [15].

Pharmacological studies have demonstrated the antifungal, antimutagenic, anti-inflammatory, and diuretic properties of *A. officinalis* [16]. Furthermore, the roots and sprouts of the plant are abundant sources of flavonoids, oligosaccharides, steroidal saponins, and amino acid derivatives [4]. Some findings have also confirmed the biological functions of *A. officinalis*, including the alleviation of alcohol hangover and protection of liver cells against toxic agents [17]. According to a research in this regard, *A. officinalis* could be used in the treatment of diabetic nephropathy [18].

The present study aimed to evaluate the possible protective effects of the *A. officinalis* extract against BPA-induced oxidative stress in the liver and kidneys of male Wistar rats. These organs have been widely exploited by researchers as models for toxicological assessment. This is the first study to investigate the association between BPA-induced toxicity and the possible protective effects of *A. officinalis* against BPA-induced liver and kidney damage.

2. Materials and methods

Preparation of *Asparagus officinalis* extract (AOE): For preparation of *Asparagus officinalis* extract, obtained from several different farms in the Dezful region of Iran. The young shoots and leaves were removed and air-dried at room temperature (25 °C) The dried samples (100 g) were then extracted with 1 L of boiling distilled water for 2 h at 100 °C and then the extracts were passed through a filter. The hot water extracts were then freeze-dried and stored at −20 °C until use, all the procedure were according to D. B. Park et al. [5]. HPLC was performed to detect and control the extract.

Animals and experimental design: Forty male Wistar rats (initially weighting 200 ± 20) were used in the present study. They were obtained from Dezful University of Medical Science Animal house (Dezful, Iran) and were used in an experimental completely randomized design. The study was approved by Dezful University Ethics Committee (IR.DUMS.RFC.1395.4), and all the experiments were performed in accordance with the guidelines for the safe working of animals. Rats were housed in controlled light and dark condition (12-hour light/dark cycle) and room temperature (25 ± 2 °C), during the study and were fed with commercial plated food with free access to water. They were acclimatized to the laboratory environment for 1 week prior to the experiments and then were divided into 5 groups (n = 8). All were treated daily and orally for 8 weeks. Group 1 control (normal saline); group 2 vehicle (olive oil, 5 ml/kg b.wt./day) [19]; group 3 (400 mg AOE/kg b.wt./day) [20]; group 4 (10 mg BPA/kg b.wt./day, dissolved in 5 ml/kg olive oil) [21]; group 5 (BPA + AOE with mentioned dose). Bisphenol A (CAS No. 80-05-7 purity of 97%) were purchased from Sigma-Aldrich Company, (USA, Saint Louis) and dissolved in olive oil (vehicle).

Collection of serum and tissue samples: After 24 h of the last administration, rats anaesthetized with sodium thiopental (30 mg/kg), weighed and were scarified. Blood samples were collected from the heart with the help of a 2-ml syringe without anticoagulant and centrifuged at 3000 rpm for 10 minutes, for serum separation and then stored at −20 °C for analysis. Liver and kidneys of each rat weighed and were kept in 10% formalin saline for the histopathological examination. The 5–6 μ sections were made using paraffin embedding techniques and stained by hematoxylin-eosin for the histomorphometric and histopathological examination. For the histomorphometric study photos were taken from sections using an Olympus optical microscope equipped with a Dino lit camera at a magnification of 4 ×, 10 × and 40 × at four random points and Dino lit software was used for extracting the data.

Liver and kidney function biomarkers in the serum: Liver function was investigated by measuring alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and total bilirubin. ALT and AST were determined depending on incubation of substrate with the enzyme to produce phenyl hydrazine which absorbs at 546 nm. The amount of phenyl hydrazine formed is directly proportional to the enzyme quantity[22]. ALP also was assayed, where phenyl phosphate is transformed into phenol and phosphate in the presence of the enzyme. The liberated phenol is measured at 520 nm in the presence of 4-aminophenazone and potassium ferricyanide[23]. Total bilirubin was measured depending on the reaction between bilirubin in the sample and the diazonium salt of sulphanilic acid to produce azo bilirubin which shows a maximum absorption at 533 nm in an acid medium [24]. Kidney function also was investigated by serum urea (BUN) and creatinine (Cr) levels were measured using the colorimetric method of Fawcett and Soctt [25] and Peters [26], respectively.

Determination of serum lipid peroxidation product, malondialdehyde (MDA), levels: The collected serum samples were also utilized for the estimation of biochemical markers such as lipid peroxidation study and measurement malondialdehyde (MDA) [27].

Estimation of antioxidant parameter: thiol protein (G-SH) concentration were determined in serum according to Beutler et al. [28]. Colored complex, which produced, measured by spectrophotometry in 450 nm wavelength. All of the above chemical material were purchased from Merck Company of Germany, Darmstadt.

Determination of serum total antioxidant capacity (TAC): The total antioxidant defense was measured by the ferric reducing ability of plasma (FRAP) assay [29,30].

Statistical analyses: All the analyses were performed using SPSS version 22. Group's variance were analyzed by one-way Analysis of Variation (ANOVA) and Fisher least significant difference test (LSD) was tested for significant differences between groups. $P \leq 0.05$ was considered statistically significant.

3. Results

Effects of BPA exposure alone and after AOE administration on body and relevant organs weight: The final body weights and organ weights, of male rats in control and treatment groups are given in Table 1. There were no significant differences ($P > 0.05$) in final body weight of BPA, BPA + AOE, AOE and Olive oil groups when compared with the control group. The statistical analysis showed a significant increase ($P \leq 0.05$) in liver and kidney weight, after consumption BPA, compare to the control group. Whiles There were no significant differences ($P > 0.05$) in mentioned organ weight, of BPA + AOE group compared with the control group.

Effects of BPA exposure alone and after AOE administration on serum biomarkers related to hepatic function: The activities of liver marker enzymes and the level of total bilirubin in the serum of control and treated rats are shown in Table 2. Exposure to BPA, ultimately damaged the liver, as indicated by significant increase ($P \leq 0.05$) in activities of AST, ALT, ALP and bilirubin. Whiles the results revealed significant changes ($P \leq 0.05$) in these biomarkers in BPA + AOE administered rats compare to BPA alone. These data shown improved liver functioning in this group. There were no significant differences in AOE

Table 1
Body weight (g) and relevant organs weights (g), of control and treated rats.

Parameter Groups	Body weight (g)	Liver (g)	kidney (g)
Group1 (control)	245 ± 1.5	7.46 ± 1.2^{b}	1.59 ± 3.4^{b}
Group2 (vehicle)	239 ± 1.5	7.24 ± 3.3^{b}	1.64 ± 1.3^{b}
Group3 (AOE)	235.3 ± 1.4	7.29 ± 4.2^{b}	1.58 ± 4.1^{b}
Group4 (BPA)	228 ± 2.7	9.35 ± 3.5^{a}	3.51 ± 2.3^{a}
Group5(BPA + AOE)	234 ± 1.5	7.88 ± 4.1^{b}	1.63 ± 3.7^{b}

Values are presented as mean ± S.E. (n = 8 animals/group). Letters a and b in each column indicate significant differences at $p \leq 0.05$.

Table 2
Effects of BPA exposure alone and after AOE administration, on liver function biomarker in the serum.

Parameter Groups	AST (UL^{-1})	ALT (UL^{-1})	ALP (UL^{-1})	Bilirubin ($mg\ dL^{-1}$)
Group1 (control)	141.8 ± 4.05[b]	71.4 ± 1.08[b]	413 ± 2.05[b]	0.28 ± 0.44[b]
Group2 (vehicle)	173.4 ± 2.72[b]	77 ± 1.69[b]	553 ± 1.92[b]	0.26 ± 0.54[b]
Group3 (AOE)	171.6 ± 4.15[b]	68.4 ± 1.27[b]	491 ± 1.4[b]	0.28 ± 0.44[b]
Group4 (BPA)	627.4 ± 1.1[a]	151.6 ± 4.76[a]	1239 ± 4.46[a]	0.72 ± 1.3[a]
Group5(BPA + AOE)	171.8 ± 3.94[b]	87.1 ± 4.65[b]	680 ± 3.82[b]	0.3 ± 0.7[b]

Values are presented as mean ± S.E. (n = 8 animals/group). Letters a and b in each column indicate significant differences at $p \leq 0.05$.

Table 3
Effects of BPA exposure alone and after AOE administration on serum urea and creatinine levels of control and treated rats.

Parameter Groups	Urea ($mg\ dL^{-1}$)	Creatinine ($mg\ dL^{-1}$)
Group1 (control)	22 ± 1.7[b]	0.74 ± 0.54[b]
Group2 (vehicle)	25.8 ± 3.27[b]	0.8 ± 0.7[b]
Group3 (AOE)	23.8 ± 0.83[b]	0.76 ± 0.5[b]
Group4 (BPA)	47.2 ± 4.79[a]	2.76 ± 1.1[a]
Group5(BPA + AOE)	27 ± 3.8[b]	0.76 ± 0.54[b]

Values are presented as mean ± S.E. (n = 8 animals/group). Letters a and b in each column indicate significant differences at $p \leq 0.05$.

alone treated rats, as compare to the control ($P > 0.05$).

Effects of BPA exposure alone and after AOE administration on serum biomarkers related to kidney function: In Table 3, Urea and creatinine levels exhibited a significant increase ($P \leq 0.05$) in BPA group compared to control group. Supplementation with AOE, significantly ($P \leq 0.05$) normalized these marker levels in the BPA treated rats.

Effects of BPA exposure alone and after AOE administration on serum biomarkers related to antioxidative status: As shown in Table 4, serum MDA levels were significantly higher ($P \leq 0.05$) in BPA group when compared to control group. Also there was significant decrease ($P \leq 0.05$) in TAC and G-SH in the BPA treated rats. Administration of AOE to BPA treated rats resulted in a significant decrease ($P \leq 0.05$) in the level of MDA compare to the BPA group. AOE also increased ($P \leq 0.05$) the level of G-SH and TAC in BPA + AOE group, compare to BPA alone. It is worth to mention that AOE supplementation alone, has a non-significant ($P > 0.05$) effect on the serum antioxidative status of rats compare to the control group.

3.1. Effects on histopathological changes of investigated organs

BPA administration alone, induced histopathological changes in the liver and kidneys of exposed rats. However, AOE exposure ameliorated these alterations by variable grades. (Figs. 1 and 2)

3.1.1. 1- Effects on the liver

Histopathological examination and comparison with the control (Fig. 1(a)), revealed that BPA administration induced necrotic changes of hepatocytes (Fig. 1(b)), dilated and congested central veins (Fig. 1(c)), dilated sinusoids with increased proliferation of kupffer cells (Fig. 1(d)), lymphocytic infiltration and mild inflammatory areas (Fig. 1(e)). In BPA + AOE group markedly reduced in the hepatocellular changes was shown as compared with those in the BPA group, and the morphology was not dissimilar to that of the AOE group (Fig. 1(f)). The liver morphology of the AOE group was comparable with that of the control group.

Table 4
Effects of BPA exposure alone and after AOE administration, on MDA, G-SH and AOA in the serum.

Parameter Groups	MDA ($nmol\ ml^{-1}$)	G-SH ($\mu mol\ ml^{-1}$)	TAC
Group1 (control)	501 ± 6.4[b]	45.4 ± 6[a]	538 ± 3.12[a]
Group2 (vehicle)	498 ± 3.3[b]	48.2 ± 3.6[a]	521 ± 1.28[a]
Group3 (AOE)	487 ± 5.4[b]	46.5 ± 1.4[a]	539 ± 2.4[a]
Group4 (BPA)	687 ± 3.1[a]	28.6 ± 4.3[b]	472 ± 3.2[b]
Group5(BPA + AOE)	513 ± 1.4[b]	40.3 ± 5.6[a]	505 ± 4.6[a]

Values are presented as mean ± S.E. (n = 8 animals/group). Letters a and b in each column indicate significant differences at $p \leq 0.05$.

3.1.2. 1- Effects on the kidney

In microscopic examination, three sections from each rat in every group, and four fields from each sections were randomly examined, the cases investigated as the indicator of kidney tissue damage include: Presence of cast in urinary tubules, acute tubular necrosis (ATN), cell swelling, the mean of the ratio of outer diameter to the inner diameter of the proximal urinary tubules and glomerular congestion. The recorded renal histopathological alterations induced by BPA alone and ameliorating effect of AOE treatment are shown in Fig. 2. Kidney of normal saline and olive oil treated rats, showed normal renal glomeruli and tubules with slight cell swelling (Fig. 2(a)). Kidney of AOE-treated rats showed more or less normal renal glomeruli and tubules with slight cell swelling. The kidney sections of BPA-exposed rats showed glomerular congestion (Fig. 2(b)), swelling in proximal convoluted tubules and the greatest amount of cast which increased considerably compared to the control group (Fig. 2(c)) and acute tubular necrosis that determined in sections with damaged epithelial cells in this group (Fig. 2(d)). Administration of AOE to BPA treated rats resulted in ameliorated most of the observed changes in renal morphology. This was represented by slight glomerular congestion, cell swelling with more or less normal renal tubules and acute tubular necrosis level did not differ much from the control group (Fig. 2(e))

4. Discussion

According to the previous studies in this regard, some chemical compounds, such as carbon tetrachloride and deltamethrin, could induce hepatotoxicity and nephrotoxicity [31]. Additionally, researchers have proposed that some plants, such as *Bauhinia hookeri* [32] and *Cupressus macrocarpa* [33], exert protective effects against oxidative stress through enhancing the antioxidant defense status, reducing lipid peroxidation, and protection against the pathological changes in the liver and kidney tissues.

BPA is a chemical compound that infiltrates the environment as a result of continuous distribution. The current research aimed to evaluate whether BPA exposure could induce liver and kidney damages and investigate the potential benefits of AOE in the protection against BPA-induced damages in these organs. According to the findings, oral exposure of adult male rats to BPA was associated with no significant difference in the body weight of the test animals compared to the control group, which is consistent with the results obtained by Bindhumol et al. [34].

On the other hand, Yamasaki et al. [35] reported a statistically significant reduction in the body weight of the rats administered with BPA ($\geq 466\ mg\ kg^{-1}\ day^{-1}$). Interestingly, the results of the mentioned research disclosed a significant increase in the weight of the liver and

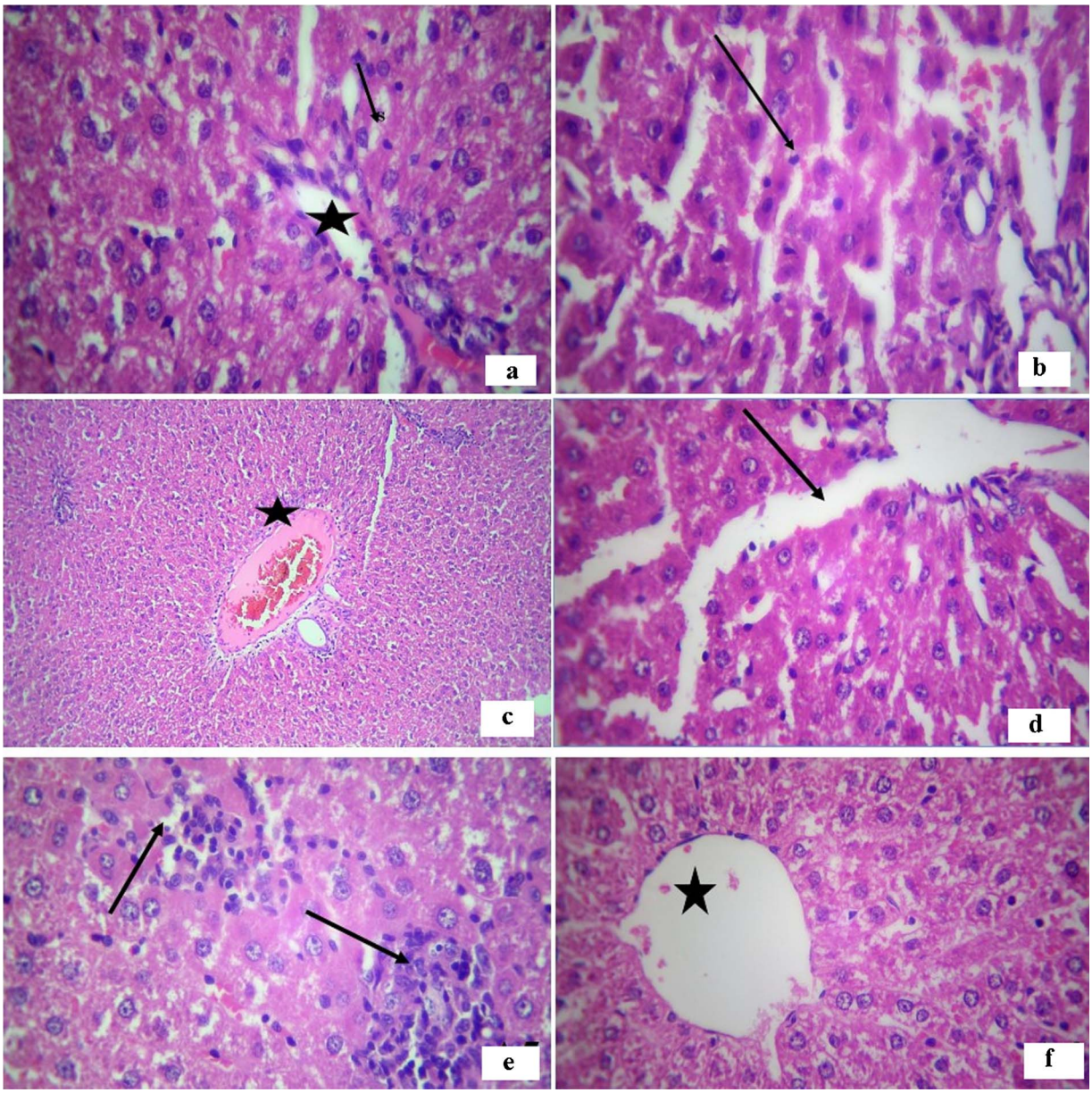

Fig. 1. Light photomicrographs of the liver: (a) Control group: Shows a central vein (star) with hepatocyte arranged in cords. Cords of hepatocytes enclose blood sinusoids (arrow); (H&E, X400). (b) BPA treated group: Some hepatocytes show dark nuclei and dense acidophilic cytoplasm (arrow); (H&E, X400). (c) BPA treated group: Dilated and congested central veins (star): (H&E, X100). (d) BPA treated group: Dilated sinusoids with increased proliferation of kupffer cells (arrow); (H&E, X400). (e) BPA treated group: shows lymphocytic infiltration and mild inflammatory areas (arrows); (H&E, X400). (f) BPA + AOE group: Shows normal central vain (star) without any congestion and ameliorated cords of hepatocytes enclose blood sinusoids (arrow); (H&E, X400).

kidneys. According to the study by Schulte-Hermann, since liver is the primary site for the elimination of xenobiotics, increased weight in the mentioned study may represent a homeostatic mechanism to deliver more BPA into the liver for detoxification [36], or it could be due to the combination of hepatocyte hypertrophy and smooth endoplasmic reticulum proliferation, which is presumed to stimulate a hepatic physiological adjustment proportionate to the increased workload request [9]. In addition, since BPA is a xenoestrogen and the kidneys have several receptors for estrogen, BPA could stimulate the receptors, thereby leading to epithelial cell proliferation. On the other hand, BPA might increase the volume of proximal and distal tubule and cause hydronephrosis.

According to the findings of the current research, BPA adversely affects the liver as indicated by the increased activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total serum bilirubin. High levels of these indicators are associated with the increased membrane integrity of the hepatocyte extinct and cellular leakage [37], suggesting that BPA may have devastating effects on the plasma membrane.

Increased levels of ALT, ALP, and AST have also been mentioned in the previous studies in this regard, which is in line with the results of the current research [38]. Accordingly, BPA could induce hepatic damage and mitochondrial dysfunction through increasing oxidative stress in the liver. Moreover, the increased activity of the liver biomarkers in the BPA group confirmed the histopathological findings, such as hepatocyte swelling and nuclear degeneration, sinusoidal dilatation and congestion of the blood, and increased number of the Kupffer cells. These findings are in congruence with the results of the previous studies in this regard [39].

According to our findings, AOE treatment significantly reduced the BPA-induced increase in the mentioned liver indices. Serum reduction of hepatic enzyme leakage by the AOE could be attributed to the

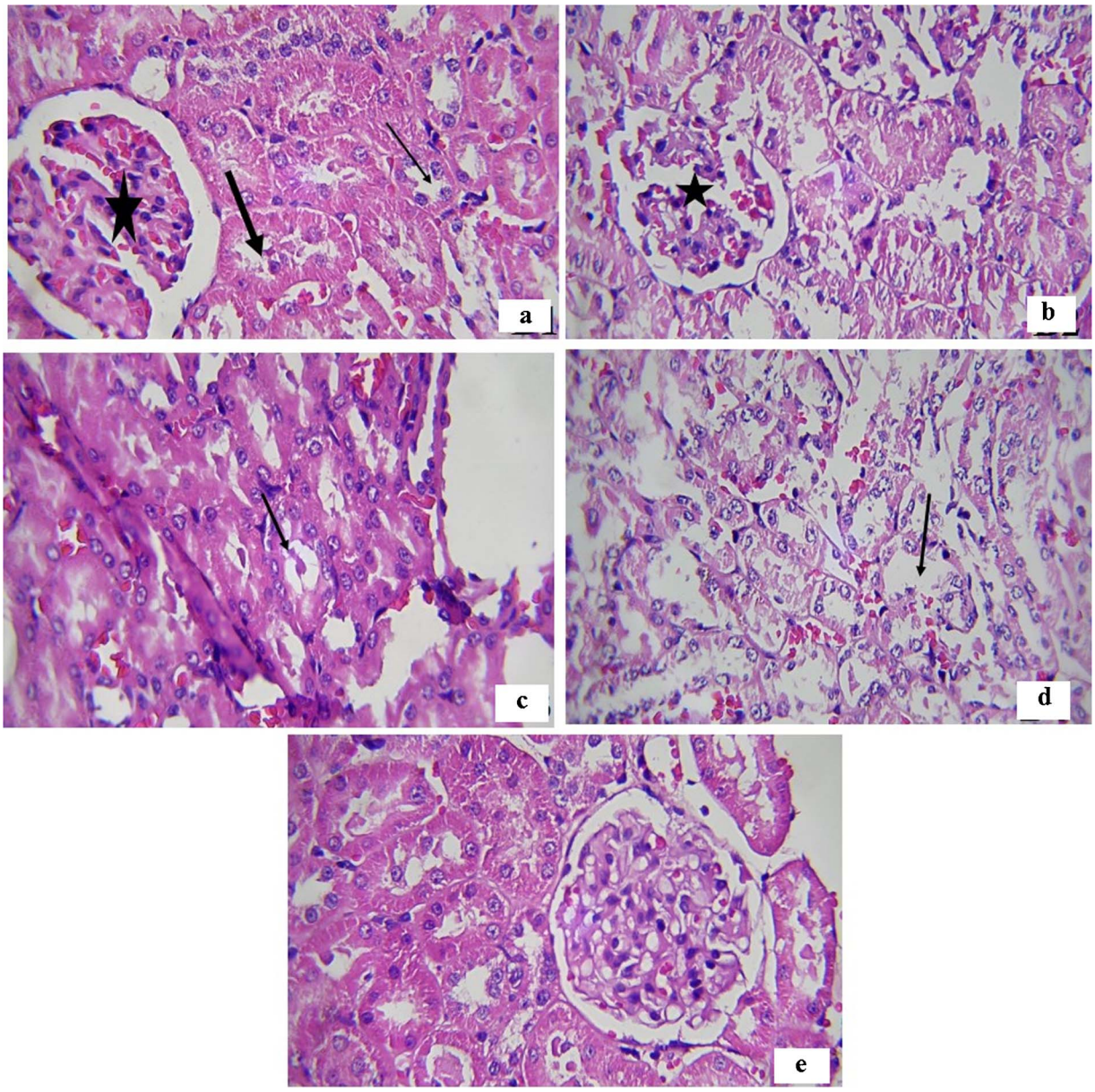

Fig. 2. Light photomicrographs of the kidney: (a) Control group: normal renal glomeruli (star) and proximal convoluted tubules (Thick arrow), distal tubules (Thin arrow); (H&E, X400). (b) BPA treated group: glomerular destruction and congestion (star); (H&E, X400). (c) BPA treated group: showing hyaline casts (arrow), in some tubules (H&E, X400). (d) BPA treated group: some tubules with damaged epithelial cells (arrow); (H&E, X400). (e) BPA + AOE group: Shows normal renal glomeruli and tubules, without any congestion or damaged cells (H&E, X400).

protection of the liver against the damages induced by BPA, such as the recovery of the hepatic tissue lesions caused by BPA. This is consistent with the results of the study of Daniela et al. that they indicating the hepatoprotective effects of AOE [40] and histopathological findings confirming the marked amelioration of hepatic tissues with the co-administration of AOE.

According to the present study, BPA may adversely affect the kidneys due to the increased serum levels of blood urea nitrogen (BUN) and creatinine (Cr). Elevated levels of these biomarkers in the current research due to BPA administration were also confirmed by the renal histopathological alterations, including the presence of casts in the urinary tubules, acute tubular necrosis, and glomerular congestion. These changes and elevated BUN and Cr levels could be due to the damage and destruction of the podocyte foot process.As a result, their contact with the glomerular base membrane reduced, followed by the degradation of filtration [41].

In a research in this regard, Walaa et al. claimed that BPA induced severe impairment in the metabolism of the proteins and mucopolysaccharides, leading to the increased levels of BUN and Cr; this finding could properly justify the mentioned results. In terms of renal histopathological changes, the mentioned research proposed similar data to the present study [24]. Consistent with our findings, Korkmaz et al. observed BPA-induced oxidative stress in the renal tissues of male rats, reporting that the co-administration of vitamin C and an antioxidant agent could effectively prevent feasible oxidative stress.

According to the results of the current research, co-administration of AOE and BPA improved the histopathological alterations in the kidneys and biochemical markers [25]. Furthermore, a parallel study [5] demonstrated that the improvement could also be due to the reduced lipid peroxidation and increased antioxidant capacity. The antioxidant properties of AOE may be attributed to the presence of flavonoids and polyphenols [42]. In this regard, Dartsch concluded that AOE could be used to support the aquaretic kidney function and enhance renal infiltration [43].

Findings of the present study revealed the associations of oxidative stress, antioxidant capability, and tissue damage. Accordingly, serum malondialdehyde (MDA) significantly increased in the BPA group, while serum thiol protein (G-SH) and total antioxidant capacity (TAC) decreased; this is in line with the previous studies in this regard [9,44]. Increased MDA level might denote cellular damage, endothelial lesion, and cell membrane damage [45], which could justify the pathological lesions in the BPA group in the present study.

G-SH is a critical reactive oxygen species (ROS) scavenger, which was observed to decrease in the BPA group, as denoted by the increased utilization of G-SH in the scavenging of the BPA-generated ROS [9]. TAC plays a pivotal role in the protection of cells against free radical-mediated oxidative damage [46]. In the current research, the level of TAC was higher in the group co-administered with BPA and AOE compared to the BPA group, which confers increased resistance to oxidative stress [39]. Evidently, these antioxidant capacity markers are restored in the combination of BPA and AOE. Furthermore, the mentioned tissue damages were attenuated by AOE administration, suggesting that AOE could act as a free radical scavenger. This finding is similar to the investigations conducted by Dartsch [27].

5. Conclusion

According to the results, AOE exerts protective effects against BPA-induced liver and kidney damages, as well as the BPA toxicity induced by oxidative stress in male rats. The tissue-protective effects of AOE could probably be accomplished via preventing G-SH depletion, inhibiting lipid peroxidation, and enhancing antioxidative capacity. Therefore, the potency and efficiency of AOE render it a potential candidate for protecting tissues (e.g., liver and kidneys) against various toxicants, including BPA. It is recommended that further investigations in this regard focus on the molecular mechanisms of the protective effects of AOE against toxicants.

Conflict of interest

None of the authors have any conflict of interests to disclose.

Author's Contribution

Poormoosavi & Najafzadeh: For conception and design.

Behmanesh: For acquisition of data, analysis and interpretation of data.

Amirgholami: Materials.

Acknowledgments

The authors would like to acknowledge Dezful University for financially supported.

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