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Original Research Article

Hesperidin Protects Against Bisphenol-A-Induced Renal Damage in Adult Male Wistar Rats

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ABSTRACT

Bisphenol-A (BPA), a common environmental contaminant, is linked to kidney toxicity through mechanisms involving inflammation and oxidative stress. Hesperidin, a bioactive compound found in citrus fruits, exhibits antioxidant and anti-inflammatory properties. This study investigated the protective role of hesperidin against BPA-induced renal damage. Thirty (30) male Wistar rats were randomly divided into six groups (n=5). Group A served as the normal control. Group B received 50 mg/kgBPA orally for 14 days. Groups C, D, and E were pre-treated with hesperidin at 50 mg/kg, 100 mg/kg, and 200 mg/kg, respectively, for 14 days, followed by BPA for another 14 days. Group F received 200 mg/kghesperidin alone for 28 days. After the treatment period, kidney and blood samples were collected for biochemical and histological assessments. Data analysis was performed using one-way ANOVA with Tukey's post hoc test ($p < 0.05$). BPA administration significantly increased ($p < 0.05$) pro-inflammatory markers (IL-6, TNF-α), malondialdehyde (MDA), and serum levels of creatinine, urea, and uric acid, while antioxidant enzymes (SOD, Catalase, GPx) were reduced. Histological analysis revealed structural kidney damage in the BPA group. Hesperidin treatment significantly reversed these effects, showing reductions in inflammation and oxidative stress, along with improved kidney histology and function. These results suggest that hesperidin provides protective effects against BPA-induced renal toxicity by mitigating oxidative stress and inflammation and preserving kidney function.

Keywords: Hesperidin, Bisphenol A (BPA), Oxidative stress markers, Kidney Toxicity, Inflammation.

Introduction

Bisphenol A (BPA) is an industrial chemical that is primarily used in the production of epoxy resins and polycarbonate plastics, which are widely employed in the production of thermal paper receipts, food and drink containers, and other products. [1,2,3] As a Food Contact Material (FCM), BPA is used in the manufacturing of plastics for products that come into direct contact with food, such as kitchenware, plastic packaging, jar cap coatings, and can walls that separate food from metal to stop corrosion. [1,4,5] Owing to its classification as an endocrine-disrupting chemical (EDC), BPA can interfere with hormone regulation and have a variety of detrimental consequences on the neurological, reproductive, and immunological systems.[6,3] By interacting with several biological receptors, such as the thyroid hormone receptor (THR), androgen receptor (AR), and estrogen receptor (ER), BPA has been shown to have endocrine-disrupting effects on humans.[4,7]

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As a result, these disruptive effects lead to health risks for the immune system, metabolic system, reproductive system, brain system, and developmental process. [7.] Human exposure to bisphenol commonly occurs through food packaging materials such as coated tin cans, plastic takeout containers, and water bottles. BPA is a white powder or colourless crystals and can leach into food and beverages, especially when plastic containers are heated or exposed to acidic or alkaline conditions. [8,9] Heating food in packaging or infant bottles significantly increases the rate at which BPA leaches into food, potentially rendering polycarbonate plastics hazardous. In addition to ingestion, individuals may also be exposed to BPA through dermal contact and inhalation. Environmental exposure can occur via contaminated soil, water, and air due to BPA's widespread use in thermal paper recycling and various industrial processes. [8,9]

Previous studies have linked BPA exposure to adverse effects on multiple organ systems, including the reproductive, neurological, and urinary systems. Both experimental and epidemiological evidence indicate that high levels of BPA exposure are associated with a wide range of disorders, including neurological, metabolic, cardiovascular, pulmonary, renal, developmental, and reproductive conditions[10,11,12,13] Notably, it has been demonstrated that BPA induces kidney damage by promoting oxidative stress, inflammation, and apoptosis in renal tissues, ultimately leading to structural and functional impairment of the kidneys.[3,14] The tendency of BPA to trigger the creation of ROS (reactive oxygen species) renders kidney cells increasingly vulnerable to oxidative cell damage. ROS can directly harm DNA, proteins, and lipids in cells, which can cause inflammation and apoptosis. [14,15,16.] It is imperative to investigate therapeutic approaches to mitigate the detrimental impacts of toxins like BPA on kidney health, particularly in

light of the global increase in kidney-related illnesses.
Hesperidin, a bioactive flavonoid predominantly found in citrus fruits such as oranges and lemons. It has been extensively documented for its antioxidant, anti-inflammatory, antihypertensive, antimicrobial, and hypolipidemic properties. [17,18,19,20]. As a potent scavenger of ROS, *hesperidin* has shown promise in protecting cells from oxidative damage. Additionally, it has been documented to affect inflammatory pathways, including the nuclear factor-kappa B (NF-κB) pathway, which is vital for immunological responses and inflammation. Owing to these properties, *hesperidin* could be able to protect kidney cells from the inflammatory and oxidative damage caused by BPA exposure. However, while *hesperidin* has significant therapeutic potential, more study is required to completely comprehend its mechanisms of action and practical use in averting kidney damage induced by BPA. This study seeks to uncover the protective potential of *hesperidin* in mitigating kidney damage triggered by BPA exposure, with a specific emphasis on its anti-oxidative and anti-inflammatory roles.
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Materials and Methods

Reagents and chemicals
Bisphenol A (CAS No. 80-05-7) and *Hesperidin* (CAS No. 520-26-3) (purity > 98%) were procured from Sigma Aldrich (St. Louis, MO, USA). All other reagents used for this study were of analytical grade.

Experimental Animals
Thirty (30) adult male Wistar rats (200-220g) were procured for this research. The animals were housed and acclimated to optimal light and temperature conditions for 14 days before the start of the administration period. The rats were housed in a temperature-controlled space with a 12-hour light/dark cycle at the Department of Anatomy at the University of Nigeria with unlimited access to routine animal feed and water. The procedure of this research work adhered strictly to compliance with the Institutional Animal Ethics Committee's (IAEC) recommendations and the National Institutes of Health's (NIH) standards.

Animal Grouping and Design of the experiment
We randomly divided the experimental rats into six groups of five rats each after two weeks of acclimatization and administration protocol as shown in Table 1. All treatments were administered by oral gavage. BPA was dissolved in olive oil, while *hesperidin* was suspended in normal saline.

Sample Collection
Following the final administration, the animals were fasted overnight, mildly anesthetized using ether, and sacrificed via cervical dislocation. Blood samples were collected from each group through cardiac puncture, allowed to clot at room temperature, and subsequently centrifuged for 10 minutes to obtain serum. The kidneys were excised, rinsed with ice-cold saline, and divided into portions for biochemical and histological analyses. For biochemical analysis, one portion was stored in a plastic container at −20°C. The second portion was fixed in 10% neutral buffered formalin for histopathological evaluations.

Biochemical Analysis
Serum Kidney Function Markers
The levels of creatinine, urea, and uric acid were measured in blood serum using commercially available kits, following specific instructions and guidelines from manufacturers and by previously documented methods. [21, 22, 39]

Oxidative Stress and Antioxidant Markers
Kidney tissue homogenates were prepared in ice-cold phosphate buffer (0.1 M, ph 7.4) using a tissue homogeniser. According to previously documented procedures. [21, 23,24] The following antioxidant enzymes and oxidative stress markers were evaluated: the level of Malondialdehyde (MDA) was measured as an index of lipid peroxidation using the thiobarbituric acid reactive substances (TBARS) method. The inhibition of pyrogallol auto-oxidation was assessed spectrophotometrically to quantify Superoxide Dismutase (SOD) activity. GSH and catalase (CAT) activity were measured by a documented protocol. [25]

Inflammatory Markers
We assessed the level of pro-inflammatory cytokines Interleukin-6 (IL-6) and Tumour Necrosis factor-alpha (TNF-α) using enzyme-linked immunosorbent assay (ELISA) kits in adherence to the manufacturer's instructions. The values were recorded in ng/ml and pg/ml, respectively.[41]

Table 1: Showing study Design and Treatment

Groups	Treatment	Dosage/Duration
A(Normal control)	Normal Saline	0.5ml/28 days
B	50 mg/kgBPA only	50 mg/kgBPA only for 14 days
C	50 mg/kgHSD +50 mg/kgBPA	50 mg/kgHSD for 14 days 50 mg/kgBPA for 14 days
D	100 mg/kgHSD +50 mg/kgBPA	100 mg/kgHSD for 14 days 50 mg/kgBPA for 14 days
E	200 mg/kgHSD+50 mg/kgBPA	200 mg/kgHSD for 14 days 50 mg/kgBPA for 14 days
F	200 mg/kgHSD only	200 mg/kgHSD only for 14 days

*n=5, HSD-*Hesperidin*, BPA-Bisphenol-A

Histological Examination and Photomicrography
To maintain structural integrity, we used 10% neutral buffered formalin to preserve the kidney samples. We dehydrated the samples using a graded series of alcohol, embedded them in paraffin and sectioned them into 5 µm slices using a microtome. Haematoxylin and Eosin were used to stain the section to enhance visualisation of cellular and structural details.[23] Histological analysis was performed using a light microscope (magnification X40) to identify structural changes, and photomicrographs were captured with a Leica ICC50 camera for detailed documentation.

Statistical Analysis
We used GraphPad Prism (version 9.0) to analyse and visualise the data from this study, and the results were presented as mean ± standard error of the mean (SEM). The comparison between groups was done with a one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test. $p < 0.05$ was considered statistically significant.

Results and Discussion

Effects of *hesperidin* on antioxidant enzymes and oxidative stress marker levels
In Figure 1a-1d. The results showed a significant decreased ($p<0.05$) in SOD, CAT, and GPx and a significant increase ($p<0.05$) in MDA levels in group B when compared to the control group.

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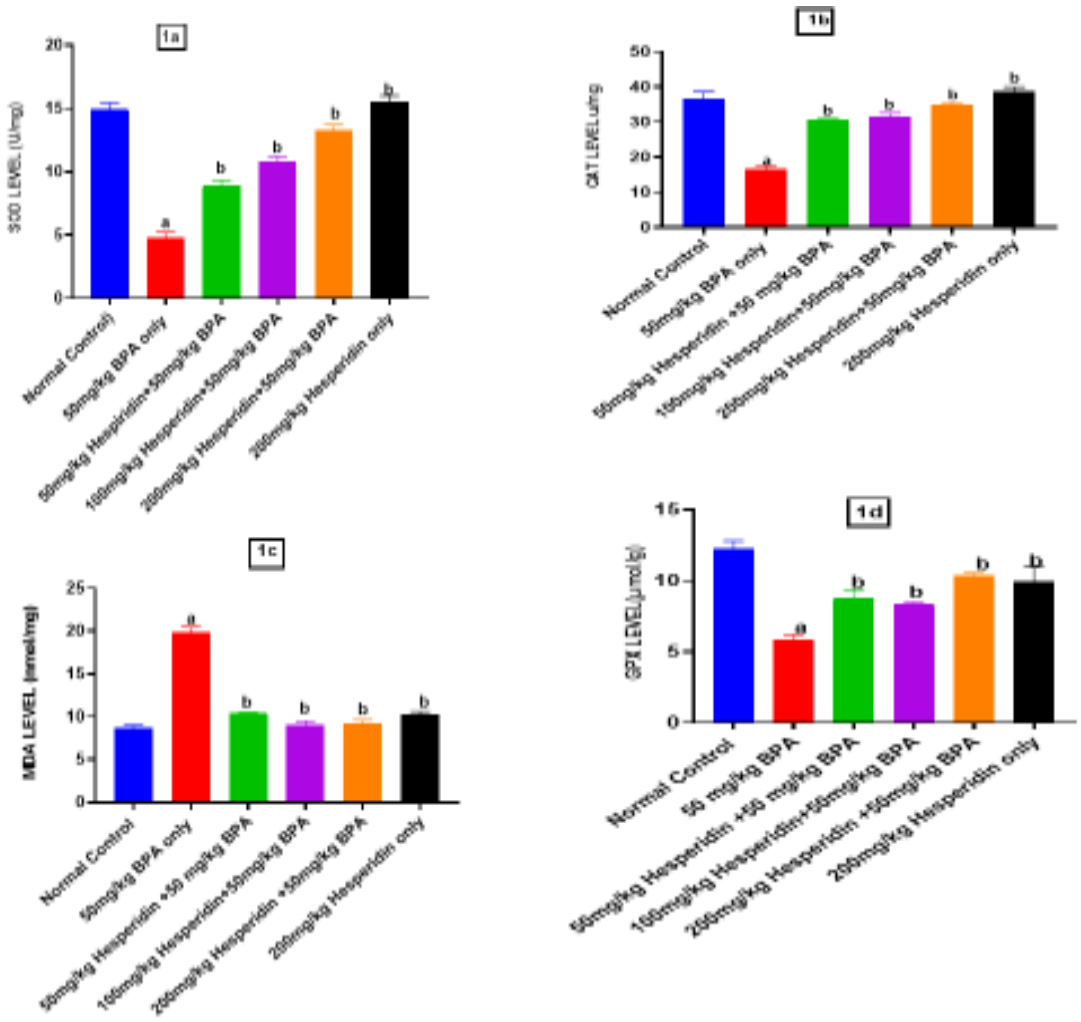

Figure 1a–d: Effects of *hesperidin* on antioxidant enzymes and oxidative stress marker levels. **(1a)** Effect of hesperidin on superoxide dismutase (SOD) activity. **(1b)** Effect of hesperidin on catalase (CAT) activity. **(1c)** Effect of hesperidin on malondialdehyde (MDA) levels. **(1d)** Effect of hesperidin on glutathione peroxidase (GPx) activity. Values are expressed as mean ± standard error of the mean (SEM). [a] indicates statistically significant difference compared to the normal control group ($p < 0.05$).[b] Indicates statistically significant difference compared to the 50 mg/kgBPA-only group ($p < 0.05$).

Exposure to BPA caused a major disruption in renal oxidative balance, as evidenced by increased levels of malondialdehyde (MDA), a crucial marker of lipid peroxidation, and a marked decrease in the activity of vital antioxidant enzymes like superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). These alterations suggest that BPA induces oxidative stress in kidney tissues, potentially contributing to renal dysfunction and structural damage. The kidneys are particularly vulnerable to oxidative stress because of their high metabolic activity, extensive vasculature, and role in toxin filtration, which exposes them to reactive oxygen species (ROS). Oxidative stress-related mediators and oxidative stress itself are responsible for many of the adverse effects of kidney damage.[26] This indicates that rats administered with BPA had increased ROS levels, which may eventually lead to renal oxidative stress and kidney damage. These findings concurred with earlier research that highlighted oxidative stress as one of the primary reasons associated with BPA's nephrotoxicity.[14,27] Administration of *hesperidin* and/or co-administration of *hesperidin* after BPA exposure showed that *hesperidin* significantly restored these oxidative alterations, demonstrating its strong antioxidant capabilities. Our findings showed Considerably decreased in lipid peroxidation (MDA) and enhanced the activity of antioxidant enzymes (SOD, CAT, and GPX). According to a previous study by [17,28,29]. *Hesperidin* has been shown to scavenge free radicals and boost the activity of natural antioxidant enzymes; it appears to be essential in keeping kidney tissues from becoming oxidatively damaged.

Effect of hesperidin on Serum kidney markers (Creatinine, Urea and Uric acid)

The assessment of serum biomarkers for renal function tests, which include creatinine, urea, and uric acid, is shown in (Figure 2a-2c). In rats administered with BPA only, our results showed significant ($p<0.05$) elevated levels of creatinine, urea, and uric acid, which are indicative of impaired renal function and these observed increases were significant in comparison to the normal control group, however, these alterations were significantly in all *hesperidin* treated groups.

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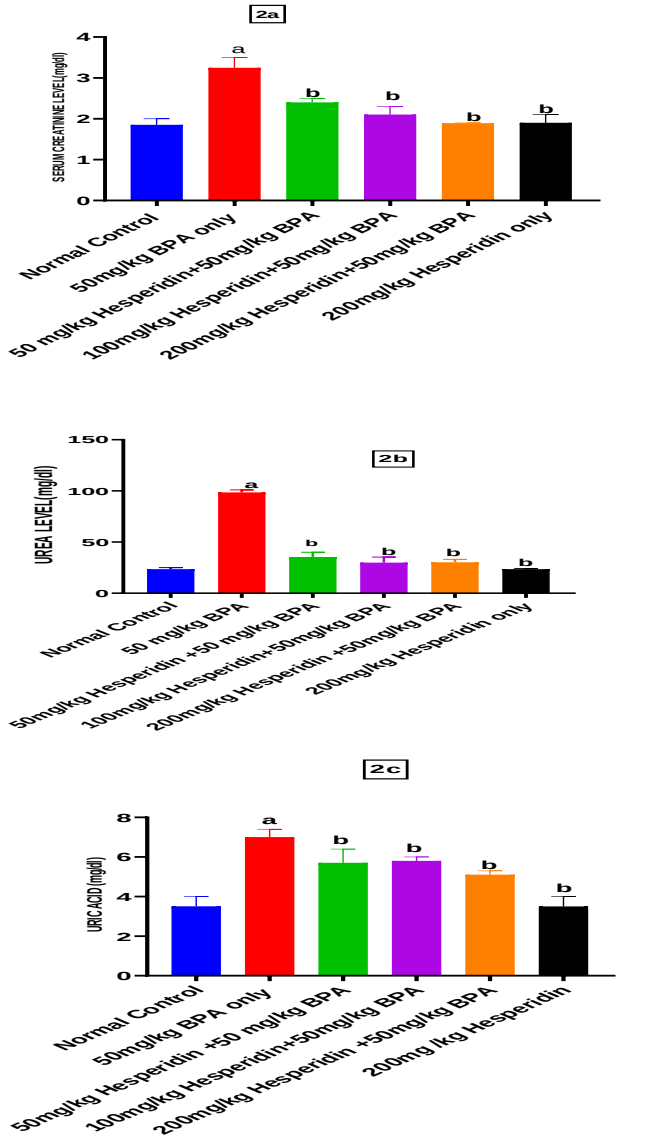

Figure 2a–c: Effects of *hesperidin* on renal function parameters. Figure 2a shows the effect of *hesperidin* on serum creatinine levels, 2b shows the effect on serum urea levels, and 2c shows the effect on serum uric acid levels. Values are expressed as mean ± standard error of the mean (SEM). *a* indicates a statistically significant difference compared to the normal control group ($p < 0.05$), and *b* indicates a statistically significant difference compared to the 50 mg/kgBPA-only group ($p < 0.05$).

Uric acid, urea, and creatinine levels are used to evaluate how effectively the kidneys are functioning. The nitrogenous material, creatinine, is produced by phosphocreatine and creatine and is primarily removed through glomerular filtration, whereas urea is a consequence of protein metabolism. Reduced creatinine clearance, increased urea, uric acid and creatinine are indicators of harmful oxidative damage to the renal cells. [27,30,39,40] BPA's harmful effects on the kidney and its contribution to the increase in renal function indicators have been previously documented. [16,31,] and this was also in line with the findings of our study.

In groups administered with 200 mg/kgof *hesperidin* only, co-treatment with 50 mg/kgof BPA+100 mg/kgof *hesperidin* and co-treatment with 50 mg/kgof BPA+ 200 mg/kgof *hesperidin* significantly ($p<0.05$) revealed reduction in creatinine, urea and uric level compared to the BPA only group, this observation compared to the normal control group showed that *hesperidin* influences normality in the renal function biomarkers. It is widely known that *hesperidin* plays an important role in preventing renal tissues from oxidative damage by scavenging free radicals and improving the activity of endogenous antioxidant enzymes. [17,19,32,33.]

Effect of hesperidin on inflammatory markers (TNF-α, IL-6 levels).

Pro-inflammatory cytokines- TNF-α and IL-6 were markedly elevated by BPA exposure as shown in Figure 3a-3b. According to these results, in comparison to the control group, BPA significantly increased the inflammatory response ($p<0.05$). TNF-α and IL-6 are important cytokines that mediate inflammatory processes, and their elevated levels imply that exposure to BPA may cause tissue damage by triggering inflammatory pathways.[34] According to research, BPA is an endocrine disruptor that replicates estrogenic activity; by altering immune cell signalling pathways and immunological responses, it can cause immune deregulation.[34] By aggravating cellular stress and damage, this inflammatory cascade induced by BPA can aid in the onset of kidney damage. The possible function of BPA in inducing inflammation-driven tissue injury is highlighted by the observed increase in TNF-α and IL-6, as also reported by other studies.[14,27] IL-6 and TNF-α levels were significantly decreased in the group that received 200 mg/kgof *hesperidin* only. This was also observed well in groups with 100 mg/kgand 200 mg/kgof *hesperidin* following BPA exposure, compared to the groups exposed to BPA alone. According to the study's findings, hesperidin has strong anti-inflammatory qualities that may mitigate the detrimental impacts of BPA exposure. The decrease in TNF-α and IL-6 levels in the groups treated with hesperidin suggests that hesperidin may help regulate the inflammatory pathways that BPA causes, reducing inflammation and tissue damage. This was consistent with earlier research [38,39] and further supports the potential therapeutic efficacy of *hesperidin* in decreasing inflammation caused by BPA. The observed dose-dependent response showed a greater reduction at 200 mg/kg.

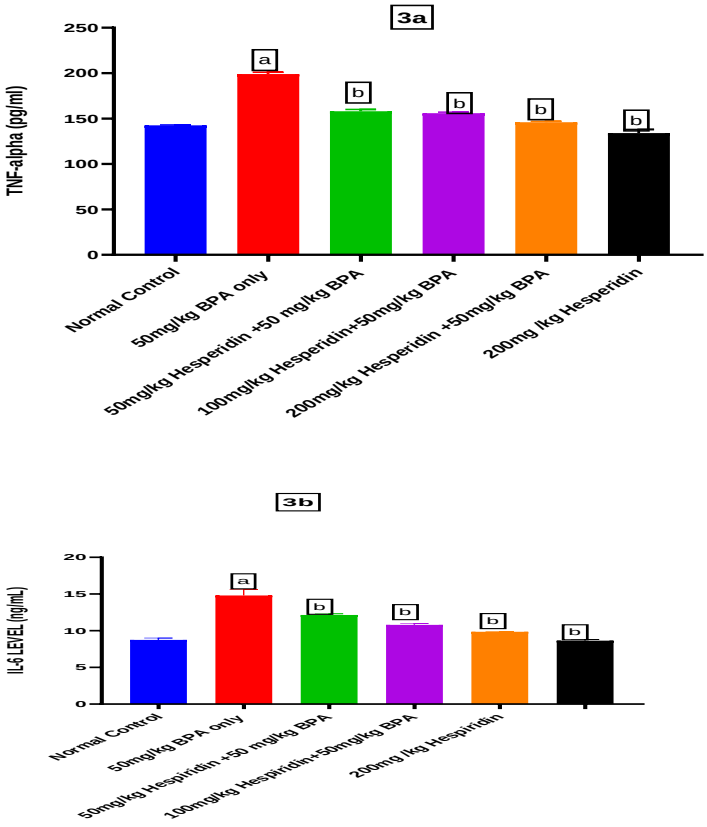

Figure 3a–b: Effects of *hesperidin* on anti-inflammatory markers. Figure 3a shows the effect of *hesperidin* on Tumor Necrosis factor-alpha (TNF-α) levels, while Figure 3b shows the effect on Interleukin-6 (IL-6) levels. Values are expressed as mean ± standard error of the mean (SEM). *a* indicates a statistically significant difference compared

to the normal control group ($p < 0.05$), and *b* indicates a statistically significant difference compared to the 50 mg/kgBPA-only group ($p < 0.05$).

Effect of hesperidin on histology of the kidney.

Photomicrographs of the kidney histology are shown in Figure 4(A-F). In the control group, the histology of the kidney showed a normal microanatomy of the kidney with a well-defined glomerulus and proper renal architecture with no signs of congestion, necrosis, or structural disruption. In group B, BPA exposure to 50 mg/kgonly resulted in marked renal damage. Kidney tissues showed significant histopathological change, tubular necrosis and a damaged basal membrane are signs of severe structural damage that impairs the kidneys' ability to function. Signs of vascular congestion were present, a sign of decreased blood flow that could make damage to the kidneys more severe. Additionally, the kidney histology of the BPA-only group showed epithelial swelling in the proximal convoluted tubule and degenerative changes that indicate coagulative necrosis, including pyknosis. Numerous investigations have documented the histological distortion caused by BPA toxicity.[14, 35, 36, 37] Groups C and D received 100 mg/kgand 200 mg/kgof *hesperidin,* respectively, after exposure to 50 mg/kgof BPA, which showed slightly improved kidney histology than the BPA-only group. The histological features show significant signs of restoration of the kidney histology. This implies that BPA-induced damage may have been somewhat mitigated, as a result of reduced doses or partial defensive mechanisms. However, it is noteworthy that kidney histology revealed a normal kidney with characteristics comparable to the control group in group (E), which received a greater dose of hesperidin following 50 mg/kgBPA exposure. Also, group F was treated with only 200 mg/kgof *hesperidin* kidneys showed no signs of damage or alteration. This shows that *hesperidin* at a higher dose of 200 mg/kgmitigates the kidney damage caused by BPA exposure. The anti-oxidative and anti-inflammatory properties of *hesperidin* likely played a pivotal role in mitigating oxidative stress and promoting cellular repair. The lack of necrotic or degenerative alterations in these groups emphasises *hesperidin's* potential as a treatment to prevent kidney damage brought on by environmental pollutants such as BPA. These findings are similar to previous reports, which reported that *hesperidin* protects kidney histology from damage due to its rich pharmacological properties.[19,28,29,32]

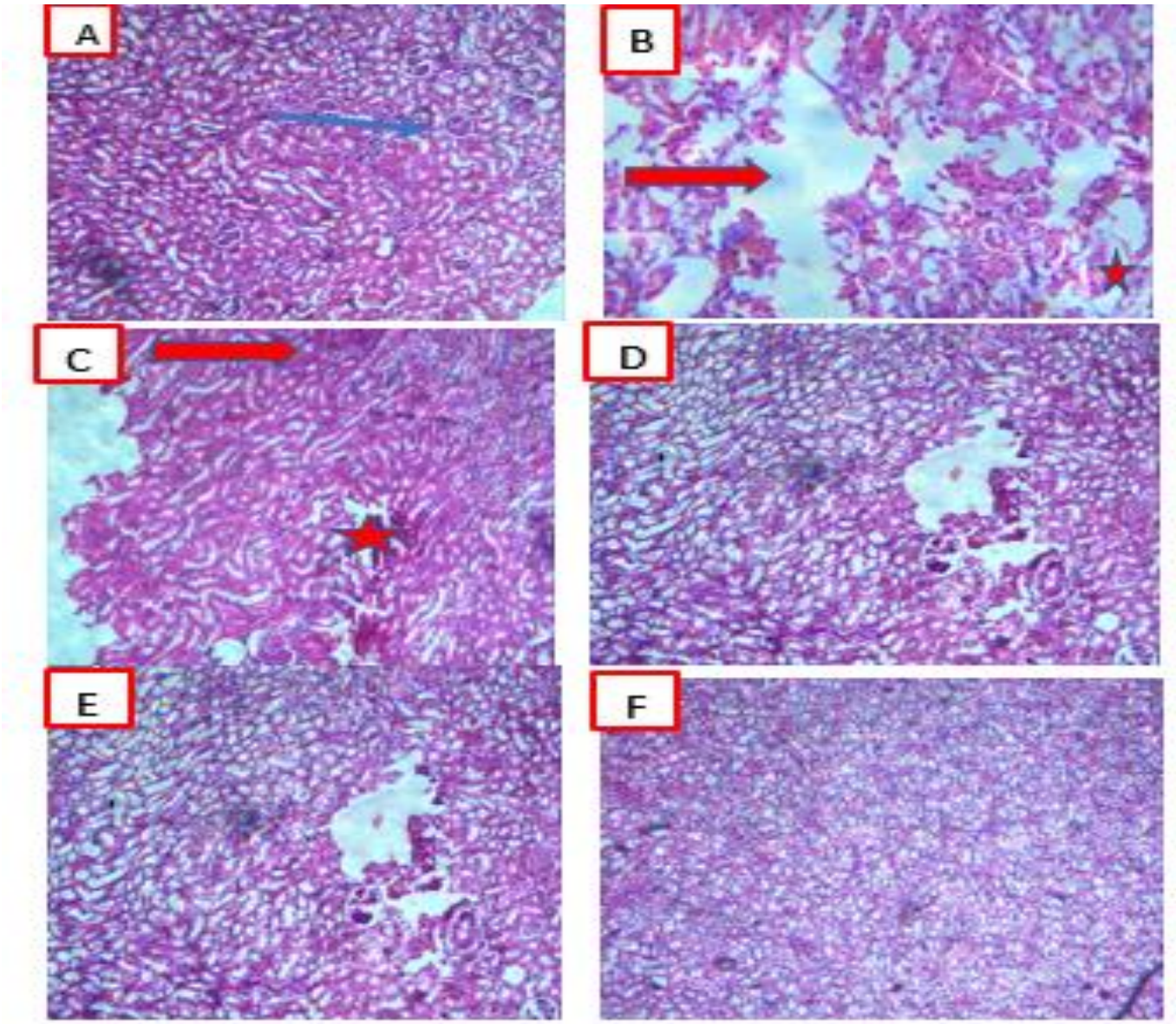

Figure 4 (A–F): Photomicrographs showing the histological architecture of the kidney across experimental groups A to F. A: Normal control group showing a normal kidney histology with well-defined and compact glomerulus, no sign of congestion B; BPA only group, with abnormal histology of the kidney characterized by disrupted basal membrane, tubular necrosis, vascular congestion, degenerative changes in the and swelling of the epithelium of proximal convoluted tubule, coagulative necrosis (pyknosis)-red arrow and star. C-D- shows slight normal histology of the kidney with mild distortion in the glomerulus. E-F: (200 mg/kgHSD+50 mg/kgBPA,200 mg/kg*HSD only*) shows a normal kidney with a spherical glomerulus and a well-shaped Bowman's capsule. (H&E X40).

Conclusion

In conclusion, this study demonstrates that BPA exposure induces renal toxicity through oxidative stress, inflammation, and impaired kidney function. *Hesperidin* administration significantly counteracted these effects, as evidenced by improved antioxidant enzyme activity, reduced inflammatory markers, normalization of renal biomarkers, and restoration of kidney histology. These results underscore *hesperidin's* potential as a protective agent against BPA-induced nephrotoxicity.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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