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Bifenthrin Causes Kidney Damage via Induction of Oxidative Stress, Activation of Pro-Inflammatory Cytokines, and Up-Regulation of Apoptosis in Wistar Rats

Ujong Peter Ujong & Mbang Edet Ibor
University of Cross River State, Calabar, Nigeria; University of Calabar, Nigeria
ujongpeteru@gmail.com

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Abstract

This study investigated the role of oxidative stress, inflammation, and apoptosis in bifenthrin-induced kidney damage in Wistar rat models. Adult male rats (110-300g) were divided into three groups of 10 rats each. Group 1 served as the normal control, while groups 2-3 were orally given 1 mg/ kg body weight bifenthrin for 14 and 28 days respectively. The results revealed that bifenthrin administration caused a significant ($p<0.05$) decrease in renal antioxidant enzymes such as superoxide dismutase, catalase, glutathione, glutathione S-transferase, and glutathione peroxidase. Conversely, malondialdehyde levels were significantly ($p<0.05$) increased. Pro-inflammatory cytokines TNF-α, IL1-β, IL-6, COX-2, iNOS, LTE B4, and PGE2 were significantly ($p<0.05$) elevated, highlighting an inflammatory response. Additionally, the apoptotic markers, caspase-3, and BAX were significantly ($p<0.05$) increased, while BCL-2, an anti-apoptotic protein, was significantly ($p<0.05$) decreased, indicating enhanced apoptosis. Renal function markers, creatinine, and urea were also significantly ($p<0.05$) elevated in bifenthrin-induced groups. Furthermore, the histopathology results revealed

morphological damages in the kidneys of groups 2 and 3 animals These findings demonstrate bifenthrin's potential to cause significant oxidative stress, inflammation, apoptosis, and structural damage in renal tissues.

Keywords: Kidney damage, Bifenthrin, Oxidative Stress, Apoptosis, Inflammation

INTRODUCTION

Bifenthrin, a synthetic pyrethroid insecticide, is extensively utilized in agricultural and residential settings for its effectiveness against a broad spectrum of insect pests (Singh *et al.,* 2022). Despite its widespread application, concerns regarding its potential adverse effects on human and animal health have emerged (Yadav *et al.,* 2021). Recent studies have highlighted the nephrotoxic properties of bifenthrin (Abdel-Wahhab *et al.,* 2024), emphasizing the need for a deeper understanding of its underlying toxicological mechanisms.

Pyrethroids, including bifenthrin, are known to exert their toxic effects primarily through disruption of neuronal sodium channels, leading to prolonged nerve excitation and subsequent neurotoxicity (Mohammadi *et al.,* 2019). However, non-neuronal toxic effects have also been documented, with particular attention to the liver and kidneys, organs crucial for detoxification and excretion (Wang *et al.,* 2024). Bifenthrin-induced nephrotoxicity have been observed in various in vivo and in vitro studies, but the precise molecular pathways involved remain to be fully elucidated.

Inflammation is a critical component of the body's response to toxic insults and is mediated by a complex network of signaling molecules, including pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) (Miliopoulos *et al.,* 2022). These cytokines play a pivotal role in initiating and propagating inflammatory responses, leading to cellular damage and organ dysfunction (Kany *et al.,* 2019). The up-regulation of pro-inflammatory cytokines has been implicated in the pathogenesis of nephrotoxicity induced by various xenobiotics (Soliman *et al.,* 2022); this is suggestive of a possible similarity in the pathogenic pathway of bifenthrin toxicity.

Oxidative stress, characterized by the overproduction of reactive oxygen species (ROS) and a concomitant depletion of antioxidants (Sachdev *et al.,* 2021), is another critical factor contributing to bifenthrin-induced organ damage. The imbalance between ROS and antioxidant defenses can lead to oxidative damage to cellular macromolecules, including lipids, proteins, and DNA, ultimately triggering cell death pathways such as apoptosis (Juan *et al.,* 2021). Caspase-3, a key executioner caspase in the apoptotic cascade, and gasdermin E (GSDME), a mediator of pyroptosis, are crucial regulators of programmed cell death (Jiang *et al.,* 2020). The modulation of the caspase-3/GSDME pathway by bifenthrin could provide insights into the mechanisms of cell death associated with its toxicity.

The intricate interplay between inflammation, oxidative stress, and cell death pathways forms the basis of bifenthrin-induced nephrotoxicity. This study aims to elucidate the role of pro-inflammatory cytokine up-regulation and the modulation of antioxidant defenses and caspase-3/GSDME signaling in bifenthrin-induced renal inflammation. Understanding these molecular mechanisms is essential for developing strategies to mitigate the adverse effects of bifenthrin exposure and for establishing safer guidelines for its use.

MATERIALS AND METHODS

Acquisition of Bifenthrin

Bifenthrin (97% TC) with batch number 20211012 was received as a generous gift from Dr. Babajide O. Ajayi, of Ajayi Crowder University, Oyo, Nigeria; who originally acquired the compound from Nanjing Essence Fine-Chemical Co., Ltd. China.

Experimental animals and study design

Ethical approval for treating and handling experimental animals was obtained from the Faculty of Basic Medical Science Animal Ethical Committee University of Cross River State, Okuku Campus with an approval number; FBMS/UNICROSS/22/10. Thirty (30) male Wistar rats ranging in weight between 110 and 300g were acquired from the University of Cross River State's Okuku Campus's Animal House, within the Faculty of Basic Medical Sciences. Following acclimatization to handling and experimental environment, they were housed in standard plastic cages (60cm by 40cm dimension) provided with top mesh wire covers, under relative humidity (45%) and room temperature

(26°C). The rats were fed with Mazuri pelletized rat chow and allowed access to water *ad libitum* throughout the experimental period.

Animal grouping and treatment

The animals were divided into three (3) groups of 10 Wistar rats each and were treated in line with the scheme in Table 1.

Table 1: Experimental design, animal grouping, and treatment

Groups	Number of animals	Treatment
1	10	0.5ml of vehicle (Tween 80 + Canola Oil in the ratio 1:10)
2	10	1mg/kg body weight bifenthrin for 14 days
3	10	1mg/kg body weight bifenthrin for 28 days

Termination of experiment and Collection of samples for analysis

At the end of the experimental period, rats were subjected to an overnight fast, and were euthanized under chloroform anesthesia, and kidney samples were harvested for biochemical assays and histopathology study.

Homogenization of kidney Tissues

The organs collected were washed in ice-cold 1.15% KCl solution, blotted with filter paper, and weighed using an electronic weighing balance. They were then homogenized while on ice, in 4 ml phosphate buffer (homogenizing buffer) of 7.4, employing a laboratory mortar and pestle. The ensuing homogenate was centrifuged at 10,000g for a quarter-hour at 4°C employing a cold centrifuge, to get the post mitochondrial fraction. The supernatant was collected and kept in a laboratory freezer at -20°C until needed for biochemical analyses.

Estimation of Renal activities of SOD, CAT, MDA, GSH, GST and GPx

The activity of Superoxide dismutase (SOD) was determined as described by Liu *et al.*, (2021). The activity of Catalase (CAT) was estimated using the method outlined by Rubio-Riquelme *et al.,* (2020). Glutathione (GSH) was estimated according to the methods of Nuhu *et al.,* (2020). Glutathione S-transferase (GST) was estimated according to the method of Buratti *et al.,* (2021). Glutathione peroxidase (GPx) was determined according to

the method outlined by Ahmed *et al.,* (2021). Malondialdehyde (MDA) was carried out according to the method of Morales & Munné-Bosch, (2019).

Estimation of Renal levels of TNF-a, IL 1-β, IL-6, COX-2, iNOS, PGE 2, LTE B4, CASPASE 3, BAX and BCL-2

Protocols in Cusabio ELISA kits (Cusabio Technology LLC, Houston, TX, USA) were followed. Briefly, samples, and standards were added into the wells already pre-coated with antibody specific for TNF-α, IL 1-β, IL-6, COX-2, iNOS, PGE 2, LTE B4, CASPASE 3, BAX and BCL-2. Unbound substances were removed, and a biotin-conjugated antibody specific for TNF-α, IL 1-β, IL-6, COX-2, iNOS, PGE 2, LTE B4, CASPASE 3, BAX and BCL-2 was added to the well. After washing, avidin-conjugated Horseradish Peroxidase (HRP) was added to the wells, followed by the addition of a substrate solution to give a color proportional to the amount of TNF-α, IL 1-β, IL-6, COX-2, iNOS, PGE 2, LTE B4, CASPASE 3, BAX and BCL-2 bound in the initial step. Color development was stopped and the intensity of the color was measured at 450 nm.

Estimation of Renal urea, creatinine concentration

Urea and creatinine were estimated following the method described by Bhatia *et al.,* (2019).

Hematoxylin and Eosin (H&E) staining

The Kidney tissues were fixed in 10 % neutral buffered formalin and embedded in paraffin, sectioned into 5-µm thick slices, deparaffinized, and stained with hematoxylin and eosin (H&E), and examined and photographed using a microscope at 400X magnification.

Statistical analysis

All data were expressed as mean ±SEM. Statistical analysis using Analysis of Variance and complemented with Duncan post hoc using GraphPad Prism statistics, version 8.0. Differences were considered statistically significant at $p < 0.05$.

RESULTS

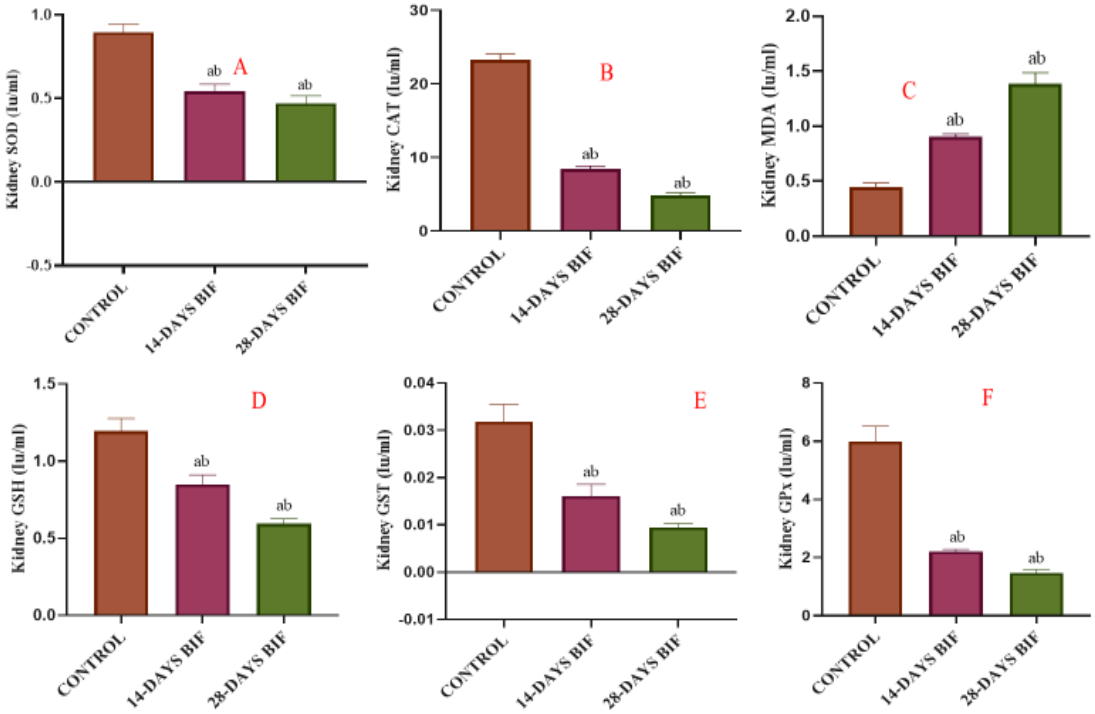

Figure1: Effect of Bifenthrin on Renal SOD, CAT, MDA, GSH, GST and GPx activities

Values are given as mean ± SEM; n=10.

Significant differences from the control group are denoted by ^{ab} ($p<0.05$)

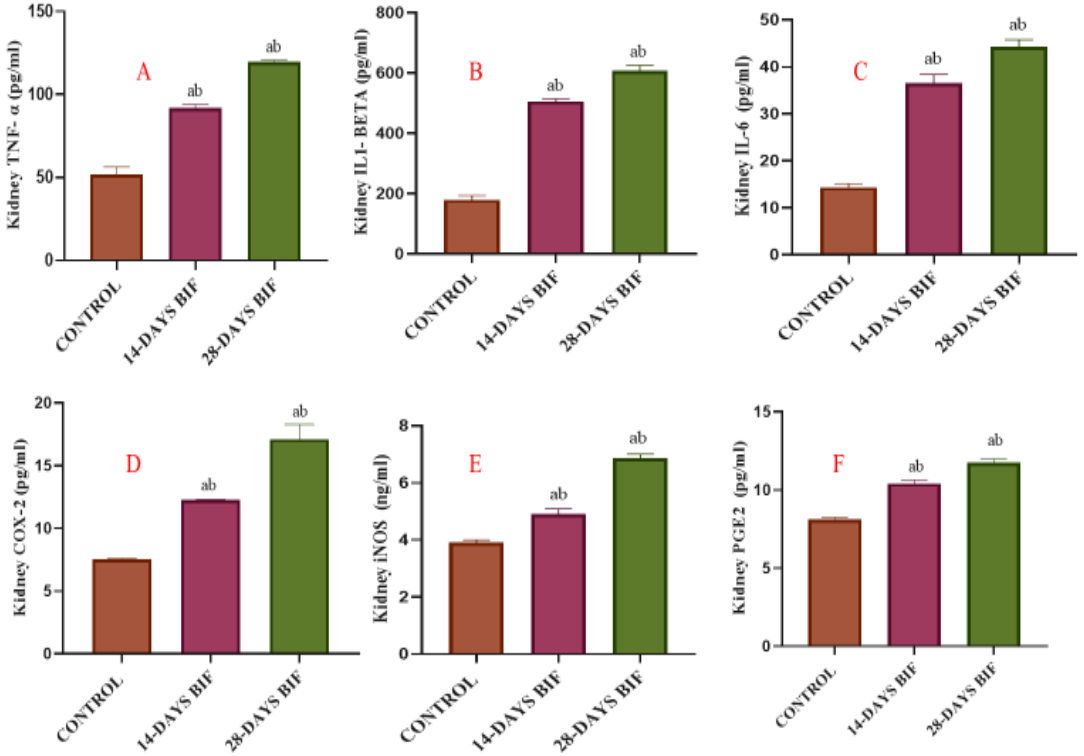

Figure 2: Effect of Bifenthrin on Renal TNF-α, IL1-β, IL-6, COX-2, iNOS and PGE2

Values are given as mean ± SEM; n=10.

Significant differences from the control group are denoted by [ab] ($p<0.05$)

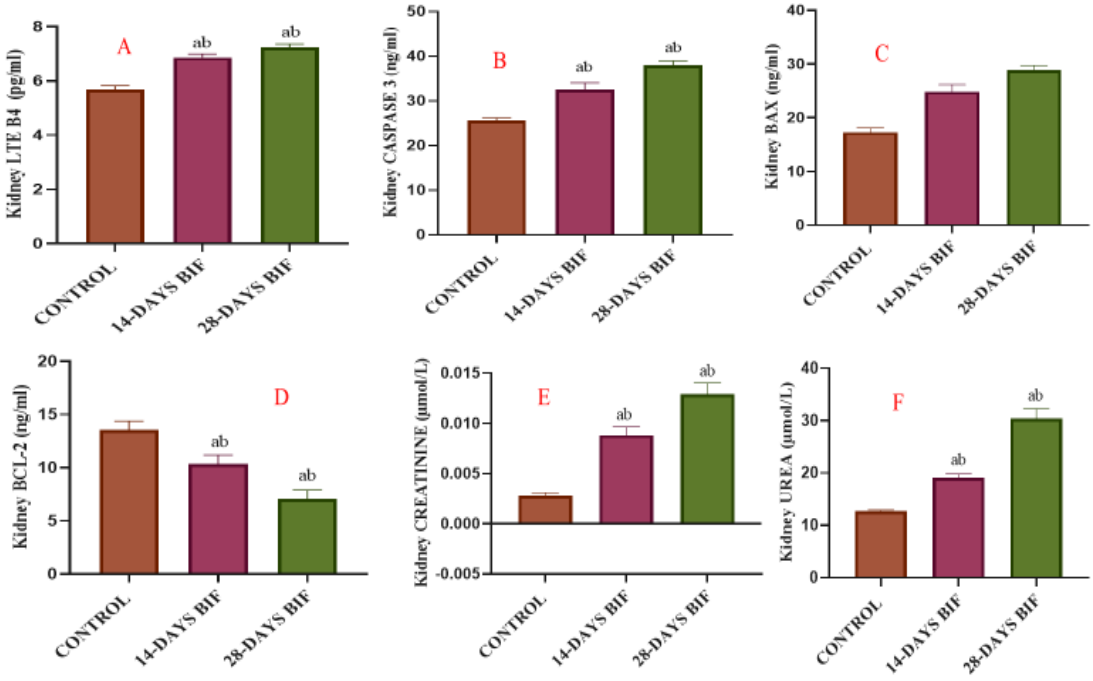

Figure 3: Effect of Bifenthrin on Renal LTE B4, CASPASE 3, BAX, BCL-2 Creatinine and Urea

Values are given as mean ± SEM; n=10.

Significant differences from the control group are denoted by [ab] ($p<0.05$)

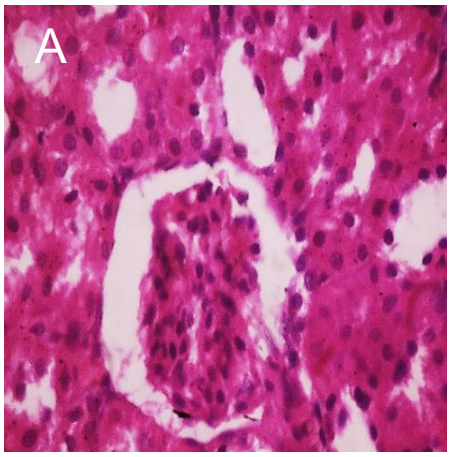

PLATE 1: Photomicrograph of Group A (Normal Control) H & E. X 400

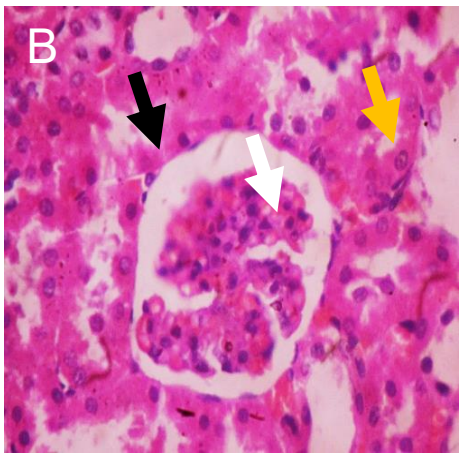

PLATE 2: Photomicrograph of Group B (14-days Bifenthrin) H & E. X 400

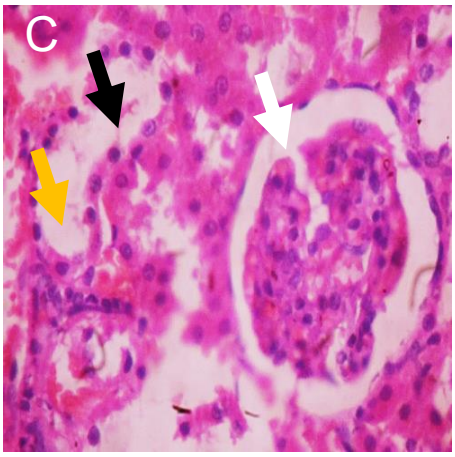

PLATE 3: Photomicrograph of Group C (28-days Bifenthrin) Bifenthrin) H & E. X 400

Effect of Bifenthrin on Renal SOD, CAT, MDA, GSH, GST and GPx activities

The activities of renal SOD, CAT, GSH, GST, and GPx (Fig 1 a, b, d, e, and f) were significantly ($p<0.05$) decreased in 14 days and 28 days bifenthrin groups compared with control. The activity of renal MDA (Fig 1 c) was significantly ($p<0.05$) increased in 14 days and 28 days bifenthrin induced groups compared with control.

Effect of Bifenthrin on Renal levels of TNF-a, IL1-β, IL-6, COX-2, iNOS and PGE2

The levels of renal TNF-α, IL1-β, IL-6, COX-2, iNOS, and PGE2 (Fig 2 a-f) were significantly ($p<0.05$) increased in 14 days and 28 days bifenthrin groups compared with control.

Effect of Bifenthrin on Renal levels of LTE B4, CASPASE 3, BAX, and BCL-2

The levels of renal LTE B4, CASPASE 3, and BAX (Fig 3 a-d) were significantly ($p<0.05$) increased in 14 days and 28 days bifenthrin induced groups compared with control. Renal BCL-2 (Fig. 16) levels were significantly ($p<0.05$) decreased in 14 days and 28 days bifenthrin induced groups compared with control.

Effect of Bifenthrin on Renal Levels of Creatinine and Urea

The levels of renal Creatinine and Urea (Fig 3 e and f) were significantly ($p<0.05$) increased in 14 days and 28 days bifenthrin groups compared with control.

Effect of bifenthrin on histopathology of the kidney

A hematoxylin and eosin-stained section of the kidney shows the following observations: In the control group (A), no histological abnormalities were observed. In the BIF (14 days) group (B), there is interstitial and glomerular hemorrhage. There is a widening of Bowman's capsule. The glomerulus is inflamed and sclerotic with tubular detachment (white arrow). the proximal convoluted tubule is distorted (Black arrow). In the BIF (28 days) group (C) there is severe tubular and glomerular hemorrhage white and yellow arrow). There is a widening of Bowman's capsule. The glomerulus and tubules are markedly inflamed and the glomerulus is sclerotic with tubular detachment (white arrow). the proximal convoluted tubule is distorted (Black arrow) with debris in the tubular lumen (yellow arrow).

DISCUSSION

Bifenthrin, a widely used pyrethroid insecticide, is known for its efficacy in pest control. However, its potential nephrotoxic effect has become a significant concern. Hence, this study sought to investigate the impact of bifenthrin exposure on various renal biomarkers, including antioxidant enzymes, oxidative stress markers, inflammatory cytokines, apoptotic markers, renal function indicators, and histopathology of the kidney. The findings reveal significant biochemical and physiological changes in the renal tissues of the groups of Wistar rats exposed to bifenthrin when compared to control.

The activities of renal superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), glutathione S-transferase (GST), and glutathione peroxidase (GPx) were significantly decreased in bifenthrin-induced groups. These enzymes play critical roles in the detoxification of reactive oxygen species (ROS). SOD catalyzes the dismutation of superoxide radicals into oxygen and hydrogen peroxide, while CAT further decomposes hydrogen peroxide into water and oxygen (Madkour, 2019). The observed reductions in these enzymes suggest a compromised antioxidant defense system, leading to increased ROS accumulation. Glutathione (GSH) and its related enzymes GST and GPx are crucial for cellular redox balance and detoxification processes (Vašková *et al.,* 2023). GSH directly scavenges free radicals, and GST conjugates xenobiotic compounds with GSH, facilitating their excretion (Georgiou-Siafis & Tsiftsoglou, 2023). GPx reduces hydrogen peroxide and lipid peroxides using GSH as a substrate (Ursini & Maiorino, 2020). The significant decrease in the activities of these enzymes indicates impaired detoxification processes, making renal cells more susceptible to oxidative damage. Concomitantly, the activity of malondialdehyde (MDA), a marker of lipid peroxidation, was significantly increased. Elevated MDA levels indicate enhanced oxidative stress and membrane lipid damage, corroborating the reduced antioxidant enzyme activities (Liakopoulos *et al.,* 2019). This imbalance between ROS production and antioxidant defenses highlights bifenthrin's role in inducing oxidative stress in renal tissues. These findings are consistent with the previous study of Dar *et al.* (2019). Who reported increased production of reactive oxygen species (ROS) due to bifenthrin exposure in wistar rats.

The levels of renal pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and enzymes (COX-2, iNOS, PGE2) were significantly increased in bifenthrin-induced groups. TNF-α, IL-1β, and IL-6 are key mediators of inflammation, promoting the recruitment and activation of

inflammatory cells (Wang & He, 2020). TNF-α is a multifunctional cytokine that promotes the expression of adhesion molecules on endothelial cells, facilitating the migration of leukocytes to sites of inflammation (Calabriso *et al.,* 2023). Its elevated levels in bifenthrin-induced kidneys indicate an acute inflammatory response aimed at combating perceived injury or stress induced by the toxin. IL-1β is another potent pro-inflammatory cytokine that is involved in a variety of cellular activities, including cell proliferation, differentiation, and apoptosis. It is primarily produced by activated macrophages and plays a significant role in the inflammatory process by inducing the expression of various other inflammatory mediators (Migliorin *et al.,* 2020). The increased IL-1β levels in the kidney following bifenthrin exposure suggest a heightened state of inflammation, possibly contributing to tissue damage and functional impairment. IL-6 acts both as a pro-inflammatory cytokine and an anti-inflammatory myokine. It is secreted by T cells and macrophages to stimulate immune response, particularly during infection and after trauma. Elevated IL-6 levels are indicative of systemic inflammation and have been associated with chronic inflammatory diseases (Rogeri *et al.,* 2020). The surge in IL-6 levels in bifenthrin-exposed kidneys reinforces the notion of a significant inflammatory reaction, which might have systemic implications beyond the renal tissue.

Cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) are enzymes involved in the inflammatory response. COX-2 catalyzes the synthesis of pro-inflammatory prostaglandins, while iNOS produces nitric oxide, a potent inflammatory mediator (Ferrer *et al.,* 2019; Saini & Singh, 2019). The increased levels of these enzymes indicate upregulated inflammatory pathways, contributing to renal inflammation and damage. Prostaglandin E2 (PGE2), a product of COX-2 activity, further amplifies the inflammatory response (Yao & Narumiya, 2019). The interplay between COX-2 and iNOS is significant in the context of inflammation-induced renal damage (Kucukler *et al.,* 2021). The kidney, with its intricate network of blood vessels and filtration units, is particularly susceptible to inflammatory insults (Diaz-Ricart *et al.,* 2020). Upregulated COX-2 activity in renal tissues results in increased PGE2 synthesis, which not only perpetuates inflammation but also influences renal blood flow and glomerular filtration rate (Diaz-Ricart *et al.,* 2020). Concurrently, heightened iNOS expression leads to excessive NO production, exacerbating oxidative stress and contributing to cellular damage. The synergistic effect of these enzymes thus plays a critical role in the progression of renal inflammation and associated pathologies (Diaz-Ricart *et al.,* 2020). this result is consistent with that of previous study

(Aouey *et al.,* 2017) that demonstrated that low doses of bifenthrin can lead to a significant increase in the level of inflammatory cytokines in the kidney.

This study also observed a significant increase in renal leukotriene B4 (LTB4) levels in bifenthrin-induced groups. LTB4 is a potent inflammatory mediator known for its role in recruiting and activating leukocytes, thus exacerbating inflammatory responses (Sasaki & Yokomizo 2019). This elevation in LTB4 levels suggests that bifenthrin exposure triggers an inflammatory cascade within the renal tissues. The recruitment of leukocytes, driven by heightened LTB4, likely contributes to renal tissue damage and inflammation, which could further compromise renal function.

Concomitantly, the study observes an increase in caspase 3 levels, indicating enhanced apoptotic activity. Caspase 3 is a crucial executioner enzyme in the apoptosis pathway, responsible for the cleavage of various cellular substrates, leading to the systematic dismantling of the cell (Araya *et al.,* 2021). The observed rise in caspase 3 levels signifies that bifenthrin exposure induces apoptosis in renal cells. This apoptotic response could be a cellular defense mechanism to eliminate damaged cells, but excessive apoptosis may lead to renal dysfunction and contribute to the overall cytotoxicity of bifenthrin.

Furthermore, the study notes an increase in BAX levels and a decrease in BCL-2 levels in bifenthrin-induced groups. BAX is a pro-apoptotic protein that plays a crucial role in promoting apoptosis (Chota *et al.,* 2021). BCL-2 is an anti-apoptotic protein that plays a pivotal role in regulating cell death by inhibiting the mitochondrial pathway of apoptosis (Qian *et al.,* 2022). Lower levels of BCL-2 suggest a reduced capacity to prevent apoptosis, thus facilitating the apoptotic process initiated by increased caspase 3 and BAX activity. The downregulation of BCL-2, coupled with elevated caspase 3 and BAX, underscores a shift in the cellular equilibrium towards apoptosis, potentially exacerbating renal injury and dysfunction.

The levels of renal creatinine and urea, markers of renal function, were significantly increased in bifenthrin-induced groups. Elevated creatinine and urea levels indicate impaired renal function and reduced glomerular filtration rate, suggesting that bifenthrin exposure adversely affects renal health (Vistisen *et al.*, 2019). This observation runs in line with recent studies (Pylak-Piwko & Nieradko-Iwanicka, 2021).

The renal histology of the control group appears normal with no detectable abnormalities. This group serves as the baseline, representing healthy kidney tissue without any exposure

to bifenthrin. Key structures such as the glomerulus, Bowman's capsule, and proximal convoluted tubules exhibit typical morphology. There is an absence of hemorrhage, inflammation, or any structural deformities. This normalcy establishes a reference point against which pathological changes in the experimental groups can be measured. In the Bifenthrin- induced (14 days) group, significant histological alterations are observed. Notably, an interstitial and glomerular hemorrhage, indicating damage to the blood vessels within the kidney. The Bowman's capsule, which encases the glomerulus, is widened, suggesting an inflammatory response or edema (Schult *et al.,* 2023). The glomerulus itself is inflamed and shows signs of sclerosis, a hardening that impairs its filtering ability. Tubular detachment is evident, reflecting severe damage to the tubular structure and its connections. Additionally, the proximal convoluted tubule, which plays a crucial role in reabsorbing nutrients from the filtrate, is distorted, likely compromising its function. In the Bifenthrin-induced (28 days) group, the histopathological damage is even more pronounced. There is severe hemorrhage both in the tubules and glomeruli, indicating extensive vascular damage (Schult *et al.,* 2023). Similar to the 14-day exposure, the Bowman's capsule is widened, but to a greater extent, suggesting progressive inflammation or increased fluid accumulation. The glomerulus and tubules are markedly inflamed, with significant sclerosis and tubular detachment. This detachment indicates that the structural integrity of the tubules is severely compromised, impairing their function. The proximal convoluted tubule remains distorted, and there is also debris present in the tubular lumen, which can further obstruct and impair renal function (Schult *et al.,* 2023).

CONCLUSION

The observations recorded from this study provide deep insight into the mechanisms of bifenthrin nephrotoxicity. The significant decrease in antioxidant enzyme activities and increase in oxidative stress markers highlight the role of oxidative damage in bifenthrin's nephrotoxic effects. Elevated levels of inflammatory cytokines and enzymes indicate a strong inflammatory response, while changes in apoptotic markers suggest enhanced apoptosis. The impaired renal function, evidenced by increased creatinine and urea levels, underscores the detrimental impact of bifenthrin on kidney health. These results emphasize the need for further research to develop potential therapeutic interventions to mitigate its adverse effects.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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