Cinnamic Acid through Reduction of Oxidative Injury and Modulation of Nrf2 Pathway Ameliorates Bisphenol A-induced Nephrotoxicity in Male Wistar Rats

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Abstract
Bisphenol A is an environmental pollutant that induces oxidative stress in the kidney. Phytochemicals such as cinnamic acid have been demonstrated to possess antioxidative properties that could mitigate against oxidative stress. The current study investigates underlying pathways that may help elucidate the protective role of cinnamic acid (CA) against bisphenol A (BPA)-induced nephrotoxicity. Rats were divided randomly into five groups. Group 1 was the control. Group 2 took BPA only. Group 3 was given BPA combined with CA (50 mg/kg), while group 4 had BPA and cinnamic acid (100 mg/kg). Group 5 received cinnamic acid only (100 mg/kg). Antioxidant parameters and protein expression levels were evaluated. Bisphenol A at 100 mg/kg significantly increased urea concentration and lipid peroxidation. Glutathione (GSH) level decreased, and superoxide dismutase (SOD), catalase, and glutathione-S-transferase (GST) presented lower activities than in the control ($P>0.05$). Cinnamic acid improved renal function by significantly reducing urea levels. Oxidative stress was reduced, as evidenced by lower malondialdehyde and higher antioxidant marker levels (GSH, SOD, catalase, and GST) compared with the BPA-administered group. qRT-PCR results showed a decline in Nrf2 expression in BPA-treated rats compared with the control ($P<0.05$). However, this decline was reversed upon CA treatment. Cinnamic acid at 100 mg/kg to rats treated with bisphenol A preserved the structural integrity of the kidney. The data obtained suggests that cinnamic acid's protective effect against BPA-induced nephrotoxicity may be driven by its ability to decrease oxidative stress and reduce inflammation through regulation of Nrf2 signaling pathway.

Keywords: cinnamic acid; bisphenol A; antioxidants; oxidative stress; signaling pathways

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Introduction

Bisphenol-A is a common industrial compound widely used in producing industrial plastics and refillable bottles. BPA is an emerging contaminant found in surface water, groundwater, and wastewater (Ologundudu *et al.*, 2025) that can leach into substances it contacts. Its presence in the aquatic environment has been reported to be harmful and detrimental to human health (Wu *et al.*, 2015). This raises concerns, and studies have shown its potential effects on liver, kidney, and neurobehavioral diseases (Street *et al.*, 2018).

Studies have linked BPA exposure to renal damage, causing abnormalities in the function and structure of the kidney that could potentially lead to chronic kidney disease (Priego *et al.*, 2021). The molecular mechanisms by which BPA induces nephrotoxicity include oxidative stress, inflammation, and apoptosis (Yuan *et al.*, 2019). In addition, renal toxicity caused by BPA is associated with ferroptosis, characterized by lipid peroxidation and necrotic cell death (Bao *et al.*, 2022). Further, BPA is involved in the modulation of nuclear factor erythroid 2-related factor (Nrf2)/heme oxygenase-1 (HO-1) expression, which is a crucial part of defense against oxidative damage and inflammation (Chiang *et al.*, 2022). Nrf2 is a main regulator of the body's antioxidant defenses. It is translocated to the nucleus under oxidative stress, where it activates the production of antioxidant enzymes and anti-inflammatory actions as a cytoprotective measure in tissues (Strom *et al.*, 2016). It plays a crucial role in maintaining intracellular redox homeostasis and regulating inflammation (Saha *et al.*, 2020).

Flavonoids and phytochemicals can enhance cellular antioxidant defenses by activating the Nrf2 signaling pathway, thus protecting against cisplatin-induced toxicity in organs such as the kidneys (Zhang *et al.*, 2025). Cinnamic acid is a natural organic phytochemical known to reduce oxidative stress and the expression of pro-inflammatory cytokines (Jia *et al.*, 2025). Its ameliorative effects on renal dysfunction and its role in mitigating oxidative stress and inflammation activation through the Nrf2 pathway

are described by Alotaibi *et al.* (2025). Thus, it is reasonable to think that cinnamic acid may provide renal protection against BPA-induced kidney damage.

Therefore, the study aims to investigate whether cinnamic acid could reduce renal impairment in rats exposed to BPA. The mechanism by which cinnamic acid ameliorates BPA-induced renal toxicity has not been explored. We hypothesized that cinnamic acid might ameliorate BPA-induced renal damage by mitigating oxidative stress and regulating the Nrf2/IL-6 signaling pathway.

Materials and Methods

Materials

Chemicals and Reagents

Reduced glutathione, Ellman's reagent, Bisphenol A, thiobarbituric acid and trichloroacetic acid were obtained from Sigma, USA. Cinnamic acid was procured from Lobal Chemie, India. All biochemical commercial kits were obtained from Randolph Laboratories (Crumlin, UK).

Experimental Subjects

Forty male Wistar rats (150-200g) were acclimatized for 14 days. The rats were kept in plastic cages in a room with a 12-hour light/12-hour dark cycle. They were fed a commercial diet with unlimited access to clean water. The animals were treated ethically according to established guidelines for the care and use of laboratory animals (NRC, 2011) for animal experiments.

Methodology

Experimental Plan

Rats were distributed into 5 groups of 5 rats each. Group 1 was administered corn oil (1 ml/kg). Group 2 was dosed with bisphenol A (100 mg/kg). The second group was given BPA co-administered with cinnamic acid (50 mg/kg). Group 4 was given BPA co-administered with cinnamic acid (100 mg/kg). The fifth group received cinnamic acid only (100 mg/kg). Cinnamic acid and bisphenol A were co-administered orally for 14 days.

Preparation of Homogenate

The rats were sacrificed via cervical dislocation. The kidney extracted was homogenized in a cold phosphate buffer, centrifuged for 15 minutes at 10,000g, and 4℃. The post-mitochondrial fractions were kept at 4℃ and subsequently used for biochemical assays.

Estimation of Antioxidant Parameters

Glutathione-S-Transferase Activity

The activity of GST was measured using the protocol described by Habig *et al.* (1974). This involves reacting the GST with 1-chloro-2,4-dinitrobenzene (CDNB) and reduced glutathione. The reaction is monitored spectrophotometrically at 340 nm by monitoring the change in absorbance.

Superoxide Dismutase Activity

SOD activity was determined spectro-photometrically by the method of Misra and Fridovich (1972), where a unit of SOD activity defines the amount of SOD necessary to cause 50% inhibition of the oxidation of adrenaline to adrenochrome in 60 seconds.

Determination of Catalase Activity

This was determined by using the method of Asru (1972). The hydrogen peroxide content was determined kinetically. The results are expressed as mmol H_2O_2 consumed/min/mg/protein.

Determination of Protein Concentration

The protein content in tissues was quantified using the principle of Lowry *et al.* (1951) and the standard used was prepared by the biuret method.

Lipid Peroxidation Level

This was determined by quantifying the thiobarbituric acid reactive substances (Varshney and Kale, 1990). Absorbance was taken at 532 nm. The malondialdehyde level was determined. Lipid peroxidation was computed using a molar extinction coefficient of 1.56×10^5 $M^{-1}cm^{-1}$.

Determination of Reduced Glutathione Level

The method of (Beutler *et al.*, 1963) was adopted for estimating the reduced glutathione level, which was determined using Ellman's reagent as described by (Jollow *et al.*, 1974). Absorbance was taken at 412 nm. GSH concentration was directly proportional to the absorbance obtained from the GSH standard.

Gene Expression

Isolation of Total RNA

Total RNA was isolated from tissue samples using the Quick-RNA MiniPrep™ Kit (Zymo Research).

cDNA Conversion
1 µg of DNA-free RNA was utilized to synthesize cDNA by reverse transcriptase reaction with cDNA synthesis kit based on ProtoScript II first-strand technology (New England BioLabs) in a three-step reaction (Elekofehinti *et al.*, 2020).

PCR Amplification and Agarose Gel Electrophoresis
Polymerase chain reaction (PCR) for the amplification of the gene of interest was run with OneTaqR2X Master Mix (NEB) using the following primers (Inqaba Biotec, Hatfield, South Africa). Quantification of band intensity was done using "image J" software (Elekofehinti *et al.*, 2020).

Histological Studies
A section of the kidney was fixed in 10% neutral formalin solution, dehydrated in graded alcohol and embedded in paraffin to obtain fine for light microscopic analysis. The slides were examined by a histopathologist and photographs were taken.

Results

Biochemical Analysis

Kidney Function Test
The urea level of the BPA-treated group was enhanced compared with the control group ($P<0.05$). The combination of cinnamic acid with bisphenol A decreased urea level significantly when compared with when BPA only was administered ($P<0.05$) (Figure 1a). However, the creatinine level of the rats dosed with BPA declined when compared with the control. Cinnamic acid elevated the creatinine level when co-administered with BPA at 100 mg/kg (Figure 1b).

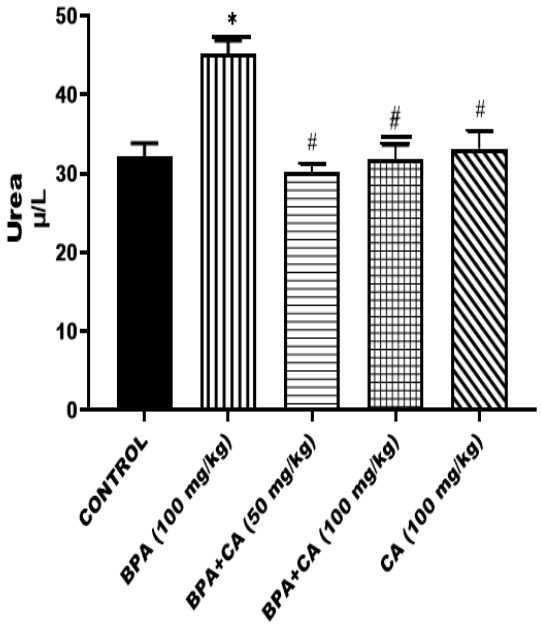

Fig. 1a: Effect of cinnamic acid on PBA-induced changes in the urea level. Values expressed as mean ± standard error of mean (SEM) for five rats per group. *Significantly different from control ($P<0.05$); #Significantly different from PBA-treated rats ($P<0.05$).

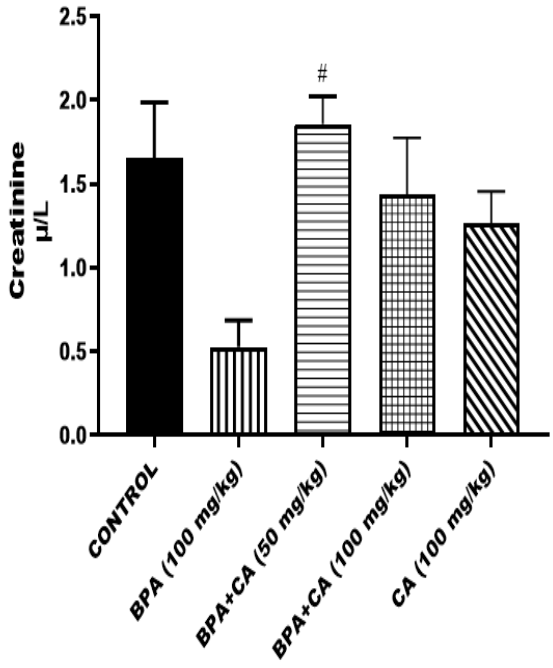

Fig. 1b: Effect of cinnamic acid on PBA-induced changes in the creatinine level. Values expressed as mean ± standard error of mean (SEM) for five rats per group. #Significantly different from PBA-treated rats ($P<0.05$).

Measurement of Kidney Oxidative Stress

Oxidative stress induced by BPA in the kidney was investigated by determining the GSH level and extent of lipid peroxidation. Lipid peroxidation level was significantly higher in the kidney of rats treated with 100 mg/kg of bisphenol A than the control (P< 0.05). This increase was notably reduced in the group co-administered with BPA and cinnamic acid compared with the BPA-only group (Figure 2a). A decline in glutathione content was noticed in BPA only group. Co-administration of BPA with cinnamic acid slightly raised the glutathione level when compared to rats treated with BPA only (Figure 2b).

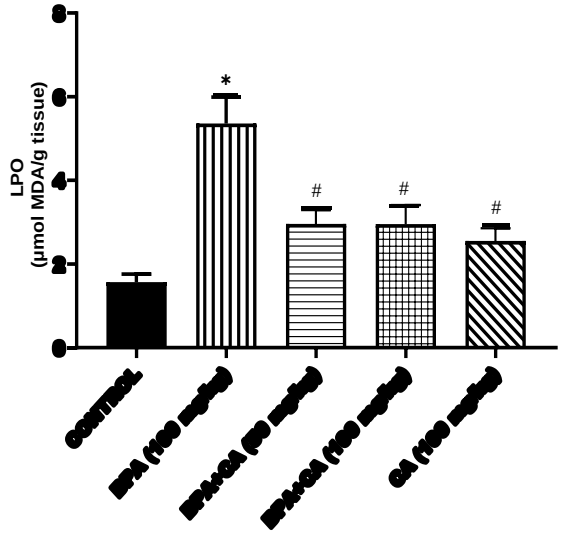

Fig. 2a: Effect of cinnamic acid on PBA-induced changes in the lipid peroxidation level. Values expressed as mean ± standard error of mean (SEM) for five rats in each group. *Significantly different from control (P<0.05); #Significantly different from PBA-treated rats (P<0.05).

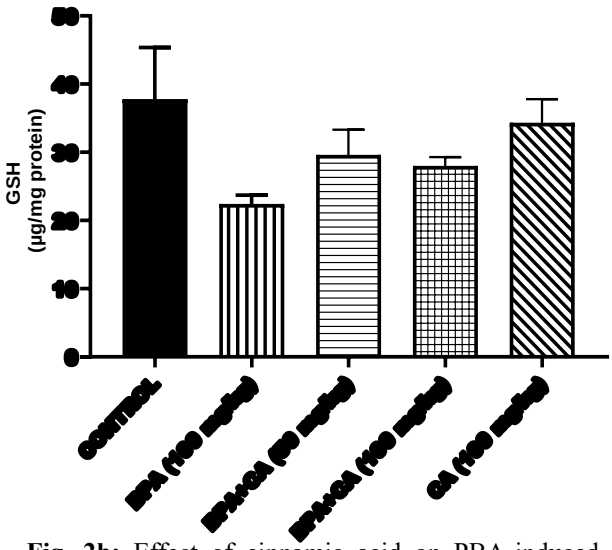

Fig. 2b: Effect of cinnamic acid on PBA-induced changes in the GSH level. Values expressed as mean ± standard error of mean (SEM) for five rats in each group. (P>0.05) in all groups compared.

Renal Antioxidants

Figures 3a and 3b show the effect of cinnamic acid on the CAT and SOD activities in the kidney of rats treated with bisphenol A. There was inhibition of catalase and superoxide dismutase activities in rats treated with 100 mg/kg of PBA in comparison to the control animals (P>0.05). However, the inhibition of CAT and SOD activities in the BPA-treated group was reversed by co-administration with cinnamic acid. Although this reversal was not significant (P>0.05). The cinnamic acid only at 100 mg/kg increased the levels of CAT and SOD when compared with the control (P>0.05).

Figure 3c shows the effect of cinnamic acid on GST activity in the kidneys of rats treated with bisphenol A. The GST activity declined, although not significantly, in the group given 100 mg/kg of BPA. Co-administration with cinnamic acid dose-dependently increased the GST activity compared to the BPA-treated group (P>0.05). GST activity was elevated in the group that received cinnamic acid only at the highest concentration in comparison to the control (P>0.05).

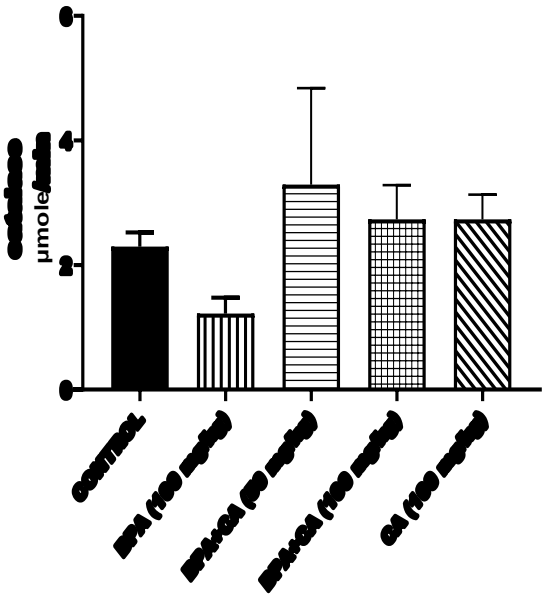

Fig. 3a: Effect of cinnamic acid on PBA-induced changes in the activities of catalase. Values expressed as mean ± standard error of mean (SEM) for five rats in each group. (P>0.05) in all groups compared.

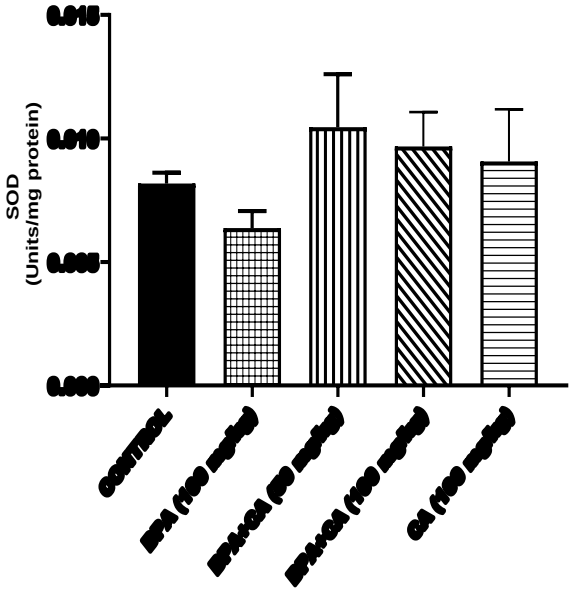

Fig. 3b: Effect of cinnamic acid on PBA-induced changes in the activities of superoxide dismutase. Values expressed as mean ± standard error of mean (SEM) for five rats in each group. (P>0.05) in all groups compared.

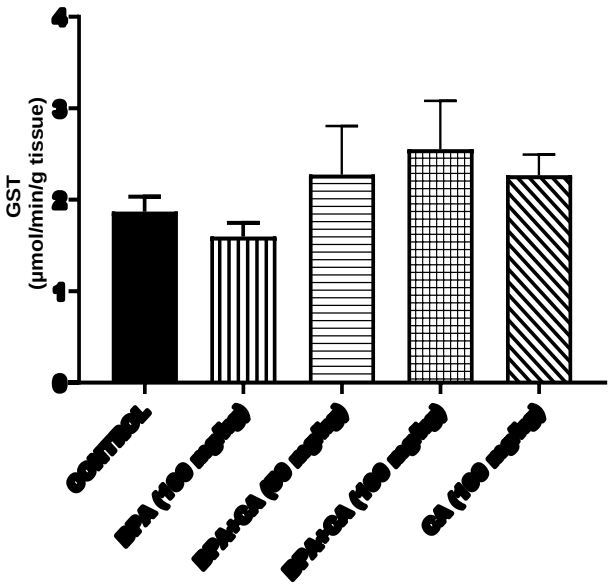

Fig. 3c: Effect of cinnamic acid on PBA-induced changes in the activities of GST. Values expressed as mean ± standard error of mean (SEM) for five rats in each group. (P>0.05) in all groups compared.

Gene Expression

Figure 4a shows that KIM1 gene expression during BPA exposure was lower than in the control group (P<0.05). Co-administration of cinnamic acid with BPA increased KIM1 levels compared to the BPA-only group (P<0.05). Cinnamic acid alone at 100 mg/kg maintained an expression level similar to the control.

Expression of the NGAL gene in bisphenol A-exposed rats was reduced in comparison with the control rats (P<0.05), as shown in Figure 4b. However, there was an increase in its expression in the kidney when PBA was combined with cinnamic acid (P<0.05).

TNF-α concentration was lower in rats administered PBA than in the control animals (P<0.05). A combination of cinnamic acid and bisphenol A significantly raised TNF-α levels relative to the BPA-only group (Figure 4c).

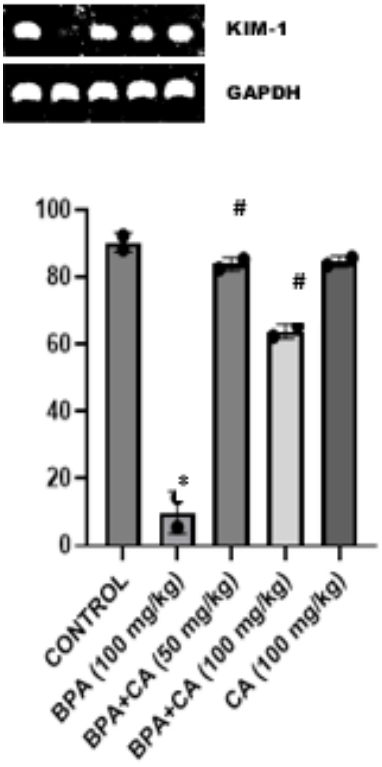

Fig. 4a: Effect of cinnamic acid on KIM1 gene in bisphenol A-exposed rats. Values expressed as mean ± standard error of mean (SEM) for five rats per group. *P<0.05 when compared to the control; #P<0.05 when compared to the BPA only.

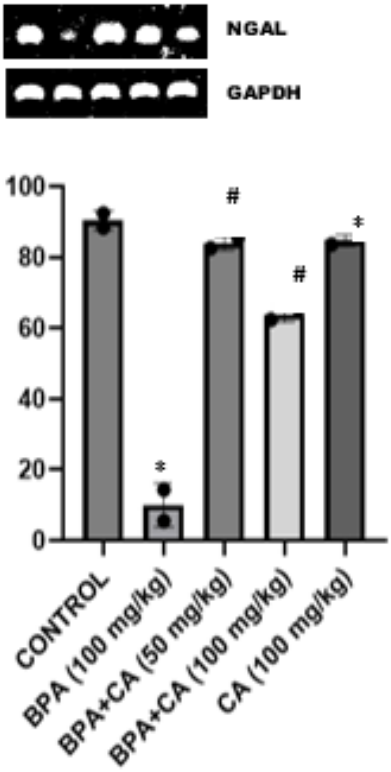

Fig. 4b: Effect of cinnamic acid on NGAL gene in bisphenol A-exposed rats. Values expressed as mean ± standard error of mean (SEM) for five rats in each group. *P<0.05 when compared to the control; #P<0.05 when compared to the BPA only.

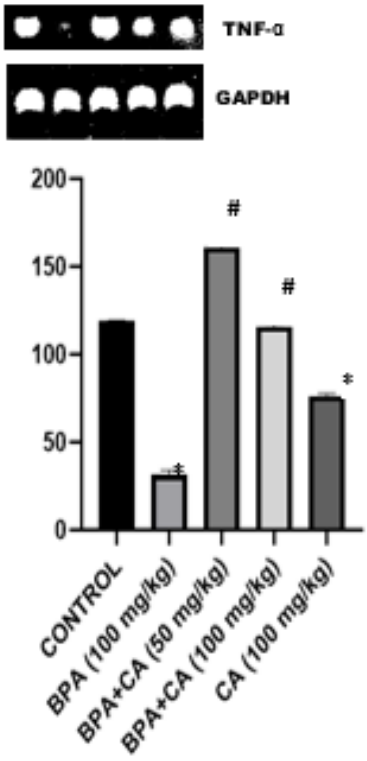

Fig. 4c: Effect of cinnamic acid on renal TNF-α in bisphenol A-exposed rats. Values expressed as mean ± standard error of mean (SEM) for five rats per group. *P<0.05 when compared to the control; #P<0.05 when compared to the BPA only.

Expression of IL-6 was lower in the kidney of the BPA-exposed group when compared with the control (P<0.05). Co-administration of cinnamic acid with BPA increased IL-6 expression in the rat kidney when compared to BPA-only treated rats (P<0.05) as shown in Figure 5a.

The BPA group showed a significant drop in NRF2 level compared with the control (P<0.05). The combined administration of cinnamic acid and BPA led to a notable increase in NRF2 level compared with the BPA group (P<0.05) (Figure 5b).

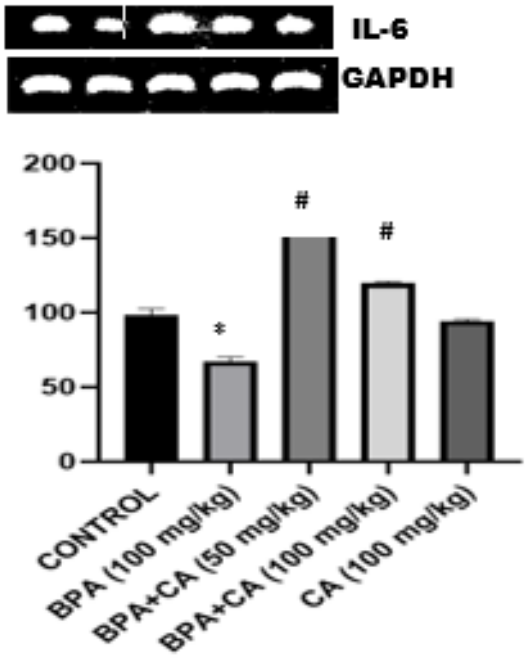

Fig. 5a: Effect of cinnamic acid on the expression of IL-6 in bisphenol A-exposed rats. Values expressed as mean ± standard error of mean (SEM) for five rats per group. *P<0.05 when compared to the control; #P<0.05 when compared to the BPA only.

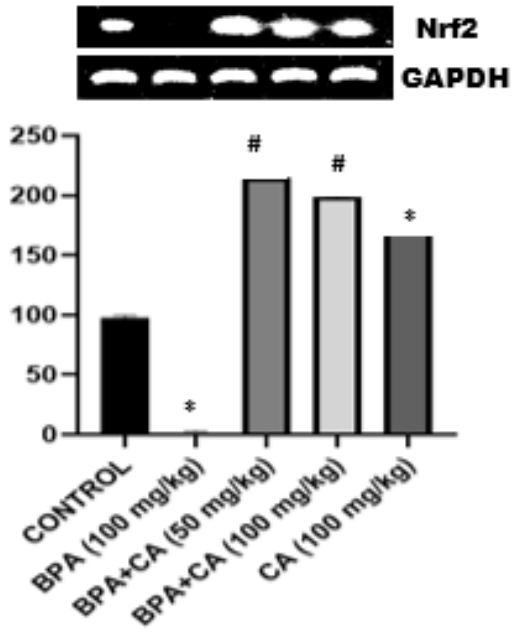

Fig. 5b: Effect of cinnamic acid on renal NRF-2 in bisphenol A-exposed rats. Values expressed as mean ± standard error of mean (SEM) for five rats per group. *P<0.05 when compared to the control; #P<0.05 when compared to the BPA only.

Histology

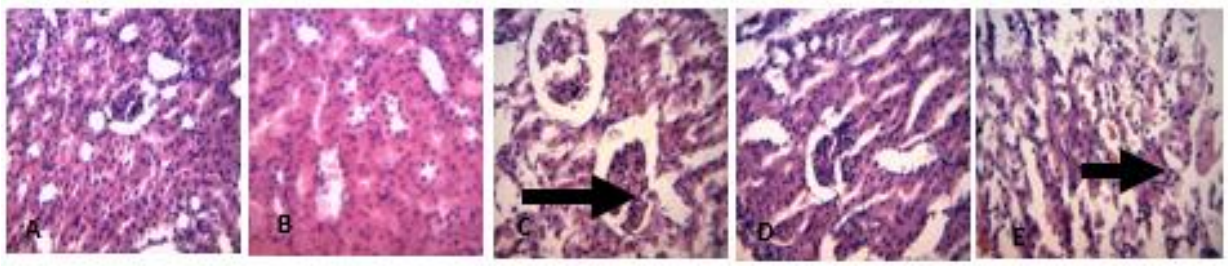

Fig. 6: The photomicrographs (×400) of rats' kidney treated with BPA and CA: (A) Control group with corn oil displays no visible lesions (B) Group given BPA only shows no noticeable lesions (C) group administered with BPA (100 mg/kg) and CA (50 mg/kg) presents glomeruli that appears slightly congested (D) group treated with BPA and CA (100 mg/kg each) shows no visible lesions (E) group treated with CA only (100 mg/kg) shows moderate to severe tubular degeneration and necrosis.

Discussion

The current study evaluated the renoprotective effects of cinnamic acid and its combination with bisphenol A in a rat model of BPA-induced nephrotoxicity. It also investigated the mechanisms involved in BPA-induced kidney damage, focusing on the Nrf2/oxidative stress pathway. Results showed that kidney function may have worsened, as evidenced by a significantly higher serum urea level in the BPA-treated group compared with the control group. This indicates that BPA negatively affects glomerular functions,

which can impair the kidney's ability to excrete waste products. Previous research by Abdelrazik *et al.* (2022) demonstrated that BPA exposure causes deterioration of kidney function, associated with a significant increase in urea levels. However, there was a decrease in creatinine level. This finding may be explained by *increased* glomerular filtration rate, known as hyperfiltration, in early BPA exposure, which can make serum creatinine *appear* normal or low and mask the damage. A study on the renal effects of BPA in mice (Moreno-Gómez-Toledano *et al.*, 2022) also showed that BPA-treated mice did not show an increase in serum creatinine. However, cinnamic acid co-administration induced a significant decrease in urea level. The decrease in serum urea level following cinnamic acid treatment may be associated with improvement of glomerular filtration rate and renal filtration barrier function, in alignment with the proposed antioxidant mechanism (*Abd-Elhamid et al., 2018).*

The data obtained in this study revealed a disturbance in the antioxidant defensesystem due to exposure to BPA, as evidenced by a marked increase in lipid peroxidation and a depletion in GSH level. Along with this, the activities of SOD, catalase and GST diminished following the administration of BPA. Therefore, the data obtained in this study verified the contribution of oxidative stress in the toxicity induced by BPA. The ability of BPA to inhibit the gene expression of antioxidant enzymes and alter their activities has been described (Kang *et al.*, 2025; Linillos-Pradillo *et al.*, 2023). Also, its implication in the generation of reactive oxygen species, leading to oxidative stress and tissue damage, has been reported by Yoo *et al.* (2022). Excessive generation of free radical species and the failure of the redox machinery to eliminate these radical products, which can impair the cellular defense system, might explain the elevation in MDA level, an index of lipid peroxidation (Linillos-Pradillo *et al.*, 2023; Tiwari and Vanage, 2017).

The finding in this study is in accordance with previous studies showing that cinnamic acid can ameliorate oxidative stress in different pathological conditions (Hemmati *et al.*, 2018) and this can be associated with its reactive oxygen species scavenging activity (Pontiki and Hadjipavlou-Litina, 2019). Cinnamic acid is a known antioxidant with protective effects against oxidative stress and inflammatory diseases *in vitro* and *in vivo*. Its antioxidant activity against oxidative stress is based on its property as a polyphenol, which can stabilize the resulting phenoxyl radical by giving an electron or hydrogen atom to the medium, and this can strongly inhibit lipid peroxidation (Santos and Vieira, 2013) or block the amplification of lipid peroxidation (Theodoridis *et al.*, 2025).

Further, we sought to elucidate the molecular mechanisms by which cinnamic acid exerts its protective function against BPA toxicity in the kidney. To this end, we targeted the Nrf2, TNF-α, IL-6, KIM1, and NGAL pathways, given their critical roles in modulating cellular responses to oxidative stress and inflammation. It was observed that BPA did not activate the expression of TNF-α, IL-6, KIM1, and NGAL in the kidney. However, our data showed that BPA significantly downregulated renal Nrf2 expression, accompanied by oxidative stress. Studies have shown that BPA can repress the Nrf2 pathway, further enhancing oxidative stress and inflammation (Loboda *et al.*, 2018; Yukta *et al.*, 2026). Cinnamic acid significantly enhanced Nrf2 in the BPA-treated group. This was corroborated by findings from Wang *et al.* (2019), who demonstrated cinnamic acid's ability to enhance Nrf2 nuclear translocation in diabetic kidneys. Similarly, cinnamic acid's role in modulating oxidative stress and inflammation through Nrf2 activation in diabetic rats was highlighted (Bai *et al.*, 2018). These studies align with our findings and underscore Nrf2 activation as a central factor in the protection of cinnamic acid against BPA-induced kidney toxicity.

The photomicrograph of the kidney treated with bisphenol A showed no observable lesions. Even without the immediate visible structural changes, this might still not rule out evidence of no adverse effect. The findings of this study revealed evidence of biochemical changes that supported that BPA induced damage in the kidney. Moreover, the biochemical changes induced by the BPA in the kidney likely preceded the manifestation of histopathological damage. Administration of cinnamic acid at 100 mg/kg to the group that received bisphenol A maintained the structural integrity of the kidney. In conclusion, cinnamic acid showed protective effects against nephrotoxicity induced by bisphenol A through its antioxidant and anti-inflammatory properties.

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Statements and Declarations

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Data Availability
All data supporting the findings of this study are available on reasonable request.