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Original Research Article

Lycopene suppresses α-cypermethrin nephrotoxicity: An insight into its modulatory effect on oxidative stress-mediated pro-inflammation, DNA damage and caspase apoptosis in Wistar rats

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Abstract

Objective: Cypermethrin (CPM) is a synthetic pyrethroid pesticide with ubiquitous use in agriculture, but well associated with nephrotoxicity induction. However, CPM exposure is linked with human and animal systemic toxicity. Lycopene (LYP) is a lipid-soluble potent antioxidant abundant in tomatoes. The investigation thus explored whether LYP could mitigate CPM-induced nephrotoxicity via related mechanisms.

Materials and Methods: The study design featured 4 groups: Control, LYP (10 mg/kg/day), CPM (25 mg/kg bw /day) and LYP (10 mg/kg bw /day) + CPM (25 mg/kg bw /day). The treatments of LYP and CPM were given for consecutive 28 days . Urea, uric acid and creatinine levels were estimated in serum, while glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) activities, and malondialdehyde (MDA), DNA damage, cytokines, interleukin-10 (IL-10), interleukin-6 (IL-6), interleukin-4 (IL-4), and tumor necrosis factor-α (TNF-α), caspase-9 and caspase-3 levels were estimated in the renal tissue sample. Histopathology and its amelioration were analyzed.

Results: The sub-acute CPM exposure provoked renal damage with significantly elevated levels of creatinine, uric acid, and urea. Renal antioxidant homeostasis was markedly impaired via depressed GPx, CAT, and SOD renal activities, and increased MDA level. Marked DNA damage and profound increases in the renal levels of caspase-9, IL-6, TNF-α, and caspase-3 were found, whereas the renal IL-4 and IL-10 levels were evidently reduced in comparison to the control. Interestingly, the LYP co-administration abrogated the CPM-induced oxidative stress, proinflammation, apoptosis, and DNA fragmentation.

Conclusion: Our findings indicate that LYP supplementation may protect the kidney from oxidative stress-related attacks of CPM.

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Introduction

Cypermethrin (CPM) is a pesticide classified by the World Health Organization (WHO) as a moderately hazardous synthetic class II pyrethroid (Vardavas et al. 2016; Famurewa et al. 2023). It is ubiquitously applied to control household insects such as ectoparasites and mites, veterinary use and killing of pests. In the target insects and pests, pyrethroid CPM causes selective toxicity on the nervous system leading to death (Ali et al. 2020). Due to CPM wide spectrum of action against insects and various pests, it is frequently used in medical, agricultural and veterinary applications (Hassouna 2020), and therefore human exposure is inevitable. The technical grade of CPM is a racemic mixture of 8 isomers out of which two are referred to as alpha-CPM, the most active form of the isomers (Arafa et al. 2015a). Alpha-CPM is widely used as ectoparaticide and as an important insecticide in food production and several public health programs. Thus, its exposure could occur during spray, dipping, ingestion or via the ingestion of exposed foods/crops (Arafa et al. 2015).

Moreover, reports of CPM-induced toxicity in humans and animals exist in the literature, and its neurotoxic and genotoxic effects have been confirmed (Ali et al. 2020; Hassouna 2020). The ovarian reserve was depleted via CPM-induced mitochondrial dysfunction in granulosa cells (Wang et al. 2019). Organ toxicity such as hepatotoxicity, neurotoxicity, nephrotoxicity, hematotoxicity, testicular toxicity and pulmonary toxicity triggered by CPM have been reported (Arafa et al., 2015; Hussain et al., 2023; Kašuba et al., 2022). The underpinning mechanisms of the deleterious effects of CPM on the organs have been linked with oxidative inflammation and apoptotic cascades. The hepatic catabolites of CPM excreted in the urine with CPM are reported to accumulate in the body tissues, including the kidney (Anwar et al. 2020; Hussain et al. 2023; Manna et al. 2005). Thus, they generate reactive oxygen species (ROS)to causing oxidative stress triggering oxidative damage via lipid peroxidation of cellular membrane, DNA damage and protein oxidation, which further activate cytokine inflammation in the kidney and other organs (Afolabi et al. 2019; Arafa et al. 2015a). CPM is implicated to cause oxidative nephrotoxicity demonstrated by increased creatinine, total bilirubin, and urea levels, depressed antioxidant homeostasis and elevated inflammation; however, apoptotic effect is sparsely reported (Abdou et al. 2012; Afolabi et al. 2019; Anwar et al. 2020).

Natural antioxidant could mediate cell protection against oxidation and pro-inflammation that may be induced by CPM. Lycopene (LYP) is a bioactive natural product with potent antioxidant efficacy; it belongs to the carotenoids in vegetables and red fruits (Ibrahim et al. 2022). LYC is a red color and waxy character compound abundant in tomato, tomato products, apricots, cranberries, grapes, peaches, watermelon and other vegetables. It is attracting increasing attention due to its various pharmacological effects against pathologies (Ibrahim et al. 2022). LYP modulates a number of signaling pathways for exhibition of antioxidant, anti-inflammatory and antiapoptotic mechanisms (Abdel-naim et al. 2023). However, the hallmark of LYP defense strategy is associated with scavenging of two types of ROS, singlet molecular oxygen ($^1O^2$) and peroxyl radicals to abrogate lipid peroxidation and redox imbalance (Aly et al. 2012). The oxidative mitochondrial impairment in spermatogenesis was reversed by LYP (Aly et al. 2012). LYP prevents phthalate plasticizer mitophagy and oxidative stress by stabilizing the mitochondrial homeostasis (Shen et al. 2023). Literature demonstrates that LYP inhibits oxidative stress and related inflammatory reactions induced by fluorouracil (Alhoshani et al., 2022), acrylamide (Reshmitha and Nisha 2021), fluoride (Mansour and Tawfik

2012), carbon tetrachloride (Altu et al. 2008), diabetes mellitus (Ali and Agha 2009), toxic metals and other toxins (Hedayati et al. 2019). Interestingly, the hepatotoxicity induced by organophosphate pesticide, chlorpyrifos, was halted by LYP via improved antioxidant and antiapoptotic mechanisms (Abdel-naim et al. 2023).

However, there is paucity of data on the apoptotic effect of CPM. More importantly, although there is a report of LYP against CPM toxicity in fish (Yonar 2013), there is no report on the possible effect of LYP on CPM-induced nephrotoxicity. Thus, the present study was undertaken to investigate whether LYP could suppress CPM-induced nephrotoxic oxidative stress, cytokine inflammation and apoptosis in rats.

Materials and Methods

Chemicals

Alpha-cypermethrin (CAS number 52315-07-8) was purchased from Sigma-Aldrich (St Louis MO, USA). Lycopene (deep red powder; CAS No. 502-65- 8) was purchased from Sigma-Aldrich (St. Louis, MO, USA). Commercial kits used in this study were procured from Jiancheng Co (Nanjing, China) and Biodiagnostics, Cairo, Egypt, including superoxide dismutase (SOD, Cat. No. SD2520), catalase (CAT, Cat. No. CA2516), glutathione peroxidase (GPx, Cat. No. GP2524), and malondialdehyde (MDA, Cat. No. MD2528).

Animals

Twenty-four (24) adult albino male rats (180-200 g) were bought from the Faculty of Science, King Faisal University in Saudi Arabia. The experimental protocols were carried out based on research ethics protocols of King Faisal University, Saudi Arabia (Reference number: KFU-REC-2023-FEB-ETHICS582). Stainless steel cages were used to keep the animals at 22±3°C and 55±5% relative humidity, 12-hr light/12-hr dark cycle basis. We provided water and feed without restrictions to the rats.

Experimental design

After a 2-week acclamation period, the male rats were divided blindly and randomly into four (4) experimental groups (6 rats/group) as shown below:

Group 1 (Control): Rats was given the vehicle oil (corn oil) orally.

Group 2 (LYP): Rats received LYP in corn oil (10 mg/kg bw), orally daily for 28 days.

Group 3 (CPM): Rats received CPM in corn oil (25 mg/kg bw) orally daily for 28 days.

Group 4 (LYP + CPM): Rats received LYP in corn oil (10 mg/kg bw) orally daily for 28 days + CPM in corn oil (25 mg/kg bw) orally for 28 days.

The dose of CPM was selected according to a published work (Mohasina et al. 2022). The dose of LYP was selected according to a published work (Oguz et al. 2015). On the morning of the 29th day, the rats were anesthetized for the collection of blood. The blood was collected into clean tubes without an anticoagulant. After clot formation for 30 min, the samples of blood were subjected to centrifugation at 1500 × g for 15 min at 4^{o}C. The serum samples were stored at -20^{o}C till the analyses. The rats were euthanized using 100 mg/kg ketamine HCl and 10 mg/kg xylazine. Kidney samples were collected for biochemical and histological studies. Kidney homogenate samples were prepared with 100 mg kidney tissue in 0.9 ml of phosphate buffered saline (PBS)solution. The tissue homogenate was cold centrifuged (4^{o}C) at 5000 rpm for 20 min. The clear supernatant at the top was stored in -80^{o}C for biochemical analyses.

Estimation of kidney function serum markers (urea, creatinine and urea)

Serum creatinine, urea, and uric acid levels were estimated by the colorimetric protocols of commercial kits.

Estimation of oxidative stress markers

The estimation of renal oxidative stress markers were determined using the respective kits.

Estimation of renal pro-inflammation markers

The renal levels of cytokines of inflammation, interleukin-6 (IL-6, Cat No R016), tumor necrosis factor-α (TNF-α, Cat No R019) and anti-inflammatory cytokines, interleukin-10 (IL-10, Cat No R017) and interleukin-4 (IL-4, Cat No R013) were determined in the supernatant samples using respective ELISA kits purchased from Jiancheng Co (Nanjing, China) and Biodiagnostics, Cairo, Egypt.

Estimation of renal apoptotic markers

Renal caspase 9 (Cat No: A069) and caspase 3 (Cat No: A064) were estimated in renal supernatant with ELISA kits for rats following the directives of the kit manufacturers.

DNA fragmentation analysis

The fragmentation of DNA was analyzed by agarose gel electrophoresis. The kidney was used to extract the DNA using Wizard Genomic DNA Purification Kit (Promega Corporation Company, WI, USA) based on the instruction of the manufacturer. The purity and amount of DNA was detected by with the use of spectrophotometer at 260 and 280 nm. The DNA was electrophoresed on 2% agarose gel and stained with ethidium bromide (0.5 µg/ml) (Zhivotovsky et al. 2001). DNA fragmentation pattern was photographed using a gel documentation system.

Renal histology

The kidney samples were fixed in 10% formalin and dehydrated in ethanol and then, embedded in paraffin blocks. The blocks were cut into 5-µm sections using a microtome instrument, fixed on slides and stained with hematoxylin and eosin (H&E). The observation of the slides was carried out under light microscope. The histopathological changes in the kidney sections were graded semi-quantitatively in at least 3 photomicrographs from each group: normal structure (0), mild (1), moderate (2) and severe (3) following evident histopathological changes (Bancroft & Gamble, 2002)

Statistical analyses

The data from this study was analyzed using GraphPad prism statistical software package (version 8; GraphPad Software Inc., San Diego, CA, USA). Data were compared using one-way ANOVA followed by Tukey test. Level of significant differences was set at $p<0:05$. The data is presented as mean ± SEM (n = 6).

Results

LYP enhanced kidney function in CPM-exposed rats

Table 1 depicts the effects of LYP and CPM the serum levels of creatinine, urea, and uric acid in CPM-exposed rats. We observed that CPM significantly ($p<0.05$) increased the urea, creatinine and uric acid levels in the CPM group in comparison to the control group. However, the LYP co-administration in the LYP + CPM group significantly ($p<0.05$) decreased the serum markers in comparison to the CPM group.

LYP suppressed renal oxidative stress in CPM-exposed rats

Table 2 presents the effects of LYP and CPM on renal activities of SOD, CAT, and GPx, and levels of MDA in CPM-exposed rats. Our results showed that CPM induced prominent ($p<0.05$) suppression in the renal activities of SOD, CAT, and GPx compared to the control. CPM also caused a marked increase in the level of MDA compared to the control. Conversely, LYP in the LYP + CPM group reversed the oxidative effect of CPM via significant increases in the activities of SOD, CAT and GPx, whereas MDA level reduced noticeably ($p<0.05$) compared to the CPM group.

Table 1. Effect of LYP and CPM on kidney function markers in CPM-exposed rats

Group	Urea (mg/dl)	Creatinine (mg/dl)	Uric acid (mg/dl)
Control	31.20 ± 0.85	0.49 ± 0.02	1.72 ± 0.05
LYP	32.10 ± 1.27	0.48 ± 0.01	1.73 ± 0.06
CPM	56.20 ± 1.82*	0.89 ± 0.01*	4.44 ± 0.05*
LYP + CPM	40.60^{c} ± 1.22$^{\#}$	0.69^{c} ± 0.02$^{\#}$	2.62^{c} ± 0.04$^{\#}$

Data are shown as mean ± SEM (n = 6 rats/group). LYP: lycopene; CPM: Cypermethrin; *p<0.05: significant compared to the control group in the same column. #p<0.05: significant compared to the CPM group in the same column.

Table 2. Effect of LYP and CPM on renal oxidative stress in CPM-exposed rats

Group	SOD	CAT	GPx	MDA
Control	79.60 ± 1.08	57.04 ± 1.38	75.40 ± 1.44	32.22 ± 0.78
LYP	78.20 ± 1.43	56.80 ± 1.46	74.80 ± 1.62	33.80 ± 1.07
CPM	34.03 ± 1.09*	35.20 ± 1.46*	45.20 ± 1.74*	63.09 ± 1.14*
LYP + CPM	58.59 ± 1.05$^{\#}$	45.60 ± 1.63$^{\#}$	58.43 ± 1.58$^{\#}$	43.12 ± 0.72$^{\#}$

Data are shown as mean ± SEM (n = 6 rats/group). LYP: lycopene; CPM: Cypermethrin; *p<0.05: significant compared to the control group in the same column. #p<0.05: significant compared to the CPM group in the same column.

LYP induced anti-inflammatory effect against CPM renal inflammation in rats

Figure 1 presents the effects of LYP and CPM on renal levels of pro-inflammatory (IL-6 and TNF-α) and anti-inflammatory (IL-10 and IL-4) markers in rats exposed to CPM. We found that CPM triggered significantly (p<0.05) elevated renal levels of IL-6 and TNF-α, while the anti-inflammatory IL-10 and IL-4 levels decreased markedly (p<0.05) in comparison to the control. The concomitant administration of LYP significantly reversed the cytokine levels in comparison to the CPM group.

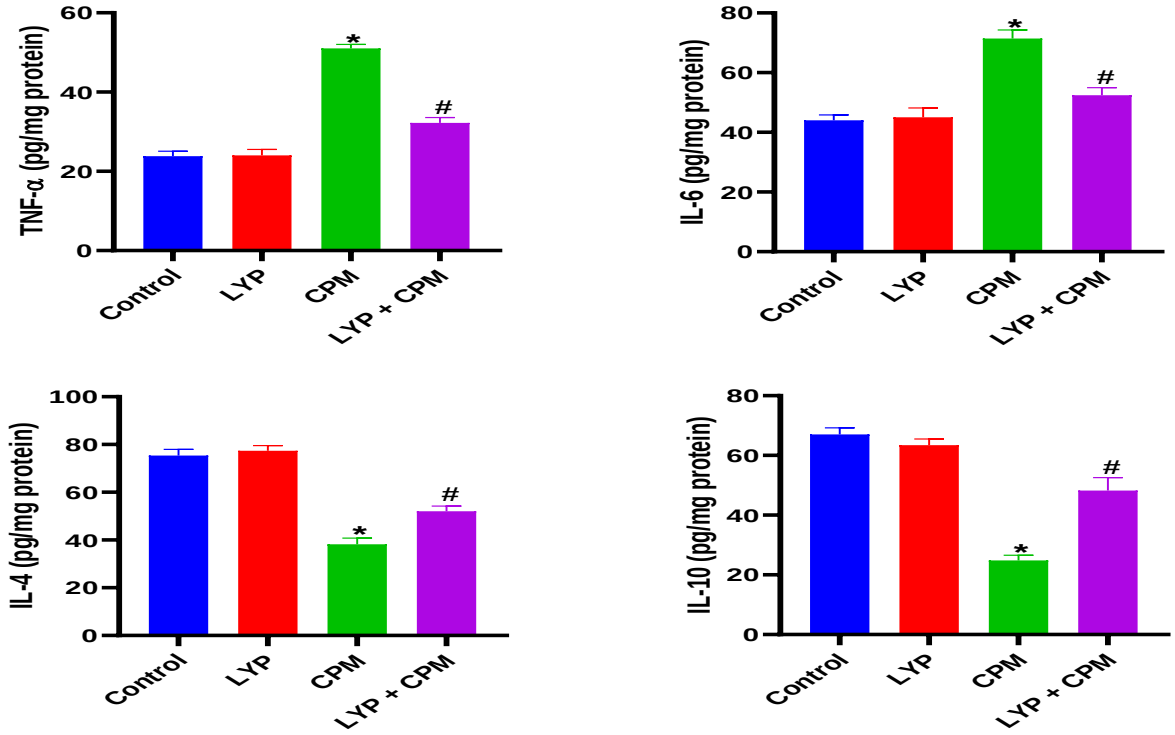

Figure 1. Effects of LYP and CPM exposure on renal levels of cytokines in CPM-exposed rats. Data are shown as mean ± SEM (n = 6 rats/group). LYP: Lycopene; CPM: Cypermethrin; *p<0.05: significant when compared to the control group. #p<0.05: significant when compared to the CPM group

LYP inhibited caspase-dependent apoptosis in CPM-exposed rats

Figure 2 shows the impact of LYP and CPM on renal caspase-3/-9 in CPM-exposed rats. CPM significantly elevated the renal levels of caspase-9, -3 in comparison to the control ($p<0.05$). Conversely, LYP significantly blocked the renal apoptosis depicted by prominent decrease in the renal levels of caspase-9 and caspase-3 compared to the CPM group.

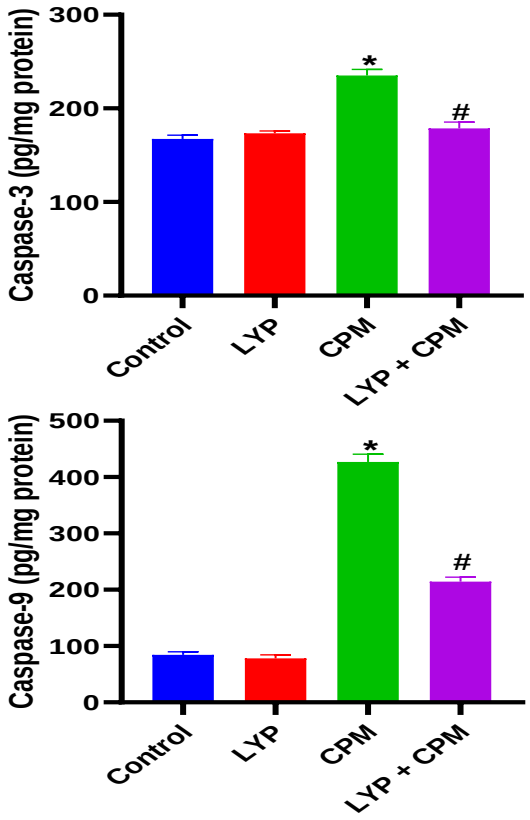

Figure 2. Effects of LYP and CPM exposure on renal levels of caspase 3/-9 in CPM-exposed rats. Data were displayed as mean ± SEM (n = 6 rats/group). LYP: Lycopene; CPM: Cypermethrin; *$p<0.05$: significant when compared to the control group. #$p<0.05$: significant when compared to the CPM group.

LYP ameliorated renal DNA fragmentation in CPM-exposed rats

Figure 3 reveals the effects of LYP and CPM on kidney DNA integrity in rats exposed to CPM. It was observed that the CPM caused higher stain in DNA damage or DNA fragmentation evidenced by intense stain in comparison to the control. LYP ameliorated the DNA damage compared to the CPM group.

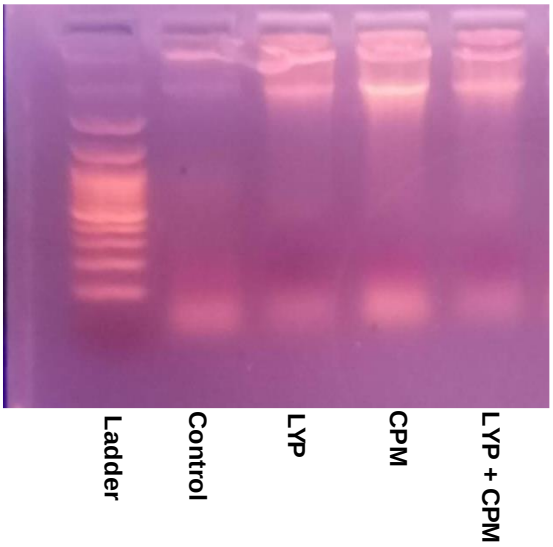

Figure 3. Electrogram for LYP-mediated protection from CPM-induced DNA fragmentation in rat kidney. Effects of LYP and CPM on DNA fragmentation/damage in CPM-exposed rats. LYP: Lycopene; CPM: Cypermethrin.

CPM exposure induced histopathological abrasions

Effects of LYP and CPM on renal histology are presented in Figure 4. The control as well as the LYP control tissues revealed normal structures according to histopathological evaluations. Histopathological lesions were found in the CPM group shown by marked hypertrophy, congestion and degeneration of glomeruli. In LYP + CPM group, there was a significant amelioration in the renal architecture compared to the CPM renal histology.

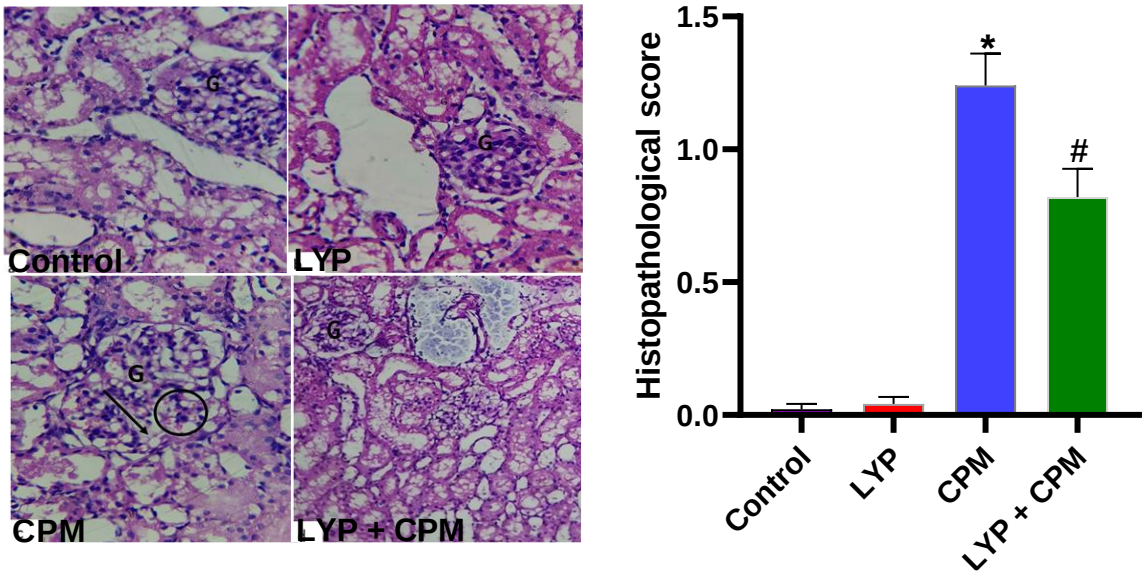

Figure 4. Effect of LYP and CPM on renal histological structures in CPM-induced nephrotoxicity. Control and LYP: showing normal renal corpuscle with typical renal histology (G: Glomerulus). CPM: showing congested tubules (circle), hypertrophy, congestion and degeneration of glomeruli (G).

Discussion

In this investigation, CPM adversely depressed the renal function as demonstrated by considerably decreased levels of serum creatinine, uric acid, and urea in comparison to the control group (Table 1).

The kidneys act as biological sieve for blood to remove metabolic wastes via renal glomerular filtration and selective reabsorption. Due to the impairment, the removal of creatinine, urea or uric acid becomes ineffective and thus, these wastes accumulated in the blood and resulted in the increased levels of serum creatinine, uric acid, and urea found in our study in agreement with the literature (Afolabi et al. 2019; Anwar et al. 2020). Therefore, CPM is nephrotoxic and caused histopathological lesions observed in the renal histology (Abdou et al. 2012). Interestingly, LYP inhibited the CPM-mediated renal damage and consequently, significantly reversed the levels of the renal markers in this study. Specifically, the capacity of LYP to protect the kidney from impaired renal function has been reported earlier against toxicity of gentamicin (Patil et al. 2020), renal ischemic reperfusion (Hussien et al. 2020), rifampicin and isoniazid (Bedir et al. 2021).

The renal GPx, CAT, and SOD activities were prominently suppressed by the CPM exposure for 28 days in agreement with the reports of previous studies (Table 2) (Anwar et al. 2020; Hussain et al. 2023). This resulted into DNA breaks and a significant increase in the MDA level, a well-known marker of lipid peroxidative reaction *in vivo* (Anwar et al. 2020). GPx, CAT and SOD are the enzymes that scavenge superoxide ion, hydroxyl ions and peroxyl radicals, respectively. By implication, the suppression of these antioxidant enzymes would allow ROS to accumulate and thus resulted in CPM-induced redox imbalance and/or oxidative stress. However, studies have implicated CPM as a generator of free radicals in targeted tissues (Ashafaq et al. 2023). Abundant evidence demonstrates the deleterious effects of free radicals on macromolecules, membrane lipids, DNA integrity and cell signaling pathways (Abir et al. 2023). ROS exerts its oxidative attack on the cell's antioxidant pool comprising of GSH, SOD, GPx, CAT and other GSH-containing reducing cellular apparatus (Alabbad et al. 2023). ROS oxidizes the bilayer system in membrane fatty acids to yield MDA as a by-product. As a result, the

cell membrane structure weakens and its permeability is pathologically affected (Seven et al. 2022). In the event that the ROS-mediated oxidative attack is overwhelming, it consumes the antioxidant enzymes and redox apparatus leading to their depressed activities and emergence of oxidative stress (Sedky and Famurewa 2024). This might be responsible for the depressed activities of GPx, CAT, SOD and DNA fragmentation herein and the consequent elevated MDA levels. Our results are consistent with other studies that have suggested CPM-triggered renal oxidative stress (Afolabi et al. 2019; Anwar et al. 2020; Ashafaq et al. 2023; Ileriturk et al. 2022). However, it is noteworthy that LYP mitigated the oxidative stress milieu orchestrated by the CPM exposure. This was confirmed by our observation of the notably elevated renal activities of GPx, CAT and SOD, whereas the renal MDA level depreciated conspicuously. The level of DNA fragments was also reduced compared to the CPM group. This implies that LYP impressed antioxidant efficacy against the DNA damage and oxidant tendency of CPM in the kidney. It has been reported that LYP possesses antioxidant effect against cardiotoxicity (Shen et al. 2023), renal ischemia (Hussien et al. 2020), isoniazid nephrotoxicity (Bedir et al. 2021), metabolic syndrome (Albrahim and Robert 2022), liver diseases and disorders associated with aging (Abir et al. 2023; Ibrahim et al., 2022). This result confirm that LYP is an antioxidant carotenoid compound that scavenges ROS and/or suppresses oxidative stress (Abir et al. 2023; Ibrahim et al. 2022).

The crosstalk of inflammation and oxidative stress is a pathological occurrence in disease and toxicity. Oxidative stress triggers inflammatory stress often signaled by increased levels of cytokines and tissue infiltration of immune cells. In the current study, oxidative proinflammation was found and evident by marked increases in renal IL-6 and TNF-α consistent with significant decreases in anti-inflammatory cytokines of IL-10 and IL-4 in comparison to the control group. The oxidative inflammatory degeneration of the glomerulus was observed in the renal histology (Figure 4). The opposite changes in the cytokines strongly suggest induction of inflammatory cascades in the kidney of rats exposed to CPM only (Figure 1). According to the study of Abdou and Sayed (2019), CPM increased hepatic TNF-α, C-reactive protein, and IL-1β levels. Ileriturk et al. (2022) reports that CPM upregulated mechanistic pathways leading to elevated levels of IL-6, TNF-α, IL-1β and induced nitric oxide synthase (iNOS) in the lungs. In the brain and kidney, the levels of inflammation have been found elevated coexisting with oxidative stress in previous studies (Afolabi et al. 2019; Ali et al. 2020; Ashafaq et al. 2023).

Although our study did not explore the possible upregulation in nuclear factor-κB (NF-κB) widely reported to trigger cytokine expression (Arafa et al. 2015), the elevation of IL-6 and TNF-α and depression of IL-10 and IL-4 levels confirm inflammatory signaling and potential of CPM. However, the elevated TNF-α is suggested to initiate mitochondrial impairment (Ashafaq et al. 2023; Sedky and Famurewa 2023). Mitochondrial impairment aggravates mitochondrial stress that stimulates apoptotic cascades linked to cytochrome C and caspase expression (Hussain et al. 2023). In fact, a study suggests that CPM can directly exert mitochondrial dysfunction and consequently induces apoptosis (Wang et al. 2019). This could explain the increased level of apoptosis in this study, whereby the assayed caspase-3 and caspase-9 were significantly increased by CPM in comparison to the control (Figure 2), in agreement with earlier studies. The DNA damage observed in our study is also well reported as a prime trigger of apoptosis (Abdou et al. 2012). In earlier literature, the apoptotic potential of CPM has been indicated in various organs (Arafa et al. 2015; Ashafaq et al. 2023; Wang et al. 2019) in parallel with our findings here.

Herein, we show that CPM could induce apoptosis in the kidney. Intriguingly, LYP was observed to inhibit and reverse the CPM inflammatory and apoptotic disruptions. The renal levels of IL-6, TNF-α, IL-10 and IL-4 as well as that of caspase-9 and -3 were markedly restored compared to the CPM group levels in this study. The anti-inflammatory and antapoptotic effect of LYC may be due to its ability to reduce ROS attack, inhibition of cytokine expression and amelioration of mitochondrial dysfunction (Albrahim and Robert 2022; Bayomy et al. 2017; Hedayati et al. 2019; Ibrahim et al. 2022).

In conclusion, the current study reports the nephroprotective effect of LYP against CPM nephrotoxicity and DNA damage. Our data show that the beneficial effect could be connected with the antioxidant, renal anti-inflammatory and renal antiapoptotic mechanisms orchestrated by LYP against CPM-triggered pro-inflammation and oxidative stress and apoptosis in the kidney of Wistar rats.

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Conflicts of interest

The authors declare no conflict of interests

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Ethical Considerations

All experimental procedures were done according to the research ethics at King Faisal University with reference number KFU-REC-2023-FEB-ETHICS582

Code of Ethics Reference number: KFU-REC-2023-FEB-ETHICS582

Data availability statement

Data is available at the reasonable request from the corresponding author

Authors' Contributions

HE and AS conceptualized and designed the study. NA and MA performed the experiment and analyzed the data. HE and AS wrote the first draft of the manuscript. All authors made corrections and approved the final
manuscript.

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