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Combined extracts of *Curcuma longa* and *Curcuma zedoaria* ameliorates cisplatin-induced kidney damage in rats

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ABSTRACT

Background: Cisplatin (CIS) is a highly effective chemotherapeutic drug. However, it is associated with various side effects, including kidney damage, due to its nephrotoxic properties.

Aim: This study aimed to evaluate the renoprotective potential of the combined extract of *Curcuma longa* and *Curcuma zedoaria* in reducing nephrotoxicity by examining its effects on tumor necrosis factor-alpha (TNF- α), KIM-1, and caspase-3 levels.

Methods: Twenty-five rats were divided into normal control groups (NS), CIS control groups, and three treatment groups that received doses of the combined extract at 100, 200, and 400 mg/kg (CUR100, CUR200, and CUR400), respectively, on day 1–20. All groups, except the NS group (receiving normal saline i.p.), received intraperitoneal CIS (1 mg/kg) on days 7 and 14 of the 20-day extract treatment.

Results: Compared with the rats in the CIS group, rats given the combined extract had a considerable gain in body weight and decreased TNF- α , KIM-1, and caspase-3 expression levels. Histopathological examination revealed that the extract group experienced less kidney damage than the CIS group. The combined extract, administered at 200 mg/kg, exerted the most apparent protective effect, decreasing renal TNF- α , KIM-1, and caspase 3.

Conclusion: The combined extract of *C. longa* and *C. zedoaria* has the potential to be a therapeutic agent for reducing nephrotoxicity by suppressing TNF- α , KIM-1, and caspase-3 levels. Further research is required to determine the potential of this combination therapy in humans.

Keywords: Cisplatin, *Curcuma longa*, *Curcuma zedoaria*, Inflammation, Nephrotoxicity.

Introduction

Curcuma longa, also known as turmeric, is indigenous to India, Indonesia, and South Asia. Numerous conditions involving endocrine, neurological, cardiovascular, digestive, pulmonary, renal, and other systems can be reversed by curcumin (Mantzorou *et al.*, 2018). The Zingiberaceae family member *Curcuma zedoaria* tends to be referred to as “white

turmeric” or “Zedoary” and contains various plants that are frequently used in traditional treatments (Sharifi-Rad *et al.*, 2017). Curcumin has been isolated from *C. longa* and *C. zedoaria*. It also has a broad spectrum of pharmacological activities, including anti-inflammatory, antioxidant, antibacterial, and antineoplastic effects. Considerable scientific interest has been shown in the study of Zhang *et al.*,

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2023. Although *C. longa* and *C. zedoaria* have anti-inflammatory properties, much more must be learned about their combined actions and underlying molecular pathways to mitigate renal damage caused by cisplatin (CIS).

We examined whether these plant anti-inflammatory qualities could lessen the well-known nephrotoxic adverse effects of CIS. The chemotherapy drug CIS (cis-diamminedichloroplatinum II) was administered. Nevertheless, substantial adverse effects, especially nephrotoxicity, accompanying kidney deposits, and CIS biotransformation limit its therapeutic efficacy. Nephrotoxicity is the main adverse effect affecting dosage and is a significant clinical issue, highlighting the significance of studies on the prevention of CIS-induced kidney damage (Volarevic et al., 2019).

Apoptosis and inflammation are critical components of the pathophysiology of renal damage caused by CIS. Inflammation is the primary cause of kidney damage caused by CIS. Studies have demonstrated that CIS increases tumor necrosis factor- α (TNF- α) levels. Several studies have shown that anti-inflammatory drugs can inhibit CIS-induced inflammation (Ramesh and Brian Reeves, 2002).

It has been hypothesized that DNA damage, decreased protein synthesis, and mitochondrial damage leading to apoptosis are the main causes of the adverse effects of CIS. Apoptosis, the primary cause of inflammation, has been linked to several kidney diseases caused by nephrotoxic medications (Santos et al., 2007).

Current strategies for mitigating CIS-induced nephrotoxicity are frequently inadequate because of their limited effectiveness, unfavorable side effects, and inability to specifically target the pathways causing kidney damage. Thus, the development of innovative treatment approaches is urgently required. Numerous studies have examined the effects of these difficulties on CIS-induced nephrotoxicity. This study aimed to evaluate the renoprotective potential of the combined extract of *C. longa* and *C. zedoaria* in reducing nephrotoxicity by examining its effects on TNF- α , KIM-1, and caspase-3 levels.

Materials and Methods

Plant material and extract preparation

We obtained and confirmed taxonomically authenticated rhizomes of *C. longa* and *C. zedoaria* (document number 306/IT3. L. P13/TA.00.03/M/B/2023, No. 305/IT3. L. P13/TA.00.03/M/B/2023) from the Tropical Biopharmaca Research Center of IPB University, Bogor, West Java, Indonesia. The extraction process for *Simplicia* used the maceration method with pharmaceutical-grade 96% ethanol for three consecutive periods of 24 hours each. A 1:10 sample-to-solvent ratio was established (Kemenkes, 2017), and extracts from *C. longa* and *C. zedoaria* were combined in equal amounts to create a 1:1 blend.

CIS injection preparation

CIS was purchased from PT. Dankos Farma, Indonesia. Each vial containing 50 mg/50 ml of water is included in each vial. The amount of CIS administered was determined based on the animal's body weight (BW). CIS (1 mg/kg) was added without dilution.

Animal and experimental design

The rats were procured from the PT. Biofarma, Indonesia. The rats were housed in an animal care facility with a 12-hour day-and-night cycle before the investigation, standard feed, unlimited access to water, temperature (20°C–25°C), and humidity levels (40%–70%) for 1 week to allow them to become acclimated to their environment.

Twenty-five male *Wistar* albino rats were aged 12 weeks (weight range: 175–200 g). Five random groups ($n = 5$ each) of rats were established: normal control (NS), CIS control, extract100 + CIS (CUR100), extract200 + CIS (CUR200), and extract400 + CIS (CUR400). The rats in the extract-treated groups were orally administered 100, 200, and 400 mg/kg of the combined extract of *C. longa* and *C. zedoaria* every day from day 1 to 20. Similarly, normal saline was administered to the NS and CIS groups. Two doses (1 mg/kg BW in saline solution) of CIS-induced kidney damage were administered at 7-day intervals (on days 7 and 14) and injected intraperitoneally (i.p.) in all groups, except the NS group, which received an intraperitoneal injection of saline. The dose of 1 mg/kg CIS and extracts was based on a previous study (John et al., 2009; El-Waseif et al., 2022) with modifications. The rats were administered a mixture of ketamine (80 mg/kg BW) and xylazine (10 mg/kg BW) on the 21st day of the experiment to induce their unconsciousness. The left kidney was stored at 80°C until molecular analysis, whereas the right kidney was maintained in 10% buffered neutral formalin for histological evaluation.

Body and renal weight

Each rat's BW was measured at four time points: days 0, 7, 14, and 21 (final day) when the rat was sacrificed. The weight of each kidney was measured after kidney removal, divided by the weight of the body (g), and then multiplied by 100 (Nosrati et al., 2021).

Histological examination

The kidney tissue was cut into 5 μ m slices and stained with hematoxylin and eosin (H&E). Hematoxylin and eosin (H&E) staining was performed by deparaffinizing the kidney tissue sections with xylol, followed by rehydration using graded ethanol. Preparations were stained by immersing them in Mayer's H&E. The tissues were then dehydrated using absolute and 96% ethanol. The tissue was immersed in xylol for cleaning. Glass cover and gum attachment were the final steps in the observation of histopathology (Etriwati et al., 2023). An Olympus BX-51 light microscope (Olympus Corp., Tokyo, Japan) was used for inspection. Blinded, 200x magnification images of the renal cortical regions were acquired to assess the results.

RNA isolation and quantitative real-time polymerase chain reaction (qRT-PCR) assay

The kidney tissue samples were processed for RNA extraction using a Tiangen Biotech kit (product number: 4992858). The RNA concentration was measured using a NanoDrop spectrophotometer (Thermo Fisher Scientific). Then, 10 µl of entire RNA was transferred to cDNA using the Sisco Research Laboratories cDNA Synthesis Kit (94837) according to the manufacturer's instructions. qRT-PCR was performed using an Applied Biosystems 7500 Fast qRT-PCR system (Applied Biosystems, USA) to assess the expression levels of TNF-α, caspase 3, and KIM-1 RNA. The PCR mixture comprised 2 µl of cDNA, 100 ng of both forward and reverse primers, and 10 µl the KAPA SYBR Fast rox low qPCR kit (KK4619) from Kapa Biosystems (MA, USA) and nuclease-free water to a final volume of 20 µl. The cycling steps of PCR amplification were as follows: initial denaturation (95°C, 3 minute), with subsequent 40 cycles of amplification, denaturation (95°C, 5seconds), and annealing (57°C, 30 seconds). The procedure was performed in triplicate for each sample. The relative expression was calculated as follows: $\Delta\text{Ct} = \text{Average Ct (ERCC1)} - \text{Average Ct (ACTB)}$, $\text{Relative Expression} = 2^{-\Delta\text{Ct}}$ (Takemoto et al., 2019). Table 1 lists the primer sequences for the target genes and the housekeeping gene, β-actin, in rats.

Statistical data analysis

The body and relative kidney weights are presented as averages with standard deviations. A one-way ANOVA followed by Tukey's *post hoc* test was used to assess the importance of data disparities and determine *p*-values. Statistical significance was set at $p < 0.05$. For quantitative real-time RNA expression analysis, data are presented as means accompanied by standard errors of the mean (SEM). Data analysis was performed using SPSS software (version 29.0) running on a Windows environment.

Ethical approval

The Maintenance and Ethics Commission for Animal Use of Indonesia's National Research and Innovation Agency approved the animal experiments (Approval Number: 087/KE.02/SK/05/2023). Each step followed the recommendations of the Manual for Laboratory Animal Care and Use.

Results

The combination of extract affected body and renal weight in CIS-treated rats

The BW of each rat was measured at four time points: day 0, 7, 14, and 21 (Fig. 2). All groups experienced fluctuations in BW. The measured data show a decrease in BW over the observation period in the CIS group due to CIS injection (Fig. 2). In the measurement of the difference in BW at the beginning and end of the study, the CUR200 group experienced significant weight gain compared with the CIS group, which experienced weight loss (Table 2). The kidney weight index did not differ significantly among the study groups (Fig. 3). The results of this study indicate that the combination of *C. longa* and *C. zedoaria* extracts can reduce the negative impact of CIS on BW, which is consistent with the anticipated protective effect.

Histopathological result

Rat kidney photomicrographs from this study are shown in Figure 4; the tubules in the NS group appeared normal and showed no histological alterations. The tubules in the cortex had a standard histological structure (H&E, × 400). H&E staining revealed tubular epithelial cell alterations in the CIS group, including areas exhibiting enlarged tubules with thinning of the epithelial cell layer (Fig. 4A), hyaline casts (Fig. 4B) within several proximal tubule lumens, cellular degradation (Fig. 4C) characterized by fluid-filled spaces, and localized tubular necrosis (Fig. 4D).

Rats administered a combined extract of *C. longa* and *C. zedoaria* at 100 mg/kg BW (CUR100 group) for 20 days and 1 mg/kg of CIS intraperitoneally on days 7 and

Table 1. qRT-PCR test primer sequences.

Name	Sequences	Accession number
TNF-α	Forward	TTCGGAAGTCACTGGATCCC
	Reverse	GGAACAGTCTGGGAAGCTCT
KIM-1	Forward	GTGAGTGGACCAGGCACACA
	Reverse	AATCCCTTGATCCATTGTTTCTT
Caspase-3	Forward	CCGACTTCCTCTATGCTTACTC
	Reverse	CGTACAGTTTCAGCATGGC
β-actin	Forward	AGGAGTACGATGAGTCCGGC
	Reverse	CGCAGCTCAGTAACAGTCCG

qRT-PCR, quantitative real-time polymerase chain Rraction; TNF-α, tumor necrosis factor alpha; KIM-1, kidney injury molecule-1.

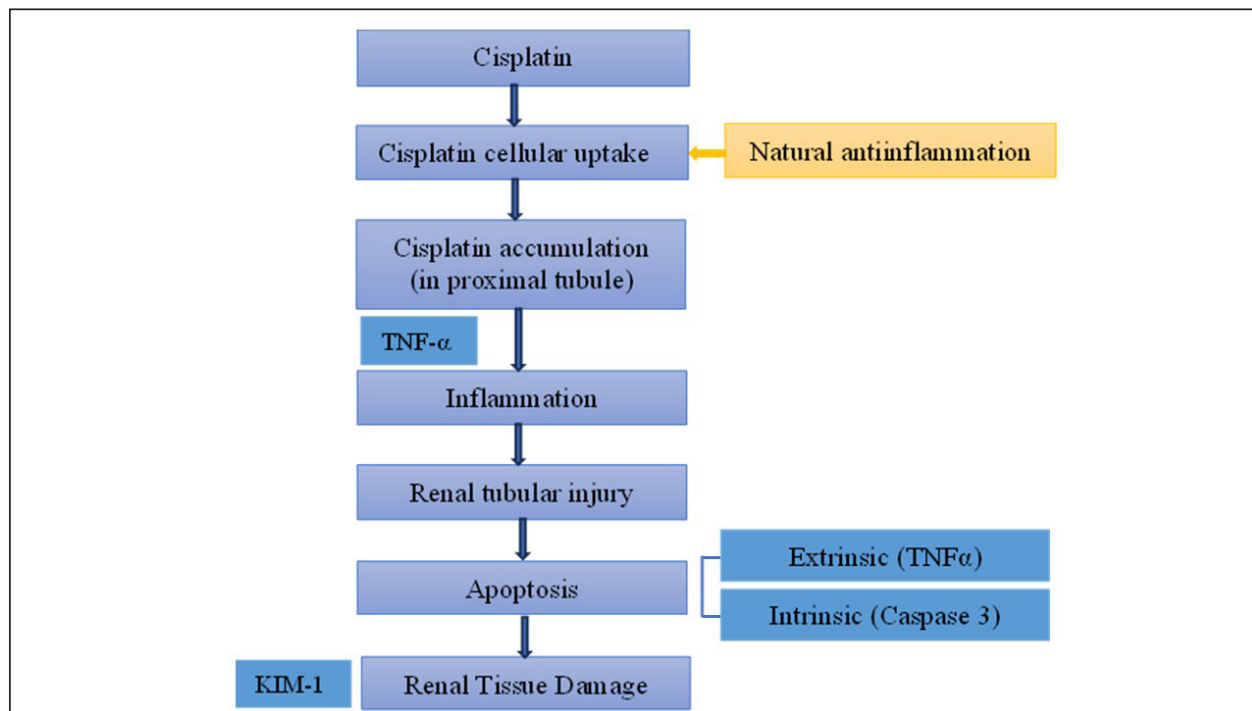


Fig. 1. Pathophysiological mechanisms underlying CIS-induced kidney damage. A pathophysiological diagram illustrates the primary molecular mechanisms involved in CIS-induced kidney damage. Although the interplay between these key pathways remains unclear, the accumulation of platinum in renal tissue is believed to be the main cause of CIS's harmful nephrotoxic effects. CIS accumulation leads to enhanced production of TNF- α (Ramesh and Brian Reeves, 2002; Zhang *et al.*, 2007), which in turn promotes inflammatory responses (Liu *et al.*, 2020) and activates apoptotic cascades (Ni *et al.*, 2019). These apoptotic processes subsequently damage kidney tissue, resulting in the characteristic clinical signs of nephrotoxicity. TNF- α , tumor necrosis factor alpha; KIM-1, kidney injury molecule 1.

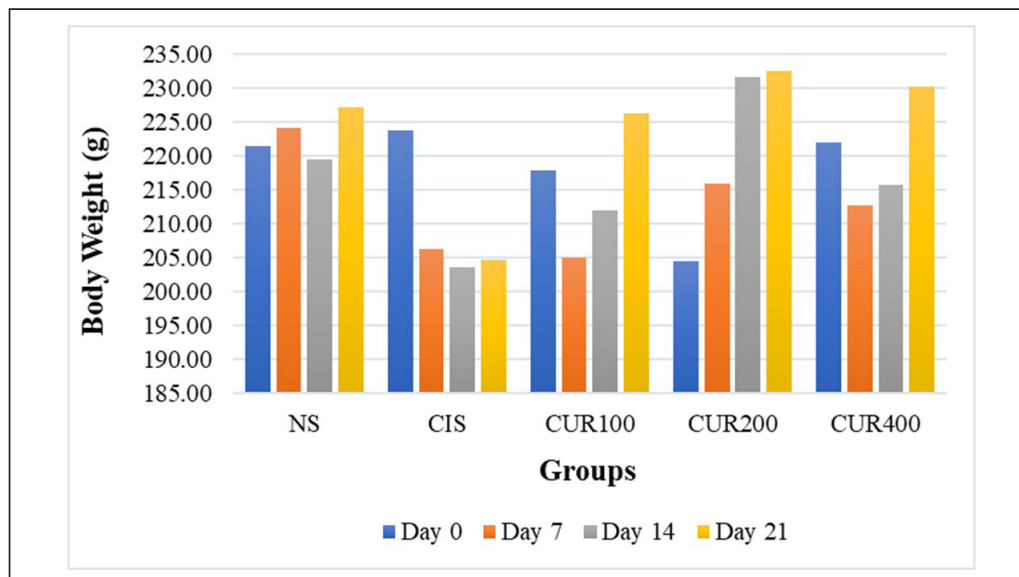


Fig. 2. The effects of the combined extract of *C. longa* and *C. zedoaria* on BW were assessed weekly from day 0 to 21 of the trial. TNF- α , tumor necrosis factor alpha; KIM-1, kidney injury molecule 1; NS, normal control; CIS, cisplatin control; CUR100, extract100 + cisplatin; CUR200, extract200 + cisplatin, and CUR400 extract400 + cisplatin.

Table 2. Effect of combined extract of *C. longa* and *C. zedoaria* administration on the CIS-induced rats' BW in a treatment group.

Groups	Day 0 BW (g)	Day 21 BW (g)	Weight difference (Days 0–21)
NS	221.5 ± 3.39 ^b	227.17 ± 15.09 ^b	+5.67 ± 13.48 ^{ab}
CIS	223.83 ± 5.84 ^b	204.67 ± 15.56 ^{ab}	-19.17 ± 10.67 ^a
CUR100	218 ± 11.33 ^{ab}	226.33 ± 8.50 ^{ab}	+8.33 ± 14.61 ^{ab}
CUR200	204.5 ± 12.94 ^a	232.5 ± 23.96 ^b	+28 ± 29.18 ^b
CUR400	222 ± 7.24 ^b	230.17 ± 1,085 ^{ab}	+8.17 ± 8.91 ^{ab}

(+): increased; (-): decreased. Data presented as mean ± SD, one-way analysis of variance, and Tukey's *post hoc* tests. Values not sharing the same letters in one column differ significantly from each other ($p < 0.05$). TNF- α , tumor necrosis factor alpha; KIM-1, kidney injury molecule 1; NS, normal control; CIS, cisplatin control; CUR100, extract100 + cisplatin; CUR200, extract200 + cisplatin, and CUR400 extract400 + cisplatin.

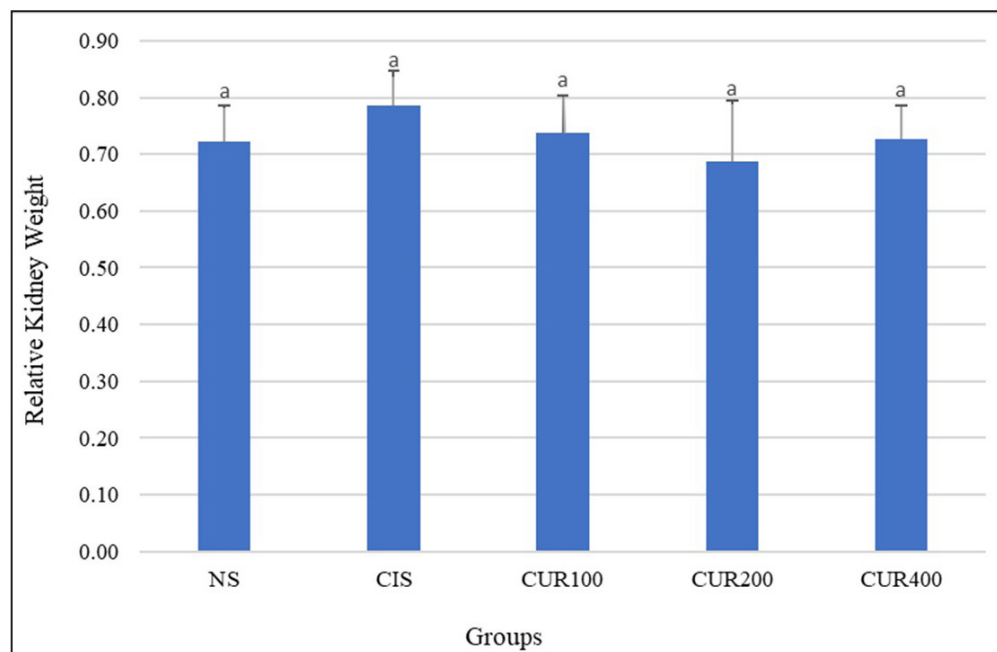


Fig. 3. The combined extracts of *C. longa* and *zedoaria* affect the relative kidney weight. Significant differences are indicated by bars with different superscript characters ($p < 0.05$). TNF- α , tumor necrosis factor alpha; KIM-1, kidney injury molecule 1; NS, normal control; CIS, cisplatin control; CUR100, extract100 + cisplatin; CUR200, extract200 + cisplatin, and CUR400 extract400 + cisplatin.

14 experienced moderate proximal tubule alterations. However, only slight changes were observed in the CUR200 and CUR400 groups. Rats treated with the combined extract exhibited less structural damage on histological examination than rats treated with the CIS extract alone. Rats administered a combined extract at 100, 200, or 400 mg/kg BW (respectively) did not exhibit substantial pathological alterations in their kidneys.

qRT-PCR results

To evaluate and compare the results, qRT-PCR was performed by measuring changes in the gene expression cycle thresholds of TNF- α , KIM-1, and caspase 3. The results showed that the CIS group exhibited an

increased mRNA expression of these markers compared with the NS group. However, as shown in Fig. 5A–C, the groups treated with the combined extract of *C. longa* and *C. zedoaria* showed significantly reduced expression levels, with the most pronounced decreases observed in the CUR200 and CUR400 groups.

Discussion

This study investigated the potential protective effects of combined *C. longa* and *C. zedoaria* extracts on rat kidneys against CIS-induced damage. This investigation focused on examining TNF- α , KIM-1, and caspase 3 markers to assess the efficacy of this herbal combination in mitigating the adverse renal

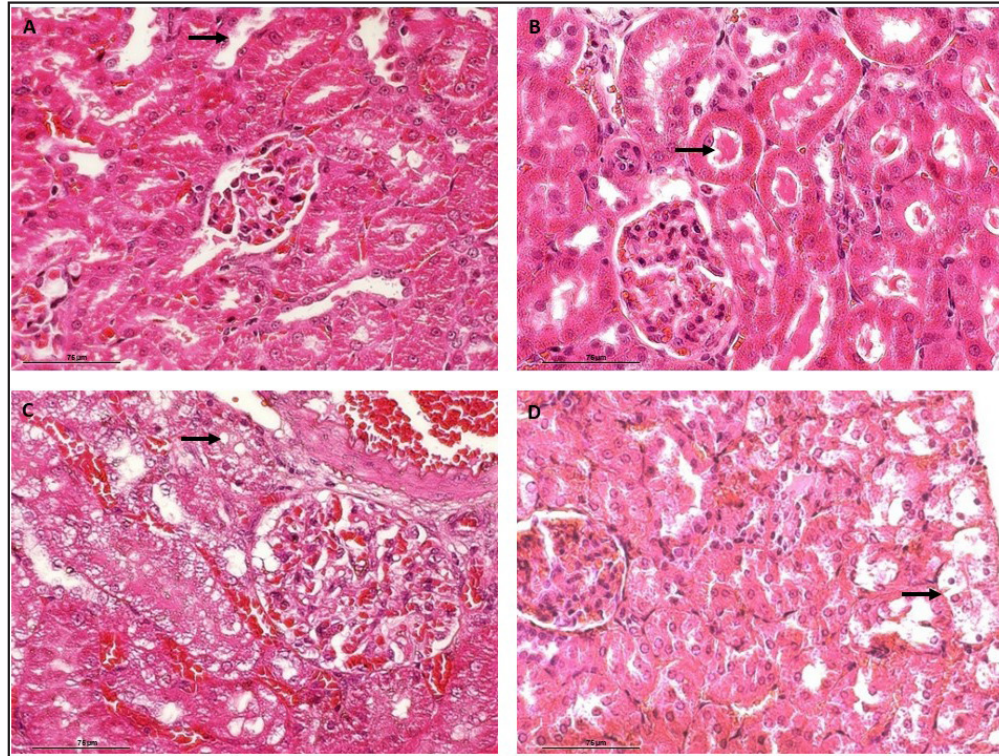


Fig. 4. Photomicrographs of H&E-stained kidney sections from rats treated with *C. longa* and *C. zedoaria* extracts after CIS-induced nephrotoxicity. (A). Enlarged tubules with thinning of the epithelial cell layer (black arrow), (B) hyaline casts (black arrow), (C) cellular degradation (black arrow) characterized by fluid-filled spaces, and (D) localized tubular necrosis (black arrow). Bars = 75 μ .

effects of CIS. A pathophysiological diagram illustrates the primary molecular mechanisms involved in CIS-induced kidney damage (Fig. 1). The combined extract was administered in multiple doses for 20 days in a row, with the first dose of CIS administered on the seventh day and subsequent intraperitoneal injection of CIS (1 mg/kg) administered 1 week later.

The administration of *C. longa* and *C. zedoaria* resulted in BW fluctuations, with an overall upward trend observed at the end of the experiment. However, the NS group exhibited continuous weight gain throughout the study period. In contrast, the CIS group consistently decreased in weight every week until the end of the experiment (Fig. 2). These results are consistent with those of previous studies in which repeated i.p. administration of CIS 1 mg was associated with weight loss, reduced kidney weight, and increased kidney weight/BW ratio (El-Waseif *et al.*, 2022). Changes in organ and BW are commonly used to indicate potential harmful effects in toxicological studies (Shafaei *et al.*, 2015). Decreased renal tubular cell counts may contribute to decreased BW (Basile *et al.*, 2012). The capacity of the manifold to absorb water may be diminished by renal tubular cell necrosis, which increases the amount of fluid lost in urine (Corman *et al.*, 1981).

By identifying inflammatory mediators such as TNF- α , CIS causes an inflammatory response in kidney tubular cells, as shown in both *in vivo* and *in vitro* studies (Domitrović *et al.*, 2013; Teng *et al.*, 2015). Studies have demonstrated the important roles of renal cell apoptosis and programmed cell death in CIS-induced acute kidney damage (Jin *et al.*, 2020). Our findings revealed high TNF- α , KIM-1, and caspase 3 expression in the CIS group. At the same time, the administration of 200 mg/kg BW after two injections of CIS administered 7 days apart reduced the expression of TNF- α , caspase 3, and KIM-1, as the combined extract of *C. longa* and *C. zedoaria* effectively countered these changes. The results align with previous research demonstrating that TNF- α plays a crucial role in tubulointerstitial injury, CIS-induced nephrotoxicity, acute kidney injury (AKI), and chronic kidney disease in animal models, which is associated with elevated levels of TNF- α (Ramesh and Brian Reeves, 2002; Pabla and Dong, 2008; El-Waseif *et al.*, 2022; Widowati *et al.*, 2022).

The well-known anti-inflammatory properties of the combined extract components may explain why the combined extract of *C. longa* and *C. zedoaria* fully or partially restored TNF- α levels to baseline (Pan *et al.*, 2019). Renal epithelial cells, rather than immune cells, can generate TNF- α in urine and blood after

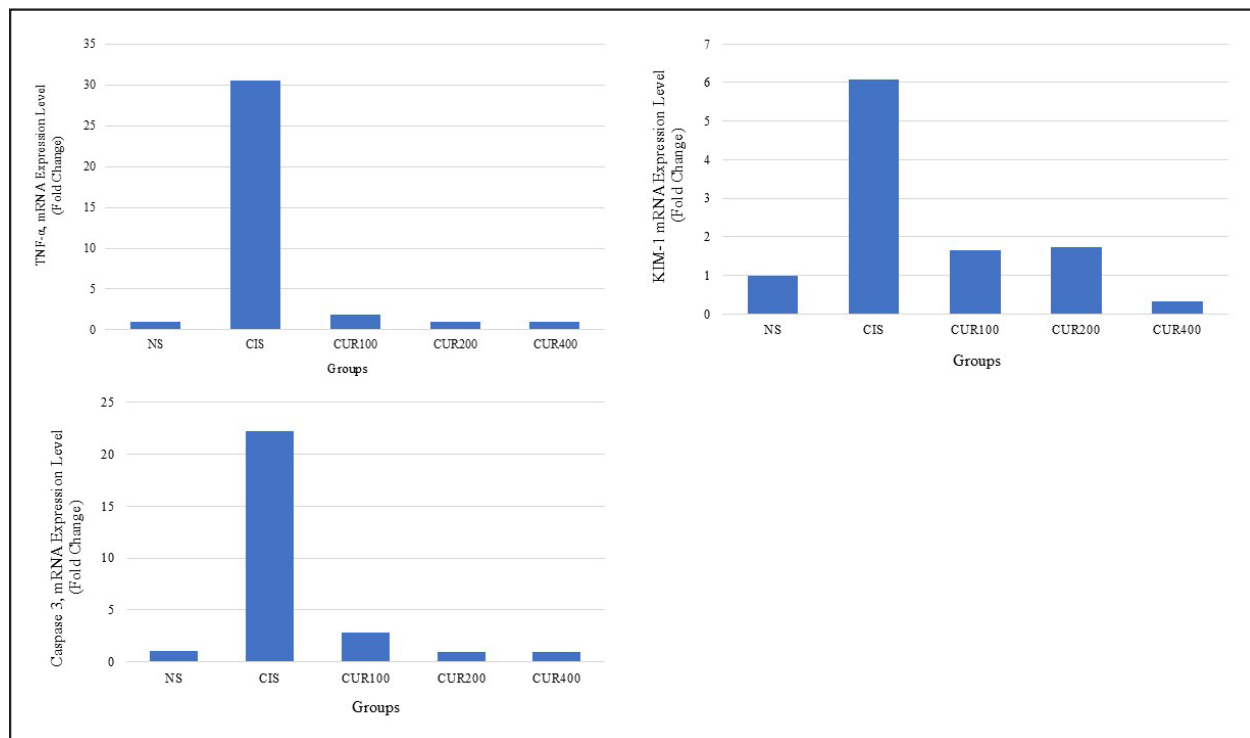


Fig. 5. Kidney quantitative qRT-PCR histogram of TNF- α (A), KIM-1 (B), and caspase 3 (C) gene expression in the rats treated with *C. longa* and *C. zedoaria* extracts after CIS-induced nephrotoxicity. The CIS group had significantly higher TNF- α , caspase 3, and KIM-1 expression levels than the control group. Furthermore, compared with the CIS group, all groups treated with the combined extract showed reduced TNF- α , cCaspase 3, and KIM-1 expression. The data ($n = 5$) are presented as the mean \pm SEM. TNF- α , tumor necrosis factor alpha; KIM-1, kidney injury molecule 1; NS, normal control; CIS, cisplatin control; CUR100, extract100 + cisplatin; CUR200, extract200 + cisplatin, and CUR400 extract400 + cisplatin.

CIS treatment. TNF- α also produces reactive oxygen species, triggering nuclear factor kappa light-chain enhancer of activated B cells (NF- κ B) (Zhang *et al.*, 2007). Subsequently, this transcription factor produces pro-inflammatory cytokines, such as TNF- α . TNF- α is essential for nephrotoxicity caused by CIS (Ramesh and Brian Reeves, 2002).

The regulation of kidney cell populations during the development and progression of renal disease is significantly influenced by apoptosis (Havasi and Borkan, 2011). Numerous nephrotoxins can induce apoptosis in AKI. CIS, a commonly used drug, as well as other anticancer therapies, can result in severe kidney toxicity, which restricts their therapeutic effectiveness (Pabla and Dong, 2008; Miller *et al.*, 2010). The findings of this study revealed that caspase-3 expression was highest in the CIS (CIS) group and lowest in the extract-treated group.

KIM-1 is a biomarker of kidney injury in renal epithelial cells with proximal tubule damage (Li *et al.*, 2019; Siddiqui *et al.*, 2019). The current study demonstrated an increase in KIM-1 concentration in the CIS group. This increase could be mitigated by introducing a combined extract of *C. longa* and *C. zedoaria*, with

particularly effective outcomes observed at 400 mg/kg twice daily. The proximal tubules exhibited a higher frequency of cytoplasmic and nuclear degenerative alterations than the distal tubules. This difference can be explained by the fact that the proximal tubules are the primary locations for reabsorption and active transport processes (Curthoys and Moe, 2014).

Hyaline casts are formed from altered tubular epithelial cells that undergo molecular changes and contain cellular debris. The formation of these casts occurs when loose cells and fragments from the tubular basement membrane combine with proteins found in the lumen of the tubule. In addition, injury to the tubular epithelium leads to decreased sodium reabsorption, resulting in increased sodium levels in the tubule lumen. Elevated sodium concentrations facilitate protein polymerization and contribute to cast formation (Abuelo, 2007).

The preventive effect of the combined extract of *C. longa* and *C. zedoaria* at 200 mg/kg BW, which considerably reduced tubular degeneration caused by CIS injection, was confirmed by histological testing. Clinically, CIS dosage can cause varying degrees of nephrotoxicity. Renal failure, which cannot be reversed,

may occur in patients undergoing repeated therapy sessions (Cornelison and Reed, 1993). Furthermore, studies on drug behavior in the body have shown that the primary factors contributing to kidney damage are prolonged buildup of CIS in the renal tissue and its extensive distribution throughout the body (Ibrahim et al., 2019). This study revealed a correlation between the dosage of combined extracts and histological changes in CIS-induced nephrotoxicity. The combined extracts mitigated damage to epithelial cells within the proximal tubules of the kidneys. As CIS concentrates in renal tissue, it causes epithelial cell death, leading to their gradual detachment and formation of protein-rich casts (Yang et al., 2018).

Conclusion

In conclusion, the above data indicated that the combined extract dose had beneficial renoprotective effects against CIS-induced nephrotoxicity. Its action may involve by suppressing TNF- α , KIM-1, and caspase-3 levels.

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Conflict of interest

The authors declare no conflicts of interest.

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Authors contributions

PRI, SA, HF, FE, AI, LAL, UAN, SS, SSM, LNS, AS, and EH developed the concepts and designs. PRI, SA, HF, SSM, LNS, AS, and EH contributed to the data analysis/interpretation. PRI, SA, HF, FE, AI, LAL, UAN, SS, SSM, LNS, AS, and EH drafted the manuscript. PRI, SA, HF, FE, AI, LAL, UAN, SS, SSM, LNS, AS, and EH contributed to the critical revision of the manuscript. PRI, SSM, LNS, AS, and EH contributed to the statistical analysis. PRI, HF, FE, SSM, LNS, AS, and EH contributed to admin, technical, or material support. PRI, SSM, LNS, AS, and EH supervised this study. PRI, SA, HF, FE, AI, LAL, UAN, SS, SSM, LNS, AS, and EH contributed to the final approval.

Data availability

All data required to substantiate the findings of this research are included in the manuscript.

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