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Channa striata Extract Dose-Dependently Improves Renal SOD and Histopathology in CCl_4-Treated Wistar Rats

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Abstract

Carbon tetrachloride (CCl_4)-induced oxidative stress contributes to renal injury by disrupting endogenous antioxidant defenses and promoting histopathological alterations. *Channa striata* contains potentially bioactive constituents with antioxidant properties; however, its effects on renal antioxidant activity and tissue morphology during CCl_4 exposure remain insufficiently characterized. This study aimed to evaluate the effects of different doses of *Channa striata* extract on renal superoxide dismutase (SOD) activity and histopathological alterations in CCl_4-exposed Wistar rats. Twenty-five male Wistar rats were randomly allocated into five groups (n = 5): a normal control (K1), a CCl_4 control (K2), and three groups receiving CCl_4 alongside oral *Channa striata* extract at 100 (K3), 150 (K4), or 200 mg/kg body weight (K5) during a 14-day experimental period. Renal SOD activity was measured spectrophotometrically, while histopathological alterations were assessed using hematoxylin and eosin staining. Mean renal SOD activity was lower in K2 (11.17 ± 0.45 U/mL) than in K1 (22.10 ± 0.30 U/mL). Extract administration was associated with progressively higher SOD activity in K3, K4, and K5 (13.83 ± 0.35, 16.13 ± 0.35, and 18.77 ± 0.40 U/mL, respectively). The corresponding reported total histopathological scores were 3.40 ± 0.31, 2.60 ± 0.31, and 0.80 ± 0.31, compared with 5.20 ± 0.31 in K2. These findings indicate a descriptive dose-related pattern, with higher renal SOD activity and lower histopathological injury scores at increasing extract doses. Concurrent *Channa striata* extract administration may attenuate selected biochemical and morphological alterations during CCl_4 exposure, although statistical confirmation of the histopathological differences and dose-response trend remains necessary.

Keywords: *Channa striata*; Carbon Tetrachloride; Nephroprotection; Superoxide dismutase; Histopathology.

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INTRODUCTION

Oxidative stress plays a central role in the development of kidney injury following exposure to toxic substances, including carbon tetrachloride (CCl_4). Excessive generation of reactive oxygen species (ROS) disrupts cellular redox homeostasis, promotes lipid peroxidation, and contributes to inflammatory responses and cellular damage. These processes can impair endogenous antioxidant defense systems, including superoxide dismutase (SOD), catalase, and glutathione peroxidase, which are essential for maintaining cellular redox balance (Liu et al., 2023). Recent evidence has highlighted the complex role of redox signaling in renal pathophysiology, emphasizing that excessive ROS production can contribute to cellular dysfunction, inflammation, and progressive tissue injury (Kishi et al., 2024; Amin et al., 2024). SOD acts as a primary antioxidant enzyme by catalyzing the dismutation of superoxide radicals into hydrogen peroxide and molecular oxygen, thereby limiting the accumulation of superoxide

radicals. When oxidative stress exceeds the capacity of antioxidant defense mechanisms, renal tissues become vulnerable to structural damage, including glomerular alterations, tubular epithelial degeneration, and inflammatory cell infiltration (Habashy & Abu-Serie, 2024). Evidence from clinical investigations has also demonstrated the importance of antioxidant and inflammatory biomarkers in evaluating oxidative stress-related kidney disorders, although findings from chronic kidney disease cannot be directly extrapolated to acute experimental nephrotoxicity (Supriyadi et al., 2023). Therefore, evaluating renal SOD activity alongside histopathological alterations provides complementary information regarding biochemical antioxidant responses and structural changes associated with oxidative kidney injury.

Carbon tetrachloride (CCl_4) is widely used in experimental animal models to investigate oxidative stress-mediated organ injury and evaluate the potential protective effects of antioxidant interventions (Essa et al., 2026). Following its biotransformation through cytochrome P450-dependent pathways, CCl_4 generates reactive intermediates, particularly trichloromethyl (CCl_3•) and trichloromethyl peroxy (CCl_3OO•) radicals, which initiate lipid peroxidation and contribute to cellular membrane disruption and tissue injury (Manhar et al., 2025). Although the liver is the primary target of CCl_4 toxicity, renal tissues are also susceptible to oxidative damage associated with disturbances in antioxidant defense mechanisms. Experimental investigations have reported renal biochemical and structural alterations following CCl_4 exposure, supporting the use of this compound in experimental nephrotoxicity studies (Baig & Khan, 2023; Dassarma et al., 2025). In a rat model, Shaban et al. (2024) demonstrated that antioxidant interventions could modify CCl_4-associated oxidative, inflammatory, and morphological alterations in renal tissue. Similarly, Aziz et al. (2022) reported changes in renal oxidative stress markers, inflammatory indices, and histopathological findings following an experimental intervention in CCl_4-exposed rats. In experimental nephrotoxicity models, reductions in renal SOD activity may indicate impaired antioxidant defense, whereas histopathological examination enables the identification of morphological alterations involving renal glomeruli, tubules, and interstitial tissues. The integration of these biochemical and histological assessments provides a broader characterization of renal responses to toxic exposure than either parameter alone, although these indicators do not directly establish renal functional impairment or recovery (Kitada et al., 2020; Okokon et al., 2024).

Natural products containing bioactive compounds have received increasing attention as potential sources of antioxidant interventions against oxidative stress-associated tissue injury. Among these, *Channa striata* (snakehead fish) is recognized for its nutritional composition and potential biological activities. Previous studies have identified albumin, essential amino acids, and fatty acids among the nutritional constituents of *Channa striata*, suggesting their possible involvement in physiological processes related to tissue maintenance and recovery (Hapsari & Tjandrawinata, 2025). A systematic review by Lee et al. (2022) reported that *Channa striatus*-derived preparations have been investigated in several inflammatory conditions, while emphasizing the need to identify the active constituents responsible for their biological effects. Clinical and experimental investigations have also explored the biological effects of snakehead fish preparations in wound healing, inflammatory responses, and nutritional recovery (Sahid et al., 2018; Taslim et al., 2022). However, the observed outcomes vary across experimental models, preparations, and clinical conditions, indicating that their effects cannot be generalized to other organs without direct investigation. Additional research has examined *Channa striata* supplementation in clinical conditions involving inflammatory and immune-related outcomes, further illustrating the diversity of its investigated applications (Setiawan et al., 2024; Anjani et al., 2026).

The potential antioxidant properties of *Channa striata* may be associated with biologically active components derived from its protein-rich tissues. Investigations of snakehead fish-derived protein hydrolysates have demonstrated antioxidant activity in

chemical assays, providing preliminary evidence of the potential functional properties of its peptides (Kardinan et al., 2024). Furthermore, Musliha et al. (2024) investigated Striatin, a bioactive protein fraction isolated from *Channa striata*, and reported effects on pathways associated with albumin regulation and inflammation using in silico and in vitro approaches. These findings complement previous investigations of the functional properties and antioxidant potential of *Channa striata*-derived preparations (Mardiah et al., 2025). Nevertheless, the biological activity of these preparations may depend on their composition, extraction procedures, and processing conditions. Consequently, antioxidant activity demonstrated in chemical assays or biological effects observed in nonrenal models cannot establish that the specific extract used in the present study protects renal tissue during CCl_4 exposure. Direct evaluation of renal biochemical and histopathological outcomes is therefore necessary.

Despite growing evidence regarding the biological potential of *Channa striata*, its effects on renal antioxidant defense and histopathological injury remain insufficiently characterized. Previous investigations have primarily focused on wound healing, nutritional recovery, and other physiological responses, while studies directly examining renal biochemical and histopathological outcomes are comparatively limited (Lailaseptiani & Prameswari, 2025). Experimental investigations of other antioxidant interventions have demonstrated the relevance of assessing oxidative stress markers and renal morphology together. For example, Dai et al. (2023) reported that nootkatone supplementation attenuated CCl_4-associated renal injury in mice, accompanied by changes in oxidative and inflammatory signaling. Eassawy and Ismail (2024) also evaluated the effects of plant-derived extracts on biochemical and histopathological outcomes in an experimental model involving CCl_4 and gamma irradiation. These studies provide evidence that antioxidant interventions can influence renal responses to experimentally induced oxidative injury, although their findings are not directly transferable to *Channa striata* extract. Other experimental studies have similarly emphasized the importance of combining biochemical measurements with histopathological assessments to characterize kidney tissue responses (Alrashdi et al., 2025; Yulizal et al., 2026). However, evidence remains limited regarding whether *Channa striata* extract administered at different doses produces corresponding changes in renal SOD activity and histopathological injury during CCl_4 exposure. Specifically, the relationship between increasing extract doses and the simultaneous modulation of renal antioxidant responses and tissue alterations has not been sufficiently characterized under comparable experimental conditions. Addressing this gap would help clarify the potential dose-related renal tissue-protective effects of *Channa striata* extract.

Therefore, this study aimed to evaluate the effects of *Channa striata* extract administered at doses of 100, 150, and 200 mg/kg body weight on renal SOD activity and histopathological alterations in male Wistar rats exposed to CCl_4 during a 14-day experimental period. By comparing a normal control group, a CCl_4-exposed control group, and three CCl_4-exposed groups receiving different extract doses, the study investigated whether increasing doses were associated with progressively higher renal SOD activity and reduced histopathological injury. We hypothesized that concurrent administration of *Channa striata* extract during CCl_4 exposure would attenuate the reduction in renal SOD activity and decrease the severity of histopathological alterations, with more pronounced protective responses at higher extract doses. The principal contribution of this study is the integrated evaluation of renal antioxidant activity and histopathological injury across three doses of *Channa striata* extract within the same CCl_4-induced renal injury model. These findings are expected to provide preliminary experimental evidence regarding the potential dose-related renal tissue-protective properties of *Channa striata* extract and establish a basis for further investigation of its biological mechanisms and effects on renal function.

METHOD

Study Design and Ethical Approval

This study employed an experimental approach using a post-test-only control group

design. The experimental procedures were developed in accordance with the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines, covering the allocation of experimental groups, standardization of animal housing conditions, and blinded histopathological assessment to minimize potential observational bias. The study received approval from the Health Research Ethics Committee of Universitas Prima Indonesia (Approval No. 052/KEPK/UNPRI/X/2025). All experimental procedures were conducted in compliance with applicable institutional standards regarding the welfare, handling, and use of laboratory animals.

Animals and Husbandry

This experiment involved 25 healthy male Wistar rats (*Rattus norvegicus*), aged 6–8 weeks, with initial body weights ranging from 170 to 190 g. Male animals were used to limit biological variation potentially associated with sex-related differences; however, this did not eliminate all possibilities of hormonal variation. Before the experimental treatments, the animals underwent a 7-day acclimatization period to adjust to the housing environment and research procedures (Rinwa et al., 2024). Each rat was housed individually in a polypropylene cage at a controlled temperature of 25 ± 2°C, with a 12-hour light/dark cycle. Standard pellet feed and drinking water were provided *ad libitum*. Cage bedding was changed every 3 days, while feed and fluid intake, general behavior, and signs of discomfort were monitored daily.

Test Material Preparation

The test material used was *Channa striata* powder extract, produced by PT Herbal Nusantara Solo and distributed by PT Mega Medica Pharmaceutical. The extract was suspended in a 0.5% carboxymethyl cellulose (CMC) solution to produce a homogeneous oral preparation. Three treatment doses were prepared 100, 150, and 200 mg/kg of body weight (BW) with individual doses adjusted according to the body weight of each animal.

CCl_4 Induction and Group Allocation

Following the acclimatization phase, the test animals were randomly assigned to five experimental groups, each consisting of five rats. Randomization was performed using a simple lottery method. The experimental groups were as follows:

1. K1 (normal control): received the vehicle only, without CCl_4 induction.
2. K2 (CCl_4 control): received CCl_4 induction and the extract vehicle.
3. K3 (treatment 1): received CCl_4 induction and *Channa striata* extract at a dose of 100 mg/kg BW.
4. K4 (treatment 2): received CCl_4 induction and *Channa striata* extract at a dose of 150 mg/kg BW.
5. K5 (treatment 3): received CCl_4 induction and *Channa striata* extract at a dose of 200 mg/kg BW.

Carbon tetrachloride (CCl_4) exposure was conducted in experimental groups K2–K5 during the 14-day study period. CCl_4 was prepared as a 10% (v/v) solution in corn oil and administered orally at a volume of 1 mL/kg body weight (BW) per administration, equivalent to 0.1 mL/kg BW of pure CCl_4. Groups K3, K4, and K5 received *Channa striata* extract at doses of 100, 150, and 200 mg/kg BW, respectively, during the CCl_4 exposure period. The CCl_4 control group (K2) received the extract vehicle without *Channa striata*, whereas the normal control group (K1) received an equivalent volume of corn oil without CCl_4 induction. This experimental design enabled the evaluation of dose-related differences in renal superoxide dismutase (SOD) activity and histopathological alterations associated with *Channa striata* extract administration during CCl_4 exposure.

Intervention Procedure

During the 14-day treatment period, rats in groups K3, K4, and K5 received *Channa striata* extract orally via gastric gavage once daily at doses of 100, 150, and 200 mg/kg body weight, respectively. The administration volume was 1 mL per rat per day. Rats in groups K1

and K2 received the extract vehicle 0.5% CMC at a volume of 1 mL per rat per day. For groups K2–K5, the administration of the extract or vehicle coincided with the period of CCl_4 exposure, in accordance with their respective dosing schedules. Body weight was recorded weekly to adjust dosages based on weight and to monitor the general condition of the test animals (Fortea et al., 2018).

Anesthesia and Tissue Collection

Following the treatment period, the animals were fasted overnight but maintained free access to drinking water. Anesthesia was induced in each rat using a combination of ketamine (80–100 mg/kg body weight) and xylazine (10 mg/kg body weight) administered intraperitoneally. The depth of anesthesia was assessed based on the absence of a pedal withdrawal response. Once adequate anesthesia was confirmed, euthanasia was performed via cervical dislocation in accordance with procedures approved by the ethics committee. The abdominal cavity was then opened aseptically to harvest the kidneys.

The left kidney was removed from each animal for biochemical analysis and histopathological examination (Dil et al., 2023). The organ was immediately rinsed with cold physiological saline to remove residual blood. Renal cortical tissue was then separated and divided into appropriate sections for the measurement of SOD activity and histopathological examination.

Renal SOD Activity Measurement

Superoxide dismutase (SOD) activity in renal tissue was measured using renal cortical tissue homogenates. A 0.2 g tissue sample was finely minced and homogenized in a cold phosphate buffer solution (pH 7.4). The homogenate was then centrifuged at 3,000 rpm for 10–15 minutes at 4°C, and the supernatant was separated for analysis. SOD enzymatic activity was measured spectrophotometrically at a wavelength of 560 nm using a commercial assay kit from Cayman Chemical (USA). Each specimen was analyzed in duplicate, and the results were reported as U/mL of homogenate.

Histopathological Processing and Scoring

Renal cortex samples were fixed for 24 hours in 10% neutral buffered formalin and subsequently processed using the conventional paraffin method. Paraffin blocks were sectioned at a thickness of 4 μm, followed by deparaffinization, rehydration, and hematoxylin-eosin (H&E) staining according to laboratory procedures. Microscopic examination was performed using a light microscope at 400× magnification. Assessments were conducted by a qualified pathologist blinded to the experimental group assignments, ensuring that group identity did not influence the interpretation of the specimens.

Statistical Analysis

Statistical analysis was performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). The distribution of SOD activity data was assessed using the Shapiro–Wilk test, while the homogeneity of variance was checked using Levene's test. Differences in SOD activity between groups were analyzed using one-way ANOVA, provided the analysis assumptions were met. If a significant overall difference was found, pairwise comparisons were conducted using the Tukey Honestly Significant Difference (HSD) post-hoc test. Histopathological scores were analyzed as ordinal data and presented as median (range). Differences in histopathological scores between groups were analyzed using the Kruskal–Wallis test. If a significant overall difference was found, pairwise comparisons were performed using the Mann–Whitney U test with Bonferroni adjustment to control for the risk of error associated with multiple testing. SOD activity data are presented as mean ± standard deviation (SD), whereas histopathological scores are presented as median (range). A p-value < 0.05 was set as the threshold for statistical significance.

RESULTS AND DISCUSSION

Renal Superoxide Dismutase (SOD) Activity

Renal superoxide dismutase (SOD) activity varied across the five experimental groups following the 14-day experimental period. As presented in Table 1, the normal control group (K1) exhibited the highest mean SOD activity (22.10 ± 0.30 U/mL), whereas the CCl_4-exposed control group (K2) showed the lowest activity (11.17 ± 0.45 U/mL). Compared with K1, mean SOD activity in K2 was approximately 49.5% lower, indicating a substantial reduction in renal antioxidant enzyme activity following CCl_4 exposure.

Table 1. Renal SOD activity in each experimental group

Experimental group	SOD activity (mean ± SD), U/mL
K1 — Normal control	22.10 ± 0.30
K2 — CCl_4 control	11.17 ± 0.45
K3 — CCl_4 + *Channa striata* extract 100 mg/kg BW	13.83 ± 0.35
K4 — CCl_4 + *Channa striata* extract 150 mg/kg BW	16.13 ± 0.35
K5 — CCl_4 + *Channa striata* extract 200 mg/kg BW	18.77 ± 0.40

Note: Values are presented as mean ± standard deviation (SD), with five animals per group (n = 5). SOD = superoxide dismutase; BW = body weight.

Administration of *Channa striata* extract during CCl_4 exposure was associated with progressively higher renal SOD activity across the three treatment groups. The mean activities in K3, K4, and K5 were 13.83 ± 0.35, 16.13 ± 0.35, and 18.77 ± 0.40 U/mL, respectively. Relative to the CCl_4 control group, mean SOD activity increased by approximately 23.8%, 44.4%, and 68.0% in the groups receiving 100, 150, and 200 mg/kg BW, respectively.

The reported one-way analysis of variance (ANOVA) indicated a significant overall difference in SOD activity among the experimental groups ($F = 569.4$; $p < 0.001$). The reported Tukey honestly significant difference (HSD) post-hoc analysis further indicated significant differences between K2 and each extract-treated group (K3, K4, and K5; $p < 0.001$). Among the extract-treated groups, K5 exhibited the highest mean SOD activity, although its value remained below that of the normal control group.

These findings demonstrate an increasing pattern of mean renal SOD activity across the tested extract doses. However, the observed pattern should be interpreted as a descriptive dose-related response because a formal statistical trend analysis has not been verified.

Renal Histopathological Findings

Histopathological examination of hematoxylin and eosin (H&E)-stained renal tissue sections revealed differences in the severity of renal morphological alterations among the experimental groups. These alterations were assessed using lesion and inflammatory scores, with higher values indicating greater histopathological injury. The reported scores are summarized in Table 2, while representative renal tissue sections are presented in Figure 1.

The normal control group (K1) exhibited relatively preserved glomerular and tubular structures, distinct Bowman's spaces, and no apparent inflammatory cell infiltration. The reported lesion, inflammatory, and total histopathological scores in this group were 0.00 ± 0.00.

In contrast, the CCl_4 control group (K2) showed more pronounced renal tissue alterations, including glomerular morphological changes, tubular epithelial damage, and interstitial inflammatory cell infiltration. This group had the highest reported lesion score (2.80 ± 0.20), inflammatory score (2.40 ± 0.24), and total histopathological score (5.20 ± 0.31).

Table 2. Histopathological Scores of Renal Tissue in Experimental Groups

Histopathological parameter	Normal control (K1)	CCl_4 control (K2)	100 mg/kg BW (K3)	150 mg/kg BW (K4)	200 mg/kg BW (K5)
Lesion score	0.00 ± 0.00	2.80 ± 0.20	1.80 ± 0.20	1.40 ± 0.24	0.60 ± 0.24
Inflammatory score	0.00 ± 0.00	2.40 ± 0.24	1.60 ± 0.24	1.20 ± 0.20	0.20 ± 0.20

Histopathological parameter	Normal control (K1)	CCl_4 control (K2)	100 mg/kg BW (K3)	150 mg/kg BW (K4)	200 mg/kg BW (K5)
Total histopathological score	0.00 ± 0.00	5.20 ± 0.31	3.40 ± 0.31	2.60 ± 0.31	0.80 ± 0.31

Note: Values are reproduced as reported in the original study (mean ± SD; n = 5 per group). K3, K4, and K5 received CCl_4 and *Channa striata* extract at 100, 150, and 200 mg/kg BW, respectively. Higher scores indicate more severe renal histopathological alterations. The reported dispersion measure and the statistical analysis of ordinal scores require verification against the original animal-level data.

The administration of *Channa striata* extract was associated with progressively lower reported histopathological scores at higher treatment doses. Total histopathological scores decreased from 3.40 ± 0.31 in K3 to 2.60 ± 0.31 in K4 and 0.80 ± 0.31 in K5. Both the lesion and inflammatory components showed similar patterns, with the lowest reported scores among the treated groups observed at 200 mg/kg BW.

These results indicate a descriptive association between increasing extract doses and less severe renal histopathological alterations during CCl_4 exposure. Nevertheless, the statistical significance of these differences remains undetermined because the Kruskal–Wallis and adjusted post-hoc results have not been verified.

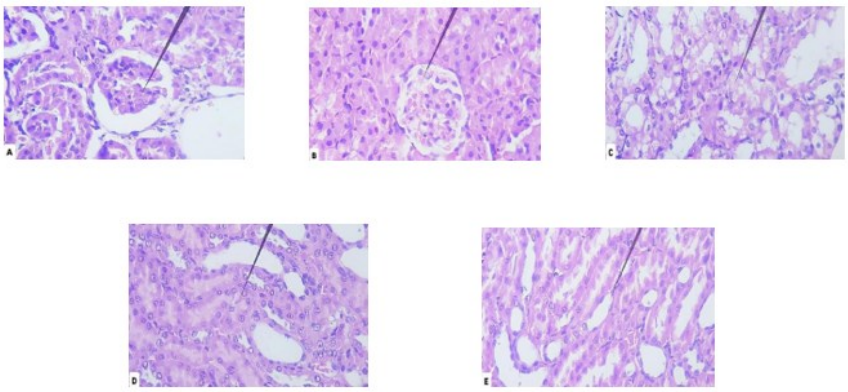


Figure 1: Renal Tissue Histopathology

Microscopic examination revealed relatively preserved glomerular and tubular morphology in K1, whereas K2 exhibited more pronounced renal tissue alterations involving the glomeruli, tubular epithelium, and interstitial tissue. Among the extract-treated groups, histopathological alterations appeared less severe at higher extract doses. The renal tissue appearance in K5 most closely resembled that of the normal control group among the extract-treated groups.

These morphological observations were consistent with the patterns of histopathological scores reported in Table 2. However, the descriptive findings do not independently establish statistically significant histological improvement or complete restoration of renal tissue architecture.

Comparative Biochemical and Histopathological Responses Across Extract Doses

To examine the consistency of biochemical and morphological responses across treatment groups, the differences in mean renal SOD activity and reported total histopathological scores were calculated relative to the CCl_4 control group (K2). These descriptive comparisons are presented in Table 3.

Table 3. Descriptive comparison of renal SOD activity and total histopathological scores relative to the CCl_4 control group

Experimental group	Increase in mean SOD (U/mL)	Relative increase in mean SOD (%)	Reduction in mean total histopathological score
K3 100 mg/kg BW	2.66	23.8	1.80
K4 150 mg/kg BW	4.96	44.4	2.60
K5 200 mg/kg BW	7.60	68.0	4.40

As shown in Table 3, the increase in mean renal SOD activity relative to the CCl_4 control group was greatest in K5 (7.60 U/mL), followed by K4 (4.96 U/mL) and K3 (2.66 U/mL). Similarly, the largest reduction in the reported mean total histopathological score was observed in K5 (4.40 points), followed by K4 (2.60 points) and K3 (1.80 points).

The parallel increase in mean renal SOD activity and reduction in reported histopathological injury scores across the tested extract doses suggests a consistent dose-related pattern involving both biochemical and morphological outcomes. However, these group-level observations do not establish a statistical correlation between SOD activity and histopathological scores or a formally significant dose-response relationship. Such conclusions would require analysis of the corresponding individual-animal data.

Discussion

Renal Oxidative Stress and SOD Activity Following CCl_4 Exposure

The present study demonstrated that carbon tetrachloride (CCl_4) exposure was associated with a substantial reduction in renal superoxide dismutase (SOD) activity and more pronounced histopathological alterations in male Wistar rats. The CCl_4 control group exhibited a mean renal SOD activity of 11.17 ± 0.45 U/mL, approximately 49.5% lower than the normal control group (22.10 ± 0.30 U/mL). This finding suggests that CCl_4 exposure was associated with a marked alteration in renal antioxidant defense under the experimental conditions.

The reduction in SOD activity is consistent with the established involvement of oxidative stress in chemically induced kidney injury. CCl_4 undergoes cytochrome P450-mediated biotransformation, generating trichloromethyl and trichloromethyl peroxy radicals that promote lipid peroxidation, disrupt cellular membrane integrity, and contribute to tissue injury (Unsal et al., 2021; Lamia et al., 2021). Excessive reactive oxygen species production may overwhelm endogenous antioxidant systems and contribute to renal cellular dysfunction and inflammatory responses (Hosohata, 2016). Experimental investigations have also reported CCl_4-associated renal oxidative alterations and tissue damage, supporting the relevance of this model for evaluating antioxidant interventions (Baig & Khan, 2023; Dassarma et al., 2025).

Similar biochemical responses have been investigated in studies involving natural antioxidant preparations. Iqbal et al. (2023) examined the effects of *Andrographis paniculata* on CCl_4-mediated renal oxidative damage in rats, providing further experimental context for the relationship between toxic exposure and antioxidant defense. Nevertheless, SOD activity represents only one component of the antioxidant system. Because the present study did not assess other oxidative stress indicators, including malondialdehyde, glutathione, catalase, or glutathione peroxidase, the specific biochemical mechanisms underlying the observed reduction in SOD activity cannot be established.

Dose-Related Effects of Channa striata Extract on Renal SOD Activity

Administration of *Channa striata* extract during CCl_4 exposure was associated with progressively higher mean renal SOD activity across the three treatment doses. Mean SOD activity increased from 13.83 ± 0.35 U/mL at 100 mg/kg BW to 16.13 ± 0.35 U/mL at 150 mg/kg BW and 18.77 ± 0.40 U/mL at 200 mg/kg BW. Compared with the CCl_4 control group, these values represented increases of approximately 23.8%, 44.4%, and 68.0%, respectively. The highest extract dose produced the greatest increase in mean SOD activity, although the value remained below that of the normal control group.

These findings suggest that *Channa striata* extract administration may influence renal antioxidant responses during CCl_4 exposure. The reported ANOVA and Tukey post-hoc results indicated differences in SOD activity between the CCl_4 control and extract-treated groups. Similar antioxidant-related renal responses have been described following administration of other natural compounds in experimental CCl_4 models. Ding et al. (2025) investigated fucoxanthin in relation to oxidative stress and ferroptosis, while Wei et al. (2022) examined the effects of *Mori fructus* aqueous extracts on renal injury and antioxidant-related

mechanisms. Dai et al. (2023) also investigated the attenuation of CCl_4-associated nephrotoxicity following nootkatone supplementation. These studies support the relevance of antioxidant modulation in experimental renal injury, although differences in test compounds and experimental procedures limit direct comparisons of efficacy.

The progressively higher SOD values across the three extract doses suggest a dose-related biochemical response within the tested range. Studies involving other plant-derived preparations, including *Humulus lupulus* and *Cola hispida*, have also examined differences in renal injury indicators across treatment doses during CCl_4 exposure (Rahimi et al., 2026; Ani et al., 2026). However, the findings of these studies cannot establish the dose-response relationship of *Channa striata* extract. Furthermore, the reported ANOVA and Tukey results do not independently confirm a statistically significant linear or monotonic trend. Therefore, the present findings should be interpreted as a descriptive dose-related pattern rather than definitive evidence of an optimal dose or a statistically established dose-response relationship.

Effects of Channa striata Extract on Renal Histopathological Alterations

Histopathological examination revealed more pronounced renal tissue alterations in the CCl_4 control group than in the normal control group. The reported abnormalities included glomerular morphological changes, tubular epithelial damage, and interstitial inflammatory cell infiltration. The CCl_4 control group also exhibited the highest reported total histopathological score (5.20 ± 0.31), indicating greater tissue injury based on the study's scoring system.

These morphological observations are consistent with previous investigations describing renal structural abnormalities following CCl_4 exposure (Sarwar et al., 2025; Mansour et al., 2024). Other experimental studies have reported that antioxidant interventions may attenuate biochemical and histopathological manifestations of CCl_4-induced renal injury. Aziz et al. (2022) examined the effects of *Pulicaria crispa* on renal oxidative, inflammatory, and structural indicators, while Shaban et al. (2024) investigated antioxidant compounds in CCl_4-associated renal and pulmonary toxicity. Noah et al. (2024) evaluated *Hippocratea africana* root extract and its fractions in a model of CCl_4-associated kidney injury, whereas Ekpo et al. (2024) investigated the potential protective effects of quercetin and hesperidin against hepatorenal toxicity. These studies provide comparative evidence that renal morphological alterations may accompany changes in oxidative stress-related parameters.

In the present study, administration of *Channa striata* extract was associated with progressively lower reported total histopathological scores as the dose increased. The scores decreased from 3.40 ± 0.31 at 100 mg/kg BW to 2.60 ± 0.31 at 150 mg/kg BW and 0.80 ± 0.31 at 200 mg/kg BW. Both the lesion and inflammatory components followed a similar descriptive pattern, suggesting that higher extract doses were associated with less severe histopathological alterations during CCl_4 exposure.

The most favorable histopathological findings were observed in the 200 mg/kg BW group, in which the reported tissue characteristics most closely resembled those of the normal control group among the extract-treated groups. However, the histopathological scoring criteria, dispersion measures, and nonparametric statistical results require verification using individual animal-level data. Consequently, these findings should be interpreted as descriptive evidence of potentially reduced tissue injury rather than statistically confirmed restoration of renal architecture.

Potential Antioxidant and Anti-Inflammatory Mechanisms of Channa striata

The potential biological activity of *Channa striata* extract may be related to the nutritional and functional properties of compounds derived from snakehead fish. Previous investigations have described albumin, amino acids, and fatty acids among the constituents of *Channa striata*, suggesting potential roles in tissue maintenance and biological recovery processes (Azemi et al., 2021). Amino acids involved in glutathione synthesis may contribute

to cellular antioxidant defense, while certain fatty acids have been associated with modulation of inflammatory responses (Panjaitan et al., 2025; Stanescu et al., 2025). Experimental investigations of renal injury have also highlighted the relevance of inflammatory signaling pathways, including nuclear factor kappa B (NF-κB), in oxidative stress-related tissue alterations (Albukhari et al., 2025).

Additional studies involving snakehead fish-derived peptides and protein fractions provide a rationale for investigating the antioxidant properties of *Channa striata*. Issac et al. (2021) examined the effects of a peptide derived from *Channa striatus* on antioxidant defense in cellular systems and apoptosis-related responses in zebrafish larvae. Kardinan et al. (2024) investigated antioxidant peptides obtained through enzymatic hydrolysis of snakehead fish proteins, while Musliha et al. (2024) explored the biological properties of Striatin, a bioactive protein fraction derived from *Channa striata*. These investigations suggest that certain snakehead fish-derived preparations possess biologically relevant activities, although their effects cannot be directly generalized to renal injury.

The biological properties of *Channa striata* preparations may also depend on extraction methods and product composition. Zubairi et al. (2024) characterized a *Channa striatus* water extract and investigated its biological properties in a cell-based model, illustrating the importance of considering preparation-specific characteristics when interpreting experimental outcomes. In the present study, the administered extract was not characterized for its concentrations of albumin, amino acids, fatty acids, or antioxidant peptides. Therefore, the observed effects cannot be attributed to specific constituents.

Furthermore, the study did not assess glutathione concentrations, NF-κB activity, inflammatory cytokines, or antioxidant-related signaling proteins. Although antioxidant and anti-inflammatory mechanisms have been investigated in studies involving other nephroprotective interventions (Albadrani et al., 2024), their involvement in the effects of *Channa striata* extract remains hypothetical. Additional mechanistic investigations are needed to identify the biologically active components of the extract and determine whether they influence oxidative stress, inflammatory signaling, or other pathways associated with renal tissue injury.

Integrated Biochemical and Histopathological Responses and Scientific Implications

An important contribution of the present study is the simultaneous evaluation of renal SOD activity and histopathological injury across three doses of *Channa striata* extract within the same CCl_4-exposure model. The highest extract dose was associated with the greatest increase in mean renal SOD activity and the largest reduction in the reported mean total histopathological score relative to the CCl_4 control group. These parallel patterns suggest that favorable biochemical and morphological responses may occur together during extract administration.

The integrated assessment of biochemical and histopathological outcomes provides a broader description of renal tissue responses than either parameter alone. Experimental studies involving antioxidant interventions have similarly emphasized the importance of evaluating both oxidative stress indicators and renal morphology when examining tissue injury associated with CCl_4 exposure (Gadhoumi et al., 2024; Kadhom, 2025). Nevertheless, agreement between group-level patterns does not establish a statistical correlation between individual SOD measurements and histopathological scores. Such an association would require paired animal-level observations and an appropriate correlation analysis.

The concurrent administration schedule also influences the interpretation of these findings. Because *Channa striata* extract was administered during the 14-day period of CCl_4 exposure, the observed changes are more appropriately interpreted as potential protective effects during ongoing toxic exposure rather than therapeutic reversal of established kidney injury. Different intervention schedules, including pretreatment and treatment after injury induction, may produce different biological responses and should not be considered equivalent.

Furthermore, the present study did not measure renal functional parameters such as serum creatinine, blood urea nitrogen, or glomerular filtration indicators. Therefore, the observed increases in SOD activity and reductions in histopathological scores do not establish complete preservation or recovery of renal function. The findings instead provide preliminary evidence that *Channa striata* extract may influence selected renal biochemical and morphological outcomes during CCl_4 exposure. This distinction is important when considering the potential nephroprotective relevance of the extract and designing subsequent investigations.

Study Limitations and Future Research Directions

Several limitations should be acknowledged when interpreting the findings. First, the relatively small sample size of five rats per group limits the precision of effect estimates and the characterization of biological variability. Second, the exclusive use of male Wistar rats restricts the generalizability of the findings to female animals and other experimental populations. Third, the lack of chemical characterization of the administered extract prevents identification of the constituents potentially responsible for the observed biochemical and morphological responses.

Fourth, the available experimental description requires further clarification regarding the frequency of CCl_4 administration and the timing of tissue collection. Fifth, the histopathological scoring criteria and the corresponding statistical analyses require verification using individual animal-level data. Sixth, although the biochemical and histopathological outcomes followed an ordered pattern across extract doses, a formal statistical dose-response analysis was not available. Finally, additional antioxidant, inflammatory, and renal functional biomarkers were not measured, limiting mechanistic and physiological interpretation.

The use of left renal tissue for both biochemical and histopathological assessments provided consistency in the anatomical source of the samples. However, this procedure does not eliminate inter-animal biological variability or establish that the observed changes represent the condition of both kidneys. Standardized tissue collection and processing remain important methodological considerations in experimental research (Qu et al., 2024).

Future investigations should use adequately justified sample sizes, standardized and chemically characterized *Channa striata* preparations, clearly documented CCl_4 administration protocols, and validated renal histopathological scoring systems. Formal statistical trend analyses should also be conducted to evaluate whether increasing extract doses produce significant and reproducible changes in renal outcomes. Additional measurements of renal function, oxidative stress biomarkers, and inflammatory mediators would help clarify the biological significance of the observed responses. Studies involving treatment initiated after confirmed renal injury are also needed to distinguish potential protective effects during toxic exposure from therapeutic effects on established kidney damage.

Overall, the present study provides preliminary evidence that concurrent administration of *Channa striata* extract during CCl_4 exposure is associated with progressively higher renal SOD activity and lower reported histopathological injury scores across the tested doses. The most favorable biochemical and morphological responses were observed at 200 mg/kg BW, supporting further investigation of the potential dose-related renal tissue-protective properties of the extract. However, confirmation of statistical dose-response trends, histopathological comparisons, extract composition, and renal functional outcomes is necessary before definitive conclusions regarding nephroprotective efficacy can be established.

CONCLUSION

The present study demonstrated that concurrent administration of *Channa striata* extract during carbon tetrachloride (CCl_4) exposure was associated with progressively higher renal superoxide dismutase (SOD) activity and lower reported histopathological injury scores in male Wistar rats across the tested doses of 100, 150, and 200 mg/kg body weight. The most favorable biochemical and morphological responses were observed at 200 mg/kg, with renal

SOD activity reaching 18.77 ± 0.40 U/mL and the reported total histopathological score decreasing to 0.80 ± 0.31. These findings suggest that *Channa striata* extract may attenuate selected oxidative stress-associated biochemical and structural alterations in renal tissue during CCl_4 exposure. However, the observed dose-related pattern requires confirmation through formal statistical trend analysis and verification of the histopathological comparisons. Furthermore, because renal functional parameters and specific molecular mechanisms were not evaluated, the findings cannot establish complete restoration of kidney function or definitive nephroprotective efficacy. Overall, this study provides preliminary experimental evidence supporting further investigation of the potential dose-related renal tissue-protective effects of *Channa striata* extract.

RECOMMENDATION

Future studies should investigate the potential nephroprotective effects of *Channa striata* extract using larger and adequately justified sample sizes, broader dose ranges, and clearly standardized experimental protocols. Particular attention should be given to verifying the dose-response relationship through appropriate statistical trend analyses and validated histopathological scoring procedures. Standardization and chemical characterization of *Channa striata* extract, including the identification and quantification of potentially active constituents, are also necessary to improve experimental reproducibility and clarify the components associated with the observed biological responses.

Further investigations should incorporate renal functional parameters, including serum creatinine and blood urea nitrogen, alongside additional oxidative stress biomarkers such as malondialdehyde, catalase, glutathione peroxidase, and glutathione. Assessment of inflammatory mediators and signaling pathways, including NF-κB, TNF-α, and IL-6, may help clarify the mechanisms potentially underlying the biochemical and histopathological changes. Future experimental designs should also distinguish protective effects during CCl_4 exposure from therapeutic effects after renal injury has been established. These approaches would provide more comprehensive evidence regarding the biological mechanisms, dose-response characteristics, and potential functional nephroprotective properties of *Channa striata* extract.

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AUTHOR CONTRIBUTIONS STATEMENT

Name of Author	C	M	So	Va	Fo	I	R	D	O	E	Vi	Su	P	Fu
Ok Yulizal	✓	✓				✓								
Yohanes V. T. Hutapea	✓	✓				✓	✓			✓		✓		
Yolanda E. P. Lubis							✓				✓			

CONFLICT OF INTEREST STATEMENT

Authors state no conflict of interest.

INFORMED CONSENT

We have obtained informed consent from all individuals included in this study.

ETHICAL APPROVAL

The experimental procedures were developed in accordance with the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines, including the allocation of experimental groups, standardization of animal housing conditions, and blinded histopathological assessment to minimize potential observational bias. The study protocol was reviewed and approved by the Health Research Ethics Committee of Universitas Prima Indonesia (UNPRI), Indonesia (Approval No. 052/KEPK/UNPRI/X/2025). All experimental procedures were conducted in compliance with applicable institutional ethical standards for the care, handling, and use of laboratory animals.

Every effort was made to minimize animal suffering throughout the experimental period.

DATA AVAILABILITY

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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