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(RESEARCH ARTICLE)

AMELIORATIVE EFFECT OF CHRYSIN AGAINST POTASSIUM DICHROMATE-INDUCED NEPHROTOXICITY IN MALE RATS

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ABSTRACT

This study investigated the protective effect of Chrysin, a naturally occurring flavone, against potassium dichromate ($K_2Cr_2O_7$)-induced nephrotoxicity in male Wistar rats. Thirty-two adult rats were allocated to four groups (n = 8 per group): control, potassium dichromate (7.5 mg/kg/day), potassium dichromate + Chrysin low dose (25 mg/kg/day), and potassium dichromate + Chrysin high dose (50 mg/kg/day). Renal function (serum urea, blood urea nitrogen and creatinine), renal oxidative stress and antioxidant status (malondialdehyde, reduced glutathione and superoxide dismutase), and renal histopathology were assessed. Rats exposed to potassium dichromate alone exhibited marked renal dysfunction, with serum creatinine, urea and blood urea nitrogen approximately three-fold, 1.8-fold and 2.3-fold higher, respectively, than controls, together with a pronounced elevation of malondialdehyde and depletion of reduced glutathione, and severe histopathological lesions including glomerular capillary hemorrhage, swelling of the glomerular tuft with obliteration of Bowman's space, and cloudy swelling of the renal tubules. Superoxide dismutase activity did not differ significantly among groups (P = 0.33). Co-administration of Chrysin produced a dose-dependent improvement in all measured renal function and oxidative stress parameters, with the high dose restoring blood urea nitrogen, serum urea and malondialdehyde to levels statistically indistinguishable from controls, and producing the greatest degree of histological protection, characterized by mild residual tubular degeneration with relatively preserved renal architecture. These findings indicate that Chrysin exerts significant, dose-dependent nephroprotective effects against potassium-dichromate-induced renal injury, most plausibly attributable to its antioxidant and anti-inflammatory properties.

Keywords: Chrysin, Potassium Dichromate, Nephrotoxicity, Oxidative Stress, Renal Histopathology and Rats

1 INTRODUCTION

Potassium dichromate ($K_2Cr_2O_7$) is a highly soluble hexavalent chromium [Cr(VI)] compound and an important environmental and occupational toxicant. It is widely used in industrial processes such as electroplating, metal processing, pigments and chemical manufacturing. Cr(VI) is considerably more toxic than other chromium forms because it can readily enter cells and undergo intracellular reduction, generating reactive oxygen species (ROS) and reactive chromium intermediates. The kidney is particularly susceptible to chromium toxicity because it plays a major role in chromium elimination and is therefore exposed to the toxicant following systemic absorption. The intracellular reduction of Cr(VI) promotes excessive ROS generation, resulting in an imbalance between oxidants and endogenous

antioxidant defenses. This oxidative stress can induce lipid peroxidation, protein and DNA damage, mitochondrial dysfunction and cellular injury {1,2 }. Renal tubular cells are particularly vulnerable because of their high metabolic activity and dependence on mitochondrial energy production. Potassium dichromate-induced oxidative injury has been associated with increased malondialdehyde (MDA), a marker of lipid peroxidation, together with depletion of reduced glutathione (GSH) and alterations in antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) . Recent experimental evidence has further confirmed that potassium dichromate induces dose-dependent renal oxidative injury, accompanied by increased MDA, impaired antioxidant defenses and renal structural damage {3 }.

Oxidative damage produced by Cr(VI) is also associated with impaired renal function. Tubular and glomerular injury may reduce normal renal filtration and excretion, resulting in increased serum urea, blood urea nitrogen (BUN) and creatinine. Histopathological changes in potassium-dichromate-exposed kidneys further demonstrate the structural consequences of this biochemical injury {2,3} Natural flavonoids have received considerable attention as potential protective agents against oxidative tissue injury. Chrysin (5,7-dihydroxyflavone) is a naturally occurring flavone found in several plant sources, including honey and propolis. It possesses antioxidant, anti-inflammatory and anti-apoptotic activities and has demonstrated protective effects in experimental models of renal and hepatorenal injury {4,5 }. Chrysin has been reported to reduce oxidative damage and improve antioxidant defenses in experimental nephrotoxicity, while more recent studies demonstrated its protective effects against paclitaxel-, gentamicin- and isoniazid-induced renal injury {6, 7, 8 }

Although the renoprotective properties of Chrysin have been investigated against several nephrotoxic agents, its protective effect specifically against potassium-dichromate-induced renal oxidative injury remains insufficiently characterized. In particular, limited information is available regarding the dose-related effects of Chrysin on the combined biochemical, oxidative and histopathological consequences of potassium dichromate exposure. Therefore, the present study investigates the protective effects of two doses of Chrysin against potassium-dichromate-induced renal injury in rats by assessing renal function (urea, BUN and creatinine), oxidative stress and antioxidant status (MDA, GSH and SOD), and renal histopathology. The novelty of the study lies in evaluating the dose-dependent renoprotective potential of Chrysin against potassium dichromate using an integrated biochemical and histopathological approach.

2 MATERIAL AND METHODS

2.1 Chemicals and Reagents

Analytical-grade potassium dichromate ($K_2Cr_2O_7$; CAS No. 7778-50-9; Cat. No. 207802; purity ≥99%) and chrysin (5,7-dihydroxyflavone; CAS No. 480-40-0; Cat. No. C80105; purity ≥96.5%) were purchased from Sigma-Aldrich (St. Louis, MO, USA). Potassium dichromate was freshly prepared in distilled water (7.5 mg/mL; 7.5 mg/kg, 1 mL/100 g). Chrysin was prepared in 1% carboxymethylcellulose sodium (CMC-Na) at 2.5 and 5 mg/mL (25 and 50 mg/kg) and freshly prepared with continuous mixing before administration.

Commercial kits (Elabscience Biotechnology Inc., Houston, TX, USA) were used to measure serum urea/BUN, creatinine, and renal oxidative stress markers (MDA, GSH, T-SOD, CAT, and GSH-Px). All assays were performed according to the manufacturers' instructions.

All other reagents for tissue processing, homogenization, biochemical assays, and histopathology were analytical grade from certified suppliers.

2.2 Experimental Animals

Thirty-two healthy adult male Wistar rats, weighing approximately 180–220 g, were used in the present study. Animals were obtained from an accredited animal house and housed under standard laboratory conditions with controlled temperature, adequate ventilation, and a 12 h light/12 h dark cycle. Standard commercial pellet diet and tap water were provided ad libitum. The animals were allowed to acclimatize for 7–14 days before the beginning of the experiment. All experimental procedures were conducted in accordance with institutional guidelines for the care and use of laboratory animals.

2.3 Experimental Design

The rats were randomly allocated into four equal groups (n = 8 per group):

- Group I – Control: Rats received the vehicle used for administration throughout the experimental period.
- Group II – Potassium dichromate: Rats received potassium dichromate ($K_2Cr_2O_7$) at a dose of 7.5 mg/kg body weight/day.

- Group III – Potassium dichromate + Chrysin low dose: Rats received potassium dichromate at 7.5 mg/kg/day together with Chrysin at 25 mg/kg/day.
- Group IV – Potassium dichromate + Chrysin high dose: Rats received potassium dichromate at 7.5 mg/kg/day together with Chrysin at 50 mg/kg/day.

The potassium dichromate dose was selected based on a recent experimental model demonstrating reproducible renal oxidative stress, biochemical renal dysfunction and histopathological alterations following daily administration of 7.5 mg/kg for 14 days {3 }.Chrysin doses of 25 and 50 mg/kg were selected based on previous experimental studies demonstrating renoprotective and antioxidant effects at these doses in rats {5, 9 }.

2.4 Preparation and Administration of Treatments

Potassium dichromate was freshly dissolved in an appropriate vehicle before administration. Chrysin was prepared immediately before administration using a suitable vehicle to ensure adequate dispersion and consistent dosing. Treatments were administered once daily according to the assigned experimental groups. The exact route and treatment sequence were maintained consistently among all animals.

For the protective-design protocol, Chrysin administration began before or concurrently with potassium dichromate exposure and continued throughout the experimental period. The same administration schedule was applied consistently to the corresponding treatment groups.

2.5 Body Weight

Body weight was recorded at the beginning of the experiment and at predetermined intervals throughout the experimental period. The change in body weight was calculated as the difference between the final and initial body weights to monitor the general effects of the experimental treatments {9 }.

2.6 Blood and Kidney Sample Collection

At the end of the experimental period, animals were anesthetized according to the approved experimental protocol. Blood samples were collected and centrifuged to obtain serum, which was stored at −20°C until biochemical analysis. Following blood collection, the animals were euthanized and the kidneys were carefully removed. Kidney tissue intended for biochemical analysis was washed with cold physiological saline, whereas representative portions were fixed in 10% neutral buffered formalin for histopathological examination {10 }.

2.7 Assessment of Renal Function

Serum urea, blood urea nitrogen (BUN), and creatinine were determined as biochemical indicators of renal function using commercially available diagnostic kits according to the manufacturers' instructions {10 }.

2.8 Oxidative Stress and Antioxidant Status

Renal tissue samples were homogenized in an appropriate ice-cold buffer and centrifuged to obtain the supernatant. Renal oxidative stress and antioxidant status were evaluated by measuring malondialdehyde (MDA), reduced glutathione (GSH), and superoxide dismutase (SOD). The assays were performed according to the manufacturers' instructions for the respective commercial kits {9 }.

2.9 Histopathological Examination

Representative kidney specimens were fixed in 10% formalin, dehydrated through graded ethanol, cleared in xylene, embedded in paraffin wax, sectioned at approximately 5 μm thickness, and stained with hematoxylin and eosin (H&E). The sections were examined microscopically for renal tubular and glomerular alterations, including tubular degeneration, tubular necrosis, inflammatory cell infiltration, vascular congestion and other pathological changes {11}.

2.10 Histopathological Scoring

Histopathological lesions were semi-quantitatively scored according to the severity of tubular degeneration, tubular necrosis and interstitial inflammatory changes, allowing objective comparison among the experimental groups {12 }.

2.11 Statistical Analysis

Data were expressed as mean ± standard deviation (SD). Differences among the experimental groups were analyzed using one-way analysis of variance (ANOVA), followed by Tukey's multiple-comparison test. A probability value of $P < 0.05$ was considered statistically significant {13}.Within each figure, groups not sharing the same superscript letter differ significantly from one another.

3 RESULTS

3.1 Effect on Renal Function Parameters

Rats exposed to potassium dichromate alone (Group II) showed a clear, significant elevation ($P < 0.05$) in all measured renal function parameters relative to the control group. Serum creatinine reached 2.4 ± 0.13 mg/dL versus 0.8 ± 0.03 mg/dL in the control group (an approximately three-fold increase), while blood urea nitrogen (BUN) rose from 22 ± 0.21 to 50 ± 0.43 mg/dL, and serum urea rose from 30 ± 0.85 to 55 ± 0.70 mg/dL. All three parameters in Group II carried the statistical letter (a), significantly different from the other groups, reflecting marked impairment of glomerular filtration and tubular function.

Combined treatment with Chrysin produced a dose-dependent improvement in all three parameters. Serum creatinine decreased to 1.7 ± 0.10 mg/dL with the low dose (25 mg/kg, Group III) and to 1.2 ± 0.04 mg/dL with the high dose (50 mg/kg, Group IV); both values carried the letter (b) and differed significantly from the potassium-dichromate-only group. BUN and serum urea returned to levels not significantly different from control in the high-dose group (27 ± 0.53 and 34 ± 0.61 mg/dL, respectively; letter c, matching the control), while both markers remained at a significantly intermediate level in the low-dose group (letter b). This pattern is illustrated in Figure 1.

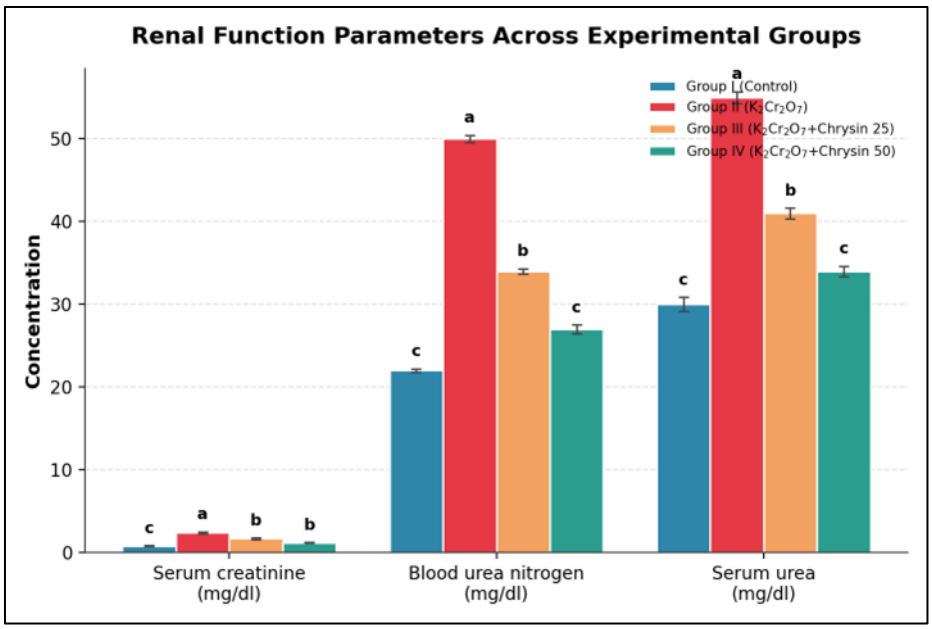

Figure 1: Serum creatinine, blood urea nitrogen (BUN), and serum urea levels across the four experimental groups. Values are mean ± SD; bars not sharing the same superscript letter differ significantly at $P < 0.05$.

3.2 Renal Reduced Glutathione (GSH)

Renal GSH concentration decreased markedly in Group II to 91.65 ± 45.17, compared with 413.53 ± 25.80 in the control group, a reduction of approximately 78% ($F = 61.76$, $P < 0.001$), reflecting acute depletion of the non-enzymatic antioxidant reserve following potassium dichromate exposure. Chrysin treatment produced a significant, partial restoration at the low dose (257.83 ± 58.35) and a near-complete restoration at the high dose (377.50 ± 26.70), with GSH levels in Group IV not differing significantly from the control group, while all other groups differed significantly from one another (Figure 2).

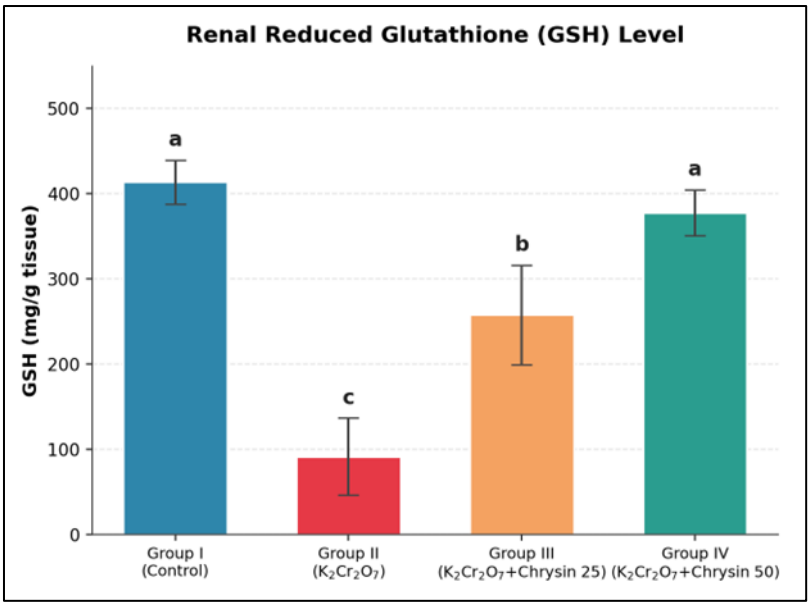

Figure 2: Renal reduced glutathione (GSH) levels across the four experimental groups. Values are mean ± SD; bars not sharing the same superscript letter differ significantly at P < 0.05.

3.3 Malondialdehyde (MDA)

Renal MDA, the principal marker of lipid peroxidation, increased sharply and significantly in Group II (255.72 ± 19.97), approximately 4.5-fold above the control value (56.28 ± 2.10) ($F = 77.20$, $P < 0.001$). This elevation was significantly reduced in both Chrysin-treated groups, with values not differing significantly from control at either the low dose (93.18 ± 39.66) or the high dose (61.72 ± 17.80); no significant difference was observed between the two Chrysin doses, indicating a strong protective effect against lipid peroxidation even at the lower dose (Figure 3).

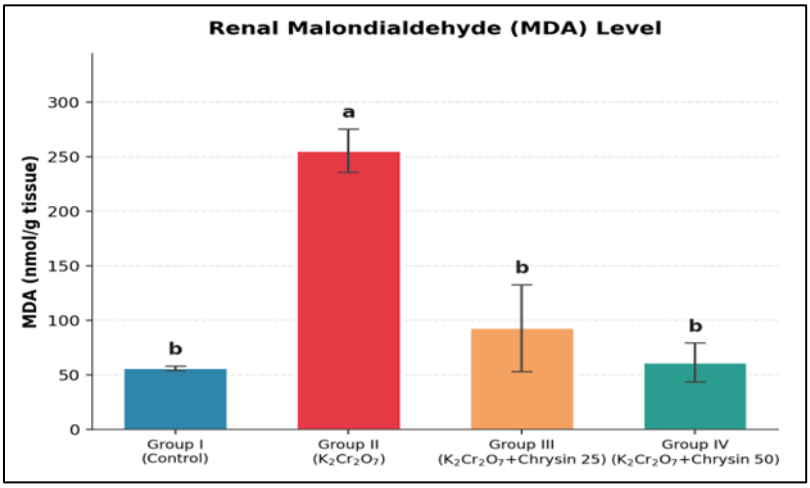

Figure 3: Renal malondialdehyde (MDA) levels across the four experimental groups. Values are mean ± SD; bars not sharing the same superscript letter differ significantly at P < 0.05.

3.4 Superoxide Dismutase (SOD) Activity

Unlike GSH and MDA, one-way ANOVA revealed no statistically significant difference in renal SOD activity among the four groups ($F = 1.24$, $P = 0.33$); mean values ranged from 1.17 ± 0.49 U/mg protein in the control group to 1.99 ± 0.76 U/mg protein in the potassium-dichromate group, with considerable inter-individual variability within each group (Figure 4).

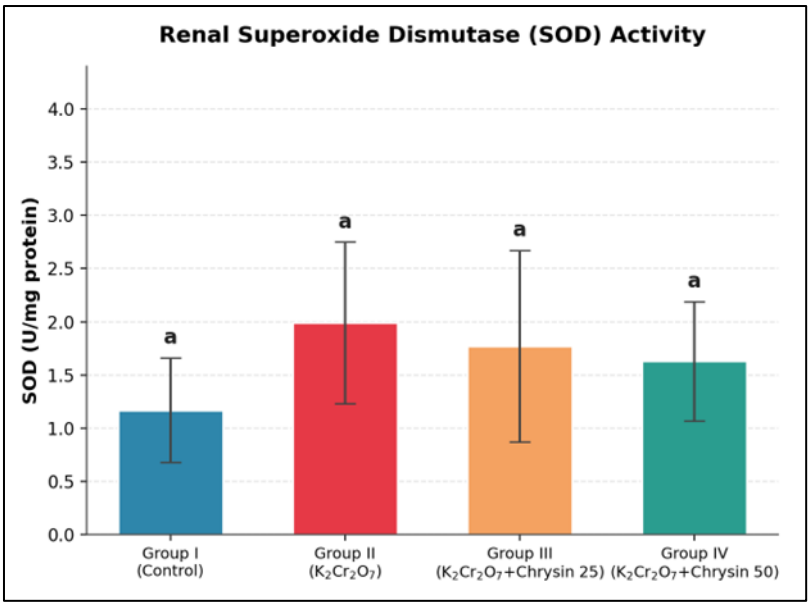

Figure 4: Renal superoxide dismutase (SOD) activity across the four experimental groups (no statistically significant differences, P > 0.05).

3.5 Histopathological Findings

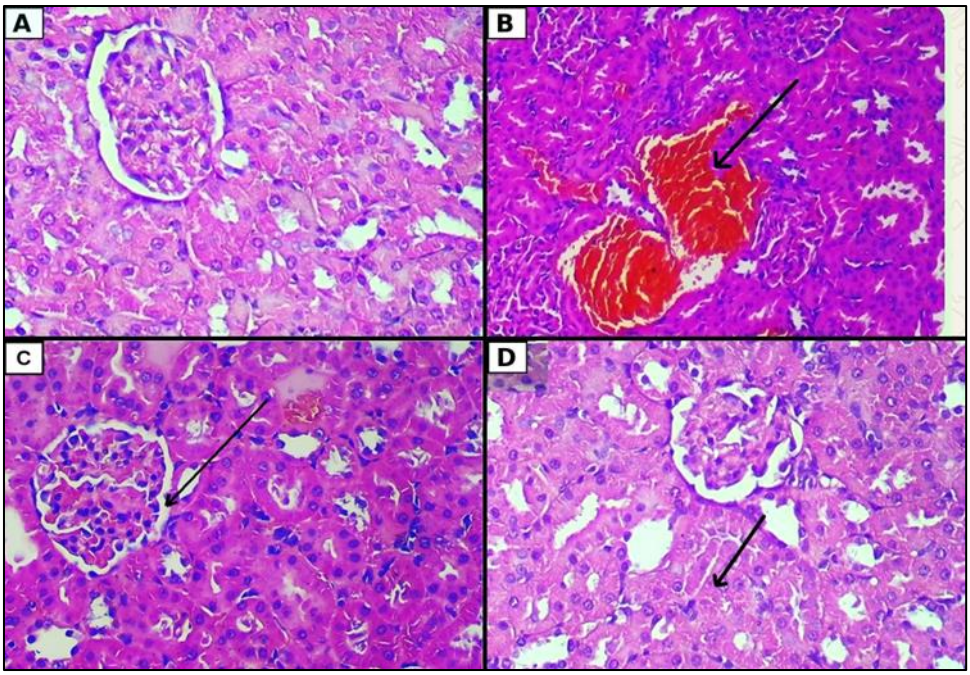

Figure 5: Representative photomicrographs of H&E-stained kidney sections (×400) from rats of the different experimental groups. (A) Control group (Group I) showing normal glomerular tuft, patent Bowman's space, and normal renal tubular epithelium (arrow). (B) Potassium dichromate group (Group II) showing severe glomerular capillary hemorrhage and swelling of the glomerular tuft with obliteration of Bowman's space, together with cloudy swelling of the renal tubules (arrow). (C) Potassium dichromate + Chrysin low-dose group (Group III) showing mild tubular epithelial degeneration and focal tubular dilatation, with partial restoration of the renal architecture (arrow). (D) Potassium dichromate + Chrysin high-dose group (Group IV) showing mild residual tubular degeneration with relatively preserved renal architecture (arrow).

Microscopic examination of H&E-stained kidney sections revealed normal renal corpuscles, patent Bowman's space, and well-preserved tubular epithelium in the control group (Fig. 5A). Rats exposed to potassium dichromate alone displayed severe histopathological alterations, characterized by marked glomerular capillary hemorrhage and swelling of the glomerular tuft leading to obliteration of Bowman's space, together with cloudy swelling of the renal tubular epithelium (Fig. 5B). Co-administration of the low dose of Chrysin (25 mg/kg) with potassium dichromate was associated with marked histological improvement relative to the potassium-dichromate-only group, with sections

showing only mild tubular epithelial degeneration and focal tubular dilatation, accompanied by partial restoration of the renal architecture (Fig. 5C). Rats receiving the high dose of Chrysin (50 mg/kg) together with potassium dichromate exhibited the greatest degree of histological protection among the treated groups, with sections showing mild residual tubular degeneration but relatively preserved overall renal architecture (Fig. 5D). These findings indicate a dose-dependent attenuation of potassium-dichromate-induced renal histopathological injury by Chrysin, consistent with the biochemical and oxidative stress findings described above.

4 DISCUSSION

The present findings confirm that sub-acute exposure to potassium dichromate produces marked renal functional impairment and oxidative injury in male rats, consistent with the well-established nephrotoxic profile of hexavalent chromium. Cr(VI) readily crosses cell membranes owing to its high solubility and subsequently undergoes intracellular reduction, generating reactive oxygen species (ROS) and reactive chromium intermediates that induce acute oxidative stress {14 }. This was clearly reflected in the sharp elevation of MDA and the parallel depletion of GSH observed in the potassium-dichromate-only group, indicating excessive lipid peroxidation and depletion of non-enzymatic antioxidant defenses, consistent with the biochemical and histological pattern reported by {15 }using the same dose (7.5).

The renal functional impairment, reflected in elevated serum creatinine, BUN and urea in potassium-dichromate-exposed animals, is attributable to direct oxidative injury of tubular and glomerular cells, which reduces glomerular filtration efficiency and impairs normal excretion of nitrogenous metabolic waste { 16,3}.The proportionally greater rise in creatinine relative to BUN suggests prominent tubular injury, consistent with the presumed mechanism of Cr(VI) nephrotoxicity.

Chrysin (5,7-dihydroxyflavone) exerted a clear, dose-dependent protective effect on all measured functional and oxidative parameters, with the high dose (50 mg/kg) achieving near-complete restoration of GSH, MDA, BUN and serum urea to levels statistically indistinguishable from control, while the low dose (25 mg/kg) achieved a statistically significant partial improvement. This dose-response pattern is consistent with previous reports of the renoprotective effect of Chrysin against arsenic-induced nephrotoxicity {17}and adenine-induced chronic kidney disease {4 }, in which the protective activity was attributed to the antioxidant, anti-inflammatory and anti-apoptotic properties of Chrysin.

The likely molecular basis of this protection is further supported by the findings of {7 },who demonstrated that Chrysin attenuates gentamicin-induced nephrotoxicity through modulation of the antioxidant Nrf2/AKT pathway and the anti-inflammatory NF-κB/KIM-1 pathway — pathways plausibly also implicated in potassium-dichromate nephrotoxicity given the shared mechanism of ROS generation. Additional recent studies support this protective role, including attenuation of paclitaxel-induced hepatorenal toxicity through suppression of oxidative stress, inflammation and apoptosis {6}, protection against isoniazid-induced nephrotoxicity {8 }, and protection against bortezomib-induced nephrotoxicity accompanied by endoplasmic reticulum stress and apoptosis {9 }, collectively reinforcing the consistency between the present findings and the accumulated literature on the renoprotective role of Chrysin across multiple models of nephrotoxicity.

The absence of a statistically significant difference in SOD activity among groups ($P = 0.33$), despite a trend toward higher relative values in the potassium-dichromate group, may be attributable to substantial inter-individual variability and the limited sample size ($n = 5$), or to an early compensatory upregulation of SOD during the initial phase of acute oxidative stress that is not yet exhausted, a phenomenon described in some heavy-metal toxicity models {1, 18}. Clarifying this pattern would benefit from comparison with catalase and glutathione peroxidase activities in future work.

The histopathological findings of the present study parallel and reinforce the biochemical results. The severe glomerular capillary hemorrhage, glomerular tuft swelling, obliteration of Bowman's space, and cloudy swelling of the tubular epithelium observed in the potassium-dichromate-only group reflect the direct cytotoxic consequences of intracellular Cr(VI) reduction described above, while the dose-dependent histological improvement observed with Chrysin co-treatment — from mild tubular degeneration with partial architectural restoration at the low dose, to mild residual changes with relatively preserved architecture at the high dose — mirrors the corresponding dose-dependent normalization of renal function and oxidative stress markers. Taken together, the concordant biochemical, oxidative and structural findings indicate that oxidative stress-mediated injury to glomerular and tubular epithelial cells is the principal mechanism underlying potassium-dichromate nephrotoxicity in this model, and that the antioxidant and anti-inflammatory properties of Chrysin underlie its dose-dependent renoprotective effect {19,3 }

5 CONCLUSION

Sub-acute exposure to potassium dichromate (7.5 mg/kg/day) produced significant renal functional impairment, oxidative stress, and severe histopathological injury in male Wistar rats, evidenced by elevated serum creatinine, BUN and urea, increased MDA, depleted GSH, and marked glomerular and tubular lesions. Co-administration of Chrysin attenuated these changes in a clearly dose-dependent manner, with the high dose (50 mg/kg) producing the greatest degree of biochemical and histological protection, in several parameters restoring values statistically indistinguishable from control. These findings indicate that Chrysin possesses meaningful, dose-dependent nephroprotective potential against potassium-dichromate-induced renal injury, most plausibly mediated through its antioxidant and anti-inflammatory properties. Further studies incorporating additional antioxidant enzymes (catalase, glutathione peroxidase) and molecular pathway analyses are warranted to fully characterize the underlying protective mechanisms.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Acknowledgments

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Disclosure of conflict of interest

The authors declare no conflict of interest.

Statement of ethical approval

All experimental procedures were approved by the Animal Care and Ethics Committee, College of Science, Al-Qasim Green University (Approval No. qgec/8 /2025). Animal care and experimental procedures were conducted in accordance with internationally recognised guidelines for the use of laboratory animals.

Data Availability

All data supporting the findings of this study are contained within the manuscript.

Author Contributions

H.M.M. conceived and designed the study, conducted all experimental work and animal handling, performed the biochemical and histopathological analyses, analyzed and interpreted the data, and drafted, reviewed and approved the final manuscript.

Generative AI Statement

The authors declare that no Gen AI/DeepSeek was used in the writing/creation of this manuscript.

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