



Quercetin Attenuates Cadmium-induced Renal Injury in Chickens *via* Suppression of Apoptosis and NLRP3 Inflammasome Activation

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10.18805/IJAR.BF-2047

ABSTRACT

Background: Research has demonstrated that the heavy metal cadmium (Cd) causes significant damage to the kidneys. In contrast, the natural flavonoid quercetin (Que) possesses a variety of pharmacological effects that can alleviate the toxic effects of Cd. However, the specific effects of Que on Cd-induced kidney inflammation, particularly regarding the NLRP3 inflammasome, remains unclear.

Methods: Sixty-four male Hylan brown chickens were with fed for 30 days with the test substances. Serum and kidney samples were collected for evaluation of kidney function, oxidative stress levels, histology, apoptosis and inflammation.

Result: Cd exposure in chickens led to reduced body weight, increased renal coefficient, renal dysfunction, histopathological damage and oxidative stress. Results from TUNEL staining, RT-qPCR and Western blot analysis confirmed that Cd induced apoptosis and inflammation in kidneys through mitochondria-mediated apoptosis and NLRP3 inflammasome activation. Que alleviated these effects by inhibiting both mitochondria-mediated apoptosis and inflammasome activation, thereby reducing Cd-induced kidney injury.

Key words: Apoptosis, Cadmium, Kidney, NLRP3 inflammasome, Quercetin.

INTRODUCTION

Cadmium (Cd) is a toxic heavy metal originated from industrial discharge, agricultural fertilization and other anthropogenic activities. Exposure to Cd damages multiple organs, including the liver, kidneys, testicles, ovaries and bones (Ali *et al.*, 2021; Ammari *et al.*, 2024). Entry occurs mainly through contaminated food and water, after which Cd enters the bloodstream and reaches the liver, inducing metallothionein expression. The resulting Cd-metallothionein complex is filtered by the glomeruli and reabsorbed in proximal renal tubules, leading to long-term accumulation and nephrotoxicity (Yan and Allen, 2021). Consequently, the kidney is a major target of Cd toxicity (Zhu *et al.*, 2019; Al-Zharani *et al.*, 2025). Prolonged exposure results in kidney dysfunction, polyuria and proteinuria (Vervaet *et al.*, 2017). Structural changes include swelling and increased volume of proximal tubular cells in the renal cortex (Kim *et al.*, 2018). The principal mechanisms underlying Cd-induced kidney injury involve oxidative stress, apoptosis and inflammation (Li *et al.*, 2020).

Pyroptosis, a unique lytic cell death mechanism differing from apoptosis and necrosis, significantly contributes to various disease developments. The typical pyroptosis process is mainly mediated by inflammasome and is particularly dependent on caspase-1 activation. Activated caspase-1 proteolytically processes pro-inflammatory cytokines such as interleukin-1 β (IL-1 β) and interleukin-18 (IL-18) (Li *et al.*, 2024), enabling their extracellular release. The NLRP3 inflammasome, as an important intracellular inflammatory signaling molecule, is mainly composed of Nod-like receptor heat protein domain-associated protein 3 (NLRP3), apoptosis-associated

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How to cite this article: Shi, Y., Zhu, H. and Wang, J. (2025). Quercetin Attenuates Cadmium-induced Renal Injury in Chickens *via* Suppression of Apoptosis and NLRP3 Inflammasome Activation. *Indian Journal of Animal Research*. 1-9. doi: 10.18805/IJAR.BF-2047.

Submitted: 17-07-2025 **Accepted:** 01-12-2025 **Online:** 16-12-2025

speck-like protein containing a CARD (ASC) and pro-cysteiny aspartate specific proteinase-1 (pro-caspase-1). After the NLRP3 inflammasome is activated, ASC binds to it and promotes ASC aggregation. This mechanism activates caspase-1 by cleaving pro-caspase-1, leading to the cleavage and secretion of inflammatory mediators like IL-18 and IL-1 β (Yang *et al.*, 2019). Notably, Multiple research findings indicate notable NLRP3 inflammasome activation in animal models subjected to Cd exposure (Li *et al.*, 2023; Li *et al.*, 2024). For example, (Antar *et al.*, 2024) confirmed through experiments that Cd may exacerbate inflammatory injury in the mouse heart by activating the NLRP3 inflammasome, thereby impacting heart function (Antar *et al.*, 2024).

Quercetin (Que) is a polyhydroxyl flavonoid, with the chemical formula C₁₅H₁₀O₇. It is commonly found in fruits, Chinese herbs and vegetables. Studies have confirmed

that in addition to its powerful antioxidant effect, Que also has wide-ranging pharmacological activities, including kidney protection, antibacterial, anticancer, antiviral and immune regulation (Granato *et al.*, 2017; Patel *et al.*, 2021). Researchers such as Beken confirmed that Que, through its antioxidant and anti-inflammatory properties, can effectively alleviate the OS and inflammatory response of human keratinocytes in atopic dermatitis models (Beken *et al.*, 2020). Scholars such as Wu have revealed that Que has an improving effect on acute liver failure by regulating the apoptosis and inflammatory processes induced by mitochondrial dysfunction (Wu *et al.*, 2024). In contrast to conventional medications, Que has found applications in the food industry, healthcare and animal husbandry and other fields due to its distinctive biological activity and lack of toxic side effects. (Alshammari *et al.*, 2021) reported that Que can reduce liver steatosis and liver fibrosis caused by Cd exposure (Alshammari *et al.*, 2021).

However, research on the potential of Que to mitigate Cd-induced damage to chicken kidneys by inhibiting apoptosis and the NLRP3 inflammasome response remains limited. Therefore, in this study, Hyland white laying hens were chosen as the experimental model to investigate Cd-induced nephrotoxicity and the protective effects of Que on Cd-induced nephrotoxicity.

MATERIALS AND METHODS

Main reagents and instruments

Cadmium chloride semi-pentahydrate (CdCl₂, purity 99.95%) was purchased from Aladdin Chemical (Shanghai, China). Quercetin (Que, purity 97%) was purchased from Yien Chemical (Shanghai, China). Creatinine (CRE), uric acid (UA), blood urea nitrogen (BUN), catalase (CAT), malondialdehyde (MDA), glutathione (GSH), total superoxide dismutase (T-SOD) and total antioxidant capacity (T-AOC) kits were purchased from Nanjing Jiancheng Bioengineering Institute (Nanjing, China). Western Blot Antibodies, including Caspase-3, Bax, ASC, IL-18 and IL-1β were sourced from Wanleibio. Cytc and Caspase-9 were sourced from Servicebio, while Bcl-2, NLRP3 and Caspase-1 were sourced from Proteintech.

Experimental animals and sample collection

After 3 days of adaptive feeding, 64 male Hylan brown chickens were randomly divided into four groups, each containing sixteen animals (Table 1). Each group was given free water. At this time, according to the experimental age

of 1 d. After 4 weeks, the weight was recorded, blood was collected using ether anesthesia, serum was obtained through low-speed centrifugation and the serum was refrigerated for subsequent experiments. The kidney was excised using sterile scissors, weighed and the kidney coefficient was calculated. A portion of kidney tissue was extracted and placed in a tissue-fixation solution and kidney histology was observed.

Detection of renal function and antioxidant levels

About 100 mg of kidney tissue was added to 9 parts normal saline, ground at low temperature and centrifugal collection of supernatant. Serum concentrations of CRE, UA and BUN and kidney tissue levels of MDA, GSH, T-SOD, T-AOC and CAT, were measured using a full-wavelength light-absorption enzyme spectrometer (Infinite M Nano, TECAN) and an ultraviolet spectrophotometer (UV-1800, MAPADA).

Renal histopathology was observed by HE staining

Small pieces of fresh kidney tissue were fixed with 4% paraformaldehyde. Various concentrations of ethanol were utilized to dehydrate the tissue and immerse it in xylene and thus to achieve tissue transparency. The transparent tissue blocks were then placed in melted paraffin wax for tissue embedding. A microtome was used to slice the embedded tissue into 0.5 μm sections. These sections were transferred onto slides and allowed to dry at 45°C. The sections were dewaxed in xylene and alcohol, hematoxylin-stained, dehydrated in pure alcohol, cleared with xylene, mounted and microscopically examined.

Renal cells apoptosis was observed through TUNEL staining

The prepared paraffin sections were incubated at an appropriate temperature, soaked in xylene and hydrated with gradient ethanol from high to low. After treatment with protease K, washed with PBS, supplemented with TdT enzyme reaction solution and incubated in a dark environment. The reaction buffer was added following by washing with PBS three times and then 0.05% DAB solution was applied for 10 min. Rinsing with PBS or distilled water was performed during each step. Then, the sample was re-dyed with methyl green for 10 min, dehydrated in xylene, sealed and dried. Finally, a photo was taken is taken using a light microscope.

RT-qPCR was used to detect the mRNA expression of genes related to apoptosis and inflammation

The kidney tissue of appropriate size was placed in 800 μL of TriZol solution for complete lysis, after which the total

Table 1: Animals and treatment.

For short	Group	Experimental treatment
Control	Control group	Daily free access to water and food
Cd	150 mg/kg CdCl ₂ group	150 mg/kg of CdCl ₂ is added to the feed
Cd + Que	150 mg/kg CdCl ₂ + 250 mg/kg Que group	A mixture of 150 mg/kg of CdCl ₂ and 250 mg/kg of Quercetin is added to the feed
Que	250 mg/kg Que group	250 mg/kg of Quercetin is added to the feed

RNA from the chicken kidney tissue was extracted and reverse transcribe the extracted total RNA into cDNA. Primer 5 was used to design primers (Table 2). The instructions of a 2×RealStar Fast SYBR qPCR Mix (Genstar) kit was followed. Treatment of the samples in each group was repeated three times and the samples were analysis using a C1000 Touch system (Bio-Rad). The mRNA expression levels of the detected genes were calculated using the $2^{-\Delta\Delta Ct}$ method.

Western blot analysis

We collected 0.4 g of kidney tissue and added 400 μ L of lysate (RIPA lysate: protease inhibitor cocktail: Phosphatase inhibitor cocktail A). The mixture was ground using a high-speed tissue grinder, the supernatant was extracted and the protein concentration was measured. The final sample was obtained by denaturing water through boiling. The protein was immobilized onto a PVDF film through SDS-PAGE mediated electrophoretic and transfer. The appropriate primary antibody concentration was selected for incubation at 4°C for 15 h. The corresponding rabbit or mouse antibody was incubated for 45 min, during which TBST was used three times. Exposure was performed using a chemiluminescent gel imager (Omega Lum G, Aplegen). Image software was used to analyze the gray values.

Data analysis and mapping

All statistical calculations were performed using SPSS version 26.0. One-way analysis of variance (ANOVA) was

applied, followed by post hoc comparisons using the least significant difference (LSD) method. Results are expressed as the mean $\pm$ standard error of the mean (SEM). Graphs were generated through GraphPad Prism 8. Differences with $P>0.05$ were considered statistically insignificant, while differences with $P<0.05$ or $P<0.01$ were considered significant or extremely significant.

RESULTS AND DISCUSSION

Effects of Que and Cd on chicken weight and kidney coefficient

The body weight of chickens across different groups was tracked (Table 3). Relative to the control, chickens exposed to Cd experienced progressive weight loss by 10.64%, 19.15% and 25.37% on days 14, 21 and 28, respectively ($P<0.01$). However, Que supplementation in the Cd + Que group led to a weight recovery of 6.12%, 14.4% and 14.72% at the same time points, with significant improvements ($P<0.05$). Additionally, assessment of kidney indices showed that Cd exposure raised the kidney coefficient by 52.24% ($P<0.01$) compared to the control. Que intervention effectively reduced the kidney coefficient by 13.53% compared to the Cd-only group ($P<0.01$).

Effects of Que and Cd on renal function indices in chicken serum

Serum levels of UA, BUN and CRE were evaluated and kidney injury was informed (Fig 1 A-C). In chickens exposed to Cd, levels of UA, BUN and CRE were markedly elevated

Table 2: Primer sequences for the target genes.

Gene	Primers sequences (5' → 3')	Product length	NCBI Reference sequence
<i>Cytc</i>	F: GGTGGTGCTGGACCTGAAG R: CACTGGCAGGTGCGTTGAG	107 bp	NM_001005843
<i>Caspase-9</i>	F: CCGAAGGAGCAAGCACG R: AGGTTGGACTGGGATGGAC	243 bp	XM_046931415
<i>Caspase-3</i>	F: TGGTGGAGGTGGAGGAGC R: CATCTTCCCCTGAGCGTGG	213 bp	NM_204725
<i>Bax</i>	F: GTGATGGCATGGGACATAGCTC R: TGGCGTAGACCTTGCGGATAA	90 bp	XM_046922136
<i>Bcl-2</i>	F: ATCGTCGCCTTCTTCGAGTT R: ATCCCATCCTCCGTTGTCCT	150 bp	NM_205339
<i>NLRP3</i>	F: GTTTGAGGAGATGAACCAGAGG R: GTTTGAGGAGATGAACCAGAGG	169 bp	NM_001348947
<i>Caspase-1</i>	F: CGCAGCCTCATAGACACCG R: GGGCACTGCTGTATCCACTG	212 bp	XM_040650618
<i>IL-18</i>	F: GCAGTACGGCTTAGAGAAA R: GTACATTCCACTGCCAGATT	199 bp	XM_015297946
<i>IL-1β</i>	F: GTGAGGCTCAACATTGCGCTGTA R: TGTCCAGGCGGTAGAAGATGAAG	214 bp	NM-204525
<i>ASC</i>	F: ATGTTGGAGTTTACGACCGC R: GGTTCGCATCCTGCCCT	155 bp	NM_001040467
<i>β-actin</i>	F: CCGCTCTATGAAGGCTACGC R: CTCTCGCTGTGGTGGTGAA	128 bp	NM_205518

by 93.95, 89.62 and 154.97%, respectively ($P<0.01$). Notably, Que supplementation reversed these trends, decreasing UA by 17.77, BUN by 30.82 and CRE by 37.23% compared to the Cd group ($P<0.01$). Histopathological analysis of the kidneys (Fig 1D) demonstrated that glomerular structures remained intact in the control and Que-treated groups. In contrast, chickens subjected to Cd exposure exhibited severe pathological changes, including blurring of glomerular boundaries, significant inflammatory infiltration and massive erythrocyte accumulation. Treatment with Que partially restored glomerular morphology and substantially mitigated inflammatory and erythrocytic infiltration.

Effects of Que and Cd on OS and MDA in kidney tissues

As depicted in Fig 2, compared to the control group, Cd exposure led to substantial declines in CAT (28.1%), T-AOC

(25.74%) and T-SOD (25.9%) activities, while promoting significant elevations in GSH (153.75%) and MDA (33.26%) ($P<0.01$). In contrast, chickens treated with Que exhibited increased activities of CAT (25.35%), T-AOC (24.69%) and T-SOD (27.84%), alongside reductions in GSH (31.77%) and MDA (21.72%) levels compared to the Cd group ($P<0.01$).

The effects of Que and Cd on renal tissue apoptosis

Apoptotic cells in renal tissues were visualized by TUNEL staining (Fig 3A) and at the same time RT-qPCR and Western blot analysis (Fig 3B-H) revealed that mRNA and proteins levels of Cytc, Caspase-3, Caspase-9 and Bax were significantly increased in the Cd group, whereas Bcl-2 expression was suppressed compared to Control exposure alone ($P<0.01$). Intervention with Que effectively down-regulated Cytc, Caspase-3, Caspase-9 and Bax, while up-

Table 3: Effects of Que and Cd on the body weight and kidney coefficient of chickens at different ages.

Project		Control	Cd	Cd + Que	Que
Weight	1 th day	49.3±2.09	49.08±1.14	49.47±2.12	50.17±1.58
	7 th day	96.15±6.19	89.45±7.31	93.75±6.45	97.58±7.08
	14 th day	195.58±9.33	174.78±8.65**	185.48±7.05#	203.15±8.59
	21 th day	284.52±14.9	230.05±13.55**	263.17±17.17##	288.12±12.32
	28 th day	414.48±20.97	309.33±24.64**	354.85±21.61##	416.97±16.64
kidney coefficient		1.01±0.03	1.52±0.32**	1.13±0.14##	0.96±0.1

Values are expressed as the Mean ± SEM. n=6. * $P<0.05$ or ** $P<0.01$: compared with the control group. # $P<0.05$ or ## $P<0.01$: compared with the Cd group. The following is the same.

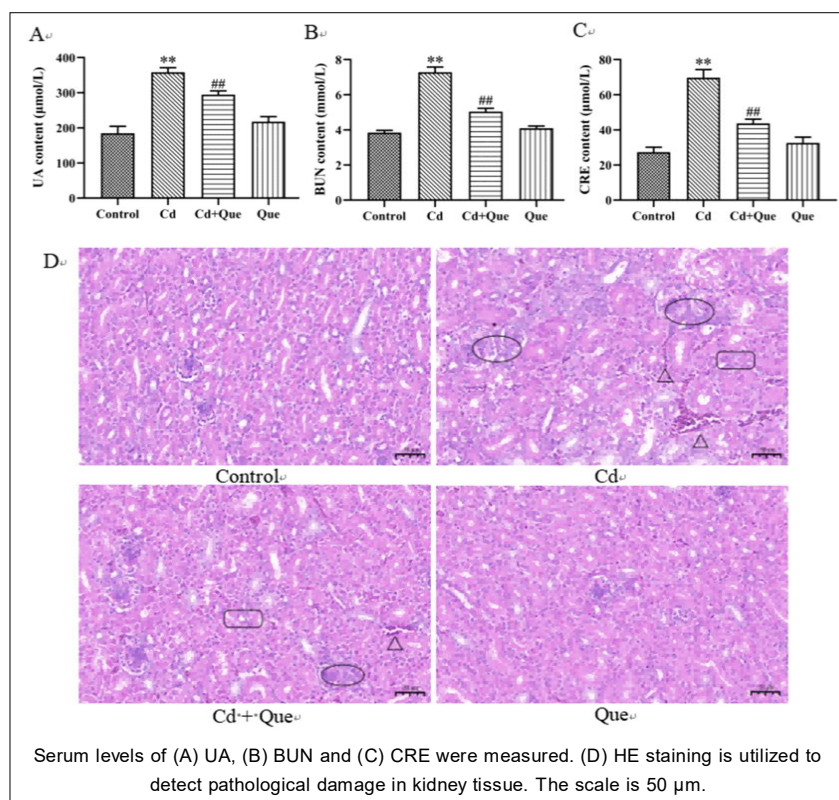


Fig 1: Effects of Que and Cd on renal function, histopathology and antioxidant function in chickens.

regulating Bcl-2, restoring the balance between pro- and anti-apoptotic signals compared to Cd exposure alone ($P<0.01$).

Effects of Que and Cd on the mRNA and proteins expression of NLRP3 inflammasome pathway-related genes in kidney tissues

The RT-qPCR and Western blot results demonstrated (Fig 4 A-G) that the Cd group exhibited pronounced up-

regulation of NLRP3, Caspase-1, ASC, IL-18 and IL-1 β ($P<0.01$). Treatment with Que significantly reduced ($P<0.01$) the expression of these inflammatory mediators compared to the Cd group ($P<0.05$).

Cd primarily enters the human body through inhalation, with ingestion of contaminated food and water serving as another major route, while skin absorption is negligible. Once inside, Cd circulates *via* the bloodstream and

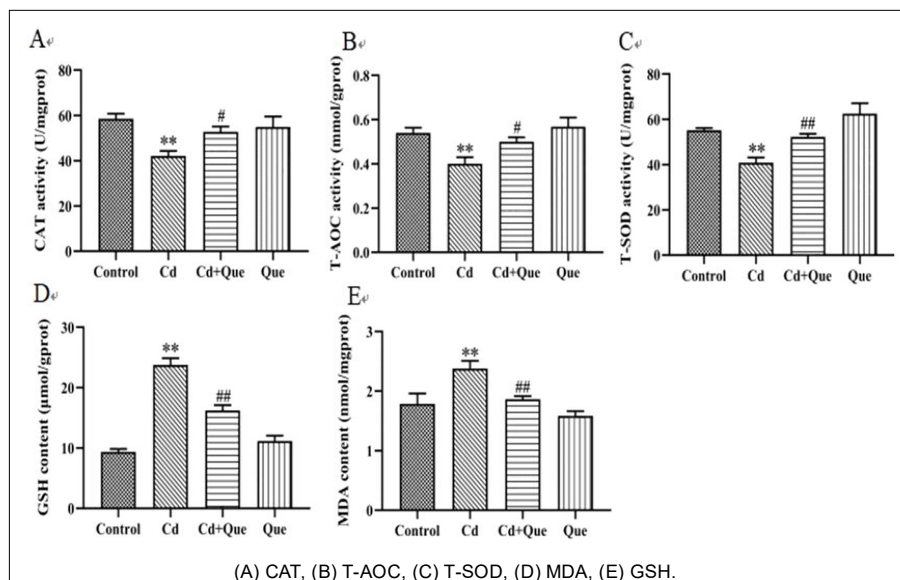


Fig 2: Effects of Que and Cd on oxidative stress indexes of chicken kidney.

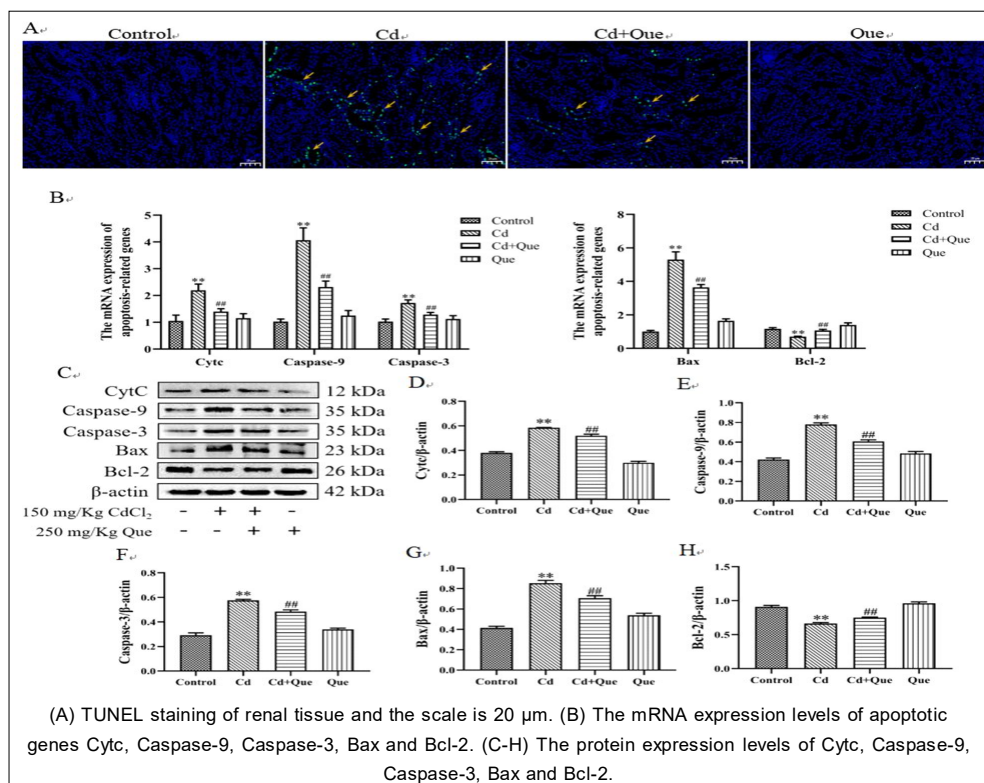


Fig 3: Effects of Que and Cd on apoptosis of renal tissue.

preferentially accumulates in organs, particularly the kidneys, where it exerts chronic toxic effects (Genchi *et al.*, 2020). The kidney is a critical site of Cd accumulation and its metabolism in this organ is extremely slow, with a half-life extending up to 45 years (Kar and Patra, 2021; Sotomayor *et al.*, 2021). In toxicology, body weight and organ coefficient are key indicators of systemic toxicity. Weight gain depends on nutrient absorption and utilization (Bhattacharya and Haldar, 2012), yet Cd poisoning has been shown to impair digestive enzyme activity, thereby disrupting absorption (Asagba, 2010). In this experiment, Cd exposure led to body-weight loss and an increased kidney coefficient, likely due to impaired nutrient assimilation. However, supplementation with Que improved body weight and reduced kidney coefficient, suggesting its protective role through appetite improvement and mitigation of Cd-induced renal damage.

As an essential detoxification organ in the body, the kidney plays a crucial role in eliminating metabolic waste and in maintaining electrolyte balance and acid-base equilibrium. Among them, UA, BUN and CRE serve as key indicators of kidney function. Elevated UA levels often indicate abnormal kidney function (Fathallah-Shaykh and Cramer, 2014). Our results indicated that the serum levels of UA, BUN and CRE were significantly increased in chickens after Cd was added to the diet, indicating that Cd can harm the kidneys by affecting the filtration capacity of the glomeruli. This finding was consistent with those of (Sanjeev *et al.*, 2019; Aqeel *et al.*, 2020). After adding Que, the levels of UA, BUN and CRE decreased, suggesting that Que can mitigate the kidney damage inflicted by Cd. At

the same time, exposure to Cd can also cause pathological damage to kidney tissue. For example, (Chen *et al.*, 2021) found that exposure to Cd may lead to incomplete kidney-tubule structure (Chen *et al.*, 2021). In this work, histopathological analysis of kidney tissue revealed a significant presence of inflammatory cell infiltrations in the kidney sections of the Cd group, along with red cell infiltration in the kidney interstitium. These findings suggested that Cd can potentially inflict kidney injury to some extent. The number of erythrocyte infiltrations also decreased after adding Que, further indicating that Que can alleviate the kidney injury caused by Cd.

Research indicates that OS plays a crucial role in the mechanism of Cd-induced kidney injury (Luo *et al.*, 2017). After Cd enters the animal's body it disrupts the body's redox balance, inducing OS, lipid peroxidation and ultimately causing kidney function impairment and cell apoptosis (Gobe and Crane, 2010; Yan and Allen, 2021). In this experiment, after exposure to Cd, the activities of CAT, T-SOD and T-AOC in chicken kidney tissue significantly decreased, whereas the contents of GSH and MDA increased. This result is consistent with (Ding *et al.*, 2024). However, contrary to the results of (Wang *et al.*, 2020) the increase in GSH content may be attributed to the compensatory increase in the body's resistance to Cd toxicity (Wang *et al.*, 2020). After adding Que, the activities of CAT, T-SOD and T-AOC in kidney tissue significantly increased, whereas the levels of GSH and MDA decreased. Therefore, Que can significantly mitigate the oxidative damage caused by Cd and reduced the damage to chicken kidneys through its powerful antioxidant function.

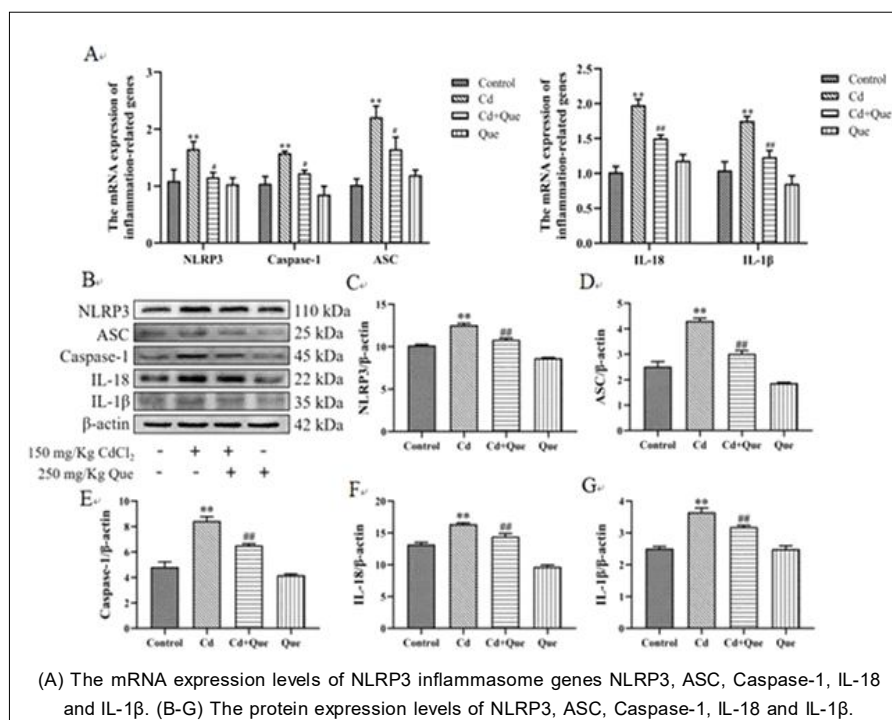


Fig 4: Effects of Que and Cd on the NLRP3 inflammasome in chicken kidney tissue.

Apoptosis is a crucial biological mechanism for maintaining homeostasis, it is coordinated regulation by multiple genes, with Bcl-2 and the Bax playing key regulatory functions (Opferman and Kothari, 2018). Studies have shown that Caspase-3 is regarded as a critical executor in the apoptotic signaling pathway (Wu *et al.*, 2020). In the apoptotic pathway, when initiator caspases or other molecules involved in the signal transduction cascade are activated, they subsequently activate Caspase-3 (Wang *et al.*, 2023). In this experiment, TUNEL staining detected elevated apoptosis in group Cd. Conversely, the mRNA and protein expression levels of mitochondrial pathway Bax, Cytc, Caspase-9 and Caspase-3 increased, whereas those of Bcl-2 decreased. These results indicated that Cd exposure may trigger apoptosis in chicken renal cells. Furthermore, Que addition significantly reduced apoptotic cells as observed by TUNEL staining. The mRNA and protein expression levels of Bax, Cytc, Caspase-9 and Caspase-3 also decreased, whereas those of Bcl-2 increased. These results showed that Que can reduce Cd-induced cell apoptosis by alleviating OS.

In recent years, the NLRP3 inflammasome has garnered significant attention as an important multiprotein complex; its abnormal activation can trigger excessive inflammatory responses, thereby exacerbating the progression of various pathological conditions (Wang and Hauenstein, 2020). Numerous studies have demonstrated that kidney injury caused by Cd is significantly linked to the activation of the NLRP3 inflammasome (Li *et al.*, 2021; Dong *et al.*, 2024). Our results indicated that the mRNA and protein expressions of NLRP3, ASC, Caspase-1, IL-18 and IL-1 β were significantly elevated following exposure to Cd. This indicates that Cd may induce kidney damage by activating the inflammatory response mediated by the NLRP3 inflammasome. Conversely, the mRNA and protein levels of NLRP3, ASC, Caspase-1, IL-18 and IL-1 β were decreased after the addition of Que, indicating that Que may mitigate Cd-induced kidney injury by inhibiting the NLRP3 inflammasome. This finding aligns with the experimental data of (Wang *et al.*, 2023).

CONCLUSION

In summary, Cd exposure can cause toxic damage to the kidneys. The mechanism of action is associated with apoptosis induced by the mitochondrial apoptosis pathway and the NLRP3 inflammasome. Concurrently, Que demonstrated a degree of protective effect against kidney injury caused by Cd. This study establishes a theoretical foundation for the protective mechanism of Que in renal injury induced by Cd through the inhibition of apoptosis and the regulation of the NLRP3 inflammasome; however, its protective pathways and regulatory mechanisms require further clarification.

ACKNOWLEDGEMENT

The present study was supported by grants from National Natural Science Foundation of China (No. 32473106, 32273083).

Disclaimers

The views and conclusions expressed in this article are solely those of the authors and do not necessarily represent the views of their affiliated institutions. The authors are responsible for the accuracy and completeness of the information provided, but do not accept any liability for any direct or indirect losses resulting from the use of this content.

Informed consent

All experimental operations were conducted in accordance with the recommendations of the National Research Council's "Guidelines for the Care and Use of Experimental Animals" and were approved by the Animal Ethics and Welfare Committee of Henan University of Science and Technology (Approval code: 20240315).

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this article. No funding or sponsorship influenced the design of the study, data collection, analysis, decision to publish, or preparation of the manuscript.

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