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Quercetin Ameliorates Clothianidin-Induced Cardiotoxicity in Rats

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Abstract

Background & Objectives: Clothianidin, a widely used neonicotinoid insecticide, has raised environmental and health concerns due to its potential toxicity. Quercetin, a flavonoid abundant in various dietary sources, exhibits potent antioxidant properties and effectively scavenges reactive oxygen species (ROS). The present study aimed to evaluate the potential protective effects of quercetin against clothianidin-induced cardiotoxicity in a rat model.

Materials & Methods: Forty-two rats were randomly assigned to six groups: (1) Normal control group: rats received 0.9% NaCl intraperitoneally (IP); (2) Vehicle control group: rats were administered 5% dimethyl sulfoxide (DMSO) IP daily; (3) Clothianidin group: rats received clothianidin (20 mg/kg/day) every three days for 21 days (seven injections); (4–6) Treatment groups: rats received clothianidin as in group 3, concurrently with quercetin at doses of 2.5, 5, or 10 mg/kg IP daily for 35 days. Serum enzyme activities of creatine kinase-MB (CK-MB) and lactate dehydrogenase (LDH) were measured. In cardiac tissue, total antioxidant capacity (TAC), malondialdehyde (MDA), and nitrate/nitrite levels were assessed. Histopathological evaluations of cardiac tissue were also conducted.

Results: Clothianidin administration induced significant cardiac injury, evidenced by decreased TAC and increased levels of MDA, nitrate/nitrite, CK-MB, and LDH. Quercetin at a dose of 10 mg/kg significantly mitigated the cardiotoxic effects of clothianidin, as indicated by reduced CK-MB and LDH levels. Furthermore, quercetin enhanced TAC and reduced MDA and nitrate/nitrite concentrations in cardiac tissue compared to the clothianidin-only group.

Conclusion: Histopathological and biochemical analyses suggest that quercetin at 10 mg/kg exerts cardioprotective effects against clothianidin-induced toxicity, likely through its antioxidant mechanisms.

Keywords: Cardiotoxicity, Clothianidin, Oxidative stress, Quercetin, Rat

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Introduction

Clothianidin (CTD), a broad-spectrum insecticide, belongs to the neonicotinoid family. It is widely used in agriculture and has been increasingly associated with environmental and health concerns (1). One of the potential mechanisms underlying its toxicity is the generation of reactive oxygen species (ROS) (2), which occurs in various tissues, including the heart, leading to oxidative damage of cellular components such as lipids, proteins, and DNA. This oxidative damage ultimately results in cellular dysfunction and apoptosis (3). Studies

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have demonstrated that clothianidin exposure can induce oxidative stress, neurotoxicity, and immunotoxicity in various species, including mammals (4). Oxidative stress, in particular, is a key mechanism of clothianidin-induced toxicity, as it disrupts the balance between ROS production and the cellular antioxidant defense system (5). This imbalance can lead to lipid peroxidation, DNA damage, and apoptosis, ultimately compromising cellular integrity and physiological function (6). Research has shown that clothianidin exposure increases ROS levels and depletes antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) in animal models, resulting in significant cellular damage (7). These findings highlight the urgent need to identify effective strategies to mitigate the adverse effects of clothianidin exposure.

ROS adversely affect myocardial function by impairing calcium handling, inducing arrhythmias, and triggering pathological remodeling, including hypertrophy, apoptosis, and necrosis. The heart's high metabolic demand and relatively low intrinsic antioxidant capacity make it particularly vulnerable to ROS-induced injury. Therefore, compared to other tissues, the unique physiological characteristics of the heart render it more susceptible to the detrimental effects of ROS (4-7). Given these findings, the impact of ROS on cardiac tissues is especially relevant when evaluating the consequences of CTD exposure.

Recently, the therapeutic potential of natural products and herbal medicines has been explored for the treatment of toxin-induced cardiotoxicity. Herbal remedies and their bioactive constituents have been employed to reduce ROS generation and manage cardiotoxicity associated with pesticide exposure (8). Quercetin (3,3',4',5, 7-pentahydroxyflavone), a widely distributed polyphenol found in numerous food sources, possesses notable antioxidant properties and functions as a potent free radical scavenger, effectively combating oxidative stress (9). Quercetin is commonly consumed through dietary intake of vegetables and fruits such as onions and apples. A wide range of scientific studies, including both in vitro and in vivo experiments, have documented its diverse biological effects. These include antioxidative, anti-inflammatory, immunoprotective, and anti-carcinogenic activities (10). Quercetin scavenges superoxide anion radicals and lipid peroxides (11). Moreover, it protects cardiomyocytes from H_2O_2-induced oxidative stress (11).

Quercetin provides significant cardioprotective effects, including inhibition of low-density lipoprotein (LDL) oxidation, endothelium-independent vasodilatory properties, reduction of adhesion molecules and other inflammatory markers, preservation of nitric oxide (NO) activity, and enhancement of endothelial function under oxidative stress conditions. It also inhibits neuronal oxidative and inflammatory injury (12). Quercetin has been demonstrated to attenuate oxidative stress and inflammation in animal models exposed to various environmental toxins, including pesticides (13). Its protective effects are mediated through modulation of signaling pathways such as NF-κB and Nrf2 (14). These properties make quercetin a promising candidate for alleviating the toxic effects of clothianidin.

Quercetin has also been shown to inhibit apoptosis by modulating key signaling cascades, including the PI3K/Akt and MAPK pathways, which are essential for cell survival (15). Through activation of these pathways, quercetin enhances the expression of anti-apoptotic proteins such as Bcl-2 while suppressing pro-apoptotic proteins including Bax and caspase-3 (16). The phenolic structure of quercetin enables it to donate hydrogen atoms to lipid radicals, thereby terminating the chain reaction of lipid peroxidation (17). Furthermore, quercetin enhances the activity of antioxidant enzymes such as SOD, GPx, and catalase, which collectively reduce ROS levels and protect

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cellular membranes from oxidative damage (14). It also directly scavenges NO and peroxynitrite ($ONOO^-$) and inhibits the expression and activity of inducible nitric oxide synthase (iNOS), the enzyme responsible for excessive NO production under pathological conditions (14).

Studies have consistently shown that clothianidin exposure increases ROS production and depletes antioxidant enzymes such as SOD and GPx in animal models, resulting in significant oxidative damage (7). Additionally, clothianidin has been reported to cause neurotoxicity by disrupting acetylcholine signaling and inducing mitochondrial dysfunction, thereby exacerbating oxidative stress (17). These findings further underscore the critical need for effective countermeasures against the toxic effects of clothianidin.

For instance, quercetin has been shown to protect against imidacloprid-induced hepatotoxicity, another neonicotinoid, by reducing oxidative stress and inflammation (18). Similarly, it has been reported to alleviate chlorpyrifos-induced neurotoxicity through its antioxidant and anti-apoptotic mechanisms (18). These findings support the notion that quercetin's protective effects extend to various models of pesticide-induced toxicity, including clothianidin-associated cardiotoxicity.

However, the effects of quercetin in animal models of clothianidin-induced cardiotoxicity have not yet been investigated. Therefore, the aim of this study was to examine the potential cardioprotective effects of quercetin against clothianidin-induced cardiotoxicity in a rat model.

Materials and Methods

Very carefully and meticulously edit this research article text regarding grammar, punctuation, collocation, prepositions, style, and word choice. The edited text must be perfectly error-free and as if written by an expert native writer and must be suitable to be published in a highly scholarly journal. Bold the changed parts:

Chemicals: Clothianidin (PESTANAL®, 33589, SPELCO, Darmstadt) and quercetin were purchased from (Sigma-Aldrich, Darmstadt, Germany). Lactate dehydrogenase (LDH) and creatine kinase (CK-MB) assessment kits were purchased from the Pars Azmoon Co. (Tehran, Iran). Furthermore, total antioxidant capacity (TAC), malondialdehyde (MDA), and nitrate-nitrite quantitation kits were purchased from Navand Salamat (Urmia, Iran) and Cib Biotech Co (Tehran, Iran), respectively.

Animals: A total number of 42 mature male Wistar rats (weight: 250±50 gr) dedicated for the current study. The rats were kept in polyethylene cages under normal preservation conditions of temperature (25± 2 ºC) and 12 h light/dark circulations. Animals had free access to commercial pellet and water. The study was done in agreement with the animal research methods established by the Ethics Committee of Faculty of Veterinary Medicine, Urmia University (IR-UU-AEC-747/PD/3).

Experimental Design: The rats were randomly allocated into 6 groups (n=7) as follow:

1. Normal control group: rats received 0.90% NaCl intraperitoneally (IP). 2. Vehicle control group: rats received dimethyl sulfoxide (DMSO; 5%) daily. Rat in group 3, received clothianidin (20 mg/kg/day) every 3 days for 21 days (seven injections). Rats in groups 4, 5, and 6 received CTD such as group 3, concurrent with 2.5, 5, and 10 mg/kg quercetin on a daily basis for 35 days (2).

Blood collection and tissue preparation: The rats were fasted overnight at the end of the experiment and anesthetized using a combination of ketamine (70 mg/kg/body weight; Alfasan, Woerden, The Netherlands) and xylazine (Alfasan, Woerden, and The Netherlands; 5 mg/kg /body weight) intraperitoneally. Blood samples were taken from the heart and their serum samples were separated by centrifugation at 3000 rpm for 5 minutes and kept at -20 °C until evaluation.

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The hearts of the animals were immediately isolated and washed with 0.9% Nacl solution and prepared for more analysis. Subsequently, approximately 0.5 g of heart tissue was transferred to a tube containing 2 mL of Tris-HCl buffer. The sample was homogenized using Ultra Turrax (IKA Labortechnic, Germany) at 14,000 rpm for 3 minutes in PBS (50 mM, pH 7). Then, the homogenate was centrifuged at 4°C for thirty minutes. Next, supernatant was stored at -80 °C for biochemical analyses. The second part of heart tissue was fixed using 10 % neutral buffered formalin for 48 h in order for histopathological investigation.

Biochemical Analysis: The serum activity of the creatine kinase-MB (CK-MB) and Lactate dehydrogenase (LDH) enzymes in samples were measured using an automated biochemical analyzer (Biotecnica, BT1500, Rome, Italy) and using the commercial kits (Pars Azmoun, Tehran, Iran).

Heart tissue determination of Total antioxidant capacity, Malondialdehyde and nitrate-nitrite levels: Total amounts of TAC and MDA in cardiac tissues were determined using the commercially available kits (Navand Salamat, Urmia, Iran) and by means of spectrophotometer (DANA-3200; Garni Medical Engineering Co., Tehran, Iran), as manufacturer's instructions. In brief, the thiobarbituric acid (TBA) method, based on the reaction of MDA with TBA, was used to measure MDA in the heart tissue. The ferric reduction antioxidant power (FRAP) assay was used to quantify TAC (13).

The NO level in heart tissue was assessed in terms of total nitrate and nitrite (NOx), which are the primary stable metabolites of NO, via an assay kit (Cib Biotech Co, Tehran, Iran) according to manufacturer's guidelines (19).

Histopathological Studies: For histopathological examination, heart tissue was removed and embedded in paraffin after being fixed with 10% formalin. Serial sections (thickness 4 µm) were prepared and stained with hematoxylin and eosin. The slides were examined by light microscopy (15).

Statistical Analysis: Statistical analyses were conducted utilizing SPSS software (ver.22) (SPSS Inc., Chicago-USA). To determine statistical significance, a one-way analysis of variance (ANOVA) was used, followed by the post hoc Tukey test. The data were presented as the mean±SD. The level of significance was considering $p < 0.05$.

Results

Serum CK-MB and LDH Activities: As shown in Figure 1, CTD administration was associated with a significant increase in serum creatine kinase-MB (CK-MB) and lactate dehydrogenase (LDH) levels compared to the control groups ($p < 0.05$). However, co-treatment with quercetin (10 mg/kg) significantly attenuated the elevated enzyme levels relative to the CTD group ($p < 0.05$).

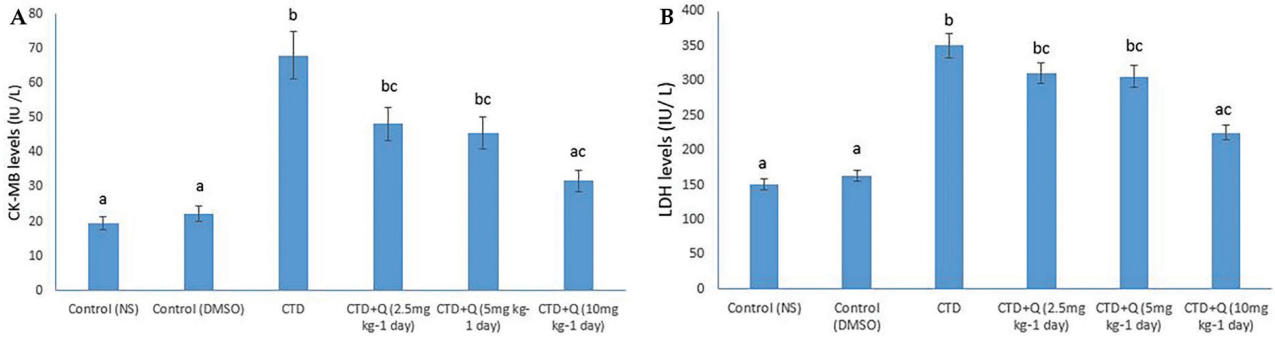


Figure 1. Effect of Quercetin treatment against the toxic effects of CTD on serum cardiac biomarkers (A) Creatine kinase-MB (CK-MB) and (B) Lactate dehydrogenase (LDH). [a,b,c] Different superscript letters indicate significant difference ($p < 0.05$). NS: Normal saline; DMSO: Dimethyl sulfoxide, CTD: Clothianidin, Q: Quercetin.

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Oxidative Stress Biomarkers in Cardiac Tissue: To further explore the pathophysiological effects of CTD, oxidative stress markers in cardiac tissue were evaluated. The results demonstrated that clothianidin exposure led to a significant reduction in cardiac total antioxidant capacity (TAC) levels in comparison with the control groups ($p < 0.05$). Co-administration of quercetin (10 mg/kg) significantly restored TAC levels compared to the CTD group ($p < 0.05$, Figure 2).

Malondialdehyde (MDA) Levels in Cardiac Tissue: Measurement of MDA concentrations in cardiac tissue across different groups revealed that CTD exposure alone resulted in a significant increase in MDA levels ($p < 0.05$). In comparison with the CTD group, quercetin co-treatment (10 mg/kg) significantly decreased MDA concentrations in rat cardiac tissue ($p < 0.05$, Figure 3). Although MDA levels were also reduced in other treatment groups, these reductions did not reach statistical significance when compared to the CTD group.

Nitrate-Nitrite Levels: The concentration of nitrate-nitrite in cardiac tissue showed a marked increase in the CTD group relative to the control group ($p < 0.05$). Co-treatment with quercetin (10 mg/kg) significantly decreased nitrate-nitrite levels in heart tissue compared to the CTD group ($p < 0.05$, Figure 4).

Histopathological Findings: Heart tissue from the control groups exhibited no histopathological abnormalities (Figure 5A, B). In contrast, the CTD-treated group demonstrated notable alterations, including changes in myocardial vessels and edema in the outer layer

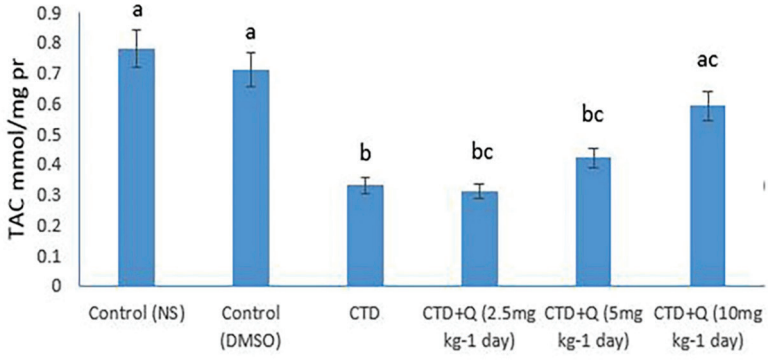


Figure 2. Total antioxidant capacity levels in the cardiac tissue of experimental groups. [a,b,c] Different superscript letters indicate significant difference ($p < 0.05$). NS: Normal saline; DMSO: Dimethyl sulfoxide; CTD: Clothianidin; Q: Quercetin; TAC: total antioxidant capacity.

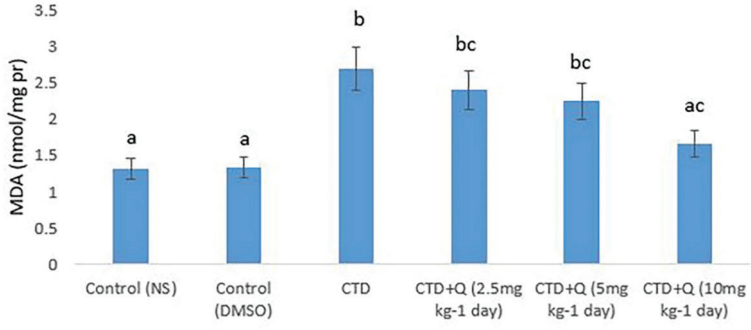


Figure 3. Malondialdehyde concentrations in the cardiac tissue of experimental groups. [a,b,c] Different superscript letters indicate significant difference ($p < 0.05$). NS: Normal saline; DMSO: Dimethyl sulfoxide; CTD: Clothianidin; Q: Quercetin; MDA: Malondialdehyde.

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(adventitia) of the vessel (black arrow), along with cardiomyolysis of myocardial fibers (red arrow) (Figure 5C). Co-treatment with quercetin (10 mg/kg) markedly improved the histological structure of cardiac tissue, evidenced by reduced edema between myocardial fibers and only mild, localized pathological changes compared to the CTD group (Figure 5F).

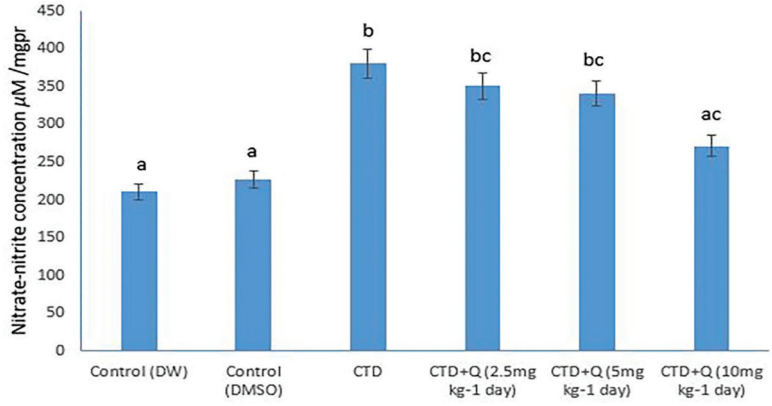


Figure 4. Nitrate-nitrate levels in the cardiac tissue of experimental groups. [a,b,c] Different superscript letters indicate significant difference ($p < 0.05$). NS: Normal saline; DMSO: Dimethyl sulfoxide; CTD: Clothianidin; Q: Quercetin.

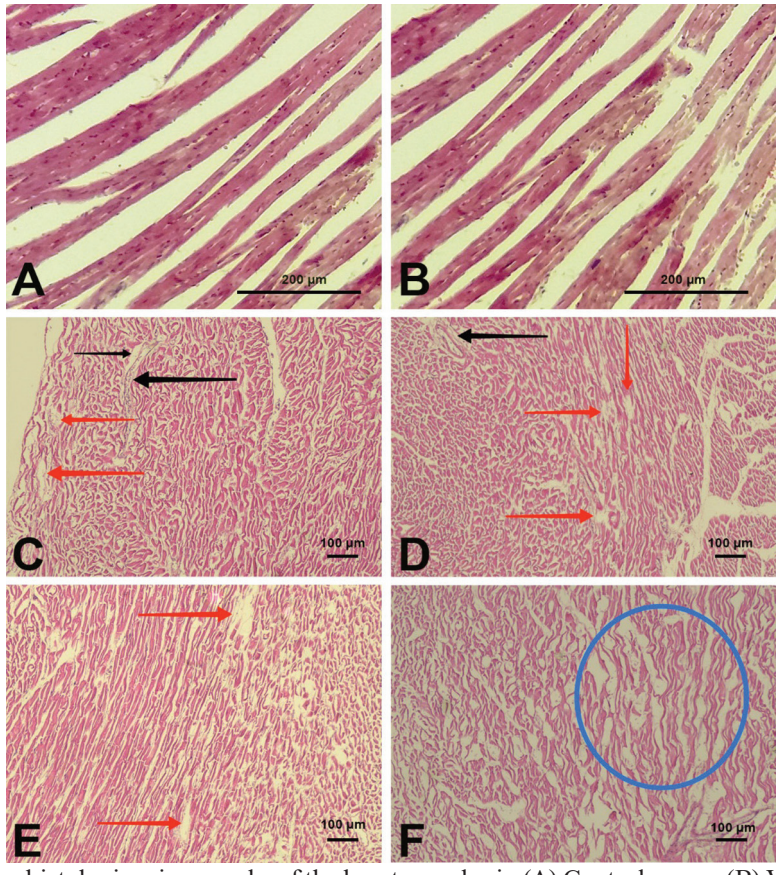


Figure 5. Representative histologic micrographs of the heart samples in (A) Control group; (B) Vehicle group, Certainly unremarkable histopathologic findings in heart sections from controls rats were obvious; (C) CTD group, changes in myocardial vessels and edema in the outer layer (adventitia) of the vessel (Black arrow), Along with cardiomyolysis of heart muscle fibers (Red arrow) were observed; (D) the CTD + Quercetin (2.5 mg/kg) group; (E) CTD + Quercetin (5 mg/kg) group; (F) CTD + Quercetin (10 mg/kg) group, an improvement in the histological heart tissue, as edema in the middle of heart muscle fibers (Blue circle) and signs of mild and minor changes were observed compared to CTD group.

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Discussion

The repeated use of chemicals such as insecticides has led to significant environmental degradation and adverse effects on human health. Clinical and experimental studies have demonstrated that pesticides increase the risk of cardiac damage and congestive heart failure, primarily through the generation of reactive oxygen species (ROS). Previous research has demonstrated that quercetin is effective in neutralizing free radicals and enhancing antioxidant activity in rat myocardial tissue (4). Quercetin has also been shown to reduce myocardial injury and oxidative stress in diabetic murine models (20). In the present study, quercetin was evaluated for the first time for its protective effects against clothianidin (CTD)-induced cardiotoxicity in rat heart tissue. When cardiac cells are exposed to free radicals, an imbalance in energy metabolism occurs, leading to cellular dysfunction and death (21). Additionally, quercetin has been found to prevent apoptosis in the heart, primarily as a result of its ability to counteract oxidative stress and inflammation. Earlier studies have highlighted quercetin's free radical-scavenging and iron-reducing capabilities (21), suggesting its potential as a natural antioxidant with cardioprotective properties against pesticide-induced myocardial damage.

The current investigation revealed that CTD induced myocardial injury in rats. Damage to myocardial cells results in the leakage of enzymes due to compromised plasma membrane integrity (16, 22). In this study, the CTD-treated group exhibited a significant increase in serum levels of cardiac biomarkers (CK-MB and LDH) compared to the control groups. Elevated plasma concentrations of these biomarkers are indicative of cardiomyocyte necrosis and an increased risk of myocardial infarction (22). Studies involving other pesticides, such as imidacloprid and chlorpyrifos, have similarly reported elevated CK-MB and LDH levels due to pesticide-induced myocardial damage. Alruhaimi (2023) found that chlorpyrifos exposure increased CK-MB and LDH levels in rats, effects that were ameliorated by antioxidant co-treatment (23, 24).

Co-administration of quercetin significantly improved serum cardiac enzyme profiles in CTD-treated rats, suggesting that quercetin protects the myocardium by preserving membrane integrity and preventing enzyme leakage. Furthermore, quercetin administration reduced CTD-induced cardiotoxicity in rats by maintaining cardiac biomarker levels close to those of untreated controls. Quercetin's free radical-scavenging properties also contribute to the preservation of cardiomyocyte structural integrity by inhibiting lipid peroxidation (25).

CTD administration in the present study led to a significant increase in malondialdehyde (MDA) levels, a key marker of lipid peroxidation, thereby reflecting excessive ROS formation and oxidative lipid damage. This finding is consistent with previous reports (26-28). Results of the current study demonstrated that quercetin co-treatment (10 mg/kg) markedly attenuated lipid peroxidation and cardiac tissue injury, likely due to its potent antioxidant activity, which reduces oxidative damage to cellular lipids (16).

Antioxidants have traditionally served as the primary line of defense against the deleterious effects of free radicals (29, 30). The current study also demonstrated that CTD exposure significantly decreased TAC levels compared to the control groups. This reduction in TAC may be attributed to increased utilization of antioxidants in response to oxidative stress, leading to their depletion.

Research on other neonicotinoids, such as imidacloprid, has shown similar oxidative stress responses. El-Ela et al. (2019) reported that imidacloprid increased MDA levels and decreased antioxidant enzyme activities in rat tissues—effects that were reversed with quercetin supplementation (29).

Quercetin administration in CTD-treated rats produced robust antioxidant effects, as evidenced

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by a significant increase in total antioxidant capacity. By reducing ROS generation and enhancing the antioxidant defense system, quercetin's flavonol structure has been shown to effectively restore antioxidant status. It has been found that quercetin increases the activity of antioxidant enzymes and restores TAC while reducing the concentration of lipid peroxidation byproducts in cardiac tissue. These findings are in agreement with previous studies (2).

CTD exposure also significantly increased nitrate-nitrite levels compared to controls. This elevation was mitigated by co-treatment with quercetin (10 mg/kg). Moreover, nitrate-nitrite levels in the CTD + quercetin group were significantly lower than those observed in the CTD-only group. Intracellular oxidative stress appears to stimulate NO production, resulting in excessive nitrite synthesis and reduced cell viability (2). Due to increased oxygen demand, mitochondrial dysfunction may further enhance the generation of both ROS and reactive nitrogen species (RNS), contributing to oxidative and nitrosative stress-mediated tissue injury (28). In CTD-treated rats, quercetin reduced nitrate-nitrite production, enhancing its cardioprotective efficacy.

Previous studies involving imidacloprid and thiacloprid also reported significant increases in nitrate-nitrite and nitrotyrosine levels in the brain and liver of rats. These findings underscore the role of oxidative stress and reactive nitrogen species in organ toxicity induced by pesticide exposure. The increase in nitrate-nitrite is a common feature of pesticide-induced oxidative stress, as ROS stimulate NO synthesis. Quercetin's capacity to reduce nitrate-nitrite levels highlights its anti-nitrosative properties, likely involving the inhibition of inducible nitric oxide synthase (iNOS) or scavenging of peroxynitrite radicals (28, 29).

Histopathological examination revealed significant myocardial damage resulting from CTD treatment, characterized by alterations in myocardial vessels and edema in the adventitial layer of the vessel, along with cardiomyolysis of myocardial fibers (14, 29). A study by Abdollahi-Karizno et al. (2024) on chlorpyrifos-induced cardiotoxicity in rats reported similar myocardial alterations, which were alleviated by co-treatment with antioxidants such as curcumin (29).

The preservation of cardiac membrane structure against ROS-induced injury may be attributed to the antioxidant activity of quercetin. Quercetin has the potential to function as an effective electron donor, reacting with free radicals and converting them into more stable, less reactive molecules (30). Its ability to mitigate cellular damage further reinforces its role in maintaining cardiac tissue integrity, likely through its combined antioxidative and anti-inflammatory effects.

Quercetin enhances total antioxidant capacity (TAC) while reducing both lipid peroxidation and nitrate-nitrite levels. It also attenuates histopathological alterations in cardiac tissue, highlighting its potential as a therapeutic agent against CTD-induced cardiotoxicity. Quercetin has been widely studied for its antioxidant and cardioprotective effects. For instance, Hashish et al. (2016) demonstrated that quercetin mitigated doxorubicin-induced cardiotoxicity by enhancing antioxidant enzyme activity and reducing lipid peroxidation (31). Similarly, quercetin has been shown to confer protection against diabetic cardiomyopathy by attenuating oxidative stress and inflammation (Roslan et al., 2018) (32). Bioactive compound stigmasterol has also shown anticancer activity (33).

The cardioprotective effects of quercetin appear to be mediated through both antioxidative and anti-nitrosative pathways, which are crucial for safeguarding cardiac cells. However, further investigation is warranted to fully elucidate the effects of quercetin on CTD-induced cardiotoxicity. Limitations of this study include interspecies physiological and metabolic differences, the short duration of exposure, and

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the lack of assessment of CTD's effects on other organ systems. Future research should prioritize long-term exposure models, comprehensive multi-organ toxicity evaluations, mechanistic studies employing advanced molecular techniques, and detailed pharmacokinetic and pharmacodynamic profiling.

Innovative methodologies, such as molecular approaches and in vitro models, could offer deeper insight into the mechanisms underlying quercetin's cardioprotective effects.

Overall, findings from both histopathological and redox status assessments indicate that quercetin at a dose of 10 mg/kg exhibits cardioprotective activity against the toxic effects of clothianidin in a rat model.

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Conflict of Interest

The authors declare no conflict of interest.

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Ethical Considerations

This study utilized laboratory animal samples, and we ensured all procedures were ethically complete by securing approval from Ethical Committee, as indicated by the specified code.

Code of Ethics

The ethical approval code (IR-UU-AEC-747/PD/3) was issued by the Veterinary Ethics Committee of Urmia University.

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