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Article

The Role of Quercetin in Mitigating Cisplatin-Induced Cardiac Oxidative Stress and Inflammation in Rats

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Abstract: Cisplatin has proven to be among the top chemotherapies for many cancer kinds but, the very heart of its utility is its capacity to cause cardiotoxicity, nephrotoxicity, and other side effects which are a result of the drug's action, and it is the only partially understood mechanism behind all those effects that really hinder its clinical application. Despite considerable progress in guideline-directed cardiovascular therapy, the risk of cardiovascular disease persists, attributable in part to oxidative stress, chronic inflammation, endothelial dysfunction, and mitochondrial damage — side effects of this drug that current medications do not fully address. This experimental study aimed to comprehensively evaluate the protective antioxidant and anti-inflammatory role of quercetin in reducing cisplatin-induced cardiotoxicity in male albino rats. Forty male albino rats ($200–250\ g$) were randomly allocated into four equal groups (10 rats each): a healthy control group, a cisplatin group, a quercetin group, and a cisplatin + quercetin group. Acute injury was induced by a single intraperitoneal injection of cisplatin ($7\ mg/kg$), and quercetin (50 mg/kg) was administered orally once daily for 14 days Cardiac function markers, inflammatory marker, oxidative stress, and lipid/ DNA damage markers together with antioxidant markers such as glutathione, superoxide dismutase and catalase were analyzed ., together with histopathological examination using haematoxylin and eosin (H&E) staining. The results showed that cisplatin administration caused a significant ($p < 0.05$) increase in serum cardiac-injury markers ($Troponin\ I, LDH$), oxidative-stress and lipid/DNA-damage markers ($MDA, 8-Isoprostane, 8-OHdG$), and the pro-inflammatory factor ($TNF-\alpha$), accompanied by a sharp decline in enzymatic and non-enzymatic antioxidants (GSH, SOD, CAT). In contrast, treatment with quercetin showed high efficacy in restoring biochemical, physiological, and histological balance, as injury, inflammation, and oxidation markers decreased significantly while cellular antioxidants increased, with a marked improvement in the H&E-stained histological picture of the cardiac muscle. We conclude that quercetin possesses a high cardioprotective capacity through suppression of oxidative stress and inflammatory pathways.

Keywords: Quercetin, Cisplatin, Cardiotoxicity, Oxidative Stress, Inflammation

Introduction

Cisplatin (a platinum compound with two chlorine atoms bound to the metal in a square planar coordination environment) is among the oldest and most frequently chemotherapeutic drugs employed in hospitals today ,The main cytotoxic effect of the drug is caused by its ability to form cross-links in

the DNA molecules which disrupt DNA replication and transcription. As a result, the integrity of a cell is threatened and its damage ensues [1,2]. Despite its high pharmacological efficacy, its use is limited by systemic toxicity directed at healthy, metabolically active tissues, most notably the kidney, heart, and liver — a toxicity that constitutes the dose-limiting factor in practical application [3, 4].

Nephrotoxicity is the most prominent and dangerous consequence associated with cisplatin, as the drug accumulates in the epithelial cells of the proximal renal tubules at concentrations several times higher than in the blood, causing mitochondrial dysfunction, oxidative stress, inflammation, and cell death [5, 6, 7]. Estimates indicate that about 25–35% of patients treated with cisplatin develop acute kidney injury (AKI), a condition that may progress to a decline in glomerular filtration rate, electrolyte imbalance, and acute renal failure [6, 8]. The consequences of this renal impairment extend beyond the kidney itself; the retention of nitrogenous products and acid–base and electrolyte imbalance impose additional stress on the cardiovascular system, widening the circle of damage to include other organs [9, 4].

In parallel with the historical focus on nephrotoxicity, recent studies have established that cisplatin causes clinically significant cardiotoxicity, with an incidence ranging between 6% and 30% of patients depending on the treatment regimen [10, 11]. This toxicity manifests as cardiac arrhythmias, ischemia, myocardial infarction, and even congestive heart failure, with elevation of cardiac-injury biomarkers such as cardiac troponin (Troponin I) and lactate dehydrogenase (LDH) [12, 13].

Oxidative stress and the inflammatory response are at the forefront of the molecular mechanisms responsible for this toxicity. Cardiomyocytes are very rich in mitochondria, and cisplatin accumulation in them leads to disruption of the electron transport chain and excessive generation of reactive oxygen species (ROS) [14, 15, 16]. These radicals attack the unsaturated fatty acids in membranes, producing malondialdehyde (MDA) and 8-isoprostane, and cause oxidative damage to nucleic bases, producing the marker 8-hydroxy-2′-deoxyguanosine ($8-OHdG$) [17, 18, 19]. Oxidative stress activates the transcription factor NF-κB, which stimulates the secretion of inflammatory cytokines, most notably tumor necrosis factor alpha ($TNF-\alpha$), aggravating tissue inflammation and inflammatory-cell infiltration [20, 21].

Given the limited pharmacological solutions available to alleviate cisplatin toxicity without compromising its efficacy, research has turned toward natural antioxidants as a promising strategy for cellular protection. Several compounds such as quercetin, curcumin, and a number of flavonoids have shown the ability to scavenge free radicals, boost the antioxidant defense system, and suppress inflammatory pathways in cisplatin-toxicity models [22, 12, 23]. The $Nrf2/ARE$ pathway, the main regulator of the cellular antioxidant response, is a central target for these compounds [24, 8].

Quercetin (2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-chromen-4-one), with the molecular formula $C15H10O7$, stands out as one of the active natural flavones, present in high concentrations in apples, red grapes, and cherries. Its hydroxyl groups at positions $C-5$ and $C-7$ give it the ability to directly scavenge free radicals and regulate intracellular signaling pathways, so it possesses antioxidant, anti-inflammatory, and anti-apoptotic properties [25, 26]. Previous studies have documented its protective role against doxorubicin-induced cardiac damage [27], against cisplatin-induced renal and intestinal toxicity [28, 29], and against paracetamol-induced renal injury [30]. However, its bioavailability remains limited owing to poor oral absorption and rapid metabolism, which represents an ongoing research challenge [31, 32]. Quercetin is known to possess antioxidant and anti-inflammatory properties, and research shows to have a cardioprotective effect in some studies of cardio toxicity [33].

Based on the foregoing, this study was conducted to precisely investigate the ability of quercetin to reduce cisplatin-induced oxidative and inflammatory damage in rat cardiac muscle, through the

measurement of a comprehensive panel of cardiac ($Troponin\ I, LDH$), oxidative ($MDA, 8-Isoprostane, 8-OHdG$), and inflammatory (TNF-α) markers and antioxidants (GSH, SOD, CAT), coupled with the histopathological study of the cardiac muscle.

Materials and Method

Laboratory Animals and Experimental Design

Forty male albino (Wistar) rats, aged 16–18 weeks and weighing $200–250\ g$, were used. The animals were obtained from the animal housing unit at the College of Veterinary Medicine, University of Tikrit, and the study was carried out in the animal house of the College of Veterinary Medicine. All animals underwent a two-week acclimatization period before the start of the experiment, and laboratory animal care procedures were applied according to approved guidelines [16]. The animals were randomly distributed into four equal experimental groups (10 rats each) as follows:

- **Group 1 (Normal control):** received distilled water for 14 days without any additional experimental intervention.
- **Group 2 (Cisplatin):** received a single intraperitoneal dose of cisplatin (7 mg/kg) on the first day to induce oxidative stress and cardiotoxicity.
- **Group 3 (Quercetin):** treated with quercetin by oral gavage at a daily dose of (50 mg/kg for 14 consecutive days.
- **Group 4 (Cisplatin + Quercetin):** injected with cisplatin (7 mg/kg) on the first day of the experiment, with daily oral gavage of quercetin (50 mg/kg) for 14 consecutive days.

Cisplatin and pure quercetin ($\geq$ 98%) were obtained from approved commercial sources. The $ELISA$ kits for Troponin $I, LDH, TNF-\alpha$, 8-Isoprostane, $8-OHdG$, and the antioxidants (GSH, SOD, CAT) were prepared according to the recommendations adopted in comparable reference studies [23, 30, 13]. Quercetin was dissolved in 0.5% carboxymethyl cellulose (CMC), and cisplatin was prepared fresh in physiological saline (0.9% $NaCl$) immediately before injection.

Blood Sample Collection and Histopathological Examination

At the end of the fourteenth day of the experiment, the rats were fasted for 12 hours (with water allowed) and then anesthetized using chloroform. Blood samples were immediately collected by cardiac puncture and transferred to anticoagulant-free tubes. To separate the serum, blood samples were centrifuged at 3000 rpm for 15 minutes; the resulting serum was then divided into small aliquots and stored in new plastic tubes at $-20\ °C$ until further biochemical analyses. The animals were then dissected, and their hearts were carefully excised, washed with cold PBS (PH 7.4), and immersed in 10% diluted neutral formalin solution for 48 hours for fixation. After fixation, tissue samples were washed with running water and preserved in 70% ethanol until later tissue processing and sectioning for microscopic examination, according to the standard protocols described by Suvarna et al. (2024).[34]

The doses of cisplatin (7 mg/kg single intraperitoneal injection) and quercetin (50 $mg/kg/day$ oral administration) were taken from the previously established experimental studies [35, 36, 15].

Statistical Analysis

Data are presented as mean standard deviation (SD). Differences between experimental groups were examined one-way analysis of variance ($ANOVA$) coupled with Duncan's new multiple range test. Those changes were regarded as statistically significant at ($p < 0.05$) [37].

Results and Discussion

Physiological and Biochemical Parameters

A. Troponin I, LDH, and TNF-α Concentrations

Table 1. Comparison of Troponin I, LDH, and TNF-α levels among the experimental groups treated with cisplatin, quercetin, and (cisplatin + quercetin) (Mean ± SD). Different letters indicate significant differences at ($p < 0.05$)

Group	Troponin I (ng/mL)	LDH (U/L)	TNF-α (pg/mg)
Control	0.12 ± 0.02 c	185.4 ± 12.3 c	24.5 ± 3.1 c
Cisplatin	1.85 ± 0.15 a	542.1 ± 35.6 a	112.4 ± 8.9 a
Quercetin	0.11 ± 0.01 c	178.2 ± 10.5 c	22.1 ± 2.8 c
Cis + Quercetin	0.48 ± 0.05 b	265.8 ± 18.4 b	48.2 ± 4.5 b

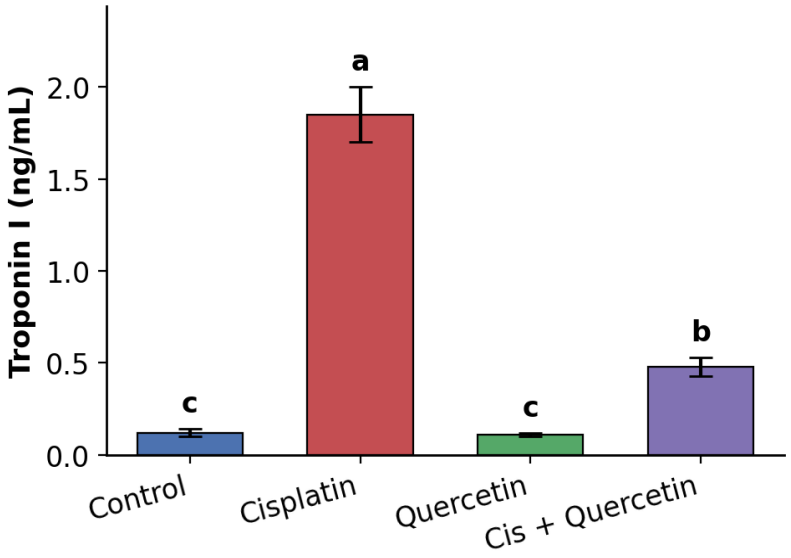

Figure 1. Serum Troponin I concentration in the experimental groups (different letters indicate significant differences at ($p < 0.05$) n = 10 per group.

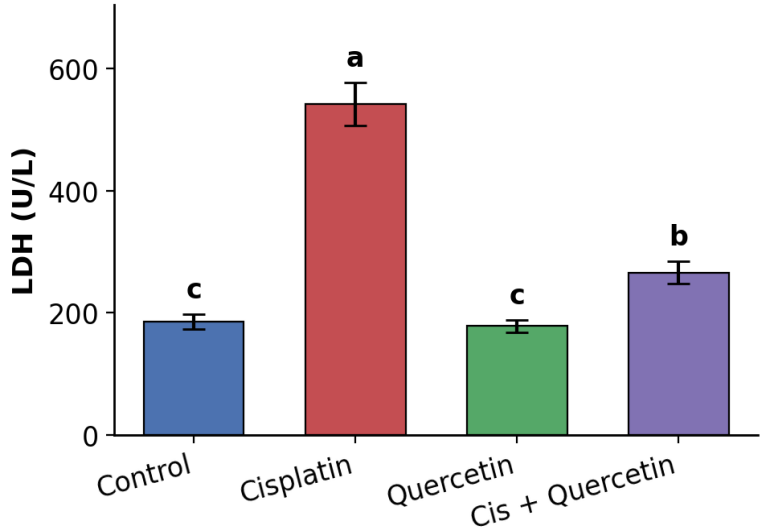

Figure 2. Serum LDH concentration in the experimental groups (different letters indicate significant differences at ($p < 0.05$) n = 10 per group.

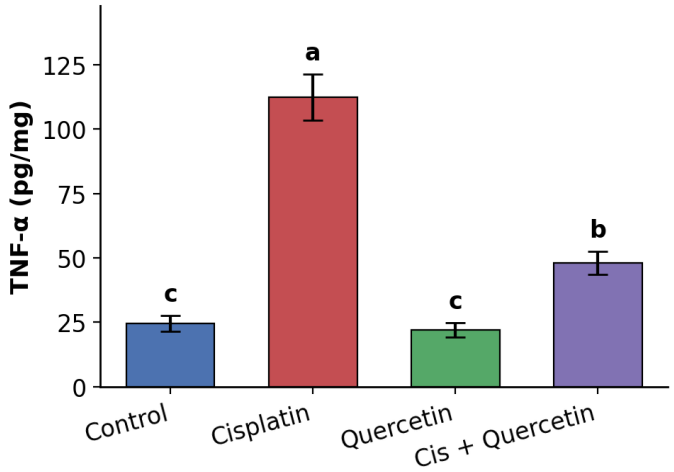

Figure 3. TNF-α concentration in the experimental groups (different letters indicate significant differences at ($p < 0.05$) n = 10 per group.

The results shown in Table (1) and Figures (1, 2, 3) demonstrate that cisplatin injection in the second experimental group caused a significant ($p < 0.05$) increase in Troponin I (from $0.12\ to\ 1.85\ ng/mL$) and in lactate dehydrogenase LDH (from $185.4\ to\ 542.1\ U$/L) compared with the control group. This is attributed to the membrane dysfunction resulting from free-radical attack, which increases the permeability of the cardiac cell membrane and leaks these specific proteins into the serum, a pattern consistent with what has been observed in cisplatin-toxicity models.

Cisplatin is one of the most notable successes in the "war on cancer"; since its accidental discovery four decades ago, it has been used widely in chemotherapy and has shown efficacy against a broad spectrum of tumors, including testicular, ovarian, cervical, bladder, and lung cancers, as well as solid tumors resistant to other treatment regimens [23]. Cisplatin is distinguished by its high efficacy, achieving one of the highest cure rates — for example, more than 90% in cases of testicular cancer [38]. The cytotoxic effect of cisplatin is believed to arise mainly from its interaction with DNA through the formation of covalent bonds between specific DNA bases and the platinum complex [1].

Unfortunately, however, cisplatin treatment suffers from numerous problems, most importantly its severe side effects, the most prominent of which is the dose-limiting cumulative nephrotoxicity, It is also commonly associated with cardiotoxicity [39]. the cardiac complications reported in many studies may include electrocardiographic changes, cardiac arrhythmias, myocarditis and cardiomyopathy, and congestive heart failure [40]. These changes occur as a result of increased oxidative stress and apoptosis due to increased reactive oxygen species (ROS), which damage the cardiomyocyte membrane, resulting in the leakage of troponin protein — found exclusively in cardiac muscle fibers — into the serum. An increase in its serum concentration is a highly sensitive standard marker of cardiotoxicity and cardiac cell membrane damage [41]. so both the cytoplasmic troponin pool and the myofilament-bound troponin leak into the bloodstream. These are among the most important factors contributing to the cardiotoxicity that limits the clinical use of cisplatin as an anti-tumor drug [13, 27, 10].

The increase in LDH concentrations can also be attributed to the fact that LDH is a cytoplasmic enzyme found in most body cells, especially the heart, liver, kidney, and skeletal muscle; its presence in serum indicates cell-membrane breakdown and general tissue necrosis. As a result of the decrease in cellular energy (ATP) and the accumulation of ROS, the membrane permeability of these organs is destroyed, so LDH leaks heavily from the damaged cells into the serum [13].

The increase in $TNF-\alpha$, one of the most important mediators promoting the inflammatory response, reflects the acute systemic inflammatory response induced by the drug. Cisplatin-induced

oxidative stress activates the $NF-\kappa B$ pathway in immune cells such as macrophages and in the cells of the affected tissues (heart, kidney), Activation of this pathway stimulates transcription and abundant synthesis of $TNF-\alpha$, which in turn induces further oxidative stress and recruits immune cells to the damaged tissues, amplifying apoptosis through the TNF-R1 death-receptor pathways [42]. TNF-α also rose from 24.5 to 112.4 pg/mg, reflecting activation of the tissue inflammatory response via the $NF-\kappa B$ pathway [43].

In contrast, the fourth group treated with quercetin showed a significant decrease in Troponin I ($0.48\ ng/mL$), LDH ($265.8\ U/L$), and TNF-α ($48.2\ pg/mg$), confirming the protective ability of quercetin to preserve membrane integrity and suppress the inflammatory pathway, consistent with its documented role as an anti-inflammatory and antioxidant. Flavonoid compounds are abundant in plants, with more than 4000 different types identified, including flavonols, flavones, flavanones, catechins, anthocyanidins, and isoflavones, Quercetin is classified within the flavonol group, one of the five main subclasses of dietary flavonoids. The hydroxyl group at the third carbon atom, the double bond between the second and third carbon atoms, the carbonyl group at the fourth carbon atom, and the polyhydroxylated aromatic A and B rings play a key role in the antioxidant properties of these compounds [44,45]. The catechol group on the B ring enables the formation of intramolecular and intermolecular hydrogen bonds, giving quercetin a high capacity to donate electrons and hydrogen ions, making it an excellent free-radical acceptor. Owing to this high capacity for tissue repair through its antioxidant and anti-inflammatory pathways, quercetin in the fourth group reduced the cardiac-injury markers (troponin, LDH, and the inflammatory $TNF-\alpha$) caused by a single effective dose of cisplatin [46, 25, 30].

Oxidative Stress and DNA Damage Markers

Table 1. Comparison of MDA, 8-Isoprostane, and 8-OHdG levels among the experimental groups treated with cisplatin, quercetin, and (cisplatin + quercetin) (Mean ± SD). Different letters indicate significant differences at ($p < 0.05$)

Group	MDA (nmol/mg)	8-Isoprostane (pg/mg)	8-OHdG (ng/mg DNA)
Control	1.42 ± 0.11 c	12.3 ± 1.1 c	0.85 ± 0.08 c
Cisplatin	5.88 ± 0.42 a	48.6 ± 3.8 a	3.92 ± 0.25 a
Quercetin	1.35 ± 0.09 c	11.8 ± 0.9 c	0.79 ± 0.06 c
Cis + Quercetin	2.31 ± 0.18 b	21.4 ± 1.8 b	1.64 ± 0.12 b

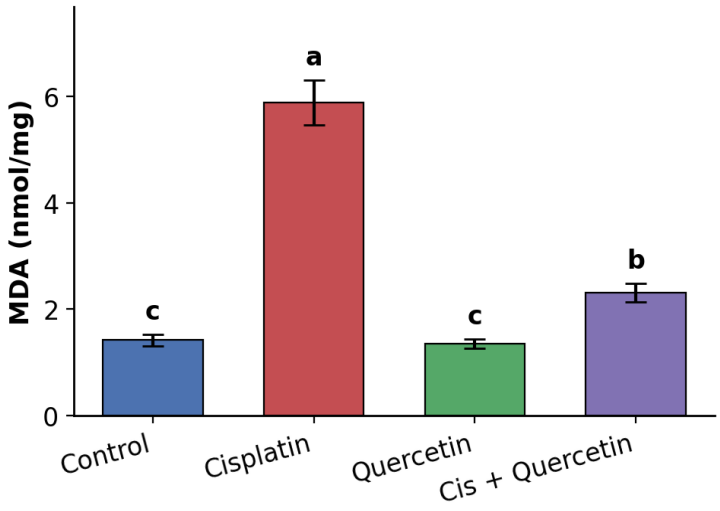

Figure 4. MDA concentration in the experimental groups (different letters indicate significant differences at ($p < 0.05$) n = 10 per group.

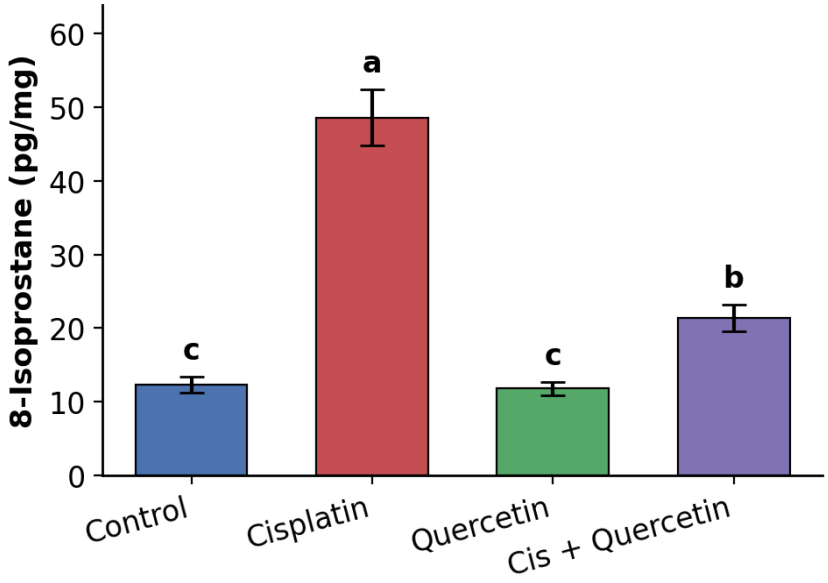

Figure 5. 8-Isoprostane concentration in the experimental groups (different letters indicate significant differences at ($p < 0.05$) n = 10 per group.

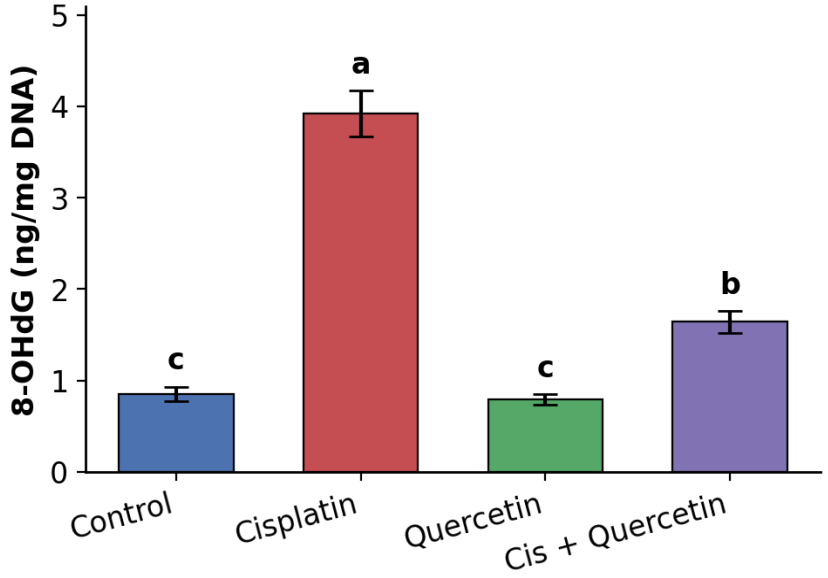

Figure 6. 8-OHdG concentration in the experimental groups (different letters indicate significant differences at ($p < 0.05$) n = 10 per group.

The results shown in Table (2) and Figures (4, 5, 6) revealed a significant ($p < 0.05$) increase in the cisplatin-treated second group, reflecting a destructive effect of cisplatin on membrane lipids and DNA. MDA rose by more than 300% compared with the control group, and 8-isoprostane — the specific product of arachidonic-acid oxidation and one of the most accurate markers of lipid peroxidation — rose from 12.3 to 48.6 pg/mg [19, 32]. 8-OHdG also rose from 0.85 to 3.92 ng/mg, confirming oxidative damage to the genome of cardiac cells; it is the most widely used marker for estimating oxidative DNA damage [47, 17].

The rise in the unsaturated-lipid aldehyde malondialdehyde (MDA), produced by lipid peroxidation; in 8-isoprostane, formed by the non-enzymatic oxidation of arachidonic acid; and in 8-hydroxy-2′-deoxyguanosine ($8 - OHdG$), which reveals oxidative DNA damage, can all be attributed

to the accumulation of reactive oxygen species (ROS). Upon entering cells, cisplatin undergoes dechlorination and replacement with water, giving it a highly reactive positive charge; it targets the mitochondria, destroys $mtDNA$, and affects the electron transport chains. This leads to electron leakage and the generation of enormous amounts of the superoxide radical, which is converted into hydrogen peroxide (H2O2), as well as the accumulation of the highly toxic hydroxyl radical. All these oxidants deplete antioxidants such as glutathione (GSH), catalase (CAT), and superoxide dismutase (SOD) [48]. Hydrogen peroxide (H_2O_2) also reacts with iron ions through the Fenton reaction, and the hydroxyl radical has a high capacity for structural destruction: it abstracts hydrogen atoms from polyunsaturated fatty acids in the mitochondrial and cell membranes, triggering a chain of lipid-peroxidation reactions that produce MDA as the end product, which is used as a reliable indicator of the severity of oxidative membrane damage; the more ROS produced, the higher the serum MDA concentration [9]. 8-Isoprostane is formed by the non-enzymatic oxidation of arachidonic acid present in the membrane phospholipids by free radicals, so its rise is one of the most sensitive and accurate markers of in-vivo lipid peroxidation [49]. The increase in $8-OHdG$, one of the most widely used markers for detecting oxidative DNA damage, results from free radicals — especially the hydroxyl radical — oxidizing the guanine base in DNA to form $8-OHdG$; the accumulation of this compound disrupts genetic-material stability and activates DNA-repair pathways or apoptosis, so its increased concentration reflects the severity of oxidative genetic damage caused by ROS overproduction [46].

The results in the same Table (2) also revealed a significant ($p < 0.05$) decrease in the fourth group treated with quercetin, with MDA falling to 2.31 nmol/mg and 8-isoprostane to 21.4 pg/mg, and with DNA protection reflected by a decline in 8-OHdG to 1.64 ng/mg DNA. This reflects the direct role of quercetin as a free-radical scavenger and an inducer of protective cellular mechanisms [28, 29, 26]. This decrease can be attributed to quercetin, a flavonoid that acts as a cytoprotectant and an excellent antioxidant through the direct scavenging of free radicals, as it has a chemical structure containing catechol groups and multiple hydroxyl groups on the A, B, and C rings. It donates hydrogen atoms to free radicals, immediately halting the lipid-oxidation chain and thereby reducing MDA and 8-isoprostane levels. It also binds iron ions and prevents their participation in the Fenton reaction, thereby preventing hydroxyl-radical formation at its source and protecting DNA from oxidation, targeting a reduction in $8-OHdG$ [50,33]. The observed reduction in oxidative stress markers may be linked to in reality flavonols such as quercetin, when present as flavonoid glycosides, can donate hydrogen atoms and electrons to quench free radicals through various mechanisms. [51,52].

Cellular Antioxidant Markers

Table 3. Comparison of GSH, SOD, and CAT levels among the experimental groups treated with cisplatin, quercetin, and (cisplatin + quercetin) (Mean ± SD). Different letters indicate significant differences at $p < 0.05$)

Group	GSH (μmol/g)	SOD (U/mg)	CAT (U/mg)
Control	8.65 ± 0.54 a	42.3 ± 3.1 a	28.4 ± 2.1 a
Cisplatin	2.91 ± 0.22 c	15.2 ± 1.4 c	10.1 ± 0.9 c
Quercetin	8.92 ± 0.61 a	44.1 ± 2.8 a	29.8 ± 1.8 a
Cis + Quercetin	6.48 ± 0.39 b	31.5 ± 2.2 b	21.3 ± 1.5 b

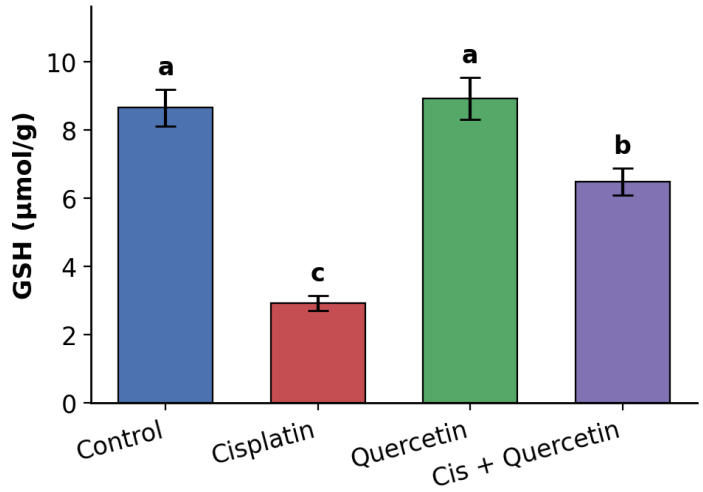

Figure 7. GSH concentration in the experimental groups (different letters indicate significant differences at ($p < 0.05$) n = 10 per group.

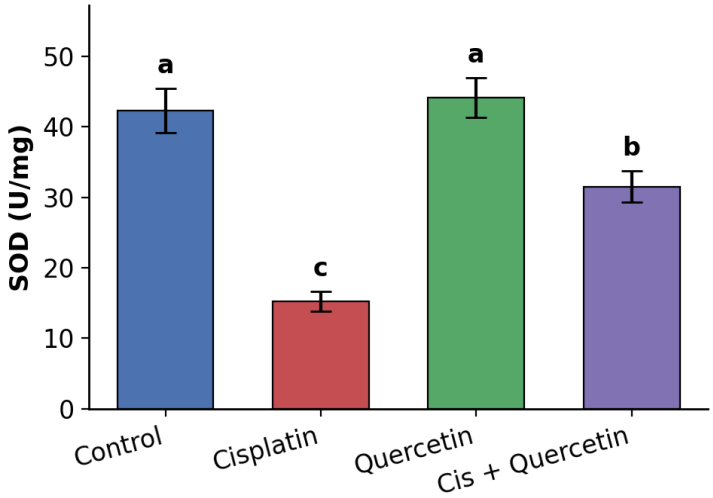

Figure 8. SOD activity in the experimental groups (different letters indicate significant differences at ($p < 0.05$) n = 10 per group.

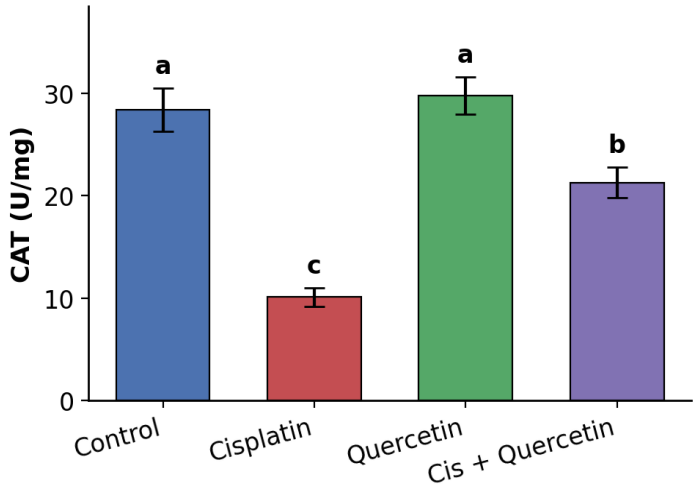

Figure 9. CAT activity in the experimental groups (different letters indicate significant differences at ($p < 0.05$) n = 10 per group.

The results shown in Table (3) and Figures (7, 8, 9) revealed a significant ($p < 0.05$) decrease in the concentration of glutathione (GSH) and a decrease in the activity of both superoxide dismutase (SOD) and catalase (CAT) by more than 60%. This is attributed to the excessive consumption and acute depletion of these antioxidants as a result of their work in neutralizing the enormous amounts of reactive oxygen species (ROS), in addition to the inhibition of the gene expression of antioxidant enzymes [53, 22].

This decrease in antioxidants in the cisplatin-treated group can be explained by the fact that, after entering the cardiac cell, the drug penetrates the mitochondria and binds to mitochondrial DNA, causing dysfunction and increasing the production of ROS by disrupting the cellular respiratory chain, which may be more important than DNA damage in cisplatin-induced cell death [54,55]. Cisplatin affects the normal transport of electrons in the oxidative respiratory chain and generates a large amount of free radicals that can form ROS, At the same time, a decrease in the activity of cytochrome c oxidase (COX) can generate ROS and release them from the mitochondria into the cytosol, an important factor in cell damage [56]. The resulting oxidative stress leads to an imbalance between the production and accumulation of ROS in cells and the cells' ability to neutralize these reactive products using antioxidant molecules, leading to their depletion , At low to moderate concentrations, ROS play a crucial role in cell signaling, gene expression, mitogenic responses, and apoptosis [57]. ROS include superoxide (O_2^-), hydroxyl radical ($HO^\bullet$), hydrogen peroxide (H_2O_2)), peroxynitrite (ONOO−), and nitric oxide ($NO^\bullet$), The drug toxicity resulting from the cisplatin injection generated free radicals as by-products during its breakdown or metabolism, leading to excessive production of ROS [58]. Cells protect themselves from ROS-induced damage by activating an antioxidant defense system composed of enzymatic components — SOD, GSH, CAT, and glutathione peroxidase (GPx) — which decreases their serum concentration due to their defensive action; however, in some cases the antioxidant defense system cannot eliminate or neutralize the excessive ROS, causing oxidative damage and disease [52].

The fourth group treated with quercetin showed a significant ($p < 0.05$) increase in antioxidant levels, as GSH rose to 6.48 μmol/g and SOD and CAT recovered most of their activity (31.5 and 21.3 U/mg, respectively).This enhancement probably arises from the ability of phenolic OH groups in flavonols to act as hydrogen donating agents and electron donating agents which is one of the major ways by which they quench free radicals. This also leads to a decrease in lipid peroxidation and this way minimizes the oxidative stress [31, 8]. Quercetin possesses five hydroxyl (–OH) groups that give it a high capacity to donate electrons or hydrogen atoms, neutralizing reactive oxygen species (ROS) and reactive nitrogen species (RNS) such as the superoxide radical, nitric oxide, and the hydroxyl radical. The catechol group on the B ring donates a hydrogen ion to the free radical, forming the quercetin radical, which is energetically stabilized by electron resonance [59,60,61]. Quercetin also induces the dissociation of the transcription factor Nrf2 from the inhibitory protein Keap1, allowing Nrf2 to translocate to the cell nucleus, where it binds to the Antioxidant Response Elements (ARE) and stimulates the gene expression of many antioxidant enzymes such as GSH, SOD, CAT, and NAD(P)H. This response strengthens cellular defenses against oxidative stress and reduces cell damage, Quercetin also raises the concentration of reduced glutathione — the most important intracellular antioxidant — through its intracellular synthesis, thereby increasing the removal of free radicals and improving the antioxidant capacity within body cells, which explains the increase in antioxidants in the fourth group treated with quercetin [62,49].

Histological Results

A. Control Group (Normal Structure)

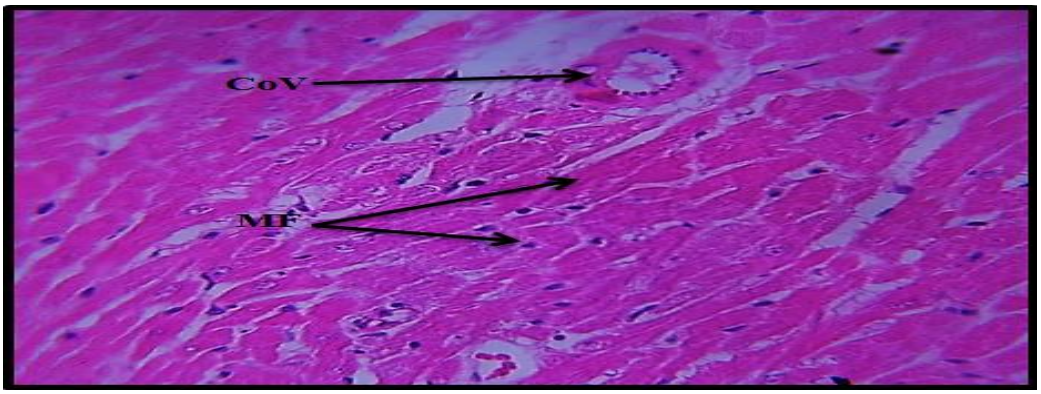

Image 10. The histological examination of the cardiac muscle in the healthy control group showed the normal appearance of the myocardial fibers (MF), characterized by their branching bundles and a single central nucleus. The transverse striations of the cardiac muscle and the coronary vessels (CoV) could also be distinguished. (H&E, 400X)

B. Cisplatin Group

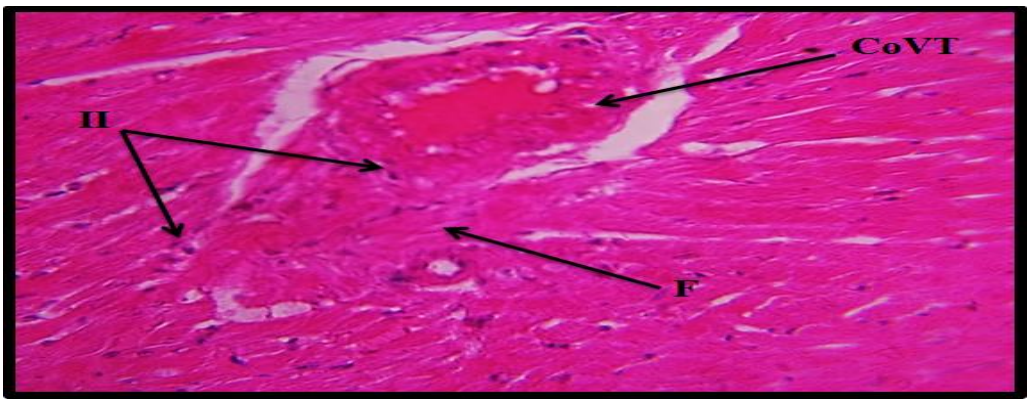

Figure 11. A section of the heart of the cisplatin-treated group showing infiltration of inflammatory cells (II) between the cardiac muscle fibers, with dissociation (DIS) and degeneration (MFD) of the cardiac muscle fibers. ($H\&E, 400X$)

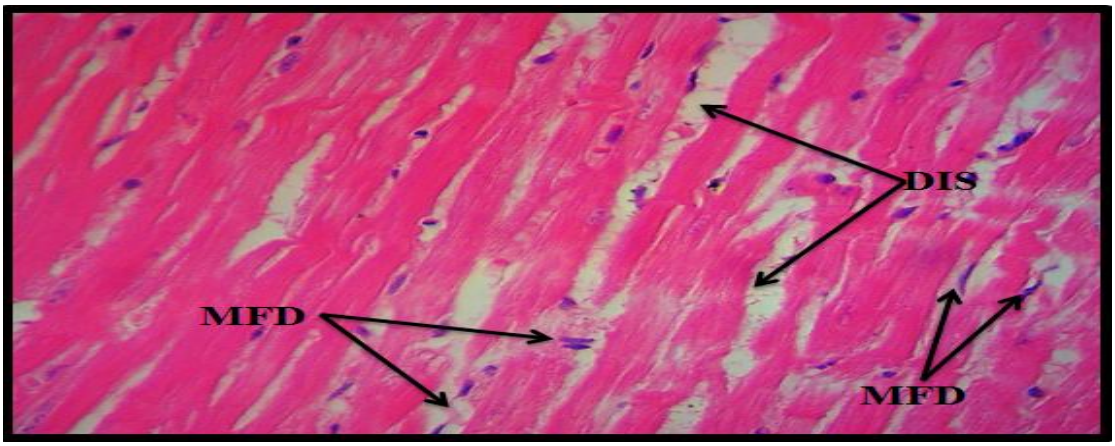

Figure 12. A section of the heart of the cisplatin-treated group showing dissociation (DIS) between the cardiac muscle fibers with degeneration (MFD) of the cardiac muscle fibers. (H&E, 400X)

Cardiac muscle in photomicrographs (Image (2) and (3)) revealed the presence of inflammatory-cell infiltrate apart from the dissociation of the cardiac myofiber and degenerations of those cardiac muscle fibers.

There was no remarkable histopathological abnormality at the level of the dose These changes in the cardiac muscle tissue can be attributed to the cardiac, vascular, and hematological toxicity caused by cisplatin, a phenomenon explained by overlapping biochemical and histological mechanisms. The main cause of this toxicity is excessive oxidative stress, mitochondrial damage, chronic inflammatory activation, and direct cell-membrane toxicity resulting from cisplatin accumulation within cardiomyocytes [13].Oxidative stress and increased free oxygen radicals oxidize the phospholipids in the cell membrane, leading to loss of membrane integrity and dissociation and degeneration of the myofibrils [63]. Cisplatin also attacks mitochondrial DNA, disrupting mitochondrial membrane permeability and releasing cytochrome c, which activates the apoptotic pathway [13].

As a result of the loss of a large number of cardiomyocytes through degeneration and cell death, the remaining cells undergo mechanical stress and a compensatory signaling response stimulated by pathways such as NF-κB and MAPK/ERK, causing hypertrophy of the cardiomyocytes in an attempt to maintain cardiac output, The death of the degenerated cardiac cells also releases intracellular molecules that stimulate the immune system, such as DAMPs, which act together with ROS to activate the transcription factor NF-κB within the endothelial tissue cells, promoting the gene expression of pro-inflammatory factors such as TNF-α, interleukin-1 (IL-1), and interleukin-6 (IL-6)[21]. This is accompanied by the recruitment of immune cells through the vascular adhesion molecules VCAM-1 and ICAM-1 on the vessel walls, facilitating the migration and infiltration of lymphocytes, macrophages, and neutrophils between the cardiac muscle fibers (inflammatory infiltration) [37]. Cisplatin also oxidizes and damages the endothelial cells lining the coronary arteries, reducing beneficial nitric oxide (NO) and releasing vasoconstrictor factors such as endothelin-1. The imbalance between nitric oxide, endothelin, and the released inflammatory cytokines stimulates the migration and proliferation of smooth muscle cells from the medial layer to the intimal layer of the arterial wall. As a result of the stimulated inflammatory state, collagen and fibronectin deposition in the coronary artery walls increases, resulting in hypertrophy of the medial layer and thickening of the vessel wall [10, 21, 34, 13].

C. Quercetin Group

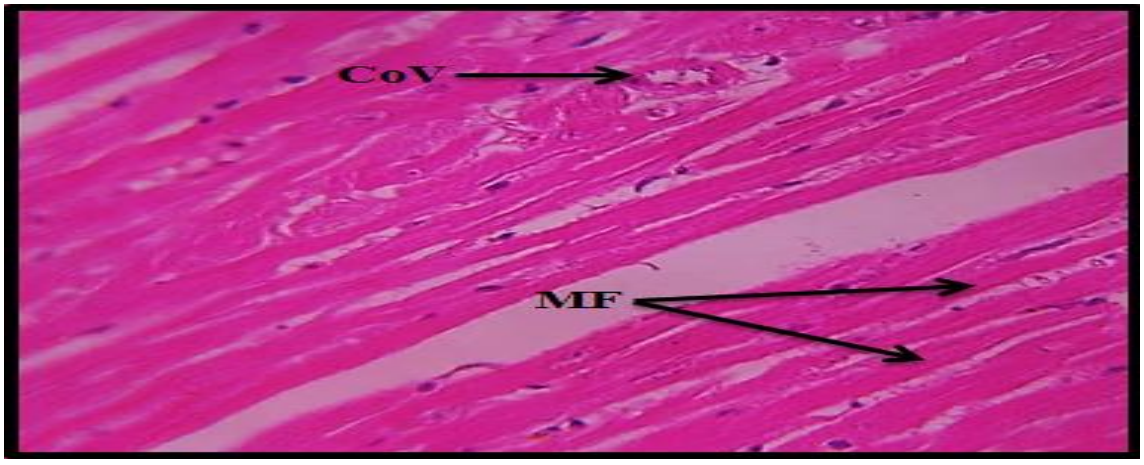

Figure 13. The quercetin group showed a normal histological section of the cardiac muscle similar to that of the healthy control group, retaining the normal structure of the fibers and nuclei without lesions, There was no remarkable histopathological abnormality at the level of the dose [14, 10]. (H&E, 400X)

3.4.D. Cisplatin + Quercetin Group

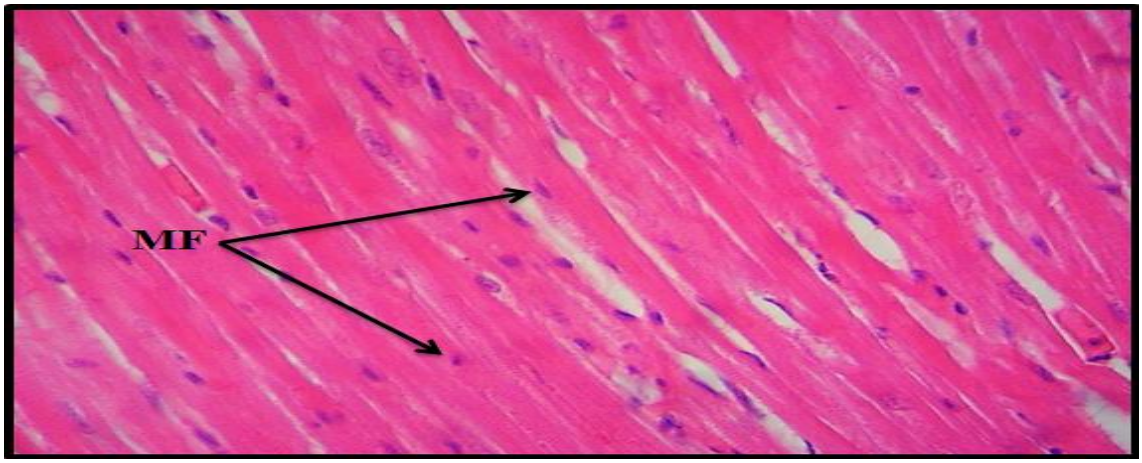

Figure 14. The fourth group treated with quercetin showed clear improvement in the histological appearance of the cardiac muscle tissue, with marked improvement and high protection and only slight residual histological changes; most fibers regained their organization and transverse striations, with almost complete disappearance of necrosis and degeneration and a sharp decrease in edema and inflammatory infiltration compared with the second (cisplatin) group, translating the biochemical protection into structural histological protection [37, 27, 36]. (H&E, 400X)

Quercetin has demonstrated protective, reparative, and restorative effects on the cardiac muscle tissue in the treated group against cisplatin toxicity. This effect is likely due to the mechanism of quercetin as it directly scavenges reactive oxygen species and suppresses free radicals. Also, the antioxidant capability of quercetin can aid in alleviating oxidative stress and maintaining the structural architecture of heart muscle fibers [64].

And, the action of quercetin in combating inflammatory and oxidative damages is also a possible reason for decreased number of invasive inflammatory cells and better histological features seen in the cisplatin + quercetin group [8,65].

Conclusion

The present study demonstrated that cisplatin induces significant cardiac injury in rats, characterized by increased cardiac, inflammatory, and oxidative stress markers, along with reduced GSH, SOD, and CAT levels and marked histopathological alterations Quercetin administration significantly alleviated these biochemical and structural changes, restoring antioxidant defenses and improving myocardial architecture. Overall, quercetin showed a clear cardioprotective effect against cisplatin-induced cardiac toxicity, mainly through reducing oxidative stress and inflammation.

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