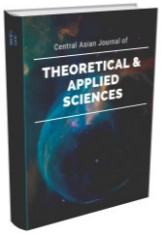

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Article

Evaluation of the Protective Effect of Quercetin against Cisplatin-Induced Acute Kidney Injury in Rats: A Biochemical and Histopathological Study

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Abstract: Acute kidney injury is among serious drug-induced adverse reactions. Cisplatin is one of the leading drugs causing nephrotoxicity mainly by generating free radicals and inflaming acute tissues. Excessive reactive oxygen species (ROS) production results in disruption of the redox balance, promotes lipid peroxidation, and consumes antioxidant systems like glutathione (GSH). Simultaneously, (SOD). activity decreases. Taken together, all these changes cause the failure of mitochondrial functions, loss of membrane integrity, and induction of proinflammatory pathways like that of B (NF-κB) and tumor necrosis factor-alpha (TNF-α). Besides that, these effects are reflected as histopathological changes, such as inflammatory cell infiltration congestion cellular degeneration and even necrosis in the worst cases. Antioxidants and anti-inflammatory properties are found in a few types of herbs like quercetin and they may have become important agents which reduce the risk of oxidative damage and inflammation, and they help to keep tissue together. This is achieved through boosting our natural ability to fight oxidative stress and altering the body's inflammatory mechanism, this way protecting the cells of the body. Yet, there is not enough clinical evidence to support the use of plants with such properties in all forms of kidney failure at this time, because of this, their usage remains confined to certain clinical support cases. Researches currently are concentrated on examining the protective effects of the natural antioxidant and anti-inflammatory flavonoid, the quercetin, in cisplatin-related severe kidney damage in the rat together with the changes that occur in the rat tissue structure due to this damage. Forty male Wistar rats weighing 200-250 g were randomly divided into four equal groups: a healthy control group, a cisplatin group, a quercetin group, and a cisplatin + quercetin group. Acute injury was induced via a single intraperitoneal injection of cisplatin (6 mg/kg), while quercetin (50 mg/kg) was administered daily for 14 days. After treatment, blood and tissue samples were taken for biochemical and histopathological studies. Measured serum levels of renal function markers included creatinine, urea and total protein, inflammatory mediators were)TNF-α,NF-κB,IL-1β), and antioxidant markers:)GSH,SOD(. All this was backed by histopathological analysis using Hematoxylin and Eosin (H&E) staining of the tissues. Cisplatin-treated animals showed a marked ($p < 0.05$) increase in the serum levels of creatinine, urea and inflammatory mediators while simultaneously a decrease in serum protein glutathione and superoxide dismutase was observed as evidenced by their blood tests. Their renal tissues, as examined microscopically, showed severe damage in tubular cells. Administration of queringetin with quite successfully reversed some of the pathological and biomorphological changes observed in cisplatin-treated group. The study concludes that quercetin offers a protective role against cisplatininduced nephrotoxicity and this may be due to the antioxidant and anti-inflammatory features of the compound.

Keywords: Quercetin, Acute kidney injury, Cisplatin, Inflammation, Rats

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1. Introduction

Acute kidney injury (AKI) is a frequent yet severe clinical syndrome which happens when a person has a sudden drop in kidney functioning In AKI, kidney function gets temporarily impaired which results in problems with the excretion of metabolic waste products and disturbances in the fluid and electrolyte homeostasis of the body, A person with AKI may expect his quality of life is going to be worse than the normal and he will be more vulnerable to death. In addition, he may be more likely to develop chronic kidney disease after this event and be prone to other system-wide complications [1].

When the glomerular filtration rate gets slowed down or blocked completely, nitrogenous waste products, like creatinine and urea, are not effectively cleared and accumulate in the body. AKI is one of the serious health issues in the world that is linked to higher rates of mortality and morbidity, longer stay in hospital, a greater likelihood of the development of chronic kidney disease with renal failure as a consequence, and serious cardiovascular complications. [2], [3]. The available treatment options still are limited and often focus on the causative agent removal or on renal substitute therapy, which highlights why it is very important to find out safe protective agents. [4].

Cisplatin is one of the most potent drugs that lead to kidney damage. Although a very effective therapeutic agent, its use is limited because severe kidney damage happens. Since the kidney is the main organ for eliminating drugs, it takes up cisplatin in the proximal convoluted tubule cells at up to five to six times higher concentrations than in blood, where cisplatin leads to changes in DNA and mitochondrial function. [5], [6], [7]. The disease-causing process involves an excessive production of reactive oxygen species (ROS) and a depletion of natural antioxidants in the body like glutathione (GSH), the enzyme superoxide dismutase (SOD). This is followed by lipid peroxidation and damage to membranes with subsequent cell death through necrosis and apoptosis. [8], [9], [10], [11].

Oxidative stress results in a dramatic increase in inflammatory mediators driven by nuclear factor $NF-\kappa B$ which is responsible for activating the production of pro-inflammatory cytokines, among which are tumor necrosis factor alpha ($TNF-\alpha$) and interleukin-1 beta ($IL-1\beta$). This cascade of events together can cause kidney cell death and damage, increase creatinine and urea levels, and cause serum protein loss. [12], [9].

This paragraph can be rewritten in a more human voice below: since there have not been enough successful traditional treatments to save the kidneys, scientists are now investigating naturally sourced compounds which have the power of both antioxidants and anti-inflixamines in a laboratory setting. In their search, these researchers cite epidemiological studies that show a decreasing occurrence of kidney injuries as a person's diet becomes higher in antioxidant nutrients. [3]. Some compounds have been found to reduce a major side effect of cisplatin treatment nephrotoxicity without decreasing the anti-tumor efficacy. [13], [14], [15], [16], [17].

Quercetin can be recognized among the most well studied flavonoids of all and is found in abundance of foods like cruciferous vegetables (e. g. cabbage), allium vegetables (e. g. onions), grapes that are red, cherries and apples [18]. It has antioxidant, anti-inflammatory, and anti-apoptotic properties and can inhibit the NF-B pathway because of this reducing $TNF-\alpha$ and IL-1β secretion. [19], [20], [21]. Multiple studies have documented its renoprotective role against the toxicity of cisplatin, arsenic, cadmium, lead, gentamicin, and doxorubicin, and in chronic kidney disease [15], [17], [22], [23], [24]. In line with this, the purpose of the current study was to evaluate the protective effects of quercetin on the kidney about physiological, biochemical, and histopathological aspects. These effects were examined using different parameters: renal-function markers (creatinine, urea, and total protein), inflammatory markers ($TNF-\alpha$, $NF-\kappa B$, $IL-1\beta$), and antioxidants (GSH, SOD). Besides, the study included the histopathology assessment of renal tissue via H&E staining among four experimental groups.

2. Materials and Methods

2.1 Laboratory Animals and Experimental Design

Forty twelve-to-fourteen week-old male albino (Wistar) rats weighing *200-250g*, have participated in this study. Animals were supplied from College of Veterinary Medicine, University of Tikrit. The study was conducted in animal house, College of Veterinary Medicine. All animals had a two-week acclimatization period before the initiation of the experiment, and laboratory animal care procedures were followed as the guidelines [25]. The animals were randomly distributed into four equal experimental groups (10 rats/group) as follows:

a. **Group 1 (Normal control):** received distilled water for 14 days without any chemical treatment.
b. **Group 2 (Cisplatin):** received a single intraperitoneal dose of cisplatin ($6\ mg/kg$) on the first day to induce acute kidney injury [26], [9].
c. **Group 3 (Quercetin):** treated with quercetin by oral gavage at a daily dose of 50 mg/kg for 14 consecutive days [15], [23].
d. **Group 4 (Cisplatin + Quercetin):** injected with cisplatin ($6\ mg/kg$) on the first day of the experiment, with daily oral gavage of quercetin ($50\ mg/kg$) for 14 consecutive days.

2.2 Blood Sample Collection and Histopathological Examination

At the end of the 14-day experimental period, the rats were 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. After this, animals were dissected, then the kidneys were carefully removed and directly plunged into a neutral formalin dilution solution (10%) for the period of 50 h so that the sample remains fixed. After fixation, tissue samples were washed with running water and preserved in 70% ethanol until later processing and sectioning for microscopic examination, according to the standard protocols described by Suvarna et al. [27]. Renal-function markers (creatinine, urea, total protein) were measured using spectrophotometric kits, while inflammatory markers (NF-κB, $TNF-\alpha$, IL-1β) were estimated by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions [19], [28]. The antioxidant glutathione (GSH) concentration in serum was measured using the modified method of Rahman et al. [29], and superoxide dismutase (SOD) activity was measured by the indirect inhibition method of Marklund & Marklund [30].

2.3 Statistical Analysis

Statistical analysis was expressed as the arithmetic mean ± standard deviation (*Mean ± SD*). Differences between groups were analyzed using one-way analysis of variance (One-way ANOVA) followed by Duncan's multiple range test to determine statistically significant differences between the experimental groups. Differences were considered significant *at* ($p < 0.05$) [31].

3. Results

3.1. Physiological and Biochemical Parameters

3.1.A. Renal-Function Marker Concentrations

Table 1. Comparison of creatinine, urea, and total protein levels among the experimental groups treated with cisplatin, quercetin, and (cisplatin + quercetin) (Mean ± SD).

Groups	Creatinine (mg/dL)	Urea (mg/dL)	Total protein (g/dL)
Control	*0.62 ± 0.05*	*31.40 ± 2.80*	*7.10 ± 0.35*
Cisplatin	*2.45 ± 0.18*	*98.60 ± 6.10*	*4.85 ± 0.28*
Quercetin	*0.60 ± 0.04*	*29.80 ± 2.40*	*7.25 ± 0.30*
Cis + Quercetin	*1.15 ± 0.09*	*52.30 ± 3.90*	*6.30 ± 0.25*

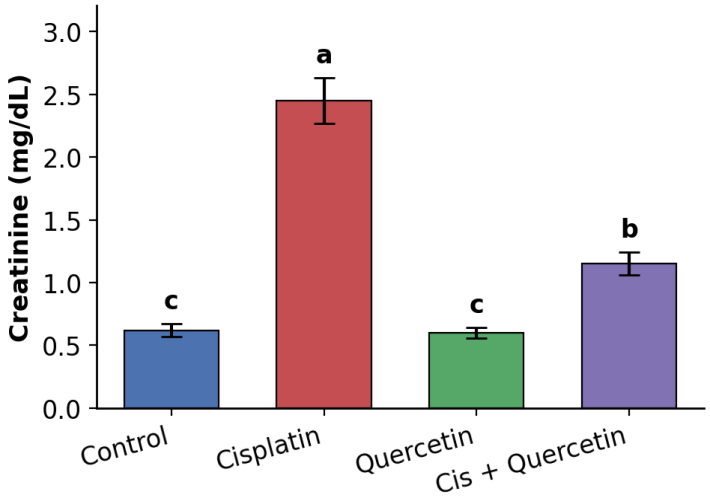

Figure 1. Serum creatinine concentration in the experimental groups (different letters indicate significant differences at ($p < 0.05$) n = 10 per group.

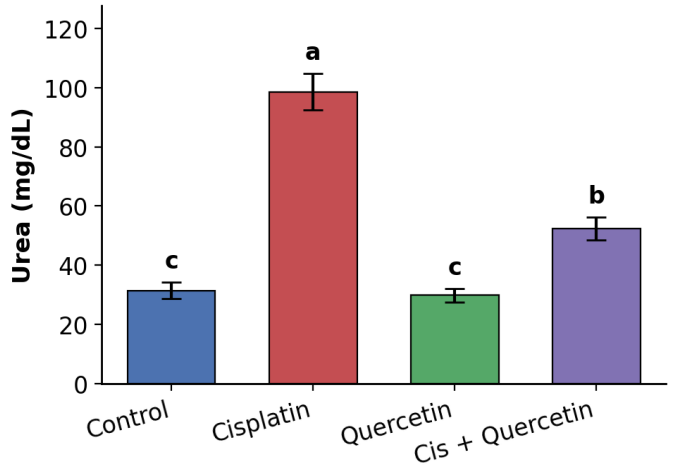

Figure 2. Serum urea concentration in the experimental groups (different letters indicate significant differences at ($p < 0.05$) n = 10 per group.

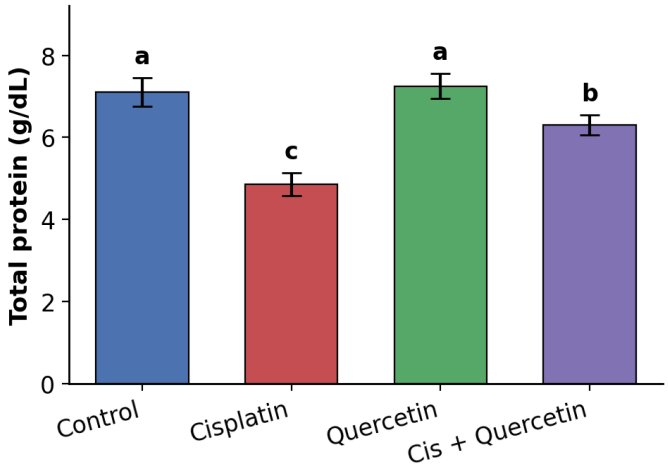

Figure 3. Serum total protein concentration in the experimental groups (different letters indicate significant differences at ($p < 0.05$) n = 10 per group.

According to the findings in Table (1), a single dose of cisplatin ($6\ mg/kg$) led to a substantial ($p < 0.05$) elevation in creatinine ($2.45\ mg/dL$) and urea ($98.60\ mg/dL$) levels versus the control group. And, the drastic rise in serum creatinine and urea, and the renal tissue changes noticed, indicate the occurrence of cisplatin-induced acute kidney injury.

The results show the significant reduction of total protein to $4.85\ g/dL$ when compared to the control group, which could be an evidence for modification in serum proteins level upon cisplatin-induced renal injury. Exposure to toxic substances can cause nephrotoxicity; owing to the kidney's special biological structure and physiological role, In addition, the kidney is responsible for drug excretion, which makes it the most susceptible organ to nephrotoxic agents. including antibiotics, anti-tumor agents, and chemotherapeutics such as cisplatin, an inorganic compound with anti-tumor activity whose pharmacological mechanism relies on forming a covalent bond with nitrogen, thereby preventing cell division and inducing programmed cell death [32].

Because of its drug toxicity, the use of cisplatin is limited, with its nephrotoxicity being the main dose-limiting factor. This toxicity is due to accumulation of the drug in the kidney, where cisplatin reduces the glomerular filtration rate and decreases blood flow within the renal vessels, causing renal ischemia, impaired kidney function, and eventually renal failure. Severe renal damage leads to failure in clearing creatinine and urea, resulting in their accumulation in serum. The copper transporter ($Ctr1$) and the organic cation transporter ($OCT2$) are the main mediators of cisplatin entry into renal tubular cells owing to their high affinity for this drug, so its concentration in the epithelial cells of the proximal tubule is about five times higher than in plasma, leading to damage of the proximal renal tubular epithelial cells. This accumulation causes severe oxidative stress, DNA damage, mitochondrial dysfunction, activation of inflammatory pathways, apoptosis, and necrosis, resulting in acute renal tubular necrosis and a reduced glomerular filtration rate (GFR), which lowers the kidney's ability to excrete nitrogenous metabolites such as creatinine and urea, so they accumulate in serum and rise markedly. Creatinine is eliminated primarily by glomerular filtration ($about$ 99%) and to a lesser extent by tubular secretion; it is a non-reabsorbed waste product affected by several factors, most importantly kidney disease and drug use, and is one of the most accurate tests for detecting the integrity of kidney function [24].

In contrast, treatment with quercetin in the fourth group led to a significant ($p < 0.05$) reduction in creatinine and urea to (*1.15)* and (52.30*),* respectively, compared with the cisplatin group, with a marked improvement in total protein levels toward *6.30 g/dL*, being the control value ($6.30\ g/dL$). From this, one can infer that quercetin helped in restoring the loss of cisplatin's harmful effects on the kidney and partly enhanced the renal functional parameters that were studied, and these results are consistent with previous

studies that established the protective effect of quercetin on kidney function against various toxic agents [15], [17], [22], [23].

Quercetin is a flavonoid naturally present in many fruits and vegetables, characterized by diverse biological properties, most notably its antioxidant, antiviral, antibacterial, anti-inflammatory, and anti-tumor activities. It acts to inhibit the inflammatory response, enhance the antioxidant system, and exert anti-apoptotic effects. The mechanisms of the protective effect of quercetin involve restoring the balance of antioxidant systems and modulating renal biomarkers through its ability to counter oxidative stress and inflammation, specifically targeting reactive oxygen species (*ROS*) and certain cytokines involved in impaired glomerular filtration [21], [33]. Quercetin also allows healthy tubular cells to proliferate and repair damaged tissue and reduces the production of inflammatory cytokines, thereby decreasing the infiltration of inflammatory cells and creating a suitable environment for cell repair. In addition, it preserves *ATP* production and prevents mitochondrial damage and the release of pro-apoptotic molecules, which improved kidney function, evident from the reduced creatinine and urea concentrations in the quercetin-treated group and the return of total protein to a near-normal level [23].

3.1.B. Serum Inflammatory Marker Concentrations

Table 2. Comparison of TNF-α, NF-κB, and IL-1β levels among the experimental groups treated with cisplatin, quercetin, and (cisplatin + quercetin) (Mean ± SD).

Groups	TNF-α (pg/mL)	NF-κB (ng/mL)	IL-1β (pg/mL)
Control	24.50 ± 2.10	1.12 ± 0.10	18.20 ± 1.50
Cisplatin	112.80 ± 8.40	4.85 ± 0.35	86.40 ± 5.20
Quercetin	22.10 ± 1.80	1.05 ± 0.08	16.90 ± 1.30
Cis + Quercetin	48.60 ± 3.70	2.10 ± 0.18	34.50 ± 2.80

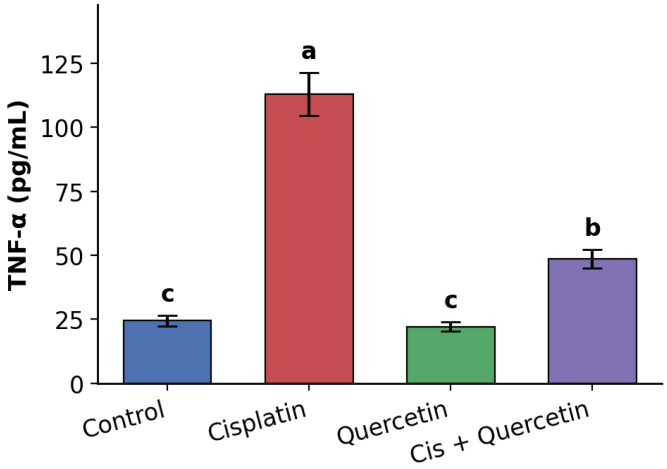

Figure 4. TNF-α concentration in the experimental groups (different letters indicate significant differences at ($p < 0.05$) n = 10 per group.

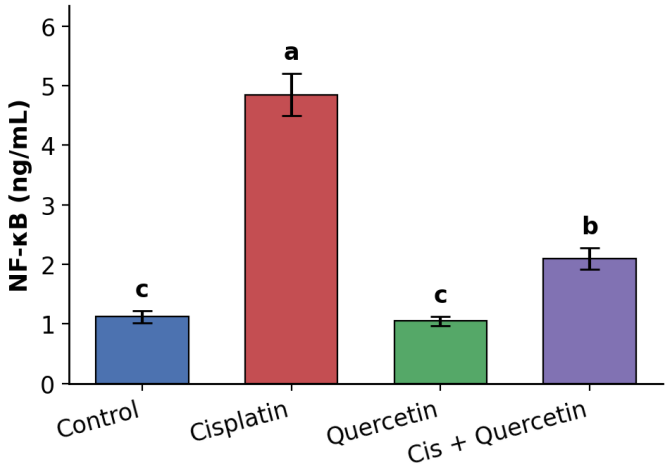

Figure 5. NF-κB concentration in the experimental groups (different letters indicate significant differences at ($p < 0.05$) n = 10 per group.

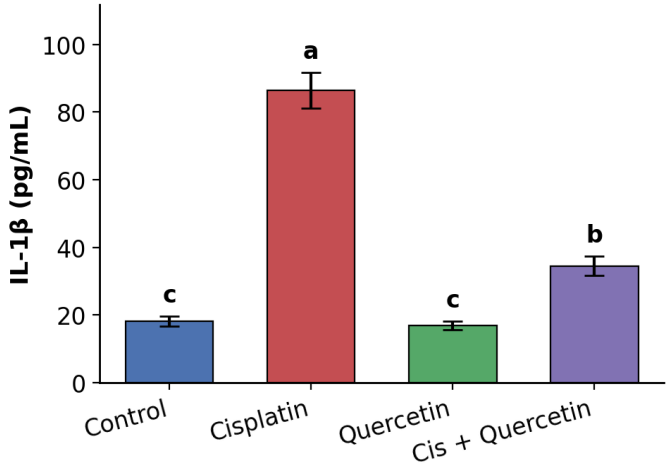

Figure 6. IL-1β concentration in the experimental groups (different letters indicate significant differences at ($p < 0.05$) n = 10 per group.

The results shown in Table (2) revealed marked inflammatory stimulation in the cisplatin-treated group, as $NF-\kappa B$ rose to (*4.85 ng/mL*), accompanied by a sharp increase in $TNF-\alpha$ (*112.80 pg/mL*) and *IL-1β (86.40 pg/mL*) compared with the control group.

Presently, our study confirmed a marked surge in the inflammatory response and showed it as a key player in the development and the progression of kidney disease. Besides its role in activating the kidney pathological response, inflammatory response itself may could accelerate renal injury. Cisplatin induces kidney injury in two stages. After its administration, it is mainly excreted from the body by the kidneys. This results in high concentrations of the drug in the renal cells and is the main reason of damage to these cells which eventually results in kidney failure. Injection of rats with cisplatin led to a marked increase in the gene expression of genes encoding pro-inflammatory cytokines and chemokines, such as $TNF-\alpha$ and *IL-1β*, whose expression increases in kidney tissue after ischemia and acute nephropathy [34]. Nuclear factor kappa B ($NF-\kappa B$) is a transcription factor family member that has vital functions in the start and development of inflammation under abnormal conditions, and the aforementioned key inflammatory factors cause additional damage to the renal tubules [35].

Inflammation makes a difference in the pathology of cisplatin-induced AKI. It starts as cisplatin is carried by transporters into the nearest kidney epithelial cells (*OCT2*/*CTR1*) and it may also involve $OAT1/3$. Mitochondrial damage caused by the entering of cisplatin

into the renal cells worsens the problem. Cisplatin causes a range of cellular organelles related events which include damage to mitochondria (the powerhouse of the cell) and generation of oxidative stress. A consequence here is the damage to mitochondrial DNA together with destruction of membrane components. Such mitochondria damage would then give way to the mitochondrial level defects manifested via respiratory-chain complex activities falling, ATP production going down, amongst other disruptions. [36]. The occurrence of such imperfections is responsible for the massive production and efflux of *ROS*, which represent the byproducts of metabolic activation first and foremost from mitochondria, after which they are released to the cytosol. Experimental results have revealed that exposition to cisplatin leads to a huge increase in *ROS* production by mitochondria in the proximal cells of the renal tube and also results in imbalance between cellular oxidants and antioxidants together with damage to various biomolecules, while then again, *ROS* have the ability to act as "a second messenger" triggering inflammatory effects and thereby aggravating the inflammation condition. In addition, *ROS* can also act as a key messenger activating the *NLRP3* inflammasome. [35].

Investigations of the kidney tissue found that cisplatin causes assembly of *NLRP3* and activation of caspase-1 by oxidative modification which results in maturation and release of IL-1. Broken-up mitochondria themselves can also give out pro-inflammatory messages; in models of cisplatin-induced AKI, pieces of DNA from mitochondria that are released into the cytosol, become damage-associated molecular patterns (*DAMPs*) detectable by DNA sensors in the kidney, like toll-like receptor 9 (*TLR9*) and cyclic $GMP-AMP$ synthase (*cGAS*), further boosting the inflammatory responses. Beside ROS-mediated signaling, cisplatin itself can be conjugated with glutathione (GSH) and degraded enzymatically on the luminal surface of the renal tubules [9]. So basically cisplatin gets to the mitochondria and is metabolically activated within kidney cells, leading to a cascade of *ROS* release and an abnormally elevated level of it [36]. Such oxidative stress signals lead to inflammatory reactions within the kidney cells right from the beginning, initiating inflammatory pathways at very initial stage of damage and then leading to immune-cell infiltration and the inflammation of the whole kidney. As a result, mitochondrial dysfunction and the inflammation triggered by *ROS* constitute the key elements of cisplatin-induced renal injury , which explains the increase in the concentrations of all the inflammatory factors studied in our present research [9], [36].

Treatment with quercetin in the fourth group succeeded in curbing this inflammatory burst, reducing $NF-\kappa B$ by more than 56% compared with the cisplatin group, with a sharp decline in $TNF-\alpha$ *and IL-1β to (48.60) and (34.50*), respectively, compared with the cisplatin group, the reduction being significant at $p < 0.05$.

The decline in serum $NF-\kappa B$ levels in the cisplatin + quercetin group might be due to quercetin's anti-inflammatory property and its reported capability to alter the activity of inflammatory signals linked to *NF-κB.*

Flavonoids, and quercetin in particular, are potent antioxidants known to modulate the activities of various enzyme systems through their interactions with diverse biomolecules. Studies have shown that quercetin markedly reduces the gene expression and secretion of $IL-1\beta$ by inhibiting the $TLR4/NF-\kappa B$ pathway, as well as inhibiting activation of the inflammasome complex responsible for the maturation and secretion of $IL-1\beta$, thereby reducing renal inflammation and limiting renal tissue damage [36]. Quercetin also inhibits $TNF-\alpha$ production by preventing the phosphorylation and degradation of the IκB-α protein, thereby preventing the translocation of the transcription factor $NF-\kappa B$ to the nucleus [21], which reduces transcription of the gene responsible for $TNF-\alpha$ production. Quercetin also inhibits the MAPK pathways (*ERK, JNK, p38*) involved in the production of inflammatory cytokines, contributing to a reduced inflammatory response and improved renal function [20]. Furthermore, quercetin activates the antioxidant $Nrf2/HO-1$ pathway, which in turn inhibits $NF-\kappa B$ activity [33]. Stopping $TNF-\alpha$, an inflammatory factor, from interacting with its receptor can be

the turning point for healing a damaged kidney. Studies show experimentally that, when the activity of $TNF-\alpha$ was completely stopped or even when $TNF-\alpha$ gene was entirely absent, the inflammatory cascade triggered by cisplatin did not take place and as a result kidneys were fully protected against damage. Quercetin also reduces cisplatin-induced lipid peroxidation, and its protective effect may also be attributed to its ability to interact with and penetrate lipid bilayers [22], [28], [33].

3.1.C. Serum Antioxidant (GSH and SOD) Concentrations

Table 3. Comparison of the antioxidants glutathione (GSH) and superoxide dismutase (SOD) among the experimental groups treated with cisplatin, quercetin, and (cisplatin + quercetin) (Mean ± SD).

Groups	GSH (µmol/L)	SOD (U/mL)
Control	4.18 ± 0.22	50.32 ± 3.10
Cisplatin	2.07 ± 0.15	30.75 ± 2.20
Quercetin	4.25 ± 0.20	51.00 ± 3.00
Cis + Quercetin	3.20 ± 0.18	48.10 ± 2.90

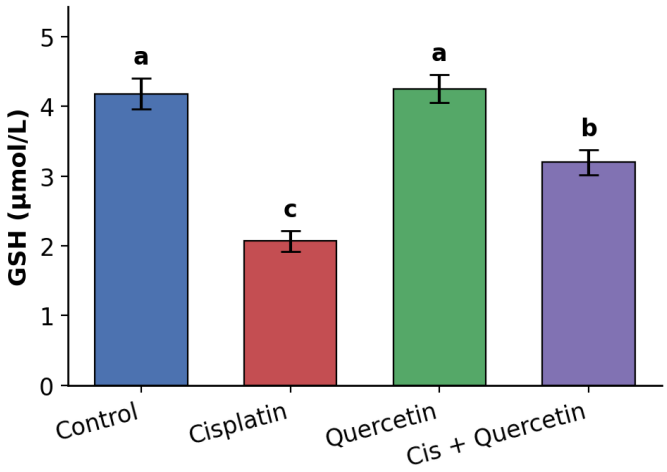

Figure 7. Serum glutathione (GSH) concentration in the experimental groups (different letters indicate significant differences at ($p < 0.05$) n = 10 per group.

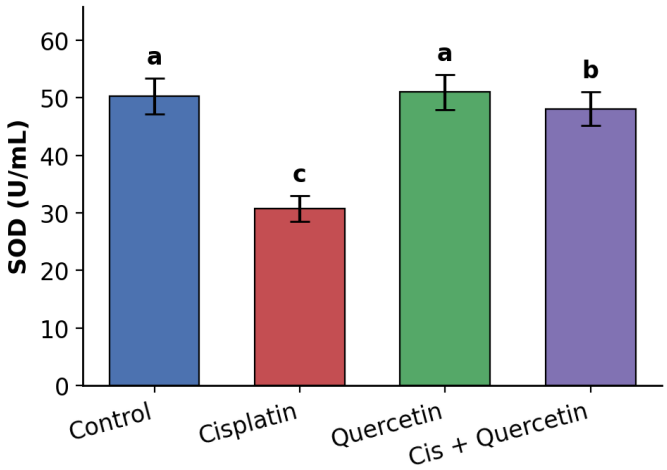

Figure 8. Serum superoxide dismutase (SOD) activity in the experimental groups (different letters indicate significant differences at ($p < 0.05$) n = 10 per group.

The results shown in Table (3) revealed a significant ($p < 0.05$) decrease in the concentration of the antioxidant glutathione (GSH) (*2.07*) in the cisplatin-treated group compared with the control group *(*4.18*),* and in the enzyme superoxide dismutase (SOD) (30.75) in the cisplatin-treated group compared with the control group (*50.32).*

The decrease in antioxidants in this group after cisplatin treatment is caused by Truth is, once the medication enters a cell, it goes into the mitochondria and binds to mitochondrial DNA thereby causing mitochondrial malfunction which disrupts the function of the respiratory chain, the production of reactive oxygen species (*ROS*) increases as a result, a possible pathway for the death of cells induced by cisplatin which seems even more significant than actual damage of DNA [37]. Cisplatin interferes with the normal transport of electrons in the oxidative respiratory chain and generates a great quantity of free radicals which can generate *ROS*. Besides this, a fall in the activity of cytochrome c oxidase (*COX*) can also give rise to and liberate *ROS* from the mitochondria into the cytosol, an important factor in cell damage [18]. The imbalance resulting from oxidative stress is the production and accumulation of excess reactive oxygen species (*ROS*) in cells beyond the cellular antioxidant capacity to eliminate these reactive metabolites and so leading to the depletion of antioxidants. When *ROS* concentration is low or moderate, *ROS* are important mediators of intracellular signals, gene expressions, stimulation of mitoses, execution of apoptosis, and resistance to infection. [38]. 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 injection of cisplatin generated free radicals as by-products during its breakdown or metabolism, leading to excessive production *of ROS* [7]. *ROS* production increase is the cause of the disturbed redox balance and oxidative stress. To defend themselves, the cells activate several antioxidant defense mechanisms which are enzymes, for example: *SOD* which breaks down the superoxide radical into oxygen and hydrogen peroxide, *GSH* is involved in maintaining of redox balance of the cells and in the detoxification processes and *CAT* which degrades hydrogen peroxide to water and oxygen, while *GPx* helps to break down glutathione and the hydroperoxide into less aggressive species like alcohol. which may contribute to alterations in antioxidant levels and activity under conditions of oxidative stress. However, in some cases, the antioxidant defense system cannot eliminate or neutralize excessive ROS, causing oxidative damage and disease [22].

The combination of cisplatin and quercetin resulted in a significant *(*$p < 0.05$*)* raise in glutathione level *(3.20)* as oppose to the cisplatin group *(2.07)* and a rise in SOD activity level *(48.10)* rather than the cisplatin group (*30.75).* The rise in serum GSH level of and *SOD* activity after treatment with cisplatin + quercetin implies a better antioxidant status for cisplatin alone. This observation confirms the antioxidant activity of naturally occurring compound quercetin which may contribute in the alleviation of oxidative stress and reinforcing the body's natural antioxidant mechanisms.

But, the current study evaluated *GSH* and *SOD* levels only in serum and did not look at the genes and activities of these antioxidant enzymes in the kidney directly.

3.2 . Histological Results

3.2.A. Control Group (Normal Structure)

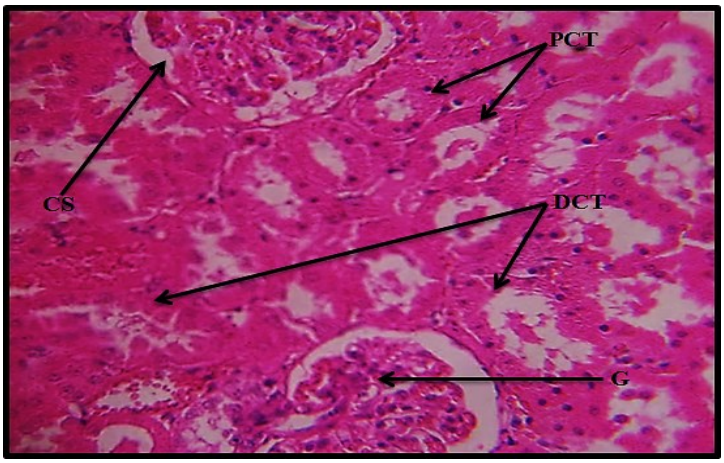

Image 1. The control group showed normal renal histological features, with intact glomeruli (G) surrounded by the (CS)capsular (Bowman's) space, and the normal appearance of the proximal convoluted tubule (PCT) and distal convoluted tubule (DCT) lined by cuboidal cells with viable nuclei and a distinct brush border, without congestion or exudation. (H&E, 400X)

3.2.B. Cisplatin Group

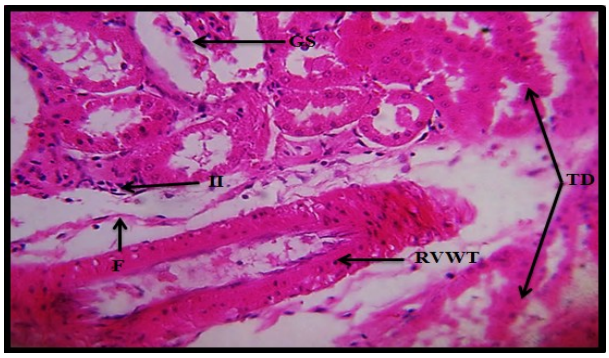

Image 2. A renal tissue section from the Cisplatin-treated group shows desquamation (DES), fibrosis (F), and renal vascular wall thickening (RVWT) within the renal tubules, along with tubular lumen blockage (TLB) observed in some tubules (H&E, 400X)

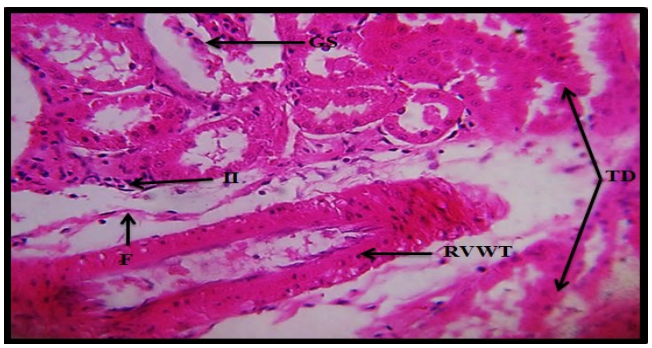

Image 3."A renal tissue section from the Cisplatin-treated group shows glomerular shrinkage (GS), tubular damage (TD), renal vascular wall thickening (RVWT), and fibrosis (F) within the renal tissue, accompanied by inflammatory cell infiltration (II).(H&E,400X)

Nephrotoxicity is functional impairment or kidney disease resulting directly or indirectly from chemical treatments and drugs. Chemical drugs are known to cause an imbalance in the functional homeostasis of the kidney and to increase the levels *of ROS* at the expense of a decline in the body's antioxidant systems. Cisplatin treatment led to oxidative stress and weakening of the antioxidant defense system, causing damage to kidney tissue as a result of the selective accumulation of cisplatin within the epithelial cells of the proximal convoluted tubules, where it stimulates *ROS* production and depletes cellular antioxidants (*GSH, SOD*), leading to increased oxidative stress, lipid peroxidation, and damage to proteins and DNA [39]. It also causes mitochondrial dysfunction and stimulates the inflammatory response via $NF-\kappa B$ and increased production of $TNF-\alpha$, *IL-1β*, and *IL-6*. These mechanisms are reflected in histological changes including tubular cell necrosis, loss of the brush border, dilation of the urinary tubules, infiltration of inflammatory cells, expansion of the capsular space, inflammatory edema, vascular congestion in the interstitial tissue, detachment of the renal capsule from the cortex, and degeneration of the epithelial cells [40], [41], [42].

3.2.C. Quercetin Group

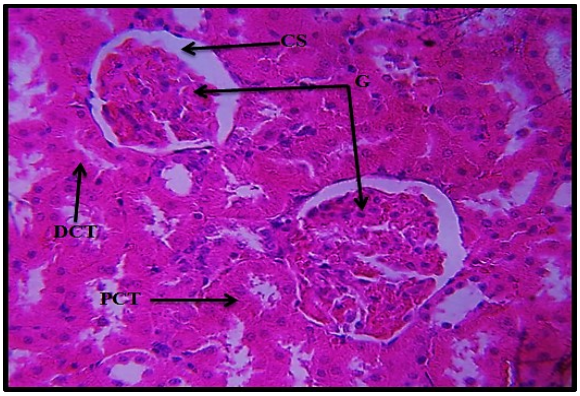

Image 4. The quercetin-treated group matched the control group, containing glomeruli that were intact in shape and structure and surrounded by the capsular space. The glomeruli were surrounded by the proximal convoluted tubules, and the distal convoluted tubules appeared lined with simple cuboidal epithelial cells, with wide tubular lumens. (H&E, 400X)

3.2.D. Cisplatin + Quercetin Group

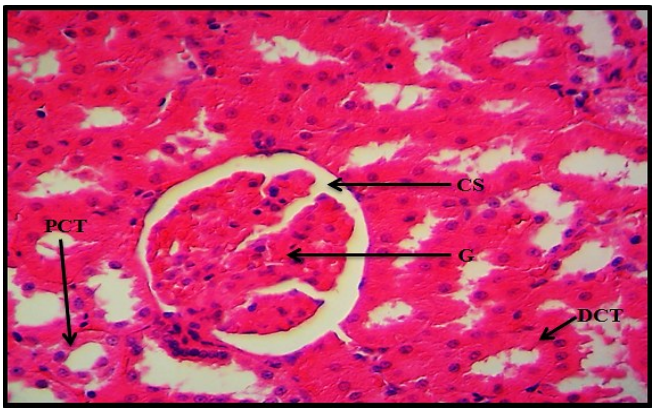

Image 5."A renal tissue section from the Cisplatin + Quercetin-treated group shows proximal convoluted tubules (PCT), distal convoluted tubules (DCT), renal glomeruli (G), and capsular space (CS).(H&E,400X)

The fourth group, treated with Cisplatin + quercetin, showed a high degree of reparative improvement, reducing shrinkage of the glomeruli and tubules, decreasing thickening of the renal vessel walls, and alleviating detachment, vascular congestion, and inflammatory-cell infiltration. It markedly reduced the obstruction of lumens, with a marked decrease in necrosis and vacuolar degeneration, disappearance of interstitial inflammatory aggregates, and restoration of the epithelial cells to their normal texture and viable nuclei. (H&E, 400X)

The histological amelioration observed in this group suggests a protective role of quercetin against the cisplatin-induced damage in the renal tissues. Such an improvement could presumably result from the antioxidant and anti-inflammatory effects of quercetin, mechanisms already documented by some investigators [15], [17].

4. Discussion

The results obtained within the scope of the current study suggest that the capital allocation strategy is a decisive factor in the effectiveness of utility-scale energy infrastructure investment decisions [24]. According to the results, renewable energy projects have the highest priority among investment projects (27%), whereas the second place is taken by the grid modernization projects (20%), and the third place goes to the development of the transmission infrastructure (16%). The high priority of renewable energy and modern electricity network infrastructure is a consequence of the transformation of the energy industry into the cleaner, safer, and technologically advanced sector [25]. Therefore, investors tend to allocate financial resources to projects that will provide them with economic, environmental, and operational advantages. The increasing attention paid to the issues of sustainability and future electricity demand demonstrates that the investment process becomes more strategic and sustainable [26]. One of the significant outcomes of the research is the fact that the expected financial return (25%) turned out to be the main influencing factor of capital allocation decision-making, after which go investment risk assessment (20%) and regulatory support (16%).It is also important for regulatory stability because the presence of the predictable investment environment boosts the level of investor's trust. Consequently, decisions about investment are not made on the basis of financial performance only but they are backed up with proper risk evaluation and favorable conditions for making decisions [27].

Correlation analysis gives additional evidence for these connections. Capital Allocation Strategy had the most positive correlation with Infrastructure Investment Performance ($r = 0.731$) meaning that organizations with good resource allocation strategies usually have good results with their projects. Investment Decision Efficiency had the best connection with Infrastructure Investment Performance ($r = 0.744$) which proves the effectiveness of systematic planning and making decisions when it comes to investment. Strong relationship between Financial Performance and Infrastructure Investment Performance ($r = 0.683$) emphasizes the importance of having financial strength through all the process of project development. Despite the fact that the correlations between Investment Risk Assessment ($r = 0.611$) and Regulatory Support ($r = 0.528$) are rather moderate, these two factors are still very significant.Moreover, the regression analysis reveals the degree of contribution of every predictor variable to the result [28]. The total explanatory power of the regression equation is 67.2%, as revealed by R squared value ($R^2 = 0.672$). It can be noted that the highest standardized coefficient is recorded for the Capital Allocation Strategy ($\beta = 0.334$), which indicates that proper allocation of financial resources is crucial for the investment success. The next predictor in importance is the Financial Performance ($\beta = 0.281$), followed by Investment Risk Assessment ($\beta = 0.194$) and Regulatory Support ($\beta = 0.147$). The results reveal that organizations with the ability to combine financial planning and proper risk management are expected to enjoy better investment performance in the infrastructure development projects [29]. From the practical standpoint, the results of the analysis provide guidance for investors and policymakers, financial institutions and utility companies, since increasing investment into renewable energy, electricity transmission systems, energy

storage facilities and smart grids presupposes the transparency of the financial planning and proper frameworks for the capital allocation process [30]. Moreover, decision makers should consider the economic potential of projects together with their risk exposure and regulatory support. Enhancing institutional backing and regulatory conformity would help further increase private investments by minimizing the uncertainties in financing big infrastructure projects.

5. Conclusion

The findings of this study demonstrate that cisplatin induces acute kidney injury in rats, as evidenced by elevated serum creatinine, urea, and inflammatory markers, together with depletion of GSH and reduced SOD activity and marked histopathological alterations in renal tissue. Co-administration of quercetin substantially attenuated these biochemical and structural changes, improving renal-function parameters, reducing inflammatory responses, and restoring antioxidant status. Histopathological examination further confirmed the protective effect of quercetin, with marked recovery of glomerular and tubular architecture and reduced inflammatory infiltration, congestion, and tissue degeneration. Overall, the results indicate that quercetin has a significant renoprotective effect against cisplatin-induced acute kidney injury, mainly through its antioxidant and anti-inflammatory activities.

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