Effect of Antioxidant Activity of Naringin and CoQ10 Against Acetaminophen-Induced Nephrotoxicity in Male Rats

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Abstract: Acetaminophen overdose is a known cause of nephrotoxicity, primarily through oxidative stress mechanisms. This study evaluated the potential renoprotective effects of the antioxidants naringin and coenzyme Q10 (CoQ10) against acetaminophen-induced kidney damage. Forty-two male rats were divided into six groups (n=7): control, acetaminophen (1g/kg), naringin (100mg/kg), CoQ10 (100mg/kg), acetaminophen + naringin, and acetaminophen + CoQ10. Treatments were administered orally for 60 days. Serum levels of urea, creatinine, calcium, phosphate, and the activities of antioxidant enzymes (SOD, GPx) and malondialdehyde (MDA) were assessed. Acetaminophen administration caused a significant ($p<0.05$) decrease in SOD, GPx, calcium, and phosphate levels, alongside an increase in MDA, urea, and creatinine levels compared to the control. Co-treatment with both naringin and CoQ10 significantly ameliorated these changes. Notably, naringin exhibited a more potent protective effect, normalizing kidney function parameters and oxidative stress markers to levels comparable with the control group. The findings demonstrate that naringin and CoQ10 confer protection against acetaminophen-induced nephrotoxicity by attenuating oxidative stress. Naringin proved to be a more effective therapeutic agent in this model, suggesting its potential for clinical application in preventing drug-induced kidney injury.

1 INTRODUCTION

Free radicals are uneasy molecules characterized by having an unpaired electron in their outer shell, which makes them highly reactive to cells, proteins, and DNA within the body. These molecules are generated during normal metabolic functions or through external factors like pollution, radiation, and smoking. The body's antioxidant defense system is crucial in counteracting their damaging effects [1].

An increase in free radicals because of a weakened antioxidant system can result in cellular damage and contribute to the onset of various chronic diseases, including cancer, heart disease, and arthritis. Unregulated oxidation also accelerates aging and can lead to nervous system disorders [2].

Naringin exhibits protective properties against chemotherapy-induced kidney toxicity by mitigating oxidative stress, cell apoptosis, autophagy, and oxidative DNA damage [3]. Naringin has a protective effect against nephrotoxicity in male rats by modulating lipid peroxidation, enhancing antioxidant defenses, and suppressing pro-inflammatory cytokines, while also lowering urea and creatinine concentrations. The findings demonstrated an improvement in mitochondrial activity and a decline in lipid peroxidation, confirming naringin's potential to safeguard the kidneys from drug-induced toxicity [4]. Studies have also demonstrated that naringin boosts the action of antioxidant enzymes, including glutathione peroxidase (GPx) and catalase (CAT), thereby enhancing the kidneys' defense against oxidative stress and preventing cellular damage [5].

CoQ10 is essential for electron transfer in mitochondrial oxidative phosphorylation. It functions as a powerful antioxidant, stabilizes cellular membranes, and serves as a crucial cofactor in ATP synthesis through oxidative phosphorylation, protecting proteins and DNA from oxidative damage [6]. CoQ10 is used to prevent oxidative stress caused by cisplatin, which causes inflammation, necrosis, and apoptosis in kidney tissues through its antioxidant actions. Similarly, CoQ10 is used to mitigate the poisoning of anthracyclines, tamoxifen, and doxorubicin [7]. levels of Coenzyme CoQ10 in the Plasma are significantly depressed in patients with chronic kidney disease (with or without

dialysis), in contrast to normal levels, and there is evidence that the supplementation of CoQ10 may ameliorate kidney function and lower the need for dialysis in chronic kidney disease patients [8].

Acetaminophen is one of the most widely consumed over-the-counter antipyretic and painkiller drugs [9]. Although the drug's mechanism of action remains unclear, it has historically been classified with "non-steroidal anti-inflammatory drugs" due to its suppression of the pathway of the cyclooxygenase (COX) enzyme [10]. Acetaminophen-induced kidney injury involves activation of the cytochrome P450 enzyme pathway, specifically in the renal cortex, binding of the drug to prostaglandin endo-peroxidase, formation of a toxic metabolite (NAPQI) in the renal medulla, deacetylation of the drug by N-deacetylase enzymes, and generation of harmful free radicals that cause renal necrosis [11]. This review aims to determine the role of naringin and the enzyme CoQ10 as antioxidants and their ability to reduce the negative effects of oxidative stress on the kidneys and improve their function.

2 MATERIALS AND METHODS

2.1 Preparation of Solution

2.1.1 Acetaminophen

The dosage of 1 g /kg [12], was obtained from the pharmacy. A stock solution was then prepared and the corresponding dose was administered to each male animal based on its weight.

2.1.2 The Naringin

The extract, at a concentration of 0.1 g/kg [13], was obtained from the pharmacy and dissolved in 10 ml of 0.9% normal saline to prepare the stock solution. Based on the body weight of the animals, the appropriate dose was administered orally.

2.1.3 The Coenzyme CoQ10

In relation to CoQ10, the concentration was 0.1g/kg [14], purchased from the Al-Razi Laboratory Supplies Store." It was dissolved in 10 ml of normal saline 0.9% to get the stock, then adjusted according to their individual's body.

2.2 Experimental Design

Following a one-week acclimatization period, a total of forty-two (42) male rats were randomly allocated into six experimental groups (n=7 per group). The groups were designed as follows:

- The control group: They were orally administered normal slain 0.9 % for 60 day.
- Naringin group: Dosage with Naringin at 0.1g/ kg orally only for 60 day.
- CoQ10 group: received orally CoQ10 (0.1g/ kg) only for 60 day.
- Acetaminophen group: received orally acetaminophen at dose of 1 g/kg 60 day.
- Acetaminophen + Naringin: received acetaminophen 1 g/kg, then after 4 h given Naringin at a concentration 0.1g/ kg orally for 60 day.
- Acetaminophen + CoQ10 group: gave orally acetaminophen 1g/kg after 4h given CoQ10 0.1g/ kg for 60 day.
- * seven rats in each group.

2.3 Indicators and Antioxidants. Estimation of Action Glutathione Peroxidase (GPx) in the Serum

The level of selenium-dependent glutathione peroxidase was estimated according to the method [15].

2.3.1 Determination of Malondialdehyde in the Serum

Malondialdehyde levels in serum were estimated using a modified method developed by researchers [16]. Absorbance intensity is measured at 532 nm.

2.3.2 Estimation of Superoxide Dismutase (SOD) Activity in the Serum

SOD enzyme activity was estimated using a spectrophotometer [17].

2.4 Kidney Function Indicators

2.4.1 Assessment of Urea Level in the Blood Serum

Urea levels were estimated using a spectrophotometer according to [18].

2.4.2 Estimation Level of Creatinine in the Blood Serum

Serum creatinine levels were estimated based on [19]. using the colorimetric method (Jaffe's reaction), where creatinine reacts with basic buffers to produce a colored compound. The absorbance was measured using a spectrophotometer.2

2.5 Estimation Levels of Ion in the Serum

2.5.1 Assessment Levels of Calcium Ion in Serum

The calcium ion level in serum was estimated using the Roche (COBAS C311) device. According [20].

2.5.2 Estimation of Phosphate Ion Level in the Serum

Ion level was estimated using the (COBAS C311) device from Roche/Hitachi. measured according to [21].

2.6 The Analysis

Concerning the analysis of study results, the " Statistical Program for Social Sciences (SPSS), version 22 and ANOVA test were used to extract the significant differences between all the groups. The LSD at P-values (<0.05) were dependent in the present study [22].

3 RESULTS

3.1 Effect of Treatment with Coenzyme CoQ10, Naringin, and Acetaminophen on the Action of SOD, MDA, and GPX

Through statistical analysis of study results, acetaminophen led to a decrease ($P \leq 0.05$) in contrast to the control group and the rest of the study groups, while the treatment with CoQ10 showed a slight rise in antioxidant levels contrast to the drug group. The naringin treatment was more effective, as an increase in levels of antioxidants was observed compared to the group that received both acetaminophen and CoQ10 Table 1.

3.2 Effect of the Treatment with Coenzyme CoQ10, Naringin, Anddrug of Acetaminophen on Levels of Creatinine, Urea, Calcium, and Phosphate

Table 2 shows an increase ($P \leq 0.05$) in creatinine and urea levels in the group treated with acetaminophen only, compared to the control and other groups. On the other hand, a decrease in creatinine and urea levels was observed in the groups treated with naringin or CoQ10, respectively, when compared to the drug-treated group.

Table 1: Effect of coenzyme CoQ10, naringin and acetaminophen on the action of SOD, MDA, and GPX.

Groups of study	Mean ± SD			
	Samples Number	SOD (IU/ L)	MDA (IU/ L)	GPX (IU/ L)
Control	7	43.28±1.14 b	49.11± 0.04 c	56.23± 0.07 b
Naringin (100mg/ kg)	7	48.26± 1.17 a	31.94± 1.02 d	62.13± 1.08 a
Q10 (100mg/ kg)	7	44.11± 0.45 b	51.35± 0.07 c	54.88±1.67 b
Acetaminophen (1g/ kg)	7	29.85± 0.08 d	65.46± 0.39 a	38.77± 1.06 d
Acetaminophen + Naringin	7	42.89± 0.05 b	50.69± 0.09 c	54.95± 1.02 b
Acetaminophen + Q10	7	38.45± 1.33 c	58.09±1.33 b	38.45± 1.33 c
LSD		3.91	6.57	5.18

Different letters show significant differences through of the study groups in P-value <0.05.

Table 2: Effect of coenzyme CoQ10, naringin and acetaminophen on levels of creatinine, urea, calcium, and phosphate.

Groups of study	Mean ± SD				
	Samples Number	Creatinine (mg/dl)	Urea (mg/dl)	Calcium (mmol/L)	phosphate (mmol/L)
Control	7	0.29±0.12 c	28.23± 1.11 c	9.68± 1.18 a	5.51± 0.17 a
Naringin (100mg/ kg)	7	0.27±0.03 c	23.56± 1.07 c	9.97± 1.23 a	5.59± 0.29 a
Q10 (100mg/ kg)	7	0.32±0.13 c	30.09± 1.09 c	9.35± 0.23 a	5.23± 1.01 a
Acetaminophen (1g/ kg)	7	0.65±0.09 a	41.15± 0.750 a	7.16± 0.06 c	3.21± 0.06 c
Acetaminophen + Naringin	7	0.30±0.06 c	28.69± 1.12 c	9.57± 0.65 a	5.45± 0.18 a
Acetaminophen + Q10	7	0.41±0.049 b	35.19± 0.06 b	8.56± 0.03 b	4.49± 0.67 b
LSD		0.08	4.95	0.78	0.69

Different letters show significant differences through of the study groups in P-value <0.05.

In contrast, showed a significant decrease in levels of calcium and phosphate ($P \leq 0.05$) in group that received the drug only, compared to the other experimental groups. An increase in calcium and phosphate levels was observed when the animals were treated with naringin and CoQ10 compared to the group that received acetaminophen. Table 2.

4 DISCATION

The results display a decrease in the antioxidants (GPX) and (SOD), accompanied by a significant increase in (MDA) level in the group treated with the drug acetaminophen only when compared with the control group. The results are similar to the study [23], which measured the level of GSH and GPx1, as well as the level of MDA. These results were consistent with the study [24], in which a reduced level of glutathione and an increased level of malondialdehyde were detected. This may be explained by the fact that the 1g/kg dose may have induced oxidative stress in kidney tissues by promoting lipid peroxidation, thereby increasing the formation of different free radical species that cause histological damage in the kidneys. The high production of the reactive compound NAPQI after a high dose leads to the depletion of cellular glutathione and damage to mitochondrial proteins, leading to the induction of oxidative stress, which can result in DNA damage, cell necrosis, and cell death. The result is that the dose causes damage to the kidney cells [25]. The increase in the levels of these parameters in the serum is an indicator of the drug-induced nephrotoxicity in the kidneys of animals, as acetaminophen depleted the antioxidant enzymes in kidney tissue and increased lipid peroxidation, which led to a disruption of the homeostasis process, cell death, tissue necrosis and, finally, functional impairment in the kidney, which leads to the accumulation of metabolic wastes in the serum, as shown by some studies [26].

In addition to the above, the results also showed that treating rats with acetaminophen + CoQ10 resulted in a significant increase in (SOD) and (GPX), while significantly decreasing the (MDA) compared to the drug group, because CoQ10 acts as an antioxidant, but it can become a pro-oxidant when oxidants are present, as occurs after high doses of acetaminophen. Acetaminophen affects the body's antioxidant system, damaging the liver and kidneys via toxic metabolites such as NAPQI, which interact with and deplete glutathione, leading to decreased levels of GPX and SOD, along with increased MDA. Alternatively, CoQ10 may exacerbate oxidative stress when the natural antioxidant system is impaired, leading to increased peroxides, notably MDA and changes in GPX [27].

In contrast to the above, the results also showed that treating rats with acetaminophen + naringin extract led to no significant change in the enzymes (SOD) and (GPX), and in the level of (MDA) compared to the control. The current research is somewhat in agreement with the study [28]. This is due to the effectiveness of the chemical compounds of naringin extract, which remove free radicals and prevent inflammatory responses by inhibiting the production of inflammatory cytokines, thus preventing cell damage by enhancing the natural

defenses of antioxidants such as glutathione (GSH), catalase, and SOD [29].

In light of the results of the current study, an elevation in the levels of creatinine and urea was observed in the group treated with acetaminophen. These results were consistent with those of some studies [30]. This increase may be explained by the toxic effect of acetaminophen, which causes a decline in the function of the renal glomeruli. As a result, filtration rates decline due to oxidative stress induced by the drug's toxicity. Several histopathological changes in renal tissue have been documented, triggered by acetaminophen consumption, such as hemorrhage in some convoluted tubules of renal tissue and necrosis of the lining epithelium, along with edema within the interstitial tissue of the renal cortex and shrinkage of some renal glomeruli, which may cause significant increases in creatinine and urea levels. Some studies have indicated shrinkage of renal glomerular cells, resulting in a reduction in the total filtration surface area and consequently a decrease in filtration rate and waste excretion [31].

Contrary to the above, a significant reduction in calcium ion and phosphate levels was observed in the aforementioned group when compared with the control. This is because of the fact that high doses of acetaminophen can lead to nephrotoxicity, limiting the kidneys' ability to reabsorb calcium and phosphate, leading to decreased levels in the blood. Damage to the renal tubules can also cause increased loss of calcium and phosphate. Alternatively, it may be due to acetaminophen-induced oxidative stress in the kidneys, which leads to increased consumption of vital minerals such as calcium and phosphate for cellular recovery and regeneration.

As for the group treated with acetaminophen + coenzyme CoQ10, a decrease in urea and creatinine was observed when compared with the drug group. This improvement can be attributed to the significant role that CoQ10 plays in protecting the interstitial tissue of the renal cortex from damage caused by oxidative stress by reducing the free radicals and their harmful effect on the kidney tissue, which results in an improvement in its functions, restoring its normal composition, and returning urea and creatinine to their normal levels [32]. CoQ10 also plays an important role in regenerating antioxidants, including (vitamins E and C). Vitamin C plays a role in reducing inflammation and oxidative stress on the kidneys, and improving the function of the renal tubules or nephrons [33].

Additionally, CoQ10 treatment resulted in an increase in calcium and phosphate levels compared with the control and drug groups. The results were somewhat consistent with a study [34]; CoQ10 also has a role as an antioxidant that includes scavenging ROS and thus reducing the oxidation of low-density lipoprotein and protecting the kidney tissue from renal damage [34].

In contrast, urea and creatinine levels did not show a significant change in the group that was treated with acetaminophen + naringin compared to the control. This lack of change could be attributed to the fact that naringin has a clear role in protecting the kidneys under multiple abnormal pathological conditions [35]. Although acetaminophen triggers oxidative stress by activating the generation of reactive oxygen species, studies have indicated the protective effects of naringin's chemical components with antioxidant activity, such as phenols, polyphenols, and flavonoid glycosides [36]. Thus, it may have played a substantial role in enhancing the physiological function of the kidneys, which was positively reflected in the absence of a significant difference in the creatinine and urea levels in rats of this group.

Calcium and phosphate levels in the blood did not demonstrate a notable change in this group compared to the control. This is because calcium and phosphate levels are linked to kidney function, and the unchanged levels of these in the blood indicate that naringin plays a role in protecting the kidneys from oxidative stress [37]. Studies have also indicated that naringin plays a substantial role in bone protection by affecting estrogen receptors and promoting mineral deposition. It also increases calcium absorption and promotes its deposition in bones [38].

5 CONCLUSIONS

This study demonstrates that acetaminophen at a dose of 1 g/kg induces significant nephrotoxicity in male rats, as evidenced by increased oxidative stress (elevated MDA, decreased SOD and GPx), impaired kidney function (elevated urea and creatinine), and disrupted electrolyte balance (decreased calcium and phosphate).

Both naringin and coenzyme Q10 showed a protective effect against acetaminophen-induced kidney damage due to their antioxidant properties. They significantly attenuated the oxidative stress and restored kidney function parameters and ion levels towards normal.

Notably, naringin exhibited a more potent renoprotective effect than coenzyme Q10. The group receiving naringin in combination with acetaminophen showed results that were not statistically different from the healthy control group across most parameters, indicating almost complete prevention of kidney damage. In contrast, the coenzyme Q10 group showed a significant improvement compared to the acetaminophen group, but not a full return to baseline.

In conclusion, naringin can be considered a highly effective natural agent for protection against drug-induced nephrotoxicity. Further clinical studies are warranted to explore its potential therapeutic application for humans.

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