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Original article

Naringenin ameliorates Cyclophosphamide-induced nephrotoxicity in experimental model

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ABSTRACT

Cyclophosphamide (CP) is widely described in the management of several nonneoplastic and neoplastic disorders. Renal damage is the most reported toxic effect of CP in clinical practice.

Our study aimed to evaluate the effect of Naringenin (NG) in attenuating renal damage induced by CP in an experimental model.

A total of 32 rats were divided into four groups (n = 8): negative control: rats fed on a basal diet, positive control: rats injected intraperitoneally with CP 50 mg/kg of body weight/day, NG 100: rats treated with NG 100 mg/kg/day body orally with concomitant administration of CP as described before, and NG 200: rats treated with NG 200 mg/kg/day body orally daily + CP. At the end of the experimental protocol (21 days), blood creatinine and urea levels were measured. The antioxidant activities and lipid peroxidation products were measured in the renal tissues as indicators of oxidative damage. Histopathological examination and immunohistochemistry staining were also performed on renal tissues.

Coadministration of NG along with CP significantly ($p < 0.001$) improved the renal function and antioxidant capacities compared with positive control animals. Furthermore, histopathological, and immunological examination of renal tissue confirmed the protective effect of NG against CP-induced nephrotoxicity.

The current study showed that NG has the potential to protect CP-induced renal damage, which may be beneficial for further studies and the design of NG analogs to be useful in clinical practice against CP-induced nephrotoxicity.

1. Introduction

Malignancies are chronic mostly noncurable diseases especially if discovered lately and they end up with severe serious outcomes. Moreover, in order to suppress the violation of the disease, highly toxic drugs are used. Cyclophosphamide (CP) is a chemotherapy and an immunosuppressive drug that is used in the management of autoimmune as well as malignant diseases (Ahlmann and Hempel, 2016).

However, Renal dysfunction and damage are well-reported side effects of CP in a dose-limiting manner that limits the effectiveness of CP (Kopecna, 2001). The CP metabolites were found to be increased several inflammatory pathways leading to the production of proinflammatory cytokine (Caglayan et al., 2018; Zarei and Shivanandappa, 2013).

Moreover, CP promotes the generation of harmful species "reactive nitrogen species (RNS), reactive oxygen species (ROS)", as well as downregulates antioxidant defenses, which lead to nitrosation of cellular macromolecules and lipid peroxidation, resulting in activation of apoptotic cascades leading to necrosis of renal tubular cells (Abraham and Rabi, 2011; Caglayan et al., 2018). Vice versa, several antioxidant compounds showed promising efficacy against CP-induced renal damage (Estakhri et al., 2013; Mahipal and Pawar, 2017).

Naringin (N) is a natural flavanone glycoside specific to citrus fruits and is highly rich in bioflavonoids. N showed a very strong capacity against inflammatory and oxidative damage in many experimental studies (Zaidun et al., 2018). Many experimental

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studies showed a significant effect of N against renal damage induced by cisplatin (Chtourou et al., 2016) cadmium (Renugadevi and Prabu, 2009), carbon tetrachloride (Hermenean et al., 2013), and gentamicin-induced renal damage in rats (Fouad et al., 2014).

The clinical problem faced by the researchers is N cannot easily be absorbed in the gastrointestinal tract due to its large hydrophilic structures which reflects negatively on the desired outcomes of flavanones (Felgines et al., 2000). Interestingly, active N form conjugated flavanones (Naringenin [NG]) which can be obtained by removing a glucose molecule through a hydrolysis of N with Naringinase (Felgines et al., 2000). "N is hydrolyzed into prunin and rhamnose by the Nringinase exhibiting α-lrhamnosidase activity, and then β-D-glucosidase catalyzes the hydrolysis of prunin to glucose and NG" (Vila-Real et al., 2011).

Attenuation of the nephrotoxicity effect of CP could offer the possibility of increasing cancer cure rates by increasing the therapeutic doses of CP. Thus, this study was designed to evaluate the effect of NG as naturally occurring plant (bioflavonoid) against the structural and functional changes in CP-induced renal damage in the animal model.

2. Materials and methods

2.1. Chemicals

2.1.1. Preparation of Naringenin

Grapefruit was obtained locally from Saudi shop. It was cleaned in a washing machine with purified water. The fresh grapefruit peel was then taken off, dried, and ground into a fine powder.

Furthermore, cold-method extraction of 50 g of grapefruit peel material was steeped in 250 ml of petroleum ether and macerated for two days to remove nonpolar components from the extract, such as waxes, resin aromatic oil, and fatty acids.

Then, petroleum ether extract was put in a filter paper and extracted via Soxhlet for 3 h with 300 ml of 90% ethanol to separate the polar compounds such as glycosides and flavonoids. Through the rotary evaporator, the filtrate was reduced to a negligible level. This quantity was converted to NG by acidified to pH 3–4 with 20 ml of 6% acetic acid solution (Ahmed et al., 2019; Lahmer et al., 2015).

Methyl alcohol (50 ml), hydrochloric acid (2 ml of 50%), and NG (2 g) were mixed, stirred, and heated for 60 min. The final homogenous mixture was concentrated one to four times, standardized, frozen, moved twice with 15 ml of chloroform, and isolated to the separator funnel. The chloroform layer was decanted, and NG precipitate was cleaned with acetone, and filtered at 60 °C for dried (Hassan et al., 2019).

2.2. Experimental protocol

2.2.1. Design

A total number of 32 male Wistar rats, weight between 200 and 250 g (between Three and five months), was obtained from King Faisal University. The proposal of the present study was reviewed and approved by the University research board (IRB 2023–01-030). All animals were kept at standard environment facilities including 12 h of light/dark cycle and 24 ± 1○C, 45 ± 5% humidity. All rats were given the standard laboratory pellet chow and free access to sterilized water and were left to acclimatize for seven days prior to the experiments (Al-Hariri et al., 2019).

All animals were assigned at random into four groups (n = 8), the negative control group: rats fed on a basal diet. To induce nephrotoxicity, the remaining rats (24 rats) were intraperitoneally (i.p.) injected with CP (Sigma-Aldrich, USA), 50 mg/kg/day, dismantled in 5 ml/kg 1.0% carboxymethyl cellulose (CMC), for four days. These remaining rats were divided into three equal groups, the positive control group, which had been subjected to kidney injury and received a vehicle; the third and fourth groups separately treated orally 100 and 200 mg/kg/day (respectively). The NG doses have been chosen based on a previous report that showed a significant nephroprotective effect (Wang et al., 2019). NG was emulsified in 5% CMC immediately before administration (Refaie et al., 2022).

At the end of the experiment (21 days), animals were anesthetized using Sevoflurane by inhalation (Sevorane, Abbott Laboratories, Ireland) as described in previous research ("Neurotoxicity of Inhalation Anesthetics in the Neonatal Rat Brain: Effects on Behavior and Neurodegeneration in the Piriform Cortex," n.d.). Blood was withdrawn from the greater vessel (aorta) and then centrifuged (3000 rounds/minute) for 15 min. Then kidney was extracted and washed with ice-cold saline solution (Alaqeel et al., 2022).

2.3. Biochemical markers

Antioxidant enzymes "Catalase enzyme (CAT) and Superoxide dismutase (SOD)" were determined in the serum as documented previously (Sairam et al., 2003). In addition. serum Glutathione antioxidant (non-enzyme) activity (GSH) was assessed as described by Kalantar et al. (2016). The serum lipid peroxidation (thiobarbituric acid reactive substances) was determined calorimetrically by calculating the amount of malondialdehyde (MDA) produced as previously described by Moore and Roberts (1998). Moreover, we measured serum total antioxidant capacity (TAC) as described by Erel (2004). Finally, assessment of kidney function markers (creatinine and urea) were evaluated as previously reported by Salem et al. (2018).

2.4. Histopathological studies

The extracted kidney was fixed in a 10% formalin solution. After dehydrating them, they were embedded in paraffin with varying alcohol concentrations. Eosin and Hematoxylin and (E and H) were used to stain 4 m slices (El Agawany et al., 2012). Then, the histological alterations in these sections were scrutinized.

2.5. Immunohistochemistry examination

Hydrogen peroxide (3%) in methanol was employed to inhibit peroxidase after the sections had been deparaffinized and rehydrated in citrate buffer. Sections were pre-treated in buffer citrate (10 mM, pH 6.0) in a microwave and incubated with rabbit polyclonal antibodies against rat inducible nitric oxide synthase (iNOS) (Thermo Scientific, USA; 1:100), and kidney injury molecule-1 (KIM-1) (1:50; Thermo Scientific, USA). Slices were incubated with streptavidin peroxidase, biotinylated goat anti-polyvalent, and lastly with DAB as a chromogen. A light microscope was used to identify immunostaining after counterstaining with hematoxylin (Sheth et al., 2018).

2.6. Statistical analysis

All the results were presented as mean ± standard error (SE). Moreover, mean comparisons and analysis of variance (ANOVA) were applied, $p < 0.05$ was considered significant. All statistics were calculated using SPSS software (Chicago, Illinois, USA, V.24) for computer program.

3. Results

3.1. Effect of Naringenin on renal functions

Creatinine and urea were measured in all study animal groups and the results were presented in Table 1. CP treatment caused as expected a significant ($p < 0.05$) decline in renal function. This finding is a typical sign of CP-related nephrotoxicity. The coadministration of NG at a dose of 100 mg/kg and CP showed a statistically significant ($p < 0.05$) decline in creatinine and urea. Interestingly, NG at a higher dose (200 mg/kg) showed a higher significant ($p < 0.05$) improvement in renal function.

3.2. Effects of Naringenin on oxidative status and antioxidant capacity

CP treatment induced an increase ($p < 0\ 0.05$) of MDA significantly and lower the enzymatic (CAT and SOD) and nonenzymatic (GSH) antioxidant activities as well as the total antioxidant activities (TAC) in animals as compared with the negative control group. While co-treatment with NG showed a significant reduction ($p < 0.05$) of lipid peroxidation production, and this effect is magnified by increasing the dose of NG (200 mg/kg) in comparison to the positive control group. Additionally, our result also found that the administration of NG can preserve the antioxidant activities significantly ($p < 0.05$) of all the study parameters. However, at a higher dose (200 mg/kg) NG exhibited more antioxidant activities compared to the lower dose (NG 100 mg/kg) as presented in Table 2.

3.3. Effects of Naringenin on histological experimental

On examination of histopathological analysis of kidney tissue, normal histology was determined in the negative control group. CP primarily influenced the proximal convoluted tubules. Moreover, extensive necrosis with epithelial desquamation, dilatation, intraluminal cast formation as well as vacuolar degeneration were identified in the positive control group. In contrast, both doses of NG (100 and 200 mg/kg, respectively), reduced the CP-induced renal tissue damage, with a histological profile similar to the negative group. Additionally, NG reduced CP-induced renal tubular necrosis (Fig. 1).

3.4. Immunohistochemical findings of Naringenin

Evaluation of immunohistochemical analysis of the control and NG-treated groups showed that CP considerably increased the expression of iNOS and KIM-1 in the renal tissues when compared with the negative group. As well as, in CP-challenged rats, NG 100 mg and 200 mg/kg, respectively, dramatically reduced the expressions of renal iNOS and KIM-1 (Fig. 2 and Fig. 3).

Table 1
Effect of Naringenin on kidney functions in cyclophosphamide-induced nephrotoxicity in rats.

Groups	Means ± SD	
	Ceatinine (mg/dl)	Urea (mg/dl)
Negative Control	0.5 ± 0.04[b]	26 ± 2.21[b]
Positive Control	1.13 ± 0.09[a]	42 ± 3.35[a]
Narginine 100 mg /kg	0.8 ± 0.07[b]	35 ± 2.16[b]
Narginine 200 mg /kg	0.6 ± 0.05[bc]	27 ± 2.74[c]

[a] Significantly different from the negative control.
[b] Significantly different from the positive control.
[c] Significantly different from the Narginine 100 mg /kg.

4. Discussion

To the best of our knowledge, this is the first paper that study the effect of NG (as the major metabolite of N) against CP-induced nephrotoxicity in animal model. Our findings showed that administration of NG at different doses (100 mg/kg and 200 mg/kg), significantly attenuated the nephrotoxicity induced by CP as confirmed by the high level of creatinine and urea, in addition to the increase in the antioxidant capacity as well as decrease in the lipoperoxidation among the affected animals. In addition, histopathological and immunohistochemical studies with NG co-treatment confirm the protective role of NG against the signs of nephrotoxicity with a maximum effect obtained at higher NG dose (200 mg/kg).

The nephrotoxicity of CP is unfortunately overlooked because creatinine level did not disturb significantly (Estakhri et al., 2013). Coadministration of NG along with CP showed significant nephroprotective properties reflected through the significant drop in the creatinine and urea levels as compared with the positive control group. Similar findings confirm the nephroprotective role of NG in other nephroprotective animal models (Ahmed et al., 2019; Hermenean et al., 2013).

The anti-malignant properties of CP are likely related to its active toxic metabolites (phosphoramide and acrolein), that delay the growth of malignant cells. Phosphoramide is accountable for the mutagenic action of CP. Acrolein inhibits the cellular antioxidant defense loop, resulting in the formation of highly ROS which interacts with body amino acids, result in physiological and morphological changes (Caglayan et al., 2018; Kim et al., 2014).

Our finding indicates that, treatment with CP decreases SOD, CAT, and TAC (enzymatic) activities and GSH (non-enzymatic) levels while increasing MDA levels in the tissues of kidney in comparison to the negative control group levels. Both NG doses (100 mg/kg and 200 mg/kg), boost the antioxidant capacity in the damaged kidney which could be explained the nephroprotective mechanisms of NG on CP-induced renal damage. These findings are in agreement with a previous report (Ahmed et al., 2019).

The anti-nephrotoxic potential of NG could be attributed to the navel orange peel which contains a significant concentration of flavonoids that interact with and neutralize ROS and RNS (Cavia-Saiz et al., 2010). In accordance with our results, several published evidence stated that citrus fruit extracts and NG have the potential to suppress oxidative stress, metal chelating, and anti-free radical scavenging activities as well as enhance the antioxidant defense system in kidneys (Cavia-Saiz et al., 2010; Guimarães et al., 2010). Interestingly, pretreatment with NG showed significant nephroprotective effects against carbon tetrachloride-induced injuries in the animal model (Hermenean et al., 2013).

CP results in the desquamation and necrosis of the kidney tubules' lining epithelial cells. Tubular degeneration is characterized by cortical degeneration, inflammation, and cell infiltration. Furthermore, the injured animal's kidney developed interstitial edema and bleeding from CP-induced cortical tubular acidophilic material accumulation and vacuolization, as well as glomerulonephritis (Dobrek et al., 2017). The observed nephroprotective effects of NG in the current study were accompanied with the amendment of the histological and architecture integrity of the study renal tissue, which reflects the ameliorative properties of NG on the injured kidney.

KIM-1 is a brand-new biomarker for renal injury brought on by ischemia or any number of nephrotoxic substances. In cases of kidney injury, the cell membrane glycoprotein KIM-1, which serves as a receptor for apoptosis, and is unregulated in kidney tubular, cells (Ichimura et al., 2012). Because of its high expression in damaged kidney tissue, it is considered a remarkably sensitive indicator of nephrotoxicity (Bonventre, 2009). The over expression of KIM-1

Table 2
Effects of Naringenin on oxidative status and antioxidant capacity.

Groups	Means ± SD				
	GSH (U/L)	SOD (U/L)	CAT (U/L)	TAC mmol Trolox equiv/L	MDA (nmol/ml)
Control negative	20.83 ± 1.36[b]	14.37 ± 1.34[b]	9.42 ± 0.91[b]	0.85 ± 0.03[b]	18.47 ± 1.34[b]
Control positive	10.42 ± 0.91[a]	5.54 ± 0.32[a]	4.69 ± 0.12[a]	0.67 ± 0.01[a]	30.52 ± 2.52 [a]
Narginine 100 mg /kg	16.12 ± 1.12[b]	9.67 ± 0.82[b]	6.58 ± 0.27[b]	0.75 ± 0.02[b]	24.75 ± 1.71[b]
Narginine 200 mg /kg	19.61 ± 1.15[b]	13.87 ± 1.12[b,c]	8.97 ± 0.46[a]	0.81 ± 0.03[b]	18.64 ± 1.68[b,c]

GSH = Glutathione, SOD = superoxide dismutase, CAT = catalase, TAC = total antioxidant capacity, MDA = malondialdehyde.
[a] Significantly different from the negative control.
[b] Significantly different from the positive control.
[c] Significantly different from the Narginine 100 mg /kg.

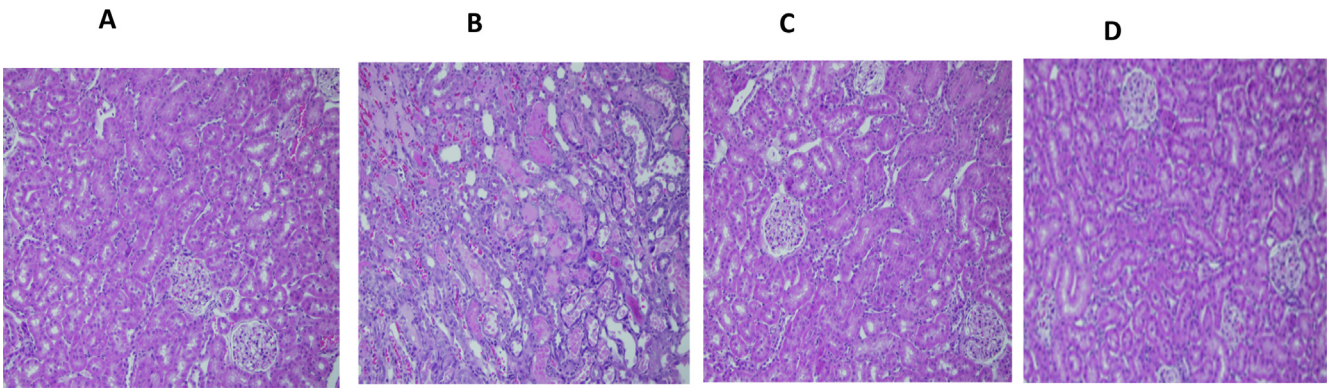

Fig. 1. Rat kidney histopathology (H&E, 200) from the following groups: (A) negative control group demonstrating normal kidney histology; (B) positive control group demonstrating marked distortion of kidney architecture, widespread necrosis of renal tubules, tubular dilatation, epithelial desquamation, vacuolization, and coagulative necrosis; (C) Naringenin 100 mg/kg + cyclophosphamide and (D) Naringenin 200 mg/kg + cyclophosphamide groups, respectively, demonstrating that normal kidney architecture is preserved.

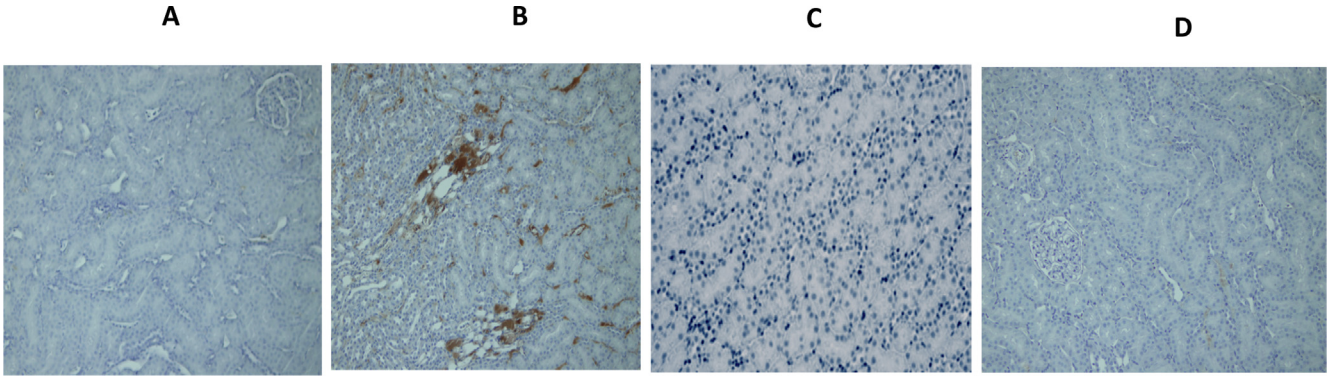

Fig. 2. Immunohistochemistry (200x) of inducible nitric oxide synthase (iNOS) of rat kidneys from (A) negative control group showing no staining (NS); (B) positive control group showing an obviously increased level of iNOS immunostaining in brown color; (C) Naringenin 100 mg /kg + cyclophosphamide group showing a marked decrease in iNOS positivity, and (D) the Naringenin 200 mg /kg + cyclophosphamide group showing no staining (NS).

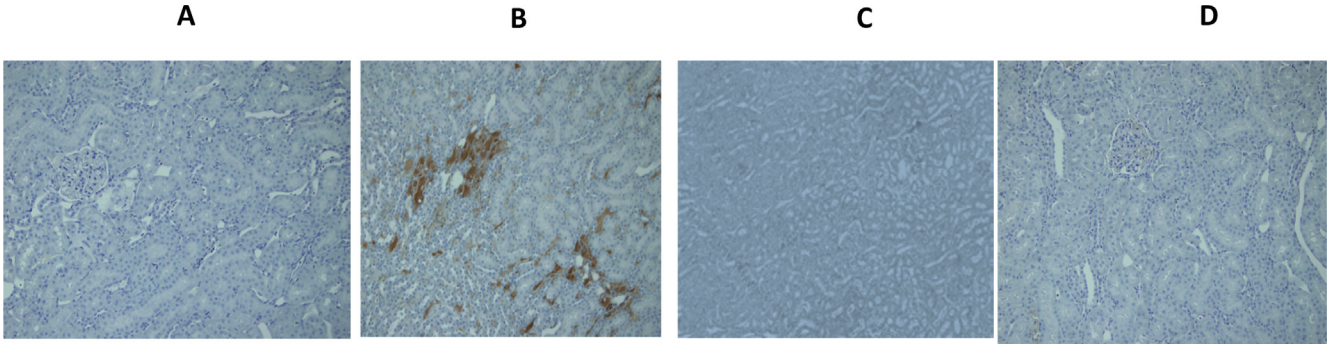

Fig. 3. Kidney injury molecule-1 (KIM-1) immunohistochemistry of rat kidneys from (A) The negative control group exhibits no staining (NS); (B) the positive control group exhibits a clear rise in KIM-1 immunostaining in a brown hue, (C) the Naringenin 100 mg /kg + cyclophosphamide group exhibits a conspicuous decrease in KIM-1 positivity, and (D) the Naringenin 200 mg /kg + cyclophosphamide group exhibits no staining (NS).

in response to exposure to several nephrotoxic substances indicates that this protein could be a useful test for renal injury as well as the repairing mechanism (Ichimura et al., 2004). Consistent with previously reported model, NG significantly reduced KIM-1 expression in the affected animals (Khan et al., 2020).

5. Conclusions

The current study's findings showed that NG has significant potential properties against CP-induced renal damage, which were evidenced by amelioration of the renal function parameters and antioxidant activities as well as mending the histopathological and immunohistochemical changes in rats. The current results may provide new interesting opportunities for the development of natural interventions against CP-induced renal injury.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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